World Health Organization

Department of Immunization, Vaccines and Biologicals (IVB)

SAGE

April 2013

Strategic Advisory Group of Experts
9-11 April 2013

CCV, Geneva

SAGE April 2013

This booklet contains key background documents for the meeting of the Strategic Advisory Group of Experts on Immunization (SAGE), 9-11 April 2013.

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

http://apps.who.int/immunization/sage/meetings/2013/april/en/

For password, please send an e-mail to:
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World Health Organization

Draft Agenda
Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)
9 – 11 April 2103
CCV/CICG, Geneva

Tuesday, 9 April 2013

Time	Session	Purpose of session, target outcomes and questions for SAGE	
9:00	**Welcome - introduction** H. Rees, Chair of SAGE		20 min.
9:20	**Report from Director, IVB - Session 1** Global report including key updates and challenges from regions, J.-M. Okwo-Bele, WHO, 40 min. Discussion: 1h 50 min.	**FOR INFORMATION**	2h 30 min.
10:30	**Coffee/tea break**	**Break**	**30 min.**
11:00	**Report from Director, IVB - Session 1, (Contd.)**		
12:20	**Reports from other Advisory Committees on Immunization - Session 2** Report of the Global Advisory Committee on Vaccine Safety (GACVS), M. Wharton, Chair of GACVS, 10 min. Discussion: 10 min. Report of the Immunization Practices Advisory Committee (IPAC), S. Deeks, Chair of IPAC, 10 min. Discussion: 10 min.	**FOR INFORMATION**	40 min.
13:00	**Lunch**	**Break**	**1h**

14:00	**Dengue - Session 3** Introduction to dengue epidemiology and disease burden, C. Simmons, Hospital for Tropical Diseases, Ho Chi Minh City, 10 min. Current status of dengue vaccine development, J. Roehrig, US Centers for Disease Control and Prevention, 20 min. Critical issues for future vaccine introduction, P. Palihawadana, SAGE member, 10 min. Discussion: 50 min.	**FOR INFORMATION** • Update on disease and vaccine development status • Initial feedback from SAGE on: - Data needs for future recommendations on vaccine use - Critical issues in preparation for future vaccine introduction	1h 30 min.
15:30	**Coffee/tea break**	**Break**	**30 min.**
16:00	**Global polio eradication initiative - Session 4** Polio Eradication and Endgame Strategic Plan: Issues for SAGE decisions in 2013-15. B. Aylward, WHO, 10 min. Discussion: 10 min. Detection and interruption of poliovirus transmission: progress and contingency planning to address insecurity and social acceptance in the last endemic areas. H. Jafari, WHO, 20 min. Discussion: 30 min. Planning for OPV2 withdrawal: status of pre-requisites and Polio Working Group priorities for 2013-14. E. Miller, Chair of SAGE Polio Working Group, 20 min. Discussion: 30 min. Polio legacy planning in the Polio Strategic Plan 2013-2018, TBD, 10 min. Discussion: 20 min.	**FOR DISCUSSION** - To orient SAGE on the key technical decisions which will be required during the coming 36 months, to facilitate SAGE and Regional TAG planning. - To seek SAGE advice on managing the two major emerging risks to eradication in the last endemic areas: insecurity and social acceptance. - To seek SAGE concurrence on the workplan of the SAGE Polio Working Group. - To outline current thinking on GPEI legacy planning and seek input from SAGE in advance of developing a discussion paper for 2013 Regional Committee Meetings.	2h 30 min.
18:30	**Cocktail**		

Wednesday, 10 April 2013

08:00	**Yellow fever - Session 5** Introduction and status report on yellow fever control, O. Tomori, Chair of SAGE working group on Yellow Fever vaccines, 10 min. Questions: 10 min. Evidence review with respect to the duration of protection and vaccine safety in special populations, E. Staples, SAGE working group on Yellow Fever vaccines, 30 min. Discussion: 20 min. Other evidence reviewed by the SAGE working group. A. Barrett, SAGE working group on Yellow Fever vaccines, 15 min. Discussion: 15 min. Proposed recommendations. O. Tomori, Chair of SAGE working group on Yellow Fever vaccines, 10 min. Discussion on the proposed recommendations: 40 min.	**FOR DECISION** Present SAGE with the report of the SAGE working group on yellow fever vaccines and request SAGE's endorsement of the proposed recommendations. Specifically, SAGE will be asked to: • Reconsider the need for booster doses every 10 years; • Review the safety profile of the vaccines and update the recommendations in the context of safety issues including in particular with respect to immunization of HIV infected populations and immunocompromised, in pregnant or lactating women, people over 60 years old and in context of viscerotropic and neurological diseases; • Review the role of routine vaccination versus outbreak control; • Review the impact of the combined vaccination strategy (routine immunization and preventive campaigns); • Review of interference between yellow fever and other vaccines and co-administered vaccination. SAGE will also be asked to identify critical research questions. SAGE recommendations on vaccine use will then be used to update the 2003 WHO position paper on the use of yellow fever vaccines.	2h 30 min.
10:30	**Coffee/tea break**	**Break**	**30 min.**

11:00	**Non-specific effects of vaccines on childhood mortality - Session 6** Why are we reviewing the evidence on non-specific effects of vaccines on mortality in children under 5 years of age and update on the related SAGE working group? T. Nolan, Chair of SAGE Working Group on Non-Specific Effects of Vaccines, 15 min. Sequence of vaccination in Low and Middle Income Countries – data from DHs and MICs surveys, C. Sanderson, London School of Hygiene and Tropical Medicine, UK, 15 min. Systematic reviews protocols: A. Reingold, University of California, Berkeley, USA, 15 min. Discussion: 45 min.	**FOR INFORMATION AND DISCUSSION** To update SAGE on the establishment and proceedings of the SAGE WG on Non-Specific Effects of Vaccines. To get SAGE's input on the key related questions from the global immunization policy perspective? Ask SAGE if the proposed protocols suitable to inform these questions? What adjustments are appropriate? Get SAGE's input on what other evidence should be critically appraised and synthetized.	1h 30 min.
12:30	**Lunch**	**Break**	**1h**
13:30	**Overcoming vaccine hesitancy - Session 7** SAGE working group on vaccine hesitancy: terms of reference and process of work, X. Liang, Chair of the SAGE working group on vaccine hesitancy, 10 min. Vaccine hesitancy: definitions, scope, context specific causes and impact. B. Gellin, Member of the SAGE working group on vaccine hesitancy, 20 min. Discussion: 20 min. Strategies to address hesitancy, success and failures stories. S. Goldstein, Member of the SAGE working group on vaccine hesitancy, 15 min. Discussion: 20 min. Conclusions, recommendations and proposed way forward. X. Liang, Chair of the SAGE working group on vaccine hesitancy, 15 min. Discussion: 50 min.	**FOR DISCUSSION** Present SAGE with a report of the SAGE working group on vaccine hesitancy on activities implemented to date. SAGE's agreement on the definitions, scope and overall approach to vaccine hesitancy. SAGE's feed-back on: the review of strategies to address vaccine hesitancy and its determinants and on further planned work. the proposed list of questions for the assessment of vaccine hesitancy. the proposed list of questions for the assessment of vaccine hesitancy. the draft landscape analysis of organizations dealing with vaccine hesitancy. Review and discuss the conclusions , current recommendations and way forward proposed by the working group in relation with its terms of reference.	2h 30 min.

15:30	**Coffee/tea break**		**30 min.**
16:00	**Vaccine hesitancy – Session 7 (Contd.)**		
16:30	**Report from GAVI - Session 8** Report from the GAVI Alliance, S. Berkley, GAVI Alliance, 20 min. Discussion: 20 min.	**FOR INFORMATION**	40 min.
17:10	**End of day**		

Thursday, 11 April 2013

08:00	**Optimization of *Haemophilus influenza* type b immunization schedules - Session 9** Why are we reviewing the evidence on Hib vaccine and what are the questions for SAGE today? J. Abramson, SAGE member, 10 min. What evidence is available (from long term impact studies in 35 countries, observational studies and RCTs) on the number of doses, age at administration, interval between doses, duration of protection and combination vaccines. R. Hajjeh, US Centers for Disease Control and Prevention, 25 min. Adjusting the Impact and assessment of incremental benefits of various Hib vaccines schedules given the disease epidemiology and the actual age at vaccination, A. Clark, London School of Hygiene and Tropical Medicine, 10 min. Questions for clarification: 15 min. What are the optimal schedules for Hib vaccines for children living in different epidemiological settings? J. Abramson, SAGE member, 10 min. Discussion: 50 min.	**FOR DECISION** What are the optimal schedules for Hib vaccines for children living in different epidemiological settings? How many primary doses, need for boosters? Age at first dose, interval between doses? Does the type of vaccine influence the choice of schedule? Effect of type of Hib vaccine on effectiveness. Effect of wP and aP on Hib vaccine effectiveness.	2h
10:00	**Coffee/tea break**	**Break**	**30 min.**
10:30	**Update on RTS,S/AS01 and the malaria vaccines pipeline - Session 10** Status of RTS,S/AS01 project. D. Kaslow, Malaria Vaccine Initiative, 15 min. Assessment and critical issues for policy assessment. P. Smith, (By telephone connection), Chair of the Joint Technical Expert Group on malaria vaccines (JTEG), TBC, 20 min. Discussion: 45 min. Updated Malaria Vaccine Roadmap and Development of malaria vaccine preferred product characteristics (for prevention of disease young children and for achievement of elimination). P. Alonso, Member of the Malaria Policy Advisory Committee, 10 min. Discussion: 30 min.	**FOR DISCUSSION** Update SAGE on on RTS,S/AS01 and the malaria vaccines pipeline. Request SAGE's input into WHO/JTEG actions required to prepare for 2015 policy decision on RTS,S/AS01 malaria vaccine. Request SAGE's input on the development of preferred product characteristics.	2h
12:30	**Closing**		
12:50	**End of meeting**		

World Health Organization

Meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization
9 – 11 April 2013
Geneva, Switzerland

SAGE members

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CURRENT SAGE WORKING GROUPS

1. 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, Chair of Working Group. Health Protection Agency, United Kingdom
- Jon Abramson, 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, United States of America
- Janet Englund, Seattle Children's Hospital, United States of America
- 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, United Kingdom
- Barry Schoub, National Institute for Communicable Diseases, South Africa

WHO Secretariat

- John Tam
- Philippe Duclos
- Cuauhtémoc Ruiz-Matus
- Nahoko Shindo, replaced by Anthony Mounts in October 2011

2. 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

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

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

WHO Secretariat

- Bruce Aylward
- Rudi Tangermann
- Roland Sutter
- Tracey Goodman
- Philippe Duclos

3. SAGE Working Group on vaccination in humanitarian emergencies (June 2011)

Terms of Reference

Develop a framework for public health decision-making for vaccination in humanitarian emergencies, to be reviewed by SAGE in April 2012.

The specific question that needs to be addressed:

What key scientific, ethical, economic, public health, operational and political criteria should be part of a decision-making framework to guide the use of vaccines in emergencies?

The approach to address this question may include:

Reviewing experiences with vaccination in humanitarian emergencies, compile the available data, identify the information gaps, guide the work required to address the information and action gaps, and prepare for a SAGE review of the general guidance on vaccination in humanitarian emergencies.

Specific issues to review in support of this approach would be:

- Defining the scope of humanitarian emergencies;

- Review of vaccination experiences in humanitarian emergencies with particular focus over the last 10 years and with respect to the political, ethical, public health/scientific, operational and economic aspects:
- Vaccine preventable disease (VPD) burden and other available interventions for the prevention and control of these diseases;
- Public health/scientific issues (evidence for effectiveness; purpose individual protection and/or interruption of transmission)
- Economic aspects
- Opportunity costs (due to competing public health priorities);
- Availability of vaccines and acceptability range of cost per person immunized;
- Operational/Programmatic Feasibility - supply availability, logistics need, procurement process and funding, human resources need and availability, cold chain space, training needs, supervision, injection safety, waste management, security, vaccine characteristics, regimens, regulatory issues; etc.
- Ethical issues.

Composition

SAGE Members

- Helen Rees, Chair of Working Group. University of Witwatersrand, South Africa
- Zulfiqar Bhutta, The Aga Khan University, Pakistan
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia
- Xiaofeng Liang, Chinese Center for Disease Control and Prevention, China
- Narendra Arora, International Clinical Epidemiology Network, India

Experts

- Brenton Burkholder (Member until November 2011. In December 2011, Dr Burkholder was recruited by WHO and as such is no longer eligible to serve as a formal member of the working group).
- Jorge Castilla, Health Sector Expert, European Commission DG for Humanitarian Aid, Kenya
- Francesco Checchi, London School of Hygiene and Tropical Medicine, UK.
- Alejandro Cravioto, Executive Director, International Centre for Diarrhoeal Disease Research, Bangladesh.
- Rebecca Freeman Grais, Epicentre, France.
- Keymanthri Moodley, Bioethics Unit, Faculty of Health Sciences, University of Stellenbosch, South Africa.
- Gopinath Nair, Scientific and Administrative Head of National Institute of Cholera and Enteric Diseases, India (resigned for personal reasons in September 2011).
- Robin Nandy, Polio Eradication, UNICEF.
- Muhammad Ali Pate, National Primary Health Care Development Agency, Nigeria.
- Ronald Waldman, Global Health Bureau, Avian and Human Influenza Unit, US Agency for International Development, USA.

WHO Secretariat

- Peter Mala
- Peter Strebel
- Pem Namgyal
- Claire-Lise Chaignat
- Michelle Gayer

4. SAGE working group on yellow fever vaccines (established September 2011)

Terms of reference

Review the evidence and prepare recommendations related to the use of yellow fever vaccines and contained in the 2003 WHO position paper for SAGE review, and subsequent publication of an updated vaccine position paper.

The questions particularly to be addressed include the following:
1. Reconsider the need for booster doses every 10 years including for travellers in the context of the International Health regulations;
2. Review the impact of routine vaccination versus outbreak control;
3. Review the impact of the combined vaccination strategy (routine immunization and preventive campaigns);
4. Review the safety profile of the vaccines and update the recommendations in the context of safety issues including in particular with respect to immunization of HIV infected populations and immunocompromised, in pregnant or lactating women, people over 60 years old and in context of viscerotropic and neurological diseases;
5. Review of interference between yellow fever and other vaccines and co-administered vaccination.

Composition

SAGE Members

- Claire-Anne Siegrist, University of Geneva, Switzerland
- Piyanit Tharmaphornpilas, National Immunization Program, Ministry of Public Health, Thailand
- Oyewale Tomori, Chair of Working Group. Redeemer's University, Nigeria

Experts

- Chantal Akoua-Koffi, Virologist Head, Department of Biology, University of Bouake, Côte d'Ivoire
- Alan Barrett, Virologist, Director, Sealy Center for Vaccine Development, USA
- Li Dexin, Director, National Institute of Viral Diseases Control and Prevention, Centers for Disease Control, China
- Eduardo Gotuzzo, Clinician and Yellow Fever specialist, Department of Medicine, Universidad Peruana Cayetano Heredia, Peru
- Dede Kusmiaty, National Agency of Drug and Food Control, Indonesia
- Maryanne Neill, Retired, Monitoring Officer, Immunizations UNICEF, USA
- Matthias Niedrig, Virologist, Robert Koch Institute, Germany
- Jennifer Staples, Epidemiologist Centers for Disease Control and Prevention, USA
- Pedro Vasconcelos, Virologist and Epidemiologist, Instituto Evandro Chagas, Brazil

WHO Secretariat

- Sergio Yactayo
- Joachim Hombach
- Philippe Duclos

5. 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., QUIVER 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
- David Durrheim, Hunter New England Area Health Service and Professor of Public Health, Australia
- Peter Figueroa, Chair of Working Group. University of the West Indies, Jamaica
- Helen Rees, University of Witwatersrand, South Africa

Experts

- Hyam Bashour, Department of Family and Community Medicine, Damascus University, Syria
- Natasha Crowcroft, Surveillance and Epidemiology, Public Health Ontario, Canada
- Heidi Larson, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, United Kingdom
- 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

WHO Secretariat

- Alya Dabbagh
- Robert Perry
- Peter Strebel

6. 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
- Arthur Reingold, University of California at Berkeley, U.S.A.

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, U.S.A.
- Susan Goldstein, Soul City: Institute for Health and Development Communication, South Africa
- Heidi Larson, London School of Hygiene and Tropical Medicine, England
- Noni MacDonald, Dalhousie University, Canada
- Mahamane Laouali Manzo, Ministry of Health, Niger
- 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

WHO Secretariat

- Philippe Duclos
- Melanie Schuster

7. 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 (IVIR) Advisory Committee (formerly known as QUIVER).

Composition

SAGE Members

- Jon Abramson, Chair of Working Group, Department of Paediatrics, Wake Forest University School of Medicine, U.S.A.
- 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, U.S.A.
- 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, U.S.A.
- 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)

WHO Secretariat

- Philippe Duclos

8. 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 new-borns

- 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

- Elizabeth Miller (Working Group Chair), Immunisation Department, Colindale, UK
- Claire-Anne Siegrist, Department of Pediatrics, University of Geneva, Switzerland
- 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

WHO Secretariat

- Philippe Duclos
- Jose Mauricio Landaverde

9. 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, NICED, ICMR, Kolkata, India

WHO Secretariat

- Ana-Maria Henao-Restrepo

Strategic Advisory Group of Experts (SAGE)
Terms of reference

Functions

SAGE serves as the principal advisory group to the World Health Organization (WHO) for development of policy related to vaccines and immunization. SAGE is charged with advising WHO on overall global policies and strategies, ranging from vaccine and technology research and development, to delivery of immunization and linkages between immunization and other health interventions. The mandate of SAGE is to provide strategic advice rather than technical input, and is not restricted to childhood vaccines and immunization but extends to the control of 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 Global Immunization Vision and Strategy (GIVS);
2. major issues and challenges to be addressed with respect to achieving the goals of GIVS;
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 GIVS 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, and 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, including the Chairperson, shall be appointed to serve for an initial term of three years. Such three-year terms may only be renewed once.

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 interest 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 agreement(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 the 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 twice annually. The frequency of meetings may, however, be adjusted as necessary. Decisions or recommendations will, as a rule, be taken by consensus.

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 in exceptional situations to help address specific questions identified by SAGE when the issue is particularly complicated and could not be addressed by 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 participations will be expected from all SAGE members throughout the year, including participation in SAGE working groups, video and telephone conferences as well as 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 further translated and posted on the IVB Departmental website.

Annex 1: **DECLARATION OF INTERESTS FOR WHO EXPERTS**

The assistance of distinguished authorities knowledgeable in a variety of medical and scientific professions is essential to the solution of international health issues. **It is expected that persons qualified to serve as an expert for the World Health Organization (WHO) may have private interests related to the subject of their expertise. At the same time, it is imperative that situations be avoided in which such interests may unduly affect, or may be perceived to affect, an expert's impartiality or the outcome of work in which he/she was involved.**

To assure the highest integrity, and hence public confidence, in the activities of the Organization, WHO regulations and policies require that all experts serving in an advisory role disclose any circumstances which could give rise to a **potential conflict of interest** (i.e., any interest which may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). Accordingly, in this Declaration of Interest form, you are requested to disclose any financial, professional or other interest relevant to the subject of the work or meeting in which you will be involved and any interest that could be significantly affected by the outcome of the meeting or work. You are also asked to declare relevant interests of others who may, or may be perceived to, unduly influence your judgment, such as immediate family members, employers, close professional associates or any others with whom you have a substantial common personal, financial or professional interest.

Kindly complete this form and submit it to WHO Secretariat, well in advance of the meeting or work. You are also asked to inform the Secretariat of any change in this information that occurs before or during the course of the meeting or work. If WHO considers that a potential conflict of interest exists, one of several outcomes can occur, depending on the circumstances involved: (i) you may be invited to continue to participate in the meeting or work, provided that your interest would be publicly disclosed; (ii) you may be asked not to take part in the portion of the meeting, discussion or work related to your interest, or not participate in related decisions; or (iii) you may be asked not to take part in the meeting or work altogether. Non-completion of the DOI form would preclude further consideration of an expert's participation.

Experts are requested to agree that any relevant conflicts may be **publicly disclosed** to other meeting participants and in the resulting report or other work product. The Secretariat will assume that you consent to such a disclosure, unless you check "no" in the space provided on the last page of this form. The information disclosed by you **may later be made available** to persons outside of WHO if the objectivity of the work or meeting in which you are involved is questioned and the Director-General considers disclosure to be in the best interests of the Organization, although only after discussion 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):

_____

_____

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, your employer and your immediate family members (i.e., spouse (or partner with whom you have a similar close personal relationship) and your minor children). "Commercial entity" includes -- aside from any commercial business -- an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources having 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 3 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work? Please also report any application or negotiation for future work.

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

RESEARCH SUPPORT

Within the past 3 years, have you or your department or research unit received support or funding from a commercial entity or other organization with an interest related to the subject of the meeting or work? Please also report any application or award for future research support.

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

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

INVESTMENT INTERESTS

Do you have current investments (valued at more than US$10 000 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.

3a Stocks, bonds, stock options, other securities (e.g., short sales) Yes ☐ No ☐

3b Commercial business interests (e.g., proprietorships, partnerships, joint ventures) Yes ☐ No ☐

INTELLECTUAL PROPERTY

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

4a Patents, trademarks, or copyrights (also include pending applications) Yes ☐ No ☐

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

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 ☐ No ☐

5b Have you held an office or other position, paid or unpaid, where you may be expected to represent interests or defend a position related to the subject of the meeting or work? Yes ☐ No ☐

ADDITIONAL INFORMATION

6a *If not already disclosed above, have you worked for the competitor of a product which 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 financial or commercial competitive advantage?* Yes ☐ No ☐

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, financial or professional interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes ☐ No ☐

6c Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes ☐ No ☐

Yes ☐ No ☐

7. ***TOBACCO OR TOBACCO PRODUCTS*** (answer without regard to relevancy to the subject of the meeting or work)

Within the past 3 years, have you had employment or received research support or other funding from the tobacco industry 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 provide, the amount or value of the interest, where requested, it will be assumed to be significant.

Nos. 1 - 4: 7 **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. The Secretariat will assume that you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product, unless you check "no" in the space provided here. If you check "no", the Secretariat will not disclose the information without your prior approval, although this may result in your not being able to participate in the meeting or conference. **No:** ☐

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 due to the fact that I acquire additional interests, I will notify the responsible staff of WHO and complete a new declaration of interests detailing the changes. This includes any change which occurs before or during the meeting or work itself and through the period up to the publication of the final results.

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.

Signed:

Signature……...

Name…….
(print or type)

CONFIDENIALITY1.

Annex 3: Purpose, structure and functioning of the Strategic Advisory Group of Experts on Immunization (SAGE) Working Groups

Working Group Purpose and decision to establish SAGE Working Groups

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

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

The need and charge for a working group is discussed and agreed during SAGE meetings.

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 meeting leading to the establishment of the working group.

TORs and proposed related expertise to serve on the Working Group are developed jointly by the SAGE member serving as Working group Chair and the Lead WHO technical staff. Final decision is taken jointly by the SAGE Chair 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 Groups charged with responsibility in the identified areas of conflict.

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

A public call for nomination of Working group members will be posted on the SAGE website together with the relevant terms of reference of the Working Group and indication of the desirable expertise. SAGE members, regional offices, WHO staff and key partner organization will also be approached for potential nominations. From the pool of nominees, the Working Group Chair 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.

Individuals other than SAGE members and organization representatives may participate in SAGE Working Groups meetings only by secretarial invitation in consultation with either Chairs of SAGE or of the Working Group. Occasionally the Working Group Chair, in consultation with the Lead WHO staff and the SAGE Chair, may request the participation of additional disease / vaccine experts who are not members of the working group. These may include SAGE members, organization representatives, industry representatives/experts, public health officials and faculty of academic institutions. Other experts, including representatives of vaccine manufacturers may be asked to provide information to the Working Groups on an ad hoc basis and as needed.

WHO staff perform, coordinate, or identify scientific studies and outbreak investigations to address questions that arise regarding appropriate vaccine policy decisions; conduct analysis of data addressing efficacy, effectiveness, safety, feasibility, and economic aspects of immunization policy.

Modus Operandi

SAGE Working Groups are not allowed to render consensus advice or recommendations directly to the WHO DG. 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 the 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 terminating in development of group consensus and recommendations must occur in the open public forum of SAGE meetings.

Working Group Process.

Effective communication and a strong working collaboration between the Working Group Chair and the Lead WHO staff are significant determinants of the effectiveness of a Working Group. The development of a brief (1-2 pages) summary of each Working Group meeting by one of these people will facilitate the function of the Working Group. Summaries should be provided to the SAGE Executive secretary so that IVB senior staff, immunization Regional Advisers and SAGE members can be informed in real time of progress and issues.

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 allows 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 scheduled in association with SAGE meetings and should be anticipated at least 2 months in advance of the SAGE meeting. WHO routinely supports travel costs for the duration of SAGE meetings for SAGE members, chairs of regional technical advisory groups, WHO Regional Advisers and any experts invited to present at SAGE. WHO may support travel for additional persons for the purpose of a WG meeting. Such requests should be brought to the SAGE Executive Secretary for consideration on a case by case basis, with justification for the increased costs.

As issues mature, proposals for presentation to the SAGE should be submitted to the SAGE Executive secretary at least 10 weeks ahead of each SAGE meeting for circulation to SAGE members and to WHO staff. At this stage, formal interaction between the SAGE Working Group Chair, lead WHO staff, SAGE Executive secretary and the SAGE Chair should occur allowing for a briefing on the issue at hand and ensuring that areas of potential conflict are recognized prior to the meeting itself.

Decision to proceed with tabling the issue at the next SAGE meeting will then be taken jointly by the Chair of SAGE and IVB Director after consideration of issues raised during the consultative process.

Management of Conflict of Interest / Undue Influence

When a SAGE Working Group is formed, and at the start of each Working Group meeting, participants should respond to a request to report conflicts of interest relevant to the focus of the Working Group. This is done using the eDOI. SAGE members, organization representatives or WHO staff who have conflicts of interest may not participate in the Working Group. Persons who serve as consultants, may participate in the Working Group despite conflicts of interest if, in the judgment of the SAGE Chair, SAGE Executive Secretary, Working Group Chair and lead WHO staff they bring specific expertise that is essential to the efforts of the Working Group. However, conflicts, both personal and those of their liaison organization (in the case of liaison representatives), must be declared and recorded at the beginning of each Working Group meeting. Participation of all persons with declared conflicts will be restricted by the Working Group Chair and lead WHO staff to that necessary for the Working Group to benefit from the expertise provided by the consultant. No person with an identified conflict of interest should participate in drafting policy options or policy recommendations.

All consultants participate in Working Groups at the discretion of the Working Group Chair and lead WHO staff. The value and impact of SAGE recommendations and WHO policies and recommendations are critically dependent upon public trust in the integrity of the process. Thus, participation of any consultant may be curtailed, even in the absence of a declared conflict of interest, if in the judgment of the Working Group Chair and the lead WHO staff a potential for the appearance of undue influence exists.

Strategic Advisory Group of Experts (SAGE) on Immunization
9 - 11 April 2013
CICG/CCV

Provisional List of Participants

SAGE member

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Meeting of the Strategic Advisory Group of Experts on immunization, November 2012 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization[1] met on 6–8 November 2012 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

In 2011, globally 90% of children received the first dose of diphtheria-tetanus-pertussis (DTP) containing vaccine. However, high drop-out rates between the first dose (DTP1) and the third dose (DTP3) remained problematic in several countries, resulting in global DTP3 coverage estimated at only 83%. In 64 of the 194 WHO member states, DTP3 coverage was <90%. If every child who received DTP1 also completed the primary vaccination series, an additional 30 countries would reach the goal of 90% DTP3 coverage. Concerns were expressed over vaccine coverage, which has remained level over the last few years, and the degree of uncertainty in global coverage estimates, which is not reported. The degree of uncertainty both in terms of precision and potential bias is needed to avoid misinterpretation and a negative impact on policy formulation and implementation.

The African Region (AFR) will celebrate the vaccination of 100 million persons with a meningococcal A conjugate vaccine. To date, not a single case of meningococ-

[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 6–8 November 2012 together with summarized declarations of interests provided by SAGE members are available at http://www.who.int/immunization/sage/meetings/2012/november/en/index.html; accessed in November 2012.

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, novembre 2012 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) sur la vaccination[1] s'est réuni du 6 au 8 novembre 2012 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

À l'échelle mondiale en 2011, 90% des enfants ont reçu la première dose du vaccin contre la diphtérie, le tétanos et la coqueluche (DTC). Néanmoins, le problème des taux d'abandon élevés entre la première dose (DTC1) et la troisième (DTC3) a subsisté dans plusieurs pays, entraînant une couverture mondiale du DTC3 estimée à seulement 83%. Dans 64 des 194 États Membres de l'OMS, la couverture du DTC3 était <90%. Si chaque enfant auquel le DTC1 est administré terminait également la série de la primo-vaccination, 30 pays supplémentaires atteindraient l'objectif d'une couverture du DTC3 de 90%. Des inquiétudes ont été exprimées à propos de la couverture vaccinale, qui n'évolue plus ces dernières années, et du degré de confiance des estimations de la couverture mondiale qui n'est pas indiqué. Il est nécessaire d'avoir le niveau d'incertitude, en termes de précision comme de biais potentiel, pour éviter les erreurs d'interprétation et un effet négatif sur l'élaboration et la mise en œuvre des politiques.

La Région africaine va célébrer la vaccination de 100 millions de personnes avec le vaccin conjugué contre le méningocoque A. À ce jour, aucun cas de méningite à ménin-

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

[2] La série complète des communications et des documents de travail de la réunion du SAGE tenue du 6 au 8 novembre 2012, 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/2012/november/en/index.html; consultée en novembre 2012.

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cal serogroup A meningitis has been reported in vaccinated individuals.

The Region of the Americas (AMR) celebrated the 10th anniversary of the Vaccination Week which has now become a global event. The process to document and verify the absence of endemic measles, rubella and congenital rubella syndrome is progressing well with the majority of countries and territories having submitted their elimination reports for review by the verification commission. The Emergency Plan of Action to maintain measles/rubella regional elimination in the Americas was developed to maintain high quality surveillance and high levels of immunization coverage, and ensure effective outbreak response.

The Eastern Mediterranean Region (EMR) has successfully sustained high immunization rates due to high levels of population demand, including in those countries which have recently experienced civil unrest; however there is concern that reductions in coverage may occur over the longer term if insecurity is prolonged. The Regional Committee reaffirmed the importance of pooled vaccine procurement for non-GAVI eligible low-middle-income countries (LMICs). This initiative will now help these countries to procure pneumococcal conjugate (PCV), rotavirus and *Haemophilus influenza* type b (Hib) vaccines through the UNICEF procurement systems.

The European Region (EUR) reported that failure to close the gaps in measles immunization coverage (mostly in older age groups) has led to the recent European outbreaks.

The South-East Asia Region (SEAR) reported that most countries carried out activities related to the Regional Committee initiative that declared 2012 as the year for Intensification of Routine Immunization, focusing on increasing access to hard-to-reach, underserved, marginalized and migrant populations.

The Western Pacific Region (WPR) reported serosurveys confirming that nearly all 30 countries have achieved a reduction in the prevalence of HBs antigen carrier rate from 8% to <2% in children aged <5 years. A new milestone – HBs antigen seroprevalence of less than 1% by 2017 – is now proposed by the Regional Technical Advisory Group on immunization, for review and endorsement by the Regional Committee in 2013.

SAGE acknowledged the global successes in the control of vaccine-preventable diseases but noted that determined efforts were still needed to sustain and enhance these achievements. SAGE stressed that country ownership of immunization as an integral component of primary care is essential as well as the need to assure corresponding political commitment to this approach from the highest levels of government.

A constraint experienced across Regions was that 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. The need for SAGE to address this issue was noted.

gocoque du sérogroupe A n'a été signalé chez les sujets vaccinés.

La Région des Amériques a fêté le dixième anniversaire de la Semaine de la Vaccination qui est devenue désormais un évènement mondial. Le processus pour prouver et vérifier l'absence de rougeole endémique, de rubéole et de syndrome de rubéole congénitale progresse bien dans la majorité des pays et territoires ayant soumis leurs rapports d'élimination à l'examen de la commission de vérification. Le Plan d'action d'urgence pour le maintien de l'élimination régionale de la rougeole et de la rubéole dans les Amériques a été élaboré, pour entretenir une surveillance de grande qualité et des niveaux élevés de couverture vaccinale et pour garantir une riposte efficace aux flambées.

Grâce à une forte demande des populations, la Région de la Méditerranée orientale a réussi à maintenir des taux élevés de vaccination, y compris dans les pays ayant récemment connu des troubles civils; on s'inquiète cependant de l'éventualité d'une baisse de la couverture sur le long terme si la situation d'insécurité se prolonge. Le Comité régional a réaffirmé l'importance des achats groupés de vaccins pour les pays à revenu intermédiaire – tranche inférieure (PRITI) ne remplissant pas les conditions pour un soutien de l'Alliance GAVI. Cette initiative aidera désormais ces pays à se procurer le vaccin conjugué contre le pneumocoque (VCP), le vaccin anti-rotavirus et le vaccin contre *Haemophilus influenza* de type b (Hib) par le biais des systèmes d'achat de l'UNICEF.

La Région européenne a signalé que le fait de ne pas arriver à combler les lacunes pour la couverture de la vaccination anti-rougeoleuse (surtout dans les groupes plus âgés) a provoqué les flambées récentes en Europe.

La Région de l'Asie du Sud-Est a indiqué que la plupart des pays ont mené des activités en relation avec l'initiative du Comité régional qui avait déclaré l'année 2012 comme étant celle de l'Intensification de la vaccination systématique, en mettant l'accent sur l'amélioration de l'accès aux populations difficiles à atteindre, mal desservies, marginalisées ou migrantes.

La Région du Pacifique occidental a fait état d'enquêtes sérologiques confirmant que pratiquement l'ensemble des 30 pays sont parvenus à ramener les taux de prévalence des porteurs de l'antigène HBs de 8% à <2% chez les enfants <5 ans. Une nouvelle étape, avec une séroprévalence de l'antigène HBs inférieure à 1% d'ici 2017, est désormais proposée par le groupe consultatif technique régional de la vaccination pour examen et approbation au Comité régional en 2013.

Le SAGE a reconnu les succès mondiaux de la lutte contre les maladies à prévention vaccinale mais il a aussi relevé que des efforts déterminés étaient encore nécessaires pour soutenir et développer ces réalisations. Il a souligné que l'appropriation de la vaccination par les pays en tant qu'élément faisant partie intégrante des soins de santé primaires est essentielle, de même que la volonté politique correspondante pour cette approche aux plus hauts niveaux des gouvernements.

Les pénuries à répétition dans l'approvisionnement en vaccins sont une difficulté vécue dans toutes les régions, pour les programmes de vaccination existants (notamment pour les vaccins contenant le DTC) comme pour les vaccins nouveaux/émergents; elles ont un impact sur la couverture vaccinale dans plusieurs pays. Le besoin, pour le SAGE, de s'occuper de ce problème a été noté.

At country level, key issues to sustain and enhance vaccination coverage include the strengthening of routine immunization by strengthening management activities and revitalization of basic processes such as inter-agency coordinating committees and national immunization technical advisory groups.

SAGE expressed strong concern that despite high coverage with primary and booster pertussis vaccination, there has been a recent resurgence of pertussis in some industrialized countries including among the very young. Reasons for this are complex but may include more rapid waning of immunity with acellular pertussis (aP) vaccines compared to whole cell vaccine. It was agreed that SAGE would establish a working group on pertussis to prepare for a SAGE review of the data and to consider updating current pertussis vaccine recommendations. As it will take a year to formulate this advice SAGE advised countries considering a switch from whole cell to aP vaccines to await further SAGE guidance, or to themselves carefully review the latest evidence on aP pertussis vaccine effectiveness and the possibility that such a switch may lead to a less favourable outcome in terms of pertussis disease control. Countries having already switched to aP vaccines are advised to continue vaccinating and await further guidance before making any further modifications to their programme.

Further to the November 2011 SAGE recommendation, a technical expert group was established to provide advice to WHO on the evaluation of tuberculosis vaccines. This group will provide guidance on the data that is needed from clinical trials to enable an assessment of the possible public health impact of new tuberculosis vaccines. The group will also guide interpretation of data from Phase II, III and IV trials, with a particular focus on the assessment of long-term safety and effectiveness.

The SAGE working group on vaccine hesitancy has produced a definition of confidence, developed a matrix of vaccine confidence drivers, and proposed hesitancy-related indicators for the Global Vaccine Action Plan (GVAP). Other activities under development include a review paper on the causes of hesitancy and the confidence gap, a systematic review on strategies to improve confidence and their impact, including best practices and unpublished success stories from countries, and a set of indicators to measure vaccine confidence.

Report from the GAVI Alliance

In June 2012, the GAVI Board approved a revised new vaccine introduction grant to help countries better prepare for the introduction of new vaccines, with increased support for infant vaccines, operational support for campaigns, and support for human papilloma virus (HPV) vaccine introductions. The Board also approved new windows of support for measles elimination, building on the original US$ 200 million GAVI investments in measles through the Measles Initiative and support for introduction of measles second-dose routine immunization. Additionally, support was approved for the use of measles-rubella vaccine through wide-age campaigns,

Au niveau des pays, les principaux points pour maintenir et développer la couverture vaccinale ont trait au renforcement de la vaccination systématique en développant les activités de gestion et à la revitalisation des processus de base comme les comités de coordination interorganisations et les groupes techniques consultatifs nationaux sur la vaccination.

Le SAGE s'est vivement inquiété du fait que, malgré une couverture élevée de la primovaccination contre la coqueluche et du rappel, il y a eu récemment une résurgence de cette maladie dans certains pays industrialisés, y compris chez les très jeunes. Les raisons en sont complexes mais pourraient comporter une disparition plus rapide de l'immunité avec les vaccins anticoquelucheux acellulaires qu'avec ceux à germes entiers. Il a été convenu que le SAGE allait créer un groupe de travail sur la coqueluche pour préparer un examen des données et envisager une réactualisation des recommandations actuelles sur la vaccination contre la coqueluche. Comme cela va prendre un an pour formuler cet avis, le SAGE a conseillé aux pays envisageant de passer des vaccins à germes entiers aux vaccins acellulaires d'attendre les nouvelles orientations qu'il donnera ou d'examiner eux-mêmes minutieusement les données les plus récentes sur l'efficacité des vaccins anticoquelucheux acellulaires et la possibilité que ce changement pourrait entraîner des résultats moins favorables en termes de lutte contre la maladie. Pour les pays qui sont déjà passés aux vaccins acellulaires, il est conseillé de poursuivre la vaccination et d'attendre les nouvelles orientations avant d'entreprendre d'autres modifications de leur programme.

Suite à la recommandation du SAGE en novembre 2011, un groupe technique d'experts a été mis en place pour donner un avis à l'OMS sur l'évaluation des vaccins antituberculeux. Ce groupe fournira des indications sur les données nécessaires à partir des essais cliniques pour permettre une évaluation des retombées possibles des nouveaux vaccins antituberculeux en santé publique. Il guidera également l'interprétation des données des essais en phases II, III et IV, en mettant plus particulièrement l'accent sur l'évaluation de l'innocuité et de l'efficacité sur le long terme.

Le groupe de travail du SAGE sur la réticence face à la vaccination a produit une définition de la confiance, a mis au point une matrice des inducteurs de confiance et proposé des indicateurs liés à la réticence pour le Plan d'action mondial pour les vaccins (GVAP). Parmi d'autres activités en cours d'élaboration, il y a un document examinant les causes de la réticence et du manque de confiance, un examen systématique des stratégies pour améliorer la confiance et de leurs retombées, avec les meilleurs pratiques et des exemples non publiés de succès dans les pays, ainsi qu'une série d'indicateurs pour mesurer la confiance dans les vaccins.

Rapport de l'Alliance GAVI

En juin 2012, le Conseil de l'Alliance a approuvé une révision de la subvention pour l'introduction de nouveaux vaccins, afin d'aider les pays à mieux s'y préparer, avec une augmentation de l'appui pour les vaccins destinés aux nourrissons, une aide opérationnelle pour les campagnes et une assistance pour les introductions du vaccin contre le papillomavirus humain (HPV). Le Conseil a également approuvé de nouvelles possibilités d'aide pour l'élimination de la rougeole, en s'appuyant sur les investissements de départ de US$ 200 millions de l'Alliance GAVI dans la rougeole, par le biais de l'Initiative contre la rougeole et l'appui à l'introduction de la vaccination systématique par une seconde dose de vaccin antirougeoleux. De plus, une aide a été acceptée pour l'utilisation du

and controlling and preventing measles and rubella outbreaks in 6 high-risk countries.

Looking ahead, the Board priorities will include: the approval of the 2013–2014 business plan of the Alliance; reviewing the next vaccine investment strategy; exploring support for inactivated polio vaccine (IPV) pending SAGE guidance; and adopting tailored approaches to supporting fragile states. On market shaping, new tenders are in process including the first tender for HPV and joint work with UNICEF on options to use market shaping for non-GAVI eligible LMICs. The December 2012 GAVI partners forum and 2013 data summit were highlighted.

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

SAGE was presented with a report of the June 2012 GACVS meeting.[3] SAGE acknowledged the detailed review of thiomersal conducted over the years and the accumulated evidence that strongly supports the safety of its use as a preservative for inactivated vaccines. With respect to the safety of vaccines during pregnancy, SAGE welcomed the early conclusions from GACVS following the review of available evidence on live rubella and trivalent inactivated influenza vaccines. The review confirmed the absence of identified risk to the mother or fetus from the use of these vaccines, and the additional health benefits that result from their use. SAGE highlighted the urgent need for a safety review of other important vaccines that could be used during pregnancy. The new causality assessment scheme recommended by GACVS for adverse events following immunization was also received with great interest and SAGE requested that this system be pilot tested and reported upon in the future.

Expert Committee on Biological Standardization (ECBS)

SAGE was presented with the outcome of the October 2012 ECBS meeting. This included the adoption of revised recommendations for oral poliovirus vaccines; diphtheria, tetanus, and combined vaccines with DTP antigens; live attenuated Japanese encephalitis vaccines; and a new guideline for candidate malaria vaccines. ECBS will also initiate the establishment of global standards for vaccines against enterovirus 71, which are being developed in one part of the world with potential for broad public health use.

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. Further to this request, ECBS was asked to prepare guidance for national regulatory authorities (NRAs) on studies needed to support evidence-based off-label use of vaccines which benefit

[3] See Nº 6, 2012, pp. 53–59.

vaccin contre la rougeole et la rubéole dans le cadre de campagnes visant un large éventail de tranches d'âges et pour la prévention des flambées de rougeole et de rubéole dans 6 pays à haut risque.

Pour ce qui est de l'avenir, les priorités du Conseil comprendront l'approbation du plan d'activité de l'Alliance pour 2013-2014, l'examen de la prochaine stratégie d'investissement dans les vaccins, l'examen de l'appui au vaccin antipoliomyélitique inactivé (VPI) en attendant les indications du SAGE et l'adoption d'approches sur mesure pour aider les États fragiles. En matière de structuration du marché, de nouveaux appels d'offres sont en cours, y compris le premier pour le HPV et un travail conjoint avec l'UNICEF sur les options pour avoir recours à l'infléchissement des marchés à l'intention des PRITI ne remplissant pas les conditions de l'aide de l'Alliance GAVI. Le Forum des partenaires de l'Alliance en décembre 2012 et le sommet de 2013 sur les données ont été rappelés.

Rapport du Comité consultatif mondial de la Sécurité vaccinale (GACVS)

Un rapport sur la réunion du GACVS de juin 2012[3] a été présenté au SAGE. Celui-ci a pris note de l'examen détaillé du thiomersal mené sur plusieurs années et des données factuelles accumulées plaidant pour la sécurité de son utilisation comme conservateur dans les vaccins inactivés. Pour ce qui est de l'innocuité des vaccins pendant la grossesse, le SAGE a salué les premières conclusions du GACVS à la suite de l'examen des données disponibles sur le vaccin vivant contre la rubéole et sur le vaccin trivalent inactivé contre la grippe. Cet examen a confirmé l'absence de risques reconnus pour la mère et le fœtus liés à l'utilisation de ces vaccins et les avantages supplémentaires pour la santé qui en résultent. Le SAGE a souligné le besoin urgent d'examiner l'innocuité d'autres vaccins importants susceptibles d'être administrés pendant la grossesse. Il a manifesté un grand intérêt pour le nouveau système d'évaluation de la causalité recommandé par le GACVS pour les manifestations indésirables postvaccinales et demandé de faire des essais pilotes et de recevoir des rapports à ce sujet à l'avenir.

Comité d'experts de la standardisation biologique (ECBS)

Le SAGE a pris connaissance des résultats de la réunion d'octobre 2012 de ce Comité, parmi lesquels l'adoption de recommandations révisées pour les vaccins antipoliomyélitiques oraux, pour les vaccins antidiphtériques, antitétaniques et les vaccins associant les antigènes DTC, pour les vaccins vivants atténués contre l'encéphalite japonaise et une nouvelle ligne directrice pour les vaccins candidats antipaludiques. Le Comité va également entreprendre l'établissement de normes mondiales pour les vaccins contre l'entérovirus 71, qui sont en cours de développement dans une partie du monde et ont le potentiel d'être largement utilisés en santé publique.

Précédemment, le SAGE avait demandé la rédaction d'un document décrivant les circonstances dans lesquelles on peut recommander l'utilisation d'un vaccin en dehors des spécifications, tout en précisant les différences entre les décisions réglementaires et les recommandations de la santé publique. Suite à cette demande, le Comité a été chargé de préparer des orientations à l'intention des autorités nationales de réglementation (ANR) sur les études nécessaires pour étayer une utilisation des vaccins

[3] Voir Nº 6, 2012, pp. 53-59.

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 (NITAGs) 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. SAGE also noted that there is also a need for a communication paper to explain the different perspectives of NRAs and NITAGs at country level.

Immunization Practices Advisory Committee (IPAC)

SAGE was presented with the conclusions and recommendations of the April[4] and October[5] 2012 IPAC meetings.

SAGE considered that the finalization of field guidance for the use of a controlled temperature chain for meningococcal A conjugate vaccine (MenAfrivac®) in a campaign setting was an important milestone, providing great potential for reaching target populations. SAGE noted IPAC's programmatic considerations of alternatives to thiomersal-containing vaccines and reinforcement of the key messages on thiomersal, and commended IPAC for having pursued further review of the programmatic implications of administering IPV as an intradermal dose. SAGE expressed support for the ongoing work to promote the use of solar refrigeration systems for vaccine storage, and encouraged IPAC to pursue other innovative technologies and strategies that improve vaccine management and delivery, such as cell-phone technology.

Immunization and Vaccine Related Implementation Research Advisory Committee (IVIR)

The IVIR chair summarized the outcome of the September 2012 IVIR meeting. SAGE endorsed the recommendation from IVIR that "while value of statistical life (VSL) may provide valuable information, there are technical challenges to the measures. Therefore, VSL should not be used as the primary basis for priority setting for vaccines".

Polio eradication

SAGE commended the countries and the Global Polio Eradication Initiative (GPEI) on the overall encouraging progress towards interrupting wild poliovirus transmission, but noted the increased number of poliomyelitis cases in some districts in Nigeria and Pakistan in 2012 compared to 2011. SAGE commended the level of detailed attention given to polio campaign planning and implementation with clear indications that best practices are being systematically applied. There is an impressive increase in the use and strengthening of accountability frameworks, training and optimization of polio worker skills, and a visibly improved engagement of leaders and decision-makers at all administrative levels.

[4] See http://www.who.int/entity/immunization_delivery/systems_policy/IPAC_2012_April_report.pdf

[5] See http://www.who.int/immunization_delivery/systems_policy/IPAC_2012_October_report.pdf

en dehors des spécifications, mais avantageuse pour la santé publique. Il a été noté que, pour les responsables de la réglementation, les données spécifiques des produits sont primordiales. Le SAGE a demandé de préparer un document supplémentaire pour conseiller les groupes techniques consultatifs nationaux sur la vaccination (GTCV) sur le type de données susceptibles d'étayer une recommandation politique d'utiliser un vaccin en dehors du calendrier homologué, afin d'obtenir des avantages pour la santé publique tels que la simplicité opérationnelle ou des économies de coût. Le SAGE a également noté qu'un article de communication était nécessaire pour expliquer les perspectives des ANR et des GTCV au niveau des pays.

Comité consultatif sur les pratiques vaccinales (IPAC)

Le SAGE a pris connaissance des conclusions et recommandations des réunions de ce comité en avril[4] et en octobre 2012.[5]

Il considère que la finalisation d'un guide de terrain sur l'utilisation d'une chaîne de contrôle de la température pour le vaccin conjugué contre le méningocoque A (MenAfrivac®) en situation de campagne est une étape importante apportant un grand potentiel pour couvrir les populations ciblées. Le SAGE a pris note des considérations programmatiques du comité concernant les produits de substitution aux vaccins contenant du thiomersal et le renforcement des messages essentiels sur celui-ci et félicité l'IPAC d'avoir poursuivi l'examen des implications programmatiques de l'administration du VPI en dose intradermique. Le SAGE a exprimé son soutien aux travaux en cours pour promouvoir l'utilisation des systèmes solaires de réfrigération pour la conservation des vaccins et a encouragé le Comité à rechercher des technologies et stratégies innovantes qui améliorent la gestion et la délivrance des vaccins, comme le téléphone cellulaire.

Comité consultatif sur la recherche pour la mise en œuvre de la vaccination et des vaccins (IVIR)

Le Président du Groupe a résumé les résultats de la réunion du comité en septembre 2012. Le SAGE a approuvé la recommandation selon laquelle «si la valeur statistique d'une vie humaine peut donner des informations utiles, il y a des difficultés techniques pour la mesurer. Cette valeur ne devrait donc pas servir de base principale pour l'établissement des priorités pour les vaccins».

Éradication de la poliomyélite

Le SAGE a félicité les pays et l'Initiative mondiale pour l'éradication de la poliomyélite (IMEP) pour l'ensemble des progrès encourageants accomplis en vue de l'interruption de la transmission du poliovirus sauvage, mais il a relevé le nombre croissant de cas de poliomyélite dans certains districts du Nigéria et du Pakistan en 2012 par rapport à 2011. Il a salué le niveau détaillé d'attention accordé à la planification et à la mise en œuvre des campagnes, avec des indications claires montrant une application systématique des meilleures pratiques. Il y a une hausse impressionnante de l'utilisation et du renforcement des cadres de responsabilisation, de la formation et de l'optimisation des qualifications des agents travaillant sur la poliomyélite et un engagement visiblement meilleur des dirigeants et des décideurs à tous les niveaux administratifs.

[4] Voir http://www.who.int/entity/immunization_delivery/systems_policy/IPAC_2012_April_report.pdf

[5] Voir http://www.who.int/immunization_delivery/systems_policy/IPAC_2012_October_report.pdf

SAGE welcomed the long-term vision of the draft GPEI Polio Eradication and Endgame Plan, 2013–2018, and commended the GPEI for the extensive consultative process used to develop the plan. SAGE endorsed the 4 major components of the plan: (i) interruption of remaining wild type 1 and 3 polio transmission, (ii) withdrawal of the type 2-component of oral polio vaccine (OPV2) use, (iii) containment and certification, and (iv) legacy planning and associated strategic approaches. SAGE supported the priority given to vaccine-associated polio disease (vaccine-associated paralytic poliomyelitis and circulating vaccine-derived poliovirus).

SAGE recommended that the draft Polio Eradication and Endgame plan be revised to include recommendations from current stakeholder consultations. The plan should be reviewed, completed and shared with other partners one month prior to the meeting of the WHO Executive Board in January 2013. The updated plan should provide more explanation for the rationale and public health benefit of the introduction of IPV, the global approach to switching from trivalent OPV (tOPV) to bivalent OPV (bOPV), and the current efforts and future plans to use ongoing polio activities to strengthen routine immunization systems. The plan should be expanded to highlight, for all major objectives, the importance of using appropriate social mobilization and communication strategies.

SAGE was deeply appreciative of the diligent work of the SAGE polio working group and impressed by the progress achieved by the group in refining the evidence base for introducing IPV to mitigate risks associated with OPV2 withdrawal when replacing tOPV with bOPV for routine immunization ("OPV2 cessation"). SAGE concurred with the main recommendations of the working group.

SAGE recommended that all countries should introduce at least 1 dose of IPV in their routine immunization programme to mitigate the risks associated with the withdrawal of OPV2. SAGE accepted the detailed scientific evidence presented to illustrate the risk-mitigating benefits of IPV use in the context of OPV2 withdrawal, specifically the evidence to show that, following OPV2 withdrawal, IPV vaccination will help to (i) prevent poliomyelitis in IPV-vaccinated individuals exposed to vaccine-derived poliovirus type-2 (VDPV2) or wild poliovirus type-2 (WPV2), (ii) improve the response to monovalent OPV type-1 (mOPV1) or an additional dose of IPV in a type 2 polio outbreak, (iii) reduce the transmission of a reintroduced type 2 poliovirus, and (iv) accelerate wild poliovirus eradication by boosting immunity to wild poliovirus types 1 and 3.

In the context of interrupting wild poliovirus transmission before the end of 2014, SAGE will review progress every 6 months on achieving the prerequisites for OPV2 withdrawal, including the availability of affordable IPV products to ensure the earliest possible date for OPV2 withdrawal but with sufficient advance notification to ensure programmatic readiness and vaccine availability. SAGE recommended that an IPV supply and funding strategy be established for timely introduction of IPV using existing whole dose products for a transition period if needed. For its next meeting SAGE requested (i) additional details on the scientific evidence for, and

Le SAGE a salué la vision sur le long terme du projet de plan de l'IMEP pour l'éradication de la poliomyélite et «l'assaut final» couvrant la période 2013-2018 et a félicité l'IMEP pour le processus de consultation approfondie auquel elle a eu recours pour élaborer ce plan. Il en approuve les 4 principales composantes: i) interruption de la transmission restante des poliovirus sauvages de types 1 et 3, ii) retrait du type 2 des vaccins antipoliomyélitiques oraux (VPO2), iii) confinement et certification, iv) planification de «l'héritage» et des approches stratégiques qui s'y associent. Il soutient la priorité donnée à la poliomyélite associée au vaccin (poliomyélite paralytique associée au vaccin et poliovirus circulant dérivant d'une souche vaccinale).

Le SAGE a recommandé de réviser le projet de plan pour l'éradication et l'assaut final afin d'y inclure les recommandations émanant des consultations actuelles avec les parties prenantes. Le plan doit être examiné, complété et communiqué aux autres partenaires un mois avant la session du Conseil exécutif de l'OMS de janvier 2013. Le plan actualisé doit donner davantage d'explications sur la justification et l'avantage de l'introduction du VPI pour la santé publique, sur l'approche mondiale pour passer du VPO trivalent (VPOt) au VPO bivalent (VPOb) et sur les efforts actuels et les plans futurs pour utiliser les activités en cours contre la poliomyélite en vue de renforcer les systèmes de vaccination systématique. Le plan doit être étendu pour souligner, pour tous les grands objectifs, l'importance d'appliquer des stratégies de mobilisation sociale et de communication adaptées.

Le SAGE a vivement apprécié l'action diligente de son groupe de travail sur la poliomyélite et a été impressionné par les progrès réalisés par celui-ci pour affiner la base factuelle en vue de l'introduction du VPI, afin d'atténuer les risques liés au retrait du VPO2 au moment de remplacer le VPOt par le VPOb dans la vaccination systématique («arrêt du VPO2»). Il a souscrit aux principales recommandations du groupe de travail.

Le SAGE a recommandé à tous les pays d'introduire au moins une dose de VPI dans leurs programmes de vaccination systématique pour atténuer les risques liés au retrait du VPO2. Il a accepté les données scientifiques détaillées présentées pour illustrer l'avantage de l'administration du VPI en matière d'atténuation des risques dans le cadre du retrait du VPO2, notamment celles qui montrent qu'après ce retrait, la vaccination par le VPI aidera à i) éviter la poliomyélite chez les sujets vaccinés par le VPI et exposés au poliovirus dérivés de souches vaccinales de type 2 (PVDV2) ou au poliovirus sauvage de type 2 (PVS2); ii) améliorer la réponse au VPO monovalent type 1 (VPO1m): ou à une dose supplémentaire de VPI au cours d'une flambée de poliomyélite de type 2; iii) réduire la transmission d'un poliovirus de type 2 réintroduit; iv) accélérer l'éradication du poliovirus sauvage en renforçant l'immunité contre les poliovirus des types 1 et 3.

Dans le cadre de l'interruption de la transmission du poliovirus sauvage d'ici fin 2014, le SAGE examinera tous les 6 mois les progrès pour réunir les conditions préalables au retrait du VPO2, notamment la disponibilité de produits VPI abordables garantissant le plus vite possible le retrait du VPO2 mais avec une notification préalable suffisamment en avance pour que les programmes soient prêts et le vaccin disponible. Le SAGE a recommandé de mettre en place une stratégie de fourniture et de financement du VPI pour introduire en temps utile ce vaccin, en s'appuyant sur l'utilisation en dose entière des produits disponibles actuellement pendant une certaine période de transition si nécessaire. Pour sa prochaine réunion, le SAGE demandera

programmatic implications of, targeting expanded age groups during polio campaigns in endemic areas, (ii) a report on the vision for the legacy planning, and (iii) noting the circulation of VDPV in Somalia and Chad, a report of progress in these countries.

SAGE expressed grave concern that because of funding shortfalls, OPV campaigns have been cancelled or scaled back in over 25 high-risk countries in 2012, which poses a threat to the success of the overall programme. This perennial problem exerts considerable pressure on the programme at a time when eradication is in sight.

Decade of Vaccines Global Vaccine Action Plan (GVAP)[6]

The session included an overview of progress in putting the GVAP into operation since the 65th World Health Assembly (WHA) in May 2012. Discussions have begun at the Regional level to update regional immunization plans in alignment with GVAP and to establish processes to monitor and report progress to the respective Regional Committees each year. The WHO and UNICEF guidance for preparation of national multi-year and annual plans for immunization are being updated to align them with the guiding principles and strategic objectives of GVAP and to foster greater alignment with national health sector plans.

The proposed structure and process for monitoring the implementation of the GVAP through a Monitoring & Evaluation /Accountability Framework was described. The framework has 3 elements: (i) monitoring results (based on the indicators for the GVAP Goals and Strategic Objectives); (ii) monitoring commitments and resources; and (iii) an independent review of progress.

Progress was described in the efforts to finalize monitoring indicators, establish operational definitions, sources of data, and the reporting process. SAGE was presented with the changes made to the indicators since its April 2012 meeting and the rationale for doing so, and was specifically asked for comments and recommendations. SAGE discussions mainly focused on: (1) the feasibility and need for surveys to validate district level vaccine coverage measures; (2) adding an indicator of DTP3 coverage ≥80% for ≥3 years; (3) proposed indicators to measure "confidence in immunization"; (4) retention of indicator on district level DTP3 coverage; (5) choice of drop-out rate between the first dose of DTP and first dose of measles containing vaccine (MCV1) (DTP1-MCV1), or between the first and third dose of DTP vaccine (DTP1-DTP3); (6) addition of a surveillance indicator; (7) addition of an indicator to measure integration of immunization within health systems; and (8) addition of a vaccine price indicator.

SAGE was presented with plans for mechanisms to document and track commitments to GVAP and resources invested in immunization by national governments and their development partners for low and middle income countries. In addition, the plans to up-

i) des détails supplémentaires sur les données scientifiques et les implications pour les programmes en rapport avec le fait de cibler des tranches d'âge plus larges au cours des campagnes de vaccination dans les zones d'endémie, ii) un rapport sur la planification de «l'héritage» et, iii) relevant la circulation de PVDV en Somalie et au Tchad, un rapport sur la situation dans ces pays.

Le SAGE s'est vivement inquiété du fait que, à cause des déficits de financement, des campagnes d'administration du VPO ont été annulées ou réduite dans >25 pays à haut risque en 2012, ce qui est une menace pour le succès de l'ensemble du programme. Ce problème persistant fait peser une pression considérable sur le programme au moment où l'éradication est en vue.

Décennie de la vaccination: Plan d'action mondial pour les vaccins (GVAP)[6]

La session a comporté un examen général des progrès pour la mise en opération du Plan depuis la 65e Assemblée mondiale de la Santé en mai 2012. Des discussions ont commencé au niveau des Régions pour actualiser les plans régionaux de vaccination en les alignant sur le GVAP et pour instituer des procédures de suivi et de présentation de rapports de situation aux comités régionaux respectifs chaque année. Le guide de l'OMS et de l'UNICEF pour la préparation de plans nationaux annuels et pluriannuels est en cours de remise à jour pour les aligner sur les principes directeurs et les objectifs stratégiques du GVAP, afin de renforcer l'alignement avec les plans nationaux du secteur de la santé.

La structure et le processus proposés pour le suivi de la mise en œuvre du GVAP au moyen d'un cadre de suivi et d'évaluation/responsabilisation ont été décrits. Ce cadre a 3 éléments: i) suivi des résultats (sur la base des indicateurs pour les buts et les objectifs stratégiques du GVAP; ii) suivi des engagements et des ressources; iii) examen indépendant des progrès.

Les progrès dans les efforts pour finaliser les indicateurs de suivi et pour créer des définitions opérationnelles, des sources de données et des processus de notification ont été décrits. Le SAGE a pris connaissance des modifications apportées aux indicateurs depuis sa réunion d'avril 2012 et des raisons les justifiant et il lui a été spécifiquement demandé de faire des observations et des recommandations. Ses discussions ont porté principalement sur: 1) la faisabilité et le besoin des enquêtes pour valider les mesures de la couverture vaccinale au niveau des districts; 2) l'ajout d'un indicateur de la couverture du DTC3 ≥80% pour au moins 3 ans; 3) des indicateurs proposés pour mesurer la «confiance dans la vaccination»; 4) le maintien de l'indicateur sur la couverture du DTC3 au niveau des districts; 5) le choix du taux d'abandon entre la première dose du DTC et la première dose d'un vaccin à valence rougeole (MCV1) (DTP1-MCV1) ou entre la première et la troisième dose de DTC (DTC1-DTC3); 6) l'ajout d'un indicateur de surveillance; 7) l'ajout d'un indicateur mesurant l'intégration de la vaccination dans les systèmes de santé; et 8) l'ajout d'un indicateur sur le prix des vaccins.

Le SAGE a pris connaissance des plans pour des dispositifs visant à documenter et à suivre les engagements pour le GVAP, ainsi que les ressources investies dans la vaccination par les gouvernements nationaux et leurs partenaires de développement dans les pays à revenu faible ou intermédiaire. De plus,

[6] *Draft global vaccine action plan* (WHA 65/22), available at: http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_22-en.pdf

[6] *Projet de plan d'action mondial pour les vaccins* (WHA65/22) disponible sur: http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_22-fr.pdf

date the costing, financing and impact work included in the GVAP, specifically addressing areas SAGE had previously outlined, were reported. SAGE provided feedback on the proposed activities for the technical group to take into consideration as they begin their work. SAGE was pleased to see the work being proposed, including the economic analysis, and the plan to ensure external validation.

Finally, a summary of the process to review and report progress on the implementation of GVAP at the national, regional and global levels was presented. This included the constitution of a SAGE working group that will undertake a detailed review of progress and prepare a report to SAGE on an annual basis. The report, incorporating feedback from SAGE, will form the basis of the WHO secretariat annual reports to the Executive Board and the WHA. The reports to the WHA will also be shared with the independent Expert Review Group for the United Nations Secretary General's Global Strategy for Women's and Children's Health. An open call for nominations of experts to serve on the working group will be initiated. Members will serve in their personal capacities and will be chosen by a selection panel including representation from the lead agencies for the implementation of GVAP and a representative of the Civil Society Organizations.

SAGE made the following recommendations on the proposed Monitoring & Evaluation/Accountability Framework:

Monitoring indicators

SAGE made specific comments and recommendations on the following:

Goal 3: Meet vaccination coverage targets in every region, country and community.

SAGE noted that district level coverage data are important for monitoring equity in delivery of immunization within countries and for operational and planning purposes. However, SAGE recognized the important resource requirement for conducting surveys to generate coverage estimates for all districts in a country and proposed that as an alternative, countries may choose to conduct such surveys in selected "high risk" districts that are likely to have low coverage. Such surveys should be done at least twice in the decade.

Strategic objective 2: Individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility.

SAGE accepted the 2 proposed indicators – % of countries that have assessed (or measured) the level of confidence in vaccination at subnational level with implementation of activities to improve it; and % of un- and under-vaccinated persons in whom lack of confidence was a factor that influenced their decision – but asked that the last part of the indicator which reads "…with implementation of corrective actions" be deleted. SAGE recommended that these indicators be piloted in AMR and EUR and that the results of the pilots should be reviewed before final acceptance for global use.

les plans inclus dans le GVAP pour actualiser l'estimation des coûts, le financement et le travail sur l'impact, qui couvrent spécifiquement les domaines décrits auparavant par le SAGE, ont été présentés. Le SAGE a fait des observations sur les activités proposées à prendre en compte par le groupe technique au moment de commencer ses travaux. Il a salué les travaux proposés, avec l'analyse économique et le plan pour s'assurer une validation externe.

Enfin, une synthèse du processus d'examen et de notification des progrès de la mise en œuvre du GVAP aux niveaux national, régional et mondial a été présentée. Elle comprenait la constitution d'un groupe de travail du SAGE chargé d'entreprendre un examen détaillé des progrès et de préparer chaque année un rapport destiné au SAGE. Ce document, intégrant les observations du SAGE, formera la base des rapports annuels présentés par le Secrétariat de l'OMS au Conseil exécutif et à l'Assemblée mondiale de la Santé. Les rapports à l'Assemblée seront également communiqués au Groupe d'examen indépendant, constitué d'experts, pour la Stratégie mondiale du Secrétaire général de l'organisation des Nations Unies pour la santé de la femme et de l'enfant. Un appel ouvert pour la désignation d'experts sera lancé. Les membres serviront à titre personnel et seront retenus par un groupe de sélection comprenant des représentants des principales institutions pour la mise en œuvre du GVAP et un représentant des organisations de la société civile.

Pour le projet de cadre de suivi et évaluation/responsabilisation, le SAGE a fait les recommandations suivantes:

Indicateurs de suivi

Le SAGE a fait des observations et recommandations spécifiques sur les points suivants:

But 3: Atteindre les cibles en matière de couverture vaccinale dans chaque Région, pays et collectivité.

Le SAGE a relevé que les données sur la couverture au niveau des districts sont importantes pour surveiller l'équité dans la délivrance de la vaccination à l'intérieur des pays, ainsi qu'à des fins opérationnelles et pour la planification. Il a néanmoins reconnu les besoins importants en ressources pour mener des enquêtes produisant des estimations de la couverture pour tous les districts d'un pays et a proposé, en remplacement, que les pays pouvaient choisir de faire de telles enquêtes dans certains districts «à haut risque», où la couverture est probablement faible. Ces enquêtes doivent être faites au moins 2 fois pendant la décennie.

Objectif stratégique 2: Les individus et les collectivités comprennent la valeur des vaccins et réclament la vaccination à la fois comme un droit et comme une responsabilité.

Le SAGE a accepté les 2 indicateurs proposés – le pourcentage des pays ayant évalué (ou mesuré) le niveau de confiance dans la vaccination au niveau infranational avec la mise en œuvre d'activités pour l'améliorer; et le pourcentage de personnes non ou sous vaccinées pour lesquelles le manque de confiance a été un facteur influant sur leur décision – mais a demandé d'enlever la dernière partie de l'indicateur «…avec l'application de mesures correctrices». Le SAGE a recommandé que des essais pilotes de ces indicateurs soient menés dans la Région des Amériques et la Région européenne et que les résultats de ces essais soient examinés avant l'acceptation définitive pour un usage mondial.

Strategic objective 3: The benefits of immunization are equitably extended to all people.

SAGE recommended that:

- it would be relevant to repeat the indicator on percentage of districts with ≥80% coverage under Goal 3 and Strategic objective 3;
- accepted the recommendation that coverage by wealth quintiles be collected for all countries and that in addition, countries also collect and report coverage data by other appropriate equity indicators;
- recommended that the SAGE working group consider the possibility of an indicator that would measure equity across as well as within countries

Strategic objective 4: Strong immunization systems are an integral part of a well-functioning health system

SAGE - agreed that an indicator to show sustained high immunization coverage be added, but recommended that the indicator should measure sustained DTP3 coverage of ≥90% for 3 or more years, rather than ≥80%, in order to ensure consistency with other coverage targets;

- accepted the proposal to use DTP1–DTP3 drop-out rate instead of DTP1–MCV1 as the indicator for this strategic objective;
- accepted the proposal to add a surveillance indicator, but recommended that the definition of surveillance be expanded to include other vaccine-preventable diseases;
- accepted in principle the need for an indicator that would measure integration of immunization systems into broader health systems and coordination between immunization and other primary health care programmes. Such an indicator may be developed for presentation to the SAGE DoV GVAP working group in 2013.

Strategic objective 5: Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies.

SAGE reviewed the request for inclusion of an indicator on vaccine price but recognized the difficulties involved in developing an indicator that would track prices in all low and middle-income countries. SAGE recommended that an annual narrative report should be prepared on vaccine price trends for low and middle-income countries, including self-procuring countries, as well as progress on supporting vaccine procurement mechanisms.

Other proposed changes were accepted with the proviso that the SAGE working group should continuously review the need for reformulation of the indicators or mechanisms for collection and reporting of data.

Monitoring commitments and resources and updating the cost and impact analysis for the Decade of Vaccines

SAGE recognized the importance for updating the cost and impact estimates and for setting benchmarks. However, SAGE also recognized the complexity of the analysis and suggested that IVIR and other expert groups

Objectif stratégique 3: Les bénéfices de la vaccination sont équitablement étendus à tous les individus.

Le SAGE a:

- estimé qu'il serait utile de répéter l'indicateur sur le pourcentage de districts ayant une couverture ≥80% au troisième but et au troisième objectif stratégique.
- accepté la recommandation de collecter les données sur la couverture en fonction des quintiles de richesse dans tous les pays et qu'en plus, les pays recueillent aussi les données selon d'autres indicateurs appropriés d'équité et fassent des rapports à ce sujet.
- recommandé que le groupe de travail du SAGE envisage la possibilité d'un indicateur mesurant l'équité entre les pays comme dans les pays.

Objectif stratégique 4: Des systèmes de vaccination solides font partie intégrante d'un système de santé performant

Le SAGE a: – accepté qu'un indicateur soit ajouté pour montrer la pérennité de la couverture élevée de la vaccination, mais il a recommandé que cet indicateur mesure une couverture durable du DTC3 ≥90% pendant au moins 3 ans, plutôt que ≥80%, afin d'assurer la cohérence avec les autres cibles de la couverture.

- accepté d'utiliser le taux d'abandon DTC1-DTC3 plutôt que DTP1-MCV1 comme indicateur pour cet objectif stratégique;
- accepté la proposition d'ajouter un indicateur de la surveillance, mais il a recommandé d'étendre la définition de la surveillance pour y inclure d'autres maladies à prévention vaccinale;
- accepté en principe la nécessité d'un indicateur qui mesurerait l'intégration des systèmes de vaccination dans le cadre plus large des systèmes de santé et de la coordination entre la vaccination et d'autres programmes de soins de santé primaires. Un tel indicateur pourra être élaboré pour présentation en 2013 au groupe de travail du SAGE pour le GVAP de la Décennie de la vaccination.

Objectif stratégique 5: Les programmes de vaccination disposent d'un accès durable à un financement prévisible, à un approvisionnement de qualité et à des technologies innovantes.

Le SAGE a examiné la demande d'inclure un indicateur sur le prix des vaccins mais il a reconnu les difficultés inhérentes à son élaboration pour suivre les prix dans tous les pays à revenu faible ou intermédiaire. Il a recommandé qu'un rapport descriptif annuel soit préparé sur les tendances des prix des vaccins dans les pays à revenu faible ou intermédiaire, y compris dans les pays se procurant eux-mêmes les vaccins, ainsi que sur les progrès concernant le soutien aux dispositifs d'achat.

Les autres modifications proposées ont été acceptées à la condition que le groupe de travail du SAGE examine continuellement la nécessité de reformuler les indicateurs ou les dispositions pour la collecte et la transmission des données.

Suivi des engagements et des ressources et actualisation du coût et de l'analyse d'impact pour la Décennie de la vaccination

Le SAGE a reconnu l'importance d'actualiser les coûts, les estimations de l'impact et de définir des points de référence. Toutefois, il a également reconnu la complexité de l'analyse et proposé de consulter régulièrement l'IVIR, d'autres groupes d'experts et

and individuals who have experience with such analysis be consulted on an ongoing basis. SAGE also recognized the urgency for having approximate estimates and recommended that the technical group provide preliminary estimates for SAGE review in November 2013.

Optimization of *Haemophilus influenzae* type b (Hib) conjugate vaccine schedules

Hib conjugate vaccines have been in use for >20 years with remarkable success. By 2011, 179 (92%) of countries worldwide had introduced Hib-containing vaccines. However, WHO estimates that only 43% of infants worldwide received at least 3 doses of Hib-containing vaccine in 2011, given the large populations of children in some countries not yet using Hib vaccine and the lack of full implementation or coverage in others with routine use.

SAGE was requested to consider the optimal Hib immunization schedules for children in different epidemiological settings. SAGE discussion was informed by: (i) 3 systematic reviews (2 independent RCTs reviews, 1 on case-control and cohort studies) of the effect of Hib-containing vaccines on the immune response and on various disease outcomes, (ii) a global review of the epidemiology of Hib disease in children, (iii) a systematic review of Hib vaccine herd effects and, (iv) a review of the long term impact of Hib vaccine in 34 countries which had introduced the vaccine more than 5 years ago. The outcomes of these reviews were used to define the parameters for a model incorporating the potential of various immunization schedules and of improvements in vaccine delivery timeliness and coverage, in order to assess impact on disease burden.

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. In particular, the experience of the United Kingdom, where the introduction of Hib vaccine into the childhood immunization programme in 1992 led to an initial reduction in the incidence of Hib disease in all age groups followed by a subsequent resurgence, needs to be further evaluated. There were a number reasons that may have contributed to the Hib resurgence: these include waning immunity after a 2/3/4 month priming schedule possibly exacerbated by the use of combination vaccines containing aP, together with the lack of boosting due to the herd immunity effect of the UK programme on Hib carriage (achieved as a result of high coverage and a catch-up programme to 4 years of age). This illustrated the complexity of the issues surrounding recommendations as to the optimal schedule for use of Hib vaccines in different epidemiological settings.

SAGE considered that the information regarding the interval between doses should also be re-analysed and that additional immunological studies should be considered. A more in-depth evaluation of duration of protection after each dose of Hib containing vaccine was

des personnes ayant l'expérience de ce type d'analyses. Il s'est aussi rendu compte de l'urgence d'avoir des estimations approximatives et recommandé au groupe technique de lui fournir des estimations préliminaires pour l'examen en novembre 2013.

Optimisation des calendriers d'administration des vaccins conjugués contre *Haemophilus influenzae* de type b (Hib)

Les vaccins conjugués contre le Hib sont utilisés avec un succès remarquable depuis >20 ans. En 2011, 179 pays (92%) dans le monde avaient introduit des vaccins à valence Hib. Pourtant, l'OMS estime que seulement 43% des nourrissons dans le monde ont reçu au moins 3 doses d'un vaccin à valence Hib en 2011, compte tenu des nombreuses populations d'enfants dans certains pays qui n'utilisent pas encore de vaccin anti-Hib et d'une mise en œuvre ou d'une couverture incomplète dans d'autres où le vaccin est inclus dans le programme de vaccination.

Il a été demandé au SAGE d'étudier les calendriers de vaccination optimaux contre le Hib pour les enfants dans différentes situations épidémiologiques. Pour ces discussions, il s'est appuyé sur: i) 3 examens systématiques (2 examens indépendants d'essais contrôlés randomisés, 1 sur des études cas-témoins et de cohortes) de l'effet des vaccins à valence Hib sur la réponse immunitaire et sur les issues des maladies, ii) un examen mondial de l'épidémiologie de l'infection à Hib chez l'enfant, iii) un examen systématique des effets de groupe de la vaccination contre le Hib et iv) un examen de l'impact du vaccin anti-Hib sur le long terme dans 34 pays l'ayant introduit il y a plus de 5 ans. Les résultats de ces examens ont été utilisés pour définir les paramètres d'un modèle intégrant le potentiel de divers calendriers de vaccination et des améliorations à apporter dans le respect du calendrier et dans la couverture, afin d'évaluer l'impact sur la charge de morbidité.

Au cours de la discussion, les membres du SAGE ont relevé que les données sur le nombre des premières doses et le besoin de doses de rappel nécessitaient une évaluation complémentaire avant de pouvoir faire des recommandations pour l'optimisation du calendrier actuel. L'expérience du Royaume-Uni en particulier, où l'introduction du vaccin anti-Hib en 1992 dans les programmes de vaccination des enfants a amené une diminution initiale des maladies à Hib dans tous les groupes d'âge, suivie d'une résurgence, doit être évaluée de manière approfondie. Un certain nombre de raisons pourraient avoir contribué à la recrudescence du Hib: un déclin de l'immunité après un calendrier de primovaccination à 2/3/4 mois, éventuellement exacerbé par l'association avec le vaccin acellulaire contre la coqueluche, ainsi qu'une absence de stimulation, due à l'immunité de groupe obtenue par le programme au Royaume-Uni et à son effet sur le portage du Hib (obtenu grâce à une couverture élevée et à un programme de rattrapage jusqu'à l'âge de 4 ans). Cela illustre la complexité des questions autour des recommandations sur le calendrier optimal d'administration des vaccins anti-Hib dans différentes situations épidémiologiques.

Le SAGE a estimé qu'il fallait aussi analyser de nouveau les informations sur l'intervalle entre les doses et que des études immunologiques supplémentaires devaient être prises en considération. Une évaluation plus approfondie de la durée de protection après chaque dose de vaccin Hib est par ailleurs nécessaire. Il

also necessary. SAGE also recommended additional review of evidence on the potential effect of Hib combination vaccines including those that include aP.

The outcomes of the above reviews should also be used to refine the model assumptions and parameters. A refined version should be submitted once more for appraisal by Hib experts to ensure that the revised assumptions and parameters have made it more realistic.

SAGE recommended that a revised summary of the evidence, including a critical appraisal of the evidence with GRADE tables and justification for proposed recommendations, should be presented to SAGE in April 2013.

Measles and rubella

SAGE commended countries and Regions for the remarkable progress made in reducing measles mortality globally during the last 3 decades, contributing significantly to the 4th Millennium Development Goal. This progress would not have been possible without country commitment and the support of many partners. AMR has achieved elimination of both measles and rubella and the WPR is approaching interruption of endemic measles transmission. In addition, the number of countries using rubella vaccine in their routine childhood immunization programme has been steadily increasing. However, despite this progress, a careful assessment of the comprehensive reports presented indicates that 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 urged countries and partners to raise the visibility of measles and rubella elimination activities and to ensure that they receive adequate priority and resources as a central component of the GVAP.

In keeping with the GVAP target of measles and rubella elimination in at least 5 WHO Regions by 2020, SAGE urged SEAR to establish a measles elimination goal and AFR, EMR, SEAR and WPR to work towards establishing regional rubella elimination goals.

SAGE endorsed the Global Measles and Rubella Strategic Plan for 2012–2020 and recommended full implementation of the key strategies in a manner that promotes country ownership, strengthens the immunization system, promotes equity and reinforces linkages with polio eradication and other programmes. SAGE noted that some key components of the strategic plan remain under-funded and urged countries and partners to work towards closing this funding gap.

In 2011, >20 million children did not receive their first dose of measles vaccine on time and countries with low routine immunization coverage continue to experience the highest burden of measles. SAGE noted the innovative use of measles supplementary immunization

a aussi recommandé un nouvel examen des données sur les effets potentiels des vaccins associant le Hib, y compris avec ceux comportant le vaccin acellulaire contre la coqueluche.

Les résultats des examens mentionnés ci-dessus seront utilisés pour affiner les hypothèses et les paramètres du modèle. Une version perfectionnée sera soumise une fois de plus à des experts du Hib pour approbation, afin de s'assurer que les hypothèses et paramètres révisés ont rendu le modèle plus réaliste.

Le SAGE a recommandé qu'une synthèse révisée des données lui soit présentée en avril 2013, avec une évaluation critique comportant des tableaux GRADE et la justification des recommandations proposées pour prendre en compte ce qui précède.

Rougeole et rubéole

Le SAGE a félicité les pays et les Régions pour les progrès remarquables accomplis à l'échelle mondiale dans la réduction de la mortalité due à la rougeole au cours des 3 dernières décennies, ce qui a apporté une contribution significative pour l'objectif du Millénaire pour le développement n° 4. Ces progrès n'auraient pas été possibles sans l'engagement des pays et l'appui de nombreux partenaires. La Région des Amériques est parvenue à éliminer à la fois la rougeole et la rubéole et le Pacifique occidental s'approche de l'interruption de la transmission endémique de la rougeole. De plus, le nombre de pays administrant aux enfants le vaccin contre la rubéole dans leurs programmes de vaccination systématique est en augmentation constante. Pourtant, malgré ces progrès, une évaluation soigneuse des rapports complets qui ont été présentés indique que, 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 prie instamment les pays et les partenaires d'accroître la visibilité des activités d'élimination de la rougeole et de la rubéole et de veiller à ce qu'elles bénéficient d'une priorité et de ressources suffisantes, en tant qu'élément central du GVAP.

Conformément à la cible du GVAP d'éliminer la rougeole et la rubéole dans 5 Régions de l'OMS au moins d'ici à 2020, le SAGE a demandé instamment à l'Asie du Sud-Est de fixer un but pour l'élimination de la rougeole et 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 approuvé le Plan stratégique mondial contre la rougeole et la rubéole pour 2012-2020 et a recommandé la pleine mise en œuvre des stratégies essentielles d'une manière qui favorise une appropriation par les pays, renforce les systèmes de vaccination, développe l'équité et consolide les liens avec l'éradication de la poliomyélite et d'autres programmes. Il a relevé que certains éléments clefs du Plan stratégique manquent encore des financements nécessaires et il a demandé instamment aux pays et aux partenaires de travailler pour combler ce déficit.

En 2011, >20 millions d'enfants n'ont pas eu à temps leur première dose de vaccin antirougeoleux et les pays ayant une faible couverture de la vaccination systématique continuent de connaître la charge la plus lourde pour cette maladie. Le SAGE a noté le recours innovant à des activités de vaccination supplé-

activities to improve routine immunization service delivery and recommended that countries and partners should plan and implement specific strategies to strengthen routine immunization systems as part of measles and rubella control and elimination activities.

Despite increases in MCV1 coverage and the introduction of MCV2 as part of routine immunization programmes, large outbreaks have occurred in a number of countries in Europe, Africa and Asia over the past 24 months. SAGE noted the changing epidemiology of measles, with a shift in age distribution of cases towards older age groups, which is consistent with a programme that primarily targets young children. SAGE urged countries to conduct in-depth investigations of their outbreaks to determine the underlying reasons and the role of these older age groups in sustaining transmission, and to develop approaches to target these older age groups as appropriate. In considering age groups for measles vaccination, rubella susceptibility in older age groups also needs to be addressed.

SAGE noted the gaps in the immunization coverage and surveillance data needed to guide the programme. Regions and countries are urged to strengthen reporting of district-level vaccination coverage, strengthen an integrated measles and rubella case-based, laboratory-supported surveillance of fever and rash illness, and introduce surveillance of congenital rubella syndrome.

Closer linkages between measles and rubella programme activities and the GPEI has well-recognized benefits. As GPEI elaborates its legacy planning as a component of its endgame strategic plan, SAGE recommended that countries and global immunization partners assess the potential synergies and take active steps, where appropriate, to adapt and apply the polio infrastructure and lessons learnt to support achievement of measles and rubella elimination targets and strengthening of routine immunization programmes.

SAGE welcomed recent GAVI investments in measles and rubella control which provide significant additional resources for increasing routine coverage, measles-rubella and measles supplementary immunization activities, and timely outbreak response vaccination. SAGE recommends that countries seize this unique opportunity and commit additional national resources to ensure that programme planning and implementation is of the highest quality. Each campaign should follow established "best practices" and be independently evaluated to ensure homogeneous vaccination coverage of >95%.

SAGE endorsed the working group's plan that includes: refining immunization strategies to address the changing epidemiology of measles and rubella; strategies to strengthen surveillance and monitoring, including the definition of an appropriate indicator of district-level coverage; and development of a prioritized list of research topics.

mentaires contre la rougeole, afin d'améliorer la prestation des services de vaccination systématique et a recommandé aux pays et aux partenaires de planifier et de mettre en œuvre des stratégies spécifiques pour renforcer les systèmes de vaccination systématique dans le cadre des activités pour combattre et éliminer la rougeole et la rubéole.

Malgré des augmentations de la couverture du MCV1 et l'introduction du MCV2 dans les programmes de vaccination systématique, de grandes flambées se sont produites dans un certain nombre de pays d'Europe, d'Afrique et d'Asie au cours des 24 derniers mois. Le SAGE a noté le changement de l'épidémiologie de la rougeole, avec une répartition des cas passant vers des tranches d'âge plus élevées, ce qui correspond à un programme ciblant principalement les jeunes enfants. Il a prié instamment les pays de mener des investigations approfondies sur leurs flambées, afin de déterminer les raisons sous-jacentes et le rôle de ces groupes d'âge plus élevés dans le maintien de la transmission, et d'élaborer des approches pour les cibler comme il convient. En étudiant les groupes d'âge pour la vaccination antirougeoleuse, il faudrait aussi s'occuper de la sensibilité à la rubéole dans les tranches d'âge supérieures.

Le SAGE a noté les lacunes dans la couverture de la vaccination et les données de la surveillance nécessaires pour guider le programme. Il prie instamment les Régions et les pays de renforcer la notification de la couverture vaccinale au niveau des districts, la surveillance intégrée des cas de rougeole et de la rubéole sur la base d'une surveillance des syndromes de fièvre et d'éruption cutanée, en s'appuyant sur les laboratoires, et d'introduire la surveillance du syndrome de rubéole congénitale.

Le renforcement des liens entre les activités des programmes s'occupant de la rougeole et de la rubéole et l'IMEP a des avantages reconnus. Alors que l'IMEP élabore la planification de l'héritage qu'elle laissera en tant qu'élément de son plan stratégique pour l'assaut final, le SAGE a recommandé aux pays et aux partenaires mondiaux de la vaccination d'évaluer les synergies potentielles et de prendre activement des mesures, suivant le cas, pour adapter et appliquer les infrastructures de la poliomyélite et les enseignements pour aider à atteindre les cibles d'élimination de la rougeole et de la rubéole et renforcer les programmes de vaccination systématique.

Le SAGE s'est félicité des investissements récents de l'Alliance GAVI dans la lutte contre la rougeole et la rubéole, qui apportent des ressources supplémentaires conséquentes pour améliorer la couverture de la vaccination systématique, les activités de vaccination supplémentaires contre la rougeole, seule ou en association avec la rubéole, et les campagnes de vaccination en temps utile pour riposter aux flambées. Il recommande aux pays de saisir cette occasion unique et d'engager des ressources nationales supplémentaires pour garantir une planification et une mise en œuvre du programme de la meilleure qualité possible. Chaque campagne doit suivre les «meilleures pratiques» établies et être évaluée de manière indépendante pour garantir une couverture vaccinale homogène >95%.

Le SAGE a approuvé le plan du groupe de travail comportant le perfectionnement des stratégies de vaccination pour tenir compte de l'évolution de l'épidémiologie de la rougeole et de la rubéole, des stratégies pour renforcer la surveillance et le suivi, avec la définition d'un indicateur adapté de la couverture au niveau des districts, et l'élaboration d'une liste de priorités sur les sujets de recherche.

SAGE reviewed and endorsed the draft framework for verification of measles and rubella elimination and encourages regions and countries, as they approach elimination, to adopt this approach. The framework should be evaluated and adjusted over time, based on country experience.

SAGE was concerned by the challenges and high costs resulting from the continuous importation of measles into countries which have achieved elimination, and suggested that the possibility that international travel regulations could potentially reduce the likelihood of measles importation be explored.

SAGE welcomed the report from the measles aerosol project. This project, led by WHO, aims to achieve licensing of at least one method for respiratory delivery of a currently licensed measles vaccine. SAGE was presented with data from clinical studies, especially on a Phase II/III trial in India. The results from the pivotal non-inferiority immunogenicity trial showed that the per-protocol seropositivity in the aerosol arm was 85.4% (95% CI: 82.5%, 87.9%) as compared to 94.6% (95% CI: 92.7%, 96.1%) in the subcutaneous arm, with the difference in seropositivity being -9.2% (95% CI: -12.2%, -6.3%). This difference and the upper limit of the confidence interval were both greater than the non-inferiority margin of 5% defined in the study protocol. SAGE members concluded that the tested aerosol vaccine may not be suitable for primary vaccination of infants against measles.

Nevertheless, SAGE recognized the potential benefits of a measles aerosol vaccine because it could be used by non-health-care workers in low-resource settings in the context of outbreaks, acute emergencies and outreach. It advised that the development of a combined measles-rubella aerosol vaccine should be pursued, including demonstration studies of field acceptability and potential to contribute to increasing coverage in resource-limited settings, expansion of safety data, additional studies to adjust the dose delivered, and cost-effectiveness. SAGE also noted the potential usefulness of the aerosol route for administration of other vaccines.

Vaccination in humanitarian emergencies

In April 2012, SAGE was presented with a draft framework on the use of vaccination during humanitarian emergencies. Although the framework could not be pilot tested during real emergencies, as requested by SAGE in April, a field exercise was carried out in the Horn of Africa. The draft framework was applied to a situation in South Sudan to decide on the appropriate use of PCV and Hib vaccines among displaced populations. Active feedback was solicited and received from key stakeholders. A proposed final draft of the framework incorporating all feedback received was presented to SAGE for approval. It was noted that this framework should not override other guidelines for specific vaccine-preventable diseases (VPDs), though in most cases (e.g. measles) the framework is compatible and complementary.

Il a examiné et approuvé le projet de cadre pour la vérification de l'élimination de la rougeole et de la rubéole et encourage les Régions et les pays, en vue de l'élimination, à adopter cette approche. Le cadre sera évalué et ajusté en temps utile sur la base de l'expérience des pays.

Le SAGE est inquiet des difficultés et des coûts élevés résultant de l'importation continue de la rougeole dans les pays qui ont atteint l'élimination et il a proposé d'examiner la possibilité qu'un règlement applicable aux voyages internationaux puisse réduire la probabilité d'importation de cette maladie.

Le SAGE a salué le rapport du projet de vaccination antirougeoleuse par aérosol. Celui-ci, dirigé par l'OMS, vise à homologuer au moins une méthode d'administration par voie respiratoire d'un vaccin antirougeoleux actuellement homologué. Il a pris connaissance des données d'études cliniques, notamment d'un essai en Phase II/III en Inde. Les résultats de l'essai pivot de non-infériorité de l'immunogénicité a montré que la séropositivité dans le groupe de l'aérosol était de 85,4% (IC à 95%: 82,5%–87,9%) contre 94,6% (IC à 95%: 92,7%–96,1%) dans le groupe de l'administration sous-cutanée, la différence de séropositivité s'établissant à -9,2% (IC à 95%: -12,2%, -6,3%). Cette différence et la limite supérieure de l'intervalle de confiance dépassent toutes deux la marge de non-infériorité de 5% définie dans le protocole de l'étude. Les membres du SAGE ont conclu que l'aérosol testé ne convenait sans doute pas pour la primovaccination des nourrissons contre la rougeole.

Néanmoins, le SAGE a reconnu les avantages potentiels d'un vaccin antirougeoleux en aérosol car, en situation de ressources limitées et dans le cadre des flambées, des situations d'urgence et des services de proximité, il peut être utilisé par des personnes qui ne sont pas des agents de santé. Il conseille de poursuivre le développement d'un vaccin en aérosol associant la rougeole et la rubéole, avec des études démontrant l'acceptabilité sur le terrain et la contribution potentielle à l'accroissement de la couverture en situation de ressources limitées, des études pour étendre les données sur l'innocuité, des études complémentaires pour ajuster la dose administrée et d'autres sur le rapport coût-efficacité. Le SAGE a aussi relevé l'utilité potentielle des aérosols comme voie d'administration pour d'autres vaccins.

Vaccination dans les situations d'urgence humanitaire

En avril 2012, un projet de cadre sur l'utilisation des vaccinations dans les situations d'urgence humanitaire a été présenté au SAGE. Bien que le cadre n'ait pas pu faire l'objet d'essais pilotes en situation d'urgence réelle, comme le SAGE l'avait demandé en avril, un exercice sur le terrain a eu lieu dans la Corne de l'Afrique. Le projet de cadre a été appliqué dans une situation au Soudan du Sud pour décider de l'utilisation appropriée du VCP et du vaccin anti-Hib dans les populations déplacées. Les principales parties prenantes ont été priées de faire activement des observations et ont donné leur avis. Une proposition de projet définitif de cadre, intégrant toutes les observations reçues, a été présentée au SAGE pour approbation. Il a été noté que ce cadre ne devait pas l'emporter sur d'autres lignes directrices pour certaines maladies à prévention vaccinale (mPV) bien que, dans la plupart des cas (rougeole par exemple), il soit compatible et complémentaire.

The framework comprises 3 steps which should be applied iteratively as the humanitarian emergency evolves: (i) an assessment of the epidemiological risk posed by each VPD; (ii) for those VPDs with a high-risk burden, consideration of the vaccine properties and a context-specific analysis of logistics for a mass campaign; and (iii) for vaccines judged to be suitable for intervention, prioritization in relation to other urgent public health actions and in light of contextual factors such as political realities, security issues, as well as available human and financial resources.

The revised framework is provided for expert analysts at the coordination/policy level rather than front line health-care workers. It is intended to guide decision-making processes to ensure the most effective use of vaccines in emergency settings. SAGE proposed that the current approach covering only acute emergencies could be extended to more chronic emergency situations where normal services have not resumed after the acute emergency is over and there may be opportunities for other vaccine interventions, such as to non-immunized populations, or where polio eradication is a priority.

SAGE endorsed the revised framework 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 and proceed with further pilot tests before finalization.

Administrative and financial issues often present difficulties for vaccination delivery in humanitarian emergencies. Procurement, as specified in the document, is limited to prequalified vaccines and it was suggested that the use of vaccines in humanitarian emergencies should not be restricted to such prequalified vaccines. This should be further reflected in the framework to assist with procurement and development of fast-track registration processes for donated vaccines and the potential off-label use of vaccines. SAGE noted that a cross reference to other WHO guidelines for emergencies including the use of other interventions, and for the use of vaccine donations, would be useful. High level messages about other priority interventions should be emphasized.

SAGE noted that the list of VPDs to be considered as part of the framework should be extended to include rabies, and that the current categorization of vaccines should be changed to focus on the mode of transmission of the pathogen. SAGE also requested that the document give consideration to herd immunity, and that the list of risk factors of the epidemiological risk assessment as noted in step (i) be extended to consider chronic diseases as a general risk factor for VPDs. The key ethical consideration of non-maleficence should be clarified as referring to risk-benefit in these settings. SAGE noted that ethical issues were embedded in the framework, but agreed that an extended explanation of

Le cadre comporte 3 étapes à appliquer successivement à mesure que la situation humanitaire évolue: i) évaluer le risque épidémiologique posé par chaque mPV; ii) pour celles ayant une forte charge de morbidité, étudier les propriétés du vaccin et faire une analyse spécifique du contexte pour ce qui est de la logistique en vue d'une campagne de masse; iii) pour les vaccins jugés souhaitables pour une intervention, établir la priorité par rapport à d'autres mesures urgentes de santé publique et en tenant compte de facteurs contextuels comme les réalités politiques, les problèmes de sécurité, ainsi que les ressources financières et humaines disponibles.

Le cadre révisé est destiné à des analystes experts au niveau de la coordination/de la politique, plutôt qu'aux agents de santé en première ligne. Il doit guider le processus de prise de décision pour garantir l'utilisation la plus efficace possible des vaccins dans les situations d'urgence. Le SAGE a proposé d'étendre l'approche actuelle, qui ne couvre que les urgences aiguës, pour englober les situations d'urgence plus chroniques où les services normaux n'ont pas repris leurs activités après la situation aiguë et où il pourrait y avoir des possibilités pour d'autres interventions vaccinales, pour des populations non vaccinées par exemple ou lorsque l'éradication de la poliomyélite est une priorité.

Le SAGE a approuvé le cadre révisé en tant qu'étape majeur du progrès et considère qu'il comble une lacune, tout en reconnaissant qu'il est centré sur la vaccination, alors qu'elle n'est qu'une des priorités à prendre en considération en situation d'urgence humanitaire. Il a fortement affirmé l'utilité potentielle de ce cadre et recommandé de faire des essais pilotes sur le terrain. Il a demandé au groupe de travail d'adapter le document et de procéder à d'autres essais pilotes avant la finalisation.

Les questions administratives et financières sont souvent des sources de difficultés pour la délivrance de la vaccination dans les situations d'urgence humanitaire. Comme le précise le document, les achats sont limités aux vaccins présélectionnés et il a été proposé de ne pas se restreindre à ces produits dans de telles situations. Ce point devrait davantage ressortir dans le cadre pour faciliter les achats et mettre au point des procédures accélérées pour l'homologation des vaccins qui ont été donnés et pour des utilisations hors spécifications. Le SAGE a noté qu'une référence croisée à d'autres lignes directrices de l'OMS pour les situations d'urgence, y compris le recours à d'autres interventions, et à l'utilisation des dons de vaccins serait utile. Il faudrait insister sur les messages à haut niveau sur d'autres interventions prioritaires.

Le SAGE a noté que la liste des mPV à envisager dans le cadre devrait être étendue pour y inclure la rage et que la catégorisation actuelle des vaccins devrait être changée pour être centrée sur le mode de transmission de l'agent pathogène. Il a également demandé que le document prenne en considération l'immunité de groupe et que la liste des facteurs de risque pour l'évaluation du risque épidémiologique, comme il est noté dans l'étape i) soit étendue, afin d'envisager les maladies chroniques en tant que facteur de risque général pour les mPV. La considération éthique essentielle de ne pas nuire doit être éclaircie en relation avec le rapport risques-avantages dans ces situations. Le SAGE a noté que les questions d'éthique étaient intégrées dans le cadre, mais il a convenu qu'il fallait inclure une

ethical principles and ethical guidance for informed consent should be included.

Consideration was given to the potential inclusion of case studies in the documents but this was debated, as disasters are very diverse. It was left to the working group to decide whether these should be included.

New vaccine introduction in middle-income countries (MICs): current initiatives to address financial challenges

In 2008[7] and 2010[8] the SAGE made a number of recommendations to WHO regarding assessing and addressing the challenges faced by middle-income countries (MICs) in immunization, particularly in the introduction of new vaccines.

SAGE was presented with a draft paper entitled *"Global Support for New Vaccine Implementation in Middle-Income Countries"*. The information provided in the paper was complemented by presentations from WHO, the former Yugoslav Republic of Macedonia, and UNICEF.

SAGE noted that the MICs have a combined population of 5 billion and an annual birth cohort of 96 million and are home to nearly 75% of the world's poorest populations. Providing support to MICs for immunization programmes and new vaccine introduction is critically important for equity, both between and within countries.

Since 2000, 40 of the 111 MICs have received support from the GAVI Alliance, 3 countries have graduated from support, and a further 16 will graduate in 2015–2016. SAGE noted that significant health gains have been made by those countries eligible for GAVI support, gains not apparent in countries which have not had access to either GAVI funding or to technical assistance from partners. Those MICs graduating from GAVI support will require assistance from development partners in the transition from that support. SAGE noted that some of the MICs are struggling to introduce new vaccines, in part due to an inability to access pricing appropriate to the country's economic status. As an example, a dose of HPV vaccine was reported to cost 4 times less in one Western industrialized European country than in one Eastern European developing country.

SAGE noted that the constraints for non-GAVI eligible MICs to introduce new vaccines extend beyond pricing and procurement, and include equity, sustainability, regulation, capacity building and partner support. The focus of development partners on a restricted group of countries and subsequent concentration of technical support and capacity building in these areas has limited the support available for other countries. MICs in the EUR also report a lack of capacity to address negative attitudes towards new vaccines among parents and medical workers.

explication plus complète des principes et des orientations de l'éthique pour le consentement éclairé.

L'inclusion potentielle d'études de cas dans les documents a été envisagée, mais elle a prêté à débat, les catastrophes étant de nature très diverse. Il revient au groupe de travail de décider s'il faut en inclure ou pas.

Introduction de nouveaux vaccins dans les pays à revenu intermédiaire (PRI): initiatives actuelles pour remédier aux difficultés financières

En 2008[7] et en 2010,[8] le SAGE a fait un certain nombre de recommandations à l'OMS concernant l'évaluation des difficultés rencontrées par les pays à revenus intermédiaire (PRI) pour la vaccination, notamment pour l'introduction de nouveaux vaccins, et les solutions à y apporter.

Le SAGE a pris connaissance d'un projet de document intitulé *«Global Support for New Vaccine Implementation in Middle-Income Countries»* (Appui mondial pour la mise en œuvre des nouveaux vaccins dans les pays à revenu intermédiaire). Les informations présentées dans ce document ont été complétées par des présentations de l'OMS, de l'ex-République yougoslave de Macédoine et de l'UNICEF.

Le SAGE a relevé qu'ensemble, les PRI ont une population de 5 milliards d'habitants, une cohorte annuelle de 96 millions de naissances et qu'ils concentrent près de 75% des populations les plus pauvres du monde. Du point de vue de l'équité, à l'intérieur des pays comme entre eux, il est d'une importance cruciale d'apporter aux PRI un appui pour les programmes de vaccination et l'introduction de nouveaux vaccins.

Depuis 2000, 40 des 111 PRI ont reçu une aide de l'Alliance GAVI, 3 se sont affranchis de l'aide et 16 autres parviendront à ce stade en 2015-2016. Le SAGE a relevé les progrès sanitaires importants accomplis par les pays remplissant les conditions pour une aide de la GAVI, mais qui n'ont pas été constatés dans les pays n'ayant pas accès au financement de la GAVI ou à une assistance technique de la part de partenaires. Ces PRI qui s'affranchissent de l'aide de la GAVI auront néanmoins besoin de l'assistance de partenaires du développement pendant une phase de transition. Le SAGE a noté que certains PRI luttent pour introduire de nouveaux vaccins, en partie à cause de leur incapacité à accéder à des tarifs convenables pour leur situation économique. Par exemple, on a signalé qu'une dose de vaccin anti-HPV avait coûté 4 fois moins cher dans un pays industrialisé d'Europe de l'Ouest que dans un pays en développement d'Europe de l'Est.

Le SAGE a relevé que les problèmes d'introduction de nouveaux vaccins pour les PRI ne remplissant pas les conditions de la GAVI vont au-delà du prix et de l'achat et portent aussi sur l'équité, la pérennité, la réglementation, le renforcement des capacités et l'appui de partenaires. L'accent mis par les partenaires du développement sur un groupe restreint de pays et la concentration de l'aide technique et du renforcement des capacités dans ces zones qui en a découlé ont limité l'aide disponible pour d'autres pays. Les PRI dans la Région européenne signalent aussi un manque de capacités pour combattre les attitudes négatives envers les nouveaux vaccins de la part des parents et des professions médicales.

[7] See N° 22, 2008, pp. 193–208.

[8] See N° 1-2, 2011, pp. 1–16.

[7] Voir N° 22, 2008, pp. 193-208.

[8] Voir N° 1-2, 2011, pp. 1-16.

Specific projects such as the Vaccine Product Price and Procurement Project (V3P), EMR pooled vaccine procurement efforts, activities within the Pan American Health Organization (PAHO) revolving fund, and the UNICEF MIC strategy (including pooling demand from MICs and defining ceiling prices) are ongoing or under development. SAGE acknowledged their importance and potential as they represent bold steps in moving forward.

In complement to the efforts made by AMRO/PAHO and UNICEF on vaccine price transparency, SAGE considered that the V3P project would allow for improved availability of reliable information on vaccine products, prices and procurement to be used for countries' decision-making. To optimize the outcomes from these projects, SAGE noted the need for significant country capacity building.

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.

The proposed coordination policy and strategy outlined in the GVAP paper included options for how to optimize outcomes by seeking an enabling environment through capacity building, technical assistance, and system strengthening, as opposed to direct financial assistance or charity. SAGE noted that if partners worked together it would be possible to build on existing efforts and capacities, and use the comparative advantage of each partner to create new synergies. SAGE recommended, as a priority, the creation of a task force convened by WHO as a mechanism for inclusive stakeholder engagement and forum for harmonization and implementation of projects and activities.

SAGE recommended continued efforts towards improving the transparency of vaccine pricing. Actions should also include ensuring that manufacturing capacity is sufficient to meet the increasing needs of MICs.

SAGE noted that with a modest investment technical assistance and capacity building could be significantly strengthened.

SAGE noted that the lack of access to life-saving vaccines in MICs has not significantly improved since this was first raised in 2008 and that rapid action is now required. SAGE requested that this issue and achievements be revisited in a subsequent meeting. ■

Des projets spécifiques, comme le Projet sur le prix et les achats de produits vaccinaux (*Vaccine Product Price and Procurement Project* – V3P), les efforts de groupements d'achats dans la Région de la Méditerranée orientale, les activités dans le cadre du fonds auto-renouvelable de l'Organisation panaméricaine de la Santé (OPS), et la stratégie de l'UNICEF pour les PRI (comprenant un groupement des demandes des PRI et la définition de prix plafonds) sont en cours ou en voie de mise au point. Le SAGE a reconnu leur importance et leur potentiel, car ils représentent des étapes hardies pour progresser.

En complément des efforts faits par le Bureau régional de l'OMS pour la Région africaine/OPS et l'UNICEF sur la transparence des prix des vaccins, le SAGE a considéré que le projet V3P allait permettre d'améliorer, pour la prise de décisions par les pays, la disponibilité des informations fiables sur les produits vaccinaux, les prix et les achats. Pour optimiser les résultats de ces projets, le SAGE a noté le besoin d'un renforcement important des capacités dans les pays.

Le SAGE a apprécié les efforts faits par l'OMS, l'UNICEF, l'Alliance GAVI et d'autres partenaires pour étendre les discussions sur l'approvisionnement en vaccins et les prix pour les PRI suivant le cas, ainsi que l'adaptation de certaines activités pour satisfaire les besoins spécifiques de ces pays. Il a en revanche relevé avec inquiétude que ces efforts sont fragmentés et n'arrivent pas à optimiser les synergies dans l'action entreprise par chaque institution.

La politique de coordination proposée et la stratégie décrite dans le document du GVAP comportent des options sur la manière d'optimiser les résultats en cherchant à établir un environnement favorable au moyen du développement des capacités, de l'assistance technique et du renforcement du système, par opposition à l'aide financière directe et à la charité. Le SAGE a noté que, si les partenaires travaillaient ensemble, il serait possible de tirer parti des efforts et moyens existants et d'utiliser l'avantage comparatif de chaque partenaire pour créer de nouvelles synergies. Il a recommandé comme une priorité la création d'un groupe spécial, réuni par l'OMS en tant que dispositif pour l'engagement inclusif des parties prenantes et forum pour l'harmonisation et la mise en œuvre des projets et activités.

Le SAGE a recommandé de poursuivre les efforts pour améliorer la transparence de la fixation des prix des vaccins. Il faudrait également prendre des mesures garantissant des capacités de fabrication suffisantes pour répondre aux besoins croissants des PRI.

Le SAGE a relevé qu'avec un investissement modeste, on pouvait renforcer sensiblement l'assistance technique et le développement des capacités.

Il n'a pas constaté d'amélioration sensible au niveau du manque d'accès aux vaccins indispensables pour sauver des vies dans les PRI, depuis que ce problème a été soulevé pour la première fois en 2008, et il a noté qu'il fallait désormais agir rapidement. Le SAGE a demandé de réexaminer cette question et les progrès accomplis lors d'une prochaine réunion. ■

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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 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. During 2012, EMRO provided support to Libya for reviewing the vaccination schedule in preparation for introduction of PCV and rotavirus vaccine. EMRO has conducted effective vaccine management assessment in Egypt and 2 workshops for implementation of the recommendations took place February 2013. Egypt is also being supported for preparing for introduction of pentavalent vaccine. EMRO is also supporting conducting vaccination cluster coverage survey in Egypt to identify any negative effect on routine vaccination coverage. EMRO has provided support to Syria for implementation of MMR and Polio SIAs in November 2012. EMRO continued to support Yemen in implementation of integrated outreach activities to improve routine vaccination coverage, specially in hard to reach areas and follow up measles SIAs targeting children 9 months-10 years was successfully conducted in Yemen in April 2012. EMRO is supporting Tunisia for preparing for Measles/Rubella SIAs for control of the rubella outbreak.
General	SAGE requested that cold chain and vaccine management, thiomersal and the non-specific effects of vaccines also be discussed by SAGE in the future.	Agenda item	Nov 2011	Ongoing	A specific session Information on vaccines for an Intergovernmental Negotiating Committee to prepare a global legally binding instrument on the use of mercury took place at the April 2012 SAGE meeting. It discussed thiomersal and alternative preservatives and presentations. A preliminary session on the non-specific effects of vaccines is slotted for April 2013 to discuss the proposed approach. A SAGE working group on non-specific effects was established and held its first teleconference on 12 March 2013. It is expected that the full analysis will be presented to SAGE in November 2013 or April 2014. Other agenda items have been added on the master list of items to be discussed by SAGE and will be ready for discussion in the next 2 years.
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. Expected early 2013. Report not still recieved.
General	SAGE noted the important potential of immunization programmes for strengthening the overall health system, suggesting that good examples be documented and shared.	Action	Nov 2011	Ongoing	An analysis of health systems impact of new vaccine introduction was presented to SAGE in April 2012. SAGE endorsed revised principles for adding a vaccine to a national immunization system while strengthening the immunization and health systems and endorsed the proposal that the 2005 WHO Vaccine Introduction Guidelines be updated to assist decision-makers and managers with identifying and taking opportunities to strengthen the health system through new vaccines introduction.
General	SAGE recommended that new approaches, such as periodic intensification of routine immunization, be carefully evaluated prospectively to determine their effectiveness and cost-effectiveness.	Action	Apr 2009	Ongoing	Work with Immunization Basics to document country experiences is wrapping up. Mission to observe Zimbabwe Child Health Days which included routine catch up doses was undertaken in June 2009. Final report available (17 June 2010). Mission to Macedonia was undertaken in April/May 2010 to document the European Immunization Week (EIW) (draft report has been reviewed by WHO and will be finalized shortly). This topic has been referred to the WHO Immunization Practices Advisory Committee (IPAC) which has discussed it intensively at its meetings June and November 2010, particularly the issue of no longer being able to use the delivery strategy to reliably disinguish whether a dose is routine and supplementary. Jointly WHO & UNICEF prepared a Guidance Note outlining four criteria to determine if a given vaccination is a routine or supplemental dose. IPAC endorsed the Guidance Note at its meeting September 27-28, 2011. WHO/UNICEF are now proceeding to disseminate the criteria and consult with stakeholders regarding the consequences.

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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 behaviours 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. TIP was piloted in Bulgaria in 2012. The Toolkit is being further pilot tested in Sweden among migrants, marginalized and anthroposophic communities. The toolkit will be launched during EIW2013 (April 22-27, 2013) 2. Strengthening the ability of member states to handle crises in vaccine confidence and trust through a guidelines document on vaccine safety communication. It is to be launched during European Immunization Week 2013 (April 22-27, 2013). This was done at the request of EPI managers. 3. Advocating through Immunization Week, which began in 2006. Activities are independent for each country. 4. Strengthening the use of new media. Well-ranked bloggers who write in Russian and English will be brought in to dialogue about how to better engage around vaccine confidence. A vaccines social media strategy is under development and an smart-phone immunization tracker/reminder 'app' for parents will be launched on April 24, 2013. 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 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 SAGE November 2012 meeting, SAGE further requested ECBS to 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.
General - 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 selection process for the DoV SAGE Working Group is still ongoing and should be finalized prior to the April 2013 SAGE meeting. Once established the Working Group will review the GVAP indicators and mechanisms.
General - GVAP	SAGE requested consideration of the establishment of a SAGE standing working group to monitor GVAP implementation.	Action	Apr 2012	Ongoing	Terms of Reference for a SAGE DoV-GVAP standing working group were discussed at the November 2012 SAGE meeting. A call for nominations and selection of working group members was launched in January 2013. The selection panel is to review all nominations on March 25 and the composition of the group should be settled prior to the April 2013 SAGE meeting.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
General - 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.
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	Activities to lead to better vaccine price information and vaccine pricing transparency are being considered and under discussion for funding. Contribution of WHO to the DoV work stream on global access. IVB staff are actively participating 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. Discussions have taken place with DCVMN as such and individual DCVMN members to consult on potential and actual role of emerging manufactuers in supplying affordable vaccines . This could be followed by offering the possibility for bilateral meetings with manufacturers to discuss this issue as well as exchange on strategic orientations as this is already being done with some members of The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). General discussions on the process of technology transfers are taking place under the leadership of the Evidence Information and Research Cluster. IVB has launched a new project on vaccine product, price and procurement. The purpose of the project is to support GAVI graduating and lower and middle income countries to accelerate the introduction of new vaccines through the provision of improved vaccine product and price information for decision-making. It is a 3-year project funded by the BMGF.
Childhood mortality	SAGE noted the recommendation by QUIVER (now 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.

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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	Ongoing	A meeting on use of oral cholera vaccines in complex emergencies was held in early May 2011, and the WHA passed a resolution on mechanism for cholera control and prevention was passed in the May 2011 assembly. In addition, a meeting on cholera vaccine stockpile was held in Geneva from 6 to 7 September 2011. A meeting on the experience of Zanzibar to use cholera vaccine as a preventive tool was held in February and the Zanzibar Government is keen to use the vaccine island-wide if support is forthcoming. Cholera vaccine has been introduced as a pilot in Haiti as well as in Guinea. The preliminary reports from both appear highly encouraging on the utility of vaccine to prevent cholera. In 2012 the WHO Pandemic and Epidemic Diseases Dept convened an expert working group to develop SOPs for implementation of the cholera vaccine stockpile for outbreak response, including definition of specific criteria for deployment of vaccine from the stockpile. Financial support has been identified (EU-ECHO, USAID–OFDA and three private entities). A request for procurement has been issued in a closed bid for 2 million doses of vaccine with closure of the bid being 5th of April 2013. The planned AFRO regional stockpile preparations are underway with the stockpile anticipated to be active 01 July 2013.
Decade of Vaccines	IVR was encouraged to contribute actively to the research component of the DoV.	Action	Apr 2011	Ongoing	IVR participates in the Research and Development subgroup, and tracks research issues emerging from delivery group. R&D working group meeting was held on 29 September 2011. Tentative list of research priorities short, mid and long-term was developed. IVR leads on coordinating R&D agenda with partners agencies. A formal memorandum was signed. Progress on establishing a vaccine research forum and implementation strategies in support of GVAP R&D related activities.
Feedback from IPAC	IPAC update.	Information	Nov 2011	Ongoing	The last IPAC meeting was held in October 2012, and feedback was provided on this meeting as well as the April 2012 meeting, to SAGE in November 2012. The next IPAC meeting will occur April 2013, one week prior to the SAGE meeting. Key topics on IPAC upcoming agenda include solar refrigeration guidance to countries, development of unvaccinated framework, health worker checklist piloting and controlled temperature chain (CTC) application with Meningococcal A vaccine MenAfriVac.
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. Despite some progress, the challenges are enormous on the financial aspects as well as on ownership, decision making, capacity, pricing and procurement aspects. The establishment of a pooled procurement in EMRO has been decided by the Regional Committee in 2012 and in 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 have been drafted, potential composition has been identified and contact with key partners are underway to set up the SAGE recommended task force.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Financing	SAGE requests that WHO conduct further situation analysis of financial challenges for low or middle-income countries and consultation with countries concerned & partners to distil issues to more actionable activities.	Action	Apr 2008	Ongoing	A Request for Proposal (RFP) has been drafted and submitted to the BMGF for funding. This was accepted, the RFP was issued in March 2009 and selection was made in June 2009. R4D was selected to conduct the study on LMIC to be launched early November 2009. Preliminary results were presented at the GIM and NUVI meeting in 2008 and 2010, findings and initial conclusions and recommendations will be presented to the SAGE in November 2010. Actionable activities will be then adopted and discuss with partners for implementation. Work is now underway to consider ways of addressing the potential obstacles and issues faced by the 16 graduating countries from GAVI support. A Sharepoint on Middle-Income Countries and new vaccine introduction was created by IVB-WHO to facilitate data collection and exchange between the Middle-Income Country working group members. A Middle-Income Country presentation by EMRO during the 2009 WHA took place and was well received - the May 2008 WHA resolution on immunization referred explicitly to Middle-Income Countries. Sessions on Middle-Income Country was held during the NUVI meeting in June 2008 and 2010, an updated background document was discussed and an action plan for 2009-12 was approved with all concerned parties (vaccine industry, country and region representatives, WHO and UNICEF, Gates Foundation, ...). Ongoing discussions are taking place with UNICEF, BMGF and other entities to implement the R4D study recommendations. The draft GVAP has partly addressed some the issues but more clarity and consistency is needed. A brainstorming meeting was organized on the lower-middle-income countries activity information and coordination on 12-13 March at HQ. On this occasion we discussed concepts, general approaches and specific plans for MIC with the ultimate objective of developing a platform and way forward for engagement and co-ordination with partners. The results of this and other consultations was presented at the November 2012 SAGE. A session was held on Middle-Income countries. A draft paper entitled "Global Support for New Vaccine Implementation in Middle-Income Countries" was presented to SAGE. The information provided in the paper was complemented by presentations from WHO, the former Yugoslav Republic of Macedonia, and UNICEF. Given the importance of the topic, SAGE requested that this issue and achievements be revisited in a subsequent meeting.
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 first annual meeting in November 2012. A portfolio of activities is being developed to cover all 8 strategic objectives.

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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 moderate 31.2% level of efficacy in preventing HIV infection and 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 held in June 2010 in Istanbul for the Eastern Europe region and Kuala Lumpur for the Asian region. This consultation allowed for the development of recommendations and drafting a new guidance point to be included in the new edition of the WHO/UNAIDS Ethics Guidelines. 2. In support of regulatory frameworks, WHO/IVR/HVI and UNAIDS have initiated a project on the development of policy/discussion paper to facilitate national decision making with regard to the novel strategies for testing HIV vaccines, namely, the recently proposed Adaptive Trail Design). A background working paper was developed and discussed at an expert group meeting co-organized in collaboration with WHO, UNAIDS, IAVI, NIH and the Global HIV Vaccine Enterprise. The expert group meeting took place on 10-11 February 2011 in New York. As an outcome of this meeting a technical discussion paper has been developed targeting the national regulatory authorities in countries where this type of trials are being planned in the coming years. This paper has been submitted to the journal Vaccine for review. A written update will be provided on the progress of HIV-vaccine research for the November 2013 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 2012 epidemiological situation was provided to WHO. There is still no identified breakthrough case among vaccinated children since the introduction of hepatitis A in the national immunization program in 2005. A slight increase in the number of reported cases in 2012 mostly in those 45 years of age and over may in part be due to a surveillance artifact as surveillance keeps improving and the result of natural (or due to the impact of vaccination) evolution of the risk in those too old to have been vaccinated. These 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. Both health system and societal costs prevented totaled ~US$ 137 million with health systems cost ~US$ 44 million. Based on the Argentinian's experience, in 2012 both Colombia and Paraguay introduced a single dose national immunization schedule for 1 year old children.

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. 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.
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	WHO HQ has completed and disseminated a new global viral hepatitis strategy. EMRO is working with Member States to ensure achievement of the Regional Committee goal for HBsAg reduction in vaccinated children. In 2012, WPR TAG endorsed the region's Hepatitis B Expert Resource Panel (ERP) proposal to set 2017 as the target year to achieve the goal of reducing childhood hepatitis B prevalence to <1%. SEARO has a draft regional strategy and will convene two meetings in 2012 to finalize. AFRO has convened a regional hepatitis TAG and will bring their input to the Regional Committee in 2012. 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.
Hib	SAGE recommended that a revised summary of the evidence, including a critical appraisal of the evidence with GRADE tables and justification for proposed recommendations, should be presented to SAGE in April 2013.	Action	Nov 2012	Ongoing	A revised summary of evidence including all the aspects suggested by SAGE along with the GRADE tables have been included in the SAGE Yellow Book for the April 2013 meeting and will be discussed at the meeting.

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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	- 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) Working on recommendations to minimize primary, secondary, and tertiary container packaging. 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 final administrative arrangements should be finalized in the coming weeks. - 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 (not recommends) the use of needle cutters but their introduction should come with training of HCWs on their use. An RCT on hub cutters has subsequently been completed in Ghana with WHO collaboration. Following this study a project proposal from GEF was submitted to the Gates Foundation Grant Challenge and granted (100,000 USD). This project will start with a pilot in one district. Used syringes will be collected and decontaminated by autoclave and supplied to a manufacture for recycling. As of today the project is waiting for the purchase of an autoclave.
Immunization schedules	SAGE endorsed continuing work in the related research areas, with refinement of the research agenda undertaken by the research component of IVB, under the oversight of the research advisory bodies of WHO. SAGE asked to be kept informed of progress and results.	Information	Apr 2007	Ongoing	Work in progress. Presentation of the PCV evidence was done at the SAGE November2011 meeting resulting in the updating of the pneumococcal conjugate vaccines position paper in April 2012. Evidence on rotavirus vaccines was presented at the April 2012 meeting and the updated rotavirus position paper will be published in January 2013. Evidence on Hib was presented 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. Hib will be revised during the SAGE April 2013 meeting.
Immunization schedules	SAGE requested that the models reflect operational realities – for example, delays in vaccine administration.	Action	Nov 2010	Completed	Models to examine these factors have been developed. Their application to PCV was presented in Nov 2011. The implication of coverage and timeliness by age on rotavirus vaccine impact was presented at the April 2012 SAGE meeting.

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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 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 will be published in February 2013. Hib: No resources for model and/or ICEA. Evidence review is being completed; an ad hoc consultation will be 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 will be 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).
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 3 countries was conducted by LSHTM in 2011-12 to gather further information. 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, which is to be published after external review in early 2013.
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 which are to be published in early 2013 as a result of the proceedings of the ad hoc working group are being vetted by the partner agencies and will be endorsed by their senior personnel.
Influenza	SAGE recommended that the Influenza Vaccines and Immunization Working Group develop a research agenda.	Action	Nov 2010	Ongoing	The Global Influenza Programme (GIP) presented their development of a WHO Public Health Research Agenda for Influenza (PHRAI) in the August 2011 SAGE WGIVI meeting. The WG acknowledged the extensive coverage of influenza research topics in the PHRAI and activities of the SAGE WGIVI can serve as one avenue to inform the RA. One area that may need further development is on vaccine communication and risk communication issues. It is recognized that communication is population-specific and how generalizable are the research work in this area would be an important topic to address. SAGE WGIVI also suggested that experiences from industry on the information gathered from countries on impact and lessons learned in view of research activities to inform the PHRAI. The importance of evidence-based recommendations was stressed and the PHRAI would be an important tool. There is also a need to identify more detailed research needs for influenza vaccines and the SAGE WGIVI encourages close collaboration with the PHRAI in addressing this need.

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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. Further discussion by the SAGE working group for influenza vaccine and immunization will have to wait for the outcome of discussions in the PIP framework.
Japanese encephalitis	Commercial kits for detection of JE-specific IgM should be compared and validated. Valuable experience had been gained from linking surveillance of encephalitis to detection of acute flaccid paralysis.	Action	Apr 2006	Ongoing	Assessment using serum carried out by PATH, published Am J Trop Med Hyg July 07. Field validation of serum and CSF in India and Bangladesh assessed in a joint WHO/CDC meeting, SEARO, February 2008. Nepal and Cambodia field evaluation of JE assays is complete and paper 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, Chengdu, China, 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 too 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.
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	Planning and fundraising efforts are ongoing in the Regions. Control goals have currently not been formulated. A literature review on the JE burden of disease has been conducted, estimating the burden of JE to some 67,000 clinical cases and a CFR of above 20%. This was Published in the Bulletin of WHO, Bull World Health Organ 2011;89:766–774. Identification of target populations are being discussed in the context of country control strategies, and a review has been conducted at the 2011 biregional JE meeting. An update of the JE position paper (from 2006) is being planned that will comprise a review of immunization strategies.
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	Some studies are being initiated by PATH, and planned by Governments considering introduction of the vaccine. Issue of interference with measles vaccination discussed at the December 2007 GACVS meeting. Measles co-administration (S Gatchalian, Vaccine 2008) had to be redone due to assay inconsistencies - results still pending. Number of doses required (one or two doses for primary immunization with live JE vaccine) has been assessed through case control studies in Nepal and India (the Nepal study is published and India study published as a note to the editor, 2 April 2009 in NEJM). A comprehensive review of the vaccine performance is planned in conjunction with an update of the JE position paper from 2006.

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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, projects and initiative to explore what are the 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 in supporting activities but they are still hesitating and trying to identify the best approaches. 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. 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. 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 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 in 2013 the EMR Initiative on pooled procurement and to contribute to the UNICEF SD initiative on MIC and new vaccines. Some results are expected during the second half of 2013.
Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE recommended, as a priority, the creation of a task force convened by WHO as a mechanism for inclusive stakeholder engagement and forum for harmonization and implementation of projects and activities.	Action	Nov 2012	Ongoing	Terms of Reference have been drafted, potential composition has been identified and contact with key partners are underway to set up the SAGE recommended task force.
Lower middle-income countries: sustainable adoption and financing for new vaccines	SAGE noted that the lack of access to life-saving vaccines in MICs has not significantly improved since this was first raised in 2008 and that rapid action is now required. SAGE requested that this issue and achievements be revisited in a subsequent meeting.	Action	Nov 2012	Ongoing	Various initiatives are underway to facilitate access to new vaccines in middle income countries: UNICEF SD is consulting with Vaccine Industry and with countries to supply PCV, RV and HPV to middle income countries and to set up a ceiling price. The regional Committee of EMR has decided to establish a pooled vaccine procurement to support introduction of priority vaccines in middle income countries and to collaborate with UNICEF SD on its MIC initiative GAVI board retreat in March discussed to options to support access to GAVI prices for graduating countries as well as lower middle income countries. Concrete efforts and results are still to be seen. Coordinated effort, consistent policy and financial support are needed to translate those initiatives into reality for countries.

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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 Phase 3 trial of RTS,S/AS01E completed enrollment Jan 2011 with 15,460 infants enrolled in 11 sites in 7 African countries. Two sets of results were published in Oct 2011 and Nov 2012. These are 12 month follow-up data post dose 3 for young children aged 5-17 months of age with no co-administration, and for infants aged 6-12 weeks in co-administration with DTwP/HepB/Hib and OPV respectively. Both age groups received 3 i.m. doses of RTS,S/AS01 at 4 week intervals. In each age group there were three trial arms, with one arm including a fourth (booster) dose 18 months post dose 3. In 5-17 month olds 55% efficacy (95% CI 50-59) was reported against all episodes of clinical malaria, and 47% (95%CI 22-64) efficacy against severe malaria. In 6-12 week olds the equivalent figures were 33% efficacy (95% CI 26-39) for all episodes of clinical malaria, and 37% (95% CI 5-58) efficacy for severe malaria. Immunogenicity was 3-fold higher in the older age group, in terms of antibodies to the malaria antigen present in RTS,S. The authors report an excess of febrile seizure within 7 days of vaccination in the RTS,S/AS01 groups, for the older age group only. A full safety review will be performed by GACVS, tentatively scheduled for June 2015. The full trial results will be available in late 2014 and will include information on 30 months of follow-up, the safety and efficacy of an 18 month booster dose and site-specific clinical malaria efficacy. The Joint Technical Expert Group on malaria vaccines (JTEG) met in Oct 2012 and has advised that this 2014 data may support policy recommendation in 2015. The first regulatory submission will be to the European Medicines Agency under the article 58 procedure. The first wave of 5 national regulatory submissions will be to Kenya, Tanzania, Ghana, Senegal and Burkina Faso, where Phase 4 studies of safety and effectiveness are planned. The dates for regulatory submissions remain unconfirmed, with a recent indication that the regulatory submission timing would be consistent with a possible "For Decision" session in Q4 2015. This is planned to be a joint Session between SAGE and the Malaria Policy Advisory Committee. The vaccine development partnership has been encouraged to fully explore optimal schedules and age groups for possible administration of this vaccine. An additional schedule study is ongoing in Malawi, with several 3 dose schedules. Previously published RTS,S/AS01 co-administration studies in children younger than 12 months of age have reported that non-inferiority criteria have been met for D, T, wP, Hep B, Hib, Measles and Yellow Fever. A major issue for communication will be the need to evaluate RTS,S/AS01 as an addition to, not a replacement for, existing preventive measures, particularly long-lasting insecticidal nets and the need for ongoing availability of rapid diagnostic tests, and effective antimalarial drugs after any possible use of this vaccine in the future.
Measles and rubella	SAGE requested that the measles and rubella working groups should merge and monitor progress, oversee the research agenda required for eradication and report back to SAGE regularly. The working group should liaise with QUIVER and IPAC to address relevant quantitative issues as well as those related to immunization practices. This activity has been included in the draft terms of reference for the combined measles and rubella working group.	Action	Nov 2010	Completed	The working group on measles and rubella was formed in late 2011. Peter Figueroa is the chair of the working group and as of 27 September 2012, the group has held monthly conference calls and 2 face-to-face meetings (22 March and 20-21 September 2012). The working group prepared a session on measles and rubella at the November 2012 SAGE meeting. The session included a report on progress, challenges, lessons learnt, and opportunities for achieving measles and rubella targets. In addition, there was a presentation on aeorsol measles vaccination and a brief update on the planned outputs from the working group in 2013. SAGE endorsed the Global Measles and Rubella Strategic Plan 2012 - 2020.

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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	Ongoing	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.
Optimizing pneumococcal conjugate vaccine (PCV) schedules	SAGE requested that available evidence and guidelines to facilitate decision-making at country and regional level be posted on the WHO website.	Action	Nov 2011	Completed	A BETA version of the proposed approach to summarize the evidence and of the website was presented to SAGE during the April 2012 meeting: http://perso.epita.fr/~costa_k/RotavirusProjectVersion2/
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	Pending	The initial offer of the pertussis strains made by Dr Nicole Guiso from the Institut Pasteur (IP) was not presented to the ECBS in 2010 due to the lack of information regarding the use of the strains and the related data. The proposal is currently subject to the official decision regarding the future of these strains that the Institut Pasteur needs to make. A possibility for maintaining the strains in the IP repository is one of the options under consideration. Update March 2013: As cooperation with the IP due to administrative issues has shown to be complicated, the value of taking this issue to another center will be discussed by the newly established SAGE Pertussis Working Group.
Pertussis control	Establish a working group on pertussis.	Action	Nov 2012	Completed	A SAGE Working Group on Pertussis vaccines was established in March 2013. The first teleconferences of the working group took place on 11th of March 2013.
Polio eradication	SAGE recommended that WHO/GPEI continue to work with GAVI to ensure financing is available within 18 months for any GAVI-eligible countries wanting to introduce a low-cost IPV option as part of the switch strategy.	Action	Apr 2012	Ongoing	The financial requirements for the 'Endgame' are projected to be US$ 5.5 billion for the period 2013-2018; this reflects substantial work under various scenarios and is the consensus position of the core GPEI partners, in consultation with the relevant global, regional and country stakeholders. The proportion across key budget categories, which include the introduction of IPV, surveillance and laboratory costs, outbreak response capacity & vaccine stockpiles, as well as containment certification costs, will be adjusted as progress against key polio eradication milestones is evaluated. Adjusting the estimated year of interruption will increase/decrease costs accordingly. The financial needs of this plan will be met by implementing a resource mobilization, communications and advocacy strategy jointly developed by GPEI partners with the guidance of the relevant executive groups in the GPEI architecture, particularly the Polio Partners' Group and the Polio Emergency Steering Committee. Discussions with GAVI are ongoing to ensure financing for the introduction of a low-cost IPV option as part of OPV2 cessation for GAVI-eligible countries.
Polio eradication	SAGE recommended that the draft Polio Eradication and Endgame plan be revised to include recommendations from current stakeholder consultations.	Action	Nov 2012	Completed	The draft 2013 to 2018 GPEI Polio Eradication and Endgame was extensively revised, following a series of in-depth stakeholder consultations; the draft will be made available to SAGE at the April 2014 meeting.
Polio eradication	SAGE recommended that an IPV supply and funding strategy be established for timely introduction of IPV using existing whole dose products for a transition period if needed. For its next meeting SAGE requested additional details on the scientific evidence for, and programmatic implications of, targetng expanded age groups during polio campaigns in endemic areas.	Action	Nov 2012	Ongoing	Work focusing on the establishment of the required IPV supply and funding strategy with stakeholders and with GAVI has continued to allow the introduction of whole-dose IPV in time before the planned cessation of OPV2. The polio session during the April 2014 SAGE meeting will also include an update on the programmatic implications of new strategies during polio SIAs in priority countries.

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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	WHO continues to assess the feasibility of using international mechanisms to implement such vaccination requirements and travel advisories. It is currently envisioned, that such measures ((e.g. an IHR standing recommendation on vaccination of travelers) would be considered for any area with continuing poliovirus transmission at end-2014. Additionally, as in previous years, WHO has updated its International Travel and Health publication, providing vaccination recommendations to travellers based on the most up-to-date global polio epidemiology.
Polio eradication	SAGE recommended that WHO/GPEI work with vaccine manufacturers to develop both options and with regulatory authorities to initiate fast track review of ID IPV immediately, to ensure that a low-cost IPV option is available within a year.	Action	Apr 2012	Ongoing	The SAGE Polio WG updated SAGE during the November 2012 meeting in detail on the outcome of discussions about the ongoing work towards achieving options for affordable IPV, including on the WGs direct interaction with four IPV manufacturers and discussions with regulatory authorities. The WG will report to SAGE in April 2013 on progress made along several 'workstreams' towards achieving the prerequisites for OPV2 withdrawal,and on the anticipated timeline towards OPV2 cessation.
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	Ongoing	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, 2013-2018 and endorsed the 4 major components.
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	Ongoing	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 - will be presented at the April 2013 SAGE meeting.
Polio eradication	SAGE requested that WHO/GPEI undertake further consultation with countries and regions to document the policy and programmatic implications of introducing an IPV dose (whether IM or ID) as part of the strategy to switch from tOPV to bOPV and to facilitate individual country decision-making.	Action	Apr 2012	Ongoing	A review of operational differences between using IPV as a full dose (IM) vs. application as fractional dose (ID), comparing differences relating to service delivery, cold chain and logistics, management, training, supervision, and cost. The assessment included detailed interviews with EPI managers from Asia (India), and Africa (one West and one East African country). Results of this investigation were reported to the SAGE Polio Working Group, and at the October 2 meeting of the Immunization Practices Advisory Committee (IPAC). Special sessions on the 'polio endgame', focusing in particular on the plans for OPV2 cessation (i.e. the switch from tOPV to bOPV for routine immunization) have been conducted at the EMRO EPI manager's meeting (September 2012) and are planned for the 4th quarter of 2012 at the regional EPI meetings in the South-East Asian and African Regions. During the November 2012 meeting, SAGE recommended that all countries should introduce at least 1 dose of IPV in their routine immunization programme to mitigate the risks associated with the withdrawal of OPV2.

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Polio eradication	SAGE strongly encouraged the Global polio Eradication Initiative (GPEI) to proceed with its full IPV research agenda, in particular to clarify the duration and quality of the priming immune response to inform the work of the SAGE IPV working group.	Action	Apr 2011	Ongoing	The WHO polio eradication research team is coordinating additional research in this area, including further analysis of Cuba study data (e.g., titre of neutralizing Ab after one and two doses of IPV), and potential collaboration with the International Vaccine Institute (IVI), Korea, to measure mucosal and systemic antibody-secreting cell (ASC) responses against polio vaccines in young infants after one and two doses of IPV. The data have been shared on multiple occasions both with the SAGE WG, and the full SAGE. In addition, a manuscript has been published that summarizes these data from Cuba. (Resik S et al. Priming after a fractional dose of inactivated poliovirus vaccine. NEJM.2013;368:416-24).
Reports from other advisory committees	SAGE recommended appointment of appropriate programmatic and implementation expertise to QUIVER's membership including representation of experts from low and middle-income countries.	Action	Nov 2011	Ongoing	The new QUIVER AC called Immunization and Vaccines related Implementation Research (IVIR) advisory committee has been expanded to 15 members with programmatic and implementation research expertise. It remains a challenge to include representatives from low and middle-income countries. Four of the five new members nominated are from LMICs with expertise in vaccine implementation issues and vaccine trials.
Reports from other advisory committees on immunization	WHO and NIBSC should develop with other stakeholders, a business plan to assure long-term security of global public health resource and additional efforts 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.
Thiomersal	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	Discussions with donors has advanced well and planning for meeting on new vaccine technologies being initiated. Further work on the report is still pending. Internal QSS-EPI discussions are in progress.
Thiomersal	SAGE endorses the proposal for a scientific meeting on alternatives to thiomersal prior to the fourth session of the Intergovernmental Negotiating Committee to prepare a global legally binding instrument on Mercury (INC4), as this would support the aims of the INC and avert concerns that developing countries are using products no longer used in industrialized countries. SAGE asked GACVS to present a review of the safety of alternative preservatives. SAGE will also consider the broader implications of alternative preservatives for global immunization policy.	Action	Nov 2011	Completed	A scientific meeting was held on 3-4 April 2012 to develop further guidance on vaccines for the UNEP-convened Intergovernmental Negotiating Committee meeting 4, and the conclusions of this meeting were reported to SAGE on April 2012 for a specific session Information on vaccines for an Intergovernmental Negotiating Committee to prepare a global legally binding instrument on the use of mercury took place at the April 2012 SAGE meeting. It discussed thiomersal and alternative preservatives and presentations. In early 2103 the Intergovernmental Negotiating Committee finally agreed to exclude vaccines containing thiomersal from the scope of the new international convention that will reduce the harmful health effects of mercury.
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	Pending	Written update was provided for the November 2013 SAGE meeting.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
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	A 3-year grant from the Bill and Melinda Gates to the Coalition against Typhoid (CaT) and Sabin Vaccine Institute ends in 2013 and an application has been initiated to seek a supplementary grant to 2016. CaT, WHO and other partners will continue to implement and support typhoid control and prevention activities, including immunization as well as water, sanitation and hygiene (WASH) strategies. A major international conference on 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. As previously reported to SAGE, WHO pre-qualified the sanofi pasteur Vi polysaccharide vaccine in June 2011, the first typhoid vaccine to be WHO prequalified. However Vi polysaccharide vaccine uptake has remained low for multiple reasons including funding. In November 2011 the GAVI Board re stated its 2008 commitment to 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 conjugate typhoid vaccine is available. The first typhoid conjugate vaccine likely to be presented for WHO pre-qualification is projected to be licensed in 2015. WHO and its expert groups are currently developing guidelines on the quality, safety and efficacy of typhoid conjugate vaccines, expected to be presented to the ECBS in Oct 2013 for approval (public consultation of the draft document now available with a deadline of 19 April at http://who.int/biologicals/WHO_TyViPSconj_Draft.01.06_cl_web.pdf).
Typhoid	Need for feedback from WHO's regional offices and countries to determine how countries could implement SAGE recommendations.	Action	Nov 2007	Ongoing	A full report was presented to the November 2010 meeting of SAGE. SAGE reiterated that countries should consider introduction of existing typhoid vaccines and not necessarily wait for surveillance systems to be in place. Further, to take the typhoid agenda forward, the Bill and Melinda Gates Foundation awarded a three year grant to the Sabin Vaccine Institute, Washington DC,to coordinate all stakeholders interested in typhoid and to develop a global agenda for the control and prevention of typhoid fever. WHO will work closely with Sabin in this process. Since typhoid vaccine is one of the 7 vaccines that GAVI listed as their priority vaccines for support, for the November 2011 meeting of the GAVI Board, a case was made for typhoid vaccine support. The GAVI Board finally issued a clear statement that GAVI will not support the Vi-polysaccharide vaccine and will wait for a conjugate vaccine to be available. Given this stand there is clearly no appepite for any donors to support ViPS typhoid vaccine. Thus all activities related to encouraging countries to consider ViPS are stopped. Focus is now on supporting the development of conjugate vaccine and strengthening surveillance in countries to generate better data on typhoid.
Un/under-immunized children	SAGE recommended that the targeted approaches undertaken by Tanzania and Ethiopia to reduce to number of un/under-immunized children should be appropriately adapted for use in other countries.	Action	Apr 2011	Ongoing	The targeted approaches undertaken by Tanzania and Ethiopia to reduce to number of un/under-immunized children have been incorporated in the framework to reduce unvaccinated children. In addition a case study from India has also been included. The final draft of the framework is complete. A follow-up meeting with the WHO regions and partners was heldd on the 4th October 2012 to review the in-depth tools that are being put together. Another meeting has been scheduled on the 3rd April 2013.
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 has been conceptualized. In addition to the work on the framework at HQ, the EURO, AMRO/PAHO and AFRO regional offices of WHO are working on operational guidelines and demand generation side documents respectively. A framework to increase coverage has been drafted and was presented to a small group comprising of representatives from EURO (2), AFRO (1), HQ and Dr David Durrheim, member of SAGE. The final draft of the framework is complete. A follow-up meeting with the WHO regions and partners was held on the 4th October 2012 to review the in-depth tools that are being put together. The initial diagnostic tool is in its draft final stage. A follow-up meeting has been scheduled on the 3rd April 2013.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Un/under-immunized children	SAGE recommended that WHO prioritize the ongoing work on the development of the framework to guide countries in identifying determinants of low immunization coverage and institute corresponding local solutions.	Action	Apr 2011	Ongoing	The work has been prioritized. A framework to increase coverage has been drafted and was presented to a small group comprising of representatives from EURO (2), AFRO (1), HQ and Dr David Durrheim, member of SAGE. The final draft of the framework is complete. A follow-up meeting with the WHO regions and partners was held on the 4th October 2012 to review the in-depth tools that are being put together. Another meeting has been scheduled on the 3rd April 2013.
Vaccination in humanitarian emergencies	SAGE requested that the finalized framework be presented to the November 2012 SAGE meeting for consideration.	Action	Apr 2012	Ongoing	The draft was presented at the November 2012 SAGE meeting. SAGE endorsed the revised framework as a major step forward and considers that it fills an existing gap.
Vaccination 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 and proceed with further pilot tests before finalization.	Action	Nov 2012	Ongoing	Finalization of the document based on feedback received from the SAGE meeting of November 8th, 2012 is in progress. The document has been revised and is currently being review by the members of the working group before finalization.
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	Emergency Risk Management and Humanitarian Response (ERM) Department staff do consider that the framework approach for other health interventions in emergencies is a good recommendation from SAGE. ERM will explore this issue in the second half of 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 20 Feb to solidify the workplan, and work started in 2012 to combine WHO and UNICEF databases on vaccine forecasting, supply and distribution in countries is ongoing. It was agreed to have a joint discussion on DTP, HepB mono and TT/Td supply in Q2 2013. WHO will also take part in the global forecasting discussions in September 2013.
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 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 (details available from: www.gatesfoundation.org/vaccines/Pages/rfp-immunity-assessment-tool.aspx).
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 consultant has been recruited to review currently available biomarkers and draft a guideline 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. For each selected disease study populations, sampling methods, data/specimen collection, laboratory/statistical analysis, and implications of results was summarized in a 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.

Topic	Recommendations/Action item	Category	Meeting Date	Status	Comments and Follow up
Vaccine coverage	SAGE recommended that WHO explore alternative survey methods to improve the precision, reduce the cost and improve the usefulness of survey results to national and local immunization programmes.	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, the UNICEF Multiple Indicator Cluster Surveys and the WHO Immunization Cluster Survey to accommodate changes in immunization system strategies.
Vaccine preventable disease 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 also noted that country ownership should be enhanced and that Ministries of Health should be encouraged to increase their own funding for surveillance. SAGE appealed for sustained financial support to ensure quality for sentinel site surveillance. SAGE underscored the importance of ensuring the representativeness of sentinel sites.	Action	Nov 2011	Ongoing	Since the previous update on the November 2011 SAGE session on VPD surveillance, WHO has conducted the following activities as aligned with SAGE recommendations: NUVI surveillance mission statements & objectives have been developed; In December 2011, WHO began the dissemination five (5) agreed minimal criteria for funding, which will be enforced as of 2014 funding. WHO has received funding from CDC to strengthen data management capacity during 2013. The methodology to estimate a denominator for Tier 1 IB VPD sentinel sites was piloted in 4 countries, reviewed technicially, and is being developed into a field guide; WHO continues to sustain the global and regional reference laboratories for training, quality assurance, and PCR testing of culture negative specimens; and reviewers have commented on the draft global IB-VPD SOPs, and comments will be incorporated during 2013. WHO will be closely assessing the status of the NUVI surveillance networks during 2013. Funding beyond 2013 remains uncertain.
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.
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, hopefully prior to the April 2013 SAGE meeting.Consideration was given to the potential inclusion of case studies in the documents but this was debated, as disasters are very diverse. It was left to the working group to decide whether these should be included.

World Health Organization

SIXTY-SIXTH WORLD HEALTH ASSEMBLY **A66/19**
Provisional agenda item 16.1 **22 March 2013**

Global vaccine action plan

Report by the Secretariat

1. The Executive Board at its 132nd session in January 2013, considered and noted an earlier version of this report.[1] The present document has been amended in response to Board members' comments and updated to include details of recent developments. It also reports on the status of progress made towards achieving the goals of the Decade of Vaccines.

2. Four sets of activities are essential to put the plan into practice and to turn the actions into results: (1) development of guidance for putting the plan into practice; (2) completion and implementation of a mechanism for evaluation and accountability in alignment with the accountability framework for the United Nations Secretary-General's Strategy for Women's and Children's Health;[2] (3) securing commitments from stakeholders; and (4) publicizing the opportunities, while acknowledging the challenges, offered by the Decade of Vaccines. This report summarizes the progress made in these areas.

OPERATIONALIZING THE GLOBAL VACCINE ACTION PLAN

3. During the past few months, all regions have held technical meetings to review the strategies proposed in the action plan and the actions required at regional level. Progress in immunization activities and in implementing regional multi-year strategies and plans for immunization in alignment with the global plan will be reported to the respective regional committees in 2013.

4. WHO/UNICEF's guidance for developing multi-year and annual national immunization plans[3] is being updated in order to facilitate alignment with the global action plan's goals and strategic objectives. The updated guidance will set out how the different elements of health systems can be used to ensure that multi-year immunization plans align better with broader national health sector plans. Guidance for Member States to develop national monitoring, evaluation and accountability processes that align with the corresponding regional and global processes will also be included in the update.

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[1] See document EB132/18 and the summary records of the Executive Board at its 132nd session, tenth meeting, section 3.

[2] Commission on Information and Accountability for Women's and Children's Health. *Keeping promises, measuring results*. Geneva, World Health Organization, 2011 (http://www.who.int/woman_child_accountability/en/; accessed 13 December 2012).

[3] *WHO-UNICEF guidelines for developing a comprehensive multi-year plan (cMYP)*. Geneva, World Health Organization, 2005.

PROPOSED FRAMEWORK FOR MONITORING, EVALUATION AND ACCOUNTABILITY

5. In resolution WHA65.17, the Health Assembly urged Member States to report every year to the regional committees on lessons learnt, progress made, remaining challenges and updated actions to reach the national immunization targets. The proposed framework for monitoring, evaluating and accountability in the implementation of the global vaccine action plan is intended to guide the content of annual progress reports submitted to the regional committees and the Health Assembly through the Executive Board.

6. Following the guidance of the Strategic Advisory Group of Experts on immunization, the proposed framework will be applied to: (1) monitoring results (defined as progress towards the action plan's goals and strategic objectives); (2) documenting and monitoring stakeholders' commitments to the action plan; (3) tracking resources invested in vaccines and immunization; and (4) inclusion of independent oversight and review of progress, through the Strategic Advisory Group of Experts, in the reporting to the governing bodies.

7. This proposed framework is designed to be aligned with the Accountability Framework for the United Nations Secretary-General's Global Strategy for Women's and Children's Health[1] and also to provide for reporting to the independent Expert Review Group[2]. The Accountability Framework refers to a cyclical process of monitoring, review and remedial action, in which progress is assessed, success documented, problems that need to be rectified identified, and prompt action taken as and where needed. It is structured around the 10 recommendations made by the Commission on Information and Accountability that are categorized as: (1) better information for better results; (2) better tracking of resources for women's and children's health; and (3) better oversight of results and resources. A similar cyclical process of monitoring, review and action is proposed for the framework for the global vaccine action plan.

Monitoring results

8. Progress towards the goals and strategic objectives of the action plan as measured by the respective indicators will serve as the basis for monitoring results throughout the decade.

9. Following the endorsement of the action plan by the Health Assembly, its monitoring indicators were reviewed, with consideration being given to the comments made by Member States during the Sixty-fifth World Health Assembly.[3] Relevant disease-control programmes and technical experts were consulted in order to review and refine the existing indicators, develop operational definitions for each indicator, define the source(s) of data if they exist or how data may be collected, and to establish baselines, milestones and targets, as appropriate. Additional consultations were held by in person, by telephone or online, and feedback on the draft indicators was elicited from more than 600 people, representing different stakeholders, including representatives of civil society organizations and vaccine manufacturers. The indicators revised through this process were in turn reviewed and approved by the

[1] Commission on Information and Accountability for Women's and Children's Health. *Keeping Promises, Measuring Results.* World Health Organization 2011 (http://www.who.int/woman_child_accountability/en/; accessed 13 December 2012).

[2] http://www.everywomaneverychild.org/resources/independent-expert-review-group (accessed 28 November 2012).

[3] Document WHA65/2012/REC/3, summary record of the third meeting (section 6) and fourth meeting (section 2) of Committee B.

Strategic Advisory Group of Experts on immunization at its most recent meeting (Geneva, 6–8 November 2012). The updated list of indicators is annexed to this report.

10. In addition to the indicators for the action plan, a report on trends in vaccine prices, classified according to the procurement mechanisms used, will be presented for review by the Strategic Advisory Group of Experts. The Advisory Group will also be requested to advise on an appropriate indicator for monitoring such price trends.

11. Progress, as measured by the indicators, except those for research and development, will be reported annually to the Health Assembly through the Board. Progress towards the research and development goals and strategic objectives will be reported biennially.

Documenting and monitoring commitments for immunization

12. For monitoring commitments made to immunization activities, it is proposed to take advantage of the process used for the commitments to the Global Strategy for Women's and Children's Health. However, to enable the commitments earmarked for immunization to be tracked, they have to be explicit. Following the guidelines used for making commitments towards the Global Strategy for Women's and Children's Health, the Secretariat has formulated specific guidelines for making commitments related to immunization; these exemplify the types of commitment that could be made towards the Decade of Vaccines.

13. The types of commitment could include financial pledges, policy and service delivery. Efforts will be made to secure commitments from a broad range of stakeholders, including national governments, development partners, global agencies, civil society organizations, academia and professional societies, vaccine manufacturers and the private sector.

Monitoring resources invested in immunization

14. Resources invested in immunization will be tracked and monitored on a yearly basis throughout the decade, using the framework of the OECD/EUROSTAT/WHO System of Health Accounts 2011,[1] the global standard for reporting spending in the health sector. The development process for the monitoring of resources invested in immunization will involve an emphasis on strengthening country capacity and creating a single platform for collecting and analysing all health expenditures, including those on priority diseases or programmes like immunization, and for preparing an annual report. This effort is intended to unify under a single platform other resource-tracking initiatives, such as those being undertaken on national health accounts, and those for (i) the Commission on Information and Accountability for Women's and Children's Health and (ii) 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 will also promote accountability and sustainability for immunization financing.

15. Activities to track resources will focus on evaluating funding flows to support immunization programmes from national governments, development partners and, to the extent possible, civil society organizations at the global, regional and country levels. Findings will be reported for the 94 countries, territories and areas identified in the costing and financing analysis of the global vaccine

[1] Available at http://www.who.int/nha/sha_revision/en/ (accessed 26 February 2013).

action plan.[1] These countries, territories and areas include those classified as low-income or lower-middle-income at the time of the analysis and those that will continue receiving support from the GAVI Alliance for part of the Decade of Vaccines. Annual reporting by countries will be phased in, with an increasing number of countries reporting annually as national capacity is enhanced. Sources of data for the resource-tracking exercise include government reports, and records of expenditures incurred by development partner agencies and civil society organizations engaged in immunization activities, insurance providers, private entities and households. Funding flows will be evaluated both in total and, to the extent possible, with disaggregated data on expenditures for vaccines and delivery. Other possible disaggregation will be explored as the quality and breadth of data are examined more fully.

Oversight, review of progress and next steps

16. The regional and global level review will use WHO's existing processes. At the global level the review process will be through the Strategic Advisory Group of Experts on immunization and to the Health Assembly through the Board. The proposed mechanism for the review and reporting at the global level is through the constitution of a working group on the Decade of Vaccines by the Strategic Advisory Group of Experts on immunization. The working group would consist of eight individuals with the technical expertise to review each component of the framework for monitoring, evaluation and accountability and would have the appropriate geographical and gender representation.

17. It is proposed that the Secretariat prepare and transmit annual reports on the Decade of Vaccines to the working group for detailed review, and that the assessment report and any draft recommendations for corrective actions from this working group be submitted to the Strategic Advisory Group for further review, on the basis of which the progress report for the Board and Health Assembly will be prepared.

18. At the regional level, WHO's regional offices are considering the mechanisms for review and reporting to the regional committees. Member States would need to consider the review and reporting modalities at the country level. It is envisaged that countries will develop a national-level framework to monitor performance of immunization programmes as well as a review process to document best practices, identify problems and make recommendations for corrective action. At the country level, the National Immunization Technical Advisory Groups and the Interagency Coordination Committees may have important roles to play in this regard.

19. The process for collecting and synthesizing data based on the proposed framework has been initiated, with the first substantive report to the Strategic Advisory Group of Experts for immunization due in 2013. Following that, a report based on the assessment of progress by the Advisory Group will be provided to the governing bodies in 2014. The reports, once considered by the Health Assembly,

[1] Afghanistan, Angola, Armenia, Azerbaijan, Bangladesh, Belize, Benin, Bhutan, Bolivia (Plurinational State of), Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Cuba, Democratic People's Republic of Korea, Democratic Republic of the Congo, Djibouti, Egypt, El Salvador, Eritrea, Ethiopia, Fiji, Gambia, Georgia, Ghana, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Iraq, Kenya, Kiribati, Kyrgyzstan, Lao People's Democratic Republic, Lesotho, Liberia, Madagascar, Malawi, Mali, Marshall Islands, Mauritania, Micronesia (Federated States of), Mongolia, Morocco, Mozambique, Myanmar, Nepal, Nicaragua, Niger, Nigeria, Pakistan, Papua New Guinea, Paraguay, Philippines, Republic of Moldova, Rwanda, Samoa, Sao Tome and Principe, Senegal, Sierra Leone, Solomon Islands, Somalia, South Sudan, Sri Lanka, Sudan, Swaziland, Syrian Arab Republic, Tajikistan, Timor-Leste, Togo, Tonga, Turkmenistan, Tuvalu, Uganda, Ukraine, United Republic of Tanzania, Uzbekistan, Vanuatu, Viet Nam, Yemen, Zambia, Zimbabwe, and Kosovo (in accordance with Security Council resolution 1244(1999)) and the West Bank and Gaza Strip.

will also be sent to the independent Expert Review Group[1] for inclusion in its report to the United Nations Secretary-General on the Global Strategy for Women's and Children's Health.

20. Available data on progress made toward achieving the goals for the Decade of Vaccines as of 2011 are summarized below. Progress made on poliomyelitis eradication is described in a separate report.[2]

21. Between 2000 and 2011, the reported incidence of measles at global level decreased by 65% from 146 to 52 cases per million population. In 2011 reported measles incidence was lowest in the Region of the Americas (2 cases per million), followed by the Western Pacific Region (12 cases per million), the South-East Asia Region (36 cases per million), the European Region (43 cases per million), the Eastern Mediterranean Region (61 cases per million) and the African Region (227 cases per million). However, despite this progress, a careful assessment of the comprehensive reports presented indicates that based on current trends and programme performance, the 2015 targets for immunization coverage and mortality reduction will not be met. On the same basis, it is also likely that the regional elimination targets for three regions will not be met by their respective target years: the European Region (2015), the Eastern Mediterranean (2015) and the African Region (2020).

22. By the end of 2011, 23 of the 58 countries targeted had been validated as having eliminated neonatal tetanus.[3] Supplemental immunization activities targeting women of reproductive age are being implemented in the remaining countries to enable them to achieve the elimination target.

23. An estimated 83% of infants worldwide received at least three doses of diphtheria-tetanus-pertussis-containing vaccine (DTP3) in 2011; 130 Member States achieved national coverage of at least 90% and 113 of them had sustained this level of coverage for three or more years. However, only 50 of them achieved coverage of at least 80% in each district or equivalent administrative unit; 49 did not achieve this target and 31 did not report subnational coverage data. Five countries (Ethiopia, India, Indonesia, Nigeria and Pakistan) accounted for 62% of all unvaccinated or under-vaccinated children in the world.

24. In 2011, 33 of the 141 Member States classified as low- or middle-income countries by the World Bank added one or more new or underutilized vaccines to their national immunization schedule.

25. Under-five mortality is declining. Among the 74 so-called Countdown countries,[4] 24 are now on track to achieve the Millennium Development Goal 4.

[1] The independent Expert Review Group reports regularly to the United Nations Secretary-General on the results and resources related to his Global Strategy for Women's and Children's Health and on progress in implementing this Commission's recommendations (available at http://www.who.int/woman_child_accountability/about/ierg/en/index.html, accessed 26 February 2013).

[2] Document A66/18.

[3] The countries validated were: Bangladesh, Benin, Burundi, Comoros, Congo, Egypt, Eritrea, Ghana, Liberia, Malawi, Mozambique, Myanmar, Namibia, Nepal, Rwanda, Senegal, South Africa, Togo, Turkey, Uganda, Viet Nam, Zambia, Zimbabwe.

[4] The Countdown countries consist of the States that bear the highest burden of child and maternal mortality and whose progress towards achievement of the Millennium Development Goals is monitored by a group of United Nations agencies through the countdown process.

COMMUNICATING THE OPPORTUNITIES OF AND CHALLENGES TO THE DECADE OF VACCINES

26. In order to ensure progress towards the achievement of the goals and objectives of the Decade of Vaccines, coordinated advocacy and communication strategies and consistent messages will be required. These efforts will need to demonstrate the value of vaccines and secure the necessary commitments from all stakeholders, including national governments and communities. The 5th GAVI Alliance Partners' Forum – which was held in Dar es Salaam, United Republic of Tanzania, from 5–7 December 2012 – provided an opportunity to advocate in support of the Decade of Vaccines and to the participants with update about developments since the endorsement of the global vaccine action plan by the Health Assembly.

27. WHO is working with UNICEF, the National Institute of Allergy and Infectious Diseases in the United States of America, the GAVI Alliance and the Bill & Melinda Gates Foundation and other partners to develop a communications strategy for World Immunization Week, the designation of which was requested by the Health Assembly in resolution WHA65.18. The Secretariat will produce a new information pack for World Immunization Week, which will take place from 24 to 30 April 2013. The pack will include multimedia features, a campaign essentials toolkit for event organizers, and relevant info-graphics.

28. A Global Vaccine Summit will be held in Abu Dhabi, United Arab Emirates on 24 and 25 April to coincide with World Immunization Week. The Global Vaccine Summit will continue the momentum of the Decade of Vaccines.

29. The Global Vaccine and Immunization Research Forum, to be held approximately every 18 months, will serve as an opportunity to track progress and to stimulate debate on the research agenda of the action plan. The Forum will be co-hosted by WHO, the United States National Institute of Allergy and Infectious Diseases, and the Bill & Melinda Gates Foundation in close collaboration with other major stakeholders. The first Forum will be held in early 2014.

ACTION BY THE HEALTH ASSEMBLY

30. The Health Assembly is invited to take note of the report, including the proposed framework for monitoring and evaluation and accountability.

ANNEX

SUMMARY OF PROPOSED INDICATORS

Goal-level indicators and targets[1]

Goal	Target by 2015	Target by 2020
Achieve a world free of poliomyelitis	• Interrupt wild poliovirus transmission globally (by 2014)	• Certification of poliomyelitis eradication (by 2018)
Meet global and regional elimination targets	• Neonatal tetanus eliminated in all WHO regions • Measles eliminated in at least four WHO regions • Rubella/congenital rubella syndrome eliminated in at least two WHO regions	• Measles and rubella eliminated in at least five WHO regions
Meet vaccination coverage targets in every region, country and community	• Reach 90% national coverage and 80% in every district or equivalent administrative unit with vaccines containing diphtheria-tetanus-pertussis	• Reach 90% national coverage and 80% in every district or equivalent administrative unit with all vaccines in national programmes, unless otherwise recommended
Develop and introduce new and improved vaccines and technologies	• At least 90 low- and middle-income countries have introduced one or more new or underutilized vaccines	• All low- and middle-income countries have introduced one or more new or underutilized vaccines • Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases • Licensure and launch of at least one platform delivery technology
Exceed the Millennium Development Goal 4 target for reducing child mortality	• Reduce by two thirds, between 1990 and 2015, the under-five mortality rate (Target 4.A)	• Exceed the Millennium Development Goal 4 Target 4.A for reducing child mortality

[1] The working group of the Strategic Advisory Group of Experts on immunization on the Decade of Vaccines that will review the annual report of progress made in putting the global vaccine action plan into practice will also consider the development and addition of indicators that measure equity in access to vaccines between countries and an indicator to monitor integration of immunization systems into broader health systems.

Strategic objective-level indicators

Global vaccine action plan's strategic objective	Indicators
All countries commit themselves to immunization as a priority	• Domestic expenditures per person targeted • Presence of an independent technical advisory group that meets defined criteria
Individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility	• Percentage of countries that have assessed (or measured) confidence in vaccination at subnational level[1] • Percentage of unvaccinated and under-vaccinated people in whom lack of confidence was a factor that influenced their decision
The benefits of immunization are equitably extended to all people	• Percentage of districts with 80% or greater coverage with three doses of diphtheria-tetanus-pertussis-containing vaccine • Reduction in coverage gaps between lowest and highest wealth quintile and another appropriate equity indicator
Strong immunization systems are an integral part of a well-functioning health system	• Dropout rate between first dose and third dose of diphtheria-tetanus-pertussis-containing vaccines • Sustained coverage with diphtheria-tetanus-pertussis-containing vaccines ≥ 90% for three or more years • Immunization coverage data assessed as high quality by WHO and UNICEF • Number of countries with case-based surveillance for vaccine-preventable diseases that meets quality standards
Immunization programmes have sustainable access to predictable funding, quality supply and innovative technologies[2]	• Percentage of doses of vaccine used worldwide that are of assured quality[2]
Country, regional and global research and development innovations maximize the benefits of immunization	• Progress towards development of vaccines against HIV infection, tuberculosis and malaria • Progress towards a universal influenza vaccine (protecting against drift and shift variants) • Progress towards institutional and technical capacity for conducting vaccine clinical trials • Number of vaccines that have either been re-licensed or licensed for use in a controlled-temperature chain at temperatures above the traditional 2–8 ºC range • Number of vaccine-delivery technologies (devices and equipment) that have received WHO prequalification compared to 2010

[1] Provisional indicator to be finalized in light of the outcomes of pilot assessments in selected regions.

[2] The report on progress will also narrate advances in vaccine supply, pricing and procurement.

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Global Advisory Committee on Vaccine Safety, December 2012

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 27th meeting in Geneva, Switzerland, on 5–6 December 2012.[2] The committee reviewed: the safety profile of varicella vaccines; the risk of narcolepsy related to use of Pandemrix® and that of Guillain-Barré syndrome (GBS) with multiple influenza A(H1N1)pdm09 vaccine use; and safety aspects of development of dengue vaccines. GACVS also reviewed progress with implementation of the Global Vaccine Safety Blueprint through the Global Vaccine Safety Initiative.

Varicella vaccines

A systematic post-licensure review of the varicella vaccine Varivax® (Merck) safety in the United States of America (USA) was presented in preparation for an update of the WHO position paper on varicella vaccines.[3] A summary of the 2011 US Institute of Medicine (IOM) report,[4] a literature review from December 2010 to October 2012, and review of key post-licensure observational studies from the US Centers for

[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 (US Food and Drug Administration), Rockville, MD, USA; Centers for Diseases Control and Prevention Dengue Branch, San Juan, Puerto Rico; London School of Hygiene and Tropical Medicine, London, United Kingdom; Merck & Co, Upper Gwynedd, PA, USA; National Institute for Health and Welfare, Helsinki, Finland; Sanofi Pasteur, Lyon, France; Shantha Biotechnics Limited, Hyderabad, India; University of California, Los Angeles, CA, USA; University of Cincinnati, OH, USA; University of Laval, Quebec, Canada.

[3] See No. 32, 1998, pp. 241–248.

[4] Stratton K et al., eds. *Adverse events of vaccines: evidence and causality*. Washington, DC, Institute of Medicine of the National Academies. August 2011.

Comité consultatif mondial de la Sécurité vaccinale, décembre 2012

Le Comité consultatif mondial de la Sécurité vaccinale (GACVS), un organe consultatif composé de spécialistes des questions scientifiques et cliniques, a été créé par l'OMS pour donner un avis indépendant et scientifiquement rigoureux sur des problèmes de sécurité vaccinale pouvant avoir une importance mondiale.[1] Le GACVS a tenu sa 27e réunion à Genève (Suisse) les 5 et 6 décembre 2012.[2] Il a examiné: le profil d'innocuité des vaccins antivaricelleux; le risque de narcolepsie associé au vaccin Pandemrix® et le risque de syndrome de Guillain-Barré (SGB) lié à l'utilisation répétée du vaccin antigrippal A(H1N1)pdm09; et les aspects relevant de la sécurité de la mise au point des vaccins contre la dengue. Le GACVS a également passé en revue les progrès dans la mise en œuvre du Projet mondial pour la sécurité des vaccins par le biais de l'Initiative mondiale pour la sécurité des vaccins.

Vaccins antivaricelleux

Un examen post-autorisation systématique de l'innocuité du vaccin antivaricelleux Varivax® (Merck) aux Etats-Unis a été présenté en préparation de la mise à jour de la note de synthèse de l'OMS sur les vaccins antivaricelleux.[3] Un résumé du rapport de 2011 de l'Institut de Médecine des Etats-Unis (IOM),[4] une revue de la littérature de décembre 2010 à octobre 2012 et une revue de certaines études d'observations post-autorisation clés, produites

[1] Voir No 41, 1999, pp. 337-338.

[2] Le GACVS a invité d'autres experts pour qu'ils présentent et discutent les preuves relatives à des sujets particuliers. Parmi ces experts, figuraient des personnes affiliées aux institutions suivantes: Center for Biologics Evaluation and Research (US Food and Drug Administration), Rockville, MD, États-Unis; aux Centers for Diseases Control and Prevention, Dengue Branch, San Juan, Puerto Rico; London School of Hygiene and Tropical Medicine, London, Royaume-Uni; Merck & Co, Upper Gwynedd, PA, États-Unis; National Institute for Health and Welfare, Helsinki, Finlande; Sanofi Pasteur, Lyon, France; Shantha Biotechnics Limited, Hyderabad, Inde; University of California, Los Angeles, CA, États-Unis; University of Cincinnati, OH, États-Unis; Université de Laval, Québec, Canada.

[3] Voir No 32, 1998, pp. 241-248.

[4] Stratton K et al., eds. *Adverse events of vaccines: evidence and causality*. Washington DC, Institute of Medicine of the National Academies, août 2011.

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Disease Control and Prevention and Merck were included. The focus of the review was to update the safety profile of the varicella vaccine, especially for events considered significant. The IOM committee addressed 15 potential adverse events by a comprehensive review of the literature from 1950 to December 2010. Five events were assessed as having convincing evidence in support of a causal relationship with the vaccine: disseminated varicella infection (widespread chickenpox rash shortly after vaccination); disseminated varicella infection with subsequent infection resulting in pneumonia, meningitis or hepatitis; vaccine strain viral reactivation (appearance of chickenpox rash months to years after vaccination); vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis; and anaphylaxis. While the risks for these adverse events were not quantified in the IOM review, GACVS reviewed evidence from case series and other studies that demonstrated them to be rare events. Ten other adverse events were assessed to have insufficient evidence to support causality: encephalopathy, seizure, cerebellar ataxia, acute disseminated encephalomyelopathy, transverse myelitis, GBS, small fibre neuropathy, new onset arthropathy, stroke, and thrombocytopenia.

A review of more recent post-licensure safety studies of the combination measles, mumps, rubella (MMR) and varicella vaccine, which contains the same Oka strain as Varivax® (ProQuad®), identified a new risk of febrile seizures after vaccination among children aged 12–23 months, compared with children receiving separate MMR and varicella vaccination. In addition, Merck's pregnancy registry for Varivax® revealed no cases of congenital varicella syndrome during 16 years of vaccine use and the data do not support a signal of an increased risk of spontaneous abortion or birth defects. Finally, a comprehensive literature review from 2010 to 2012 revealed no additional safety concerns.

GACVS raised several questions not covered by this review. These included: (1) whether varicella vaccination increases the risk of shifting varicella disease to older age groups, where disease is generally more serious, and whether this potential risk depends on the number of vaccine doses administered (i.e. would a single dose lead to greater risk than 2 doses and would additional booster doses be required?); (2) whether risks from currently available varicella vaccines remain similar to those described earlier; and (3) what the risk–benefit ratio of varicella vaccine use would be in low and middle income countries (LMICs) with a high proportion of undetected immunocompromised people, especially children with HIV, cancer and other immunodeficiencies. GACVS recommended that additional data are needed to determine the full safety profile of varicella vaccine if it is to be deployed in LMICs. GACVS recom-

par les *Centers for Disease Control and Prevention* des Etats-Unis et par Merck, y ont été inclus. L'examen portait principalement sur la mise à jour du profil d'innocuité du vaccin antivaricelleux, et notamment des considérations portant sur les manifestations considérées comme importantes. Le comité de l'IOM a examiné 15 manifestations indésirables potentielles en procédant à une revue complète de la littérature des années 1950 à décembre 2010. Il a été estimé que pour 5 manifestations, il existait des preuves convaincantes d'une relation de causalité avec le vaccin, notamment de l'infection varicelleuse disséminée (éruption varicelleuse étendue très peu de temps après la vaccination); de l'infection varicelleuse disséminée accompagnée d'une infection secondaire débouchant sur une pneumonie, une méningite ou une hépatite; de la réactivation de la souche virale vaccinale (apparition d'une éruption varicelleuse quelques mois à quelques années après la vaccination); de la réactivation de la souche virale vaccinale accompagnée d'une infection secondaire conduisant à une méningite ou une encéphalite; et de réactions anaphylactiques. Bien que les risques d'apparition de ces manifestations secondaires ne soient pas quantifiés dans le rapport de l'IOM, le GACVS a analysé les données provenant de séries de cas et d'autres études, ce qui l'a amené à conclure que ces manifestations étaient des événements rares. Pour 10 autres manifestations indésirables, il a été estimé que les preuves disponibles n'étaient pas suffisantes pour corroborer l'existence d'un lien de causalité: encéphalopathie, convulsions, ataxie cérébelleuse, encéphalomyélopathie disséminée aiguë, myélite transverse, SGB, neuropathie des petites fibres, nouvelle apparition d'arthropathies, AVC et thrombocytopénie.

Une revue des études post-autorisation plus récentes de l'innocuité de l'administration combinée du vaccin contre la rougeole, les oreillons et la rubéole (ROR) et du vaccin antivaricelleux contenant la même souche Oka que le Varivax® (ProQuad®) a mis en évidence un nouveau risque de convulsions fébriles suite à la vaccination des enfants de 12 à 23 mois, par rapport à la situation des enfants recevant séparément le ROR et la vaccination antivaricelleuse. En outre, le registre des grossesses de Merck tenu pour le Varivax® n'avait recensé aucun cas de syndrome varicelleux congénital pendant les 16 années d'utilisation du vaccin et les données n'étayaient aucun indice d'un risque accru d'avortement spontané ou d'anomalie congénitale. Enfin, une revue complète de la littérature de 2010 à 2012 n'a fait ressortir aucune inquiétude supplémentaire concernant l'innocuité.

Le GACVS a soulevé plusieurs questions non traitées dans cette revue: (1) dans quelle mesure la vaccination antivaricelleuse augmenterait-elle le risque de déplacement de la varicelle vers des tranches d'âges supérieures, parmi lesquelles cette maladie est généralement plus grave et le risque potentiel correspondant dépendrait-il du nombre de doses de vaccin administrées (une dose unique comporterait-elle un plus grand risque que 2 doses et une dose de rappel supplémentaire serait-elle nécessaire?); (2) les risques associés aux vaccins antivaricelleux actuellement disponibles restent-ils similaires à ceux décrits auparavant; et (3) quel serait le rapport risque/bénéfice de l'utilisation de ce vaccin dans les pays à revenu intermédiaire – tranche inférieure (PRITI) où l'on trouve une forte proportion de personnes immunodéprimées non détectées, notamment des enfants vivant avec le VIH, cancéreux ou présentant d'autres déficits immunitaires. Le GACVS a recommandé de réunir des données supplémentaires pour déterminer le profil d'innocuité complet

mended conducting surveillance for varicella disease to assess the effectiveness, as well as enhanced vaccine adverse event monitoring if varicella vaccine is introduced in LMICs.

Noting that substantial new safety evidence has accumulated since the last WHO report in 1998, GACVS concluded that additional data should be gathered and reviewed to complete the full benefit–risk assessment of varicella vaccine globally.

Pandemic influenza vaccines

GACVS reviewed 2 safety updates on influenza A(H1N1) pdm09 vaccines, which included associations with narcolepsy and with GBS. The association between use of the adjuvanted pandemic vaccine Pandemrix® (GlaxoSmithKline) and abrupt juvenile narcolepsy has thus far been confirmed in 4 countries (Finland, Ireland, Norway and Sweden) with high uptake of vaccine among children and adolescents. In all these countries the absolute risk was low but the relative risk was significantly raised, ranging from 6.6 (95% confidence interval [CI]: 3.1–14.5) in Sweden to 13.0 per 100 000 (95% CI: 4.8–34.7) in Ireland. An association in adults has so far been observed only in France. Additional studies are also being finalized in the United Kingdom (UK) and Canada. Although this vaccine is no longer being used and all lots of Pandemrix® (2009 H1N1) have now expired, GACVS considered that research should continue to better characterize the possible underlying biological mechanisms of this association. Most cases of narcolepsy, with or without exposure to Pandemrix®, occur in subjects who carry the HLA DQB1*0602 allele. The importance of understanding the triggers and causes of this association will be crucial, especially since new vaccines will be required to protect against future pandemics.

The association between GBS and influenza vaccine first emerged following swine influenza vaccination in the USA in 1976 (attributable risk: around 1 case of GBS per 100 000 vaccinations). GBS is a relatively rare (1–2 cases per 100 000 persons annually) acute peripheral immune-mediated neuropathy. In up to two-thirds of cases, GBS is preceded by an infectious illness, particularly a gastrointestinal or respiratory infection. The most frequently identified pathogen associated with subsequent GBS is *Campylobacter jejuni* (estimated at 1 GBS case per 3000 infectious episodes).

After 1976, several studies demonstrated no increased or a slightly increased risk of GBS after use of human seasonal influenza vaccines but vigilance remains high and GBS was carefully monitored during the influenza A(H1N1)pdm09 pandemic vaccination campaign.

GACVS has reviewed published and unpublished active surveillance studies that monitored GBS cases during influenza A(H1N1)pdm09 pandemic vaccination. The data are from single countries such as Canada, France,

du vaccin antivaricelleux dans la perspective de son déploiement éventuel dans les PRITI. Il a aussi préconisé une surveillance de la varicelle maladie pour évaluer l'efficacité du vaccin et un renforcement de celle de ses manifestations indésirables en cas d'introduction dans un PRITI.

Notant que des éléments importants concernant l'innocuité se sont accumulés depuis le dernier rapport de l'OMS en 1998, le GACVS a conclu qu'il convenait de réunir des données supplémentaires et de les étudier pour achever de dresser le bilan risques/bénéfices complet du vaccin antivaricelleux à l'échelle mondiale.

Vaccins contre la grippe pandémique

Le GACVS a examiné 2 mises à jour concernant l'innocuité des vaccins contre la grippe A(H1N1)pdm09, qui portaient notamment sur les associations avec la narcolepsie et le SGB. Le lien entre l'utilisation du vaccin pandémique adjuvanté Pandemrix® (GlaxoSmithKline) et la narcolepsie juvénile soudaine a ainsi été confirmé dans 4 pays (Finlande, Irlande, Norvège et Suède), où le vaccin est fortement utilisé chez les enfants et les adolescents. Dans tous ces pays, le risque absolu est faible et le risque relatif significativement élevé, allant de 6,6 pour 100 000 [intervalle de confiance (IC) à 95%: 3,1-14,5] en Suède à 13,0 pour 100 000 (IC à 95%: 4,8-34,7) en Irlande. Jusqu'à présent, une telle association a été observée chez les adultes uniquement en France. D'autres études sont en cours de finalisation au Royaume-Uni et au Canada. Bien que le Pandemrix® (2009 H1N1) ne soit plus utilisé et que tous les lots de ce vaccin soient maintenant périmés, le GACVS considère que les recherches doivent se poursuivre pour mieux caractériser les mécanismes biologiques potentiellement sous-jacents à cette association. La plupart des cas de narcolepsie, avec ou sans exposition au Pandemrix®, apparaissent chez des sujets porteurs de l'allèle HLA DQB1*0602. Il est crucial de comprendre les facteurs déclenchants et les causes intervenant dans cette association, compte tenu notamment de la nécessité d'élaborer de nouveaux vaccins pour se protéger des pandémies à venir.

L'association entre le SGB et le vaccin antigrippal est apparue pour la première fois suite à la campagne de vaccination contre la grippe porcine menée en 1976 aux Etats-Unis (risque attribuable: environ 1 cas de SGB pour 100 000 vaccinations). Le SGB est une neuropathie périphérique aiguë à médiation immunitaire relativement rare (1 à 2 cas pour 100 000 personnes et par an). Dans une proportion des cas allant jusqu'à 75%, le SGB est précédé par une maladie infectieuse, et notamment par une infection gastro-intestinale ou respiratoire. L'agent pathogène le plus fréquemment identifié en association avec l'apparition ultérieure d'un SGB est *Campylobacter jejuni* (fréquence estimée: 1 cas de SGB pour 3000 épisodes infectieux).

Après 1976, plusieurs études ont démontré l'absence d'augmentation ou un accroissement léger du risque de SGB après l'utilisation de vaccins contre la grippe saisonnière humaine, mais la vigilance est restée forte et le syndrome a fait l'objet d'une surveillance étroite pendant la campagne de vaccination contre la grippe pandémique A(H1N1)pdm09.

Le GACVS a analysé des études de surveillance active publiées et non publiées ayant suivi l'apparition des cas de SGB pendant les campagnes de vaccination contre la grippe pandémique A(H1N1)pdm09. Les données provenaient de pays isolées tels

Germany, Sweden, the UK and the USA as well as a multinational European Union study and a global study. Some but not all of these studies have shown a relative incidence of GBS of 2.28 to 3.76 following both unadjuvanted and adjuvanted influenza A(H1N1)pdm09 pandemic vaccines. Overall, the data available are compatible with a small increased risk of GBS after influenza A(H1N1)pdm09 vaccination that is substantially lower than that observed following the 1976 swine influenza vaccination campaign in the USA.

Live attenuated dengue vaccines

GACVS reviewed progress with the development of tetravalent recombinant live dengue virus vaccines, of which at least one chimeric candidate with a yellow fever virus genetic backbone is undergoing phase III studies. The objective was to appraise the safety assessment plans proactively in order to determine the data critical to safety should the vaccine attain authorization for use in populations where the burden of dengue is significant.

To date, no serious vaccine-related events have been documented in the 41 700 subjects who have participated in different phases of the dengue vaccine trials. In addition, among vaccine recipients, no excess cases of dengue fever or severe dengue attributable to the vaccine virus have been demonstrated compared with control groups. Published results from a phase 2b study conducted among school-age children in Thailand indicated an overall efficacy of 30% but there was evidence of greater protection against 3 of the 4 serotypes.[5] GACVS agreed that the safety profile observed up to date is encouraging but efficacy to protect against dengue remains a critical factor to be confirmed.

GACVS recognized that several issues will remain challenges for the evaluation of the safety of dengue vaccines if phase III studies indicate efficacy against clinical disease, in particular the lack of harmonization of dengue case classifications and the lack of consensus on the follow-up time or exposures to different dengue virus types needed to monitor the theorical risk of vaccine-mediated enhanced severe disease outcomes. Safety evaluation of dengue vaccines is also complicated by the rarity of suspected adverse events that could be readily attributable to the vaccine, i.e. neurotropic or viscerotropic disease from the yellow fever vaccine virus backbone, and severe dengue from natural infection potentially induced by incomplete vaccine protection.

In 2008, WHO issued technical recommendations to guide the development of dengue vaccines. GACVS concurs that long-term follow-up of vaccinated and unvaccinated cohorts, including those in randomized double-

[5] Sabchareon A et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet*, 2012, 380:1559–1567.

que l'Allemagne, le Canada, les Etats-Unis, la France, le Royaume-Uni et la Suède, d'une étude multinationale réalisée par l'Union européenne et d'une étude mondiale. Certaines de ces études, mais pas toutes, ont mis en évidence une incidence relative du SGB de 2,28 à 3,76 suite à l'utilisation des vaccins contre la grippe pandémique A(H1N1)pdm09 adjuvantés et non-adjuvantés. Globalement, les données disponibles sont compatibles avec une faible augmentation du risque de SGB après la vaccination contre la grippe A(H1N1)pdm09 substantiellement inférieure à celle observée après la campagne de vaccination contre la grippe porcine de 1976 aux Etats-Unis.

Vaccins vivants atténués contre la dengue

Le GACVS a examiné les progrès dans la mise au point de vaccins vivants tétravalents recombinants contre le virus de la dengue, parmi lesquels au moins un vaccin candidat chimérique utilisant comme squelette génétique le virus de la fièvre jaune est en cours d'essai de phase III. Son objectif était d'apprécier de manière proactive les plans d'évaluation de l'innocuité pour déterminer quelles données seraient essentielles pour cette évaluation si le vaccin venait à atteindre le stade de l'autorisation en vue d'une utilisation parmi des populations que la dengue affecte de manière importante.

À ce jour, aucune manifestation postvaccinale grave n'a été enregistrée parmi les 41 700 sujets ayant participé aux différentes phases des essais de vaccins contre la dengue. En outre, aucun excès de cas de dengue ou de dengue sévère attribuable au virus vaccinal n'a été mis en évidence chez les bénéficiaires de la vaccination par rapport à des groupes témoins. Les résultats publiés d'une étude de phase 2b conduite en Thaïlande chez des enfants d'âge scolaire indiquaient une efficacité globale de 30%, mais il existait des éléments en faveur d'une protection plus importante contre 3 des 4 sérotypes.[5] Le GACVS a admis que le profil d'innocuité observé à ce jour est encourageant, mais l'efficacité du vaccin en termes de protection contre la dengue reste un élément critique, qui reste à confirmer.

Le Comité a reconnu que plusieurs aspects continueraient de poser problème dans l'appréciation de l'innocuité des vaccins contre la dengue si les études de phase III venaient à indiquer une efficacité de ces vaccins contre la maladie clinique, et notamment le manque d'harmonisation entre les classifications des cas de dengue et l'insuffisance du consensus sur la durée du suivi ou sur les types de virus auxquels il faudrait être exposé pendant le suivi pour évaluer le risque théorique d'aggravation éventuelle des issues de la dengue sévère induit par le vaccin. L'évaluation de l'innocuité des vaccins contre la dengue est aussi compliquée par la rareté des manifestations indésirables suspectées que l'on pourrait facilement imputer au vaccin, à savoir un neurotropisme ou un viscérotropisme dû à la présence du squelette viral appartenant au virus de la fièvre jaune et la survenue de formes graves de l'infection naturelle potentiellement induite par une protection vaccinale incomplète.

En 2008, l'OMS a publié des recommandations techniques pour guider la mise au point des vaccins contre la dengue. Le GACVS convient qu'il faudrait s'efforcer de suivre à long terme des cohortes de personnes vaccinées et non vaccinées, y compris

[5] Sabchareon A et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet*, 2012, 380:1559–1567.

blind controlled trials, should be sought to help determine the safety of dengue vaccines when exposed to several natural infection cycles. In addition, storage of adequate samples of sera and peripheral blood mononuclear cells will be important for future studies on the immune mechanisms of protection or of sensitization conferred by dengue vaccines. Post-licensure studies will also provide estimates of the long-term effectiveness of immunization against multiple dengue virus serotypes in large populations; assess the risk of vaccine virus escape and any herd effects of vaccination; help establish whether booster immunization is needed; and indicate any potential age shifts in dengue presentations. GACVS identified several approaches that should be considered in designing those studies: collection of background dengue surveillance data; use of phased introduction (e.g. stepped wedge designs); use of case-control and case-only methods (to detect rare early adverse events); and epidemiological exploration of signals as the most appropriate way to establish causality for potentially related adverse events following immunization.

Global Vaccine Safety Initiative

In 2011, WHO and a group of partners developed the Global Vaccine Safety (GVS) Blueprint, a strategic document with a vision of establishing effective vaccine pharmacovigilance systems in all countries.[6] The GVS Blueprint is a part of the Global Vaccine Action Plan, which was endorsed by the World Health Assembly in May 2012. The Global Vaccine Safety Initiative (GVSI) was set up to implement the Blueprint and is advised by the GVSI planning group. The Blueprint strategic goals, which GVSI is expected to achieve during 2012–2020, include: (1) ensuring minimal capacity in vaccine safety for all LMICs; (2) promoting enhanced vaccine pharmacovigilance activities in countries with specific needs; and (3) establishing a global technical support structure.

GACVS reviewed the development of the GVSI workplan and the display of its products through its website.[7] The GVSI identified activities to cover the 8 strategic goals of the Blueprint through a broad network of stakeholders engaged in global vaccine pharmacovigilance. An activity portfolio has been developed as a management tool for implementing the Blueprint. In the portfolio, activities are prioritized based on their expected impact, feasibility and desirability. The portfolio provides initiators, managers and donors of each activity with due recognition for their respective roles. It is also a resource for all stakeholders in global pharmacovigilance to help identify ongoing efforts, allow for better synergies, minimize duplications and enable resource

[6] See http://extranet.who.int/iris/restricted/bitstream/10665/70919/1/WHO_IVB_12.07_eng.pdf.

[7] See http://www.who.int/vaccine_safety/initiative/en/

les sujets participant à des essais randomisés en double aveugle, pour contribuer à la détermination de l'innocuité des vaccins contre la dengue lorsque ces sujets sont exposés à plusieurs cycles d'infection naturelle. En outre, il sera important de conserver des échantillons appropriés de sérum et de cellules mononucléaires du sang périphérique pour étudier dans l'avenir les mécanismes immunitaires de protection ou de sensibilisation introduits par les vaccins contre la dengue. En outre, les études post-autorisation fourniront des estimations de l'efficacité à long terme de la vaccination contre plusieurs sérotypes de virus de la dengue dans des populations de grande ampleur; évalueront le risque d'échappement du virus vaccinal et tous les effets éventuels de protection indirecte que pourrait avoir la vaccination; permettront de trancher quant à la nécessité d'une dose de rappel; et indiqueront tout déplacement éventuel dans les tranches d'âges touchées par la dengue. Le GACVS a identifié plusieurs démarches à envisager dans la conception de ces études: collecte de données de fond par la surveillance de la dengue; recours à une introduction par étapes (études de type par étapes, par exemple); application de la méthode cas-témoins ou basée sur les cas seulement (pour détecter des manifestations indésirables précoces et rares); et étude épidémiologique des signaux, en tant que moyens les plus appropriés pour établir un lien de causalité avec certaines manifestations postvaccinales indésirables.

Initiative mondiale pour la sécurité des vaccins

En 2011, l'OMS et un groupe de partenaires ont mis au point le Projet mondial pour la sécurité des vaccins (GVS Blueprint), un document stratégique ayant pour ambition de mettre en place des systèmes de pharmacovigilance à l'égard des vaccins efficaces dans tous les pays.[6] Le GVS Blueprint est une composante du Plan d'action mondial pour les vaccins approuvé par l'Assemblée mondiale de la Santé en mai 2012. L'Initiative mondiale pour la sécurité des vaccins (GVSI) a été mise sur pied pour réaliser ce projet et bénéficie des conseils du groupe de planification de la GVSI. Les objectifs stratégiques du projet que l'on s'attend à voir atteindre par la GVSI sur la période 2012–2020 sont entre autres: (1) l'obtention d'une capacité minimale en matière de sécurité des vaccins dans tous les PRITI; (2) la promotion d'activités de pharmacovigilance renforcées pour les vaccins dans les pays ayant des besoins spécifiques; et (3) la mise en place d'une structure d'assistance technique à l'échelle mondiale.

Le GACVS a examiné la mise au point du plan de travail de la GVSI et la présentation de ses produits par le biais de son site web.[7] La GVSI a identifié des activités permettant de remplir les 8 objectifs stratégiques du projet grâce à la participation d'un réseau étendu de parties prenantes exerçant une pharmacovigilance à l'égard des vaccins à l'échelle mondiale. Un portefeuille d'activités a été constitué en tant qu'outil de gestion pour la mise en œuvre du projet. Au sein de ce portefeuille, les activités ont été affectées de priorités en fonction de leur impact attendu, de leur faisabilité et de leur désirabilité. Le portefeuille reconnait dûment les rôles respectifs des initiateurs, des gestionnaires et des donateurs pour chaque activité. C'est aussi une ressource pour toutes les parties prenantes à la pharmacovigilance mondiale, qui les aide à connaître les efforts en cours, favorise

[6] Voir http://extranet.who.int/iris/restricted/bitstream/10665/70919/1/WHO_IVB_12.07_eng.pdf

[7] Voir http://www.who.int/vaccine_safety/initiative/en/

mobilization. The WHO regional offices lead country support in capacity building and in addressing vaccine safety concerns. Currently, the portfolio includes 94 activities, 31 of which have been identified in the first priority category.

GACVS examined areas of interactions between its mandate to advise on vaccine safety issues of global importance and that of the GVSI to support and strengthen global vaccine pharmacovigilance capacity. GACVS recognizes that the GVSI strategies are required to improve vaccine safety systems and develop networks to strengthen the monitoring, evaluation and response to vaccine safety issues. The rapid development of activities expected to be associated with the GVSI will also generate a complex network of stakeholders where roles and responsibilities should be defined as clearly as possible. The GVSI addresses many aspects that intersect with the work of other established groups. The complementarity of advice from vaccine safety bodies with that of other immunization and public health advisory groups requires particular attention, both at global and regional levels. GACVS identified several areas where the GVSI should clearly outline the leading role of WHO as a global convener in health monitoring and systems. In addition, efforts should include: involving regional and national immunization technical advisory groups with vaccine safety assessment and communication efforts; use of existing academic and educational institutions to expand vaccine safety training resources, engagement of vaccine producers in promoting information exchange; and active development of a roster of vaccine pharmacovigilance experts with appropriate cultural awareness and geographical proximity to support country demands.

The GVSI proposes solutions for a number of unmet needs in vaccine safety. The Blueprint framework has the potential to involve many new players in a broad collaborative effort. Yet the increased volume of activities and attention will generate competition and competency issues, requiring clear accountability and quality assurance. GACVS therefore proposed a thorough analysis of how the complex needs for vaccine safety can best be addressed and development of an accountability framework for all stakeholders participating in the GVSI. The role of GACVS with respect to the GVSI will remain at the consultancy and advisory level, providing independent evaluation of the evidence for the global vaccine safety issues identified by and for WHO. The rapidly increasing number of proposed activities will also require a more comprehensive system of prioritization with appropriate criteria. The committee is well positioned to help set those criteria, with a focus on ensuring that technical partners' activities meet the needs of LMICs in strengthening their vaccine safety capacities. ■

de plus grandes synergies, limite la duplication des activités et permet la mobilisation des moyens. Les bureaux régionaux de l'OMS dirigent le soutien aux pays dans le renforcement des capacités et la résolution des problèmes de sécurité vaccinale. Actuellement, le portefeuille comprend 94 activités, dont 31 ont été reconnues comme devant bénéficier de la plus forte priorité.

Le GACVS a examiné les domaines d'interaction entre son mandat consistant à fournir un avis sur des questions en rapport avec la sécurité des vaccins d'importance mondiale et celui de la GVSI, qui est d'appuyer et de renforcer les capacités mondiales de pharmacovigilance à l'égard des vaccins. Il a reconnu que les stratégies de la GVSI étaient nécessaires pour améliorer les systèmes de sécurité vaccinale et pour développer des réseaux permettant d'améliorer la surveillance et l'évaluation des problèmes de sécurité vaccinale, ainsi que la réponse à ces problèmes. Le développement rapide des activités qui devraient accompagner l'Initiative mondiale pour les vaccins fera également apparaître un réseau complexe de parties prenantes, dont les rôles et les responsabilités seront à définir aussi clairement que possible. La GVSI intervient dans plusieurs directions qui recoupent les domaines d'activité d'autres groupes établis. La complémentarité des avis émis par les organes chargés de la sécurité des vaccins et de ceux d'autres groupes consultatifs dans les domaines de la vaccination et de la santé publique doit faire l'objet d'une attention particulière, tant au niveau mondial que régional. Le GACVS a identifié plusieurs domaines dans lesquels la GVSI devrait clairement indiquer le rôle directeur de l'OMS en tant qu'organisateur mondial de la surveillance sanitaire et des systèmes de santé. Les efforts doivent notamment aussi porter sur l'implication des groupes techniques consultatifs nationaux sur la vaccination dans l'évaluation de l'innocuité des vaccins et la communication concernant les activités; le recours à des institutions de formation et d'enseignement supérieur existantes comme autres moyens pour former à la sécurité des vaccins, l'engagement des fabricants de vaccins à poursuivre les échanges d'informations et le développement actif d'une liste d'experts de la pharmacovigilance à l'égard des vaccins suffisamment sensibilisés aux problèmes culturels et proches sur le plan géographique pour répondre aux besoins des pays.

La GVSI propose des solutions pour un certain nombre de besoins non satisfaits en matière de sécurité vaccinale. Le cadre du projet GVS Blueprint permet d'impliquer un grand nombre de nouveaux acteurs dans un effort collaboratif de grande envergure. Néanmoins, l'accroissement du volume d'activités et de l'intérêt suscité générera une compétition et des problèmes de compétences nécessitant des obligations redditionnelles claires et une assurance de la qualité. Le GACVS a donc proposé une analyse approfondie des moyens pour répondre aux besoins complexes en matière de sécurité vaccinale et l'élaboration d'un cadre d'obligations redditionnelles pour l'ensemble des parties prenantes à la GVSI. Á l'égard de la GVSI, le GACVS gardera un rôle d'expertise et de conseil en fournissant une évaluation indépendante des données relatives aux problèmes de sécurité vaccinale de portée mondiale identifiés par l'OMS ou à son intention. Le nombre rapidement croissant d'activités proposées nécessitera aussi un système plus complet de priorisation, s'appuyant sur des critères appropriés. Le Comité est bien placé pour aider à définir ces critères, en veillant à ce que les activités des partenaires techniques répondent aux besoins des PRITI en matière de renforcement de leurs capacités pour assurer la sécurité vaccinale. ■

Table: Dengue vaccine candidates in clinical development[1]

Vaccine type Technological approach	**Development stage** Selected current trials	**Developer**	**References**[2]
Live attenuated vaccine YF17D/DEN chimeric viruses	**Phase 3** NCT01373281 NCT01374516	Sanofi Pasteur	[1],[2]
Live attenuated vaccine Attenuated DEN2 PDK-53 virus and DEN/DEN intertypic chimeric viruses	**Phase 2** NCT01511250	Inviragen	[3]
Live attenuated vaccine Targeted mutagenesis of DEN viruses and DEN/DEN intertypic chimeric virus	**Phase 2** NCT01696422	Butantan Institute National Institute of Allergy and Infectious Diseases	[4],[5]
Recombinant subunit vaccine Truncated E protein	**Phase 1** NCT01477580	Merck	[6]
Purified inactivated virus vaccine	**Phase 1** NCT01702857 NCT01666652	GlaxoSmithKline Oswaldo Cruz Foundation Walter Reed Army Institute of Research	
DNA vaccine Expression of prM and E proteins	**Phase 1** NCT01502358	Naval Medical Research Center Walter Reed Army Institute of Research	[7],[8]

[1] Active clinical development projects as of February 2013

[2] Selected recent publications of clinical trial results and review articles

References

1. Sabchareon, A., Wallace, D., Sirivichayakul, C., Limkittikul, K., Chanthavanich, P., Suvannadabba, S., Jiwariyavej, V., Dulyachai, W., Pengsaa, K., Wartel, T.A., et al. (2012). Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet *380*, 1559-1567.
2. Guy, B., Barrere, B., Malinowski, C., Saville, M., Teyssou, R., and Lang, J. (2011). From research to phase III: Preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine. Vaccine *29*, 7229-41.
3. Osorio, J.E., Huang, C.Y., Kinney, R.M., and Stinchcomb, D.T. (2011). Development of DENVax: A chimeric dengue-2 PDK-53-based tetravalent vaccine for protection against dengue fever. Vaccine *29*, 7251-7260.

4. Durbin, A.P., Kirkpatrick, B.D., Pierce, K.K., Elwood, D., Larsson, C.J., Lindow, J.C., Tibery, C., Sabundayo, B.P., Shaffer, D., Talaat, K.R., et al. (2013). A Single Dose of Any of Four Different Live Attenuated Tetravalent Dengue Vaccines Is Safe and Immunogenic in Flavivirus-naive Adults: A Randomized, Double-blind Clinical Trial. J Infect Dis. Epub ahead of print 31 Jan.
5. Durbin, A.P., Kirkpatrick, B.D., Pierce, K.K., Schmidt, A.C., and Whitehead, S.S. (2011). Development and clinical evaluation of multiple investigational monovalent DENV vaccines to identify components for inclusion in a live attenuated tetravalent DENV vaccine. Vaccine *29*, 7242-50
6. Coller, B.A., Clements, D.E., Bett, A.J., Sagar, S.L., and Ter Meulen, J.H. (2011). The development of recombinant subunit envelope-based vaccines to protect against dengue virus induced disease. Vaccine *29*, 7267-7275.
7. Danko, J.R., Beckett, C.G., and Porter, K.R. (2011). Development of dengue DNA vaccines. Vaccine *29*, 7261-7266.
8. Beckett, C.G., Tjaden, J., Burgess, T., Danko, J.R., Tamminga, C., Simmons, M., Wu, S.J., Sun, P., Kochel, T., Raviprakash, K., et al. (2011). Evaluation of a prototype dengue-1 DNA vaccine in a Phase 1 clinical trial. Vaccine *29*, 960-968.

World Health Organization

Questions and Answers on Dengue Vaccines: Phase IIb study of CYD-TDV

September 2012

What is the current status of dengue vaccine development?

No licensed dengue vaccine is currently available. However, there is a significant and continually growing public health need for effective interventions against dengue.[1] A safe, effective and affordable dengue vaccine would represent a major advance for the control of the disease. Several vaccine candidates are currently at different stages of preclinical or clinical development.[2] The candidate currently at the most advanced clinical development stage is a live attenuated tetravalent dengue vaccine developed by Sanofi Pasteur (CYD-TDV), which is under evaluation in phase II and phase III clinical studies.

What are the main objectives of the phase IIb study of CYD-TDV in Thailand?[3]

The primary objective of the phase IIb study is to assess the efficacy of CYD-TDV in preventing dengue disease, after completion of the vaccination schedule of three doses given 6 months apart. Additional objectives include the evaluation of vaccine safety and immunogenicity. The study population consists of 4,002 children aged 4 to 11 years in Ratchaburi Province, Thailand. Efficacy, safety and immunogenicity results, as available one year after completion of the vaccination schedule, are described in a recent publication.[3] The study protocol includes a follow-up period of two additional years, which is currently ongoing.

What conclusions can be drawn from the results of the phase IIb study?

This is the first study conducted to evaluate the efficacy of any dengue vaccine candidate against clinical dengue disease in a population naturally exposed to dengue, which represents a significant advance for the field of dengue vaccine research. The results are therefore of considerable interest to the vaccine research community.

Phase IIb studies are generally designed to provide initial proof-of-concept data, to be corroborated in larger phase III studies. Interpretation of phase IIb study results should therefore be undertaken with caution.

The primary efficacy analysis, as defined in the protocol for this study, is based on the number of dengue cases in vaccinated and control subjects, during a one year observation period following completion of the vaccination schedule. The reported vaccine efficacy result of 30.2% (95% confidence interval: -13.4% to 56.6%) is not statistically significant, and the vaccine efficacy therefore remains inconclusive.

Additional analyses were carried out to explore efficacy after at least one vaccine dose, and against individual dengue virus serotypes. Statistically significant efficacy estimates were reported for three of the four dengue virus serotypes after at least one vaccine dose, but not after three doses. These exploratory analyses, which are based on relatively small numbers of dengue cases, must be interpreted cautiously.

According to a WHO advisory group of experts[4], the recently published data from this phase IIb study do not yet prove nor disprove efficacy of CYD-TDV against disease caused by any of the four dengue virus serotypes. Further studies in larger populations and different epidemiological settings are needed to assess conclusively the efficacy of this vaccine candidate.

Based on the recently published data, the safety profile of CYD-TDV is satisfactory, for an observation period of 25 months after the first vaccine dose. Continued follow-up of participants in this and other studies will be critical to generate data towards an assessment of long-term safety of CYD-TDV.

Antibody responses to each of the four dengue virus strains in the vaccine were observed in vaccinated subjects. Evaluation of antibody persistence over time will require continued follow-up of participants in this and other studies. Detailed data on the relationship between antibody responses and protection against clinical dengue disease in this study, such as comparisons of antibody levels in vaccinated subjects who developed dengue versus those who did not, remain to be published. Other efficacy studies in different epidemiological settings should also contribute to addressing this critical question.

What are the implications for phase III studies and potential future licensure?

The recently published data from a phase IIb study support the continued evaluation of this vaccine candidate in phase III studies. Phase III efficacy studies of CYD-TDV are currently underway in 31,000 children and adolescents in 10 countries in Asia and Latin America. These large-scale, multi-centre studies in a variety of epidemiological settings will be important to obtain pivotal efficacy results, additional safety data, and further insight into the relationship between vaccine-induced immune responses and protection against clinical dengue disease.

Future licensure of any dengue vaccine candidate will depend on the assessment of quality, safety and efficacy data by national regulatory agencies. Based on currently available evidence, WHO believes that the public health value of CYD-TDV remains to be demonstrated, and further studies are therefore needed.

How is WHO involved in dengue vaccine research efforts?

The role of WHO is to advise and guide the dengue vaccine development activities of the global research community. This includes scientific consensus-building, guidance on vaccine evaluation, and assessment of the evidence base for policy recommendations on vaccine introduction and use. WHO also provides guidance to national regulatory agencies on approaches and methodologies related to the assessment and licensure of vaccines and post-licensure surveillance. In addition, WHO prequalification is a mechanism to ensure that a vaccine meets international standards for quality, safety and efficacy and is appropriate for the target population. Only WHO prequalified vaccines can be supplied to countries through UN agencies.

More information on dengue vaccine development and related WHO activities is available at http://www.who.int/vaccine_research/diseases/dengue/dengue_vaccines/en/index.html.

References

[1] World Health Organization (2012). Fact sheet: Dengue and severe dengue. Accessible online at http://www.who.int/mediacentre/factsheets/fs117/en/index.html

[2] Special Issue (2011): The Development of Dengue Vaccines. *Vaccine*, Volume 29, Issue 42, Pages 7219-7284.

[3] Sabchareon A. et al. (2012). Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *The Lancet* (Published online September 11).

[4] WHO Technical Advisory Group on Dengue Vaccines in Late Stage Development. Further information at http://www.who.int/vaccine_research/committees/dengue_tag/en/index.html

Long-term safety assessment of live attenuated tetravalent dengue vaccines

Introduction

WHO estimates that approximately 2.5 billion people are at risk from dengue, and 50 to 100 million dengue infections occur annually. 500,000 of those are severe dengue cases who require hospitalization.

There is no licensed dengue vaccine and prevention is exclusively through vector control. However, several vaccine candidates with a variety of vaccine constructs are in the pipeline with the most advanced being a live attenuated chimeric vaccine (developed by sanofi pasteur) that employs the yellow fever 17D-backbone which is currently in Phase III trials in Asia and the American region.

WHO held an expert consultation in October 2011 to review long-term safety considerations of dengue vaccines, and in particular the current scientific evidence regarding a hypothetical concern (based on the natural history of dengue) of an increased risk of severe dengue resulting from vaccination with the live attenuated vaccine. The experts convened also considered broadly various methodological approaches that could potentially be used for the long-term assessment of vaccine safety.

Safety issues

It has long been recognized that infection with a specific DENV serotype (of the 4 distinct serotypes) produces life-long serotype-specific immunity whereas immunity against the other serotypes is short-lived for about 3 to 6 months. Severe disease occurs most commonly after secondary infections and the most important risk factor is infection with a different serotype than the previous infection(s). There is additional evidence of an increased risk of severe disease in dengue-infected infants born to dengue-immune mothers associated with decline in maternally-derived neutralizing antibodies. While mechanisms for this increased immunopathology are not well understood, non-neutralizing antibodies or sub-neutralizing antibody titres are believed to constitute a critical element. To date, clinical trials have not observed an increased risk of severe dengue following vaccination. In addition, trials to date have shown the live dengue vaccine candidates to be well-tolerated (some studies showed more local and systemic reactions after the first dose than subsequent doses and more frequent fever than in adults) and have not reported dengue-like illness caused by the vaccine.

Current WHO guidelines and considerations for future assessments

Previous WHO guidelines for the clinical evaluation of dengue vaccines in endemic areas (2008), and guidelines on the quality, safety and efficacy of live attenuated tetravalent dengue vaccines (2012) have recommended follow-up of dengue-vaccinated and control subjects for at least 3 to 5 years after completion of primary vaccination in Phase II and Phase III trials. Ongoing clinical trials for candidate vaccines take into account this WHO guidance, however, post-licensure vaccine introduction strategies may need to include longer-term assessments in order to extend and provide more robust safety (and effectiveness) data.

The WHO consultation discussed a number of methodological considerations, including factors for or against the potential use of case-control, cohort, randomised control or stepped wedge study designs. Key issues to be considered in selecting an appropriate study design and planning long-term studies will include the feasibility of accurate ascertainment of vaccination status and infection exposure, the ascertainment of severe dengue and diagnostic challenges, a need to conduct studies in a variety of settings with different dengue transmission intensities, and ethical challenges for including unvaccinated comparison groups in long-term studies after an effective vaccine is licensed.

Key conclusions of the expert consultation included that (a) reliable data on the long-term safety of dengue vaccines will be critical to identify and manage unsubstantiated safety concerns that could emerge after vaccine introduction; (b) a coordinated approach should be established to ensure such safety assessment (most likely in sentinel sites); (c) efforts should be made to enhance dengue surveillance in countries where the vaccine is introduced given that cases of severe dengue are less likely to be captured by the current adverse event surveillance systems in many endemic countries; (d) dengue vaccine introduction provides an opportunity to further strengthen routine post-marketing surveillance of AEFI (e.g., through the Global Vaccine Safety Initiative); and (e) the collection and long-term storage of serum or other samples from vaccinees should be encouraged to facilitate further studies (e.g. for correlates of protection and possible booster needs). It was also noted that close collaboration will be needed between licensing national regulatory authorities and with respective vaccine sponsors.

A more detailed report of the consultation has been accepted for publication.

Polio's Last Stand?

Report of the **Independent Monitoring Board** of the **Global Polio Eradication Initiative**

November 2012

CONTENTS

EXECUTIVE SUMMARY

1. When the Independent Monitoring Board (IMB) issued its first report early in April 2011:

    - 99% of polio had been eradicated a decade previously but 1% had remained since then.
    - Four countries had 'endemic' disease: India, Pakistan, Nigeria and Afghanistan.
    - Three countries that had previously been free of disease had 're-established transmission' for more than six months: Angola, Chad and the Democratic Republic of Congo.
    - There had been 14 outbreaks in other countries since the start of 2010.

2. In its series of meetings and reports, the IMB has challenged affected countries and those leading the Global Polio Eradication Initiative (we use the term 'the Programme' for the sum total of these people and activities) to look critically at performance and improve it. The IMB has pushed the Programme to broaden its thinking and approach to embrace more strongly the 'people factors' that are critical to this endeavour. Traditionally, the Programme's strengths have lain with technical and epidemiological disease control interventions and activities. The IMB has raised questions, directed attention and recommended action in areas such as:

    - Are the right people in the right jobs?
    - Is there political commitment and alignment from national to regional to local level?
    - Are governmental leaders working effectively with traditional and religious leaders?
    - Is the management of local vaccination days achieving a consistent standard of best practice?
    - Are front-line vaccinators properly trained and valued?
    - Is the Programme receiving the level of priority attention needed for success?
    - Is everybody focusing on why vaccination days repeatedly miss the same children, and on what can be done about it?
    - What can be done to eliminate refusals and increase community demand?
    - Does the Programme think and act too much in isolation, missing opportunities for strong and effective alliances?

3. The IMB has been pleased that the Programme has responded positively to our guidance. We have seen its leadership reflect, learn, change its emphasis, and increase its urgency.

4. As we issue this, our sixth report:

    - All but 0.1% of polio has been eradicated globally: there were 350,000 cases in 1988; there have been just 175 so far in 2012.
    - Polio is more tightly confined than ever before – affecting just 94 districts in four countries so far this year.
    - The Programme is enjoying an unprecedented level of priority and commitment, much of it stemming from the World Health Assembly's declaration of polio eradication as an emergency for global public health.

5. The IMB was established to monitor the Programme's 2010-12 Strategic Plan. This aimed to stop global polio transmission by the end of 2012. The Programme will now clearly not achieve this goal.

6. Despite it missing yet another deadline, the IMB judges the Programme's prospects to be more positive than ever. If this level of progress had been achieved at the start, not the end, of the 2010-12 period, transmission could have been stopped by now.

7. History shows how cruel polio can be – that it resurges more easily than it is contained. There is a significant risk of having more polio cases in 2013 than in 2012, and in more countries. The Programme must receive a level of priority to not just mitigate this risk, but to achieve another year of major progress towards stopping transmission.

8. The challenge ahead is huge for each of the four countries where polio transmission persists:

    - Nigeria is the only country to have had more polio transmission this year than last. There is finally some evidence that more children are being vaccinated. With its personnel surge and well-constructed plan, the Nigerian Programme may be on the brink of a breakthrough. Over the next six months, the world will be watching. If case numbers are not reduced, spread to other countries is all but inevitable. The fate of polio in Nigeria – and therefore Africa – now lies in the hands of the Nigerian Programme – from President to vaccinator. The Local Government Area Chairmen and Traditional Leaders of the north are crucial in leading this mission. The Programme needs to do everything possible to encourage and support them.
    - Pakistan's chances of stopping polio have been transformed over the last year. Its Programme reorientated and case numbers plummeted in 2012 as a result. But an election looms, which could distract government at every level and allow the virus to resurge. This, and a complex security situation, are the major risks in Pakistan in 2013.
    - Afghanistan has surely, but too slowly, made progress over the last two years. Its slow pace of improvement is worrying, particularly because the country's security landscape faces uncertainty as international troops withdraw.
    - Chad has rebuilt its Polio Programme over the last year, suffering just five cases so far in 2012. It now needs to build on its turnaround, to create a programme that can see every last bit of polio virus gone from the country.

9. Each country will stop polio transmission if its leaders, at every level, take to heart the mission to protect their country's children from being blighted by polio. The word 'ownership' encapsulates what is required. The Indian Government and the Indian people truly 'own' the task of protecting children and families from the scourge of polio. India did not want its image as a modern, vibrant, successful nation to be tarnished by harboring a virus that has been vanquished in most countries of the world. India seized 'ownership' of the polio eradication effort and as a direct consequence has interrupted transmission for the first time in its history.

10. We make ten recommendations to the Global Programme:

- Every time a child or adult travels abroad from Afghanistan, Nigeria or Pakistan, they risk carrying the polio virus with them. We recommend that the International Health Regulations Expert Review Committee urgently issue a standing recommendation by May 2013 that will introduce pre-travel vaccination or vaccination checks in each of these countries until national transmission is stopped. No country should allow a citizen from any endemic polio state to cross their border without a valid vaccination certificate.

- The low season over the next six months is a crucial time. Each of the four affected countries has many actions planned, amongst which the priorities could get lost. Countries that have successfully stopped transmission offer vital lessons about what these priorities should be. We recommend that each affected country rapidly considers its plan, and best practice elsewhere, to set out a list of no more than five priority goals that they absolutely commit to achieve by the end of April 2013, and maintains the focus and pace necessary to do so.

- When the same children are missed by one vaccination campaign after another, frequent campaigns may not be the best way to stop polio transmission. We recommend that an analysis be urgently commissioned to examine the relationship between the frequency and quality of vaccination campaigns, to guide programmatic decisions about the optimum interval between campaigns.

- Mothers and fathers are critical to the Programme's success, but do not have a voice within it. We recommend that every endemic country district-level task force (or equivalent) should be constituted to include a parent, representing parents of the district.

- Too many communities see polio vaccination as an imposition with no benefit. We recommend that every opportunity be taken to 'pair' other health and neighbourhood benefits with the polio vaccine.

- The Programme cannot afford for vaccine supply issues to dictate when campaigns can and cannot be held. The IMB requests a report on vaccine supply at each of its future meetings.

- Capturing the learning, both positive and negative, from polio eradication for future public health programmes is essential. It is an important and distinct part of the legacy of the Polio Programme. This learning needs to be rigorous and comprehensive, needs to involve other partners in immunisation, and it needs to start now. We recommend that the Programme accelerate planning to set out how the learning from polio eradication can be captured and disseminated as part of the strategic legacy plan, overseen and funded with minimal distraction to current work.

- It would be dangerous to assume that polio will remain confined to four countries. Population movement and poor immunity leave a great number of other nations and areas at risk of importation, particularly Yemen, Libya, the Horn of Africa, Somalia, Ukraine, Uganda and Kenya. We recommend that an intensive 'Polio Watch' be established in the countries at highest risk of a polio outbreak. We further recommend that the responsible WHO Regional Offices should issue within the next month an action plan for strengthening vaccination coverage and surveillance in these areas.

- In India, maintaining the hard-earned polio-free status is crucial. We recommend that India plans for a simulation exercise to test the readiness of its emergency response plans. We recommend that the exercise should begin, on an unannounced date in mid-2013, by selecting a sample of districts at random and carrying out real-time simulation-based scrutiny of their emergency response capability.

- An Emergency Operations Centre is being established in Nigeria. We recommend that a continual live audiovisual feed should be broadcast online from here, with a facility for the world's polio experts and the IMB to observe and provide input at any time.

11. The Programme ends 2012 in a complex position: deadline missed, but strong progress made. What happens next? The Programme is developing a strategic plan. Aspirations are no longer good enough – this needs to be a rigorous manifesto for success. Asking for a US$5.5 billion investment, it needs to robustly address the question: why can this Programme now achieve what it has so far failed to deliver? The body of this report sets out the strategic areas that need thorough development. These include ensuring clarity and realism about how the Programme relates to routine immunisation, and making sure that the mission of eradication is truly led by the countries where polio persists.

12. As 2012 draws to a close, the IMB congratulates those who have made the year a success for the Polio Programme. We also pay great tribute to the memory of those who have tragically lost their lives in the pursuit of polio eradication.

13. The Programme has never been in a stronger position, but how history looks back on 2012 will depend what happens next. The remaining polio virus now sits on just 0.2% of the Earth's land mass. Are we seeing its last stand? Only a fool would say this for certain. The virus has fought back and outwitted the Programme many times. Its survival guide is well-established – weak leadership, poor parental engagement, flawed microplans, under-financing. The time is momentous for pubic health history. A final concerted effort could indeed mean writing the story of polio's last stand.

EXECUTIVE SUMMARY

Since its launch at the World Health Assembly in 1988, the Global Polio Eradication Initiative (GPEI) has helped reduce the global incidence of polio by more than 99 per cent and the number of countries with endemic polio from 125 to three. More than 10 million people are walking today who would otherwise have been paralyzed.

At the beginning of 2013, polio – a highly infectious viral disease which causes irreversible paralysis – was a distant memory in most of the world. The year 2012 ended with the fewest polio cases in the fewest countries ever, making now the best moment the world has ever had to put an end to this terrible, yet preventable, disease.

On 26 May 2012, the World Health Assembly (WHA), declared ending polio a "programmatic emergency for global public health." Noting India's success using available tools and technology, the threat to the global community of on-going poliovirus transmission in the last three endemic countries, and the growing knowledge about and risk of circulating vaccine-derived poliovirus (VDPV), the WHA called on the WHO Director-General to develop and finalize a comprehensive polio endgame strategy.

The *Polio Eradication and Endgame Strategic Plan 2013-2018* (the Plan) was developed to capitalize on this opportunity. It accounts for the parallel pursuit of wild poliovirus eradication at the same time as VDPV, while planning for the backbone of the polio network to be used for delivery of other health services to the world's most vulnerable children.

ADVANCES AGAINST POLIO IN 2012

The year 2012 was largely a one of tremendous advances for the program, setting up the opportunity to end polio for good. Among the most significant advances, in February 2012, India celebrated one year without wild poliovirus (WPV) transmission. India was arguably the most technically challenging place to eliminate polio and a large source of outbreaks. India's success was due to the ability of the program to repeatedly reach all children, use of bivalent oral polio vaccine (bOPV), sustained political commitment and accountability, societal support and the availability of resources needed to finish the job. It remains polio-free today.

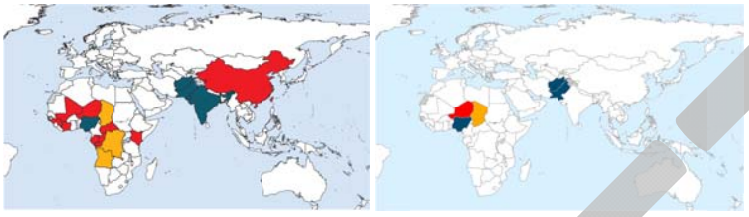
By the end of 2012, the total number of polio cases worldwide plunged to 223. Three of the four countries that had re-established WPV transmission (Angola, the Democratic Republic of the Congo, Sudan) did not have a single case in 2012. The fourth, Chad, has not reported a case since June 2012.

To tackle VDPV, new knowledge and tools have been developed over the past few years, including bOPV, strengthened surveillance to detect VDPVs, and the promise of new, more affordable IPV. In an important step, the Strategic Advisory Group of Experts (SAGE), the world's chief policy guidance body

for immunization has recommended the global withdrawal of the type 2 component of OPV as soon as possible from routine immunization programmes[1].

In September 2012, leaders at all levels of government in the endemic countries, donor countries and the UN Secretary General declared ending polio a top priority, signalling the political commitment needed to effectively implement national Emergency Action Plans and capitalize on the progress to date.

Countries with endemic or re-established transmission or outbreaks of polio



2011 2012

In addition to declining cases in Afghanistan and Pakistan, evidence demonstrates that these countries and Nigeria showed marked improvement in increasing vaccination coverage in 2012, putting them on a trajectory to interrupt transmission by the end of 2014. This will hold true if trends continue and current security challenges do not cause a prolonged or increased impact on operations.
In Pakistan, the proportion of highest-risk districts achieving the estimated target threshold of 95 per cent increased from 59 per cent in January 2012 to a peak of 74 per cent in October 2012.

In Nigeria, though overall cases increased in 2012, the quality of campaigns has improved dramatically over the past year through revised micro-plans, better team selection, improved monitoring and strong oversight at the national and state level. The proportion of very high-risk local government areas in which vaccine coverage reached the target threshold increased from 10 per cent in February 2012 to 70 per cent in February 2013.

In Afghanistan, permanent polio teams operate in the key high-risk areas of Helmand, Kandahar, and Farah. Intense outreach efforts continue to community leaders to ensure the polio programme can safely access all children, including those that had not been reached for more than three years. By end 2012, approximately 15,000 were unreachable, down from 80,000 in 2011.

Tragically, at the end of 2012 and beginning of 2013, the targeting killings of health workers in Pakistan and Nigeria forced the programme to make adjustments for their safety in specific insecure areas.

PLANNING FOR THE END OF POLIO

The Plan was created by GPEI in extensive consultations with national health authorities, global health initiatives, scientific experts, donors and other stakeholders. Its goal is the complete eradication and

[1] Informed by the eradication of wild poliovirus type 2 in 1999 and the fact that over 90% of circulating VDPVs are type 2.

containment of all wild, vaccine-related and Sabin polioviruses, such that no child ever again suffers paralytic poliomyelitis.

Discussions to create the Plan started with a frank assessment and acknowledgement of the failures, incorrect assumptions, and lessons learned from past eradication plans and reasons for missed deadlines. In the process, the following became evident:

1. *One size does not fit all*: While core principles of eradication are global and the vast majority of all polio-endemic countries stopped transmission within two-three years, the tactics needed in the remaining countries need to be carefully tailored to adapt to a range of factors.

2. *Technological innovation cannot overcome gaps in political support, management and community engagement*: It is necessary to create and foster strong political support, as programme management and accountability. In addition, social mobilization must be focused on a micro-level to increase community trust and reach chronically missed children.

3. *A combination of innovations tailored to country context can deliver success in even the most challenging conditions*: India's success highlighted operational best practices to ensure highest quality polio vaccination campaigns. These included: careful micro-planning; strengthened monitoring; a massive and well-managed social mobilization effort; strict accountability measures; community and local leadership engagement; and, a mass increase of human resources at district and sub-district levels.

On January 25, 2013, the WHO Executive Board reviewed and strongly endorsed the Plan's goal, objectives and timelines. Major elements that distinguish this Plan from previous GPEI strategic plans:

- Strategic approaches to end all polio disease (wild and vaccine-related)
- An urgent emphasis on improving routine immunization systems in key geographies
- The introduction of new, affordable IPV options for managing long-term poliovirus risks and potentially accelerating wild poliovirus eradication
- Risk mitigation strategies to address new risks, particularly insecurity, in some endemic areas, and contingency plans should there be a delay in interrupting transmission in such reservoirs
- A concrete timeline to complete the programme

The Plan outlines the steps to harness the GPEI infrastructure to deliver other critical health and development resources and, ultimately, complete the GPEI programme.

Four Main Objectives of the Plan

1. Poliovirus Detection and Interruption. The first objective is to stop all wild poliovirus transmission by the end of 2014 and any new outbreaks of VDPV within six months of the first case. The primary geographic focus is in the three endemic countries and the countries at highest risk of importation in Africa and southern Asia. Activities will focus on enhancing global poliovirus surveillance, improving OPV campaign quality to reach children in the remaining endemic countries, and ensuring rapid outbreak response. This objective also addresses the risks that have become increasingly important in late 2012, particularly insecurity, as the programme is now reaching chronically underserved places and

populations more systematically. This global objective complements the tailored emergency action plans being implemented in each endemic country.

2. Routine Immunization Strengthening and OPV Withdrawal. This objective will help hasten the interruption of wild poliovirus transmission, reduce the risk of wild and vaccine-derived poliovirus importation and spread, and help build a strong system for the delivery of other lifesaving vaccines.

To achieve this objective, the GPEI will commit at least 50 per cent of the time of its field personnel to strengthen routine immunization systems by end-2014 in 10 countries. These include the three polio endemic countries plus seven other countries at high risk of WPV outbreaks and recurrent VDPV emergence – Angola, Chad, the Democratic Republic of the Congo, Ethiopia, India, Somalia, and South Sudan. The goal is to contribute to at least a 10 per cent improvement in coverage rates in the worst-performing districts annually. GPEI staff responsibilities will be specifically directed towards strengthening local and national capacity on management of programmes, micro-planning, mobilization of communities and influencers and monitoring of programme performance. These efforts will be carried out in collaboration with national governments and immunization partners such as the GAVI Alliance.

This objective also affects all 144 countries which currently use OPV in their routine immunization programmes, since success depends on the eventual withdrawal of OPV, beginning with the withdrawal of the type 2 component of trivalent oral polio vaccine (tOPV). OPV withdrawal entails strengthening routine immunization systems, introducing at least one dose of affordable IPV into the routine immunization schedule globally and *then* replacing the trivalent OPV with bivalent OPV in all OPV-using countries.

3. Containment and Certification. All 194 Member States of the World Health Organization will be affected by work under this objective, which aims to certify the world polio-free and ensure that all poliovirus stocks are safely contained. This includes finalizing international consensus on long-term bio-containment requirements for polioviruses. Making sure that these standards are applied is a key element of certifying global eradication.

4. Legacy Planning. This objective will ensure that the investment in polio eradication provides public health dividends for years to come. At present, polio eradication staff comprise the single largest source of external technical assistance for immunization in low-income countries. Staff are responsible for reaching hundreds of millions of the world's most vulnerable children with the polio vaccine and other health interventions such as Vitamin A supplements. Careful planning is essential to ensure that lessons learned during polio eradication, as well as the assets and infrastructure built in support of the effort, are transitioned responsibly to benefit other development goals and global health priorities. This will require thorough consultation with a range of stakeholder groups.

Implementing the Plan

An important aspect of the Plan's success is putting the right checks and balances in place to ensure that milestones are met, and that the program is administered with the greatest efficiency and effectiveness possible to achieve results.

A Monitoring Framework will be used to assess progress against the four objectives and corresponding milestones laid out in the Strategic Plan. This framework outlines the high level areas of work required to achieve the four objectives of the Plan and the details of the activities to be implemented under each area of work, their milestones and how they will be measured. While interruption cannot be guaranteed by a particular date, these trends in progress and commitment toward ending polio suggest the potential to stop transmission of wild polio virus by 2014, and certification of the end of wild poliovirus transmission by 2018.

The World Health Assembly (WHA), comprised of all WHO Member States, provides the highest level of governance of the GPEI. The Regional Committees of WHO allow for more detailed discussion by Member States, and provide input to the WHO Executive Board (EB) and the WHA meeting.

National authorities in polio-affected countries have primary responsibility at all levels of the government for the achievement of the Plan's first three major objectives. National governments in the three WHO Regions certified as polio-free, and polio-free member states in the three remaining polio-endemic Regions, also play a critical role in maintaining high population immunity, including through strengthened routine immunization, and sensitive surveillance for AFP.

The Plan also identifies a set of independent advisory bodies and a wider group of stakeholders across the international health community that advise and monitor the plan's implementation. These groups inform the decision-making of the governing bodies and provide oversight of the management bodies.

Strategic Plan - Objectives	Advisory & Monitoring
Objective 1: Poliovirus Detection & Interruption	Independent Monitoring Board (IMB)
Objective 2: Routine Immunization Strengthening & OPV 2 withdrawal	Strategic Advisory group of Experts (SAGE)
Objective 3: Containment & Certification	Global Certification Commission (GCC)
Objective 4: Legacy Planning	WHO Regional Committees & World Health Assembly (WHA)

- **The Polio Oversight Board (POB)** provides oversight of the management and implementation of the GPEI. Heads of GPEI partner agencies meet quarterly to review GPEI operations and ensure high-level accountability across the GPEI partnership.
- **The Polio Partners Group (PPG)** informs the decisions of the POB, represents GPEI stakeholders and donors and ensures GPEI has the necessary political commitment and financial resources to reach the goal of polio eradication.

Overcoming Risks

Unexpected factors and external risks can delay or undermine the GPEI's ability to achieve the Plan's four major objectives.

Recognizing risks, identifying mitigation options and articulating contingency plans enhance the GPEI's ability to rapidly react to problems, adjust its strategies as needed and minimize setbacks. Six major forward-looking risks have been identified under input and implementation risks:

INPUT RISKS	IMPLEMENTATION RISKS
Insufficient funding	Inability to operate in areas of insecurity
Inability to recruit/ retain the right people	Decline in political and/or social will
Insufficient supply of appropriate vaccines	Lack of accountability for quality activities

Current insecurity in Pakistan and Nigeria have caused tragic losses and pose a new and real threat to the programme. However, GPEI has previously faced periods of instability in various countries, and has learned from these experiences. The leaders of Pakistan, Afghanistan, and Nigeria remain fully committed, at all levels, to stop transmission of polio in their country, with urgent efforts underway to address serious insecurity challenges.

Through end-2014, the GPEI will use an overarching framework for operating in insecure areas while tailoring that approach in each setting, continuing its efforts to institutionalize the programme and maintain its neutrality. The basic elements include:

1. *Operational adjustments*: reduce the programme's and vaccinators' exposure to potential threats (e.g. phased or low-profile campaigns).
2. *Programme safety and security*: enhance coordination between civilian and security services and integrate local security assessments into operational plans to improve the physical safety of vaccinators and facilities.
3. *Community demand*: improve local community demand to increase access to vaccination and basic health services through a combination of awareness-raising activities around the disease, its consequences and its prevention, and ideally by coupling OPV with the delivery of other services/interventions.
4. *Religious leaders advocacy*: markedly step up advocacy by Islamic leaders and institutions at the local, national and international levels to ensure all Muslims (i.e. including aggressors) are aware of their obligation to ensure the vaccination/protection of children against polio, the sanctity of health workers , and the neutrality of health services.
5. *Measures to prevent spread*: reduce the risk of spread from insecure areas (e.g. by intensive vaccination in surrounding areas and vaccination of travelers in/out of infected areas).

Financing the Plan

Efficient and effective implementation of the Plan requires as much funding at the outset of the plan as possible to allow for certainty and predictability of resources. Full funding of the plan is critical to:

- Help protect the gains GPEI has made to date
- Enable allocation of resources to ensure the greatest impact over the long term
- Allow GPEI to implement the major objectives of the plan concurrently, creating greater opportunity for success.

A thorough budget analysis was conducted by GPEI estimating a budget of US$5.5 billion to achieve the Plan's objectives through 2018.

The budget includes the cost of reaching and vaccinating more than 400 million children multiple times every year in at least 20 countries, monitoring and surveillance in more than 70 countries, and developing an infrastructure that allows for other health and development programs to flourish. The costs for the programme are directly related to the number and quality of vaccination campaigns. It requires more (and higher quality) campaigns to boost the immunity levels of children in the hardest-to-reach areas of Nigeria, Pakistan, and Afghanistan. As the number and quality of campaigns to reach those children increase, the costs of the programme increase as well.

A detailed section on financial resources describes the assumptions made when calculating the costs of the programme, and the margins built in to anticipate a potential rise in funding required. The financial requirements for the period will be presented in a Financial Resource Requirements (FRR) document with corresponding costs and underlying assumptions per major budget category. The FRR information will be reviewed and updated every four months.

A strategy is in place to obtain long-term, predictable funding for the 2013-2018 period, to ensure that lack of funding is not a barrier to implementation and thus to eradication.

ENDING POLIO FOR ALL TIME

Ending one of the world's most enduring diseases will change the course of history and extend benefits beyond protecting future generations from this debilitating, preventable disease. The GPEI is responsible for identifying and reaching more than 2.5 billion children living in some of the most challenging areas and in vulnerable communities worldwide. GPEI staff and its infrastructure have served as a vehicle for the distribution of other global and country health priorities including anti-measles vaccines, vitamin A, malaria bed nets, anti-helminthics (de-worming), and surveillance for epidemics such as yellow fever and avian influenza in areas with fragile health systems. Full implementation of this plan will enable those benefits to multiply, improving immunization rates of children who never before have been reached with life-saving vaccines. Beyond ending polio, it will lay the groundwork for transitioning the extensive GPEI infrastructure to deliver additional public health dividends.

Ending polio also will produce economic benefits. A 2010 study in *Vaccine*[1] estimated that the GPEI's efforts will generate net benefits of $40-50 billion**,** largely savings from avoided treatment costs for paralytic polio and gains in productivity. Approximately 85 per cent of the savings will be in developing countries. The disease surveillance networks and improved vaccine delivery systems created by polio eradication efforts add economic benefits.

While polio harms a relatively small number of children worldwide, it is an epidemic-prone disease. On-going endemic transmission in three countries will continue to threaten polio-free areas everywhere, unless it is eradicated entirely. From 2009 to 2011, approximately half of all polio cases were due to international spread of polio from endemic areas to polio-free countries, and approximately one-third of the 2011 GPEI budget was spent on outbreak response in previously polio-free countries. Failure to eradicate polio now could result in as many as 200,000 new cases every year, within ten years.

Support from the global community to fully fund the *Polio Eradication and Endgame Strategic Plan 2013-2018* will pay dividends for generations to come by providing the resources needed to effectively and efficiently implement the Plan. Success will mean that this global partnership developed a workable, scalable model for global vaccination—a blueprint for success that can be used time and again to reach children throughout the developing world with other health resources, clean water and education. This partnership will end a disease and prove that together we can achieve even more ambitious goals in the future.

[1] Duintjer Tebbens DJ, Pallansch MA, Cochi SL, Wassilak SGF, Linkins J, Sutter RW, et al. Economic analysis of the global polio eradication initiative. Vaccine. 2010; 29 (2):334-343.

Background Paper on Yellow Fever Vaccine

SAGE Working Group

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Introduction

Yellow fever is a vector-borne disease resulting from the transmission of yellow fever virus to a human from the bite of an infected mosquito. It is endemic to sub-Saharan Africa and tropical South America. Infection in humans is capable of producing hemorrhagic fever and is fatal in 20-50% of person with severe disease. Because no treatment exists for yellow fever disease, prevention is critical to lower disease risk and mortality.

Yellow fever vaccine has been used since 1937 in the prevention of yellow fever disease with more than 600 million doses of the vaccine having been delivered worldwide. Currently all yellow fever vaccines in use are live attenuated viral vaccine from the 17D lineage. The vaccine has been proven to be highly immunogenic and a single dose provides long-term protection against yellow fever. In general, the vaccine is well tolerated inducing mild local and systemic side effects in up to a third of recipients. However, rare but serious side effects have been observed following yellow fever vaccination including: 1) immediate hypersensitivity or anaphylactic reactions; 2) yellow fever vaccine-associated neurologic disease (YEL-AND); and 3) yellow fever vaccine-associated viscerotropic disease (YEL-AVD). YEL-AND is a group of neurologic conditions that are either due to direct viral invasion of the central nervous system by the vaccine virus resulting in meningitis or encephalitis or due to an autoimmune reaction resulting in conditions such as Guillain-Barré syndrome or acute disseminated encephalomyelitis. YEL-AVD results from the replication and dissemination of the vaccine virus similar to the wild-type virus. YEL-AVD cases typically develop multi-organ system dysfunction or failure and over 60% of cases have been fatal. To date, YEL-AND and YEL-AVD only have been reported in primary vaccine recipients.

Yellow fever vaccine is recommended for person aged ≥9 months who are living in or traveling to areas at risk for yellow fever virus transmission in South America and Africa. Because of the risk of spread of the virus through infected mosquitoes or more likely infected humans, policies regarding the use of yellow fever vaccination are included in International Health Regulations (IHR). Under IHR (2005), countries can require proof of yellow fever vaccine receipt from persons upon entry. Individuals who arrive in a country with a yellow fever vaccination entry requirement without proof of vaccination may be quarantined for up to 6 days. Per IHR, a single dose of yellow fever vaccine is consider to provide protection against yellow fever virus infection starting 10 days following the administration of the vaccine and continuing for 10 years when a booster dose of the vaccine should be given.

The SAGE Working Group on Yellow Fever Vaccines was tasked with reviewing evidence and preparing recommendations related to the use of yellow fever vaccines in order to update the 2003 WHO position paper for SAGE review. This report reviews the evidence related to main topics considered by the working group, including:

1. Need for booster doses every 10 years to maintain protection against yellow fever
2. Safety of the vaccine in selected special populations
    a. Persons aged 60 years and older
    b. HIV-infected persons
    c. Persons with other immunocompromising conditions
    d. Pregnant women
    e. Lactating women, specifically the safety of vaccine exposure in their breastfed infants

3. Interference between yellow fever and other co-administered vaccines
4. Impact of vaccination strategies on control of yellow fever
    a. Routine vaccination versus outbreak control
    b. Combined routine immunizations and preventive campaigns

Methodology

To update the 2003 WHO position paper on yellow fever vaccine, the SAGE working group for yellow fever vaccination considered several key issues (outlined above). To address these issues and review current data relating to yellow fever vaccination, the working group first met in December 2011 conducting monthly teleconferences through July 2012 and having two face-to-face meetings conducted in April 2012 and January 2013. Published, peer-reviewed studies were the primary source of data used. When relevant to issues under discussion, unpublished data available to WHO also were considered.

To address the question related to the need of a booster of yellow fever vaccine and safety of yellow fever vaccine in persons age 60 years and over, the WHO Secretariat collaborated with both external (Eduardo Gotuzzo and Gabriela Córdova) and internal investigators (Ellen Rafferty) to review available data. This work was also supplemented by the following questions that were assessed by personnel from the WHO Secretariat using the GRADE approach:

- Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection?
- Is there evidence that elderly individuals over 60 years of age in endemic settings are at greater risk of YEL-AVD?
- Is there evidence that elderly travelers over 60 years of age are at greater risk of YEL-AVD?

Findings and Recommendations

The findings and recommendations of the working group for each of the main topics reviewed are presented below in distinct sections. Each section includes key findings, more in-depth information, and the recommendations of the working group.

Booster Doses

Key Findings

- No efficacy study has been performed for yellow fever vaccine; however, neutralizing antibodies have been used as a surrogate to indicate a protective immune response.
- The current recommendation of a booster dose of yellow fever vaccine every ten years has been in place under IHR since 1965 and was determined based on limited evidence.
- Data suggest that the majority of vaccine recipients will develop a protective antibody titer against yellow fever virus within 28 days of vaccination and will maintain protective antibody titers for potentially several decades, or possibly life-long, following vaccination.
- Children less than 2 years of age have lower seroconversion rates following a single dose of yellow fever vaccine.
- Very few primary vaccine failures following yellow fever vaccination have been reported and there are no reports of secondary vaccine failures due to time elapsed after immunization.
- Recent data suggest that, in addition to neutralizing antibodies, both innate and cell-mediated immunity also contribute to the initial immune response and the maintenance of long-term protection against yellow fever virus in those who are vaccinated.

Although no human efficacy studies have been performed with yellow fever vaccine, several observations support yellow fever vaccine being protective in humans, including: 1) the reduction of laboratory-associated infections in vaccinated workers; 2) the observation following initial use of the vaccine in Brazil and other South American countries that yellow fever only occurred in unvaccinated people; 3) the rapid disappearance of cases during yellow fever vaccination campaigns initiated during epidemics, and 4) the protection of rhesus monkeys against virulent yellow fever virus by neutralizing antibodies generated in response to yellow fever vaccination [1, 2].

From the dose-response study conducted in rhesus monkeys, a minimal level of neutralizing antibodies needed to protect the monkeys against virulent yellow fever virus was established. Testing using a $\log_{10}$ neutralization index (LNI) demonstrated that LNI >0.7 was correlated strongly with protection [1]. Although the amount of serum needed for LNI testing is suitable for animal studies or clinical trials, it precludes routine screening among humans [3]. Therefore, a similar test, plaque reduction neutralization test (PRNT), is used most frequently in diagnostic tests and follow-up studies to determine the absence or presence of neutralizing antibodies and the specific serum antibody titer.

Clinical trials have found 80% to 100% of vaccinated individuals develop yellow fever virus neutralizing antibodies by 10 days after vaccination [4-6]. Most studies find >99% of the vaccinated individuals developed neutralizing antibodies by 28 days after vaccination [3].

Yellow fever vaccine is recommended for persons aged ≥9 months who are traveling to or living in areas where there is a risk of yellow fever virus transmission. Per IHR (2005), a single dose of yellow fever vaccine is consider to provide protection against yellow fever virus infection starting 10 days following the administration of the vaccine and continues for 10 years [7]. The booster dose requirement for yellow fever vaccine was put into place in 1959 under the precursor to IHR, International Sanitary Regulations, with booster doses initially being required every 9 years based on available data [8, 9]. The booster dose interval was changed in 1965 to every 10 years based published studies that showed

neutralizing antibodies were present in the majority of vaccine recipients for at least 10 years after vaccination (Table 1) [10, 11].

A systematic review conducted by external collaborators and WHO secretariat identified at least 6 additional studies on the presence of neutralizing antibodies in yellow fever vaccine recipients 10 or more years since vaccination [12-18]. Although different techniques and assay PRNT cutoff values were used in the studies, most studies document a high proportion of vaccine recipients (>90%) with detectable levels of serum neutralizing antibodies up to 20 years post vaccination (Table 1). Studies that have looked at persons 20 or more years after vaccination have found that approximately 80% of vaccine recipients still have detectable levels of neutralizing antibodies [12, 14, 15, 17]. One of these long-term immunity studies was conducted among U.S. military veterans from World War II and found that more than 80% of military personnel had neutralizing antibody 30-35 years following a single dose of yellow fever vaccine [12]. In a separate study, neutralizing antibodies were detected in one vaccine recipient 60 years following their vaccination [17].

Since the 1930s when yellow fever vaccine was first used, only 12 cases of yellow fever disease have been identified among vaccine recipients of over 600 million doses of the vaccine administered (Table 2) [19-23]. Of the 12 cases, some (n=3) lacked any laboratory data to confirm them as yellow fever cases while others had questionable or inadequate laboratory findings (n=7). Two of the yellow fever disease cases occurred in person who received the vaccine within two weeks of their illness onset and thus may not have had adequate time to develop neutralizing antibodies against the vaccine before being exposed to wild-type yellow fever virus. For these cases, nucleotide sequencing was performed and identified wild-type yellow fever virus rather than vaccine virus (i.e., not YEL-AVD cases) [23]. All 12 of the cases of yellow fever disease among vaccine recipients developed within 5 years of vaccination suggesting that secondary vaccine failures due to waning immunity do not occur.

In addition to the systematic review, the following question related to the need for a booster dose of yellow fever vaccine was evaluated using GRADE: 1) Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection? (Table 3). The conclusions from GRADE were that healthy persons rarely fail to develop neutralizing antibodies after vaccination. Despite some observed time-dependent waning, neutralizing antibody titers can be found in the vast majority more than 10 years after vaccination. Further evidence suggests that even with no detectable neutralizing antibodies, protective immunity might be induced due to cell-mediated immunity. Post-licensing monitoring of break-through infections is missing yet observational studies attest the effectiveness of the vaccine. In endemic settings high primary vaccination coverage (60-80%) is sufficient to prevent yellow fever outbreaks and waning of antibody titers seems not to be relevant in affected regions. In immunocompetent persons, there is no demonstrated need for a booster dose every ten years. However, the confidence in the estimate of the effect on the outcome is limited.

Working Group Discussion and Conclusions

The need and timing of booster doses of yellow fever vaccine was discussed by the previous SAGE Yellow Fever Working Group that provided the recommendations for the 2003 yellow fever vaccine position paper. It was noted at that time that the booster dose recommendation predominantly applied to travelers, most of which were traveling from non-endemic areas.

The current working group reviewed information: 1) collected through the systematic review [18]; 2) from outbreaks of the yellow fever disease in endemic countries; and 3) on the mechanism of

immunologic memory following yellow fever vaccination. The working group agreed that the information collected from the systematic review (presented above) suggest that immunity following yellow fever vaccination is likely to be life-long. The working group also noted the rarity of primary vaccine failures and the lack of identified secondary vaccine failures in persons from endemic areas or in travelers who have been vaccinated against yellow fever. However, the working group did note issues and concerns with interpreting published study data as different PRNT levels (e.g., 50% to 90% cutoff) were used in the various studies and the lack of a clear correlate of protection in the immune response to yellow fever vaccination. It was also noted that persons living in an endemic area are likely to have some degree of "boosting" that occurs due to exposure either to yellow fever virus or to related viruses, such as dengue, West Nile, or Zika viruses. Furthermore, endemic populations are likely to have some effect of herd immunity in regards to protection as humans are a potential amplifying reservoir of yellow fever virus. So if there is adequate vaccine coverage, an unvaccinated individual may be "protected" due to decrease in amplifying reservoirs around them. Another potential concern raised by working group members are data suggesting that children (<2 years) do not seem to develop the same high level of neutralizing antibodies as is seen in adults and this could lead to some yellow fever cases among persons who received the vaccine as a child if a booster dose is not given [24]. However, this observation is confounded by the fact that seroprotective levels of neutralizing antibodies, using a PRNT, have not been determined.

In regards to outbreaks of yellow fever disease, the working group discussed unpublished data from the large outbreaks of yellow fever that occurred in Nigeria during the 1980s. Nigeria had good levels of yellow fever vaccination in their population until the 1960s, when routine vaccination was discontinued. In the 1980s, large outbreaks of the disease were seen in several areas of the country and hundreds of thousands of persons were believed to develop disease [25, 26]. During these outbreaks, yellow fever disease only occurred in unvaccinated individuals and persons who received yellow fever vaccine several decades previously were protected from developing yellow fever disease (Tomori, personal communication).

In response to concerns over the lack of a correlate of protection and potential waning antibody titers against yellow fever virus over time following yellow fever vaccination, the working group briefly discussed the mechanism of immunologic memory following vaccination. Recent research suggests cellular immunity and innate immunity contribute to the initial immune response and sustaining the immune memory to yellow fever vaccination [27, 28]. Therefore, the working group felt that a lack of detectable neutralizing antibodies may not mean a lack of protection against yellow fever viral infection among yellow fever vaccine recipients; however, detection of neutralizing antibodies was clearly associated with a protective immune response.

Finally, the working group noted that yellow fever surveillance needs to be improved and maintained in order to detect potential yellow fever cases due to vaccine failure. Testing of acute samples for viral RNA will be critical for these cases to differentiate vaccine failures from other causes of jaundice and hemorrhage.

Recommendations: Based on currently available data, a single dose of yellow fever vaccine appears to confer life-long protective immunity against yellow fever disease. Therefore, a booster dose of yellow fever vaccine is not needed to maintain immunity. However, further study is needed

in certain groups, who may have suboptimal seroconversion rates following a single dose of the vaccine to determine if they may benefit from a single booster dose.

References

1. Mason RA, et al. Yellow fever vaccine: direct challenge of monkeys given graded doses of 17D vaccine. Appl Microbiol. 1973; 25: 539-544.
2. Staples JE, et al. Centers for Disease Control and Prevention (CDC). Yellow fever vaccine: recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm Rep. 2010; 59: 1-27.
3. Monath T, Gershman MD, Staples JE, Barrett AD. Yellow fever vaccine. In: Plotkin SA, Orenstein, W.A., Offit, P.A., editor. Vaccines. 6th ed: Saunders Elsevier; 2013.
4. Courtois G. Time of appearance and duration of immunity conferred by 17D vaccine. In: Yellow Fever Vaccine. WHO Series. Geneva, Switzerland; 1956.
5. Monath TP. Neutralizing antibody responses in the major immunoglobulin classes to yellow fever 17D vaccination of humans. Am J Epidemiol. 1971; 93: 122-129.
6. Monath TP, et al. Clinical proof of principle for ChimeriVax: recombinant live, attenuated vaccines against flavivirus infections. Vaccine. 2002; 20: 1004-1018.
7. World Health Organization. International Health Regulations (2005). Switzerland; 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf, Accessed February 19, 2013.
8. Courtois G. [Duration of immunity following yellow fever vaccination.] Ann Soc Belg Med Trop. 1954; 34: 9-12.
9. Dick GWA, Gee FL. Immunity to yellow fever nine years after vaccination. Trans Roy Soc Trop Med Hyg. 1952; 46(4): 449-458.
10. Groot H, Riberiro RB. Neutralizing and haemagglutination-inhibiting antibodies to yellow fever 17 years after vaccination with 17D vaccine. Bull World Health Organ. 1962; 27: 699-707.
11. Rosenzweig EC, et al. Immunological studies with group B arthropod-borne viruses. IV. Persistence of yellow fever antibodies following vaccination with 17D strain yellow fever vaccine. Am J Trop Med Hyg. 1963; 12: 230-235.
12. Poland JD, et al. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ. 1981; 59: 895-900.
13. Reinhardt B, et al. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. J Med Virol. 1998; 56: 159-167.
14. Niedrig M, et al. Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. Trop Med Int Health. 1999; 4: 867-871.
15. Gomez SY, Ocazionez RE. [Yellow fever virus 17D neutralizing antibodies in vaccinated Colombian people and unvaccinated ones having immunity against dengue.] Rev Salud Publica. 2008; 10: 796-807.
16. de Melo AB, et al. Description of a prospective 17DD yellow fever vaccine cohort in Recife, Brazil. Am J Trop Med Hyg. 2011; 85: 739-47.
17. Coulange Bodilis H, et al. [Long-term persistence of yellow fever neutralizing antibodies in persons aged 60 years and older]. Bull Soc Pathol Exot. 2011; 104: 260-265.
18. Gotuzzo E, et al. Efficacy and duration of immunity following yellow fever vaccine: a systematic review on the need of yellow fever booster every 10 years. *Manuscript in preparation*.
19. Elliott M. Yellow fever in the recently inoculated. Trans Roy Soc Trop Med Hyg. 1944; 38: 231-234.
20. Ross RW, et al. A fatal case of yellow fever in a European in Uganda. East Afr Med J. 1953; 30: 1-11.
21. Nolla-Salas J, et al. Imported yellow fever in vaccinated tourist. Lancet. 1989; 334: 1275.
22. Tuboi SH, et al. Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998-2002. Trans Roy Soc Trop Med Hyg. 2007; 101: 169-175.
23. de Filippis AM, et al. Isolation and characterization of wild type yellow fever in cases temporally associated with 17DD vaccination during an outbreak of yellow fever in Brazil. Vacc. 2004; 22: 1073-1078.
24. Nascimento Silva JR, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps, and rubella. Vaccine. 2011; 29: 6327-6334.
25. DeCook KM, et al. Epidemic yellow fever in eastern Nigeria, 1986. Lancet. 1988; 1(8586): 630-633.

26. Nasidi A, et al. Urban yellow fever epidemic in western Nigeria, 1987. Trans Roy Soc Trop Med Hyg. 1989; 83: 401-406.
27. Wrammert J, et al. Human immune memory to yellow fever and smallpox vaccination. J Clin Immunol. 2009; 29(2): 151-157.
28. Kohler S, et al. The early cellular signatures of protective immunity induced by live viral vaccination. Eur. J. Immunol. 2012; 42: 2363–2373.

Table 1. Studies documenting long-term immunity following yellow fever (YF) vaccination. *(Adapted from reference 18)*

Study author – year published[reference]	Number of subject evaluated	Population	Time since yellow fever vaccination	Laboratory test*	Findings
Courtois - 1954 [8]	79	Endemic population; adult males	12 years	Mouse protection	Protective immunity documented in 76/79 (96%)
Dick - 1952 [9]	202	Endemic population; children and adults	~9 years	Mouse protection	156/202 (77%) were immune to YF; 36/57 (63%) of children and 120/145 (83%) of adults
Groot - 1962 [10]	108	Nonendemic area of Brazil; All ages	17 years	Mouse protection	82 (76%) strong positive neutralizing antibody results; 23 (21%) weak positive neutralizing antibody results; 3 (3%) negative neutralizing results
Rosenzweig - 1963 [11]	29	Traveler population; Adult U.S. military	6-15 years	Mouse protection	All with protective antibody titers; 6-15 years mean LNI† 3.9, range 3.5-4.4; 16-19 years mean LNI 4.2, range 2.6-5.0
Poland - 1981 [12]	116	Traveler population; Adult U.S. military	30-35 years	$PRNT_{90}$	90/116 (78%) with detectable PRNT titer (≥2); titers varied by service between 60 and 97% with detectable titers. Not all could be confirmed to be vaccinated. OF NOTE: Also ran mouse protection studies and found test to be less sensitive than PRNT.
Reinhardt - 1988 [13]	5	Traveler population; adults	10 years	$PRNT_{90}$	All vaccinees had neutralizing antibodies at 10 years post vaccination; Mean titer 72 (SE ± 11.2); all above 40.
Niedrig - 1999 [14]	59	Traveler population; children and adults	11-38 years	$PRNT_{90}$	At 11-38 years, 38/51 (75%) were seroprotected (titer ≥10).
Gomez - 2008 [15]	19	Endemic population; children and adults	5-24 years	$PRNT_{75}$	13/19 (68%) had seroprotective (titer ≥10) levels of antibodies
de Melo - 2011 [16]	20	Endemic population;	10 years	$PRNT_{50}$	All had protective levels (≥20) of

		aged 16-83 years			neutralizing antibodies with a GMT of 113 (95%CI = 102–188) and a range of titers from 20 to 320
Coulange Bodilis - 2011 [17]	84	Traveler population; 60-89 years	1-60 years	$PRNT_{80}$	80/84 (95%) of cases had seroprotective (≥10) titers; 13/15 (87%) of those vaccinated ≥20 years previously had seroprotective titers; 25/27 (93%) between 10-19 years were seroprotected

*PRNT = plaque reduction neutralization test. $PRNT_{\#}$ is the reciprocal of the highest serum dilution at which #% of virus is inhibited.

†LNI = log neutralization index; LNI > 0.7 is seroprotective.

Table 2. Reports of yellow fever vaccine failures. (*Adapted from reference 18)*

Subject [reference]	Evidence of yellow fever vaccine	Time from vaccination to disease onset	Date of disease onset	Outcome	Testing
32 yo male solider (traveler) [19]	Unknown*	1 year, 4 months	Jan 1942	Died	None; diagnosed based on clinically compatible illness
35 yo male solider (traveler) [19]	Unknown	1 year, 3 months	Feb 1942	Died	None; diagnosed based on clinically compatible illness
25 yo male solider (traveler) [19]	Unknown	1 year, 4 months	Feb 1942	Recovered	None; diagnosed based on clinically compatible illness
39 yo male traveler [20]	Unknown	4 years, 81 days	Jan 1952	Died	Testing inconclusive; postmortem findings consistent
37 yo female traveler [21]	Written evidence of vaccination	5 years	Oct 1988	Recovered	Antibody testing with complement fixation
21 yo male endemic area [22]	Written evidence of vaccination	8 months	1998-2002†	Recovered	Confirmed‡
20 yo female endemic area [22]	Written evidence of vaccination	5 years, 2 months	1998-2002†	Recovered	Confirmed‡
17 yo female endemic area [22]	Written evidence of vaccination	1 year, 6 months	1998-2002†	Recovered	Confirmed‡
62 yo male endemic area [22]	Written evidence of vaccination	1 year	1998-2002†	Died	Confirmed‡
30 yo female endemic area [22]	Written evidence of vaccination	5 months	1998-2002†	Died	Confirmed‡
39 yo male endemic area [23]	Vaccinated in reactive campaign	2 days	March 2001	Died	Yellow fever virus isolation and sequencing
69 yo male endemic area [23]	Vaccinated in reactive campaign	14 days	March 2001	Died	Yellow fever virus isolation and sequencing

*Not clearly stated in article how proof of vaccination was verified

†Does not specify a specific date of disease onset in article

‡Clinically compatible illness with laboratory data of yellow fever infection (e.g., IgM antibodies, isolation of yellow fever virus, histopathologic changes in liver consistent with yellow fever, four-fold rise in yellow fever virus-specific antibodies, yellow fever virus antigen detected in tissue); death within 10 days of symptom onset in someone with a clinically compatible illness but no laboratory testing was also considered a confirm case.

GRADE Table 3. Need for a booster dose of yellow fever vaccine in immunocompetent individuals

Population : Immunocompetent individuals
Intervention : Primary yellow fever vaccination
Comparison : No primary vaccination
Outcome : Duration of immunity

Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		10/ observational[1]	2
	Factors decreasing confidence	Limitation in study design	None Serious[2]	0
		Inconsistency	None serious	0
		Indirectness	None serious[3]	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 outcome is limited.**
Conclusions	In total over 540 million doses of yellow fever have been used globally(1) . So far only 12 cases of secondary vaccine failure have been reported in literature (2-6)[4]. Healthy persons rarely fail to develop neutralizing antibodies after vaccination (7). Despite some observed time-dependent waning, neutralzing antibody titers can be found in the vast majority more than 10 years after vaccination (8-19). Further evidence suggests that even with no detectable neutralizing antibodies, immunity might be given due to cell-mediated protective effects (13;15). Post-licensing monitoring of break-through infections is missing yet observational studies attest the effectiveness of the vaccine. In endemic settings high primary vaccination coverage (60-80%) is sufficient to prevent yellow fever outbreaks and waning of antibody titers seems not to be relevant in affected regions (20). In immunocompetent persons there is no demonstrated need for a booster dose every ten years.			

[1] 6 observational studies reported 74.5-100% neutralizing antibody (NTAb) ≥10years after vaccination. One small study reported 65% (n=13/20) with protective NTAb after 10 years (De Melo et al. 2011). One study (Gomez SY et al. 2008) reported NTAb in >68% in vaccinees after ≥4years post vaccination. One study (Veit et al.2009) reported 88% NTAb 1-10 years after vaccination and one study reported 73% with NTAb 3- 4 years after vaccination (Gibney et al. 2012).
[2] Limitations in only 2 of 8 studies/therefore no downgrading: No clear description of method and incomplete medical records of vaccinated (Poland et al. 1981). Non-standardized methods such as mouse-protection test used (Groot et al. 1962).
[3] Serological marker as proxy to assess level of clinical protection, yet overall agreement in the assumption that titer>1:10 in plaque reduction neutralization test is associated with protective immunity (Hepburn at al. 2006; Monath et al. 2005), therefore no downgrading.
[4] Reporting of 10 cases of secondary vaccine failure, with disease onset >5 month after vaccination (3-6).Two cases with onset of disease 2-14 days after vaccination (Fillipis et al.2004).

Reference List for GRADE table 3

(1) Barrett AD, Teuwen DE. Yellow fever vaccine - how does it work and why do rare cases of serious adverse events take place? Curr Opin Immunol 2009 Jun;21(3):308-13.

(2) Filippis AM, Nogueira RM, Jabor AV, Schatzmayr HG, Oliveira JC, Dinis SC, et al. Isolation and characterization of wild type yellow fever virus in cases temporally associated with 17DD vaccination during an outbreak of yellow fever in Brazil. Vaccine 2004 Mar 12;22(9-10):1073-8.

(3) Nolla-Salas J, Saballs-Radresa J, Bada JL. Imported yellow fever in vaccinated tourist. Lancet 1989 Nov 25;2(8674):1275.

(4) ROSS RW, HADDOW AJ, RAPER AB, TROWELL HC. A fatal case of yellow fever in a European in Uganda. East Afr Med J 1953 Jan;30(1):1-11.

(5) Tuboi SH, Costa ZG, da Costa Vasconcelos PF, Hatch D. Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998-2002. Trans R Soc Trop Med Hyg 2007 Feb;101(2):169-75.

(6) M.Elliott. Yellow Fever in the recently inoculated. Transactions of The Royal Society of Tropical Medicine and Hygiene - TRANS ROY SOC TROP MED HYG , 1944;38(3):231-4.

(7) Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg 2002 May;66(5):533-41.

(8) Coulange BH, Benabdelmoumen G, Gergely A, Goujon C, Pelicot M, Poujol P, et al. [Long term persistence of yellow fever neutralising antibodies in elderly persons]. Bull Soc Pathol Exot 2011 Oct;104(4):260-5.

(9) de Melo AB. Description of a prospective 17DD yellow fever vaccine cohort in Recife, Brazil. 2011 Oct.

(10) Gomez SY, Ocazionez RE. [Yellow fever virus 17D neutralising antibodies in vaccinated Colombian people and unvaccinated ones having immunity against dengue]. Rev Salud Publica (Bogota) 2008 Nov;10(5):796-807.

(11) Groot H, RIBERIRO RB. Neutralizing and haemagglutination-inhibiting antibodies to yellow fever 17 years after vaccination with 17D vaccine. Bull World Health Organ 1962;27:699-707.

(12) Hepburn MJ, Kortepeter MG, Pittman PR, Boudreau EF, Mangiafico JA, Buck PA, et al. Neutralizing antibody response to booster vaccination with the 17d yellow fever vaccine. Vaccine 2006 Apr 5;24(15):2843-9.

(13) Niedrig M, Lademann M, Emmerich P, Lafrenz M. Assessment of IgG antibodies against yellow fever virus after vaccination with 17D by different assays: neutralization test, haemagglutination inhibition test, immunofluorescence assay and ELISA. Trop Med Int Health 1999 Dec;4(12):867-71.

(14) Poland JD, Calisher CH, Monath TP, Downs WG, Murphy K. Persistence of neutralizing antibody 30-35 years after immunization with 17D yellow fever vaccine. Bull World Health Organ 1981;59(6):895-900.

(15) Reinhardt B, Jaspert R, Niedrig M, Kostner C, L'age-Stehr J. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. J Med Virol 1998 Oct;56(2):159-67.

(16) Rosenzweig EC, BABIONE RW, Wisseman CL, Jr. Immunological studies with group B arthropod-borne viruses. IV. Persistence of yellow fever antibodies following vaccination with 17D strain yellow fever vaccine. Am J Trop Med Hyg 1963 Mar;12:230-5.

(17) Veit O, Niedrig M, Chapuis-Taillard C, Cavassini M, Mossdorf E, Schmid P, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. Clin Infect Dis 2009 Mar 1;48(5):659-66.

(18) Gibney KB, Edupuganti S, Panella AJ, Kosoy OI, Delorey MJ, Lanciotti RS, et al. Detection of anti-yellow Fever virus immunoglobulin m antibodies at 3-4 years following yellow Fever vaccination. Am J Trop Med Hyg 2012 Dec;87(6):1112-5.

(19) DICK GW, GEE FL. Immunity to yellow fever nine years after vaccination with 17D vaccine. Trans R Soc Trop Med Hyg 1952 Jul;46(4):449-58.

(20) Weekly Epidmiological Record. (http://www.who.int/wer). Yellow fever fact sheet. No. 5, 2010, 85, 29-36.

Special Populations

Use of yellow fever vaccine in people over 60 years old

Key Findings

- There are published reports identifying a higher risk of serious adverse events following immunization (AEFI), namely YEL-AVD, in persons 60 years old and older compared to younger persons who are receiving the vaccine for travel to an endemic area.
- There are insufficient data to determine if the risk of serious AEFI may be elevated among elderly persons who reside in an endemic area and receive yellow fever vaccine.

Previous studies have suggested that there is a higher risk of serious adverse events following immunization (AEFI) with yellow fever vaccine, in particularly YEL-AVD, among the elderly [1, 2, 3]. These studies primarily used age-specific reporting rates (RRs) and reporting rate ratios (RRRs) as proxies for determining risk in the elderly population and have used a variety of case definitions for YEL-AVD and YEL-AND. A systematic review was conducted by the WHO secretariat that utilized the recently published Brighton case definition for viscerotropic disease in order to better quantitate the current risk of YEL-AVD among the elderly for both travelers and endemic populations [4].

The review found that the crude number of reported cases of YEL-AVD among the elderly (≥60) was quite high (n=19) compared to all the other age groups combined (n=24) (Table 4). After applying the Brighton Classification for both diagnostic certainty and causality to published studies on travelers, the re-calculated RRs were statistically significant and remained the highest among persons aged 70 years or older but also were higher in those aged ≥60 years as well with significant RRR with ratios of 34 to 47 (Table 5) [1, 2]. Currently, there is only one published article that calculates age-specific RRs of YEL-AVD in an endemic country (Table 6) [5]. Although this study does demonstrate a slightly higher RR of YEL-AVD among the elderly than the average RR, the calculated RRR [RRR=2.57, 95% CI (0.57, 8.54)] showed no significant difference for those aged ≥60 years compared to those aged 15-59 years (reference population). From these data, the systematic review concluded that: 1) there are data to support an increased risk of YEL-AVD among elderly travelers; and 2) the evidence of increased risk of YEL-AVD in older endemic population is undetermined.

In addition to the systematic review, two questions related to the use of yellow fever vaccine in elderly were as evaluated using GRADE: 1) Is there evidence that elderly individuals 60 years of age and older in endemic settings are at greater risk of YEL-AVD than those less than 60 years? and 2) Is there evidence that elderly travelers 60 years of age and older are at greater risk of YEL-AVD than those less than 60 years? Relative to the question on yellow fever vaccine use in elderly individuals living in endemic areas, the conclusion from GRADE found age-related tendencies between YEL-AVD and older age in endemic settings can be seen, yet the evidence is limited (Table 7). For yellow fever vaccine use in elderly travelers, the conclusion from GRADE was age-related tendencies showed an association between higher rates of serious adverse events after yellow fever vaccination in travelers ≥60 years than those <60 years (Table 8). Yet the evidence to support association is limited. Further research was felt to be necessary to support either hypothesis.

Working Group Discussion and Conclusions

The working group felt the main difference between endemic and traveler populations that might account for the higher rates of AEFIs in travelers is that travelers are more likely to be immune naïve to yellow fever virus (both vaccine and wild-type virus) and thus are potentially more "susceptible" to developing serious AEFIs than those living in endemic areas. The association between serious AEFIs, like YEL-AVD, and primary vaccination is likely due to the fact that primary vaccine recipients often become viremic following vaccination while viremia has not been documented in persons receiving a booster dose of yellow fever vaccine. A recent study also found more frequent viremia with a higher yellow fever vaccine RNA copy numbers in elderly when compared to younger naïve vaccine recipients [6]. In addition, there was also a delayed antibody response seen among the elderly. The authors hypothesized that slower antibody response and increase in viremia may lead to an increased risk of developing serious AEFI, such as YEL-AVD, and therefore could explain the higher rates of serious AEFI in the elderly population. Based on the current data, the working group concluded that caution be used when vaccinating persons aged ≥60 years who have not received the vaccine previously regardless if they live in an endemic area or not. They also concluded that further research is needed on this topic as well as exploring the age-specific rates of YEL-AND.

Recommendations: Based on the currently available data, it is advisable to recommend caution in vaccinating persons ≥60 years of age against yellow fever if they have not been previously vaccinated. A risk-benefit assessment for yellow fever vaccination should be performed for any person ≥60 years of age who has not been vaccinated but for whom the vaccine is recommended. The risk assessment should take into account risk of acquiring yellow fever disease (e.g., location, season, duration of exposure, occupational and recreational activities, and local rate of virus transmission in the potential area of exposure) versus the risk of a potential adverse event following immunization (e.g., age, underlying medical conditions, medications). Further research is needed to better quantitate the risk for vaccine recipients who is ≥60 years and might reside in or near a yellow fever endemic area.

References

1. Martin M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis. 2001; 7(6): 945-951.
2. Khromava AY, et al. Yellow fever vaccine: An updated assessment of advanced age as a risk factor for serious adverse events. Vaccine. 2005; 23(25): 3256-3263.
3. Lindsey NP, et al. Adverse event reports following yellow fever vaccination. Vaccine 2008; 26(48):6077-6082.
4. Rafferty E, et al. Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: A systematic review. *Manuscript in preparation*.
5. de Menezes Martins R, et al. Yellow fever vaccine post-marketing surveillance in Brazil. Procedia Vaccinol. 2010; 2(2): 178-183.
6. Roukens AH, et al. Elderly subjects have a delayed antibody response and prolonged viraemia following yellow fever vaccination: A prospective controlled cohort study. PLoS One. 2011; 6(12): e27753.
7. Gershman MD, et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2012; 30(33): 5038-5058.
8. Lawrence GL, et al. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell. 2004; 28(2): 244-248.
9. Monath TP, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin. 2005; 1(5): 207-214.
10. Fitzner J, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast. Vaccine. 2004; 23(2): 156-62.

11. Struchiner CJ, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect. 2004; 132(5): 939-946.
12. Belmusto-Worn VE, et al. Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru. Am J Trop Med Hyg. 2005; 72(2): 189-197.
13. Whittembury A, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine. 2009; 27: 5974-5981.
14. Breugelmans G, et al. Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010.Vaccine. Epub 2013 Feb 7.

Table 4. Number of yellow fever vaccine associated-viscerotropic disease cases by age group and by the Brighton viscerotropic case definition for diagnostic certainty and yellow fever vaccine causality [7] (*Table adapted from reference 4)*

Age group (years)	Traveler Population			Endemic Population			Total		
	Both*	One†	Neither‡	Both*	One†	Neither‡	Both*	One†	Reported
0-9	-¶	-	-	2	-	-	2	-	2
10-19	-	-	-	1	2	1	1	2	4
20-29	3	1	-	3	-	1	6	1	8
30-39	-	-	-	-	-	1	-	-	1
40-49	-	1	-	1	1	2	1	2	5
50-59	1	1	2	-	-	-	1	1	4
60-69	3	6	2	1	-	1	4	6	13
≥70	1	2	2	1	-	-	2	2	6
Subtotal <60 years	*4*	*3*	*2*	*7*	*3*	*5*	*11*	*6*	*24*
Subtotal ≥60 years	*4*	*8*	*4*	*2*	*-*	*1*	*6*	*8*	*19*
Total	**8**	**11**	**6**	**9**	**3**	**6**	**17**	**14**	**43**

*Both = met both diagnostic criteria (any level) AND causality (any level)

†One = met either diagnostic criteria (any level) OR causality (any level)

‡Neither = met neither diagnostic criteria (any level) OR causality (any level)

¶No cases

Table 5. Reporting rates (RRs) and reporting rate ratios (RRRs) based on the Brighton viscerotropic case definition for diagnostic certainty and yellow fever vaccine causality for yellow fever vaccine-associated viscerotropic disease (YEL-AVD) in elderly travel population (*Table adapted from reference 4)*

Reference	Population Years Surveillance type	Number of YEL-AVD cases	Original RR*	New RR* Diagnostic criteria	RRR* Diagnostic criteria	New RR* Causality	RRR* Causality
Martin et al. [1]	USA 1990-1998 Passive	4	serious AEFI 15-24 = 1.05 25-44 = 0.29 45-64 = 1.13 65-74 = 3.48 ≥75 = 9.06	15-24 = 0 25-44 = 0 45-64 = 0.23 65-74 = 1.16 ≥75 = 9.05	15-64 = Ref (n=1 357 434) ≥65 = 47.23 (95%CI 4.91, 454) (n=86 222)	15-24 = 0 25-44 = 0 45-64 = 0.26 65-74 = 0 ≥75 = 4.53	15-64 = Ref (n=1 357 434) ≥65 = 15.74 (95%CI 0.98, 252) (n=86 222)
Khromava et al. [2]	USA 1990-2002 Passive	7	YEL-AVD 1-18 = 0 19-29 = 0.2 30-39 = 0.3 40-49 = 0 50-59 = 0.3 60-69 = 1.1 ≥70 = 3.2	1-18 = 0 19-29 = 0.23 30-39 = 0 40-49 = 0 50-59 = 0 60-69 = 1.6 ≥70 = 3.2	<60 = Ref ≥60 = 34.49 (95%CI 4.03, 295)	1-18 = 0 19-29 = 0.2 30-39 = 0.3 40-49 = 0 50-59 = 0.3 60-69 = 1.1 ≥70 = 3.2	<60 = Ref ≥60 = 13.8 (95%CI 1.25, 152)
Lawrence et al. [8]	Australia 1993-2002 Passive	1	serious AEFI 15-24 = 0 25-44 = 2.49 45-64 = 8.21 ≥65 = 22.26	15-24 = 0 25-44 = 0 45-64 = 2.05 ≥65 = 0	<65 = Ref ≥65 = 0 (95%CI 0, 427)	15-24 = 0 25-44 = 0 45-64 = 2.05 ≥65 = 0	<65 = Ref ≥65 = 0 (95%CI 0, 427)
Monath et al. [9]	UK 1995-1999 Active/Passive	Unknown	serious AEFI <15 = 0 15-24 = 2.09 25-44 = 3.05 45-64 = 5.55 65-74 = 8.58 ≥75 = 0	NA†	NA	NA	NA
Lindsey et al. [3]	USA 2000-2006 Passive	6	YEL-AVD ≤18 = 0 19-29 = 0.5 30-39 = 0 40-49 = 0	NA	NA	NA	NA

	50-59 = 0 60-69 = 1.0 ≥70 = 2.3

* by age group in years and reports per 100,000 doses

† Not available (e.g., not enough information available to perform the calculations)

Table 6. Reporting rates (RRs) and reporting rate ratios (RRRs) based on the Brighton viscerotropic case definition for diagnostic certainty and yellow fever vaccine causality for yellow fever vaccine-associated viscerotropic disease (YEL-AVD) in elderly endemic population (*Table adapted from reference 4)*

Reference	Population Years	Number of YEL-AVD cases	Original RR*	New RR*	RRR*
De Menezes Martins et al. [5]	Brazil 1999-2009	20	YEL-AVD <1 = 0 1 = 0 2 = 0 3 = 0.053 4 = 0.098 5-9 = 0.018 10-14 = 0.017 15-59 = 0.019 ≥60 = 0.047	NA†	15-59 = Ref ≥60 = 2.53 (95%CI 0.56, 8.54)
Fitzner et al. [10]	Ivory Coast 2001	0	YEL-AVD 0	0	0
Struchiner et al. [11]	Brazil 1991-2001 1998-2001	4	YEL-AVD 0.0056 to 0.213	NA	NA
Belmusto-Worn et al. [12]	Peru No year	0	YEL-AVD 0	0	0
Whittembury et al. [13]	Peru 2007	5	YEL-AVD 7.9	6.3	NA
Breugelmans et al. [14]	Benin, Cameroon, Liberia, Mali, Senegal, Sierra Leone 2007-2010	5	YEL-AVD 0.013	NA	NA

* by age group in years and reports per 100,000 doses

† Not available (e.g., not enough information to be able to classify cases based on the Brighton case definition or to perform the calculations)

GRADE Table 7. Yellow fever vaccination in elderly living in endemic areas

Population: Elderly individuals ≥ 60 years of age in endemic settings
Intervention: Yellow Fever Vaccination ≥ 60 years of age
Comparison: Yellow Fever Vaccination < 60 years of age
Outcome: Yellow Fever vaccine-associated viscerotropic disease

Is there evidence that elderly individuals 60 years of age older in endemic settings are at greater risk of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) than those younger than 60 years?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ 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	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 outcome is limited.**
	Conclusion			**Age-related tendencies between YEL-AVD and older age in endemic settings can be seen, yet the evidence to support association between older age and YEL-AVD in endemic populations is limited. Further research is needed to support the hypothesis.**

[1] Only 1 observational study reported a non-significant relation of increased YEL-AVD incidence for elderly in an endemic population (Martins RdM et al. 2010). Some additional trials included reports of YEL-AVD in elderly, but these are either in non-endemic populations or do not include age-related analysis (Martin et al.2001, Monath et al.2005; Lawrence et al 2004; Lindsey et al. 2008, Khromava et al.2005, Fitzner et al. 2004; Struchiner et al. 2004; Whittembury et al.2009).

Reference List for GRADE table 7

(1) Fitzner J, Coulibaly D, Kouadio DE, Yavo JC, Loukou YG, Koudou PO, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast, 1. Vaccine 2004 Nov 25;23(2):156-62.$

(2) Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005 May 9;23(25):3256-63.

(3) Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell 2004;28(2):244-8.

(4) Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination, 1. Vaccine 2008 Nov 11;26(48):6077-82.

(5) Martin M, Weld LH, Tsai TF, Mootrey GT, Chen RT, Niu M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis 2001 Nov;7(6):945-51.

(6) Martins RdM, Maia MdLd, Santos EMd, Cruz RLd, dos Santos PR, Carvalho SMD, et al. Yellow Fever Vaccine Post-marketing Surveillance in Brazil. Procedia in Vaccinology 2010;2(2):178-83.

(7) Monath TP, Cetron MS, McCarthy K, Nichols R, Archambault WT, Weld L, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin 2005 Sep;1(5):207-14.

(8) Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JG, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect 2004 Oct;132(5):939-46.

(9) Whittembury A, Ramirez G, Hernandez H, Ropero AM, Waterman S, Ticona M, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine 2009 Oct 9;27(43):5974-81.

GRADE Table 8. Yellow fever vaccination in elderly travelers

Population: Elderly travelers ≥ 60 years of age
Intervention: Yellow Fever Vaccination ≥ 60 years of age
Comparison: Yellow Fever Vaccination < 60 years of age
Outcome: Yellow Fever vaccine-associated viscerotropic disease

Is there evidence that elderly travelers 60 years of age and older are at greater risk of yellow fever vaccine-associated viscerotropic disease (YEL-AVD) than those younger than 60 years?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ observational[1]	2
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None Serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[3]	1
		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 outcome is limited.**
	Conclusion			**Age-related tendencies showing association between higher rates of serious adverse events after yellow fever vaccination in travelers can be seen. Yet the evidence to support association between older age and YEL-AVD in travelers is limited. Further research is needed to support the hypothesis.**

[1] Two observational studies reported reporting rate ratio of YEL-AVD in elderly travelers (Khormava et al.2005, Lindsey et al.2008). Some additional trials included reports of YEL-AVD in elderly, but either in endemic settings or no age-related analysis (Martin et al.2001, Martins RdM et al. 2010, Monath et al.2005; Lawrence et al 2004;,Fitzner et al. 2004; Martins et al. Struchiner et al. 2004; Whittembury et al.2009*)*.
[2] Source of data was from passive public health surveillance. Reporting rate ratio possibly overestimated if the true rate for elderly travelers increased since 1998.
[3] RRR significantly higher compared to reference group 5.9 (95%CI 1.6-22.2) for 60-69 years of age and 10.4 (95%CI 2.7-40.2) for ≥70 years (Khormava et al.2005).

Reference List for GRADE table 8

(1) Fitzner J, Coulibaly D, Kouadio DE, Yavo JC, Loukou YG, Koudou PO, et al. Safety of the yellow fever vaccine during the September 2001 mass vaccination campaign in Abidjan, Ivory Coast 1. Vaccine 2004 Nov 25;23(2):156-62.

(2) Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005 May 9;23(25):3256-63.

(3) Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell 2004;28(2):244-8.

(4) Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination, 1. Vaccine 2008 Nov 11;26(48):6077-82.

(5) Martin M, Weld LH, Tsai TF, Mootrey GT, Chen RT, Niu M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis 2001 Nov;7(6):945-51.

(6) Martins RdM, Maia MdLd, Santos EMd, Cruz RLd, dos Santos PR, Carvalho SMD, et al. Yellow Fever Vaccine Post-marketing Surveillance in Brazil. Procedia in Vaccinology 2010;2(2):178-83.

(7) Monath TP, Cetron MS, McCarthy K, Nichols R, Archambault WT, Weld L, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin 2005 Sep;1(5):207-14.

(8) Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JG, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect 2004 Oct;132(5):939-46.

(9) Whittembury A, Ramirez G, Hernandez H, Ropero AM, Waterman S, Ticona M, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine 2009 Oct 9;27(43):5974-81.

Use of yellow fever vaccine in HIV-infected persons

Key Findings

- Data on the safety and immunogenicity of yellow fever vaccines in HIV-positive persons are from a limited number of small studies and case reports, mainly among travelers with CD4 counts >200 cells/mm^3.
- Monitoring vaccination campaigns in countries where the prevalence of HIV is about 1–5% has identified only a few HIV-positive individuals among those with any serious AEFI.
- Data suggest that the immunologic response to yellow fever vaccine in HIV-infected individuals wanes more rapidly than non-infected vaccinated persons.

Language below is from the Weekly Epidemiological Record (No. 5, 2011, 86, 37–44) that summarized the GACVS Meeting from December 2010 where yellow fever vaccine use in HIV-infected persons was discussed [1]. The benefits of mass vaccination campaigns for yellow fever are recognized in endemic countries, and millions of individuals are vaccinated against the disease every year in countries where the prevalence of HIV is 1–5% among those aged 15–49 years. In many places access to laboratory testing and other resources for diagnosing and treating HIV infection is poor, and many people with undiagnosed advanced HIV infection are likely to have received the vaccine.

Published studies on the safety and immunogenicity of yellow fever vaccines in HIV-positive people are limited to small studies and case reports, mainly of travelers with CD4 counts >200 cells/mm^3. With the exception of 1 case of fatal meningoencephalitis, these studies did not detect any other serious [AEFI] among HIV-positive individuals. However, little evidence has accumulated about the safety of this vaccine in people with advanced HIV infection. Data about the immune response to the vaccine are scarce but show consistent immunogenicity in HIV positive people with CD4 [counts] >200 cells/mm^3.

In West and Central Africa, between 2007 and 2010, 10 countries undertook vaccination campaigns against yellow fever, during which about 50 million people were vaccinated. In these countries, surveillance efforts have been implemented in collaboration with national health authorities and local expert committees. Analyses of the safety data are continuing in 7 countries, but so far around 194 serious AEFI have been reported, and more than three quarters of patients have been tested for HIV. Only a few individual cases of serious AEFI have occurred in HIV-positive individuals. Similar findings have been reported from vaccination campaigns in Latin America.

In summary, monitoring vaccination campaigns in countries where the prevalence of HIV is about 1–5% has identified only a few HIV-positive individuals among those with any serious AEFI; no clear risk has been identified that precludes the use of yellow fever vaccine in people infected with HIV. However, the sensitivity of these studies to detect serious AEFI has not been established. In addition, GACVS is awaiting data about the completeness of case investigation, the classification of serious AEFI and the HIV status of those cases.

No changes have been suggested by GACVS to WHO's recommendation that individuals known to be severely immunocompromised should not receive yellow fever vaccine; the available data do not identify a significant problem with mass vaccination in populations where a moderate proportion of individuals are HIV-positive. However, GACVS strongly recommends that additional data on safety and immunogenicity should be obtained on the effect of vaccination in HIV-positive individuals, and

especially in those with advanced HIV infection. Also, additional clinical studies of yellow fever vaccines administered to HIV-positive individuals should be conducted.

Working Group Discussions and Conclusions

The working group reviewed published and unpublished data from the large preventive campaigns that have been conducted in West and Central Africa [2]. These data did not suggest additional safety concerns beyond those noted by GAVCS previously. The working group also reviewed new data on the immunologic response to yellow fever vaccine in HIV-infected travelers. In a recent retrospective cohort study, 65 (83%) of 78 HIV-infected persons developed specific antibodies against yellow fever virus in the first year after vaccination; however this was significantly lower than vaccinated persons without HIV infection (97%, 64/66) [3]. An older study noted that, only 3 (17%) of 18 HIV-infected infants in developing nations developed yellow fever virus-specific neutralizing antibodies within 10 months of vaccination compared to 42 (74%) of 57 HIV-uninfected controls matched for age and nutritional status [4]. The mechanisms for the diminished immune response in HIV-infected persons are uncertain but appear to be correlated with HIV RNA levels and CD4+ cell counts [5]. Further studies are required to assess the relevance of these findings.

Recommendations: *[Maintain current language]* Yellow fever vaccine is contraindicated for severely immunocompromised persons, including persons with AIDS or CD4+ counts < 200 cells/mm^3. Yellow fever vaccination may be offered to asymptomatic HIV-infected persons with CD4+ counts ≥200 cells/mm^3 who require vaccination. Additional data on safety and immunogenicity should be obtained on the effect of vaccination in HIV-positive individuals.

References

1. World Health Organization. Meeting of the Global Advisory Committee on Vaccine Safety, December 2010: Yellow fever vaccine and HIV infection. Wkly Epidemiol Rec. 2011; 86 (5): 37–44.
2. Sidibe M, et al. Immunogenicity and safety of yellow fever vaccine among 115 HIV-infected patients after a preventive immunisation campaign in Mali. Trans Roy Soc Trop Med Hyg. 2012 Jul; 106(7): 437-444.
3. Veit O, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. Clin Infect Dis. 2009; 48: 659-666.
4. Sibailly TS, et al. Poor antibody response to yellow fever vaccination in children infected with human immunodeficiency virus type 1. Pediatr Infect Dis J. 1997; 16: 1177-1179.
5. Veit O, et al. Yellow fever vaccination in HIV‐infected patients. HIV Ther. 2010; 4(1): 17–26.

Use of yellow fever vaccine in persons with immunocompromising conditions (other than HIV)

Key Findings

- The contraindication of yellow fever vaccine in persons with immunocompromising conditions is based on historical experience with vaccines as a whole rather than yellow fever vaccine specifically.
- There are limited data on the safety and immunogenicity of yellow fever vaccine in persons with specific immunocompromising conditions.

Although there have been case reports and case series published regarding the safe use of yellow fever vaccine in immunocompromised persons, clinical trials with control groups and appropriate surveillance data with clear numerator and denominator data are lacking. The rationale behind contraindicating yellow fever vaccine in immunocompromised persons is based on historical experience with live attenuated vaccines, rather than yellow fever vaccine specifically, and is from the observation that immunocompromised persons may not mount an appropriate immune response to live vaccines and thus the vaccine could cause disease similar to the wild-type disease it is meant to prevent. The only condition where yellow fever vaccine has been associated with an increased risk of serious AEFIs is thymus disease. Four (17%) of the initial 23 YEL-AVD reported cases were noted to occur in persons who had had thymectomies performed for thymomas [1].

Currently, all yellow fever vaccine manufacturers note that yellow fever vaccine is contraindicated in immunocompromised individuals in their package inserts. They note that yellow fever vaccine poses a risk of encephalitis or other serious adverse events to patients with illnesses that commonly results in immunosuppression or patients whose immunologic responses are suppressed by treatments/drugs. Furthermore, they note that persons with a history of thymus dysfunction should not be vaccinated.

Working Group Discussion and Conclusions

The working group reviewed available data on the use of yellow fever vaccine in persons with immunocompromising conditions and did not find any evidence to change the current recommendation that contradicts the use of yellow fever vaccine in persons who are severely immunocompromised. The working group did, however, think that additional clarity is warranted about the specific conditions that might contraindicate or require special caution for the use of yellow fever vaccine. The working group considered the following conditions and treatments to be severely immunocompromising:

1. Severe primary immunodeficiencies (i.e., conditions affecting IgG and/or T cell responses)
2. Thymus disorder
3. Symptomatic HIV-infection or CD4+ T-lymphocyte values < 200 per mm^3 (*see previous section*)
4. Malignant neoplasm being treated with chemotherapy
5. Recent (< 2 years) hematopoietic stem cell transplantation
6. Drugs with known immunosuppressive or immunomodulatory properties (e.g., high-dose systemic corticosteroids*, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent, or other monoclonal antibodies targeting immune cells)
7. Current or recent radiation therapies that target immune cells

* Dose of either ≥2 mg/kg of body weight or a total ≥ 20 mg/day of prednisone or its equivalent for persons who weigh >10 kg when administered for ≥2 weeks is considered sufficiently immunosuppressive to contraindicate the use of live-attenuated vaccines. Corticosteroids are not a contraindication when administration is under any of the following circumstances: short-

term (i.e., < 2 weeks); a low-to-moderate dose (<20 mg of prednisone or its equivalent per day); long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy); or administered topically (skin or eyes), inhaled, or by intra-articular, bursal, or tendon injection.

Recommendations: [*Maintain current wording from 2003 position paper but further clarify possible immunocompromising conditions*] Contraindications against yellow fever vaccination include… severe immunodeficiency. Conditions and treatments that would be considered severely immunocompromising include: certain primary immunodeficiencies, thymus disorder, symptomatic HIV-infection or CD4+ T-lymphocyte values < 200 per mm^3, malignant neoplasm treated with chemotherapy, recent hematopoietic stem cell transplantation, drugs with known immunosuppressive or immunomodulatory properties (e.g., high-dose systemic corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent, or other monoclonal antibodies targeting immune cells), and current or recent radiation therapies targeting immune cells.

References

1. Barwick R. History of thymoma and yellow fever vaccination. Lancet. 2004; 364: 936.

Use of yellow fever vaccine in pregnant women

Key Findings

- Based on the available albeit limited data, yellow fever vaccine is believed to represents minimal risk to a pregnant woman and her fetus.
- Immune response to yellow fever vaccine may be suboptimal for pregnant women and may depend on the timing of vaccination during pregnancy.

There are no specific data on the yellow fever disease risk for pregnant women and their fetuses. However, from available surveillance and outbreak data, pregnant women do not appear to be at risk for more severe yellow fever disease.

The use of yellow fever vaccine during pregnancy has not been studied in a large prospective trial. Limited data are available from several small studies where pregnant women were either inadvertently vaccinated or given the vaccine in outbreak settings. Since the last position paper, two studies have been published regarding yellow fever vaccine and pregnant women [1, 2]. In the first study, 304 infants born to women who were vaccinated with yellow fever vaccine early in their pregnancies were examined for malformations [1]. There was no increased risk of major malformations found. However, there was an increased risk for minor malformations (e.g., pigmented nevi) but the authors suggested that the finding could have resulted from assessment bias. The second study involved the same mother-child cohort and it did not find an increased risk of fetal death (7.4/1,000 in vaccinated women versus 18.5/1,000 unvaccinated women in the general population) among 441 women inadvertently vaccinated early in their pregnancy [2]. These findings do not support an earlier study that suggested a potential increased rate of spontaneous abortions among pregnant women who received the vaccine [relative risk of 2.3 (95% confidence intervals 0.7-8.0)] [3].

The second study also examined the rates of yellow fever virus IgG antibodies formed in pregnant women and found that 98% of 433 women vaccinated predominantly in the first trimester developed IgG antibodies [2]. These findings differ from that of a previous study which found only 39% of 101 pregnant women receiving yellow fever vaccine predominantly in their third trimester had evidence of seroconversion to yellow fever virus [4]. These findings suggest that proportion of women vaccinated during pregnancy who develop antibodies against yellow fever is variable and may be related to trimester in which they received vaccine.

Recommendations: [*Maintain wording from 2003 position paper*] On theoretical grounds, [yellow fever] vaccine is not recommended during pregnancy. However, pregnant women may be vaccinated during epidemics when the risk of yellow fever virus transmission may be very high.

References

1. Cavalcanti DP, et al. Early exposure to yellow fever vaccine during pregnancy. Trop Med Int Health. 2007; 12: 833-837.
2. Suzano CE, et al. The effects of yellow fever immunization (17DD) inadvertently used in early pregnancy during a mass campaign in Brazil. Vaccine. 2006; 24: 1421-1426.
3. Nishioka Sde A, et al. Yellow fever vaccination during pregnancy and spontaneous abortion: a case-control study. Trop Med Int Health. 1998; 3: 29-33.
4. Nasidi A, et al. Yellow fever vaccination and pregnancy: a four-year prospective study. Trans R Soc Trop Med Hyg. 1993; 87(3): 337-339.

Use of yellow fever vaccine in lactating women

Key Findings

- Three infants less than 6 weeks of age developed encephalitis as a result of infection with yellow fever vaccine virus potentially transmitted to them via breastfeeding from their recently-vaccinated mothers.
- Potential risk of transmission may vary depending on whether mothers are vaccinated for the first time or have been previously vaccinated.

Language below is from the Weekly Epidemiological Record (No. 30, 2010, 85, 285–292) that summarized the GACVS Meeting from June 2010 where the use of yellow fever vaccine and breastfeeding was reviewed [1].
The [GACVS] reviewed recent data suggesting that 3 neonates (aged 10 days, 23 days and 5 weeks) developed encephalitis as a result of infection with yellow fever vaccine virus transmitted to them from their recently-vaccinated mothers. All 3 infants were being breastfed, but the mode of transmission has not been established. All 3 mothers had received the vaccine for the first time during the infant's first month of life. Further research is needed to quantify the potential risk of transmission of yellow fever vaccine virus from mothers to infants, including the possibility of transmission through breast milk.

Mass vaccination campaigns being conducted in West Africa provide an opportunity to conduct studies that will clarify these issues. Such studies might test breast milk from vaccinated mothers for the presence of vaccine virus, and test infants for evidence of seroconversion to the vaccine virus. The potential risk of transmission may vary depending on whether mothers are vaccinated for the first time or have been previously vaccinated.

In areas where yellow fever is endemic, or during outbreaks, the Committee believes that the benefits of vaccinating nursing mothers are likely to far outweigh the risk of potential transmission of vaccine virus to infants; the Committee also believes that the benefits of breastfeeding far outweigh the alternatives for infant feeding. Nursing mothers who are considering travel to endemic areas should be counseled regarding the benefits and potential risks of vaccination. Vaccination is recommended if vaccination is indicated for a breastfeeding woman and travel cannot be avoided or postponed.

Working Group Discussion and Conclusions
The working group reviewed the available literature, which included published case reports for each of the cases reviewed by GACVS [2, 3, 4]. The working group agreed with GACVS' assessment, recommendations, including the call for more study on yellow fever vaccine use among breastfeeding women.

Recommendations: *[Per GAVCS]* In areas where yellow fever is endemic, or during outbreaks, the benefits of vaccinating nursing mothers are likely to far outweigh the risk of potential transmission of vaccine virus to infants. Nursing mothers who are considering travel to endemic areas should be counseled regarding the benefits and potential risks of vaccination. Vaccination is recommended if vaccination is indicated for a breastfeeding woman and travel cannot be avoided or postponed.

References

1. World Health Organization. Global Advisory Committee on Vaccine Safety, 16–17 June 2010: Yellow fever vaccine and breastfeeding. Wkly Epidemiol Rec. 2010; 85 (30): 285–292.

2. Centers for Disease Control and Prevention. Transmission of yellow fever vaccine virus through breast-feeding — Brazil, 2009. MMWR. 2010; 59(5): 130-132.
3. Kuhn S, et al. Case report: probable transmission of vaccine strain of yellow fever virus to an infant via breast milk. CMAJ. 2011; 183(4): E243-E245.
4. Traiber C, et al. Infant meningoencephalitis caused by yellow fever vaccine virus transmitted via breast milk. J Pediatr (Rio J). 2011; 87(3): 269-272.

Co-administration of yellow fever and other vaccines

Key Findings

- Co-administration of yellow fever vaccine and other vaccines typically has no impact on safety.
- Co-administration of yellow fever vaccine and other vaccines generally elicits a good immune response to yellow fever; notable exception is combined measles, mumps, and rubella vaccine.
- Additional co-administration studies are needed yellow fever vaccine with several vaccines where co-administration data are lacking or incomplete.

Data were reviewed by the working group from both published and unpublished literature regarding the safety and immunogenicity of yellow fever vaccine when co-administered (given on the same day but in different locations and in different syringes) with other vaccines. Yellow fever vaccine co-administration has been studied for at least unique 17 antigens (Table 9). Twenty-eight published articles or abstracts on the co-administration of yellow fever vaccine were identified since 1964, which includes articles on the co-administration with 10 inactivated vaccines and 10 live-attenuated vaccines (*see more specific report on web for more details*). There are also several (n=11) available vaccines for which there are no co-administration data available (Table 9).

Based on the available data for inactivated vaccines (Table 10), there are no safety concerns with the co-administration of yellow fever vaccine and inactivated vaccines. Immunogenicity for most vaccines appears not to be compromised when yellow fever vaccine is co-administered with inactivated vaccines. Potential limitations of the studies include: 1) most studies were conducted several decades ago, using different vaccine preparation than what might be currently available; 2) individual studies often contained low number of subjects; 3) studies do not include all potential targeted populations (e.g., children or adults); and 4) no studies were performed in special populations.

Based on the available data for co-administration of yellow fever vaccine with other live-attenuated vaccines (Table 11), there are no safety concerns with co-administration with most vaccines. However, data from two studies on the co-administration of yellow fever vaccine and a dengue chimeric vaccine based on the yellow fever vaccine backbone found increased rates of both systemic and local adverse events [1, 2]. Although there was no increase in serious adverse events noted, there was limited power to detect serious AEFIs. Immunogenicity for most vaccines is also not compromised when yellow fever vaccine is co-administered with other live-attenuated vaccines. The most notable exception was with the co-administration of yellow fever vaccine and the combined measles, mumps, and rubella vaccine (MMR) to children 12-23 months of age [3]. The study found a significant decrease in the seroconversion rates and geometric mean titers obtained against yellow fever, mumps, and rubella when the vaccines were co-administered versus administered 28 days apart; no decreases were noted in the immune response to measles. Another exception was from a study involving persons who received yellow fever vaccine one year before the chimeric tetravalent dengue vaccine based on the yellow fever vaccine backbone [4]. The study found an initial delay in the antibody response to dengue 1 among yellow fever vaccine-primed persons. Potential limitations of the studies on the co-administration of yellow fever vaccine and live vaccines are similar to those noted for inactivated vaccines.

Working Group Discussion and Conclusions

In reviewing available data, the working group found that co-administration of yellow fever vaccine and other vaccines typically have no impact on safety and generally elicit a good immune response to yellow

fever vaccine. A notable exception is the co-administration of MMR vaccine and yellow fever vaccine where immune response is decreased to several antigens when they are co-administered versus administered 28 days apart. The working group suggests additional studies are needed on the co-administration of yellow fever vaccine and vaccines that are likely to be given at the same time as yellow fever vaccine and where there are no, limited, or conflicting data. Priority co-administration studies identified by the group include:

1. MMR vaccine – Only study performed showed decrease immune response to several antigens [3]. MMR will be increasing used in yellow fever endemic countries and based on current timing of measles vaccine, these vaccines will be co-administered.
2. Meningococcal A or quadrivalent meningococcal vaccine – Currently there are no or very limited data on the co-administration with yellow fever vaccine. It is expected that yellow fever and meningococcal vaccines will be co-administered in the EPI of several African countries where both diseases are endemic or prone to causing epidemic disease. *Note: One study has been conducted but the results are currently pending.*
3. Other considerations: Haemophilus influenzae b (Hib) and pneumococcal vaccines are being increasing used in the EPI and final doses in the series for these vaccines may coincide with yellow fever vaccine delivery. Malaria and dengue vaccines are in development but once available are likely to be used in the same populations (endemic and travelers) and may be co-administered with yellow fever vaccine.

Recommendations: Currently available data suggest that there is minimal impact on the reactogenicity and immunogenicity when yellow fever vaccine is co-administered with other vaccines. One notable exception is the co-administration of yellow fever vaccine and MMR vaccine in young children, where immunogenicity appears to be compromised against several antigens. Additional studies are warranted on the co-administration of yellow fever vaccine and other vaccines, in particularly MMR and meningococcal A vaccines.

References

1. Poo J, et al. Live-attenuated tetravalent dengue vaccine in dengue-naïve children, adolescents, and adults in Mexico City. Pediatr Infect Dis. 2011; 30: e9-e17.
2. Guirakhoo F, et al. Live attenuated chimeric yellow fever dengue type 2 (ChimeriVax-DEN2) vaccine: phase I clinical trial for safety and immunogenicity: effect of yellow fever pre-immunity in induction of cross neutralizing antibody responses to all 4 dengue serotypes. Hum Vaccin. 2006; 2: 60-67.
3. Nascimento Silva JR, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps, and rubella. Vaccine. 2011; 29: 6327-6334.
4. Qiao M, et al. Priming effect on dengue and yellow fever vaccination on the immunogenicity, infectivity, and safety of a tetravalent dengue vaccine in humans. Am J Trop Med Hyg. 2011; 85: 724-731.

Table 9: Vaccines either studied or available for co-administration with yellow fever vaccine listed by whether data are present on co-administration

Data present		*No data available*
Inactivated Vaccines	***Live (attenuated) vaccines***	
Cholera*	Bacillus Calmette-Guérin (BCG)	Anthrax
Diphtheria	Cholera*	Haemophilus Influenzae b; Hib
Hepatitis A	*Dengue chimera - recruiting*	Human papillomavirus
Hepatitis B	Measles	Influenza (lv)*
Influenza*	Mumps	Japanese encephalitis (iv)*
Meningococcal - *recruiting*	Japanese encephalitis chimera*	*Malaria - recruiting*
Polio*	Polio*	Pneumococcal
Pertussis	Rubella	Rabies
Tetanus	Smallpox	Rotavirus
Typhoid*	Typhoid*	Tick-borne encephalitis
		Varicella/Zoster

* Both live and inactivate forms of vaccine; Abbreviations: iv = inactivated viral; lv = live viral; *Italic* indicate vaccines not yet licensed; ClinicalTrials.gov was used to determine if there were on-going studies and are indicated with “recruiting”

Table 10: Immunogenicity and reactogenicity of yellow fever (YF) vaccine and inactivated vaccines

Vaccines[*]	# of Studies	Years studies published	# of subjects (type)[†]	Immune Response YF Vaccine[‡]	Reactogenicity[¶]	Immune Response Other Vaccine[‡]
Cholera	2	1973, 1986	500 A predominantly	50%	+	50%
Diphtheria	3	1973, 1986 (2)	800 A/C	+	+	+
HepA	5	1993, 1996 (2), 1997, 1999	650 A only	+	+	90%
HepB	2	1986 (2)	400 C only	75%	+	+
Influenza	1	1993	65 A only	+	Not assessed	78-80%
Meningococcal	1[§]	1996	Unknown A only	(+)	(+)	(+)
Pertussis	1	1973	550 C only	+	+	+
Polio	2	1986 (2)	450 A/C	+	+	Not assessed
Tetanus	4	1973 (2), 1986 (2)	1405 A/C	+	+	50%
Typhoid	3[§]	1996, 1997, 2002	360 A only	+	+	+

[*] Listed by antigen component rather than specific vaccines; the specific vaccine and manufacturer often varied between studies;
[†] type of subjects: A=adults; C=children (definition of children variable by study but typically less than 18 years of age);
[‡] + = No difference between co-administration immune response and immune response administered non-simultaneously or in some cases seroconversion rates of higher than 90% for participants receiving co-administered vaccines, ##% indicates the decrease from vaccines administered "alone" or proportion that showed seroconversion, ( ) = specific data not given;
[¶] + No impact on safety profile when co-administered, ( ) = specific data not given;
[§] Indicates that at least one of the studies was a published abstract from a meeting rather than data from a full manuscript

Table 11: Immunogenicity and reactogenicity of yellow fever (YF) vaccine and other live-attenuated vaccines

Vaccines*	# of studies	Year studies published	# of subjects (type)†	Immune Response YF Vaccine‡	Reactogenicity¶	Immune Response Other Vaccine‡
BCG	1	1973	600 C only	+	+	(+)
Cholera	1	1997	150 A only	+	+	+
Dengue Chimeric	3	2006 (2), 2011	217 A/C	(+)	(-)	+
JE Chimeric	2	2003, 2010	120 A only	(+)	+	50%
Measles (Only)	8	1973 (2), 1986, 1989, 1990, 1991, 1996, 1999	2000 C only	+	+	+
MMR	1	2011	1828 C only	-	+	66%
Polio	2	1984, 1986	440 A only	+	+	Not assessed
Smallpox	4	1964, 1972, 1973 (2)	2000 A/C	+	+	(+)
Typhoid	2§	1996, 1997	150 A only	+	+	+

* Listed by antigen component rather than specific vaccines; the specific vaccine and manufacturer often varied between studies;
† type of subjects: A=adults; C=children (definition of children variable by study but typically less than 18 years of age);
‡ + = No difference between co-administration immune response and immune response administered non-simultaneously or in some cases seroconversion rates of higher than 90% for participants receiving co-administered vaccines, - = Statistically significant decrease in the immune response when vaccines is co-administered, ##% indicates the decrease from vaccines administered "alone" or proportion that showed seroconversion, ( ) = specific data not given;
¶ + No impact on safety profile when co-administered, - Significant impact (worsening) of the safety profile when co-administered, ( ) = specific data not given;
§ Indicates that at least one of the studies was a published abstract from a meeting rather than data from a full manuscript

Impact of vaccination strategies on the control of yellow fever

Key Findings

- Data from yellow fever endemic countries support the combined use of yellow fever vaccine through Expanded Program on Immunization (EPI) and mass vaccination campaigns as an effective approach to prevent yellow fever and control outbreaks of the disease.
- There is a continued need to improve and strengthen yellow fever disease surveillance and improve vaccination coverage.
- Current yellow fever vaccination strategies are cost-effective and the costs do not vary substantially between the various strategies (e.g., EPI, preventive, or reactive campaigns).
- Vaccine supply issues need to be considered when determining the optimal vaccination strategies.

The WHO-recommended control strategy for yellow fever centers on preventing, detecting and controlling outbreaks [1, 2]. This strategy includes ensuring the quality and sensitivity of the epidemiological surveillance system for yellow fever and delivery of yellow fever vaccine through systematic organized programmes, such as the EPI, or mass prevention and response campaigns.

Yellow fever vaccination in routine EPI

Immunization against yellow fever through EPI is an effective strategy for disease control [1]. Significant progress had been made since 1998 when WHO and UNICEF recommended introducing yellow fever vaccine into the routine immunization schedule of countries considered to be at risk. By 2008, 23 of the 33 yellow fever endemic countries in the African Region and 9 of the 13 endemic countries in American Region were offering yellow fever vaccine through EPI. Although gap between coverage of yellow fever vaccine and measles vaccine is decreasing, EPI coverage rates have varied by country and in certain countries is <50% [1]. One major limitation to the EPI coverage has been shortages of the vaccine [1, 2].

Preventive mass vaccination campaigns

Immunization against yellow fever through EPI requires several years to raise population immunity to a level that is sufficient to prevent outbreaks. To obtain faster and broader population coverage, routine (EPI) immunization may be complemented by preventive mass immunization campaigns. This combined strategy (routine EPI plus preventive campaigns) has proved to be highly effective in reducing the mortality and morbidity associated with yellow fever and reducing the risk of outbreaks [1, 2]. A good example of this approach has been in The Gambia that had several large outbreaks of yellow fever disease including one in 1978 when 271 cases and 63 deaths were reported [3]. Estimations from subsequent studies suggested that there were likely more than 8,000 cases and 1,700 deaths in the 1978 outbreak. Following this outbreak a mass campaign vaccination targeting the whole country was conducted with a vaccine coverage > 95%. Starting in 1979, yellow fever vaccine was introduced into the EPI for children > 9 months. In 2009, 96% coverage was reported. Despite ongoing risk that has been documented through unvaccinated travelers to Gambia becoming ill with yellow fever, no autochthonous cases have been reported in the country since 1978.

In 2005, the GAVI Alliance invested US$ 58 million to decrease the risk of yellow fever epidemics in Africa by vaccinating millions of people in 12 African countries (Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Ghana, Guinea, Liberia, Mali, Nigeria, Senegal, Sierra Leone and Togo) [1]. To date 11 of the original 12 countries as well as Central Africa Republic have undergone preventive mass vaccination campaigns. Nigeria is the only remaining country to have a preventative mass vaccination campaign mostly due to larger than anticipated vaccine needs. The country is currently scheduled to undergo a mass vaccination campaign from 2013-2016. The same preventive mass vaccination campaign strategy has been used as well in the American Region, namely in Bolivia, Brazil, and Peru. As was seen with The Gambia, there have been no outbreaks reported in areas receiving preventive campaigns.

Reactive mass vaccination campaigns

Reactive mass vaccination campaigns have been successful in the past years at controlling outbreaks of yellow fever disease in places with inadequate vaccination coverage [1]. There is currently an emergency vaccine stockpile of roughly 6 million doses funded by the GAVI Alliance, which allows for a more effective response to outbreaks. Since 2007, the vaccine stockpile has been used by a number of countries that experienced an outbreak of the disease in areas where the disease has been silent for decades, such as Southern Brazil, Paraguay, Sudan, and Uganda. In each instance, no subsequent cases of the disease were noted among vaccinated persons following the reactive campaigns. However, with the outbreaks in Brazil and Paraguay in 2008, the vaccine stockpile was depleted by February of that year. Although the stockpile was eventually restocked in the following months, this situation stressed the need for countries to: 1) continue to optimize their current vaccine coverage in populations at risk; and 2) develop a national stock of vaccine in areas where significant proportions of their population are outside the endemic area and therefore are unvaccinated (e.g., the Americas).

Cost-effectiveness of the various vaccination strategies

Following a review of the various vaccination strategies that are available, the working group assessed the cost of each strategy to determine if any of the strategies are more cost-effective or cost-prohibitive. Although older data suggest differential costs between EPI and reactive (outbreak control) vaccination strategies, current available data suggest that cost per dose of yellow fever vaccine is similar for various strategies. Cost was estimated to be approximately US$ 0.67/dose for each strategy but the breakdown of cost (e.g., cold chain, vaccine price) varied based on strategy. Given these data, it was decided that vaccine utilization strategies should be driven by factors other than cost (e.g., vaccine availability).

Recommendations: Control strategy for yellow fever should include sound epidemiologic surveillance and delivery of yellow fever vaccine through a complementary and optimized combination of EPI and mass preventive campaigns. Reactive campaigns should be conducted in response to yellow fever outbreaks if there is inadequate vaccination coverage within the population.

References

1. World Health Organization. Update on progress controlling yellow fever in Africa, 2004–2008. Wkly Epidemiol Rec. 2008; 83(50): 450–458.

2. Pan American Health Organization. XVIII Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases – Final Report 2009. Available at: http://www2.paho.org/hq/dmdocuments/2010/tag18_2009_Final%20Report_Eng.pdf. Accessed on February 4, 2013.
3. World Health Organization. Expanded Programme on Immunization (EPI): Inclusion of yellow fever vaccine in the EPI. Wkly Epidemiol Rec. 1996; 71(24): 181-185.

Summary

Over the last 75 years, yellow fever vaccine has been the most effective means of preventing of yellow fever disease. The vaccine has been proven to be highly immunogenic and a single dose provides long-term protection against yellow fever. However, rare but serious side effects have been observed following the administration of this live attenuated viral vaccine.

The SAGE Working Group on Yellow Fever Vaccine carefully reviewed and weighed all available data regarding the use of yellow fever vaccine to reach the following conclusions and recommendations:

1. Booster dose of yellow fever vaccine is not needed to maintain immunity as a single dose of yellow fever vaccine appears to confer life-long protective immunity against yellow fever disease.
2. Caution should be used in vaccinating pregnant women, lactating women, and persons >60 years of age against yellow fever if they have not been previously vaccinated.
3. Yellow fever vaccine is contraindicated for severely immunocompromised persons, including persons with AIDS or CD4+ counts < 200 cells/mm3, certain primary immunodeficiencies, thymus disorder, malignant neoplasm being trated with chemotherapy , recent hematopoietic stem cell transplantation, drugs with known immunosuppressive or immunomodulatory properties (e.g., high-dose systemic corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent, or other monoclonal antibodies targeting immune cells), and current or recent radiation therapies targeting immune cells.
4. There is minimal impact on the reactogenicity and immunogenicity when yellow fever vaccine is co-administered with other vaccines. One notable exception is the co-administration of yellow fever vaccine and MMR vaccine.
5. Control strategy for yellow fever should include sound epidemiologic surveillance and delivery of yellow fever vaccine through a combination of EPI, preventive campaigns, and reactive campaigns.

In addition to the conclusions and recommendations above, the working group also noted several areas where additional research is warranted to address critical gaps related to the safety and immunogenicity of yellow fever vaccine (Table 12).

Table 12: Overview of potential studies to be conducted on live attenuated yellow fever (YF) vaccine to address gaps in safety or efficacy of the vaccine that were identified by the SAGE YF working group

Studies are listed below according to the target population where evidence based advice regarding safety and efficacy of YF vaccine are most needed.

Study topics regarding the safety and efficacy of YF vaccine identified by the SAGE YF working group	Studies to be initiated in Developing countries		Developed countries
	YF endemic	YF non endemic	
Transmission of YF vaccine virus by breastfeeding[a]	X		
Efficacy of YF and meningococcal vaccines when co-administered in EPI[b]	X		
Efficacy of YF and combined measles, mumps, and rubella (MMR) vaccines when co-administered in EPI[c]	X		
Efficacy of YF and OPV vaccines when co-administered in EPI[d]	X		
Safety and immunogenicity of YF vaccine in persons with advanced HIV[e]	X		X
Safety of YF vaccine in people ≥60 years[f]	X	X	X
Safety of YF vaccine in people with immunocompromising conditions[g]	X		X
Duration of protective immunity against YF in children[h]	X		
Duration of protective immunity against YF in adults[i]	X	X	X
Development of diagnostic assays for YF outbreaks[j]			X
Evaluation of diagnostic assays for YF outbreaks[j]	X		

[a] ***Transmission of YF vaccine virus by breastfeeding.*** Research question(s): Is the YF vaccine virus transmitted by breastfeeding from a vaccinated mother to her baby? How often this transmission does occur and what are the consequences for the baby? Are there any health risks for the baby? Study: An estimated number of 100 breastfeeding mothers in an YF vaccination campaign have to be thoroughly investigated for transmission via breastfeeding.

[b] ***Efficacy of YF and meningococcal vaccines when co-administered in EPI.*** Research question(s): Does the simultaneous administration of YF and meningococcal vaccine in the EPI influence the protective immune response generated against each vaccine? Study: An estimated number of 1000 children in a YF vaccination campaign have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[c] ***Efficacy of YF and MMR vaccines when co-administered in EPI.*** Research question(s): Does the simultaneous administration of YF and MMR vaccine in the EPI influence the protective immune response generated against each vaccine? Study: An estimated number of 1000 children in an YF vaccination campaign have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[d] ***Efficacy of YF and OPV vaccines when co-administered in EPI.*** Research question(s): Does the simultaneous administration of YF and oral polio vaccine in the EPI influence the protective immune response generated against each vaccine? Study: An estimated number of 1000 children in an YF vaccination campaign have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[e] ***Safety and immunogenicity of YF vaccine in persons with advanced HIV***. Research question(s): What is the impact of advanced HIV infection on the safety, magnitude, and duration of immunity following YF vaccination? Study: An estimated number of 200-400 HIV infected persons have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data. Since the HIV therapeutic regime has great impact on the quality of the immune system separate studies in developing and undeveloped countries are necessary.

[f] ***Safety of YF vaccine in people ≥60 years.*** Research question(s): Are there higher numbers of serious AEFIs in elderly persons compared to younger persons due to a less competent immune system? Study: This requires continuous notification, analysis and investigation of side effects after YF vaccination. Since the rate of side effects after YF vaccination is in the range of a few cases per thousand vaccinees (1/100,000) the limiting factor to obtain statistically robust data is the total number of YF vaccine administered to people >60 years over the years.

[g] ***Safety of YF vaccine in people with immunocompromising conditions***. Research question(s): Are there higher numbers of serious AEFIs in immunocompromised persons due to a less competent immune system? Study: This

requires continuous notification, analysis and investigation of side effects after YF vaccination. Since the rate of side effects after YF vaccination in immunocompromised is very low and the range of diseases causing immunosuppression is very different it is not possible to give an estimated number of cases to be investigated to get statistically valid data.

[h]***Duration of protective immunity against YF in children***. Research question(s): What is the duration the protection against YF in children receiving YF vaccine in the EPI? Study: An estimated number of 1000 adolescents and adults with a well-documented history of receiving YF vaccine as a child have to be thoroughly investigated for neutralizing/protective antibodies to get statistically valid data.

[i]***Duration of protective immunity against YF in adults***. Research question(s): What is the duration of protection against YF in adults who receive YF vaccine? Study: An estimated number of 200-400 vaccinees with a well-documented YF vaccination have to be thoroughly investigated per time interval for the presence of neutralizing/protective antibodies to get statistically valid data.

[j]***Development and evaluation of diagnostic assays for YF outbreaks*** *(NOTE: topics discussed in the working group but not presented in the background document)*. Research question(s): Which kind of assay provides a sensitive and reliable diagnostic analysis of YF infections in case of a suspected outbreak? Study: An estimated number of 50 – 100 acute YF cases have to be thoroughly investigated for IgM/IgG antibodies and YF RNA detection to get statistically valid data.

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Yellow fever vaccine

WHO position paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO is issuing a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; limited vaccination, as executed mostly in the private sector, may be a valuable supplement to national programmes, but is not emphasized in these policy documents. The position papers summarize essential background information on the respective diseases and vaccines and conclude with the current WHO position concerning their use in the global context. The papers have been reviewed by a number of experts within and outside WHO and are designed for use mainly by national public health officials and immunization programme managers. However, the position papers may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community and the scientific media.

Summary and conclusions

Yellow fever (YF) is a mosquito-borne, viral haemorrhagic fever that is endemic in tropical regions of Africa and South America. *Aedes aegypti* is the vector of YF virus in the urban human-to-human cycle of transmission, whereas in the jungle (forest, sylvatic) monkey-to-monkey – and accidentally monkey-to-human – cycle, several different mosquito species are involved. About 90% of an estimated 200 000 annual cases of YF occur in Africa, where outbreaks are common and where both the urban and the jungle type of transmission operate. In South America, the jungle type of YF predominates, either in individual cases or localized outbreaks. Sup-

Vaccin antiamaril

Note d'information de l'OMS

Conformément à son mandat qui l'appelle à conseiller les Etats Membres sur les questions de politique sanitaire, l'OMS publie une série de notes d'information régulièrement mises à jour sur les vaccins et associations de vaccins contre des maladies affectant la santé publique au niveau international. Ces notes concernent avant tout l'utilisation de vaccins dans le cadre de programmes de vaccination à grande échelle; elles ne mettent pas l'accent sur la vaccination limitée telle qu'elle est pratiquée principalement dans le secteur privé et qui peut compléter utilement les programmes nationaux. Les notes d'information présentent de manière succincte les données fondamentales de base sur les différents vaccins et maladies et précisent la position actuelle de l'OMS concernant l'utilisation des vaccins dans le contexte mondial. Elles ont été examinées par une série d'experts de l'OMS et de l'extérieur, et s'adressent principalement aux responsables nationaux de la santé publique et aux responsables des programmes de vaccination. Toutefois, elles peuvent aussi intéresser les organismes internationaux de financement, les fabricants de vaccins, les médecins et les revues scientifiques.

Résumé et conclusions

La fièvre jaune est une fièvre hémorragique virale transmise par des moustiques, qui est endémique dans les zones tropicales de l'Afrique et de l'Amérique du Sud. Dans le cycle de transmission interhumaine, le vecteur du virus amaril est *Aedes aegypti*, alors qu'en milieu selvatique, où le cycle de transmission est de singe à singe, avec accidentellement un cycle de singe à l'homme, plusieurs espèces de moustiques interviennent. Quelque 90% du nombre total de cas annuels de fièvre jaune – estimé à 200 000 – concernent l'Afrique où les flambées sont fréquentes et où l'on observe à la fois la transmission urbaine et selvatique. En Amérique du Sud, c'est la fièvre jaune selvatique qui prédomine et l'on observe

pression of *Ae. aegypti* in densely populated settlements may drastically reduce the number of YF cases, but mosquito control is impractical in thinly populated jungle districts. There is no specific antiviral treatment for the YF virus. A highly efficacious, live attenuated vaccine (17D) has been available for 60 years. One month following immunization, up to 99% of vaccinees show protective levels of neutralizing antibodies, and the immunity is likely to last for decades. Adverse events following YF vaccination are usually minor, although hypersensitivity to vaccine components may occasionally occur, and very rare cases of viral encephalitis or multiple organ failures have been reported. The rare adverse events should not deter the appropriate use of this highly valuable vaccine. In countries at risk[1] for YF, this vaccine is recommended for individual and outbreak prevention as well as outbreak control. The vaccine is also widely used for the protection of travellers to YF-endemic areas. Although there is no current shortage of YF vaccine at the global level, supplies may not be sufficient in the event of multiple large outbreaks in urban centres.

In countries at risk for YF, the use of the 17D vaccine is the main strategy recommended to rapidly build up YF immunity in the population at large. This prevention strategy has two components. The first component is the inclusion of the 17D vaccine in national childhood immunization programmes. For convenience and improved coverage, the YF vaccine should be administered simultaneously with the measles vaccine at approximately 9–12 months of age, but in a separate syringe and at a different injection site.

The second component is the implementation of mass preventive vaccination campaigns to protect susceptible older age groups. In the event of limited resources, assessment of the degree of risk can help prioritize areas for mass preventive campaigns.

During YF epidemics, outbreak response vaccination campaigns should be carried out with minimum delay in order to limit the spread of the disease. The occurrence of an epidemic reflects incomplete implementation of prevention strategies, which therefore need to be strengthened following the outbreak. Appropriate measures to control *Ae. aegypti* should accompany all efforts to improve immunization coverage.

YF vaccine should be offered to all travellers to and from at-risk areas, unless they belong to the group of individuals for whom YF vaccination is contraindicated. There is currently insufficient scientific evidence to support a change in the *International health regulations* for travellers to endemic areas demanding proof of valid YF vaccination within the preceding ten years. However, in at-risk countries, vaccination resources should be directed to ensuring good primary vaccination coverage rather than to providing booster doses.

[1] At risk for yellow fever is defined as areas where evidence for presence of the virus has been demonstrated and where ecological factors can support yellow fever virus transmission to man.

soit des cas isolés ou des flambées locales. La suppression de *Ae. aegypti* dans les zones densément peuplées peut permettre une réduction considérable du nombre des cas, mais la lutte contre le moustique n'offre pas une solution pratique dans les zones selvatiques à faible densité de population. Il n'existe pas de traitement antiviral spécifique. Par contre, un vaccin vivant atténué très efficace (17D) est disponible depuis 60 ans. Un mois après la vaccination, on observe chez 99% des vaccinés des titres protecteurs en anticorps neutralisants, et l'immunisation dure généralement plusieurs décennies. Les événements indésirables de la vaccination antiamarile sont généralement mineurs, mais l'on observe parfois des cas d'hypersensibilité aux composants du vaccin ainsi que quelques cas très rares d'encéphalite virale ou de défaillance multiviscérales. Les événements indésirables, qui restent rares, ne doivent pas inciter à renoncer à un usage approprié de ce vaccin très utile. Dans les pays à risque de fièvre jaune[1], le vaccin est recommandé aussi bien pour les individus que pour prévenir et combattre les flambées. Il est également largement utilisé pour protéger les voyageurs qui se rendent dans des zones d'endémie. S'il n'y a pas actuellement de pénurie de vaccin antiamaril au niveau mondial, les stocks pourraient ne pas être suffisants en cas de flambées importantes et multiples dans des centres urbains.

Dans les pays à risque de fièvre jaune, l'utilisation du vaccin 17D est la principale stratégie recommandée pour renforcer rapidement l'immunité antiamarile dans la population en général. Cette stratégie comporte deux points, le premier consistant à intégrer le vaccin 17D au programme national de vaccination de l'enfant. Par commodité et pour améliorer la couverture, le vaccin antiamaril doit être administré en même temps que le vaccin antirougeoleux, à environ 9-12 mois, mais avec une seringue distincte et dans un site d'injection distinct.

Quant au deuxième point de cette stratégie, il s'agit de la mise en œuvre de campagnes de vaccination préventive pour protéger les groupes réceptifs les plus âgés. En cas de ressources limitées, une évaluation du degré de risque peut aider à donner la priorité à certaines zones pour des campagnes de vaccination de masse.

Au cours d'une épidémie, des campagnes de vaccination doivent être menées sans retard afin de limiter la propagation. Une épidémie reflète une application incomplète des stratégies de prévention, qui doivent donc être renforcées. Des mesures appropriées de lutte contre *Ae. aegypti* doivent accompagner tous les efforts visant à améliorer la couverture vaccinale.

Le vaccin antiamaril doit être proposé à tous les voyageurs à destination et en provenance d'une zone à risque, à moins qu'ils n'appartiennent à l'un des groupes d'individus pour lesquels la vaccination contre la fièvre jaune est contre-indiquée. Les données scientifiques actuellement disponibles ne justifient pas une modification du *Règlement sanitaire international* en ce qui concerne la présentation d'une attestation de vaccination valable au cours des dix années précédentes pour les voyageurs qui se rendent dans les zones d'endémie. Toutefois, dans les pays à risque, les ressources doivent privilégier la couverture vaccinale par la primovaccination plutôt que l'administration de rappels.

[1] On définit les zones à risque de fièvre jaune comme des zones où la preuve de la présence du virus a été faite et qui présentent des facteurs écologiques propices à la transmission du virus de la fièvre jaune à l'homme.

The various clinical presentations of YF may be mistaken for those of a number of other infectious diseases that occur in YF at-risk countries. This underscores the importance of having a sensitive, case-based YF surveillance system, supported by laboratory diagnostic facilities. The timely notification and investigation of patients with acute febrile illness and jaundice, with or without haemorrhagic manifestations, is recommended to increase the sensitivity of surveillance to detect the circulation of YF virus. The early detection of YF virus circulation would prompt timely implementation of outbreak response activities.

Improved surveillance and reporting of any potential adverse event following vaccination is recommended in order to correct any programmatic errors that may be involved and to facilitate improved understanding of the pathogenic mechanisms causing the recently described serious adverse events.

Mechanisms should be found to provide incentives for manufacturers of YF vaccine to sustain or increase their production capacity to ensure rapid delivery of sufficient quantities in the event of a major YF outbreak.

Background

Public health aspects

Yellow fever is a mosquito-borne, viral haemorrhagic fever that is endemic in tropical areas of Africa and South America, where it has caused outbreaks at irregular intervals for centuries. Like plague and cholera, YF is subject to control measures outlined in the *International health regulations*. WHO estimates that a total of 200 000 cases of YF occur each year, with about 30 000 deaths. More than 90% of YF cases occur in Africa, where over 500 million people live in the YF at-risk zone between 15° north and 15° south of the equator. Furthermore, YF is a significant risk to more than 3 million travellers who visit areas affected with YF each year.

Exposure of susceptible persons to bites from infected mosquitoes is the only significant mode of YF transmission. An urban and a jungle (forest, sylvatic) form of YF can be distinguished by differences in their respective transmission cycles. Urban YF, which frequently occurs as large outbreaks, is transmitted from infected to susceptible humans by *Ae. aegypti,* a mosquito species that breeds in the proximity of human habitats. The urban form of transmission is found mainly in Africa. The jungle form of YF is primarily an enzootic viral disease of non-human primates, but the various mosquito vectors involved may occasionally cause individual cases or small outbreaks of YF among humans in the forested savanna of Africa and in jungle areas of South America. As a result of high vector density, the risk of contracting YF is usually greatest towards the end of the rainy season and at the beginning of the dry season, particularly with the jungle type of transmission. The YF virus is maintained during the dry season by transovarial transmission in mosquitoes.

Since the beginning of the 1980s, the incidence of YF has increased dramatically, particularly in Africa. In Nigeria, more than 20 000 cases, notably in children, were reported in successive outbreaks between 1986 and 1994. The

Les différents tableaux cliniques de la fièvre jaune peuvent être confondus avec ceux de maladies infectieuses qui touchent les pays à risque de fièvre jaune. Il est donc important de disposer d'un système sensible de surveillance de la fièvre jaune fondé sur les cas, et appuyé par des moyens de diagnostic au laboratoire. Une modification en temps voulu et l'examen des patients souffrant de maladie fébrile aiguë ou d'ictère, avec ou sans manifestations hémorragiques, sont recommandés afin d'augmenter la sensibilité de la surveillance pour dépister la circulation du virus de la fièvre jaune. Le dépistage précoce de la circulation du virus de la fièvre jaune inciterait à la mise en place en temps voulu des activités de lutte contre les flambées.

Une amélioration de la surveillance et de la notification des manifestations indésirables potentielles suivant la vaccination est recommandée afin de corriger les erreurs de programme éventuelles et de faciliter une meilleure compréhension des mécanismes pathogéniques provoquant les événements indésirables graves récemment décrits.

Il faut trouver des moyens d'inciter les fabricants de vaccin antiamaril à maintenir ou accroître leur capacité de production afin d'assurer un approvisionnement rapide de stocks de vaccin suffisants en cas de flambée majeure.

Données fondamentales

Aspects concernant la santé publique

La fièvre jaune est une fièvre hémorragique virale transmise par des moustiques, qui est endémique dans les milieux tropicaux d'Afrique et d'Amérique du Sud, où depuis des siècles, elle provoque des flambées à des intervalles irréguliers. Tout comme la peste et le choléra, la fièvre jaune peut être combattue par les mesures décrites dans le *Règlement sanitaire international.* L'OMS estime que 200 000 cas de fièvre jaune surviennent chaque année, dont 30 000 sont mortels. Plus de 90% des cas touchent l'Afrique où plus de 500 millions de personnes vivent dans la zone à risque située entre 15° de latitude nord et 15° de latitude sud. La fièvre jaune constitue également un risque important pour plus de 3 millions de voyageurs qui se rendent chaque année dans les zones touchées.

L'exposition de sujets réceptifs aux piqûres de moustiques infectés est le seul mode de transmission significatif de la fièvre jaune. On distingue la forme urbaine de la forme selvatique de la maladie par les différences des cycles de transmission. La fièvre jaune urbaine, qui provoque souvent d'importantes flambées, est transmise d'un sujet infecté à un sujet réceptif par *Ae. aegypti*, une espèce de moustique qui se reproduit à proximité de l'habitat humain. La forme urbaine de transmission concerne principalement l'Afrique. La forme selvatique constitue avant tout une virose enzootique des primates non humains, mais les différents vecteurs moustiques concernés peuvent occasionnellement provoquer des cas humains isolés ou des flambées réduites dans la savane forestière africaine et dans les zones selvatiques sud-américaines. En raison de la forte densité vectorielle, le risque de fièvre jaune est généralement le plus élevé vers la fin de la saison des pluies et au début de la saison sèche, surtout en ce qui concerne la transmission le type selvatique. Le virus amaril se maintient au cours de la saison sèche par transmission transovarienne chez le moustique.

Depuis le début des années 80, l'incidence de la fièvre jaune a augmenté très fortement, surtout en Afrique. Au Nigéria, plus de 20 000 cas, surtout chez l'enfant, ont été notifiés lors de flambées successives entre 1986 et 1994. Dans ce pays, les flambées ont princi-

Nigerian outbreaks were mainly caused by urban-type YF, but small outbreaks due to the jungle transmission cycle are believed to cause thousands of YF cases in Africa each year. During outbreak periods in Africa, about 20–40% of the population in affected areas show serological evidence of YF infection. The ratio of infection to clinical illness was found to be 3.8:1 and 7.4:1 respectively, in two separate epidemics.

By 1940, successful vector control had resulted in the disappearance of urban YF in Argentina, Bolivia, Brazil, Ecuador, Panama, Paraguay, Peru and Uruguay. However, the urban vector (*Ae. aegypti*) was never eliminated in the Guyanas, Trinidad and Tobago and Venezuela. In recent years, reinfestation of *Ae. aegypti* resulted in the reappearance of urban YF in Bolivia, and, if the vector is re-established widely across South America, there is a significant threat of reappearance of urban YF on this continent. Jungle YF has a permanent enzootic cycle throughout the region encompassing the great river basins, and cases (generally a few hundred per year) have continued to occur annually in Brazil, Bolivia, Colombia, Ecuador, the Guyanas, Peru, Trinidad and Tobago and Venezuela. The reported national incidence figures concerning YF are believed to significantly underestimate the true incidence. In fact, during outbreak periods, about 1–3% of the population in affected regions of South America shows serological evidence of YF infection.

Whereas urban YF can be successfully eliminated by large-scale vaccination and measures to suppress *Ae. aegypti*, vaccination is the only means of controlling the jungle form. In Africa, *Ae. aegypti* is widespread in rural villages as well as in towns and cities, and vector control is therefore inefficient.

The pathogen and etiological diagnosis

Yellow fever virus is the prototype of the genus *Flavivirus*, which comprises about 70 different viruses, most of which are arthropod-borne. The core of the small (35–45 nm), enveloped YF virus contains a positive-sense, single-stranded RNA of 10 233 nucleotides, which encode three structural and eight non-structural proteins. The viral envelope protein plays an essential role in cell tropism, virulence and immunity, and mutations in the envelope gene may alter these functions. Based on sequence analysis, wild-type YF virus strains have been classified into at least seven genotypes: five in Africa and two in South America. The genotypic variation is not accompanied by antigenic differences across strains, and the 17D vaccine is therefore effective against all YF virus genotypes in both continents. Yellow fever virus can be inactivated by lipid solvents (ether, chloroform), heating at 56 °C for 30 minutes and with ultraviolet light.

Following a bite from an infected mosquito, YF virus first replicates at the site of inoculation and spreads from there to the local lymph nodes, liver, spleen, bone marrow and myocardium, but very rarely to the brain (i.e. viscerotropic rather than neurotropic affinity). The virus is present in the blood during the incubation period and early stage of illness at levels capable of infecting blood-feeding *Ae. aegypti*.

No commercial test is available for the laboratory diagnosis of YF, but WHO coordinates training and the provision of reagents for the Centers for Disease Control and Prevenpalement été provoquées par le type urbain, mais l'on estime que de petites flambées dues au cycle de transmission selvatique provoquent chaque année en Afrique des milliers de cas de fièvre jaune. Au cours des périodes de flambées en Afrique, la sérologie révèle l'infection amarile chez 20 à 40% de la population des zones touchées. Le rapport observé entre le nombre de personnes infectées et le nombre de personnes cliniquement malades dans deux épidémies distinctes a respectivement été de 3,8:1 et de 7,4:1.

En 1940, la lutte antivectorielle a permis de faire disparaître la fièvre jaune urbaine en Argentine, en Bolivie, au Brésil, en Equateur, au Panama, au Paraguay, au Pérou et en Uruguay. Mais le vecteur urbain (*Ae. aegypti*) n'a jamais été éliminé dans les Guyanes, à la Trinité-et-Tobago et au Venezuela. Ces dernières années, la réinfestation de *Ae. aegypti* a entraîné une réapparition de la fièvre jaune urbaine en Bolivie et une large réimplantation du vecteur dans toute l'Amérique du Sud pourrait entraîner un risque considérable de réapparition de la forme urbaine sur ce continent. La forme selvatique dispose d'un cycle enzootique permanent dans la région, qui comprend de grands bassins fluviaux, et l'on a continué d'observer chaque année des cas au Brésil, en Bolivie, en Colombie, en Equateur, dans les Guyanes, au Pérou, à la Trinité-et-Togabo et au Venezuela (généralement quelques centaines par année). L'incidence nationale notifiée est généralement considérée comme bien inférieure à l'incidence réelle. En fait, au cours des flambées, la sérologie révèle l'infection amarile chez 1 à 3% de la population des zones touchées d'Amérique du Sud.

Si la fièvre jaune urbaine peut être éliminée par une vaccination à grande échelle et des mesures de lutte contre *Ae. aegypti,* la vaccination est le seul moyen de lutte contre la forme selvatique. En Afrique, *Ae. aegypti* est très répandu en milieu rural, au même titre que dans les villes, et la lutte antivectorielle n'est donc pas efficace.

L'agent pathogène et le diagnostic étiologique

Le virus de la fièvre jaune ou virus amaril est typique du genre *Flavivirus*, lequel comporte environ 70 virus différents, dont la plupart sont des arbovirus. Le nucléoïde de ce petit virus enveloppé (35-45 nm) contient un ARN monocaténaire positif de 10 233 nucléotides, qui code pour trois protéines structurales et huit protéines non structurales. La protéine de l'enveloppe virale joue un rôle capital dans le tropisme cellulaire, la virulence et l'immunité, et les mutations du gène d'enveloppe peuvent modifier ces fonctions. Le séquençage montre que les souches de virus amaril sauvage peuvent être classées en au moins sept génotypes: cinq sont observés en Afrique et deux en Amérique du Sud. La variation génotypique ne s'accompagne pas de variation antigénique et le vaccin préparé à partir de la souche 17D est par conséquent efficace contre tous les virus amarils, quel que soit leur génotype, sur les deux continents. Le virus amaril peut être inactivé par les solvants des lipides (éther, chloroforme), par chauffage à 56 °C pendant 30 minutes et par l'exposition au rayonnement ultraviolet.

Après piqûre par un moustique infecté, le virus commence par se multiplier au site d'inoculation puis migre vers les ganglions lymphatiques régionaux, le foie, la rate, la moelle osseuse et le myocarde, mais rarement vers l'encéphale (le virus est plus viscérotrope que neurotrope). Le virus est présent dans le sang pendant la période d'incubation et au début de la maladie, en nombre suffisant pour infester un moustique hématophage de l'espèce *Ae. aegypti*.

Il n'existe aucun test de diagnostic de la fièvre jaune dans le commerce, mais l'OMS assure, dans le cadre de son réseau de laboratoires pour la fièvre jaune, la formation et la fourniture de réactifs

tion (Atlanta, USA) capture IgM assay to the WHO Yellow Fever Laboratory Network. A single IgM-positive serum sample obtained in the absence of recent vaccination provides a presumptive YF diagnosis. As cross-reactions occur between the YF virus and other flaviviruses, it is recommended that all presumptive positive cases are confirmed by the regional reference laboratory (RRL) within seven days. The RRL has the capacity to confirm the positive result using a battery of methods, including testing with potentially cross-reacting antigens, virus isolation and polymerase chain reaction (PCR). In specialized laboratories, YF virus may be isolated by intracerebral inoculation of suckling mice, intrathoracic inoculation of mosquitoes or inoculation into cell cultures. PCR can also be used to detect the viral genome in clinical samples, including serum taken in the first month after onset of illness.

In emergency situations, WHO, through its network of Collaborating Centres for Arboviruses and Haemorrhagic Fevers, can organize diagnostic assistance to affected countries.

Immune response

Infection with YF virus is followed by a rapid immune response. IgM antibodies appear during the first week of illness, peak during the second week and decline over the next 1–2 months. Specific neutralizing antibodies, which are the principal mediators of protection, appear at the end of the first week and persist for many years. Neutralizing antibodies bind to epitopes on the viral envelope protein and interfere with both viral attachment to the host cell membrane and the subsequent internalization of the virus. Some non-structural viral proteins (NS1 and NS2) are associated with the infected host cell membrane, where they are targets for immune elimination. Antibodies to NS1 contribute to protective immunity by lysing infected cells, whereas NS3 is a target for cytotoxic T-cells. Wild-type YF virus induces lifelong protection against subsequent infection, but relatively little is known about the cellular responses in humans to infection by this virus. Previous infection with certain heterologous flaviviruses, in particular dengue virus, appears to modulate disease expression and severity of YF. Determination of the presence of neutralizing antibodies is the only useful test for immunity to YF.

Clinical features

Following a bite from an infected mosquito, the incubation period is approximately 3–6 days. This is followed by either subclinical infection, nonspecific illness, transient influenza-like disease, a febrile illness with jaundice or fatal haemorrhagic fever. Disease onset is typically abrupt and characterized by fever, chills, malaise, headache, lower back pain, generalized nausea and dizziness. Congestion of the conjunctiva and face, as well as relative bradycardia, is commonly found. In patients with a transient, non-icteric infection, the average duration of fever is 3–4 days, followed by complete recovery. However, in approximately 15% of cases, the disease progresses, with or without a brief (24–48 hours) remission, to a more severe form, with fever, vomiting, epigastric pain, jaundice, renal failure and haem-

pour la recherche des IgM par capture utilisée par les *Centers for Disease Control and Prevention* (Atlanta, Etats-Unis d'Amérique). Un seul échantillon de sérum positif pour la recherche des IgM, obtenu à distance d'une vaccination, permet de porter un diagnostic présomptif de fièvre jaune. Dans la mesure où des réactions croisées entre le virus de la fièvre jaune et d'autres flavivirus sont possibles, il est recommandé de confirmer dans un délai maximal de sept jours, tous les cas présumés positifs auprès du laboratoire régional de référence (LRR). Le LRR peut confirmer un résultat positif en utilisant une batterie de méthodes, notamment la recherche d'antigènes susceptibles de donner des réactions croisées, l'isolement du virus et la PCR (*polymerase chain reaction*). Dans les laboratoires spécialisés, le virus amaril peut être isolé par inoculation intracérébrale chez le souriceau à la mamelle, inoculation intrathoracique chez le moustique et inoculation en culture cellulaire. La PCR peut également être utilisée pour déceler la présence du génome viral dans les prélèvements cliniques, notamment les échantillons de sérum prélevés dans le mois qui suit le début de la maladie.

En situation d'urgence, l'OMS peut organiser une aide au diagnostic dans les pays touchés, grâce à son réseau de centres collaborateurs pour les arbovirus et les fièvres hémorragiques.

Réponse immunitaire

L'infection par le virus amaril est suivie d'une réponse immunitaire rapide. Les IgM apparaissent pendant la première semaine de la maladie, atteignent leur maximum au cours de la deuxième semaine, puis diminuent au cours des 1 à 2 mois suivants. Les anticorps neutralisants spécifiques, qui sont les principaux médiateurs de la protection, apparaissent à la fin de la première semaine et persistent plusieurs années. Les anticorps neutralisants se lient aux épitopes de la protéine d'enveloppe virale et interfèrent à la fois avec la fixation du virus à la membrane de la cellule hôte, et avec son internalisation. Certaines protéines virales non structurales (NS1 et NS2) sont associées à la membrane de la cellule hôte infectée, où elles constituent des cibles appropriées à l'élimination par le système immunitaire. Les anticorps dirigés contre la protéine NS1 contribuent à l'immunité protectrice en lysant les cellules infectées, tandis que la protéine NS3 est une cible pour les cellules T cytotoxiques. Le virus amaril de type sauvage suscite une protection définitive contre les infections ultérieures, mais les réponses cellulaires à l'infection par ce virus sont assez mal connues chez l'homme. Une infection antérieure par certains flavivirus hétérologues, le virus de la dengue notamment, semble moduler l'expression de la maladie et la gravité de la fièvre jaune. La mise en évidence des anticorps neutralisants est le seul test utile pour rechercher une immunité vis-à-vis de la fièvre jaune.

Tableau clinique

Après piqûre par un moustique infecté, la période d'incubation est d'environ 3 à 6 jours. Elle est suivie soit par une infection infraclinique, soit par un syndrome non spécifique, soit par une affection résolutive pseudogrippale, soit par une affection fébrile accompagnée d'ictère ou une fièvre hémorragique fatale. Le début de la maladie est classiquement brutal, avec un tableau caractéristique de fièvre, frissons, syndrome général, céphalées, douleurs lombosacrées, des nausées et vertiges. Conjonctives injectées et faciès vultueux ainsi que bradycardie modérée sont fréquemment observés. Dans les formes résolutives non ictériques, la durée moyenne de la fièvre est de 3 à 4 jours, et la guérison est complète. Cependant, chez environ 15% des cas, la maladie évolue avec ou sans brève période de rémission (24 à 48 heures), vers une forme plus grave, avec fièvre, vomissements, douleurs épigastriques, ictère, défaillance rénale et

orrhagic manifestations. The haemorrhagic manifestations are caused by reduced synthesis of clotting factors as well as by a consumptive coagulopathy. Encephalitis due to YF virus is exceedingly rare. About 20–50% of patients with hepato-renal failure die, in most cases 7–10 days after onset of disease. Case-fatality rates are highest among young children and the elderly. Patients surviving YF may experience prolonged weakness and fatigue, but healing of the liver and kidney injuries is usually complete. The specific pathogenic mechanisms involved in human YF remain poorly defined.

Justification for vaccine control

Yellow fever is a very serious disease and a major public health problem for hundreds of millions of people in large parts of tropical Africa and South America. Millions of travellers to at-risk areas are also at risk of YF infection. In recent years, there has been a dramatic increase in the number of YF cases. No drug treatment is available against YF virus, and mosquito control is impractical in areas of jungle-type transmission.

For unvaccinated individuals entering an area of epidemic activity in Africa, the risks of YF illness and death have been estimated at 1:267 and 1:1333, respectively, for a two-week trip, although the risks vary considerably according to the season. The corresponding figures for South America are likely to be 10 times lower.

Immunization is the single most effective means of obtaining protection against YF. For decades, a safe and effective 17D vaccine has been available and is recommended by WHO for large-scale use by residents of and visitors to at-risk countries. This live attenuated vaccine provides long-lasting protection after one injection and its routine use in children in at-risk countries has a favourable cost–benefit ratio. Furthermore, a valid certificate of vaccination is required under the *International health regulations* for entry into most YF-endemic countries or for travel from endemic countries to countries at risk for introduction of YF virus.

Yellow fever vaccine

The yellow fever 17D vaccine is the only commercially available vaccine against YF. The vaccine is based on a wild-type YF virus (the Asibi strain) isolated in Ghana in 1927 and attenuated by serial passages, principally in chicken embryo tissue culture. Numerous mutations in the viral structural and non-structural genes have resulted in the attenuated variant 17D. This attenuated vaccine virus exists in the two sub-strains (17D–204 and 17DD), which share 99.9% sequence homology. Nucleotide sequencing has shown differences between the wild-type Asibi strain and the attenuated sub-strains affecting 20 amino acids. Many of the substitutions involve the envelope protein, and the resulting phenotypic changes make the sub-types non-transmissible by mosquitoes.

The 17D–204 and 17DD sub-strains are both used in vaccines and produced in embryonated chicken eggs in several countries. The production procedures include testing of both primary and secondary seed lots for viscerotropic and neurotropic activity.

manifestations hémorragiques. Celles-ci sont dues à la fois à une diminution de la synthèse des facteurs de coagulation et à une coagulopathie de consommation. Le virus de la fièvre jaune est très rarement à l'origine d'une encéphalite. Environ 20-50% des patients atteints d'insuffisance hépato-rénale décèdent, le plus souvent dans les 7-10 jours qui suivent le début de la maladie. C'est chez l'enfant et la personne âgée que le taux de létalité est le plus élevé. Quand le patient survit à la fièvre jaune, la convalescence peut s'accompagner d'une asthénie prolongée mais la guérison des lésions hépatiques et rénales est en général complète. Les mécanismes pathogéniques spécifiques de la fièvre jaune humaine restent mal connus.

Justification de la lutte antiamarile par la vaccination

La fièvre jaune est une maladie très grave et un problème de santé publique majeur pour des centaines de millions de personnes habitant des zones étendues de l'Afrique tropicale et de l'Amérique du Sud. Des millions de voyageurs se rendant dans les zones à risque sont également exposés au risque d'infection par le virus amaril. Le nombre de cas de fièvre jaune a considérablement augmenté ces dernières années. Il n'existe aucun traitement médicamenteux contre le virus amaril, et la lutte antivectorielle n'est pas applicable dans les régions où la transmission est de type selvatique.

Le sujet non vacciné qui pénètre en zone d'activité épidémique en Afrique a un risque de fièvre jaune ou de décès estimé respectivement à 1:267 et 1:1333 pour un séjour de deux semaines; le risque varie cependant considérablement avec la saison. Les chiffres correspondants pour l'Amérique du Sud seraient environ 10 fois inférieurs.

La vaccination est le seul moyen efficace de se protéger contre la fièvre jaune. Il existe depuis des dizaines d'années un vaccin utilisant la souche 17D, sûr et efficace, recommandé par l'OMS pour la vaccination de masse des résidents et des voyageurs dans le pays à risque. Ce vaccin vivant atténué confère une protection durable après une seule injection, et en vaccination systématique chez l'enfant des pays d'endémie son rapport coût/avantage est intéressant. En outre, un certificat de vaccination en cours de validité est exigé par le *Règlement sanitaire international* à l'entrée de la plupart des pays à risque ou en cas de voyage d'un pays d'endémie vers un pays dépourvu d'endémie où existe un risque d'introduction du virus amaril.

Le vaccin antiamaril

Le vaccin antiamaril 17D est le seul vaccin existant dans le commerce contre la fièvre jaune. Le vaccin est fabriqué à partir d'un virus amaril de type sauvage (souche Asibi) isolé au Ghana en 1927 et atténué par passages en série, essentiellement en culture de tissus d'embryon de poulet. Les nombreuses mutations des gènes de structure et des gènes non structuraux ont abouti au variant atténué 17D. Ce virus vaccinal atténué existe sous deux formes, les sous-souches 17D-204 et 17DD, dont les séquences sont homologues à 99,9%. Le séquençage des nucléotides a mis en évidence des différences entre la souche Asibi de type sauvage et les sous-souches atténuées portant sur 20 acides aminés. Nombre de ces substitutions touchent la protéine d'enveloppe et les modifications phénotypiques qui en résultent rendent ces sous-types non transmissibles par les moustiques.

Les sous-souches 17D-204 et 17DD sont toutes les deux utilisées comme souches vaccinales et cultivées dans plusieurs pays sur œuf de poule embryonné pour produire le vaccin. La production comporte un test de détermination du viscérotropisme et du neurotropisme des lots de semence primaire et secondaire.

The YF vaccine is given as a single subcutaneous or intramuscular injection (0.5 ml per dose), although the subcutaneous route is preferred. According to current WHO requirements, a YF vaccine that has been held at 37 °C for 14 days must (i) maintain the minimal potency of >1000 MLD_{50} per dose and (ii) show a mean loss of titre <1 log 10 MLD_{50}. These requirements necessitate the addition of stabilizers such as sorbitol and gelatin. The lyophilized vaccine requires proper storage under cold-chain conditions, and reconstituted vaccine must be kept on ice and used within six hours.

Effectiveness. Protective levels of neutralizing antibodies (log neutralization index of at least 0.7) are found in 90% of vaccinees within 10 days and in 99% within 30 days. In most cases, protection appears to last for 30–35 years or more. Since there is no interference between YF vaccine and other vaccines, YF vaccine may be administered simultaneously, but in different syringes and at different sites, with the following vaccines: measles, polio (oral polio vaccine), diphtheria–tetanus–pertussis, hepatitis B, hepatitis A, oral cholera and oral or parenteral typhoid. When not given simultaneously, live vaccines should be administered at least one month before or one month after the YF vaccination. This recommendation is based on the assumption that interferon released in response to the first vaccine may have a temporary inhibitory effect on other live virus vaccines.

Safety. About 400 million doses of YF vaccine have been administered worldwide with an excellent record of safety, although mild systemic reactions such as headache, myalgia, malaise and weakness occur during the first few days after vaccination in 10–30% of vaccinees. Severe adverse reactions are extremely rare, but when they do occur infants (encephalitis) and the elderly (multiple-organ failure) seem more susceptible than the YF-vaccinated population at large. Three distinct types of serious adverse reactions to the 17D vaccine have been described:

1. *Hypersensitivity reactions*. The rate of serious allergic reactions, particularly those of anaphylactic reactions, is very low. However, the vaccine is produced in embryonated chicken eggs and is contraindicated for persons with a history of oral egg intolerance or strong allergic reactions to egg-based products. In persons without egg allergy, systemic allergic reactions are known to occur, although very rarely. Sensitivity to gelatin, which is commonly used to stabilize the vaccine, may explain at least some of these cases.

2. *Vaccine-associated neurotropic disease*. Since 1945, a total of at least 26 cases of proven or probable post-vaccinal encephalitis have been reported, of whom 16 were infants aged under 7 months. Of these 26 patients, 24 recovered without sequelae. Vaccine virus obtained from the brain of one fatal case in a 3-year-old child showed mutations in the envelope gene of the virus and increased neurovirulence in animal studies. It is unknown whether the other cases were caused by similar mutations of the vaccine strains. The other fatality was in an HIV-infected adult patient who was immunosuppressed.

Le vaccin antiamaril est administré en une seule injection, sous-cutanée ou intramusculaire (0,5 ml par dose); on préfère toutefois la voie sous-cutanée. D'après les normes actuelles de l'OMS, un vaccin antiamaril conservé à 37 °C pendant 14 jours doit avoir les propriétés suivantes: i) avoir conservé une activité minimale >1000 DL_{50} pour la souris et ii) montrer une perte moyenne du titre <1 log 10 DL_{50}. Pour être respectées ces normes exigent l'addition de stabilisants, sorbitol et gélatine par exemple. Le vaccin lyophilisé doit être conservé conformément aux exigences de la chaîne du froid, et, une fois reconstitué, être maintenu dans la glace et utilisé dans les six heures.

Efficacité. On observe chez 90% des vaccinés dans les 10 jours qui suivent la vaccination et chez 99% des vaccinés dans les 30 jours de la vaccination des titres protecteurs en anticorps neutralisants (logarithme de l'indice de neutralisation d'au moins 0,7). Dans la plupart des cas, la protection semble avoir une durée de 30-35 ans, voire plus. Dans la mesure où il n'y a pas d'interférence entre le vaccin antiamaril et les autres vaccins, celui-ci peut être administré en même temps, mais avec une autre seringue et en un site d'injection différent, que le vaccin contre la rougeole, la poliomyélite (vaccin antipoliomyélitique oral), la diphtérie-tétanos-coqueluche, l'hépatite B, l'hépatite A, le vaccin anticholérique oral et le vaccin antityphoïdique oral ou parentéral. S'ils ne sont pas administrés simultanément, les vaccins vivants seront administrés au moins un mois avant ou après la vaccination antiamarile. Cette recommandation s'appuie sur l'hypothèse que l'interféron libéré en réponse à la première vaccination, pourrait avoir un effet inhibiteur temporaire sur les autres vaccins à virus vivant.

Innocuité. 400 millions de doses de vaccin antiamaril ont été administrées dans le monde avec une excellente sécurité, même si des réactions générales bénignes ont lieu dans les premiers jours qui suivent la vaccination chez 10-30% des vaccinés: céphalées, myalgies, syndrome général et asthénie. Les réactions indésirables sévères sont extrêmement rares, mais lorsqu'elles surviennent, le nourrisson (encéphalite) et la personne âgée (défaillance multiviscérale) apparaissent plus sensibles que la population générale vaccinée contre le virus amaril. Trois types distincts de réactions indésirables graves au vaccin 17D ont été décrits:

1. *Réactions d'hypersensibilité*. La fréquence des réactions allergiques graves, des réactions anaphylactiques en particulier, est très faible. Cependant, le vaccin est produit par culture sur œuf de poule embryonné et il est contre-indiqué chez les personnes ayant des antécédents d'intolérance orale à l'œuf ou de réaction allergique forte aux produits à base d'œuf. En cas d'allergie aux protéines de l'œuf, la survenue de réactions d'allergie généralisées est possible, bien que très rare. La sensibilité à la gélatine, fréquemment utilisée comme stabilisant du vaccin, peut expliquer au moins un certain nombre de ces cas.

2. Maladie postvaccinale neurotrope. Depuis 1945, on connaît au total 26 cas au moins d'encéphalite postvaccinale prouvés ou probables, dont 16 chez des nourrissons de moins de 7 mois. Parmi ces 26 patients, 24 ont guéri sans séquelle. Le virus vaccinal isolé à partir de l'encéphale d'un cas fatal survenu chez un enfant de 3 ans était porteur de mutations du gène d'enveloppe du virus et une augmentation de sa neurovirulence a été mise en évidence dans les études chez l'animal. On ignore si les autres cas sont dus à des mutations comparables de la souche vaccinale. Un autre cas fatal est survenu chez un adulte immunodéprimé infecté par le VIH.

3. *Vaccine-associated viscerotropic disease.* During 1996–2001, 7 cases of YF vaccine-associated viscerotropic disease (including 6 deaths) occurred in Australia (1 case), Brazil (2 cases) and the United States (4 cases). Subsequently, 11 additional suspected or probable cases (including 2 deaths) have been reported from different countries. During 1996–2001, approximately 150 million doses of the vaccine were administered worldwide, of which 54 million doses were given in Brazil, where 2 cases of vaccine-associated viscerotropic disease were identified. Careful investigation of the first 7 cases reported suggested that an atypical host response, rather than genomic instability of the attenuated vaccine virus, caused the serious reactions. The risk of YF vaccine-associated viscerotropic disease appears to be limited to the first immunization against YF. The frequency of such reactions remains uncertain, although estimates based on Brazilian experience (including routine childhood immunization) indicate a risk in the order of 1 per 10 million doses. Comparative risk estimates from the United States (mainly protection of adult travellers) are 1 per 200 000–300 000 doses and 1 per 40 000–50 000 doses for vaccinees above 60 years of age.

Indications for YF vaccine

All persons aged 9 months or older and living in YF at-risk areas should receive YF vaccine. Highest priority should be given to those persons most likely to be exposed, such as forestry and agricultural workers, and to those living in villages or towns with a history of previous outbreaks. Immigrants to such regions from non-endemic areas should also be vaccinated against YF. During YF outbreaks, mass immunization should be instituted at the earliest possible stage and according to locally defined priorities. Travellers should be vaccinated at least 10 days before arrival in the at risk area.

Contraindications to YF vaccination

The vaccine is contraindicated in children aged under 6 months and is not recommended for those aged 6–8 months, except during epidemics when the risk of YF virus transmission may be very high. It is also contraindicated for persons with severe allergy to egg and for severely immunocompromised persons. On theoretical grounds, the 17D vaccine is not recommended during pregnancy. However, pregnant women may be vaccinated during epidemics when the risk of YFV transmission may be very high.

General WHO position on new vaccines

Vaccines for large-scale public health use should:

- meet the quality requirements as defined in the current WHO policy statement on vaccine quality;
- be safe and have a significant impact against the actual disease in all target populations;
- if intended for infants or young children, be easily adapted to the schedules and timing of national childhood immunization programmes;
- not interfere significantly with the immune response to other vaccines given simultaneously;
- be formulated to meet common technical limitations, e.g. in terms of refrigeration and storage capacity;

3. Maladie postvaccinale viscérotrope. De 1996 à 2001, on a observé 7 cas de maladie viscérotrope associées au vaccin antiamaril (dont 6 décès), 1 en Australie, 2 au Brésil et 4 aux Etats-Unis d'Amérique. Par la suite, 11 autres cas probables ou présumés (dont deux décès) ont été signalés dans différents pays. De 1996 à 2001, environ 150 millions de doses de vaccin ont été administrées dans le monde, dont 54 millions au Brésil, où 2 cas de maladie postvaccinale viscérotrope ont été identifiés. Une investigation soigneuse de ces 7 premiers cas signalés donne à penser que la gravité des réactions est due à une réponse atypique de l'hôte plutôt qu'à une instabilité génomique du virus vaccinal atténué. Le risque de maladie viscérotrope associé au vaccin antiamaril semble être limité à la première injection du vaccin. La fréquence de ces réactions reste mal connue; d'après les estimations reposant sur l'expérience brésilienne (y compris la vaccination systématique de l'enfant) le risque serait de l'ordre de 1 pour 10 millions de doses. Les estimations comparatives du risque à partir des données des Etats-Unis d'Amérique (protection des voyageurs adultes essentiellement) sont de 1 pour 200 000-300 000 doses et de 1 pour 40 000-50 000 doses chez les personnes vaccinées ayant plus de 60 ans.

Indications concernant le vaccin antiamaril

Toute personne âgée de neuf mois ou plus, vivant dans une zone à risque, doit être vaccinée. La priorité doit être donnée aux personnes dont le risque d'exposition est le plus élevé, par exemple les travailleurs forestiers et agricoles et la population des villages ou des villes touchés par de précédentes flambées. Les immigrants provenant de zones indemnes doivent également être vaccinés. Pendant une flambée la vaccination de masse doit être pratiquée le plus rapidement possible selon des priorités définies localement. Le voyageur doit être vacciné au moins 10 jours avant son arrivée dans une zone à risque.

Contre-indications à la vaccination

Le vaccin est contre-indiqué chez l'enfant âgé de moins de 6 mois et il n'est pas recommandé entre 6 à 8 mois, sauf pendant des épidémies où le risque de transmission du virus peut être très élevé. La vaccination est également contre-indiquée en cas d'allergie grave à l'œuf et chez les sujets gravement immunodéprimés. Le vaccin 17D n'est théoriquement pas recommandé pendant la grossesse, mais la femme enceinte peut être vaccinée en cas d'épidémie lorsque le risque de transmission est très élevé.

Position générale de l'OMS concernant les nouveaux vaccins

Les vaccins destinés à un usage à grande échelle aux fins de la santé publique doivent:

- répondre aux exigences concernant la qualité définies dans la déclaration actuelle de l'OMS sur la qualité des vaccins;
- être sûrs et avoir un effet considérable contre la maladie dans toutes les populations cibles;
- s'ils sont destinés au nourrisson ou au jeune enfant, être facilement adaptés au calendrier des programmes nationaux de vaccination de l'enfant;
- ne pas perturber gravement la réponse immunitaire aux autres vaccins donnés en même temps;
- être formulés de façon à tenir compte des contraintes techniques courantes, par exemple en ce qui concerne la réfrigération et la capacité de stockage;

- be appropriately priced for different markets.

WHO position on yellow fever vaccine

In 1988, the joint United Nations Children's Fund/WHO Technical Group on Immunization in Africa recommended that countries at risk for YF incorporate the 17D vaccine into their national immunization programme. Unfortunately, in most at-risk African countries, routine YF vaccination coverage remains low. In the at-risk countries of South America, YF vaccination has been used for decades, although national coverage and immunization strategies vary considerably. Coverage rates of more than 70% have been achieved in enzootic areas of Brazil and Bolivia whereas coverage of only about 30% has been reached in some other endemic areas.

The recent increase in YF incidence both in Africa and in areas of Latin America, where the disease had been under control for centuries, is alarming, particularly since the tools to prevent YF outbreaks are well known, safe and of documented effectiveness. When promoting increased use of YF vaccine in at risk areas, the outstanding safety and effectiveness profile, the long duration of protection and the cost-effectiveness of the 17D vaccine should continue to be emphasized. However, recent reports of severe, but very rare, vaccine-associated adverse events highlight the importance of careful post-licensure surveillance, even for well established vaccines. Enhanced surveillance of such events and careful molecular analyses of the 17D strains isolated from potential new cases as well as from the actual vaccine batches should contribute to the understanding of the pathogenetic mechanisms involved.

In countries at risk of YF, YF vaccine is recommended for use in all children aged at least 9–12 months of age. In addition, preventive vaccination of older children and adults is recommended in at risk areas. Vaccination for YF is also recommended for travellers aged above 9 months who plan to visit areas at risk for YF. Contraindications against YF vaccination include age less than 6 months, severe hypersensitivity to egg antigens and severe immunodeficiency. Whereas it is relatively easy to avoid immunization of the first two categories, the principal contraindications against immunization during pregnancy and in severe immunodeficiency cause significant practical problems. Fortunately, the few published cases of congenital infection caused by 17D have not been associated with fetal abnormalities. Similarly, no adverse events occurred in a small study of HIV-infected children with low CD4+ counts who received the vaccine. These observations are important considering the likelihood that many pregnant women and HIV-positive individuals, including children, will be immunized inadvertently during large-scale immunization activities in at-risk countries.

For international travellers, where laboratory and other resources are available, YF vaccination may be offered to asymptomatic HIV-infected persons with CD4+ counts above 200 cells/mm^3 who require vaccination for unavoidable travel. Individual expert assessments are required before YF vaccination may be offered to persons taking high-dose corticosteroids or antineoplastic drugs. If possible,

- pouvoir être achetés à des prix appropriés pour différents marchés.

Position de l'OMS concernant le vaccin de la fièvre jaune

En 1988, le Groupe technique commun UNICEF/OMS sur la vaccination en Afrique a recommandé l'intégration du vaccin 17D au programme national de vaccination des pays à risque. Malheureusement, dans la plupart des pays africains à risque, la couverture vaccinale antiamarile systématique reste faible. Dans les pays d'endémie sud-américains la vaccination antiamarile est utilisée depuis des décennies mais la couverture et les stratégies de vaccination nationales varient considérablement. Des taux de couverture de plus de 70% ont été atteints en Bolivie et au Brésil dans les zones enzootiques, alors qu'ailleurs, on ne dépasse pas 30% environ.

L'incidence accrue observée récemment en Afrique et dans certaines parties d'Amérique latine où la maladie était maîtrisée depuis des siècles est d'autant plus alarmante que les outils permettant d'éviter les flambées sont bien connus, sûrs et efficaces. Pour promouvoir l'usage accru du vaccin dans les zones à risque, il faut continuer de mettre l'accent sur l'innocuité et l'efficacité remarquables, la durée de protection très longue et le rapport coût/efficacité très favorable du vaccin 17D. Toutefois, certaines informations faisant état d'événements indésirables graves mais très rares associés au vaccin soulignent bien l'importance de la pharmacovigilance, même dans le cas de vaccins bien établis. Une surveillance accrue de ces événements et des analyses moléculaires approfondies des souches 17D isolées chez les nouveaux cas suspects, de même que sur les lots de vaccins, devrait aider à mieux comprendre les mécanismes pathogéniques.

Dans les pays à risque de fièvre jaune, la vaccination antiamarile est recommandée chez tout enfant âgé d'au moins 9 à 12 mois. En outre, des campagnes de vaccination préventives chez l'enfant plus âgé et l'adulte sont recommandées dans les zones à risque. La vaccination est également recommandée chez les personnes âgés de plus de 9 mois qui ont l'intention de se rendre dans une zone à risque. Les contre-indications à la vaccination concernent notamment l'enfant de moins de 6 mois, les cas d'hypersensibilité aux antigènes de l'œuf et les sujets gravement immunodéprimés. S'il est relativement facile d'éviter la vaccination des deux premières catégories, les principales contre-indications de la vaccination pendant la grossesse et en cas d'immunodéficience grave posent d'importants problèmes pratiques. Fort heureusement, les quelques cas publiés d'infection congénitale provoquée par le 17D n'ont pas été associés à des anomalies fœtales. De même, aucun événement indésirable n'a été mis en lumière dans le cadre d'une étude restreinte sur la vaccination d'enfants infectés par le VIH, ayant une numération basse de CD4+. Ces observations sont importantes compte tenu du fait que de nombreuses femmes enceintes et de nombreux VIH-positifs, et notamment des enfants, seront vaccinés accidentellement dans le cadre d'activités de vaccination à grande échelle dans les pays à risque.

Dans le cas des voyageurs internationaux, on peut, lorsqu'on dispose de moyens de laboratoire et d'autres ressources, proposer le vaccin à des personnes infectées par le VIH asymptomatique dont la numération CD4+ dépasse 200 par mm^3 qui ont besoin d'une vaccination pour un voyage auquel ils ne peuvent se soustraire. Une évaluation par un spécialiste s'impose avant que la vaccination ne soit proposée à des personnes prenant d'importantes doses de cor-

tests should be performed to ensure that protective levels of neutralizing antibodies have been achieved, as primary vaccination failure is common in immunodeficient individuals.

According to the *International health regulations* and the *WHO International certificate of vaccination*, a booster-dose of YF vaccine is required every 10 years. However, in most cases, the duration of protection following the first dose of YF vaccine seems to be at least 30–35 years and possibly lifelong. For this reason, it has been proposed to limit vaccination against YF to a single dose. In order to clarify this matter, WHO organized a consultation with a group of YF experts in March 2003. This group reviewed relevant literature and available data and concluded that, at present, the evidence for protective immunity beyond 10 years was insufficient to justify a change in the current YF vaccination policy for international travellers. However, in at-risk countries, vaccination resources should be directed to ensuring good primary vaccination coverage rather than to providing booster doses. For the purposes of international travel, only YF vaccinations performed at nationally authorized YF vaccination sites and using WHO pre-qualified YF vaccines may be entered into the International Certificate of Vaccination. Each year, 9 million travellers from areas not at risk travel to YF at-risk countries in Africa and South America, and at least 3 million of these persons may visit regions where YF transmission is ongoing. Estimates from the United States indicate that only 10–30% of such travellers have been vaccinated against YF. On the other hand, the number of imported cases to non-endemic regions is remarkably low, probably indicating that the percentage of vaccinated persons is considerably higher among those visiting the most YF-affected areas. Given the very rare, but potentially severe, adverse effects, YF vaccine for travellers should be administered on strict indications only, particularly in the elderly. Restriction of YF vaccination to authorized centres is likely to promote the appropriate use of YF vaccine.

A serious international shortage of the vaccine was demonstrated in connection with the YF outbreak in Guinea in 2000. Concerned international organizations have agreed to build up an emergency stockpile of YF vaccine that should be retained for outbreak response in Africa and South America. A stockpile of 6 million doses is now reserved for this purpose. Mechanisms should be found to provide incentives for manufacturers of YF vaccine to sustain or increase their production capacity to ensure rapid delivery of sufficient quantities in the event of a major YF outbreak.

Stockpiling of vaccine for emergency use is necessary but does not solve the underlying problem. To avoid devastating outbreaks of YF in the future, YF vaccine must be fully introduced into well functioning childhood vaccination programmes. In addition, childhood vaccination should be combined with pre-emptive YF vaccination campaigns in at-risk areas, and in urban areas control efforts directed against *Ae. aegypti* should be increased. In areas of predominantly jungle-type transmission, YF vaccination of persons belonging to the high-risk groups is strongly recommended.

In most countries, YF occurs in remote regions where human and technical resources are limited. For this reason, annual reports on the incidence of YF greatly underesti-

ticoïdes ou des antitumoraux. Si possible, des tests doivent être effectués pour vérifier que les titres protecteurs en anticorps neutralisants ont été atteints car l'échec de la primovaccination est fréquent chez les sujets immunodéprimés.

Le *Règlement sanitaire international* et le *Certificat international de vaccination de l'OMS* prévoient qu'un rappel de vaccination s'impose tous les 10 ans. Toutefois, dans la plupart des cas, la durée de la protection après l'administration de la première dose de vaccin semble être d'au moins 30 à 35 ans, voire pour le reste de la vie. Pour cette raison, il a été proposé de limiter la vaccination antiamarile à une dose unique. Afin de clarifier la question, l'OMS a organisé une consultation avec un groupe d'experts de la fièvre jaune en mars 2003. Le groupe a fait le point sur la littérature et les données disponibles, et a conclu qu'à l'heure actuelle les éléments concernant l'immunité protectrice au-delà de 10 ans étaient insuffisants pour justifier une modification de la politique de vaccination actuellement applicable aux voyageurs internationaux. Toutefois, dans les pays à risque, les ressources doivent viser à assurer une bonne couverture par la primovaccination plutôt qu'à administrer des rappels. Aux fins des voyages internationaux, seules les vaccinations effectuées dans des centres de vaccination autorisés sur le plan national utilisant des vaccins présélectionnés de l'OMS peuvent être inscrites sur le certificat international de vaccination. Chaque année, 9 millions de voyageurs de zones indemnes se rendent dans des pays à risque en Afrique et en Amérique du Sud, et au moins 3 millions de ces personnes se rendent dans des régions à transmission de la fièvre jaune. Les estimations aux Etats-Unis indiquent que 10 à 30% seulement de ces voyageurs ont été vaccinés contre la fièvre jaune. En revanche, le nombre de cas importés dans des zones exemptes de l'endémie reste remarquablement faible, ce qui indique probablement que le pourcentage de vaccinés est considérablement plus élevé chez les personnes se rendant dans les zones les plus touchées. Etant donné le caractère très rare mais potentiellement grave des effets indésirables, le vaccin antiamaril ne doit être administré aux voyageurs que selon des indications strictes, notamment en ce qui concerne les personnes âgées. La restriction de la vaccination aux centres autorisés devrait promouvoir l'usage approprié du vaccin.

Une grave pénurie internationale du vaccin est apparue lors de la flambée de fièvre jaune en Guinée, en 2000. Les organisations internationales concernées ont convenu de constituer des stocks d'urgence de vaccin, devant être maintenus pour faire face à des flambées en Afrique et en Amérique du Sud. Des stocks de 6 millions de doses sont actuellement maintenus à cette fin. On devrait trouver des moyens d'inciter les fabricants de vaccins à maintenir ou accroître leur capacité de production afin d'assurer un approvisionnement rapide de quantités de vaccins suffisantes en cas de flambée majeure.

Le stockage du vaccin à des fins d'urgence s'impose, mais ne résout pas le problème sous-jacent. Pour éviter des flambées dévastatrices de fièvre jaune à l'avenir, le vaccin doit être entièrement intégré aux programmes de vaccination de l'enfant qui donnent satisfaction. D'autre part, dans les zones à risque, la vaccination de l'enfant doit être associée avec des campagnes de rattrapage préventives et, en milieu urbain, des efforts de lutte accrus devraient être menés contre *Ae. aegypti*. Dans les zones à transmission avant tout selvatique, la vaccination des sujets appartenant aux groupes à hauts risques est fortement recommandée.

Dans la plupart des pays, la fièvre jaune survient dans des zones reculées où les ressources humaines et techniques sont limitées. C'est pour cela que des rapports annuels sur l'incidence de la mala-

mate the true burden disease. WHO recognizes the urgent need for improved surveillance of YF in at-risk countries. In terms of clinical presentation, however, individual cases of YF may not be differentiated easily from other haemorrhagic fevers or from diseases such as malaria, influenza and typhoid fever, all of which occur in countries endemic for YF. There is therefore an urgent need for rapid laboratory confirmation of diagnosis in clinically suspected cases. WHO recommends extended use of the filter-paper method for blood collection because it improves safety of the procedure and simplifies both collection and transportation of the samples. Dried blood on filter-paper allows testing for PCR products as well as for YF virus-specific IgM. ■

die ont tendance à sous-estimer fortement la charge réelle de morbidité. L'OMS reconnaît la nécessité d'améliorer d'urgence la surveillance dans les pays à risque. Toutefois, en ce qui concerne la présentation clinique, il n'est pas facile de différencier les cas individuels des cas d'autres fièvres hémorragiques ou de maladies telles que le paludisme, la grippe et la fièvre typhoïde qui, toutes, touchent les pays à risque. Il est donc urgent de disposer de moyens permettant de confirmer rapidement au laboratoire le diagnostic chez des cas suspects cliniques. L'OMS recommande un plus large usage de la méthode du confetti pour recueillir les prélèvements de sang car elle améliore la sécurité et simplifie à la fois la recueil et le transport des prélèvements. Les confettis permettent de pratiquer la PCR et la recherche des IgM spécifiques du virus amaril. ■

New, affordable vaccine stops meningitis – now WHO appeals for funds

An inexpensive new meningitis vaccine has been made available in record time and, on 25 September 2003, WHO issued an appeal for the funds to buy millions of doses of the vaccine before the start of the meningitis season.

Each year, meningitis sweeps across sub-Saharan Africa, with outbreaks sometimes involving 100 000 people or more. Vaccination is the only effective public health weapon to combat these outbreaks. Two years ago, however, those battling the disease suffered an enormous setback with the emergence of the W135 strain, for which no affordable vaccine existed. The response was the development by GlaxoSmithKline, in record time, of a new vaccine specifically for these outbreaks. It is being made available to WHO at reduced cost, to allow the building of an emergency response stockpile for African countries. Funds are now urgently needed for production of the new vaccine before the next wave of meningitis begins. Production constraints mean that funds to purchase 6 million doses must be found within days.

This is an urgent public health situation – one that forces quick action. If the appeal is successful, enormous suffering can be prevented, lives saved, and hope given to tens of thousands of people who live in the direct path of this disease.

Every year, the disease ravages people living in Africa'a "meningitis belt" – a swathe stretching from Ethiopia to Senegal and with a population of 350 million. At least 10% of those infected die, and many others are left permanently disabled. The new threat – strain W135 – exploded in Burkina Faso in 2002, striking more than 13 000 people and killing at least 1500.

With the emergence of W135 as a major threat, WHO went to work with GlaxoSmithKline, and later with the Bill & Melinda Gates Foundation, to develop, test, and license a new vaccine. That work is now done, and meningitis, even in its newest and most threatening form, can be slowed significantly if there is money to buy the vaccine.

However, the tragedy of meningitis will be compounded is this new vaccine cannot be made available to those who need it most.

Un nouveau vaccin d'un prix abordable barre la route à la méningite – l'OMS lance un appel de fonds

Un nouveau vaccin bon marché contre la méningite a été mis à disposition en un temps record et le 25 septembre 2003, l'OMS a lancé un appel afin d'acheter des millions de doses de ce vaccin avant le début de la saison de la méningite.

Chaque année, la méningite ravage l'Afrique subsaharienne, déclenchant parfois des flambées pouvant toucher 100 000 personnes ou davantage. La vaccination est la seule arme de santé publique efficace pour combattre ces flambées. Toutefois, il y a deux ans, ceux qui se battaient contre cette maladie ont essuyé une déconvenue de taille avec l'émergence de la souche W135, contre laquelle il n'existait aucun vaccin d'un prix abordable. Mais en un temps record, un nouveau vaccin spécifiquement destiné à lutter contre ces flambées a été mis au point par GlaxoSmithKline. Il est mis à la disposition de l'OMS à prix réduit afin de constituer un stock d'urgence destiné aux pays africains. Aujourd'hui, il est urgent de trouver des fonds pour produire ce nouveau vaccin avant le début de la prochaine vague de méningite. A cause des impératifs de production, il faut trouver en quelques jours de quoi acheter 6 millions de doses.

Il s'agit d'une situation sanitaire d'urgence qui oblige à prendre des mesures rapides. Si cet appel s'avère être une réussite, il sera possible d'éviter de grandes souffrances, de sauver des vies et d'apporter de l'espoir aux dizaines de milliers de personnes qui sont les plus exposées à cette maladie.

Chaque année, la méningite sévit parmi les populations vivant dans la ceinture africaine de la méningite, une bande qui s'étend de l'Ethiopie au Sénégal et dans laquelle vivent 350 millions de personnes. Elle tue 10% au moins de ceux qui sont infectés et elle handicape à vie de nombreuses autres personnes. La nouvelle menace que fait peser la W135 a explosé au Burkina Faso en 2002, frappant plus de 13 000 personnes et en tuant au moins 1500.

Lorsqu'elle a mesuré l'importance de cette nouvelle menace, l'OMS s'est associée à GlaxoSmithKline, puis à la Fondation Bill et Melinda Gates, afin de mettre au point, de tester et d'homologuer ce nouveau vaccin. Ce travail est achevé et aujourd'hui la méningite, même sous sa forme la plus nouvelle et la plus menaçante, pourrait être considérablement freinée si l'on disposait des moyens voulus pour acheter le vaccin.

Le problème de la méningite sera encore plus grave si nous ne sommes pas en mesure de procurer ce nouveau vaccin à ceux qui en ont le plus besoin.

PROTOCOL FOR A SYSTEMATIC REVIEW –EPIDEMIOLOGY OUTCOMES

Title: Systematic review of the nonspecific effects of BCG, DTP and standard titre measles containing vaccines on deaths from infections other than those conditions that the given vaccine is designed to prevent and, on all-cause mortality in children under five years of age.

Authors: Reingold A, Higgins J, Sterne J, Low N, Soares-Weiser K, Riveros X and Henao-Restrepo AM

Date: March 18, 2012

Overall aim

- To determine if the current evidence is sufficiently compelling 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.

Review Objectives: To systematically identify, assemble, and review all published and grey literature concerning epidemiological studies addressing "non-specific" effects of BCG, measles and, DTP-containing vaccines on: (i) survival/deaths from infections other than those conditions that the vaccine is designed to prevent and, (ii) on all-cause mortality in children under five years of age and ; to critically appraise the evidence using existing guidelines.

1. The protocol	
1.1 Primary questions	a. Is the administration of BCG in infancy associated with an effect on survival /deaths from infections other than those conditions that the vaccine is designed to prevent in children up to five years of age? b. Is the administration of DTP in infancy associated with an effect on survival/deaths from infections other than those conditions that the vaccine is designed to prevent in children up to five years of age? c. Is the administration of Measles in infancy associated with an effect on survival/ deaths from infections other than those conditions that the vaccine is designed to prevent in children up to five years of age?
1.2 Secondary questions	a. Is administration or non-administration of BCG vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age? b. Is administration or non- administration of DTP-containing vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age? c. Is administration or non- administration of measles-containing vaccine in infancy associated with an effect on all-cause mortality/deaths from all causes in children up to five years of age? For each question we will also assess if the effect is modified by gender, number of doses, age at vaccination, sequence/order in which vaccines are given and/or prior, or co-administration of vitamin A.
2. Methods	
2.1 Criteria for selecting studies for this review	Types of studies included • RCT or quasi-randomized controlled trials • Observational epidemiological studies: case-control studies and, prospective, historical and ambi-directional cohort studies.
Types of **P**articipants	Children up to five years of age
Types of **I**nterventions	Vaccination with BCG, DTP and measles-containing vaccines
Types of **O**utcome measures	• survival/all-cause mortality/deaths from infections other than those conditions that the vaccine is designed to prevent and, • death from all causes (e.g. all-cause mortality, child survival)

2.2 Search methods for identification of studies	There will be no restrictions on language, study design (except as noted above), length of follow-up, and report characteristics (e.g. date of publication or listing, publication status). We will search in electronic databases, grey literature, conduct manual searches, and contact lead authors and search on specialized websites.
Sampling strategy	Comprehensive strategy to identify all articles on: (i) effect of vaccines on survival/deaths from infections other than those conditions that the vaccine is designed to prevent and, (ii) effect of vaccines on or all-cause mortality
Type of studies	No restrictions, all study types included
Approaches	Electronic search in various databases plus: • Grey literature • Hand searches • Contact lead authors in the field
Range of years (start date and end date)	No restrictions From the beginning of each candidate database to December 15, 2012.
Limits	No limits
Inclusions and exclusions	No inclusions or exclusions applied
Terms used	See Full version of protocol
Electronic sources	See Full version of protocol
3.Data Collection and Analysis	
Data extraction	Data extraction sheet using predefined data fields for extracting consistent data from eligible articles. The sheet will also include variables that will permit assessment of the risk of bias of each individual study informed by key elements from two methods papers on nonspecific effects of vaccines (Fine et al 2009 and Farrindon P et al 2009)
Assessment of risk of bias of included studies	RCTs: COCHRANE-Risk of bias tool Observational studies: a new tool will be developed specifically for this review drawing on a new tool under development within the Cochrane Collaboration
Data analysis (summary)	For each study, the rate ratio (RR) for vaccinated compared with unvaccinated individuals, with 95% confidence interval (CI) will be derived. If only hazard ratios are available for a study, we use these instead. If only 2×2 data (rather than person-years) are available we will estimate risk ratios. We will assume that these approximate to rate ratios provided that overall mortality risk is low. For case-control studies we will derive odds ratios: we will assume that these approximate to rate ratios in the general population. Where possible, we will compare published estimates with those directly calculated from raw data. Where data are available for two or more time periods we will plot RRs and 95% CIs over time. Where studies are considered substantively similar enough for meta-analysis to be appropriate, both fixed- and random-effects analyses will be carried out. Heterogeneity (differences between the true vaccine effects in the different studies) will be quantified by estimating the between-study variance $\tau 2$. Factors that may bias estimates from case-control studies will be examined by displaying the results in forest plots stratified by these factors and their effects will be estimated in meta-regression analyses. These factors include whether a matched design has been ignored in the analysis (giving "crude" estimates from studies that have a matched design), and whether the controls were sampled from the same population as the cases. As sensitivity analyses we will report analyses restricted to studies assessed as at low, and low or unclear, risk of bias if this is feasible
4.Assessment of the strength of conclusions	We will use the GRADE approach, as modified by WHO Strategic Advisory Group of Experts (SAGE), to assess the evidence in support of various hypothesized associations between various vaccines and (i) survival/all-cause mortality/deaths from infections other than those conditions that the vaccine is designed to prevent and/or; (ii) on all-cause mortality/deaths by all causes/survival in children less than five years of age in all settings. Results will be summarized in GRADE tables.

PROTOCOL FOR A SYSTEMATIC REVIEW –IMMUNOLOGY OUTCOMES

Title: Systematic review of the nonspecific effects of selected routine childhood immunizations.

Authors: Andrew Pollard and Karlijn De Nie, Department of Paediatrics, University of Oxford

Date: March 18, 2012

Overall aim

- To determine if the current evidence is sufficiently compelling 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.

Review Objectives: To systematically identify, assemble, and review all available studies and data addressing the possible "non-specific" or "heterologous" effects of BCG, measles, DPT, including studies with immunologic endpoints and, to critically appraise the evidence using the GRADE approach, as modified by WHO Strategic Advisory Group of Experts (SAGE).

1. The protocol	
1.1 Primary questions	a. What is the effect of BCG vaccine given before 5 years of age on immune response markers? b. What is the effect of measles vaccine given before 5 years of age on immune response markers? c. What is the effect of DPT vaccine given before 5 years of age on immune response markers? d. What is the effect of any of these three vaccines under review given before 5 years of age on the T helper cell type 1/ T helper cell type 2 balance? e. If, in infancy, one of the three vaccines under review is given first, does that effect the antibody response to a second different vaccine?
1.2 Secondary questions	a. Do the effects on immune response markers, if any, of any of the vaccines under review vary by gender of the child? b. Do the effects on immune response markers, if any, of any of the vaccines under review vary by age at which they are delivered? c. Do the effects on immune response markers, if any, of any of the vaccines under review vary by co-administration of Vitamin A? d. Do the effects on the T helper cell type 1/ T helper cell type 2 balance, if any, of any of the vaccines under review vary by gender, age or co-administration of vitamin A.
2. Methods	
2.1 Criteria for selecting studies for this review	Types of studies included • randomized controlled trials (RCTs), quasi-randomized control trials, clinical trials, • cohort studies, case-control studies, case series and case reports. .
Types of **P**articipants	Children up to five years of age
Types of **I**nterventions	Vaccinations with all BCG and standard titre measles containing vaccines, all diphtheria and tetanus toxoids, and Bordetella pertussis containing vaccines..
Types of **O**utcome measures	• immune response markers • T helper cell type 1/ T helper cell type 2 balance
2.2 Search methods for identification of studies	There will be no restrictions on language, study design (except as noted above), length of follow-up, and report characteristics (e.g. date of publication or listing, publication status). We will search in electronic databases, grey literature, conduct manual searches, and contact lead authors and search on specialized websites.
Sampling strategy	Comprehensive strategy to identify all articles on effect of vaccines on immunological markers

Type of studies	No restrictions, all study types included
Approaches	Electronic search in various databases plus, Grey literature, Hand searches, Contact lead authors in the field
Range of years (start date and end date)	No restrictions From the beginning of each candidate database to December 15, 2012.
Limits	No limits
Inclusions and exclusions	No inclusions or exclusions applied
Terms used	See Full version of protocol
Electronic sources	See Full version of protocol
3.Data Collection and Analysis	
Data extraction	We will develop forms for extracting consistent data about: • exposures and outcomes (including methods or criteria for diagnosis); • tests used to assess outcomes, any cut-off points used in the assessment of immunogenicity and the time between last vaccination and outcome assessment; • presence of disease that might affect immunogenicity outcomes; • co-administration of other vaccines or vitamin A; • potential confounders if relevant; • background data (e.g. geographic and demographic information); • methodological and reporting quality (specific for each type of study design and based on published checklists of items likely to cause bias); and other potentially relevant information such as funding source.
Assessment of risk of bias of included studies	RCTs: COCHRANE-Risk of bias tool Observational studies: a new tool will be developed specifically for this review drawing on a new tool under development within the Cochrane Collaboration
Data analysis (summary)	We will produce descriptive tables summarizing information about study design, study quality, and results of all included studies. If there is more than one study reporting an exposure-outcome relationship, or the frequency of an outcome, we will present the results using forest plots and consider combining the data statistically in a meta-analysis. We will examine heterogeneity of the results first using X2 test and I2 test (Higgins JP and Thompson SG, quantifying heterogeneity in a meta-analysis Stat Med 2002.21 (11):p. 1539-58). If a meta-analysis is appropriate we will calculate summary weighted effects measures and 95% CI using random effects models (Der Simmonian R Laird N Meta-analysis in clinical trials. Control Clin Trials, 1986. 7 (3): p177-88). If sufficient data are available, results will also be examined for apparent bias in a reporting/publication of studies using funnel plots and Egger's test (Egger M Davies-Smith G and Altman H. Systematic Review in health care, Meta-analysis in context (2001, London: BMJ books).
4.Assessment of the strength of conclusions	We will use the GRADE approach, as modified by WHO Strategic Advisory Group of Experts (SAGE), to assess the evidence in support of various hypothesized associations between various vaccines and heterologous effects.

What influences vaccine acceptance: A model of determinants of vaccine hesitancy

Definition of vaccine hesitancy

Vaccine hesitancy is a behavior, influenced by a number of factors including issues of **confidence** (do not trust vaccine or provider), **complacency** (do not perceive a need for a vaccine, do not value the vaccine), and **convenience** (access). Vaccine hesitant individuals are a heterogeneous group who hold varying degrees of indecision about specific vaccines or vaccination in general. Vaccine hesitant individuals *may accept* all vaccines *but remain concerned* about vaccines, some may refuse or delay some vaccines, but accept others; some individuals may refuse all vaccines.

Definition of vaccination confidence

Trust in the effectiveness and safety of vaccines and in the system that delivers them, including the reliability and competence of the health services and health professionals and having trust in the motivations of the policy-makers who decide which vaccines are needed and when they are needed. Vaccination confidence exists on a continuum, ranging from zero-to-100% confidence. Vaccination confidence is only one of a number of factors that affect an individual's decision to accept a vaccine.

Definition of vaccine complacency

Vaccine complacency exists where perceived risks of vaccine-preventable diseases are low and vaccination is not deemed a necessary preventive action. Besides perceptions of the threat of disease severity and/or transmission, complacency about a particular vaccine or about vaccination in general can be influenced by under-appreciation of the value of vaccine (effectiveness and/or safety profile) or lack of knowledge. Immunization program success may result in complacency and ultimately, hesitancy, as individuals weigh risks of vaccines against risks of diseases that are no longer common as a result of immunization.

Definition of vaccination convenience

The quality of the service (real and/or perceived) and the degree to which vaccination services are delivered at a time and place and in a way that is considered appealing, affordable, convenient and comfortable, also affects the decision to vaccinate. Vaccination convenience and complacency are also determined by the priority that an individual places on vaccination.

Vaccine decision making by a caregiver or patient is a complex process with many factors influencing this both directly and indirectly. Some factors may be more important in certain contexts than in others. Experience and circumstances may change the weight of a factor(s) in different settings.

CONTEXTUAL INFLUENCES **Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors**	**a.Communication and media environment** *Media and social media can create a negative or positive vaccine sentiment and can provide a platform for lobbies and key opinion leaders to influence others; social media allows users to freely voice opinions and experiences and it can facilitate the organization of social networks for or against vaccines .*	**b. Influential leaders, gatekeepers and anti- or pro-vaccination lobbies** *Community leaders and influencers, including religious leaders in some settings, celebrities in others, can all have a significant influence on vaccine acceptance or hesitancy.*	**c.Historical influences** *Historic influences such as the negative experience of the Trovan trial in Nigeria can undermine public trust and influence vaccine acceptance, as it did for polio, especially when combined with pressures of influential leaders and media. A community's experience isn't necessarily limited to vaccination but may affect it.*	**d.Religion/culture/gender/socio-economic** *A few examples of the interplay of religious/cultural influences include:* *Some religious leaders prohibit vaccines* *Some cultures do not want men vaccinating children* *Some cultures value boys over girls and fathers don't allow children to be vaccinated),*	**e. *Politics/policies*** *(Mandates)* *Vaccine mandates can provoke vaccine hesitancy not necessarily because of safety or other concerns, but due to resistance to the notion of forced vaccination*	**f.Geographic barriers** *A population can have general confidence in a vaccine and health service, and be motivated to receive a vaccine but hesitate as the health center is too far away or access is difficult.*	**g.Pharmaceutical industry** *Industry may be distrusted and influence vaccine hesitancy when perceived as driven only by financial motives and not in public health interest; This can extend to distrust in government when perceived that they are also being pushed by industry and not transparent.*

<u>INDIVIDUAL and GROUP INFLUENCES</u> **Influences arising from personal perception of the vaccine or influences of the social/peer environment**	**a. Experience with past vaccination** *Past negative or positive experience with a particular vaccination can influence hesitancy or willingness to vaccinate. Knowledge of someone who suffered from a VPD due to non-vaccination may enhance vaccine acceptance. Personal experience or knowledge of someone who experienced an AEFI can also influence hesitancy.*	**b.Beliefs, attitudes about health and prevention** *Vaccine hesitancy can result from 1) beliefs that vaccine preventable diseases (VPD) are needed to build immunity (and that vaccines destroy important natural immunity) or 2) beliefs that other behaviors (breastfeeding, traditional/alternative medicine or naturopathy) are as or more important than vaccination to maintain health and prevent VPDs.*	**c.Knowledge/awareness** *Decisions to vaccinate or not are influenced by a number of the factors addressed here, including level of knowledge and awareness. Vaccine acceptance or hesitancy can be affected by whether an individual or group has accurate knowledge, a lack of awareness due to no information, or misperceptions due to misinformation. Accurate knowledge alone is not enough to ensure vaccine acceptance, and misperceptions may cause hesitancy, but still result in vaccine acceptance.*	**d. Health system and providers-trust and personal experience.** *Trust or distrust in government or authorities in general, can affect trust in vaccines and vaccination programmes delivered or mandated by the government. Past experiences that influence hesitancy can includes system procedures that were too long or complex, or personal interactions were difficult.*	**e. Risk/benefit (perceived, heuristic)** *Perceptions of risk as well as perceptions of lack of risk can affect vaccine acceptance. Complacency sets in when the perception of disease risk is low and little felt need for vaccination. E.g. Patient's or caregiver's perceptions of their own or their children's risk of the natural disease or caregivers' perceptions of how serious or life threatening the VPD is.*	**f. Immunisation as a social norm vs. not needed/harmful** *Vaccine acceptance or hesitancy is influenced by peer group and social norms*

VACCINE/ VACCINATION -specific issues **Directly related to vaccine or vaccination**	**a. Risk/ Benefit (scientific evidence)** *Scientific evidence of risk/benefit and history of safety issues can prompt individuals to hesitate, even when safety issues have been clarified and/or addressed e.g. suspension of rotavirus vaccine due to intussusception; Guillain-Barre syndrome following swine flu vaccine (1976) or narcolepsy (2011) following (A)H1N1 vaccination; milder, local adverse events can also provoke hesitancy.*	**b. Introduction of a new vaccine or new formulation** *Individuals may hesitate to accept a new vaccine when they feel it has not been used/tested for long enough or feel that the new vaccine is not needed, or do not see the direct impact of the vaccine (e.g. HPV vaccine preventing cervical cancer). Individuals may be more willing (i.e. not complacent) to accept a new vaccine if perception of the VPD risk is high.*	**c. Mode of administration** *Mode of administration can influence vaccine hesitancy for different reasons. E.g. oral or nasal administrations are more convenient and may be accepted by those who find injections fearful or they do not have confidence in the health workers skills or devices used.*	**d. Design of vaccination program/Mode of delivery** *Delivery mode can affect vaccine hesitancy in multiple ways. Some parents may not have confidence in a vaccinator coming house-to-house; or a campaign approach driven by the government. Alternatively if a health centre is too far or the hours are inconvenient*	**e. Reliability and/or source of vaccine supply** *Individuals may hesitate if they do not have confidence in the system's ability to provide vaccine(s) or might not have confidence in the source of the supply (e.g. if produced in a country/culture the individual is suspicious of) ; health workers may also be hesitant to administer a vaccine (especially a new one) if they do not have confidence that the supply will continue as it affects their clients trust in them. Caregivers may not have confidence that a needed vaccine and or health staff will be at the health facility if they go there.*	**f. Vaccination schedule** *Although there may be an appreciation for the importance of preventing individual vaccine preventable diseases, there may be reluctance to comply with the recommended schedule (e.g. multiple vaccines or age of vaccination).* *Vaccination schedules have some flexibility that may allow for slight adjustment to meet individual needs and preferences. While this may alleviate hesitancy issues, accommodating individual demands are not feasible at a population level.*	***g. Costs*** *An individual may have confidence in a vaccine's safety and the system that delivers it, be motivated to vaccinate, but not be able to afford the vaccine or the costs associated with getting themselves and their child(ren) to the immunization point. Alternatively, the value of the vaccine might be diminished if provided for free.*	**h. Role of healthcare professionals** *Health care professionals (HCP)are important role models for their patients; if HCPs hesitate for any reason (e.g. due to lack of confidence in a vaccine's safety or need) it can influence their clients' willingness to vaccinate*

While some of the factors presented in this matrix could easily be understood as mostly convenience issues (e.g. costs, geographic distance to vaccination clinic), to some extent all of these factors can affect confidence (e.g. if I have to pay for the vaccine it can make me hesitate to accept it, because "if it was really important, it would be included in the publicly funded program"). Some factors could also be included in the three Cs, depending on the context. For instance, "vaccination schedule" could be understood as a confidence issue (e.g. if parents lack confidence in it – "too many vaccines, too early"), as a convenience issue (e.g. if parents have transport problems to come for all visits needed to fully immunize their child) or as complacency issue (e.g. if parents don't think that it is important for their child to receive booster doses). Indeed, confidence, complacency and convenience issues can all result in vaccine hesitancy.

Understanding how barriers to vaccine uptake belong to one or many of the Cs is important in the design of activities and strategies that could have a positive impact on vaccine hesitancy. The varied drivers of hesitancy require different type of interventions (convenience issues call for activities and strategies such as reducing costs or enhancing geographic access to vaccination services, etc. whereas issues around low confidence may require trust building strategies such as improved dialogue).

Vaccine Hesitancy – Literature Review

21 March 2013

A review of vaccine hesitancy

A literature review was undertaken to "explore vaccine hesitancy in different settings including its context-specific causes, its expression and its impact" as outlined in the SAGE Working Group's terms of reference. Specific objectives were to:

1) Identify factors that act as either barriers or promoters of vaccination; and
2) Map these onto the "Model of determinants of vaccine hesitancy" as developed by the SAGE WG to assess its relevance and guide its further development.

This literature review was undertaken by researchers of *The Vaccine Confidence Project* (VCP)[1], based at the London School of Hygiene and Tropical Medicine, with input from members of the working group.

Key Findings:

- Research about trust and confidence in, and hesitancy towards, vaccines and vaccination programmes has doubled in the last five years;
- Issues around trust, confidence and hesitancy are of global interest – studies from all WHO regions were identified – although studies about the WHO EUR and AMERICAS regions dominate the field. Of concern is the limited research available in regions where the majority of the world's population of children live;
- A variety of factors are identified as being associated with vaccine hesitancy but their independent and relative strength of influence is complex and context-specific – varying across time, place and vaccines;
- The literature does not yet quantify the overall impact of vaccine hesitancy;
- There are no established metrics for vaccine hesitancy. Factors examined in the quantitative literature are often drawn from the core theoretical constructs of classic social cognitive models (e.g., Health Belief Model, Theory of Planned Behaviour), which do not adequately account for the influence of broader contextual features and limit interpretation around the complex multi-factorial relationships at play.

[1] http://www.vaccineconfidence.org/

A literature review of vaccine hesitancy:
its causes, its expression and its impacts

Introduction

Vaccination is often heralded as one of the most important achievements of public health; however, this success has always been accompanied by opposition to its practice (1). Historical reasons for objection have never been singular nor straight-forward, drawing motivation from several frames of reference including religious, scientific and political (2,3). Present day issues around vaccination share the same diversity but are arguably, more complex, as more vaccines are available, and the world takes on a more global profile (4). One observed impact of this growing complexity is an increase in the expression of public concerns and sense of uncertainty around vaccines; both have been linked in developed countries to an increase in the number of people seeking alternative vaccination schedules (5,6) and decisions to delay or even refuse vaccination (7).

In recent years, this phenomenon has been labeled and investigated as 'vaccine hesitancy' (8-10). Vaccine-hesitant individuals have been defined as a heterogeneous group in the middle of a continuum ranging from total acceptance to complete refusal; these individuals may refuse some vaccines, but agree to others; delay vaccines or accept vaccines but are unsure of doing so (11,12).

Several systematic reviews offer insight into the factors that influence vaccine hesitancy across different populations and vaccines (13-16). However, there is also evidence to suggest that not all potentially relevant factors have been identified or thoroughly investigated (17,18). As such, the purpose of this first-phase literature review is to adopt a more panoramic lens in order to frame a broad selection of factors that have been identified as potential influencers of vaccine hesitancy and help bring into focus what these factors look like globally.

Figure 1. Overview of SAGE Working Group (WG) "Model of determinants of Vaccine Hesitancy"

Methods

Search strategy and selection criteria

The *Vaccine Confidence Project* (VCP) is currently running a global systematic review investigating public trust in vaccines and vaccination programmes (Part A). Given the broad scope of this review, which includes vaccine hesitancy and confidence, a subset of studies was extracted to support the SAGE WG literature review (Part B and C).

Part A

VCP Systematic Review

Published articles in all languages were identified using multidisciplinary mainstream and regional electronic databases *(Table 1)*.

Table 1. Electronic databases searched

Database	Date Range
Medline	1946 – November Week 2 2012
Embase Classic & Embase	1947 - 2012 November 19
PsychInfo	1806 - November Week 2 2012
Cochrane	1993 - 12 November 2012
CINAHL Plus	1937 – 12 November 2012
Web of Science	1970 – November Week 1 2012
IBSS	1951 – November Week1 2012
LILACS	1982 – November Week 1 2012
AfricaWideInfo	19th century – 19 November 2012
IMEMR	1984 – 12 November 2012

The search strategy included an extensive list of keywords *(Table 2)* and related MeSH/subject headings in an effort to capture the many dimensions and expressions of trust, as well as related subject headings adjusted accordingly to each database. The search strategy was first developed in Medline and then adapted as necessary across each database; the full search strategy, including MeSH terms, is laid out in Appendix 2. The search first run in October 2011 and updated on 19 July 2012.

Table 2. Keywords used in search strategy for literature review on vaccine hesitancy

vaccin*	**AND**	anxiety	doubt*	trust	intent*	dilemma*
		attitude*	distrust	mistrust	controvers*,	objector*
		awareness	dropout*	Perception*	misconception*	uptake
immunis*		behavi*r	exemption *	refus*	misinformation	barrier*
		belief*	fear*	rejection	opposition	choice*
immuniz*		criticis*	hesitanc*	rumo*r	delay	mandatory
		accept*	concern*	compulsory	knowledge	
		confidence	decision making	anti-vaccin*	parent* con*	

Once retrieved, articles were screened by title and abstract according to a set of inclusions and exclusion criteria *(Box 1).* After an initial round of screening using this set of criteria, articles that were purely about knowledge and awareness were also excluded as it was felt that these elements did not sufficiently investigate nor represent the complex nature of trust on their own.

Box 1. Inclusion and exclusion criteria applied to articles for literature review

Inclusion Criteria

- Articles that include research on the following:
  - Public trust/distrust, perceptions, concerns, confidence, attitudes, beliefs about vaccines and vaccination programmes by individuals (such as parents, health care workers), groups or communities.
- Peer reviewed research
- Location: Global
- Publication Years: Up to November 2012
- Study period: Any
- Vaccine: All vaccines and vaccination programmes of communicable diseases.
- Concerns: All concerns
- Populations: All

Exclusion Criteria

- Not about vaccines
- Non-Human vaccines
- Vaccines not currently available, such as HIV vaccine.
- Non-peer reviewed papers such as editorials, letters, comment/opinion, protocol (no data), pilot studies (E.g. MMWR, Med let CDC FDA, New York Times)
- Research and Development; unless about public trust, confidence or concern.
  - Safety research
  - Serologic investigations
  - Immunogenicity Studies
  - Efficacy trials
  - Pre-clinical trial research
  - Cost-benefit analysis or cost effectiveness trials
  - Evaluations of mandates
  - Knowledge and awareness as sole variables investigated
- Papers without abstracts

Part B

SAGE WG literature review on dealing with vaccine hesitancy

The above search and screening was repeated in November 2012 to bring the body of studies to be included in the literature review up-to-date. A subset of articles was extracted, limited to the publication date period January 2007 – November 2012 and restricted to the six UN languages – Arabic, Chinese/Mandarin, English, French, Russian and Spanish. The keywords of the search strategy were also translated into French and run across the following databases: Medline (via PubMed), Embase, PsychInfo, CINAHL, Cochrane, IBSS, IMEMR, REPERE, Academic search premier and JSTOR.

Summary descriptive analyses

All articles (all UN languages) were screened and coded by year of publication, country, WHO region (Appendix 4), vaccine, study group and population methodology (i.e., statistical analyses employed) and theoretical approach. Study group was identified using either keyword searches in RefWorks (reference management software) or manually. Keywords included: multivariate, multivariable, regression, factor analysis, systematic, qualitative, focus group, mixed method, univariate, bivariate and descriptive. To assess the degree to which different facets of vaccine hesitancy had been investigated, keyword searches, also using RefWorks, were run across all articles. Keywords included: Hesitan*, accept* barrier, delay, missed, partial, refus*, timeliness, unsure, confidence. Descriptive analyses of all articles were run to enable an appreciation of the global distribution of research on this topic.

Factor analysis – Barriers and Promoters of Vaccination

Multivariate studies were reviewed to identify any factors found to be significantly associated with vaccination behaviour as either barriers or promoters. Each significant factor was then mapped onto the vaccine hesitancy model developed by the SAGE Working Group in order to position them within an overarching framework. This was an important step as the concept of vaccine hesitancy is complex and much of the research tends to focus on one or only a few model elements rather than the entire scope. For this first-phase review, all studies on childhood vaccines (all vaccines administered ≤7 years old) were reviewed. However, in order to reflect vaccine hesitancy across a broad range of the public and vaccines, this reach will be extended to include both seasonal influenza and the human papilloma virus (HPV) vaccines in subsequent stages.

Part C

Qualitative analysis – AFR region (Childhood, Adolescent and Adult vaccines)

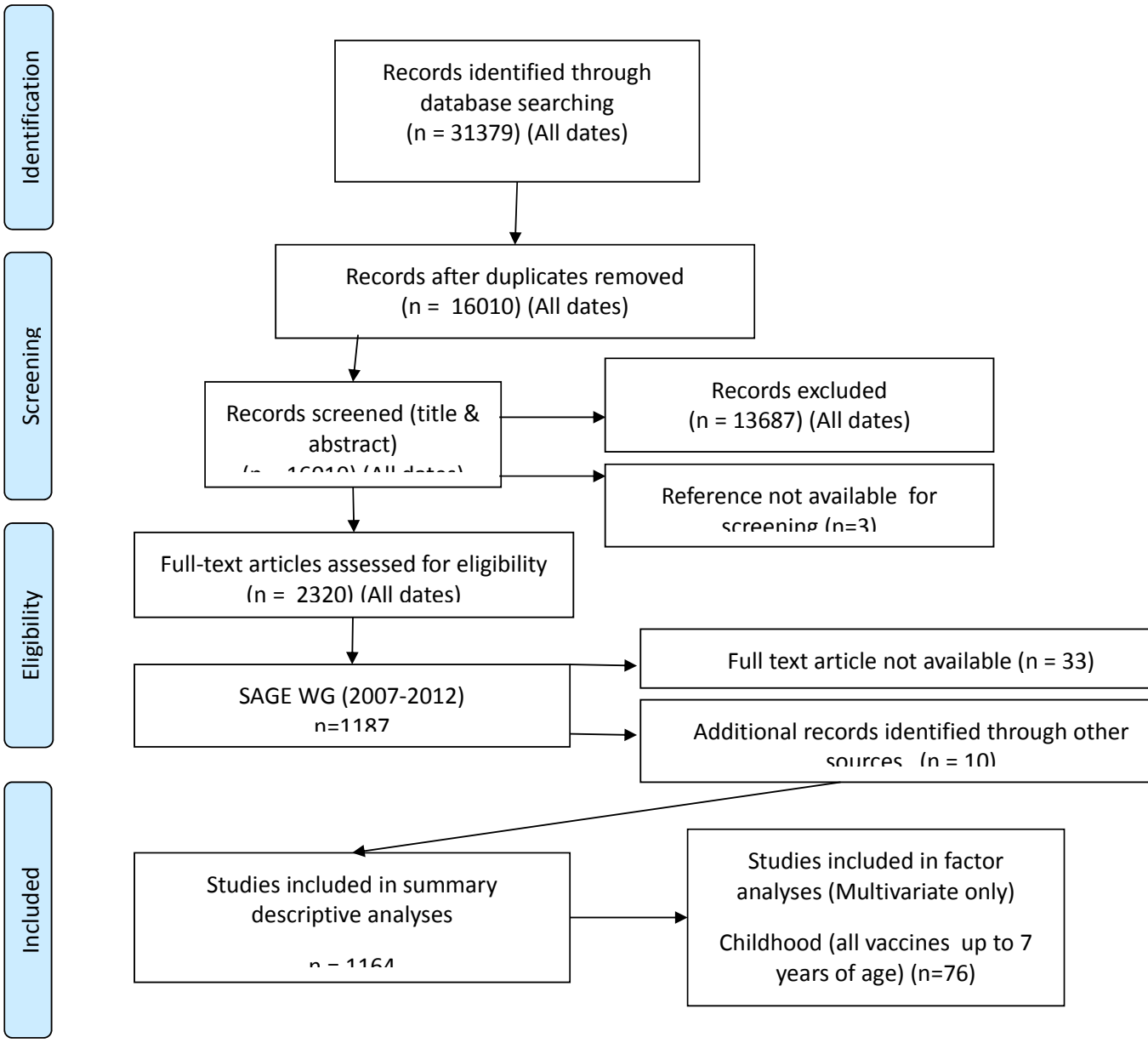
A small, nested analysis of qualitative studies about the WHO AFR region was performed to complement the larger literature review. This study was undertaken because of the paucity of peer-reviewed quantitative research from this region and it was hoped that the qualitative data could add to the understanding of vaccine confidence, hesitancy and barriers to the use of vaccines in the region.

Papers were identified using the original literature review search and filtered by year of publication (2007-2012), WHO region (AFR) and Study group (qualitative and mixed method). The themes from each study were examined and the arising common themes from the 19 papers were selected. These themes were then grouped according to the three primary domains of the model of determinants of vaccine hesitancy: Contextual influences, vaccine and vaccination-specific issues and individual/social group influences.

Results

31,379 records (all languages) were identified from the databases using the combined searches *(Figure 2).* After the removal of duplicates, 16,010 records were shortlisted for screening by title and abstract, of which 2,320 were included for full-text assessment. Once the additional criteria were applied for the purposes of the SAGE Working Group literature review, 1,187 articles remained, of which 33 were not available in full text. An additional 10 articles were added from other sources, which summed to a total of 1,164 articles on public trust, confidence or hesitancy to be analysed in this literature review. All of these articles were included in the summary descriptive analyses. For the factor analyses, in order to focus on the most robust and relevant articles, only those articles that used multivariate analyses were included (n=76 for childhood vaccines).

Figure 2. Flow diagram for systematic review on public trust in vaccines incorporating subset for SAGE literature review

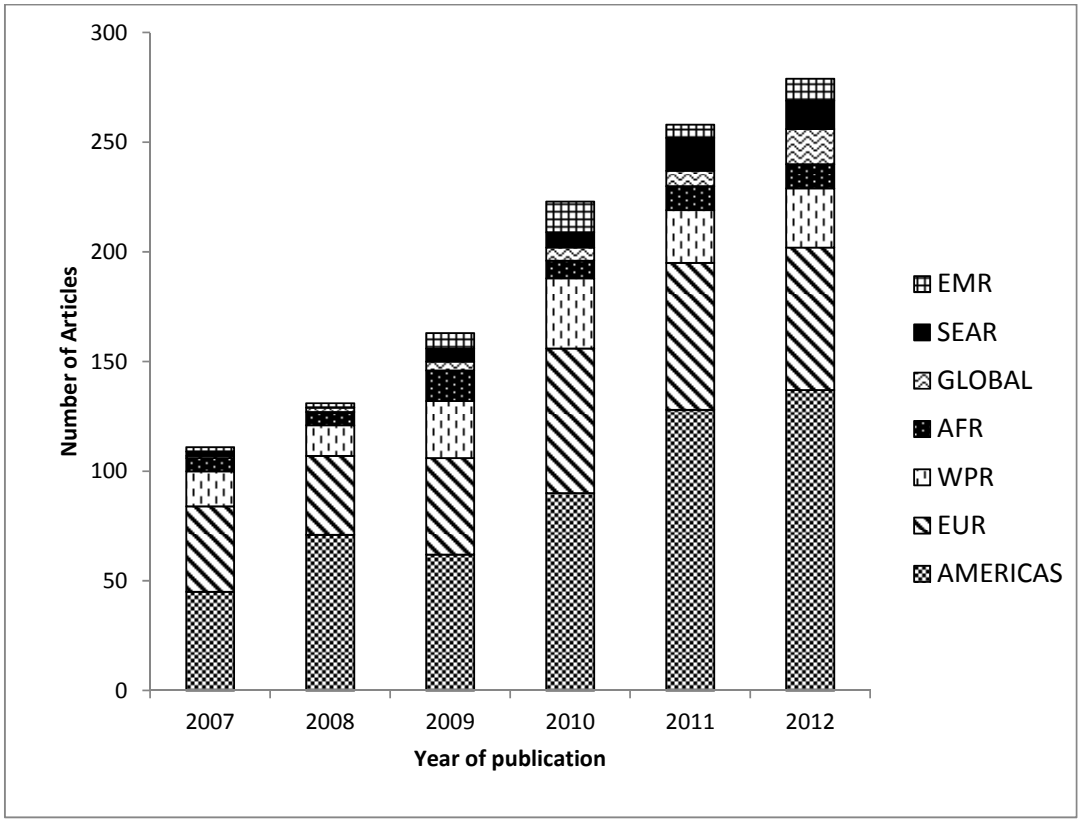


Summary descriptive analyses

Research on the many different facets of public confidence in vaccines and vaccination programmes were found across all WHO regions but the majority originated from the AMERICAS, EUR and WPR regions *(Figure 3*). Over the period 2007-2012, there has been a marked increase in research on this topic, particularly within the AMERICAS and EUR regions. The full concept and expression of 'vaccine hesitancy' is however relatively new, especially as a core topic, with only 6 articles found using this term in either the title or abstract, most of which were published in the last two years (8-10,19-21). Historically, it has been more

common for issues of vaccination behaviour to be discussed in terms of acceptance, barriers and refusals with some covering middle-continuum aspects of vaccine hesitancy including delay, missed, partial and timeliness.

Figure 3. Articles about public trust, confidence or hesitancy in vaccines by year (2007-2012) and WHO region (n=1164)

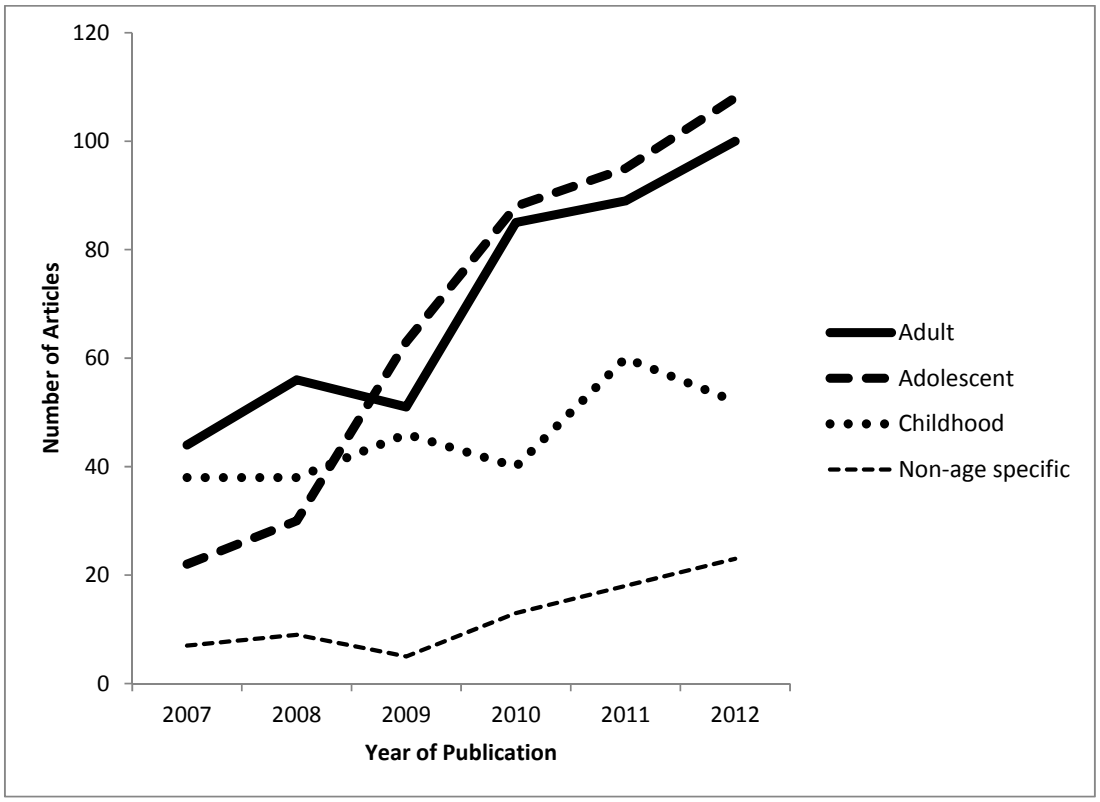


NB: Number exceed total number of articles reviewed as some articles discuss more than one region. Data is non-cumulative.

Across all WHO regions over the period 2007-2012, there has also been an interesting shift in vaccines of interest. Childhood vaccines have remained a steady focal point with an increase in the last couple of years as well as non-age specific (i.e., studies about vaccination in general), but the real divergence was seen for both adult and adolescent vaccines *(Figure 4).* For these age groups there has been a special interest in influenza vaccines – both pandemic and seasonal – and the newly introduced HPV *(Figure 5)*. There have been a greater proportion of articles published on adult and adolescent vaccines in the more developed regions – AMERICAS, EUR and WPR; whereas childhood vaccines continue to be the mainstay of in this area in less developed regions – AFR, SEAR and EMR *(Figure 6).* Importantly, the introduction of HPV and the expanded recommendations for Influenza (H1N1) led to a three-fold increase in the literature around issues of acceptance and barriers to vaccination during the period 2006-2011. Taking a retrospective view, this increase

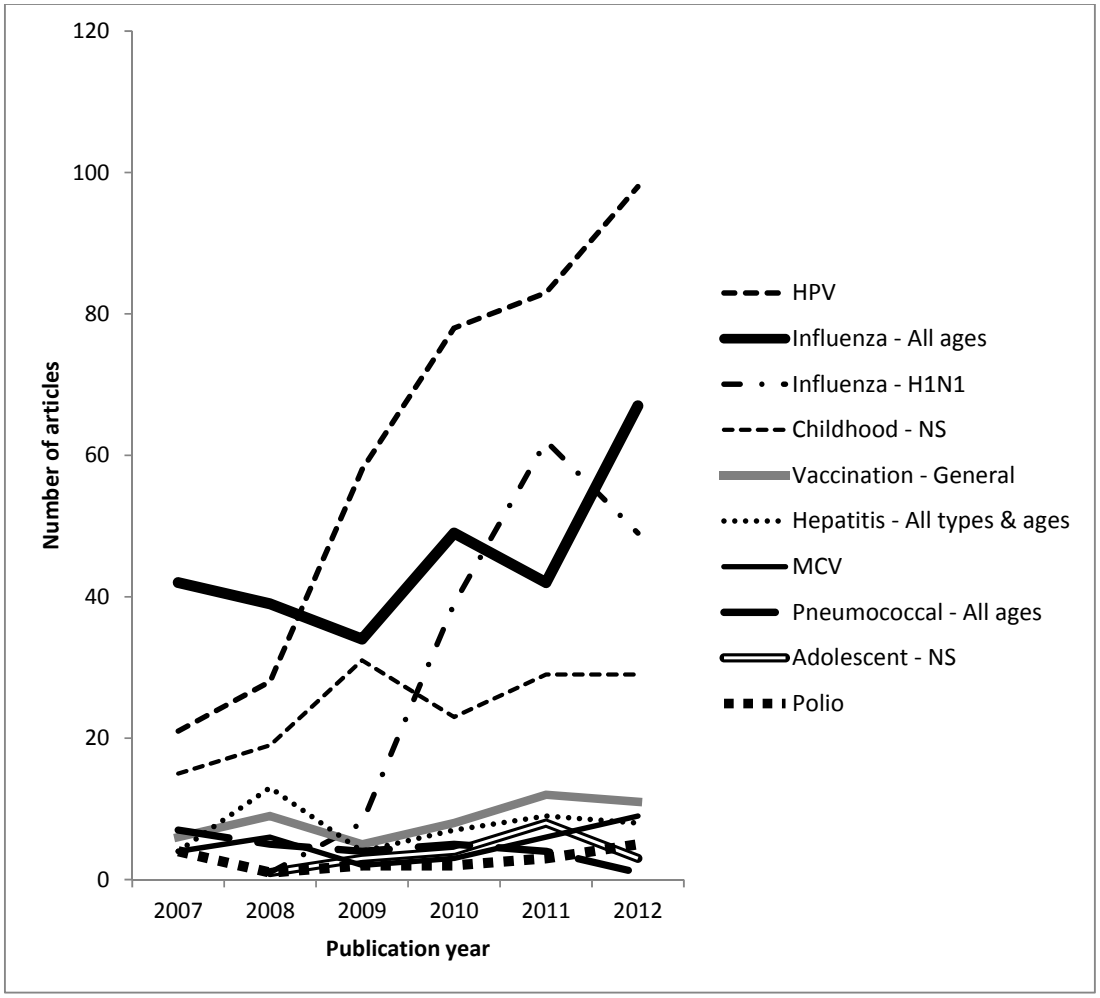
reflects the widespread challenges faced around uptake of the pandemic (H1N1) vaccine and the varied debates around the introduction of the HPV vaccines and the implications for vaccine confidence.

Figure 4. Articles about trust, confidence or hesitancy grouped by age over time (2007-2012) (n=1164)



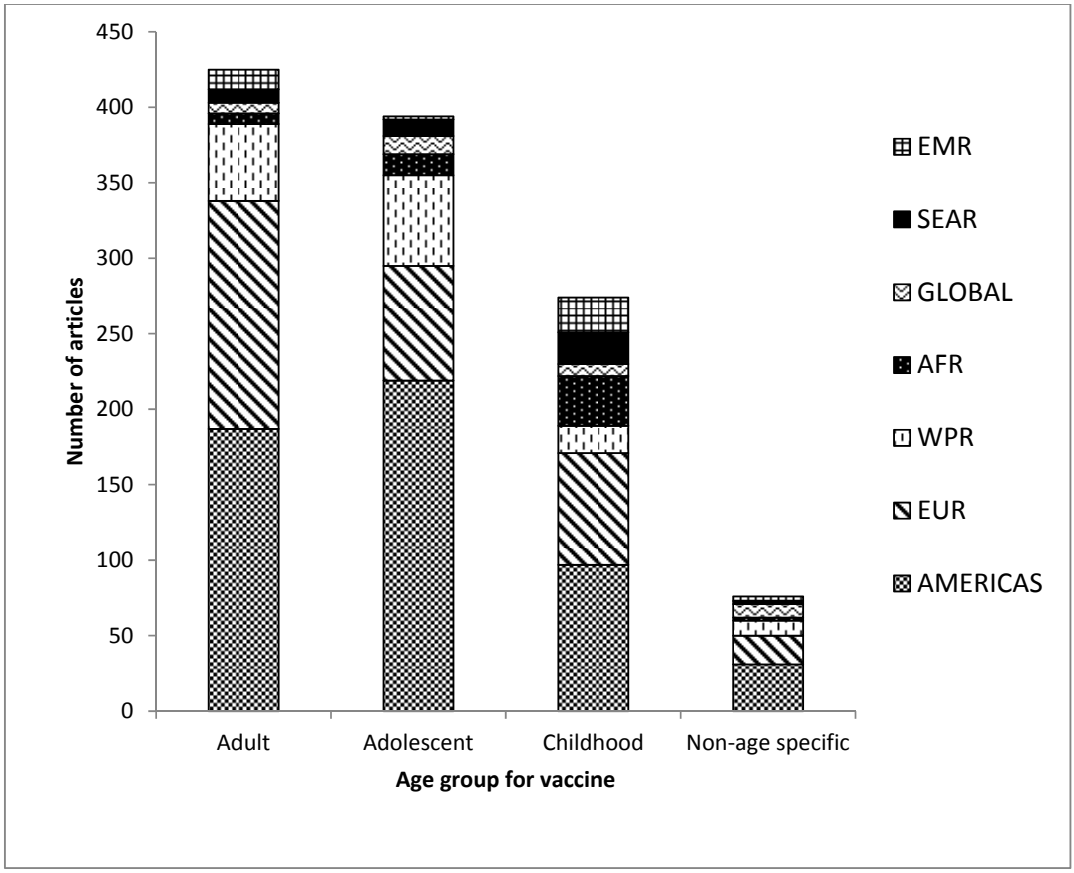
NB: Data is non-cumulative.

Figure 5. Articles on all vaccines (over 15 articles) grouped by year of publication (2007-2012)



NB: NS = Non-specific – vaccines in general; Influenza – All ages = Seasonal influenza only across all age groups; Influenza – H1N1 = Pandemic vaccine only

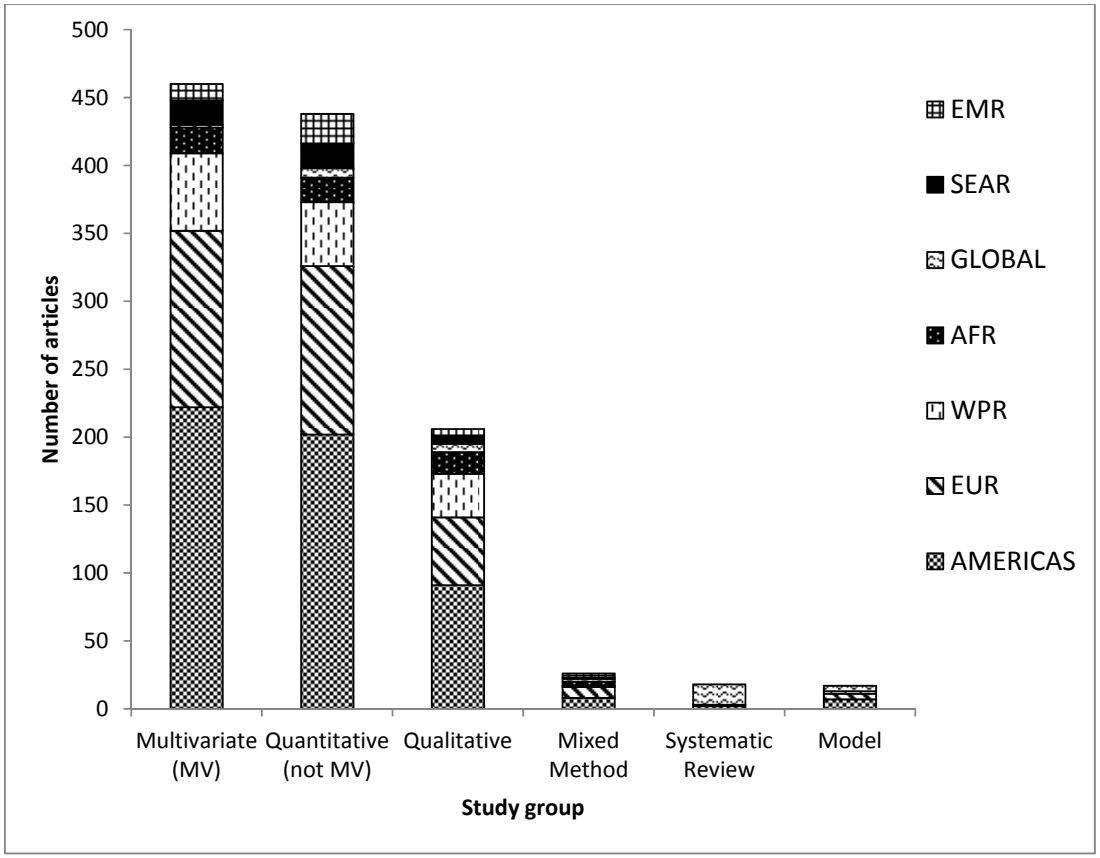
Figure 6. Articles about trust, confidence or hesitancy in vaccines grouped by WHO region and by age (2007-2012) (n=1164)



NB: Number exceeds total number of articles reviewed as some articles discuss vaccines across more than one age group.

A review of the methodological approaches used in the articles analysed showed that the majority of studies were multivariate, followed by other quantitative and qualitative methods *(Figure 7).* A higher proportion of all these studies have been conducted about the AMERICAS and EUR regions with much less representation from the other regions.

Figure 7. Articles about trust, confidence or hesitancy in vaccines grouped by WHO region and study type (2007-2012) (n=1164)

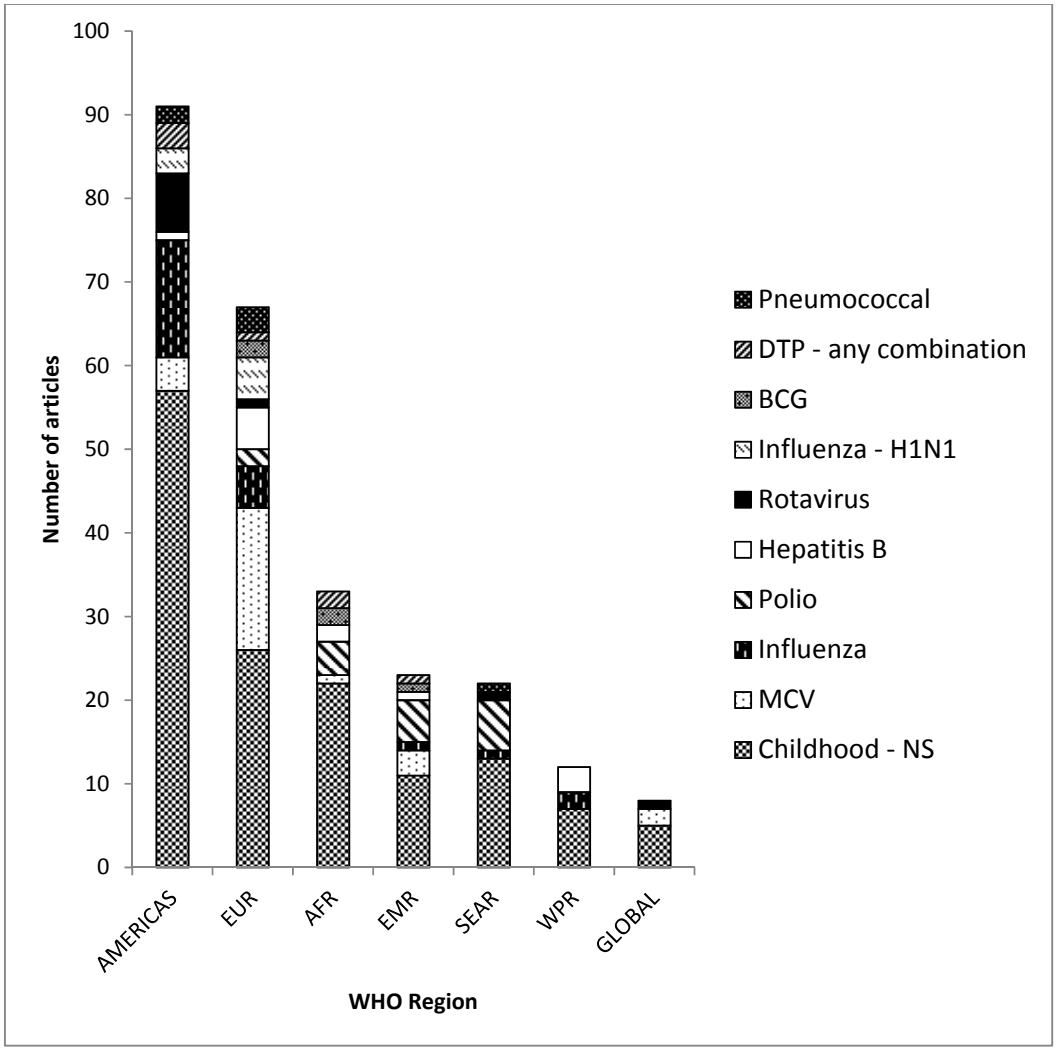


NB: One article was also identified as a 'Survey instrument' but not included on this graph; Mixed Method = both qualitative and quantitative approaches were applied; Quantitative = all quantitative methods other than those employing multivariate analyses e.g., descriptive, bivariate.

Vaccine-specific analyses - Childhood

Among the studies on childhood vaccines, the majority looked at vaccines in general and were not specific to one vaccine *(Figure 8).* Vaccine-specific studies were mostly about Influenza and Rotavirus in the AMERICAS, and measles in EUR. Polio was a key vaccine of interest across AFR, EMR and SEAR regions. Most of the studies were conducted with parents / primary caregiver (n=60). 16 studies examined the perspectives of healthcare workers (e.g., general practitioners, paediatricians and nurses on childhood vaccines, and the extent to which different factors influenced their intention or practice of recommending vaccines.

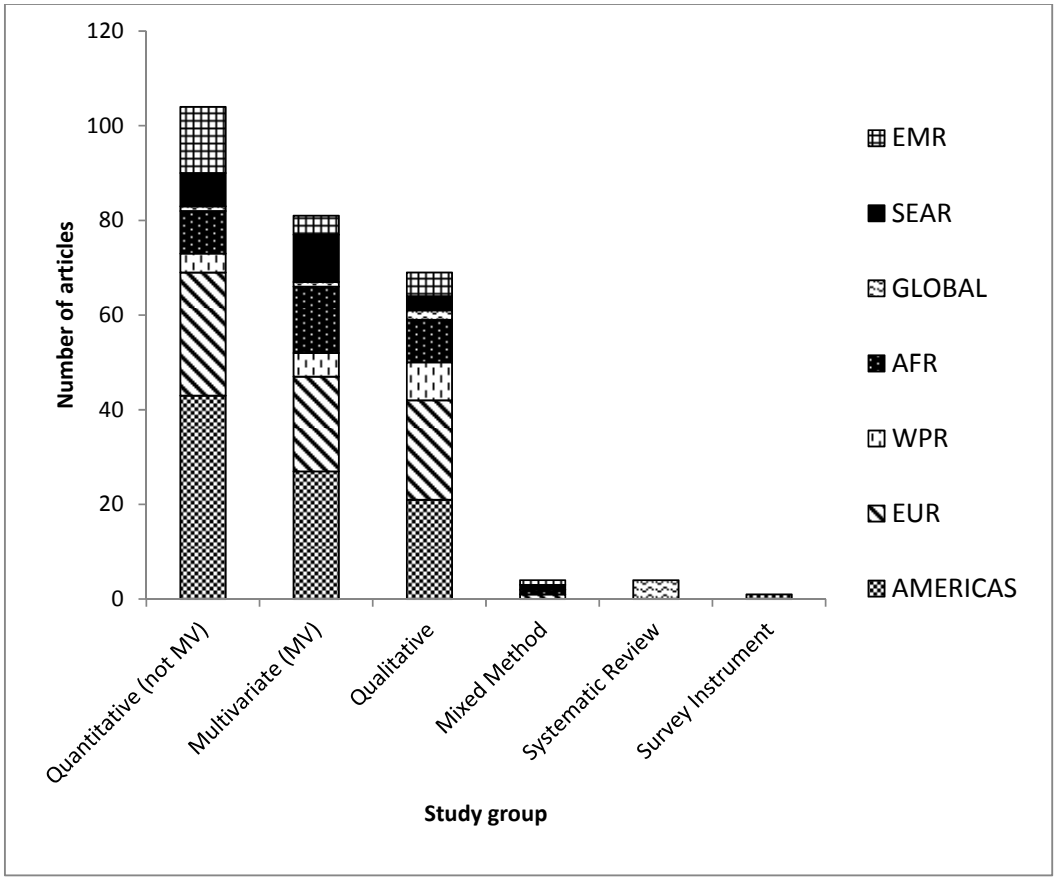
Figure 8. Articles about trust, confidence or hesitancy in childhood vaccines by WHO region and Childhood vaccines (2007-2012)



NB: One article could apply across multiple VPD groups; Includes only VPDs covered in six or more articles (n=256) from a total of 262.

For childhood vaccines, the majority of studies across all regions were quantitative (70%) *(Figure 9)*. Multivariate analyses were used in 44% of the quantitative studies, and identified across all regions.

Figure 9. Articles about trust, confidence or hesitancy in childhood vaccines, by WHO region and study group (2007-2012) (n=262)



Quantitative factor analysis – Childhood vaccines

Several determinants of vaccine hesitancy were frequently observed in relation to childhood vaccines (Appendix 3). These predominantly clustered around the core constructs of popular social cognitive models (e.g., Health Belief Model and Theory of Planned Behaviour) as more often than not, these were the approaches adopted to explore the issues around vaccination behaviour. With respect to Objective 2 of this review, these findings help validate the inclusion of these factors as determinants of vaccine hesitancy but due to the framing of questions in these models (e.g., HBM, TPB), they risk missing other important factors captured in the broader vaccine hesitancy model.

1. Contextual influences

Socio-economic

Level of income/Socio Economic Status (SES) was identified as a significant explanatory factor in eight studies across three regions. In two studies about the USA (AMERICAS), both high (22) and low (23) income/SES were indicated as barriers to vaccination. In Nigeria (AFR), low income/SES was identified as both a barrier (24) and promoter (25), and in Burkino Faso (AFR), two studies identified high income/SES as a promoter (26,27). In India (SEAR), higher income was noted as a promoter (28) and in Bangladesh (SEAR), both high and low income/SES was found to promote vaccination and middle income was non-significant (29). The reasons why this factor is of influence are not always explained, and when they are, it is usually not in isolation. For example, lower income in the USA was linked to issues of trust with the health provider (23) and in Nigeria (24) it was a barrier because it related to both low education, and therefore a lack of knowledge of childhood diseases, as well as access issues, as poorer women are less likely to hold decision-making power.

Level of education presents an equally mixed set of results. Six studies about India (SEAR) consistently found caregivers' higher education to be a promoter (28,30-34). Studies about China (WPR) (35), Lebanon (EMR) (36), Israel (EUR) (37), Bangladesh (SEAR) (29) and USA (AMERICAS) (22) all identified higher education as a potential barrier, whereas studies about Greece (EUR) (38), The Netherlands (39), Nigeria (AFR) (40) and Pakistan (EMR) (41,42) identified it as a promoter of vaccination. Low education was identified as a barrier in studies about Nigeria (AFR) (24,25,43,44), India (SEAR) (30,45), China (WPR) (46), Kyrgyzstan (EUR) (47), and as both a promoter (48) and barrier (49) in the USA (AMERICAS). In the DR Congo (AFR), both high and low education were represented as barriers (50). It is interesting to note that low education manifests different effects; in India, illiteracy indicates more of an issue with knowledge whereas in Nigeria and Kyrgyzstan, low education was associated with higher levels of anti-vaccination attitudes. The evidence from this review suggests that factors should not be considered in isolation as contextual influences are at play.

Communication and media environment

Regular exposure to vaccination stories / messages through mass media, newspapers or community sources was identified as a promoter of vaccination in Nigeria (AFR) (24,43,51), India (SEAR)(28) and Bangladesh (SEAR) (29). This positive influence may relate to the more basic issues of low knowledge about vaccination in these countries. Exposure to news stories about vaccination, particularly negative ones, in the mass media acted as a barrier in Taiwan (WPR) (52) and Canada (AMERICAS) (53).

2. Vaccine and vaccination-specific issues

Costs

Different types of costs were identified in the studies reviewed including financial, time, administrative and general accessibility. In DR Congo (AFR) (50), having the father pay the transport fare to the vaccination clinic acted as a promoter. In Nigeria (AFR)(43), India (SEAR)(45), Pakistan (SEAR)(54) and Greece (EUR)(38), longer distances from vaccination delivery point, either real or perceived, were a significant barrier. In Nigeria, knowledge was reported as the more important barrier over different costs for any level of vaccination. However, the factors of influence were different in relation to partial and non-immunisation status. Specifically, supply-side issues such as maternal and familial availability appeared to explain partial immunisation whereas for non-immunisation, ideational and normative factors, such as parental disapproval, held sway (43). One study from the USA (AMERICAS)(55) reported several costs perceived by health providers which acted as barriers to recommendation of the rotavirus vaccine. These included extra time needed to explain safety profile with patients and additional financial and administrative burdens.

3. Individual/social group influences

Immunisation as a social norm vs immunisation not needed / harmful

Encouragement from others, either social or professional (e.g., co-workers, government or health professional recommendation) or belief that immunisation should be a social, familial or workplace norm was a promoter across all studies in which immunisation as a social norm was identified as a factor. The studies were split across the USA (55-57) and Canada (53,58,59) in the AMERICAS; the UK (18) and The Netherlands (60) in EUR; as well as Taiwan (WPR) (52) and Nigeria (43,51) and DR Congo (50) in AFR. These findings suggest that perceptions of social and professional support around vaccination behaviour, whether it be positive or negative, is an important explanatory factor with universal appeal.

Beliefs, attitudes & motivation about health and prevention.

Greater health knowledge in general was found to promote vaccination in India (SEAR) (34) whereas health knowledge, influenced by myths or rumours in Nigeria (AFR) (43) or anthroposophic beliefs and alternative medicine in The Netherlands (EUR) (32,61), acted as a barrier. Belief in scientific medicine promoted vaccination in Germany (EUR) (62). Predictably, having a positive attitude to, and seeing value in vaccination was found to be a promoter in studies about Italy (EUR) (63), UK (EUR) (18), Canada (AMERICAS) (59,64), The Netherlands (EUR) (60), and Switzerland (EUR) (30,65). Similarly, feeling a sense of self-efficacy and comfort about getting vaccinated acted as a promoter in both The Netherlands (EUR) (60) and Canada (AMERICAS) (59) whereas anticipating barriers to immunization acted as a barrier in the USA (AMERICAS) (66,67) and Taiwan (WPR) (52) respectively. On the flipside, either ignoring vaccination as a health behaviour or generally opposing vaccination acted as a barrier in Senegal (AFR) (68) and Taiwan (WPR) (52). However, one study in the USA (AMERICAS) (69) showed that is it possible to have a positive attitude to vaccination yet decide for exemption.

In terms of health behaviours, studies about Nigeria (AFR) (43), India (SEAR)(30,32), Burkino Faso (AFR) (27), China (WPR) (67), practicing one or more of the following supported vaccination: Accessing antenatal care (27,28,51), giving birth at a health facility (27,30,32,43,51,67), and having an immunization card (26,51). In Senegal (AFR) (68) and China (WPR) (67), not having an immunization card acted as a barrier to vaccination. Further, accessing vaccination through a private clinic or regularly accessing healthcare were both found to be promoters in Nigeria (AFR) (70) and The Netherlands (EUR) (39). In one study in the USA (AMERICAS) (23), planning on breastfeeding was reported as a barrier, as was being a smoker in Turkey (EUR) (71).

Outside of health behaviours, a study in India (SEAR) (34) found that membership of/in a development organisation promoted vaccination.

Knowledge / awareness of why / where / what / when vaccines are needed

Two studies about Nigeria (AFR) identified awareness of a vaccine-preventable disease (VPD) as a promoter (43,51). Similarly, a perception that the VPD is dangerous promoted vaccination in Taiwan (WPR) (52) as did having had experience of or caring for someone with a VPD in DR Congo (AFR) (50). Knowledge about vaccine recommendations and schedule was acted as a promoter in India (SEAR) (28) but as a barrier in DR Congo (AFR) (50) and China (WPR) (67). Interestingly, most of the other studies identifying aspects of knowledge as explanatory factors related to health providers responsible for vaccination. Specifically, a greater sense of confidence in personal knowledge and training in vaccination was found to act as a promoter, in terms of recommending vaccines, in France (EUR) (72), Canada (AMERICAS)(64,73), New Zealand (WPR) (74) and Pakistan (EMR) (54). Perceived medical severity of the VPD by health providers was also found as a promoter in USA (AMERICAS) (75), Canada (AMERICAS) (64,73) and The Netherlands (EUR) (60), and when considered less severe, became a barrier in the USA (AMERICAS) (55).

Qualitative analysis – AFR region

20 relevant papers were identified; one of these was not available, but was a second paper on the same study already in the sample. A total of 19 papers were reviewed. The studies (n=19) came from 10 countries – only five of which are in the top ten countries for highest number of unimmunised children – including, South Africa (n=4) (76-79), Uganda (n=3) (80-82), Nigeria (n=2) (83-85), Tanzania (n=3)(86-88), Ethiopia (n=1) (89), Gabon (n=1) (90), Kenya (n=1) (91), Burkina Faso (n=1) (92), Benin (n=1) (93) and Zimbabwe (n=1) (94). The majority of papers were about childhood vaccines (non-specific) (n=7; 37%) (80,82,89,90,92-94) and HPV and preparedness for vaccine introduction (n=5 ; 26%)(77-79,81,86), followed by polio (n=3; 11%)(83-85), cholera (n=2 ; 11%) (87,88), and one each for adolescent (non-specific) (76) and Influenza – H1N1 (91). The most commonly used qualitative approaches were focus group discussion and in-depth interviews (n=13; 68%), and five (26%) studies used a mix of both quantitative and qualitative methods.

1. Contextual influences

Despite the general willingness of caregivers to have children vaccinated, the studies noted a number of barriers. Geographical distance was common to many, as well as the costs of getting to the health centre. Opportunity costs were mentioned in many papers; these were mainly the time taken to get a child vaccinated (often a whole day) when there is a lot of work to be done at home and in the fields.

Social barriers were mentioned in relation to the social support needed to take a child for vaccination. If a male partner or elderly relative is against vaccination, for instance, it is difficult for a mother to then take the child for vaccination (though some mentioned doing so nevertheless). Elderly support for vaccination was mentioned a number of times. In the AFR region, given the important place of older relatives in child rearing and decision making, the elderly are an important group of people with whom to build vaccine confidence. In some cases lack of support resulted in intimate partner

> ***Also it is the mother who should really make sure your child is immunised. If you follow the man's advice and you don't immunise the child, when that child falls sick it is you the mother who will spend sleepless nights when the child is sick. He will be snoring and the doctors will abuse you as he is not around the hospital. Yet you followed his advice. You the mother have to stick to your guns. Let him fight with you, but after your child has been immunised.***
>
> *(Older mother, Kampala, Uganda)*

violence. One woman, for instance, was reportedly put out of her house because the child became ill after being vaccinated.

Health service barriers were mentioned in a number of the papers. These related to being shamed by the health workers (and sometimes other mothers) if one was dressed poorly; if the child failed to thrive; if the child was not well dressed; if one arrived late (after having to wait for the water of a river to subside to enable crossing) or just being humiliated for no reason. Most respondents said after such an experience they would not return to complete their vaccination.

Other health service barriers included the clinic being too far away and the queues being too long. Not having a mobile clinic coming to an area was a predictor of incomplete vaccination in Malawi.

2. Vaccine and vaccination-specific issues

Poverty and the costs associated with vaccination were fairly consistent across the papers. Anxiety about the side effects of vaccination was also a common theme, though the studies found that this did not necessarily deter respondents from being (or having their children) vaccinated. The side effects mentioned were mostly localised swellings, or the child becoming ill.

Routine immunisation was preferred over mass campaigns in a few studies. Interestingly the reasons given were that the health workers could be found in case of a problem and held accountable, whereas in a campaign follow up afterwards is difficult for an individual.

In Benin a study with a number of religious sects examined the strong religious beliefs that led to their refusal to vaccinate their children. Striking about the study was the low level of formal education among all responders.

Mistrust of the vaccine was mentioned a number of times, in one context it was believed that the vaccines in Africa are not of as high standard as those in the first world. Another related to rumours and myths about infertility, illness and HIV caused by vaccines.

Some of the barriers were very specific to the country or the vaccine. For example, the study on Nigeria described the political, religious and social resistance to the polio eradication campaign in 2003. In Nigeria there were also concerns about the high number of campaigns and the belief that children could get a vaccine overdose.

3. Individual / social group influences

The most prominent theme across the studies was a general lack of knowledge – about vaccine-preventable diseases, vaccines, and the appropriate schedule of administration. Nonetheless, despite respondents' lack of knowledge, they were generally well disposed towards vaccination to prevent illness and were keen to know more.

Limitations

Quantitative analysis

This review only included peer-reviewed literature that related to stated dimensions (see Appendix 1) of vaccine trust, confidence or hesitancy. The exclusion of studies that only looked at knowledge or awareness and grey literature may have undermined a fuller examination of the explanatory factors in SEAR, especially India, and AFR regions, where issues around knowledge are recognized by experts as a very common problem. The exclusion of articles on mandates may also have influenced findings around the influence of policies and politics. There is also a clear publication bias with the majority of studies investigating populations in the EUR and AMERICAS regions. Despite regional databases being included, the database searches were only conducted in natural language for English and French which may have impacted on the sensitivity of searches for articles in other UN languages.

The majority of the studies reviewed applied cross-sectional questionnaires based on similar theoretical approaches. This presents issues in terms of ecological bias and limits the extent to which the relative strength of individual factors can be assessed and interpreted at a general level. In an effort to balance these shortcomings a set of qualitative studies from the AFR region have been included in this review, however, in order to further validate the vaccine hesitancy model and enhance understanding around explanatory factors, a review of the remaining qualitative literature and input from subject-matter experts in all regions would be extremely useful. This extension would not only help highlight gaps in knowledge and overcome the regional publication bias that currently exists, but also help qualify and quantify the extent to which vaccine hesitancy is an issue across the regions – it is essential that in exploring and directing action on vaccine hesitancy that immunisation resources allocated elsewhere are not unjustifiably put at risk.

Qualitative analysis – AFR

This extension piece highlighted that there were very few papers directly investigating the issue of vaccine hesitancy, despite including a broader range of vaccines. Further, the inclusion of adolescent and adult vaccines, whilst useful from a general perspective, made up the majority of the articles analysed so comparability with childhood-only vaccines is limited. Some of the studies also looked at health worker's perceptions of reasons for vaccine hesitancy as opposed to the more direct interrogation of parents and caregivers in the quantitative analysis, although investigation from this perspective could prove useful in relation to communication strategies. There were also some issues around sample-bias, with some studies only being facility-based, which would exclude those not able to reach the facility, and other studies purposively selected populations known to be hesitant. This means that the results need to be interpreted with this in mind.

Discussion

Quantitative analysis

Until further review of alternative studies and sources is conducted, it is difficult, and perhaps unwise, to make inferences about the relative importance of individual factors or how they are incorporated into decision-making processes. Part of the difficulty in understanding the relative importance of individual factors to vaccine hesitancy, is the definition of vaccine hesitancy itself. For example, a study on the timeliness of children's vaccination (95) – just one aspect of the vaccine hesitancy continuum – found that children's vaccinations varied widely between and within 45 low- and middle-income countries (96). Similarly, a study in Nigeria found that partial immunisation was most influenced by supply-side factors, such as maternal availability, and lack of knowledge, whereas non-immunization largely related to demand factors, such as parental disapproval (43), and in Greece (EUR) (38), socioeconomic factors, such as number of other siblings and father's education were the most important predictive factors of both under- and delayed childhood vaccination, and parental attitudes and beliefs about vaccinations were found to be non-significant in this regard. The picture by individual vaccines is no simpler; a study on MMR in the UK found that different factors or the same factors by different degrees influenced decision-making at each dose (18).

To engage with this issue in the immediate term, one option could be to perform a closer review of the hierarchy of factors identified in multivariate studies, but not without significant caveats. In addition, further consideration of the qualitative literature and a review of models around decision-making could be of use. Essentially, the dominating fact is that vaccine hesitancy is a complex issue and is driven by very context-specific factors which require a multidisciplinary approach to be better understood.

Qualitative analysis

The AFR region has high numbers of unimmunised children but there is little information about the demand side reasons for this. There is no information at all in 50% of the countries with the highest number of unimmunised children.

The most striking aspect of these data is that there were many common issues across the studies, such as the lack of knowledge about vaccination and about the illnesses under discussion, the general acceptance of the vaccines, and fear or concern about the side effects. However despite the lack of information, many papers described that the study participants were willing to learn and that they were keen to vaccinate their children to protect them from illness, often despite the many health service barriers.

There were areas of mistrust, particularly in areas where there were repeated mass immunisation campaigns. The mistrust related to believing that “western powers” wanted to sterilise the population or introduce certain diseases like AIDS.

There were different issues relating to different age groups and different vaccines, for example the issues relating to polio vaccination in Nigeria were quite specific, issues relating to cholera vaccination in Zanzibar were a little different but the difference is a matter of emphasis rather than different issues.

What is clear is that more research is needed to elucidate the confidence/ hesitancy around vaccines in the AFR region, but the limited indications are that there is not a huge problem relating to lack of vaccine confidence, and the weight of these is difficult to determine while the numerous structural barriers to immunisation persist.

Future research

Encouragingly, there are signs of expansion in the mode of approach adopted by researchers on this topic. For example, a recent study in Pakistan (EMR), sought to understand the mechanisms, or ‘pathways’ of true impact factors, through which vaccination choices are derived. Using this method the study was able to disaggregate broad factors like ‘education’ and assess its influence on health outcomes over time. In this example, the education level of the father had a greater influence on childhood immunization and that of the mother’s on longer term health outcomes, such as height and weight (97). In the same vein, a recent study in India (SEAR) (34) examined the broader influence of maternal education in terms of human, social and cultural capital, as well as empowerment, to explore the pathways in which these factors affect child health.

Similarly, studies that attempt to identify the influence of layers beyond the individual would be worthwhile. For example, one study in northern Nigeria (AFR) used the behavioural-ecological model to explore the influence of factors at five levels of BCG immunization; these included: intrapersonal, interpersonal, institutional, community and public policy (51). This approach allowed for both broad identification of relevant factors and their relative strength. In this case, maternal (e.g., use of prenatal care, knowledge about immunization) and household factors (e.g., social influence) were more important than child characteristics, and vaccine supply factors were least important. In parallel with multidisciplinary approaches, research like this, which is broad in scope but context-specific, would greatly support global understanding of vaccine hesitancy.

References

(1) Wolfe RM, Sharp LK. Education and debate. Anti-vaccinationists past and present. BMJ 2002 08/24;325(7361):430-432.

(2) Durbach N. 'They might as well brand us': Working-class resistance to compulsory vaccination in Victorian England. Social History of Medicine 2000 Apr;13(1):45-62.

(3) Porter D, Porter R. The politics of prevention: Anti-vaccinationism and public health in nineteenth-century England. Med Hist 1988 1988;32(3):231-252.

(4) Larson HJ, Cooper LZ, Eskola J, Katz SL, Ratzan S. Addressing the vaccine confidence gap. Lancet 2011 08/06;378(9790):526-535.

(5) Dempsey AF, Schaffer S, Singer D, Butchart A, Davis M, Freed GL. Alternative vaccination schedule preferences among parents of young children. Pediatrics 2011 Nov;128(5):848-856.

(6) Robison SG, Groom H, Young C. Frequency of alternative immunization schedule use in a metropolitan area. Pediatrics 2012 Jul;130(1):32-38.

(7) Gust DA, Darling N, Kennedy A, Schwartz B. Parents with doubts about vaccines: which vaccines and reasons why. Pediatrics 2008 10;122(4):718-725.

(8) Luthy KE, Beckstrand RL, Peterson NE. Parental hesitation as a factor in delayed childhood immunization. J Pediatr Health Care 2009 2009;23(6):388-393.

(9) Opel DJ, Mangione-Smith R, Taylor JA, Korfiatis C, Wiese C, Catz S, et al. Development of a survey to identify vaccine-hesitant parents: the parent attitudes about childhood vaccines survey. Hum vaccin 2011 Apr;7(4):419-425.

(10) Mirdamadi K, Einarson A. H1N1 and influenza viruses: why pregnant women might be hesitant to be vaccinated. Canadian Family Physician 2011 Sep;57(9):1003-1004.

(11) Opel DJ, Mangione-Smith R, Taylor JA, Korfiatis C, Wiese C, Catz S, et al. Development of a survey to identify vaccine-hesitant parents The parent attitudes about childhood vaccines survey. Human Vaccines 2011 Apr;7(4):419-425.

(12) Benin AL, Wisler-Scher D, Colson E, Shapiro ED, Holmboe ES. Qualitative analysis of mothers' decision-making about vaccines for infants: the importance of trust. Pediatrics 2006 05;117(5):1532-1541.

(13) Falagas ME, Zarkadoulia E. Factors associated with suboptimal compliance to vaccinations in children in developed countries: a systematic review. Curr Med Res Opin 2008 06;24(6):1719-1741.

(14) Rainey JJ, Watkins M, Ryman TK, Sandhu P, Bo A, Banerjee K. Reasons related to non-vaccination and under-vaccination of children in low and middle income countries: findings

from a systematic review of the published literature, 1999-2009. Vaccine 2011 Oct 26;29(46):8215-8221.

(15) Prematunge C, Corace K, McCarthy A, Nair RC, Pugsley R, Garber G. Factors influencing pandemic influenza vaccination of healthcare workers--a systematic review. Vaccine 2012 Jul 6;30(32):4733-4743.

(16) Trim K, Nagji N, Elit L, Roy K. Parental Knowledge, Attitudes, and Behaviours towards Human Papillomavirus Vaccination for Their Children: A Systematic Review from 2001 to 2011. OBSTET GYNECOL INT 2012;2012:921236-921236.

(17) Mills EJ, Montori VM, Ross CP, Shea B, Wilson K, Guyatt GH. Systematically reviewing qualitative studies complements survey design: An exploratory study of barriers to paediatric immunisations. J Clin Epidemiol 2005 Nov 2005;58(11):1101-1108.

(18) Brown K, Fraser G, Ramsay M, Shanley R, Cowley N, Wijgerden Jv, et al. Attitudinal and demographic predictors of measles-mumps-rubella vaccine (MMR) uptake during the UK catch-up campaign 2008-09: cross-sectional survey. PLoS ONE 2011(May):e19381.

(19) Healy C, M., Pickering L, K. How to Communicate With Vaccine-Hesitant Parents. Pediatrics 2011 05/02:S127-33.

(20) Luthy KE, Beckstrand RL, Clark-Callister L. Parental Hesitation in Immunizaing Children in Utah. Public Health Nursing 2010;27(1):25-31.

(21) Opel DJ, Taylor JA, Mangione-Smith R, Solomon C, Zhao C, Catz S, et al. Validity and reliability of a survey to identify vaccine-hesitant parents. Vaccine 2011 Sep 2;29(38):6598-6605.

(22) Wei F, Mullooly JP, Goodman M, McCarty MC, Hanson AM, Crane B, et al. Identification and characteristics of vaccine refusers. BMC Pediatr 2009;9:18-18.

(23) Wu AC, Wisler-Sher D, Griswold K, Colson E, Shapiro ED, Holmboe ES, et al. Postpartum mothers' attitudes, knowledge, and trust regarding vaccination. Matern Child Health J 2008 11;12(6):766-773.

(24) Antai D. Faith and child survival: the role of religion in childhood immunization in Nigeria. J Biosoc Sci 2009;41(1):57-76.

(25) Antai D. Gender inequities, relationship power, and childhood immunization uptake in Nigeria: a population-based cross-sectional study. 2012;16:E136-E145.

(26) Sanou A, Simboro S, Kouyaté B, Dugas M, Graham J, Bibeau G. Assessment of factors associated with complete immunization coverage in children aged 12-23 months: a cross-sectional study in Nouna district, Burkina Faso. BMC international health and human rights 2009 01/01.

(27) Sia D, Kobiane J-, Sondo BK, Fournier P. Individual and environmental characteristics associated with immunization of children in rural areas in Burkina Faso: A multi-level analysis. Cahiers Sante 2007 October/November/December 2007;17(4):201-206.

(28) Patra N. A probe into the ways to stimulate childhood immunisation in India: Findings from National Family Health Survey-III . International Journal of Child and Adolescent Health 2012;5(1):65-84.

(29) Rahman M, Obaida-Nasrin S. Factors affecting acceptance of complete immunization coverage of children under five years in rural Bangladesh. Salud Publica de Mexico 2010 March-April 2010;52(2):134-140.

(30) Kumar D, Aggarwal A, Gomber S. Immunization status of children admitted to a tertiary-care hospital of north India: reasons for partial immunization or non-immunization. J Health Popul Nutr 2010 06;28(3):300-304.

(31) Phukan RK, Barman MP, Mahanta J. Factors associated with immunization coverage of children in Assam, India: over the first year of life. J Trop Pediatr 2009 Aug;55(4):249-252.

(32) Chhabra P, Nair P, Gupta A, Sandhir M, Kannan AT. Immunization in urbanized villages of Delhi. Indian J Pediatr 2007 Feb;74(2):131-134.

(33) Rammohan A, Awofeso N, Fernandez RC. Paternal education status significantly influences infants' measles vaccination uptake, independent of maternal education status. 2012;12.

(34) Vikram K, Vanneman R, Desai S. Linkages between maternal education and childhood immunization in India. Soc Sci Med 2012 Jul;75(2):331-339.

(35) Zhang S, Yin Z, Suraratdecha C, Liu X, Li Y, Hills S, et al. Knowledge, attitudes and practices of caregivers regarding Japanese encephalitis in Shaanxi Province, China. Public Health 2011 Feb;125(2):79-83.

(36) Sinno DD, Shoaib HA, Musharrafieh UM, Hamadeh GN. Prevalence and predictors of immunization in a health insurance plan in a developing country. Pediatrics International 2009 August 2009;51(4):520-525.

(37) Muhsen K, Abed El-Hai R, Amit-Aharon A, Nehama H, Gondia M, Davidovitch N, et al. Risk factors of underutilization of childhood immunizations in ultraorthodox Jewish communities in Israel despite high access to health care services. Vaccine 2012 Mar 9;30(12):2109-2115.

(38) Danis K, Georgakopoulou T, Stavrou T, Laggas D, Panagiotopoulos T. Socioeconomic factors play a more important role in childhood vaccination coverage than parental perceptions: a cross-sectional study in Greece. Vaccine 2010 17 Feb 2010;28(7):1861-1869.

(39) Uwemedimo OT, Findley SE, Andres R, Irigoyen M, Stockwell MS. Determinants of influenza vaccination among young children in an inner-city community. Journal of

Community Health: The Publication for Health Promotion and Disease Prevention 2012 Jun;37(3):663-672.

(40) Oladokun RE, Lawoyin TO, Adedokun BO. Immunization status and its determinants among children of female traders in Ibadan, South-Western Nigeria. Afr J Med Med Sci 2009 Mar 2009;38(1):9-15.

(41) Mitchell S, Andersson N, Ansari NM, Omer K, Soberanis JL, Cockcroft A. Equity and vaccine uptake: a cross-sectional study of measles vaccination in Lasbela District, Pakistan. Bmc International Health and Human Rights 2009 Oct;9.

(42) Siddiqi N, Siddiqi A, Nisar N, Khan A. Mothers' knowledge about EPI and its relation with age-appropriate vaccination of infants in peri-urban Karachi. Journal of the Pakistan Medical Association 2010 November, 2010;60(11):940-944.

(43) Babalola S. Maternal reasons for non-immunisation and partial immunisation in northern Nigeria. J Paediatr Child Health 2011 05;47(5):276-281.

(44) Oladokun RE, Adedokun BO, Lawoyin TO. Children not receiving adequate immunization in Ibadan, Nigeria: what reasons and beliefs do their mothers have?. Nigerian journal of clinical practice 2010 Jun 2010;13(2):173-178.

(45) Patel TA, Pandit NB. Why infants miss vaccination during routine immunization sessions? Study in a rural area of Anand District, Gujarat. Indian J Public Health 2011 Oct-Dec;55(4):321-323.

(46) Wang YY, Wang Y, Zhang JX, Kang CY, Duan P. [Status of mother's KAP on child immunization in minority areas, Guizhou Province]. Beijing da Xue Xue Bao.Yi Xue Ban/Journal of Peking University.Health Sciences 2007;39(2):136-139.

(47) Akmatov MK, Mikolajczyk RT, Kretzschmar M, Kramer A. Attitudes and beliefs of parents about childhood vaccinations in post-soviet countries: The example of kyrgyzstan. Pediatr Infect Dis J 2009 July 2009;28(7):637-640.

(48) Kim SS, Frimpong JA, Rivers PA, Kronenfeld JJ. Effects of maternal and provider characteristics on up-to-date immunization status of children aged 19 to 35 months. Am J Public Health 2007 Feb;97(2):259-266.

(49) Stockwell MS, Irigoyen M, Martinez RA, Findley S. How parents' negative experiences at immunization visits affect child immunization status in a community in New York City. Public Health Rep 2011 2011;126(SUPPL. 2):24-32.

(50) Kayembe K, Piripiri L, Nyandwe K, Mapatano MA. Immunisation-related knowledge, attitudes and practices of mothers in Kinshasa, Democratic Republic of the Congo. South African Family Practice 2008 05/21;50(2):61-61e.

(51) Babalola S, Lawan U. Factors predicting BCG immunization status in northern Nigeria: a behavioral-ecological perspective. J Child Health Care 2009 03;13(1):46-62.

(52) Chen M, Wang R, Schneider JK, Tsai C, Jiang DD, Hung M, et al. Using the Health Belief Model to understand Caregiver factors influencing childhood influenza vaccinations. J Community Health Nurs 2011 Jan;28(1):29-40.

(53) Morin A, Lemaitre T, Farrands A, Carrier N, Gagneur A. Maternal knowledge, attitudes and beliefs regarding gastroenteritis and rotavirus vaccine before implementing vaccination program: Which key messages in light of a new immunization program? 2012;30:5921-5927.

(54) Mitchell S, Andersson N, Ansari NM, Khalid Omer, Legorreta Soberanis J, Cockcroft A. Equity and vaccine uptake: a cross-sectional study of measles vaccination in Lasbela District, Pakistan. (Special Issue: The fallacy of coverage: uncovering disparities to improve immunization rates through evidence. The Canadian International Immunization Initiative Phase 2 (CIII2) operational reSEARch grants.). BMC International Health and Human Rights 2009;9:Su.

(55) Kempe A, Patel MM, Daley MF, Crane LA, Beaty B, Stokley S, et al. Adoption of rotavirus vaccination by pediatricians and family medicine physicians in the United States. Pediatrics 2009 November 2009;124(5):e809-e816.

(56) Daley MF, Crane LA, Chandramouli V, Beaty BL, Barrow J, Allred N, et al. Misperceptions about influenza vaccination among parents of healthy young children. Clin Pediatr 2007 Jun;46(5):408-417.

(57) Thorpe EL, Zimmerman RK, Steinhart JD, Lewis KN, Michaels MG. Homeschooling parents' practices and beliefs about childhood immunizations. 2012;30:1149-1153.

(58) Gilca V, Boulianne N, Dube E, Sauvageau C, Ouakki M. Attitudes of nurses toward current and proposed vaccines for public programs: A questionnaire survey. Int J Nurs Stud 2009 Sep;46(9):1219-1235.

(59) Dube E, De Wals P, Gilca V, Boulianne N, Ouakki M, Lavoie F, et al. New vaccines offering a larger spectrum of protection against acute otitis media: Will parents be willing to have their children immunized?. Int J Pediatr Otorhinolaryngol 2009 July 2009;73(7):987-991.

(60) Harmsen IA, Lambooij MS, Ruiter RAC, Mollema L, Veldwijk J, van Weert Y, et al. Psychosocial determinants of parents' intention to vaccinate their newborn child against hepatitis B. 2012;30:4771-4777.

(61) Mollema L, Wijers N, Hahne SJM, van der Klis, F. R. M., Boshuizen HC, de Melker HE. Participation in and attitude towards the national immunization program in the Netherlands: data from population-based questionnaires. 2012;12.

(62) Kriwy P. Similarity of parents and physicians in the decision to vaccinate children against measles, mumps and rubella. International Journal of Public Health 2012 Apr;57(2):333-340.

(63) Anastasi D, Di Giuseppe G, Marinelli P, Angelillo IF. Paediatricians knowledge, attitudes, and practices regarding immunizations for infants in Italy. BMC Public Health 2009;9:463-463.

(64) Dube E, Gilca V, Sauvageau C, Bradet R, Lavoie F, Boulianne N, et al. Acute otitis media and its prevention by immunization A survey of canadian paediatricians' knowledge, attitudes and beliefs. Human Vaccines 2011 Apr;7(4):429-435.

(65) Agyeman P, Desgrandchamps D, Vaudaux B, Berger C, Diana A, Heininger U, et al. Interpretation of primary care physicians' attitude regarding rotavirus immunisation using diffusion of innovation theories. Vaccine 2009 30 Jul 2009;27(35):4771-4775.

(66) Misperceptions about influenza vaccination among parents of healthy young children. CLIN PEDIATR 2007 06;46(5):408-417.

(67) Zhou Y, Wang H, Zheng J, Zhu X, Xia W, Hipgrave DB. Coverage of and influences on timely administration of hepatitis B vaccine birth dose in remote rural areas of the People's Republic of China. American Journal of Tropical Medicine & Hygiene 2009 Nov;81(5):869-874.

(68) Ndiaye NM, Ndiaye P, Diedhiou A, Gueye AS, Tal-Dia A. Factors related to failure to complete immunization of children aged 10-23 months in Ndoulo (Senegal). Sante 2009;19(1):9-13.

(69) Gaudino JA, Robison S. Risk factors associated with parents claiming personal-belief exemptions to school immunization requirements: Community and other influences on more skeptical parents in Oregon, 2006. 2012;30:1132-1142.

(70) Odusanya OO, Alufohai EF, Meurice FP, Ahonkhai VI. Determinants of vaccination coverage in rural Nigeria. BMC Public Health 2008;8:381.

(71) Ozkaya E, Eker HH, Aycan N, Samanci N. Impact of maternal anxiety level on the childhood vaccination coverage. Eur J Pediatr 2010 November 2010;169(11):1397-1401.

(72) Rossignol L, Guthmann J-, Kerneis S, Aubin-Auger I, Lasserre A, Chauvin P, et al. Barriers to implementation of the new targeted BCG vaccination in France: A cross sectional study. Vaccine 2011 18 Jul 2011;29(32):5232-5237.

(73) Dube E, Gilca V, Sauvageau C, Bradet R, Bettinger JA, Boulianne N, et al. Canadian paediatricians' opinions on rotavirus vaccination. Vaccine 2011 Apr 12;29(17):3177-3182.

(74) Goodyear-Smith F, Grant C, York D, Kenealy T, Copp J, Petousis-Harris H, et al. Determining immunisation coverage rates in primary health care practices: a simple goal but a complex task. Int J Med Inf 2008;77(7):477-485.

(75) Kempe A, Daley MF, Crane LA, Barrow J, Chandramouli V, Beaty BL, et al. Misperceptions regarding influenza vaccine safety for individuals with chronic medical illness. Prev Med 2007 07;45(1):80-82.

(76) Zipursky S, Wiysonge CS, Hussey G. Knowledge and attitudes towards vaccines and immunization among adolescents in South Africa. Human Vaccines 2010 June 2010;6(6):455-461.

(77) Harries J, Moodley J, Barone MA, Mall S, Sinanovic E. Preparing for HPV vaccination in South Africa: Key challenges and opinions. Vaccine 2009 01 Jan 2009;27(1):38-44.

(78) Nelson JA, Francis SA, Liverpool J, Soogun S, Mofammere N. Healers in a non-traditional role; a focus group study of Sangoma's knowledge of and attitudes to cervical cancer prevention and screening in Johannesburg, South Africa. Sexual & reproductive healthcare: official journal of the Swedish Association of Midwives 2010 01/01.

(79) Francis SA, Nelson J, Liverpool J, Soogun S, Mofammere N, Thorpe,Roland J.,,Jr. Examining attitudes and knowledge about HPV and cervical cancer risk among female clinic attendees in Johannesburg, South Africa. Vaccine 2010 01/01.

(80) Babirye JN, Rutebemberwa E, Kiguli J, Wamani H, Nuwaha F, Engebretsen IMS. More support for mothers: a qualitative study on factors affecting immunisation behaviour in Kampala, Uganda. Bmc Public Health 2011 Sep;11.

(81) Katahoire RA, Jitta J, Kivumbi G, Murokora D, Arube WJ, Siu G, et al. An assessment of the readiness for introduction of the HPV vaccine in Uganda. Afr J Reprod Health 2008 01/01;12(3):159-172.

(82) Braka F, Asiimwe D, Soud F, Lewis RF, Makumbi I, Gust D. A Qualitative Analysis of Vaccine Safety Perceptions and Concerns Among Caretakers in Uganda. 2012;16:1045-1052.

(83) Obute JA, Arulogun OS. Parents' awareness and perception of the polio eradication programme in Gombe Local Government Area, Gombe State, Nigeria. INT J HEALTH PROMOT EDUC 2007 08;45(3):81-86.

(84) Arulogun OS, Obute JA. Health workers' perception about the supplemental immunization activities in Gombe local government area, Gombe state. Afr J Med Med Sci 2007 Mar 2007;36(1):65-70.

(85) Olufowote JO. Local resistance to the global eradication of polio: newspaper coverage of the 2003-2004 vaccination stoppage in northern Nigeria. Health Commun 2011 Dec;26(8):743-753.

(86) Remes P, Selestine V, Changalucha J, Ross DA, Wight D, de Sanjose S, et al. A qualitative study of HPV vaccine acceptability among health workers, teachers, parents, female pupils, and religious leaders in northwest Tanzania. 2012;30:5363-5367.

(87) Schaetti C, Ali SM, Hutubessy R, Khatib AM, Chaignat C-, Weiss MG. Social and cultural determinants of oral cholera vaccine uptake in Zanzibar. Human Vaccines and Immunotherapeutics 2012 September 2012;8(Cancer Commentary Series.):1223-1229.

(88) Schaetti C, Ali SM, Chaignat C-, Khatib AM, Hutubessy R, Weiss MG. Improving community coverage of oral cholera mass vaccination campaigns: Lessons learned in Zanzibar. PLoS ONE 2012 Article Number: e4;7 (7) , 2012:ate of Pubaton: 23 Ju 2012.

(89) Tadesse H, Deribew A, Woldie M. Explorative assessment of factors affecting child immunization in Wonago district, Gedeo zone, South Ethiopia. Archives of Medical Science 2009;5(2):233-240.

(90) Schwarz NG, Gysels M, Pell C, Gabor J, Schlie M, Issifou S, et al. Reasons for non-adherence to vaccination at mother and child care clinics (MCCs) in Lambarene, Gabon. Vaccine 2009 27 Aug 2009;27(39):5371-5375.

(91) Oria PA, Matini W, Nelligan I, Emukule G, Scherzer M, Oyier B, et al. Are Kenyan healthcare workers willing to receive the pandemic influenza vaccine? Results from a cross-sectional survey of healthcare workers in Kenya about knowledge, attitudes and practices concerning infection with and vaccination against 2009 pandemic influenza A (H1N1), 2010. Vaccine 2011 Apr 27;29(19):3617-3622.

(92) Dugas M, Dube E, Kouyate B, Sanou A, Bibeau G. Portrait of a lengthy vaccination trajectory in Burkina Faso: from cultural acceptance of vaccines to actual immunization. Bmc International Health and Human Rights 2009 Oct;9.

(93) Fourn L, Haddad S, Fournier P, Gansey R. Determinants of parents' reticence toward vaccination in urban areas in Benin [West Africa]. BMC international health and human rights 2009 01/01.

(94) Chadambuka A, Chimusoro A, Apollo T, Tshimanga M, Namusisi O, Luman ET. The need for innovative strategies to improve immunisation services in rural Zimbabwe. Disasters 2012 Jan 2012;36(1):161-173.

(95) Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. The Lancet 2009 20090502;373(9674):1543-1549.

(96) Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet (British edition) 2009;373(9674):1543-1549.

(97) Aslam M, Kingdon GG. Parental education and child health-understanding the pathways of impact in Pakistan. World Dev 2012 Oct 2012;40(10):2014-2032.

Appendix 1 - Search strategy for systematic review of public trust in vaccines and vaccination programmes – Ovid MEDLINE(R) 1948 to November Week 3 2012

1. ((vaccin$ or immunis$ or immuniz$) adj5 (anxiety or attitude$ or awareness or behavio?r or belief$ or criticis$ or doubt$ or distrust or dropout$ or exemption$ or fear$ or hesitanc$ or trust or mistrust or perception$ or refus$5 or rejection or rumo?r$ or intent$5 or controvers$ or misconception$ or misinformation or opposition or delay or dilemma$ or objector$)).ti,ab.
2. ((vaccin$ or immunis$ or immuniz$) adj3 (uptake or barrier$ or choice$ or mandatory or compulsory or concern$ or accepta$ or knowledge or parent$ con$)).ti,ab.
3. (((vaccin$ or immunis$ or immuniz$) adj5 confidence) not confidence interval).ti,ab.
4. ((vaccin$ or immunis$ or immuniz$) adj5 decision making).ti,ab.
5. ((vaccin$ or immunis$ or immuniz$) and (anti-vaccin$ or antivaccin$)).ti,ab.
6. 1 or 2 or 3 or 4 or 5
7. exp vaccination/
8. Vaccines/
9. Mass Vaccination/
10. Immunization/
11. exp Immunization Programs/
12. 7 or 8 or 9 or 10 or 11
13. Public Opinion/
14. Attitude to Health/
15. Attitude/
16. Health Knowledge, Attitudes, Practice/
17. "Patient acceptance of health care"/
18. Treatment Refusal/
19. Parental Consent/
20. Decision Making/
21. Prejudice/
22. Internet/
23. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 12 and 23
25. 6 or 24
26. limit 25 to humans
27. ((vaccin$ or immunis$ or immuniz$) adj5 (anxiety or attitude$ or awareness or behavio?r or belief$ or criticis$ or doubt$ or distrust or dropout$ or exemption$ or fear$ or hesitanc$ or trust or mistrust or perception$ or refus$5 or rejection or rumo?r$ or intent$5 or controvers$ or misconception$ or misinformation or opposition or delay or dilemma$ or objector$)).ti,ab.
28. ((vaccin$ or immunis$ or immuniz$) adj3 (uptake or barrier$ or choice$ or mandatory or compulsory or concern$ or accepta$ or knowledge or parent$ con$)).ti,ab.

29. (((vaccin$ or immunis$ or immuniz$) adj5 confidence) not confidence interval).ti,ab.
30. ((vaccin$ or immunis$ or immuniz$) adj5 decision making).ti,ab.
31. ((vaccin$ or immunis$ or immuniz$) and (anti-vaccin$ or antivaccin$)).ti,ab.
32. 27 or 28 or 29 or 30 or 31
33. exp vaccination/
34. Vaccines/
35. Mass Vaccination/
36. Immunization/
37. exp Immunization Programs/
38. 33 or 34 or 35 or 36 or 37
39. Public Opinion/
40. Attitude to Health/
41. Attitude/
42. Health Knowledge, Attitudes, Practice/
43. "Patient acceptance of health care"/
44. Treatment Refusal/
45. Parental Consent/
46. Decision Making/
47. Prejudice/
48. Internet/
49. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. 38 and 49
51. 32 or 50
52. limit 51 to humans

Appendix 2. WHO Regions and countries[2]

WHO Western Pacific Region	WHO African Region	WHO EURpean Region	WHO Region of the Americas	WHO Eastern Mediterranean Region	WHO South-East Asia Region
Australia	Algeria	Albania	Antigua and Barbuda	Afghanistan	Bangladesh
Brunei Darussalam	Angola	Andorra	Argentina	Bahrain	Bhutan
Cambodia	Benin	Armenia	Bahamas	Djibouti	Democratic People's Republic of Korea
China	Botswana	Austria	Barbados	Egypt	India
Cook Islands	Burkina Faso	Azerbaijan	Belize	Iran (Islamic Republic of)	Indonesia
Fiji	Burundi	Belarus	Bolivia (Plurinational State of)	Iraq	Maldives
Japan	Cameroon	Belgium	Brazil	Jordan	Myanmar
Kiribati	Cape Verde	Bosnia and Herzegovina	Canada	Kuwait	Nepal
Lao People's Democratic Republic	Central African Republic	Bulgaria	Chile	Lebanon	Sri Lanka
Malaysia	Chad	Croatia	Colombia	Libya	Thailand
Marshall Islands	Comoros	Cyprus	Costa Rica	Morocco	Timor-Leste
Micronesia (Federated States of)	Congo	Czech Republic	Cuba	Oman	
Mongolia	Côte d'Ivoire	Denmark	Dominica	Pakistan	
Nauru	Democratic Republic of the Congo	Estonia	Dominican Republic	Qatar	
New Zealand	Equatorial Guinea	Finland	Ecuador	Saudi Arabia	
Niue	Eritrea	France	El Salvador	Somalia	
Palau	Ethiopia	Georgia	Grenada	South Sudan	
Papua New Guinea	Gabon	Germany	Guatemala	Sudan	
Philippines	Gambia	Greece	Guyana	Syrian Arab Republic	
Republic of Korea		Hungary		Tunisia	
Samoa		Iceland		United Arab Emirates	
Singapore		Ireland		Yemen	
Solomon Islands		Israel			
Tonga		Italy			
		Kazakhstan			
		Kyrgyzstan			
		Latvia			
		Lithuania			
		Luxembourg			

[2] Source: http://www.who.int/about/regions/en/index.html

Tuvalu Vanuatu Viet Nam	Ghana Guinea Guinea-Bissau Kenya Lesotho Liberia Madagascar Malawi Mali Mauritania Mauritius Mozambique Namibia Niger Nigeria Rwanda Sao Tome and Principe Senegal Seychelles Sierra Leone South Africa Swaziland Togo Uganda United Republic of Tanzania Zambia Zimbabwe	Malta Monaco Montenegro Netherlands Norway Poland Portugal Republic of Moldova Romania Russian Federation San Marino Serbia Slovakia Slovenia Spain Sweden Switzerland Tajikistan The former Yugoslav Republic of Macedonia Turkey Turkmenistan Ukraine United Kingdom Uzbekistan	Haiti Honduras Jamaica Mexico Nicaragua Panama Paraguay Peru Saint Kitts and Nevis Saint Lucia Saint Vincent and the Grenadines Suriname Trinidad and Tobago United States of America Uruguay Venezuela (Bolivarian Republic of)		

Appendix 3. Determinants of vaccine hesitancy identified in relation to childhood vaccines and vaccination.

Figure 11. Factors identified as either barriers (B) to or promoters (P) of childhood vaccination and mapped onto Vaccine Hesitancy model (multivariate studies reviewed, n=76)

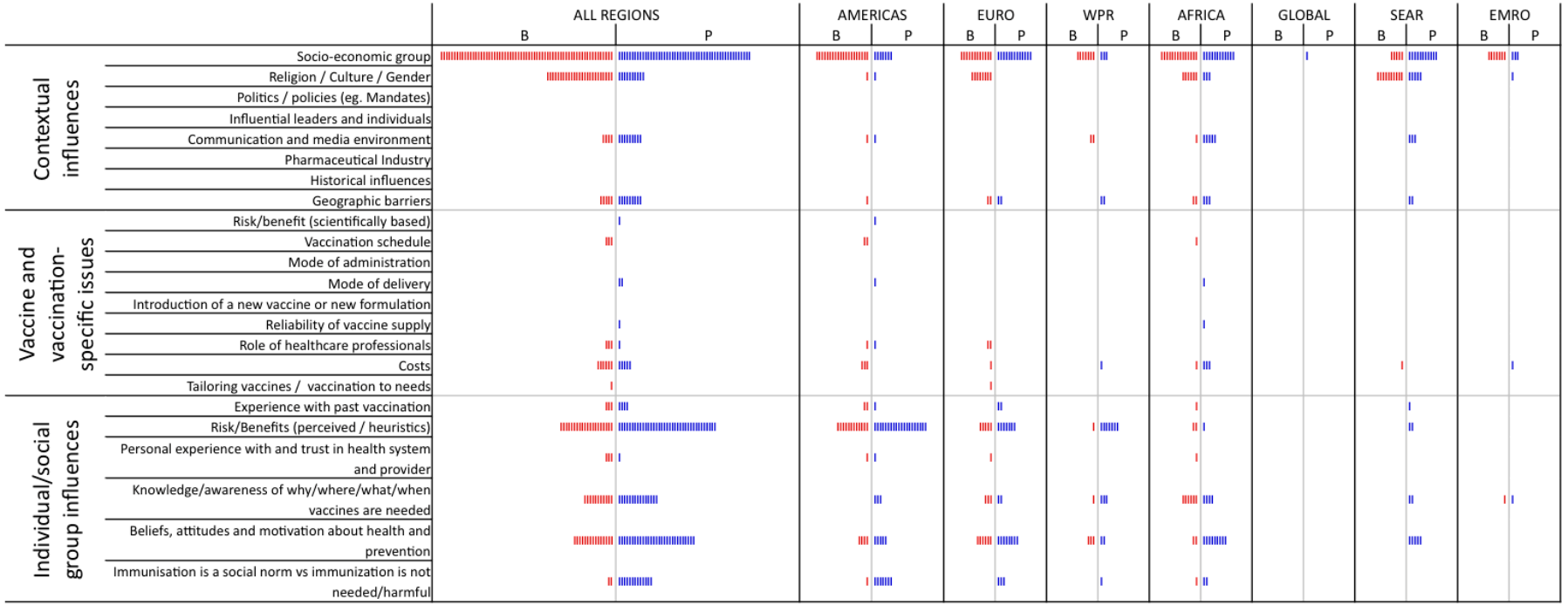


Figure 12. Breakdown of factors identified as 'Contextual Influences' (see above) for childhood vaccines

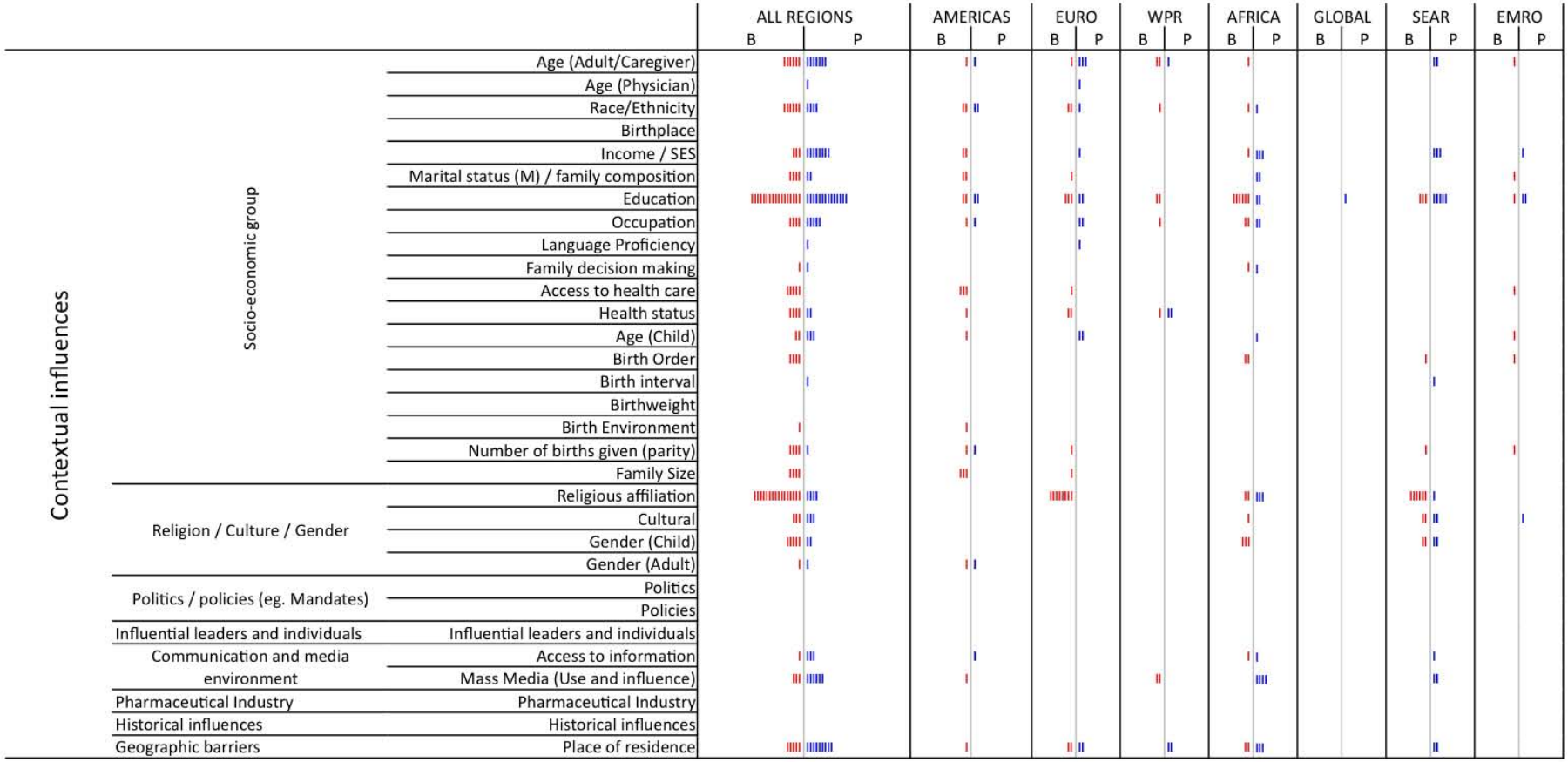


Figure 13. Breakdown of factors identified as 'Vaccine & vaccination-specific issues' (see above) for childhood vaccines

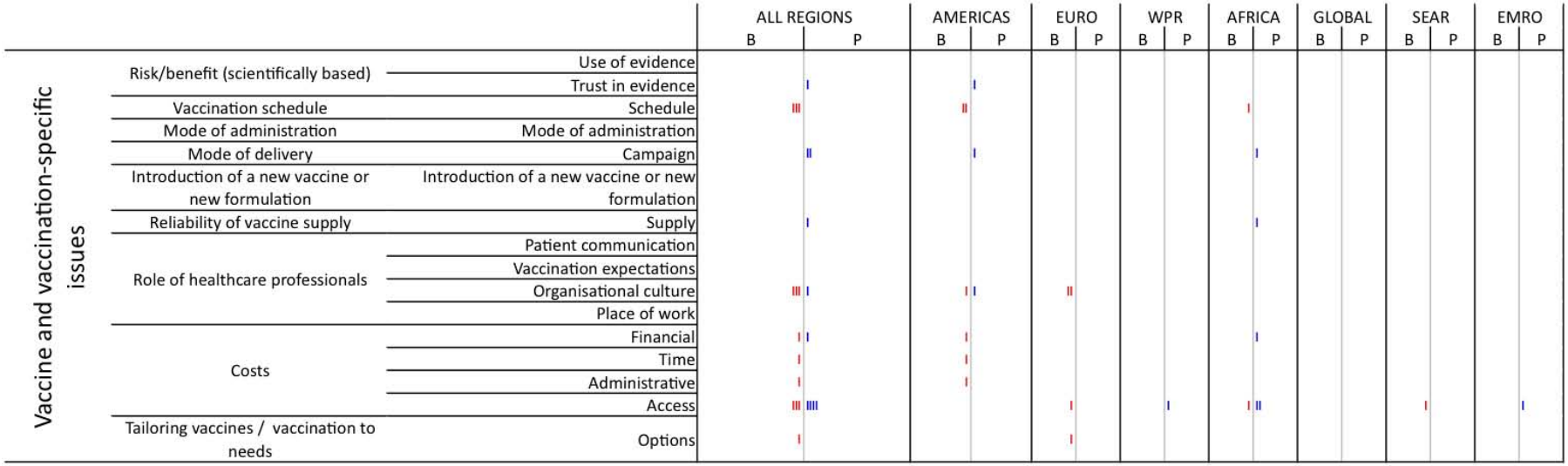
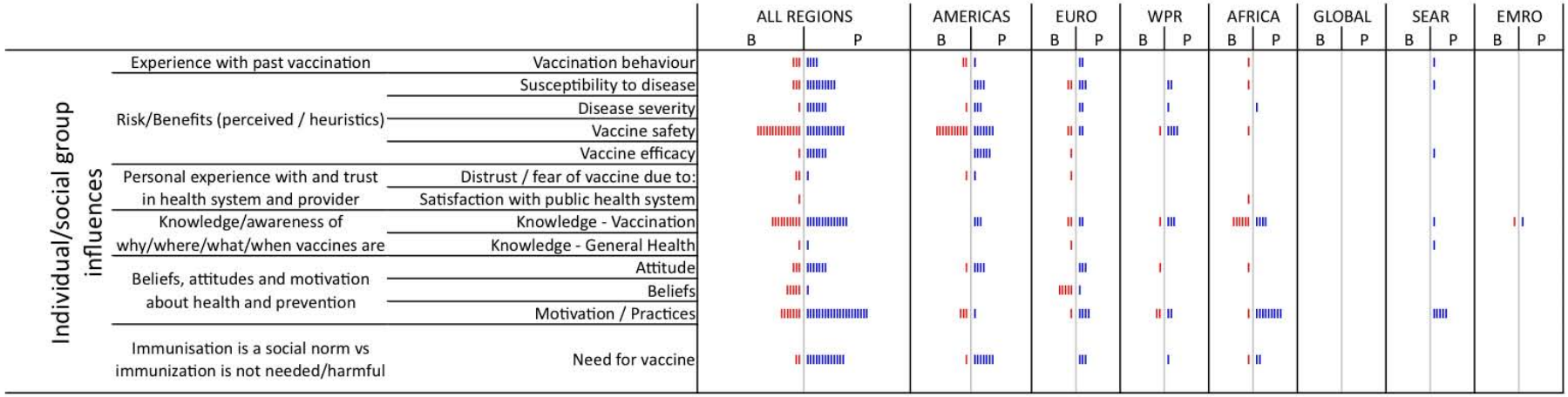


Figure 14. Breakdown of factors identified as 'Individual / social group influences' (see above) for childhood vaccines



Vaccine Hesitancy Landscape Analysis of organisations working on the issue of Vaccine Hesitancy[1]

SAGE Working Group on Vaccine Hesitancy
March 2013

[1] Work in progress. No claims can be made about the completeness or adequacy of the contents of this document .

Table of Contents

Background:

Vaccine hesitancy is one of several concepts and ideas that relate to the demand side of vaccine usage, synonymously following terms can be used: vaccine acceptance, vaccine confidence and vaccine refusal, among others. This landscape analysis attempts to take a relatively broad view of vaccine hesitancy by including all actors working on any of these concepts. However, for the purposes of simplicity, all concepts are grouped under the umbrella term of 'vaccine hesitancy'.

The purpose of this document is to stimulate the compilation of a list of organizations involved in vaccine hesitancy work. This document presents a reference list which includes examples from many different types of organizations at many different levels. The intention is that the list becomes more populated and evergreen as stakeholders, organizations, institutes and communities respond with suggested additions. This currently initial list should be shared with country level partners for their additional input. As the list becomes more robust it will be become more useful to meet the indicated objectives.

Five categories and **four** sub-categories of actors were determined to represent the groups working on the issue of vaccine hesitancy, including *Government* (national and regional), *Not-for-profit*, *Donors*, *Research Organisations* and *Multinationals.* An *Other* category was included to represent any actor that did not fit in the above categories but was still producing important work related to vaccine hesitancy. Industry was not included as its own category in this framework. Although industry has a major stake in vaccine hesitancy, industry vaccine groups share similar interests in combating vaccine hesitancy and therefore conduct comparable work on the issue. Consequently, limited benefit is seen in analysing each member of vaccine industry individually. Instead, the vaccine industry was included as one entity in the 'other' category, so their work and interests as a group may be presented in the Landscape Analysis.

Excluded were concepts, frameworks or strategies addressing vaccine hesitancy which are not a solitary entity but composed of different organizations, stakeholders or collaborators. In this context especially the "'Decade of Vaccines' Collaboration/ Global Vaccine Action Plan" needs to be mentioned. One of their strategic objectives is that individuals and communities understand the value of vaccines and demand immunization both as a right and a responsibility. Goal is to develop an indicator measuring vaccine hesitancy[i].

Objectives:

- Allow to identify what organisations are working on the issue of vaccine hesitancy in various settings/countries.
- Allow those working on the issue of vaccine hesitancy to identify potential partners, donors and collaborators in the field.
- Allow people to identify the regions where work is being done on vaccine hesitancy and what kind of work is being done in each area.
- Be a regularly updated resource on work currently being done in the field of vaccine hesitancy
- Help identify research and funding gaps—particularly in countries where there are more significant vaccine hesitancy issues.

Methods:

Areas of work:

7 areas of work and/or interest were identified being carried out by actors working on the issue of vaccine hesitancy, these included:

- *research*
- *policy recommendation*
- *intervention*
- *education & promotion*
- *collaboration*
- *goal setting*
- *social mobilisation*

Search strategies:

Two main strategies were used:

1. *Literature Search*
   a. Databases/Search engines used:
      i. Google: Canadian (google.ca), United States (google.com), United Kingdom (google.co.uk) and Hong Kong (google.com.uk)
         - First 5 pages of google were searched for relevant actors
      ii. Pubmed
      iii. Refworks database for the systematic review on the rubric of trust and confidence in vaccines currently being produced by the London School of Hygiene and Tropical Medicine (LSHTM).
      iv. WHO database: Global Information Full Text project (GIFT), more than 10,000 priced and open access journals
   b. Search terms
      i. Google (Canadian, US, German and UK), GIFT and Pubmed
         - Used the following search terms: vaccin*, immunization, shot AND hesitan*, resistan* refusal, confidence, acceptance, promotion AND initiative* OR organization* OR strateg*
      ii. Google (Hong Kong)
         - Used the same search terms as above, translated into Chinese:
            - 疫苗=vaccine
            - 犹豫=hesitant/hesitancy
            - 抗拒=refuse/resist
            - 信心=confident/confidence
            - 接受=accept/acceptance
            - 研究=research
            - 组织=organization/institution
      iii. Refworks
         - Searched full database, using term: vaccin*, immunization, shot AND hesitan*

2. *Snowballing technique*

Furthermore, we obtained unpublished information through personal communication with colleagues and experts.

a. Asked main players working on the issue of vaccine hesitancy (i.e. people in SAGE WG on vaccine hesitancy, and players identified through initial literature search) and colleagues familiar with regional/local circumstances
    i. Feedback from:
        - Julie Leask, University of Sydney
        - Heidi Larson, member SAGE working group (WG) on vaccine hesitancy
        - Noni MacDonald, member SAGE WG on vaccine hesitancy
        - Susan (Yuquing) Zhou, member SAGE WG on vaccine hesitancy
        - Mahamane Laouali Manzo, member SAGE WG on vaccine hesitancy
        - Dr. Bettinger, vaccine researcher at the Child & Family Research Institute at the BC Children's Hospital and UBC, Canada
b. Based on these responses collaborators and affiliates of players of vaccine hesitancy that were mentioned were looked up and it was determined if/how they were involved in vaccine hesitancy.
c. The main players working on the issue of vaccine hesitancy also provided additional contact information for other actors working on this issue.

Inclusion/exclusion criteria:

Inclusion:

i. Actors doing work in at least two of the seven areas of work/interest specified in the introduction.
ii. Actors give *specific* examples of activities they are engaged relating to the issue of vaccine hesitancy (i.e. not simply stating general mandates).

Exclusion:

iii. Actors promoting vaccine hesitancy or who are part of the anti-vaccination lobby.
iv. Actors that have not worked on the issue of vaccine hesitancy in the last 5 years

Results:

Table 1. Key actors working on vaccine hesitancy

Categories		Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
Gov.	National	China CDC (CCDC)	• Research • Policy Recommendations Interventions	• Research: ○ Survey of KAP (knowledge, attitudes and practices) of measles[2] (MOH and WHO) ○ Survey on KAP of Hepatitis B among health care staff [16] (MOH and UNICEF) ○ Survey on EPI KAP among highly educated population [16] (CCDC) ○ Person to person communication intervention strategies[16] (MOH and UNICEF) ○ Evaluation of parents KAP on immunization[16] (MOH, WHO and US CDC) • Social marketing campaign ○ 25 April- Children's Immunization Day[3](MOH, CCDC and provincial health bureau and provincial CDC) ○ Information sheets/brochures for parents and caregivers, to address any vaccine concerns.[4] (MOH, CCDC) ▪ Guide providing info about general knowledge, the benefits of vaccination, situations when not to receive vaccination, preparation work for parents, adverse events, etc.[18] (MOH, CCDC)	China	• Provincial health bureau and CDC • WHO • US CDC • UNICEF China Ministry of Health (MOH)
		China MOH	• Research • Interventions • Education & Promotion	• Social Marketing: ○ ImmunizationDay[17] (MOH ,national wide health bureau and CDC and government) ▪ Theme: Vaccination is the responsibility of each household in 2012, each year has different theme based on the priority of work (MOH) • Promotion methods [18] (CCDC and Local CDC) ○ Central governor and Local governor attend initiating ceremony ○ Improve awareness and promotion through competitions about vaccine knowledge, expert visits, as well as art and cultural performances (CCDC) ○ Involvement of organisational leaders, including attending vaccine promotion activities, improve cooperation between education and social media departments, motivate village leaders and committee members to promote to the community	China	• China CDC • Provincial health bureau and CDC Central and local governments

† Areas of work/interest within vaccine hesitancy including: research, policy recommendation, intervention, education/promotion, collaboration, goal setting.
‡ Actions: examples of current vaccine hesitancy activities the actors are engaged in
§ Where (country/setting) where the organization is based and/or where their work on vaccine hesitancy is focused.
** Only organization that consistently collaborated on vaccine hesitancy or worked on key project related to vaccine are shown in the 'Collaborators and Affiliates' section.

Categories		Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
				about the efficacy and safety of the vaccine(MOH, PROVINCIAL HEALTH BUREAU and CDC) ○ Arrange visits to rural areas and visits of minorities which health information may not reach conveniently (CDC) ○ Enforce education to village committees, village doctors, school teachers, and parents CDC ○ Systematically collect and manage information of promotion activities CDC ○ *Please note that many of these projects were undertaken in concert by both the China Department of Health and the China CDC.		
		Department of Health, Belize	• Policy • Intervention • Research	○ Public Health strategy to meet with all parents whose children not immunized in timely fashion. The workers will meet parents in their homes. [5]	Belize	Canadian Centre for Vaccinology
		Federal Centre for Health Education (Bundeszentrale für Gesundheitliche Aufklärung, BZgA)	• Education & Promotion • Research	• Health education and health promotion • Research on parental knowledge, behaviour and attitude concerning vaccinations and the need for information material[6]	Germany	• German Ministry of Health • National Public Health Institute
		National Centre for Immunisation Research and Surveillance (NCIRS)	• Research • Policy Recommendations • Interventions • Education & Promotion	• Workshops and conferences ○ *2012- Ethical Issues in Immunisation Seminar*[7] ▪ Presentation on 'How far can government go in promoting vaccination?' and 'A little bit more ethics on power an persuasion in immunisation' • Social Research ○ Descriptive, identifying immunisation-related beliefs, attitudes and practices of consumers and health professionals, as well as mass communication research. [8] ▪ Survey tracking parental attitudes to vaccination[9] ▪ *MMR Decision Aid*[10] • Used to help parents to decide whether to immunise their child with MMR the vaccine. *Please note that the NCIRS is directly linked with the University of Sydney, however because of its varied work on the issue of vaccine hesitancy it was included as its own actor.	Australia	• Australian Technical Advisory Group on Immunisation (ATAGI) • Australian Government Department of Health and Ageing • University of Leeds
		AFRICAN REGION: Ministries of Health and Communication	• Policy/Recommendation • Intervention • Education& promotion • Collaboration	• Solemn declaration by President (swearing on the Koran at Niger) on the safety of the vaccine to overcome reluctance • Launching ceremonies of immunization campaigns by heads of state: (Niger,Nigeria,Benin,Burkina Faso,Mali)A meeting is organized, all stakeholders are taking part and there are media reports. • Media coverage of immunization sessions where families of authorities(health and	Africa	• UNICEF

Categories		Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
		(Niger,Benin,Nigeria,Mali,Burkina Faso,Kenya, Guinée Conakry)	• Goal setting.	government) are vaccinated: Niger,Nigeria • Integration of home visits in the "minimum package" of health center service delivery: Niger, Benin, Burkina Faso ,Mali • Broadcast television radio messages explaining the different vaccinations during the EPI immunization schedule and the importance of respecting it (reports by religious association„chief associations and MOH): Niger, Benin, Burkina Faso ,Mali,Nigeria • Capacity building of EPI managers: WHO and UNICEF support it in most of African region. • Production of information material (National EPI, National Directorate of Health Education with lean of UNICEF) and distribution of educational media information to raise awareness (pagivoltes, booklets, posters): health workers, religious and chief association		
		Romania National Institute of Public Health	• Policy/Recommendation • Research	Project: Strategic Directions for the Development of the vaccination program and Promotion of vaccination Identifying issue related to vaccine hesitancy and developing a national strategy with best practice and recommended methodologies to tackle caregiver hesitancy.	Romania	
		UK Department of Health	• Research • Interventions • Policy Recommendations	• *Joint Committee on Vaccination and Immunisation* (JCVI) ○ Research on attitudes on influenza vaccination in children[11] • Immunisation Market Research Section ○ State: "feedback on attitudes and awareness of immunisation is vital to help inform and shape the work" on successfully promoting and administrating vaccines. [12] ○ Parent tracking research and health professionals surveys[13] ○ Studies of attitudes towards HPV (e.g. for girls, mother, nurses administrating the vaccine)[14] ○ Evaluation of vaccine hesitancy campaigns[15] • *Arm Against Cervical Cancer* campaign A national media campaign "designed to inform mums and girls about the virus and vaccination program, offer reassurance of the vaccine's safety, counteract possible negative press attention and maximise take up of the vaccine." [16] (p.1)	UK	• Health Protection Agency
		US Centers for Disease Control and Prevention (CDC)	• Research • Interventions • Policy Recommendations	• National Center for Immunization and Respiratory Diseases (NCIRD) Online tool for Catch-up Scheduling for Childhood Immunization (www.vacscheduler.org) • Funds collaborations and initiatives focusing on vaccine hesitancy: ○ *Immunization Action Coalition*[17] ○ *Vaccine Confidence Project* (LSHTM)[18] • Clinical Immunization Safety Assessment (CISA) ○ To enhance public confidence in sustaining immunization benefits for all populations	USA	• US Department of Health and Human Services State public health departments
		US Department of Health and Human Services	• Research • Policy Recommendations	• *National Vaccine Advisory Committee (*NVAC) ○ *Recommendations on Strategies to Achieve the Healthy People 2020 Annual Influenza Vaccine Coverage Goal for Health Care Personnel*[19]	USA	CDC

Categories		Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
			• Goal Setting • Education & Promotion	○ Vaccine Hesitancy working group now being established ▪ In report, individuals raised concerns over adverse events, vaccine effectiveness, vaccine safety, etc. ○ *A Pathway to Leadership for Adult Immunization: Recommendations of NVAC*[20] ▪ Identified 9 categories of barriers to adult immunization, including 'lack of public knowledge', 'health literacy', and 'concerns about adverse events' ▪ One recommendation- increase 'community demand for vaccinations' • *2010 National Vaccine Plan*[21] ○ Goal 3: Support communications to enhance informed vaccine decision-making Priorities for implementation include "increase awareness of vaccines, vaccine-preventable diseases, and the benefits/risks of immunization among the public, providers, and other stakeholders"[3]		
	Regional	Department of Health and Wellness, Nova Scotia, Canada	• Research • Interventions	• Projects to decrease vaccine hesitancy: [22,23] ○ Campaign to mitigate pain with immunization based upon evidence– aimed at parents, adults, HCP anxious about immunization • Campaign to increase uptake flu vaccine by pregnant women	Nova Scotia, Canada	• Can Centre for Vaccinology HELPinKIDS Canada
		Institut National de Santé Publique de Québec	• Policy/Recommendation • Research • Intervention • Goal setting	• *Plan Québécois de Promotion de la Vaccination* (Feb 2010) ○ *Action Plan for Vaccination Promotion- Phase* II (April 2012)[24] ▪ Phase II addresses goals 3 and 4 of the action plan which related directly to vaccine hesitancy • Goal 3: Encourage positive attitudes toward vaccination among health professionals and encourage such professionals to be vaccinated themselves • Goal 4: Encourage positive attitudes toward vaccination in the general population ▪ To achieve these goals • Identify knowledge, attitudes, beliefs and practices of general population and health professionals, • Identify interventions to encourage positive attitudes toward vaccination • Strategies to train health professionals on vaccination, and update their immunization competencies	Québec, Canada	• L'Université Laval
		• Regional governors, prefects and mayors • Regional and departmental public health Direction • Traditional and religious	• Education & Promotion • Interventions • Policy	• Organizing Meeting with communities around the reasons of vaccine hesitancy: MOH and, religious and chief association. Discussions with community, religious and traditional leaders, various associations, • Organization of home visits by health centers through Community women: (Volunteer Community mobilizes) Niger, Nigeria, Mali, Benin,Burkina Faso • Organization of meetings in neighborhoods, villages and health centers: health workers, religious association and traditional chief ,community health committee • Debates and broadcasts messages on local radio stations: health workers, religious association and traditional chief ,community health committee • Use of media for promotion and surveillance of campaigns: local radio, text messaging and	Africa	• MOH • UNICEF

Categories	Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
	leaders (Imams, Pastors) •Health committees		daily evening meetings during campaigns to spot and correct refusals and other problems encountered (e.g. Guinée Conakry) • Providing rewards e.g. "hygiene kit during immunization session" in Kenya .to women whose children are fully immunized financed by MOH,UNICEF. • Reward health centers with the best performance vaccination financed by MOH,UNICEF		
	California Immunization Coalition	• Education &Promotion • Interventions	• Improving immunization rates (coverage) for Californians of all ages and achieving Healthy People goals relating to immunization rates across the lifespan. • Offering leadership in policy development and advocacy with an emphasis on promoting community based advocacy through support of local coalitions. • Supporting local coalitions. • Providing educational activities/opportunities for health care professionals, community stakeholders and the public. e.g. shotbyshot.org • Promoting use of immunization registries. • Reducing health disparities and improving access to vaccines by addressing barriers that prevent or limit access to immunizations. •	California, USA	•
	Canadian Association for Immunization Research and Evaluation	• Research • Intervention	• CAIRE actively participates and promotes vaccine related investigations • Conferences • Immunization Competencies Education Program (ICEP), training for Health Professionals • CAIRE offers a "second scientific home" to researchers who work in the field of applied vaccinology.	Canada	• Public Health Agency of Canada (Centre for Immunization and Respiratory Infectious Diseases)
	Canadian Pediatric Society	• Education& Promotion Collaboration	• Education materials for parents and health care professionals: Caring for kids Collaboration: provincial governments, PHAC at the Federal Government	Canada	
	Global Polio Eradication Initiative	• Research • Interventions • Education &Promotion • Research	• Data and monitoring ○ Household survey[25] ▪ Asking about reasons why child was not immunized (e.g. Refusal- religious belief, vaccine safety, no felt need) ○ Polio Pipeline: KAP studies- understanding barriers to immunization[26] ▪ Studies conducted in Nigeria, India, Pakistan in 2008 and Afghanistan in 2009 • National Polio Surveillance Programme in India[27] : • Resistant issues in endemic areas • Surveys looking at what children are not being vaccinated and why?	Polio infected countries	• UNICEF • WHO • US CDC • Rotary International • National governments • LSHTM
	•National Association offices of	• Policy/Recommendation • Intervention	• Traditional chief and religious (Muslim and Christian) have an Association in most African countries. Taking the example of Niger: National association of traditional chiefs named Association des Chefs Traditionnels du Niger(ACTN) or Association Islamic du Niger	Africa	MOH, WHO UNICEF

Categories	Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
	traditional chief and religious leaders.	•	(AIN). • Advocacy on media • Preaching in villages • Face-to-face contact with reluctant individuals		
	National Foundation for Infectious Diseases (US)	• Education & Promotion • Collaboration •	• Professional educational program on immunization 2 times per year – 3 hours devoted to hesitancy each course for now > 5 years[28]	USA	CDC and others
	Trust for Vaccines and Immunization	• Education Intervention	• Several mass vaccination campaign against typhoid fever of children and adults in towns in the province of Karachi	Pakistan	• International Vaccine Institute • Ministry of Health – Govt of Sindh • Expanded Programme on Immunization • Ministry of Education – Govt of Sindh • City District Government Karachi
Donors	Bill and Melinda Gates Foundation	• Research • Intervention • Education & Promotion	• Funding ○ Initiatives related to vaccine hesitancy, as well as vaccine acceptance and promotion[29] ▪ E.g. *Vaccine Confidence Index* from LSHTM (global surveillance system to identify and track rumours/misinformation related to immunization. ○ Supporting organisations that are working in the area of vaccine hesitancy. ▪ E.g. WHO, UNICEF, LSHTM	Global	
	Robert Wood Johnson Foundation	• Research • Intervention	• Grants ○ Funding publications and research[30] ▪ E.g. 'Protecting public trust in immunization'	US	
Research Organisations	Canadian Centre for Vaccinology	• Research • Education & Promotion	• Vaccine hesitancy[31] ○ pain mitigation, ○ school based vaccine programs ○ hard to reach and their hesitancy, ○ health care professional undergrad curriculum ○ HCP hesitancy for flu vaccine policy and hesitancy	Canada	• Variety of local, regional and national partners- both NGOs and govt's

Categories	Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
	Harvard University	• Research • Collaboration	• Working with the American Academy of Arts and Science on a vaccine hesitancy project	USA	• American Academy of Arts and Science
	John Hopkins School of Public Health	• Research • Collaboration	Research parental attitudes, studied the effectiveness of providing vaccination education materials to pregnant women and women who have just delivered to see if that would make them less hesitant. He has also collaborated with the CDC and Kaiser on several studies.	USA	• CDC • Kaiser Permanente
	London School of Hygiene and Tropical Medicine	• Research • Intervention • Promotion & Education	• *Vaccine Confidence Project*[32] • *MOTIV Think Tank: Motors of Trust in Vaccination* • Developing systematic review on vaccine confidence, acceptance, hesitance, etc.	UK	• Wide variety of global partners
	Ottawa Hospital Research Institute	• Research • Education & Promotion	○ Research on evolution of controversies concerning pediatric vaccination (Kumanan Wilson, MD, FRCPC, MSc)	Canada	
	Sherbrooke University (Quebec) and University of Victoria (British Columbia).	• Research • Education & Promotion	• Book title on Vaccine Hesitancy (working title): Cultural and Religious Roots of Vaccine Hesitancy: Explanations and Implications for Canadian Health Care. ▪ Objectives and target readership: 1) Report on various aspects of phenomenon of vaccine hesitancy (VH) and its features; 2) Propose theories for understanding VH; 3) Support public health (PH) practices and decisions for health professionals facing VH. PH authorities, health professionals and graduate students are targeted.	Canada	• Researchers across Canada
	University of British Columbia (Vaccine Evaluation Center)	• Research • Education & Promotion	• The main research themes involve disease burden studies, vaccine clinical trials, and studies to fine tune public immunization programs, including ongoing assessment of vaccine safety	Canada	
	University of Leeds (UK)	• Research • Intervention	• *MMR Decision Aid* (with NCIRS) ○ *Detailed Evaluation of a Childhood Immunisation Decision Aid* (D.E.C.I.D.A study)[33] •	UK	University of Sydney
	University of Sydney	• Research • Interventions Education & Promotion	• Working with the NCIRS and other partners on a variety of projects related to vaccine hesitancy, acceptance and promotion.[34] ○ E.g. *MMR Decision Aid Tool*[35] • Provide classes related to vaccine hesitancy and acceptance ○ E.g. PUBH5416 Vaccines in Public Health[36] Content- "risk communication and immunisation myths and realities"	Australia	• University of Leeds NCIRS
	University of Washington School of	• Research • Promotion& Education	• Research in the field of vaccine refusal/ attitude towards vaccination ○ Parental delay or refusal of vaccine doses, childhood vaccination coverage at 24 months of age, and the Health Belief Model.[37]	USA	

Categories	Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
	Medicine Seattle, Washington	•	○ Washington State Pediatricians Attitudes Towards Alternative Childhood Immunization Schedules[38]		
	VAX Northwest	• Research • Intervention • Promotion & Education	• Social marketing campaign ○ Increase timely immunizations from birth to age 24 months in Washington State[39,40] ▪ Focus: vaccine hesitant parents ▪ Provider toolkit ▪ Outreach to parents/social norms[41]	Washington State, USA	• Within Reach Immunization Action Coalition of WA • Washington State Department of Health • Seattle children's hospital • Community pediatric foundation of Washington.
Multinationals	UNICEF	• Research • Policy Recommendations • Education & Promotion • Intervention •	• Works with GAVI on the *Advocacy & Communication Task Force* (ACTF)- See GAVI above • UNICEF works with governments, partners and communities to increase demand for immunization • Vaccine strategies include engaging communities: ○ Communication strategies that include advocacy, communication, and social mobilisation ○ Rapid inquiry into attitudes about PCV and introduction in Rwanda • Financial and technical support for evidence-based social mobilization and communication for immunization e.g. in countries like Niger,Nigeria,Benin,Tchad,Guinée,Gabon) •	Global	• Wide variety of global partners • GAVI • WHO
	WHO	• Research • Policy Recommendations • Collaboration • Education & Promotion	• *Strategic Advisory Group of Experts* (SAGE) on immunization ○ Vaccine Hesitancy SAGE Working Group (estabL. March 2012) • Publications and information: ○ E.g. Behavioural Factors in Immunization (Department of Mental Health and Substance Dependence ○ Vaccine Safety Net ▪ "websites providing information on vaccines which adhere to good information practices" • Surveys: ○ EPI Coverage Survey ▪ Reasons for immunization failure cluster form, includes reasons such as 'fear of side reactions', 'no faith in immunisations', 'rumours', etc. • Capacity building e.g. of mid-level managers (MLM)in most of African country	Global	• Wide variety of global partners

Categories	Key Actors	Areas of Work/Interest†	Actions‡	Region§	Collaborators and Affiliates**
			• Procure and assure vaccine safety and effectiveness		
	WHO EURO	• Intervention • Collaboration • Policy Recommendations • Goal setting	• Developing TIP (Tailoring Immunization Programme) Toolkit to identify behavioural determinants of vaccination (and barriers) and recommend promising practices to address or respond to such barriers. Includes caregiver hesitancy and presents diagnostic framework for pin-pointing reasons for acceptance, hesitancy and refusal. • Vaccine Hesitancy as subcomponent of *Communication Strategy* • Factsheets ○ Talking with parents about vaccines for children' ○ Understanding the risk and responsibilities of not vaccinating your child. European Immunization Week media and caregiver publications : ie. 7 Key Reasons to Vaccinate and documents dispelling the myths that generate hesitancy. Launching a mobile phone ápp'in 2013 to allow parents to track their child immunization status, remind them to vaccinate on time, and serve as a recall system in countries where physicians do not carry out this service. Addresses a consistently reported reason for hesitancy – lack of reminder or recall system (forgetfulness/apathy)	Europe	• Variety of partners
Other	Vaccine Industry	• Research • Intervention	• GlaxoSmithKline (GSK) supports the development of an education tool on how physicians' should address vaccine hesitancy and resistance. ○ Developer was a consultant for 8 different vaccine manufacturers • Supporting researchers working on vaccine hesitancy ○ E.g. Gary S. Marshall (including but not limited to Merck, GSK, Sanofi Pasteur, etc) Wrote article on 'Navigating Parental Vaccine Hesitancy'	Global	•

Discussion:

It is important to note some specific attributes and limitations of this framework. A broad variety of groups focusing on the promotion of vaccines and therefore addressing vaccine hesitancy in the population were found, yet according to our inclusion/exclusion criteria we only listed groups focusing on generating research/studies or implementation/evaluation of interventions where specific examples on the scope of their work could be identified.

There were several cases where actors and their interests could potential fit in more than one category. For instance, as CDC is both a subsidiary of the US national government and it donates money it could have fit in either the *Governmental*- National Category or the *Donors* category. In these cases the actors were organised based on how they identify themselves, and in which of the categories they produce most of their work on the issue of vaccine hesitancy. Therefore, in the case of the CDC, they were placed within the Government- National category, as they identify themselves as a major operating component of the Department of Health and Human Services in the US government and produce most of their work on vaccine hesitancy as a part of the US government.

Furthermore, many of the projects on the issue of vaccine hesitancy were conducted with the help of collaboration between multiple partners. This collaboration can make it difficult to demarcate which organisations are working on which vaccine hesitancy projects.

In these cases organisation taking the lead on the project were tried to be identified and classified the action under them. If two groups were highly connected it was noted that many of their projects would be interlinked in the action section.

Retrieving information on developing countries conducting work on the issue of vaccine hesitancy was difficult to find, possibly due to language or publication issues. Therefore Working Group members were asked to share their knowledge on country activities. In addition, the help of the Working Group members contributed to extending research to languages other than English.

The above framework illustrates that many advisory committees and organizations have started to deal with the issue of vaccine hesitancy, including encountering and defining the problem of lack of confidence in vaccines, gathering information on the problem and suggesting potential strategies to deal with this issue. However, although organisations are starting to view vaccine hesitancy as an important topic many organizations discuss and highlight the issue without making meaningful contributions (e.g. research, interventions, recommendation). In fact, many organizations working on vaccines state in their mandates that they will work to promote the use and acceptance of vaccines among both the public and health professionals. However it is rarely specified how they will achieve this vaccine demand section of their mandate. Few examples of current projects relating to vaccine promotion/acceptance are given.

This landscape analysis, along with the development of indicators of vaccine hesitancy, demonstrates that there are not many global vaccine reporting or surveillance systems currently measuring demand-side indicators, such as vaccine hesitancy. In addition, most of the vaccine-related work indicated in this landscape analysis is on supply side criteria, rather than demand-side criteria. For example, most of the grants given to vaccine-related work by The Bill & Melinda Gates Foundation in 2012 were to projects that focused on vaccine development, production and safety, as well as health systems strengthening, whereas there were only a few projects that focused on the demand-side factors (e.g. vaccine acceptance, confidence and hesitancy).

References

[i] WHO. (May 2012). *Report by the secretariat: Sixty-fifth world health assembly, provisional agenda item 13.12. Draft global vaccine action plan.* Geneva, Switzerland.

[2] Personal communication from Yuqing Zhou

[3] http://www.chinacdc.cn/jkzt/ymyjz/4y25rqgetyfjzr/201204/t20120413_59805.htm

[4] http://www.chinacdc.cn/jkzt/ymyjz/myghcbcl/200605/t20060531_24616.htm

[5] Personal communication from Noni McDonald…need to get more information.

[6] (www.impfen-info.de) Study on parental attidude : http://www.bzga.de/forschung/studien-untersuchungen/studien/?sid=10&sub=64

[7] Ethical issues in immunization Seminar, NCIRS, Centre for values, ethics and the law in Medicine. Monday 26 March, 2012. Official program.

[8] http://ncirs.edu.au/research/social/index.php NCIRS Social research section, last updated 16th November 2009

[9] http://www.ncirs.edu.au/research/social/current.php Social research- current progects, last updated 01 August 2012

[10] http://ncirs.edu.au/immunisation/education/mmr-decision/index.php MMR Decision aid. Copyright NCIRS 2009, last updated 16 Sept 2009

[11] JCVI meeting: April 2012 http://transparency.dh.gov.uk/2012/05/25/jcvi-meeting-april-2012/

[12] The national archives website of the department of health. Immunisation- Market research section 2011 http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publichealth/Immunisation/Marketresearch/index.htm

[13] Parent tracking survey, child immunization wave 33. Conducted by BMRB (January/February 2010. COI Research Management Summary on behalf of the Department of health

[14] HPV Attitudinal Research conducted by Solutions, February 2009. UK deparment of health. COI research management summary on behalf of the department of health.

[15] UK department of health. COI Research management summary on behalf of the department of health. HPV Campaign Evaluation conducted by IFF research (2009)

[16] UK Department of Health. COI research management summary on behalf of the department of health. Direction of the HPV Arm Against Cervical Cancer Campaign by 2CV (July 2009)

[17] Immunization Action Coalition Website

[18] Vaccine confidence project at LSHTM website

[19] *Recommendations on Strategies to Achieve the Healthy People 2020 Annual Influenza Vaccine Coverage Goal for Health Care Personnel.* http://www.hhs.gov/nvpo/nvac/reports/index.html

[20] A pathway to leadership for adult immunization: recommendations of the National Vaccine Advisory Committee

[21] 2010 National Vaccine Plan

[3] 2010 National Vaccine Plan, p.19

[22] Personal communication Noni McDonald,

[23] Health policy and translation Group. (n.d.). Project areas. *Canadian Center for Vaccinology.* Retrieved on 22 Sept 2012. From http://www.centerforvaccinology.ca/project-areas.html

[24] Action Plan for Vaccination Promotion – Phase II (Direction des risques biologiques et de la santé au travail. Institut national de santé publique du Québec. April 18th, 2012. Eve Dubé

[25] Polio Global Eradication Initiative. (2012) *Global guidelines- Independent monitoring of polio supplementary immunization activities (SIA) July 2012*. Geneva, Switzerland.

[26] Global Polio Eradication Initiative. KAP studies – understanding barriers to immunization. *Global Polio Eradication Initiative.* Retrieved on 22 Sept 2012. From http://www.polioeradication.org/Research/PolioPipeline/No2Autumn2008/KAPstudies.aspx

[27] National Polio Surveillance Program in India. (2012). National Polio Surveillance Project. *National Polio Surveillance Program in India.* Retrieved on 3 Oct 2012. From http://www.npspindia.org/
[28] National Foundation for Infectious Diseases. (n.d.). Professional Education. *National Foundation for Infectious Disease*. Retrieved on 22 Sept 2012. From http://www.nfid.org/professional-education
[29] Bill and Melinda Gates Foundation. (2012). Grants Overview. *Bill and Melinda Gates Foundation*. Retrieved on 10 Aug 2012. From http://www.gatesfoundation.org/grants/Pages/overview.aspx
[30] Robert Wood Johnson Foundation. (n.d.) Grants. *Robert Wood Johnson Foundation.* Retrieved on 10 Aug 2012. From http://www.rwjf.org/pr/product.jsp?id=33483
[31] Health Policy and Translation Group. (n.d.) *Canadian Center for Vaccinology*. Retrieved on 2 Oct 2012. From http://www.centerforvaccinology.ca/
[32] London School of Hygiene and Tropical Medicine. (2012). Project to monitor public confidence in immunization programs. *London School of Hygiene and Tropical Medicine.* Retrieved on 10 Aug 2012. From http://www.lshtm.ac.uk/eph/ide/research/vaccinetrust/
[33] Leeds Institute of Health Sciences. (2012). DECIDA- Detailed Evaluation of a Childhood Immunisation Decision Aid. *University of Leeds*. Retrieved on 3 Oct 2012. From http://www.leeds.ac.uk/hsphr/research/AUHE/decida.html
[34]Director, Marketing and Communications. (26 Sept 2012). *University of Sydney.* Retrieved from 10 Aug 2012. From http://sydney.edu.au/index.shtml
[35] University of Leeds. (8 July 2008). Leeds project to boost parents' confidence in MMR choices as measles rates rise. *University of Leeds.* Retrieved on 10 Aug 2012. From http://www.leeds.ac.uk/news/article/348/leeds_project_to_boost_parents_confidence_in_mmr_choices_as_measles_rates_rise
[36] Director, Student Recruitment. (3 Oct 2012). Vaccines in Public Health PUBH 5416. *University of Sydney*. Retrieved on 4 October 2012. From http://sydney.edu.au/courses/uos/PUBH5416/vaccines-in-public-health
[37] Public health reports (Washington, D.C. : 1974) , 2011: 126(Suppl 2): 135-46
[38] Pediatrics , 2011: 128(6)1094-99
[39] Ginny Heller. (n.d.) Powerpoint presentation- turning the tide: addressing vaccine hesitancy through a social marketing campaign. *Washington Department of Health. Retrieved* on 22 Sept 2012. From http://www.pkids.org/files/webinars/turningthetideonvaccinehesitancy.pdf
[40] Opel. (2009). Social marketing as a Strategy to Increase Immunization Rate. *Archive of Pediatric Adolescent Medicine*, 261(5):432-437.
[41] http://www.ncbi.nlm.nih.gov/pubmed/21763384

The determinants of vaccine hesitancy: Sample survey questions

As countries increasingly face varied issues of vaccine hesitancy and sometimes refusal, more in-depth understanding of the issues driving hesitancy will be needed. The global polio eradication initiative has conducted the most in-depth research on reasons for vaccine refusals, but the resources required for such detailed analysis are unlikely to be available for all vaccines. The Working Group is developing a list of possible survey questions that countries can use to better understand the drivers of vaccine hesitancy in specific settings or around vaccines – specifically or in general. We propose the clustering of questions in same domains identified for the model of determinants of vaccine hesitancy.

The questions below are only suggestive, and are selected from survey questions identified through the peer-reviewed literature review as well as from the ongoing review of grey literature. These are examples, and are not an exhaustive list, but illustrate the types of questions being identified. More detailed lists of questions will be developed by the Working Group to address specific determinants in each of these domains, as outlined in the full model of determinants of vaccine hesitancy. Key questions will be identified and suggestions how to analyze the identified questions will be added.

CONTEXTUAL INFLUENCES **Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors**	**a. Communication and media environment** What is the most common information source you turn to for information about vaccines? When you hear a negative rumour related to vaccine(s), do you: ask a friend what they think? Ask a health worker? Go to the internet? Other? Who do you trust the most for information? Who do you trust the least?	**b.Influential leaders, gatekeepers and anti- or pro-vaccination lobbies** Some groups do not agree to vaccination for different reasons. In general, do you agree with these groups?	**c.Historical influences** Do you remember any events in the past that would discourage you from getting a vaccine(s) for yourself or your child(ren)? Can you describe it?	**d.Religion/culture/gender/socio-economic** Do you know anyone who does not take a vaccine because of religious or cultural reasons? Do you think they are risking their health or the health of their child? The community?	**e. *Politics/policies*** *(Mandates)* Do you trust that your government is making decisions in your best interest with respect to what vaccines are provided? Do you think vaccines should be compulsory?	**f.Geographic barriers** If you have to spend more than one hour getting a vaccine, are you willing to take the time you think it is an important vaccine? What is the maximum amount of time you would be willing to spend to get a vaccine that you want for yourself or your child(ren)?	**g.Pharmaceutical industry** Do you trust the motives of pharmaceutical industry? Do you believe that drug companies have your and your children's best health interests at heart?

INDIVIDUAL and GROUP INFLUENCES **Influences arising from personal perception of the vaccine or influences of the social/peer environment**	**a. Experience with past vaccination** Do you have any experience of not getting vaccination for your child? why? Do you know anyone who has had a serious reaction to a vaccine? Do you know anyone who has a child who has had a serious reaction to a vaccine? Do you know anyone who has a child who had a serious vaccine preventable disease because they were not vaccinated?	**b.Beliefs, attitudes about health and prevention** Do you believe that there are other (better) ways to prevent vaccine preventable diseases than with a vaccine? Do you think vaccines strengthen the immune system? Do you think it is possible to have too many vaccines?	**c. Knowledge/awareness** Do you feel that you know which vaccines you should get for yourself? your child(ren)? Have you heard about the HPV vaccine? Do you think the polio vaccine is still needed? Do you understand how vaccines work? Have you ever felt confused about number/scheduling of vaccines?	**d. Health system and providers-trust and personal experience.** Are you satisfied with the HCW' s answers for your questions related on immunization? Do you trust your health care provider to honestly tell you about the risks and benefits of vaccines? And, about the risks of vaccine preventable disease for you and your children? Do you trust the vaccine advice your main health care provider gives you? Do you believe your health care provider has your and your children's best health interests at heart?	**e. Risk/benefit (perceived, heuristic)** Which vaccine(s), if any, do you think are important for you? For your child(ren)? For your community? Do you believe vaccine preventable diseases can be serious? Which one(s)? Are you concerned about any risk with vaccines? What kind of risks? Do you think that vaccine benefits, in general, are larger than their risks? Do you consider other activities (going to market, work, etc.) more important than getting a vaccine? Or, taking your child for vaccination? Do you believe vaccines are safe for yourself? Your child/children? For those in your community?	**f. Immunisation as a social norm vs. not needed/harmful** Do you think it is important for everyone to get recommended vaccines for themselves and their children? Did you feel social pressure to get the vaccine? Do most people you know are being vaccinated / are getting their children vaccinated?

VACCINE/ VACCINATION - specific issues **Directly related to vaccine or vaccination**	**a. Risk/ Benefit (scientific evidence)** Do you think there is adequate safety information? As far as you know are side effects or adverse reactions kept track of in your country? How confident are you in the system for tracking adverse reactions or side effects to vaccinations in your country?	**b. Introduction of a new vaccine or new formulation** When a new vaccine is introduced, do you want to be the first to get it? Would you rather wait and see what other people do? What is the first thing you want to know when a new vaccine is introduced or announced? Do you think that newer vaccines are as safe as older vaccines?	**c. Mode of administration** Do you prefer a vaccine that is injected, taken orally, or with a nasal spray? Is there any mode of vaccination you would not want?	**d. Design of vaccination program/Mode of delivery** Is access to immunization easy? Convenient in location? Is the process of being immunized welcoming? What are the barriers for receiving vaccine(s) on time for you? For your child(ren)?	**e. Reliability and/or source of vaccine suppl** Do you feel confident that the health center or doctors office will have the vaccine you need, when you need them?	**f. Vaccination schedule** Do you think it is possib to have too many vaccines? Is it better for a child to have multiple vaccines in one shot with fewer injections or to have individual vaccines?	***g. Costs*** Would the cost of a vaccine prevent you from getting it, even if you felt you or your child needed it?	**h.Role of healthcare professionals** Did a healthcare professional recommend that you receive a vaccine

EXPANDING THE POTENTIAL IMPACT OF

Haemophilus influenzae type b vaccines (Hib)

BY OPTIMIZING IMMUNIZATION SCHEDULES

What are optimal immunization schedules for *Haemophilus influenzae* type b vaccines (Hib) for children living in different epidemiological settings?

March 26, 2013

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IMPLICATIONS FOR IMMUNIZATION POLICY

Hib conjugate vaccine 2p+1, 3p+0 and 3p+1 schedules are likely to provide direct protection from Hib disease but the optimal schedule, and overall impact population is likely to depend on setting characteristics. For example, in countries where the burden of severe Hib disease lies in young infants it is more appropriate to provide three doses of Hib vaccine early in life. The first dose should be given at 6 weeks of age or soon after and the interval between primary doses should be at least 4 weeks. However, in settings where the greatest disease morbidity and mortality occur later, in the presence of herd immunity or, where a resurgence of Hib cases is seen after the introduction of Hib vaccine, it might be advantageous to use a schedule where the third dose is given as a booster e.g. at 11 months of age or during the second year of life. Programmatic considerations are also likely to influence the choice of Hib vaccine schedule, as most Hib vaccines are administered as combined vaccines, which mean that the scheduling of the other co-administered vaccines must also be taken in to account when choosing a Hib vaccine schedule.

SUMMARY

Selecting the optimal schedule for Hib containing vaccines is a complex process. It requires understanding of the efficacy and effectiveness of various schedules from clinical trials and observational studies. Choice of vaccine schedule depends on the age-distribution of Hib disease and the potential to achieve high and timely coverage of each dose. The choice of schedule should also take into account programmatic considerations including but not limited to: (i) vaccine presentation in use (especially since many countries are using Hib vaccines in combination forms, often as pentavalent with DTwP and HepB), (ii) potential to administer all recommended doses on time and achieve high coverage and, (iii) contact opportunities for provision of other health interventions and other vaccines. In addition, the experience to date in various countries has demonstrated that the interplay between carriage rates in the pre-vaccine era, reduction of carriage and potential for natural boosting after vaccine introduction, herd immunity and the force of infection, and immunological memory are also key factors to determine the potential impact on disease and immunological outcomes of various immunization schedules. Moreover, Hib vaccine effectiveness may be reduced as a result combining it with certain vaccines.

Hib conjugate vaccines have been in use for over 20 years with remarkable success. Hib vaccine has been recommended for universal introduction by WHO since 2006. The current WHO recommendation for Hib includes a three doses primary schedule with no booster (3p+0) and states that immunization should start as early as possible after the age of 6 weeks and that in countries where the vaccine is being introduced, consideration should be given to offering a one-time dose to all eligible children aged 12-24 months.

Countries are currently using Hib vaccines in routine immunization programmes as part of a combination product (often as pentavalent presentation e.g. Hib-DTwP-HepB). The Hib containing immunization schedules (as reported in the JRF, data as 31st December 2011) can be summarized as follows. 8.8% countries out of 194 reporting countries have not introduced Hib vaccine in the routine immunization programme, 56.2% countries (mostly non-industrialized countries representing 76.9% of the global birth cohort of ~135 million infants) use 3 primary doses without booster schedule(3p+0); 28% of countries (most of them industrialized countries) use 3 primary doses plus a booster (3p+1) and, 5.7% of countries (most of them industrialized countries representing 1.4% of the global birth cohort) use 2 primary doses plus a booster (2p+1). There are 41 countries using a combination that includes acellular pertussis (aP) vaccine, 36 of them with a schedule that includes a booster dose in the second year of life (6 as 2p+1 and 30 as 3p+1), the majority of which are from industrialized countries, (see further information on page 18). However in practice the actual age at vaccination may vary from recommended ages[1] .

NUMBER OF PRIMARY DOSES

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two primary doses?	
Conclusion	**Data suggest that at least three doses of Hib vaccine are required to achieve high effectiveness**. (See further information on pages 18-28).
Summary statement	**From the studies identified, data available do not clearly favour a 3p+0 or 2p+0 schedule in terms of disease outcomes or immunogenicity for various Hib vaccine types [except for PRP-OMP].** The observed marginal increase in efficacy and effectiveness was considerably greater between the first and second dose, than between second and third dose, when assessed as part of the primary series. The data found did not show significant differences by type of Hib vaccine conjugate (except PRP-OMP conjugate as reported efficacy and effectiveness with one or two doses was reported as > 90%) or for combination vaccines using wP or aP. Data available from RCTs suggest that a booster dose after a 2p primary series results in high levels of proportion above a set threshold (i.e. > 1.0 ug/ml)). If a two primary doses schedule is selected, evidence suggests that efficacy and effectiveness over time will be high. There is some evidence that DTaPHib vaccines may be less effective and less immunogenic that DTwPHib vaccines.
Quality of evidence	**We are uncertain about the estimate of the effect.** We were unable to identify data from RCTs or observational studies reporting direct comparison between 2 and 3 primary doses for disease outcomes for any of the conjugates, and using different vaccine combination types such as aP containing vaccines. In terms of immunological outcomes, seven RCTs provided immunological data to compare two doses versus three primary doses. There was also information from observational studies.

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two primary doses?	
Caution	Estimates of vaccine efficacy from different trials in terms of immunogenicity cannot be compared directly as evidence of equivalence or superiority of one particular schedule and there were too few trials for a network metanalysis which would allow such a comparison. It is important to note that most of the evidence on effect on disease outcomes is drawn from observational studies and few RCTs comparing schedule versus no vaccination. The observational studies took place when the vaccine was in routine use and other children in the community may have received 3 or more doses. There is no experience from any country using a 2p+0 schedule.

NEED FOR A BOOSTER DOSE

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
Conclusion	**In some countries, administering a booster dose during the child's second year of life has been deemed necessary to sustain overall disease control in population and direct protection of toddlers. However, the need for booster doses in non-industrialized countries requires further evaluation.** (See further information on pages 30-35).
Summary statement	Available data suggest that after 5 years of vaccine introduction using a 3p+0 schedule a significant reduction in meningitis in young children was observed in a number of developing countries. A recent evaluation from four South American countries reported that Hib meningitis rates were similar 6-10 years post introduction in countries with and without boosters. There is similar data from a dozen of non-industrialized countries that have used a 3p+0 schedule for at least 6 years. However, the UK had a different experience: after the introduction of a 3p+0 schedule (2, 3, 4 months) in 1992 with PRPT-conjugate alongside a catch-up campaign for toddlers 12-48 years of age (with HbOC conjugate vaccine), the UK had an initial decline in cases, but started observing an increase in Hib over a decade after an initial decline in cases. As a result of this, a Hib vaccination booster campaign using (PRP-T conjugate) was conducted between May and September 2003, offering one dose of vaccine to all children who were aged between 6 months and 4 years on 1 April 2003 and to those children who reached 6 months of age during the campaign. A routine booster dose in the vaccine schedule was introduced in 2006. Following these interventions cases declined again. Data from industrialized countries suggest that immunogenicity may be lower with PRPT conjugate and aP containing vaccine and this could have an impact on duration of protection. Emerging reports on some resurgence of Hib cases in older children in The Gambia (3p + 0) highlight the need for further evaluation of duration of protection and of the role of a booster dose in non-industrialized country settings [e.g. 10 years after introduction of Hib vaccine in combination with whole cell pertussis vaccine]. If boosters are deemed necessary (i.e. as

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
	part of a 2p+1 or 3p+1 schedule), an alternative to routine booster at 11 months or later may be to implement catch-up campaigns targeting toddlers. The UK experience suggests that they have resulted in important reductions of overall carriage
Quality of evidence	**We are moderately confident on the estimate of the effect. 3primary doses vs 2p+1→ low quality of evidence (GRADE table 6)** Assessment of the need for booster doses is challenging because (a) there are no data directly comparing clinical effectiveness between similar primary schedules with and without booster No data are currently available from developing country settings using aP containing combination vaccines without a booster dose.
Caution	The situations in which a booster dose should be used remain unclear, and it would depend on various factors including local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

INTERVAL BETWEEN DOSES

Does using Hib conjugate vaccine schedule with a longer interval between primary doses (e.g. 8 weeks or more) have a greater effect on disease or immunological outcomes than a schedule with a shorter interval (i.e. 4 weeks) between doses?	
Conclusion	**Limited data available showed no consistent or clinically relevant differences between shorter (e.g. 4 weeks) and longer (e.g. ≥ 8 weeks) intervals between primary doses of Hib vaccines.** (See further information on page 55-57).
Summary statement	In most reported schedules, 3 primary doses were separated by either one month (e.g. 6, 10, 14 weeks and 2, 3, 4 months) or two months (e.g. 2, 4, 6 months) whereas 2-dose schedules essentially included 8-weeks intervals. Available data on proportion achieving a set threshold (i.e. ≥ 0.15mcg/ml and ≥1.0 mcg/ml) show no significant difference between short interval [e.g. 4 weeks] vs. longer interval [e.g. ≥ 8 weeks] in the primary series on immunogenicity outcome for different types of Hib conjugates. There was no clear difference in effectiveness against Hib meningitis, invasive Hib disease or radiologically confirmed pneumonia between observational studies using different dosing intervals or different Hib conjugates. Two months intervals between doses in the primary schedule were not shown to be consistently more immunogenic than one month interval in the observational studies. From long term impact studies both a 4 week and 8 week interval have been used in a number of countries with good sustained long term impact.
Quality of evidence	**We are moderately confident on the estimate of the effect.** There were no RCTs or observational studies that compared various intervals and, types of vaccine conjugate and that reported effect on various disease outcomes.
Caution	Not enough evidence on schedules using 2p+1 at short intervals (e.g. 4 weeks)

DURATION OF PROTECTION

Does using 2 or 3 primary doses plus a booster of Hib conjugate vaccine has a greater effect on duration of protection than using three primary doses without a booster?	
Conclusion	**Although there is some evidence for decrease over time in the proportion above a set threshold (i.e. >0.15mcg/ml and >1.0 mcg/ml) there is limited evidence for this decline being associated with an increase in disease.** (See further information on page 37-39).
Summary statement	The rationale for the 3p+0 schedule is predicated on the induction of sufficient primary antibody responses after three doses in infancy to reduce carriage and thus confer indirect protection through the early childhood years when susceptibility is greatest. In the UK over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, using PRP-T conjugate) and at the same time a catch up campaign with single dose of Hib (HbOC conjugate) given to those aged 13 months to 4 years, vaccine failures were observed primarily in children age 1-4 years who completed the primary vaccination series, despite the induction of immune memory. An increased in disease in previously non immunized children over 15 years of age was also seen, confirming the resurgence of Hib circulation. Enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign conducted when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis . This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant
Quality of evidence	**We are uncertain about the estimate of the effect** Although there is some evidence for decrease over time in proportion above a set threshold there is limited evidence to date for this decline being associated with increase in disease, except in the UK
Caution	As mentioned above, available data from developing countries on long-term duration of protection requires further evaluation. This is a complex issue. With high sustained vaccine coverage with a highly effective vaccine and a low force of infection, carriage may be reduced to a low level which results in less opportunity for boosting antibody levels by exposure but also a very low risk of disease. If VE in children drops then this might allow Hib to re-emerge. In countries, such as those in the developing world, with lower coverage and a higher force of infection, carriage of Hib may be still likely to be sufficiently common to result in continued boosting and maintenance of antibody levels and thus longer duration of direct protection in an individual but no indirect protection.

Hib combination vaccines: The above statements are based on evidence related to all the currently available Hib conjugate vaccines and to both combination and monovalent vaccines. There are limited data comparing the effect on Hib disease between vaccination schedules that include acellular vs. whole cell vaccine combinations. There is some evidence of lower immunogenicity (and limited data on lower clinical effectiveness outside the UK) when Hib vaccines are combined with acellular pertussis as compared to whole cell pertussis combinations. (See further information on page 55).

Sources of evidence

Although the systematic reviews used to inform this summary assessed several schedules with different numbers of primary doses and boosters, the summary below focus on information from studies that used 3p+0, 2p+1 and 3p+1. Full details of analyses and studies descriptions are available in each individual systematic review report. Hib conjugate vaccines of the following types were eligible for inclusion in this summary: PRP-HbOC (diphtheria CRM 197 protein conjugate), PRP-OMP (outer membrane protein (Neisseria meningitides conjugate) and PRP-T (tetanus toxoid conjugate).

Table 1. List of main articles used to inform this summary of evidence

Author (Year)	Title	Type of review	Number of studies included [time period]
Scott, P. et al. (2013)[2]	*Haemophilus influenzae* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules	Systematic review and meta-analysis	40 randomized clinical trials [earliest citation - June, 2012]
Griffiths, U. et al. (2012)[3]	Dose-specific efficacy of *Haemophilus influenzae* type b conjugate vaccines: a systematic review and meta-analysis of controlled clinical trials	Systematic review and meta-analysis	8 randomized clinical trials [not stated, search conducted March, 2011]
Jackson, C. et al. (2013)[4]	Systematic review of observational data on effectiveness of *Haemophilus influenzae* type b vaccines to allow optimization of vaccination schedules	Systematic review and meta-analysis	33 observational studies (20 case-control, 9 cohort, 4 other) [earliest citation - June, 2012]
Watt, J. et al. (2012)[5]	*Haemophilus influenzae* type b conjugate vaccine: review of observational data on long-term impact to inform recommendation for vaccine schedules	Systematic review	38 studies including data from 34 countries [earliest citation - June, 2012]
Garcia, S. et al.	Impact of vaccination against *Haemophilus influenzae* type b with and	Descriptive	Sentinel site surveillance data and

Author (Year)	Title	Type of review	Number of studies included [time period]
(2012)[6]	without a booster dose on meningitis in four South American countries	review	cross-sectional carriage surveys [not stated]

In addition, to ensure completeness we consulted the following reviews and individual articles:

Author (Year)	Title	Type of review	Number of studies included [time period]
Sanderson, C. et al. (2013)	Age at Hib disease, and the impact of delayed vaccination - report to WHO 2012 [7]	Systematic review	17 studies
Bar-On, E. (2012)[8]	Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, Hepatitis B and *Haemophilus influenzae* B (HIB) (Review)	Systematic review and meta-analysis	20 randomized clinical trials [Jan, 1966 - Nov, 2011]
Dhillon, S. et al. (2008)[9]	DTaP/IPV/Hib Vaccine (Pentacel)	Descriptive review	8 randomized clinical trials [not stated]
Chandran, A (2012)[10]	*Haemophilus influenzae* vaccines, in Vaccines 6th ed.	Textbook chapter	
Decker, M. et al. (2012)[11]	Combination vaccines, in Vaccines 6th ed.	Textbook chapter	
Peltola, H. et al. (1999)[12]	A five-country analysis of the impact of four different *Haemophilus influenzae* type b conjugates and vaccination strategies in Scandinavia	Descriptive review	Routine surveillance data from 5 countries [not stated]
Ladhani S. et al. (2010)[13]	Invasive *Haemophilus influenzae* disease, Europe 1996-2006	Descriptive review	
Mc Vernon J. et al (2007)[14]	Understanding the impact of Hib conjugate vaccine on transmission, immunity and disease in the UK	Mathematic model	
Mc Vernon J. et al (2004)[15]	Trends in *Haemophilus influenzae type b* infections in adults in England and Wales: surveillance study	Descriptive review	
Ladhani S. et al. (2009)[16]	*Haemophilus influenza* serotype b conjugate vaccine failure in twelve countries with established national childhood immunisation programmes	Descriptive review	

Burden of Hib disease[17]

Estimated Hib and pneumococcal deaths, children under 5 years of age for year 2008

In March 2012, the World Health Organization released estimates for global and regional year 2008 deaths from Haemophilus influenzae and Streptococcus pneumoniae among children under 5 years of age that update the estimates from year 2000. It is estimated that in 2008 globally there were 203,000 (uncertainty range: 139,000 - 287,000) child deaths due to Hib (*Haemophilus influenzae* type b) among those under 5 years, of which 199,000 (uncertainty range: 136,000 - 281,000) occurred among HIV-negative children. It is also estimated that there were 541,000 (uncertainty range: 376,000- 594,000) global child deaths due to pneumococcal (Streptococcus pneumoniae) infections among those under 5 years, of which 476,000 (uncertainty range: 333,000 – 529,000) occurred among HIV-negative children. Hib and pneumococcal global and regional mortality estimates by syndrome and HIV infection status are provided in Annex I. An update of the year 2000 pneumococcal and Hib case estimates has not been done for year 2008; Hib and pneumococcal case fatality ratios combining year 2008 deaths and year 2000 cases should not be done as there are important methodologic and key input differences in the year 2000 and year 2008 models. Based on the World Health Organization estimates of 8.8 million deaths among children under 5 years of age globally in the year 2008, (of which 5.2 million occurred in the non-neonatal period), Hib is estimated to cause 2% of all cause-child mortality under five and 4% of non-neonatal mortality while pneumococcus is estimated to cause 5% of all cause-child mortality under five and 9% of non-neonatal mortality. The year 2000 and 2008 Hib and pneumococcal mortality values are shown in Annex II. Although part of the reduction in number of deaths from Hib can be attributed to the introduction of Hib vaccine into the national immunization schedule of 68 countries between 2000 and 2008, the change in values should not be interpreted as a time-series or used as the values to infer the impact of Hib vaccine. Although the Hib mortality differences do include the effect of vaccine introduction, differences in the mortality estimates between the two time periods are deeply impacted by significant changes in the value of model input parameters (e.g. population size, child mortality, pneumonia mortality). Specifically the all-cause pneumonia death estimates by WHO declined from 1.8 million in 2000 to 1.2 million in 2008. This change is attributable to changes in estimation methods and model input values. The year 2008 Hib and pneumococcal mortality estimates, like the year 2000 estimates, do not incorporate any impact from PCV, which was not yet in use in the developing world by 2008.

Epidemiology of *Haemophilus influenzae* type b (Hib) meningitis in the pre-vaccine era [7]

Aim: To seek existing data on age at invasive Hib disease and Hib meningitis, with age groups small enough for assessment of the population impact of vaccination according to different schedules.

Age at Hib disease i) Re-examine an earlier literature review of the burden of Hib disease covering the period 1980-2005 (Watt et al 2009), and conduct a literature review for the period 2005-12; ii) identify papers with relevant data on age at Hib and/or authors' contact details; iii) seek authors' cooperation in supplying age distributions or raw data; iv) tabulate %s aged < 6m and < 12m if available; v) for finely stratified datasets, fit gamma distributions to

summarize results from each population and deal with reporting anomalies; vi) fit regression models for each gamma parameter with independent variables such as GDP (World Bank); and vii) use these models to estimate age distributions in countries without data.
A case of invasive Hib disease was defined as a child <5 years of age with *H. influenzae* type b isolated from a normally sterile site (i.e., blood, cerebrospinal fluid (CSF) or pleural fluid, etc.). A case of Hib meningitis was defined as a child <5 years of age with laboratory-confirmation by culture or identification (i.e. by Gram stain or antigen detection methods) of Hib in the CSF, pleural fluid or from the blood, in a child with a clinical syndrome consistent with bacterial meningitis (WHO, 2003).

Age at vaccination: i) Obtain data from recent DHS and MICS surveys; ii) impute missing data and carry out survival analyses to estimate age-specific coverage; iii) fit lognormal curves to the age-coverage curves; iv) fit regression models for each lognormal parameter, with independent variables including GNI & skilled birth attendants (World Bank), the difference between coverage of DPT1 and DPT3, and WHO-CHOICE subregion (WHO); v) use these models to estimate timeliness in countries without surveys.

Results age at Hib disease. The earlier literature review included 209 studies, of which 97 had relevant data on Hib and 35 had author contact details. The new review produced 1492 studies, 28 with relevant Hib data and 11 with author contact details. A further 14 investigators were identified as having unpublished data. Attempts were made to contact 60 authors/investigators, and 7 (12%) sent more detailed data. We found 16 published studies, and 6 unpublished datasets, with age bands <=3m, and 17 of these included more than 100 cases aged < 60m. In 67 studies there were data from studies with n > 30 on the percentages of all cases aged < 60m who were also aged < 6m and < 12m. Results from these are shown in Table 2.

Table 2: Age at invasive Hib disease and Hib meningitis: studies reporting % < 6m and % < 12m

					of all cases aged < 60m	
	Region	*n of studies*	*median year study started*	*median n of cases aged < 6m*	*median % aged < 6m*	*median % aged < 12m*
Invasive Hib	AMR	1	1992	180	41.5%	74.4%
	EMR	3	1993	258	39.5%	75.0%
	EUR	8	1990	193	17.0%	35.3%
	SEAR	1	1993	517	39.3%	92.5%
	WPR	5	1992	212	19.2%	41.0%
Hib meningitis	AFR	10	1990	52	37.0%	73.1%
	AMR	10	1989	200	26.0%	60.2%
	EMR	3	1999	51.5	39.7%	84.6%
	EUR	7	1981	151	15.3%	46.3%
	SEAR	4	1993	64	26.5%	85.5%
	WPR	5	1994	79	26.8%	59.3%

Figure 1: Age at invasive Hib disease & meningitis: studies with age bands of 2m or less, and fitted curves.

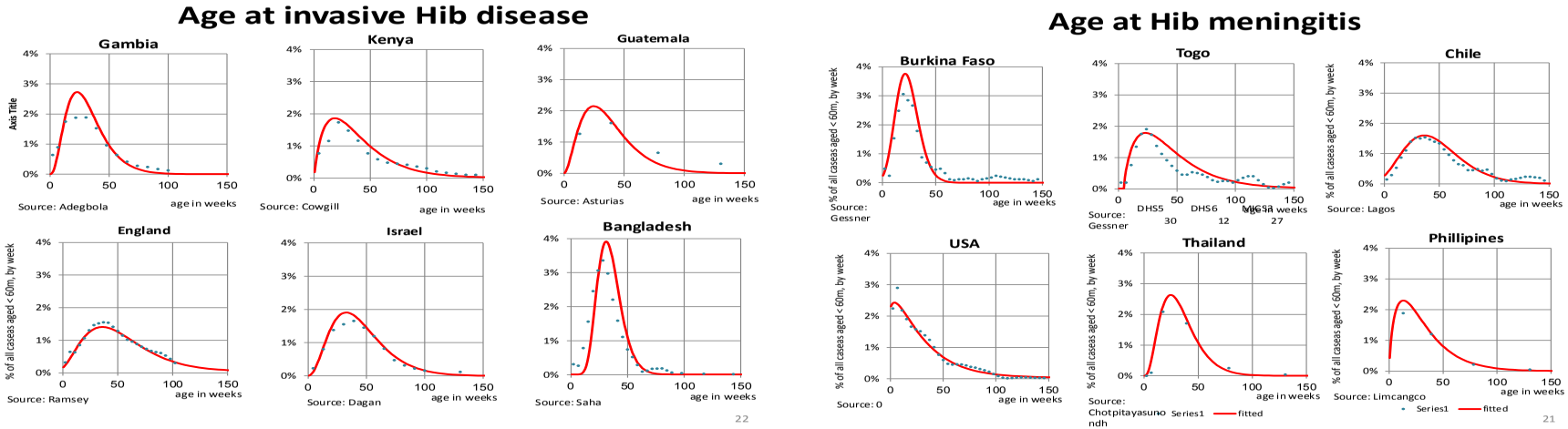
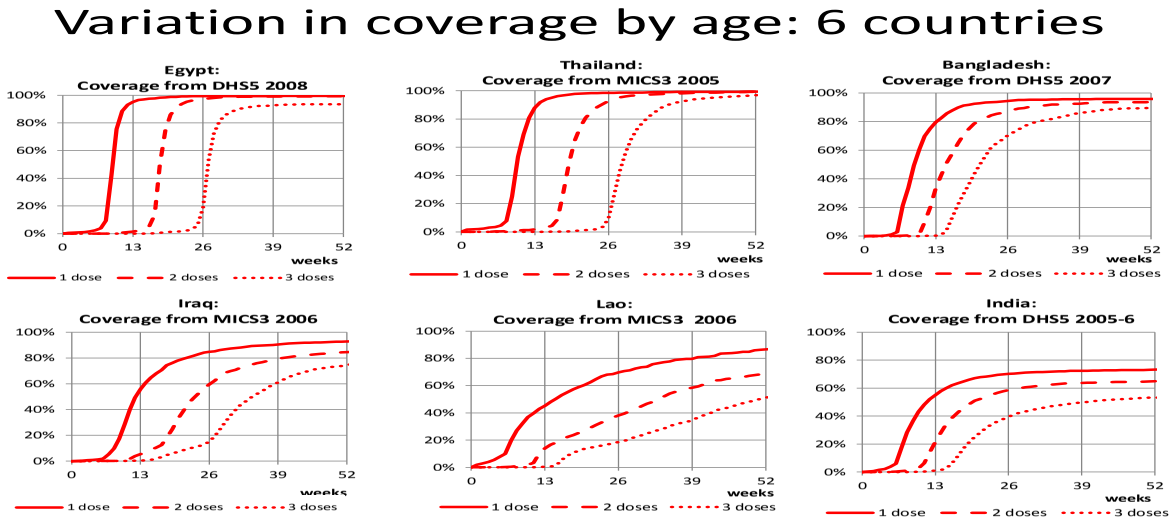


Figure 2: Age at vaccination: There were usable data in 42 DHS and 25 MICS surveys



WHO Recommendations for Routine Immunization (2006)[18]

"National immunization schedules differ depending upon local epidemiological and programmatic considerations. In general, three-dose primary series is given at the same time as the primary series of DTP. The first dose may be given to infants as young as 6 weeks of age, and the second and third doses may be given at 4–8-week intervals along with DTP. For children aged 12–24 months who have not received their primary series of immunizations, a single dose of the vaccine is sufficient. When Hib vaccine is introduced into a country, the implementation of catch-up vaccination of children aged 12–24 months will likely result in a more rapid decline of disease incidence. The vaccine is not generally offered to children aged >24 months owing to the limited burden of Hib disease among them. In most developed countries, a booster dose is recommended at 12–18 months of age; in developing countries, the need for and timing of booster has not yet been defined. Although immunization against Hib disease is not routinely recommended for individuals aged >24 months, older children and adults who are at an increased risk for invasive Hib infection should be vaccinated where resources are available. Such high-risk individuals include those with HIV infection or immunoglobulin deficiency, recipients of stem cell transplants, patients undergoing chemotherapy for malignant neoplasms and those with asplenia (for example, due to sickle-cell disease or splenectomy). Although vaccines are generally less immunogenic in immunocompromised individuals, people who have not previously been vaccinated and who have one of the aforementioned conditions or similar immunodeficiency should be given at least 1 dose of a conjugate Hib vaccine. (…). Evidence suggests that an immunization series started with one type of conjugate Hib vaccine may be completed using another formulation of conjugate Hib vaccine. Hib vaccine has not been associated with any serious adverse effects. "

Table 3. Recommended Routine Immunizations for Children (http://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

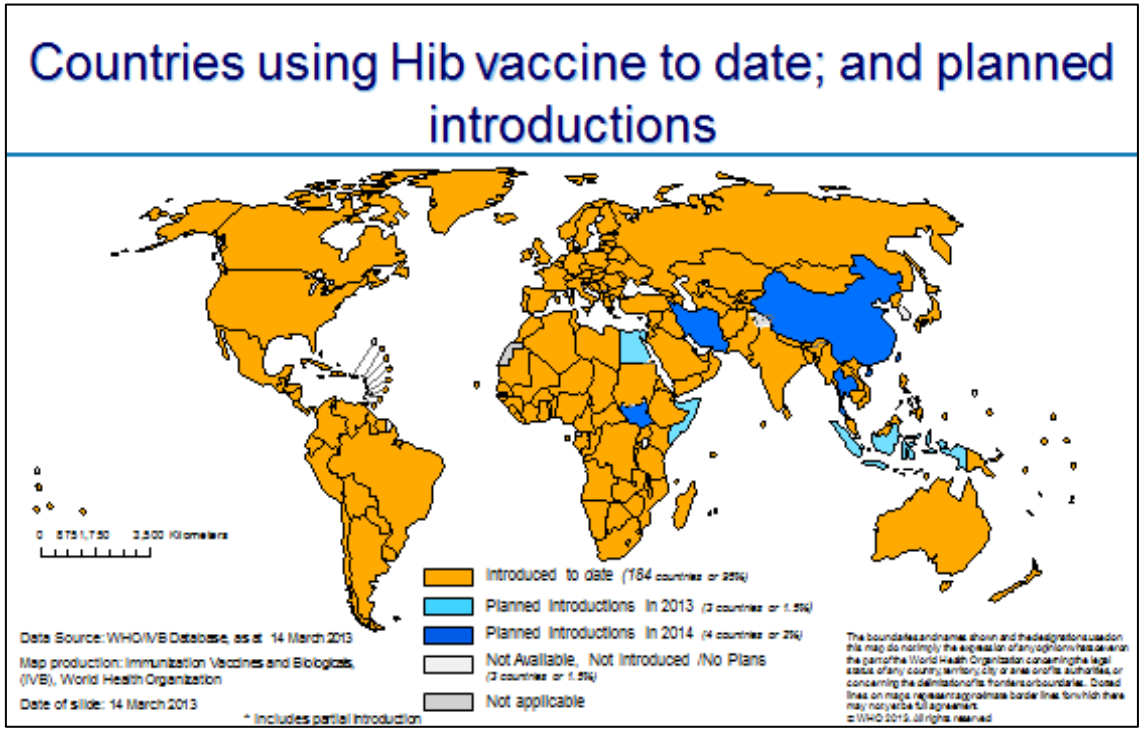
Antigen	Age at 1st dose	Doses in primary series	Interval between doses		Considerations (see footnote)
			1st to 2nd	2nd to 3rd	
Haemophilus influenza type b[1]	6 weeks (min) with DTP1, 24 months (max)	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3	Single dose if > 12 months of age. Delayed/ interrupted schedule.

[1] Position paper reference: Weekly Epid. Record (2006, 81: 210-220)

Immunization should start as early as possible after the age of 6 weeks. The 3-dose primary series is given at the same time as the DTP primary series often in combination vaccines. The vaccine is not generally offered to children aged >24 months owing to the limited burden of Hib disease among children older than that age. Delayed series - if a child 12-24 months of age has not received their primary vaccination series, a single dose of the vaccine is sufficient. Booster dose may be administered to children aged between 12-18 months although there is no WHO recommendation on this yet.

Progress with the introduction of Hib vaccines globally and vaccines and schedules in use

In 1997, 31 countries had introduced or partially introduced Hib containing vaccines. Mainly in the region of the Americas and Europe; South Africa, Australia and New Zealand also introduced the vaccine by that year. 31 of them are high-income countries and 18 middle-income countries. By March 2013, 184 (95%) of the countries introduced Hib containing vaccines, 3 countries are planning introduction in 2013 and 4 countries are planning introduction in 2014 (Figure 2). Data is not available or there are no introduction plans from 3 countries. Note that on a global level only 74% of all infants are receiving Hib vaccine.



Countries are currently using Hib vaccines in routine immunization programmes as part of a combination product (often as pentavalent vaccine presentation) using one of 3 different schedules:

- 56.2% of countries (mostly developing countries) use 3 primary doses (3p+0),
- 28% of countries (most of them industrialized countries) use 3 primary doses plus a booster (3p+1),
- 5.7% of countries (most of them industrialized countries) use 2 primary doses plus a booster (2p+1).

There are 41 countries using a combination that includes acellular pertussis vaccine, all with a schedule that includes a booster dose in the second year of life, the majority of which are from the European Region.

Table 4. Summary of Hib containing vaccine delivery as reported in the JRF, data as at 31st December 2011

	Total		AFR		AMR		EMR		EUR		SEAR		WPR	
	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort	number of countries	birth cohort
No Hib	17	34,785,830	2	6,484,206	1	266,231	5	4,700,496	0	-	6	6,376,862	3	16,958,035
3 doses	109	77,103,805	41	23,143,673	23	6,607,251	10	9,730,506	14	1,790,237	5	31,224,881	16	4,607,256
2 doses + 1 booster	11	1,410,202	0	-	0	-	0	-	9	1,406,360	0	-	2	3,842
3 doses + 1 booster	55	20,008,149	3	1,781,140	11	8,629,986	7	1,323,878	28	6,249,073	0	-	6	2,024,072
other	2	1,689,399	0	-	0	-	0	-	2	1,689,399	0	-	0	-
use with combination of aP	41	8,197,901	2	1,068,886	2	461,012	1	23,405	32	5,693,936	0	-	4	950,662
use with combination of Wp	117	83,207,665	42	23,855,927	29	10,435,040	14	10,855,856	11	2,228,704	5	31,224,881	16	4,607,256
Other (some doses with ap and others with wp) * see notes	10	5,390,841	0	-	3	4,341,185	2	175,123	5	874,533	0	-	0	-
Hib mono only	8	1,726,195	0	-	0	-	0	-	4	648,943	0	-	4	1,077,252
ap combination Hib only	35	6,985,332	2	1,068,886	2	461,012	1	23,405	29	4,852,907	0	-	1	579,122
wp combination Hib only	115	82,603,869	42	23,855,927	28	10,325,398	14	10,855,856	10	1,734,551	5	31,224,881	16	4,607,256
ap combination Hib + Hib mono for booster	5	451,499	0	-	0	-	0	-	2	79,959	0	-	3	371,540
wp combination Hib + Hib mono for booster	2	603,795	0	-	1	109,642	0	-	1	494,153	0	-	0	-
other	12	7,840,865	0	-	3	4,341,185	2	175,123	7	3,324,557	0	-	0	-

Notes:

1. The list of countries that have introduced Hib includes the ones that have introduced in some parts of the country, which are Belarus, India and the Philippines. This explains the large birth cohort for SEAR that is for the entire country for India

2. The 17 countries not having introduced Hib are: China, Egypt, Equatorial Guinea, Haiti, Indonesia, Iran (Islamic Republic of), Iraq, Republic of Korea (the), Democratic People's Republic of Korea (the), Maldives, Myanmar, Nigeria, Singapore, Somalia, Thailand, Timor-Leste, South Sudan. Since then, the following countries introduced (but did not yet report to WHO their JRF with the schedule): Haiti, Iraq, DPRK, Maldives, Myanmar; Nigeria (in some parts of the country) and Timor-Leste.

3. Are not counted here the 8 countries that are using Hib monovalent only + Russia that is using Hib mono only with only 2 doses schedule

Number of primary doses

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two primary doses?	
Conclusion	**Data suggest that at least three doses of Hib vaccine are required to achieve high effectiveness**.
Summary statement	**From the studies identified, data available do not clearly favour a 3p+0 or 2p+0 schedule in terms of disease outcomes or immunogenicity for various Hib vaccine types [except for PRP-OMP].** The observed marginal increase in efficacy and effectiveness was considerably greater between the first and second dose, than between second and third dose, when assessed as part of the primary series. The data found did not show significant differences by type of Hib vaccine conjugate (except PRP-OMP conjugate as reported efficacy and effectiveness with one or two doses was reported as > 90%) or for combination vaccines using wP or aP. Data available from RCTs suggest that a booster dose after a 2p primary series results in high levels of proportion above a set threshold (i.e. > 1.0 ug/ml)). If a two primary doses schedule is selected, evidence suggests that efficacy and effectiveness over time will be high. There is some evidence that DTaPHib vaccines may be less effective and less immunogenic that DTwPHib vaccines.
Quality of evidence	**We are uncertain about the estimate of the effect.** We were unable to identify data from RCTs or observational studies reporting direct comparison between 2 and 3 primary doses for disease outcomes for any of the conjugates, and using different vaccine combination types such as aP containing vaccines. In terms of immunological outcomes, seven RCTs provided immunological data to compare two doses versus three primary doses. There was also information from observational studies.
Caution	Estimates of vaccine efficacy from different trials in terms of immunogenicity cannot be compared directly as evidence of equivalence or superiority of one particular schedule and there were too few trials for a network metanalysis which would allow such a comparison. It is important to note that most of the evidence on effect on disease outcomes is drawn from observational studies and few RCTs comparing schedule versus no vaccination. The observational studies took place when the vaccine was in routine use and other children in the community may have received 3 or more doses. There is no experience from any country using a 2p+0 schedule.

Effect of 3p+0 and 2p+0 schedules on selected disease outcomes

Table 5. Summary of studies reporting on Hib vaccine efficacy (PRPT-conjugate) and effectiveness on Hib disease: studies comparing 3p+0 or 2+0 schedule versus no vaccination

We found no data from RCTs or observational studies that directly compare 3p+0 vs. 2p+0 schedules.

PRP-T vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
RCTs- two RCTs (Gambia –Mulholland 1997[19] and Chile – Lagos 1996[20]) **Observational studies** – four studies (Gambia–Adegbola 2005[21], Chile-Lagos 1996[20], Germany–Kalies 2008[22] and Germany-Kalies 2004[23]). All used combined Hib vaccines including wP vaccine with the exception of the German studies that used aP.	**RCTs-** no RCTs **Observational studies** – six studies (Uganda-Lee 2008[24], Dominican Republic-Lee 2008[25], Uganda-Lewis-2008[26], Malawi-Daza 2006[27], The Gambia-Adegbola 2005[21], Bangladesh-Baqui 2007[28]). All used combined Hib vaccines including wP vaccine.	**RCTs**- two RCTs (Gambia-Mulholland 1997[19], Chile-Lagos 1996[20], reported on radiologically defined pneumonia and one RCT (Indonesia - Gesner 2005[29]) reported on clinical pneumonia. **Observational studies –** two studies (Colombia-de la Hoz 2004[30] and Bangladesh-Baqui 2007[28]) after 3p+0. All used combined Hib vaccines including wP vaccine except for Colombia which used monovalent Hib vaccine.
The Gambia -Mulholland 1997[19] reported PP VE after 3p+0 was 95% (95%CI 67-100). Chile-Lagos 1996[20] reported PP VE after 3p+0 was 91.7% (95%CI 64.8, 100). A case control study that compared 2p+0 vs. 3p+0 (The Gambia-Adegbola 2005[21]) reported no statistically significant difference between both schedules. Cohort studies (Chile-Lagos 1996[20], [2]Germany–Kalies 2008[22] and Germany-Kalies 2004[23]) reported VE against invasive Hib disease as follows: 90.4 (95% CI 70.6-96.8) (Germany 2008[22]),	In the observational studies, VE against Hib meningitis after two or more doses ranged from 65% (95% CI-190 to 100%)[28] to 99% (95% CI 92-100%)[24]. Excluding the estimate of 65%, the lowest reported effectiveness against Hib meningitis after 2 or 3 doses was 87% (95% CI 14-100%)[25]. Meta-analysis (Jackson C et al 2012)[4] using community controls produced estimates of VE against Hib meningitis of 55% (95% CI 2-80%), 94% (95% CI 65-99%) and 94% (95% CI 18-100%) for 1, 2	In the RCTs, the reported PP VE against radiologically defined pneumonia was 22.4% (95%CI -1.9, 38.6) for the individually randomized trial (Gambia –Mulholland 1997[19]) and 23% (95%CI1, 40) in the cluster-randomized trial (Chile-Lagos 1996 [20]). ITT VE estimates were similar to PP estimates. In the RCT that reported ITT VE against clinical pneumonia was 4% (95%CI 0.7,7.1) In an observational study in Colombia [30]

[2]

PRP-T vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
91.7 (95% CI 64,8-100) (Chile 1996[20]) and, 96.7 (95% CI 87.7-99.1) (Germany 2004[23]) for 3p+0. Acellular pertussis was used in the two German studies, all studies used combination vaccines. VE for 1-2 doses ranged from 68.4 (95% CI 19-87.6) in Germany 2008[22] to 89.6% (95% CI 67-96.7) in Germany 2004[23]. Based on the screening method, in England & Wales during 1993-2003, when the intended schedule was 3p+0 (at 2, 3, 4 months) and PRPT was used, VE against invasive Hib disease for full primary vaccination or a single catch-up dose at age $\geqslant$13 months was estimated to be 57% (95% CI 42 to 67%), or 72% in a sensitivity analysis which assumed that vaccination coverage in the population was 2% than reported (UK – Ramsay 2003[31]). VE against invasive Hib disease was only 49% (95% CI 32 to 64%) when vaccinees were defined only as children who received their 3 primary doses. VE overall (full primary vaccination plus catch up) and VE restricted to full primary vaccinees only were both higher within two years of scheduled vaccination (66%, 95% CI 51-76%) than after two years (37% 95% CI 3-62%). VE was estimated to be higher in children vaccinated at	and 3 doses, respectively. The estimates using hospital controls were similar: 53% (95% CI -14-81%), 92% (95% CI 75-97%) and 94% (95% CI 65-99%). There was no or very limited heterogeneity between studies using community controls; in studies using hospital controls, the one-dose estimates were moderately heterogeneous (I^2 = 35.8%). For Hib meningitis, one Danish study (published in 2004 and using data from 1991-1999), which used various schedules over the study period and which did not specify what vaccines were used, presented dose specific VE which suggest high VE was achieved after a single dose: VE 1 dose: 97.74% (90.77–99.45%); 2 doses 98.94% (95.71–99.74%); 3 doses 99.29% (94.87–99.90%)[33]	effectiveness of 3p+0 was reported to be 55% (95% CI 7-78%). In Bangladesh [28], VE after 3p+0 were estimated to be 44% (95% CI 16-63%) or 32% (95% CI -2 to 54%) effective against radiologically confirmed pneumonia, based on hospital and community controls, respectively[3].

[3] These estimates are based on cases of pneumonia diagnosed both by study personnel and by an independent paediatrician who reviewed the radiograph. If the VE estimate is instead based on cases diagnosed by only study personnel or by only the independent paediatrician, then the estimate is lower than that stated above, potentially as low as 16% (95% CI -11 to 37%) based on community controls diagnosis by the independent paediatrician.

PRP-T vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
more than one year of age compared with those vaccinated during infancy (HbOC vaccine was predominantly used in the catch-up campaign in the UK). It is important to note that during the 2000-2002 period approximately half of the conjugate Hib vaccine was in combination with aP vaccine. This later vaccine has reportedly associated with lower Hib immunogenicity. A German screening method study[32] reported VE against invasive Hib disease during 1998 and 1999, when the intended schedule was DTaP-Hib or DTaP-IPV-Hib given at 2, 3 and 4 months followed by a booster at 11-15 months. VE estimates were, 95.4% (92.7; 97.2) for two doses and 98.9% (98.3; 99.3) for three doses, compared to 0 doses).		

Table 6. Summary of studies reporting on Hib vaccine (PRP-OMP conjugate) efficacy and effectiveness on Hib disease: studies comparing 3p+0 or 2p+0 schedule versus no vaccination

We found no data from RCTs or observational studies that directly compare 3p+0 vs. 2p+0

PRP-OMP vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
RCTs –one RCT (USA-Santosham 1991[34]) using monovalent wP **Observational studies**- two (USA- Harrison 1994[35] and USA-Vadheim-1994[36]) .	**RCTs**- one RCTs (USA- Santosham 1991[34]) **Observational studies -** no observational studies	**RCTs**- no RCTs **Observational studies-** no observational studies
Data from the RCT in the USA-Santosham 1991[34] was collected from individuals with onset of invasive Hib disease before their second dose. This trial reported PP VE 100% (95%CI 15,100) for one dose and 93% (95%CI 53, 98) for two doses. One case control study (USA-Harrison 1994[35]) reported not statistically significant difference between 2p+0 (99% 95%CI 69-100) and 3p+0 (99% 95%CI -57-100) schedules. Another case control study (USA-Vadheim 1994[36]) reported not statistically significant difference between 1p+0 (100% 95%CI 39-100) and 2p+0 (100% 95% CI -68-100) schedules.	No data found	No data found

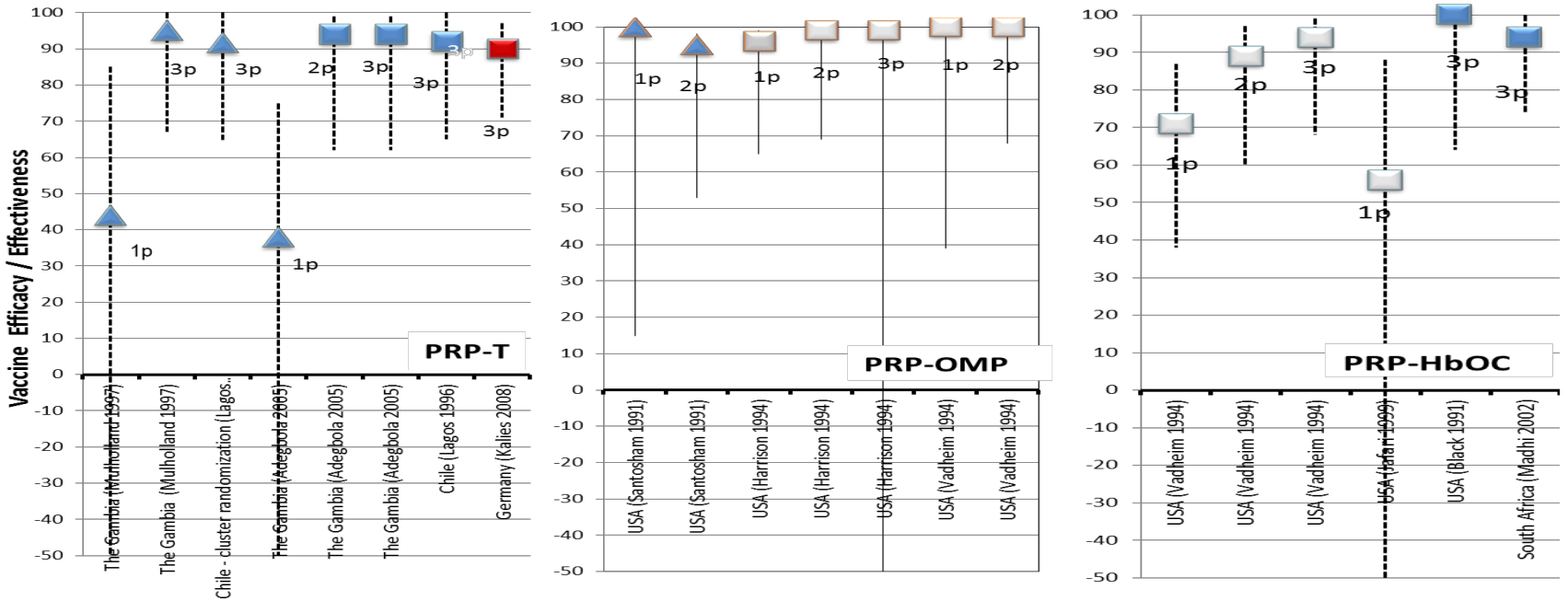
Table 7. Summary of studies reporting on Hib vaccine (HbOC conjugate) efficacy and effectiveness on Hib disease: studies comparing 3p+0 or 2p+0 schedule versus no vaccination

We found no data from RCTs or observational studies that directly compare 3p+0 vs. 2p+0

PRP-HbOC-vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
RCTs– no RCTs **Observational studies** – Four studies (USA-Vadheim 1994[36], USA –Jafari 1999[37], USA-Black 1991[38] and South Africa-Madhi 2002[39]).	**RCTs–** no RCTs **Observational studies- -** no observational studies	**RCTs–** no RCTs **Observational studies-** one observational study (Brazil-de Andrade 2004[40]).
The observational studies that compared 3p+0 vs. no vaccination reported vaccine effectiveness above 94% and one study that compared 2p+0 vs. no vaccination reported vaccine effectiveness of 89%. One study (USA-Vadheim 1994) reported not statistically significant difference between 2p+0 and 3p+0. The pooled estimates from meta-analysis (Jackson C et al 2012[4]) of studies that used PRP-T or PRP-HbOC vaccines were 59% (95% CI 30-76%) for one dose and 99% (95% CI 77-100%) for three doses (only two studies which used PRP-T or PRP-HbOC vaccines reported two-dose VE against invasive Hib disease, so meta-analysis was not performed). There was high heterogeneity in the three-dose estimates (I2 = 79.8%) but not in the one-dose estimates (I2 = 0%). Sufficient data for meta-analysis of vaccine effectiveness from cohort studies that used PRP-T or PRP-HbOC were identified only for three doses against invasive Hib disease. The South African study [39] stratified VE estimates by HIV status;	No data found	The observational study from Brazil [40] reported the effectiveness of two or more doses against radiologically confirmed pneumonia as 31% (95% CI -9 to 57%), based on an intended schedule of 2, 4, 6 months and using HbOC. All of these estimates of effectiveness against radiologically confirmed pneumonia [28 30 40]are lower than those of the effectiveness of two or three doses against invasive Hib disease and Hib meningitis. Unfortunately the VE estimates from Indonesia Lombok trial for radiological pneumonia were published without confidence intervals therefore they could not be included in meta-analysis[29]. Reviewers also assessed the data presented to see if they could calculate VE with

PRP-HbOC-vaccines		
INVASIVE HIB DISEASE	**HIB MENINGITIS**	**RADIOLOGICALLY DEFINED PNEUMONIA**
only the estimate for HIV-uninfected children is included in the meta-analysis. The pooled VE estimate was 94% (95% CI 88-97%), with little heterogeneity (I2 = 0%).		confidence intervals but could not do so without making substantial assumptions. The reported VE point estimates were -4.9 (ITT) and -12.0 (PP).

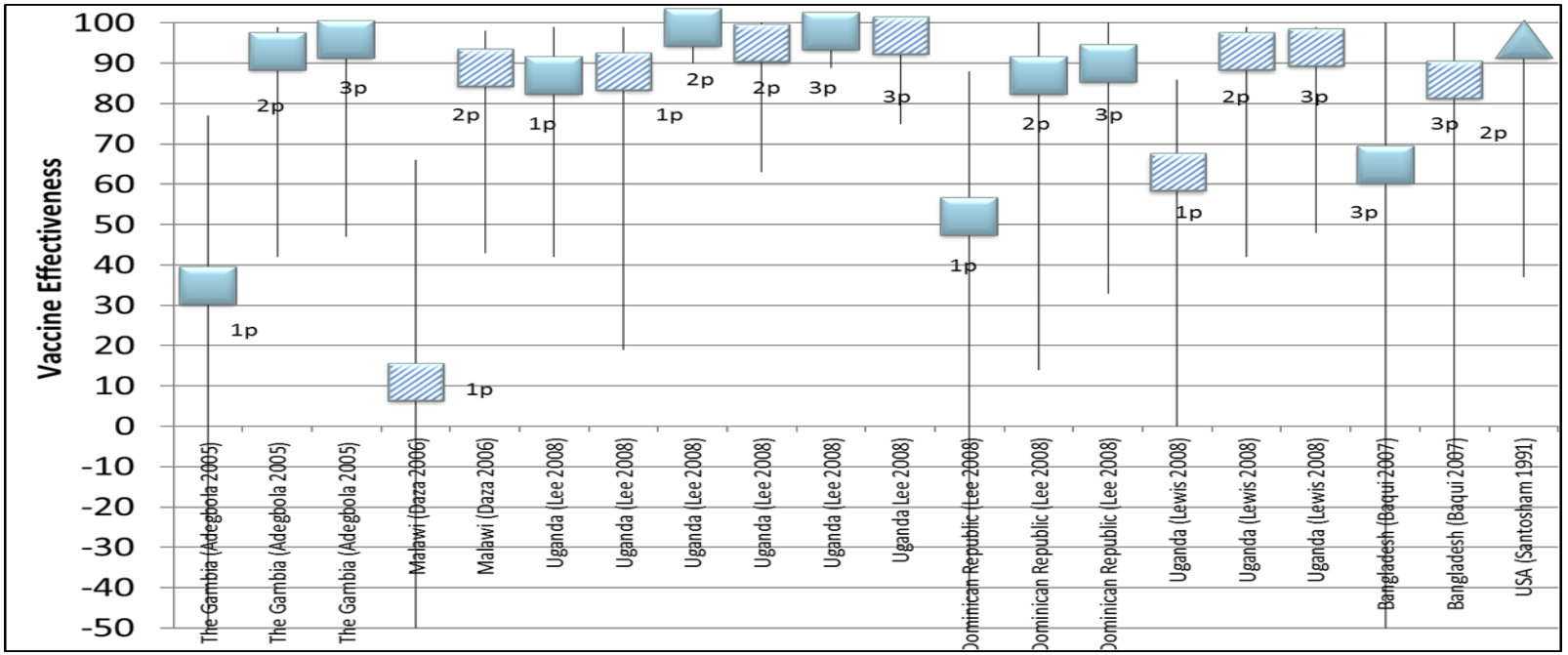
Figure 3. Studies reporting on Hib vaccine efficacy and effectiveness on invasive Hib disease - studies comparing schedule versus no vaccination



Triangle = RCT, Square = Observational study, Blue= wP, Red= aP, Grey= not stated.NB: Data from the RCT in the USA-Santosham 1991 was collected from individuals with onset of invasive Hib disease before their second dose. The Gambia -Mulholland 1997 data for 1p+0 is reported for outcomes with onset after one dose. Onset before second dose also but not included in this summary.

Figure 4. Studies reporting on Hib vaccine effectiveness on Hib meningitis - studies comparing schedule versus no vaccination

All studies are case control studies except Santosham which is an RCT. All studies used PRP-T conjugate combined with wP (shown in squares) except the USA-Santosham 1991[34], which used monovalent Hib PRP-OMP conjugate vaccines (shown in triangle).

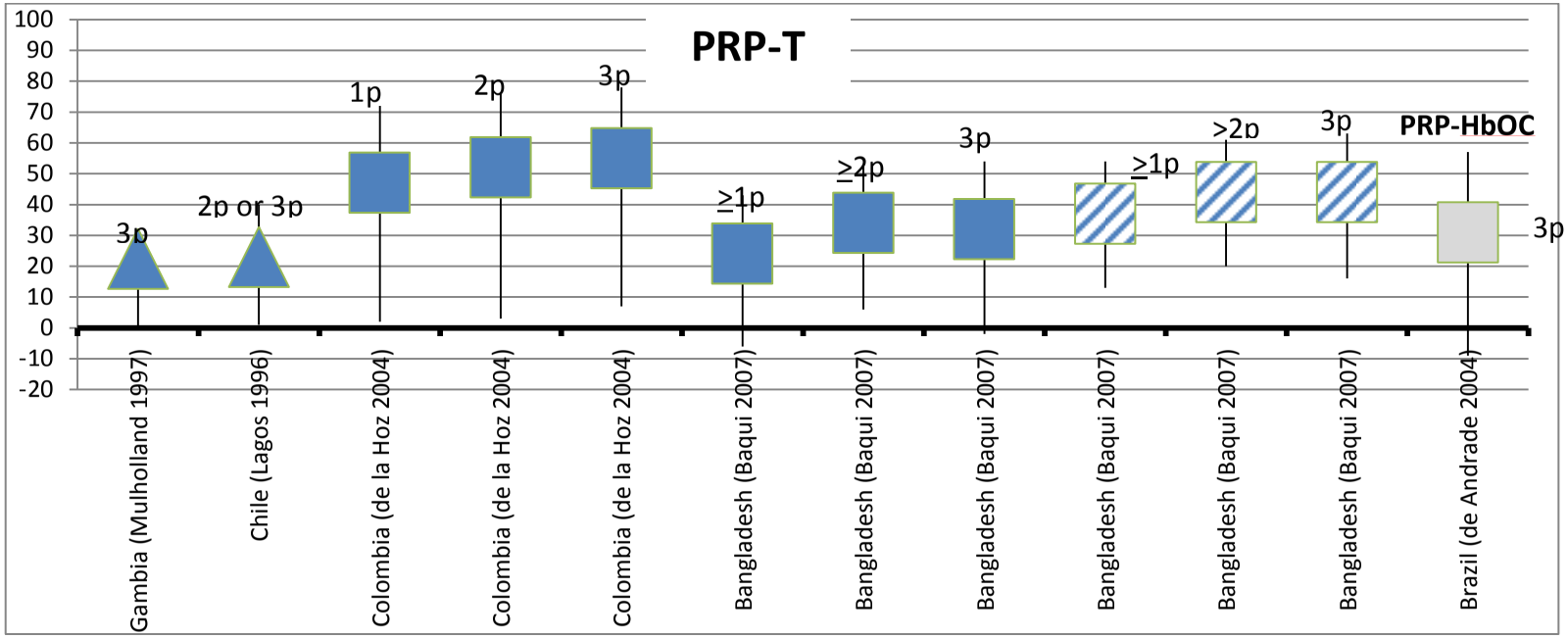


Solid marker = Community controls; Striped marker = Hospital control

Blue= wP
Red= aP
Grey= not stated

Figure 5. Studies reporting on Hib vaccine efficacy and effectiveness on radiologically defined pneumonia - studies comparing schedule versus no vaccination

All studies used PRP-T conjugate combined with wP except the Colombia-De la Hoz 2004[30] that used monovalent Hib PRPT and Brazil-de Andrade 2004[40], which used monovalent Hib PRP-HbOCvaccine .



Triangle = RCT, Square = Observational study, Blue= wP, Red= aP, Grey= not stated, solid= community control, hatches= hospital control

Effect of 3p+0 or 2p+0 on selected immunological outcomes

Table 8: Summary of studies reporting proportion above a set threshold (i.e. ≥1.0 ug/ml) and/or risk difference at the set threshold after 1 or 6 month post primary and/or geometric mean Concentrations (GMCs)

Three primary doses (3p) vs. two primary doses (2p)
PRP-T vaccines - six trials provided immunological data for this comparison (Chile –Lagos 1998[41], Chile Lagos 1998[42], Guatemala-Asturias 2009[43], Netherlands-Labadie 1996[44], Niger Campagne 1998[45], Sweden Carlsson 1998[46]). In three trials examining (Chile4 –Lagos 1998[41], Niger Campagne 1998[45], Sweden Carlsson 1998[46]), the proportion above a set threshold around 1m after vaccination was high for both 3p and 2p schedules at 0.15µg/ml. The proportions above a set threshold were lower at the 1.0µg/ml threshold and at 6m after last dose in the primary schedule. Neither the 2p nor the 3p schedule was consistently favored in analyses. By six months after the last primary dose, there was no statistical evidence of a difference between the schedules at the 1.0µg/ml threshold (pooled risk difference -0.02, 95%CI -0.10, 0.06, I^2 0%) but it remained high at the 0.15µg/ml threshold (pooled risk difference 0.02 95%CI -0.10, 0.14, I^2 75%). A case-control study performed at the time demonstrated an increased risk of vaccine failure in those who received the DTaP-Hib combination (Ramsay et al., 2003[31]). Despite intensive study and the supposition that Hib carriage must have increased in the period, associated with increased disease, adequately powered studies of Hib carriage in various age groups failed to reveal significant Hib carriage in the United Kingdom population during this period (Heath & McVernon, 2002[47]). Trotter and colleagues (Trotter et al., 2003[48]) studied serum samples obtained from different birth cohorts and showed that Hib antibody titres beyond the first year of life in cohorts immunized after the catch-up campaign did not differ significantly from titres in similarly aged children in the pre-vaccine era. McVernon and colleagues (McVernon et al., 2004b[49]) analysed anti-PRP IgG titres in the serum stored from adults in the United Kingdom, spanning the period 1991 to 2003, and showed that titres in adults declined and remained low following the introduction of Hib conjugate. This was presumably as a result of reduced exposure to Hib due to the reduction in carriage associated with the introduction of conjugate. Low circulating titres in toddlers and adults may thus explain the increase in invasive disease in the United Kingdom between 1999 and 2002, which suggests that immune memory alone in a vaccinated child is unable to provide robust protection against invasive Hib disease. A catch-up campaign was undertaken in the United Kingdom in 2003 for all children under the age of five years, and the incidence of invasive Hib disease reduced. A routine Hib booster dose was introduced into the United Kingdom schedule in 2006[50].

Three primary doses (3p) vs. two primary doses (2p)
A UK study (Southern 2007[51]) recruited, through immunisation clinics, 388 children aged 6 months to 4 years who had previously received their full primary Hib vaccine series and were given a booster dose in a catch-up campaign. Amongst these children, the GMC before the booster decreased with time since vaccination, and thus age. Despite this, the post-booster GMC increased with age at boosting: 29.87µg/ml, 68.41µg/ml and 182.36µg/ml in each group one month after booster. All but one of the 344 participants who had a blood sample taken one month after the booster had a titre ⩾0.15µg/ml one at that time, and all but three had a titre ⩾1.0µg/ml.
PRP-OMP vaccines – we did not find RCTs for this vaccine type. An observational study in the USA (Shehab 1991[52]) which used PRP-OMP vaccine did find an increase in GMT after a single dose. The GMT increased from 0.11 to 1.75 µg /ml after a single dose administered at the age of 2-3 months. The GMT increased further in all age groups following the second dose, e.g. to 3.5 µg /ml in those vaccinated at 2-3 months of age. The fold increases in GMT were 15-31, depending on age group after the first dose and 2-3 after the second. There was little difference between age groups in the percentage of children whose antibody titres reached 1.0 µg /ml after the first dose (76%, 75% and 72% of children aged 2-3 months, 4-5 months and 6-11 months at vaccination) or the second (91% of children aged <6 months and 92% of children aged 6-11 months).
PRP-HbOC vaccines – two trials examined PRP-HbOC (USA Lieberman 1995[53] and Chile –Lagos 1998[41]). One trial (Chile –Lagos 1998[41]) examined PRP-HbOCand presented seropositivity data. Point estimates favored the 3p group but the confidence interval crossed the null effect at both two and six months after the last dose and for both thresholds. The trial which reported only GMC (USA Lieberman 1995[53]) examined PRP-HbOCand compared a birth dose plus doses at 2 and 4 months of age to doses at 2 and 4 months of age. Two months after the last dose, the GMC in the 3p group (birth-dose group) was 0.93µg/ml (95%CI 0.48, 1.69) and 0.20µg/ml (95%CI 0.10, 0.29) in the 2p group. In an observational study of the immunogenicity of HbOC and PRP-D vaccines carried out in Finland (Käyhty 1989[54]), 46 children received HbOC at ages 4 and 6 months, and 25 of these received a booster dose at 14 months. Blood samples were taken before each vaccination and one month after the second and third doses, and anti-PRP antibody titres measured. There was no increase in GMT after the first dose of HbOC (0.07µg/ml before, 0.09µg/ml after); after the second dose, GMT increased to 4.32µg/ml and all children had a titre >0.15µg/ml.

Use of Hib vaccines and observation of their clinical efficacy in practice has questioned the relevance of the ≥0.15 ug/ml and ≥1.0 ug/ml (ref)concentration as surrogates of protection following conjugate vaccination (Eskola et al., 1999[55]) although they are still widely used today for licensure purposes.
The fact that conjugate vaccines induce memory, suggests that irrespective of the antibody concentrations achieved after vaccination, priming for memory responses may provide protection of longer duration, particularly if ongoing exposure to Hib is able to maintain circulating antibody concentration.
Protection against invasive Hib disease in the face of vaccine induced memory but the absence of circulating antibody is not clearly established (Galil et al., 1999[56]) and is illustrated with experience in the United Kingdom.

An increase in antibody avidity following primary immunization and boosting has been demonstrated in Hib conjugate immunogenicity trials (Goldblatt, Vaz & Miller, 1998[57]; Anttila et al., 1999[58]). Avidity measurements have thus been proposed as a surrogate marker for the successful generation of immunological memory. The relative importance of memory versus circulating antibody levels for clinical protection by conjugate vaccines is unclear. During the development and evaluation of Hib conjugate vaccines, two thresholds were identified, one that predicted short-term and one that predicted long-term protection respectively (i.e. ≥0.15 ug/ml and ≥1.0 ug/ml).

Need for a booster dose

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
Conclusion	**In some countries, administering a booster dose during the child's second year of life has been deemed necessary to sustain overall disease control in population and direct protection of toddlers. However, the need for booster doses in non-industrialized countries requires further evaluation.**
Summary statement	Available data suggest that after 5 years of vaccine introduction using a 3p+0 schedule a significant reduction in meningitis in young children was observed in a number of developing countries. A recent evaluation from four South American countries reported that Hib meningitis rates were similar 6-10 years post introduction in countries with and without boosters. There is similar data from a dozen of non-industrialized countries that have used a 3p+0 schedule for at least 6 years. However, the UK had a different experience: after the introduction of a 3p+0 schedule (2, 3, 4 months) in 1992 with PRPT-conjugate alongside a catch-up campaign for toddlers 12-48 years of age (with HbOC conjugate vaccine), the UK had an initial decline in cases, but started observing an increase in Hib over a decade after an initial decline in cases. As a result of this, a Hib vaccination booster campaign using (PRP-T conjugate) was conducted between May and September 2003, offering one dose of vaccine to all children who were aged between 6 months and 4 years on 1 April 2003 and to those children who reached 6 months of age during the campaign. A routine booster dose in the vaccine schedule was introduced in 2006. Following these interventions cases declined again. Data from industrialized countries suggest that immunogenicity may be lower with PRPT conjugate and aP containing vaccine and this could have an impact on duration of protection. Emerging reports on some resurgence of Hib cases in older children in The Gambia (3p + 0) highlight the need for further evaluation of duration of protection and of the role of a booster dose in non-industrialized country settings [e.g. 10 years after introduction of Hib vaccine in combination with whole cell pertussis vaccine]. If boosters are deemed necessary (i.e. as part of a 2p+1 or 3p+1 schedule), an alternative to routine booster at 11 months or later may be to implement catch-up campaigns targeting toddlers. The UK experience suggests that they have resulted in important reductions of overall carriage
Quality of evidence	**We are moderately confident on the estimate of the effect.** Assessment of the need for booster doses is challenging because (a) there are no data directly comparing clinical effectiveness

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?	
	between similar primary schedules with and without booster No data are currently available from developing country settings using aP containing combination vaccines without a booster dose.
Caution	The situations in which a booster dose should be used remain unclear, and it would depend on various factors including local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

Effect of 3p+1 and 2p+1 on selected disease outcomes

We did not identify RCTs or observational studies that compared these schedules to a 3p+0 schedule. The conclusions below are based on data from long term impact post vaccine introduction (Watt J et al 2012[5]) that are described in page 38 of the 3p+1 or the 2p+1 regimens.

In some countries, administering a booster dose during the child's second year of life has contributed to sustain overall disease control in population and direct protection of toddlers. However, the need for booster doses in non-industrialized countries requires further evaluation. Data from industrialized countries suggest that immunogenicity is lower with an aP containing vaccine and this could have an impact on duration of protection.

No data are currently available from developing country settings using aP containing combination vaccines without a booster dose. Available data suggest that after 5 years of vaccine introduction using a 3p+0 schedule a significant reduction in meningitis in young children has been observed in a number of developing countries.

A recent evaluation from four South American countries reported that Hib meningitis rates were similar 6-10 years post introduction in countries with and without boosters. However, the UK after the introduction of a 3p+0 schedule (2, 3, 4 months) with the PRPT-conjugate alongside a catch-up campaign for toddlers 12-48 years of age (with HbOC conjugate) experienced an increase in Hib cases several years after an initial decline in cases. Cases again declined after two booster campaigns and the introduction of a routine booster dose to the vaccine schedule. (see pages 31-36).

The situations in which a booster dose should be used remain unclear, and might relate to local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

Emerging reports on cases of Hib disease from the Gambia highlight the need for further evaluation of duration of protection and of the role of a booster dose in some settings [e.g. 10 years after introduction of Hib vaccine in combination with whole cell pertussis vaccine]. See pages 39-48.

If boosters are deemed necessary, an alternative to routine booster is to implement catch-up campaigns targeting toddlers. The UK experience suggests that they have resulted in important reductions of overall carriage. See page 49.

Table 9. Summary of studies reporting on Hib vaccine efficacy and effectiveness on selected disease comparison of 3p+0 versus schedules including a booster dose.

Hib invasive disease	Hib meningitis	Hib pneumonia
Three primary doses (3p+0) vs. two or three primary doses and a booster (2p+1 or 3p+1)		
No data from RCTs or observational studies that directly compared three primary doses with other primary doses and a booster schedules	No data from RCTs or observational studies that directly compared three primary doses with other primary doses and a booster schedules	No data from RCTs or observational studies that directly compared three primary doses with other primary doses and a booster schedules
Two or three primary doses and a booster vs. no vaccination (2p+1 or 3p+1 vs. no vaccination)		
PRP-T vaccines – No data from RCTs or observational studies	**PRP-T vaccines** – No data from RCTs or observational studies	**PRP-T vaccines** – No data from RCTs or observational studies
PRP-OMP vaccines – No data from RCTs or observational studies	**PRP-OMP vaccines –** No data from RCTs or observational studies	**PRP-OMP vaccines –** No data from RCTs or observational studies
PRP-HBOC vaccines – No data from RCTs or observational studies	**PRP-HBOC vaccines –** No data from RCTs or observational studies	**PRP-HBOC vaccines –** No data from RCTs or observational studies

Effect of 3p+1 or 2p+1 on selected immunological outcomes

A booster dose after a primary series of either two or three doses of Hib conjugate vaccine results in high levels of seropositivity. There was no evidence from trials that the age at which the booster dose is given, or the interval between the primary series and the booster dose affect the level of seropositivity. Proportion above a set threshold levels in children after a booster dose are much higher than in children who received the same primary schedule without a booster. The interval between the last vaccine dose and blood draw is, however, shorter in children receiving the booster than in those who received only the primary schedule, and it is not clear if differences in antibody levels can be interpreted as differences in protection from Hib disease. The UK experienced an increase in Hib cases several years after an initial decline in cases subsequent to the introduction of a 3p+0 schedule (2, 3, 4 months) alongside an early catch-up campaign. Cases again declined after two booster campaigns and the introduction of a routine booster dose to the vaccine schedule.

Table 10. Summary of studies reporting on Hib vaccine efficacy on selected immunological outcomes: comparison of 3p+0 versus for schedules including a booster dose.

Three primary doses (3p+0) vs. two primary doses and a booster (2p+1)	Three primary doses (3p+0) vs. three primary doses and a booster (3p+1)
PRP-T vaccines - One trial provided immunological data for this comparison (Sweden-Carlsson 1998[46]) using PRP-T. This trial reported seropositivity and GMC data. At 13 months of age (seven months after the 3p group received their last primary dose and one month after the 2p+1 group received their booster); the 2p+1 schedule resulted in higher proportions above a set threshold than the 3p schedule at both the 0.15µg/ml and 1.0µg/ml thresholds. The risk difference was -0.79 (95%CI -0.87, -0.71) at the 1.0µg/ml threshold (favors the 2p+1 schedule) and -0.20 (95%CI -0.27, -0.13) at 0.15µg/ml. The proportion above the 0.15µg/ml threshold	**PRP-T vaccines -** two trials provided immunological data for this comparison (Canada-Scheifele 2005[59], Europe- Knuf 2011[60]). Both examined PRP-T, and one reported seropositivity data (Europe-Knuf 2011[60]). Both trials reported GMC. At 13 months of age (one month after the 3p+1 group received their booster dose), the 3p+1 schedule resulted in higher proportions above a set threshold than the 3p schedule at both the 1.0µg/ml (risk difference 0.59, 95%CI 0.52, 0.67) and 0.15µg/ml thresholds (risk difference 0.16, 95%CI 0.11, 0.22).

Three primary doses (3p+0) vs. two primary doses and a booster (2p+1)	Three primary doses (3p+0) vs. three primary doses and a booster (3p+1)
remained high at around 6 months after a 3p schedule. This proportion was lower at the 1.0µg/ml threshold. Additionally, six trials included in this review reported data for an individual trial arm receiving a 3p schedule or a 2p+1 schedule (Chile4 –Lagos 1998[41], Chile5-Lagos 1998[42], Guatemala-Asturias 2009[43], Netherlands-Labadie 1996[44], Niger-Campagne 1998[45], Sweden-Carlsson 1998[46]). High proportions of individuals remained above the 0.15µg/ml threshold 6 months after a 3p schedule. The proportion was lower at the 1.0µg/ml threshold but there was variability between trials.	One trial reported only GMC (Canada-Scheifele 2005[59]). At 16 months of age a group which received a 3p schedule with a booster dose at 15 months of age achieved a GMC of 29.2µg/ml (95%CI 24.58, 36.43) and a group which had received a 3p schedule with no booster dose by 16 months of age achieved a GMC of 0.32µg/ml (95%CI 0.25, 0.41). A UK study (Southern 2007[51]) recruited, through immunisation clinics, 388 children aged 6 months to 4 years who had previously received their full primary Hib vaccine series and were given a booster dose in a catch-up campaign. Amongst these children, the GMC before the booster decreased with time since vaccination, and thus age. Despite this, the post-booster GMC increased with age at boosting: 29.87µg/ml, 68.41µg/ml and 182.36µg/ml in each group one month after booster. All but one of the 344 participants who had a blood sample taken one month after the booster had a titre ≥0.15µg/ml one at that time, and all but three had a titre ≥1.0µg/ml.
PRP-OMP vaccines – We did not find RCTs for this vaccine type. A study, carried out in Alaska Native infants (Bulkow 1993), compared three different Hib conjugate vaccines and also found that geometric mean antibody titres were increased after one dose of PRP-OMP intended to be given at the age of 2 months, and increased further after a second dose intended to be given at 4 months. However, vaccination with HbOC or PRP-T required 3 doses (intended to be given at 2, 4 and 6 months) for a substantial rise in GMT, although the results are influenced by the timing of sample collection (samples were taken 2 months after doses 1 and 2, but 1 month after dose 3.)	**PRP-OMP vaccines –** We did not find RCTs for this vaccine type.

Three primary doses (3p+0) vs. two primary doses and a booster (2p+1)	Three primary doses (3p+0) vs. three primary doses and a booster (3p+1)
PRP-HbOC vaccines – We did not find RCTs for this vaccine type. In the Finnish study (Käyhty 1989[54]) of 25 children given a primary series of HbOC at 4 and 6 months with a booster at 14 months, the GMT immediately prior to the booster dose was 1.12µg/ml. This increased to 58.3µg/ml following the booster.	**PRP-HbOC vaccines –** We did not find RCTs for this vaccine type.

Impact of Hib vaccines on carriage

The mechanism of protection against carriage is not well understood, but high levels of serum anti-PRP IgG (>5 lg/mL) have been associated with protection against carriage, and the presence of anti-PRP antibodies in saliva is associated with high serum levels of anti-PRP antibody. Vaccination strategies that elicit higher post-vaccination anti-PRP levels may therefore be more effective in reducing Hib carriage and transmission. The reduction in Hib carriage directly determines herd immunity and significantly contributes to the protection of the vaccinated population. However, in a non-vaccinated population, Hib encountered in the course of childhood may contribute to immunity by repeated stimulation of antibody production thereby inducing both individual and herd immunity. Thus in a vaccinated population reduction in carriage results in a decrease in natural boosting and, in the absence of further doses of vaccine, serum antibody concentrations wane. Initial efficacy trials, involving only a subset of the population may have underestimated this effect (reference Goldblatt et al 2007[61]).

There were no eligible carriage outcome data from trials that compared different schedules of Hib vaccination. One trial presented data about carriage for 1p1= vs. no doses (Gambia-Mulholland 1997[19]). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was low (I2 0%). The point estimate showed slightly less carriage with one dose of PRP-T compared to no doses but confidence intervals were very wide (pooled odds ratio 0.82, 95%CI 0.14, 4.71). This trial also reported about carriage for 2p+0 vs. no doses although it was randomized trial of a 3p schedule (Gambia-Mulholland 1997[19]). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was moderate (I2 47%). The point estimate showed less carriage with two doses of PRP-T compared to no doses but confidence intervals were very wide (pooled odds ratio 0.52, 95%CI 0.08, 3.37). Again, this trial, comparing three primary doses of PRP-T at 2, 3 and 4 months with no Hib doses, reported carriage data (Gambia-Mulholland

1997[19]). Carriage was measured in the second and third years of the trial (different children each year) and in urban and rural locations. Heterogeneity between settings and years of the trial was low (I2 0%). The combined odds ratio comparing three doses of PRP-T to no doses was 0.36 (95%CI 0.25, 0.53, I2 0%).

A case-control study conducted in three rural Alaskan villages found no evidence of an effect of Hib vaccine on carriage of Hib. Based on 16 carriers and 32 controls (matched on age and village), 62% of carriers and 62% of controls had received at least one dose of a Hib conjugate vaccine, implying 13% effectiveness of at least one dose against carriage but with an extremely wide confidence interval (95% CI -1000 to 93%). Restricting the analysis to children born after conjugate vaccine became available in this setting, there was no evidence of an effect on carriage of either PRP-OMP, HbOC or the time since last vaccination (<82 or $\geqslant$82 days, the median value). However, the number of carriers and controls was small and the confidence intervals wide[62].

A study in Turkey compared the prevalence of carriage in fully vaccinated, partially vaccinated and unvaccinated children (the intended vaccination schedule was 2, 4, 6 and 18 months, using PRP-T) 53. 19/57 (33%) fully vaccinated children carried Hib in the oropharynx, compared to none of 17 partially vaccinated and 46/85 (54%) unvaccinated children. After adjusting for previous respiratory infection, having a sibling aged <5 years, breastfeeding and recent antibiotic use, the OR comparing unvaccinated to fully vaccinated children was 3.76 (95% CI 1.61 – 8.80). This implies a VE of 73% (95% CI 38-89%). This estimate is not adjusted for age, time since vaccination or socioeconomic status (although the authors state that there was no association between carriage and parental job)[84]

A study in Native American children[63] reported the prevalence of carriage in relation to age and the number of doses of PRP-OMP received (intended to be given in 3 doses at ages 2, 4 and 12-15 months). Overall, 65% of carriers and 80% of non-carriers had received at least one dose before the swab was taken; 13% of carriers and 36% of non-carriers had received the intended number of doses for their age. The point estimate of the prevalence of carriage was highest in unvaccinated children in all age groups (Figure 6) but confidence intervals were wide (the number of carriers was <10 in each group) and there was no apparent dose-response relationship. After adjusting for age and the presence of a respiratory infection at the time of swabbing, the OR comparing children who were not age-appropriately vaccinated to those who were, was 2.66 (95% CI 1.00 – 7.05, p = 0.05) 54. This implies a VE against carriage of 62% (95% CI 0 – 86%).

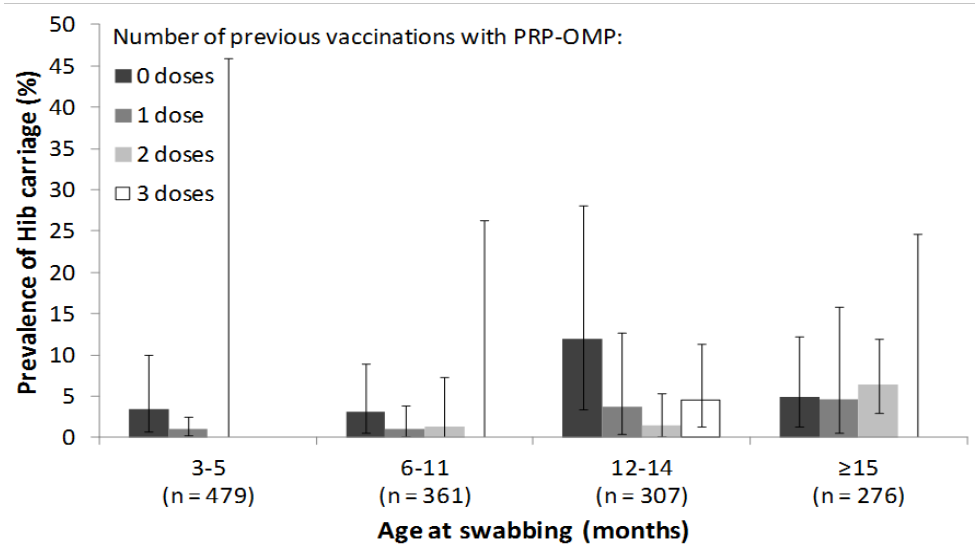


Figure 6: Prevalence of oropharyngeal carriage of Hib by Native American children, by age and number of previous doses of PRP-OMP. Error bars show 95% exact binomial CIs (or one-sided 97.5% CIs if the point estimate is zero) [63]

In the UK, carriage was assessed in 143 children (recruited via computerised immunisation records) who had received three doses of Hib-containing vaccine in relation to the number of doses given as DTaP-Hib 51. Only three carriers were identified: one had received no doses of DTaP-Hib and two had received three doses. These small numbers do not allow a comparison of the effects of DTaP-Hib versus other vaccines on effectiveness against carriage. The studies included here which report the prevalence of carriage according to the number of vaccine doses received did not suggest an obvious dose-response relationship, but the number of carriers was usually small. However, these studies of Hib vaccination indicate some reduction in carriage, perhaps with an effectiveness of 60-70%. They are thus consistent with population data showing dramatic impacts of Hib vaccines against invasive disease in several populations.

Duration of protection and considerations for immunization schedule selection

Does using 2 or 3 primary doses plus a booster of Hib conjugate vaccine has a greater effect on duration of protection than using three primary doses without a booster?	
Conclusion	**Although there is some evidence for decrease over time in the proportion above a set threshold (i.e. >0.15mcg/ml and >1.0 mcg/ml) there is limited evidence for this decline being associated with an increase in disease.**
Summary statement	The rationale for the 3p+0 schedule is predicated on the induction of sufficient primary antibody responses after three doses in infancy to reduce carriage and thus confer indirect protection through the early childhood years when susceptibility is greatest. In the UK over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, using PRP-T conjugate) and at the same time a catch up campaign with single dose of Hib (HbOC conjugate) given to those aged 13 months to 4 years, vaccine failures were observed primarily in children age 1-4 years who completed the primary vaccination series, despite the induction of immune memory. An increased in disease in previously non immunized children over 15 years of age was also seen, confirming the resurgence of Hib circulation. Enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign conducted when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis . This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant
Quality of evidence	**We are uncertain about the estimate of the effect** Although there is some evidence for decrease over time in proportion above a set threshold there is limited evidence to date for this decline being associated with increase in disease, except in the UK
Caution	As mentioned above, available data from developing countries on long-term duration of protection requires further evaluation. This is a complex issue. With high sustained vaccine coverage with a highly effective vaccine and a low force of infection, carriage may be reduced to a low level which results in less opportunity for boosting antibody levels by exposure but also a very low risk of disease. If VE in children drops then this might allow Hib to re-emerge. In countries, such as those in the developing world, with lower coverage and a higher force of infection, carriage of Hib may be still likely to be sufficiently common to result in continued boosting and maintenance of antibody levels and thus longer duration of direct protection in an individual but no indirect protection.

The rationale for the 3p+0 schedule is predicated on the induction of sufficient primary antibody responses after three doses in infancy to reduce carriage and thus confer indirect protection through the early childhood years when susceptibility is greatest.

In the UK over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, using PRP-T conjugate) and at the same time a catch up campaign with single dose of Hib (HbOC conjugate) given to those aged 13 months to 4 years, vaccine failures were observed primarily in children age 1-4 years who completed the primary vaccination series, despite the induction of immune memory. An increased in disease in previously non immunized children over 15 years of age was also seen, confirming the resurgence of Hib circulation. Enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign conducted when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis . This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant. Although there is some evidence for decrease over time in proportion above a set threshold (i.e. >0.15mcg/ml and >1.0 mcg/ml) there is limited evidence for this decline being associated with increase in disease, except in the UK.

As mentioned above, available data from developing countries on duration of protection requires further evaluation. In the UK, over a decade after Hib vaccine introduction of a 3p+0 schedule (at 3, 4 and 5 months, mostly PRP-T conjugate), vaccine failures were occurring primarily in children aged one to four years who completed the primary vaccination series, but an increase in disease in those over 15 years of age was also seen.

In addition to the information on proportion above the set thresholds over time described above, we reviewed data on vaccine failures from observational studies.

Furthermore, we discussed recent information from vaccine failures in the UK, South Africa and The Gambia in the section on experience with Hib vaccines use and long term impact of various schedules.

Two case-control studies presented data on children who developed Hib disease despite having been vaccinated[24 36]. In one of these studies, from Uganda[24], three children developed Hib meningitis after receiving two doses of Hib vaccine with DTwP, all within one year of the second dose. Three children who had received three doses developed Hib meningitis within three years of the third dose.
These six vaccine failures ranged in age from 17 to 157 weeks (Lee et al 2008[24]).

The second case-control study to include data on vaccine failures was from the USA and reported 27 vaccine failures in total (Vadheim 1994[36]). Eighteen children were diagnosed with invasive Hib disease after a single vaccine dose, all within one year of vaccination. Six and three children developed disease after two and three doses, respectively, again within one year of the most recent dose.

Three cohort studies included data on the time since the last vaccine dose in vaccine failures (Kalies 2008[22], Kalies 2004[23], Madhi 2005[64] and Madhi 2002[39]). In two of these studies (from South Africa and Germany), Hib vaccine was given with DTwP [34, 36, 37.] All children in the German study, and all but one of the South African children not infected with HIV, developed disease within a year of receipt of their final dose of Hib vaccine (irrespective of the total number of doses). In the South African study, children infected with HIV appeared to develop disease later than vaccine failures who were not HIV-infected, e.g. four HIV-infected children developed disease $\geqslant$2 years after receiving two or three doses (Madhi 2005[64] and Madhi 2002[39]).

Amongst cohort studies in which Hib vaccine was given with DTaP[22 23], almost all vaccine failures occurred within two years of receipt of the last dose of vaccine. Vaccine failures also occurred in two children who received two doses of monovalent Hib vaccine (12-23 months after the second dose) and one child who received two doses of DT-Hib.

Experience with Hib vaccine use and impact of various schedules

Observational studies in countries using Hib conjugate vaccine for at least five years suggest that various Hib vaccination schedules in use worldwide have been very effective (Watt J et al 2012[5]). There are limited data available to assess the interaction of different epidemiologic settings and vaccination schedule. Because instances of diminished vaccine effectiveness are few, there are limited data available to assess the relationships between different epidemiologic settings, vaccination coverage levels, vaccination schedules and vaccine effectiveness. To illustrate the impact of various vaccination schedules in different parts of the world we summarized the experience from a selected number of countries in each region.

Table 11. Summary of evidence on long term impact of Hib vaccines with schedules with and without a booster dose

	Schedules without a booster dose	Schedules including a booster dose
Non – industrialized countries	Most developing countries have implemented a primary series only (3p+0), with good effectiveness. In Kenya Hib disease incidence has declined since vaccine introduction. Reports indicate that Anti-PRP Geometric Mean Concentration has declined and yet nasopharyngeal carriage prevalence of H. influenzae has remained low. In The Gambia preliminary reports of an increase in number of cases of Hib disease have led local investigators to ponder whether Hib disease protection may be waning 15 years after introduction. In South Africa following vaccine introduction, there was a substantial decrease in the number of Hib cases, however, from 2003-2009 investigation on vaccine failures suggested a possible resurgence of Hib disease. South Africa introduced a booster dose in 2010.	Data from four Latin American countries found no difference in vaccine impact in the two countries which use a booster dose (Argentina and Uruguay) compared with the two which do not (Chile and Colombia).
Industrialized countries	Limited data are available on the use of a schedule without a booster dose (3p+0) in industrialized countries. The United Kingdom, experienced a resurgence of Hib disease approximately 6 years after vaccine introduction using a 3p + 0 schedule. While multiple factors likely contributed to this resurgence, addition of a booster dose resulted in decreased disease incidence.	With a few exceptions, industrialized countries have implemented schedules that include a primary series and a booster dose (3p+1). In general, schedules used in industrialized countries have been highly effective. Data from Finland and other Scandinavian countries suggest that two vaccine doses in early infancy, followed by a late booster (2p+1), are efficacious in protecting children from *Haemophilus influenzae* type b (Hib) infection, and will practically eliminate Hib meningitis. In Italy, Hib vaccination using a 2p+1 schedule has been in use since 1999. Overall, pediatric H. influenzae disease has become less common whereas there has been a slight increase of disease in the elderly. Among industrialized countries in Watt et al 2012, all but Italy (2p+1) and the Czech Republic (3p+0) reported higher disease incidence among children less than one year of age compared with children 1-4 years of age.

Watt J and colleagues (2012[5]) reviewed data on invasive Hib disease at least 5 years following vaccine introduction[4]. They limited the analysis to countries with at least 100,000 live births per year so that disease incidence estimates for young children would be stable. One hundred two countries introduced Hib conjugate vaccine into their routine infant immunization schedule on or before January 1, 2006. Of these, 50 (49%) had at least 100,000 live births in 2010. Data on Hib disease at least 5 years after vaccine introduction were available from 34 (68%) of these 50 countries. By WHO region, data were available from 4 countries in the African region, 18 countries in the Americas, 11 in the European region, and 1 in the Western Pacific region. Data on disease incidence at least 5 years after vaccine introduction was available from 21 countries. Data on case characteristics from sentinel sites was available from an additional 13 countries.

Table 12. Description of Hib vaccine schedules in selected countries with data on Hib disease at least 5 years following vaccine introduction.

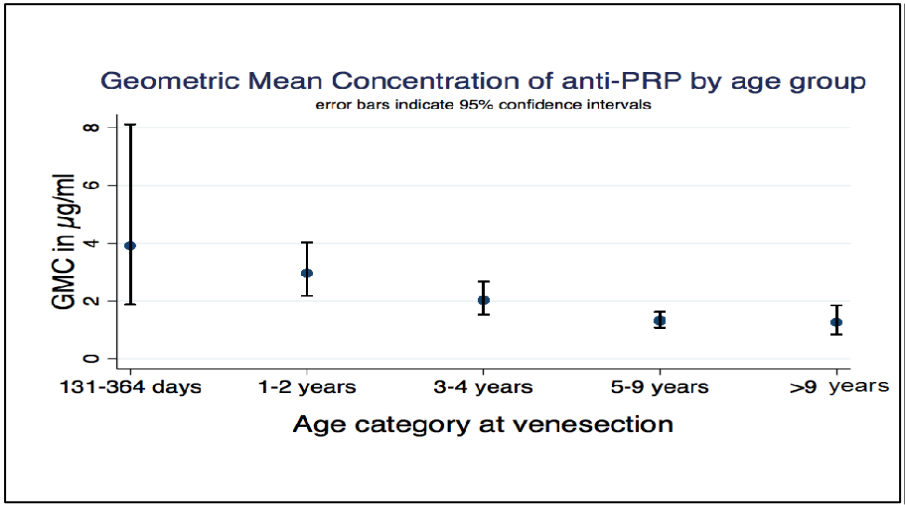
Country	WHO region	Year of introduction	Vaccine presentation	Current type of pertussis vaccine	Schedule	Primary schedule	Booster dose	DATA TYPE AVAILABLE
Kenya	AFRO	2001	DTP/HepB/Hib	wP	3p+0	6, 10, 14 wks.	None	Incidence
The Gambia	AFRO	1997	DTP/HepB/Hib	wP	3p+0	2, 3, 4 mos	None	Incidence
Malawi	AFRO	2002	DTP/HepB/Hib	wP	3p+0	6,10,14 wks	None	Case
Uganda	AFRO	2002	DTP/HepB/Hib	wP	3p+0	6,10,14 wks	None	Case
South Africa	AFRO	1999	DTP/Hib until 2008. DTaP/Hib/IPV from 2009	aP	3p+1	6, 10, 14 wks.	Booster dose added 2010.	Incidence
Chile	AMRO	1996	Hib until 2006. DTP/HepB/Hib from 2007.	wP	3p+0	2, 4, 6, mos	None	Incidence
Colombia	AMRO	1998	Hib until 2002. DTP/HepB/Hib from 2003.	wP	3p+0	2, 4, 6, mos	None	Incidence
Brazil	AMRO	1999	Hib until 2002. DTP/Hib from 2003.	wP	3p+0	2, 4, 6, mos	None	Incidence
Canada	AMR	1986	DTaP/Hib/IPV	aP	3p+1	2, 4, 6, mos	18 mos	Incidence
United States of America	AMR	1991	Various	aP	3p+1	2, 4, 6, mos	12-15 mos	Incidence

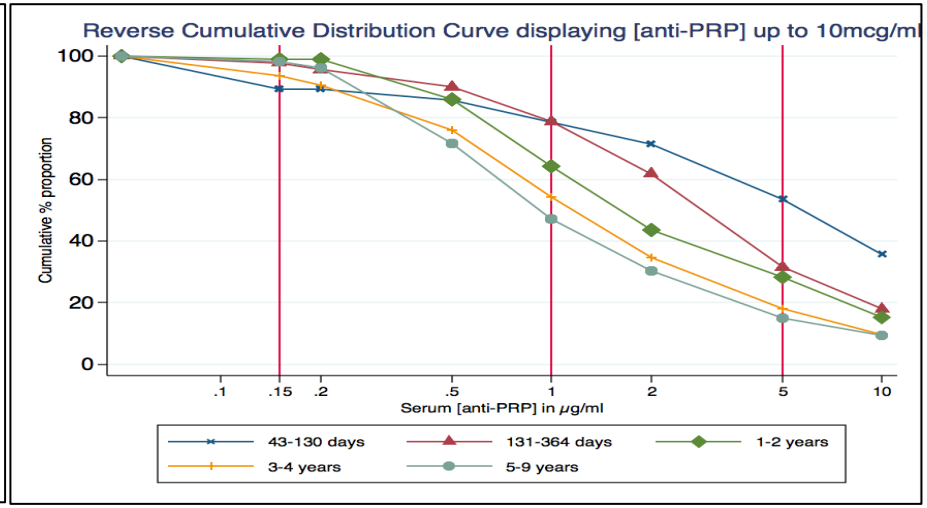
[4] This time range was selected based on the experience in the United Kingdom where disease resurgence was observed beginning 6 years after vaccine introduction. Five years was selected as the threshold to increase the amount of data for review.

Country	WHO region	Year of introduction	Vaccine presentation	Current type of pertussis vaccine	Schedule	Primary schedule	Booster dose	DATA TYPE AVAILABLE
Uruguay	AMR	1994	DTP/HepB/Hib	wP	3p+1	2, 4, 6, mos	12 mos	Incidence
Argentina	AMR	1997	DTP/Hib	wP	3p+1	2, 4, 6, mos	18 mos	Incidence
Sweden	EUR	1992	Various		2p+1	3, 5 mos	12 mos	Incidence
Italy	EUR	1999	Various DTaP/Hib combinations	aP	2p+1	3, 5 mos	11-12 mos	Incidence
Czech Republic	EUR	2001	Hib monovalent until 2006. DTaP/Hib/HepB/IPV from 2007	wP	3p+0	9, 13, 17 wks.	18 mos	Incidence
United Kingdom	EUR	1992	DTP/Hib until 1999. DTaP/Hib combinations from 1999	aP	3p+1	2, 3, 4 mos	12 mos (added in 2003)	Incidence
Netherlands	EUR	1993	Hib monovalent until 2002. Switched to DTP/Hib/IPV in 2003. Switched to DTaP/Hib/IPV or DTaP/Hib/HepB/IPV in 2005	aP	3p+1	2, 3, 4 mos	11 mos	Incidence
Israel	EUR	1994	DTP/Hib/IPV until 2001. DTaP/Hib/IPV from 2002 onwards.	aP	3p+1	2, 4, 6 mos	12 mos	Incidence
Australia	WPR	1993	DTaP/Hib/HepB/IPV Hib/HepB (PRP-OMP, indigenous children)	aP	3p+1	2, 4, 6 mos and 2,4 mos	12 mos	Incidence

Kenya (3p+0)[5]

In November 2001, Kenya, Hib vaccine was introduced as part of a pentavalent using a 3p+0 schedule (at 6, 10, and 14 weeks of age). A catch-up campaign was not conducted. Coverage with three doses of vaccine by 12 months of age was estimated to be 87% in 2004 (Ndirtu BMC Pub Health 2006). Culture-based surveillance for invasive Hib disease at Kilifi District Hospital has been conducted from 2000 through present. Antibodies to Polyribosylribitol Phosphate (PRP), were assessed by ELISA on serum samples collected in 2009, from 471 children aged 0 to 15 years residing in the KDHSS. Long-term protective anti-PRP titres (>1mcg/ml) were detected amongst 75.8% (95% CI 57.7-88.9) of children aged <1 year, 71.3% (64.0-77.7) of children aged 1-5 years and 52.9% (46.4-59.4) of children aged 5-15 years. Anti-PRP Geometric Mean Concentration declined from 3.9mcg/ml (95% CI 1.9-7.8) amongst children aged <1 year to 2.4mcg/ml (2.0-3.0) amongst children aged 1-5 years to 1.3mcg/ml (1.1-1.6) amongst children aged 5-15 years (preliminary analyses). (See GMC values and reverse cumulative distribution curves (below.). Analysis of anti-PRP antibodies is ongoing for ~1000 serum samples collected from children in 1998 – 2007. Nasopharyngeal carriage prevalence of H. influenzae has been assessed in cross-sectional surveys conducted in the KHDSS in 2004, 2009, 2010, 2011, and 2012. The prevalence of Hib carriage in children <5 years of age in the KHDSS was 6 (1.7%)/349 in 2004 (Abdullahi PIDJ 2006) and 1(0.2%)/623 in 2009-2012 (preliminary analysis, personal communication A Scott and L Hermit[65]).





[5] Summary courtesy of Dr L Hammit Johns Hopkins Bloomberg School of Public Health, USA and Dr A Scott London School of Hygiene and Tropical Medicine, UK

South Africa (3p+0 and then 3p+1)[6]

South Africa introduced Hib conjugate vaccine in 1999 as a 3 dose primary series without a booster dose. The initial vaccine was a PRP-T combination vaccine with a whole cell pertussis component. In 2009, this vaccine was replaced with a combination vaccine containing an acellular pertussis component and inactivated polio vaccine (IPV).(Von Gottberg, 2012[66]) Following vaccine introduction, there was a substantial decrease in the number of Hib cases identified by the national surveillance system (Von Gottberg, 2006[67]) However, from 2003 through 2009, despite high vaccination coverage, detection rates of Hib disease in children <5 years increased from 0.7 per 100,000 population in 2003 to 1.3/100,000 in 2009 ($p < 0.001$). Among 263 episodes of invasive Hib disease among children with known vaccination status, 135 (51%) were classified as vaccine failures. Of vaccine failures, 55% occurred among case patients ⩾18 months old. HIV status was documented for 90 children with vaccine failure; 53% were not HIV infected. Vaccine failures, which occurred in both HIV-infected and -uninfected children, comprised half of the rise in invasive Hib disease. In November 2010, children in South Africa began receiving a booster dose of HibCV as part of a pentavalent vaccine (Von Gottberg 2012[66]). The introduction of the booster dose was driven by polio prevention since IPV was being used and not a response to change in Hib disease incidence.

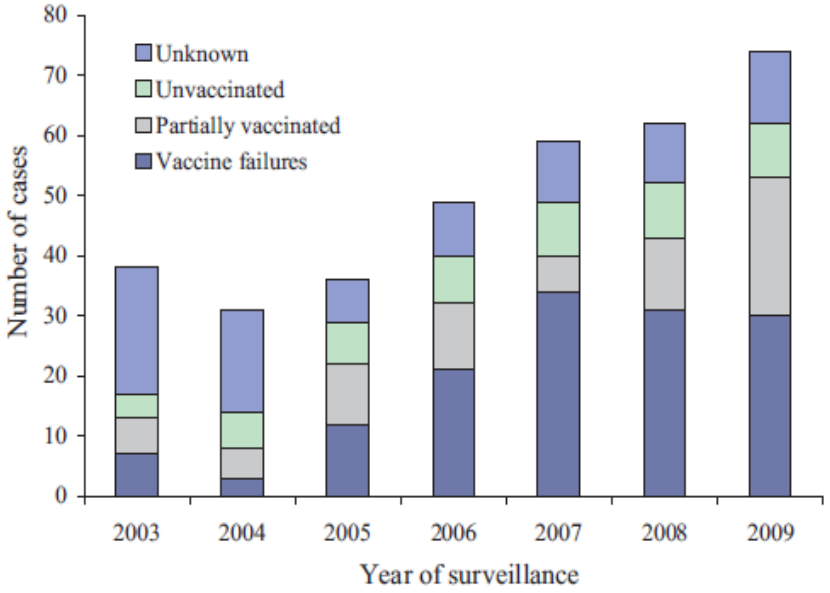


Fig. 2. Number of children <5 years with confirmed invasive *Haemophilus influenzae* serotype b disease ($n = 349$) by vaccination history and year, South Africa, 2003–2009.

[6] Summary prepared using information kindly provided by Dr A von Gottberg, Centre for Respiratory Disease and Meningitis, National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service, South Africa

Figure 10: Number of reported cases of invasive Haemophilus influenzae (Hi) disease in children <5 years (n=1455), by serotype and year, South Africa, 2003-2009.

Invasive pneumococcal disease (IPD) documented for children <5 years is depicted for the same time period. Serotype b = *H. influenzae* serotype b; Non-typeable = non-encapsulated H. influenzae; other encapsulated Hi = *H. influenzae* serotypes a, c, d, e, and f.

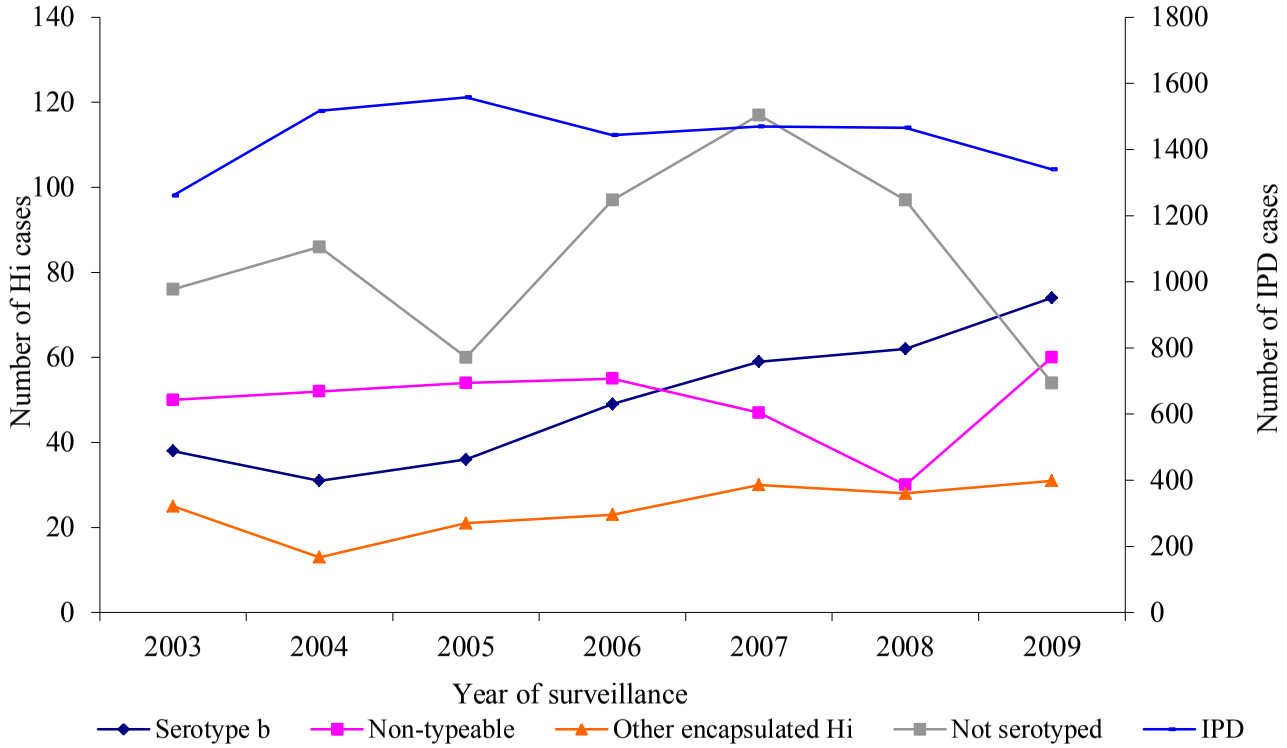


Figure 11: Number of children <5 years with confirmed invasive *Haemophilus influenzae* serotype b disease (n=349) by vaccination history and year, South Africa, 2003-2009

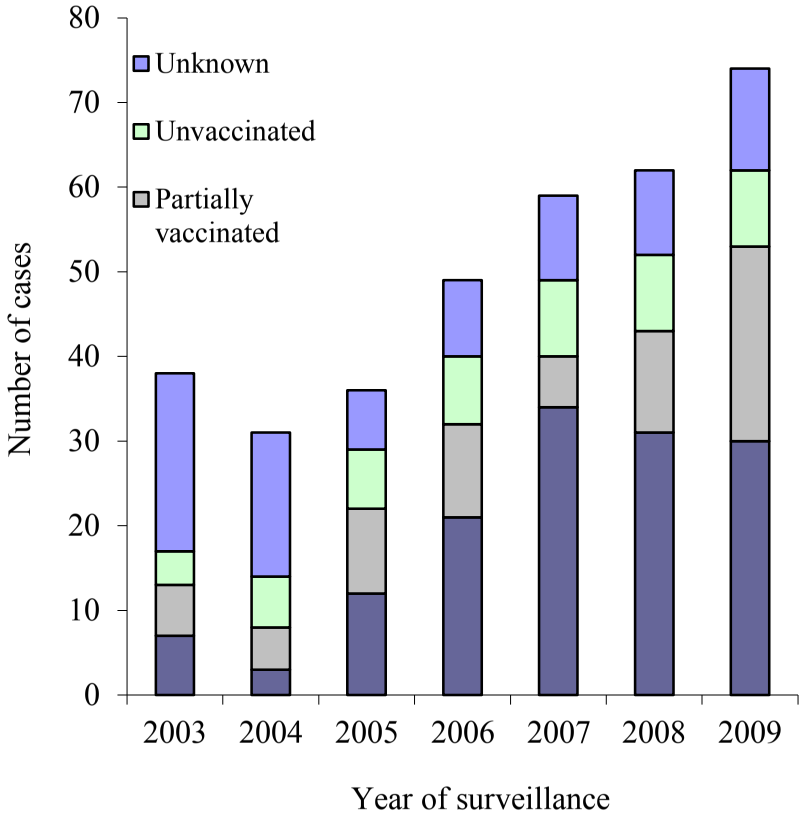


Figure 12: Number of children with confirmed invasive *Haemophilus influenzae* serotype b disease, reported by age and known vaccination status (n=263), South Africa, 2003-2009

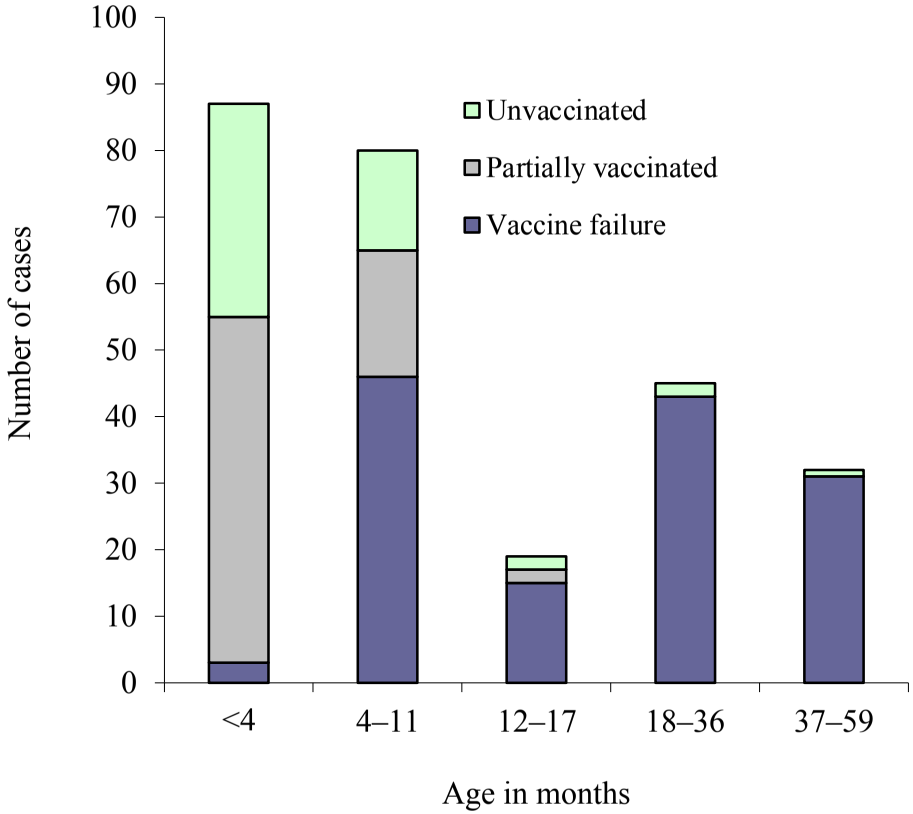
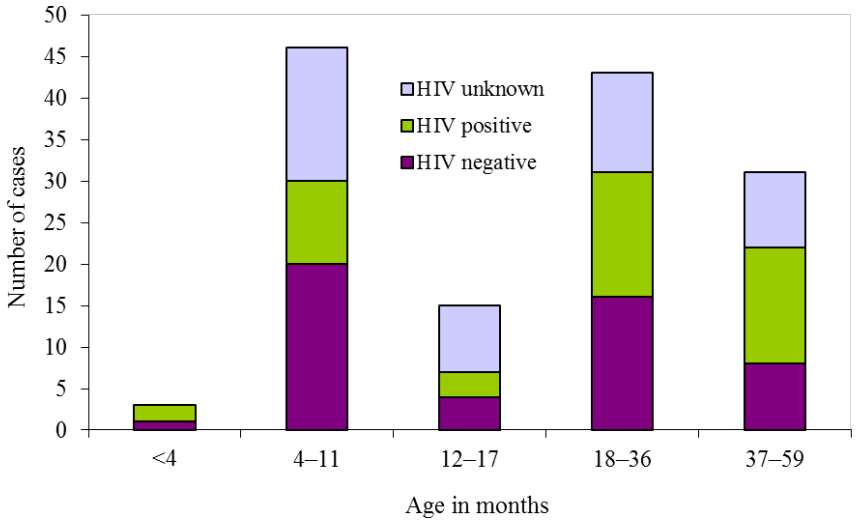


Figure 13: Number of *Haemophilus influenzae* serotype b vaccine failures (n=138) by age and HIV infection, South Africa, 2003-2009



The Gambia- (3p+0) Routine conjugate Hib vaccination with a 3-dose primary series was introduced into The Gambia in 1997, the first introduction in Africa, with virtual elimination of Hib disease by 2002. Sporadic cases were observed thereafter through incidental detection in hospitals but formal surveillance in The Western Region from 2007-2010, extending 14 years after introduction, confirmed a low incidence of invasive disease (Hib meningitis <3 per 100,000 under 5), a low rate of carriage (0.9% in 1 year olds), high community seroprotection (99.3% of 2-5 year olds with protective antibody levels), and high

vaccine coverage (92% having 3 doses at 1 yo). These observations were not suggestive that a booster dose was required. In 2011 and 2012 formal clinical and microbiological surveillance in Eastern Gambia associated with PCV introduction (Aug 2009) detected over 20 cases, having detected one in the previous 2 years; this was accompanied by incidentally detected hospital cases in the Western Region where formal surveillance had stopped in 2010. Around half had had 2 or more doses of vaccine and half were under 1 year of age. Local investigators suggest that this resurgence raises the question of the need for a booster dose, and reinforces the need for continuing high quality surveillance of Hib disease

Table 13. Overview of key milestones in the Hib immunization programme of The Gambia

Time period	Vaccination coverage	Surveillance system	Hib disease incidence	Age distribution of cases	Carriage
Before 1997	Pre-routine vaccination	Western Region (formal clinical/microbiological surveillance)	meningitis 70 per 100,000 children <5 years (1990)	80% <12 months of age	12% (1-2 year olds)
2002, 5 years after introduction,	2000 for 1-2 yo: 3 doses 68%, 2 doses 84%, 1 dose 94%; Median age at 1st, 2nd, 3rd doses (2000): 3.4m, 6.5m, 8m	Western Region (formal clinical/microbiological surveillance)	meningitis 0 per 100,000 children <5 years		0.25% (1-2 year olds)
2006		no formal surveillance		Western Region, hospital cases detected incidentally	Cases: N=5 ; median age 15 months
2007-2010	1-2 yo - 3 doses 92% Median age at 1st, 2nd, 3rd doses: 2.6m, 4.3m, 6.0m	Western Region formal clinical/microbiological surveillance (funded by Hib Initiative)	meningitis 0.8-2.3 per 100,000 children <5 years (all invasive Hib 0.8-3.7/100k)		0.9% (1-2 year olds)
2009 Introduction pentavalent DPT-HepB-Hib vaccine					
2011-2012 Provisional data		Eastern Gambia formal clinical/microbiological surveillance, Western Region (no formal surveillance)	>20 culture +ves cases in Eastern Gambia with latex agglutination typing (only 1 case 2009/10,), half with 2+ doses a handful of incidentally detected cases Western Gambia	half <1 yo;	

South America – (3p+1 or 3p+0)

To evaluate potential impact of use of a booster dose, we used surveillance data to compare trends in Hib meningitis incidence among children <5 years in four countries, two of which had a 3p+0 schedule (Chile and Colombia) and two of which had a 3p+1 schedule (Argentina and Uruguay). Surveys of nasopharyngeal carriage were conducted among children in Argentina and Colombia to compare prevalence of Hib colonization several years after introduction of Hib conjugate vaccines (Garcia S et al 2012[6]). Following Hib vaccine introduction, rates of Hib meningitis declined and were sustained at low levels through the study period in all four countries. Incidence of Hib meningitis during the post-vaccine study period varied from 2.3 to 1.2 cases per 100,000 among children <1 year and 0.5 to 0 cases per 100,000 among 1–4 year olds. Surveillance data from all four countries demonstrated that Hib meningitis cases continued to occur, albeit at low levels, 6–10 years following vaccine introduction. Contrasting Hib meningitis incidence during the post-vaccine period with the prevaccine base-line period, relative rates were similar in countries with and without booster doses.

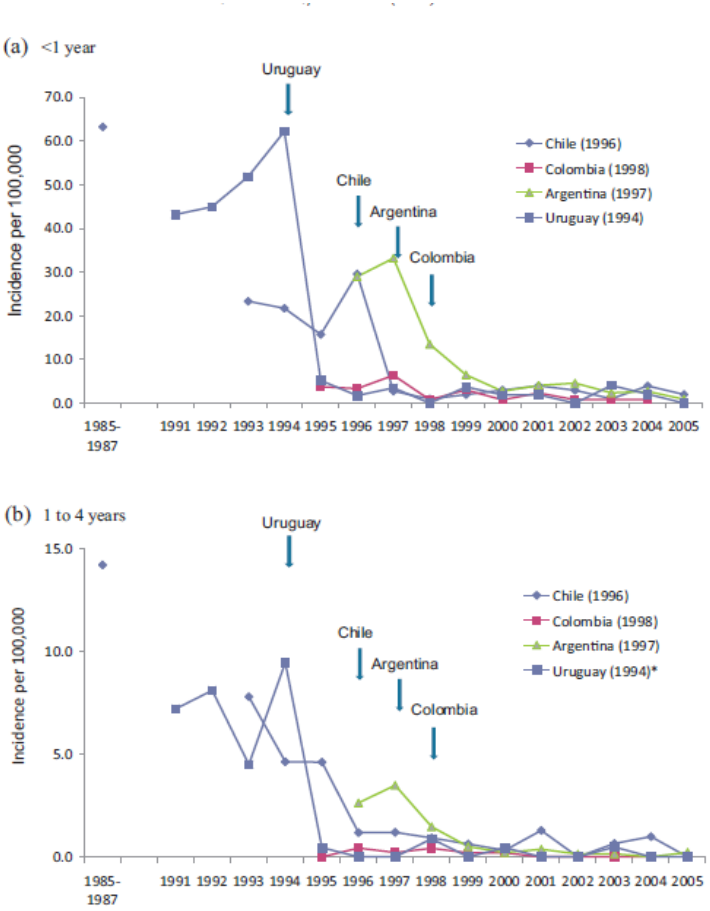


Fig. 1. Trends in Hib meningitis incidence in 4 South American countries before and after introduction of Hib vaccines in national immunization programs: (a) <1 year; (b) 1–4 years of age. *In 2005 the age groups used for reporting changed; from 2005 to 2009 the cases among children aged 48–59 are included in the 1–4-year-old group.

United States (3p+1)

In the United States prior to Hib vaccine introduction, the annual incidence of H. influenzae meningitis was approximately 50-60/100,000, 25-35/100,000 and 5/100,000 for children <1 year of age, 1 year of age and 2-4 years of age, respectively.(Adams, 1993[68]) Hib conjugate vaccine was introduced as a single dose at 18 months of age in 1987. Following vaccine introduction, there were declines in the incidence of Hib disease in vaccinated age groups. Incidence also declined in infants who were too young to be vaccinated, reflecting an indirect impact of the vaccine. (Adams, 1993[68]) Infant vaccination was introduced in 1990. In the United States, a number of different vaccines and combinations and schedules have been used. However, since 1990, the basic approach to scheduling has been to use a 3p+1 schedule. Disease incidence has remained low. Of note, there was a resurgence of invasive Hib disease among Alaska Native children reported in 1996 associated with a change in Hib conjugate vaccine. Prior to vaccine introduction, Alaska Native children had among the highest rates of invasive Hib disease reported worldwide. Use of PRP-OMP vaccine, which is more immunogenic after a single dose than other Hib conjugate vaccines, resulted in a large decline in disease incidence. However, disease incidence increased after a switch to PRP-CRM197 vaccine, which is less immunogenic until the third dose of the primary series. The resurgence of Hib disease in Alaska Native children was associated with ongoing circulation of the organism in pre-school and school aged children, despite several years of routine vaccination. (Galil, 1999[56]; Singleton, 2000[69]) Disease incidence declined following reinstitution of a PRP-OMP based schedule.

Italy- (2p+1)

In Italy, Hib vaccination using a 2p+1 schedule (at 3, 5, and 11 months of age) was introduced in 1999 and coverage by 24 months of age was estimated to be 95.6% in 2009. An "Active Surveillance of Invasive H. influenzae Disease" was carried out in a sample of Italian regions during the period 1997–2002 and extended nationally following the rapid decline in Hib incidence. From 2003 to 2006, data on cases of invasive H. influenzae disease were detected through the National Surveillance Network of Bacterial Meningitis but, since January 2007, they have been collected as a part of the National Surveillance of Invasive Bacterial Disease. Both the latter surveillances used a passive reporting system. Ten years after Hib vaccination was introduced, the annual incidence of invasive H. influenzae infection was 0.06/100,000 in 2007, 0.08/100,000 in 2008 and 0.09/100,000 in 2009 in all age groups. A slight increase in disease incidence has been observed in adults ⩾65 years since 2007 (Giufre M et al 2011)[70].

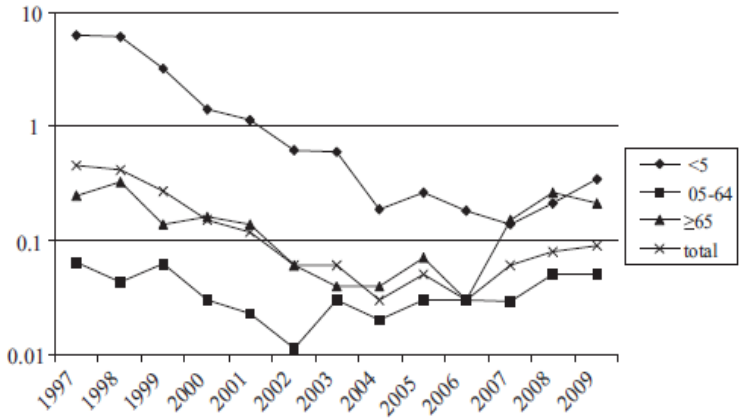


Fig. 1. Age-specific incidence (cases per 100,000 inhabitants, semi-logarithmic scale) for invasive disease caused by *Haemophilus influenzae* in Italy, during the period 1997–2009.

United Kingdom – (3p+0 the 3p+1)[7]

Prior to the introduction of routine vaccination, the incidence of invasive Hib disease in children aged <5 years in the UK was estimated to be 21–44/100,000. In October 1992, the UK introduced the Hib conjugate vaccine into the national immunisation programme. A Hib-tetanus toxoid conjugate vaccine (Hib-PRP-T) was offered to infants at 2, 3 and 4 months of age alongside DTwP. At the same time, a catch-up campaign lasting 12 months took place, where three dose of Hib-PRP-T vaccine were offered to infants and a single dose of Hib CRM197 conjugate vaccine (HbOC) was given to those aged 13 months to 4 years. Unlike many other industrialised countries, a Hib booster in the second year of life was not recommended. Coverage of over 90% was rapidly achieved in infants and coverage in the catch up campaign was above 85% in most cohorts. This Hib vaccination programme led to a rapid decline in the incidence of invasive Hib disease within two years, initially in the age group targeted for vaccination, but soon followed by a reduction in all other age groups through indirect (herd) protection. In 1996, a Hib-OC conjugate vaccine was licensed to be mixed with DTwP but, in 1997, a combination vaccine containing Hib-PRP-T with DTwP was introduced.

By 1998, invasive Hib incidence fell to its lowest level: 0.63/100,000 in children aged <5 years. From 1999, however, enhanced national surveillance in England and Wales observed an increase in the number of reported invasive Hib disease cases in all age groups – peaking at 120 cases in children aged <5 years in 2002. The reasons for this increase included a decline in indirect protection offered by catch-up campaign that was offered to children up to 4 years of age when the vaccine was introduced in 1992, a greater than expected decline in vaccine effectiveness among children who were only vaccinated in infancy and a temporary change in the Hib vaccine combination offered to young infants. During 2000-2001, a shortage of combined vaccines containing whole cell pertussis meant that less than half the infants received DTP-Hib combination vaccines containing acellular pertussis (aP). This vaccine was known to have reduced Hib immunogenicity, but this was not felt to be clinically significant.

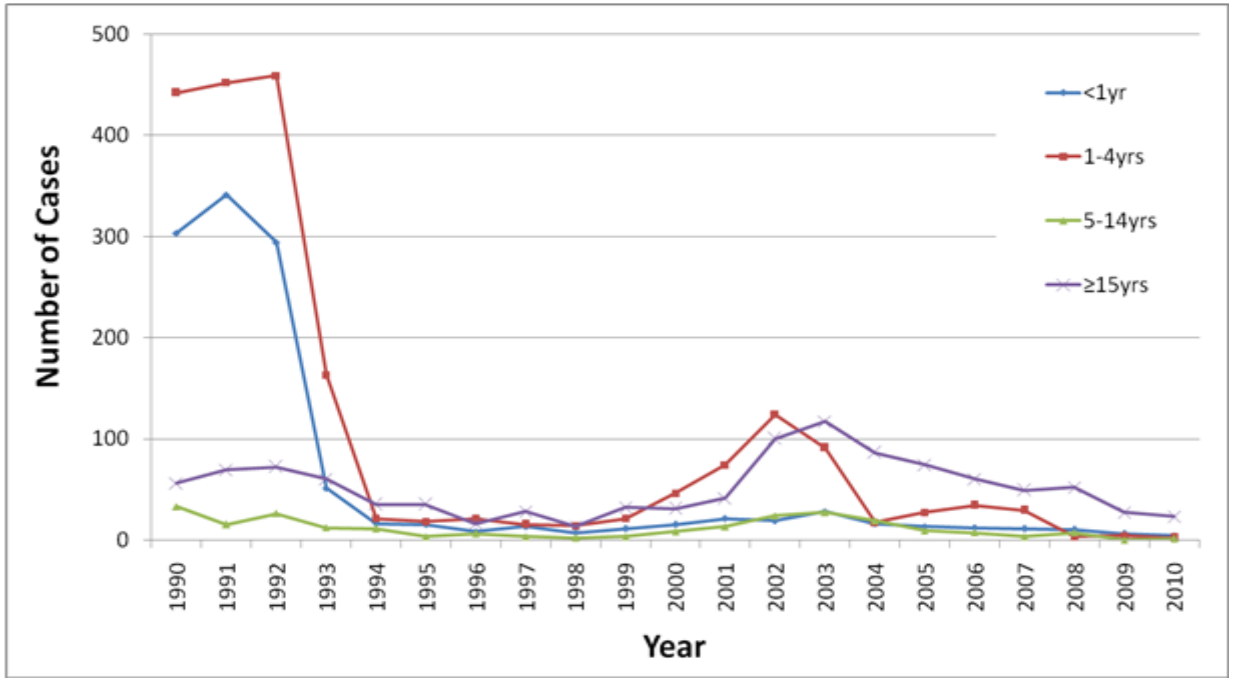
As a result of the increase, a number of control measures were taken. The implicated DTaP vaccine was withdrawn and DTwP vaccines were resumed. In addition, a Hib vaccination booster campaign using PRP-T was conducted between May and September 2003, offering one dose of vaccine to all children who were aged between 6 months and 4 years on 1 April 2003 and to those children who reached 6 months of age during the campaign. In September 2004, the infant combination vaccine was changed to one containing DTaP, inactivated polio and Hib. This vaccine has a different acellular pertussis component to the one previously used and was shown to have a satisfactory immune response against Hib. Together, these measures resulted in a rapid reduction in cases, initially in toddlers, but soon followed by a reduction in the other age groups.

[7] Summary courtesy of Drs M Ramsay and S Ladhani, Immunisation, Hepatitis and Blood Safety Department, Health Protection Agency , UK

From September 2006 onwards, a routine 12-month Hib booster administered as a Hib-MenC-PRP-T was introduced. After the 2003 booster campaign, however, an increase in Hib cases among 1–3-year-old children was noted (from 13 cases in 2004 to 32 cases in 2006), children too young to be vaccinated in the 2003 booster campaign and too old for the routine 12-month booster in September 2006. This group of approximately 1.5 million children, was subsequently targeted in a separate programme when a dose of Hib was given at pre-school age (3 years 4 months to 5 years of age) between September 2007 and 3 March 2009,

Currently, control of Hib in the UK is the best that has ever been achieved. In 2010, there were only 30 invasive Hib disease cases across all age groups, with only 6 cases in children under 5 years. Hib cases in adults were also at their lowest levels since 1998 (n=23).

Figure 16. Number of cases of invasive Hib disease in different age-groups diagnosed in England and Wales (1990-2010).
Source: Health Protection Agency Centre for Infection



Australia (3p+1 and 2p+1)

Australia introduced Hib conjugate vaccine in 1993. Currently, an acellular pertussis PRP-T combination vaccine is used with a schedule of 2, 4, 6 and 12 months for non-indigenous children. Indigenous children receive PRP-OMP vaccine at 2, 4, and 12 months of age. Horby et al. reported national surveillance data showing that invasive Hib disease incidence fell sharply following vaccine introduction and remained low (<2/100,000 children less than 5) from mid-1996 through mid-2000.(Horby, 2003[71]) Australia also participated in the EU-IBIS surveillance system from 1999-2006. Between these years, reported Hib disease incidence in children less than 5 years of age remained low, ranging from 0.5-1.6 cases per 100,000. Of note, incidence rates in indigenous populations living in Northern Australia who had very high levels of disease in the pre-vaccine era have fallen considerably, but remain higher than in non-indigenous persons (Menzies, 2008[72]).

Effect of age at administration of first dose of Hib vaccine on selected outcomes

Limited available evidence suggest that schedules starting earlier (i.e. at 4-6 weeks of age) are comparable to schedules starting later (i.e. > 2 months of age).Trade-offs may exist between initiating vaccination earlier versus later in infancy in settings where Hib disease epidemiology data suggest that a large proportion of cases occur before 8 weeks of age. Another consideration in the choice of the age at first dose is the recognition of delays with the actual age at vaccination. There is no evidence to firmly determine the age limit for initiating vaccination but three years seems appropriate as it is in line with the evidence on the age distribution of Hib disease cases in the pre-vaccine era.

Immunization schedules starting later (i.e. > 2 months of age) vs. immunization schedules starting earlier (i.e. at 4-6 weeks of age)

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

A study which reported only GMC (Gambia- Mulholland 1994[19]) examined PRP-T and compared doses at 2 and 4 months of age to doses at 1 and 3 months of age. GMC was measured 1 month after the last dose of vaccine. The GMC was 0.41µg/ml (95%CI 0.28-0.61) in the 2 and 4 month group and 0.26µg/ml (95%CI 0.19-0.35) in the 1 and 3 month group. There a few additional studies assessing the immunogenicity of neonatal doses of Hib vaccines.

In a Finnish[73] (Kurikka 1995) study Hib capsular polysaccharide (PS)-tetanus toxoid conjugate vaccine (PRP-T) was given to 120 neonates at 2 days of age, followed by PRP-T or the Hib PS vaccine at 4 months and a PRP-T booster at 14 months. Their anti-Hib PS concentrations were compared with those in children receiving PRP-T at 2 and 4 months or at 4 months. TS: The geometric mean concentration of anti-Hib PS at the age of 2 days was 0.34 micrograms/mL and at 4 months was 0.12 µg/mL. This was significantly more than the concentration in unimmunized infants at this age and 3.5 times more than expected, taking into account the natural decay of transplacentally acquired antibodies. Such a response was not seen in infants with a high (greater than 3.0 micrograms/mL) neonatal antibody concentration. The PRP-T vaccine given at 4 months elicited an antibody response in all infants and Hib PS in 62%, indicating immunologic priming. At 14 months, a higher percentage of the infants who had received PRP-T at 2 days and 4 months than of those who had received PRP-T at 4 months only had anti-Hib PS concentrations greater than 0.15 µg/mL. All infants responded well to the booster at 14 months. There was no evidence of immunologic tolerance.

A study in Papua New Guinea evaluated the safety and immunogenicity of a lyophilized and a liquid form of Hib polysaccharide-tetanus toxoid conjugate vaccines (PRP-T) given in the same syringe as diphtheria-tetanus-pertussis (DTP) vaccine (Lehmannmexy D, 2001[74]). As part 1 of the study 209 children were randomized to receive at ages 1, 2 and 3 months either DTP alone or a liquid formulation of DTP/PRP-T or lyophilized PRP-T dissolved in DTP suspension. A further 75 children were given the liquid DTP/PRP-T formulation at ages 2, 3 and 4 months as part 2 of the study. 54 children aged 15-18 months were given a booster of the same preparation of PRP-T/DTP as they had received during Part 1. Blood for antibody assays was collected at enrolment, before (Part 1 only) and one month after the third dose, then just before and 3 weeks after the booster dose. Results. Follow-up to age of 12 months showed that PRP-T was safe with no evidence of impaired response to individual vaccine components when combined with DTP.

Geometric mean titres (GMTs) of anti-PRP antibody before vaccination (n=64, mean age 41 days), after 2 doses (mean age 99 days) and after 3 doses (mean age 132 days) of the lyophilized formulation were 0.21, 1.48 and 5.04 µg/ml, respectively, with 58% and 89% having anti-PRP antibody titres ⩾1.0 µg/ml after 2 and 3 doses, respectively. Anti-PRP antibody responses to the liquid Hib vaccine formulation were lower (GMT post-dose 3 = 0.48 µg/ml) than to the lyophilized formulation, but better responses were elicited from older children (Part 2; GMT post-dose 3 = 0.78 µg/ml, with 79% ⩾0.15 µg/ml). Both PRP-T preparations elicited excellent booster responses suggesting that children are likely to be protected if exposed to Hib infection. The liquid DTP/PRP-T formulation showed a lower immunogenicity than in earlier studies with this vaccine, which might have been due to exposure to low temperature during shipment or the younger age at immunization. Serum antibody responses to three Hib capsular polysaccharide protein conjugate vaccines (PRP-OMP HbOC and PRP-T) were evaluated in 102 Filipino infants. Vaccination was carried out at 6, 10 and 14 weeks of age based on the national Expanded Programme on Immunization (EPI) schedule together with diphtheria-tetanus-pertussis, hepatitis B and oral poliomyelitis vaccines. Sera were collected at 6 weeks and I month after each vaccination. Anti-Hib polysaccharide antibody concentrations were determined by Farrtype radioimmunoassay (RIA) and

enzymeimmunoassay (EIA). Following the first dose, the geometric mean concentrations (, pgml-') for PRP-OMP HbOC and PRP-T were 0.69, 0.27 and 0.38, respectively after two doses, there was a significant response (PcO.05) to PRP-OMP and PRP-T (0.89 and 1.47) but not for HbOC (0.37). Differences in the GMC after the primary series were significant (pair-wise PcO.05): GMC was highest for PRP-T (4.0) followed by HbOC (1.6) and PRP-OMP (1.1). All three Hib vaccines were immunogenic when given in the local EPI schedule in Filipino infants although significant differences in the kinetics and magnitude of antibody responses were noted. The anti-Hib antibody concentrations determined by RIA and EL4 were also compared in order to validate the latter for use in laboratories where it is feasible. There was a good correlation (r' = 76%; P = 0.0001) in the Hib antibody titres obtained by both assays.

There is limited evidence from observational studies. Six cohort studies with intended age at initiation ranging from 6 weeks to 2-5 months provided VE estimates. Estimated VE may increase slightly with intended age at initiation. In Denmark, the intended age at initiation of vaccination 3 or 5 months of age, as opposed to 2 months of age in the other cohort studies which reported the intended schedule[33 75] . In the Danish study 3-dose vs. 0 dose VE for PRP-T against Hib meningitis was 99.3% (94.87–99.90%)[33]. In the South African study, in which age at initiation of vaccination was intended at 6 wks., 3- dose vs. 0 dose VE against invasive Hib was estimated to be 83.2 % (60.3–92.9%); there was a high prevalence of HIV infection in the children in this study and effectiveness of 3 doses vs. none was estimated as 96.5% (74.4–99.5%) in children who were not HIV-infected[39]. The 3-dose (vs. 0 dose) VEs against invasive Hib from the Chilean, English and German studies, which all had intended age at initiation of 2 months, were slightly higher than the overall estimate from the South African study (ranging from 90.4 to 97.6%)[20 22 23].

From long term impact studies, we found that there is limited variability in first dose timing in currently used schedules. Developing countries recommend the first dose at 6 or 8 weeks. Industrialized countries recommend the first dose mainly at 8 weeks with a few at 12 weeks. Hib continues to cause disease in all countries reviewed, with incidence highest in the first year of life. This suggests ongoing risk in young infants. No clear evidence of the superiority of either schedule.

Effect of the interval between doses on selected outcomes

Effect of the interval between primary doses of Hib vaccine on selected outcomes

Does using Hib conjugate vaccine schedule with a longer interval between primary doses (e.g. 8 weeks or more) have a greater effect on disease or immunological outcomes than a schedule with a shorter interval (i.e. 4 weeks) between doses?	
Conclusion	**Limited data available showed no consistent or clinically relevant differences between shorter (e.g. 4 weeks) and longer (e.g. ≥ 8 weeks) intervals between primary doses of Hib vaccines.**
Summary statement	In most reported schedules, 3 primary doses were separated by either one month (e.g. 6, 10, 14 weeks and 2, 3, 4 months) or two months (e.g. 2, 4, 6 months) whereas 2-dose schedules essentially included 8-weeks intervals. Available data on proportion achieving a set threshold (i.e. ≥ 0.15mcg/ml and ≥1.0 mcg/ml) show no significant difference between short interval [e.g. 4 weeks] vs. longer interval [e.g. ≥ 8 weeks] in the primary series on immunogenicity outcome for different types of Hib conjugates. There was no clear difference in effectiveness against Hib meningitis, invasive Hib disease or radiologically confirmed pneumonia between observational studies using different dosing intervals or different Hib conjugates. Two months intervals between doses in the primary schedule were not shown to be consistently more immunogenic than one month interval in the observational studies. From long term impact studies both a 4 week and 8 week interval have been used in a number of countries with good sustained long term impact.
Quality of evidence	**We are moderately confident on the estimate of the effect.** There were no RCTs or observational studies that compared various intervals and, types of vaccine conjugate and that reported effect on various disease outcomes.
Caution	Not enough evidence on schedules using 2p+1 at short intervals (e.g. 4 weeks)

Immunization schedules with short (i.e. 4 weeks) versus longer (> 8 weeks) intervals between primary doses

There were no RCTs that compared these schedules and reported invasive disease, pneumonia or carriage data.

The trial which compared two-month intervals to one-month intervals using PRP-OMP reported GMC results only and could not be included in seropositivity graphs. This study used alternation for assignment of interventions and was therefore quasi-randomized. The mean age at first vaccination was unintentionally older in the two-month-interval group than in the one-month-interval group (4.1 months and 3.2 months respectively). Age adjusted

GMCs one month after the second vaccinations were 3.95µg/ml (95%CI 2.63-5.92) in the two-month-interval group and 2.32µg/ml (95%CI 1.48-3.64) in the one-month-interval group. The reviewers concluded that it has methodological problems (e.g. randomization was not effective) which should be mentioned noted.

In most reported case control studies, doses were separated by either one month (6, 10, 14 weeks and 2, 3, 4 months) or two months (2, 4, 6 months and 2, 4, 12 months). There was no clear difference in effectiveness against Hib meningitis, invasive Hib disease or radiologically confirmed pneumonia between studies using different intended dosing intervals. A study carried out in Colombia[30] compared the time between doses of Hib vaccine in pneumonia cases and controls17. The median delay between both doses 1 and 2 and doses 2 and 3 was slightly greater for cases than for controls, but the study did not find evidence against these being chance findings (p = 0.08 and p = 0.18 for doses 1 and 2 and doses 2 and 3, respectively). An interval of >90 days between doses 1 and 2 was associated with an increased risk of pneumonia (OR = 2.1, 95% CI 1.1 – 3.5, adjusted for "factors related to pneumonia. There are limited data from cohort studies to inform the optimal interval between doses. A Chilean[20] had a schedule with 2-month intervals: the VE for 3 doses vs. 0 doses, quadrivalent vaccine, was 91.7% (64.8 - 100%). A German [22 23], English and South African[64] studies included schedules that have 1-month intervals and report VE for 3 doses vs. 0 doses which ranges from 83.2% and 97.6 %9 50 10 . Since the VE estimate for a 2-month interval is nested within the range of VE estimates for a 1-month schedule, there is no strong evidence from cohort studies for a difference in VE according to dosing interval.

From long term impact studies, both 4 week and 8 week intervals have been used in a number of countries with good sustained long term impact.

Effect of interval between last primary dose and booster dose on selected disease outcomes

We found no evidence of significant differences in effectiveness with various intervals between the primary doses and the booster dose

Immunization schedules with long (> 8 weeks) vs. short (i.e. 4 weeks) intervals between primary doses

No immunological data from RCTs: Minimal difference seen between the schedules. Schedules with a booster dose given in the second year of life have shown good sustained long term impact. Schedules with the booster dose ranging from 11 months to 18 months of age have all been successful. No clear evidence of the superiority of booster dose timing between 11 months and 18 months of age[5].

Effect of combination vaccines

The available data do not suggested clinically relevant decreases in Hib efficacy or interference with other antigens with the use of combination vaccines compared with monovalent vaccines. There is some evidence of lower immunogenicity against Hib with the use of aP vaccines compared to wP vaccines, though little evidence of interference with other antigens in either combination. The clinical relevance of lower immunogenicity is unclear, as is the necessity of a booster dose with the use of aP containing vaccines.

Combination vs. monovalent vaccines

A recent COCHRANE meta-analysis[8] including data from twenty RCT's (N=5874 children for immunogenicity analysis, N=5232 for reactogenicity analysis) concluded that the overall level of evidence comparing combination and monovalent vaccines was low, and could not conclude that the immune response to combination vaccines was different from or equivalent to monovalent vaccines. No studies presented data on clinical outcomes. Antibody responses to diphtheria, pertussis, polio, and hepatitis B were not significantly different. Antibody response to Hib and tetanus was lower in children receiving combination vaccines. However, when the results were analyzed distinguishing aP and wP combination vaccines, the differences in immunogenicity were seen only in the aP vaccines; wP vaccines had equivalent of better immune responses, although no differences were statistically significant. There was no significant difference in the number of serious adverse events. A small but statistically significant increase in pain and redness at the injection site was noted for combination vaccines.

A review found in the textbook Vaccine (Plotkin, 6th ed.[76]) concluded that geometric mean titers for Hib/PRP have been seen to be lower in combination vaccines; however, there is no evidence that these differences are clinically meaningful as most (>95%) of children achieve antibody levels >1.0 ug/ml even with combination vaccines and observational and surveillance data do not support the hypothesis of lower effectiveness of combination vaccines.

A review of 41 studies[77] evaluating proportion of vaccine recipients achieving seroprotection, as opposed to GMT levels, found no consistent differences. 13 studies reported a significantly significant difference in seroprotection for one or more antigens; 8 found decreased seroprotection with combination vaccines while 5 found increased seroprotection with combination vaccines.

Acellular vs. whole cell pertussis component

A Cochrane meta-analysis[8] found significantly lower Hib seroprotection in recipients of aP containing vaccines, but not in wP vaccines. Studies have consistently documented this reduced immune response in terms of GMT following the primary series, however, following a booster dose all combination vaccines are highly immunogenic[76]. In general, aP vaccines do not show additional interference with other antigens, although the meta-analysis did note a decrease in seroprotection against tetanus with aP.

Most developed countries use aP vaccines and have effectively controlled Hib disease. The use of a booster dose in most of these countries may serve to augment lower immunogenicity such that the vaccine remains effective.

Hib vaccines and herd immunity

Available data suggest a very strong indirect effect with Hib vaccine, even at medium to low levels of coverage. Hib conjugate vaccines also have been shown to reduce carriage in vaccinated children. Widespread use of conjugate vaccines has led to decreases in disease incidence that were greater than rates of vaccination coverage and to decreases in Hib disease in unvaccinated age groups.

The impact of herd effect can be seen by the tenfold reduction in Hib disease rates in the United Kingdom in unvaccinated children <1 year of age in 1998 compared with rates in similarly aged children before vaccination began (Heath et al., 2000b[78]). Another reflection of herd effect is the impact of childhood Hib vaccination on adult Hib disease. A review of adult cases of Hib disease in five English regions between 1990 and 1995 showed a halving of case numbers between the first three-year period and the last two-year period (Sarangi et al., 2000[79]). Ongoing surveillance for Hib disease by Moulton and colleagues (Moulton et al., 2000[80]) demonstrated that immunization of 40% of Navajo Indian infants (USA) between the years 1988 to 1992 resulted in a 75% reduction of Hib disease among infants that were living in the same community. This demonstrates that countries that implement Hib immunization programmes may receive greater benefits at the community level than those hitherto seen due to the direct protection conferred on the individual through vaccination.

In Canada after several Hib vaccines were introduced within the last two decades. In Ontario, Canada authors reported that the incidence of invasive Hib disease in children, reflected in the submission of invasive Hib isolates to Ontario's Public Health Laboratory-Toronto, has fallen sharply since the introduction of the Hib conjugate vaccine (Adam HJ 2010[81]) . Furthermore, they concluded that herd effects were acting on all age groups in the population; using data to document a reduction in the risk of invasive Hib infection in older (unvaccinated) adults following vaccine introduction. Authors argued that this is a result of a reduced force of infection due to less Hib colonization among children.

A systematic literature search for studies which included impact data (pre- and post-introduction measure(s) of disease), vaccine coverage, and sufficient methodology detail to judge study quality was conducted (Walker N et al 2012-personal communication[82]). Direct effect of vaccine was calculated as efficacy x coverage; indirect effect was calculated as study observed effect - calculated direct effect. Eight out of 10 included studies showed higher observed impact on Hib disease than would be expected given coverage levels of the vaccine, suggesting indirect effects (herd immunity). Excluding the studies with a negative effect, the calculated indirect effects ranged from 7% to 63%, representing 13% to 76% of the total vaccine impact in some settings. The lowest level of vaccine coverage was in Brazil in 1999, at 8%. At this coverage level a 26% reduction in Hib meningitis was observed. Most studies which showed a negative indirect effect (observed impact was lower than would be expected at the given coverage levels) were conducted in the first year of vaccine introduction and reported maximum coverage levels for that year, as opposed to median-year coverage. This likely caused an over-estimation of the true coverage for most of that year, and thus an overestimation of the expected direct effect.

Limitations of the evidence

Number of doses of Hib vaccine: Clinical and carriage data: no direct RCTs with comparisons within individual trials between these 2 schedules. Studies randomizing to 2p schedules are PRP-OMP, and those to 3p are PRP-T and PRP-HbOC. Limited control for confounding (particularly in cohort studies). There is no direct comparison of the two schedules from impact studies. Few countries use a 2p+1 schedule. Comparisons must be made between countries which may result in confounding. Comparisons are difficult because there are no long term data from developing countries using a 2p+1 schedule and few developing countries are using a booster dose at all. Also, no industrialized countries reviewed are currently using a 3p schedule. Likely long term effectiveness must be inferred from immunogenicity and efficacy data. Reasons for increases in incidence in countries using 3p are not known. There are no impact data on use of a booster dose prior to 11 months of age.

Age at first dose: Clinical and carriage data: no data from RCTs, immunological data only: Only PRP-T and PRP-OMP in comparisons of proportion above a set threshold. Few data about birth dose and conclusions about birth dose differ depending on control group used (e.g. Lieberman 1995[53], HbOC).Observational Studies mainly reported intended schedules rather than actual age at vaccination. Limited range in intended age at first dose (6 weeks, 2 months or 2-5 months). The one study with intended age at initiation of 6 weeks and relatively low three-dose VE (83%) was carried out in a population with a high prevalence of HIV infection. Regarding impact studies, there is limited variability in first dose timing in currently used schedules. Developing countries recommend the first dose at 6 or 8 weeks. Industrialized countries recommend the first dose mainly at 8 weeks with a few at 12 weeks. Hib continues to cause disease in all countries reviewed, with incidence highest in the first year of life. This suggests ongoing risk in young infants. No clear evidence of the superiority of either schedule.

Interval between doses

Clinical and carriage data from RCTs: no data. Immunological data: Only proportion above a set threshold data from PRP-T studies. One study (Lenoir 1987[83], PRP-OMP) showed 2m interval better but 2m group vaccinated later. Limited evidence from observational studies. Comparison of VE estimates between studies. One case-control study compared intervals between doses in cases and controls. No evidence to favour any particular interval based on intended schedules. The one case-control which provided actual dosing intervals found no evidence of a different in the median interval between doses in cases and controls, but found an increased risk of pneumonia with a longer interval between doses (OR 2.1 if >90 days interval between doses 1 and 2 in a three-dose schedule). Both 4 week and 8 week intervals have been used with good sustained long term impact. There are no direct comparisons of different age at first dose using long term impact as an outcome. Data on the age and vaccine receipt in cases that persist in countries using vaccine for >5 years has not been systematically assessed.

Interval between last primary dose and booster dose

Clinical and carriage data from RCTs: no data. Immunological data: Data about PRP-T only. No data are available on earlier use of the booster dose from observational studies. Few countries recommend a booster dose prior to the first birthday. Comparisons must be made between countries which could result in confounding. Schedules with a booster dose given in the second year of life have shown good sustained long term impact. Schedules with the booster dose ranging from 11 months to 18 months of age have all been successful. No clear evidence of the superiority of booster dose timing between 11 months and 18 months of age.

HIV infected children

Limited data to inform policy. There are not studies to assess various immunization schedules

Research needs

Main research priorities include: ongoing surveillance for impact and possible disease resurgence in a small number of high quality surveillance sites; Evaluation of need for booster in HIV infected children; assessment of any impact on disease of switching to aP with various conjugate Hib vaccines, especially PRP-T.

In addition, we list below additional research questions that will help address some of the identified evidence gaps are listed below:

Studies are required to further assess the effect on Hib vaccine efficacy and effectiveness as well as carriage of co-administration with acellular pertussis vaccines (by type of aP), schedules, including assessing the need for a booster. It is important to conduct special studies to further monitor disease impact and evaluate disease surveillance systems. This evidence will help to inform policy as it will provide evidence on any changes on the age distribution of the cases and would provide further evidence on the impact of Hib immunization in various epidemiological settings.

Over the long term, there is a need further assess the impact of various schedules, particularly looking at disease at later ages, ad secondarily serotype replacement. Therefore, there is a need to expand ongoing review of Hib disease surveillance data to assess vaccine impact by schedule. Planning of such studies should bear in mind the opportunities offered by ongoing or planned research including but not limited to carriage studies on Streptococcus pneumonia.

Additional studies are needed (e.g. observational studies) to further assess vaccine effectiveness after various immunization schedules in low and middle income countries including: number of doses with or without booster, early vs. late start schedules, interval between doses and; duration of protection of primary series with and without booster. In addition, supplementary evidence on the immunogenicity of 1st dose at 4 weeks would be informative. In addition, we need to better understand the effect of vaccine coverage and force of infection on the optimal schedule. For example, some argue that in the UK they may have experienced and increase in Hib disease among older people because coverage was too high relative to baseline Hib carriage, leading to a lack of natural boosting. However, maybe in developing countries, a lower coverage with occasional boosting using a 3p+0 schedule will result in acceptable levels of Hib disease control.

Over the short term, it is also important to assess what vaccine coverage is necessary and with what distribution through the population to achieve elimination or near elimination.

Given the limited data on the Hib disease epidemiology and Hib vaccine response among HIV infected individuals studies to assess both elements are critical to define future immunization schedules. In order to determine whether a booster dose should be given to HIV-infected children in developing countries, well-designed studies need to be conducted to better determine the persistence of protective antibody concentrations, response to booster doses of

vaccine as well as timing of and risk factors for vaccine failure in HIV-infected children both treated and naive to antiretroviral drug therapy (ART), though these studies are becoming more difficult to conduct due to prenatal ART programs.

As the data on Hib vaccination in emergency settings are absent, generating such evidence is important. Evaluation of potential role of Hib vaccines should be conducted together with the evaluation of the impact of other health interventions. Lastly, evaluation should consider the effectiveness of different Hib vaccines.

APPENDIX 1 Hib and pneumococcal global and regional mortality estimates by syndrome and HIV infection status

Table 1: Estimated Hib deaths for children under 5 years of age, 2008

	GLOBAL			AFR			AMR			EMR			EUR			SEAR			WPR		
	Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range	
		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound
TOTAL																					
Deaths	203,000	139,000	287,000	98,600	68,200	135,000	1,400	900	2,000	31,600	21,700	45,700	2,600	1,800	3,700	51,700	34,300	74,900	17,300	11,800	25,800
§ Total Deaths in HIV +	4,300	3,000	5,400	4,100	2,800	5,100	<100	<100	<100	<100	<100	<100	<100	<100	<100	100	<100	100	<100	<100	<100
§ Total Deaths in HIV -	199,000	136,000	281,000	94,500	65,400	129,000	1,400	900	1,900	31,600	21,600	45,700	2,600	1,800	3,700	51,600	34,300	74,700	17,300	11,800	25,800
Pneumonia																					
Deaths	161,000	113,000	234,000	72,600	51,100	105,000	1,200	800	1,700	26,500	18,600	38,600	2,000	1,400	2,900	43,300	30,400	63,100	15,300	10,800	22,300
§ Deaths in HIV +	3,200	2,200	3,900	3,000	2,100	3,700	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	100	<100	<100	<100
§ Deaths in HIV -	158,000	111,000	230,000	69,600	49,000	102,000	1,200	800	1,700	26,400	18,600	38,600	2,000	1,400	2,900	43,200	30,300	63,000	15,300	10,700	22,300
Meningitis																					
Deaths	42,100	25,400	52,400	25,900	17,100	29,100	200	<100	200	5,100	3,000	7,100	600	400	800	8,400	3,900	11,700	2,000	1,000	3,500
§ Deaths in HIV +	1,200	700	1,400	1,100	700	1,400	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	40,900	24,700	50,900	24,800	16,300	27,700	200	<100	200	5,100	3,000	7,000	600	400	800	8,300	3,900	11,600	2,000	1,000	3,500
NPNM																					
Deaths	200	100	300	<100	<100	100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV +	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	200	100	300	<100	<100	100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100

Global and regional results are the sum of country results. Global and regional totals have been rounded and reported with three significant digits, and never more specific than hundreds of cases or deaths.

Table 2: Estimated Pneumococcal deaths for children under 5 years of age, 2008

	GLOBAL			AFR			AMR			EMR			EUR			SEAR			WPR		
	Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range		Estimate	Uncertainty Range	
		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound		Lower bound	Upper bound
TOTAL																					
Deaths	541,000	376,000	594,000	309,000	208,000	336,000	13,700	9,400	15,900	68,900	49,700	75,900	6,800	5,000	7,800	108,000	79,400	119,000	33,700	23,900	39,400
§ Total Deaths in HIV +	64,900	44,500	72,800	62,300	42,700	69,900	400	300	400	600	400	600	<100	<100	<100	1,400	1,000	1,400	300	200	300
§ Total Deaths in HIV -	476,000	333,000	529,000	247,000	167,000	274,000	13,400	9,200	15,500	68,300	49,400	75,300	6,800	5,000	7,800	107,000	78,500	118,000	33,400	23,600	39,100
Pneumonia																					
Deaths	485,000	354,000	526,000	273,000	200,000	296,000	10,300	7,300	10,900	64,100	46,900	69,700	5,700	4,100	6,100	101,000	73,600	109,000	31,200	22,900	33,900
§ Deaths in HIV +	57,400	42,000	62,400	55,000	40,300	59,800	300	200	300	500	400	500	<100	<100	<100	1,300	900	1,300	300	200	300
§ Deaths in HIV -	427,000	312,000	464,000	218,000	159,000	237,000	10,000	7,100	10,500	63,600	46,600	69,100	5,700	4,100	6,000	99,400	72,700	108,000	30,900	22,600	33,600
Meningitis																					
Deaths	38,800	12,900	43,600	28,100	6,100	28,300	1,700	1,100	2,600	3,300	1,800	4,100	600	500	900	3,900	2,900	4,900	1,300	500	2,700
§ Deaths in HIV +	5,600	1,800	7,600	5,500	1,700	7,400	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	33,200	12,900	43,600	22,600	6,100	28,300	1,700	1,100	2,600	3,200	1,800	4,200	600	500	900	3,800	2,900	4,900	1,200	500	2,700
NPNM																					
Deaths	17,400	8,400	24,500	8,600	2,600	11,500	1,700	1,000	2,400	1,500	1,000	2,100	600	400	800	3,700	2,900	4,900	1,200	500	2,800
§ Deaths in HIV +	1,900	700	2,800	1,800	600	2,700	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100	<100
§ Deaths in HIV -	15,500	7,700	21,600	6,800	2,000	8,800	1,700	1,000	2,400	1,500	1,000	2,000	600	400	800	3,700	2,800	4,800	1,200	500	2,700

Global and regional results are the sum of country results. Global and regional totals have been rounded and reported with three significant digits, and never more specific than hundreds of cases or deaths.

APPENDIX 2 –OVERVIEW OF STUDIES INCLUDED IN THIS SUMMARY

Table 1. Results of studies reporting on Hib vaccine efficacy and effectiveness on invasive Hib disease Hib-PRPT conjugate): studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
The Gambia (Mulholland 1997)[19]	RCT	-85	85	44	1p vs. 0	1 vs. no doses	PRP-T	Combined[1], wP*
The Gambia (Adegbola 2005)[21]	Case control - community	-58	75	38	1p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Germany (Kalies 2008)[22]	Cohort	19	88	68	1p or 2p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined aP
Germany (Kalies 2004)[23]	Cohort	67	97	90	1p or 2p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined aP
The Gambia (Adegbola 2005)[21]	Case control - community	62	99	94	2p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
The Gambia (Mulholland 1997)[19]	RCT	67	100	95	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined[1], wP*
Chile - cluster randomization (Lagos 1996)[20]	RCT	65	100	92	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined[3], wP*
The Gambia (Adegbola 2005)[21]	Case control - community	62	99	94	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Chile (Lagos 1996)[20]	Cohort	65	100	92	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Germany (Kalies 2008)[23]	Cohort	71	97	90	3p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined, aP
Germany (Kalies 2004)[23]	Cohort	88	99	97	3p vs. 0	2, 3, 4, 11-14 vs. no doses	PRP-T	Combined aP

Table 2. Results of studies reporting on Hib vaccine (PRP-OMP conjugate) efficacy and effectiveness on Hib invasive disease: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
USA (Santosham 1991)[34]	RCT	15	100	100	1p vs. 0	1.5-3 vs. no doses	PRP-OMP	Monovalent, wP*
USA (Harrison 1994)[35]	Case control - community	65	99	96	1p vs. 0	not stated	PRP-OMP	Not stated
USA (Vadheim 1994)[36]	Case control - community	39	100	100	1p vs. 0	2, 4, 12 months	PRP-OMP	Not stated
USA (Santosham 1991)[35]	RCT	53	98	95	2p vs. 0	1.5-3, 2.5-5 vs. no doses	PRP-OMP	Monovalent,, wP*
USA (Vadheim 1994)[36]	Case control - community	68	100	100	2p vs. 0	2, 4, 12 months	PRP-OMP	Not stated
USA (Harrison 1994)[35]	Case control - community	69	100	99	2p vs. 0	not stated	PRP-OMP	Not stated
USA (Harrison 1994)[35]	Case control - community	-57	100	99	3p vs. 0	not stated	PRP-OMP	Not stated

Table 3. Results of studies reporting on Hib vaccine (PRP-HbOC conjugate) efficacy and effectiveness on Hib invasive disease: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
USA (Vadheim 1994)[36]	Case control - community	38	87	71	1p vs. 0	2, 4, 6, 15 months	PRP-HbOC	Not stated
USA (Jafari 1999)[37]	Case control - community	-63	88	56	1p vs. 0	2, 4, 6 vs. no doses	PRP-HbOC	Not stated
USA (Vadheim 1994)[36]	Case control - community	60	97	89	2p vs. 0	2, 4, 6, 15 months	PRP-HbOC	Not stated
USA (Vadheim 1994)[36]	Case control - community	68	99	94	3p vs. 0	2, 4, 6, 15 months	PRP-HbOC	Not stated
USA (Black 1991)[38]	Case control -community	64	100	100	3p vs. 0	2, 4, 6 vs. no doses	PRP-HbOC	wP
South Africa (Madhi 2002)[39]	Cohort	74	100	97	3p vs. 0	6, 10, 14 weeks vs. no doses	PRP-HbOC	wP

Table 4. Results of studies reporting on Hib vaccine (PRPT and PRP-OMP conjugates) efficacy and effectiveness on Hib meningitis: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
USA (Santosham 1991)[34]	RCT	37	100	96	2p vs. 0	1.5 - 3 or 2.5 -5 vs. no doses	PRP-OMP	Monovalent ,wP
The Gambia (Adegbola 2005)[21]	Case control - community	-84	77	35	1p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - community	42	99	87	1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - hospital	19	99	88	1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Dominican Republic (Lee 2008)[25]	Case control -community	-63	88	52	1p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Uganda (Lewis 2008)[26]	Case control - hospital	0	86	63	1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Malawi (Daza 2006)[27]	Case control - hospital	-151	66	11	1p vs0	6, 10, 14 weeks	PRP-T	Combined, wP
The Gambia (Adegbola 2005)[21]	Case control - community	42	99	93	2p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Malawi (Daza 2006)[27]	Case control - hospital	43	98	89	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - community	90	100	99	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - hospital	63	100	95	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Dominican Republic (Lee 2008)[25]	Case control -community	14	100	87	2p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Uganda (Lewis 2008)[26]	Case control - hospital	42	99	93	2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
The Gambia (Adegbola 2005)[21]	Case control - community	47	100	96	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined, wP
Uganda (Lee 2008)[24]	Case control - community	89	100	98	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Uganda Lee 2008)[24]	Case control - hospital	75	100	97	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Dominican Republic (Lee 2008)[25]	Case control -community	33	100	90	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Combined, wP
Uganda (Lewis 2008)[26]	Case control - hospital	48	99	94	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - community	-190	100	65	3p vs. 0	6, 10 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	-8	100	86	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP

Table 5. Results of studies reporting on Hib vaccine (PRP-T and PRP-OMP conjugates) efficacy and effectiveness on radiologically defined pneumonia: studies comparing schedule versus no vaccination

Study (author, year)	Study design	Reported VE			Schedule	Intended schedule	Conjugate	Formulation
		95% CI		VE				
		lower limit	upper limit					
Colombia (de la Hoz 2004)[30]	Case control	2	72	47	1p vs. 0	2, 4, 6 vs. no doses	PRP-T	Monovalent
Bangladesh (Baqui 2007)[28]	Case control - community	-6	43	24	≥1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	13	54	37	≥1p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - community	6	53	34	≥ 2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	20	61	44	≥ 2p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Chile (Lagos 1996)[20]	RCT	1	40	23	2p or 3p vs. 0	2, 4 or 2, 4, 6 vs. no doses	PRP-T	Combined[2], wP*
Colombia (de la Hoz 2004)[30]	Case control	3	76	52	2p vs. 0	2, 4, 6 vs. no doses	PRP-T	Monovalent
Colombia (de la Hoz 2004)[30]	Case control	7	78	55	3p vs. 0	2, 4, 6 vs. no doses	PRP-T	Monovalent
Gambia (Mulholland 1997)[19]	RCT	0.61	0.98	22.4	3p vs. 0	2, 3, 4 vs. no doses	PRP-T	Combined[1], wP*
Bangladesh (Baqui 2007)[28]	Case control - community	-2	54	32	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Bangladesh (Baqui 2007)[28]	Case control - hospital	16	63	44	3p vs. 0	6, 10, 14 weeks	PRP-T	Combined, wP
Brazil (de Andrade 2004)[40]	Case control -	-9	57	31	≥ 2p vs. 0	2, 4, 6 vs. no doses	PRP-HbOC	Monovalent

Table 6. Results of studies reporting proportion above a set threshold (i.e. ≥1.0 ug/ml) at different time points after vaccination with Hib vaccines containing PRP-T conjugate.

Study	Schedule	Time since vaccination	Proportion above set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Niger1[45]	2p + 0	1m after	83	71	92	4.5 m	2.5, 3.5	PRP-T	Combined, wP
Sweden[46]	2p + 0	1m after	44	35	54	6 m	3, 5	PRP-T	Combined, 2 component aP
Chile4[41]	2p + 0	2m after	95	87	99	8m	4, 6	PRP-T	Separate, wP
Chile5[42]	2p + 0	2m after	95	89	98	7m	3, 5	PRP-T	Separate, 2 component aP
Guatemala Kaqchikel[43]	2p + 0	3m after	87	74	95	12 m	7, 9	PRP-T	Separate, wP 2, 4, 6 m
Guatemala Ladino[43]	2p + 0	3m after	100	92	100	12 m	7, 9	PRP-T	Separate, wP 2, 4, 6 m
Netherlands[44]	2p + 0	4m after	81	73	87	11 m	6, 7	PRP-T	Separate, wP
Niger1[45]	2p + 0	5.5 m after	67	51	81	9 m	2.5, 3.5	PRP-T	Combined, wP
Chile4[41]	2p + 0	6 m after	56	44	67	12 m	4, 6	PRP-T	Separate, aP
Sweden[46]	2p + 0	7 m after	21	14	30	12 m	3, 5	PRP-T	Combined, 2 component aP
Belgium[84]	3p + 0	1m after	87	75	95	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
Belgium[84]	3p + 0	1m after	92	80	98	6 m	3, 4, 5	PRP-T	Separate, 2 component aP
Chile5[42]	3p + 0	1m after	96	92	99	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
France[85]	3p + 0	1m after	62	55	69	5 m	2, 3, 4	PRP-T	Combined, 2 component aP
France[85]	3p + 0	1m after	73	66	80	7 m	2, 4, 6	PRP-T	Combined, 2 component aP
Niger1[45]	3p + 0	1m after	89	75	96	4.5 m	1.5, 2.5, 3.5	PRP-T	Combined, wP
Sweden[46]	3p + 0	1m after	67	58	76	7 m	2, 4, 6	PRP-T	Combined, 2 component aP
Turkey[84]	3p + 0	1m after	97	91	100	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
Turkey[84]	3p + 0	1m after	96	89	99	6m	3, 4, 5	PRP-T	Separate, 2 component aP
Chile4[41]	3p + 0	2m after	84	74	92	8 m	2, 4, 6	PRP-T	Separate, wP
Niger1[45]	3p + 0	5.5 m after	76	59	88	9 m	1.5, 2.5, 3.5	PRP-T	Combined, wP
Chile4[41]	3p + 0	6 m after	53	41	65	12 m	2, 4, 6	PRP-T	Separate, wP
Guatemala	3p + 0	6 m after	95	90	98	12 m	2, 4, 6	PRP-T	Combined, wP

Study	Schedule	Time since vaccination	Proportion above set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Kaqchikel[43]									
Guatemala Ladino[43]	3p + 0	6 m after	89	82	93	12 m	2, 4, 6	PRP-T	Combined, wP
Netherlands[44]	3p + 0	6 m after	40	32	48	11 m	3, 4, 5	PRP-T	Separate, wP
Sweden[46]	3p + 0	7 m after	17	10	25	13 m	2, 4, 6	PRP-T	Combined, 2 component aP
Europe[60]	3p + 0	unclear time after	39	32	47	13 m	3p	PRP-T	Combined, 3 component aP
France[85]	3p + 0	9-11 m after	26	19	33	15-17 m	2, 4, 6	PRP-T	Combined, 2 component aP
France[85]	3p + 0	11-13 m after	40	32	48	15-17 m	2, 3, 4	PRP-T	Combined, 2 component aP
China1[86]	3p + 0	13-15 m after	75	69	80	18-20 m	3, 4, 5	PRP-T	Combined, 2 component aP
China1[86]	3p + 0	14-16 m after	74	68	79	18-20	2, 3, 4	PRP-T	Combined, 2 component aP
Netherlands[44]	2p + 1	1m after	98	94	100	14 m	6, 7 + b13	PRP-T	Separate, wP
Sweden[46]	2p + 1	1m after	95	90	98	13 m	3, 5 +b12	PRP-T	Combined, 2 component aP
Sweden[46]	2p + 1	4.5 year after	44	33	55	5.5 y	3, 5 +b12	PRP-T	Combined, 2 component aP
Canada3[59]	3p + 1	1m after	98	97	99	17/18 m	3p + b16/17	PRP-T	Combined, 5 component aP
Canada3[59]	3p + 1	1m after	99	98	100	18/19	3p +b17/18	PRP-T	Combined, 5 component aP
Chile5[42]	3p + 1	1m after	99	96	100	13 m	2, 4, 6 +12	PRP-T	Separate, 2 component aP
Chile5[42]	3p + 1	1m after	100	97	100	13 m	3, 5, 7 +b12	PRP-T	Separate, 2 component aP
China1[86]	3p + 1	1m after	100	99	100	19-21 m	2, 3, 4 + b18-20 m	PRP-T	Combined, 2 component aP
China1[86]	3p + 1	1m after	100	98	100	19-21 m	3, 4, 5 + b18-20	PRP-T	Combined, 2 component aP
Europe[60]	3p + 1	1m after	98	95	100	13 m	3p + 12	PRP-T	Combined, 3 component aP
Europe[60]	3p + 1	1m after	97	94	99	14 m	3p + 13	PRP-T	Combined, 3 component aP
France[85]	3p + 1	1m after	98	95	100	16-18 m	2, 3, 4 + b15-17	PRP-T	Combined, 2 component aP
France[85]	3p + 1	1m after	98	95	100	16-18 m	2, 4, 6 + b15-17	PRP-T	Combined, 2 component aP
Netherlands[44]	3p + 1	1m after	98	95	100	12 m	3, 4, 5 + b11	PRP-T	Separate, wP
Sweden[46]	3p + 1	1m after	99	95	100	14 m	2, 4, 6 + b13	PRP-T	Combined, 2 component aP
Canada1[87]	3p + 1	1.5m after	98	92	100	13.5 m	2, 4, 6 + b12	PRP-T	Combined wP

Study	Schedule	Time since vaccination	Proportion above set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Canada1[87]	3p + 1	1.5m after	95	88	99	16.5 m	2, 4, 6 + b15	PRP-T	Combined, wP
Canada1[87]	3p + 1	1.5m after	100	95	100	19.5 m	2, 4, 6 +b18	PRP-T	Combined, wP
Europe[60]	3p + 1	2m after	97	93	99	14 m	3p +12	PRP-T	Combined, 3 component aP
Sweden[46]	3p + 1	4.5 year after	38	27	49	5.5 y	2, 4, 6 + b13	PRP-T	Combined, 2 component aP

Table 7. Results of studies reporting proportion above a set threshold (i.e. >1.0 ug/ml) at different time points after vaccination with Hib vaccines containing PRP-OMP and PRP-HbOC conjugates.

Study	Schedule	Time since vaccination	proportion above a set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Gambia1[88]	2p + 0	1m after	54	43	65	4m	1, 3	PRP-OMP	Separate, wP 2, 3, 4 m
Gambia 1[88]	2p + 0	1m after	61	47	74	5m	2, 4	PRP-OMP	Separate, wP 2, 3, 4 m
USA4[89]	2p + 0	1m after	58	41	74	7m	3, 6	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	3m after	38	23	55	7m	2, 4	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	9m after	22	9	40	15m	3, 6	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	11m after	9	2	24	15m	2, 6	PRP-OMP	Separate, wP according to guidelines
Gambia1[88]	2p + 0	14m after	26	15	40	18m	2, 4	PRP-OMP	Separate, wP 2, 3, 4m
Gambia1[88]	2p + 0	15m after	27	17	39	18m	1, 3	PRP-OMP	Separate, wP 2, 3, 4m
Chile4[41]	2p + 0	2m after	64	52	74	8m	4, 6	PRP-HbOC	Separate, wP
Chile4[41]	2p + 0	6m after	30	20	41	12m	4, 6	PRP-HbOC	Separate, wP
Chile4[41]	3p + 0	2m after	76	64	85	8m	2, 4, 6	PRP-HbOC	Separate, wP
Chile4[41]	3p + 0	6m after	33	22	45	12m	2, 4, 6	PRP-HbOC	Separate, wP

Table 8. Results of studies reporting proportion above a set threshold (i.e. ≥1.0 ug/ml) at different time points after vaccination with Hib vaccines containing PRP-T conjugate.

Study	Schedule	Time since vaccination	proportion above a set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Niger1[45]	2p + 0	1m after	83	71	92	4.5 m	2.5, 3.5	PRP-T	Combined, wP
Sweden[46]	2p + 0	1m after	44	35	54	6 m	3, 5	PRP-T	Combined, 2 component aP
Chile4[41]	2p + 0	2m after	95	87	99	8m	4, 6	PRP-T	Separate, wP
Chile5[42]	2p + 0	2m after	95	89	98	7m	3, 5	PRP-T	Separate, 2 component aP
Guatemala Kaqchikel[43]	2p + 0	3m after	87	74	95	12 m	7, 9	PRP-T	Separate, wP 2, 4, 6 m
Guatemala Ladino[43]	2p + 0	3m after	100	92	100	12 m	7, 9	PRP-T	Separate, wP 2, 4, 6 m
Netherlands[44]	2p + 0	4m after	81	73	87	11 m	6, 7	PRP-T	Separate, wP
Niger1[45]	2p + 0	5.5 m after	67	51	81	9 m	2.5, 3.5	PRP-T	Combined, wP
Chile4[41]	2p + 0	6 m after	56	44	67	12 m	4, 6	PRP-T	Separate, sP
Sweden[46]	2p + 0	7 m after	21	14	30	12 m	3, 5	PRP-T	Combined, 2 component aP
Belgium[84]	3p + 0	1m after	87	75	95	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
Belgium[84]	3p + 0	1m after	92	80	98	6 m	3, 4, 5	PRP-T	Separate, 2 component aP
Chile5[42]	3p + 0	1m after	96	92	99	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
France[85]	3p + 0	1m after	62	55	69	5 m	2, 3, 4	PRP-T	Combined, 2 component aP
France[85]	3p + 0	1m after	73	66	80	7 m	2, 4, 6	PRP-T	Combined, 2 component aP
Niger1[45]	3p + 0	1m after	89	75	96	4.5 m	1.5, 2.5, 3.5	PRP-T	Combined, wP
Sweden[46]	3p + 0	1m after	67	58	76	7 m	2, 4, 6	PRP-T	Combined, 2 component aP
Turkey[84]	3p + 0	1m after	97	91	100	7 m	2, 4, 6	PRP-T	Separate, 2 component aP
Turkey[84]	3p + 0	1m after	96	89	99	6m	3, 4, 5	PRP-T	Separate, 2 component aP
Chile4[41]	3p + 0	2m after	84	74	92	8 m	2, 4, 6	PRP-T	Separate, wP
Niger1[45]	3p + 0	5.5 m after	76	59	88	9 m	1.5, 2.5, 3.5	PRP-T	Combined, wP
Chile4[41]	3p + 0	6 m after	53	41	65	12 m	2, 4, 6	PRP-T	Separate, wP
Guatemala Kaqchikel[43]	3p + 0	6 m after	95	90	98	12 m	2, 4, 6	PRP-T	Combined, wP
Guatemala Ladino[43]	3p + 0	6 m after	89	82	93	12 m	2, 4, 6	PRP-T	Combined, wP

Study	Schedule	Time since vaccination	proportion above a set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Netherlands[44]	3p + 0	6 m after	40	32	48	11 m	3, 4, 5	PRP-T	Separate, wP
Sweden[46]	3p + 0	7 m after	17	10	25	13 m	2, 4, 6	PRP-T	Combined, 2 component aP
Europe[60]	3p + 0	unclear time after	39	32	47	13 m	3p	PRP-T	Combined, 3 component aP
France[85]	3p + 0	9-11 m after	26	19	33	15-17 m	2, 4, 6	PRP-T	Combined, 2 component aP
France[85]	3p + 0	11-13 m after	40	32	48	15-17 m	2, 3, 4	PRP-T	Combined, 2 component aP
China1[86]	3p + 0	13-15 m after	75	69	80	18-20 m	3, 4, 5	PRP-T	Combined, 2 component aP
China1[86]	3p + 0	14-16 m after	74	68	79	18-20	2, 3, 4	PRP-T	Combined, 2 component aP
Netherlands[44]	2p + 1	1m after	98	94	100	14 m	6, 7 + b13	PRP-T	Separate, wP
Sweden[46]	2p + 1	1m after	95	90	98	13 m	3, 5 +b12	PRP-T	Combined, 2 component aP
Sweden[46]	2p + 1	4.5 year after	44	33	55	5.5 y	3, 5 +b12	PRP-T	Combined, 2 component aP
Canada3[59]	3p + 1	1m after	98	97	99	17/18 m	3p + b16/17	PRP-T	Combined, 5 component aP
Canada3[59]	3p + 1	1m after	99	98	100	18/19	3p +b17/18	PRP-T	Combined, 5 component aP
Chile5[42]	3p + 1	1m after	99	96	100	13 m	2, 4, 6 +12	PRP-T	Separate, 2 component aP
Chile5[42]	3p + 1	1m after	100	97	100	13 m	3, 5, 7 +b12	PRP-T	Separate, 2 component aP
China1[86]	3p + 1	1m after	100	99	100	19-21 m	2, 3, 4 + b18-20 m	PRP-T	Combined, 2 component aP
China1[86]	3p + 1	1m after	100	98	100	19-21 m	3, 4, 5 + b18-20	PRP-T	Combined, 2 component aP
Europe[60]	3p + 1	1m after	98	95	100	13 m	3p + 12	PRP-T	Combined, 3 component aP
Europe[60]	3p + 1	1m after	97	94	99	14 m	3p + 13	PRP-T	Combined, 3 component aP
France[85]	3p + 1	1m after	98	95	100	16-18 m	2, 3, 4 + b15-17	PRP-T	Combined, 2 component aP
France[85]	3p + 1	1m after	98	95	100	16-18 m	2, 4, 6 + b15-17	PRP-T	Combined, 2 component aP
Netherlands[44]	3p + 1	1m after	98	95	100	12 m	3, 4, 5 + b11	PRP-T	Separate, wP
Sweden[46]	3p + 1	1m after	99	95	100	14 m	2, 4, 6 + b13	PRP-T	Combined, 2 component aP
Canada1[87]	3p + 1	1.5m after	98	92	100	13.5 m	2, 4, 6 + b12	PRP-T	Combined wP
Canada1[87]	3p + 1	1.5m after	95	88	99	16.5 m	2, 4, 6 + b15	PRP-T	Combined, wP
Canada1[87]	3p + 1	1.5m after	100	95	100	19.5 m	2, 4, 6 +b18	PRP-T	Combined, wP

Study	Schedule	Time since vaccination	proportion above a set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Europe[60]	3p + 1	2m after	97	93	99	14 m	3p +12	PRP-T	Combined, 3 component aP
Sweden[46]	3p + 1	4.5 year after	38	27	49	5.5 y	2, 4, 6 + b13	PRP-T	Combined, 2 component aP

Table 9. Results of studies reporting proportion above a set threshold (i.e. ≥1.0 ug/ml) at different time points after vaccination with Hib vaccines containing PRP-OMP and PRP-HbOC conjugates.

Study	Schedule	Time since vaccination	proportion above a set threshold	lower limit	upper limit	age at blood draw	intended schedule	conjugate	formulation
Gambia1[88]	2p + 0	1m after	54	43	65	4m	1, 3	PRP-OMP	Separate, wP 2, 3, 4 m
Gambia 1[88]	2p + 0	1m after	61	47	74	5m	2, 4	PRP-OMP	Separate, wP 2, 3, 4 m
USA4[89]	2p + 0	1m after	58	41	74	7m	3, 6	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	3m after	38	23	55	7m	2, 4	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	9m after	22	9	40	15m	3, 6	PRP-OMP	Separate, wP according to guidelines
USA4[89]	2p + 0	11m after	9	2	24	15m	2, 6	PRP-OMP	Separate, wP according to guidelines
Gambia1[88]	2p + 0	14m after	26	15	40	18m	2, 4	PRP-OMP	Separate, wP 2, 3, 4m
Gambia1[88]	2p + 0	15m after	27	17	39	18m	1, 3	PRP-OMP	Separate, wP 2, 3, 4m
Chile4[41]	2p + 0	2m after	64	52	74	8m	4, 6	PRP-HbOC	Separate, wP
Chile4[41]	2p + 0	6m after	30	20	41	12m	4, 6	PRP-HbOC	Separate, wP
Chile4[41]	3p + 0	2m after	76	64	85	8m	2, 4, 6	PRP-HbOC	Separate, wP
Chile4[41]	3p + 0	6m after	33	22	45	12m	2, 4, 6	PRP-HbOC	Separate, wP

APPENDIX 3 - GRADE TABLES

GRADE Table No 1: Hib vaccination schedules: three primary doses versus two primary doses

PICO Question: Does using three primary doses of Hib have a greater effect on proportion above a set immunological threshold than using two primary doses?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		6 RCTs	4
	Factors decreasing confidence	Limitation in study design	serious[8]	-1
		Inconsistency	Very serious[9]	-2
		Indirectness	None	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			We are uncertain about the estimate of effect
	Conclusion			There is no clear difference in effect on proportion above a set threshold of a three primary dose schedule over a two primary dose schedule

[8] All studies either lacked blinding of participants or failed to report it. Most studies did not report allocation concealment

[9] High level of hetereogeneity: I-squared greater than 75% (96.6%)

References

1. Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules Trials graded;

2. Chile 4 Lagos, R., et al., *Economisation of vaccination against Haemophilus influenzae type b: a randomised trial of immunogenicity of fractional-dose and two-dose regimens.* Lancet, 1998. **351**(9114): p. 1472-6.

3. Chile 5 Lagos, R., et al., *Clinical acceptability and immunogenicity of a pentavalent parenteral combination vaccine containing diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type b conjugate antigens in two-, four- and six-month-old Chilean infants.* Pediatr Infect Dis J, 1998. **17**(4): p. 294-304.

4. Guatemala: Asturias, E.J., et al., *Differences in the immune response to hepatitis B and Haemophilus influenzae type b vaccines in Guatemalan infants by ethnic group and nutritional status.* Vaccine, 2009. **27**(27): p. 3650-4.

5. Netherlands: Labadie, J., et al. *Multi-center study on the simultaneous administration of DPT-IPV and Hib PRP-T vaccines. RijksinstLituut voor Volksgezondheid en Milieu RIVM*. 1996 [accessed 2013 Jan 24]; Available from: http://www.rivm.nl/bibliotheek/rapporten/124001003.html

6. Niger: Campagne, G., et al., *Response to conjugate Haemophilus influenzae B vaccine among infants in Niamey, Niger.* Am J Trop Med Hyg, 1998. **59**(5): p. 837-42.

7. Sweden: Carlsson, R.M., et al., *Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatr Infect Dis J, 1998. **17**(11): p. 1026-33.

GRADE Table 2: Hib vaccination schedules: three primary doses versus two primary doses plus one booster dose

PICO Question: Does using three primary doses of Hib have a greater immunological effect than using two primary doses plus one booster dose?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1 RCT	4
	Factors decreasing confidence	Limitation in study design	serious[10]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	serious[11]	-1
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	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 low
	Conclusion			One trial has found that the 2p+1 schedule resulted in higher proportion above a set threshold than the 3p schedule but further research is needed to confirm whether this is a true effect.

[10] Randomization unclear, participants not blinded
[11] Only one study-low number of events

Six trials measured examined proportion above a set threshold after either 3p or 2p+1 in individual trial arms but only one trial provided a direct comparison.

References:

Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules

Trials graded;

Sweden: Carlsson, R.M., et al., *Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatr Infect Dis J, 1998. **17**(11): p. 1026-33.

GRADE Table 3: Hib vaccination schedules: three primary doses plus one booster dose versus two primary doses plus one booster dose

PICO Question: Does using three primary doses of Hib plus one booster dose have a greater immunological effect than using two primary doses plus one booster dose?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCT	4
	Factors decreasing confidence	Limitation in study design	serious[12]	-1
		Inconsistency	Not serious	0
		Indirectness	none	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	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
	Conclusion			Both schedules induced high proportions above a set threshold and there was little difference between the two groups

[12] [12] Randomization unclear or not reported, participants not blinded

References: Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules

Trials graded:

Netherlands: Labadie, J., et al. *Multi-center study on the simultaneous administration of DPT-IPV and Hib PRP-T vaccines. RijksinstLituut voor Volksgezondheid en Milieu RIVM*. 1996 [accessed 2013 Jan 24]; Available from: http://www.rivm.nl/bibliotheek/rapporten/124001003.html

Sweden: Carlsson, R.M., et al., *Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatr Infect Dis J, 1998. **17**(11): p. 1026-33.

GRADE Table 4: Hib vaccination schedules: three primary doses plus one booster versus three primary doses only

PICO Question: Does using three primary doses of Hib plus one booster dose have a greater immunological effect than using three primary doses only?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCT	4
	Factors decreasing confidence	Limitation in study design	serious[13]	-1
		Inconsistency	None	0
		Indirectness	None	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	-	0
		Dose-response	-	0
		Antagonistic /mitigated bias and confounding	-	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**
	Conclusion			The 3p+1 schedule induced higher proportion above a set threshold than the 3p schedule

[13] Randomization unclear or not reported, participants not blinded

Notes
Adapted from: Scott, P. et al *Haemophilus influenza* type b conjugate vaccines: a systematic review of data from randomized controlled trials of childhood schedules

References:Trials graded: Canada3: Scheifele, D.W., et al., *Safety and immunogenicity of a pentavalent combination vaccine (diphtheria, tetanus, acellular pertussis, polio, and haemophilus influenzae type B conjugate) when administered as a fourth dose at 15 to 18 months of age.* Hum Vaccin, 2005. **1**(5): p. 180-6

Europe: Knuf, M., et al., *An investigational tetravalent meningococcal serogroups A, C, W-135 and Y-tetanus toxoid conjugate vaccine co-administered with Infanrix hexa is immunogenic, with an acceptable safety profile in 12-23-month-old children.* Vaccine, 2011. **29**(25): p. 4264-73.

References

[1] Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. Lancet. 2009 May 2;373(9674):1543-9. doi: 10.1016/S0140-6736(09)60317-2. Epub 2009 Mar 19.

[2] Scott P, Redmond S, Ruthes A, Matthias E, Low N. . *Haemophilus influenzae type b conjugate vaccines: a systematic review of schedule related RCTs.* Draft report to WHO 2013. Unpublished data.

[3] Griffiths UK, Clark A, Gessner B, Milners A, Sanderson C, Sedyaningsih ER, Mulholland KE. *Dose-specific efficacy of Haemophilus influenzae type b conjugate vaccines: a systematic review and meta-analysis of controlled clinical trials.* Epidemiol Infect 2012; 140(8):1343-55.

[4] Jackson C, Mann a, Mangtani P, Fine P. Systematic review of observational data on effectiveness of *Haemophilus influenzae* type b (hib) vaccines to allow optimization of vaccine schedules. London School of Hygiene and Tropical Medicine 2012.

[5] Watt JP, Chen S, Santosham M, *Haemophilus inflIuenzae type b conjugate vaccine: Review of observational data on long term vaccine impact to inform recommendations for vaccine schedules.* Report to WHO 2012.

[6] Garcia S, Lagos R, Muñoz A, Picón T, rosa R, Alfonso A, Abriata G, Gentile A, Romanin V, Requeira M, Chiavetta L, Agudelo CI, Castañeda E, De la Hoz F, Higuera AB, Arce P, Cohen AL, Verani J, Zuber P, Gabastou JM, Pastor D, Flannery B, Andrus J. Impact of vaccination against *Haemophilus influenzae* type b with and without a booster dose on meningitis in four South American countries. Vaccine 2012;30(2):486-92.

[7] Sanderson C. et al. Age at Hib disease, and the impact of delayed vaccination - report to WHO 2012. Unpublished data.

[8] Bar-On ES, Goldberg E, Hellmann S, Leibovici L. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* B (HIB). Cochrane Database Syst Rev 2012. Apr 18;4:CD005530. doi: 10.1002/14651858.CD005530.pub3

[9] Dhillon S, Keam SJ. DTaP-IPV/Hib vaccine (Pentacel). Paediatr Drugs. 2008;10(6):405-16.

[10] Chandran A, Watt JP, Santosham M, Haemophilus influenza vaccines. Vaccines (Sixth Editions) 2013.
Vaccines (Sixth Edition. 2013 Elsevier Inc. ISBN: 978-1-4557-0090-5 .

[11] Decker MD, Edwards KM, Bogaerts HH. Combination Vaccines. Vaccines (Sixth Edition. 2013 Elsevier Inc. ISBN: 978-1-4557-0090-5 .

[12] Peltola H, Aavitsland P, Hansen KG, Jónsdóttir KE, Nøkleby H, Romanus V. Perspective: a five-country analysis of the impact of four different *Haemophilus influenzae* type b conjugates and vaccination strategies in Scandinavia. J Infect Dis. 1999 Jan;179(1):223-9.

[13] Shamez Ladhani, Mary P.E. Slack, Paul T. Heath, Anne von Gottberg, Manosree Chandra, Mary E. Ramsay, and European Union Invasive Bacterial Infection Surveillance participants. Invasive *Haemophilus influenzae* Disease, Europe, 1996–2006. Emerg Infect Dis. 2010 March; 16(3): 455–463.

[14] McVernon J, Ramsay ME, McLean AR. Understanding the impact of Hib conjugate vaccine on transmission, immunity and disease in the United Kingdom. Epidemiol Infect. 2008 Jun;136(6):800-12. Epub 2007 Aug 3.

[15] McVernon J, Trotter CL, Slack MP, Ramsay ME. Trends in *Haemophilus influenzae* type b infections in adults in England and Wales: surveillance study. BMJ. 2004 Sep 18;329(7467):655-8.

[16] Ladhani S, Heath PT, Slack MP, McIntyre PB, Diez-Domingo J, Campos J, Dagan R, Ramsay ME; Participants of the European Union Invasive Bacterial Infections Surveillance Network. *Haemophilus influenzae* serotype b conjugate vaccine failure in twelve countries with established national childhood immunization programmes. Clin Microbiol Infect. 2010 Jul;16(7):948-54. doi: 10.1111/j.1469-0691.2009.02945.x. Epub 2009 Nov 4.

[17] http://www.who.int/immunization_monitoring/burden/Pneumo_hib_estimates/en/index.html.

[18] http://www.who.int/immunization/documents/positionpapers/en/

[19] Mulholland, K., et al., *Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants.* Lancet, 1997. **349**(9060): p. 1191-7

[20] Lagos, R., et al., *Large scale, postlicensure, selective vaccination of Chilean infants with PRP-T conjugate vaccine: practicality and effectiveness in preventing invasive Haemophilus influenzae type b infections.* Pediatr Infect Dis J, 1996. **15**(3): p. 216-22

[21] Adegbola, R.A., et al., *Elimination of Haemophilus influenzae type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study.* Lancet, 2005. **366**(9480): p. 144-50.

[22] Kalies, H., et al., *Effectiveness of hexavalent vaccines against invasive Haemophilus influenzae type b disease: Germany's experience after 5 years of licensure.* Vaccine, 2008. **26**(20): p. 2545-52.

[23] Kalies, H., et al., *Four and one-half-year follow-up of the effectiveness of diphtheria-tetanus toxoids-acellular pertussis/Haemophilus influenzae type b and diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus/H. influenzae type b combination vaccines in Germany.* Pediatr Infect Dis J, 2004. **23**(10): p. 944-50.

[24] Lee, E.H., et al., *Haemophilus influenzae type b conjugate vaccine is highly effective in the Ugandan routine immunization program: a case-control study.* Trop Med Int Health, 2008. **13**(4): p. 495-502

[25] Lee, E.H., et al., *Impact of Haemophilus influenzae type b conjugate vaccine on bacterial meningitis in the Dominican Republic.* Rev Panam Salud Publica, 2008. **24**(3): p. 161-8.

[26] Lewis, R.F., et al., *Action for child survival: elimination of Haemophilus influenzae type b meningitis in Uganda.* Bull World Health Organ, 2008. **86**(4): p. 292-301.

[27] Daza, P., et al., *The impact of routine infant immunization with Haemophilus influenzae type b conjugate vaccine in Malawi, a country with high human immunodeficiency virus prevalence.* Vaccine, 2006. **24**(37-39): p. 6232-9.

[28] Baqui, A.H., et al., *Effectiveness of Haemophilus influenzae type B conjugate vaccine on prevention of pneumonia and meningitis in Bangladeshi children: a case-control study.* Pediatr Infect Dis J, 2007. **26**(7): p. 565-71.

[29] Gessner, B.D., et al., *Incidences of vaccine-preventable Haemophilus influenzae type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial.* Lancet, 2005. **365**(9453): p. 43-52.

[30] de la Hoz, F., et al., *Effectiveness of Haemophilus influenzae type b vaccination against bacterial pneumonia in Colombia.* Vaccine, 2004. **23**(1): p. 36-42.

[31] Ramsay, M.E., et al., Estimating Haemophilus influenzae type b vaccine effectiveness in England and Wales by use of the screening method. J Infect Dis, 2003. 188(4): p. 481-5

[32] Schmitt, H.J., et al., *Haemophilus influenzae type b disease: impact and effectiveness of diphtheria-tetanus toxoids-acellular pertussis (-inactivated poliovirus)/H. influenzae type b combination vaccines.* Pediatr Infect Dis J, 2001. **20**(8): p. 767-74.

[33] Hviid, A. and M. Melbye, *Impact of routine vaccination with a conjugate Haemophilus influenzae type b vaccine.* Vaccine, 2004. **22**(3-4): p. 378-82.

[34] Santosham, M., et al., *The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex.* N Engl J Med, 1991. **324**(25): p. 1767-72.

[35] Harrison, L.H., et al., *Postlicensure effectiveness of the Haemophilus influenzae type b polysaccharide-Neisseria meningitidis outer-membrane protein complex conjugate vaccine among Navajo children.* J Pediatr, 1994. **125**(4): p. 571-6.

[36] Vadheim, C.M., et al., *Protection provided by Haemophilus influenzae type b conjugate vaccines in Los Angeles County: a case-control study.* Pediatr Infect Dis J, 1994. **13**(4): p. 274-80.

[37] Jafari, H.S., et al., *Efficacy of Haemophilus influenzae type b conjugate vaccines and persistence of disease in disadvantaged populations. The Haemophilus Influenzae Study Group.* Am J Public Health, 1999. **89**(3): p. 364-8.

[38] Black, S.B., et al., *Efficacy in infancy of oligosaccharide conjugate Haemophilus influenzae type b (HbOC) vaccine in a United States population of 61,080 children. The Northern California Kaiser Permanente Vaccine Study Center Pediatrics Group.* Pediatr Infect Dis J, 1991. **10**(2): p. 97-104.

[39] Madhi, S.A., et al., *Reduced effectiveness of Haemophilus influenzae type b conjugate vaccine in children with a high prevalence of human immunodeficiency virus type 1 infection.* Pediatr Infect Dis J, 2002. **21**(4): p. 315-21

[40] de Andrade, A.L., et al., *Effectiveness of Haemophilus influenzae b conjugate vaccine on childhood pneumonia: a case-control study in Brazil.* Int J Epidemiol, 2004. **33**(1): p. 173-81.

[41] Lagos, R., et al., *Economisation of vaccination against Haemophilus influenzae type b: a randomised trial of immunogenicity of fractional-dose and two-dose regimens.* Lancet, 1998. 351(9114): p. 1472-6

[42] Lagos, R., et al., *Clinical acceptability and immunogenicity of a pentavalent parenteral combination vaccine containing diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type b conjugate antigens in two-, four- and six-month-old Chilean infants.* Pediatr Infect Dis J, 1998. **17**(4): p. 294-304.

[43] Asturias, E.J., et al., *Differences in the immune response to hepatitis B and Haemophilus influenzae type b vaccines in Guatemalan infants by ethnic group and nutritional status.* Vaccine, 2009. **27**(27): p. 3650-4

[44] Labadie, J., et al. *Multi-center study on the simultaneous administration of DPT-IPV and Hib PRP-T vaccines. Rijksinstituut voor Volksgezondheid en Milieu RIVM*. 1996 [accessed 2013 Jan 24]; Available from: http://www.rivm.nl/bibliotheek/rapporten/124001003.html

[45] Campagne, G., et al., *Response to conjugate Haemophilus influenzae B vaccine among infants in Niamey, Niger.* Am J Trop Med Hyg, 1998. **59**(5): p. 837-42.

[46] Carlsson, R.M., et al., *Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-Haemophilus influenzae type b vaccine administered at 2-4-6-13 or 3-5-12 months of age.* Pediatr Infect Dis J, 1998. **17**(11): p. 1026-33.

[47] Heath, PT; McVernon, J. *The UK Hib vaccine experience.* Archives of Disease in Childhood, 2002; 86:396-399.

[48] Trotter CL et al: *Antibody to Haemophilus influenzae type b after routine and catch-up vaccination.* Lancet 2003; 361:1523-1524.

[49] McVernon, J. et al. *Trends in Haemophilus influenzae type b infections in adults in England and Wales: surveillance study.* BMJ (Clinical research ed.) 2004;329:655-658.

[50] The Immunological Basis for Immunization Series: Module 9: *Haemophilus influenzae* type b. World Health Organization 2007. ISBN 978 92 4 159613 8.

[51] Southern, J., et al., *Immunogenicity of a fourth dose of Haemophilus influenzae type b (Hib) conjugate vaccine and antibody persistence in young children from the United Kingdom who were primed with acellular or whole-cell pertussis component-containing Hib combinations in infancy.* Clin Vaccine Immunol, 2007. **14**(10): p. 1328-33.

[52] Shehab, Z.M., et al., *Immunogenicity and reactogenicity of Haemophilus influenzae type b-meningococcus group B outer membrane protein conjugate vaccine in children 2-60 months of age.* Scand J Infect Dis, 1991. **23**(6): p. 763-9.

[53] Lieberman, J.M., et al., *Effect of neonatal immunization with diphtheria and tetanus toxoids on antibody responses to Haemophilus influenzae type b conjugate vaccines.* J Pediatr, 1995. **126**(2): p. 198-205.

[54] Kayhty, H., et al., *Immunogenicity of Haemophilus influenzae oligosaccharide-protein and polysaccharide-protein conjugate vaccination of children at 4, 6, and 14 months of age.* Pediatrics, 1989. **84**(6): p. 995-9.

[55] Eskola J, Ward J, Dagan R, Goldblatt D, Zepp F, Siegrist CA. Combined vaccination of Haemophilus influenzae type b conjugate and diphtheria-tetanus-pertussis containing acellular pertussis. Lancet. 1999 Dec 11;354(9195):2063-8.

[56] Galil K, Singleton R, Levine OS, Fitzgerald MA, Bulkow L, Getty M, Perkins BA, Parkinson A. Reemergence of invasive *Haemophilus influenzae* type b disease in a well-vaccinated population in remote Alaska. J Infect Dis. 1999 Jan;179(1):101-6. Limited efficacy of a *Haemophilus influenzae* type b conjugate vaccine in Alaska Native infants. The Alaska H. influenzae Vaccine Study Group. N Engl J Med. 1990 Nov 15;323(20):1393-401.

[57] Goldblatt D, Pinto Vaz A R J P M, Miller E. Antibody avidity as a surrogate marker of successful priming to Haemophilus influenzae type b conjugate vaccines following infant immunization. J Infect Dis. 1998;177:1112–1115.

[58] Anttila M, Eskola J, Ahman H, Käyhty H. Differences in the avidity of antibodies evoked by four different pneumococcal conjugate vaccines in early childhood. Vaccine. 1999 Apr 9;17(15-16):1970-7.

[59] Scheifele, D.W., et al., *Safety and immunogenicity of a pentavalent combination vaccine (diphtheria, tetanus, acellular pertussis, polio, and haemophilus influenzae type B conjugate) when administered as a fourth dose at 15 to 18 months of age.* Hum Vaccin, 2005. **1**(5): p. 180-6.

[60] Knuf, M., et al., *An investigational tetravalent meningococcal serogroups A, C, W-135 and Y-tetanus toxoid conjugate vaccine co-administered with Infanrix hexa is immunogenic, with an acceptable safety profile in 12-23-month-old children.* Vaccine, 2011. **29**(25): p. 4264-73.

[61] Goldblatt D et al. The Immunological Basis for Immunization Series. Module 9: *Haemophilus influenzae* type b. World Health Organization 2007. ISBN 978 92 4 159613 8

[62] Baggett, H.C., et al., Immunologic response to Haemophilus influenzae type b (Hib) conjugate vaccine and risk factors for carriage among Hib carriers and noncarriers in Southwestern Alaska. Clin Vaccine Immunol, 2006. 13(6): p. 620-6.

[63] Takala, A.K., et al., Vaccination with *Haemophilus influenzae* type b meningococcal protein conjugate vaccine reduces oropharyngeal carriage of *Haemophilus influenzae* type b among American Indian children. Pediatr Infect Dis J, 1993. 12(7): p. 593-9.

[64] Madhi, S.A., et al., Immunogenicity and effectiveness of *Haemophilus influenzae* type b conjugate vaccine in HIV infected and uninfected African children. Vaccine, 2005. 23(48-49): p. 5517-25.

[65] Scott A, Hammit L, personal communication 2013.

[66] Von Gottberg A, Cohen C, Whitelaw A, Chhagan M, Flannery B, Cohen AL, et al. Invasive disease due to *Haemophilus influenzae* serotype b ten years after routine vaccination, South Africa, 2003-2009.Vaccine. 2012 Jan 11;30(3):565-71.

[67] Von Gottberg A, de Gouveia L, Madhi SA, du Plessis M, Quan V, Soma K et al. Impact of conjugate *Haemophilus influenzae* type b (Hib) vaccine introduction in South Africa. Bull WHO 2006;84:811-8.

[68] Adams WG, Deaver KA, Cochi SL, Plikaytis BD, Zell ER, Broome CV, et al. Decline of Childhood *Haemophilus influenzae* Type b (Hib) Disease in the Hib Vaccine Era. JAMA 1993;269:221-6.

[69] Singleton R, Bulkow LR, Levine OS, Butler JC, Hennessy TW, Parkinson A. Experience with the prevention of invasive *Haemophilus influenzae* type b disease by vaccination in Alaska: The impact of persistent oropharyngeal carriage. J Pediatr 2000;137:313-20.

[70] Giufrè M, Cardines R, Caporali MG, Accogli M, D'Ancona F, Cerquetti M. Ten years of Hib vaccination in Italy: prevalence of non-encapsulated Haemophilus influenzae among invasive isolates and the possible impact on antibiotic resistance. Vaccine. 2011 May 17;29(22):3857-62. doi: 10.1016/j.vaccine.2011.03.059. Epub 2011 Apr 1.

[71] Horby P, Gilmour R, Wang H, McIntyre P. Progress towards eliminating Hib in Australia: An evaluation of *Haemophilus influenzae* type b prevention in Australia, 1 July 1993 to 30 June 2000. Communicable Dis Intel 2003;27:324-41

[72] Menzies R, Turnour C, Chiu C, McIntyre P. Vaccine Preventable Diseases and Vaccination Coverage in Aboriginal and Torres Strait Islander People, Australia 2003 to 2006. Communicable Dis Intel 2008;32:S1-67.

[73] Kurikka S, Käyhty H, Peltola H, Saarinen L, Eskola J, Mäkelä PH. Neonatal immunization: response to *Haemophilus influenzae* type b-tetanus toxoid conjugate vaccine. Pediatrics. 1995 Jun;95(6):815-22.

[74] Lehmannmexy D, Kakazo M, Saleu G, Tame J, Javati A, Namuigi P, Alpers M, Wegmüller B, Zellmeyer M et al. Safety and immunogenicity of two *Haemophilus influenzae* type b polysaccharide-tetanus toxoid conjugate vaccines (PRP-T) given with diphtheria-tetanus-pertussis vaccine to young Papua New Guinean children PNG Med J 2001 Mar-Jun;44(1-2):6-16..

[75] Hviid, A., et al., Childhood vaccination and nontargeted infectious disease hospitalization. JAMA, 2005. 294(6): p. 699-705.

[76] Plotkin S, Orenstein W, Offit P. Vaccines, 6th Edition. Saunders 2012. ISBN: 9781455700905.

[77] Kahn, G. 2013, Report to WHO – unpublished.

[78] Heath PT et al. (2000b). Clinical and immunological risk factors associated with *Haemophilus influenzae* type b conjugate vaccine failure in childhood. Clinical Infectious Diseases: an official publication of the Infectious Diseases Society of America, 31:973-980.

[79] Sarangi J et al. (2000). Invasive Haemophilus influenzae disease in adults. Epidemiology and Infection, 124:441-447.

[80] Moulton LH et al. (2000). Estimation of the indirect effect of *Haemophilus influenzae* type b conjugate vaccine in an American Indian population. International Journal of
Epidemiology, 29:753-756.

[81] Adam, H. J., Richardson, S. E., Jamieson, F. B., Rawte, P., Low, D. E. & Fisman, D. N. Changing epidemiology of invasive Haemophilus influenzae in Ontario, Canada: evidence for herd effects and strain replacement due to Hib vaccination. Vaccine 2010; 28, 4073–4078.

[82] Walker N et al 2012. Personal communication.

[83] Lenoir, A.A., P.D. Granoff, and D.M. Granoff, Immunogenicity of *Haemophilus influenzae* type b polysaccharide-Neisseria meningitidis outer membrane protein conjugate vaccine in 2- to 6-month-old infants. Pediatrics, 1987. 80(2): p. 283-7.

[84] Hoppenbrouwers, K., et al., Priming effect, immunogenicity and safety of an *Haemophilus influenzae* type b-tetanus toxoid conjugate (PRP-T) and diphtheria-tetanus-acellular pertussis (DTaP) combination vaccine administered to infants in Belgium and Turkey. Vaccine, 1999. 17(7-8): p. 875-86.

[85] GlaxoSmithKline. Co-Administration of meningococcal vaccine GSK134612 with Infanrix Hexa versus individual administration of each vaccine. NCT00508261. 2009 [accessed 2013 Jan 24]; Available from: http://clinicaltrials.gov/ct2/show/NCT00508261

[86] Li, R.C., et al., Antibody persistence at 18-20 months of age and safety and immunogenicity of a booster dose of a combined DTaP-IPV//PRP approximately T vaccine compared to separate vaccines (DTaP, PRP approximately T and IPV) following primary vaccination of healthy infants in the People's Republic of China. Vaccine, 2011

[87] Scheifele, D.W., R. Guasparini, and P. Lavigne, A comparative study of PENTA vaccine booster doses given at 12, 15, or 18 months of age. Vaccine, 1999. 17(6): p. 543-50.

[88] Campbell, H., et al., Serologic responses to an *Haemophilus influenzae* type b polysaccharide-Neisseria meningitidis outer membrane protein conjugate vaccine in very young Gambian infants. Pediatrics, 1990. 86(1): p. 102-7.

[89] Anderson, E.L., et al., Interchangeability of conjugated *Haemophilus influenzae* type b vaccines in infants. JAMA, 1995. 273(11): p. 849-53.

SUMMARY FOR STRATEGIC ADVISORY GROUPS OF EXPERTS (SAGE) RE: RTS,S/AS01 MALARIA VACCINE

February 2013: written by WHO secretariat with input from JTEG

Introduction:

The most advanced vaccine candidate against *Plasmodium falciparum*, known as RTS,S/AS01, is currently being evaluated in a Pivotal Phase 3 trial. This vaccine is being developed by GlaxoSmithKline (GSK) in partnership with PATH Malaria Vaccine Initiative (MVI) with funds from the Gates Foundation to MVI. There are about 20 other malaria vaccine projects in clinical testing; none of the other approaches have demonstrated proof of concept of efficacy in field settings.

The randomised controlled double-blind Phase III efficacy trial started in May 2009 and completed enrolment in January 2011 of 15,460 children in 7 countries in sub-Saharan Africa. These countries are: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania. The children are in two age groups: 1) 5-17 months at first immunization without co-administration and 2) 6-12 weeks at first immunization in co-administration with DTwP/HepB/Hib and OPV. Each child is followed for at least 30 months following the third dose of RTS,S/AS01. The three intramuscular doses are given in 1 month intervals followed by an 18 month booster dose in one of the 3 trial arms. The control vaccine is rabies vaccine for 5-17 months olds and meningococcal C conjugate vaccine for 6-12 week olds. The trial is occurring in the context of insectidice-treated bednet (ITN) use by most trial participants. The trial teams liaised with national authorities to maximise ITN use in the trial settings.

Phase 3 Results

The first of the three sets of results from the Phase III trial were published in October 2011 in the *New England Journal of Medicine* (NEJM)[1]. At that time clinical malaria efficacy data was reported on 6,000 infants/toddlers 5-17 months old at first immunization with RTS,S/AS01.

There was a Joint Technical Expert Group (JTEG) on Malaria Vaccines meeting on 9-10 October 2012. At this meeting GSK and MVI presented the second set of results from the Pivotal Phase 3 trial of RTS,S/AS01. These results were then published in a second NEJM article[2], which reports data from 6,537 infants aged 6-12 weeks of age randomized 2:1 to receive RTS,S/AS01 or Meningococcal C conjugate vaccine (control) in co-administration with DTwP/HepB/Hib and OPV. Duration of follow-up reported to date for both age groups is 12 months post dose 3.

[1] N Engl J Med 2011; 365:1863-1875 . November 17, 2011. www.nejm.org/doi/full/10.1056/NEJMoa1102287
[2] N Engl J Med 2012; 367:2284-2295. December 13, 2012. www.nejm.org/doi/full/10.1056/NEJMoa1208394

Efficacy & Immunogenicity: Summary Table of Per Protocol Analyses for RTS,S/AS01 Phase III Trial.

	6-12 week age group **(published Nov 2012)**	5-17 month age group **(published Oct 2011)**
Efficacy, first or only episode of clinical malaria	31%(97.5% CI 24-38)	56% (97.5% CI, 51 to 60)
Efficacy, all episodes of malaria	33% (95% CI 26-39)	55% (95%CI 50-59)
Efficacy, severe/ hospitalized malaria	37% (95% CI 5-58)	47% (95% CI 22-64)
Immunogenicity (antibody, elisa units per ml to malaria antigen).	209 (95%CI 197-222)	621 (95% CI, 592 to 652).

While much of the discussion following publication is likely to focus on the apparent difference between the efficacy figures in the 2 age groups, JTEG advised that the two age groups are not strictly comparable. This is because the numbers enrolled by site across the 11 sites differs between the 2 age groups, as does the number of malaria events. Malaria transmission intensity varies greatly across the sites. JTEG advised that site or transmission strata specific efficacy analyses are necessary to interpret the new results, and this was communicated to GSK/ MVI. Such analyses will be available to WHO by late 2014.

A potentially important finding is the three-fold lower antibody concentrations by ELISA to the malaria antigen in the younger age group. The apparent difference in efficacy between the two age groups may relate to some or all of the following factors: interference from co-administration, maternally acquired antibodies to the malaria antigen in RTS,S/AS01, differences in the prior exposure of the children to malaria, transmission intensity and seasonality. A further factor raised by the GSK/MVI partnership is that the children in the 5-17 month age category had almost all received three prior doses of hepatitis B vaccine, and this may act to prime for higher malaria antibody responses given that RTS,S is a fusion malaria-hepatitis B vaccine.

Safety and reactogenicity: In terms of reactogenicity, there was a higher proportion of fever cases (31% vs 13%) in the 7 days after vaccination in the 5-17 months age category, among those receiving RTS,S when compared to controls; and an excess frequency of about 1 in 2000 vaccine doses for febrile seizure was observed within 7 days after RTS,S vaccination.

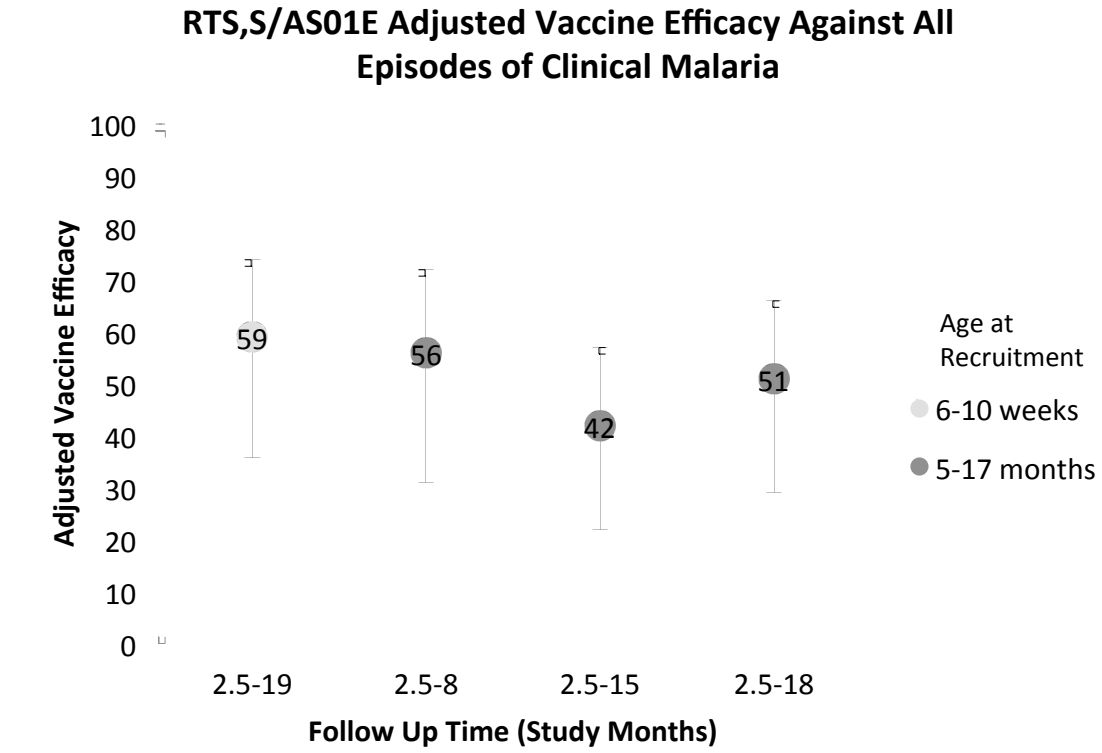
No new safety concerns were raised by the second set of results in infants aged 6-12 weeks at first dose, with no excess of febrile seizures reported in this age group. The full Phase III data will be reviewed by the Global Advisory Committee on Vaccine Safety (GACVS) prior to the "For Decision" session in 2015.

Phase 2 results

The earlier Phase 2 studies were done using a different adjuvant (AS02, an oil-in-water emulsion containing immunostimulants). Later studies were done with the AS01 adjuvant (a liposomal formulation containing the same immunostimulants, ie monophosphoryl lipid A and QS21) which

appeared to give superior IgG and cell-mediated immune responses, as well as an indication of improved efficacy in the human challenge model. AS01 is the adjuvant that is being used in the Phase 3 studies. The longest term efficacy follow-up from Phase 2 available to date is from a RTS,S/AS02 study in Mozambique. Efficacy from this study was 26% (95%CI 12 to 37) for all episodes of clinical malaria over 43 months following administration of the third dose, in children aged 1-4 years at vaccination.

Phase 2 efficacy data against all episodes of clinical malaria for RTS,S/AS01 are summarized in figure 1 (this figure was produced by WHO secretariat). These are per protocol estimates with follow-up starting 2 weeks from the third dose. The first column relates to an exploratory efficacy analysis from a three site safety and immunogenicity study conducted in Gabon, Ghana and Tanzania. The second and third column relate to pooled results from a study conducted in Kilifi, Kenya and Korogwe, Tanzania. The fourth column relates to extended follow-up in the Kilifi site only for the same trial.



Timing of further Phase 3 results

In late 2014, WHO expects to receive the full per-protocol 30 month analyses from both age groups, as well as additional pre-specified analyses requested by WHO, including data on all episodes of malaria broken down by time since vaccination and additional site or transmission strata specific analyses.

Likely timing of For Decision Joint Session of SAGE and Malaria Policy Advisory Committee (MPAC)

The new results re-emphasise the previously stated policy timings: WHO policy recommendations are expected in 2015 based on the outcome of a joint SAGE/MPAC session. This session is tentatively scheduled for Q4 2015, depending on the final regulatory submission timings. The recommendations will be based on all data available up to 2014, including the site-specific efficacy, duration of protection and 18-month booster dose data. GSK/MVI have agreed that additional analyses requested by JTEG will be performed in late 2014.

The GACVS safety review of RTS,S/AS01 data is tentatively scheduled for June 2015.

Assessment of severe malaria age patterns, in order to inform discussions about immunization schedules

IVB is working jointly with WHO Global Malaria Programme to perform an assessment of the available data on severe malaria age patterns in sub-Saharan Africa. In work with some analogies to the rotavirus schedule expansion assessment, it is planned that the age patterns for given malaria transmission settings, will be combined with immunization coverage data to provide modeled estimates of the percentage of severe malaria disease burden that would be missed by different possible schedules within the age ranges of immunization covered by the pivotal Phase 3 trial. The outcome of this work will be presented to SAGE as part of the 2015 For Decision session.

Summary of Ongoing Phase II, Phase III, and ancillary studies for the RTS,S programme

See separate 2 page document

WHO Immunization, Vaccines & Biologicals (IVB)/Global Malaria Programme (GMP)

Report of the Fourth Meeting of the Joint Technical Expert Group (JTEG) on Malaria Vaccines in Pivotal Phase 3 Trials and Beyond

9-10 October 2012

Geneva, Switzerland

This report presents a summary of the discussions by the committee members and recommendations proposed by the JTEG.

LIST OF ABBREVIATIONS

ART: Anti-retroviral therapy
ASTMH: American Society of Tropical Medicine & Hygiene
CS: Circumsporozoite
DOI: Declaration of interest
DTwP/HepB/Hib: Diptheria, tetanus, whole cell pertussis, hepatitis B, *H. influenzae* type b
EMA: European Medicines Agency
EPI: Expanded programme on immunization
GSK: GlaxoSmithKline
MPAC: Malaria Policy Advisory Committeee
MVI: Malaria Vaccine Initiative
OPV: Oral polio vaccine
PATH: Program for Appropriate Technology in Health
SAE: Serious Adverse Event
SAGE: Strategic Advisory Group of Experts on Immunization
VE: Vaccine Efficacy

Joint Technical Expert Group (JTEG) Meeting
October 10, 2012
Summary of Topics Discussed and Key Points

Session 1. Welcome, Meeting Background and Objectives/Introduction from secretariat

This was the fourth meeting of JTEG. Objectives were outlined:

- Discussion with the Malaria Vaccine Development Partnership to help interpret the new data,
- To consider additional work required by the Secretariat to prepare for upcoming data,
- To determine if additional analyses should be requested,
- To receive JTEG input on external messages that will be available around the release of new data.

With the new results, WHO policy process remains the same: no policy decisions will be made prior to 2015, based on data to become available in late 2014, and on additional analyses to be performed at WHO's request. All results are confidential and should not be discussed outside the meeting. Submitted DOIs were deemed not to represent real or perceived conflicts requiring exclusion of any members.

Session 2. Presentation of Phase III data

Overview and Clarifications

Phase III study results from two analyses were shared:

- efficacy against clinical and severe malaria, and SAEs in 6,537 infants in the 6-12 week age group with one year of follow up, and
- immunogenicity for anti-CS, unsolicited AEs and rash, and solicited reactogenicity in 2200 (200 at each site) in the 6-12 week age group.

Neither numbers of children enrolled nor numbers of malaria cases occurring were distributed evenly across sites. For example, two sites taken together were responsible for over 50% of total malaria cases from the 11 sites in the older age group (5-17 months of age).

It was clarified that all analyses are stratified by site, in the Cox regression analyses. A test for heterogeneity of efficacy by site was not performed. The protocol was written such that site-specific effects would be examined only at the end of the study. The Partnership stated that this reasoning was based on an assumption that there would be insufficient cases for earlier site-specific analyses, although the actual numbers of cases to date have been higher than the pre-trial assumptions about incidence rates. It was clarified that in the graphs of cumulative malaria incidence, the drop in the denominator at 12 months was due to some participants having their one-year follow-up at slightly less than 12 months at the time of this analysis.

Changes in VE with time since vaccination have not been analysed for all episodes of malaria but may be incorporated into analyses in 2014. For severe malaria, 65 of the 104 cases included were analyzed in the February 2012 presentation of results.

Key Discussion Points

Potential explanations for the results were discussed, as were strategies for aiding in their interpretation. It was posited that subdividing the 5-17 month age group help clarify the differences seen between the 6-12 week and 5-17 month groups. There was much discussion about the possibility of heterogeneity of efficacy by site, and what bearing the lack of analysis examining such heterogeneity may have on interpreting the current data. JTEG indicated having site or transmission strata-specific VE estimates was very important, as the results from one or two high transmission sites could greatly affect the pooled estimate of effect. GSK/MVI Partnership stated that for any additional analyses or altered timing, the protocol must be amended, and this must be reviewed by many ethical and scientific review committees. An amendment that will include VE by site (for 18 months follow up) has been submitted and, if approved, will allow for these analyses to be done by 2013[Post-meeting note March 2013: this amendment has passed. Thus all analyses dependent on the amendment will occur in 2013]. It was clarified that even this amendment will not explore VE by site over 12 months. VE will be provided by site only over the full 18 month period, not including any breakdown by time period. The VE breakdown by time period will only be available in late 2014 [Post-meeting note March 2013: the 2013 analyses will include VE by site and broken down by time period, as GSK/MVI included these requests in line with JTEG's feedback].

The substantial difference in the pooled VE estimate between the older and younger age groups was noted, and it was suggested that one possible partial explanation could be that if VE wanes with time since vaccination, then the period of highest VE would coincide with lowest incidence of malaria due to the reduced malaria risk in young infants related to maternally acquired antibodies. Another difference between age groups discussed was that the older age group was enrolled more quickly while infants were enrolled over a longer period. Thus seasonality of malaria could impact VE in the 2 age groups differently. Furthermore, different sites contributed different proportions of cases for the two age groups. Indeed two sites did not contribute any children to the previously published analysis in 5-17 month olds.

It was observed that the Kaplan-Meier curves appear different in Phase III compared to Phase II data; one possible reason was speculated to be the different transmission levels. Transmission in some sites in the Phase III trial is much higher than in any Phase II studies.

In the Phase III trial, seasonality of malaria was not taken into account in the analyses to date. Most sites show some peaks in malaria but are considered perennial, with the exception of Nanoro in Burkina Faso where malaria is both highly seasonal and there is high transmission. It was proposed that analyses of the effect of seasonality on vaccine efficacy be included in future analyses. Broader issues were also raised, such as whether RTS,S should be delivered in the routine EPI schedule or potentially outside this schedule.

Discussion of Phase III data including available data on alternative schedules, including 4 doses.

Overview and Clarifications

Key differences between the 5-17 month age group and 6-12 week age group were highlighted including:

- Approximately three-fold higher anti-CS IgG responses to vaccination in the older age group
- Co-administration with DTwP/HepB/Hib and OPV in the younger age group
- Higher proportion with presence of maternally acquired antibodies to the CS sporozoite antigen in the younger age group (as measured by pre-vaccination anti-CS IgG)
- Greater naturally acquired immunity, and higher previous exposure to malaria in the older age group
- Prior Hepatitis B priming at the time of RTS,S/AS01 vaccination in the older age group (as part of prior pentavalent immunization)

There has not been an examination of an association between immunological response and birth weight or other anthropometric indicators, but this can be done at the end of the study as the data are being collected. There are few data looking at the correlation between anti-HepB and anti-CS. There is some evidence from phase II trials that co-administration with DTwP/Hep B/Hib and OPV may adversely affect immunogenicity. The potential role of HepB as a prime for the anti-CS response was also discussed. A JTEG member pointed out that kinetics of decline of antibody responses could differ by age even when peak responses do not differ. Decline can be more rapid in infants compared to older children with some other vaccines.

Key Discussion Points

The distribution of children and cases is different between the 2 age groups and thus the pooled VE results for each of the 2 age groups are not strictly comparable. Site specific weighting in the analyses presented to date is imposed by the Cox regression model.

An important question still being explored is the relationship between anti-CS titers and vaccine efficacy. No established correlate of protection currently exists for RTS,S/AS01, but a sense of the correlation (or lack of correlation) between titer and risk of disease would be helpful from the Phase III data. Challenge studies and Phase II field trials have found consistent statistically significant associations between total IgG titers and vaccine efficacy against infection but not consistently for morbidity.

With this vaccine, it appears that the most useful immunological measure for associating with efficacy may not be peak titer, but IgG titers at the time of infection. Antibody levels at the time of infection could vary by age group. Because of the short time interval before the sporozoite reaches the liver, there is insufficient time to mount an anamnestic immune response. The Olutu et al. study in Kilifi was raised exploring the relationship between CS antibody titers and protection to assess whether it was a linear or a stepwise function/threshold effect. In that

particular setting, it appeared to be a step-wise function. However, these results have not been confirmed in other settings.

The possible contribution of immune interference from EPI vaccines was discussed. A JTEG member stated that, even in 2-week staggered schedules (done with AS02 studies), interference can occur. Adjuvant use in different vaccines given could also have an effect, but since all co-administered parenteral vaccines given were alum-based, there are unlikely to be concerns about non-specific effects that would apply differently in the studies under discussion. There is evidence that RTS,S does not affect measles titers, but no evidence was available at the meeting on the effect of the measles vaccine on RTS,S response. A JTEG member indicated that interference between RTS,S and measles is unlikely, due to the contrast between live and subunit vaccine kinetics for induction of immunogenicity.

Further analyses of association between immunogenicity and pre-existing maternal antibodies could be informative.

The issue of timing between vaccination and infection was raised as an additional complexity that has not been fully looked at. The time interval between completion of the vaccination schedule and seasonal transmission is relevant if efficacy wanes. The relationship between vaccination and seasonality is likely different by age group given the rapid enrollment of the 5-17 month age group and the longer enrollment of 6-12 week age group.

There was a discussion about RTS,S kinetics of immunogenicity, suggesting that the vaccine does not appear to induce high, long-lived plateaus of immunogenicity, with boosters perhaps likely to provide multiple primary vaccination kinetics. The reasons for this are unclear, although it was raised that with RTS,S the malaria response may be subdominant to the Hepatitis B response (note that a plateau of anti-Hep B IgG is obtained with RTS,S vaccination).

The Partnership was asked whether there were plans to test RTS,S in adults. For the moment the Partnership is prioritizing infants. The site-specific analyses should give a sense of what the potential role could be in a range of settings. Thus, the data to become available in late 2014 will only allow assessment of direct benefits against morbidity, but there may be advantages to generation of data in broader age ranges, so that whether or not there may be a role for RTS,S/AS01 as a contribution to elimination in some settings can be assessed after 2015.

Availability of next data packages

Overview and Clarifications

Assuming the current protocol amendment is approved, 18 month post dose 3 results are expected in 2013 and will include efficacy pooled and by site over 18 months. The statistical analysis plan is under development and will be sent to JTEG for input in the beginning of 2013. The last child's last visit will occur in December 2013 (all children are followed for at least 12 months post booster). The final analyses in late 2014 will include WHO pre-specified requests, i.e. additional analyses that WHO indicated would be necessary for a policy decision in 2015. A

single-blind extension has been arranged to follow up all children to 49 and 41 months post dose 1 in the 5-17 month age category and 6-12 week age category, respectively.

Key Discussion Points

There was intense discussion about the process for requiring an amendment, timelines and regulatory limitations to doing unplanned analyses. It was clear that additional clarification on all of these issues would be of use.

JTEG has previously emphasized the need for longer follow up. However, if a decline in vaccine efficacy is apparent in one year of follow up and there is evidence of low vaccine efficacy after a year or two, the pressure to follow participants longer is reduced.

Update on regulatory status & Phase 4 plans

Overview and Clarifications

Prior to the availability of these new data to the Partnership, much scenario planning and decision tree analysis had already been done by GSK/MVI in anticipation of the results. Both co-primary endpoints were met, but many questions remain as to what the optimal indication and the schedule (EPI co-administration with DTP1-3 or alternative) would be, which are important considerations for filing. The timing of regulatory submissions are under assessment. Plans for Phase IV studies are also under revision, as they will depend on the results of the Phase III trial and the indication of the vaccine.

There was clarification about the impact modeling, which is based on the Swiss Tropical and Public Health Institute model and has been reviewed by a joint QUIVER/JTEG group. A JTEG member expressed caution in some of the assumptions used by the mathematical models [Post-meeting note: a second WHO meeting to assess the status of public health impact and cost-effectiveness models for malaria vaccines is being held in May 2013].

Key Discussion Points

There was much discussion about the pros and cons of doing additional analyses not yet specified in the data analysis plan. Conducting a study in the context of submission to a stringent regulatory authority was noted to add a layer of complexity that makes data exploration more difficult. There are opportunities for scientific consultations with European Medicines Agency (EMA), but the Partnership has concerns that actions taken without a careful approval process could invalidate the file when submitted to a regulatory agency. Because of the time it takes to go through the approval process, quick answers cannot be easily obtained despite the potential usefulness of additional analyses with interpretation of the latest results. Although there do not appear to be ethical issues with the requested clarifying analyses (e.g. site-specific data), recently an ethical committee raised questions to even the 18 month analysis in the amendment, so it is not a given that such unplanned analyses would be approved [Post-meeting note March 2013: all ethical committees and national regulatory authorities did approve the amendment]. This is the only pivotal Phase III trial, and it is important not to call into question its integrity. At the same

time, waiting a year for the ability to do new analyses is a highly inefficient way to explore the important scientific questions raised by these results. It would be an ethical problem, it was argued, to have a vaccine that could save lives but was withheld because analyses were not done in a timely fashion that could have been. Furthermore some analyses could be done now, which could lead to generation of additional data that could accelerate timelines.

There were also discussions of the potential impact on sites if site-specific vaccine efficacies were known. Theoretically, this knowledge could impact how investigators at a site follow up their patients. Many meeting participants did not think this would be a problem, but did acknowledge the theoretical possibility.

The Partnership agreed to consider if there could be a different course of action that would satisfy JTEG, regulatory agencies, involved scientific and ethical review committees, and the Partnership to conduct analyses that would allow for better understanding of the latest results. It was noted that the Partnership's decision to defer the regulatory submission, will also delay policy recommendation timelines by 6 months.

Given the many questions that are raised by the latest results, it was suggested that publishing these results without further context and explanation could be misleading and confusing to the scientific community. GSK considers it is very important to publish data when they are available so no one accuses them of with-holding data, particularly data that are different than what was hoped for.

In summary, there was strong support for looking at ways to improve flexibility for additional analyses that may help explain results or suggest further analyses or studies that are needed. Delay of these additional analyses could postpone timelines and access to the vaccine, depending on the results not yet to hand. It was appreciated that regulatory considerations are paramount. There was frustration that the publication speculates on questions that could be answered by analyses that could be performed on available data.

Review of status of other Phase III and ancillary studies

Malaria Transmission Intensity Study

Overview and Clarifications

Annual cross-sectional surveys will collect blood from 800 randomly selected children and adults for four years at eight sites. The results after one annual survey were presented. The peak prevalence of *P. falciparum* infection varied from over 60% to less than 5% across the range of sites, with different age patterns for prevalence of infection in the different sites. Bednet coverage also varied by site and impacted the odds of parasitemia differently by site. The results confirm the large heterogeneity in transmission intensity by site.

Key Discussion Points

The transmission intensity study is a useful contribution that should facilitate extrapolation from the Phase III trial to non-trial settings in terms of transmission intensity. Such extrapolation may be necessary at the policy stage if VE varies with transmission intensity.

Lot-to-lot consistency study

Overview and Clarifications

The first primary objective was to establish consistency of immunogenicity between three consecutive commercial scale lots of RTS,S/AS01, and the second primary objective was to establish non-inferiority of commercial scale lots to the pilot scale lot. Both were demonstrated.

Key Discussion Points

It was pointed out that the antibody titers seen in this study were lower than seen in other studies of the same age group. The study population was 5-17 month old Nigerian children thought to be living in an area of fairly high malaria transmission (although no data on the transmission intensity was presented). There may be several reasons that immunogenicity will vary by site or even within a site. These sites were chosen in Nigeria to support a filing that would include Nigerian data, which is required for licensure in that country.

Hepatitis B indication, co-administration with Rotavirus and S. pneumoniae

Overview and Clarifications

This study, the goal of which is to establish the non-inferiority of the Hepatitis B response, is fully enrolled and in progress. Secondary objectives include establishing non-inferiority of immunogenicity in co-administration with pneumococcal and rotavirus vaccines. The results should be available in 2013.

Study in HIV-positive children

Overview and Clarifications

The primary goal of this study is safety for 14 months post dose 1. Two sites in Kenya are participating with a total of 200 study participants, and results should be available in 2013. Children are diagnosed before entering the study, and thus are on ART treatment. There is a subset of children in the Phase III trial who are now known to be HIV positive but were not diagnosed at the time of vaccination and were not on treatment. A case-control study will be done to look at safety and immunogenicity in this group of 125 children.

Immunology study

Overview and Clarifications

This study will follow the model of the HIV RV144 prime boost vaccine trial in Thailand to better understand vaccine-induced protection against malaria and identify a correlate of protection. Three working groups are involved in drafting a proposal for the study, which will be thoroughly reviewed by a number of experts. The study is framed in the larger systems biology context. Because samples are taken at a fixed time, they are not obtained at the time when infection occurs.

Key Discussion Points

It was noted that having serology at the time of infection would be helpful given the assumption that the immunological response changes over time since vaccination. Such samples will not be available, and analyses will be done using fixed timepoints for the sampling.

Genotyping study

Overview and Clarifications

The aim of the study is to better understand the mechanism of action of RTS,S/AS01 and to evaluate whether the vaccine puts selective pressure on parasites resulting in variants that may be resistant to the vaccine or lead to a change in the number of parasite types. The study, to be performed in collaboration with the Harvard School of Public Health, will occur post-unblinding of the pivotal Phase III trial.

JTEG Recommendations to WHO
JTEG indicated that the new data that have become available in Q4 2012 do not change the previously communicated policy timings. WHO policy recommendations can be expected in 2015, depending on the data available in 2014 and on the timing of regulatory submission.
RTS,S/AS01 will be evaluated as an addition to, not a replacement for, existing malaria prevention, diagnostic and treatment measures. There is a range of policy decisions possible in the 2015 timeframe, depending on the 2014 results.
JTEG highlights the following to be considered as part of the additional analyses for late 2014. These will also be revisited in review of the analysis plan for the 2013 analyses [Post-meeting note March 2013: some recommendations listed here were taken into account by GSK/MVI when the list of analyses to be conducted in 2013 was finalized] . • Site-specific and transmission strata specific efficacy analyses • Rates of disease in the vaccine vs control group broken down by time since vaccination • Explorations of correlation between immunogenicity and efficacy • Exploration of the interaction between seasonality and vaccine efficacy • Correlation between pre-existing maternally acquired antibody to CS and immunogenicity • Correlation between anti-CS and anti-Hepatitis B antibody titres
Given the results to date, contingency plans for alternative schedules should be included, minimizing the number of additional routine immunization visits whilst maximizing expected efficacy. However it is unlikely that policy recommendations for use can be made on alternative schedules without clinical trial data on those schedules.
JTEG recommends the Secretariat present to MPAC and SAGE: • Available data (as soon as embargo period is over) • Summary of issues JTEG has identified • Pipeline of additional work that is ongoing or planned
JTEG supports WHO's effort on communication about these results. JTEG could be included in such communication efforts by provision of slides.
JTEG supports in concept a systematic review of the age pattern of severe malaria in sub-Saharan Africa if possible to do, noting that age-spectrum of hospitalizations can change at the same location as transmission changes, and this must be taken into account. This work may support considerations of alternate schedules during the 2014-2015 policy discussions.

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Permission to publish on SAGE website/ in SAGE Yellow book was obtained

ORIGINAL ARTICLE

A Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Infants

The RTS,S Clinical Trials Partnership

ABSTRACT

BACKGROUND

The candidate malaria vaccine RTS,S/AS01 reduced episodes of both clinical and severe malaria in children 5 to 17 months of age by approximately 50% in an ongoing phase 3 trial. We studied infants 6 to 12 weeks of age recruited for the same trial.

METHODS

We administered RTS,S/AS01 or a comparator vaccine to 6537 infants who were 6 to 12 weeks of age at the time of the first vaccination in conjunction with Expanded Program on Immunization (EPI) vaccines in a three-dose monthly schedule. Vaccine efficacy against the first or only episode of clinical malaria during the 12 months after vaccination, a coprimary end point, was analyzed with the use of Cox regression. Vaccine efficacy against all malaria episodes, vaccine efficacy against severe malaria, safety, and immunogenicity were also assessed.

RESULTS

The incidence of the first or only episode of clinical malaria in the intention-to-treat population during the 14 months after the first dose of vaccine was 0.31 per person-year in the RTS,S/AS01 group and 0.40 per person-year in the control group, for a vaccine efficacy of 30.1% (95% confidence interval [CI], 23.6 to 36.1). Vaccine efficacy in the per-protocol population was 31.3% (97.5% CI, 23.6 to 38.3). Vaccine efficacy against severe malaria was 26.0% (95% CI, –7.4 to 48.6) in the intention-to-treat population and 36.6% (95% CI, 4.6 to 57.7) in the per-protocol population. Serious adverse events occurred with a similar frequency in the two study groups. One month after administration of the third dose of RTS,S/AS01, 99.7% of children were positive for anti-circumsporozoite antibodies, with a geometric mean titer of 209 EU per milliliter (95% CI, 197 to 222).

CONCLUSIONS

The RTS,S/AS01 vaccine coadministered with EPI vaccines provided modest protection against both clinical and severe malaria in young infants. (Funded by GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative; RTS,S ClinicalTrials.gov number, NCT00866619.)

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Considerable gains have been achieved in malaria control during the past decade.[1,2] Nonetheless, malaria remains a major public health concern. In 2010, an estimated 216 million cases of malaria and 655,000 malaria-related deaths occurred, with the vast majority of deaths occurring in African children.[1]

The RTS,S/AS01 candidate malaria vaccine targets the pre-erythrocytic stage of the *Plasmodium falciparum* parasite. It was developed to reduce clinical and severe malaria in African children. Ideally, it would be administered through the well-established Expanded Program on Immunization (EPI).

In 2011, we reported the results for the first coprimary end point from an ongoing phase 3 trial, which showed that during 12 months of follow-up, RTS,S/AS01 had an efficacy against clinical and severe malaria of 55.8% (97.5% confidence interval [CI], 50.6 to 60.4) and 47.3% (95% CI, 22.4 to 64.2), respectively, among children 5 to 17 months of age at enrollment (per-protocol analysis).[3] Vaccine efficacy against severe malaria among children 6 to 12 weeks of age and those 5 to 17 months of age combined was 34.8% (95% CI, 16.2 to 49.2) during an average of 11 months of follow-up (range, 0 to 22). We now report on the second coprimary end point from the same trial: efficacy against clinical malaria during 12 months of follow-up among infants 6 to 12 weeks of age at enrollment, when RTS,S/AS01 was coadministered with EPI vaccines.

Methods

Study Design

Details of the study methods have been described previously[3-7] and are provided in the Supplementary Appendix and the study protocol, both of which are available with the full text of this article at NEJM.org. This phase 3, randomized, controlled, double-blind trial is being conducted at 11 centers in 7 African countries with a range of malaria-transmission intensity (Fig. S1 in the Supplementary Appendix). The trial is designed to evaluate vaccine efficacy, safety, and immunogenicity for 32 months after the first dose of study vaccine in children 6 to 12 weeks of age or 5 to 17 months of age at enrollment. The trial includes three study groups in each age category: infants who received three doses of RTS,S/AS01 administered at 1-month intervals and a booster dose 18 months after the third dose, infants who received three doses of RTS,S/AS01 at 1-month intervals without a booster dose, and a control group of infants who received a non-malaria comparator vaccine. The analysis described in this report combines the first two groups (referred to as the RTS,S/AS01 group) and compares this group with the control group[6] 14 months after the first dose of vaccine administered in children 6 to 12 weeks of age (Fig. S2 in the Supplementary Appendix). The trial protocol was approved by all relevant ethics review boards and national regulatory authorities (Tables S1A and S1B in the Supplementary Appendix). Written informed consent was obtained from the children's parents or guardians. The study was undertaken in accordance with Good Clinical Practice guidelines.[8]

Study Oversight

The trial was sponsored by GlaxoSmithKline Biologicals (GSK), the vaccine developer and manufacturer, and funded by both GSK and the Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative, which received a grant from the Bill and Melinda Gates Foundation. All study centers received study grants from the Malaria Vaccine Initiative, which also provided funding for authors' travel and accommodations related to this trial. All the authors reviewed all manuscript drafts, approved the final version of the manuscript, and made the decision to submit it for publication. No GSK authors were involved in the collection or analysis of the data; the analysis was performed by an independent statistician. The authors had full access to the results. The authors remain unaware of study-group assignments in this ongoing trial and do not have access to the raw data at this point. Details of the contributions of all the authors to the study are available in the Supplementary Appendix. The Clinical Trials Partnership Committee and Writing Group vouch for the completeness and accuracy of the data presented and for the fidelity of this report to the study protocol.

Randomization and Vaccination

From December 2009 through January 2011, a total of 6537 infants 6 to 12 weeks of age were randomly assigned to one of the three study groups in a 1:1:1 ratio. Three doses of the RTS,S/AS01 or

the comparator vaccine, meningococcal serogroup C conjugate vaccine (Menjugate, Novartis), were coadministered with EPI vaccines according to the World Health Organization EPI schedule.[9] EPI vaccines comprised a diphtheria–tetanus–whole-cell pertussis–hepatitis B–*Hemophilus influenzae* type b pentavalent vaccine (Tritanrix HepB Hib, GSK) and an oral poliovirus vaccine containing serotypes 1, 2, and 3 (Polio Sabin, GSK). The study and pentavalent vaccines were administered intramuscularly at different protocol-specified injection sites.

SURVEILLANCE FOR CLINICAL AND SEVERE MALARIA

Passive surveillance for malaria began at the time of the first vaccination. Parents or guardians of the study participants were encouraged to seek care at a health facility if the child had any signs of illness, and transportation was facilitated. All participants who presented to a study facility with reported or documented fever during the previous 24 hours were evaluated for malaria.

The primary efficacy end point for this analysis was the incidence of clinical malaria, defined as an illness in a child who was brought to a study facility with an axillary temperature of 37.5°C or higher and *P. falciparum* asexual parasitemia at a density of more than 5000 parasites per cubic millimeter or a case of malaria meeting the primary case definition of severe malaria (Table S2 in the Supplementary Appendix). Different parasite thresholds were used for secondary case definitions (Table 1). Participants who were hospitalized were evaluated for severe malaria on the basis of a protocol-defined algorithm (Table S3 in the Supplementary Appendix).[4,10]

SAFETY SURVEILLANCE

Data regarding serious adverse events were recorded by means of passive surveillance beginning after the first dose of vaccine. Verbal autopsies were conducted for deaths that occurred outside study facilities.[11] Information was collected on all unsolicited reports of adverse events that occurred within 30 days after vaccination and on reactogenicity (pain, swelling, redness at the injection site, drowsiness, fever, irritability or fussiness, or loss of appetite) within 7 days after vaccination among the first 200 participants enrolled at each center. Symptom intensity was assessed with the use of standardized methods (Table S4 in the Supplementary Appendix). Information on related adverse events within 30 days after vaccination was collected for all participants. Study clinicians used clinical judgment to decide whether an adverse event was likely to be related to the vaccine. In an analysis of previous RTS,S studies, rash was observed more frequently in children vaccinated with RTS,S than in controls.[12] Rashes and mucocutaneous diseases occurring within 30 days after vaccination and seizures occurring within 7 days after vaccination were reported according to Brighton Collaboration guidelines[13,14] (see the Methods section in the Supplementary Appendix).

IMMUNOGENICITY

Anti-circumsporozoite antibodies were measured by means of enzyme-linked immunosorbent assay[15] in the first 200 infants enrolled at each study center at screening and 1 month after dose-3. An antibody titer of 0.5 EU per millimeter or greater was considered to be positive.

LABORATORY AND RADIOLOGIC PROCEDURES

Laboratory and radiologic procedures have been reported previously[5] and are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The statistical methods have been described in detail previously.[3,7] We used Cox regression models (1 minus hazard ratio) to evaluate vaccine efficacy against the first or only episode of clinical malaria, using the study center as a stratification factor that allowed for differential baseline hazards. For the coprimary end point, vaccine efficacy against clinical malaria during 12 months of follow-up in the two age categories, 97.5% confidence intervals were used, ensuring an overall two-sided alpha level of 5%. The proportionality of hazards was evaluated by means of Schoenfeld residuals and models, including time-varying covariates. Secondary analyses, which included evaluations based on other case definitions and an analysis including multiple episodes of clinical malaria, were performed with the use of negative binomial regression. Vaccine efficacy against severe malaria was defined as 1 minus the risk ratio and is presented with 95% confidence intervals and Fisher's exact P values.

Primary analyses of vaccine efficacy were based on the per-protocol population, which included all participants who received three doses

Table 1. Efficacy of the RTS,S/AS01 Vaccine against Clinical and Severe Malaria in Infants Enrolled at 6 to 12 Weeks of Age.

Variable	RTS,S/AS01 Vaccine			Control Vaccine			Protective Efficacy		Protective Efficacy Adjusted for Covariates*	
	No. of Events	Person-Yr	Event Rate	No. of Events	Person-Yr	Event Rate	% (CI)†	P Value	% (95% CI)	P Value
Clinical malaria‡										
Per-protocol population (12 mo after third dose of vaccine)										
First or only episode										
>5000 parasites/mm³ and temperature ≥37.5°C (coprimary end point)	1161	3163	0.37	714	1476	0.48	31.3 (23.6–38.3)	<0.001	31.5 (24.7–37.6)	<0.001
>0 parasites/mm³ and measured or reported fever	1475	2921	0.50	879	1328	0.66	32.4 (26.5–37.9)	<0.001	32.6 (26.7–38.0)	<0.001
>500 parasites/mm³ and temperature ≥37.5°C	1282	3073	0.42	770	1429	0.54	30.3 (23.7–36.2)	<0.001	30.4 (23.8–36.3)	<0.001
>20,000 parasites/mm³ and temperature ≥37.5°C	1005	3256	0.31	630	1535	0.41	31.4 (24.2–37.9)	<0.001	31.6 (24.4–38.1)	<0.001
All episodes, >5000 parasites/mm³ and temperature ≥37.5°C	2301	3604	0.64	1626	1790	0.91	32.9 (26.3–38.8)	<0.001	33.0 (26.4–38.9)	<0.001
Intention-to-treat population (14 mo after first dose of vaccine)										
First or only episode, >5000 parasites/mm³ and temperature ≥37.5°C	1283	4106	0.31	782	1949	0.40	30.1 (23.6–36.1)	<0.001		
All episodes, >5000 parasites/mm³ and temperature ≥37.5°C	2615	4688	0.56	1864	2345	0.79	32.9 (26.7–38.5)	<0.001		
	No. of Infants	No. Affected	Affected rate	No. of Infants	No. Affected	Affected rate	% (95% CI)	P Value		
			%			%				
Severe malaria§										
Per-protocol population (12 mo after third dose of vaccine)										
Primary case definition	3995	58	1.5	2008	46	2.3	36.6 (4.6–57.7)	0.02		
Secondary case definition	3995	63	1.6	2008	51	2.5	37.9 (8.3–57.8)	0.01		
Intention-to-treat population (14 mo after first dose of vaccine)										
Primary case definition	4358	77	1.8	2179	52	2.4	26.0 (–7.4–48.6)	0.09		
Secondary case definition	4358	83	1.9	2179	58	2.7	28.4 (–1.9–49.4)	0.06		

* In the adjusted analyses, data were stratified according to study site with adjustment for the distance to the nearest outpatient health facility.

† All end points are presented with 95% confidence intervals except for the coprimary end point, which is presented with 97.5% confidence intervals. The coprimary end point was defined as vaccine efficacy against a first or only episode of clinical malaria, according to the primary case definition.

‡ The primary case definition of clinical malaria was an illness in a child brought to a study facility with a temperature of ≥37.5°C and *Plasmodium falciparum* asexual parasitemia at a density of >5000 parasites per cubic millimeter or a case of malaria meeting the primary case definition of severe malaria.

§ The primary case definition of severe malaria was *P. falciparum* asexual parasitemia at a density of >5000 parasites per cubic millimeter with one or more markers of disease severity and without diagnosis of a coexisting illness. The secondary case definition of severe malaria was *P. falciparum* asexual parasitemia at a density of >5000 parasites per cubic millimeter with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of ≤2 (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycemia, acidosis, elevated lactate level, or hemoglobin level of <5 g per deciliter. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis on analysis of cerebrospinal fluid, bacteremia, or gastroenteritis with severe dehydration.

of a study vaccine coadministered with EPI vaccines and who were included in efficacy surveillance, starting 14 days after the third dose of a study vaccine. The modified intention-to-treat population included all participants who received at least one dose of a study vaccine. In the adjusted analyses, vaccine efficacy was adjusted for study center and distance to the nearest outpatient facility (≤5 km vs. >5 km). Data were censored 14 months after the first dose of vaccine, or at the date of emigration, withdrawal of consent, or death.

Serious adverse events were coded from clinician-assigned diagnoses according to the preferred terms of the *Medical Dictionary for Regulatory Activities*[16] and were based on available clinical and laboratory evidence.

The primary analysis of immunogenicity was based on the per-protocol population. Anti-circumsporozoite antibody titers were plotted and evaluated after the third dose of a study vaccine on the basis of seropositivity levels and geometric mean titers.

RESULTS

STUDY POPULATION

In total, 6537 infants 6 to 12 weeks of age were enrolled; 6003 (91.8%) were included in the per-protocol analysis (Fig. 1, and Fig. S3 in the Supplementary Appendix). Baseline demographic characteristics were similar in the two study groups (Table S5 in the Supplementary Appendix). The numbers of participants and malaria episodes according to study center are shown in Table S6 in the Supplementary Appendix. As expected, the majority of malaria episodes were reported by centers in areas with the highest transmission; 43.5% of all clinical malaria episodes were reported by two high-transmission sites in western Kenya. These two sites, combined with the site in Nanoro, Burkina Faso (where transmission is high but seasonal), accounted for 72.6% of clinical malaria episodes in this analysis. The rate of use of insecticide-treated nets was 85.8% overall and was similar in the two study groups. Indoor residual spraying was conducted as a public health intervention at four study centers; at those centers, spraying coverage was low (Table S7 in the Supplementary Appendix).

VACCINE EFFICACY AGAINST CLINICAL AND SEVERE MALARIA

In the per-protocol population, the incidence of a first or only episode of clinical malaria meeting the primary case definition during 12 months of follow-up was 0.37 per person-year in the RTS,S/AS01 group and 0.48 per person-year in the control group, for a vaccine efficacy of 31.3% (97.5% CI, 23.6 to 38.3). Kaplan–Meier curves are shown in Figures 2A and 2B. Vaccine efficacy was not constant over time ($P<0.001$ by Schoenfeld residuals), with efficacy higher at the beginning than at the end of the follow-up period (Table S8 in the Supplementary Appendix). Vaccine efficacy against all clinical malaria episodes was 32.9% (95% CI, 26.3 to 38.8). Estimates of efficacy against clinical malaria were consistent across all case definitions and in both adjusted and intention-to-treat analyses (Table 1).

At least one episode of severe malaria occurred in 58 of 3995 infants (1.5%) in the RTS,S/AS01 group and in 46 of 2008 infants (2.3%) in the control group, for a vaccine efficacy of 36.6% (95% CI, 4.6 to 57.7) in the per-protocol population. In the intention-to-treat population, at least one episode of severe malaria occurred in 77 of 4358 infants (1.8%) in the RTS,S/AS01 group and in 52 of 2179 infants (2.4%) in the control group, for a vaccine efficacy of 26.0% (95% CI, −7.4 to 48.6) (Table 1, and Tables S15 and S16 in the Supplementary Appendix).

SAFETY

Serious Adverse Events

Serious adverse events were reported in 17.9% (95% CI, 16.8 to 19.1) of recipients of the RTS,S/AS01 vaccine and in 19.2% (95% CI, 17.6 to 20.9) of recipients of the meningococcal vaccine (Table 2, and Table S9 in the Supplementary Appendix). A total of 94 infants died: 66 of 4358 infants (1.5%; 95% CI, 1.2 to 1.9) in the RTS,S/AS01 group and 28 of 2179 infants (1.3%; 95% CI, 0.9 to 1.9) in the control group. Causes of death were similar in the two groups; none of the deaths were thought to be related to vaccination (Table S10 in the Supplementary Appendix). Serious adverse events that were considered to be related to a study vaccine occurred in 7 infants: 4 of the 4358 infants in the RTS,S/AS01 group and 3 of the 2179 infants in the control group; 4 events (2 in each group)

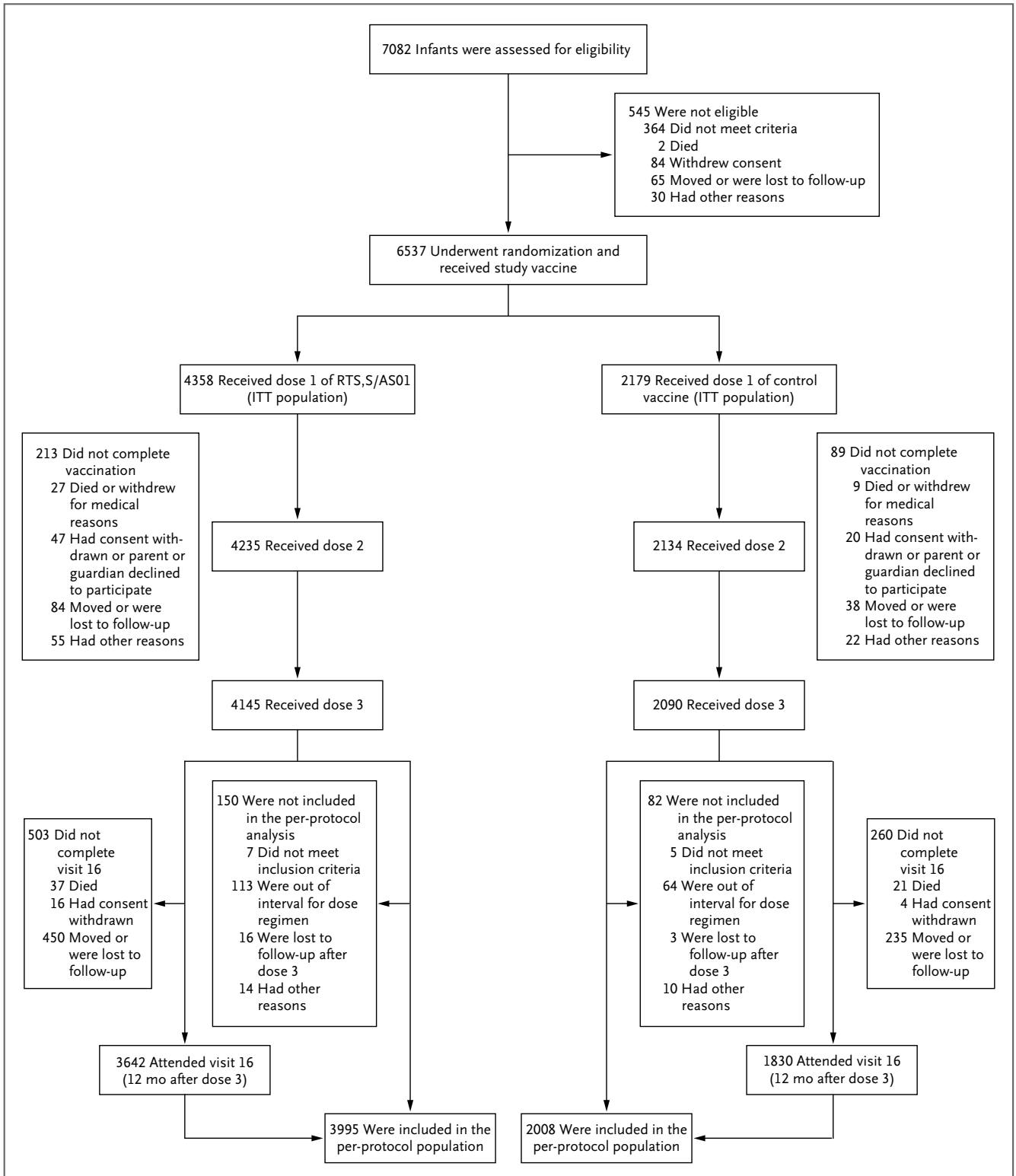
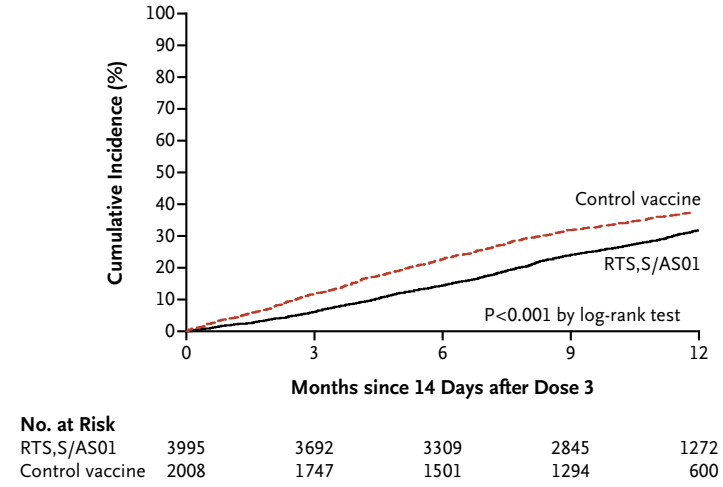


Figure 1. Enrollment of Infants 6 to 12 Weeks of Age.

ITT denotes intention to treat.



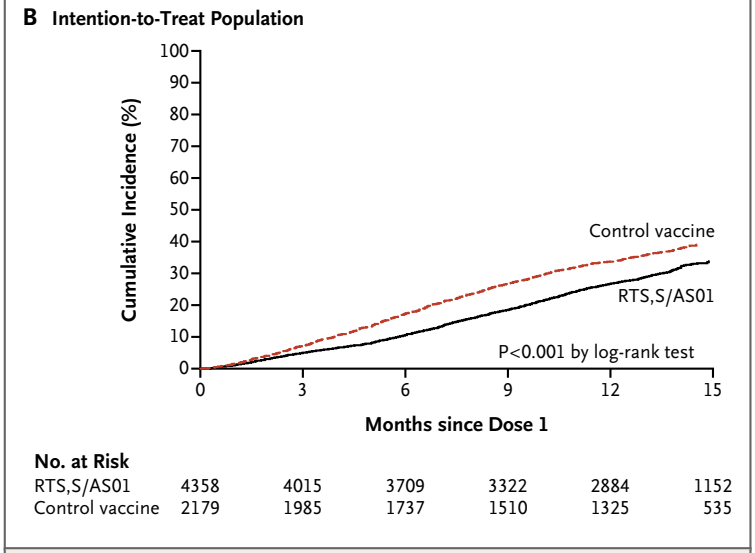


Figure 2. Cumulative Incidence of a First or Only Episode of Clinical Malaria (Primary Case Definition).

The cumulative incidence of clinical malaria in infants 6 to 12 weeks of age at enrollment is shown for the 12 months of follow-up after the third dose of a study vaccine in the per-protocol population (Panel A) and for the 14 months of follow-up after the first dose of vaccine in the intention-to-treat population (Panel B).

were episodes of fever for which infants were hospitalized for investigation. One infant (in the control group) had anaphylaxis, one infant (in the RTS,S/AS01 group) had a suspected injection-site infection related to the pentavalent vaccine, and one infant (in the RTS,S/AS01 group) had repeated febrile seizures associated with a respiratory infection. The frequency of seizures within 7 days after vaccination, reported previously, was similar in the two study groups.[3]

Meningitis of any cause was reported as a serious adverse event in 11 infants: 9 of the 4358 infants in the RTS,S/AS01 group and 2 of the 2179 infants in the control group (relative risk in the RTS,S/AS01 group, 2.3; 95% CI, 0.5 to 10.4). A pathogen was identified for 7 of the events (salmonella in 3 episodes of meningitis and pneumococcus in 4 episodes). The 4 remaining events, with no pathogen identified, were reported by a single study center (3 episodes of meningitis in the RTS,S/AS01 group and 1 episode in the control group). Of the 11 episodes of meningitis, 2 were new (1 due to pneumococcus and 1 due to salmonella); the 9 other episodes have been reported previously.[3] Investigator-driven medical review of previously reported meningitis episodes led to reclassification of 1 episode as an episode of pneumonia and reclassification of 4 episodes without cause as 2 episodes of pneumococcal meningitis and 2 of salmonella meningitis. Four of the episodes of meningitis occurred within 30 days after vaccination.

Adverse Events

Unsolicited reports of adverse events within 30 days after vaccination were recorded with similar frequency in the RTS,S/AS01 group (79.4%; 95% CI, 77.2 to 81.5) and in the control group (81.3%; 95% CI, 78.3 to 84.1). No clinically important imbalances were observed (Table S11A in the Supplementary Appendix). Information on unsolicited reports of adverse events related to the vaccine or leading to withdrawal within 30 days after vaccination is shown in Table S11B in the Supplementary Appendix. The frequency of solicited reports of local symptoms was similar among infants who received the RTS,S/AS01 vaccine and among those who received the meningococcal vaccine and was lower than that observed with the pentavalent vaccine (Table S13 in the Supplementary Appendix). Systemic reactogenicity was higher in the RTS,S/AS01 group than in the control group (Fig. 3, and Table S12 in the Supplementary Appendix). Postvaccination fever was reported after 30.6% of doses (95% CI, 29.2 to 32.0) in the RTS,S/AS01 group and after 21.1% of doses (95% CI, 19.4 to 22.8) in the control group. A temperature higher than 39°C was reported after less than 1% of doses. The incidence of mucocutaneous disease was similar in the two study groups (Table S14 in the Supplementary Appendix).

Table 2. Serious Adverse Events in Infants 6 to 12 Weeks of Age at Enrollment during 14 Months after the First Dose of Vaccine (Intention-to-Treat Population).

Variable	RTS,S/AS01 Vaccine (N=4358)		Control Vaccine (N=2179)	
	No. of Infants	% (95% CI)	No. of Infants	% (95% CI)
Serious events in all infants				
≥1 Serious adverse event	782	17.9 (16.8–19.1)	419	19.2 (17.6–20.9)
≥1 Serious adverse event, excluding malaria	760	17.4 (16.3–18.6)	407	18.7 (17.1–20.4)
≥1 Fatal serious adverse event*	66	1.5 (1.2–1.9)	28	1.3 (0.9–1.9)
≥1 Serious adverse event related to vaccine	4	0.1 (0.0–0.2)	3	0.1 (0.0–0.4)
≥1 Serious adverse event within 30 days after vaccination	192	4.4 (3.8–5.1)	96	4.4 (3.6–5.4)
Events with an incidence ≥0.5%†				
Pneumonia	302	6.9 (6.2–7.7)	152	7.0 (5.9–8.1)
Gastroenteritis	260	6.0 (5.3–6.7)	139	6.4 (5.4–7.5)
Malaria	184	4.2 (3.6–4.9)	115	5.3 (4.4–6.3)
Anemia	90	2.1 (1.7–2.5)	58	2.7 (2.0–3.4)
Febrile convulsion	82	1.9 (1.5–2.3)	46	2.1 (1.5–2.8)
Bronchiolitis	28	0.6 (0.4–0.9)	21	1.0 (0.6–1.5)
Convulsion	41	0.9 (0.7–1.3)	19	0.9 (0.5–1.4)
Bronchopneumonia	35	0.8 (0.6–1.1)	20	0.9 (0.6–1.4)
Upper respiratory tract infection	36	0.8 (0.6–1.1)	19	0.9 (0.5–1.4)
Salmonella sepsis	26	0.6 (0.4–0.9)	16	0.7 (0.4–1.2)
Malnutrition	29	0.7 (0.4–1.0)	7	0.3 (0.1–0.7)
Sepsis	26	0.6 (0.4–0.9)	10	0.5 (0.2–0.8)
HIV infection‡	27	0.6 (0.4–0.9)	9	0.4 (0.2–0.8)
Enteritis	11	0.3 (0.1–0.5)	12	0.6 (0.3–1.0)
Urinary tract infection	16	0.4 (0.2–0.6)	10	0.5 (0.2–0.8)
Measles	20	0.5 (0.3–0.7)	7	0.3 (0.1–0.7)
Pyrexia	15	0.3 (0.2–0.6)	11	0.5 (0.3–0.9)

* More than one fatal serious adverse event could be attributed to a single infant if there was more than one underlying cause of death (e.g., meningitis and sepsis).
† Events are listed according to the preferred terms in the *Medical Dictionary for Regulatory Activities*.
‡ HIV denotes human immunodeficiency virus.

IMMUNOGENICITY

Before vaccination, 34.3% and 35.2% of infants in the RTS,S/AS01 and control groups, respectively, were positive for anti-circumsporozoite antibodies but at low titers (Fig. S4 in the Supplementary Appendix). One month after the third dose of the study vaccine, 99.7% of infants in the RTS,S/AS01 group were positive for anti-circumsporozoite antibodies, with a geometric mean titer of 209 EU per milliliter (95% CI, 197 to 222).

DISCUSSION

This phase 3 trial showed that in young infants, the RTS,S/AS01 candidate vaccine provided modest protection against malaria when coadministered with EPI vaccines. The efficacy of RTS,S/AS01 reported here is lower than that observed in a phase 2 trial involving infants at three of the phase 3 trial sites, in which RTS,S/AS01 was coadministered with EPI vaccines. In that trial, geo-

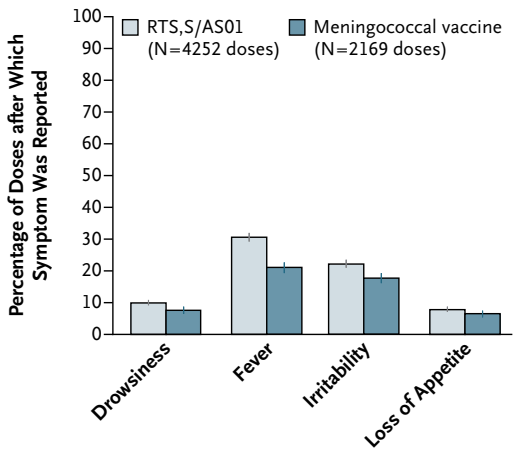


Figure 3. Incidence of Solicited Reports of Adverse Events during the 7-Day Postvaccination Period after Each Dose (Intention-to-Treat Population).

Solicited reports of adverse events during the 7-day postvaccination period were recorded and analyzed in the first 200 infants enrolled at each study site.

metric mean titers of anti-circumsporozoite antibodies after vaccination were similar to those measured here, but vaccine efficacy against clinical malaria was 61.6% (95% CI, 35.6 to 77.1).[17] Although we wish to avoid overinterpretation of the results of this previously reported small phase 2 trial with wide confidence intervals, it is notable that this higher estimate of efficacy comes from a study conducted at sites in areas with low-to-moderate malaria transmission. It is possible that the pooled estimate across the 11 centers in the phase 3 trial obscures differences in vaccine efficacy according to transmission intensity and that these two sets of results are compatible with each other.

The efficacy of the RTS,S/AS01 vaccine reported here is also lower than that reported previously among older children recruited for this trial at the same study centers.[3] A likely explanation for the lower vaccine efficacy among infants is an age-dependent differential immune response to the vaccine. This concept is supported by the lower anti-circumsporozoite antibody titers observed in infants (geometric mean titer, 209 EU per milliliter; 95% CI, 197 to 222) as compared with titers in older children (621 EU per milliliter; 95% CI, 592 to 652), reported previously.[3] Although the titer of anti-circumsporozoite antibodies is not an established correlate of the level of protection, an association with efficacy has been observed in several trials.[17-21] Infants may have mounted a lower immune response than older children owing to coadministration of RTS,S/AS01 with routine EPI vaccines, an inhibitory effect of maternally derived anti-circumsporozoite antibodies, an absence of priming with hepatitis B vaccine or with *P. falciparum* infection, or the infant's immature immune system.

Coadministration of RTS,S/AS01 with the pentavalent vaccine and the oral poliovirus vaccine might have resulted in immune interference and contributed to the lower anti-circumsporozoite antibody titers in the younger infants. Two phase 2 studies have explored the immunologic response to the related RTS,S/AS02 vaccine, either when coadministered with a diphtheria–tetanus–pertussis–hepatitis B vaccine or when given 2 weeks afterward. The geometric mean titer of anti-circumsporozoite antibodies was lower when vaccines were coadministered than when they were staggered (70 EU per milliliter [95% CI, 54 to 90] vs. 200 EU per milliliter [95% CI, 151 to 265]).[20,21] However, vaccine efficacy against infection was similar in the two trials (65.2% [95% CI, 20.7 to 84.7] during 6 months after vaccination and 65.9% [95% CI, 42.6 to 79.8] during 3 months after vaccination, respectively).

An absence of priming with hepatitis B vaccine or with *P. falciparum* infection may also have contributed to the lower anti-circumsporozoite antibody titers. In this trial, infants simultaneously received a hepatitis B surface antigen (HBsAg)–containing combination vaccine and the RTS,S vaccine, which contains HBsAg fused as a carrier protein to the circumsporozoite protein. Immune interference on concurrent administration of similar protein components has been described.[22] In contrast, in older children vaccinated against hepatitis B, memory T-cell reactivation may have enhanced the anti-circumsporozoite antibody response to RTS,S/AS01.[22] One study showed a tendency toward higher anti-circumsporozoite antibody responses in children who had been vaccinated against hepatitis B than in children who had not previously received hepatitis B vaccine.[23] Maternally derived antibodies can interfere with the immune response in young infants; such interference is common with live vaccines, such as the measles vaccine, but can also occur with some protein vaccines.[24,25] Similarly, pas-

sively acquired antibodies to either HBsAg or the circumsporozoite components of the RTS,S/AS01 vaccine might have suppressed immune responses. Finally, although most protein vaccines and polysaccharide–protein conjugate vaccines are immunogenic in young infants, improved immunogenicity and efficacy have often been achieved when vaccination has extended beyond the first few months of life.[22,26,27]

As previously reported in older children,[3] statistical models indicated nonproportionality of hazards over time. This could be due to waning vaccine efficacy, differential acquisition of natural immunity, or other factors that may influence the model,[28] such as heterogeneity of exposure, the vaccine effect at the individual level, or both.[29,30] If vaccine efficacy does wane, this might contribute to the lower observed efficacy among infants than among older children, especially because young infants may be less susceptible to malaria in the immediate postvaccination period owing to maternally acquired immunity, fetal hemoglobin, lower exposure, and other factors.[31]

The 11 sites of the phase 3 trial cover a wide range of malaria-transmission intensity. The inclusion of sites in high-transmission or seasonal-transmission areas and the large proportion of cases of severe and clinical malaria from these sites might have contributed to the lower vaccine efficacy among infants in this trial than in earlier trials involving infants. The implications of the large representation of malaria episodes from high-transmission areas may become apparent when site-specific data are analyzed at a later date, as specified by the protocol. Estimates of site-specific vaccine efficacy and the corresponding estimates of clinical or severe malaria episodes averted will help to determine what role this vaccine might have in malaria control. Exploration of factors that might affect vaccine efficacy, including the effect of maternal antibodies, the role of immune interference by EPI vaccines, the effect of the RTS,S/AS01 booster, and status with respect to previous exposure to *P. falciparum* parasites, will provide crucial information for the further development of this vaccine and for other malaria vaccines under development.[32]

Overall, fatal, or vaccine-related serious adverse events were balanced between the study groups. In the previous analysis, which included infants and older children, the incidence of meningitis was imbalanced between the RTS,S/AS01 and control groups.[3] The imbalance remains, but we now have clarified that the majority of cases had a bacterial cause. We will continue to monitor the incidence of meningitis throughout the trial. The imbalance in the incidence of rash, observed in previous RTS,S studies,[12,33] was not confirmed in this larger trial.

This phase 3 trial shows efficacy of the RTS,S/AS01 vaccine. Data from the remainder of this trial and additional studies in progress will contribute to the understanding of the complex interplay among the intensity of exposure to malaria, the immune response, and vaccine efficacy.

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APPENDIX

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REFERENCES

1. World malaria report 2011. Geneva: World Health Organization, 2011.
2. Steketee RW, Campbell CC. Impact of national malaria control scale-up programmes in Africa: magnitude and attribution of effects. Malar J 2010;9:299.
3. The RTS,S Clinical Trials Partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011;365:1863-75.
4. Vekemans J, Marsh K, Greenwood B, et al. Assessment of severe malaria in a multicenter, phase III, RTS,S/AS01 malaria candidate vaccine trial: case definition, standardization of data collection and patient care. Malar J 2011;10:221.
5. Swysen C, Vekemans J, Bruls M, et al. Development of standardized laboratory methods and quality processes for a phase III study of the RTS,S/AS01 candidate malaria vaccine. Malar J 2011;10:223.
6. Leach A, Vekemans J, Lievens M, et al. Design of a phase III multicenter trial to evaluate the efficacy of the RTS,S/AS01 malaria vaccine in children across diverse transmission settings in Africa. Malar J 2011;10:224.
7. Lievens M, Aponte JJ, Williamson J, et al. Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS,S/AS01 malaria vaccine in African children. Malar J 2011;10:222.
8. ICH harmonised tripartite guideline: guideline for Good Clinical Practice. International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). June 1996:30-3, 41-52 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf).
9. Immunization in practice module 2: EPI vaccines. Geneva: World Health Organization, 2004:26.
10. Bejon P, Berkley JA, Mwangi T, et al. Defining childhood severe falciparum malaria for intervention studies. PLoS Med 2007;4(8):e251.
11. Verbal autopsy standards: ascertaining and attributing cause of death. Geneva: World Health Organization, 2007.
12. Vekemans J, Guerra Y, Lievens M, et al. Pooled analysis of safety data from pediatric phase II RTS,S/AS malaria candidate vaccine trials. Hum Vaccin 2011;7:1309-16.
13. Beigel J, Kohl KS, Khuri-Bulos N. Rash including mucosal involvement: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5697-706.
14. Bonhoeffer J, Menkes J, Gold MS, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004;22:557-62.
15. Clement F, Van Braeckel E, Desombere I, et al. Validation of an enzyme-linked immunosorbent assay for the quantification of human IgG directed against the repeat region of the circumsporozoite protein of the parasite Plasmodium falciparum. Malar J (in press).
16. MedDRA term selection: points to consider: ICH-endorsed guide for MedDRA users. Release 4.2 (http://www.meddramsso.com/files_acrobat/ptc/9491-1410_TermSelPTC_R4_2_sep2011.pdf).

17. Asante KP, Abdulla S, Agnandji S, et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis 2011;11:741-9. [Erratum, Lancet Infect Dis 2011;11:727.]
18. Kester KE, Cummings JF, Ofori-Anyinam O, et al. Randomized, double-blind, phase 2a trial of falciparum malaria vaccines RTS,S/AS01B and RTS,S/AS02A in malaria-naive adults: safety, efficacy, and immunologic associates of protection. J Infect Dis 2009;200:337-46.
19. Olotu A, Lusingu J, Leach A, et al. Efficacy of RTS,S/AS01E malaria vaccine and exploratory analysis on anti-circumsporozoite antibody titres and protection in children aged 5-17 months in Kenya and Tanzania: a randomised controlled trial. Lancet Infect Dis 2011;11:102-9. [Erratum, Lancet Infect Dis 2011;11:159.]
20. Abdulla S, Oberholzer R, Juma O, et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. N Engl J Med 2008;359:2533-44.
21. Aponte JJ, Aide P, Renom M, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. Lancet 2007;370:1543-51.
22. Dagan R, Poolman J, Siegrist CA. Glycoconjugate vaccines and immune interference: a review. Vaccine 2010;28:5513-23.
23. Lell B, Agnandji S, von Glasenapp I. A randomized trial assessing the safety and immunogenicity of AS01 and AS02 adjuvanted RTS,S malaria vaccine candidates in children in Gabon. PLoS One 2009;4(10):e7611.
24. Hodgins DC, Shewen PE. Vaccination of neonates: problem and issues. Vaccine 2012;30:1541-59.
25. Siegrist CA. Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants. Vaccine 2003;21:3406-12.
26. Prymula R, Plisek S. Clinical experience with DTPw-HBV ad DTPw-HBV/Hib combination vaccines. Expert Opin Biol Ther 2008;8:503-13.
27. Insel RA. Potential alterations in immunogenicity by combining or simultaneously administering vaccine components. Ann N Y Acad Sci 1995;754:35-47.
28. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer, 2000.
29. White MT, Griffin JT, Drakeley CJ, Ghani AC. Heterogeneity in malaria exposure and vaccine response: implications for the interpretation of vaccine efficacy trials. Malar J 2010;9:82.
30. Halloran ME, Longini IM Jr, Struchiner CJ. Design and analysis of vaccine studies. New York: Springer, 2010.
31. Brabin B. An analysis of malaria parasite rates in infants: 40 years after Macdonald. Trop Dis Bull 1990;87:R1-R21.
32. World Health Organization. Malaria vaccine "rainbow tables" (http://www.who.int/vaccine_research/links/Rainbow/en/index.html).
33. Agnandji ST, Asante KP, Lyimo J, et al. Evaluation of the safety and immunogenicity of the RTS,S/AS01E malaria candidate vaccine when integrated in the expanded program of immunization. J Infect Dis 2010;202:1076-87. [Erratum, J Infect Dis 2011;203:1344.]

World Health Organization

Questions and Answers on Malaria Vaccines

November 2012

Malaria vaccines

What is the current status of malaria vaccine research?
There are currently no licensed malaria vaccines. Over 20 vaccine projects are in clinical trials. Of these, the most advanced vaccine is being evaluated in a Phase 3 clinical trial. This vaccine is called RTS,S/AS01 and has been developed through a partnership between GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative (MVI), with funds from the Bill & Melinda Gates Foundation to MVI. The clinical testing of RTS,S is at least 5-10 years ahead of other candidate malaria vaccines. RTS,S/AS01 is a vaccine against *Plasmodium falciparum*, with no protection expected against *P. vivax* malaria.

In what populations is the Phase 3 trial being conducted?
The Phase 3 trial of RTS,S/AS01 includes 15,460 infants and young children in seven sub-Saharan African countries namely Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania. These countries represent a range of different malaria transmission settings in order to be able to determine the vaccine's usefulness in these different settings. There are two age groups in the trial. One of these age groups is infants who receive three doses of the malaria vaccine together with other routine childhood vaccines at 6, 10 and 14 weeks of age. The other age group in the Phase 3 trial is older children aged between 5 and 17 months at first dose of RTS,S/AS01.

How well does the RTS,S/AS01 vaccine protect against malaria?
As of November 2012, two sets of results are available from the Phase 3 trial. The first results were released in October 2011 and were in children aged 5-17 months at first immunization. The estimated overall efficacy was a 55% reduction in all malaria episodes during the 12 months of follow-up, with 47% efficacy against severe, life-threatening malaria estimated in this same age group. Data for children vaccinated aged 6-14 weeks, in co-administration with other vaccines, were released in November 2012. Estimated overall efficacy in this age group over 12 months of follow-up was 33% for all malaria episodes, and 37% for severe, life-threatening malaria.

So far data from follow-up of children for 1 year after vaccination have been published. There is evidence in both age groups that protection declines during this period, and we do not know how long the vaccine's protection lasts beyond 1 year. Furthermore, we do not know if a booster dose will be needed to enhance protection. No data are available yet indicating whether or not the level of protection varies among countries with different intensities of malaria transmission. More information on all of these issues should be available by the end of the Phase 3 trial in 2014.

Why is the efficacy apparently different in the 2 age groups?

There has not yet been a detailed analysis to explore possible reasons for the apparent lower efficacy when the vaccine is given to infants rather than to older children. Possible factors that may relate to these differences include interference by co-administration with other vaccines, maternally acquired antibodies, transmission intensity and seasonality.

An initial finding is that lower immune responses are induced by the vaccine in infants aged 6-14 weeks compared to children aged 5-17 months.

The implications of these apparent differences in level of protection according to the age at which the vaccine is administered include the need for a thorough assessment of the feasibility, safety and effectiveness of different possible schedules and immunization strategies for this vaccine. No immunization visits currently exist in malaria-endemic countries to administer all the vaccine doses at 5-17 months of age. The new results also place emphasis on the importance of the site-specific efficacy and booster dose safety and efficacy information which will become available by 2014.

How is WHO involved in malaria vaccine research efforts?
WHO's role is to advise and guide the malaria vaccine development activities of the global research community. Once Phase 3 clinical trial data become available, WHO convenes its technical group to assess the safety and effectiveness of the malaria vaccine, and considers a WHO policy recommendation and prequalification, if advised that these are supported by the data. The technical group advising WHO on Phase 3 trials of malaria vaccines is the Joint Technical Expert Group on Malaria Vaccines, convened by the Immunization, Vaccines, and Biologicals Department and the Global Malaria Programme.

Joint Technical Expert Group on Malaria Vaccines

Licensing, policy recommendations and prequalification

When could the RTS,S/AS01 vaccine be available for African children?
If the results from the current Phase 3 trial provide sufficient evidence of the protective effect of the vaccine against malaria, RTS,S could be a "first generation" malaria vaccine. This means that RTS,S would be partially effective, reducing the number of cases of malaria in vaccinated children, but not preventing all episodes of the disease. There are still a number of steps that usually occur before new vaccines are introduced into immunization programmes in some endemic countries. These steps include: licensure of the vaccine by regulatory authorities; a WHO recommendation for use; WHO prequalification (for countries wishing to be supplied through the United Nations, or who use WHO prequalification as the basis for procurement eligibility); then decision-making by national public health authorities in malaria-endemic countries on introduction and use of the vaccine. An affordable price is one of the many additional factors beyond efficacy that will influence country decision-making on introduction.

Based on what we know now, and depending on the final trial results, a WHO recommendation for use and subsequent prequalification may occur in 2015.

When could the RTS,S/AS01 vaccine be licensed by a regulatory authority?
The European Medicines Agency (EMA), under a process known as article 58, will perform a scientific evaluation of this vaccine and issue what is called "a European scientific opinion". This would not be licensure or registration, but provides a scientific opinion which African regulators may use to help their own regulatory processes. It will be African national regulatory authorities which will consider licensing the vaccine in their jurisdictions. It is not clear when African regulators will consider this, but evaluation for licensure becomes relevant when sufficient efficacy data for the target population for vaccination become available.

What is article 58 and how does the EMA work with WHO in assessing the RTS,S/AS01 vaccine?
Article 58 is a specific legal basis in the European pharmaceutical legislation, allowing the EMA to perform an evaluation of medicinal products which are intended to be used only outside the EU to prevent or treat diseases of major public health significance. The same processes are used by the

EMA as those used for marketing/registration of European Union (EU) medicinal products. This evaluation is performed with WHO and with involvement of the relevant national regulatory authorities. RTS,S/AS01 will be submitted to EMA under article 58 because it is being developed by an EU manufacturer specifically for targeted populations and against a disease which occurs primarily outside the EU. It is not expected that the manufacturer will seek to license this vaccine in European countries given its targeted intended use.

When will WHO make a recommendation concerning use of the RTS,S/AS01 vaccine?
Information needed to make a recommendation for use includes how long the vaccine's protection lasts, and what the protection level is in different settings in Africa. In making recommendations, the efficacy of a booster dose may also be important. According to the vaccine development partnership's timelines, the information needed for WHO to make an assessment will become available in late 2014, to allow possible recommendation for use in 2015, depending on the results.

Vaccines that are currently licensed against human diseases are caused by either viruses or bacteria. Should RTS,S/AS01 be licensed, it will be the first ever licensed vaccine against a parasitic disease in humans. RTS,S/AS01 would therefore be a novel health intervention. The role of WHO, as the United Nations health agency, is to fully assess its safety and effectiveness; WHO will recommend RTS,S/AS01 if and when all required conditions for such a recommendation have been met. The introduction of a new vaccine is a major public health and financial decision that needs to be thoroughly assessed.

What is the difference between a WHO recommendation for use and WHO prequalification?
A WHO policy recommendation is the global equivalent of a national public health authority's decision about use of vaccines. Many countries appreciate guidance from the WHO policy recommendation process on which vaccines they should seek to introduce in their national immunization programmes. Similarly, donor agencies, such as the GAVI Alliance, require a WHO recommendation for use before funding procurement of vaccines for developing countries. Before a WHO recommendation is made, the vaccine's safety, immunogenicity and efficacy are reviewed by WHO technical expert groups and the risk/benefit to vaccinees in potential target countries is assessed. The role of new vaccines in the context of existing preventive and treatment measures plays a part in this assessment, as does cost-effectiveness.

WHO prequalification ensures that a specific vaccine from a specific manufacturer meets international standards of quality, safety and efficacy and is appropriate for the target population. Only WHO prequalified vaccines can be supplied to countries through UN agencies.

Malaria control measures

What other interventions exist for malaria control?
There are many effective interventions now available that can be used to reduce the burden of malaria in Africa. These include: prevention through mosquito vector control and use of long-lasting insecticidal bed-nets and, in some settings, indoor residual spraying with insecticides; seasonal malaria chemoprevention in some settings; intermittent preventive treatment for infants and during pregnancy; prompt diagnostic testing; and treatment of confirmed cases with effective anti-malarial medicines. These measures have dramatically lowered malaria disease burden in many African settings. The malaria disease burden can be lowered further by continuing to scale up WHO recommended control measures. Available malaria control measures represent some of the most cost-effective measures for public health.

The potential role of RTS,S/AS01 will be in addition to fully scaled-up access to and use of non-vaccine malaria preventive measures, prompt diagnostic testing and effective anti-malarial medicines.

The need for high quality, safe and effective drugs to treat malaria will continue regardless of any deployment of a first-generation malaria vaccine such as RTS,S/AS01.

Table 1 - Ongoing RTS,S/AS01 clinical and epidemiological studies

Study groups	Study and Objectives	Location	Population	Sample size	Expected data availability
Pivotal Ph III efficacy & safety study					
5-17 months: • RTS,S/AS01 (3 doses) + RTS,S/AS01 booster dose • RTS,S/AS01 (3 doses) + MenC vaccine • Rabies vaccine (3 doses) + MenC vaccine 6-12 weeks*: • RTS,S/AS01 (3 doses) + RTS,S/AS01, OPV booster • RTS,S/AS01 (3 doses) + MenC vaccine, OPV booster • MenC vaccine (3 doses) + MenC and OPV booster ** Infants in this age category receive in co-administration to the 3 doses of RTS,S/AS01 or control vaccine, 3 doses of DTPw-HepB/Hib and OPV*	Primary analysis: efficacy against clinical malaria, safety (12 months follow-up)	7 SSA countries; 11 research centres	5-17m	8923	Published (*The RTS,S Clinical Trials Partnership, 2011).*
	Primary analysis: efficacy against clinical malaria, safety (12 months follow-up)		6-12w	6537	Published *(The RTS,S Clinical Trials Partnership, 2012).*
	Secondary analysis: efficacy against clinical malaria, safety (18 months follow-up)		5-17m 6-12w	15460	2013
	Secondary analysis: efficacy against severe malaria disease (case-driven)		Combined	15460	Published (*The RTS,S Clinical Trials Partnership, 2011).*
	Final analysis: evaluation of all other secondary efficacy endpoints (30 months follow-up)		5-17m 6-12w	15460	2014
	Follow-up analysis: evaluation of secondary endpoints from the extension (follow-up to Jan 2014)		5-17m 6-12w	15460	2014

RTS,S/AS01 vaccine summary of ongoing/planned studies

March 2013

Malaria Transmission Intensity study					
6m-4y 5y-19y 20y +	Annual cross-sectional surveys of *P. falciparum* parasitemia at peak of transmission in Ph III pivotal efficacy study (Malaria-055) catchment areas, during 4 years.	6 SSA* countries; 8 research centres	6m-90y	6400	Year 1 reported, Year 2 completed, Year 3 ongoing, Final data in 2015.
Ph III study in special population					
RTS,S/AS01 Rabies vaccine	Safety and immunogenicity in HIV infected infants and children	Kenya	6w-17m	200	2014
Ph III study on HepB Indication and EPI Integration					
• RTS,S/AS01 + CoAd (DTPa/Hib + OPV + rotavirus vaccine) + pneumococcal vaccine staggered (3 groups - 3 lots) • RTS,S/AS01 + CoAd (DTPa/Hib + OPV + pneumococcal vaccine) + rotavirus staggered (3 groups - 3 lots) • RTS,S/AS01 + CoAd (DTPa/Hib + OPV) + rotavirus and pneumococcal vaccines staggered (3 groups - 3 lots) • HepB + CoAd (DTPa/Hib + OPV + pneumococcal vaccine) + rotavirus vaccine staggered • HepB + CoAd (DTPa/Hib + OPV + rotavirus vaccine) + pneumococcal vaccine staggered	Non-inferiority of Hepatitis B immune response Co-administration with 10V S. pneumoniae Co-administration with rotavirus vaccine, non-inferiority	Burkina Faso Ghana	8-12w	705	2014

*SSA – sub-Saharan Africa

RTS,S/AS01 vaccine summary of ongoing/planned studies

March 2013

Ph III lot to lot consistency study					
• RTS,S/AS01 (1600L RTS,S PB lot 1) • RTS,S/AS01 (1600L RTS,S PB lot 2) • RTS,S/AS01 (1600L RTS,S PB lot 3) • RTS,S/AS01 (20L RTS,S PB lot)	Commercial scale RTS,S vaccine lot-to-lot consistency Non-inferiority of lots from commercial scale RTS,S PB† (1600 L) versus lot from pilot scale RTS,S PB† lot (20L)	Nigeria	5-17m	320	2014
Ph II Schedule optimization study					
• RTS,S/AS01 (≤ 7d, 10w, 14w) • RTS,S/AS01 (≤ 7d, 10w, 26w) • RTS,S/AS01 (6, 10, 14 w) • RTS,S/AS01 (6, 10, 26 w) • RTS,S/AS01 (6, 10, 26 w & HepB prime at birth) • RTS,S/AS01 (10, 14, 26 w) • RTS,S/AS01 (14 w, 26 w, 9M)	Exploration of various vaccination schedules around current EPI visits.	Malawi	≤7d – 9m	480	2015

† PB: Purified bulk (= Drug substance) d = days, w = weeks; m = months, y = years of age

Table 2 – Ongoing studies ancillary to Ph III pivotal efficacy & safety trial

Study and Objectives	Principal Investigators	Expected data availability
Parasite genotyping		
Evaluate if RTS,S induces a selective pressure on parasite	S.Volkman & D.Wirth, Harvard School of Public Health and Broad Institute of Harvard	2016
Immunology		
Investigate mechanisms of RTS,S vaccine-induced protection against Malaria	C.Dobano, CRESIB	2014
Gametocytes		
Evaluate vaccine efficacy against *P.falciparum* gametocytaemia	GSK driven	2015

Table 3 – Health Economics studies

Study and Objectives	Where	Institutions	Subjects or health centers surveyed	Status
Cost of illness				
Estimation du poids économique du paludisme au Burkina Faso	Nanoro district	Health Research Institute (IRSS). Sponsored by PATH-MVI.	1 district hospital and 4 primary health facilities surveyed, 500 household surveys	Completed
Estimating economic burden of malaria in Ghana	Kintampo north and south, Asante-Akim	University of Ghana, Institute of Statistical, Social, and Economic Research (ISSER). Sponsored by PATH-MVI.	3 hospitals, 4 government clinics, 1 private clinic and 10 drug shops, 500 household surveys	Completed
Estimating the economic burden of malaria in Uganda	APAC district	Makerere University. Sponsored by PATH-MVI.	1 district hospital and 4 health centers, 500 household surveys	Completed
Estimating the economic burden of malaria in Nigeria	Achi and Oji in Enugu state, Nigeria	Health Policy Research Group, College of Medicine, University of Nigeria Enugu-Campus, Enugu, Nigeria. Sponsored by PATH-MVI.	2 hospitals, 4 primary health centers ,1 drug shop, 500 households surveys	Completed
The economic costs of malaria in children in three Sub-Saharan countries: Ghana, Tanzania and Kenya	Various sites in Ghana, Tanzania and Kenya	Sponsored by GSK.	Review of previous studies that surveyed about 150 inpatients and 150 outpatients in each country Interviews with HCP	Completed
Economic costs of malaria in children	TBD	Sponsored by GSK.	TBD	In preparation

RTS,S/AS01 vaccine summary of ongoing/planned studies

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Cost effectiveness				
Cost-effectiveness of RTS,S for a variety of delivery strategies	SSA-malaria endemic countries	Swiss Tropical and Public Health Institute (STPH). Sponsored by PATH-MVI.		Preliminary estimates
Cost-effectiveness of adding RTS,S to the existing mix of interventions	Ghana, Tanzania and Kenya, others (TBD)	Sponsored by GSK.		Preliminary estimates
Optimization Model				
Optimal mix of interventions to prevent malaria in children under budget constraint	Ghana, Tanzania and Kenya, others (TBD)	Sponsored by GSK.		In preparation
Macroeconomic Model				
Macroeconomic impact of preventing malaria in children in Ghana	Ghana	Sponsored by GSK.		In preparation
Cost of malaria case management and costs of vaccine implementation				
Cost of malaria case management (provider costs) and vaccine implementation (including a description of the methodology used to extrapolate to SSA malaria endemic countries)	SSA-malaria endemic countries	Swiss Tropical and Public Health Institute (STPH). Sponsored by PATH-MVI.		report in preparation and preliminary estimates
Cost of implementation of RTS,S	TBD	Sponsored by GSK.	TBD	In preparation

Table 4 – Post-Approval Program (Ph IV studies)

Study and Objectives	Design	Sample size	Expected data availability
Baseline study			
Define baseline incidence rates of selected diseases	Cohort monitoring event (surveillance)	Cohort of 40 000 children under surveillance	2016
Safety-surveillance study			
Safety surveillance after vaccine introduction	Cohort monitoring event (surveillance) after vaccine introduction	Cohort of 40 000 children vaccinated	2018
Effectiveness			
Effect of the RTS,S/AS01 vaccine on malaria morbidity when used in combination with other preventive measures	Step wedge design	To be determined	2018

Table 5 – Community perception studies

Completed studies	Partners	Sample size	Publications
Kenya			
Community Perceptions of malaria and vaccines in Kenya's Busia region in Western Province and South Coast in Coast Province	AMREF in Kenya	274 participants (focus group discussions, key informant interviews, ad exit interviews in maternal and child health clinics	Published *(Ojakaa, 2011).*
Mozambique			
Community Perceptions of malaria and vaccines in Mozambique's Chókwè District in Gaza Province and Massinga District in Inhambane Province	Family Health International and Institute of Traditional Medicine, Mozambique Ministry of Health	276 participants (focus group discussions and in-depth interviews)	Published *(Bingham, 2012).*
Burkina Faso			
Community perceptions of Malaria and vaccines in Kaya and Houndé	Family Health International and Institut de Recherche en Sciences de la Santé (IRSS)	308 participants (focus group discussions and in-depth interviews)	Manuscript under review
Ongoing studies	**Partners**	**Sample size**	**Publications**
Ghana			
Community perceptions of malaria and vaccines in Ghana's Ejisu Juaben district in Ashanti Region and Bolgatanga municipality in Upper-East Region	Malaria in Pregnancy team, Department of Community Health, Kwame Nkrumah University of Science and Technology (KNUST)	286 participants (focus group discussions, interviews, and semi-structured observations over 3 months at vaccination clinics).	Technical report of study close to completion; article to be later submitted for publication

References

Bingham A., Gaspar F, Lancaster K, Conjera J, Collymore Y, and Ba-Nguz A. Community perceptions of malaria and vaccines in two districts of Mozambique. Malaria Journal 2012 11:394

Ojakaa D, Yamo E, Collymore Y, Ba-Nguz A, Bingham A. Perceptions of malaria and vaccines in Kenya. Human Vaccines. 2011;7(10):1096–1099.

Ojakaa DI, Ofware P, Machira YW, Yamo E, Collymore Y, Ba-Nguz A, Vansadia P, Bingham A. Community perceptions of malaria and vaccines in the South Coast and Busia regions of Kenya. Malaria Journal. 2011;10:147

The RTS,S Clinical Trials Partnership. First results of Phase 3 trial of RTS,S/AS01 malaria vaccine in African children. New England Journal of Medicine 2011; 365: 1863-75

The RTS,S Clinical Trials Partnership. A Phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. New England Journal of Medicine 2012; 367: 2284-95

5 Mar 2013

2013 Update to the Malaria Vaccine Technology Roadmap

Introductory text

This text represents the result of a review process facilitated by WHO, and working with the malaria vaccine funders group, to update the vision and strategic goal of the Malaria Vaccine Technology Roadmap. Originally launched at the 2006 WHO Global Vaccine Research Forum, and supported by the malaria vaccine funders group, the roadmap has formed a strategic framework underpinning the activities of the global malaria vaccine R&D community.

Substantial changes in malaria epidemiology are now being observed in many, but not all, settings following reduction in malaria transmission(1) in association with scaling-up of malaria control measures. Reduced transmission is associated with a shift in the peak age of clinical malaria to older children(2) and therefore the median age of hospitalization due to malaria has increased(3, 4) in some settings**.**

In response to the recognition that the epidemiological and malaria control status have changed markedly since 2006, and acknowledging substantial changes in the strategic direction for malaria research, the roadmap has been updated to encompass the current goals of prevention of malaria disease and deaths, accompanied by consideration of the accepted goals of incremental malaria elimination and ultimately global eradication. The expanded vision and strategic goals reflect these ambitious aims of the global malaria community.

The 2015 Landmark goal remains in place, unchanged, as follows “By 2015, develop and license a first generation malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year.” Furthermore, the 11 priority areas in research, vaccine development, key capacities, policy and commercialization, all remain in place unchanged.

The priority areas outlined in the Malaria Vaccine Technology Roadmap will be updated only as necessary to reflect the new Vision and Strategic Goals, and taking into account the major progress in many of the areas since 2006.

It is noted that the following goal has been set as an indicator of success for the Global Vaccine Action Plan of the Decade of Vaccines by the 2012 World Health Assembly “Proof of concept for a vaccine that shows greater than or equal to 75% efficacy for HIV/AIDS, tuberculosis, or malaria by 2020”.

Keeping the roadmap up-to-date in future

Further reviews of the vision and strategic goals will occur at least every 5 years in light of the epidemiological and control situation at that time and progress in the development of new tools and technologies. Changes will be made only if necessary.

The malaria vaccine community should work with the malaria control and elimination communities to ensure products under development are suitable for use alongside current WHO recommended malaria prevention, diagnostic and treatment measures.

Vision

Safe and effective vaccines against *Plasmodium falciparum* and *Plasmodium vivax* that prevent transmission, disease and death to enable malaria eradication

Strategic Goals

By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* and encompassing the following two objectives, for use by the international public health community[1]:

1) Malaria vaccines with a protective efficacy of at least 70-80%[2] against clinical malaria, suitable for administration to appropriate at-risk groups in malaria-endemic areas.[3]
2) Malaria vaccines that reduce transmission[4] of the parasite and thereby substantially reduce the incidence of human malaria infection to achieve elimination in multiple settings. The vaccines should be suitable for administration to people of all ages in mass campaigns[5]

[1] While vaccines that meet or exceed these targets are acknowledged as being of major public health significance, those that do not fully meet these targets may still have substantial value. Any licensed, available malaria vaccine will undergo assessment for evidence-based policy recommendation by WHO.

[2] Relative efficacy estimates may be provided where a vaccine is tested against a licensed, available first generation malaria vaccine. In this case WHO will evaluate whether the relative efficacy estimates can be considered analogous to absolute efficacy of >70-80% (ie analogous to >70-80% efficacy from trials conducted with a traditional control arm)

[3] The efficacy measure will be an absolute reduction in incidence of all episodes of clinical malaria over at least 2 years. Booster doses will be required no more frequently than annually.

[4] The new transmission-related strategic goal does not apply only to sexual stage/mosquito antigen vaccines but to any vaccine capable of interrupting malaria transmission .

[5] For this goal the endpoints will be set through the process for development of preferred product characteristics for malaria vaccines. Although these metrics are centrally important to this goal, there is no consensus available to set the criteria at the time of this update.

Background to WHO malaria vaccine Preferred Product Characteristics

Vaccine R&D should address an unmet public health need. To do this, the unmet need must be identified and defined, and product development plans put in place. The strategic goals above provide guidance on the two highest priorities in terms of public health need for malaria vaccines.

Two sets of WHO preferred product characteristics (PPCs) will be developed in 2013-2014. The WHO PPCs will provide guidance on the characteristics of malaria vaccines that could meet the two strategic goals of the Roadmap, and could be programmatically suitable for use in malaria-endemic settings. Any malaria vaccine which becomes available for use in malaria-endemic countries will undergo evidence-based policy assessment by WHO through the standard policy processes. Those vaccines not meeting the WHO PPCs are not excluded from consideration for policy recommendation and pre-qualification by WHO. However the PPCs provide information on the desired characteristics of vaccines to meet the public health need, and to lower the burden on developing country immunization and malaria control programmes.

Target audience for this update:

- The Vision and Strategic Goals are aimed at senior leadership within international and national donor, financing and public health agencies, as well as governments of malaria-endemic countries.
- The Strategic Goals are also of interest to malaria vaccine developers in academia, government agencies, public-private partnerships and industry.
- The WHO malaria vaccine Preferred Product Characteristics are aimed at a technical audience in research & development in industry, public-private partnerships, academia and government agencies, who have an interest in development of malaria vaccines to meet the public health need in developing malaria-endemic countries.

Malaria Vaccine Technology Roadmap Priority Areas

Re-stated below are the original 11 Priority Areas. Those which are out of date will be reworded through a joint process between WHO and the malaria vaccine funders group.

Research

1. Develop a standard set of immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines.

2. Standardize clinical trial design and assessment to allow comparison of data and to determine correlates of protection.

3. Use state-of-the-art approaches, including functional genomics, to characterize the biological functions of proteins at the interface of host-parasite interactions and to identify novel potential antigen candidates.

4. Develop web-based information-sharing tools to strengthen connections between the laboratory and the clinic.

Vaccine Development

5. Establish a systematic approach for prioritizing sub-unit vaccine candidates using accepted pre-clinical criteria.

6. Pursue multi-antigen, multi-stage, and attenuated whole-parasite vaccine approaches.

Key Capacities

7. Establish readily accessible formulation and scale-up process development capacity for malaria vaccines.

8. Build and broaden good clinical practice (GCP) clinical trial capacity in Africa and other malaria-endemic regions to accommodate the growing number of trials required for malaria vaccine development.

Policy and Commercialization

9. Establish and maintain country-level dialogues to facilitate decision-making on malaria vaccine policy.

10. Secure sustainable financing for future procurement of vaccines.

11. Develop novel regulatory strategies to expedite approval while ensuring safety.

References

1. WHO. World Malaria Report. 2011. Available from: www.who.int/malaria.
2. Carneiro I, Roca-Feltrer A, Griffin JT, Smith L, Tanner M, Schellenberg JA, et al. Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. PLoS ONE. 2010;5(2):e8988.
3. O'Meara WP, Bejon P, Mwangi TW, Okiro EA, Peshu N, Snow RW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet. 2008 Nov 1;372(9649):1555-62.
4. Ceesay SJ, Casals-Pascual C, Erskine J, Anya SE, Duah NO, Fulford AJ, et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. Lancet. 2008 Nov 1;372(9649):1545-54.