

An evaluation of GAVI Alliance efforts to introduce new vaccines via the Accelerated Development and Introduction Plans (ADIPs) and the Hib Initiative (HI)

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LIST OF ABBREVIATIONS

ADIP	Accelerated Development and Introduction Plan
AMC	Advance Market Commitment
BCG	Boston Consulting Group
CDC	US Centers for Disease Control and Prevention
CEE/NIS	Central European Economies/Newly Independent States
DCVMN	Developing Country Vaccine Manufacturers Network
DTP	Diphtheria, tetanus and pertussis vaccine
EPI	Expanded Programme on Immunization
GAVI/GAVI Alliance /the Alliance	The Global Alliance for Vaccines and Immunization
GSK	Glaxo SmithKline
HI	Hib Initiative
Hib	Haemophilus influenzae type b
IFFIm	International Finance Facility for Immunization
JE	Japanese Encephalitis
MC	Management Committee (for the ADIPs)
MVP	Meningitis Vaccine Project
PAHO	Pan American Health Organization, also WHO's Americas Regional Office
PATH	Program for Advanced Technology in Health
Pneumo	<i>Streptococcus pneumoniae</i>
R&D	Research and development
RAPID	Rotavirus action program for immunization and development
RFP	Request for Proposals
Rota	Rotavirus
RVP	Rotavirus Vaccine Program
RWG	Regional Working Group
SAGE	WHO's Strategic Advisory Group of Experts, advisory to the WHO Director-General on immunization
TB	Tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization

1. EXECUTIVE SUMMARY

1.1 Scope and Methodology of Study

- o GAVI created the Accelerated Development and Introduction Plans (ADIPs) in 2002, in response to delays in uptake of new vaccines in developing countries. The vaccines to be included were proposed by GAVI's Research and Development (R&D) Task Force after an extensive process including country inputs. It was determined to focus on the "low hanging fruit" – those vaccines against diseases with high burden in developing countries and for which a product was already defined. Thus rotavirus and pneumococcal conjugate vaccines were chosen as the focus of the first ADIPs, which were approved in February 2003 with a financing of \$30M each. The mission of the Pneumo ADIP is to improve child survival and health by accelerating the evaluation of and access to new life saving pneumococcal vaccines for the world's children. The Pneumo ADIP is located at the Johns Hopkins Bloomberg School of Public Health, and managed as a small team under the leadership of Dr Orin Levine. The Rota ADIP, called the PATH Rotavirus Vaccine Program (RVP), is a partnership with the World Health Organization (WHO) and the US Centers for Disease Control (CDC). The team director, Dr John Wecker, who has management responsibility, and all management functions, are located at PATH, in Seattle. The PATH Rotavirus Vaccine Program was created to accelerate the vaccine introduction process and to make rotavirus vaccines available to children in developing countries as quickly as possible.
- o Later, because of the slow uptake of *Haemophilus Influenzae* type b (Hib) vaccine into developing countries, despite the availability of GAVI funds, the Hib Initiative (HI) was approved in June 2005, for a period of four years with a financing of \$28M, plus \$9M for the India Hib Vaccine Probe Study. Its mission is to expedite and sustain evidence-informed decisions regarding the use of Hib vaccination, in order to prevent childhood meningitis and pneumonia. It is composed of a consortium of four members, including Johns Hopkins University, CDC, WHO, and the London School of Tropical Medicine and Hygiene. The Project Director is Dr Rana Hajjeh.
- o As it enters its second phase, GAVI is critically examining the vaccine marketplace and its own role in vaccine introduction to ensure its strategies and tactics are in line with changing environments and institutional structures. To this end, GAVI has commissioned a study by HLSP London to examine the ADIPs and the HI. This study

was overseen by a Steering Committee convened by the Alliance.

- o The Terms of Reference of the study are :
 - to take stock of the way the environment for new vaccine development and introduction has evolved over the past four years,
 - to assess the progress made and highlight the lessons learnt through the innovative ADIPs approach, the Hib initiative and other new vaccine introduction related GAVI supported activities; and,
 - to make recommendations to the GAVI Board on the structure and finance [of] its continued support in this priority area in the coming years.
- o The scope of the project includes (1) a description of how the environment prevailing at the time of the launch of these initiatives has evolved and how this may have an impact on the relevance and objectives of these initiatives; (2) an evaluation of the structures themselves, in terms of their mandates, achievements, governance, and constraints; and (3) a proposal for the future role of the Alliance to continue to support the introduction of these and other new vaccines in the developing world.
- o It should be noted that the HI has been in existence for a shorter period of time, and is only midway into its implementation phase. It is therefore difficult to demonstrate or assess achievements at this stage.
- o The methodology used was consultation of available documentation and semi-structured interviews with a variety of stakeholders at country, industry, and donor level, and then fitting this information into the framework of the “virtuous cycle.” The limitations of the methodology – the fact that a controlled study with quantitative data is not possible when measuring the impact of such interventions – means that the results are of necessity limited and depend on judgements on what would have happened in the absence of the ADIPs and HI. Nevertheless, most of the observations reported were consistently noted in several different contexts.

1.2 Evaluation of environment for new vaccine development and introduction

- o In 2002, GAVI was promoting the uptake of hepatitis B and Hib vaccines in its client countries because more than 15 years after marketing approval of the current

hepatitis B and Hib vaccines in the United States, less than 10% of children in GAVI Fund-eligible countries were receiving either of these vaccines. Countries were uncertain about need (disease burden) and the price and availability of the vaccine. GAVI at the time was a relatively new organization with assured funding for only a limited number of years, and was searching for the optimal way of introducing new vaccines by building up partner cooperation in this area particularly with regard to a coherent global vaccine supply strategy, which was significantly absent.

- o The supplies of the tetravalent and pentavalent combinations, the preferred vaccines for delivering hepatitis B and Hib antigens, were severely limited. This supply constraint was exacerbated by country level delays. As a result, there was a lack of trust between the multinational manufacturers and GAVI, so that increasing industrial capacity for the GAVI market seemed an unlikely possibility. Equally important, emerging manufacturers were disregarded as a potential source of innovative vaccines.
- o The use of the existing pneumococcal vaccine, Prevnar®, in the developing world was not considered likely. A rotavirus vaccine (Rotashield® – Wyeth) had been placed on the US market in 1998, but was withdrawn by the manufacturer in 1999 after reports of association with intussusception, a rare and serious adverse reaction. Manufacturers were mindful that several older vaccines (e.g. yellow fever and rubella) were not widely used despite the establishment of disease burden and affordable prices. Most developing country policy makers had little idea of the disease burden of the diseases these newer vaccines were targeted against.
- o New vaccines for the developing world were procured and supplied in a market that was both monopsonistic (one buyer) and monopolistic (one seller) for several products. The buyer, UNICEF Supply Division, was working to obtain the lowest possible prices for countries, while the sellers were not compelled to lower prices given the uncompetitive market and that these products were not suitable for the high margin market because of product divergence. Manufacturer lead times were long and changes expensive to make. In comparison, the public sector market operated with short turn-around times, large volumes and low prices.
- o In 2005, emerging suppliers were undertaking vaccine-development activities, especially for the DTP-based combination vaccines including Hib. Of the 75 GAVI

Fund-eligible countries, only 15 had actually incorporated Hib vaccine or applied to incorporate it into their immunization programmes. 2005 also was significant in terms of financial sustainability issues as countries that had received GAVI support started to become obligated to co-pay for Hib vaccines but many did not have the resources for it. Given that the price of the pentavalent vaccine had not dropped and countries had not fully implemented financial sustainability plans, Hib vaccine financing was recognized as a priority and the Bridge Financing concept was introduced as a result. By 2005, GAVI was secure financially as it had successfully raised more than \$1.3 billion for the GAVI Fund since 1999 (not including the International Finance Facility on Immunization (IFFim) and the Advance Market Commitment (AMC)).

- o In 2007 funding has increased significantly, there are notable changes in GAVI's scope and structure, scientific and technical progress have been made, there are many new vaccines in the pipeline and an increased entry of manufacturers, both multinational and emerging suppliers, into the market.
- o The work of the ADIPs had a large impact on the entry of suppliers into the market for pneumococcus conjugate and rotavirus vaccines, given their work to develop credible demand forecasts and business cases to demonstrate and secure the availability of funding sources and the interest of countries in taking up these products. This has influenced the multinational suppliers. By working directly with the emerging suppliers in exchange of information and some technical support, the ADIPs have also encouraged these producers to invest in the development of innovative products.
- o While it is difficult to assess the absolute impact the ADIPs have had given the lack of a counterfactual, one could compare the status of rotavirus and pneumococcal conjugate vaccines today, poised to enter the GAVI market, with the status of Hib at the same stage in its life cycle to see the impact the ADIPs have had. Even if one were to compare the programme readiness of Hib four years ago, when the ADIPs were started, to the programme readiness today of rotavirus and pneumococcal conjugate vaccines, it is difficult to avoid the conclusion that there has been a contribution of the ADIPs to this process.

1.3 Achievements of ADIPs and HI

1.3.1. *Pneumo ADIP*

- o The activities of the Pneumo ADIP have led to the potential for widespread introduction of the pneumococcal vaccine into GAVI-target countries more than five years before historical precedents and the possibility that Prevnar®, Wyeth's 7-valent vaccine, will be introduced into several countries as early as 2008. More specifically:
 - The Pneumo ADIP has developed sound disease burden data for which there is international consensus; clearly communicated key messages to core stakeholders about the disease, the vaccine, and response to the vaccine based on technical information agreed by leading scientists in the field; with Wyeth, is planning a demonstration project with the 7-valent vaccine in high disease burden countries for which country commitment to participate has been seen.
 - It has encouraged Wyeth to supply to developing countries and to go through the WHO prequalification process; set the stage for additional multinational products with improved characteristics (GSK's 10-valent vaccine and Wyeth's 13-valent vaccine) to enter the market; raised interest on the part of emerging suppliers to invest in pneumococcal vaccine development, and at least one major manufacturer is already investing in significant capacity for the developing market.
 - It has obtained commitment from both multinational suppliers both for available and future vaccines to supply the products at tiered prices; obtained commitment from the GAVI Alliance to co-finance pneumococcal conjugate vaccines to developing countries; partly as a result of the ADIP's inputs, commitment was given by the G8 donors to finance an AMC of \$1.5 billion for pneumococcal vaccine.

1.3.2 *Rota ADIP*

- o Two rotavirus vaccines are now authorized for marketing and have been proven to be safe and relatively effective in industrialized countries and in some developing

countries (although not necessarily in public sector immunization programmes). The vaccine has already been introduced into a number of countries in Latin America, through the Rota ADIP's collaboration with PAHO and the Sabin Vaccine Institute. Through the work of the Rota ADIP, the vaccine could be introduced into GAVI target countries as early as 2007, one year after marketing approval was obtained in the USA and Europe, provided that sufficient safety and efficacy data are available for those countries.

- The Rota ADIP made a strong case for the cost-effectiveness of rotavirus vaccine as well as for impact on known disease burden, supporting potential early-adopter countries to take it up. It has successfully undertaken advocacy by disseminating information about expanded clinical trial safety results which have dispelled safety concerns. As a result, the vaccine is already in use in several developing countries.
- The Rota ADIP has worked with several manufacturers, both multinationals and emerging suppliers, in an effort to ensure ample competition among rotavirus vaccine producers. Ideally, this will ensure adequate supply at affordable prices. Through collaboration on clinical trials in developing countries, safety and efficacy of these vaccines in these countries could be demonstrated.
- Both multinational manufacturers have pledged to offer the product at tiered prices to the GAVI market. The GAVI Board has recommended co-financing of the product in target countries.

1.3.3. Hib Initiative

- o The HI has made progress in its communications and advocacy strategy which has helped support country decision making to take up Hib vaccine. It is providing a stronger evidence base by focusing on surveillance and impact determinations, as well as assembling cost-effectiveness data. The HI has directly reached 64 countries, and it has already met and exceeded its 2007 introduction targets: 24/49 countries in regions with well documented disease burden have introduced or approved the introduction of Hib, while about half of the eligible countries in Asia and the Central European Economies/Newly Independent States (CEE/NIS), where disease burden

data are limited, have made a decision about Hib introduction. Whilst it is not possible to demonstrate the specific contribution of the HI to these decisions, it has been able to provide relevant material to the countries concerned.

- o The HI has contributed to the revision of the WHO Position Paper so it clearly recommends use of the Hib vaccine. There have been no achievements in supply, capacity and pricing issues as a result of HI work, but they were specifically excluded from the HI mandate.

1.4 Gaps and constraints

- o The ADIPs and the HI have in some cases had to work under external constraints that limited their effectiveness. These are outlined below.

1.4.1 *Pneumo ADIP*

- o The Pneumo ADIP had projected in its original proposal that one or two new pneumococcal conjugate vaccines would be ready to use in 2007. This has been delayed and is not likely going to take place for another one to three years. Following a SAGE recommendation on the use of the 7-valent vaccine it is now undergoing the WHO prequalification process, which was delayed at the request of WHO, and will not be in use until this is final. Thus the planned pilot introduction programmes and dose and schedule optimization studies will not be completed in 2007 as planned. In the first years of the ADIP, it had to work against a remaining uncertainty about the appropriateness of the vaccine for developing countries and a lack of consensus on key technical issues, and these constraints also delayed progress, although they have now to a large extent been addressed, given a Lancet paper by major scientific experts in the field.

1.4.2 *Rota ADIP*

- o Like the Pneumo ADIP, its goals have changed in response to delays and changes in the global landscape. Rather than providing direct support to a specific emerging supplier, as envisioned in the RFP, technical assistance has been provided to a number of these manufacturers. Trials in Bangladesh were delayed as were Phase 3

trials in Africa, although the trials are now underway. While disease burden information is available and there is a SAGE position and a WHO position paper on the benefits of the vaccine, because of the delay in clinical trials, specific recommendations to some regions cannot be made, as safety and efficacy have not been confirmed in all populations. Price-volume agreements are still outstanding.

1.4.3 *Hib Initiative*

- o The HI is distinct from the ADIPs insofar as its mandate is to set a firmer basis for Hib introduction in target countries. The HI was envisioned to help countries decide whether to introduce or continue the vaccine and handle country introduction activities, on the theory that all other ADIP-like activities had already been done. They have focused this work as appropriate to facilitate country decision making, with success as outlined above. The HI has not addressed capacity of supply issues effectively, nor has it developed a credible demand forecast or entered price discussions, as these were all specifically excluded from their mandate by the GAVI Management Committee (MC). Its institutional organization, spanning different physical locations and being governed by an Executive Committee rather than by a team leader, may limit its coherence and fluidity.

1.5 Value for money

1.5.1 *Pneumo ADIP*

- o The expenditures to date of the Pneumo ADIP (about US\$ 30 million), have been used to set the stage for the introduction of Wyeth's 7-valent pneumococcal conjugate vaccine in some countries as early as 2008 and for the rapid introduction of the 10- and 13-valent products when available. This will mean an acceleration of more than five years for introduction. The Pneumo ADIP estimates that as many as three million children may be immunized against *Streptococcus pneumoniae* in this initial period, which could avert 15 000 deaths. Their effort has also leveraged US \$1.5 billion in AMC funds to accelerate the improved products at an affordable price, and, for an additional up to US\$200 million expended, the ADIP estimates that by 2025 3.9M deaths and 32M hospitalizations could be averted, along with \$690M/year in direct medical expenditures. The ADIP has refocused multinational manufacturers' efforts

toward developing country vaccines by addressing their concerns, building a solid business case, and facilitating vaccine registration and introduction issues. The ADIP has also helped established the credibility of emerging suppliers to foster future market competition.

1.5.2 *Rota ADIP*

- o The Rota ADIP, also for about \$30M, has helped accelerate the introduction of rotavirus vaccines into developing countries within three to four years after industrialized country introduction, and thus has effectively added 12 years of availability of this product. This potentially translates into 30,000 deaths averted until 2010. For an additional expenditure of about \$500M, the ADIP estimates an equivalent savings in direct medical costs plus prevention of 2.4M deaths by 2025. It has stimulated emerging suppliers to develop these innovative vaccines, and focused multinational manufacturers on the potential reward of producing vaccines for the developing world.

1.5.3 *Hib Initiative*

- o The 15 years time lag following introduction into the industrialized world has already passed. However, if the HI can set the stage for enhanced introduction of these products, even in only 10% of the children who are not yet receiving the vaccines, 300,000 cases and 40,000 deaths per year could be averted.

1.6 Roles and impact at country level

Both ADIPs and the HI are spending significant amounts of money at the global level for communications and advocacy and meetings, and the ADIPs have also invested in regulatory inputs at the global level.. The amounts given below indicate funds spent directly at country level. The response of interviewees on the impact of the ADIPs and HI at the regional and country levels has been contradictory, with some respondents clearly differentiating the three groups (as well as the two other initiatives on Japanese encephalitis and meningitis mentioned below) and others lumping them together as vertical projects that compete with

each other and overburden countries; some have particularly praised their efforts to improve disease burden data and surveillance, while others have deplored the “project” approach, not building on existing surveillance systems; some have commended the ADIPs’ work with industry, while others charge that they are working to industry’s agenda; some have complained that the ADIPs have been absent at country level, but the majority has concluded that, rather than working directly at the country level, they should work at Regional level through WHO and the Regional Working Groups (RWGs).

1.6.1 *Pneumo ADIP*

- o The Pneumo ADIP will have spent a total of \$17M, over half of its original budget, at country level by the end of 2007, or about 25% of the total budget. These expenditures are focused on tracking disease burden, surveillance, small grants to countries, and support to WHO regional staff.¹ Over 50% of those funds have been to Africa, and most of the rest to South Asia and the Middle East, tracking the highest incidence of childhood pneumonia-related mortality.

1.6.2 *Rota ADIP*

- o The Rota ADIP provided data on their 2007 budget of \$9.22M, of which \$7.58M is for clinical trials. Of the remaining \$1.64M, \$315,000, or about 20% will go directly to countries, mostly for surveillance, but with about \$10,000 for cost-effectiveness work at country level. This figure does not include staff support at Regional level.

1.6.3 *Hib Initiative*

- o The HI has proposed to spend over the entire 2006-2010 period, \$4.57M in direct expenditures at the country level, of which about \$1M is for surveillance and the rest is for assessment of vaccine impact and effectiveness. This amount is about 12% of their total expected \$37M budget, including the India probe study, and does not include staff support at the Regional level.

Based on this incomplete data, the HI seems to spend a lower share at country level, despite its focus on support to country decision making.

1.7 Other interventions

¹ To compare with the expenditures of the other initiatives, support to WHO Regional staff must be factored out, but this information was not provided.

- o We compared the ADIPs with two other interventions, the Meningitis Vaccine Project (MVP), and the Japanese Encephalitis (JE) Project, selected because they were dealing with vaccines at about similar stages of programme readiness. The MVP has served as a virtual vaccine developer in collaboration with a developing country vaccine manufacturer for conjugate meningitis type A vaccine. In addition to all vaccine development activities and clinical trials, they have worked on developing surveillance systems in Africa, where the disease is epidemic. They have spent a great deal of time on country level advocacy through collaboration with WHO to assure that countries are prepared to take up the product once it becomes available – it is now in phase 2 trials in Africa. The JE Project is also providing direct support to a developing country manufacturer, in China, encouraging clinical trials, and working in-country through PATH sites, in areas where the disease is epidemic. The projects differ from the ADIPs in their direct support to specific manufacturers, with whom they have negotiated specific low per dose prices for a specified period after eventual introduction of the products, but are using similar mechanisms in terms of surveillance and advocacy.
- o The analysis does not support the idea that these interventions have been more effective.

1.8 Governance

- o Both the ADIPs and HI are overseen by the same Management Committee (MC) composed of scientific experts, a donor organization, an individual with private sector industrial expertise, and a country health ministry official. Although the technical and scientific expertise on the MC has been helpful, this means that, of the three client groups of the ADIPs, industry, donors, and countries, the second and third groups are not well represented.² . In the HI RFP, it was specifically stated that the MC would be expanded to reflect the new mandate; this apparently has not happened. Several of those interviewed expressed a need for more country representation on the MC, to better guide all three initiatives in the preparation for introduction phase.
- o When the ADIPs were started, it was foreseen that GAVI Board members would

² For example, there are no bilateral donors or other partners working at the country level, and no specialists in primary health care service delivery at the country level.

constitute a significant proportion of the MC. This has not happened, so that the MC is the liaison between the ADIPs/HI and the GAVI Board. This situation has left the impression of lack of interest on the part of the GAVI Board. Several interviewees complained about the lack of transparency in the management structure, charging that the Board has delegated too much to the MC.

- o Until recently, there was no focal point in the GAVI Secretariat for the ADIPs/HI. This has been strongly felt. In addition, the GAVI Country Support Team has not been involved with the ADIPs/HI to the extent that they felt would be desirable.
- o The governance and oversight of the ADIPs and the HI have indicated some failures to adopt principles clearly stated in the RFPs which might have enhanced their impact. The key issues are addressed in the recommendations below.

1.9 Conclusions and recommendations

- o The team concludes that the work of the ADIPs has accelerated the process of introduction of pneumococcal conjugate and rotavirus vaccines and has thus provided value in terms of lives saved and hospitalizations averted. The HI, in place for a shorter period of time, has served more like an Implementation ADIP, and has facilitated decision making in a number of countries. However there remain capacity, demand, and pricing issues for Hib that are specifically excluded from the HI mandate that need to be addressed.
- o The team recommends that the GAVI Board consider approaches for further managing the new vaccine introduction process in three areas:
 - Scanning the pipeline (the pre-ADIP process) and keeping informed on projects in earlier stages of development;
 - Addressing the issue of the ADIP process: capacity, demand, and pricing strategies that are needed to render a vaccine “programme ready;”,
 - Addressing the implementation issues for a range of programme ready vaccines..
- o Possible approaches with the pros and cons of each are presented, through which GAVI

could better manage the life cycle of new vaccines which are being considered for inclusion within developing country immunization programmes. Whichever approaches are selected, GAVI will need to consider how best to manage them, and the following recommendations are offered related to gaps seen in the current process.

1. GAVI will need to review its mission and its working procedures to determine how best to manage these approaches and structures, either within the GAVI Secretariat, housed at a GAVI Partner organization or at an outside organization selected through an RFP process.
2. For the ADIP and implementation processes, oversight needs to involve the GAVI Board, through a Management Committee selected with appropriate skills, and with liaison through specifically charged GAVI Secretariat teams.
3. ADIPs should be focused in a single organization, with a strong manager, and be target-oriented, time-limited and milestone-driven.
4. The ADIPs should justify on a regular basis to the GAVI Board the continuing relevance of their product.
5. The ADIPs should carefully define their interactions with GAVI Partners at country level.
6. The Requests for Proposals, mandate, and the governance structures must be clear and appropriate.
7. The GAVI Board should ensure that there is collaboration and coordination among all groups performing an ADIP-like function by convening open fora where they can report latest results and resolve potential issues.

2. BACKGROUND

The Global Alliance for Vaccines and Immunization (GAVI, now called the GAVI Alliance) was founded in 1999 and launched in 2000 to increase the access of populations in developing countries to vaccines of public health importance. More specifically, GAVI's strategic objectives during its first phase in 2000-2005 were: (1) to improve access to sustainable immunization services; (2) to expand the use of all existing safe and cost-effective vaccines and promote delivery of other appropriate interventions and immunization contacts; (3) to support the national and international accelerated disease control targets for vaccine-preventable diseases; (4) to accelerate the development of new vaccines and technologies; (5) to accelerate R&D efforts for vaccines needed primarily in developing countries; and (6) to make immunization coverage a centerpiece in international development efforts.

In 2002, recognizing the need for support to bring new vaccines into immunization programmes, GAVI launched the Accelerated Development and Introduction Plans (ADIPs). In brief, the ADIPs aim to shorten the time lag between vaccine introduction and their introduction into developing countries. After an extensive analysis process which included country inputs and product evaluation, and emphasized the concept of "low-hanging fruits," pneumococcal conjugate vaccines and oral rotavirus vaccines were selected as the respective foci of the two ADIPs.³ In 2005, based on evidence that the availability of financing alone had not resulted in optimal uptake of *Haemophilus influenzae* type b (Hib) vaccine, the GAVI Alliance launched the Hib Initiative (HI), to expand the use of the Hib vaccine in developing countries.

As it enters its second phase, GAVI needs to take into account the changing vaccine market place and what this means for its operational structures, such as the ADIPs and the HI. To this end, GAVI has commissioned a study by HLSP London to examine these initiatives. This study was overseen by a Steering Committee convened by the Alliance.

The Terms of Reference of the study are as follows:⁴

³ A third vaccine, meningitis A conjugate, was also selected as a priority, but was not included in the ADIP process because there was already the Meningitis Vaccine Project providing similar activities.

⁴ GAVI Alliance Request for Proposals for Consultancy Services, July 2006, Annex 3, p. 27.

- a. to take stock of the way the environment for new vaccine development and introduction has evolved over the past four years,
- b. to assess the progress made and highlight the lessons learnt through the innovative ADIPs approach, the Hib initiative and other new vaccine introduction related GAVI supported activities and
- c. to make recommendations to the GAVI Board on the structure and finance [of] its continued support in this priority area in the coming years.

The scope of the project includes (1) a description of how the environment prevailing at the time of the launch of these initiatives has evolved and how this may have an impact on the relevance and objectives of these Initiatives; (2) an evaluation of the structures themselves, in terms of their mandates, achievements, governance, and constraints; and (3) a proposal for the future role of the Alliance to continue to support the introduction of these and other new vaccines in the developing world.

The report is structured to answer these questions. Section 3 outlines the study methodology. Section 4 will look at the global situation with the relevant vaccines when the ADIPs and the HI were set up. Section 5 analyzes the outputs of the three structures in terms of the study framework, and Section 6 considers their impacts on industry, donor, and countries, their three target audiences. Section 7 looks at the governance issues to date, and Section 8 examines whether the ADIPs and the HI have given “value for money.” Section 9 briefly considers other initiatives that are charged with tasks similar to those of the ADIPs and the HI. Section 10 summarizes the important changes in the global vaccine landscape since the initiatives were launched, and considers the impact the ADIPs have had on these elements, as well as attempts to address the counterfactual, if the ADIPs had not existed. Finally Section 11 outlines the needs for GAVI intervention and oversight in the development and introduction of new vaccines in the pipeline, and Section 12 develops possible models to fulfil these needs, along with some recommended GAVI actions whichever approaches are selected.

3. METHODOLOGY OF STUDY

The conceptual framework of the study is embodied in the virtuous cycle described by the original report presentation by McKinsey & Company which advised on establishing the

ADIPs,⁵ with additional elements (market incentives, available finance, disease burden, advocacy, supply strategy, and demand estimates added to each of the components (predictable price, predictable demand, predictable capacity), representing activities the ADIPs could do to positively impact the virtuous cycle (Figure 1).

There were three major sources of information for the work, as outlined in the original Request for Proposals (RFP)⁶ :

- a. Documents available from the GAVI Alliance or from the ADIPs themselves: the Mercer, McKinsey, and BCG studies (the Mercer study looked at the supply picture for new vaccines, the McKinsey study is the primary reference impacting the launching of the ADIPs,⁷ and the BCG study examined the role of emerging suppliers in the context of innovative vaccine supply⁸); ADIP and HI technical and financial reports and newsletters; and Management Committee (MC) and Board meeting minutes and reports.
- b. Semi-structured interviews with key stakeholders and informants (see Annex 1 for a list of these) representing donors, industry, and users. Most were interviewed using a format which sought overall impressions of the functioning of the ADIPs and the HI, including questions in the areas of context, organizational and governance effectiveness, outcomes, relationship with GAVI Partners, financing, as well as suggestions for how they could function better. Some informants, particularly those in charge of managing the ADIPs, and those working directly with them from WHO and GAVI, were interviewed a second time, to elicit more specific information on possible GAVI support and structures, and these are indicated in Annex 1.
- c. Information on other public-private partnerships designed to accelerate the development and introduction of specific vaccines: the Japanese Encephalitis

⁵ The World Bank Group/The Gates Foundation, Accelerated introduction of priority new vaccines in developing countries – from credible investment case to Accelerated Development and Introduction Plan (ADIP), September 2002.

⁶ GAVI Alliance Request for Proposals for Consultancy Services, July 2006, Annex 3, p. 27.

⁷ See Accelerated Development and Introduction of Priority New Vaccines: The case of pneumococcal and rotavirus vaccines, 8th GAVI Board Meeting, 19-20 June 2002, Paris.

⁸ Boston Consulting Group. Global Vaccine Supply: the Changing Role of Suppliers, a report commissioned for GAVI by WHO and the World Bank, 2005.

Vaccine Project and the Meningitis Vaccine Project, available from their websites, and interviews as listed in Annex 1.

These sources were supplemented by familiarity with GAVI and the evolution of the ADIPs, the incorporation of Hib, and the work of the Financing Task Force by the team members.

This information was then analyzed within the conceptual framework (Figure 1), and conclusions were used to develop potential models for future GAVI Alliance roles in new vaccine introduction and within its institutional architecture for vaccines.

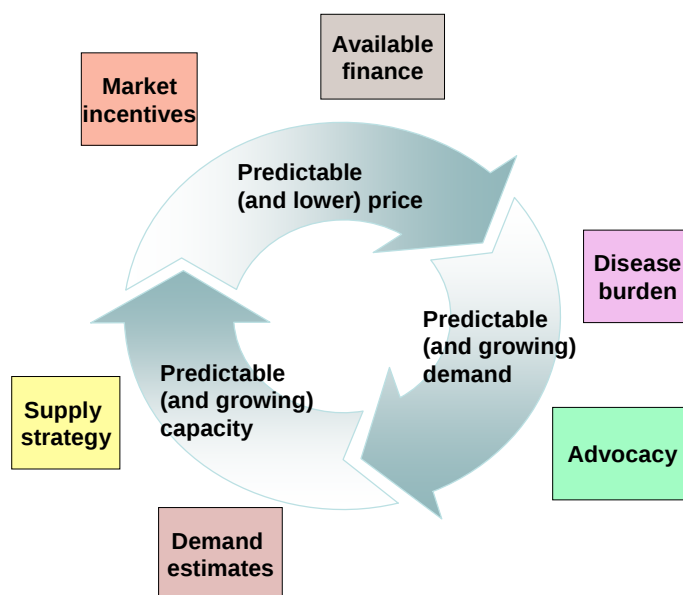


Figure 1. The virtuous cycle, with potential ADIP activities, that together form the structural framework for this analysis.

The analysis is limited by the lack of robustness of the data available. Where possible, each statement and observation is documented, but the comparability of the ADIP documents is limited by the different approaches used. A major source of information was interviews with ADIP/HI clients, which can be subjective, and it was left to the study team to determine how much credence to put to particular observations. A more rigorous study, particularly to look at impacts at the country level, would require site visits and more time and resources than available for this report. Finally, the HI was judged by the same criteria as the ADIPs, which limited the evaluation. A separate effort would be required to assess its performance as an implementation ADIP.

4. WHY ADIPS AND HI

4.1 The vaccine introduction picture in 2002

GAVI had started encouraging introduction of hepatitis B and Hib. By 2002, GAVI had been launched and was promoting the uptake of hepatitis B and Hib vaccines. At this time, more than 15 years after marketing approval of the current hepatitis B and Hib vaccines in the US, fewer than 10% of children in GAVI Fund-eligible countries were receiving either of these vaccines. The issues for countries were uncertainty about need (disease burden) and the price and availability of the vaccine.

GAVI was a relatively new organization with assured funding for only a limited number of years, and was searching for the optimal way of introducing new vaccines through partner complementation. Some of the work for new vaccine introduction had previously been done through the Financing Task Force, working with countries on the issue of financial sustainability. The Task Force was scheduled to be phased out within a short period of time.

Significantly, GAVI had no coherent vaccine supply strategy. UNICEF Supply Division was procuring WHO-prequalified vaccines, but the supplies of the preferred vaccines for delivering hepatitis B and Hib antigens, tetravalent and pentavalent combinations, were severely limited, with only one manufacturer for both of them. This supply constraint was exacerbated by delays at country level with placing orders and setting up introduction plans, and sometimes placement of orders was delayed for up to a year or more after approval of funding for the products. This led to a mutual distrust between the multinational manufacturers and GAVI, with the result that increasing industrial capacity for the GAVI market seemed an unlikely possibility. Moreover, emerging manufacturers were disregarded as a potential source of innovative vaccines.⁹ Indeed, they had not yet produced combination vaccines nor Hib vaccines, and few, if any of them, had demonstrated the capacity for R&D or process development and scale up. WHO produced a position paper on Hib vaccines in 1998:¹⁰ because of questions concerning Hib disease burden in Asia, it stopped short of a firm

⁹ The World Bank Group/The Gates Foundation, Accelerated introduction of priority new vaccines in developing countries – from credible investment case to Accelerated Development and Introduction Plan (ADIP), September 2002, p.3. This study suggests that no developing country manufacturers could make either pneumococcal conjugate vaccine or rotavirus vaccines by 2009, and then only with intensive support.

¹⁰ World Health Organization, WHO Position paper on *Haemophilus influenzae* type b conjugate vaccines. *Weekly Epidemiological Record* (March, 1998).

recommendation for their global use. WHO also had a priority project for new vaccine introduction, which was primarily focused on Hib, with funding from the Children's Vaccine Program at PATH, providing for support for a network of new vaccine officers in the WHO Regional Offices; however funding was for a limited time and was due to expire.

In terms of pneumococcal disease, there were uncertainties on disease burden complicated by debates about diagnostic methodology. One pneumococcal conjugate vaccine was on the market, the 7-valent Prevnar® product, produced by Wyeth, which had been used in the US and Europe since approval in February 2000, and was also licensed in a total of 49 countries, none of them part of the GAVI clientele. Efficacy trials had shown high efficacy with a 7-valent product in Western populations and in American Indians. The only trial to have been completed in a developing country, of a 9-valent vaccine in South Africa, showed less than expected efficacy. Two more developing country trials were underway, in the Gambia, with a 9-valent product, and in the Philippines with an 11-valent product. A 9-valent Wyeth vaccine and an 11-valent GSK product were expected to be ready for marketing in 2006 or 2007.¹¹ In addition, there was uncertainty about serotype replacement and herd immunity, and few people seriously considered there to be benefit, both because of its price and its serotype mix, of using Prevnar® in the developing world. Nevertheless, because of the importance of acute respiratory infections as a public health problem and the high pneumococcal disease burden, as well as earlier efforts by the Children's Vaccine Initiative and USAID for a pneumococcal vaccine agenda, collaboration had already been started between pneumococcal disease experts and WHO, to develop a process for moving this product forward.

Rotavirus infection reflected a major proportion of diarrheal disease in both industrialized and developing countries. Because of this a rotavirus vaccine (Rotashield® – Wyeth) had already been placed on the market in the US in 1998, but was withdrawn by the manufacturer in 1999 after reports of association with intussusception, a rare, serious adverse reaction. At the time, the vaccine had not been shown effective in most developing countries: WHO was supporting trials in Asia and Africa. Because of the discussions around the decision to withdraw the Wyeth vaccine there was much activity to try to find a suitable vaccine candidate. Both Merck and Glaxo SmithKline (GSK) had products in the late clinical stage. There was work also in

¹¹ These products are expected to be a 10-valent product from GSK and a 13-valent product from Wyeth, anticipated to receive marketing approval between 2008-2010. Two additional products, a 7-valent Merck product and an 11-valent Aventis product, had reached phase 3 trials but development had been stopped. Uncertainty of regulatory pathways played a role in this decision.

several developing countries, including India and Indonesia, to develop a product, and a lamb rotavirus vaccine had been used in China for several years, though little efficacy data had been accumulated. The key barriers identified at the time of the ADIP's initiation were the development of reliable surveillance sites in countries, the establishment of the cost-effectiveness of new products, and assurance that the new candidate vaccines would not present safety risks. Work was already going on with both multinational and developing country manufacturers, and a collaboration called RAPID (Rotavirus action program for immunization and development) was in place between GSK and the Children's Vaccine Program at PATH to support phase 1 and 2 trials in the developing world, in Bangladesh and South Africa.

There were information asymmetries related to new vaccine uptake. GAVI wanted to introduce new vaccines and offered funding to support country uptake, but countries were not rushing to take them up. In 2002, only about 70 million doses of hepatitis B vaccine and fewer than 10 million doses of Hib vaccine were used by developing countries, while demand forecasters often confused demand with need, and failed to take into account trade-offs between antigens at country level when trying to develop forecasts. Delays at the country level which could make a real difference to annual uptake, and to manufacturers' capacity, were not foreseen in the forecasting effort. Moreover, manufacturers could see that there were several older vaccines, e.g. yellow fever and rubella, for which need and disease burden had been established, and for which prices were affordable to developing countries, yet these were not being widely used. Most policy makers in developing countries had little idea of the disease burden of any of the diseases these newer vaccines were targeted against. Since disease surveillance systems were not in place, there was thus no way to demonstrate a reduction in cases due to the impact of a vaccine. Vaccines were considered to be cheap – which could translate into “of little value.” And as yet there was no vaccine supply strategy, nor even a vaccine introduction strategy.

Market imbalances continued to exist. New vaccines for the developing world were procured and supplied in a market that was both monopsonistic (one buyer) and monopolistic (one seller) for several products. The buyer, UNICEF Supply Division, was working to obtain the lowest possible prices for countries, while the sellers, in the absence of competition, saw no need to lower prices, especially since these products were not suitable for the high margin market because of product divergence. Product divergence made price tiering unattractive for the vaccine industry when there was no high end market to offset costs, so vaccine security – shortage of some key products on the public market – became a central issue. Manufacturer

lead times were long, and changes expensive, while the public sector market operated with short turnaround times, large volumes and low prices.

4.2 The charge to the ADIPs in the RFP

Funding for the ADIPs came from Window 3 of the original Vaccine Fund allocations, which was for R&D. The charge from the R&D Task Force for this window was clear: focus on “low-hanging fruit,” end stage vaccines that could be introduced in the short to medium term. The RFP¹² described the ADIP strategy, referenced in a separate document.¹³ The RFP thus discusses primarily evaluation criteria. The Summary Document specifies that “ADIP teams would execute a *product development and early introduction programme* [italics added] in coordination with a broad range of public and private GAVI Partners.” The activities were to focus on multinational manufacturers with vaccines in the late stages of clinical development.

The activity plan was to be organized around three areas: establishing value, communicating value, and delivering value, as follows:

1. Establish value: assess burden of disease, assess impact of a vaccine
2. Communicate value: develop a communications strategy including both positive and negative aspects
3. Deliver value: ensure vaccine supply, ensure funding of vaccine purchase and of delivery systems.

Although this seems clear (and it should be remembered that the Summary Document was written in collaboration with people who eventually staffed the ADIPs), there are some inconsistencies in the document and in the way it has been interpreted by the ADIPs and by the overseeing Management Committee (MC). For example, the document refers to (p.14) one of the ADIP work tracks as “clinical programme development,” while it is unclear how

¹² Global Alliance for Vaccines and Immunization, Accelerated Development and Introduction Plans (ADIPs) for Pneumococcal Conjugate and Rotavirus Vaccines. Request for Proposals. Annex 1, August 2002.

¹³ Global Alliance for Vaccines and Immunization, Accelerated Development and Introduction Plans (ADIPs) for Pneumococcal Conjugate and Rotavirus Vaccines. Summary Document. Annex 2, August 2002.

much R&D the ADIPs should support.¹⁴ Second, the activities and name imply that country introduction will be a big focus, yet the ADIPS have been specifically enjoined from specific introduction activities. In addition, while the document says (p. 8) that the focus should be on multinational manufacturers, it also mentions for rotavirus vaccines that local production may be feasible, yet the Rotavirus ADIP was told by the MC not to deal with local producers.¹⁵ Finally, the document reiterates the McKinsey study finding that demand uncertainty was the most important issue (p. 5), yet developing demand forecasts is not on the initial list of activities mentioned above, although it is included later in the document as part of a summary of demand and supply activities. The key first objective is identified as “to advise GAVI on whether to develop price-volume understandings with suppliers;” although until recently this would have been premature.

In light of this confusion, for which both ADIP Directors told us they had to go back to the MC for clarification, it is interesting that later the MC endorsed the following strategic objectives:¹⁶

1. Provide information that enables national decision-makers, the GAVI Alliance Board and its partners to make an evidence-based decision regarding vaccine use.
2. Increase the access to affordable, sustainable vaccine supply for the world's poorest countries.

It is also important to note here that the RFP and the Summary Document emphasize the need for the ADIPs to continually evaluate the relevance of the products they are working with to the GAVI mission.

Oversight was specified in the RFP to be by a “small managerial Steering Group that will include – but is not limited to – several GAVI Board members, with decision making authority delegated by the GAVI Board to approve the plan and budget and to evaluate the team’s use of resources and progress towards pre-specified milestones.” (p.3, RFP) In addition, ADIPs

¹⁴ There has been a difference in interpretation from the very beginning, in that the original Rotavirus ADIP proposal included support for manufacturers’ clinical trials, while that from the Pneumo ADIP did not.

¹⁵ This information came from interviews.

¹⁶ Accelerated Introduction of New Vaccines. GAVI Alliance Board Meeting, 20 June 2006, p.6 (noted to have been endorsed by the GAVI Alliance Board at its December 2003 Geneva meeting).

were encouraged to have their own technical oversight groups.

4.3 The Hib vaccine introduction picture in 2005

General. By 2005, there had been some changes in the general vaccine introduction landscape. Although the WHO/World Bank study on emerging suppliers performed by the consulting firm BCG had not been completed,¹⁷ it was already evident that there were vaccine development activities going on among the emerging suppliers, especially for the DTP-based combination vaccines which included Hib. In contrast, there was little movement among the multinationals, apart from Glaxo SmithKline (GSK), to develop such vaccines. GSK had taken a step to expand capacity by acquiring a Hungarian DTP producer; nevertheless, prices for tetravalent and pentavalent vaccines had not fallen. Although the supply crunch had eased off somewhat, there was no competition and prices had in fact risen.

The Hib position paper developed by WHO in 1998 still had an unclear recommendation for use for countries in Asia. Hib disease surveillance was not fully in place. There had been some efforts to promote Hib surveillance, and an additional effort by WHO to help countries arrive at disease burden estimates (the Hib Rapid Assessment Test, which was a hospital records-based disease burden estimation methodology). In some countries, notably Mali, the fourth poorest country in the world, Hib disease burden had been quantified by laboratory isolates from pediatric meningitis cases to be among the highest reported.¹⁸ The funding for the WHO priority project on new vaccine introduction had expired, and there were no longer funds for the network of WHO Regional new vaccine officers.¹⁹

In terms of financial sustainability, 2005 marked the beginning of the time period when countries would have to start co-paying for Hib vaccines, but few were able to. It was recognized that since the price of the pentavalent vaccine had not gone down, and countries had yet to fully implement financial sustainability plans, there would be a need to extend Hib vaccine financing, and the Bridge Financing concept was introduced. In contrast, by 2005,

¹⁷Boston Consulting Group. Global Vaccine Supply: the Changing Role of Suppliers, a report commissioned for GAVI by WHO and the World Bank, 2005.

¹⁸ SO Sow, S Diallo, JD Campbell, et al. [Pediatr Infect Dis J](#). 2005 Jun 24(6): 533-7 Burden of invasive disease caused by *Haemophilus influenzae* type b in Bamako, Mali: impetus for routine infant immunization with conjugate vaccine.

¹⁹ This was later addressed when the ADIPs and HI provided support in some Regions for this.

GAVI was on a much more secure financial basis, having raised more than \$1.3 billion for the GAVI Fund since 1999.

By 2005, of the 75 GAVI Fund-eligible countries, only 15 had actually incorporated Hib vaccine, or applied to incorporate it into their immunization programmes. For some of them, this decision was not necessarily sustainable after GAVI financing ran out. There were an additional 22 countries eligible with high disease burden that had not applied for Hib vaccine financial support, and another 26 countries for which the disease burden was regarded as unclear. In 2004, GAVI had set up a Hib Task Force to advise it on how best to incorporate Hib vaccine. The result of this was the launching of the Hib Initiative.

Information asymmetries and constraints on sustainable Hib use existed primarily in five areas. First, the Hib disease burden was regarded as unclear, which meant that WHO was disseminating a weak message about the desirability of incorporating Hib vaccine. This in turn meant that demand forecasts could not be robust, as demand (and need) in countries with unclear disease burden could not be quantified. Third, supply was uncertain, depending on one supplier, and there was as yet no supply strategy. The price of the vaccine had not decreased as expected since GAVI's launch. Finally, because several countries had incorporated Hib vaccine without a clear disease burden basis or a way to document impact, they were envisioning dropping Hib when GAVI funding support ran out.

Market imbalances existed in that specifically for the Hib-containing combination vaccine preferred by countries, the pentavalent vaccine, there was a monopoly seller (and a monopsony buyer). That seller had had production difficulties and was unable to meet demand – a demand that was not robust enough to justify much investment from the point of view of the seller (although GSK did invest in another DTP producer to expand their capacity). Other products containing the Hib component were not satisfactory to countries. Thus, instead of a projected price decrease as the product moved forward in its life cycle, the price in fact increased – from \$3.20 per dose in 2002-2003 to \$3.65 per dose in 2004 with a very limited supply²⁰

²⁰ The price decreased to \$3.60 in 2005-2006 as the supply became more available. UNICEF Supply Division. Product Menu for Vaccines Supplied by GAVI, at http://www.unicef.org/supply/files/UNICEF_-_Procuring_supplies_for_children_-_GAVI.pdf, accessed 9 February 2007.

4.4 Bridging the gap from early adopters

In a book entitled “Crossing the Chasm,”²¹ are included ideas that are relevant to what happened with Hib vaccine, or, for that matter, any product that is a “new technology” – it is first taken up by early adopters, but it is not until substantive changes are made that it is incorporated by the general population. This is part of the management of the product life cycle. The author states in the Preface, “...The point of greatest peril in the development of a high-tech market lies in making the transition from an *early market* dominated by a few *visionary* customers to a *mainstream market* dominated by a large block of customers who are predominantly *pragmatists* in orientation. The gap between these two markets, heretofore ignored, is in fact so significant as to warrant being called a *chasm*, and crossing this chasm must be the primary focus of any long-term high-tech marketing plan.” The Hib story implies that there were issues that were not managed up front that would have helped Hib uptake – some of these issues no doubt include disease burden, impact measurement, price, and supply. It is therefore important to note that not all of these were covered in the RFP (see next section).

4.5 The charge to the HI in the RFP

Following the recommendations of the Hib Task Force, GAVI launched the Hib Initiative in 2005. The charge was quite clear: “To ensure that countries are supported in their efforts to make evidence-based decisions regarding the continual use or introduction of Hib vaccines into their National Immunization Programmes.”²² Supply issues were not included in the purview of the Hib Initiative; later in 2005 these were then taken over by a GAVI Supply Strategy Group working with UNICEF Supply Division. WHO was specified by the RFP as an obligatory collaborator in this effort. In addition, the HI team was expected to liaise with the group doing the India Probe Study, set up to quantify Hib disease burden in India.

Project oversight was specified in the RFP to be under the ADIP Management Committee, which would be “augmented to address this important area.” (RFP, p. 11) The MC would be responsible for approving organizational and implementation plans, approving budgets, and evaluating use of resources and progress in meeting milestones. Subject to the approval of the MC, the HI could also set up an Ad-Hoc Technical Advisory Group. (RFP, p.9)

²¹ Geoffrey A Moore, *Crossing the Chasm*. Harper Business, 1991.

²² Global Alliance for Vaccines and Immunization. Hib Initiative: Supporting country decision-making. Request for Proposals. February 2005.

5. OUTPUTS²³

5.1 Major activities²⁴

The activities listed below are not exhaustive but were considered critical in leading to the achievements of these groups during their life span thus far. The headings refer to the boxes in Figure 1.

Pneumo ADIP

Demand

Disease burden: The ADIP supported surveillance networks developed by its partners in several countries and regions with collaboration from the HI; received monthly data; analyzed serotype data; developed a cost-effectiveness model which allowed incorporation of the impact of HIV; supported small grants in 16 countries on surveillance efforts; supported staff in WHO Regional Offices; provided support for the WHO Burden of Disease project on meningitis and pneumonia with the HI

Advocacy: The ADIP did surveys of decision makers to identify perceptions to craft communications strategy; set up web-site along with a regular newsletter; disseminated a short list of key messages to decision makers, along with technically-based support materials; the ADIP was featured in BBC documentaries on immunization; succeeded in getting a policy recommendation from WHO's Strategic Advisory Group of Experts (SAGE) that the data available are sufficient to support the use of the 7-valent vaccine in developing countries.

Capacity

Demand estimate: The ADIP developed a demand forecasting tool for dynamic

²³ Please see Annex 2 for a description of the structure and function of the two ADIPs and the HI

²⁴ Activities of the three Initiatives were taken from their annual reports to the MC, and from the investment cases for pneumococcal and rotavirus vaccines submitted in 2006 (GAVI's PneumoADIP at Johns Hopkins, GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries. 23 October 2006; PATH's Rotavirus Vaccine Program in collaboration with WHO and the US CDC, Accelerating the Introduction of Rotavirus Vaccines into GAVI-Eligible Countries. Investment Case for GAVI Secretariat. October 2006.)

construction of demand forecast; shared the initial forecast with stakeholders

Supply strategy: The ADIP worked with industry to assure appropriate formulations and presentations; developed potential alternative regulatory strategies; inventoried both emerging suppliers and multinationals on their pipelines; participated in GAVI Supply Strategy Group, first for Hib, and then for pneumo, after having convened their own Supply Strategy Working Group.

Pricing

Market incentives: The ADIP developed draft business cases to model affordable supply from various manufacturers; did a Cost of Goods analysis for pneumococcal conjugate and protein vaccines; projected the total global market for infant pneumococcal conjugate vaccine; constructed a net present value model of an 11-valent vaccine; contributed to work on Advance Market Commitments (AMCs).

Secure financing: The ADIP worked to develop the AMC with pneumococcal vaccine as the first test case;²⁵ developed an investment case to convince the GAVI Board to co-finance pneumococcal vaccine introduction into countries.

Rota ADIP

Demand

Disease burden: The ADIP developed and published surveillance protocols for both rotavirus disease and intussusception with WHO; established surveillance networks in several regions, with at least 40 countries participating; promoted laboratory diagnosis with establishment of regional laboratories, training, a lab manual and kits; funded a Regional Advisor in PAHO; produced global, regional and country cost-effectiveness analyses; worked successfully with PAHO and the Sabin Vaccine Institute to accelerate rotavirus vaccine introduction in Latin America.

Advocacy: The ADIP developed a web-site and an electronic newsletter;

²⁵ This was announced in Rome on 9 February, 2007. See http://www.vaccineamc.org/launch_event_01.html.

developed an information packet on rotavirus after a study of effective messaging in five countries; built linkages in diarrheal disease management community; worked with the pneumo ADIP on joint communications strategies; developed educational materials including an e-learning module.

Capacity:

Demand estimate: The ADIP developed a demand forecast based on similar methodology as used by the Pneumo ADIP; also developed a Delphi-methodology demand forecast.

Supply strategy: The ADIP partnered with two multinational developers of rotavirus vaccine to assure regulatory pathways, appropriate clinical trials; partially supported two positions in WHO on regulatory pathways; developed A *Manufacturer's Resource Guide*²⁶ to help emerging manufacturers develop the rotavirus production technology, and provided a consultant to advise them on request; worked with multinational manufacturers of licensed products to submit products for WHO prequalification; worked with regulatory bodies in developing countries where clinical trials were to be held to assure capacity building for clinical trial authorization and oversight; took part in the GAVI Supply Strategy Group

Pricing:

Market incentives: The ADIP worked with GAVI and others on the AMC strategy; identified early-adopting countries and worked with them on uptake decisions, specifically with a Latin American strategy.

Secure financing: The ADIP developed an investment case to convince the GAVI Board to support county co-financing of rotavirus vaccine.

Hib Initiative

Demand:

Disease burden: The HI is supporting, with Pneumo ADIP, WHO estimation of burden of disease as well as development of a surveillance protocol; funding surveillance and impact studies in EUR and AFR; liaising with the India Probe

²⁶ PATH's Rotavirus Vaccine Program. *A Manufacturer's Resource Guide*. March 2006.

study on impact of Hib in a country with unclear disease burden; summarizing cost-effectiveness data on use of Hib; supporting three large country proposals on decision making in Pakistan, Bangladesh, and Mozambique; and contributed to the publishing of a new WHO Position Paper in November 2006 that advocates clearly the desirability of Hib use in all countries.

Advocacy: The HI developed key consistent messages on Hib disease and Hib vaccine; developed a website (<http://www.Hibaction.org>) and an electronic bulletin; contributed to a BBC documentary on immunization; is working at the country level through Regional Offices to support decision making and to disseminate the new WHO position; has directly reached 64 countries and has sponsored national consensus meetings in some of them; and is funding WHO Regional Office staff in AFRO, EMRO, SEARO, EURO, and WPRO (pending).

Capacity:

Demand estimate: This appears not to be on the work plan, although the HI does keep a running list of countries that have been approved for funding to introduce Hib vaccine. In the recent past (presumably since the launching of the HI), three countries have introduced Hib vaccine and four more have been approved for funding.²⁷ (see below under achievements for up to date totals).

Supply strategy: The HI has no mandate to handle supply issues or work with manufacturers despite major supply issues, a newly prequalified emerging supplier's pentavalent vaccine, and several others in the late stages of the pipeline; it is liaising with UNICEF and is an active member of vaccine reference group and the Bridge Financing Team.

Pricing:

Market incentives: The HI is working with countries to increase the market; promoting use of Hib in all countries, which could expand the market in middle income countries; the HI has no direct interaction with manufacturers and there are no activities by HI on vaccine price.

²⁷ The Hib Initiative Newsletter, Announcements. Volume 2, Number 1, January 2007, @ <http://www.hibaction.org/news/newsletter/hibFocusVol2No1.pdf>.

Secure financing: The HI worked with the GAVI Bridge Financing Group to support continued co-financing for Hib vaccine.

5.2 Major achievements²⁸

Pneumo: The evaluation team concludes that the activities of the Pneumo ADIP have led to the potential introduction of the pneumococcal vaccine into GAVI-target countries more than five years before historical precedents, and the possibility that Prevnar®, Wyeth's 7-valent vaccine, will be introduced into several countries as early as 2008.

Demand: The ADIP developed firm disease burden data for which there is international consensus; clearly communicated key messages to core stakeholders about the disease, the vaccine, and response to the vaccine based on technical information agreed by leading scientists in the field;²⁹ with Wyeth, is planning a demonstration project with the 7-valent vaccine in high disease burden early adopter countries.³⁰

Capacity: The ADIP succeeded in getting commitments from a US manufacturer, Wyeth, to supply to developing countries and to go through the WHO prequalification process;³¹ set the stage for additional multinational products with improved characteristics (GSK's 10-valent vaccine and Wyeth's 13-valent vaccine) to enter the

²⁸ These achievements were primarily taken from the statements of the managers of the Initiatives and other interviewees, as well as the documents provided.

²⁹ [Levine OS, O'Brien KL, Knoll M](#), et al. Pneumococcal vaccination in developing countries. [Lancet](#). 2006 Jun 10;367(9526):1880-2.

³⁰ GAVI's PneumoADIP at Johns Hopkins, GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries. 23 October 2006. The decision to use this vaccine, which was not in the original proposal, was suggested through a study commissioned by the ADIP and approved by their advisory group. It had been one of the options described in the original documentation on which the ADIPs were based, and was endorsed by the WHO SAGE, and now has been documented in a WHO Position Paper: World Health Organization. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. Weekly epidemiologic record 82 (12) 93-104, 23 March 2007. According to information from the manufacturer cited in the Investment Case, the supplies of this product are sufficient for this early phase, after which its production would be phased out, when the 13-valent product is available, and a more programme-friendly presentation is available.

³¹ To the uninitiated this may not seem a large achievement, but for suppliers not used to the GAVI market, dealing with issues such as autodisposable syringes and Vaccine Vial Monitors presents huge issues to their regulatory people.

market; developed interest on the part of emerging suppliers to invest in pneumococcal vaccine development, and at least one major manufacturer is already investing in significant capacity for the developing market.

Pricing: The ADIP obtained commitment from both multinational suppliers both for available and future vaccines to supply the products at tiered prices; obtained commitment from the GAVI Alliance to co-finance pneumococcal conjugate vaccines to developing countries; and based on an investment case developed with the ADIP's inputs, the G8 donors committed to finance an Advance Market Commitment of \$1.5 billion for pneumococcal vaccine.

Rota: The evaluation team concludes that through the work of the ADIP the vaccine could be introduced into GAVI target countries as early as 2007, just one year after marketing approval was obtained in the USA and Europe. Introduction would depend sufficient safety and efficacy data being available for those countries. Work is underway to assess safety and efficacy in two additional regions to extend the use of the vaccine to those regions. Two rotavirus vaccines are now licensed and proved to be safe and relatively effective in industrialized countries and in some developing countries. GSK's Rotarix® has just received prequalification by WHO.³² The vaccine has already been introduced or considered for introduction into a number of countries in Latin America, through the Rota ADIP's collaboration with PAHO and the Sabin Vaccine Institute.

Demand: The ADIP made a strong case for the cost-effectiveness of rotavirus vaccine as well as for impact on known disease burden, supporting potential early-adopter countries to take it up. Moreover, advocacy messages of expanded clinical safety trial results have virtually dispelled safety concerns.³³ As a result, the vaccine is already in use in several developing countries.

³² World Health Organization, WHO list of vaccines for purchase by UN agencies as of February 2007, at http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html, accessed 16 February, 2007. The prequalification status has the following accompanying remark: "The prequalification of Rotarix is based on quality, safety and efficacy data generated in Latin America and Western Europe. GSK is committed to provide additional evidence of safety and efficacy being generated in Africa and Asia. GSK is also working on an improved presentation for the vaccine that would take less space in the cold chain."

³³ Recent communications from the ADIP and one of the manufacturers report that use of the product in the US has been associated with 28 cases of intussusception. Although there is no evidence of causality, and a recent MMWR report confirms this, it implies the ADIP's work on vaccine safety is not over.

Capacity: Through the ADIP's work with several manufacturers, both multinationals and emerging suppliers, there should be ample competition among rotavirus producers to ensure adequate supply at affordable prices; through the ADIP's collaboration on clinical trials in developing countries, the vaccines might be shown to be safe and effective in these countries.

Pricing: Both multinational manufacturers have pledged to offer the product at tiered prices to the GAVI market. The GAVI Board has recommended co-financing of the product in target countries.

Hib Initiative: The team concludes that the HI has made progress in its communications and advocacy strategy, which has helped support country decision making to take up Hib vaccine. It is providing a stronger evidence base by focusing on surveillance and impact determinations, as well as assembling cost-effectiveness data. Through directly reaching 64 countries and providing information and processes to facilitate decision making at the country level, it has exceeded its June 2007 targets, and currently 24/49 countries in regions with documented disease burden have introduced Hib or approved investment, and about half of the eligible countries in Asia and the CEE/NIS, where disease burden data are limited, have made a decision about Hib introduction.

Demand: WHO has now revised its Position Paper to give a clear recommendation on Hib use. This is a major change in the Hib landscape and one of the achievements of the HI; working through WHO to support countries in decision making processes, seven countries have been facilitated to introduce Hib.

Capacity: There were no achievements in this area; but it is not in the HI mandate

Pricing: There were no achievements in this area; but it is not in the HI mandate

5.3 What has not been achieved, and what have been the constraints?

Pneumo ADIP

The proposal in response to the RFP³⁴ from 2002 projected that one, if not two new

³⁴ Proposal to host GAVI's Pneumococcal Vaccine Accelerated Development and Introduction Plan

pneumococcal conjugate vaccines would be ready to use in 2007. This has been delayed and will not happen for one to three more years. The existing vaccine is undergoing the process for WHO prequalification, and thus will not be used before that step has been passed. This was not in the ADIP's control; however it will impact some of their timelines. Pilot introduction programmes and dose and schedule optimization studies will not be able to be done in 2007, as originally foreseen in the proposal. Also, it was originally anticipated that price negotiations would be started by now; although discussions have been ongoing, this is still premature.

The Pneumo ADIP's Scientific and Technical Constraints were due to the challenge of readying for introduction a vaccine that was not felt to be entirely appropriate for developing country use, was available in limited supply, and was selling at a price higher than the average annual income in most GAVI countries. One of their original challenges was how to involve industry in a fair way, both industrialized and developing country manufacturers. Because of the unclear scientific base, one of the ADIP's first activities was to clarify the messages to countries by achieving consensus among the leaders in the field. Another challenge was the issue of appropriate serotypes, again addressed by vetting the data with scientific leaders and getting a strong recommendation from WHO's SAGE. Finally, there was a general feeling that the cost of manufacture of the pneumococcal conjugate vaccine would price it out of the GAVI market, eliminate competition and rule out the possibility of having adequate supply. The ADIP's Cost of Goods study helped to change this feeling by showing that the vaccine might be manufactured for about \$1 per dose.

Managerial and Governance Constraints were less of an issue; however, the ADIP reported a fuzziness in the goals as stated in the RFP, with the result that their mandate, and that of the Rota ADP, was clarified by the MC in 2003.³⁵ focus on the late end stage products, set the stage for introduction, thus provide an evidence base for country decision making. One major advantage in the ADIP's work was a strong team centered in one location, and a very strong liaison with WHO, covered by a Memorandum of Understanding. However, the ADIP feels that the GAVI Country Support Team are not always passing on complete information to countries about their work – an argument for more country staff involvement in ADIP activities.

(ADIP) at John Hopkins Bloomberg School of Public Health.

³⁵ Accelerated Introduction of New Vaccines. GAVI Alliance Board Meeting, 20 June 2006, p.6 (noted to have been endorsed by the GAVI Alliance Board at its December 2003 Geneva meeting).

Rota ADIP

As for the Pneumo ADIP, some of the original goals have changed in the light of delays and changes in the global landscape. Not achieved as intended is the direct support to a specific emerging supplier envisioned in the response to the RFP, which was opposed by the MC, and instead across the board technical assistance is being provided. In addition, direct agreements with manufacturers were not used as originally envisioned. Trials in Bangladesh were delayed as were phase 3 trials in Africa, although this process is underway. While disease burden information is available, and there is a SAGE position and a WHO position paper, because of the delay in clinical trials, specific recommendations to some regions cannot be made. As noted above safety is a recurring issue, with reports of intussusception recently reported in the United States.³⁶ Finally, price-volume agreements have not been made with manufacturers.

The Rota ADIP's Scientific and Technical Constraints are related to the two products in the late stages of development that are being brought to the GAVI market. Much of the effort has been focused on assembling safety and efficacy data in the target countries. Their attempt to involve emerging suppliers in the effort was indicated by the MC as not within their mandate; nevertheless, some progress has been by these manufacturers in developing rotavirus vaccines. Another source of difficulty was GSK's decision to go for licensing of their product first in Mexico, given that its National Regulatory Authority did not have the credibility to support widespread approval of the product. Thus it was not until approval in the US and Europe that the products began to be incorporated into childhood immunization schedules. Finally, the delays in getting clinical trials completed in Asia and Africa has been a source of frustration to manufacturers who want to move the products forward.³⁷

³⁶ Centers for Disease Control. Postmarketing monitoring of intussusception after Rotateq vaccination in the United States, February 1 2006 to February 15 2007. MMWR 56 (1) 218-222, March 16, 2007.. This article concludes that in the formal postmarketing study of 28,000 vaccinated infants, no cases were seen, but since vaccine introduction there have been 35 spontaneous reports of intussusception, of which 17 were within the specified time frame after immunization. It was concluded after analysis that this number is below the background rate expected.

³⁷ In the course of our interviews, several people mentioned friction between the Rota ADIP and GSK. To the best of our knowledge, this is based on two things: (1) disagreement about GSK's strategy to go first for licensing in Mexico, and (2) the counsel of the ADIP to delay promotion of vaccine uptake in those regions where safety and efficacy had not been shown for this product.

Management and Governance Constraints for the Rota ADIP first concerned the split nature of the original group: although PATH was identified as the main home of the ADIP, the scientific director, who had been a major champion for rotavirus vaccines, was based at CDC. Handling the differing visions with this joint leadership must have been a challenge. In addition, both the pneumo and rota ADIPs reported a lack of contact with the GAVI Secretariat in the early stages, and a perception that the GAVI Board was just not interested in what they were doing.

Hib Initiative

The HI had a different mandate, which was to set a firmer basis for Hib introduction in GAVI target countries. The HI was envisioned to handle country introduction activities, on the theory that all ADIP-like activities had already been done. They have focused this work on facilitating country decision making, as well as surveillance and impact measurement, which is appropriate. The HI has not addressed capacity of supply issues, nor has it developed a credible demand forecast or entered price discussions, all of these activities having been specifically excluded from their mandate. Thus, since the key to the ADIP strategy is the achieving the virtuous cycle, the HI cannot be classified as an ADIP-like structure. The Hib rather appears to be more on the lines of an Implementation ADIP (see below).

In terms of *Scientific and Technical Constraints*, the HI has overcome a key challenge, which was the lack of a firm WHO recommendation, which has now been achieved with the revised WHO Position Paper. Perhaps the biggest challenge the HI has had was in trying to work without being able to implement a supply strategy. The supply and pricing issues with Hib needed addressing prior to introduction. This has limited the outputs of the HI. Developing good cost-effectiveness data depends on being able to make some reliable predictions about the price. To date pricing has escaped predictions.

The HI has faced *Governance and Management Constraints*. The structure of the Initiative, with an Executive Committee rather than a strong manager, as well as the geographic dispersion of the members, has made flexibility and agility difficult. Especially the obligatory partnership with WHO, though imposed with the best of intentions, has proven difficult to handle in terms of hiring staff and approving documents and budgets. Furthermore, although the HI saw its work as primarily providing support to countries, there has been some resistance from countries and partners who charge that in carrying out this work, the HI was “pushing Hib.” This is now being effectively addressed through developing a joint

Communications strategy among the three initiatives, a change suggested by the three groups themselves and recommended by the MC.

6. IMPACTS OF THE INITIATIVES

6.1 Impacts on industry

In general, the ADIPs have improved relations with the multinational industry, especially with those manufacturers who have had products in late stage development. They have incorporated industrial concerns into their strategy and kept industry informed on developments. Also there have been improved communications with the emerging suppliers, notably by participation in annual meetings of the Developing Country Vaccine Manufacturers Network (DCVMN).

In the absence of the ADIPs, most industry contacts on similar issues were with UNICEF Supply Division or WHO. With UNICEF Supply Division, the interactions of necessity were limited to procurement issues, and there was little opportunity for discussions on the larger view, the credibility of demand forecasts, production capacity, desired future products, regulatory issues. Some of this was handled by WHO, but there were few instances where a WHO staff member had a clear mandate to talk about a particular product, although to the extent that WHO is involved in epidemic prevention (as for pandemic influenza) this could change.

The formation of an ADIP sends a clear signal to industry that the public sector is interested in investing in a specific vaccine. The ADIPs have made the business case that this can be a useful and potentially profitable investment, and they are providing up-to-date and verified information on potential demand and needed product changes for public sector uses. However, unfortunately, to have all this done in time for market introduction, the ADIPs should start earlier in the development pathway. For example, presentation issues for rotavirus vaccines have caused logistics challenges: the packaging volume demands greatly increased cold storage capacity: 73 – 176 cm³/ dose, compared to 3-10 cm³/ dose for traditional vaccines.³⁸

³⁸ John Fitzsimmons. Introducción de nuevas vacunas: rotavirus y cadena de frío. TechNet Meeting, Mexico City, 26-27 October, 2006.

There were some complaints from industry that the ADIP/HI mandate is too broad: “There is too much liberty to do as they see fit.” Another complaint was related to a lack of understanding of the mandate and specifically what contacts were made with emerging suppliers when products produced by multinational companies were already available.

In addition, there was significant criticism from industry on the oversight by the MC (see section 7): “[It is the] GAVI structure more than the ADIPs structure that worries me.” However, in the words of one industry partner, “[We are] better off having a GAVI than no GAVI – better to have an ADIP than none. Are we \$30M better off?” This report will attempt to address that question in Section 8, below.

6.2 Impacts on donor organizations and developmental partners

International donors and partners. The existence of ADIPs has been attractive to international donors and partners. For example, the AMC decision mentioned above probably would not have been possible had not the ADIPs existed to provide and advocate for their investment cases to inform the G8 donors.³⁹ Moreover, it has been attractive to international technical organizations, like WHO, because the ADIPs have provided a source of funding for additional staff members and activities for collaborative effort under the ADIP umbrella. By focusing resources on a particular issue, which cannot be easily done by most international organizations, ADIPs have been able to leverage added resources.

At country level. Presumably the ADIPs would be helpful for donors at country level as sources of validated information that could help in decision making. ADIPs would ideally provide the kind of technical information that would be most useful for making vaccine introduction decisions. Several interviewees reported, however, that each initiative is focused on its particular product and perhaps countries would be better served by a group with a mandate for a basket of interventions, not necessarily limited to vaccines. Such a group might be better able to serve public health priorities and to ascertain better how vaccines could best complement public health objectives.

³⁹ Note that this could have been done, and in fact was done for some products by public-private partnerships that exist independently of GAVI. None of those to date is for childhood vaccines that are at the end stage.

6.3 Impacts at country level

ADIP work focused at country level includes such things as developing surveillance capacity, providing laboratory training, doing cost effectiveness studies, refining demand forecasts, and coordinating pilot introduction studies. Moreover, technical information is available on the websites and in the newsletters, and there has been funding for small grants at country level.

The Pneumo ADIP will have spent a total of \$17M, over half of its original budget, at country level by the end of 2007, or about 25% of the total budget. These expenditures are focused on tracking disease burden, surveillance, small grants to countries, and support to WHO regional staff. Over 50% of those funds have been to Africa, and most of the rest to South Asia and the Middle East, tracking where the highest incidence of childhood pneumonia-related mortality.⁴⁰ The Rota ADIP provided data on their 2007 budget of \$9.22M, of which \$7.58M is for clinical trials. Of the remaining \$1.64M, \$315,000, or about 20% will go directly to countries, mostly for surveillance, but with about \$10,000 for cost-effectiveness work at country level. This figure does not include staff support at Regional level.⁴¹ The HI has proposed to spend over the entire 2006-2010 period, \$4.57M in direct expenditures at the country level, of which about \$1M is for surveillance and the rest is for vaccine impact and effectiveness. This amount is about 12% of their total expected \$37M budget, including the India probe study, and does not include staff support at the Regional level.⁴²

Often these contributions have not been received by countries directly from the ADIPs, but through an organization with country representation, such as WHO or UNICEF, or in the context of national or regional workshops. The actual impact at the country level is difficult to document and it is not clear that countries are aware that the information provided comes from the ADIPs or the HI, especially since the strategy of these initiatives is to hand off the actual introduction activities to WHO.

The response of interviewees on the impact of the ADIPs and HI at the regional and country

⁴⁰ Orin Levine, personal communication, March 2007. Information to separate out the contributions for WHO Regional staff was not received..

⁴¹ John Wecker and Kelli Brooke, personal communication, March 2007.

⁴² Rana Hajjeh, personal communication, March 2007. Note that this does not include direct contributions to WHO to carry out specific country-related activities.

levels has been contradictory, with some respondents clearly differentiating the three groups (as well as the two other initiatives on Japanese encephalitis and meningitis) and others lumping them together as vertical projects that compete with each other and overburden countries; some have particularly praised their efforts to improve disease burden data and surveillance, while others have deplored the “project” approach, not building on existing surveillance systems; some have commended the ADIPs’ work with industry, while others charge that they are working to industry’s agenda; some have complained that the ADIPs have been absent at country level, and at least one interviewee specifically mentioned the country-based activities of the Meningitis Vaccine Project, but the majority has concluded that they should work at Regional level through WHO and the RWGs (see Annex 1 for list of interviewees). An interviewee from a large country which has not yet made a decision on Hib reported no contact with the HI, no surveillance system, and a real need for disease burden data; in contrast, one of the ADIPs had been in touch. Regional staff and RWG members reported ADIP/HI contacts in countries that had bypassed them. It appears that these groups need more advocacy at the country level as to what their mandate is and how they are achieving it.

7. STRUCTURE AND PROCESS

7.1 Structure⁴³

7.1.1 Best organizational practices

For the type of organization envisioned in the McKinsey study, the report itself defined the structure: a small flexible group with a strong leader, milestone driven, with clear lines of authority and oversight. The host organization should be supportive yet flexible enough to accomplish the needed transactions (hiring and firing, contracts, disbursement of funds, accounts) with the needed speed. One of the first tasks of a group like this should be to define its interactions with collaborators and partners.

7.1.2 Structure as defined in ADIP RFP

The RFP described a small team (about four people with the requisite technical expertise), a capable team leader, the ability to work within a project-milestone framework with a broad

⁴³ Information from this section came from the RFPs: Global Alliance for Vaccines and Immunization, Accelerated Development and Introduction Plans (ADIPs) for Pneumococcal Conjugate and Rotavirus Vaccines. Request for Proposals. Annex 1, August 2002; Global Alliance for Vaccines and Immunization. Hib Initiative: Supporting country decision-making. Request for Proposals. February 2005.

range of public and private collaborators. The host organization would need to provide commitment and support in areas having to do with logistics, contracting, travel, and especially for reporting outside of the organization. The RFP was specific in the need to describe how collaborative activities would be handled.

In terms of the structures described in the RFPs, the Pneumo ADIP structure appears to meet the criteria laid out. Originally the Rota ADIP was located at two organizations, with the overall director at PATH and the scientific director at CDC. The latter had been intimately involved with the McKinsey study team and was a well known rotavirus vaccine champion. This created initial problems for the ADIP management, which was solved by his departure. PATH appears to have been an effective home for other vaccine development and introduction initiatives (see part 9, below). Both ADIPs appear to have defined and implemented their partner collaborators in an effective way. Both have liaisons with WHO and with CDC, but neither has the type of consortium governance of the HI (see below)..

7.1.3 Structure as defined in HI RFP

The HI RFP also described a small, accountable target-driven team, the management of which should be under a team leader with managerial and technical expertise. The structure could be under a single host organization or a coalition, but the management and financial accountability should be described. WHO was strongly identified as a collaborator with whomever was awarded the tender; thus the stage was set for a coalition at the outset.

The HI structure as it originally existed does not meet these criteria in that the team leader up until⁴⁴ now did not have executive authority, which was held in a consortium Executive Committee. In addition, it appears that the management and financial modalities could have been worked out better in advance, because the four organization consortium has made management, particularly financial management, difficult.⁴⁵ Specific modalities for working with all collaborators, particularly WHO at its different levels (see below, Interactions), were not defined in the proposal. Both of these constraints have restricted the impact of the HI, and the team endorses the proposed changes in operation, suggesting that the MC follow up on its implementation.

7.1.4 Governance as defined in both RFPs

⁴⁴ According to one of our interviewees, this will now change.

⁴⁵ This information comes from our interviews.

Both RFPs mentioned the desirability of a technical oversight group for each organization, and each of the ADIPs/HI has such a technical advisory committee. In addition, both types of organizations were to be overseen by a “Steering Committee”, later designated as the Management Committee, reporting to the GAVI Board. The MC is the interface between these groups and the GAVI Board, and has authority over the use of funds made available to each organization plus the ability to solicit additional funds from the GAVI Board.

As originally established, the MC was chaired by the R&D Institution representative to the GAVI Board, and included scientific and technical experts,, a representative of the Bill & Melinda Gates Foundation; a representative from the Vaccine Fund, an ex-industry executive, representing an industrial point of view, and a former minister from a developing country, to provide country inputs. By 2006 the MC was somewhat changed, with Dr Tore Godal, former Executive Secretary of GAVI and former Director of the co-sponsored Programme on Tropical Disease Research based in WHO, and Mr Michel Zaffran, Deputy Executive Secretary of GAVI and former staff of WHO’s Department of Immunization, Vaccines and Biologicals joining the group, apparently accompanied by the departure of the Vaccine Fund and country representatives. Although the technical and scientific expertise on the MC has been helpful, this means that, of the three client groups of the ADIPs, industry, donors, and countries, the second and third groups are not well represented.⁴⁶ In the HI RFP, it was specifically stated that the MC would be expanded to reflect its mandate that is more country specific than that of the ADIPs: this apparently has not happened. Several of those interviewed expressed a need for more country representation on the MC, to better guide all three initiatives in the preparation for introduction phase.

The MC chair is rotating off the Board, and his replacement as R&D Institute representative cannot oversee the ADIPs as his institution is receiving funding from them. There is now a dearth of Board members on the MC, although the original RFPs specified several. In the past the Board had delegated most key decision-making power to the MC, and accepted the MC’s reports and recommendations generally without discussion. This has left the impression that the Board was not really interested in the work of the ADIPs. The team agrees that if the intent is to provide better communication between the ADIPs and the Board, then this issue should be addressed.

⁴⁶ For example, there are no bilateral donors or other partners working at the country level, and no specialists in primary health care service delivery at the country level.

7.2 Process

Functions as laid out in RFPs

The functions of the ADIPs, as outlined in the McKinsey study, were to “Establish value, communicate value, and deliver value.” The ADIPs were to leverage the work of GAVI Partners to achieve this goal, not to replace the partners, but to complete a specific task. After clarification, the ADIPs were charged with providing information to make an evidence-based decision regarding vaccine use, and to increase the access to affordable, sustainable vaccine supply for the world's poorest countries. They were also to advise the GAVI Board, through the MC, of the continuing appropriateness of a particular product for GAVI support. The HI was recommended by a GAVI Hib Task Force. Its specific mandate was to support the decision making process at country level.

7.2.1 Functions to achieve goals

The following list gives an indication of the kind of activities the initiatives have used to attain their goals. It is derived from activities in the annual reports, and from interviews.

- collaboration with WHO or other organizations at global level to develop country tools, and to set international standards, e.g. developing surveillance protocols, laboratory manuals;
- commissioning studies, such as the Demand Forecasting activities, or the Cost of Goods study;
- contracting out activities to consultant organizations, such as the *Manufacturer's Resource Guide* or visits to manufacturers;
- awarding small grants to developing country investigators;
- convening meetings at the global or regional level, or small groups of scientists;
- developing and maintaining websites and advocacy tools;
- participating in other meetings;
- leveraging decision making, for example with manufacturers;
- making country visits;
- providing process development, clinical trial and regulatory support for manufacturers;
- managing a large field study (India Probe Study);
- providing basic administration services, staff hiring and firing according to host organization policy;
- budgeting, reporting, strategic planning and analysis.

These activities were foreseen in the RFPs and the proposals received described how these were to be done; however, it is clear that a structure with multiple institutional homes will meet

more challenges in being able to effectively handle this range of activities unless it is carefully planned for.

7.2.2 Interactions

Each of the Initiatives has to interact with a number of different organizations. This section summarizes impressions from interviewees on how these interactions have gone.

The *GAVI Partners* constitute a diverse group of organizations from international organizations, such as WHO, UNICEF, the World Bank, non-governmental organizations, ranging from those set up for overall assistance to developing countries to academia; bilateral donor organizations; industry, both multinational and emerging suppliers; and health ministries in the GAVI target countries. Each of these has a different mandate, a different organizational culture, and a different way of working with its partners. This has constituted possibly the biggest challenge to the initiatives in doing their work, because they are accountable to many interests. The example of working with WHO is a case in point. WHO is not just one organization, but many: it exists at the global level, with six regional offices, and 142 country offices for its 193 member states. Moreover, each department within WHO has its own way of interacting with its collaborators. The WHO headquarters staff in immunization are responsible for developing global policy, subject to inputs from its SAGE and to approval by the World Health Assembly in some cases, while entry to countries is generally achieved through the relevant Regional Office, who often develop programmes and activities for all country offices in their Region with a particular focus. One of the challenges of working with WHO is to determine how to optimally arrange an activity such as a country visit or a meeting, balancing speed and the requisite approvals. Another is to determine how best to achieve funding and hiring within the constraints of WHO's bureaucracy. To the extent that a group can work with a specific liaison person who can facilitate these activities, this can work quite well. So can giving funds to WHO for specific activities. While the latter course means assuring buy in and commitment, crucial if an activity needs to go on at country level, it also means giving up control over the budget, the reporting timeframe, and the management of the activity. These factors have to be balanced in finding the best interaction.

Comments from the interviews suggest that activities that are further upstream, such as those of the two ADIPs, are best able to manage their interactions with the GAVI Partners, probably because issues of "turf" can be minimized. For example, in a

particularly good example of effective collaboration, the Rota ADIP worked with PAHO, the Sabin Vaccine Initiative, Merck, and Nicaragua to develop the Rotateq® introduction project now ongoing there. The HI, on the other hand, has a challenge that will also hold true for any group eventually charged with vaccine introduction, which has traditionally been the purview of WHO – how best to work at the country level? It seems apparent that involving only a WHO HQ staff as a member of an Executive Committee may not be an optimal solution, especially when most activities will need to go through the Regional Offices, which function fairly independently. A second option might be to have introduction activities implemented only by WHO and/or UNICEF, both organizations with strong country presence. A third option that GAVI might consider is developing GAVI representation at key GAVI target countries to coordinate these activities, but this option is contrary to GAVI's current mandate at the country level. A fourth option, mentioned in our interviews, was to use the Regional Offices, and, where active, RWGs, as the gateway to country activities. The possible implementation of each of these models is discussed in part 10.

One major comment we received from the interviews is that GAVI is no longer stimulating bilateral donor organizations to invest in immunization. This is evidently not true at the global level, as the GAVI Fund is wealthier than ever, but it may be true at the country level. A future challenge for GAVI and for any group charged with implementation activities at country level will be the need to mobilize in-country resources including bilateral donors. This is a challenge that has not really been met to date. In its original concept, GAVI envisioned the GAVI Partner Board structure at global level being replicated by RWGs in the regions and Interagency Coordinating Committees at country level as a focus for implementation. This has not been as effective as hoped. Several interviewers characterized the RWGs as “not effective...effective only for information exchange...WHO Regional Offices work better.” A challenge for vaccine introduction will be to appropriately involve all stakeholders at regional and country levels. Specific comments were received from industry interviewees charging the intervention of politics in the selection of home organizations for the ADIPs/HI.

Management Committee

In general, once the original clarifications on the mandate were made, the MC appears to have served its functions for the two ADIPs. The MC reports that they have been working without administrative support. Nevertheless, they have contributed to

standardizing the ADIP approach, and their recommendations are generally accepted by the Board without comments. Criticisms of the MC have been that its membership does not really reflect the skill set that would be useful for an activity managing late stage products down to introduction. There should be more country representation, ideally more knowledge about vaccine logistics and administration, as well as decision making at country level. In addition, the point of view of the emerging suppliers is probably not represented. For the HI, the MC structure has not changed to reflect its more downstream focus. We also received comments that the MC does not really add value due to the inconsistency of skills and of the lack of proactiveness of some of its members, and that there was not a good information channel between the ADIPs and the Board. Comments from industry were more explicit in the assessment of MC oversight: "The processes need to have increasing transparency to improve the progress...We don't have a structure to communicate with that person [the industry person on the MC]...We have not gotten information from the MC."

GAVI Board

Feedback from the interviews has been that there has been basically no interaction with the GAVI Board, that the Board is perceived as "not interested." This impression possibly arises because the MC is trusted to do its role. It has been noted above that generally MC recommendations are passed by the Board with no comments. As long as this does not impede progress and given strong and effective oversight by the MC, this should not present a problem. It is clearly important that the Board is interested in an activity that represents one of GAVI's key functions, for the ADIPs need high level support to work effectively. On the other hand, the lack of Board involvement with the ADIPs/HI has been interpreted by some industry personnel as a significant issue in the success of the ADIPs. "We had to demand that [the ADIPs] had to be on the agenda... The ADIP MC needs to be looked at. GAVI is not monitoring this." "The Board postponed discussion about ADIPs for 18 months...Decision making [is] consistently deferred from one Board to the next."

GAVI Secretariat

Up until early 2005, there was little interaction with the GAVI Secretariat, as the Secretariat had a limited staff and no permanent person charged with this interaction, other than the MC. Staff assigned changed responsibilities, so that the ADIPs felt they were constantly having to re-educate the Secretariat. This has been a problem for the ADIPs in communication and clarification, and has also been a problem articulated for

GAVI Partners in trying to get more information on the ADIP functions. This has changed, reportedly coincident with Michel Zaffran's joining GAVI and serving in this function. There are concerns that such an important job should not rest with just one person who has multiple management responsibilities, and it is suggested that GAVI develop an ADIP Project Team, of perhaps three people, charged with managing these initiatives. While the support from the GAVI Secretariat on upstream issues (for example, Advance Market Commitments, Supply Strategies) has been strong, there has been little contact between the ADIPs and the HI and GAVI's Country Support Team, which would seem to be desirable for more downstream activities.

Among ADIPs/HI

One of the issues mentioned was the perceived competition among the ADIPs/HI, especially at country level. Thus, interviewees reported that countries felt pressure to choose to take on an intervention ("...GAVI was being prescriptive...") without having the opportunity to consider other interventions. The ADIPs/HI, seeing this as a problem, asked the MC to support their respective communications teams to work together to put out some joint messages, and this has been done. The ADIPs/HI feel satisfied with this activity which they think has strengthened their work and their collaborations. Mentioned above are joint projects, specifically for pneumonia and meningitis surveillance in countries sponsored by the Pneumo ADIP and the HI, working with WHO. It is also evident from reading their written documentation that there is good coordination between the two ADIPs, in terms of similar formats and types of messaging, which makes it much easier for the reader to understand the information being communicated. Because of their physical proximity, there are frequent contacts between the Pneumo ADIP and the HI. Thus the team concludes that the perceived competition is not an issue.

8. VALUE FOR MONEY

8.1 Major expenditures of the three initiatives

Through the financial reports of the three initiatives we can take a comparative look at expenditures. Representative budget information compiled from their annual reports can be found in Annexes 3, 4, and 5.

The budgets and expenditures can be broken down in two ways: (1) by looking at the category of costs, that is, personnel, overhead, meetings, etc.; and (2) by looking at the proportion that went to the different planning categories, such as communication, surveillance, etc. Figure 2 below provides a comparison for the expenditures in 2005 for the three initiatives.

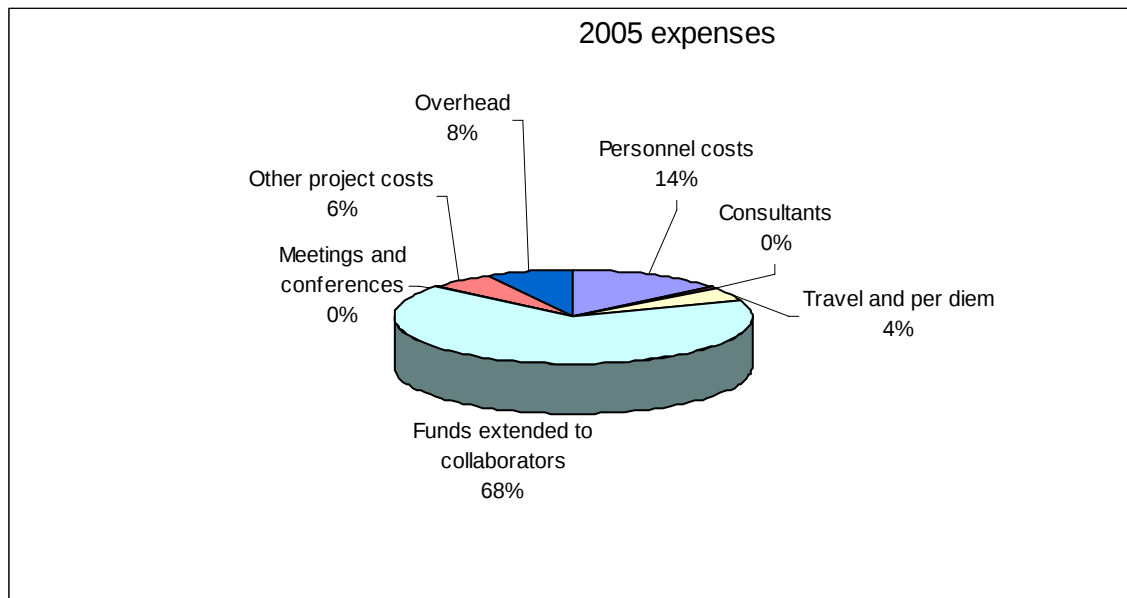


Figure 2a. 2005 expenditures by category for Rota ADIP

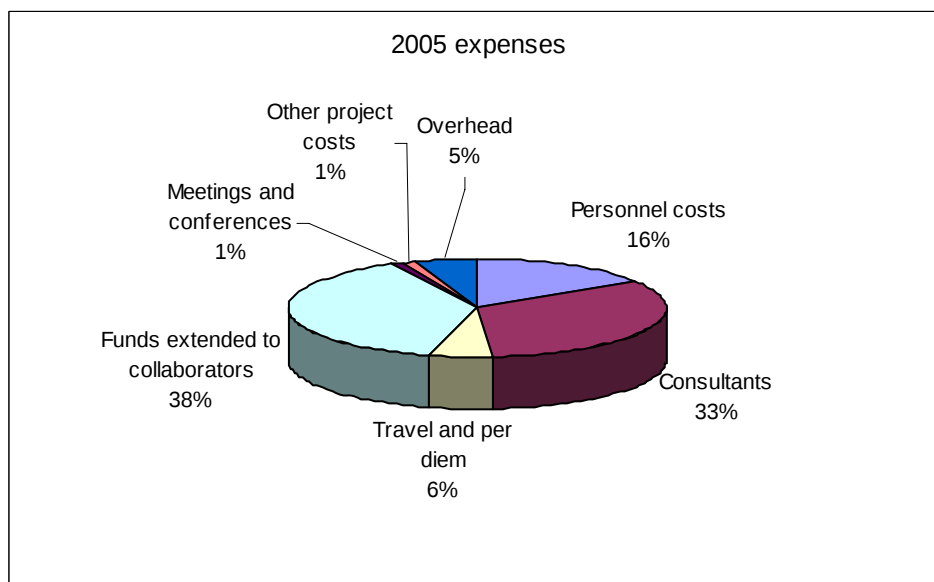


Figure 2b. 2005 expenditures by category for Pneumo ADIP

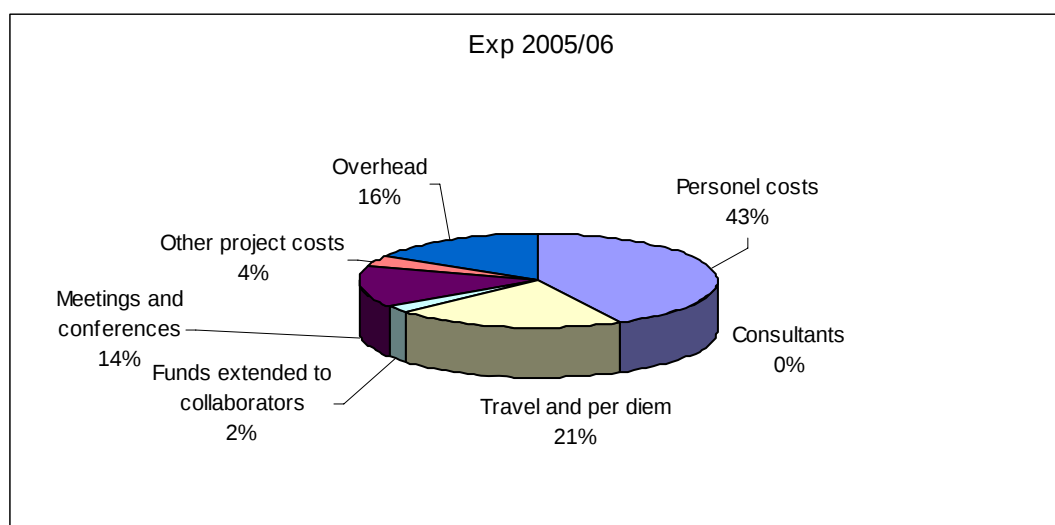


Figure 2c. 2005/2006 expenditures by category for HI

A more comprehensive breakdown for the ADIPs is included in the Annexes. However, it will be seen that their major expenditures are in “Funds extended to collaborators” and “Consultants.” This implies that the ADIPs are leveraging their work through collaborations (funding positions at WHO, for example) and consultants to complement their relatively small teams – and also implies that their major focus is gathering of information. In contrast, the HI has spent the majority of its funds on personnel costs and on travel and per diem. The personnel costs will also reflect positions in WHO, while the travel costs certainly reflect their geographical diversity as well as their more country oriented focus.

Table 1 breaks down these expenditures into programmatic areas. Both ADIPs have written their strategic plans to include activities in three areas: Establish value, Communicate value, and Deliver value. Establish value includes activities in surveillance, disease burden and vaccine development; Communicate value includes communication and advocacy; Deliver value includes activities in vaccine financing and supply and vaccine introduction. The HI has no separate supply component,⁴⁷ but these three categories can be roughly equated to their three components: Research and surveillance, Communications, and Coordination.

Research and surveillance, according to the HI 2007 Strategic Plan,⁴⁸ includes activities to:

⁴⁷ They have indicated in their proposed budget that some coordination funds would go to assist developing country manufacturers. This is surprising as it is not in their mandate.

⁴⁸ The Hib Consortium, Supporting Country Decision Making Regarding Hib Vaccine Use. Strategic Plan, 14 April 2006.

- Provide technical support to partners' efforts
- Develop estimates of Hib disease incidence
- Perform Hib cost-effectiveness studies
- Support novel methods to measure Hib burden and vaccine impact
- Generate evidence to facilitate decision-making
- Assess operational aspects of Hib introduction
- Resolve remaining questions
- Support and oversee the India probe study.

Communications includes:

- Increase awareness of Hib disease and Hib vaccine
- Advocate for Hib vaccine at all levels
- Address region-specific manufacturing issues.

Coordination includes activities to:

1. Collaborate with efforts to assure financial sustainability
2. Assist global partners and facilitate decision making
3. Support global and regional policy decisions
4. Monitor progress at country level.

Table 1 is based on expenditures in 2005 for the Rota and Pneumo ADIPs, but on budget information for 2007/2008 for the HI, in order to look at comparable times from their launch. Note that overheads are not included explicitly in the HI budget, but are contained within each category.⁴⁹ Figure 3 shows the information graphically.

Table 1. Comparison of ADIP programmatic expenditures for 2005 (or budget for 2007/2008 for HI) in US\$. See text for further information.

Category	Rota ADIP	Pneumo ADIP	HI
Establish value	5,723,298	3,147,374	4,834,492
Communicate value	681,193	1,063,894	781,996
Deliver value	954,211	1,913,951	2,843,391
Administration	309,760	749,355	--
Totals	7,688,372	6,874,574	8,459,879

⁴⁹ Figures included under "Administration" reflect institutional overheads set by the respective institutional homes.

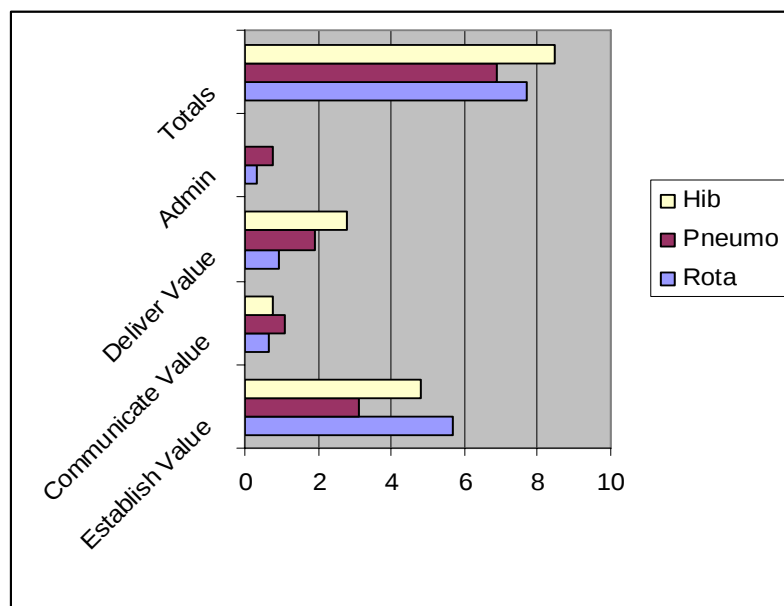


Figure 3. Graphic of information in Table 1.

It can be seen that for a similar level of expenditure, the Pneumo ADIP spends proportionately more on communicating value, while the Rota ADIP is more focused on establishing value, and the HI more on delivering value, which reflects very well their activities and achievements as covered in Part 4. However, all spend the most on establishing value, and this is the area where country level interventions would be expected to play an important role.⁵⁰

8.2 Impact of these expenditures⁵¹

8.2.1 *Pneumo ADIP*

The expenditures to date of the Pneumo ADIP, about \$30M, have served to set the stage for the introduction of Wyeth's 7-valent pneumococcal conjugate vaccine in some countries as early as 2008, and for the rapid introduction of the 10- and 13-valent products when they become available, effectively accelerating the introduction process by over five years. The Pneumo ADIP estimates that as many as 3M children may be immunized against *Streptococcus pneumoniae* in this initial period, which could avert 15,000 deaths.⁵² Their

⁵⁰ More information on country expenditures is found in Section 6.3.

⁵¹ It should be pointed out here as well that the calculations in this section are based on assumptions which may not be borne out, so the data should be regarded as indicative only.

⁵² Orin Levine, personal communication, March 2007.

effort has also leveraged \$1.5B in AMC funds to accelerate the improved products at an affordable price, and, for an additional up to \$200M expended, the ADIP estimates that by 2025 3.9M deaths and 32M hospitalizations could be averted, along with \$690M/year in direct medical expenditures.⁵³ In addition, the work of the ADIP has refocused multinational manufacturers' efforts toward developing country vaccines by understanding their issues, making a good business case, and facilitating vaccine registration and introduction issues. The ADIP has also helped established the credibility of emerging suppliers as a means to provide more competition in the future.

8.2.2 *Rota ADIP*

The Rota ADIP, with an investment of about \$30M to date, has helped accelerate the introduction of rotavirus vaccines into developing countries within three to four years after industrialized country introduction, and thus has effectively added 12 years of availability of this product, because it is available sooner than might otherwise have been the case. Until 2010, this could translate into 30,000 deaths averted. For an additional \$319-\$907M, this could mean 2.4 M deaths and 100M hospitalizations averted by 2025, with a savings of \$500M in direct medical costs.⁵⁴ The work of the ADIP has additionally stimulated emerging suppliers to develop these innovative vaccines, and focused multinational manufacturers on the potential reward of producing vaccines for the developing world.

8.2.3 *Hib Initiative*

The HI is due to receive a total of \$38M funding over four years (with \$9M for the India Probe Study); thus it will effectively have the same amount of funding as the ADIPs. In the case of the HI, the 15 years time lag following introduction into the industrialized world has already passed, as this vaccine was first used in the US in the late 1980s. However, if the HI can set the stage for enhanced introduction of these products, even in only 10% of the children who are not yet receiving the vaccines, that translates into averting 300,000 cases and 40,000 deaths per year, based on a disease burden of 3M cases per year and 400,000 Hib-related deaths.⁵⁵

⁵³ GAVI's PneumoADIP at Johns Hopkins, GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries. 23 October 2006.

⁵⁴ PATH's Rotavirus Vaccine Program, Accelerating the Introduction of Rotavirus Vaccines into GAVI-Eligible Countries. Investment Case for GAVI Secretariat. October 2006.

⁵⁵ World Health Organization (WHO), "Vaccines and Biologicals," accessed online at www.who.int/vaccines, on Nov. 3, 2005. *Haemophilus influenzae* is not related to influenza.

8.3 Trade-offs and pricing

8.3.1 *Alternatives to immunization*

One of the criteria for the ADIPs, and indeed for the selection of vaccines that GAVI would support was that the alternatives to immunization were not effective enough. Potential alternatives to immunization in the case of Hib and Pneumo include antibiotic therapy with a concomitant rise in risk of antibiotic resistance, and with the requirement that the diagnosis must first be established. For rotavirus disease, oral rehydration therapy is an alternative, but does rely on continuing access to primary health care and to clean water. For serious rotavirus disease, intravenous therapy would be needed, which would not be a cost-effective intervention compared to immunization.

8.3.2 *Pricing benefits of vaccine availability*

Both ADIPs have stated that the multinational manufacturers who have already developed the products or are in the late stages of development have already agreed to make the products available at tiered pricing. What that tiered price will be is not yet clear for either product. In the case of pneumococcal conjugate vaccines, however, for the short term the Cost of Goods study will allow some informed price negotiations, given that the price per dose to the PAHO Revolving Fund for 2006 is \$53.00.⁵⁶ For later stage vaccines, the availability of AMC funding is expected to guarantee an affordable price for at least the years that it covers.⁵⁷ For rotavirus vaccines, we are already seeing the price come down. In the US, Merck announced a price of \$187.50 for the standard three-dose regimen.⁵⁸ They are now donating the vaccine to Nicaragua for a pilot study, and then later will provide it at a “dramatically reduced price.”⁵⁹ The lowest public-sector price now known is \$14 for a two-dose treatment course in Brazil.^{60,61} One of the results of the ADIP advocacy efforts is the expansion of the use of these products in mid-income countries and in the private sector,

⁵⁶ PAHO, 2006 Revolving Fund Prices. *Immunization Newsletter*, Vol XXVIII, No. 1, February 2006.

⁵⁷ GAVI, Advance Market Commitments for Vaccines, at <http://www.vaccineamc.org>, accessed 13 February 2007.

⁵⁸ Wikipedia, Rotavirus, at <http://en.wikipedia.org/wiki/Rotavirus>, accessed 13 February 2007.

⁵⁹ Ransdell Pierson, Merck to donate rotavirus vaccine in Nicaragua, at <http://www.msnbc.msn.com/id/14936212>, accessed 13 February 2007.

⁶⁰ PATH's Rotavirus Vaccine Program, Accelerating the Introduction of Rotavirus Vaccines into GAVI-Eligible Countries. Investment Case for GAVI Secretariat. October 2006.

⁶¹ Note that the investment cases for pneumo and rota use different figures for cost per dose, but these are to date speculations.

which would further expand the market and invite competition.

For Hib vaccine, at \$3.60 per dose, the vaccine is still in a seller's market. There are only two suppliers, supply is still limited, and the newest supplier, Crucell/Rhein Biotech/Berna, has an all liquid product for which they initially charged a higher price, although now the price of the two pentavalent products are comparable. When true competition exists it is anticipated that the price will decrease, but this is a subject for consideration by the Supply Strategy group, not the HI. It appears desirable to have a true Hib supply strategy, not just for the public sector GAVI target market, to accelerate demand and to lower prices. The availability of vaccines at affordable prices is expected to expand the market, stimulating competition and further reducing prices.

9. BRIEF LOOK AT OTHER WAYS TO MANAGE AN ADIP PROCESS

Are there ways that a vaccine development and introduction project could be managed differently? The team selected two projects to examine in greater detail because, in contrast to other vaccine development projects, the vaccines were at a similar level of readiness and the target audiences were similar to those traditionally used in national immunization programmes: the Meningitis Vaccine Project (MVP) and the Japanese Encephalitis (JE) Project. The team analyzed the scopes of these two projects compared to those of the ADIPs, and at the achievements with similar amounts of funding, but somewhat different ways of working.

9.1 The Meningitis Vaccine Project (MVP)⁶²

The MVP was set up in 2001 as a partnership of WHO and PATH, with a grant from the Bill & Melinda Gates Foundation of \$70M. Its mission is "to eliminate epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, introduction, and widespread use of conjugate meningococcal vaccines." Although it was set up as a partnership, this basically refers to co-planning and oversight by a jointly selected group. Some of the activities are carried on at WHO with MVP funding, but the project is housed at PATH offices under a strong PATH manager, Dr Marc LaForce. The original intent of the project was to accelerate the development of a conjugated meningitis A vaccine for Africa.

⁶² The Meningitis Vaccine Project, at <http://www.meningvax.org>, accessed 13 February 2007

The components of the project are now four: (1) enhanced surveillance in the meningitis belt; (2) development of a vaccine using the methodology of “technology transfer” to an emerging supplier, the Serum Institute of India for an agreed number of doses at a price agreed by the African constituents, about \$0.50 per dose; (3) introduction of the vaccine when it is available; (4) communication, advocacy, and resource mobilization. The vaccine is scheduled to be on the market probably about 2009. Although the work with the manufacturer is said to be going well, there have been inevitable delays, and the product is now in phase 2 trials in two African countries. Because the MVP sees itself as a virtual vaccine developer, much of the initial work was devoted to accessing technologies and developing a clinical plan.⁶³ By developing the surveillance in advance, the vaccine introduction should be easier, but as this is an epidemic prevention vaccine, its initial use will be in mass campaigns followed by routine use, which makes demand forecasting challenging. Vaccine financing is projected to come from country budgets from the meningitis belt countries, which is why a very low price has been guaranteed. The market incentives have been provided directly by the project itself,⁶⁴ by guaranteeing a market and providing funds for the product development. This project is likely to be successful in providing a vaccine that very likely would not exist in its absence. However, ongoing financial sustainability after the initially agreed number of low-priced doses has been used remains an issue. A major focus is advocacy at the country level, starting at the inception of the project and continually, even though the vaccine is several years from being available. This was felt crucial for the success of the project.⁶⁵

9.2 The Japanese Encephalitis Project⁶⁶

The goals of this project are (1) to improve JE disease burden data; (2) to speed development of an improved JE vaccine; (3) to introduce the vaccine where it is most needed; (4) to promote investment in JE immunization. It was funded for five years with \$27M from the Bill & Melinda Gates Foundation in December 2003 at PATH. Even before the project began, the project director, Dr Julie Jacobson, was promoting the use of the Chinese live oral SA 14-14-2 vaccine. However, it should be noted that this product has been the focus of much

⁶³ According to informants at the Serum Institute of India, the technology transferred needed significant development before it was usable as a manufacturing method.

⁶⁴ Although the funds for vaccine purchase are not yet guaranteed.

⁶⁵ Marc LaForce, personal communication, March 2007.

⁶⁶ PATH's Japanese Encephalitis Project, at <http://www.path.org/je>, accessed 13 February, 2007

discussion at WHO because of its history of questionable production practices and an unclear clinical record. Dr Jacobson's influence has leveraged tremendous investment in this product which has undoubtedly led to quality improvements, and it is soon to be submitted for WHO-prequalification. The JE project has now expanded its scope beyond just promoting the use of this vaccine. The heightened surveillance includes laboratory diagnosis and a diagnostic kit. The team, which is very strong at country level, in PATH offices in six countries in Asia, besides the US and France, is working on vaccine introduction, although most of these efforts are promoting a vaccine which is not yet WHO-prequalified. Nevertheless the project has managed to enlist WHO Regional Office collaboration in Asia to move forward in JE vaccine uptake. The project is now also working with other vaccines against JE. The project has been very successful in raising the profile of JE as a public health problem, and has managed to get the Chinese vaccine introduced into several countries. Vaccine financing comes from country funds, as most of the project funding goes into vaccine production investments, developing surveillance tools, and advocacy.

9.3 Evaluation of these projects

These two projects have several things in common which differentiate them from the ADIPs, and other things which they share with the ADIPs. Table 2 summarizes these.

Table 2. Similarities and differences of MVP and JE Project to the ADIPs

Similarity to ADIP	Difference from ADIP
Led by strong technically competent teams	Developing up-front low price agreements as condition of collaboration with manufacturers
Working at WHO Regional Office level	Working with developing country manufacturers rather than multinationals
Partnering with WHO	Sited at PATH, with an extensive network of country offices
Similar amounts of funding	Country level activities have taken advantage of PATH network
Prioritizing surveillance, advocacy, demand forecasting, supply activities	Not associated with GAVI
Have GAVI commitment for vaccine purchase	Heavily concentrated on vaccine development activities, including basic technology transfer, clinical trials, and facility investment.

In learning from these observations, GAVI needs to consider whether it should manage from the start activities to accelerate the introduction of new vaccines, or whether it should use an outside organization to do this. This will be explored further in part 10. GAVI also needs to consider how best to use WHO: as a GAVI Partner, a co-collaborator, a facilitator, or an authorized liaison. Financial sustainability issues are easier if countries are paying for vaccines from the start. The approach of using emerging suppliers may make this easier because of some savings in manufacturing costs in developing countries, but it means identifying with a manufacturer up front,⁶⁷ and experience has shown that this is not the most rapid approach given some needs for infrastructure development in these countries. Finally, GAVI should consider whether it wants to continue to focus on innovative vaccines that will be developed first by multinational producers, and, if so, how it can best use the potential of emerging suppliers.

9.4 Monitoring progress of other initiatives

It will be useful to GAVI to keep up with the progress of these initiatives, first, to consider their inclusion into national immunization programmes with GAVI funding, and second, to compare achievements and obstacles in the process of vaccine readiness of these projects, and of others that might be more upstream or focused at a different audience,⁶⁸ with that of the ADIPs, to learn from that experience. This could be accomplished in a number of ways; perhaps the simplest would be a regularly convened Vaccine Forum for this purpose.

10. CHANGES IN THE IMMUNIZATION LANDSCAPE AND RELATION TO ADIPS AND HI

10.1 Changes in the landscape

10.1.1 *New sources of financing*

Public health and especially immunization seem to have entered a phase where they are attractive to donors. Some of this comes from the major focus that the Bill & Melinda Gates Foundation has given, and to what could be termed the “Hollywoodization” of infectious

⁶⁷ Something emerging suppliers told BCG study interviewers that they would welcome, if there were open competition. Note that the selection of Serum Institute of India for the MVP was a competitive selection.

⁶⁸ For example, malaria, HIV/AIDS, and tuberculosis vaccines, and human papilloma virus vaccine, respectively.

diseases and poverty – the involvement of big name stars in the fund raising effort. Some undoubtedly comes from the publicity given to newly emerging infectious diseases that are potentially vaccine preventable, such as pandemic influenza. A part of it must be due to the efforts of GAVI and its partners to increase national financial sustainability, and recognition must be paid to the brilliant work of people like Amie Batson at the World Bank and Ruth Levine at the Center for Global Development and their collaborators, who enlisted economists to consider the problem and then developed new ideas, such as the AMCs and the International Financing Facility for Immunization, IFFim.⁶⁹ For all these reasons, GAVI and its partners have a lot more money at their disposal to strengthen immunization systems and to deliver new vaccines

10.1.2 Changes in GAVI

GAVI has changed from a fragile partner alliance rising out of the death of the Children's Vaccine Initiative to a force in international public health. Because of this success, there is consideration to drastically changing the GAVI structure. Formerly administered by a Secretariat with only limited staff, GAVI will likely change to a much larger organization, with necessarily a different relationship to the GAVI Partners. This change in focus is defined in the recently approved Strategic Plan for 2007-2010.⁷⁰ This will undoubtedly have an impact on how GAVI may choose to act in influencing uptake of innovative products.

10.1.3 Scientific and technical progress

In the five years since the McKinsey study, science and technology has not stood still. Much more is known about laboratory diagnosis and molecular immunology, and about the ability to master these skills in developing countries. The concepts of ethics and Good Clinical Practice have become prerequisites for any clinical trial, and are being applied routinely in developing countries. Management of data regarding processes, population outcomes, and diagnoses are bringing epidemiology forward. Chemical techniques for biological product synthesis are changing the way vaccines are made and how they are regulated. These changes will have an impact on GAVI's mission.

10.1.4 The vaccine pipeline

⁶⁹ Credit should be also given to the efforts of the GAVI Financing Task Force and its successor organizations for this work. More information about IFFim can be found at http://www.iff-immunisation.org/pr_nov7b_06en.html, accessed 15 February 2007.

⁷⁰ GAVI Secretariat, GAVI Alliance Strategy 2007-2010, 6 June 2006.

For the first 20 years of its existence, the Expanded Programme on Immunization (EPI) had six antigens. In the decade since the mid-1990s, hepatitis B and Hib vaccine have entered many immunization programmes and yellow fever vaccine has been incorporated in areas at risk. This means that the current number of antigens is 150% of the original EPI start-up kit. We are now seeing many more options: not only the pneumococcal and rotavirus vaccines that are the subject of this paper, but human papilloma virus and meningitis conjugate vaccines and regional products like the new Japanese encephalitis product can be considered. In the next few years there will be many more: besides some of the older products like mumps, rubella, influenza and varicella, we may see new vaccines against malaria, dengue and respiratory syncytial virus. This increase is on the one hand a consequence of the advances in science and technology mentioned above, but also due to the fact that there is a known disease burden and also a market.

10.1.5 Entry of both multinational and emerging suppliers into this market

For decades, only a few European vaccine manufacturers showed interest in the developing country market. In the last decade they have undergone huge structural changes, moving from private sector vaccine producers to components of large multinational corporations. Perhaps surprisingly, most of these have continued to be concerned with the developing market. In addition, the last five years have seen two American multinational vaccine producers moving into the international market. Other firms have acquired partners in newly industrialized and developing countries as part of their investment in this market. Finally, although developing country manufacturers have been around for years, it is only really in the last five years that they represent credible sources of newer vaccines. This expansion on the supply side, in contrast to the crisis in vaccine security that emerged around the turn of the century, will have a large impact on GAVI's efforts.

10.2 Impact of the ADIPs and HI

10.2.1 New sources of financing

Although the ADIPs and the HI have probably not been responsible for the increase in funding for immunization, their existence has been a point in favor of supporting GAVI. Both ADIPs made a large contribution to the work on AMCs.

10.2.2 Changes in GAVI

Part of the reason for needed expansion of GAVI staff is because the Secretariat resources are too thin to handle the workload. Part of that workload was certainly due to the existence

of the ADIPs, the need for supply strategies, the work on the AMC, and other activities associated with the work of the ADIPs and the HI. A major part of the work, devoted to Bridge Financing and the Hib Task Force, suggests that a Hib ADIP starting about a decade ago might have avoided some of GAVI's teething problems. One major impact of the ADIPs is the recommendation, supported by the GAVI Board, to move forward with the introduction of rotavirus and pneumococcal conjugate vaccines into global immunization programmes. This could not have been accomplished without them.

10.2.3 Scientific and technical progress

The progress in science and technology would have occurred no matter what the ADIPs and the HI did. However, they have been able to harness this technology to improve their performance: for example by exploiting the ability to do laboratory diagnosis in developing countries to thus better quantify disease burden. The ADIPs have encouraged the use of developing country trial sites for quality clinical trials, and this trend will expand in future.

10.2.4 The vaccine pipeline

Similarly, the vaccine pipeline has not changed because of the work of the ADIPs and the HI. Their work has however changed the market, and this will change the motivation of manufacturers to apply science and technology (see below).

10.2.5 Entry of both multinational and emerging suppliers into this market

The work of the ADIPs has had a large impact on the entry of suppliers into this market by working to develop credible demand forecasts and business cases, and to demonstrate the availability of funding sources and the interest of countries in taking up these products. Manufacturers have reiterated their needs for better demand analyses, a more transparent procurement process, a funding commitment to make the decisions that would be necessary to become a better partner in the global market. The work of the ADIPs has begun to provide this information in a focused way for a specific product. The recent entry of both American multinational vaccine manufacturers, who had not been part of the developing market supply picture in recent years, and their willingness to submit to the full prequalification process clearly shows this change. Moreover, by working directly with the emerging suppliers in exchange of information and some technical support, the ADIPs have encouraged these producers to invest in the development of innovative products. Already three emerging suppliers have been prequalified for the supply of the DTP-based combination vaccines, and several of them are rotavirus and pneumococcal vaccines.

10.3 The Counterfactual

Because many of the changes mentioned above are the natural continuation of processes started well before the ADIPs came into existence, it is difficult to say whether all these changes would have happened at the same speed in the absence of the ADIPs. It is difficult to rule out the impact of funding and global changes in perception. But we do have a counterfactual, and that is the status of Hib. In 1997, before GAVI came into existence, Hib vaccine had been available for about 10 years. Its impact in the United States was well-documented. The Children's Vaccine Initiative and WHO, with USAID support, were actively working on a Hib agenda to support its introduction into developing country immunization programmes, with a disappointing lack of success. Even when GAVI came with financing, thus moving Hib in 2000 to approximately the same status as rotavirus and pneumococcal vaccines will have with guaranteed GAVI financing, there was no rush to take it up. The team contends that the reasons behind this related to the lack of attention to the elements of the virtual circle: capacity, demand, and pricing. Some of these elements have still not been completely resolved, although they are now being addressed to some extent. Now, seven years later, with the bridge financing guidelines and the second tranche of GAVI funds, with much better data on disease burden and vaccine cost-effectiveness, countries are starting to introduce Hib vaccine. By addressing these issues before the availability of the vaccine, the ADIPs are now shortening the time between licensure and introduction, and that is their charge. One industry interviewee noted the bottom line in the impact of the ADIPs, saying, "Rota and pneumo [vaccines] being used would mean that the ADIPs have made a difference." The same interviewee used several times the example of Hib, noting that the planning for its GAVI launch was mishandled. "Hib is the vaccine that GAVI did not succeed in its fundamental task."

10.4 Impacts of these changes on the need for ADIPs in future

These changes in the landscape, taken together, suggest that GAVI will need to continue to be proactive, and, in fact, more proactive, in managing innovative products in the future. The next section explores some possible activities.

11. FUTURE ROLE OF THE GAVI ALLIANCE IN ACCELERATING VACCINE INTRODUCTION

Each of the three stages described below has options laid out for it in the accompanying table

(Table 3), which describes possible actions for the GAVI Board and the pros and cons of each.

11.1 New vaccines in the pipeline

There is little or no role for the Alliance for vaccines where there is as yet no product – where the scientific and technical uncertainties are so large as to make introduction a distant vision, for example for AIDS or TB vaccines. When a product exists, GAVI needs to look at the scientific and market uncertainties. One possibility is that GAVI could commission a prescreening process to find which vaccines were ready to move into an ADIP – based on their market uncertainties and their scientific uncertainties, as well as the global disease burden. It should be a thorough and careful scanning of the vaccines in the pipeline, and preliminary work as necessary to set the stage, look at surveillance systems, develop a disease priority list, and inventory potential uptake and supply capacity.

In this pre-ADIP period, GAVI could: (1) commission such a scan of the vaccine pipeline or (2) wait for someone else to do this. The advantage of path (1) would be the control of the process, and the assurance that GAVI would possess the knowledge it needed when launching an ADIP seemed appropriate. Early involvement also sends a signal of credibility to industry. The disadvantages of this route are two: first, it would need to be established that this is compatible with the GAVI mission, which is generally more downstream.⁷¹ Second, it would likely be expensive.

11.2 Starting an ADIP

The act of initiating an ADIP sends a signal to industry that GAVI is seriously interested in introducing this vaccine. The charge of the ADIPS is to facilitate progress to a state of programme-readiness. GAVI could be involved for future vaccines in much the same way, but if so, it should start earlier, to be able to better set the stage, engage the industry, accelerate introduction, and influence the target product profile. Because whatever GAVI does on a particular product will signal industry, moving earlier rather than later would be helpful. Even a vaccine like Hib, which still has market uncertainties, supply issues, and some technical issues (disease burden in Asia), should have had an ADIP which covered the whole range of questions.⁷² The sections below outline some of the activities that might be important for the

⁷¹ Although GAVI's original plan was to have an R&D Window, of which the ADIPs are one activity.

⁷² GAVI's Strategic Plan for 2007-2010 specifically states that "To ensure a healthy vaccine market and a sufficient supply of reasonably priced vaccines by multiple manufacturers, the Alliance will put into

GAVI Board to take into consideration, should it decide to continue with the ADIP process.

11.2.1 Criteria

We first considered the criteria that might be used to start such an initiative. The original McKinsey study⁷³ suggested the following:

- either there is no currently-registered vaccine, or the existing vaccine has drawbacks which severely limit its utility;
- the vaccine has a high potential impact and could significantly reduce morbidity and mortality in children and/or adults in developing countries (high disease burden);
- there is a high probability of success in developing a vaccine in the short/medium term;
- the vaccine has a potential for improving immunization systems;
- the vaccine fills a strategic gap, i.e. no other effort is currently focusing on the disease, or those efforts are less cost-effective than a vaccine would be.

To these we would add the following:

- there is a potential way to measure the impact of the vaccine;
- there are potential market failures that can be addressed;
- there is an expressed need or demand from countries.

11.2.2 Structure

As for the original ADIPs the ADIP should be target oriented, time-limited, milestone driven, small, under strong management, and located at a single site that is a supportive organization. An RFP process should be used to select the organization and management team; care should be taken that the RFP is clear as to mission and governance. ADIP applicants should clearly indicate in their proposals how they intend to work with collaborators, and the details of this should be a major criterion for selection.

Because of the shortcomings in governance noted in this study, we would recommend that the GAVI Secretariat develop an ADIP Project Team Liaison Office composed of at least three people to provide the necessary support for those ADIPs now in existence and any ADIPs that will be developed.

place a supply strategy for all GAVI sponsored vaccines," GAVI Secretariat, GAVI Alliance Strategy 2007-2010, 6 June 2006, p.13.

⁷³ Accelerated Development and Introduction of Priority New Vaccines: The case of pneumococcal and rotavirus vaccines, 8th GAVI Board Meeting, 19-20 June 2002, Paris.

Because the ADIPs will be time-limited, there should be criteria for determining the end of their lifespan. It might be proposed that this be initially five years, with the charge that the ADIPs should, as before, continually evaluate the relevance of their product to the GAVI mission and justify the continuation of the ADIP at each annual report.⁷⁴ At the end of five years there could be several possible decisions, such as, to terminate the ADIP, to continue the ADIP for another defined period, or to transition the ADIP to an Implementation ADIP (see below). In the event of a transition decision, the ADIP could continue, perhaps with a reduced staff, to handle the technical issues related specifically to the product under the issues of capacity, demand and pricing.

As before, the ADIPs should each have their own scientific and technical advisory committee, but for GAVI, there should be a MC which provides oversight to all ADIPs. This should have authority for approving the expenditures up to a predefined limit and the directions of the ADIPs within certain guidelines. The MC would report regularly to the Board, but time should be given for the ADIPs to report directly to the Board, unless the MC actually includes at least three Board Members. Membership of the MC should include the relevant scientific and technical expertise for all ADIPs under its surveillance, including experience in vaccine development, vaccine production, clinical trials, surveillance/epidemiology, and programmatic issues.

11.2.3 Function

Because the ADIPs as constituted have worked well, the team sees no reason to change the functions as defined in the original McKinsey report. Specifically, that means working within the virtuous cycle framework as defined in that document and further elaborated in this report. A breakdown of activities under the rubric “Establish Value, Communicate Value, Deliver Value” seems to have worked effectively, and could be continued.

It will be important for the ADIPs to, insofar as possible, institutionalize activities that they put in place for setting the stage for introduction. For example, disease surveillance activities could be taken over by the relevant WHO Regional Offices and countries.

⁷⁴ One suggestion from industry was that an ADIP be limited initially to 18 months, noting that “the most successful ADIP is one you don’t need.”

11.3 Transition to introduction mode

An “Implementation ADIP” which can take forward and coordinate country introduction activities, laying out the landscape for countries and empowering them to select new vaccine(s) for introduction, could be a mechanism to manage this transition. Such an Implementation ADIP would coordinate partner activities, consider the communication messages, support decision making in developing countries, ideally through national Advisory Committees on Immunization, and inventory logistics, training and financing needs that individual partners at the country level could address. It should provide a service to countries, laying out the landscape so that they could then effectively make their own vaccine introduction decisions. This Implementation ADIP should be small, flexible, and accountable to GAVI for these activities.

Such a team could be (1) located within and staffed by the GAVI Secretariat; (2) located within and staffed by a GAVI Partner organization with strong country and regional contacts such as WHO or UNICEF; (3) located within an outside organization selected through an RFP process and financed by GAVI. GAVI will have to determine, based on how it sees its future roles and that of its partners, how best to move forward. A few comments: approach (1) implies significant credible GAVI presence at regional and country level with skills in introduction issues as well as an ability to work effectively with all partners. Approach (2) implies that implementation is handed off to and performed by WHO and/or UNICEF. This will still require some element of GAVI control, which will have to be defined. Approach (3) is similar to that being followed by the MVP and the JE Vaccine Project: location in an outside organization but with strong contacts with the existing infrastructure in GAVI Partner organizations. In each case, GAVI will need to assure timeliness of communication with ADIPs, clarity in mandates, elimination of unnecessary layers of authority, and clear RFPs.

11.3.1 *Criteria for transition*

What should be the criteria for transitioning to implementation? Some suggestions are:

- one vaccine licensed and appropriate, available, and in supply adequate for the early introduction phase;
- safety and efficacy data available for at least two regions of the world;
- burden of disease established in each region of the world where the vaccine is going to be introduced;
- surveillance systems set up but not finished for all countries;
- vaccine still presents field issues for its use;
- potential for country to take on vaccine (political, infrastructure, financing);

- consensus from ADIP team that the above criteria has been satisfactorily met.

11.3.2 Relationship to GAVI Secretariat

Given the opinion of the HI that they need more contact with the Country Support Group within the GAVI Secretariat, it is suggested that this might be the appropriate group to liaise with the Implementation ADIP. As suggested for the Vaccine-Specific ADIPs, this should be a project team of at least three members for this task.

11.3.3 Relationship to GAVI Board

An Implementation ADIP would still have reporting obligations to the GAVI Board and would still be overseen by a Board-designated MC. This could be the same MC as for the ADIPs, or a different one, depending on the skill sets represented. For an Implementation ADIP an oversight group would need good understanding of country contexts and how countries differ, as well as a broad understanding of public health interventions.

12. POSSIBLE MODELS AND RECOMMENDATIONS

12.1 Summary of life cycle oriented structures proposed

In this section we aim to summarize, through Table 3, possible approaches that GAVI could take in the three areas spanning the early life cycle of innovative vaccines.

Table 3. Possible GAVI Interventions during the vaccine life cycle

Stage	Option	Description	Pros	Cons
1. Pre-ADIP period – scanning the horizon	1.1 Do nothing	Let the market do its work; count on outside funding support for this	Has worked OK so far	GAVI loses control
	1.2 Be conservatively proactive	Commission a study on the pipeline and which products are most relevant to GAVI, including country input; convene a meeting to survey the market	Allows GAVI to choose when to enter the fray; promotes communications	Takes money and resources
	1.3 Be very proactive	Take charge of the process. Develop pre-ADIP study groups for every new vaccine with high disease burden	Gives GAVI optimal control over the process and better positions it to appoint ADIPs	Very expensive; moves GAVI further upstream; may result in duplication of effort
2. ADIP process	2.1 Phase out ADIP process and existing ADIPs	Agreeing with those saying the ADIPs have had no added value, rely on existing structure to develop products to a state of programme-readiness	Saves GAVI money and effort, and possibly the international community is sensitized so that these functions could go on without ADIPs	GAVI would be taking a risk in terms of vaccine introduction

	2.2 Continue the ADIP process for a limited number of vaccines	Limit those vaccines for which an ADIP is set up to no more than 2-4 at a time. Set criteria for selecting ADIPs. Have them go from as early as possible to past the country introduction stage to be sure of appropriate supply strategies, disease burden information, demand forecasting, appropriate technical messages, and issue resolution	Provides more rigor to the process, especially if ADIPs are reserved only for those instances in which there are market failures	Takes lots of GAVI resources. High transaction costs for manufacturers. Large proliferation and potential duplication of efforts
	2.3 Continue time-limited ADIP process	Have ADIPs stop when country introduction starts	Less work for GAVI	Potentially problems, especially for issues that arise after introduction (product failure, adverse events)
	2.4 Continue ADIP process, but have only one ADIP	Have a mega-ADIP for all products	Administratively easier and avoids duplication of effort and country level transaction costs	Less effective, less specific technical expertise, potential for competition between vaccines

Stage	Option	Description	Pros	Cons
3. Implementation	3.1 Do nothing	Allow existing structures to handle implementation issues	Fewer resources required	We are back where we started; most agree that existing structures cannot handle these implementation issues alone
	3.2 Specifically add implementation to the mega-ADIP charge	Put all ADIPs under a mega-ADIP as in 2.5 that spans the whole process from early development through programme-readiness	As in 2.5 and 3.2	Will not get the needed technical inputs, plus cons for 2.5 and 3.2
	3.3 Develop an implementation ADIP that will handle country advocacy activities for all products that are programme-ready.	This could be based on the HI with some structural and mandate changes, and also take on in-country implementation activities for pneumo and rota	Avoids competition and confusion at the country level for introduction activities, allows a coordinated approach providing tailored information to each country for a variety of products	Develops a new structure that must work with existing country and regional infrastructure

12.2 Recommendations

The team concludes that the work of the ADIPs has accelerated the process of introduction of pneumococcal conjugate and rotavirus vaccines and has thus provided value in terms of lives saved and hospitalizations averted. The HI, in place for a shorter period of time, has served more like an Implementation ADIP, and has facilitated decision making in a number of countries. However there remain capacity, demand, and pricing issues for Hib that are specifically excluded from the HI mandate than need to be addressed.

The team recommends that the GAVI Board consider approaches for further managing the new vaccine introduction process in three areas:

- Scanning the pipeline (the pre-ADIP process) and keeping informed on projects in earlier stages of development;
- Addressing the issue of the ADIP process: capacity, demand, and pricing strategies that are needed to render a vaccine “programme-ready;”
- Addressing the implementation issues for a range of programme-ready vaccines.

Possible approaches with the pros and cons of each are presented, through which GAVI could better manage the life cycle of new vaccines which are being considered for inclusion within developing country immunization programmes. Whichever approaches are selected, GAVI will need to consider how best to manage them, and the following recommendations are offered related to gaps seen in the current process.

1. GAVI will need to review its mission and its working procedures to determine how best to manage these approaches and structures, either within the GAVI Secretariat, housed at a GAVI Partner organization or at an outside organization selected through an RFP process.
2. For the ADIP and implementation processes, oversight needs to involve the GAVI Board, through a Management Committee selected with appropriate skills, and with liaison through specifically charged GAVI Secretariat teams.
3. ADIPs should be focused in a single organization, with a strong manager, and be target-oriented, time-limited and milestone-driven.
4. The ADIPs should justify on a regular basis to the GAVI Board the continuing relevance of their product.

5. The ADIPs should carefully define their interactions with GAVI Partners at country level.
6. The Requests for Proposals, mandate, and the governance structures must be clear and appropriate.
7. The GAVI Board should ensure that there is collaboration and coordination among all groups performing an ADIP-like function by convening open fora where they can report latest results and resolve potential issues.

ANNEX 1.**INTERVIEWS CONDUCTED**

Interviewee	Organization	Telephone Interview	In person Interview
Mercy Ahun	GAVI Secretariat	X	
Michel Zaffran	GAVI Secretariat	2X	
Julian Lob-Levyt	GAVI Secretariat	X	
Thomas Cherian	World Health Organization	2X	
Jean-Marie Okwo-Bele	World Health Organization	X	
Julian Bilous	World Health Organization	X	
Kane Ibrahim	World Health Organization, AFRO	X	
Steve Landry	Bill & Melinda Gates Foundation (Steering Committee - SC)	X	
Regina Rabinovich	Bill & Melinda Gates Foundation (MC)	X	
Violaine Mitchell	World Bank consultant	X	
Amie Batson	World Bank	X	X
Jean-Louis Sarbib	World Bank	X	
Ruth Levine	Centre for Global Health (SC)	2X	
Tore Godal	Special Adviser to the Prime Minister – Norway (MC, former GAVI Executive Secretary)		X
Rajah Nihal Abeysinghe	EPI Manager Sri Lanka	X	
Orin Levine*	Johns Hopkins (Pneumo ADIP)	2X	X
Angeline Nanni	Johns Hopkins (Pneumo ADIP)	X	
John Wecker*	PATH (Rota ADIP)	2X	
Rana Hajjeh*	Johns Hopkins/CDC (HI)	2X	X
Claire Broome	Ex head of science, CDC	X	
Bob Davis	UNICEF, East Africa	X	
Chris Lyons	UNICEF	X	
Shawn Gilchrist	Sanofi	X	
Kevin Reilley	Ex-Wyeth (MC)	X	
Walter Vandersmissen	Glaxo SmithKline	X	
Elaine Esber	Merck	X	
Robert Hecht	IAVI	X	
Jan Holmgren	U Goteborg (Chair, MC)	X	
Selina Haylock	Ruder Finn UK	X	
Marc LaForce	Meningitis Vaccine Project		X
Rehan Hafiz	EPI Manager, Pakistan		Email
Pem Namgyal	Acting Regional Adviser, WHO SEARO		Email
Jane Soepardi	EPI Manager, Indonesia		Email

* Plus multiple email contacts

ANNEX 2.

DESCRIPTION OF THE TWO ADIPS AND THE HI

The Pneumo ADIP was approved in February 2003 for a period of four years with a financing of \$30 M. In 2006, approval for an additional year plus an envelope of \$200M (to be shared for pneumococcal conjugate and rotavirus vaccine activities) was given by the GAVI Board. The Pneumo ADIP had requested these funds for activities to ensure affordable sustainable supply and evidence-based decisions at the country, regional and global levels (\$40M) and for vaccine purchase (\$127-189M).

The mission of the Pneumo ADIP is to improve child survival and health by accelerating the evaluation of and access to new life saving pneumococcal vaccines for the world's children. The Pneumo ADIP is located at the Johns Hopkins Bloomberg School of Public Health, and managed as a small team under the leadership of Dr Orin Levine.

The Rota ADIP was approved in February 2003 for a period of four years with a financing of \$30 M. In 2006, approval for an additional year plus an envelope of \$200M (to be shared for pneumococcal conjugate and rotavirus vaccine activities) was given by the GAVI Board. The Rota ADIP had requested these funds for strategic and technical activities (\$38M) and for vaccine purchase (\$13-50M)

The Rota ADIP, called the PATH Rotavirus Vaccine Program (RVP), is a partnership with the World Health Organization and the US Centers for Disease Control. The team director, Dr John Wecker, who has management responsibility, and all management functions are located at PATH, in Seattle. The PATH Rotavirus Vaccine Program was created to accelerate the vaccine introduction process and to make rotavirus vaccines available to children in developing countries as quickly as possible.

The Hib Initiative was approved in June 2005 for a period of four years with a financing of \$28M, plus \$9M for the India Hib Vaccine Probe Study. Its mission is to expedite and sustain evidence-informed decisions regarding the use of Hib vaccination, in order to prevent childhood meningitis and pneumonia.

It is composed of a consortium of four members, including Johns Hopkins University, CDC, WHO, and the London School of Tropical Medicine and Hygiene. The Project Director, Dr Rana Hajjeh, the communications director, the programme manager and support staff are all based at Johns Hopkins University. There is one epidemiologist at each of the four sites, and an economist located at the London School. An Executive Committee made up of one representative from each of the institutions represented has responsibility for management decisions.

ANNEX 3**FINANCIAL INFORMATION ON THE ROTA ADIP, TAKEN FROM ANNUAL REPORTS AND BUDGETS****Rotavirus**

	2003 expenses	2004 expenses	2005 expenses	2006 budget
Personnel costs	\$484,812	\$698,974	\$1,096,464	\$1,042,441
Consultants	\$59,599	\$146,362	\$30,069	\$36,000
Travel and per diem	\$67,868	\$317,823	\$344,353	\$294,165
Funds extended to collaborators	\$195,388	\$2,925,523	\$5,118,366	\$7,234,920
Meetings and conferences	\$7,184	\$10,245	\$11,153	\$12,900
Other project costs	\$209,956	\$264,051	\$467,924	\$460,935
Overhead	\$264,962	\$444,236	\$600,044	\$580,347
Total	\$1,289,769	\$4,807,214	\$7,668,373	\$9,661,708

Rotavirus Vaccine Program Financial Report 2005

	Budget	Expenses	Per cent
Establish value:			
Surveillance and Disease Burden	\$2,650,964	\$2,268,353	30%
Vaccine Development	\$5,245,319	\$3,454,945	45%
Subtotal	\$7,896,283	\$5,723,298	
Communicate value:			
Communication and advocacy	\$1,138,561	\$681,193	9%
Subtotal	\$1,138,561	\$681,193	
Deliver value:			
Vaccine Financing and Supply	\$571,410	\$457,692	6%
Vaccine introduction	\$1,165,068	\$496,519	6%
Subtotal	\$1,736,478	\$954,211	
Program Management and Administration	\$264,272	\$309,670	4%
Total	\$11,035,594	\$7,668,372	100%

ANNEX 4**FINANCIAL INFORMATION ON THE PNEUMO ADIP, TAKEN FROM ANNUAL REPORTS AND BUDGETS****Pneumo**

	2003 expenses	2004 expenses	2005 expenses	2006 budget
Personnel costs	\$412,417		\$1,070,707	\$1,621,148
Consultants	\$23,840		\$2,272,735	\$925,500
Travel and per diem	\$87,971		\$388,165	\$747,250
Funds extended to collaborators	\$405,974		\$2,617,845	\$3,886,247
Meetings and conferences	\$110,286		\$79,117	\$232,900
Other project costs	\$72,868		\$85,509	\$67,750
Overhead	\$222,671		\$360,497	\$733,910
Total	\$1,336,027	\$0	\$6,874,575	\$8,214,705

PneumoADIP Financial Report 2005

	Budget	Expenses	Per cent
Establish value:			
Surveillance and Disease Burden	\$4,589,149	\$3,147,374	46%
Vaccine Development	\$0	\$0	0%
Subtotal	\$4,589,149	\$3,147,374	
Communicate value:			
Communication and Advocacy	\$1,401,026	\$1,063,894	15%
Subtotal	\$1,401,026	\$1,063,894	
Deliver value:			
Vaccine Financing and Supply	\$1,061,002	\$1,913,951	28%
Vaccine introduction	\$0	\$0	0%
Subtotal	\$1,061,002	\$1,913,951	
Program Management and Administration	\$701,732	\$749,355	11%
Total	\$7,752,909	\$6,874,574	100%

ANNEX 5

FINANCIAL INFORMATION ON THE HI, TAKEN FROM ANNUAL REPORTS AND BUDGETS

Hib Initiative Work Plan Budget July 1, 2005 - June 30, 2009					
	Interim Workplan				
Strategic Areas	2005 - 06	2006 -07	2007-08	2008 -09	Total
Strategic communication		\$1,910,073	\$781,997	\$808,185	\$3,500,255
Strategic Research and Surveillance		\$8,914,459	\$4,834,490	\$5,504,291	\$19,253,240
Strategic Coordination		\$2,992,416	\$2,843,392	\$2,900,476	\$8,736,284
Total	\$5,648,979	\$13,816,948	\$8,459,879	\$9,212,952	\$37,138,758
July 1, 2006 - June 30, 2007					
	Global coordination	Regions with Doc BOD	Reg. w emerg. data (Asia)	EE, NIS, Central Asia	Total
Strategic Areas					
Strategic communication	\$663,268	\$482,268	\$577,268	\$187,268	\$1,910,072
Strategic Research and Surveillance	\$773,615	\$2,413,615	\$4,363,515	\$1,363,615	\$8,914,360
Strategic Coordination	\$748,104	\$748,104	\$748,104	\$748,104	\$2,992,416
Total	\$2,184,987	\$3,643,987	\$5,688,887	\$2,298,987	\$13,816,848
July 1, 2007 - June 30, 2008					
	Global coordination	Regions with Doc BOD	Reg. w emerg. data (Asia)	EE, NIS, Central Asia	Total
Strategic Areas					
Strategic communication	\$260,749	\$234,749	\$155,749	\$130,749	\$781,996
Strategic Research and Surveillance	\$390,873	\$560,873	\$3,536,873	\$345,873	\$4,834,492
Strategic Coordination	\$693,900	\$693,900	\$761,691	\$693,900	\$2,843,391
Total	\$1,345,522	\$1,489,522	\$4,454,313	\$1,170,522	\$8,459,879
July 1, 2008 - June 30, 2009					
	Global coordination	Regions with Doc BOD	Reg. w emerg. data (Asia)	EE, NIS, Central Asia	Total
Strategic Areas					
Strategic communication	\$262,046	\$227,046	\$182,046	\$137,046	\$808,184
Strategic Research and Surveillance	\$337,073	\$667,073	\$3,763,073	\$737,073	\$5,504,292
Strategic Coordination	\$725,813	\$723,730	\$725,813	\$725,120	\$2,900,476
Total	\$1,324,932	\$1,617,849	\$4,670,932	\$1,599,239	\$9,212,952

Hib Initiative Annual Budget and Expenditure					
	Budget	Expenditures	Encumbrances	Balance	Budget
	2005/06	2005/06	2005/06		2006/07
Personnel costs	\$1,630,987	\$1,064,357	\$474,720	\$91,910	\$2,918,210
Consultants				\$0	\$785,000
Travel and per diem	\$853,355	\$599,210	\$151,564	\$102,581	\$1,135,996
Funds extended to collaborators	\$1,082,000	\$0	\$82,000	\$1,000,000	\$5,153,000
Meetings and conferences	\$350,000	\$516,441	\$0	(\$166,441)	\$265,000
Other project costs	\$376,259	\$116,513	\$34,746	\$225,000	\$2,768,164
Overhead	\$606,378	\$383,823	\$197,612	\$24,943	\$791,578
Total	\$4,898,979	\$2,680,344	\$940,642	\$1,277,993	\$13,816,948



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