



Report to the GAVI Alliance Board

12-13 June 2012

Subject:	Continued funding for special studies
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Agenda item:	14
Category:	For Decision
Strategic goal:	SG1 - Vaccines & SG2 - Health systems

Section A: Overview

1. Purpose of the report

- 1.1 This paper outlines a request for urgent funding for continuing research studies submitted by the Accelerated Vaccine Introduction Initiative Technical Assistance Consortium (AVI-TAC).

2. Recommendations

- 2.1 The PPC reviewed four urgent special studies proposals from AVI-TAC and recommended that the GAVI Alliance Board:
- **Approve** an amount of up to US\$ 9.3 million for AVI-TAC to continue two urgent pneumococcal studies and conduct two urgent rotavirus studies over a three year period, through 2015.
- 2.2 In connection with these four urgent studies, the PPC noted that consideration should be given to the impact of the recent SAGE recommendation to loosen the age restrictions for the delivery of rotavirus vaccines. To enable an assessment of this impact, in parallel with the four urgent studies, and following the PPC, the Secretariat recommends that the Board:
- Approve**, subject to the Secretariat receiving satisfactory peer review reports, an amount of US\$ 1.8 million for AVI-TAC to conduct a study to monitor the impact of the SAGE recommendation on widening age restrictions related to rotavirus vaccine delivery.

3. Executive summary

- 3.1 The AVI-TAC Special Studies sub-team has identified urgent priority needs and submitted four study proposals to GAVI in February 2012. Because of the imperative to address these mission critical questions in a timely manner,

these study proposals require an immediate decision from GAVI on funding (see list below). In order to most expediently address these urgent needs, it is recommended to fund these four urgent studies by the PATH led consortium.

4. Context

- 4.1 In order to support the evidence base around introduction and monitor early effects of the vaccines in low resource settings, the GAVI Alliance has been funding research through the Accelerated Development and Introduction Plans (ADIPs) and the Accelerated Vaccine Introduction Initiative Technical Assistance Consortium (AVI-TAC). The rationale was that although there was a lot of research done on these vaccines in more affluent countries, little had been done to assess the effectiveness in resource poor countries.
- 4.2 As such, GAVI's investment in special studies has mostly focused on vaccine effectiveness and cost effectiveness in GAVI eligible countries.
- 4.3 In June 2008 the GAVI Alliance and Fund Boards endorsed an envelope of \$99.6M for an outsourced entity to support the work of AVI. In October of the same year, \$51.3 million of this envelope was awarded to the PATH led consortium (AVI-TAC) to implement the project. Of this, \$11.2 million was dedicated to research. The remaining \$48.3 million of the envelope was left for future special studies and was not awarded or included in future financial projections when the Alliance and Fund boards merged.
- 4.4 By the end of 2012, the majority of GAVI's current portfolio of studies funded through the AVI-TAC will conclude (see Annex 2). Recognising this, in November 2011 the GAVI Board requested that a strategy for special studies come to the Board after review by the PPC.
- 4.5 To respond this request, the Secretariat convened an expert group to help define potential applied, policy relevant research questions related to the roll out of GAVI supported vaccines. The group considered that GAVI funded research activities should have three major aims: mitigating risk to programmatic credibility of not achieving the desired impact, increasing return on investment by optimising effectiveness in real world settings, and demonstrating return on investment. The process also identified who else is funding and/or conducting these studies proposed options for GAVI engagement.¹ The report of the expert group can be found in Annex 1.
- 4.6 After review of the proposal, the PPC concluded that GAVI should not provide dedicated funding for special studies as a separate window, but rather should address any key policy related studies through the business plan.
- 4.7 In that context, the PPC also reviewed a list of studies identified as urgent by the AVI-TAC. These were identified after a review of the critical policy/strategic questions facing GAVI countries and other stakeholders

¹ List of experts, outcome of consultation and mapping exercise are available from the Secretariat upon request.

around the use of pneumococcal and rotavirus vaccines, and following a landscape analysis of ongoing studies or studies in late-stage planning. The South Africa and Kenya studies, (a) and (b) below, represent a continuation of GAVI funding for work underway and would entail consequences on staffing if funding were to cease.

- 4.8 The budget requested by AVI-TAC for these studies totals US\$ 9.3 million over a 3 year period and includes project, personnel and support costs. A short rationale for the studies is provided (full proposals and reviewer comments are available upon request).
- (a) Case control study to estimate effectiveness of a pneumococcal conjugate vaccine against invasive pneumococcal disease in South Africa (US\$ 2.0 million over 2 years). Continued funding for this study will enable site enrollment to continue uninterrupted. The study will provide the earliest possible results of PCV13 effectiveness in an African country.
 - (b) Pneumococcal conjugate vaccine impact study in Kenya (US\$ 5.9 million over 3 years). The current funding for this study will expire in December 2012. The current funding only allows for 2 years of post-vaccine surveillance (2011 and 2012) which is insufficient to observe the impact of the vaccine in its various dimensions. The requested funding will support continued surveillance of serotype replacement and impact assessment for 2013 – 2015.
 - (c) Assessment of the vaccine effectiveness of the pentavalent rotavirus vaccine in Rwanda (US\$ 0.7 million over 3 years). Rwanda is currently the only GAVI-eligible country in Africa planning to introduce the pentavalent rotavirus vaccine; therefore, it represents a unique opportunity to assess the impact of this vaccine in an African country.
 - (d) Assessment of the vaccine effectiveness of the monovalent rotavirus vaccine in an early adopter African country, Ghana (US\$ 0.7 million over 3 years). As the majority of GAVI-eligible countries are likely to use the monovalent vaccine, this study provides critical information for assessing the future potential health impact of rotavirus vaccine across GAVI countries, as well as to provide important information for advocacy purposes.
- 4.9 The studies have been peer reviewed by eight independent experts (four experts per disease area) as to their relevance, aims, urgency, study design, ethics and budget, all of whom recommended the proposals for urgent funding, pending clarification on some technical issues and more detail on the requested budgets.² In response to the reviewer feedback, AVI-TAC submitted additional detail on the proposals with regards to the technical clarifications requested, and submitted a more detailed budget. These were

² The proposals and detailed reviewer comments are available upon request.

then re-assessed by the reviewers who recommended the proposals for urgent funding.

- 4.10 With regard to the rotavirus proposals, the PPC noted that consideration should be given to consider impact of the recent SAGE recommendation to loosen the age restrictions for the delivery of rotavirus vaccines. In view of this, the Secretariat requested AVI-TAC to also put forward a proposal to monitor the impact of a recent SAGE decision on widening age restrictions related to rotavirus vaccine delivery. AVI-TAC has submitted an “add on” to the proposal described above which is currently being peer reviewed. The total additional request for funding is US\$ 1.8 million over 4 years. The Board is requested to approve in principle this study and its budget subject to a satisfactory peer review.
- 4.11 Recognizing that limited data exist on the safety of initiating rotavirus vaccination among older infants, WHO initially recommended that rotavirus vaccination be initiated before the infant reaches 15 weeks of age. This recommendation was partly based on data showing that the background rates of natural intussusception are low in the first 2–3 months of life, and thus vaccination would cause fewer excess intussusception cases if a risk exists. However, recognizing that the benefits of vaccination outweigh the potential short-term risk of intussusception, SAGE has recently recommended removing these age restrictions in developing countries to improve vaccine coverage, but also strongly recommended implementing intussusception surveillance to monitor the safety of the new rotavirus vaccine programs. GAVI funding to support active surveillance for intussusception at select, reliable sites early after the introduction of vaccine in Africa is important for proper causality assessment and evidence-based decision-making to address and mitigate real or perceived vaccine safety concerns that are likely to arise.

5. Next steps

- 5.1 If the urgent studies are approved by the Board, GAVI will award funding to the AVI-TAC consortium through the existing agreement.
- 5.2 Through the business planning process, and drawing on the areas for research identified as high priority by the expert group, the Secretariat will identify special studies which should be considered for funding in 2013-2015.

Section B: Implications

6. Impact on countries

- 6.1 Additional evidence will help strengthen decision making by countries.

7. Impact on GAVI Stakeholders

- 7.1 By adding breadth and depth to the evidence base on the impact of pneumococcal and rotavirus vaccination in GAVI supported countries, these studies will help inform policies, funding decisions and advocacy efforts.

8. Impact on the Business Plan / Budget / Programme Financing

- 8.1 The 4 urgent studies, if recommended for funding, would be an additional allocation of US\$ 9.3 million to AVI-TAC through the business plan for 2012 to 2014.

9. Risk implications and mitigations

- 9.1 There are critical questions that need to be answered for GAVI to maximise its investment in vaccines and have a strong evidence base around new vaccine introduction in low-income countries. If GAVI does not fund these areas, critical questions may remain unanswered and the risk to programmatic credibility will increase.

10. Legal or governance implications

- 10.1 Assuming the AVI-TAC proposed urgent special studies and the study to monitor the impact of the SAGE decision on widening age restrictions related to rotavirus vaccine delivery described in this report are funded, the existing agreement between PATH and GAVI would be amended to include these studies. That agreement is scheduled to continue through 2015 by which time the proposed special studies would also be completed.
- 10.2 The Secretariat shall ensure that appropriate insurance cover is in place to cover any risks to GAVI associated with these studies.

11. Consultation

- 11.1 The Secretariat worked with an expert advisory group (see Annex 3) to define the recommended areas for research. In addition, other research funders were identified and provided feedback through a questionnaire. The research and technical constituency of the Board was consulted via their Board representative.
- 11.2 The proposed studies were peer reviewed by eight independent experts (see section 4.9).

12. Gender implications / issues

- 12.1 None at this time.

13. Implications for the Secretariat

- 13.1 None at this time.

Annex 1 Priority areas for funding

This annex summarises the outcome of a consultation with the expert advisory group held over two days, 2-3 April at the GAVI Secretariat. It includes a list of the high priority areas recommended for funding by the GAVI Alliance as part of a potential funding window for research. A full report from the meeting will be available in the coming weeks.

The objective of the meeting was to review the rationale for GAVI's engagement in research and propose priority areas for research. In addition to the Chair Brian Greenwood, 13 experts participated along with two observers. Members of the Secretariat were on hand to provide support and background information as needed. Representatives from WHO, SAGE and the Decade of Vaccines (DOV) participated to ensure alignment in priority setting with other groups involved in vaccine research. The group was divided into breakout groups to discuss different research categories: Phase IV/epidemiological studies (jointly held), implementation research and health economics.

The groups were asked to: review a preliminary mapping exercise that had identified studies funded by other funders in areas relevant to the GAVI portfolio of vaccines, identify potential gaps in each category, develop a list of recommended studies and prioritise the list based on criteria that include potential for impact, relevance to GAVI and value for money.

Rationale for GAVI's investment in research

The expert group agreed that GAVI's investment in research should focus on supporting, maximising and protecting its programmatic investment in the introduction and implementation of the vaccines in its portfolio. GAVI funded research activities should have three major aims: mitigating risk to programmatic credibility of not achieving the desired impact, increasing return on investment by optimising effectiveness in real world settings, and demonstrating return on investment. Research in these areas would support GAVI's mission and four strategic goals. In addition, the group recommended key areas for strengthened investments and linkages through the GAVI business plan and areas that should be considered by other funders to help GAVI achieve its mission.

The research topics described illustrate the types of studies that GAVI should consider funding. These relate to currently funded vaccines as well as to vaccines that GAVI is considering for future implementation. Examples of the research needed for specific antigens and for specific geographical areas are given where relevant. Although some of the research areas proposed are currently being supported by other donors or by industry, most have funding gaps, particularly in areas especially relevant to GAVI eligible countries and to the goals/objectives in GAVI's business plan.

The expert group felt that three of the research questions considered below need to be explored as soon as possible, taking advantage of imminent roll out of pneumococcal vaccines to ensure that GAVI has the best possible information on which to make decisions in the near and medium term.

1. Risk of pneumococcal vaccine failure due to serotype replacement.
2. Effectiveness of pneumococcal vaccines in Asia.
3. Cost effectiveness of PCV catch-up campaigns.

AREAS OF RESEARCH IDENTIFIED AS HIGH PRIORITY

RISK MITIGATION

Exploration of the issues listed below would form a critical part of GAVI's risk mitigation strategy related to vaccine roll out.

Epidemiological/Phase IV

- Risk of pneumococcal vaccine failure due to serotype/strain replacement.
- Risk of Congenital Rubella Syndrome (CRS) resulting from rubella vaccine introduction.
- Duration of protection – Meningococcal serogroup A (Men A) conjugate vaccine.
- Safety –rotavirus vaccines (intussusception).

Implementation/Health economics

- Validity of coverage data and improved use of novel data information systems at all levels of the health system (eg. quality and timeliness of reporting and using new technologies such as mobile phone and biomarkers).
- Impact of large scale SIAs on immunisation programmes more broadly.

OPTIMISING EFFECTIVENESS AND EFFICIENCY IN REAL WORLD SETTINGS

The issues below focus on improving vaccine efficiency, maximising vaccine impact and optimising vaccine use.

Epidemiological/Phase IV studies

- Evaluation of the effectiveness of pneumococcal conjugate vaccines in Asia.
- Understanding the effectiveness of different dosing schedules (2, 3 or 2+1) of pneumococcal and rotavirus vaccines based on field experience.
- Evaluation of the potential need for booster doses of pneumococcal and meningococcal conjugate vaccines.
- Evaluation of the effects of breastfeeding/maternal antibody on the immunogenicity of rotavirus vaccines.

Implementation/Health economics

- Study of the cost effectiveness of PCV catch-up campaigns.
- Development of new methods to monitor equity in vaccine delivery and examination of their impact on vaccine related outcomes.
- Exploration of strategies for delivering additional services/commodities through SIAs.

DEMONSTRATING RETURN ON INVESTMENT

Exploration of the following issues would allow meaningful interpretation of results and demonstrate the impact of the GAVI Alliance and of vaccination in general.

Epidemiological/Phase IV

- Evaluation of the degree of herd protection provided by pneumococcal, rotavirus, Men A and rubella vaccines.
- Burden of disease estimates, for example for JE.
- Studies of the impact of vaccination on morbidity as well as mortality.

Implementation/Health economics

- Further evaluation of the broader social and economic impact of vaccination.
- Determination of the comparative cost effectiveness of introducing new vaccines vs. increasing coverage.
- Determination of the cost effectiveness/programmatic effectiveness of stockpiles.

AREAS FOR STRENGTHENED INVESTMENT AND LINKAGES THROUGH THE GAVI BUSINESS PLAN

- Surveillance (hospital surveillance for severe disease in particular for pneumonia/diarrhea; vaccine failures; mortality impact where verbal autopsy available).
- Building a learning component around key activities such as co-financing, roll out and demand creation.

KEY AREAS FOR CONSIDERATION BY GAVI ALLIANCE PARTNERS AND OTHERS

Other important areas of research related to the introduction of new vaccines and maintenance of coverage with established vaccines noted by the committee included:

- Understanding the reasons for drop out from immunisation programmes.
- Burden of disease estimates for vaccines under consideration such as typhoid and cholera.
- Characterisation of correlates of protection for rotavirus and Men A vaccines.
- Issues related to the non-specific effects of vaccines eg. DPT.
- The safety and logistics of vaccination campaigns.
- Methodologies for case control studies and their effectiveness.
- The use of pharyngeal carriage as a measure of impact (pneumococcal and meningococcal vaccines).
- The added impact of the introduction of multiple new vaccines concurrently.
- Comparison of vaccines directed at the same target eg. pneumococcal disease.
- The use of vaccines in the context of primary healthcare.
- Development of new and innovative methods for safety surveillance.
- Understanding how communities can best be engaged in generating demand for vaccination and overcoming safety concerns.

Annex 2 List of AVI-funded studies

	<i>Study</i>	<i>Location</i>	<i>Vaccine</i>	<i>Status</i>
Optimization of Dosing / Delivery (4 studies)	Landscape analysis of dosing schedules	Desk based	All pneumococcal vaccines	Completed
	Understanding the impact of breastfeeding and age of administration on the immunogenicity	Pakistan	Rotarix	9/2012
	Strain Review and meta-analysis of trial data to look at strain specific protection for rotavirus vaccine.	Desk based	Rotavirus vaccines	Completed
	Mathematical modeling of rotavirus transmission patterns to identify optimal vaccine schedules	Desk based	Rotavirus vaccines	Completed
Effectiveness (7 studies)	Assess the impact of a national introduction of vaccines among children in populations representative of GAVI-eligible countries through short-term vaccine effectiveness studies	South Africa, Nicaragua, Bolivia	Pneumococcal and rotavirus vaccines	9/2012
	Development of pneumococcal conjugate vaccine impact assessment manual and generic case-control study protocol	Desk based	Pneumococcal vaccines	Completed
Demonstration Projects to Measure Costs and Benefits (1 study)	Assessment of the economic impact of national introduction of vaccines among children in populations representative of GAVI-eligible countries through collection and evaluation of associated health care and societal costs	Ghana, Gambia	Pneumococcal, pentavalent and rotavirus vaccines	4/2012
Cost-Benefit Analysis and Acceptability (1 study)	Creation, maintenance, and country training on use of web-based tools that link disease burden and economic impact to model region and country specific estimates and enable country derived cost effectiveness analyses	Desk-based & in-country training (Senegal, Ghana)	Not vaccine specific	Completed

Annex 3 Expert advisory group membership

Name	Title
Brian Greenwood (Chair)	Professor of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine
Altat Lal	Independent consultant; DOV
Ciro de Quadros	Executive Vice President, Sabin Institute; DOV co-chair
David Bloom	Professor of Economics and Demography in the Department of Global Health and Population, Harvard School of Public Health
Heidi Larson	Senior Lecturer, London School of Hygiene and Tropical Medicine
Helen Rees	Chair of SAGE; Executive Director, Wits Institute for Sexual and Reproductive Health, HIV, and Related Disease and Professor, Dept. of Ob/Gyn
Joachim Hombach	Acting Head, WHO Initiative for Vaccine Research
Juhani Eskola	Deputy Director General, National Institute for Health and Welfare, Finland
Kim Mulholland	Professor of Child Health and Vaccinology, London School of Hygiene and Tropical Medicine, London
Prabhat Jha	University of Toronto Canada research chair of health and development at the University of Toronto
Roger Glass	Associate Director for Global Health Research, National Institutes of Health
Samba Sow	Coordinator, Center for Vaccine Development-Mali (CVD-Mali) Ministry of Health, Mali and Associate Professor of Medicine University of Maryland School of Medicine
Sania Nishtar	Chair of GAVI Evaluation Advisory Committee. Founder and president of Heartfile
Shabir Madhi	Executive Director of the National Institute for Communicable Diseases (NICD), Johannesburg
Rebecca Martin	Director of the Global Immunization Division, Center for Global Health, US CDC
Sharmila Mhatre	Program Leader, Governance for Equity in Health Systems International Development Research Centre, Canada
Abdullah Brooks	Associate Scientist, JHSPH and ICDDR
Anne Schuchat	Board member representing research and technical constituency (and Director, National Center for Immunization and Respiratory Diseases, US CDC)
Katherine O'Brien	Professor, Johns Hopkins Bloomberg School of Public Health
Ulla Griffiths	Lecturer in health economics, London School of Hygiene and Tropical Medicine
Mira Johri	Assistant Researcher with the Université de Montréal Health Administration Department
Nhan Tran (Observer)	Manager, Implementation Research Platform (IRP), WHO
Paul Fife (Observer)	Director, Department for Global Health, Education and Research, NORAD
Greg Widmyer (Observer)	Senior Program Officer, Global Health Delivery, Bill & Melinda Gates Foundation