TB Vaccine Scoping Study:
Evidence and Methodology

Part 2:

Lessons for TB from a selection of other vaccines:

Hepatitis B
Pneumococcal
human papillomavirus (HPV)
rotavirus
Haemophilus influenzae type B (Hib)

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To save the time of some readers, a decision was made to gather the lessons at the start of the report rather than leave them at the end of each section as would be expected by a reader expecting to read the whole file.

1. HEPATITIS B VACCINE LESSONS FOR TB

- As in many other cases, the incomplete awareness of the extent of the disease burden played a big role in failure to take up recently-developed vaccines.
- Low-income, intermediate-endemicity countries failed to introduce universal Hepatitis B immunization because their health administrations were not being convinced of the cost-effectiveness of the intervention even when there was good evidence that this was so.
- The role of the International Task Force for Hepatitis B is detailed in the main body of the text, including the role in building burden of disease and cost effectiveness evidence, establishing demonstration programmes in developing countries, forging consensus globally and nationally, stimulating competition between manufacturers to reduce prices, and creating international procurement funds.
- Using model projects to influence nearby countries required a great deal of attention to indigenous culture, and especially to country-level politics and hierarchy. For example, the difficulties faced with the role of PKK (woman's movement) in Indonesia required a great deal of diplomacy; and the Chinese movement towards private healthcare in the early 1990s restricted 'effective market' as Hepatitis B became the first vaccine that was not provided free of charge to all Chinese children (although China is now cited by GAVI as a 'Success Story' with accelerated immunization between 1999-2002). The main body of the text below details the case of China.
- It is also necessary to be aware of the culture when suggesting technology transfer or other entrepreneurial changes, as the Task Force faced problems when addressing the possibility of local production such as a belief that PATH was a private money-making organization.
- Cultural factors may have a significant impact on the effectiveness of vaccine campaigns. For example, the education materials were poorly managed in Indonesia where the money was wasted on booklets before it was concluded that television was more effective for raising awareness. In Sri Lanka the Ministry of Health placed an amulet on a poster**.**
- We can learn a lot about the possibilities and limitations of economic analysis from the case of Hepatitis B, and especially the pitfalls to avoid (the next dozen or so points).
- Reflecting the maldistribution of TB studies, many Hepatitis B economic evaluations mostly covered (and still cover) countries of low to medium endemicity.
- Simulation models turned out to be very important, especially in revealing the hidden chronic part of the disease and the long run cost-effectiveness of immunization.
- Discounting is still a major unresolved methodological issue in economic evaluation. The modeled impact of Hepatitis B vaccine is extremely sensitive to discounting. This is mainly because of the very long horizons between

vaccination and prevented illness and death; this is not unlike TB vaccines, especially replacement BCG vaccines given to children.

- Even for studies of the same, low-endemicity country, there can be a divergence of results. This is due to differences in underlying assumptions and methodologies:
    - Incidence
    - Disease progression after infection
    - Costs and coverage of vaccination
    - Vaccination effectiveness and duration of vaccine protection
    - Discount rate
    - Time span
- The wide range of cost-effectiveness ratios coming from these analyses raised suspicion about the validity of economic evaluation among a number of policy makers. More standardization would have helped.
- Sensitivity analyses indicated that vaccination costs, discount rate and vaccination effectiveness had the largest impact on the cost-effectiveness in the case of Hepatitis B.
- In the Beutels global revue of the literature (see reference in main text), no cost-utility analyses (health gains expressed in natural units adjusted for quality, like QALYs) was found – only cost-effectiveness and cost-benefit analysis. This may be because the additional information attained by using the values of quality weights for health gains obtained through intervention is out of proportion compared to the effort required to determine these values accurately.
- There were difficulties in comparing cost-effectiveness analyses since effectiveness is expressed in a range of ways – infections prevented, carriers prevented, deaths averted, life-years gained – making it difficult to compare CERs. This is the 'end-point' issue we find in various analyses.
- Most analysis do not account for other indirect costs such as loss of work, human suffering and travel costs. In fact many studies do not even acknowledge these factors.
- In a 'dynamic model', the force of infection can change with time as a function of the proportion of infectious people in the population. A dynamic model will cyclically recalculate the force of infection over time. However, this is difficult to construct and requires data. In a 'static model' the force of infection over time remains constant. It cannot include impact on the risk of infection and herd immunity. With a static model, CER and BERs are independent of vaccine coverage. Static models can be seen as a pragmatic alternative, but one needs to be aware of limitations. It has been argued that in analysing Hepatitis B a static model could be accepted for universal vaccination but not targeted vaccination (whereas a static model could suffice for influenza vaccination for the elderly but probably not for universal vaccination).
- Aggregate analyses of vaccination against several infectious diseases are likely to become more relevant as producers now focus more on combined vaccines – an analysis of just one of the components in a combined vaccine may become too much of an over-simplification.

- Bi- and multivariate sensitivity analyses should be standard practice, because of the multitude of uncertain parameters.
- Threshold analysis also seems important to improve the credibility of potential savings of vaccination.
- Cost-benefit analysis for China found universal Hepatitis B vaccination to be very cost-saving and a study in Gambia also concluded that Hepatitis B vaccination would be cost-saving.
- Some have argued against the discounting of effects in countries like the Gambia because mortality affects primarily the economically active part of the population with an important function in society.
- Economic evaluation is only one of the factors influencing policy decision making – medical, epidemiological, practical, historical and ethical considerations, pressure from interest groups and the public's perception are found to be other important elements.
- It proved necessary to have national 'champions', such as the Minister of Health in Indonesia 1984.
- Forecasting demand needs to be done carefully. With the recent GAVI Bridge Funding Proposals for recombinant Hepatitis B, prices were expected to decrease when they in fact increased; demand forecasts were described by GAVI as "inaccurate".
- Hepatitis B is an interesting case of tiered pricing nevertheless, with very cheap prices in the poorest of countries. However, it is not clear to what degree causality ran from cheap prices to uptake (it was not a controlled experiment and many other supportive activities were taking place and path dependencies were present).
- Supply factors also need to be carefully considered. UNICEF had limited supplies of the Hepatitis B vaccine.
- Accountability has been unclear. There needs to be consensus on institutional responsibilities.
- TRIPS has been highlighted recently as potentially causing difficulties in technology transfer.
- One should be aware of any conflicts of interest with pharmaceuticals companies and those involved in advocacy at a national (and international level), since a number of cases arose in the Hepatitis B case that needed to be dealt with at the time with great care. Further, at a national level those representing both government and international organisations may have some difficulty maintaining local credibility depending on local hierarchy. This is important in advocacy.
- Careful choices of pharmaceutical companies are required to transfer vaccine technology – the International Task Force did not succeed in their attempts in Thailand (although there was success in the adoption of the National Immunization program).
- In high endemic countries the main difficulty policy makers face is not simply a lack of awareness of the disease burden, but rather whether programmes for vaccination deserve priority over other highly cost-effective interventions, how much it would cost to sustain it, and who would be willing to pay for it.

2. PNEUMOCOCCAL VACCINE LESSONS FOR TB

- There was lack of compatibility of the 23-valent vaccine or the 'blockbuster' vaccine Prevnar that was launched originally to target the market in developing countries.
- The supply strategy for Prevnar was not ideal. Wyeth initially had problems in expanding the manufacturing procedure to supply the vaccine to those developing countries with serotype coverage that was suited to a 7-valent vaccine never mind those that were not.
- The vaccine supply was sized to meet high-income demand and can only meet a small amount of developing country demand. Furthermore, if a company had been making $70+ per dose, there was little incentive to develop low-cost technology.
- This perhaps had a knock-on effect limiting interest and ability to alter the manufacturing process for higher-valent production.
- There is a need for vaccines to match disease burden. Prevnar is a 7-valent vaccine that does not include serotypes 1 and 5, the two serotypes that are particularly prevalent in developing countries.
- The launch of a pneumococcal vaccine is a natural scientific experiment.[1] The key issues are serotype escape over time as a vaccine is used, antibiotic resistance caused by a complex reaction in the population of serotypes to the vaccine targeting a selection of serotypes, and colonization. All three are encouraged by the use of vaccines with insufficient serotypes.
- There is already evidence for the US – a country relatively better positioned to take a 7-serotype vaccine – that serotype escape is making it likely that the current vaccine will need to be replaced there. In the US serotype 19A in particular has increased in part because of an expansion of a genotype circulating in the US prior to immunization commenced – and in other countries since at least 1990 – but also, some argue, because of the emergence of a novel 'vaccine escape recombinant' pneumococcal strain.
- In data collected by the Emerging Infections Program of the US Department of Health and Human Services, while the rate of invasive disease caused by vaccine serotypes had dropped by 92% in children <2 years old, disease caused by non-vaccine types had increased by 33% in just two years. The problem is that there are 90 different serotypes and rapid possible emergence of resistant strains as the pneumococcus' adapt to selective pressures. Furthermore, molecular studies indicate that pneumococci can swap genetic material so that they can change their serotype. Some argue that this will occur more frequently with selective pressure from a vaccine. To make things more complicated, it is unclear whether the population that emerges is going to be more or less antibiotic resistant.
- There are also concerns over efficacy of vaccines when administered to HIV infected children. A study in South Africa showed that over a 10 year period the

[1] Beall, B., "Vaccination with the pneumococcal 7-valent conjugate: a successful experiment but the species is adapting" Expert Review of Vaccines, June 2007, Vol. 6, No. 3, Pages 297-300, http://www.expert-reviews.com/doi/abs/10.1586/14760584.6.3.297.

incidence of pneumococcal disease doubled as the prevalence of HIV infection in children rose to around 6%.[2] This is being addressed in clinical trials for higher-valency vaccines.

- In many countries where the burden of pneumococcal disease is high, there are many competing priorities (e.g. malaria, HIV, etc.). Yet, it is difficult to diagnose *S. pneumoniae* as the causative agent of many of the diseases that it does cause. Developing country demand is primarily driven by strong awareness of burden of disease (surveillance efforts are important particularly in sub-Saharan Africa and Asia), clinical trial results and herd immunity effects as has been illustrated by immunization in other countries. Supporting the development of surveillance to document local evidence of the burden of pneumococcal disease is a high priority as part of a market-building exercise.
- In the US, herd immunity turned out to be very high, indeed much higher than expected. However, US-style herd immunity will not likely hold in much poorer countries (for example, in poor countries there is much denser household population and contact, and many target countries suffer high levels of HIV) and even more so in poorer countries if they using a vaccine that does not contain all the most appropriate serotypes. As illustrated by the differences in immunogenicity in HIV-infected infants in the US and the Gambia trial, there may be factors more relevant to developing countries that mean that these herd immunity effects cannot be assumed to be equivalent across countries. More work is needed on this.
- However, the time lag between being aware of these demand factors in developing countries for the vaccines and both motivating national and international institutions to advocate national immunization schedules and actually being able to administer suitable vaccines (currently higher valency vaccines are not expected until a least 2010 and some recent AMC literature has put this date back even further) is clear.
- Although there have been clear signs of international support for the accelerated introduction of pneumococcal vaccines, with GAVI's PneumoADIP and the AMC, these are of course limited to some extent by the vaccine development process. The decision to remove some of the higher-valent pneumococcal vaccines from the product pipeline by some of the larger pharmaceuticals companies is another confusing signal for a product that was initially not aimed at developing countries.
- At current costing and given current capacity decisions and GAVI expenditures, there is a concern that a lot of money will go on a much smaller number of doses than originally understood, with long-term price, and therefore financial sustainability, still unclear.
- Although there are key figures from Western Governments involved in these new proposals, there is a need for more 'pioneering figures' from the developing world too in order to have a successful launch. Too much emphasis is put on the financial instrument than the local 'grassroots' engagement. This could ensure that in future, outcomes take more account of the needs of developing countries at all points of the development process.

[2] Karstaedt A, M Khoosal and H Crewe-Brown "Pneumococcal bacteremia during a decade in children in Soweto, South Africa" *Pediatric Infectious Diseases Journal* (2000) 19(5): 454-457.

- Although pneumococcal vaccines can be administered at the same time as DTP3 vaccines and also have been proven to have herd effects, there may be other difficulties in distribution. Clearly the single vial used for Prevnar is not suitable.
- Newer vaccine approaches are being developed in order to provide protective immunity against a larger number of *S. pneumoniae* serotypes, and to circumvent the complexity of manufacture of conjugate vaccines. However, most of these will arrive (if at all) after most of the recent sponsor funding has been expended. One danger is that such approaches might even be prematurely discontinued. If the ultimate best solution turns out to be a protein-based vaccine targeting a large number of serotypes, we need to take care not to disincentivise it.
- Given the fungibility of money, the AMC has enabled GAVI to push ahead with an early program of 7-serotype pneumococcal vaccine in a range of African countries. In spite of the high costs (because of issues like vaccine packaging requiring big investments in cold chain) the rationalization given is that the 7-serotype programs will help learn about later higher serotype programs and that this initiative will 'prime' the market (an argument the only came to be made quite recently). It is also helping as a filler while the AMC is delayed.
- The claim of groups like Oxfam (and, indeed of other vaccine PDPs) is that once the AMC money was sunk, and once political processes were demanding action, the process became de facto a case of bargaining, and prices were naturally higher. It is also claimed that it is not clear if long-term low prices are locked in in exchange for early high prices, or what the consequences of current arrangements will be to follow-on producers. If there is nothing in the AMC pot for cheaper emerging suppliers or developers of new vaccines (such as protein-based vaccines) and yet rich world pharmaceutical firms have expanded capacity, it is not clear how emerging suppliers will not be put at risk. It is also claimed that arrangements may potentially perversely exaggerate the monopoly position of those already in the market (opposite to what is intended if one wishes to stimulate innovation and replacement of both product and supplier).
- The original argument was for 446,000 deaths prevented by 2015 by the current arrangements. This is now 500,000-700,000 by 2019. Claims about lives saved out to longer horizons have risen over time, from 3.9 million by 2025 to 5.4 million and, just recently, 7 million by 2030. It is unclear how these numbers incorporate herd immunity issues, and what the impact on numbers will be from serotype escape, etc. Another way to look at this is that by 2030 there will be about 25 million child deaths from pneumococcal. According to the GAVI figures, the newly-funded programme will save about 20% of these. Of this 20%, if the GAVI figures stand up over time, currently committed funding will cover 2%, and reduced long-term prices will cover the remaining 18%. If this is what $2bn-$3bn achieves, it does suggest those working on TB think very seriously about how to be creative with a $2bn-$3bn budget line were it ever to get it, so as to maximize the conceivable impact.
- The recent AMC paperwork indicates that there has been two to three years of further delay while the mechanism was going through a further round of design. The start date has been put back to at least 2014 (14 years after the pneumo-7 vaccine was licensed), and the roll-out has been lengthened. This tells us that

institutions and lack of general preparedness cause delay, and not just sheer quantity of money. The years of delay between rich countries getting access to life-saving vaccines for a disease and poor countries getting access to life-saving vaccines against the same disease is still of the order of 15-20 years. By the TB vaccine field targeting a product more appropriately, and instigating market support measures sooner, can it beat delays of this order of magnitude?

- By 2015 about 80% of GAVI's resources will go towards pneumococcal. Sustainability after that date (both of GAVI and of the pneumococcal programme) will require pneumococcal vaccine prices per dose to fall strongly at that point and for newer, cheaper, production technologies (such as protein-based vaccines) to come online then and over the following ten or so years. Budget projections of GAVI (available on the web) stop at 2015, the current lifetime of GAVI. At 2015 GAVI intends to renew. GAVI has put a lot at stake on the current pneumococcal programme.

3. HPV VACCINE LESSONS FOR TB

- The example of HPV has a lot of cross-cutting lessons useful to TB, especially a range of newer thinking being carried out with regard to developing-country launch, adolescent immunization and catch-up programmes.
- There is variation in prevalence of the subtypes of HPV globally, with some implications for the differential efficacy of the vaccine and how different market and policy makers will respond.
- There has been a lack of trials in Africa, and this will slow uptake there further than would otherwise have been the case.
- PAHO has put in place a HPV vaccine introduction plan for:
    - Building political will through top-down and bottom-up advocacy
    - Disseminating information and knowledge to allow evidence-based decision-making
    - Encouraging and conducting research, e.g. economic analyses and acceptability studies
    - Designing surveillance systems and tools
    - Mobilising cross-sectional support through social marketing and communication
    - Mobilising technical and financial resources
- Harvard University is using models adapted to different epidemiological settings to estimate population impact and cost-effectiveness of various vaccination strategies in different low-resource conditions, to identify potential synergies between vaccination and screening. Merck is also modelling the effect of vaccination strategies with dynamic modelling experts.
- PATH is working on pilot HPV vaccination demonstration projects in India, Peru, Uganda and Vietnam following 12-18 months of formative research in each country, to gather information about the medical, policy, fiscal and sociocultural environment. The demonstration projects include some clinical but especially operations research, gathering information on the sociocultural, logistic, policy and clinical elements needed for HPV introduction. Of particular relevance to TB, studies will probably look at optimal age ranges to target; the differences between a school-based strategy and one based on semi-annual child health days; and the most cost-effective way to reach 14-year-old girls. For example, there is varying evidence on how successful a school-based program might be, including concerns about school drop-out rates and low school attendance by girls.[3]
- PATH is also involved in mapping decision-making processes to address potential bottlenecks, including those of international funders.
- PATH is also developing global demand estimates, encouraging dialogue between GAVI, governments and industry about price using data from the demonstration projects, and identifying logistical challenges of procuring, storing, transporting and administering vaccines. It is also reviewing how to integrate HPV into

[3] See Biddlecom A, A Bankole and K Patterson, "Vaccine for cervical cancer: reaching adolescents in sub-Saharan Africa", *The Lancet* (2006), 367(9519): 1299-1300, for a brief discussion.

existing health programs and what combination of program activities (including other interventions) could have the most impact. It is also investigating the danger that people will stop screening.

- PATH is developing selection criteria for and identifying a shortlist of early-introducer countries.
- This activity is very interesting from the point of view of TB, as it examines several of the issues that should be looked at for TB. Specifically, research to map decision-making processes; the development of selection criteria for early-introducer countries; and attitudinal research at both political and community level parallels what would be needed for TB marketing and launch studies.
- There is much needed information and further actions which have been identified. These include:
    - Information on efficacy for women over 25.
    - Impact of vaccination on disease transmission, cross-protection against other HPV types, HPV type distribution; and on existing infection.
    - Information on herd immunity in increasing effectiveness of vaccination.
    - Information on long-term duration. International efforts are underway to set guidelines for monitoring vaccination programmes.
    - Evaluation of vaccine safety and efficacy in Africa and especially areas with high HIV prevalence.
    - Health economic data, including impact of protection against low-risk types 6 and 11 on cost-effectiveness; and marginal cost-effectiveness of adding other types.
    - Better cost-effectiveness information on vaccinating men.
    - Evaluation of efficacy at school entry age or infancy; and when simultaneously administered with other vaccines (e.g. tetanus, MMR).
    - Whether a lower number of doses might give adequate immunity and what cost implications this would have.
    - Research on aerosol and oral vaccination to overcome problems of multiple injections in developing countries. Evidence so far is apparently promising.
    - Information on possible use of reproductive health networks to deliver immunisation, e.g. family planning, pre- or post-natal care, and possibility of combining this with existing (child) immunisation networks.
    - Mapping the IP ownership situation to help developing-country producers decide if vaccine development is an attractive option.
    - Alternative technologies, not using virus-like particles (VLP technology), which could reduce cost, but are many years of research away.
- Many activities being carried out, in addition to those being called for, might possibly have been done earlier in the process. Some striking examples include: dialogue on price; work to influence production capacity and international funders; research on efficacy for older women, existing infection, and other subtypes of HPV; research on the benefits for males, and the benefits of including them in vaccination programmes; work on how to influence national decision-makers, given industry's need for financial commitment. The lessons from HPV can be learned by the TB vaccine field.

4. ROTAVIRUS VACCINE LESSONS FOR TB

- Rotavirus vaccines are another good example of a vaccine that was launched in developed countries and showed a significant time-lag before becoming a serious possibility for use in developing countries.
- When analysing the effectiveness of the vaccine, it is important to bear in mind the 'end point' of the study. There has not been consistency on this in the case of rotavirus. Rotavirus vaccines are more efficacious against severe disease. This may be very relevant for surveys on (cost) effectiveness of TB vaccines.
- The case of rotavirus showed that it is important to take into consideration any possible side effects, and also whether they are the same in developed and developing world. This is both a question of the risk of actually developing the side effect (evidence suggests that the risk of developing intussusception depends on the time that the vaccines are administered) and the affect on reducing disease burden/fatalities. The pity of rotavirus is now well known. Although the exact pathogenic mechanism by which Rotashield might cause intussusception was never determined, in retrospect, had the first dose of vaccine been administered only to children less than 90 days of age the risk of intussusception could have been substantially reduced to approximately ≤1 case/30,000 vaccine recipients. In the developing world, where about 1 in 200 children die from rotavirus disease, the benefits of vaccination far exceeded the risks.
- The climatic dynamics of the disease may also be important. For example, it has been suggested that in tropical settings, vaccine efficacy may be independent of vaccine administration. The vaccine schedule is an important parameter in cost-analyses and may affect the decision-making process to launch national immunization programs.
- There has been evidence of some competition between GSK and Merck to develop the Rotavirus vaccine which has speeded up the process to some extent. However as yet progress in developing a live oral rotavirus vaccine suitable for use in Africa has been limited.
- This is due partly to the strain diversity across different countries – for example, Malawi, India and Brazil have been recognised as hosting different variants of Rotavirus disease. It is important to be aware of any variation in disease or possible variation in disease when developing the vaccine. In addition the efficacy of the vaccine against HIV is a factor that is becoming increasingly important (and with a strong political influence) with regard to vaccines in developing countries. It is possible that the rush from the big pharmaceuticals companies to get vaccines licensed in as many countries as possible may not have taken the prevalence of different strains of rotavirus into account.
- There are concerns with the perceived efficacy of rotavirus vaccine, in particular with relation to co-morbidities. In Nigeria for example, 12% children suffer from sever weigh deficiency and 120,000 are infected with HIV disease. These co-morbidities could decrease vaccine efficacy.

- It has been suggested that an important factor in limiting the uptake of Rotavirus vaccines in developing countries has been uncertainty of demand. The above suggests that it is possible that demand forecasting and encouragement of commitment to certain particular vaccines is relying on poor assumptions.
- The PPP between Bharat Bio-Tech and CDC has been delayed. Time lags in clinical trials are a problem.
- There seems to be some overlap in the international institutions' programs for accelerating development and increasing "active participation".
- Surveillance is important and has been emphasised in these initiatives, especially with the development of surveillance Networks in Asia. The ARSN was only created in 2001. Although it is designed to increase global awareness of the disease and document the profile of the disease internationally, the emphasis is that national governments need to make decisions to implement immunization programs. However, there continues to be a gap between the extent of the disease burden and the acknowledgement of it at a national level. In many countries there is little appreciation of the burden of diseases because diagnoses are rarely made and research is limited. If the emphasis is on allowing countries to make decisions of priority of rotavirus disease prevention, better knowledge at the local level of the disease burden is needed.
- There is perhaps a lack of consistency between these international programs creating a broad picture of demand for vaccines and disease burden, and the shift of the burden of responsibility for decision making onto national governments. Accountability is a problem.

5. HIB VACCINE LESSONS FOR TB

- Increasing awareness of the global burden of Hib disease has been an important contributory factor to the uptake of Hib vaccines. Diagnostics are important in quantifying the disease burden and raising awareness but they can be difficult and complicated, particularly at the local level. Recognition of Hib disease burden is not uniform across developing countries; in particular there have been problems still in parts of Asia and Africa. This is despite the WHO recommendations that Hib combination vaccines are adopted in all countries.
- It is necessary to look at the nature of the disease in different countries. For example, the age at which Hib is prevalent is important in determining the optimal vaccination strategy, and the cost and effectiveness of that strategy – but the age distribution of cases between 2 months and 2 years of age varies across countries.
- It is necessary to create a protocol for surveillance but some aspects of the WHO general protocol have been limiting for use in developing countries as the requirements for a well-defined population with high access to care and the duration of at least a year's surveillance are not easily met.
- Also the WHO protocol for surveillance cannot be used to measure the burden of Hib pneumonia. This is an 'end-point' issue in surveying the disease burden.
- HibRAT methods have been effective to some extent but rely on several assumptions to extrapolate data for population-based estimates.
- Success in getting Hib to developing countries has been limited despite the efforts to encourage combination vaccine use. In particular, the GAVI Financing Initiative ran into problems as the price of combination vaccines did not decrease when expected and are not yet comparable in cost-effectiveness to the current standard EPI vaccines. This meant that assumptions about countries increasing their allocations to health and immunization and removing the need for GAVI support proved unfounded.
- However, with successful lowering of combination vaccine prices, the vaccines would become highly cost-effective and would be a powerful addition to the standard EPI package.
- In particular, the tradeoffs involved in the choice of combination vaccines (higher price than monovalent products, limited supply base) were not fully analysed in advance, and the Phase I model did not hold.
- Five years of support was too brief to allow the market to react to the increased demand and too short a time-frame to permit countries and partners to ramp up to meet increased costs.
- Although there has been an emphasis on encouraging national decision-making processes through these international committees support networks, many countries do not yet have the information they require to make an informed decision on whether to continue Hib vaccination from the GAVI Phase I. This implies that there is a problem in national advocacy or transfer of information as well as in funding the combination vaccines (prices of which are still expected to decrease).

- It is necessary to be very careful in forecasting the time-scales such as those used in these initiatives for Bridge Financing.
- It is necessary also to make it clear where accountability amongst partners lies, as there was some lack of consensus over institutional responsibilities in the GAVI Initiative.
- Price is not everything. Those in developing countries in particular expressed a concern that vaccine introduction depends on convincing key politicians and decision-makers about the value of the vaccine, and that insufficient attention was paid to this.
- The successful implementation of the vaccine program in the Gambia (with one of the best EPIs in Africa) was due to a combined effort of government healthcare workers and researchers at the Medical Research Council Laboratory. The long involvement of the Gambian people with medical research projects make this society quite unusual and it may be wrong to extrapolate these findings to other African countries.
- Even though combination vaccines are designed to be administered at the same time as standard EPI vaccines (DTP3), it should be noted that in the Case Study conducted in the Gambia fewer than half the children came back for booster vaccines in clinical trials. Given that clinical trials can be a critical stage in increasing awareness for new vaccination programs and for advocacy at a local level, this is worrying.
- Clinical trials need to be conducted in areas which do not have a long-standing relationship with, for example, a Medical Research Council as well as those that do, in order to properly analyse perceptions and feasibility of immunization programs.
- It should be noted that financial sustainability of trial programs has been an issue, which raises the question of the commitment of finance from international funds (if priorities change) – for example this is still a challenge for the program in the Gambia.

1. HEPATITIS B VACCINE CASE DETAILS

Summary

The case of immunization programs against hepatitis B is now often referred to as an important example, because there was a significant lag between development of vaccines becoming available and actually getting them to developing countries which needed them – and this 10-year lag (seen also in vaccination against Hib) is something which the key international players are keen to avoid again. Further, the means by which the need for immunization programs was addressed was not standard at the time.

This section focuses mainly on the story of the International Task Force for Hepatitis B, which succeeded due to the concentrated endeavour of the individuals pioneering the effort for immunization against hepatitis B without waiting for standard institutional channels to do so. In illustrating the progress of the Task Force with reference both to case-specific implementation and the processes required to make progress, a key reference was found to be Muraskin (1995), as one of the few sources available focused specifically on a concentrated vaccine effort and the difficulties faced along the way. The section describes case studies and comments referring largely to Muraskin (1995) in order to best illustrate this influential process. There is then a subsection on more recent case studies.

It should be noted that not only was hepatitis B not introduced in the developing world until the involvement of the Task Force and the pioneering figures committed to its cause, but in developed countries the procedure for immunization was flawed. For example, in the US, vaccines were only given to those individuals considered 'high-risk'. This was one of the factors that limited the use of hepatitis B vaccines – the others being the high price of the vaccine (initially on the US market at $18 per dose for a three dose course), and the incomplete awareness of the extent of the disease burden.

The hepatitis B vaccine also suffered some difficulties in public support for immunization. In the 1980s the plasma-derived vaccine came up against some issues following the HIV crisis, and more recently, claims that link the DNA recombinant vaccine to possible multiple sclerosis prompted difficulties in administration in France. Now, drives for increasing vaccination against hepatitis B are largely within the context of the expanding EPI programs: the WHO recommended additional vaccination against both hepatitis B and Hib in 1992 and this coincides also with the development of combination vaccines, which are not described in detail here but are explained more thoroughly in the Hib Case Study.

1.1. The Disease

Summary of disease:

- Hepatitis B is caused by a virus that affects the liver.
- Adults who get hepatitis B usually recover.
- However, most infants infected at birth become chronic carriers i.e. they carry the virus for many years and can spread the infection to others.
- The virus is carried in the blood and other body fluids.
- It is usually spread by contact with blood.

Prevention: Recombinant DNA or plasma-derived hepatitis B vaccine - three doses given by the intramuscular route into upper thigh of infant and deltoid muscle of adult.[4]

Because the development of jaundice is a characteristic feature of liver disease, a correct diagnosis can only be made by testing patients' sera for the presence of specific anti-viral antigens or antibodies. HBV carriers can transmit the disease for many years.

- HBV transmission can occur in a variety of ways. Perinatal, horizontal transmission, sexual contact or blood contact. HBV is the only sexually transmitted infection for which there is a protective vaccine. Only people who have been vaccinated successfully or those who have developed anti-HB antibodies after HBV infection are immune.[5]
- Following acute HBV infection the risk of developing chronic infection varies inversely with age.

Disease burden

- Researchers in the early 1970s discovered that the disease was ubiquitous in Asia and sub-Saharan South Africa.
- In some countries as much as 15-20% population would become chronic carriers of the disease; an estimated 1-2m people died each year from the chronic diseases that ultimately resulted.
- There is high endemicity in SE Asia, the Pacific Basin (excluding Japan, Australia, and NZ), sub-Saharan Africa, and the Amazon Basin, parts of the Middle East, the central Asian Republics, and some countries in E. Europe. In these areas 70-90% of the population becomes HBV-infected before the age of 50 and 8-20% people are HBV carriers. In countries such as China, Senegal, Thailand, infection rates are very high in infants, and continue through early childhood. At that stage, the prevalence of HBsAg in serum may exceed 25%.
- It is far less common in the west. But still, for example, in the US, there were 200-300,000 cases of hepatitis B p.a. in 1980s.
- In other countries such as Panama, Papua New Guinea, Solomon Islands, and Greenland and in populations such as Alaskan Indians, infection rates in infants are relatively low and increase rapidly during early childhood.

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[4] WHO webpage on surveillance of hepatitis B immunization
http://www.who.int/immunization_monitoring/diseases/hepatitis/en/index.html

[5] Viral Hepatitis Prevention Board "Universal HB immunization by 1997: Where are we now?" *Viral hepatitis fact sheet no. 2* (1998)

"HBV is far more heterogeneous than is generally thought. The HBV genome seems not to be characterized by a single representative genomic molecule, but by a pool of genomes which differ both in structure and function. The public health importance of mutant hepatitis B viruses is currently under debate. Further studies and a strict surveillance to detect the emergence of these viruses are crucial for a correct evaluation of the effectiveness of current immunization strategies."[6]

1.2. Key Players

GAVI, WHO, Task Force

- In 1991 the global advisory group of the EPI recommended the integration of hepatitis B vaccine into all national immunization programmes.
- The deadline of countries with a prevalence of carriers of 8% or more was 1995 and for other countries, 1997.
- This recommendation was endorsed in May 1992 by the World Health Assembly (WHO).
- In 1994 the World Health Assembly added a disease reduction target – 80% decrease in the incidence of new hepatitis B virus carriers in children by 2001.
- In March 2002 151 countries had introduced hepatitis B vaccines into their national immunization program. However, in other countries, universal vaccination is still being postponed.
- The reasons for this (according to WHO) are weakness of social commitment to preventative medicine and vaccinations, the lack of medical and public awareness, the view of hepatitis B infection as a limited public health problem that does not justify the expense and other efforts of universal immunization, and the financial burden of national programs.[7]
- Failure of the low-income, intermediate-endemicity countries to introduce universal hepatitis B immunization may be related to their health administration not being convinced of the cost-effectiveness of this intervention.[8]
- However, in an analysis of several newer vaccines, Miller and McCann (2000) calculated that hepatitis B vaccine was the most cost-effective in all parts of the world including intermediate hepatitis B endemicity areas.[9]

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[6] WHO Epidemic and Pandemic Alert and Response webpage on hepatitis B http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index2.html

[7] WHO "Hepatitis B immunization: introducing hepatitis B vaccine into national immunization services" (2001) http://www.who.int/vaccines-documents/DocsPDF01/www598.pdf

[8] Aggarwal R, U C Ghoshal and S R Naik "Assessment of cost-effectiveness of universal hepatitis B immunization in a low-income country with intermediate endemicity using a Markov model" *Journal of Hepatology* (2003) 38(2): 215-222

[9] Miller M and L McCann "Policy analysis of the use of Hepatitis B, Haemophilus influenzae type B, Streptococcus Pneumoniae-conjugate and Rotavirus Vaccines in National Immunization Schedules" *Health Economics* (2000) 9(1): 19-35

- In most countries, hepatitis B vaccine procured through the Vaccine Fund will be supplied through the UNICEF procurement mechanism – the number of hepatitis B vaccine doses required is calculated using the size of the birth cohort, the coverage rate for DTP and the number of doses in the immunization schedule. These calculations should also include wastage and the size of the reserve stock.

Viral Hepatitis Prevention Board (Europe)[10]

- Established in 1992, its first actions related to hepatitis B as an occupational risk, under the auspices of the Society for Occupational Medicine. Its aim was to eliminate transmission of hepatitis B in all workers at risk in the industrialised world.
- 1993: a second new initiative, the European Public Health Association, focused on hepatitis B as a community health risk
- 1994, 1995: Expanded to include hepatitis A and C
- 1996: Geographically expanded to cover countries of Central and Eastern Europe, Newly Independent States
- 1997: WHO deadline for integrating hepatitis B vaccination into national immunization programmes
- Oct 1998: French authorities temporarily suspended the widespread school-based adolescent hepatitis B vaccination programmes while continuing universal infant immunization programmes – multiple sclerosis scare
- 2000: focus on behavioural issues relating to hepatitis B immunization, review of economics of immunization
- March 2001: Meeting "How to research risk groups?" – Collaboration between CDC, CVP/PATH, GAVI, UNICEF and WHO.
- May 2002: WHO informal consultation "Public Health Challenges for controlling HCV infection". Also "Prevention of viral hepatitis in Italy: lessons learnt and the way forward". Italy as a model for successful control and evaluation.
- 2003: hepatitis B vaccination safety issues
- 2004: World experts gathered to review and present their long-term vaccine trial studies, long-term efficacy, booster policy, impact of HBV mutants on hepatitis B vaccination programs. They also met to discuss France. Interestingly the vaccination scare from 1998 is still having an impact on vaccine coverage.

Members include Dr Craig Shapiro (WHO Immunizations, Vaccines and Biologicals), and Dr Mark Kane (Consultant – cost-effectiveness, combination vaccines studies).

Current status with key players

Data on surveillance, incidence etc. (2005) is available on the WHO website[11]:

- According to the 2005 WHO report (Vaccine immunization strategy 2006-2009), the Global Advisory Committee on Vaccine Safety GACVS has continued to meet twice a year. Issues considered by the committee include the purported relationship

[10] Viral Hepatitis Prevention Board webpage http://www.vhpb.org/

[11] WHO "WHO vaccine-preventable disease monitoring system, 2005 global summary" (2005) http://www.who.int/immunization_monitoring/diseases/GS_Hepatitis.pdf

between hepatitis B vaccine and multiple sclerosis, which prompted a health scare in France in 1998

- From GAVI together with Vaccine Fund:
  "…by 2007 all countries with adequate delivery systems will have introduced Hepatitis B vaccine"

The focus is now on combination vaccines.

1.3. Vaccines

Summary of vaccine development (plasma to recombinant DNA) – *Notes largely from Mahoney 2005*[12]

1970s

Hepatitis B vaccines were first developed as a result of research conducted largely at the New York Blood Centre, by Dr Alfred Prince and Dr Barry Blumberg. Prince identified an antigen that would react with serum but not the virus in Korea in 1962. Merck took leadership in developing the first commercial plasma-derived hepatitis B vaccine. A number of other countries subsequently developed these vaccines, including France and China, and Korea (Cheil Sugar Co and Korea Green Cross Co). In India Shantha Biotech, a private firm also developed a hepatitis B vaccine in collaboration with the Indian government's department of Science and Technology.

Use was limited due to

- Lack of awareness of the true extent of the burden of disease caused by hepatitis B virus infection
- High price

1980s

Dr James Maynard, Dr Rich Mahoney, and Dr Alfred Prince formed the International Task Force on Hepatitis B Immunisation.

- They realised one of the first things they would have to do was to lower the cost of plasma-derived hepatitis B vaccine.
- They bought large quantities for use in developing countries.
- The first purchase resulted in the price of hepatitis B vaccine falling to less than $1 per dose. Cheil and Green Cross in Korea offered prices at this level.
- The International Task Force bought vaccine from both Cheil and Green Cross.
- The vaccine was used in demonstration immunisation programmes in developing countries.

"The effort to establish national immunisation programmes for hepatitis B began to see global success in the late 1990s. At that time the Bill and Melinda Gates

[12] Mahoney RT "Public-Private Partnership in the Development of the Hepatitis B Vaccine in Korea: Implications for Developing Countries" *Science, Technology and Society* (2005) 10(1): 129-140

Foundation made a contribution of $750m to establish the Global Fund for Children's Vaccines. A decision was made to allocate a substantial amount of these funds to the purchase of the Hepatitis B vaccine." (Mahoney 2005[13])

This enabled the reduction in price of a recombinant hepatitis B vaccine.

Vaccines now licensed:

- The two major yeast-derived hepatitis B vaccines that are licensed in most countries are Engerix-B (Smith-Kline Beecham 1992) and Recombivax HB (Merck&Co).
- India has developed an indigenous yeast-derived, recombinant DNA vaccine, Shanvac-B (Shantha Biotech 1997). At about US$14, Shanvac-B is within reach of the EPI.
- Hepatitis B vaccines can be combined with other vaccines such as BCG and MMR, Hib and DTP-polio. Smith-Kline Beecham offers a tetravalent DTP-HepB vaccine, and a combined hepatitis A/B vaccine.

Articles such as Usonis et al[14] (combined hepatitis A/B vaccine) and Zepp et al[15] (looking at GSK Biologicals' hexavalent DPTa-HepB-IPV/Hib vaccine) suggest that coadministration does not impair immunogenicity. FitzSimons et al[16] also find positive conclusions for status and likely impact of existing and potential new combined hepatitis B vaccines (Europe).

1.4. The Story of the International Task Force

Notes largely from Muraskin 1995[17]

The hepatitis B story is important as a key example of introduction of immunization programmes in developing countries. Because the delay between succeeding to make a vaccine available and succeeding to actually get it to the areas of the world which needed it least was finally tackled by the concentrated efforts of the Task Force Program,

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[13] Ibid.

[14] Usonis V, S Meriste, V Bakasenas, I Lutsar, F Collard, M Stoffel and N Tonieporth "Immunogenicity and safety of a combined hepatitis A and B vaccine administered concomitantly with either a measles-mumps-rubella or a diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis vaccine mixed with a *Haemophilus influenzae* type b conjugate vaccine in infants aged 12-18 months" *Vaccine* (2005) 23(20): 2602-2606

[15] Zepp F, M Knuf, U Heininger, K Jahn, A Collard, P H Habermehl, L Schuerman and R Sanger "Safety, reactogenicity and immunogenicity of a combined hexavalent tetanus, diphtheria, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and *Haemophilus influenzae* type b conjugate vaccine, for primary immunization of infants" *Vaccine* (2004) 22(17-18): 2226-2233

[16] FitzSimons D, G Francois, N Emeroglu and P Von Damme "Combined Hepatitis B vaccines" *Vaccine* (2003) 21(13-14): 1310-1316

[17] Muraskin W *The war against Hepatitis B: A History of the International Task Force on Hepatitis B Immunization* (Philadelphia: University of Philadelphia Press, 1995)

hepatitis B immunization has become a reference point ("we don't want to see the 10-15 year lag that we saw with hepatitis B and Hib") for other immunization strategies.

Key elements of the innovation strategy (as described in Mahoney and Maynard 1999[18]) were:

1) Defining burden of disease and computing cost effectiveness
2) Conducting demonstration programmes in developing countries
3) Building global and national consensus for use of the vaccine
4) Stimulating competition among manufacturers to reduce prices
5) Stimulating the creation of international procurement funds for vaccine purchase.

> "The task force was able to defend the scientific legitimacy of the new Asian 'cheap' vaccines, while simultaneously working to convince Western manufacturers to accept low (unit) profits in a massive lower-class market rather than to seek high (unit) profits in a restricted elite market." Muraskin (1995)

Hepatitis B vaccines available internationally:

Manufacturer	Brand name*	Country	*Type*
Centro de Ingenieria Genetica Y Biotecnologia	Enivac-HB	Cuba	Recombinant DNA
Chiel Jedang	Hepaccine-B	South Korea	Plasma derived
Korea Green Cross	Hepavax B	South Korea	Plasma derived
Korea Green Cross	Hepavax-Gene	South Korea	Recombinant DNA
LG Chemical	Euvax B	South Korea	Recombinant DNA
Merck Sharp & Dohme	Recompivax H-B-Vax II	United States	Recombinant DNA
Merck Sharp & Dohme	Comvax	United States	Combined Hib and (recombinant)
Pasteur Mérieux Connaught	Genhevac B	France	Recombinant DNA (mammalian cell)
SmithKline Beecham	Engerix-B	Belgium	Recombinant DNA
SmithKline Beecham	Twinrix	Belgium	Combined hepatitis A and B (recombinant)
SmithKline Beecham	Tritanrix-HB	Belgium	Combined DTP and recombinant
SmithKline Beecham	Infanrix-HB	Belgium	Combined DTP (acellular P) and HB (recombinant)
Swiss Serum and Vaccines Institute	Heprecombe	Switzerland	Recombinant DNA (mammalian cell)

Numerous producers who sell only in country of production are not listed. Presence on this list does not imply endorsement of these products by the World Health Organization.

* Brand names may vary in different countries.
Abbreviations: DTP, diphteria, tetanus and pertussis; HB, hepatitis B; Hib, *Haemophilus influenza* type b.

From: Mahoney FJ and Kane M. Hepatitis B vaccine. In: Plotkin SA and Orenstein WA, eds. Vaccines, 3rd ed.

Context in which the International Task Force developed:

It followed the failure of vertical programs in general, and campaigns against fighting smallpox that initially failed (1959, 1967).

[18] Mahoney R and J Maynard "The Introduction of New Vaccines into Developing Countries" (1999) *Vaccine* 17 (7-8): 646-652

1974: The EPI program (Expanded Program on Immunization) was a vertical program with a major difference. Establishment of a permanent vaccine delivery system in the nations of the developing world has been its dedicated goal. It laboured carefully and cautiously to encourage countries in the developing world to establish their own national EPIs. The international EPI did not have the resources or the mandate to create its own centralized system. Rather, its job was to persuade local elites of the need for vaccination, then to train cadres of workers (at the international, regional, and national levels) who could establish and maintain a vaccine delivery system.

1982: UNICEF made a forceful entrance into the health field by declaring "the Children's Revolution" and proceeding to champion a series of health measures, thus infringing on an area that up to then had been the province of WHO, which was bound to cause conflict.

The growing national EPI infrastructures suggested the possibility that new vaccines could be quickly added to the network as they were developed.

Main players in the Task Force on Hepatitis B Immunization:

- WHO, EPI, UNICEF were the key international players that had to be won over for universal hepatitis B vaccination to become a reality.
- Other important players included the Task Force for Child Survival, the Rockefeller Foundation, USAID, Rotary International and the foreign aid agencies of Canada, Australia and Japan – to name just a few of the most prominent government donor groups.

The Task Force itself was Drs Alfred Prince, James Maynard, Ian Gust, and Richard Mahoney.

1.5. Model Case: Indonesia

Timeline

1984: PATH initially entered the hepatitis field in Indonesia. It found that most of the big pharmaceutical companies had already demonstrated an interest in either exporting vaccine or transferring the technology to produce it to Indonesia. (Merck, Pasteur, SmithKline) and smaller companies (Korean Green Cross Corporation = KGCC, Biotech Corporation of Singapore, the Dutch Red Cross)

1987: The Task Force recommended to the Indonesian government that a sealed international bid and tender be set up that would allow all hepatitis B vaccine manufacturers registered in Indonesia to compete for the contract to supply the vaccine.

April 1991: Nationwide adoption of a Modified Immunization Program

The model program was so successful that the Indonesian government announced its intention to institute universal hepatitis B immunization throughout Indonesia. However

the government did not follow through on the model project's commitment to give newborns the first shot in the home within seven days after birth – feeling that the hamlet/home-level extension was too expensive.

Reasons for initial choices

The Model Project for the Task Force, chosen by the McDonnell Foundation. Richard Mahoney and PATH had been investigating the possibility of local production of hepatitis B vaccine there since the Minister of Health had raised the issue of liver cancer to them in 1984.

Given that hepatitis B vaccination had to occur in the first week of life, it was hoped that not only would the model project inspire the local government to institute a nationwide program but also influence nearby countries to establish them as well. It was necessary to be very sensitive to the indigenous culture, especially the political system.

- Indonesian society's commitment to hierarchy was so deeply ingrained that initiatives from the top were more likely to motivate villagers to cooperate than popular education or direct appeals to the people.
- The Task Force could, and did, continue to stress community outreach, but it substituted educating and persuading the local political leadership as its top priority.
- The Indonesian model also reinforced the Task Force's belief that a successful program required finding a national champion, who would support the project against competitors and detractors. In Indonesia that role was played primarily by the Minister of Health (backed by the President of the Republic).

Lessons learnt – the possibility and 'politics' of local production

In trying to reach agreements with local producers, some difficulties occurred. For example, in Indonesia (with Dr Lembong, Director and President of PT Pharos, Indonesian Pharmaceuticals Company) the following issues came up:

- Question of the recombinant or plasma-derived vaccine.

  Lembong thought that Indonesia should bypass the plasma-derived vaccine and use Merck's new recombinant DNA vaccines. However, by October 1985 Mahoney was convinced that recombinant DNA vaccine was totally impractical for Indonesia. Further, the new quality control standards being discussed by the WHO would make even the first phase of production – the importation of bulk vaccine with local bottling and quality control – impossible.
- PATH's grant from USAID specifically forbad any government involvement in ventures their money funded.

  Lembong believed PATH to be a private money-making organization.
- The culture was not used to the type of entrepreneurship being suggested by the Initiative.

  Lembong had difficulty in understanding how increasing competition to improve quality and fair pricing would be beneficial for the company, as it involved a direct relationship with its competitors.
- Conflict of interest between pharmaceuticals companies

Lembong had deep personal ties to Merck. This was a potential problem particularly with PATH focussing on Cheil Sugar Co.

Benefit of a local intermediary

- PATH (Leona D'Anges in Jakarta) had a close relationship with one of Kalona's key advisors, Dr Anton Widjaya.
- This was very useful as he could act as a conduit for information from PATH to the proper officials, whilst simultaneously working to smooth over conflicts and interpret communication in a way that harmonized the two groups.
- However, the fact that Widjaya was representing both the government and PATH/the Task Force caused some conflict. Given that Widjaya's credibility depended on his primary loyalty to the Ministry of Health, PATH had to be very careful.

Lessons – vaccine price

The problem of getting Cheil to pledge itself to $1 per dose, a price favoured by the Task Force and PATH-Seattle, initially caused a great deal of consternation in the local PATH office in Jakarta.

- PATH had spent a great deal of time and effort setting up the relationship between Cheil and the pharmaceutical entrepreneur Kalona.
- An agreement had been reached that he would first import and later locally produce hepatitis B vaccine. The price would be lower than existing prices, but still substantial enough to be affordable only for the growing middle class.
- The Task Force's talk of $1 per dose threatened to undercut the market for such a venture, and Kalona made it clear that he did not look favourably on such Task Force involvement in Indonesia.

Sealed bid and tender system

- This was seen as a formality for most members of the Task Force, as Cheil would of course underbid everyone else, though it would establish a reasonable procedure for other countries.
- It was also expected that the bigger companies might not compete, as a representative of SmithKline stated that his company would be embarrassed to lose to a Korean manufacturer.
- However, the bid and tender attracted many companies (Western and Asian) including SmithKline, and all offered prices considerably below what they had previously sold for.
- Surprisingly, the lowest bid did not come from Cheil but from its chief competitor KGCC, who offered to supply the vaccine at $0.95 per dose.
- When Chairman B.C. Lee of Samsung (who owned Cheil) made his $1 dose offer, it was based on the assumption that it would require his personal subsidy to achieve the low price.
- KGCC's offer was a straight-out profit making $0.95. In addition, KGCC was willing to commit to provide the vaccine at the same price to other public sector agencies for similar quantities.

The implementation procedure

- There existed a core of deeply committed physicians on the island (Soewigno, the Health Minister and Widjaya etc) who had a long-term interest in hepatitis B.
- Lombok was an island with a population of 2.3m, 40% of which could not read Bahasa Indonesian, the national language; 90% births occurred at home and the vast majority of birth attendants were illiterate.
- Each province was headed by the Provincial Governor, the district was then headed by a Bupati, the subdistricts headed by the Camat and the village head was a respected man (not always a government employee).
- The Indonesian Village Women's Movement (PKK) played a vital role in the delivery of EPI vaccines.
- By law all births had to be officially registered within 48 hours – but in practise only 40-50% were registered.
- The health system was built around 48 stationary centres that delivered a wide range of services, including outreach services to villages periodically.
- Around 10% of the population were hepatitis B carriers. 20-30% of transmission occurred between mother and child, the rest via horizontal transmission between children.

Lessons learnt from procedure (education and PKK)

- Education materials included brilliantly composed drawings and local language.
- However, it transpired that because, for example, there is no standard Sasak lexicon, the meaning of text could be radically misinterpreted, even to the extent that the slogan could be read as "Don't Immunize" your child.
- PATH's first response was to shift the use of booklets away from parents and towards hamlet leaders, their wives, and PKK. There was considerable expense spent on the booklets.
- PATH eventually found that television was a good medium for reaching the population because despite the lack of widespread private ownership, large numbers of people had access to the sets that did exist.
- The PKK required incentives to do the work, and even with these incentives it appeared to have limited capability in carrying out the program. However due to the nature of the political hierarchies in Indonesia the problem had to be dealt with very diplomatically.
- PATH supplemented the system unofficially, getting hamlet chiefs, parents and traditional birth attendants to fill the gaps.

1.6. Other Cases

Attempts in China

Nakajima (Japanese) offered to transfer the technology to China.

- Maynard and Gust, and Umenai and Nakajima (two Japanese scientists), were all engaged in 'Kissinger-style' shuttling to and from China.

- The transfer entailed 50-100 visits by consultants over a five-year period. Nakajima arranged for Japan's Kitasato Institute to give the technology to China essentially cost-free and he raised the money for this venture from the Arab Gulf Fund, a WHO donor.
- For the Japanese, the transfer was a form of foreign assistance which helped establish a good reputation for Japanese products and technology in China.
- China set up five different vaccine-producing centres and by 1991 had produced 22m doses of vaccine.

But was the China case flawed?

- There were 5 centres for vaccine production, but the mechanisms were faulty. They could not produce sufficient vaccine for universal childhood vaccination. They could not effectively distribute.
- Hepatitis B manufacturing became a victim of China's movement to privatize pharmaceutical and health care services. It was the first infant vaccine that was not provided free of charge to all Chinese children. The production centres needed more money from the government to increase efficiency and quality. Instead the money came in the form of a loan from the Bank of China, and costs had to be met by charging a higher price than most rural Chinese could afford. In addition, with the privatization of health delivery, there was an entrepreneur not a 'barefoot doctor' – who had to be paid for services giving any new vaccine.

  "Thus the vaccine sat on the shelf for lack of an effective market."[19]

  Also, the manufacturing centres experienced major problems in production which reduced the efficacy and consistency of the vaccine, significantly impeding the fight against the epidemic.

Thailand

Thailand was a second model program for Hepatitis B immunization.

- It was more complex than expected due to scientific and government 'politics'.
- Although the Task Force achieved a major victory as the government agreed to institute a nationwide immunization program, it also suffered a great defeat as its efforts to transfer the vaccine technology collapsed.
- This was due to a poor choice (although this was only possible to see in retrospect) in using the Thai Red Cross as an institutional vehicle. The Thai Red Cross had already negotiated a hepatitis B vaccine with the Dutch.

Philippines

The launch in the Philippines is a good example of the precariousness of cooperation between WHO and the Task Force.[20]

Difficulties with big pharma

The Task Force also suffered some difficulties from the large pharmaceuticals companies, for example an attack from SmithKline, citing its attempt to impugn the safety and

[19] Muraskin "The War Against Hepatitis B: A History of the International Task Force on Hepatitis B Immunization", chapter 2

[20] For detail, see Muraskin, ibid.

efficacy of the Cheil and Korean Green Cross Vaccines. Rivalry between the pharmaceuticals companies was not uncommon. For example at this time Pasteur and Merck in Europe were engaging in activities to undermine each other, playing on public fear of AIDS.

- When SmithKline entered the market producing recombinant DNA vaccine, several members of the Task Force reacted favourably as the company seemed to be aiming for a potentially limitless mass market (not the middle class).
- However, there was a downside to this, as SmithKline became very aggressive towards its competitors.
- SmithKline also attacked the plasma-derived vaccine (Merck produced both).

1.7. More Recent Case Studies

India as a possible more recent case study for DNA recombinant vaccine[21]

- In India, there is an estimated pool of 42 million HBV carriers and 60-80% HBV-mediated hepatocellular carcinoma.
- Shantha Biotech, Hyderabad, introduced the first indigenously prepared genetic recombinant hepatitis B vaccine, called Shanvac B in India. Several other manufactures in India have also successfully produced and marketed their genetic recombinant hepatitis B vaccines.
- Objections from the health care professionals in India (also applicable to other low-income, intermediate-endemicity countries) include the range of estimates from data on carrier rates. There is concern that the vaccine may not be cost-effective in populations with lower carrier rate, and also that the coverage rate for vaccines in the existing national immunization program may be much lower than is claimed.
- They also question the WHO immunization schedule beginning a few weeks after birth (this is supported by the evidence and literature from China in particular which emphasized the importance and effectiveness of a vaccine given within 24 hours especially when dealing with mother-baby transmission). Aggarwal et al (2003) comment:

  > "In fact, we believe that our analysis underestimates the beneficial effect of the HB immunization programme."[22]

China, recently cited by GAVI as an immunization success story[23]:

- Launched in 2002. A US$76m project co-funded in equal parts by the China Ministry of Health and GAVI.

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[21] Vijayakumar V, R Hari, R Parthiban, J Mehta and SP Thyagarajan "Evaluation of immunogenicity and safety of Genevac B: a new recombinant Hepatitis B vaccine in comparison with Engerix B and Shanvac B in healthy adults" *Indian Journal of Medical Microbiology* 22(1): 34-38

[22] Aggarwal, Ghoshal and Naik "Assessment of cost-effectiveness of universal hepatitis B immunization in a low-income country with intermediate endemicity using a Markov model"

[23] GAVI, Chinese Ministry of Health, UNICEF and WHO "An Immunisation Success Story: Stopping Deadly Hepatitis B in China" http://www.gavialliance.org/resources/GAVI_China_en.pdf

- Government of China, GAVI Alliance, provincial governments, WHO, UNICEF, and CDC were involved
- Three-dose series serves 6m newborns every year, which is one third of births in China. By 2003 more than 90% of infants in the eastern and middle provinces had been immunized against hepatitis B and over 80% newborns had received a timely birth dose.
- In total the programme has reached nearly 70% newborns with the full hepatitis B vaccine series, up from 47% in 2002. It has also purchased and distributed 145.6m autodisable (AD) syringes.

  As GAVI comments:

  > "The China Ministry of Health/GAVI Hepatitis B Vaccination Project is saving lives in China's poorest and most remote regions, through an unprecedented effort that has mobilized health workers, midwives and mothers. With support from the GAVI Alliance, 11.1m infants have been immunized in three years in the poorest provinces of China, raising the nation's hepatitis B vaccine coverage which was 60% in 1999 to >90% today."[24]

Challenges:
Most progress has been made in hospitals, where more than 90% babies born receive their hepatitis B vaccine dose at birth. More than 1m babies born at home are not receiving the important birth dose (when given within the first 24 hours of life it is 95% effective in preventing virus transmission from infected mothers to their newborns).

1.8. Economic Evaluations

Economic evaluations seem mostly to cover countries of low to medium endemicity. A study by Beutels (2000[25]) highlights interesting issues from looking at methodology:

> "Simulation models unveiled the hidden chronic part of the disease and demonstrated that in the long run vaccination against it could be relatively cost-effective…On the other hand, the wide range of cost-effectiveness ratios coming from these analyses has raised suspicion about the validity of economic evaluation among a number of policy makers."

Methodology
- The study highlights discounting as a main unresolved methodological issue in economic evaluation.
- It also demonstrates a range of other assumptions – for example in countries with high endemicity (southeast Asia, the Pacific Basin, the Amazon Basin, sub-Saharan Africa, China, the Asian countries of the Newly Independent States, the

[24] Ibid.
[25] Beutels P "Economic evaluations of Hepatitis B immunization: A Global Review of Recent Studies (1994-2000)" *Health Economics* (2001) 10(8): 751-774

Arctic Rim, parts of the Middle East and some countries of Eastern Europe) HBV carrier rates range from 7% to 20% and prevalence of HBV markers from 70% to 90%.

- It looks at studies mostly on countries of low to medium endemicity.
- This of course to some extents highlights different issues, since certain factors influencing choice of vaccination procedure are of relevance – such as the question of DNA recombinant vaccines rather than those of a lower price, a higher age of vaccination, and the effect of treatment costs such as liver transplants on cost analyses.
- Even for studies of the same, low-endemicity country, there can be a divergence of results. This is due to differences in underlying assumptions and methodologies.
    - Incidence
    - Disease progression after infection
    - Costs and coverage of vaccination
    - Vaccination effectiveness and duration of vaccine protection
    - Discount rate
    - Time span
- Sensitivity analyses indicated that vaccination costs, discount rate and vaccination effectiveness had the largest impact on the cost-effectiveness.

  "Univariate sensitivity analysis should at least be complemented with bivariate sensitivity analysis of vaccination costs and discount rate (of health gains) for varying time span."
- No cost-utility analyses (health gains expressed in natural units adjusted for quality, like QALYs) were found in the Beutels search criteria – only cost-effectiveness and cost-benefit analysis. This may be because the additional information attained by using the values of quality weights for health gains obtained through intervention is out of proportion compared to the effort required to determine these values accurately.
- This may not be the case when qualifying health gains and losses for other disease, although the accuracy of values may remain a concern.
- There were difficulties in comparing cost-effectiveness analyses since effectiveness is expressed in a range of ways – infections prevented, carriers prevented, deaths averted, life-years gained – making it difficult to compare CERs. *We should be aware of this for TB, although there have been few cost-effectiveness studies – tradeoff between standardised methodology and most appropriate/efficient? This is the 'end-point' issue again.*
- Most analysis do not account for other indirect costs such as loss of work, human suffering and travel costs. In fact many studies do not even acknowledge these factors. *We should be aware of these.*

Modelling differences

- In a 'dynamic model' the force of infection can change with time as a function of the proportion of infectious people in the population. A dynamic model will cyclically recalculate the force of infection over time. However, this is difficult to construct and requires data on virus transmission.

- In a 'static model' the force of infection over time remains constant. It cannot include impact on the risk of infection and herd immunity. With a static model, CER and BERs are independent of vaccine coverage. Static models can be seen as a pragmatic alternative, but we need to be aware of limitations. Documents such as Edmunds et al (1996)[26] discuss other limits of the static model such as age shift and transmission dynamics.
- The modelled impact of HBV vaccination is extremely sensitive to discounting. Despite the range of possible discount rates, normally analyses stick to a discrete value (0%, 3%, 5%).

Suitable modelling techniques

- It is necessary to question the relevance of static versus dynamic modelling techniques.
- Beutels here argues that for HBV a static model could be accepted for universal vaccination but not targeted vaccination (whereas a static model could suffice for influenza vaccination for the elderly but probably not for universal vaccination)
- Aggregate analyses of vaccination against several infectious diseases are likely to become more relevant as producers now focus more on combined vaccines – an analysis of just one of the components in a combined vaccine may become too much of an over-simplification.
- Bi- and multivariate sensitivity analyses should be standard practice, because of the multitude of uncertain parameters.
- Threshold analysis also seems important to improve the credibility of potential savings of vaccination.

> "Once there are savings by preventing morbidity and mortality, it should not matter for the decision how great the savings really are… it seems more usual for vaccinations to be cost-saving than it is for economic evaluations of vaccinations to be truly credible to decision-makers."[27]

Application to countries with high endemicity

Cost-benefit analysis for China found universal vaccination to be very cost-saving[28] and a study in Gambia[29] also concluded that HBV vaccination would be cost-saving. Hall et al[30] argue against the discounting of effects in countries like the Gambia because HBV mortality affects primarily the economically active part of the population with an important function in society:

> "Within the framework of a static closed cohort model this argument is similar to the use of an age-weighting function, as in the disability-adjusted life-year (DALY) approach. However, in the DALY approach, life-years gained are discounted on top

[26] Edmunds WJ, GF Medley and DJ Nokes "The transmission dynamics and control of hepatitis B virus in the Gambia" *Statistical Medicine* (1996) 15(20): 2215-2233

[27] Beutels "Economic evaluations of Hepatitis B immunization: A Global Review of Recent Studies (1994-2000)"

[28] Liu ZG, SL Zhao and YX Zang "Cost-benefit analysis on immunization of newborns with hepatitis B vaccine in Jinan City" *Chinese Journal of Epidemiology* (1995) 16(2): 81-84

[29] Hall AJ, RL Robertson and PE Crivelli "Cost-effectiveness of Hepatitis B vaccine in the Gambia" *Transactions of the Royal Society of Tropical Medicine and Hygiene* (1993) 87(3): 333-336

[30] Ibid.

of being weighted for six disability classes and for age, so that the implicit 'end weights' differ greatly from the suggestion made here."[31]

There has also been a study applying the same cost-data to a dynamic simulation model (WJ Edmunds, Medley 1997) which confirms largely the study by Hall et al.

Decision making

Economic evaluation is of course only one of the factors influencing policy decision making – medical, epidemiological, practical, historical and ethical considerations, pressure from interest groups and the public's perception are cited here as other important elements. As Beutels comments, in high endemic countries the main difficulty policy makers face is not simply a lack of awareness of the disease burden, but rather whether programmes for vaccination deserve priority over other highly cost-effective interventions, how much it would cost to sustain it, and who would be willing to pay for it:

> "It seems to me that [economic evaluations] primarily role has been to justify an existing opinion, rather than to form (or to change) opinions."[32]

1.9. Political Evaluation/Advocacy

Specific Problems with Hepatitis B

From PATH (Scott Wittet on lessons learned in advocacy, communication, training[33]): hepatitis B can often be confusing because

- People become confused between hepatitis B and other forms of hepatitis.
- Because of jaundice. Hepatitis B is not the only cause of jaundice – the vaccination does not always prevent jaundice.
- Hepatitis B can cause liver cancer many years after immunization – this can sometimes make the benefits of infant immunization less clear to some parties.
- Hepatitis B is transmitted in many ways. In some countries, hepatitis B is transmitted to children when they are very young but in others transmission occurs later in life, again causing parents to question the necessity of immunizing a young child.
- There is confusion over whether adults need to be immunized – this answer "depends on evaluation of specific risk in the area".
- Some health care providers are not aware that WHO recommends that all infants receive hepatitis B vaccine.

Gauri and Khaleghian (2002) comment:

> "Now is the time to give the 'Polio Troops' a new mission in countries where National Immunisation Days are now phasing out. No-one has been more successful than the Polio Eradication Initiative in mobilizing communities for health."[34]

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[31] Beutels "Economic evaluations of Hepatitis B immunization: A Global Review of Recent Studies (1994-2000)"

[32] Ibid.

[33] Children's Vaccine Program "Hepatitis B Vaccine Introduction: Lessons Learned in Advocacy, Communication and Training" (2001) at http://www.path.org/vaccineresources/files/CVP_Occ_Paper4.pdf

Examples of differences in systems required for successful programs

- In Lombok, the **Indonesian** government experimented with systems for birth reporting and for delivery of hepatitis B vaccine within the first weeks of life. Due to changes in the roles and responsibilities of various staff, special training was required throughout the project area. Also in Lombok, research indicated that parents had lower levels of education and held many traditional (non-medical) beliefs about disease causation – therefore government messages were kept simple and focused on parental behaviour rather than on scientific information.
- In **Sri Lanka** the Ministry of Health used this association by placing an amulet on a national vaccination poster.[35]
- In the **Philippines** fewer systematic changes were envisioned, so extra training was not needed. Instead, the Department of Health made sure that hepatitis B information was disseminated through in-house publications and that it was discussed at staff meetings and regional and national conferences.

A study of the integration of hepatitis B vaccination into national immunization programmes[36] in **Europe** also highlights some interesting issues, referring to:

- The weakness of social commitment to preventative medicine and vaccines.[37]
- The lack of medical and public awareness:

  "The public does not perceive hepatitis B as a threat to the population at large, and governments, expected to respond to public demand, have not considered hepatitis B prevention as a priority and have opted for selective prevention strategies."[38]

Problems with attempts to target high-risk groups, the strategy used in low-endemicity countries since 1982: Most high-risk groups are difficult to access. There is a lack of perceived risk among those at risk; and over 30% of those with acute hepatitis B infection do not have identifiable risk factors.

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[34] Gauri V and P Khaleghian "Immunization in Developing Countries: Its political and organizational determinants" *World Development* (2002) 30(12): 2109-2132

[35] Gauri and Khalegian "Immunization in Developing Countries: Its political and organizational determinants"

[36] Van Damme P, M Kane and A Meheus "Integration of hepatitis B into national immunization programmes" *British Medical Journal* (1997) 314: 1033

[37] Citing Francis DP "The Public's health unprotected – reversing a decade of underutilization of Hepatitis B vaccine"

[38] Van Damme, Kane and Meheus "Integration of hepatitis B into national immunization programmes"

2. PNEUMOCOCCAL VACCINE CASE DETAILS

Summary

The pneumococcal vaccines currently available have been aimed at the Western industrialized world, despite the global burden of disease Both the 23-valent and 7-valent vaccines licensed in the US and Europe have demonstrated high levels of efficacy and herd immunity benefits. However vaccine development specifically for under-developed countries has been limited.

The factors that have limited the vaccine development for poorer countries are:

(**Demand-side Problems)**

- Poor estimates of disease burden. This is partly due to the difficulties in identifying *S. pneumoniae* as the cause of an illness when health workers are used to treating many variants of pneumococcal disease, and also due to a limited amount of emphasis on political agendas and from the general public.
- The burden of diseases such as HIV and malaria often also being a large health problem in those countries suffering a large pneumococcal disease burden. The current 7-valent vaccine does not offer significant protection for children that are HIV-positive, and also cannot significantly benefit HIV-positive people through herd immunity. Therefore, the demand for a pneumococcal vaccine has not been the most important of priorities in these countries.

(Supply-side Problems)

- **Manufacturers** Wyeth-Lederle and sanofi pasteur originally developed and produced conjugate vaccines for the developed world only, despite evidence of the different serotypes prevalent in Asia and Africa. Several manufacturers have developed conjugate vaccines more suitable for developing countries (notably containing serotypes 1 and 5) but the first to reach licensing is expected in 2010.
- **GAVI and WHO.** Although international organisations have emphasised the burden of pneumococcal disease, and the **Bill and Melinda Gates Foundation** has made a significant contribution to GAVI for use in the **PneumoADIP**, there is a tendency to tag pneumococcal disease onto Hib as there is much overlap between the two. Therefore, *once several countries have made the decision or been influenced to adopt Hib immunization into national programs, there will be more of an indication of how pneumococcal vaccines should be launched*.

This document describes the history of the pneumococcal vaccine and its use in both Western and developing countries. It goes on to explain the recent developments in efforts to accelerate the introduction of suitable (higher-valent) vaccines into developing countries, particularly with reference to the PneumoADIP and the recent AMC proposal. It does not however critique the AMC proposal in detail, focusing more on the 'story' of the development of the vaccine and its launch.

2.1. Introduction

From 1974 to 1990, coverage of developing countries with the six EPI vaccines increased from 5% to about 75% of children. In spite of much recent boosting in expenditure, current levels are only a few percentage points higher than 1990, at about 78%, and coverage remains highly variable with low levels particularly in a range of developing countries. For example, according to WHO/UNICEF figures from 2005, coverage is still below 50% in some sub-Saharan African countries including Ethiopia, Niger, Chad, Angola and Nigeria (only 38% EPI coverage). Progress in improvements in child health care has been further hindered by a lack of vaccines that prevent childhood pneumonia,[39] which along with deaths related to diarrhoea is one of the biggest causes of child mortality. It is only since 2000 that the burden of pneumococcal disease and its high impact on child mortality rates has been truly acknowledged and emphasis has been put on completing vaccine development for higher-valent conjugates.

Pneumococcal vaccines were originally developed and licensed in the US. The process in fact took several decades as the discovery of penicillin significantly reduced the perceived disease burden (until a new pathogen increased the incidence of pneumonia and forced recognition that penicillin was not sufficient[40]). Neither the 23-valent polysaccharide vaccine licensed in the US in 1983 or the 7-valent conjugate vaccine licensed in 2000 (both also licensed in the EU) were aimed at developing countries, although the acknowledged differences in disease burdens and prevalence of different strains for indigenous populations in developed countries did have some effect on the development of the vaccines.[41] The 7-valent vaccine is generally not deemed suitable for use in developing countries, despite a presentation from Wyeth in February 2006 indicating that Prevnar (Wyeth) helps provide more coverage than previously thought. Prevnar is marketed as Prevenar internationally, with an independent subsidiary company

[39] Shann S and S Steinhoff "Vaccines for children in rich and poor countries" *Lancet* (1999) 354: 7-11
[40] Butler J, E Shapiro and G Carlone "Pneumococcal Vaccines: History, Current Status, and Future Directions" *American Journal of Medicine* (1999) 107(1A): 69S-76S
[41] Menzies R and P McIntyre "Vaccine preventable diseases and vaccination policy for Indigenous Populations" *Epidemiological Review* (2006) 28(1): 71-80

created by Wyeth for example in India for the vaccine launch on June 30th 2006.[42,43] Prevnar is often referred to as the first 'blockbuster' vaccine, creating revenues of US$1bn in 2004, a first in the history of vaccines.[44] Some suggest that Prevnar has transformed the vaccine business as the price for a routine paediatric vaccine has jumped

> "…from a few dollars in the 1980s to over $200 for Wyeth's blockbuster vaccine Prevnar…"[45]

According to Pediatric Oncall, the 7-valent vaccine has coverage of more than 90% of serotypes in the USA, 75% in Europe, 51% in India and 45% in Pakistan. Similar figures with a 9-valent vaccine are 71% in India, 30% in Dhaka (Bangladesh) and 61% in Pakistan. For an 11-valent vaccine the figures are 75% in India, 51% in Dhaka & 61% in Pakistan. Hence for good global coverage, at least a 9- or 11-valent vaccine is required.[46] There have been some concentrated efforts to develop multivalent vaccines, as stated on the WHO Initiative for Vaccine Research website:

> "New conjugate vaccines that provide more optimal serotype coverage in (developing) countries are in clinical development, including a 9-valent Wyeth vaccine, and an 11-valent GSK and Sanofi-Pasteur vaccines."[47]

However, there have been some changes in the vaccine supply environment, as noted in the April 2006 report from the PneumoADIP – 9-valent, 11-valent and 7-valent vaccines that had been under development have been discontinued. Notably, GSK decided to focus purely on its 10-valent vaccine. This is the next multivalent conjugate vaccine that will be available. GSK filed for review by the European medicines Agency in January 2008, and PneumoADIP predicts developing country access in 2010.[48]

It has been suggested that if manufacturers had focused on creating a pneumococcal vaccine suitable for both developed and developing countries from the start, revenue gains could still have been significant. Instead the capacity to supply to developing countries was not in place and therefore the factors encouraging price discrimination and a more suitable scale to market the vaccine to developing countries (notwithstanding the high costs of technology) were also not in place. Not only were supply factors not considered in a more suitable framework for creating a vaccine for both developed and developing countries, the serotype coverage that had previously been documented was not taken into account:

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[42] Pharmabiz Article, June 30 2006, Mumbai
http://www.pharmabiz.com/article/detnews.asp?articleid=34049&sectionid=45

[43] Reuters Company Overview
http://stocks.us.reuters.com/stocks/fullDescription.asp?symbol=WYE.N&WTmodLoc=InvArt-L1-MarketView-3

[44] Gillis J, "Lives lost as vaccine programs face delays" *Washington Post* (December 2005)
http://www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069_pf.html

[45] Sheridan C "The business of making vaccines" *Nature Biotechnology* (2005) 23: 1359-1366

[46] Pediatric Oncall, Child Healthcare (for doctor reference) 2006

[47] WHO Initiative for Vaccine Research website
http://www.who.int/vaccine_research/diseases/ari/en/index5.html

[48] GAVI and World Bank "Framework Document: Pilot AMC for Pneumococcal Vaccines" (9 November 2006) http://www.vaccineamc.org/files/Framework%20Pneumo%20AMC%20Pilot.pdf p18

> "In 1980 before the 23-valent polysaccharide vaccine was formulated, serogroups 1 and 5 were considered essential in vaccines for use in Africa."[49]

However, the 23-valent PS vaccine was licensed, along with the 7-valent Wyeth conjugate vaccine, before higher-valency conjugates. Further, Wyeth initially had problems in expanding the manufacturing procedure to supply the vaccine, perhaps limiting interest and ability to alter the manufacturing process to allow for higher-valent vaccine production:

> "The company initially underestimated demand and has struggled to expand a complex manufacturing procedure… Wyeth's critical supply decisions had already been made by the time GAVI funded a $30m program at John Hopkins University to accelerate the introduction of Prevnar or a similar vaccine to poor countries."[50]

This funding from GAVI and the Vaccine Fund was given in 2003.[51]

In February 2007 a public commitment was announced by the UK, Canadian, Russian, Italian and Norwegian governments to fund a pilot Advance Market Commitment for vaccines, with pneumococcal disease as the example chosen.[52] According to the Pilot AMC Proposal (World Bank and GAVI September 2006), pneumococcal disease was chosen as the most suitable candidate as not only is there an increasing awareness of the disease burden and concern about growing antibiotic resistance (especially in the context of possible influenza pandemics), but there is also a "robust pipeline" of vaccines,[53] and testing and production capacity for these vaccines will be limited without financial support. These vaccines also fit into the existing delivery systems. However, there is some concern over the fact that the "robust pipeline" is becoming more limited than originally indicated, with three of the multinational pharmaceutical companies with higher-valency conjugate vaccine candidates in Phase III discontinuing the development of these products.

2.2. The Disease

Invasive pneumococcal infections include pneumonia, meningitis and febrile bacteria; among the common non-invasive manifestations are otitis media, sinusitis and bronchitis. Young children and the elderly are the most susceptible to severe pneumococcal disease. WHO estimates that up to 1 million children under five die each year due to

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[49] Greenwood et al "Pneumococcal serotypes in West Africa" *Lancet* (1980), cited in Gordon S, S Kanyanda, A Walsh, K Goddard, M Chaponda, V Atkinson, W Mulwafu, E Molyneux, E Zijlstra and M Molyneux "Poor Potential Coverage for 7-valent Pneumococcal Conjugate Vaccine, Malawi" *Emerging Infectious Diseases, CDC* (2003) 9(6): 747-749

[50] Justin Gillis "Lives lost as vaccine programs face delays" *Washington Post, December 2005* http://www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069_pf.html

[51] Johns Hopkins Bloomberg Public School of Health "Grant to Connect Kids with Lifesaving Vaccines" *The Gazette Online* (February 23 2003) 32(22) http://www.jhu.edu/~gazette/2003/17feb03/17grant.html

[52] GAVI Alliance Media Centre Press Releases http://www.gavialliance.org/Media_Center/Press_Releases/pr_amc_09feb2007_en.php

[53] "AMC Pilot Proposal" World Bank and GAVI under the guidance of Governments of Italy, Canada and the UK, September 2006

pneumococcal diseases, 90% of which occur in the developing world.[54, 55] In the developed world the burden of the disease tends to fall predominantly on the elderly:

> "Even in economically developed regions, invasive pneumococcal disease carries high mortality; for adults with pneumococcal pneumonia the mortality rate averages 10-20%, whilst it may exceed 50% in the high-risk groups. Pneumonia is by far the most common cause of pneumococcal death worldwide."[56]

Conditions associated with increased risk of serious pneumococcal disease include HIV infection, sickle-cell anaemia and a variety of chronic organ failures. In particular the incidence of pneumococcal disease among HIV-infected children has become a matter of concern following a study in South Africa which showed that over a 10 year period the incidence of pneumococcal disease doubled as the prevalence of HIV infection in children rose to around 6%.[57] As well as certain illnesses having a negative effect on incidence of pneumococcal disease, there have also been suggestions that there are racial disparities in incidence:

> "For years, African-American and Native Alaskan/American Indian children had rates of invasive pneumococcal disease several fold higher than that of white children in the USA. Vaccination has wiped out these health disparities and the incidence of disease is now the similar low rates in all groups."[58]

According to WHO, vaccination is the only tool available to prevent pneumococcal disease.[59] Other possible interventions are case management of pneumonia and zinc supplementation, as Edejer et al (2007) describe.[60] A recent study on the effects of zinc supplementation in Bangladesh in combination with Wyeth's Prevenar concluded that whilst a higher immunogenicity to some of the serotypes after zinc supplementation may have resulted in a more effective protection against the disease, the hypothesis is preliminary and requires more specific definitions of the role of zinc in efficacy of vaccinations in controlled trial environments.[61] The GAVI Investment Case for accelerating the introduction of pneumococcal vaccines into GAVI-eligible countries (October 2006) states further:

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[54] PneumoADIP "Pneumococcal Diseases" http://www.preventpneumo.org/diseases_vaccines/pneumococcal_diseases/index.htm

[55] PneumoADIP Press Releases "$US 1.5 Billion dollar commitment launches pilot Advance Market Commitment for pneumococcal vaccines" (9 February 2007) http://www.preventpneumo.org/pdf/PneumoADIP_AMC_9Feb07.pdf

[56] WHO Immunization, Vaccines and Biologicals WHO position paper *Weekly Epidemiological Record June 1999* http://www.who.int/wer/pdf/1999/wer7423.pdf.

[57] Karstaedt A, M Khoosal and H Crewe-Brown "Pneumococcal bacteremia during a decade in children in Soweto, South Africa" *Pediatric Infectious Diseases Journal* (2000) 19(5): 454-457

[58] PNEUMOADIP quoting B Flannery et al *JAMA* (2004), Hennesey TW et al *Vaccine* (2005) http://www.preventpneumo.org/diseases_vaccines/vaccine_health_impact/north_america.htm

[59] WHO Immunization, Vaccines and Biologicals, *ibid*

[60] Edejer T, M Aikins, R Black, L Wolfson, R Hutubessy and D Evans "Cost effectiveness analysis of strategies for child health in developing countries" *British Medical Journal* (2007) doi:10.1136/bmj.38652.550278.7C (published 10 November 2005)

[61] Osendarp S, H Prabhakar, G Fuchs, J van Raaij, H Mahmud, F Tofail, M Santosham and R Black "Immunization with the heptavalent pneumococcal conjugate vaccine in Bangladeshi infants and effects of zinc supplementation" *Vaccine* (2007), doi: 10.1016/j.vaccine.2007.01.001

"In the future zinc may be an important part of comprehensive approaches to preventing and treating pneumococcal pneumonia. However, it will likely be several years before enough data accumulates for this to happen."[62]

2.3. The Vaccine: Stages of Development

There are two types of vaccines currently licensed. Polyvalent PS vaccines contain, per dose, 25µg of purified capsular PS from each of the 23 serotypes of S.*pneumoniae* that together account for most cases (90%) of serious pneumococcal disease in Western industrialised countries.[63] Although these elicit relatively good antibody responses in healthy adults (60-70%) the immune response is mediocre in children less than two years of age and in immunocompromised individuals.

From the mid-1980s, several vaccine manufacturers have developed pneumococcal conjugate vaccines in which a number of *S. pneumoniae* polysaccharide vaccines are covalently coupled to a protein carrier:

"Conjugate vaccines elicit higher antibody levels and a more efficient immune response in infants, young children, and immunodeficient persons than the PS vaccines, as well as a significant immunological memory resulting in a booster antibody response on subsequent exposure to the antigen. Moreover, these vaccines suppress nasopharyngeal carriage of the pathogen and reduce bacterial transmission in the community through herd immunity, which adds considerable value to their implementation. Conjugate vaccines immunization followed by PS vaccine boosting might provide a foundation for lifelong protection against pneumococcal disease."[64]

The conjugate vaccine formulation currently licensed includes polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, 23F and oligosaccharide of 18C. Each saccharide is conjugated separately to a carrier protein, CRM-197, a non-toxic diphtheria mutant.
These 7 serotypes are the most common ones occurring in children in the US and in many other industrialized countries. The currently licensed vaccine, Prevnar, does not contain some of the serotypes that cause severe disease in developing countries, notably serotypes 1 and 5. New conjugate vaccines that provide more optimal serotype coverage in these countries are in clinical development, including a 10 valent GSK vaccine, and 13 valent Wyeth vaccine (currently at Phase II trials for high-risk individuals and adults >50, and Phase III trials for infants and children aged 6 months to two years). The GSK vaccine, Streptorix, contains serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F; and the Wyeth PCV 13 contains these 10 serotypes plus an additional 3 serotypes.[65]

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[62] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf p11

[63] WHO Immunization, Vaccines and Biologicals "State of the art of new vaccines: research and development" (January 2006) http://www.who.int/vaccine_research/documents/stateoftheart/en/index.html

[64] Ibid.

[65] GAVI and World Bank "Framework Document: Pilot AMC for Pneumococcal Vaccines" (9 November 2006) http://www.vaccineamc.org/files/Framework%20Pneumo%20AMC%20Pilot.pdf

Vaccine Status - Compiled from WHO IVR Status Table updated February 2006 and documents referenced

Vaccine	Manufacturer	Trial Stage	Details
Conjugate 7-valent	'Prevnar' Wyeth	Licensed; launched in 2000. Registered in >75 countries, including 5 GAVI-eligible countries (India, Indonesia, Pakistan, Honduras, Nicaragua)	Expected serotype coverage ~50% globally with regional variations[66]
Conjugate 9-valent	Wyeth	End of Phase III	Protein carrier used in CRM-197 "The 9-valent vaccine has been tested in South Africa with remarkable efficacy results in children <2, including HIV positive infants. In addition, an unexpected benefit of vaccination was the decrease of symptomatic pneumonia cases associated with a viral infection, whether influenza virus or one of the paramyxoviruses."[67] Efficacy levels were 83% for HIV-uninfected children and 65% efficacy in HIV-infected children. **Reported Discontinued, 2006**
Conjugate 10-valent	'Streptorix' GSK	Phase III completed (old formulation) /Phase II (improved formulation), Phase III 2007	Preparing for licensure in 2008, although PneumoADIP has predicted developing country access by 2010.[68] ~80% efficacy globally with less-variance than 7-valent[69,70]
Conjugate 11-valent	Sanofi Pasteur	Phase III	*Results of efficacy trial in Philippines not yet available…* Pneumococcal vaccines are not part of

[66] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf

[67] WHO Initiative for Vaccine Research "Respiratory Infections" (2005) http://www.who.int/vaccine_research/documents/Respiratory_Infections.pdf 2005

[68] GAVI and World Bank "Framework Document: Pilot AMC for Pneumococcal Vaccines" (9 November 2006) http://www.vaccineamc.org/files/Framework%20Pneumo%20AMC%20Pilot.pdf p18

[69] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf

[70] GSK Investor Presentations to ABM-AMRO (2005) http://www.gsk.com/investors/presentations/abm-amro-13062006/ABM-AMRO-13062006.pdf

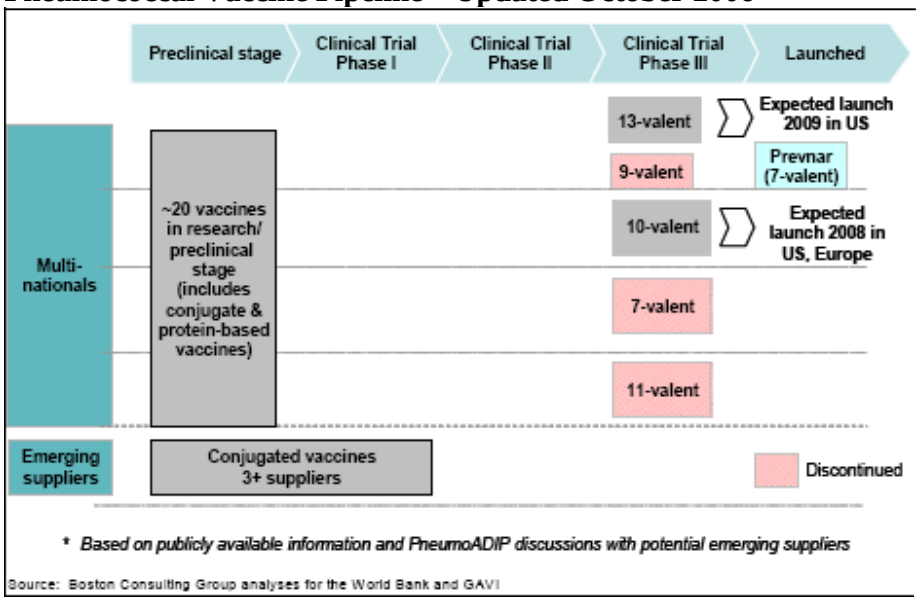
			the vaccine schedule in the Philippines (2005)[71]
Conjugate 13-valent	GSK	Phase III	~80% efficacy globally with less variance than 7-valent
BVH3/11V fusion protein	ID BioMedical	Phase I completed	September 2005, GSK acquired ID Biomedical, bringing ID BioMedical's common protein pneumococcal vaccine candidate into GSK's early vaccine pipeline. Identification of what appear to be remarkably conserved bacterial surface proteins able to induce protective anti-pneumococcal antibodies in the mouse model. A recombinant protein was engineered by fusion of part of the two genes, and successfully tested in Phase I dose ranging clinical trials in young children and elderly. A 2-dose immunization regimen was able to induce a 50-fold increase in anti-pneumococcal antibody levels. Phase II clinical trials have been initiated. This vaccine should be serotype-independent as the BVH3 and BVH11 antigens are common to all 90 serotypes of SP.[72] **Reported Discontinued, 2006**
PspA+PsaA	Sanofi Pasteur	Phase I in adults	
Pneumolysin, PspA, adhesins, PiaA, PiuA, etc, subunit or DNA vaccines	Various academic institutions	Preclinical/Phase I	"Newer vaccine approaches are being developed in order to provide protective immunity against a larger number of *S. pneumoniae* serotypes, and to circumvent the complexity of manufacture of conjugate vaccines"[73]

[71]Sanofi Pasteur Childhood immunization schedule as recommended by the Committee on Immunization, Pediatric Infectious Disease Society of the Philippines (2005) http://198.73.159.214/sanofi-pasteur-ph/ImageServlet?imageCode=13943&codeSite=AVPI_PH

[72]WHO Initiative for Vaccine Research " Respiratory Infections" (2005) http://www.who.int/vaccine_research/documents/Respiratory_Infections.pdf

[73] Ibid.

Pneumococcal Vaccine Pipeline – Updated October 2006[74]



2.4. History in the US, Brief Summary for Europe

The US - *Compiled largely from Butler and Shapiro "Pneumococcal Vaccines: History, Current Status, and Future Directions"*[75]

- In 1911, Wright et al developed a crude whole-cell pneumococcal vaccine to immunize South African gold miners, a group with an extremely high incidence of serious pneumococcal infections. The validity of these trials, and the subsequent clinical trials on the safety and efficacy of polysaccharide vaccines against pneumococci of various serotypes conducted by a number of investigators, was questionable due to methodological flaws.
- However, controlled trials of bivalent, trivalent and quadrivalent polysaccharide vaccines conducted in the 1940s provided stronger evidence for efficacy.
- Two hexavalent vaccines were later commercially produced and marketed. At about the same time, antimicrobials effective against pneumococci became available, and the outcomes of patients with pneumococcal infections improved substantially:

  "The seemingly miraculous efficacy of penicillin led to the widespread belief that pneumococcal infections were entirely curable, and clinicians, researchers and public health officials lost interest in the prevention of this previously feared pathogen."

[74] GAVI and World Bank "Framework Document: Pilot AMC for Pneumococcal Vaccines" (9 November 2006) http://www.vaccineamc.org/files/Framework%20Pneumo%20AMC%20Pilot.pdf

[75] Butler J, E Shapiro and G Carlone "Pneumococcal Vaccines: History, Current Status, and Future Directions" *American Journal of Medicine* (1999) 107(1A): 69S-76S

- By the 1950s, the pneumococcal vaccines had been withdrawn from the market, but the decline in pneumonia deaths from 1944 to 1950 were swiftly reversed with the emergence of a new pathogen (1957 pandemic influenza virus).[76]
- By 1964, complacency over pneumococcal disease ended when Robert Austrian and Jerome Gold presented cases – Austrian and others then worked together to redevelop an effective polyvalent pneumococcal polysaccharide vaccine.
- This led to the licensure of a 14-valent polysaccharide vaccine in the US in 1977 that was replaced by a 23-valent vaccine in 1983.
- Declines in pneumococcal deaths from 1966 to 1982 appear to be attributable to expanded access to medical care, notably the Medicaid legislation, and increased availability of services for lower-income populations.[77]
- In 2000 a 7-valent conjugate vaccine was licensed for routine use. Invasive pneumococcal disease in the population below 2 years old dropped by 69% during 2001 and evidence of significant herd effects became clear for the 20-39 year old group (32% decline) and those over 65 (18% decline).[78]

Europe

There has been a 23-valent vaccine available since the 1980s[79] (Pneumovax 23, Merck&Co) and the 7-valent conjugate vaccine has been licensed since 2001 in Europe (Prevnar, Wyeth). Relatively good antibody responses (60-70%) are elicited in most healthy adults within 2-3 weeks following a single intramuscular or subcutaneous immunization of 23-valent vaccine. The immune response is however mediocre in children less than two years of age and in immunocompromised individuals (HIV/AIDS).[80] The 7-valent vaccine is more appropriate for use in children under 2.

A summary of all pneumococcal vaccination schedules in national immunization programs is in the ANNEX.

2.5. Developing Countries

The success of Prevnar is hugely impressive both in terms of the revenues it produced and the continuing declines in pneumococcal disease in developed countries. Several studies have noted that herd immunity has played a significant part in this. According to Beutels (2007), the first major study to demonstrate herd effects in the US was the study

[76] Schuchat A and S Dowell "Pneumonia in children in the developing world: New challenges, new solutions" *Seminars in Pediatric Infectious Diseases* (2004) 15(3): 181-189
[77] Ibid.
[78] Whitney et al, Clinical Infectious Disease 30, cited in Schuchat A and S Dowell "Pneumonia in children in the developing world: New challenges, new solutions" *Seminars in Pediatric Infectious Diseases* (2004) 15(3): 181-189
[79] Pebody R, T Leino, H Nohynek, W Hellenbrand, S Satmaso, P Ruutu "Pneumococcal vaccine policy in Europe" *Euro Surveillance* (2005) 10(7-9): 174-178
[80] WHO Initiative for Vaccine Research "Respiratory Infections" (2005) http://www.who.int/vaccine_research/documents/Respiratory_Infections.pdf

by Whitney et al (2003)[81] showing that the vaccine was preventing illness among unvaccinated adults and unvaccinated children. Another study by Talbot et al (2004) indicated that the 7-valent conjugate vaccine was effective in reducing invasive pneumococcal disease both in vaccinated children and in non-vaccinated adults.

Referring to data from the CDC on direct and indirect effects of routine vaccination with 7-valent vaccine from 1998-2003 in the US, the framework document for the pilot AMC for pneumococcal vaccines states:

> "…more than twice as many cases of pneumococcal disease are being prevented through the herd immunity effects of vaccination than are being directly prevented by the vaccination of young children."[82]

However, the different serotype distribution in many Asian and African countries requires higher valency formulation than Prevnar offers.[83]

Malawi was taken as a country with similar patterns of serogroups to other West African countries, and has higher rates of types 1 and 5 than that reported from the US and Europe.[84] There is therefore poor potential for 7-valent vaccine to provide protection in Malawi.
Specifically, at least a 9-valent vaccine is required. The Adegbola, Mulholland analysis of the 9-valent vaccine trial in the Gambia concluded that a proposed nine-valent pneumococcal conjugate vaccine for developing countries containing conjugates of serogroups 1, 4, 5, 6, 9, 14, 18, 19 and 23 would cover 74% of cases of invasive pneumococcal disease in children resident in the Western Region of the Gambia.[85]

The October 2006 PneumoADIP report (adapted from Hausdorff 2000) summarises the valencies dominant by continent:

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[81] Beutels P, N Thiry and P Van Damme "Convincing or confusing? Economic evaluations of childhood pneumococcal conjugate vaccination – a review (2002-2006)" *Vaccine* (2007) 25(8-9): 1355-1367

[82] GAVI and World Bank "Framework Document: Pilot AMC for Pneumococcal Vaccines" (9 November 2006) http://www.vaccineamc.org/files/framework%20Pneumo%20AMC%20Pilot.pdf p13

[83] Haussdorf W, J Bryant, P Paradiso and G Siber "Which Pneumococcal Serotypes Cause the Most Invasive Disease : Implications for Conjugate Vaccine Formulation and Use, Part I" *Clinical Infectious Diseases* (2000) 30(100) : 100-121

[84] Gordon S, S Kanyanda, A Walsh, K Goddard, M Chaponda, V Atkinson, W Mulwafu, E Molyneux, E Zijlstra and M Molyneux "Poor Potential Coverage for 7-valent Pneumococcal Conjugate Vaccine, Malawi" *Emerging Infectious Diseases, CDC* (2003) 9(6): 747-749

[85] Adegbola R, S Usen, K Mulholland, S Jaffar, S Hilton, A Oparaugo, C Omosigho, G Lahai, T Corrah, A Palmer, G Schneider, M Weber, B Greenwood "Epidemiology of invasive pneumococcal disease in the Western Region, The Gambia" *Pediatric Infectious Disease Journal* (1998) 17(1) : 23-28

	Rank order of isolation frequency						
Region	1st	2nd	3rd	4th	5th	6th	7th
U.S. and Canada	**14**(27.8)	**6**(17.0)	**19** (14.3)	**18** (8.6)	**23** (7.4)	**9** (6.3)	**4** (6.3)
Asia	1 (11.7)	**19**(10.8)	**6** (9.9)	5 (9.1)	**14** (8.0)	7 (6.4)	**23** (5.3)
Africa	**6** (23.8)	**14**(18.9)	1 (12.7)	**19** (11.7)	**23** (4.2)	5 (4.0)	15 (3.8)
Europe	**14** (18.7)	**6** (15.4)	**19** (12.7)	**18** (9.6)	**23** (8.1)	**9** (6.3)	1 (6.1)
Latin America	**14** (22)	**6** (13.9)	5 (9.2)	1 (8.2)	**19** (7.9)	**23** (7.9)	**18** (5.5)
Oceania	**14** (24.0)	**6** (15.9)	**19** (14.2)	**18** (6.6)	**23** (6.4)	**9** (6.3)	**4** (4.2)

Further, the problem of pneumococcal disease is far larger in developing countries than the developed countries, both in terms of the quantity of children affected[86] and the difficulty in pinpointing the cause of pneumococcal disease. A large limiting factor is surveillance and awareness of the disease burden. If control of pneumonia among children in the developing world is to move from the 'case-management' approach advocated since the early 1980s to an approach based on the prevention of infection with specific pathogens, surveillance systems capable of measuring the burden of disease from these pathogens will be required to inform decisions on major control efforts such as the introduction of new vaccines.[87]

Surveillance in developing countries

Some efforts have been made to improve surveillance systems. The Thai Ministry of Public Health implemented the International Emerging Infections Program (IEIP) of the US CDC surveillance system (population-based throughout two provinces).

- Although the system focuses on the causes and burden of severe pneumonia requiring hospitalization, periodic community surveys measure the burden of less severe pneumonia and other respiratory illnesses.
- A focus on laboratory testing is aimed at permitting estimation of disease caused by potentially available vaccines, such as influenza vaccines and the conjugate Hib and pneumococcal vaccines.[88]

A second IEIP was aimed for Kenya in 2004 (but information is limited).

Links to Hib

As described in the section specifically on the PneumoADIP, it is expected that decisions to integrate pneumococcal vaccines into national immunization programs will be influenced by (and will follow) decisions for Hib vaccinations.

The analysis by Peltola et al. of the burden of meningitis and other severe bacterial infections of children in Africa notes the very large burden of disease, with mortality

[86] Schuchat A and S Dowell "Pneumonia in children in the developing world: New challenges, new solutions" *Seminars in Pediatric Infectious Diseases* (2004) 15(3): 181-189

[87] Ibid.

[88] Ibid.

levels of pneumococcal meningitis at 45% of 1211 patients. At 0-4 years the estimated incidence of Hib meningitis and all classic Hib diseases were 70 and 100 cases per 100,000 per year. The conclusion of the survey was that:

> "The only realistic way to combat these severe infections efficaciously would be through widespread vaccination, starting with Hib conjugates".[89]

Mulholland describes pneumococcal conjugate vaccines as being developed along lines similar to the Hib conjugate vaccines and around 10 years behind in their development. The pneumococcus is a more difficult target than Hib, because it causes disease throughout life, from the neonatal period to advanced age, and there are 90 serotypes capable of causing disease.[90]

2.6. Key Players

WHO involvement

Disease burden estimates, specifically, cases, deaths and DALYs at national, regional and global levels. This will then:

- Facilitate country-level decision-making regarding the introduction (or continued use) of pneumococcal vaccines.
- Facilitate multilateral and bilateral agencies in prioritising pneumococcal prevention activities relative to other interventions.
- Guide WHO global and regional vaccine policy and strategy.
- Inform decision-making processes related to vaccine development and production.

Recent efforts by the WHO to standardise estimates of burden of disease across program areas identify acute respiratory infections (ARIs) and have determined that ARI is the most common infectious cause of death in children under 5:

> "The magnitude of illness attributable to pneumonia is such that countries seeking to achieve (the UN Millennial Development goal of reducing mortality rates by 2/3 by 2015) will not be possible unless they give attention to pneumonia prevention and control."[91]

[89] Peltola H "Burden of Meningitis and other Severe Bacterial Infections of Children in Africa: Implications for Prevention" *Clinical Infectious Diseases* (2001) 32: 64-75

[90] Mulholland K "Evaluation of Vaccines to prevent Childhood Pneumonia: Lessons Relevant to Planning Tuberculosis Vaccine Trials" *Clinical Infectious Diseases* (2000) 30: S206-S209

[91] Schuchat A and S Dowell "Pneumonia in children in the developing world: New challenges, new solutions" *Seminars in Pediatric Infectious Diseases* (2004) 15(3): 181-189

WHO estimates of annual ARI deaths in children <5 years old, by region (Williams B et al. Lancet ID 2002)

WHO Region	Under 5 Deaths	ARI deaths	Range (000s)	% due to ARI
AFR	3,608,000	794,000	677-911	22%
AMR	436,000	60,000	47-73	14%
EMR	1,345,000	261,000	221-302	19%
EUR	217,000	24,000	17-32	11%
SEAR	3,274,000	606,000	519-694	19%
WPR	979,000	132,000	102-162	13%
Total	9,901,000	1,880,000	1582-2178	19%

Most experts consider that the vast majority of ARI deaths are likely due to bacterial pneumonia (probably 50-80%).[92]

GAVI's PneumoADIP (Accelerated Development and Introduction Plans). PneumoADIP is funded through GAVI, and based at the Johns Hopkins Bloomberg School of Public Health, and is run by Executive Director Orin Levine. It describes its activities as based around the following areas:

- Establishing value of vaccination by demonstrating the burden of meningitis and pneumonia caused by pneumococcal bacteria and demonstrating the value of prevention by vaccination.
- Communicating effectively to key decision makers the knowledge about disease burden and the value of vaccination by assuring that research data are communicated through appropriate and effective communication channels.
- Delivering the value of the vaccine by assuring that there is a predictable supply of quality vaccine at an affordable price, and an adequate system.[93]

According to the PneumoADIP report October 2006,[94] multinational manufacturers have indicated willingness to supply GAVI at tiered prices. Calculations made by researchers have estimated the total vaccine market in low-income countries to be between US$1-1.5bn annually,[95] of which the market for pneumococcal conjugate vaccines is estimated at about $250m per year (compares to $2.5bn revenue from the same volumes of 50m doses in high-income countries).

Emerging market manufacturers are developing pneumococcal vaccines and are expected to enter the market by 2015.

[92] Ibid
[93] GAVI Alliance website www.gavialliance.org
[94] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf
[95] PneumoADIP Presentation given by A Nanni, Director of Vaccine Finance and Supply "PneumoADIP's Approach to Building A Win-Win-Win Situation for Industry, Donors & Countries" (April 2006)

World Bank and GAVI – Pneumococcal Pilot AMC November 2006. In February 2007 there was announcement of commitment from the Italian, UK, Canadian, Norwegian and Russian governments.

2.7. The PneumoADIP (Accelerated Development Introduction Plan, GAVI)

The strategy suggested by PneumoADIP is to accelerate introduction of Prevnar in countries where appropriate, "laying the foundation for widespread use by 2010 of a 10-13 valent vaccine."[96] These vaccines include serotypes 1 and 5, which are important in many developing countries. In 2005, the WHO SAGE committee

> "…expressed confidence in the already available evidence of safety and efficacy of pneumococcal conjugate vaccines, in numerous settings, ranging from industrialised to developing countries, including infants with HIV infections."[97]

In addition, the evidence from clinical trials in Africa, Europe and the US has shown vaccine ability to protect HIV-infected children as well as herd immunity. Therefore, according to the PneumoADIP report October 2006,[98] further trials are not needed to prove they can protect children in GAVI-eligible countries:

> "Much of the PneumoADIP team's work will focus on supporting the collection of data to measure both the burden of pneumonia and meningitis in developing countries and the value of preventing it through vaccination. Clearly, the overlap of these activities with those that would go into Hib introduction is striking. Furthermore, country decisions to uptake Hib vaccine will influence decisions on the uptake of pneumococcal vaccine." [99]

The use of the vaccine in campaigns has been described by GAVI as an excellent way to 'front load' prevention. Vaccinating children aged 1-4 with a single dose would prevent a substantial amount of illness among children in this age group and increase the potential for herd immunity to prevent disease among unvaccinated adults and children. Also, by using the vaccine in a campaign, it helps reach children who may not be reached by routine services and may have the highest risk of pneumococcal mortality. The use of the vaccine for catch-up campaigns is a planned component of the post-introduction evaluations.[100]

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[96] Ibid
[97] WHO Immunization, Vaccines and Biologicals WHO position paper *Weekly Epidemiological Record* (6 January 2006) 81: 1-12
[98] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf
[99] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf
[100] Ibid.

ADIP role

- Summary of vaccine safety and effectiveness for the prevention of key outcomes
- Country and region-specific estimates of the burden of pneumococcal disease and cost-effectiveness of vaccinations
- Cost-effectiveness analysis, from the perspective of the Vaccine Fund, for supporting pneumococcal conjugate vaccine use between 2007-2012
- Demand forecasts and projected resource requirements for national governments, international donors, and the Vaccine Fund
- Financial analysis of the costs and risks involved in investing in alternative supply sources such as emerging market suppliers
- Analysis of the costs of delivering pneumococcal vaccine in the context of local immunization programs
- Systematic surveys of local and international decision-makers attitudes towards the attractiveness of pneumococcal vaccine.

Analyses on the contribution of specific pneumococcal serogroups to different disease manifestations indicate that pneumococcal conjugate vaccines could potentially prevent a substantial proportion of episodes of bacteraemic disease, pneumonia, meningitis, and otitis media, especially in young children.[101]

It is expected that based on the herd immunity effect already clear in the US and the efficacy proven in the Gambian trial for the 9-valent vaccine, there will be individuals and institutions advocating for routine infant pneumococcal vaccination in the poorest countries, where pneumococcal disease is a major cause of child mortality. As GAVI comments:

> "Arguments will likely characterize the situation as a 'social injustice' if the benefits of vaccination continue to accrue in richer countries where ~10% of pneumococcal deaths occur, and not in poorer countries where ~90% of pneumococcal deaths occur."[102]

Another issue particularly relevant for developing countries is the efficacy of the vaccine for HIV-infected children, which it has been suggested have a risk of incidence of invasive pneumococcal disease (IPD) that is 40-fold greater than non-HIV-infected children. It has also been suggested that HIV-infected children account for as much as 75% of cases of IPD in some sub-Saharan countries.[103] In the analysis conducted by Adegbola et al (2005) on the 9-valent Gambian trial, the authors state that

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[101] Haussdorf W, J Bryant, P Paradiso and G Siber "Which Pneumococcal Serotypes Cause the Most Invasive Disease : Implications for Conjugate Vaccine Formulation and Use, Part I" *Clinical Infectious Diseases* (2000) 30(100) : 100-121

[102] PneumoADIP at Johns Hopkins "Proposal to Host GAVI's Pneumococcal Vaccine Accelerated Development and Introduction Plan (ADIP) at Johns Hopkins Bloomberg School of Public Health" (2003) http://www.gavialliance.org/resources/pneumo_adip_web.pdf

[103] Madhi S, K Petersen, A Madhi, A Wasas and K Klugman "Impact of human immunodeficiency virus type 1 on the disease spectrum of Streptococcus pneumoniae in South African children" *The Pediatric Infectious Disease Journal* (2000) 19: 1141-47

> "…although we did not test for HIV infection…immune suppression was unlikely."[104]

Madhi et al (2006) state in their study on the long-term immunogenicity of 9-valent pneumococcal vaccine in HIV-infected children that vaccine efficacy against all serotype invasive pneumococcal disease was greater in HIV-infected (46%) than non-HIV-infected (35%) children.[105] However, there was a trend towards a greater burden of invasive pneumococcal disease due to non-vaccine serotypes among non-HIV-infected children, which almost halved the benefit of reduction in IPD associated with protection against vaccine-serotype IPD. Also, although the pneumococcal conjugate vaccine protected against pneumococcal morbidity in HIV-infected children, there was no difference in mortality in the study between HIV-infected and placebo recipients. Clearly, this area requires more robust analysis before it can be asserted unequivocally that the 9-valent conjugate vaccine increases long-term immunogenicity for HIV-infected children, despite the fact that this work and other studies indicate that the vaccine combined with a booster vaccine could be very effective in increasing long-term immunogenicity.

Cost-effectiveness

Cost-effectiveness analysis from PnemoADIP estimate that at a vaccine price of $5 per dose, pneumococcal vaccination has an average cost per DALY saved of $22, and an average cost per death averted of $691 in the 72 GAVI-eligible countries.[106] This contrasts with other analyses (Shepard et al, Vaccine 1995; Miller and McCann, Health Economics 2000) which estimated the cost per DALY saved at $57 and $20-$39 respectively.

Currently the Prevnar vaccine cost in the US is $57.59 per dose,[107] but is more expensive elsewhere. For example, Wyeth launched Prevenar in India (through an unlisted, wholly owned subsidiary Wyeth Pharmaceuticals India Ltd) with a price tag of Rs3750 + tax,[108] which is roughly US $85 per dose. As Beutels (2007) comments:

> "Where it has been licensed, PCV7 is the most expensive pediatric vaccine to date, with the assumed price of a single dose ranging from €40 to €69 in this review"[109]

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[104] Adegbola A, F Cutts, S Zaman, G Enwere, S Jaffar, O Levine, J Okako, C Oluwalana, A Vaughan, S Obaro, A Leach, K McAdarn, E Biney, M Saaka, U Onwuchekwa, F Yallop, N Pierce and B Greenwood for the Pneumococcal Vaccine Trial Group "Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial" *The Lancet* (2005) 365: 1139-46

[105] Madhi S, P Adrian, L Kuwanda, W Jassat, S Jones, T Little, A Soinen, C Cutland and K Klugman "Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster vaccine" *Vaccine* (2006) doi:10.1016/vaccine.2006.09.019

[106] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf

[107] CDC Vaccine Price List as accessed January 2007 http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm

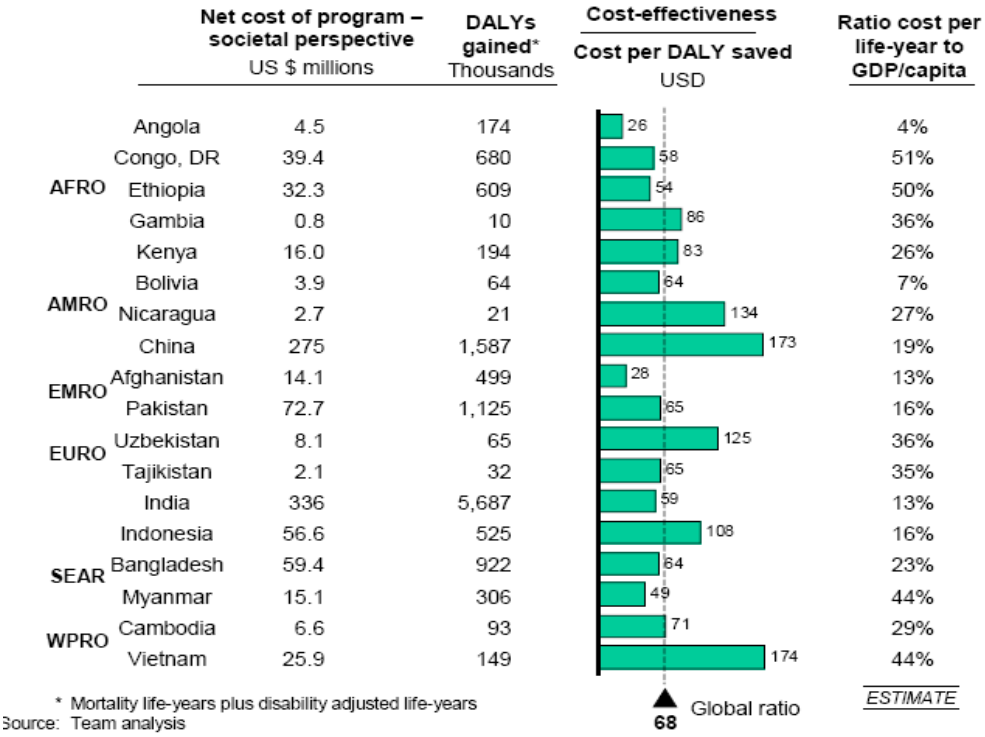
[108] Pharmabiz, June 30 2006, Mumbai http://www.pharmabiz.com/article/detnews.asp?articleid=34049&sectionid=45

[109] Beutels P, N Thiry and P Van Damme "Convincing or confusing? Economic evaluations of childhood pneumococcal conjugate vaccination – a review (2002-2006)" *Vaccine* (2007) 25(8-9): 1355-1367

The proposed pneumococcal AMC suggests that prices of the vaccines currently in the pipeline of development (the 10-valent vaccine being the closest to completion) will range from US $5-$7. Though there is no evidence of an agreement with Wyeth to ensure this price, or any other explanation of how this price will be reached. Some, such as the UK's Oxfam complain that the negotiated $7 is far higher than should have been achieved in the bargaining process with the pharmaceutical companies.

A review of economic evaluations of childhood pneumococcal conjugate vaccinations 2002-2006 by Beutels et al (2007) found a great diversity in assumptions in vaccine efficacy, incidence rates, vaccine uptake and herd effects even for the 7-valent pneumococcal vaccine when looking at studies in developed countries. This made it difficult to draw solid conclusions about the cost-effectiveness of universal infant vaccination with PCV7. It is argued by several studies that a substantial reduction in the cost of the vaccine could bring the incremental cost-effectiveness ratio into an acceptable range.[110] It should be noted perhaps that although this study was looking primarily at developed countries, the factors that influenced the cost-effectiveness analyses most substantially may be similar in developing countries.

Summary: McKinsey & Co. cost-effectiveness analysis for pneumococcal vaccine
All countries have costs per life-year gained below GDP/capita



McKinsey Analysis, PneumoADIP[111]

[110] Beutels P, N Thiry and P Van Damme "Convincing or confusing? Economic evaluations of childhood pneumococcal conjugate vaccination – a review (2002-2006)" *Vaccine* (2007) 25(8-9): 1355-1367

[111] PneumoADIP at Johns Hopkins "Proposal to Host GAVI's Pneumococcal Vaccine Accelerated Development and Introduction Plan (ADIP) at Johns Hopkins Bloomberg School of Public Health" (2003) http://www.gavialliance.org/resources/pneumo_adip_web.pdf

In the McKinsey analysis, cost-effectiveness was influenced most by price per dose, DTP coverage rate in the country and the actual disease burden (vaccine efficacy to less of an extent).

PneumoADIP analysis suggests that vaccination remains cost-effective over a range of vaccine prices (as high as $10 per dose) and is cost-saving at dose costs below $3 per dose.

Vaccine prices

It is unlikely that whilst prices for middle-income countries may be reduced, they will be in the $3-8 range that would be expected for Vaccine Fund-eligible countries:

> "Even in the event of competition between GSK and Wyeth, the price of pneumococcal conjugate vaccines for industrialized countries is likely to remain in the range of $30-$50 per dose through 2009…. As stressed by McKinsey and Co… the public sector's best approach to assuring an affordable supply of vaccine is to reduce the uncertainty of demand…"[112]

GAVI financing estimates – the AMC

GAVI's Investment Case for Accelerating the Introduction of Pneumococcal Vaccine into GAVI-Eligible Countries (October 2006) states that GAVI's financing will motivate industry to dedicate capacity for developing countries, support countries that demand pneumococcal vaccine and contribute directly to sustaining affordable vaccine prices.[113] The report suggests that without GAVI financing, a sustainable supply of pneumococcal vaccines at affordable prices is unlikely before 2020.

The Pilot AMC for pneumococcal vaccines was officially launched 9 February 2007

> "…to demonstrate both the feasibility of the AMC mechanism and its impact on accelerating vaccine development, production scale-up, and introduction. A successful pneumococcal AMC has the potential to prevent 5.4 million child deaths by 2030."[114]

The AMC proposal is an interesting illustration of the challenges and limitations of policy-making in attempts to accelerate the introduction of vaccines into developing countries. According to the GAVI documents in the run up to the launch,[115] early vaccine purchases will be the 7-valent Wyeth vaccine even though it is not fully efficacious against the pneumococcal serotypes prevalent in developing countries. Suggested funding for this component of the overall package will be between $127-$189m, where up to 79%

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[112] Ibid.

[113] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf, Executive Summary

[114] PneumoADIP Press Releases "$US 1.5 Billion dollar commitment launches pilot Advance Market Commitment for pneumococcal vaccines" (9 February 2007) http://www.preventpneumo.org/pdf/PneumoADIP_AMC_9Feb07.pdf

[115] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf p14

is for purchasing the vaccine and the remaining $40m or so for supporting GAVI partners and a health team "to support the evidence-based introduction of the vaccine and assessment of the vaccine's impact in early adopter countries". The $1.5bn funding suggested does not seem comparable to the claim made that the scheme will save 5.4m of the estimated 25m children who will die from pneumococcal disease by 2030; the GAVI Alliance figures suggest that funding is sufficient to save between 280,000 – 460,000 lives.[116] In addition to the fact that the "best-case scenario" thinking still leaves 75% of lives lost, the use of such a long horizon generates a figure that is rather arbitrary; recent supporting arguments suggested that by 2025, 4m lives could be saved, but the figure now used is 5.4m by 2030 9and has recently gone up again to 7m in AMC literature). Given that the initiative is actually fairly short-term and despite claims that there will be more money available in 2015 when this phase of financing ends, it seems that the long-term goals will be difficult to achieve when the incentive to fund has been front-loaded in this way, even possibly crowding out longer-term positive outcomes. According to the GAVI figures, 98%-99% of potential lives saveable between now and 2030 will not be picked up by the $1.5bn proposal.

Further, the money does not appear to account for costs of expansion of the cold chain needed to store and distribute the vaccine, assuming instead that "the incremental cost for delivering pneumococcal vaccine is relatively small", basing its judgement on non-vaccine costs derived from country-level finance data on routine immunization programs. In fact the AMC Proposal almost contradicts itself, stating that:

> "There are minimal technical constraints facing pneumococcal vaccines introduction. As with any additional vaccine to be administered as a separate injection, introduction will require training of health workers, social mobilization, preparation of the cold chain and addressing transport and other logistic issues"[117]

It is proposed that the scheme will encourage sustainable vaccine supplies to developing countries as a result of accurate demand forecasts and commitments to purchase. However, the funding is scheduled to run out in 2015. Emerging suppliers, and potentially more affordable technologies that might be able to counter the already high costs of providing pneumococcal vaccines to the poor, require investment, and long-term incentives may inadvertently and even perversely suffer increased risk as a result of the way the commitment has been framed. Particularly following the difficulties faced in funding combination vaccines (DTP-Hep-Hib) in several developing countries, (GAVI Bridge Funding Proposal 2005) caution needs to be taken when looking at claims from such high-profile initiatives.

Perceptions survey from PneumoADIP

A **PneumoADIP web-based "perceptions survey"**, with the 90 respondents made up of researchers, clinicians, industry, technical agencies, NGOs or in other areas was conducted in October 2005. It should be noted that these are opinions only of readers of

[116] PneumoADIP website "Pneumococcal Diseases" http://www.preventpneumo.org/diseases_vaccines/pneumococcal_diseases/index.htm (low figure) and range from supporting GAVI paperwork.

[117] GAVI and World Bank "Framework Document: Pilot AMC for Pneumococcal Vaccines" (9 November 2006) http://www.vaccineamc.org/files/Framework%20Pneumo%20AMC%20Pilot.pdf p16

PneumoFOCUS, and these are largely from industry. Opinions might be biased, in particular about how extensive the influence of researchers is on policy. The survey:

- Found that 71% of participants thought that pneumococcal conjugates could be made affordable to developing countries.
- 50% responded that it costs US$6 or more to manufacture a dose of the licensed 7-valent pneumococcal vaccine (10% responded that it costs US$20 or more and 20% responded that it costs US$2 or less to manufacture).
- 50% responded that, after 10 years of financing by GAVI, the maximum price per dose that developing countries and their donor partners can sustain is between US$1- US$2 (only 20% thought that it could be higher than US$5).
- 77% responded that researchers can influence donors and policy makers in decisions about pneumococcal vaccine introduction.
- 74% responded that companies should expect to make a profit on vaccines that are supplied to developing countries.[118]

Compared with the analysis conducted for PneumoADIP, most respondents *overestimated* the costs of manufacturing multi-valent conjugate vaccines. Only 27% of correspondents estimated a manufacturing price that was less than the "maximum" price per dose that countries can sustain.

So, despite comments made in their reports of being quite wary of reaching a suitable price for vaccine fund eligible countries, these PneumoADIP survey results are far more positive.

GAVI's Anticipated Constraints – Social and Cultural Constraints

- Lack of awareness of the burden of disease among some key audiences (this is expected to be the biggest constraint).
- According to audience research conducted by PneumoADIP, McKinsey & Co and others, despite widespread recognition of the burden of pneumonia among paediatricians, nurses and MoH officials, many politicians and the lay public may not be aware of the specific burden of pneumococcal disease in their country.
- However there is an advantage over other vaccines (such as the oral polio vaccine) where there is a risk of getting the disease from the vaccine, as pneumococcal conjugate vaccines are made from inactive particles of the vaccine. Therefore safety risks are not likely to be a major constraint to uptake.

  "However, efforts to demonstrate the vaccine's safety and value are important for ensuring acceptance."[119]

GAVI's Anticipated Constraints – Epidemiological and Environmental Constraints

[118] PneumoADIP news October 2005 http://www.pneumoadip.org/news/pneumofocus/newsletter/oct05.htm
[119] PneumoADIP at Johns Hopkins "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 23 2006) http://www.gavialliance.org/resources/19brd_IC_Pneumo.pdf

- It is difficult to diagnose *S. pneumoniae* as the causative agent of many of the diseases that it does cause.
- It is therefore a high priority to support the development of surveillance to document local evidence of the burden of pneumococcal disease.
- In many countries where the burden of pneumococcal disease is high, there are many competing priorities (e.g. malaria, HIV etc).

Technical Constraints

- Injection will require training of health workers, social mobilization, preparation of the cold-chain (much like any other vaccine administered as a separate injection).

Institutional Constraints

- "It is expected that the experiences and lessons gained during the scale-up with Hib and Hepatitis B vaccines can be built upon to anticipate and overcome many of the institutional constraints that are important in accelerating new vaccine introduction."[120]

[120] Ibid.

2.ANNEX

A) Immunization schedules for Pneumococcal Vaccines
B) Results from Survey in Israel
C) Results from Survey in Kenya

A)

	Pneumo conj.[121]	**Pneumo polysaccharide.**	
Australia	2, 4, 6, 12 months, eligible children only	18-24 months, 4 years, eligible children only	
Austria	0-1 year (3 doses), 1-2 years; children belonging to defined high-risk groups		
Canada	2, 4, 6, 12-15 months		
Israel		>65 years	
Monaco		2 months	
Spain		High-risk groups	
Additional vaccines reported			
Bahamas	2, 4, 6, 15 months (subnational)	2 years (subnational)	
Bahrain	2, 4, 6 months; high-risk groups (subnational)	>2 years; old-age and high-risk groups >2 years (subnational)	
Brazil	2, 3-5 years (CRIE indicators)	2 months (CRIE indicators)	
Cyprus		2 years; high-risk groups	
France	2, 3, 4 months; 2 years; high-risk groups kindergarten (recommended)	High-risk groups (recommended)	
Germany	High-risk groups	60 years; high-risk groups	
Iraq		High-risk groups	
Kuwait		High-risk groups	
Qatar	2, 4, 6, 18 months	Elderly, high-risk patients (subnational)	
Russian Fed		High-risk groups	
Switzerland	High-risk groups	High-risk groups	
United Arab		High-risk groups	

[121] UNICEF/WHO Immunization Summery (2006)
http://www.unicef.org/publications/files/Immunization_Summary_2006.pdf

Emirates			
USA	2, 4, 6, 12-15 months	≥65 years; high-risk medical conditions all ages	

B) ISRAEL

As noted with reference to the range of serotypes prevalent in Israel, to choose the appropriate vaccine for a national immunization program, it is important to study all groups in the population, especially those with high risk of invasive pneumococcal illness, to determine the serotype distribution associated with disease. The serotype distribution among Jewish and Bedouin children is such that the 7-valent vaccine covers only 41% and 22% of the population respectively. The addition of serotypes 1 and 5 (the 9-valent vaccine) raises the potential coverage to 67% and 63% and the 11-valent vaccine which also includes 3 and 7F raises coverage to 71% and 65%.[122]

C) KENYA

Evidence from Kenya indicates that the number of cases preventable with 7-valent vaccine (150-300 cases per 100,000 children under the age of 5) is 3 to 6 times higher than the number of cases prevented by Hib vaccine (52 cases per 100,000 children under the age of 5).[123]

[122] Fraser D et al "A Decade (1988-1998) of Paediatric Invasive Pneumococcal Disease in 2 Populations Residing in 1 Geographic Location: Implications for Vaccine Choice" *CID 2001:33*

[123] Cowgill, Ndiritu et al "Effectiveness of Haemophilus Influenzae type b Conjugate Vaccine Introduction into Routine Childhood Immunization in Kenya" *JAMA 2006* 296

3. HPV VACCINE CASE DETAILS

Summary

This section describes the activity on the ongoing launch of the recently developed vaccines for human papillomavirus (HPV), which is responsible for cervical cancer. It aims to provide an outline of key facts about HPV – the disease and its epidemiology, the main vaccine development players and products, the trials and regulatory processes, and the main players and actions with regard to eventual launch in developing countries – as a way to learn cross-cutting lessons to input into TB vaccine market thinking. HPV is one of a number of recent vaccine stories which can provide extremely useful lessons for the launch of TB and other vaccines. Although it is the most recent story and as yet incomplete, it is also interesting in the newer thinking being carried out with regard to developing-country launch. There are features of HPV that make its study as a case study particularly useful for TB, particularly in the context of boost and prime boost TB vaccines, adolescent immunization and catch-up programmes.

This section explains how HPV is broken into subtypes and how these types are connected to cancer and other diseases, and the implications for different regions of the world. It then describes the characteristics of the two main vaccine products (those developed by Merck and GSK), and outlines the history of their pre-licensure trials and regulatory approval. The final section explains activity conducted specifically with respect to developing countries: earlier WHO activity (roughly, 1999-2005), the current Bill and Melinda Gates-funded project led by PATH, activity by other players such as industry and PAHO, and finally a list of areas which are in need of action and which may not have been covered by existing plans.

For reference, some of the main players are:

- The WHO
- The main two industry players: Merck (producing Gardasil) and GSK (producing Cervarix)
- The Program for Appropriate Technology in Health (PATH), taking the lead on the Bill and Melinda Gates-funded initiative, including the 4 vaccine demonstration projects
- The Food and Drug Administration (FDA), the US regulatory body for vaccines
- The Pan American Health Organisation (PAHO)

3.1. The Disease

Human papillomavirus (HPV) has more than 100 genotypes, which can be grouped into 'high-risk' and 'low-risk' types in terms of their link to cervical cancer. HPV-16 and HPV-18 account for roughly 70% of cancer cases globally – these are the genotypes targeted by the main vaccine candidates (see below). The remaining 30% of cases are due to other high-risk HPV types (e.g. HPV-31, -33, -35, -39, -45,-51, and -66).[124]

There is some variation across the world in the breakdown of cancer cases by HPV type causing them, although type 16 has the greatest contribution to cervical cancer in all regions.[125] Some of the 'other types' are more common in the developing world.[126] The table below shows the percentage of cancer cases caused by each subtype in various regions, as quoted in a WHO study:[127]

Region	HPV-16	HPV-18	Other
Central/South America	57%	13%	30%
North America/ Europe	70%	15%	15%
Northern Africa	68%	17%	15%
South Asia	53%	26%	21%

Another WHO report cites 73.5%; 65; and 71.5% as the percentages of cancer cases caused by types 16 and 18 in Asia; Africa and central/South America; and North America and Europe respectively. It cites the next most common genotypes as 45 in Africa and Asia; 31 in Latin America; 33 in Europe and North America; and 58 and 52 in Asia [it is not clear from the document why Asia is listed twice in this list]. These differences could reduce the relevance of the main vaccines from 70% of cancer cases to around 65% in Latin America and sub-Saharan Africa, whilst a vaccine that covered the 7 most common genotypes would be relevant to 87% of cases, with little regional variation. However, adding extra genotypes might be difficult for manufacturers.[128]

Low-risk HPV subtypes, such as HPV-6 and HPV-11 referred to below, can cause genital warts. High-risk subtypes can also cause precancerous lesions.[129] These mean vaccines can have wider effects than preventing cervical cancer, and specifically could be of benefit to, and could be promoted to, males.

[124] WHO/IVR page on HPV www.who.int/vaccine_research/diseases/viral_cancers/en/index3.html accessed on 27 November 2006
[125] WHO/IVR page on HPV
[126] PATH "Introducing HPV Vaccines in Developing Countries: Overcoming the Challenges" (September 2005) www.path.org/files/RH_hpv_intro.pdf
[127] Muñoz et al (2004), cited in WHO and United Nations Population Fund "Preparing for the introduction of HPV vaccines: policy and programme guidance for countries" (Geneva: WHO, 2006)
[128] WHO "Report of the Consultation on Human Papillomavirus Vaccines, World Health Organisation, Geneva, April 2005" (2005) www.who.int/vaccine_research/documents/816%20%20HPV%20meeting.pdf
[129] WHO/IVR page on HPV

3.2. The Vaccines

There are two main products at or close to launch at time of writing:

- *Gardasil*, made by Merck, targets 4 HPV subtypes (6, 11, 16, and 18)[130] and has been licensed in several countries, including the US and the EU. It is a 3-dose vaccine given over 6 months.[131] It has 96% efficacy against persistent infection for 60 months; also 100% efficacy against cervical or genital lesions caused by the HPV subtypes it targets.[132] It is a 3-dose vaccine, and the catalogue price is $120 a dose.[133]
- *Cervarix*, made by GSK, targets 2 HPV subtypes (16, 18). GSK claims that it also has some efficacy for others: 75.4% for HPV-45, which accounts for 6.7% of cancer cases globally; 78.5% for HPV-31, responsible for 2.9% of cases; and 77.1% for HPV-52, at 2.3% of cases (these are three of the four most common cancer-causing genotypes after the main two).[134] It submitted for licensure in the EU in March 2006. Cervarix was approved in May 2007 in Australia for women ages 10 to 45, the Philippines in August 2007, and the European Union in September 2007. In March 2007 GlaxoSmithKline submitted a Biologics License Application (BLA) to the FDA in the United States of America, including data from clinical trials in almost 30,000 females aged 10 to 55 years, but awaits results of further trials. Approval in the US is expected in late 2009. For cost reasons the UK government chose Cervarix over Gardasil for its national programme of vaccination for teenage girls even though Gardasil protects against HPV strains 6 and 11 in addition to 16 and 18. Like Merck's product, *Cervarix* is a 3-dose vaccine given over 6 months.[135] It has 96% efficacy against persistent infection for 47 months.

According to PATH, the vaccines have been shown in clinical trials to be 95% effective in preventing persistent HPV infection, and 100% effective in preventing type-specific cervical lesions.[136]

There are also a number of other candidates in earlier stages of development (preclinical to Phase I). According to the WHO's Initiative for Vaccine Research, none of these target

[130] WHO/IVR "New Vaccines against Infectious Diseases: Research and Development Status" (April 2005, updated February 2006) www.who.int/vaccine_research/documents/en/Status_Table.pdf
[131] Merck Press Release "Merck Launches National Advertising Campaign for GARDASIL®, Merck's New Cervical Cancer Vaccine", 13 November 2006 www.merck.com/newsroom/press_releases/product/2006_1113.html
[132] PAHO "Important Characteristics of Prophylactic HPV Vaccines for the Prevention of Cervical Cancer" (updated 12 June 2006) www.paho.org/English/AD/FCH/IM/HPV_VaccineCharacteristics.pdf
[133] Merck Press Release "FDA Approves Merck's GARDASIL®, the World's First and Only Cervical Cancer Vaccine", 8 June 2006, www.merck.com/newsroom/press_releases/product/2006_0608.html
[134] Forbes.com "GlaxoSmithKline announces second boost to Cervarix cervical cancer drug" (4 May 2006) www.forbes.com/markets/feeds/afx/2005/05/04/afx1998456.html, refers to these three genotypes and gives a figure of "a further 12% of cervical cancers".
[135] PAHO "Important Characteristics of Prophylactic HPV Vaccines for the Prevention of Cervical Cancer"
[136] PATH "Cervical Cancer Vaccine Project" (August 2006) www.path.org/files/RH_cc_vacc_proj_fs.pdf

a wider range of HPV subtypes than the two advanced products.[137] (These use different approaches to the two main industry projects, e.g. proteins made in transgenic plants,[138] recombinant, DNA, nasal immunisation.[139] One project is for a therapeutic vaccine.[140])

3.3. Pre-Licensure Trials

In April 2005, Merck phase III trials were taking place in 34 countries.[141] One phase III trial, FUTURE II, involved women from Brazil, Colombia, Denmark, Finland, Iceland, Mexico, Norway, Peru, Poland, Singapore, Sweden, the UK and the US (including Puerto Rico). GSK phase III trials were taking place in 15 countries, and a global multi-centre trials was enrolling participants in Asia Pacific, Europe, North America and Latin America[142]. On 18 January 2007, GSK announced a "head-to-head" trial to compare the immunogenicity of its vaccine to Gardasil.[143]

WHO officials have pointed out the lack of trials in sub-Saharan Africa, and the need to understand the effect of vaccines in areas of high HIV prevalence.[144] Whilst TB vaccine development is at an earlier stage in the process, this is a possible warning that use of the vaccine in Africa may have particular problems, and it may be best not to leave the identification of these too late.

3.4. Regulatory Approval

Gardasil was first approved in Mexico on 1 June 2006, and subsequently by the US Food and Drug Administration (FDA) on 8 June 2006.[145] The application to the FDA was made on 1 December, 2005.[146] According to a Merck press release, the Mexican

[137] WHO/IVR "New Vaccines against Infectious Diseases: Research and Development Status".
[138] University of Cape Town *Monday Paper* "Funds will back preliminary test of HPV vaccine", 22 July 2002
[139] WHO/IVR "New Vaccines against Infectious Diseases: Research and Development Status".
[140] Revaz, V, "Therapeutic vaccine against Human papillomavirus type 16", Département de Gynécologie, Centre Hospitalier Universitaire Vaudois [internal Lausanne University document] http://www2.unil.ch/cyberdocuments/pratique/acces/biologie_medecine/AB_Revaz_an.pdf
[141] WHO "Report of the Consultation on Human Papillomavirus Vaccines, World Health Organisation, Geneva, April 2005"
[142] WHO, "Report of the Consultation on Human Papillomavirus Vaccines, World Health Organisation, Geneva, April 2005"
[143] GSK Press Release "GlaxoSmithKline initiates head-to-head study of cervical cancer vaccines: Study to compare immunogenicity of GSK's cervical cancer candidate vaccine, CERVARIX®, to Merck's Gardasil®", 18 January 2007 http://www.gsk.com/media/archive.htm
[144] WHO "Report of the Consultation on Human Papillomavirus Vaccines"
[145] Merck Press Release "FDA Approves Merck's GARDASIL®, the World's First and Only Cervical Cancer Vaccine"
[146] AScribe.org "Merck Submits Biologics License Application to FDA for Gardasil, the Company's Investigational Vaccine for Cervical Cancer", 5 December 2005

application was made after the FDA application,[147] so it is unclear whether getting the product licensed in Mexico first was deliberately planned (there is no evidence of this from Merck press releases from the time – the application to Mexico was not emphasised[148]).

On 29 June the US Advisory Committee on Immunization Practices (ACIP) provisionally recommended Gardasil's use for 11- and 12-year-olds girls, and for girls and women 13 to 26 years old and not previously vaccinated; and recommended that it *could* be used for 9- and 10-year-olds at the discretion of a physician.[149] As of late 2006, the vaccine had been approved in more than 40 countries, including Australia, Taiwan, Canada, New Zealand and Brazil, and the EU; and application were under review in over 50 other countries.[150]

Gardasil is not on the UN list of prequalified vaccines for purchase by UN agencies.[151] PAHO states this is an "essential prerequisite" before agencies like the PAHO Revolving Fund or UNICEF can begin purchases.[152] It is estimated that the prequalification process could add an extra year before vaccines can be introduced in developing countries.[153]

3.5. Developing Country Activity

A. Early WHO Activity

In a 2005 report,[154] WHO described its work over the previous 6 years. This included a series of technical meetings to help with vaccine trials, and other input into vaccine evaluation. It also did research on duration of protection, ethical considerations, manufacturing costs, HPV type-specific prevalence, manufacturing capacity in developing countries, IP issues, research on HIV-positive women – but see below ("4. Missing Activity?") for reported gaps in information, which implies research in these areas was not sufficient.

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www.ascribe.org/cgi-bin/behold.pl?ascribeid=20051205.045918&time=07%2044%

[147] Merck Press Release "GARDASIL®, Merck's Investigational Cervical Cancer Vaccine, to Receive Priority Review from the U.S. Food and Drug Administration", 7 February 2006, www.merck.com/newsroom/press_releases/research_and_development/2006_0207.html

[148] Also note that GSK is not promoting its product to "developing countries first".

[149] Merck Press Release "Merck Launches National Advertising Campaign for GARDASIL®, Merck's New Cervical Cancer Vaccine"

[150] Merck Press Release "Merck Launches National Advertising Campaign for GARDASIL®, Merck's New Cervical Cancer Vaccine"

[151] WHO "United Nations prequalified vaccines: WHO list for vaccines for purchase by UN agencies as of November 2006" www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html accessed 29 November 2006

[152] PAHO "Human Papillomavirus Vaccines: A New Tool for Cervical Cancer Prevention" 20 September 2005 www.paho.org/English/AD/FCH/IM/HPV-FactSheet1.pdf

[153] Pollack AE, MS Balkin and L Denny "Cervical cancer: a call for political will" *International Journal of Gynecology and Obstetrics* (2006), 94: 333-342

[154] WHO "Report of the Consultation on Human Papillomavirus Vaccines"

B. The Bill and Melinda Gates Foundation Project

The Bill and Melinda Gates-funded Program for Appropriate Technology in Health (**PATH**) launched its HPV vaccine project in June 2006.[155] A grant of $27.8m was given by the Foundation to it and partners the Harvard School of Public Health, the International Agency for Research on Cancer, and WHO/IVR. The plan was for PATH to begin to pilot 'HPV vaccination demonstration projects' in early 2008 in India, Peru, Uganda and Vietnam[156] following 12-18 months of formative research in each country, to gather information about the medical, policy, fiscal and sociocultural environment.[157]

The demonstration projects themselves include some clinical but especially operations research, gathering information on the sociocultural, logistic, policy and clinical elements needed for HPV introduction.[158] The exact nature of the projects will depend on the formative research, but it will probably have studies looking at optimal age ranges to target; the differences between a school-based strategy and one based on semi-annual child health days; the impact of vaccinating boys on acceptability; and the most cost-effective way to reach 14-year-old girls.[159] This will potentially yield many useful lessons for other vaccines, and not just HPV. One can imagine a useful cross-learning exercise for TB booster vaccines. The vaccines for the project will be provided by Merck and GSK. The countries were said to be selected because of, among other reasons, their existing commitment to cervical cancer prevention and effective childhood vaccination programmes.[160]

PATH also plans to:

- Use the introduction efforts in the 4 pilot countries to inform and support global advocacy efforts (e.g. Alliance for Cervical Cancer Prevention mechanisms), regional vaccine strategies, and introduction in other countries.[161]
- Map decision-making processes to address potential bottlenecks,[162] including those of international funders.[163]
- Provide decision-makers with information to decide whether and how to add the vaccine to health programs.[164]
- Negotiate partnerships with both the vaccine producers.[165]
- Develop a global demand estimate, to guide decisions made by manufacturers; and for GAVI, G8 AMC financing teams and other potential decision-makers.[166]

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[155] PATH News Release "PATH to pave the way for cervical cancer vaccines in the developing world", 5 June 2006 www.path.org/news/pr060606-cervical_cancer_vaccine.php
[156] PATH "Update: Cervical Cancer Vaccine Project" (December 2006)
[157] PATH "Update: Cervical Cancer Vaccine Project"
[158] PATH "Introducing HPV Vaccines in Developing Countries"
[159] PATH "Update: Cervical Cancer Vaccine Project"
[160] PATH News Release "PATH to pave the way for cervical cancer vaccines in the developing world"
[161] PATH "Cervical Cancer Vaccine Project"
[162] PATH "Updated: Cervical Cancer Vaccine Project"
[163] WHO "Report of the Consultation on Human Papillomavirus Vaccines".
[164] PATH "Cervical Cancer Vaccine Project"
[165] PATH "Introducing HPV Vaccines in Developing Countries"
[166] PATH "Cervical Cancer Vaccine Project"

- Encourage dialogue between GAVI, governments and industry about price, providing all with data from the demonstration projects.[167]
- Develop selection criteria for and identify shortlist of early-introducer countries.[168]
- Develop and disseminate strategic forecasts, investment cases (using the GAVI framework [169]), and decision-making tools to inform and influence industry production capacity and pricing decisions, international agency financing initiatives, and country government introduction plans.[170]
- Work with vaccine producers, global vaccine distributors and developing country governments to identify and resolve logistical challenges of procuring, storing, transporting and administering vaccines.[171] For instance, as the vaccine will probably be administered to pre-teen children, it cannot be part of the usual EPI schedule for infants. There is varying evidence on how successful a school-based program might be, including concerns about school drop-out rates and low school attendance by girls.[172]
- Look at introduction questions, including what sociocultural barriers exist; how to deliver the vaccine most effectively to adolescent girls; how to integrate HPV into existing health programs; what the cost implications and ultimate public-sector price of the HPV vaccine program are; what combination of program activities (including other interventions) could have the most impact.[173]
- Do formative research on community attitudes. Several potential issues have been raised, e.g.
    - belief that a vaccine for pre-teens would encourage early sexual activity;[174]
    - lack of awareness about the causal link between HPV and cervical cancer, including among healthcare providers and policymakers;[175]
    - confusion about similar acronyms like HIV, HBV and HSV,[176] and, similarly, a misconception that the vaccine will protect against all STIs;[177]
    - possible fears that a girls-only vaccine would be a fertility control device,[178] as existed with tetanus toxoid in Mexico, the Philippines and Uganda;[179]
    - danger that people will stop screening;[180] and

[167] PATH "Updated: Cervical Cancer Vaccine Project"
[168] PATH "Introducing HPV Vaccines in Developing Countries"
[169] WHO "Report of the Consultation on Human Papillomavirus Vaccines"
[170] PATH "Cervical Cancer Vaccine Project"
[171] PATH page on HPV vaccine www.path.org/projects/cervical_cancer_vaccine.php accessed 27 November.
[172] See Biddlecom A, A Bankole and K Patterson, "Vaccine for cervical cancer: reaching adolescents in sub-Saharan Africa", *The Lancet* (2006), 367(9519): 1299-1300, for a brief discussion.
[173] PATH "Cervical Cancer Vaccine Project"
[174] PATH "Introducing HPV Vaccines in Developing Countries"
[175] PATH "Introducing HPV Vaccines in Developing Countries"
[176] PATH "Introducing HPV Vaccines in Developing Countries"
[177] WHO "Report of the Consultation on Human Papillomavirus Vaccines"
[178] PATH "Introducing HPV Vaccines in Developing Countries"
[179] Kane MA, J Sherris, P Coursaget, T Aguado and F Cutts "HPV vaccine use in the developing world". *Vaccine* (2006), 24(Supplement 3): 132-139

- confusion on the difference between endpoints for Merck and GSK (only Merck includes genital warts).[181]

This activity is very interesting from the point of view of TB, as it examines several of the issues that should be looked at for TB. Specifically, research to map decision-making processes; the development of selection criteria for early-introducer countries; and attitudinal research at both political and community level parallels TB marketing and launch studies. The PATH HPV team were extremely helpful to the Oxford group with offers to collaborate further and to share learning.

Harvard University is doing policy analyses using models adapted to different epidemiological settings to estimate population impact and cost-effectiveness of various vaccination strategies in different low-resource conditions, to identify potential synergies between vaccination and screening.[182] This would again be interesting work on TB. The **International Agency for Research on Cancer** is gathering epidemiological data on prevalence (including on age of cancer sufferers, the country-specific distribution of HPV types).[183]

The **WHO** is carrying out a number of activities: standardizing laboratory procedures and creating a laboratory network to facilitate vaccine licensure and monitoring in developing countries; creating a policy platform and "setting the global agenda" in consultation with regions and countries; and creating an information centre to help country decision-making.[184] An Expert Advisory Group was set up in April 2005 to develop guidelines for accelerating safe and effective vaccine use.[185]

C. Other Activities

Merck has stated that it will make the vaccine available in the developing world at "dramatically lower prices". It also mentions a partnership with India's Council of Medical Research to study Gardasil.[186] It is modelling the effect of vaccination strategies with dynamic modelling experts.

The companies are said to be discussing early introduction into public markets, but with this being dependent on demand and financial commitment.[187] There are also said to be discussions over local production options with governments and local producers, but it is unclear if these will be fruitful.[188]

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[180] WHO "Report of the Consultation on Human Papillomavirus Vaccines"
[181] WHO "Report of the Consultation on Human Papillomavirus Vaccines"
[182] PATH "Introducing HPV Vaccines in Developing Countries"
[183] PATH "Introducing HPV Vaccines in Developing Countries"
[184] PATH "Introducing HPV Vaccines in Developing Countries"
[185] WHO "Report of the Consultation on Human Papillomavirus Vaccines"
[186] Merck Press Release **"**Merck Launches National Advertising Campaign for GARDASIL®, Merck's New Cervical Cancer Vaccine"
[187] Kane, Sherris, Coursaget, Aguado and Cutts "HPV vaccine use in the developing world"
[188] Ibid.

WHO's **SAGE** discussed HPV vaccines in its November 2005 meeting. It was supportive, as was **UNICEF**, and called for strong political commitment from country governments (to meet the cost of the vaccine).[189]

PAHO preparatory activities have included:[190]

- Engaging vaccine suppliers in technical dialogue.
- Developing a joint work-plan with internal stakeholders.
- Strengthening National Regulatory Authorities.
- Advocacy efforts to increase awareness.
- Building partnerships with external organisations.

It also has an HPV vaccine introduction plan, which has 6 components:[191]

1) Building political will through top-down and bottom-up advocacy
2) Disseminating information and knowledge to allow evidence-based decision-making
3) Encouraging and conducting research, e.g. economic analyses and acceptability studies
4) Designing surveillance systems and tools
5) Mobilising cross-sectional support through social marketing and communication
6) Mobilising technical and financial resources

A recent conference, "Stop Cervical Cancer: Accelerating Global Access to HPV Vaccines", was convened by the International Union Against Cancer (UICC), the Rockefeller Foundation, the International Planned Parenthood Federation, PATH, the AIDS Vaccine Advocacy Coalition, and IAVI. It was held 12-13 December 2006 and attended by 60 representatives from public health agencies, pharmaceutical companies, NGOs and philanthropic organizations.[192] The organisers called for urgent action over the next 12-18 months to tackle obstacles; advocacy and resource mobilisation; and a broad, results-driven campaign.[193]

D. Missing Activity?

Needed information and actions which have been identified include:

- Information on efficacy for women over 25.[194]
- Impact of vaccination on disease transmission, cross-protection against other HPV types, HPV type distribution;[195] and on existing infection.[196]

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[189] WHO "Conclusions and recommendations from the Immunization Strategic Advisory Group", *Weekly Epidemiological Record* (2006), 81, 1, pp.1-12
[190] PAHO "Human Papillomavirus Vaccines: A New Tool for Cervical Cancer Prevention"
[191] PAHO "Human Papillomavirus Vaccines: A New Tool for Cervical Cancer Prevention"
[192] Waiting for more details from conference organisers.
[193] UICC News Release "Stop cervical cancer: make new vaccines available in developing countries, roundtable says", 13 December 2006 www.uicc.org/index.php?id=975&backPID=1235&tt_news=255
[194] Van Damme P "HPV vaccination strategies: mobilize all stakeholders", presentation to satellite symposium at Eurogin 2006 conference on cervical cancer, 23-26 April 2006 www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf
[195] Ibid.

- Information on effect of herd immunity in increasing effectiveness of vaccination.[197]
- Information on long-term duration. Barnabas *et al*, in a model of disease transmission in Finland, found that vaccine protection of 3-4 decades would be needed to substantially reduce cancer incidence.[198,199] Some studies have been done, e.g. Harper *et al* found in a cohort study for GSK in North America and Brazil that high-level protection was maintained for 4 years.[200] International efforts are underway to set guidelines for monitoring vaccination programmes.[201]
- Evaluation of vaccine safety and efficacy in Africa and especially areas with high HIV prevalence.[202]
- Health economic data,[203] including impact of protection against low-risk types 6 and 11 on cost-effectiveness; and marginal cost-effectiveness of adding other types.[204]
- Better cost-effectiveness information on vaccinating men.[205] Some studies have been done.[206]
- Evaluation of efficacy at school entry age or infancy; and when simultaneously administered with other vaccines (e.g. tetanus, MMR).[207]
- Whether a lower number of doses might give adequate immunity and what cost implications this would have.[208]
- Research on aerosol and oral vaccination to overcome problems of multiple injections in developing countries. Evidence so far is apparently promising.[209]

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[196] Schiller J "HPV vaccine efficacy", training course at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf

[197] Myers E "Cost-effectiveness of HPV vaccines", training course at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf

[198] Barnabas RV, KM French, P Laukkanen, O Kontula, M Lehtinen and GP Garnett "HPV vaccination: unresolved issues and future expectations", training course at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf

[199] How applicable is this to developing countries?

[200] Harper DM, C Wheeler, EL Franco and G Dubin "Sustained Efficacy of AS04-adjuvanted HPV-16/18 L1 vaccine: results from a long term follow-up study", scientific session at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf

[201] Dillner J "Long term follow-up and monitoring of HPV vaccination programs", scientific session at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf

[202] WHO "Report of the Consultation on Human Papillomavirus Vaccines"

[203] Van Damme "HPV vaccination strategies: mobilize all stakeholders"

[204] Myers "Cost-effectiveness of HPV vaccines"

[205] Castellsagué, X "The role of men in HPV transmission and cervical carcinogenesis: should we vaccinate them?", scientific session at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf. Also Myers "Cost-effectiveness of HPV vaccines"

[206] E.g. as referred to by Jenkins D "Public health issues related to HPV vaccination", training course at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf

[207] WHO "Report of the Consultation on Human Papillomavirus Vaccines"

[208] WHO "Report of the Consultation on Human Papillomavirus Vaccines"

[209] Revaz V, D Fraillery, D Baud, J Schiller, D Lowy and DN Haefliger "Aerosol and oral vaccination against HPV16 and cervical cancer", scientific session at Eurogin 2006 conference www.eurogin.com/2006/docs/EUROGIN2006-Abstracts.pdf

- Information on possible use of reproductive health networks to deliver immunisation, e.g. family planning, pre- or post-natal care, and possibility of combining this with existing (child) immunisation networks.[210]
- Mapping the IP ownership situation to help developing-country producers decide if vaccine development is an attractive option.[211]
- Alternative technologies, not using virus-like particles (VLP technology), which could reduce cost, but are many years of research away.[212]

[210] Kane, Sherris, Coursaget, Aguado and Cutts "HPV vaccine use in the developing world"
[211] Ibid.
[212] Ibid.

4. ROTAVIRUS VACCINE CASE DETAILS

Summary

This document looks at one of the key vaccine 'failures' in getting a vaccine to developing countries. A vaccine against rotavirus, Rotashield, was launched in the US but cases of intussusception following administration of the vaccine led to its withdrawal from the market in the US.

Despite acknowledgement that in different settings this decision might not have been necessary, this undermined the potential use of Rotashield in developing countries, where the burden of disease is greater and fatalities associated with rotavirus significantly higher.

> "…in the absence of data on the effectiveness of rotavirus vaccine in developing countries and in the face of political challenges to using a vaccine withdrawn from the US market, further use of Rotashield in any country was untenable."[1]

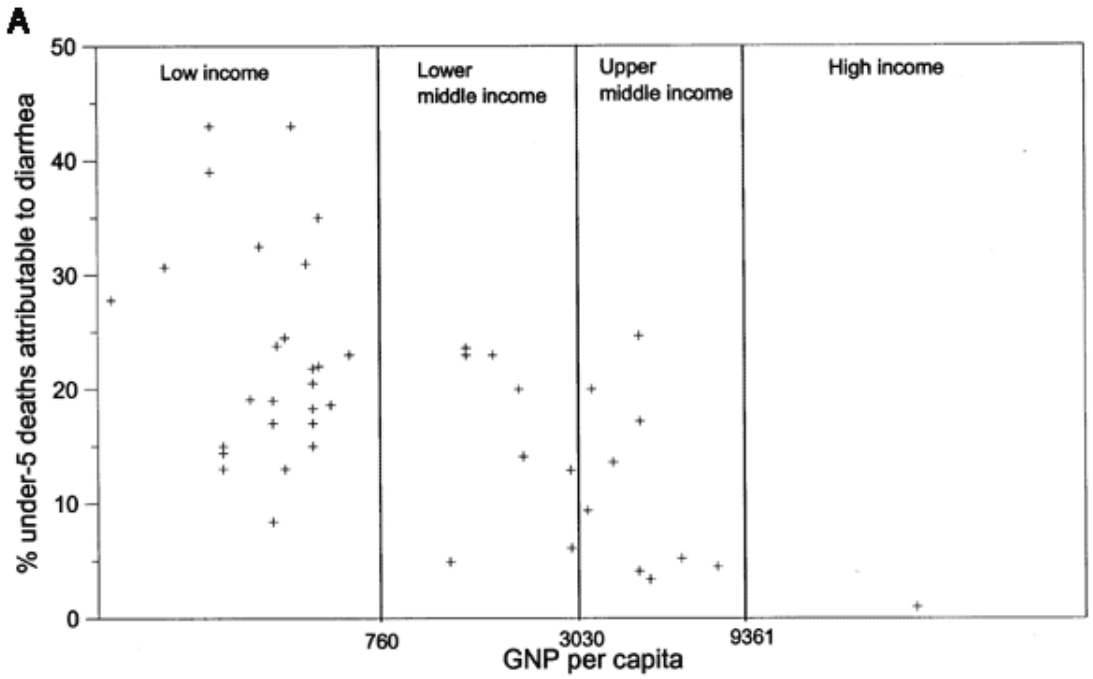
The body of scientific evidence suggests that in fact there would have been no case for withdrawal in developing countries, and further, that vaccination at less than 3 months would prevent a possible association with intussusception.

Recently, there have been some important developments in advocacy of rotavirus vaccines programs, supported by the creation of international committees with the aim of accelerating efforts. PATH, the WHO and CDC have collaborated since 2003 in their 'Rotavirus vaccine program', funded by GAVI and the Vaccine Fund. GAVI have also formed a Rotavirus ADIP and Supply Strategy Group. This coincides with the development of vaccines by Merck, GSK and Wyeth. The importance of surveillance[1] has been emphasised in these recent initiatives, with the development of Surveillance Networks in particular in Asia.

The document describes the burden of rotavirus disease and the need for vaccines before detailing the story of Rotashield. Only recently has the rotavirus vaccine become a genuine prospect for developing countries, with a new wave of vaccines reaching licensure from 2005, and Merck's supply of RotaTeq to Nicaragua (providing free technical support) being hailed as an example for encouraging integration into national immunization programs across Latin America, Asia and Africa.

4.1. Rotavirus Disease and Need for Vaccines

Since the mid 1980s, groups reviewing the need for the development of new vaccines including the WHO, the Institute of Medicine, GAVI have identified rotavirus vaccines as a priority for development. There is a great burden associated with fatal rotavirus disease (440,000 deaths a year). 90% of deaths occur in Africa and Asia, with more than 100,000 occurring in each of India and sub-Saharan Africa, and 35,000 in China.[213] The disproportionate impact in terms of deaths of children of less than five years can be seen Figure A. For comparison Figure B shows percentage of diarrhea hospitalization attributable to rotavirus by country GNP.

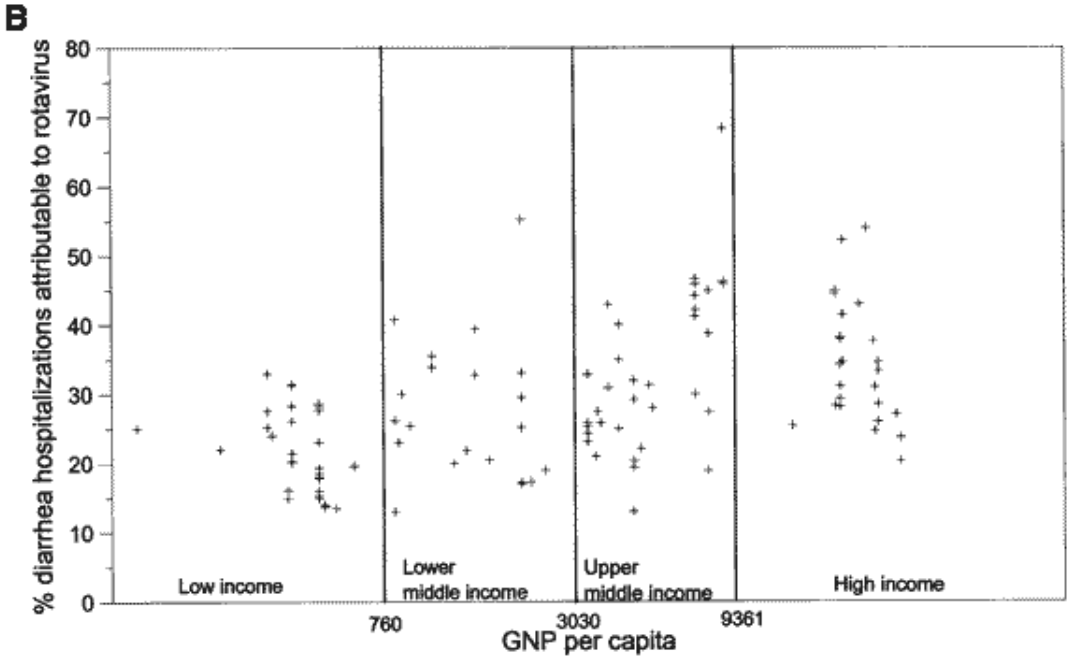


Median	21	17	9	1
IQR	17-30	11-23	5-17	NA

Figure. A. Percentage of deaths in children <5 years that are attributable to diarrhea for countries in different World Bank income groups, by gross national product (GNP) per capita of the country. IQR, interquartile range.[214]

[213] Parashar UD, JS Bresee and RI Glass "The global burden of diarrhoeal disease in children" *Bulletin of the World Health Organization* (2003) 81(4): 236

[214] Taken from Figure 1 of Parashar UD, EG Hummelman, JS Bresee, MA Miller and RI Glass "Global Illness and Deaths Caused by Rotavirus Disease in Children" *Emerging Infectious Disease* (2003) 9(5): 565-572.



Median	20	25	31	34
IQR	16-27	20-33	25-42	28-38

Figure B. Percentage of diarrhea hospitalization attributable to rotavirus for countries in different World Bank income groups, by GNP per capita of the country. IQR, interquartile range.[215]

As Bresee comments (2006):

> "Hospital-based surveillance performed in Asia, Africa and Latin America indicates that 25-55% of hospitalizations for diarrhoea among children less than 5 years of age are associated with rotavirus infection."

There is a firm scientific basis for developing live oral vaccines. Vaccination is deemed the best method for prevention as studies[216] have suggested that rotavirus infection cannot be prevented through improvements in water and sanitation:

> "Rates of rotavirus illness among children in industrialized and less developed countries are similar, indicating that clean water supplies and good hygiene have little effect on virus transmission and so further improvements in water or hygiene are unlikely to prevent the disease."[217]

[215] Taken from Figure 1 of Parashar UD et al ibid.
[216] Velazquez FR, DO Mason, JJ Calva, L Guerrero, AL Morrow and S Carter-Campbell "Rotavirus infection in infants as protection against subsequent infections" *New England Journal of Medicine* (1996) 335(14): 1022-1028
[217] Dennehy PH "Rotavirus Vaccines – An update" *Vaccine* (2007) *In Press*

Also, first infections are proven to induce immunity against severe disease after re-infection. Both these points have been made by key scientific figures such as Parashar, Hummelman, Miller, Glass and Bresee. There is a belief that increased investment in development at this time could speed the introduction of vaccines in developing countries and a measurable decrease in the number of hospitalization and deaths associated with rotavirus, i.e. a significant impact both for rotavirus and also vaccine implementation in general.

Rotavirus vaccination

- The age at which vaccine is given is an important issue (<3 months should prevent association with intussusception).
- Results show that rotavirus vaccine is more efficacious against severe disease – therefore it is recommended that the endpoint of efficacy studies should be severity of illness (rather than hospitalization) and the need for standard definitions of both a diarrhoea episode and the severity of the illness is noted.
- Seasonality is an issue in some countries. In countries where the vaccine circulates year-round (tropical settings), vaccine efficacy may be independent of time of vaccine administration.[218]

4.2. Timeline

1979: WHO's former Program for Control of Diarrhoeal Diseases listed for the first time the prevention of rotavirus disease as one of its goals.

1985: The US Institute of Medicine wrote that rotavirus vaccine development is a high priority for developing countries. Also, Feachem and DeZoysa published a paper outlining the disease burden associated with rotavirus (the results from this study were used for the next 10 years).

1996: Rotavirus was listed as a "best buy" for developing countries in a report for WHO and other agencies, chaired by Dr Tore Godal.

1996: US IOM issued a report claiming that Rotavirus was not a high priority for prevention in the US.
In reaction to this, the group of Dr Glass at the CDC conducted a series of investigations to better define the disease burden associated with rotavirus. The methods were duplicated in other developed countries to show that rotavirus was a problem worldwide.

[218] PATH Rotavirus Vaccine Program "The Development of Live, Attenuated Rotavirus Vaccines" (March 2006) http://www.rotavirusvaccine.org/documents/RotaManufResourceGuide.pdf

August 1998: RRV-TV (Rotashield) was licensed in the US by the FDA and introduced into the routine schedule of immunizations by ACIP and the American Academy of Pediatrics.

July 1999: Rotashield suspended.
WHO report (February 2000) noted that studies of safety and enhanced immunization response in India and Bangladesh commenced but were put on hold because of the investigation into the association between RRV-TV and intussusception.

June 2002: GAVI endorsed the creation of ADIPs (Accelerated Development and Introduction Plans), following McKinsey Study in January 2002 financed by the Bill and Melinda Gates Foundation and the World Bank.

January 2003: PATH proposed to take up the Rotavirus ADIP, endorsed by GAVI.
Program leaders are Director John Wecker (extensive experience in pharmaceutical industry and PPPs) and Scientific Director Roger Glass (extensive experience with the rotavirus vaccine)

2005: New rotavirus vaccines from Merck and GSK (neither showed increased risk of intussusception).

4.3. Rotashield

Summary:
Rotashield was approved by the CDC, supported by research and analysis by members of the Advisory Committee on Immunization Practices. After reports of intussusception to the Vaccine Adverse Event Reporting System, the manufacturer (in discussions with the FDA) voluntarily ceased further distribution of the vaccine. The same ACIP committee then concluded that intussusception occurs with significantly increased frequency in the first 1-2 weeks after vaccination, particularly following the first dose, and therefore stated that it no longer recommended the vaccination for vaccinations of RRV-TV at 2, 4 and 6 months of age.

For 7 years following this public withdrawal of a vaccine due to concerns over adverse effects, and questions of the vaccine safety, no vaccines against rotavirus were licensed in the US.

Approval:
31 August 1998. Licensed by FDA**.** Rotashield was manufactured by Wyeth-Lederle Vaccines and licensed by FDA in August 1998.
The document representing the first statement by the Advisory Committee on Immunization Practices on the use of an oral, live rotavirus vaccine licensed by the FDA for use among infants was the CDC Morbidity and Mortality Weekly Report.
Material in the Report was prepared for publication by

- National Center for Infectious Diseases (James M Hughes, MD, Director) Division of Viral and Rickettsial Diseases (Brian W J Mahy, PhD, Director)
- National Immunization Program (Walter A. Orenstein, MD, Director) Epidemiology and Surveillance Division (John R Livengood, MD, Director)

The report was written by CDC staff members Joseph S Bresee, Roger I Glass (both from Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases); and Charles R Vitek (Epidemiology and Surveillance Division, National Immunization Program).

Initial Report:

- Explains the decision to adopt the immunization policy. The report gave evidence of the disease burden and suggested that multivalent vaccines would be more suitable.
- States that in the US a high level of rotavirus morbidity occurs despite currently available therapies, thus it is necessary to develop a vaccine or vaccines.
- Following research to develop a safe and efficacious vaccine (monovalent and multivalent) decision to licence Rhesus-based rotavirus vaccine, a tetravalent vaccine produced by Wyeth-Lederle Vaccines and Pediatrics,
- Explains that the efficacy of monovalent vaccines varied in trials.
- Researchers postulated that a multivalent vaccine that provided serotype-specific immunity against all common human rotavirus strains might be more effective.

Studies illustrated that simultaneous administration of a three-dose series of RRV-TV did not diminish the immune response to Oral Polio Vaccine, DTP, Hib Vaccine, IPV or Hep B Vaccine (according to unpublished data from Wyeth-Lederle, 1998).

Withdrawn:

In **July 1999, CDC** recommended that health-care providers and parents postponed use of the vaccine at least until November 1999, based on reports of intussusception.

16 July 1999 FDA

Wyeth-Lederle temporarily suspended further distribution and administration of Rotashield until more data on the potential association between vaccine administration and intussusception become available. The action was taken in consultation with the Food and Drug Administration following a recommendation from the Centers for Disease Control and Prevention to postpone administration because of the reports to the Vaccine Adverse Events Reporting System (VAERS) of a possible association between the use of Rotashield and the development of intussusception.

22 October 1999 ACIP

Advisory Committee on Immunisation Practices (ACIP) reviewed scientific data “from several sources” and concluded that intussusception occurred with significantly increased frequency in the first 1-2 weeks after vaccination, particularly following the first dose. Therefore ACIP stated that it no longer recommended the vaccination for vaccinations of RRV-TV at 2, 4 and 6 months of age, although also stating that:

"…the ACIP's decision may not be applicable to other settings, where the burden of disease is substantially higher and where the risks and benefits of rotavirus vaccination could be different."[219]

RRV-TP was recommended because it was shown in pre-licensure trials to be a safe and effective vaccine. In those trials, RRV-TV prevented rotavirus in at least 50% of cases of diarrhoea and almost all of the hospitalizations.

Consensus/Comments:

- Risk for intussusception was at 1 case per 10,000 children immunized with Rotashield (Peter, Myers).[220]
- The range of estimates varied more than 100-fold – and was considered too high in the United States, a country in which deaths from rotavirus are uncommon.

As Glass et al (2005) comment:

"The exact pathogenic mechanism by which Rotashield might cause intussusception was never determined…. In retrospect, had the first dose of vaccine been administered only to children less than 90 days of age the risk of intussusception could have been substantially reduced to approximately ≤1 case/30,000 vaccine recipients."[221]

Studies by scientists (and supported by ethicists) argued that in the developing world, where about 1 in 200 children die from rotavirus disease, the benefits of vaccination far exceeded the risks.

4.4. Vaccines currently in development

Following the withdrawal of Rotashield (at which time at least 7 different live oral candidate vaccines were in development) manufacturers had to reassess whether its vaccine might cause intussusception. However, despite the circumstance surrounding the withdrawal of Rotashield, there were in fact positive outcomes. Competition between Merck and GSK accelerated development, and vaccines have been developed in China (lamb strain, Lanzhou), India and Indonesia (being considered as candidate vaccines):

"The two vaccines from the multinational vaccine manufacturers are based on different principles and will first be targeted to different markets: the GSK vaccine will be targeted for use in Latin America and the Merck Vaccine for use in the US"[222]

Merck and GSK have both had their vaccines licensed in the US and Europe respectively, and have filed for license in over 75 countries together. However there have been

[219] CDC "Withdrawal of Rotavirus Vaccine Recommendation" *Morbidity and Mortality Weekly Report* (1999) 48(43): 1007

[220] Peter G and MG Meyers "Intussusception, Rotavirus and Oral Vaccines: Summary of a Workshop" *Pediatrics* (2002) 110(6): e67

[221] Glass RI, JS Bresee, R Turcois and T K Fisher "Rotavirus Vaccines: Targeting the Developing World" *The Journal of Infectious Diseases* (2005) 192: S160-S166

[222] Ibid.

difficulties previously in vaccinations that are suitable for developing counties, with a lack of vaccine efficacy demonstrated in any live oral rotavirus vaccine in Africa or in any poor country in Asia. RIT 4237 (Smith-Kline), the first rotavirus vaccine that was highly effective in Finnish children, failed to protect children in Rwanda and the Gambia, as well as children on a Navajo reservation in the southwest US.

Vaccines Manufactured (also see Table 1 in Annex)**:**

RotaTeq (Merck)
RotaTeq was developed in the early 1990s. Plans to launch final trials (phase III) in 1999 were marred by the Rotashield link with intussusception. A comprehensive safety and efficacy trial (REST) of more than 60,000 children was launched in the US and Europe. Approval of RotaTeq was based on results of three phase III trials of the drug, which treated a combined 72,324 infants in 11 countries. The studies were designed to investigate both the efficacy of the drug and the vaccine's safety and manufacturing consistency. It was approved by the FDA in February 2006.

22 September 2006. It was announced that all infants in Nicaragua born during a three-year period will receive free vaccination with RotaTeq. Merck is also to provide technical assistance at no cost for the duration of the program. (This relates to Merck's commitment to improve access to important vaccines in the developing world – Mark Feinburg, VP of Policy, Public Health and Medical Affairs, Merck.[223]) The plan to jointly conduct this project was announced by Merck & Co. Inc and the Nicaraguan Ministry of Health during the second meeting of the Clinton Global Initiative in New York.

According to PAHO, Nicaragua experienced an increase in reported cases of diarrhoea in the beginning of 2005, with a total of 64,088 cases and 56 deaths due to diarrhoea as reported to the Nicaraguan Ministry of Health. Children less than five years of age were most affected, representing nearly three quarters of the cases. During the period of increased case reports, 253 children were evaluated for possible rotavirus infection and 59% tested positive for rotavirus.

In recent years, Nicaragua has successfully controlled the spread of other vaccine-preventable diseases by achieving and maintaining high vaccination coverage levels and adding additional vaccines to their national infant immunisation schedule, including the measles-mumps-rubella (MMR) vaccine in 1998. It should be noted that Nicaragua already had a well-reputed implementation strategy ensuring that almost 90% of children receive standard EPI.

Note. The efficacy of RotaTeq beyond the second season after vaccination was not evaluated. The safety and efficacy of RotaTeq have not been established in infants less than six weeks of age or greater than 32 weeks of age. No safety or efficacy data are

[223] Merck Press Release "Merck and Nicaragua Unveil New Rotavirus Vaccine Demonstration Project at Clinton Global Initiative", 22 September 2006
http://www.merck.com/newsroom/press_releases/product/2006_0922.html

available for the administration of RotaTeq to infants who are potentially immuno-compromised.[224] (Medical News Today)

Rotarix (GSK (with Avant))
Rotarix has been developed over a similar time-frame to RotaTeq. It can also be administered at the same time as other infant vaccines - diphtheria-tetanus-acellular pertussis vaccine (DTPa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine and pneumococcal vaccine.
Phase III trials were conducted in the third quarter of 2004, and as reported by Medical News Today:

> "The Phase III clinical study in over 60,000 infants aged 6 weeks to 6 months, conducted in 11 Latin American countries and in Finland, confirmed that Rotarix(TM) is safe and well tolerated."[225]

Smaller Phase III trials are being conducted in Asia and Africa.

12 July 2004. Licensure was obtained from the Mexican regulatory authorities, and launch began in **January 2005.** Since then more than 24 additional licenses have been granted worldwide (12 Latin American countries including Brazil; Philippines and Singapore being the first Asian countries).

Recently, Brazil and Panama included the rotavirus vaccine for the first time in their national official vaccination calendars. In Panama, the President Martin Torrijos was photographed administering vaccine to an infant (14 March 2006). As part of the government's paediatric immunization program, vaccination with Rotarix will be available free at public health clinics in Brazil and Panama.

Rotarix received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), the Scientific Committee, which evaluates the quality, safety and efficacy of medicinal products in the European Union, on 15 December 2005.

27th February 2006. European Commission granted approval of Rotarix, the first vaccine available to children in Europe for the prevention of gastroenteritis caused by rotavirus. There had been positive opinion from the Committee for Medicinal Products for Human Use (CHMP), the Scientific Committee which evaluates the quality, safety and efficacy of medicinal products in the European Union, on 15 December 2005. Rotarix is not approved in the US at the time of writing; however there are plans to file for approval in the US where discussions are ongoing with the FDA. In May 2006 it became available in Australia.

GSK trials are currently being conducted in Malawi and South Africa (Phase III for efficacy) – data from these studies are not expected until 2009 but organizations like GAVI, PATH, the WHO and the CDC are already actively engaged in accelerating the

[224] Ibid.
[225] GSK Press Release "GSK's Global Launch with Rotarix™ starts in Mexico (for rotavirus)", 9 January 2005 http://www.medicalnewstoday.com/medicalnews.php?newsid=18718

testing and introduction of rotavirus vaccines in countries where the most deaths from severe gastroenteritis occur.

13 February 2007. GSK awarded prequalification status for Rotarix by WHO. WHO prequalification facilitates vaccine supply as it encourages purchase of the vaccines by PAHO, UN agencies and other multilateral organisation, and signals the recognition of the importance of Rotavirus immunization.[226]

4.5. International Initiatives

Summary
GAVI noted the need for global immunization against rotavirus and created the Accelerated Development and Introduction Plans in 2002 (ADIP) with the long-term objective to introduce a safe and effective rotavirus vaccine through EPI to children in developing countries.[227] PATH proposed to host the ADIP for rotavirus and was accepted. PATH now describes the initiative as the Rotavirus Vaccine Program. The PATH work is also often through its Children's Vaccine Program branch.

Most recently (August 2006) GAVI created the Rotavirus and Pneumococcal Vaccines Supply Strategy Group. GAVI also has a Rotavirus Action Plan which includes work with other stakeholders.

There are some specific issues related to developing vaccines against rotavirus in developing countries, as noted in the WHO meeting February 2000.[228] Children in developing countries become infected with rotavirus much earlier in life, they more commonly have mixed infections, and they are more likely to have infections with uncommon serotypes. In particular there is evidence of unusual strain diversity in Brazil, India and Malawi (See Table 1).

2003 PATH Proposal to host ADIP:[229]

- Emphasis on the requirement for disease burden and evaluation studies – crucial for any decisions on the introduction of vaccines.
- PATH Surveillance systems were already operating in Africa and Asia (9 countries).

[226] GSK Press Release "WHO awards prequalification status to GSK rotavirus vaccine", 13 February 2007 http://www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=975
[227] PATH "Accelerated Development and Introduction Plan (ADIP) for Rotavirus Vaccines: A Final Revised Proposal to GAVI" (January 2003) www.gavialliance.org/resources/rota_adip__web.pdf
[228] WHO "Report of the meeting on future directions for rotavirus vaccine research in developing countries, Geneva, 9-11 February 2000" (2000) http://www.who.int/vaccines-documents/DocsPDF00/www531.pdf
[229] PATH "Accelerated Development and Introduction Plan (ADIP) for Rotavirus Vaccines: A Final Revised Proposal to GAVI"

- Core Surveillance Project Grants to be offered to countries with minimal or no quality data available. Funds were made available to establish hospital-based surveillance systems based on CDC/WHO's Generic Protocol.

According to the McKinsey analysis conducted on the ADIPs in 2002,[230] the single greatest obstacle to expediting testing and supply of new vaccines in developing-country settings is the uncertainty of demand for new vaccines. Therefore certain Go/No-Go decision points are highlighted, noting in particular the problem of reliable demand:[231]

- The decision to purchase rotavirus vaccine through GAVI and The Vaccine Fund.
- Commitment to procure the vaccine by GAVI and the Vaccine Fund will likely develop over time, as will the level of commitment of industry to move forward or make price-volume agreements.
- This decision to commit "would be revisited as the vaccine candidates progress and to further leverage commitments on price-volume from industry partners."[232]

Vaccine candidate-specific Go/No-Go Decision points (2003-2006)

- Does the manufacturer have a plan for vaccine evaluation of the candidate in developing countries?
- Does the manufacturer have a plan for vaccine introduction in developing countries with in an acceptable time-frame?
- Is there planned manufacturing capacity to satisfy developing-country demand? (According to demand forecasting of initial seven-year model and further developments?)
- Is there a favourable risk-benefit for vaccine introduction in developing countries?
- Is there demonstrated heterotypic serotype protection (e.g. against G9 strains) from Phase III trials? (To be included in annual work plan and then discussed with ADIP as needed)?
- Is there an acceptable price-volume agreement reached?[233]

PATH's Children's Vaccine Program (CVP)

- Rotavirus expert group advising and aiding development of rotavirus strategic plan.
- Financial support of extensive surveillance and vaccine development activities.
- A PPP between Bharat BioTech and partners in India (AIIMS/IISc) and the US (Stanford/CDC) has been initiated with support from CVP, Indo-US Vaccine Action Program and other donors. *Expected licensure data was 2006 but at time of*

[230] McKinsey & Company Report commissioned by the Gates Foundation and World Bank 2002, available at http://www.gavialliance.org/Resources_Documents/Policy_Technical/Accelerating_RD/adip.php

[231] McKinsey & Company Report commissioned by the Gates Foundation and World Bank 2002, available at http://www.gavialliance.org/Resources_Documents/Policy_Technical/Accelerating_RD/adip.php

[232] PATH "Accelerated Development and Introduction Plan (ADIP) for Rotavirus Vaccines: A Final Revised Proposal to GAVI"

[233] Ibid.

writing in late 2006: Current status is only at Phase I trials although Phase II should have been completed now.

There is significant overlap between the Rotavirus Global Agenda, CVP's rotavirus activities and the Interim ADIP strategic plan.

CVP is also "actively participating" in a creative partnership with the public sector and GSK, the Rotavirus Action Program for Immunization and Development (RAPID):

- Provides funding to program areas that cannot be met by other partners, e.g. arranging travel.
- Provides funding to Phase I and II trials in Asia (Bangladesh) and Africa (South Africa).

4.6. Surveillance

Asian Rotavirus Surveillance Network (ARSN)

- ARSN was established primarily to address the acknowledged lack (following GAVI and WHO meeting 2001) of recent, high-quality data on the burden of disease in the poorest countries with which to establish the need for vaccinations when they become available.[234]
- This gap between the extent of the disease burden and the acknowledgement of it at a national level has been discussed. For example Parashar et al note with reference to China, which has the second largest cohort of children born each year (17m) and the second largest number of rotavirus deaths per year (35,000)

  "…many countries have little appreciation of the burden of diseases in their own settings because diagnoses are rarely made and research is limited."[235]
- ARSN aims to:
  - Confirm global importance of rotavirus disease.
  - Document regional epidemiological profile of rotavirus – demonstrates that the age distribution of rotavirus disease-associated hospitalizations tends to shift toward younger ages in countries with the lowest income levels.
- The emphasis is on allowing countries to make decisions of priority of rotavirus disease prevention.

[234] Bresee J, ZY Fang, B Wang, EA Nelson, E Hummelman, R Glass et al "First report from the Asian Rotavirus Surveillance Network" *Emerging Infectious Disease* (2004) 6:988-995
[235] Parashar UD et al ibid.

4.7. Case Study – Nigeria

Melliez et al (2007) use a Markov decision tree to compare two alternatives (vaccine programme and no vaccine programme) and show that in a hypothetical Nigerian cohort from birth to age five, the vaccine programme would prevent 284,000 cases of rotavirus diarrhoea annually and 6,129 deaths due to the disease.[236]

- Because the rotavirus vaccine can be administered simultaneously with the Diphtheria-Tetanus-Polio vaccine (DTP), Melliez et al assume that the monovalent vaccine coverage rate would be approximately the rate of DTP coverage in Nigeria for the base case analysis.
- Strategies to reduce the burden caused by rotavirus diarrhoea in sub-Saharan Africa may be therapeutic or preventive.
- Sensitivity analysis shows that the vaccine coverage rate is the variable with the greatest impact on vaccine efficacy.

> "This, together with the availability of new vaccines, will make it important to promote measures to increase vaccination coverage among the population."[237]

It should be noted that there are some concerns with the perceived efficacy of rotavirus vaccine, in particular with relation to co-morbidities. In Nigeria for example, 12% children suffer from sever weigh deficiency and 120,000 are infected with HIV disease. These co-morbidities could decrease vaccine efficacy.

Phase II clinical trials of Rotarix have been started under the auspices of WHO in Bangladesh and South Africa in order to investigate the safety and immunogenicity of the vaccine when administered to HIV-infected infants, and also when given concomitantly with oral polio vaccine; as these are seen to be two factors particularly pertinent to developing countries.[238]

There are other possible cases studies in China and other parts of Asia; Glass et al have published extensively on this.

[236] Melliez H, PY Boelle, S Baaron, Y Mouton and Y Yazdanpanah "Effectiveness of childhood vaccination against rotavirus in sub-Saharan Africa: The case of Nigeria" *Vaccine* (2007) 25:298-305
[237] Ibid.
[238] Dennehy "Rotavirus Vaccines – An update"

4.ANNEX

Table 1 – Vaccines licensed and explanation

Vaccine	Manufacturer (location)	Rotavirus strains (genotype)	Status of vaccine	Efficacy
RotaTeq	Merck (United States)	Pentavalent human-bovine reassortants WC3 × WI79 (P7[5],G1), WC3 × SC2 (P7[5],G2), WC3 × W178 (P7[5],G3), WC3 × BrB (P7[5],G4), and WC3 × WI79 (P1A[8],G1)	Phase 3 trial involving >60,000 children	Pending
Rotarix	GlaxoSmithKline (Belgium)	Monovalent, attenuated human strain 89-12 (P[8],G1)	Phase 3 trial involving >60,000 children	90% in Venezuela, Brazil, and Mexico
LLR	Lanzhou Institute of Biological Products (China)	LLR strain (P[12],G10)	Licensed in China in 2000	Not evaluated in a randomized controlled trial
RV3	University of Melbourne (Australia) and Bio Farma (Indonesia)	Monovalent neonatal human strain (P2A[6],G3)	Phase 2 trial	ND
UK reassortant vaccine	NIH (United States)	Tetravalent human-bovine reassortant UK × Wa (P7[5],G1), UK × DS1 (P7[5],G2), UK × P (P7[5],G3), and UK × ST3 (P7[5],G4)	Phase 2 trial	Pending
Indian neonatal vaccines	Bharat Biotech (India)	Neonatal strains 116E (P[11],G9) and I321 (P[11],G10)	Phase 1 trial	ND
Rhesus tetravalent	BIOVIRx (United States)	Tetravalent human-rhesus reassortants RRV × D (P5[3],G1), RRV × DS1 (P5[3],G2), RRV (P5[3],G3), and RRV × ST3 (P5[3],G4)	Licensed by the US FDA but currently not manufactured	>90% in the United States and Finland and 70% in Venezuela

NOTE. FDA, Food and Drug Administration; LLR, Lanzhou lamb rotavirus; ND, not determined; NIH, National Institutes of Health; WC3, bovine rotavirus strain.

The Merck bovine-human reassortant vaccine contains five antigens (G1 to G4 and P1), whereas the GSK vaccine contains a single, attenuated human rotavirus serotype, G1P1. Both vaccines have been shown to have similar efficacy against any rotavirus gastroenteritis, to have up to 90-100% efficacy against severe rotavirus gastroenteritis, and to have heterotypic protection against multiple virus serotypes. Recent licensure of Rotarix in predominantly Latin American countries and of RotaTeq in the US will provide additional post-marketing effectiveness data against non-vaccine serotypes. Both vaccines are also in clinical trials for efficacy in developing nations.

Some other vaccine strategies being pursued include additional bovine virus-based human reassortants developed at the National Institutes of Health in Washington, DC; a rhesus rotavirus–based human reassortant (Rotashield); and vaccines based on attenuated strains of rotavirus that enter new-born nurseries in hospitals – known as neonatal strains – being developed in Australia and India.

5. HIB VACCINE CASE DETAILS

Summary

Haemophilus influenzae type B (Hib), alongside hepatitis B, is often criticised as being a disease which is vaccine-preventable but which saw a significant (10-year) time lag before introduction into developing countries.

Factors limiting the vaccine introduction in developing countries include:

(Demand-side)

- Difficulties in diagnostics of Haemophilus influenzae type B (Hib). In particular, diagnosis is risky and complicated at the local level.
- Despite high recognition of the disease burden in Latin America there is still low recognition of it in Africa/Asia (McKinsey Analysis funded by World Bank and the Bill and Melinda Gates Foundation, 2002).

(Supply-side)

- Supply to developing countries "not prioritised by manufacturers"[a]

Increasing awareness of the global burden of Hib disease and the success of efforts to introduce Hib vaccination programs in industrialized countries had led to an effort to support the introduction of Hib vaccines in EPI. There has been encouragement particularly of the use of combination vaccines.

Key players advocating the introduction of Hib vaccines include WHO, SAGE and GAVI.

- WHO identified DTP-HepB and DTP-HepB+Hib combination vaccines as a priority for programs.
- GAVI was willing to pay higher prices for combination vaccines compared to traditional EPI vaccines.

  "A core GAVI activity is support for the introduction of HepB and Hib containing combination vaccines. The recommendation to provide support for combination, rather than monovalent products was originally made by the GAVI Working Group. The choice of combination vaccines was driven by a concern for safety and programmatic ease, as DTP-based combination vaccines were considered easier to introduce than a stand alone new antigen requiring an additional injection."[b]
- SAGE (Strategic Advisory Group of Experts, Principal Advisory Group to WHO) recently recommended the global implementation of Haemophilus influenzae type B vaccine, unless robust epidemiological evidence exists of low disease burden, lack of benefit or overwhelming barriers to implementation.[c]

[a] GAVI webpage on ADIPs, www.gavialliance.org/Resources_Documents/Policy_Technical/Accelerating_RD/adip.php
[b] GAVI Supply Strategy 2005
[c] WHO *Weekly Epidemiological Record* (6 January 2006)

This section comments in some detail on the GAVI Bridge Financing Initiative, which was a global initiative designed to encourage combination vaccine usage in national immunization schedules globally. The problems highlighted are interesting not only as a specific example of combination vaccines but also for looking at increasing EPI systems and the uncertainties in forecasting and vaccine supply and finance.

5.1. The Disease (summary)

Haemophilus influenzae type b (Hib) is a bacterium which can cause meningitis and severe pneumonia. On average, 20% of children in developing countries with Hib meningitis will die (rising to an even higher percentage in Asia and Africa) and 15%-35% of children suffering from Hib meningitis will go on to develop lifelong disabilities.[239]

Not only is Hib disease difficult to diagnose but also the different conditions in which the disease occurs means that a uniform means of defining the disease (burden and incidence) may not aid decision-making:

- Virtually all Hib disease occurs in children younger than 5 years, and is uncommon in children under 2 months old, probably because of the presence of maternal antibody.
- The age distribution of cases between 2 months and 2 years of age varies in different populations. In the Gambia, Hib disease occurs at an earlier age with 45% of cases occurring in children younger than 6 months. In Finland, only 5% of Hib disease cases occur in children younger than 6 months.[240]
- The proportion of Hib disease occurring before 6 months of age has important implications for prevention with Hib conjugate vaccine.
- This affects the optimal vaccination strategy.

Surveillance

Difficulties in the diagnosis of Hib meningitis and pneumonia make it difficult to confirm Hib as the cause of illness in any situation. The WHO general protocol for Hib meningitis surveillance recommends criteria for selecting a surveillance population and provides information on laboratory, clinical, and epidemiologic methods to ensure accurate surveillance. Limits of this approach include:

- Requirement for a well-defined catchment population with high access to care.
- The need for a time-span of at least one year to conduct surveillance.
- Physicians that routinely collect CSF specimens from patients with suspected meningitis.

[239] Hib Initiative website, www.hibaction.org

[240] Watt E, OS Levine and M Santosham "Global reduction of Hib disease: what are the next steps? Proceedings of the meeting Scottsdale, Arizona, September 22-25 2002" (2003) *Journal of Pediatrics* 143(6): 163-187

- Laboratory resources to culture Hib and other organisms from CSF.
- The approach cannot be used to measure the burden of Hib pneumonia.[241]

WHO also recommend HibRAT methods, which aim to provide a framework that local decision-makers can use to assess the accuracy and reliability of existing data on Hib disease – meningitis incidence method and <5 mortality method. However, the HibRAT process relies on a number of assumptions to extrapolate disease estimates from the available data. (Nevertheless, the HibRAT enables countries that have few resources to obtain estimates of national disease burden in the absence of population-based surveillance data).

5.2. Global Prevalence

Around 78% of cases of meningitis and of all classical Hib diseases in the age group 0-4 years are prevented in the developed world (50% of the cases of Hib disease in all age groups). The worldwide figures are less impressive. Only 5.9% of cases of meningitis or 8.5% of cases of the classical Hib manifestations in children are estimated to be prevented by the present vaccination practices (Peltola 2000).

> "Hib conjugate vaccines have essentially been used only by affluent countries and people in the private sector who can afford these vaccines."[242]

> "If pneumonia is included, and for developing countries in general, the numbers fall considerably. The global impact of Hib vaccination, after more than 10 years during which conjugates have been available, has been negligible. Annually, less than 2% of cases of Hib disease are prevented worldwide." [243]

Europe

Beginning in 1996, several European countries, Israel and Australia participated in a project to monitor the incidence of invasive Hib disease, assess the impact of Hib conjugate vaccines, and improve laboratory capacity to characterize *H. influenzae* isolates[244] (increased to 19 members by 2002). Before the use of Hib conjugate vaccines, considerable diversity in the incidence of invasive Hib disease was reported from different European countries. The incidence ranged from approximately 12 to 54 cases per 100,000 children under 5 in Spain and Sweden, respectively. In general, Northern European countries reported higher incidence, whereas Southern and Eastern European

[241] WHO webpage on surveillance of HIB vaccine, http://www.who.int/vaccines-surveillance/deseasedesc/RSS_hib.htm

[242] Peltola H "Worldwide Haemophilus Influenzae Type B Disease at the Beginning of the 21st Century: Global analysis of the Disease Burden 25 Years after the use of the Polysaccharide Vaccine and a Decade after the Advent of Conjugates" *Clinical Microbiology Review* (2000) 13(2): 302-317

[243] Ibid.

[244] Watt, Levine and Santosham "Global reduction of Hib Disease: what are the next steps? Proceedings of the meeting Scottsdale, Arizona, September 22-25 2002"

countries reported lower incidence (although surveillance and laboratory methodologies differed from country to country).

- Finland
  - 1986, 1987: First trials with PRP-D conjugate.
  - 1989: Accomplished the only controlled follow-up study, in which two conjugates, PRP-D and PRP-CRM, were compared side by side.
  - Both conjugates proved effective, since no cases of HIB disease occurred in either group after three doses. The impact of vaccination was indisputable: within a few years, the incidence of all the disease in which Hib plays a major role (meningitis, epiglottitis and septic arthritis) declined to a fraction of the previous levels.
- Iceland

  1989: Launched a program of vaccination with PRP-D in 1989, and Hib diseases disappeared within 3 years.[245]
- Denmark, Norway and Sweden; Germany; Netherlands

  Later immunization programs, but in Scandinavia at least 470 cases of meningitis and 770 cases of all classical Hib diseases are prevented annually. Post-marketing studies in Germany indicate a similar trend. In the Rhein-Main area, the incidence of all Hib diseases in children aged 0-4 years decreased by 94% in the first 24 months.
- France

  Used exclusively PRP-T; steep decline in incidence.
- Other parts of Europe

  Once Ireland and Austria had started to use these PRP-T vaccines, steeply declining incidence rates were also seen. What remains is the implementation of Hib vaccines in the regular immunization program in populous countries such as Turkey, Poland, and Ukraine.

  "In fact, all Newly Independent States lack an efficacious Hib immunization program, although vaccines are available."[246]

Americas

- US

  PRP-CRM and PRPOMP were licensed for 2-month-old infants in the US in 1991, increasing the rate of decline in the incidence of Hib disease that had started as the result of vaccination at age 15-60 months by a factor of five. The overall incidence of this entity in the US has been lowered by 98% among children 4 years of age or younger and currently stands at 1.6 per 100,000 per

[245] Peltola H, P Aavitsland, K G Hansen, K E Jonsdottir, H Nokleby and V Romanus "Perspective: A Five-Country Analysis of the Impact of Four Different *Haemophilus influenzae* Type b Conjugates and Vaccination Strategies in Scandinavia" *The Journal of Infectious Diseases* (1999) 179: 223-229

[246] European Union Invasive Bacterial Infections Surveillance Network "Invasive *Haemophilus influenzae* in Europe" (2003) http://www.euibis.org/documents/2001_hib.pdf

annum. (In the pre-vaccine era the average was 88 per 100,000 children.) The savings through the use of conjugates were $500m in 1992.[247]

- Alaska (interesting case)[248]
  - In Alaska, in 1996 the Hib vaccine was changed to PRP-CM197 in conjunction with DTwP, in an effort to decrease the number of injections. After this change, the incidence of invasive Hib disease among Alaskan children increased almost threefold!
  - In 1997, a new schedule with PRP-OMP at 2 months followed by PRP-CM197 at 4, 6, and 12 months was implemented, in order to secure benefits of both vaccines. However, disease rates did not fall back to the levels previously seen in 1991-95. In part this was because there were programmatic problems in implementing a schedule with two different Hib conjugate vaccines. Several cases of invasive Hib disease occurred in children who had inadvertently been given PRP-CM197 for the first dose.
  - In 2001, the vaccine schedule was again switched to PRP-OMP (in combination with the hepatitis B vaccine) at 2, 4, 12 months. Over 2001-2002 only one case of invasive Hib disease occurred (according to unpublished data from CDC).
- Chile

  Chile was the first country in Latin America to show the benefits of Hib vaccination. PRP-T also prevented pneumonia, a phenomenon that was necessarily expected in a nonbactaeremic process such as most cases of pneumonia. A 90% decline in Hib disease was observed.[249]
- Uruguay

  The first country in Latin America to execute a successful country-wide program; the incidence of Hib meningitis in children aged 0 to 4 years declined from 17-22 per 100,000 in 1992 to 1 per 100,000 in 1996.[250]
- Brazil, Argentina, Mexico, Colombia

  The Curitiba region of Brazil is an example of successful local vaccination in a large country whose resources did not permit routine immunization for all infants at once.

Asia, Oceania and Africa

- Israel

  Began large-scale Hib vaccinations in 1992 and a 95% decrease in the incidence of Hib disease was observed.

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[247] Shinefield H and S Black "Conjugate Hib vaccines and their combinations: present success and future possibilities" *JAMA SEA* (1993) 9: S20-23 as cited in Peltola (2000)

[248] Singleton R, L Bulkow, OS Levine, J Butler, T Hennessy and A Parkinson "Experience with the prevention of invasive *Haemophilus influenzae* type b disease by vaccination in Alaska: The impact of persistent oropharyngeal carriage" *The Journal of Pediatrics* (2000) 137:3

[249] Hoppenbrouwers K, R Lagos, B Swennen, C Ethevenaux, J Knops, M Levine and J Desmyter "Safety and immunogenicity of an *Haemophilus influenzae* type b-tetanus toxoid conjugate (PRP-T) and diphtheria-tetanus-pertussis (DTP) combination vaccine administered in a dual-chamber syringe to infants in Belgium and Chile" *Vaccine* (1998) 16: 921-927

[250] Peltola H "Haemophilus influenzae type b disease and vaccination in Latin America and the Caribbean" *Pediatric Infectious Disease Journal* (1997) 16: 780-787

- Gulf

  In Qatar the decline has been 80% to date.[251] Most of the other Gulf States have also started Hib immunization, but many large countries on the Asian continent are not seriously considering wide-scale vaccinations; these nations believe Hib diseases are not a major issue there.[252] In Saudi Arabia it is thought that only compulsory vaccination will guarantee long-term effectiveness against Hib.
- Australia

  Commenced Hib vaccinations in 1992. PRP-CRM was first selected, except for the Aboriginal population, for which PRP-OMP was used.

Hib disease in Asia

Before the early 1990s, invasive Hib disease burden studies in Asia were mostly retrospective and hospital-based and showed lower incidence rates than that observed in other regions. Interpretation of these previous study results was limited by concerns regarding the adequacy of clinical and laboratory methods used.

In the mid-1990s, new efforts were initiated to assess Hib meningitis incidence by using more rigorous surveillance methods. The most notable examples of these new studies are the metacentre, population-based surveillance projects organised by the IVI in South Korea, Vietnam and China. Similarly, investigators from the University of Melbourne, PATH, and the Program of International Health at John Hopkins University developed a population-based project to assess Hib incidence and pneumonia disease burden in Thailand.

Africa

- Gambia

  Until recently (2000), Gambia was the only country in Africa that had introduced Hib vaccination into the national immunization program. This was made possible by external financial aid, stimulated by the prospective efficacy study using the PRP-T conjugate.[253]
- South Africa

  Introduced in 1999; also used PRP-Y. Gambia and South Africa are forerunners among the >50 countries in Africa, where more than 95% of the paediatric population receives no Hib vaccine.

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[251] Wenger JD, J DiFabio, JM Landaverde, OS Levine and T Gaafar "Introduction of Hib conjugate vaccines in the non-industrialized world: experience in four 'newly adopting' countries" *Vaccine* (1999) 18: 736-42

[252] Peltola H "Spectrum and burden of severe Haemophilus influenzae type b diseases in Asia" *Bulletin of the World Health Organization* (1999) 77: 878-87

[253] Adegbola RA, EK Mulholland, AG Falade, O Secka, R Sarge-Njai, T Corrah, A Palmer, G Schneider and BM Greenwood "Haemophilus influenzae type b disease in the western region of The Gambia: background surveillance for a vaccine efficacy trial" *Annals of Tropical Paediatrics* (1996) 16: 103-111

5.3. Key Global Initiatives – The GAVI Bridge Financing Initiative

The GAVI Bridge Financing Initiative was introduced to address the challenges faced by the countries that introduced the higher-priced combination vaccine products under GAVI Phase I (2001-2005). As part of the GAVI Phase I model, it was assumed that vaccine prices would decline and that countries and partners would significantly increase their allocations to health and immunization such that when GAVI support ended, the improved program would be financially sustainable.

The partners in the Bridge Financing Initiative:

- **GAVI/Vaccine Fund.** Host a multi-partner group to oversee the Bridge Financing initiative. The GAVI Secretariat will also be responsible for monitoring co-financing agreements and reporting to the GAVI Board on progress and challenges.
- **UNICEF = UNICEF Programme, Country and Supply Division Staff** Negotiation of MOUs (Memorandum of Understanding), supporting procurement process at both global and national levels
- **World Bank** In countries where the World Bank is active in the health sector, the Bank may be requested by a member government to support the development of MOUs that are consistent with the Health Sector Strategic Plan.
- **WHO** WHO officers at global regional and country level will be engaged in the development of MOUs and the monitoring and oversight of agreements.
- **Bilaterals/NGOs** Depending on the country, different bilaterals/NGOs will be engaged.

Phase I GAVI strategy

The drive for combination vaccines and the GAVI's Phase I procurement strategy did not go as expected. GAVI comments that the tradeoffs involved in the choice of combination vaccines (higher price than monovalent products, limited supply base) were not fully analysed. As the Bridge Financing Report states, the Phase I model did not hold:

> "Prices of combination vaccines did not decline, but increased. The initial five years of support was too brief a time to allow the market to react to increased demand and too short a time frame to permit countries and partners to ramp up to meet increased costs….(national) allocations have not been sufficient to meet increased costs of the expanded and improved immunization programs."[254]

The Report goes on to explain that:

- At current market prices, combination vaccines are slightly less cost-effective than a package of separate monovalent Hib, hepatitis B and DTP vaccines, although they are competitive with other widely accepted health interventions.
- The combination vaccines are not yet comparable in cost-effectiveness to the current standard EPI vaccines.

[254] GAVI Financing Task Force "Bridge Financing Investment Case" (June 2005) http://www.gavialliance.org/resources/16brd_04._Bridge_financing_investment_case.pdf

- However, with successful lowering of combination vaccine prices, the vaccines would become highly cost-effective and would be a powerful addition to the standard EPI package.

As part of the Bridge Financing proposal, flat-line support is offered to permit pentavalent countries (Guyana, Gambia, Ghana, Kenya, Uganda, and Rwanda) whose funding was scheduled to end in 2005 or 2006, so that they are able to work with the Hib Initiative to document vaccine impact; and initial tetravalent countries will have time to put country co-financing in place. When working with the Hib Initiative, countries can be supported to make evidence-based decisions on Hib vaccination.

> "Many countries do not yet have the information they require to make an informed decision whether the continuation of Hib vaccine is a national priority."[255]

All countries will be supported through the Financial Sustainability Implementation process to improve program efficiency and increase government and partner commitment to immunization and health service delivery.

Problems with GAVI Phase I

- Although a procurement strategy was in place, it had two competing objectives: quick scale-up of combination vaccines and emphasis on an affordable price.
- Despite the fact there is significant capacity for hepatitis B production and that two manufacturers had already contracted with GAVI for Hib antigen technology, significant delays exist for the manufacturing planning.
- The rapid timeline to scale up vaccine support to countries with an explicit emphasis and preference for combination products was another fault with the GAVI initial procurement round highlighted by the Mercer Management Consulting Study (2002).[256]
- There was a lack of consensus among the partners regarding institutional responsibilities and lines of accountability on the supply and procurement functions within the Alliance.
- UNICEF, as the procurement agent designated by the GAVI Board at the time (Phase I, first procurement round 2000-2001), allowed only restricted involvement and oversight by GAVI partners in the solicitation process.
- Mercer (2002) found that GAVI's first procurement round suffered from inaccuracies around demand forecasts

Current status

Efforts were made to develop a more accurate mechanism for determining projected country-level demand for GAVI-produced vaccines. WHO leads this effort, and along with UNICEF and the GAVI Secretariat, has developed a model which has significantly

[255] GAVI Financing Task Force "Investment Case for Bridge Financing: Update for GAVI Board" (April 2005) http://www.gavialliance.org/resources/15brd_BridgeICupdate.pdf

[256] Mercer Management Consulting "Lessons Learned: New Procurement Strategies for Vaccines – Final Report to the GAVI Board" (2002) http://www.who.int/immunization_delivery/new_vaccines/17.Lessons_learnt_New_strategies_for_vaccines.pdf

improved demand forecasts. An approach similar to GAVI's ADIP's was approved for Hib by the Alliance Board, the Hib Initiative.

5.4. Vaccine Supply and Finance

Funds are requested by UNICEF Supply Division from the UNICEF Trust Account. If the Trust Account does not have sufficient balance to cover the request, then the Trust Account requests funds from the GAVI Fund (a two-year rolling forecast is provided to the GAVI Fund on a quarterly basis).

There have been problems with a limited supply of Hib vaccines. See table in Annex.

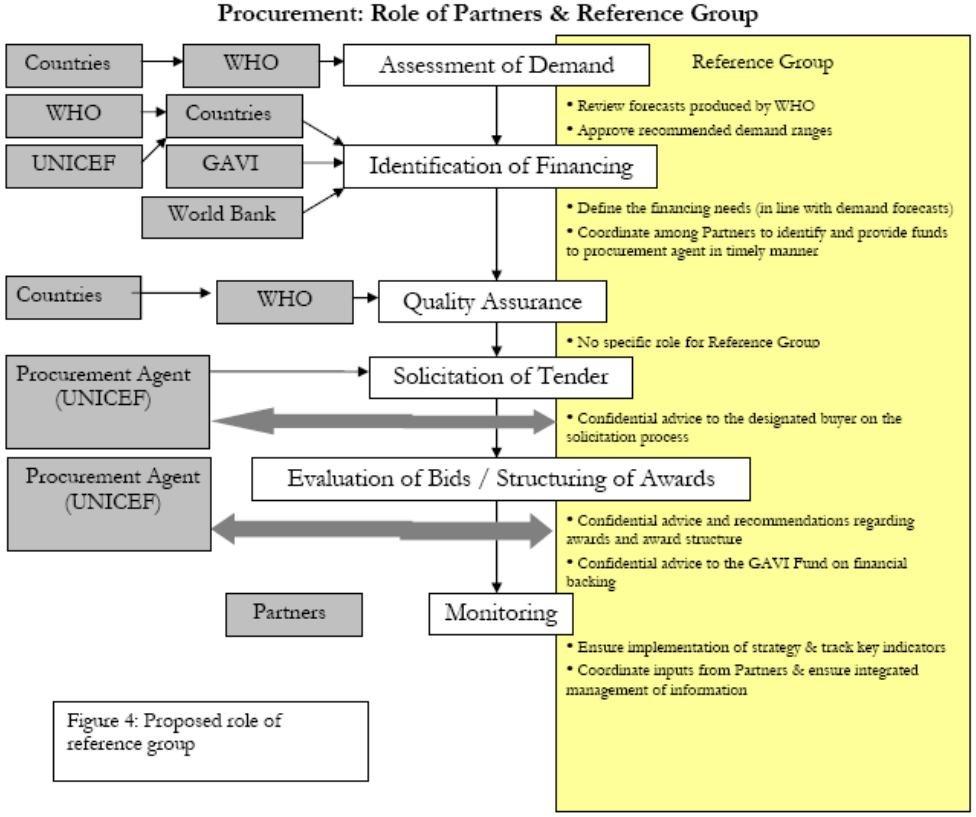


Figure 4: Proposed role of reference group

Countries with GDP <$1000 are eligible to procure vaccines through UNICEF's supply division. **DTP-Hib vaccine: $3.12 per dose in 10-dose vial**
Pentavalent vaccine: $3.60 per dose in 2-dose vial

Countries in Latin America and the Caribbean can procure through PAHO's Revolving Fund. **Hib monovalent lyophilized: $3.10 in single-dose vial**
Hib monovalent liqueis: $3.15 in single-dose vial
DTP-Hib vaccine: $3.30 in single-dose vial; $2.90 per dose in 10-dose vial

Pentavalent vaccine: $3.99 in single-dose vial

Most other countries procure vaccines independently and prices vary considerably.

The GAVI Financing Task Force is also working to identify and expand the use of other alternative financing options. In Tanzania for example, $23m from debt relief is being applied to the immunization program.

> "Although the price of Hib conjugate vaccines is frequently used as a key reason for its underutilization, participants from several developing countries stated that vaccine introduction depends on convincing key politicians and decision-makers about the value of the vaccine."[257]

Co-financing proposals

The table below shows the co-financing proposals as estimated by GAVI. The costs include vaccine and associated safety equipment costs, freight, visa and insurance charges, and UNICEF procurement fees.

Co-financing proposals summary. Data source: Hib Initiative

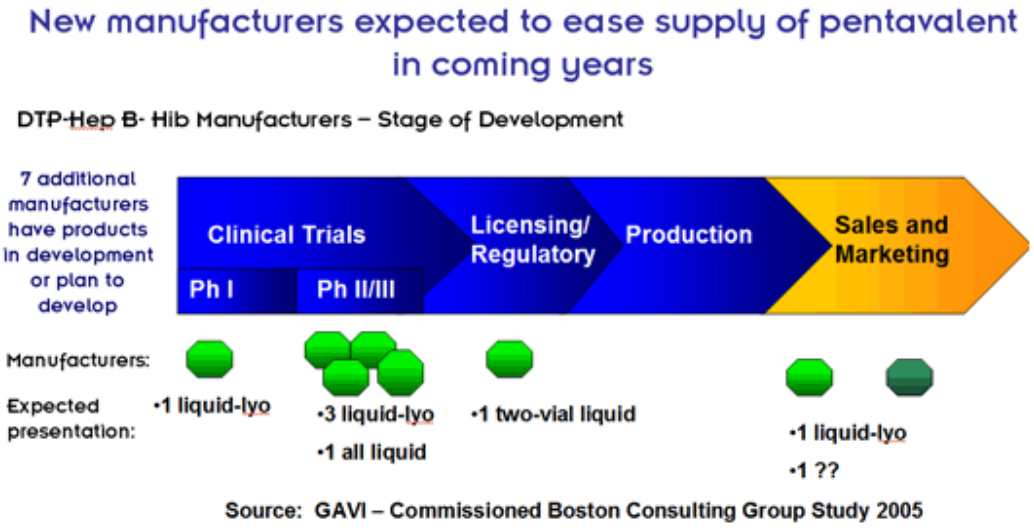
Poorest group (<$1000 2005 GNI/pc, UN classified LDC) *Myanmar, Ethiopia, Malawi, Guinea- Bissau, Rwanda, Niger, Nepal, Uganda, The Gambia, Madagascar, Mozambique, Tanzania, Togo, Guinea, Cambodia, Mali, Sao Tome and Principe, Burkina Faso, Chad, Lao PDR, Bangladesh, Zambia, Benin, Mauritania, Solomon Islands, Yemen Rep, Comoros, Senegal, Bhutan, Lesotho*		
Pentavalent DTP-HepB+Hib, Tetravalent DTP/Hib, Monovalent Hib	$0.23 min co-financing/dose	Fixed co-payment through 2010 – increases after 2010 depending on future price of vaccine
Intermediate Group (<$1000 2005 GNI/pc, not UN classified LDC) *Cuba, Korea DR, Tajikistan, Zimbabwe, Kyrgyz Republic, Ghana, Uzbekistan, Kenya, Nigeria, Vietnam, Papua New Guinea, Mongolia, Pakistan, India, Moldova, Nicaragua*		
Pentavalent DTP-HepB+Hib, Tetravalent DTP/Hib, Monovalent Hib	$0.38 min co-financing/dose	Fixed co-payment through 2010
Least poor group (>$1000 2005 GNI/pc) *Bolivia, Cameroon, Guyana, Djibouti, Kiribati, Sri Lanka, Honduras, Azerbaijan, Indonesia, Georgia, Armenia, Ukraine*		
Pentavalent DTP-HepB+Hib, Tetravalent DTP/Hib, Monovalent Hib	$0.43 min co-financing/dose	Gradually increasing co-payment to predicted long-term price

[257] Watt, Levine and Santosham "Global reduction of Hib disease: what are the next steps? Proceedings of the meeting Scottsdale, Arizona, September 22-25 2002"

Fragile States (GAVI eligible, meeting GAVI fragile state criteria) *Angola, Afghanistan, Burundi, Central African Republic, Congo Rep, Côte d'Ivoire, Democratic Republic of Congo, Eritrea, Haiti, Liberia, Sierra Leone, Somalia, Sudan, Timor-Leste*		
All eligible vaccines (except Yellow Fever)	$0.15	

There is only one manufacturer of the combined DTP-Hepatitis B-Hib pentavalent vaccine (GSK). Relatively low levels of demand have provided little incentive for additional manufacturers to enter the market.

However, following a technical review by WHO consultants, it was estimated that by the end of 2007 there could be 5 suppliers (2 MNCs and 3 emerging manufacturers) with a WHO prequalified product (DTP-HepB or DTP-HepB-Hib).[258]



5.5. Vaccines Licensed

In the literature, Hib vaccines are usually referred to by name. All vaccines use PRP as the polysaccharide; the means of vaccination is by antibody against PRP.

2001: Vaccines prequalified by WHO:

[258] Watt, Levine and Santosham "Global reduction of Hib disease: what are the next steps? Proceedings of the meeting Scottsdale, Arizona, September 22-25 2002"

PRP-T: PRP bound to tetanus toxoid - produced by SmithKline Beecham and Aventis Pasteur. A three dose primary series in the first year of life is adequate for protection, but the manufacturers recommend a booster dose in the second year.
HbOC: PRP bound to a mutant diphtheria toxoid (CRM197) produced by Wyeth Lederle. A three dose primary series in the first year of life is adequate for protection, but the manufacturer recommends a booster dose in the second year.
PRP-OMP: PRP bound to meningococcal outer membrane protein - produced by Merck. This gives early protection after a single dose, but lower levels of antibodies after a primary series in the first year of life compared to other two conjugates. There is a two dose primary series in the first year of life (there is no benefit from a third dose) and a booster dose at 12-15 months of age.

PRP-T (ActHIB) is also available combined with a cellular pertussis vaccine (DTaP Tripedia); the combined product is called TriHIBit and is licensed for use only as the fourth dose of the Hib and DTaP series in the US.

UN PREQUALIFIED VACCINES - WHO list of vaccines for purchase for UN agencies as of November 2006. Hib

Company	
Berna Biotech Korea Corp.	DTP-Hep B-Hib (fully liquid pentavalent) (Quivaxen)
GSK, Belgium	Hib DTP-HepB+Hib (Zilbrix-Hib)
Wyderle	Hib DTPw-Hib (HbOC) (Comvax)
Merck and Co. Inc, USA	Hib Hib-Hep B (PRP-OMP)
Sanofi Pasteur, France	Hib DTP-Hib combined
Chiron Vaccines, Italy	Hib DTP-Hib combined

Comments on combination vaccines
Although it is generally agreed that combination vaccines are just as effective as monovalent vaccines, there is not complete consensus. Possible issues from the simultaneous administration of multiple conjugate vaccines are:

- They may enhance or inhibit immune responses (e.g. studies by Kovel et al[259], Eskola et al, Granoff et al[260], Lieberman et al – give varying results on antibody levels).
- Also there may be interference between vaccines – this has been observed between vaccines that contain protein-PRP conjugates and acellular pertussis antigens.

[259] Kovel A, ER Wald, N Guerra, C Serdy and CK Meschievitz "Safety and Immunogenicity of acellular diphtheria-tetanus-pertussis and Haemophilus conjugate vaccines given in combination or at separate injection sites" *Journal of Pediatrics* (1992) 120(1): 84-87
[260] Granoff DM "Assessing efficacy of Haemophilus influenzae type b combination vaccines" *Clinical Infectious Diseases* (2001) 33: S278-287

- There may be cases of carrier-induced suppression.

However, combination vaccines have several advantages, including programmatic simplification and decreased number of injections, storage spaces and medical waste. Also, routine use of Hib conjugative vaccines has reduced carriage and transmission of Hib and resulted in herd immunity.

5.6. Case Study – Combination Vaccines in Costa Rica and Latin America

Costa Rica was used as a Phase III trial site for the GSK combination vaccine. Faingezicht et al[261] (2002) present the results of the analysis of Costa Rican children who had received a birth dose of hepatitis B vaccine, comparing the immunogenicity and the reactogenicity of the DTPw-HepB/Hib combination vaccine to separate injections of DTPw-HepB and Hib vaccines as primary vaccination in a group of children who had received a dose of hepatitis B vaccine at birth.

- The study was designed as a phase III observer-blind prospective randomized controlled trial in a single vaccination centre in Costa Rica. Vaccines were provided by GSK. Vaccines were released, shipped and stored according to the WHO Good Manufacturing principles. The three vaccines used were DTPw-HepB (Tritanrix-HepB), Hib (PRP-T, Hiberix) and DTPw (Tritanrix).
- At least 97.5% infants reached protective levels of antibodies against the antigens employed in the vaccines. The DTPw-HepB/Hib pentavalent vaccine is highly immunogenic as a primary vaccine in children who received a hepatitis B vaccine at birth, with the pentavalent combination inducing both persisting immunity and boostable memory. The pentavalent vaccine was safe both for primary and booster vaccines.

It can be seen that this study in Costa Rican infants supports the routine use of the pentavalent DTPw-HepB/Hib vaccine as part of childhood vaccination program. The results are described as a good indication of how the vaccinations would be successful in Latin America and the Caribbean

Comments on Latin America

Hib vaccination was introduced into Latin America in 1994, when Uruguay decided to include the Hib conjugates in its routine immunization program. While only 3.4% of all newborns in Latin America received a routine Hib vaccination in 1996, this situation has changed dramatically since then.

[261] Faingezicht I, M Avila-Aguerro, Y Cervantes, M Fourneau and S Clements "Primary and booster vaccination with DTPw-HB/Hib pentavalent vaccine in Costa Rican children who had received a birth dose of hepatitis B vaccine" *Revista Panamerica de Salud Publica* (2002) 12(4): 247-257

In 2001, over 10 million (over 90%) of Latin Americas infants routinely received a Hib vaccine. This success of introducing a novel vaccine into routine immunization was triggered by various factors:

- Leadership role of PAHO
- A surveillance network providing local disease burden data, thus increasing the disease awareness among both health care professionals and parents
- Local clinical-trial data
- Availability of vaccines in such combinations as DTPw/Hib and DTPw-HepB/Hib.

The results are very similar to the other studies in Latin America, such as those referred to in the Journal of Paediatric Child Health 1997.[262]

Advantages
An advantage that the DTPw-HepB and DTPw-HepB/Hib combinations have over the hepatitis B monovalent vaccines in the first year of life is that in the combinations with DTPw, the HepB response reaches 95% seroprotection after two doses of vaccine, with GMTs of 95mlU/mL. This compares with a 66% seroprotection rate, with a GMT of 25mlU/mL, following the second dose of monovalent hepatitis B vaccine in studies.

Problems
The biggest shortfall is that fewer than half of the children came back for booster vaccination in this study.

5.7. Case study – Vaccine Implementation and Surveillance in the Gambia

The EPI in the Gambia is regarded as one of the best in Africa, with reported rates of vaccine coverage exceeding 80%. Vaccine procurement began initially with vaccine donated by Aventis Pasteur to UNICEF and has continued with funds from GAVI.

- The evidence from recent studies in the Gambia suggests a herd effect from decreasing carriage and disease incidence in unvaccinated children.
- Ongoing studies of the impact of vaccine on colonization suggest that Hib vaccination is decreasing transmission of Hib in the Gambia.
- The success of the clinical trial was instrumental in raising awareness of disease burden among policymakers and the subsequent adoption of the Hib vaccine. Interestingly:

  > "The practical effects of a late third dose of PRP-T in this schedule (i.e., scheduled at 4 months but in practice given much later), which could act as a booster dose, may contribute to the effectiveness of this Hib vaccine program."[263]

[262] Peltola "Haemophilus influenzae type b disease and vaccination in Latin America and the Caribbean"
[263] Adegbola RA, O Secka, G Lahai, N Lloyd-Evans, A Njie, S Usen, C Oluwalana, S Obaro, M Weber, T Corrah et al "Elimination of *Haemophilus influenzae type b* (Hib) disease from The Gambia after the

The successful implementation of the vaccine program in the Gambia was due to a combined effort of government healthcare workers and researchers at the Medical Research Council Laboratory. The financial sustainability of this program after GAVI funding ends is still a challenge.

Consent procedure

An interesting study of the trial procedure by Leach, Mulholland et al[264] looks at the degree of success with which the Government/Medical Research Council Ethical Committee (est. 1978) has tried to implement the recognized international ethical standard of 'informed consent' with sensitivity to the educational and cultural background of the community.

Trial methods

The UK Medical Research Council (MRC) has worked in the Gambia since 1948 and is well known to local people for the provision of treatment facilities and for conducting research.

- The Hib trial conducted in the Gambia was a randomized, double-blind, placebo-controlled trial, and was conducted as part of the Ministry of Health's childhood immunization program.
- In the Gambia, mothers travel to attend vaccination sessions on specified days at their local health centres or outreach clinics.
- The trial was preceded by an intensive publicity campaign involving radio, newspapers and discussions with village leaders. All mothers should attend a child health clinic within the first month for the newborn to be examined and receive a BCG vaccination. At this time the Hib vaccine was explained to the mother, and she was given an information sheet (English and Arabic). At the time she returned for the first DTP vaccine at 8 weeks, the study was explained again and if the mother gave verbal consent, the trial worker signed the information sheet.

Results

- In rural areas, only 20% of mothers and 23% of fathers had primary school education. In urban areas, 35% of mothers and 55% of fathers had attended primary school.
- Before attending the clinics, the mothers had heard of the program mostly through the radio or through other mothers.
- The level of knowledge of the purpose of the vaccine was quite high, with nearly 90% of both rural and urban stating that the vaccine might prevent illness, and awareness of over 50% of participants that the vaccine may prevent pneumonia and meningitis (over 70% for both these associations in rural areas).

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introduction of routine immunization with a Hib conjugate vaccine: A prospective study" *The Lancet* (2005) 366: 144-150

[264] Leach A, S Hilton, BM Greenwood, E Manneh, B Dibba, A Wilkins and EK Mulholland "Evaluation of the informed consent procedure used during a trial of Hib conjugate vaccine undertaken in the Gambia" *Social Science and Medicine* (1999) 48(2): 139-148

- Those who did not join the study gave reasons including that the husband did not consent, that there was a fear that the vaccine might be too strong for the child and that as a test run there might not be any benefit from the vaccine.

Who should be involved in the decision making process

	Rural acceptors ($n = 73$) %	Urban acceptors ($n = 64$) %	Refusers ($n = 49$) %
Father	92	92	88
Mother	75	98[b]	74[a]
MRC staff	34	38	2[a]
Health workers	32	33	8[a]
Extended family	19	30	22
Village chief	23	2[b]	6
Imam	15	2[b]	6
Friends	10	11	2

[a]Comparison of all acceptors with refusers: $p < 0.05$.
[b]Comparison of rural acceptors and urban acceptors: $p < 0.05$

Is Gambia a good example?

The long involvement of the Gambian people with medical research projects make this society quite unusual and it may be wrong to extrapolate these findings to other African countries. However, it should be noted that Preziosi et al (1997) find similar results in Somalia.[265]

In the recent (June 2005) Lancet series, Clemens et al[266] also address the question of the broader applicability of the Gambia trial to the rest of the world.

> "Immunisation of infants with polysaccharide-protein conjugate vaccines has had a remarkable impact in bringing invasive disease due to Hib to the verge of immunisation in many industrialised countries."

Discussing the study by Adegbola et al, Clemens suggests that the size of the decline of Hib meningitis incidence could not be explained by the documented level of vaccine protective efficacy, and probably resulted in part from vaccine-induced herd immunity.

> "Whilst it is reasonable to conclude that similar levels of vaccine protection against invasive Hib disease can be expected elsewhere, it cannot be confidently predicted, in lieu of reliable disease-burden estimates, that the burden of Hib disease to be prevented by Hib vaccines will be as high in other countries as it was in the Gambia."

Possible case study – Kenya?

This would be interesting to look at more closely. From November 2001 Kenya received a combined DTP/Hepatitis B/Hib vaccine with support from GAVI. The

[265] Preziosi MP, A Yam, M Ndiaye, A Simaga and F Simondon "Practical experiences in obtaining informed consent for a vaccine trial in Rural Africa" *New England Journal of Medicine* 336(5): 370-373
[266] Clemens J and L Jodar "Hib vaccines for all the world's children?" *The Lancet* (2005) 366(9480): 101-103

KEMRI/Wellcome Trust Centre for Tropical Diseases Research in the Kilifi district is conducting a hospital-based surveillance study in an area of continuous demographic surveillance. The Wellcome Trust is study led by Dr Anthony Scott (Oxford University Centre for Clinical Vaccinology and Tropical Medicine).

5.ANNEX

Surveillance and Supply Tables

Hib-PBM Surveillance Feedback Table, 2003

(Data submitted from countries for May 2003; Table last modified 30 June 2003)

Column number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Trained	Month Started Hib Vaccine	No. suspected meningitis cases	No. (%) with lumbar puncture done		No. with CSF culture result in database		No. with CSF - turbid or WBC > 100	No. with culture positive for basic pathogen	Sensitivity of CSF culture	Total cult positive for Hib, S.pneu, N.mening	No. culture positive for Hib	Sensitivity of culture for Hib	Month of Last Report/Reported months
			n	n	% c4/c3 (target: 80%)	n	% c6/c4 (target: 80%)	n	n	% c8/c6 (target: 20%)		n	% c12/c11 (target 20% if no Hib vaccination)	
Cameroon	Trained-not reporting		103	103	100%	102	99%	34	18	53%	20	13	65%	May-03
Cen.A.fr. Rep.	Not trained													
Chad	Not trained													
Congo	Not trained													
Eq. Guinea	Not trained													
Gabon	Not trained													
Central Block														
Benin	Trained-not reporting		630	628	100%	223	36%	56	11	20%	12	7	58%	01/03-05/03
Burkina Faso	Trained-reporting		94	86	91%	70	81%	52	36	69%	38	18	47%	01/03-05/03
Cote d'Ivoire	Trained-reporting		254	242	95%	228	94%	25	9	36%	9	5	56%	01/03-05/03
Gambia	Trained-reporting	1995	86	82	95%	78	95%	10	2	20%	2	0	0%	01/03-05/03
Ghana	Trained-reporting	Dec-01	201	199	99%	192	96%	12	2	17%	2	1	50%	01/03-05/03
Guinea	Trained-reporting		59	58	98%	57	98%	9	9	100%	10	6	60%	01/03-05/03
Guinea-Bissau	Not trained													
Liberia	Not trained													
Mali	Trained-reporting		257	256	100%	256	100%	62	37	60%	38	13	34%	01/03-05/03
Mauritania	Not trained													
Niger	Trained-reporting		143	128	90%	117	91%	59	39	66%	40	15	38%	01/03-05/03
Senegal	Trained													No data for 2003
Sierra Leone	Trained-not reporting													No data for 2003

.**UNICEF Product Menu for Vaccine Supply (Source: UNICEF)**

PRODUCT MENU FOR VACCINES SUPPLIED BY UNICEF FOR THE GLOBAL ALLIANCE FOR VACCINES AND IMMUNIZATION (GAVI)

Vaccine	Form	Presentation	Number of manufacturers	Storage space (cm^3/dose)		VVM	Product availability			Weighted Average Prices per dose		
				Vaccine	Diluent		2004	2006	2008	2004	2005	2006
DTP-HepB+Hib	Liquid DTP-HepB Lyophilised Hib	2 ds	1	11.3	-	Yes		Increasing, needs planning	Needs planning	$3.66	$3.60	$3.60
DTP-HepB	Liquid	10 ds	1	3.0	-	Yes		Increasing, needs planning	Needs planning	$1.21	$1.25	$1.29
DTP+Hib	Liquid DTP Lyophilised Hib	1 ds	1	43.2	-	No		Limited	Needs planning	N/A	N/A	N/A
DTP+Hib	Liquid DTP Lyophilised Hib	10 ds	1	11.8	-	No		Limited	Needs planning	$2.58	$2.80	$3.12
DTP+Hib	Liquid	10 ds	1	2.3	-	No		Needs planning	Needs planning	N/A	N/A	N/A
Hib	Lyophilised	1 ds + diluent	1	12.4	36.8	No		Needs planning	Needs planning	N/A	N/A	N/A
Hib	Lyophilised	10 ds + diluent	1	2.4	2.4	No		Needs planning	Needs planning	N/A	N/A	N/A
Hib	Liquid	1 ds	2	14.5-16.0	-	No		Needs planning	Needs planning	N/A	N/A	N/A

Notes on general product availability

- Supply exceeds current demand.
- Limited supply. Requires planning to ensure adequate supply.
- Very limited supply.
- No established demand. Availability needs to be determined based on needs.