

GAVI ALLIANCE INVESTMENT CASE: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries

Submitted by: GAVI's PneumoADIP at Johns Hopkins October 23, 2006

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DRAFT DOCUMENT: For circulation by GAVI Secretariat



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Executive Summary

The Investment Objective

To prevent 3.9 million deaths in children under age 5 years by accelerating developing countries' access to and uptake of new, life-saving pneumococcal vaccines. Success will lead to use of pneumococcal vaccines 15 years earlier than historical precedents and will prevent at least 446,000 deaths by 2015. GAVI funding for vaccine purchase and support of introduction activities is the key to achieving this goal. GAVI's financing will:

- 1. Motivate industry to dedicate capacity for developing countries;
- 2. Support countries that demand pneumococcal vaccine;
- 3. Contribute directly to sustaining affordable vaccine prices.

Without GAVI financing, historical precedents indicate that a sustainable supply of pneumococcal vaccines at affordable prices is unlikely before 2020. With catalytic GAVI financing, the 7-valent vaccine can begin saving lives now and pave the way for the uptake of extended protection vaccines between 2010 and 2015.

The Disease

Streptococcus pneumoniae is a serious, common, and preventable global disease. Previous WHO estimates for pneumococcal deaths in children have been as high as 1 million deaths per year. The current estimate is 716,000 deaths per year in children and 1.6 million persons of all ages. This makes pneumococcal disease the No. 1 vaccine-preventable cause of child mortality.

The Vaccines

Vaccine supply. A 7-valent vaccine is currently available. The vaccine is efficacious, safe, and can be given in existing schedules. The manufacturer, Wyeth, is willing to supply it at tiered prices for GAVI-eligible countries beginning immediately.

Licensure of extended-protection vaccines with 10 and 13 serotypes is expected between 2008 - 2010. These vaccines will include serotypes 1 and 5, which are important in many developing countries. The 10- and 13-valent vaccines are expected to prevent >80% of pediatric pneumococcal disease worldwide. Multinational manufacturers have indicated willingness to supply GAVI at tiered prices. Emerging market manufacturers are developing pneumococcal vaccines and are expected to enter the market by 2015.

Efficacy and safety. In 2005 the WHO SAGE committee "expressed confidence in the already available evidence of the safety and efficacy of pneumococcal conjugate vaccines, in numerous settings, ranging from industrialized to developing countries, including in infants with HIV infection". Clinical trials in Africa, Europe, and North America, and routine use in the United States have shown these vaccines to be efficacious, well tolerated, and capable of preventing pneumococcal disease among unimmunized children and adults through herd immunity. They also have proven ability to protect HIV-infected children, who have a high risk of pneumococcal disease. Further trials are not needed to prove they can protect children in GAVI-eligible countries.

Cost-effectiveness. Cost-effectiveness analyses indicate that pneumococcal conjugate vaccines meet internationally recognized benchmarks for a "highly cost-effective" health investment. Recent analyses from Harvard University 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.

Pneumococcal vaccination remains cost-effective over a wide range of pricing and disease burden assumptions. It is most cost-effective in countries with the highest infant mortality rates.

The Challenges

The primary challenge facing accelerated pneumococcal vaccination is to motivate suppliers to invest in the capacity needed to meet GAVI demand. There is a strong potential demand in GAVI-eligible countries for pneumococcal vaccines. Existing capacity can meet GAVI's demand between 2007 and 2011, however GAVI demand is projected to outstrip global vaccine capacity between 2012-2015 unless manufacturers invest now to increase capacity. This limited supply situation, if unchanged, will keep prices high and demand low. Increased capacity to meet GAVI demand will in turn accelerate long-term sustainable pricing for countries and their local partners. History shows that unless there is a coordinated global effort with sustained financing, these vaccines will go unused in the countries that need them the most.

GAVI's PneumoADIP analyses suggest that there is a "solution space" with the pricing, financing, and timing of demand. This solution space allows the interests of countries, donors, and suppliers to align and achieve the health objectives outlined in this proposal.

To realize the demand for these vaccines, GAVI and its partners need to ensure sustainable financing for vaccination and continue to demonstrate and communicate the value of pneumococcal vaccination as a health and development investment.

The Proposed Project

This investment case outlines a 20-year strategic vision for introducing and sustaining pneumococcal vaccines. It focuses on the "first step" — the 2007 to 2010 period — and the implication for the following years 2011 to 2015.

The main goal of the 2007–2010 period is to use 7-valent vaccine in earlyadopting countries. This early introduction period is needed as a springboard for evidence-based policies in 2011-2015 when the use of next generation vaccines, 10and 13-valent expands rapidly to help meet Millennium Development Goals (MDGs) and GAVI and WHO/UNICEF Global Immunization Vision and Strategy (GIVS) objectives.

This investment case outlines the proposed costs, expected health impacts, and key assumptions for pneumococcal vaccines. These data are supported by an evidence-driven strategic demand forecast. This forecast represents a significant improvement over historical precedents for accelerated vaccine use.

Key activities to support the vaccine's introduction are also included in the investment case. These activities will ensure that:

1) An affordable, sustainable supply of safe, high quality pneumococcal vaccine is available to meet demand in GAVI-eligible countries;

2) Countries and donors can continue to see the value of pneumococcal vaccines;

3) Credible data is used to build evidence-based decisions at all levels.

The Proposed Costs

Between 2007–2010, an estimated \$127 million to \$189 million in new GAVI financing is required to begin the accelerated use of pneumococcal vaccines in GAVI-eligible countries.

This financing includes an estimated \$87 million to \$149 million to procure the volume of doses needed to meet projected demand between 2007–2010 (after 2010, additional funding will be needed to sustain vaccination in early-adopter countries). This investment case also includes a request for \$40 million to support activities that ensure affordable, sustainable supply and evidence-based decisions at the country, regional, and global levels.

Given GAVI's financing policy in Phase 2, countries are expected to co-finance new vaccine introduction. Based on current policies, the sum of country co-payments during 2007–2010 is an estimated \$6 million.

The Expected Return on Investment (Health Impacts)

By 2025, the accelerated introduction of pneumococcal vaccines will have:

- Prevented 3.9 million child deaths;
- Prevented 32 million hospitalizations;
- Saved over \$690 million per year in medical expenditures;
- Improved the lives of HIV-infected children by preventing a common, serious complication;
- Prevented additional cases of serious disease and deaths among unvaccinated children and adults through herd immunity.

Part I. The Proposed Investment

Section 1: The Objective

To prevent 3.9 million child deaths by accelerating developing country access to new, life-saving pneumococcal vaccines by ~15 years. A successful GAVI investment in accelerated pneumococcal vaccination will:

- Contribute to meeting GAVI and GIVS objectives for accelerating new vaccines
- Contribute to achieving Millennium Development Goal 4 (reducing childhood mortality) by preventing up to 446,000 child deaths by 2015 (Figure 1.)
- Prevent ~3.9 million pneumococcal-related child deaths by 2025
- Contribute to Millennium Development Goals 1 and 2 by reducing the effects of serious pneumococcal disease on health and economic systems by:
 - Decreasing hospitalization and acute care costs due to pneumococcal infections by >\$690 million per year by 2025
 - Decreasing long-term care costs and economic burden from physical and learning disabilities due to pneumococcal meningitis and severe otitis media





Section 2: Description of the Problem

2a. The Disease

The World Health Organization estimates that ~1.6 million people, including >700,000 children under the age of 5 years, die every year of pneumococcal pneumonia, meningitis and sepsis (1). In populations with high child mortality rates, pneumonia accounts for ~20–25% of all child deaths.(2) Studies from these populations consistently show *S. pneumoniae* as the leading cause of bacterial pneumonia, and highlight pneumococcal sepsis as a cause of child mortality.

HIV infection increases the risk of pneumococcal disease 20-to-40 fold, and antibiotic resistance makes treatment more difficult and more expensive.(3) Pneumococcal pneumonia also commonly follows influenza in children and adults. In

an influenza pandemic, as many as 20% of cases may be followed by a pneumococcal pneumonia episode. Thus, pneumococcal disease is a major global health problem.

Pneumococcal disease deepens poverty and increases the economic and social burdens on poor families and their communities. For poorer families, paying for the hospitalization of a child with serious pneumococcal disease often requires them to use their savings or to borrow funds. Hospitalized children also need a parent as a "bedside advocate" during their stay to feed and care for them. The lost work during this time represents a substantial opportunity cost for poor families.

When children survive pneumococcal meningitis, they are often left with life-long disabilities such as hearing loss, learning disabilities, and paralysis. Thus, children disabled by pneumococcal disease will enjoy fewer economic and educational opportunities than their peers. Pneumococcal disease, therefore, contributes to the vicious cycle of poverty to ill health to poverty.

2b. The Vaccine(s)

Vaccines, licensed and under development (see Table 1). Pneumococcal conjugate vaccines are expected to prevent the majority of serious pneumococcal diseases in children. Although the ranking of individual pneumococcal serotypes causing serious disease varies from country to country, the 7–13 serotypes included in conjugate pneumococcal vaccines are responsible for 50%–80% of all pediatric pneumococcal diseases worldwide.(4)

In a review of all published data conducted in 2000, the serogroups in the 7-valent vaccine were found to cause 70-88% of invasive pneumococcal disease in the Africa, Europe, Oceania, the US and Canada, and 63% in Latin America and 43% in Asia. The addition of serotypes 1 and 5 (which are in the 10-valent and 13-valent candidates under development) raises the proportion of disease due to vaccine serogroups to >80% in all regions except Asia (where coverage reached 66%).(5)

Vaccines		Expected serotype coverage	Stage of Development	Expected Licensure
Wyeth	7- valent	~50% globally with regional variations higher and lower	Licensed; launched in 2000	Registered in >75 countries
	13- valent	~80% globally with less variation than 7-valent	Product in Phase 3 clinical testing	2010
GSK	10- valent	~80% globally with less variation than 7-valent	Phase III completed by 2007; effectiveness study for pneumonia prevention in planning stage	2008

Table 1.	Summary:	Licensed	and Near	Licensure	Pneumococcal	Conjugate	Vaccines
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The pneumococcal conjugate vaccine pipeline is strong (see Figure 2), in part because the scientific hurdles are largely overcome and in part because there is a large global market. A 7-valent conjugate vaccine is licensed and available now. The 7-valent vaccine, called Prevnar[®] (or Prevenar) contains vaccines against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. It is manufactured by Wyeth and licensed in ~75 countries, including 5 GAVI-eligible countries (India, Indonesia, Pakistan, Honduras, and Nicaragua).

Wyeth has indicated that it is committed to supplying GAVI and has begun working with WHO on prequalification. Wyeth plans to submit an application for prequalification of 7-valent vaccine in January 2007. Prequalification by late 2007 or early 2008 is considered a realistic projection.

The next vaccine expected from the pipeline is a 10-valent conjugate vaccine from GSK that adds serotypes 1, 5, and 7F to the serotypes in the 7-valent vaccine. This candidate vaccine is in late-stage clinical development with expected licensure in 2008. A similar 11-valent candidate (that added serotype 3) was tested in a phase 3 trial in Czech Republic and shown to protect against ear infections.

GSK has indicated that it is interested in supplying vaccine for GAVI-eligible countries, and they have indicated a willingness to supply the vaccine as early as possible (in 2008 according to GSK). Whether this timeline is possible will depend in part on the results of an ongoing phase 3 trial, and the regulatory approval and prequalification processes. At this time, with the limited data available on this vaccine, it is PneumoADIP's independent assessment that GAVI access to pre-qualified 10valent vaccine in 2008 is possible but optimistic at this point because it requires an interval between initial licensure and WHO pre-qualification that is shorter than historical precedents. Access to the vaccine in 2009 is more likely, and 2010 is very realistic. Also, at this point in time, it is unclear what volumes of doses would be available for GAVI countries in those years. As additional data become available this year, this estimate can be updated and with more certainty.

A 13-valent conjugate vaccine candidate (Wyeth) is in Phase 3 testing; this vaccine adds serotypes 1, 3, 5, 6A, 7F, and 19A to the serotypes in the 7-valent. Licensure is forecasted for late 2009/early 2010. GAVI supply is projected for ~2012.

Emerging market manufacturers are developing multi-valent conjugate vaccines and are expected to supply them after 2015. A potential role for emerging market manufacturers in fill and finish is possible by 2015. Overall, more than 20 conjugate and protein-based vaccines are in early stages of product development or in research (pre-product development) phases.



Figure 2. Pneumococcal Vaccine Pipeline — Updated October 2006

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Vaccine efficacy. The efficacy of pneumococcal conjugate vaccine is wellestablished by clinical trials and surveillance following routine use in the United States. Phase 3 clinical trials have been conducted with 7-valent, 9-valent, and 11valent vaccine candidates in 7 different countries. Significant protection versus invasive disease, pneumonia, ear infections, hospitalizations and mortality have been demonstrated in some or all of the trials. Figure 3 provides an overview of the clinical trials and their results.

Two clinical trials in Africa, using a 9-valent vaccine candidate from Wyeth (the 7-valent vaccine serotypes plus serotypes 1 and 5), show that pneumococcal conjugate vaccines can improve child survival and protect the most vulnerable children.(6) A randomized, controlled trial with 9-valent vaccine candidate in The Gambia showed that vaccination reduced:

- All-cause mortality by 16% (95% CI 3–28)
- All-cause hospital admissions by 15% (95% Cl, 7–21)
- X-ray–confirmed pneumonia by 37% (95% CI, 27–45)

The mortality reduction translates into 7.4 deaths prevented for every 1000 children vaccinated.

In South Africa, a randomized, controlled trial of 9-valent vaccine was conducted that included both HIV-infected and HIV-uninfected children.(7) The main findings were:

- 83% efficacy (95% CI, 39–97) vs. vaccine-type pneumococcal disease in HIVuninfected children.
- 65% efficacy (95% CI, 24–86) vs. vaccine-type pneumococcal disease in HIVinfected children
- Vaccination reduced the incidence of pneumonia in HIV-infected children by 2566 cases per 100,000 children. That reduction translates to about 1 pneumonia case prevented for every 40 children immunized.

In short, this trial shows that pneumococcal conjugate vaccines can improve the health of HIV-infected children by pneumococcal disease.



Figure 3. Summary of pneumococcal conjugate vaccine Phase III trials and their results

Experience with vaccination in the United States, including herd immunity and serotype replacement.

In 2000, Prevnar received US approval and has since been used to safely and effectively vaccinate >30 million children in >75 countries. Since 2000, all children in the United States under 2 years are routinely vaccinated with Prevnar. The US also has strong surveillance in place, dating back to the pre-vaccination era, to monitor changes in disease following vaccination.(8-10)

The main findings from the US experience with 7-valent vaccine include:

- Routine vaccination prevents vaccine serotype disease in vaccinated children.
- Routine vaccination of children reduces vaccine serotype disease in older children and adults by reducing transmission from vaccinated children. This "herd immunity" protection has been especially pronounced among persons aged 65 years and older, and has included children too young to be vaccinated

(i.e., children under 2 months old).

- The "herd immunity" protection by routine vaccination has prevented more than twice as many cases as the direct vaccination of children.
- Rates of non-vaccine type invasive disease (i.e., serotype replacement disease) have increased but the increase has been small (~4,000 cases in 2003) relative to the overall decline in vaccine-type disease (~30,000 cases in 2003).
 - The increases in non-vaccine-type disease are generally from serotypes that frequently colonize young children (e.g., serotype 19A), not the "highly virulent" serotypes such as serotype 1 and 5.
 - Experience in Native American children is reassuring because vaccination has reduced disease rates in this population with an epidemiology similar to developing countries, i.e., high overall incidence rates and more nonvaccine serotype disease than the general US population.

These data reinforce the basis for implementing pneumococcal vaccination in developing countries now, and the importance of strong, sustained surveillance to monitor the impact of vaccination on vaccine and non-vaccine type disease.

Alternative interventions to prevent and control pneumococcal disease.

Vaccines are the only reliable, effective way to prevent pneumococcal infections. Other interventions can diminish its mortality, but do not prevent cases from occurring. Assuring early access to care and use of appropriate antibiotics for the treatment of pneumonia will substantially reduce the mortality rate but not the incidence. Improved treatment will have a less profound affect on pneumococcal meningitis, whose case-fatality rates remain high, even in industrialized countries.

Supplemental zinc is being studied as a potential treatment for severe pneumonia and as an approach to preventing pneumonia in children in developing countries. 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. Even with this data, additional challenges for successful introduction and compliance (long term, sustained dosing is required for the effect of zinc to be observed) will also need to be addressed. It is unclear if zinc has any role in treatment or prevention of meningitis. Ultimately, expanded vaccination and increased access to treatment will complement one another. Vaccines will prevent some but not all infections and reduce the negative impacts of antibiotic resistance. Antibiotics will help to prevent mortality from those infections not prevented by vaccination.

2c. The Challenge

In order to accelerate pneumococcal vaccine introduction in developing countries, an affordable, sustainable supply of vaccine must be ensured. The only way to do this is to ensure that there is sufficient global capacity to meet the demand in developing countries, i.e., supply that exceeds high- and middle-income market demands, and financing to support the developing country demand.

GAVI's PneumoADIP analyses and discussions with multinational and emerging market suppliers indicate that affordable, sustainable supply is possible if GAVI makes a firm, credible commitment to finance vaccine procurement for eligible countries and demonstrates credible efforts to build and sustain evidence-based demand.

2d. Vaccine Supply

Currently one pneumococcal conjugate vaccine, licensed in 2000 by the US FDA and registered in >75 countries is available. The vaccine Prevnar®, manufactured by Wyeth is a pneumococcal 7-valent conjugate vaccine (Diphtheria CRM₁₉₇ Protein) sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4,6B,9V,14,18C,19F,and 23F individually conjugated to diphtheria CRM₁₉₇ protein. The vaccine is manufactured as a liquid preparation. A complete product description is presented in Annex I.

Wyeth is prepared to supply and support Prevnar® introduction into GAVI-eligible countries for the period 2007-2010 from their current capacity. Demand estimates from the strategic demand forecast indicate that existing capacity is sufficient to supply GAVI-eligible countries prepared to adopt the vaccine during this period.

By 2010 the vaccines available for routine vaccination are expected to diversify with the introduction of 10 and 13 valent vaccines between now and 2015. These extended protection vaccines include serotypes 1 and 5, which are important in many developing countries, and are expected to be "global formulations". Two multinational suppliers, Wyeth and GSK have indicated their willingness to supply vaccines during this accelerated uptake period 2010-2015 and have indicated that a clear expression of GAVI's commitment to financing pneumococcal vaccines is essential. This commitment is needed for companies to assure dedicated capacity to supply GAVI demand at affordable, sustainable prices.

Between 2015 and 2020 new manufacturers are expected to enter the pneumococcal market. This includes emerging manufacturers either with alternative vaccine approaches (e.g., common protein vaccines) that may become licensed and play a role in global prevention programs, or with additional multi-valent conjugates. A complete analysis of the supply landscape conducted by GAVI's PneumoADIP is in Annex J.

2e. Price

GAVI's PneumoADIP analyses on pricing aimed to find 'solution space' in pricing and financing that could help to bring suppliers, GAVI, and countries together. For the supplier perspective, GAVI's PneumoADIP analyses took a 'business case' approach. In this analysis, a potentially acceptable price was considered one that would provide a positive return on investment after accounting for the manufacturing costs of the vaccine and discounting at 10% per annum. It assumed that revenues were the product of forecasted demand, individual supplier market share, and price.

For the GAVI and country perspectives, the 'investment case' approach was taken. Cost-effectiveness analysis, target product profile interviews, comparison with other competing uses of health and immunization resources and consideration of fiscal space were used to identify potentially acceptable prices.

Based on these analyses, the prices used in this investment case are expected to represent a 'solution space' where the needs of suppliers, GAVI, and countries converge to provide a successful business or investment case for each one. Annex K provides more information on vaccine pricing methodology.

Section 3: Description of the Proposed Project

This investment case focuses on introducing and sustaining uptake of pneumococcal vaccines in GAVI-eligible countries during the period 2007 to 2010 and includes the proposed costs and key assumptions for successful implementation.

The main goal of this period is to use the 7-valent vaccine in early-adopting countries to demonstrate expected health impact, the country's ability and willingness to introduce new vaccines into current programs and as a springboard for future evidence-based policies during 2011-2015 when use of next generation (10- and 13- valent) vaccines expand rapidly to help meet MDGs.

Key activities proposed in this project ensure that:

- 1. An affordable, sustainable supply of safe, high quality pneumococcal vaccine is available to meet demand in GAVI-eligible countries;
- 2. Countries and donors continue to see the value of pneumococcal vaccines;
- 3. Information on the vaccine and the disease is used to build evidence-based decisions at the country, regional, and global levels.

Comparison of the forecasted pneumococcal demand to the actual Hib uptake in 'similar' years shows that the forecasted introduction of pneumococcal vaccines during 2007-2015 represents a significant improvement in accelerating vaccine uptake over historical precedents (Figure 4). The pneumococcal vaccine strategic demand forecast is the basis for the proposed project and investments.



Figure 4. Pneumococcal Accelerated Demand Forecast vs. Actual Hib Introduction

Section 4: Proposal Cost and Funding Needs

4a. Cost of the Proposal (2007 – 2010)

To begin accelerated use of pneumococcal vaccination in GAVI-eligible countries will require \$127 million to \$189 million in new GAVI financing between 2007–2010. It will also require \$14 million from the existing commitments for strengthening health systems and \$6 million in country co-payments.

The majority of the funding requested (up to 79%) is for purchasing the vaccine itself. The financing requested from GAVI is mainly to subsidize the cost of the vaccine to a price that allows GAVI-eligible countries the ability to demand it.

The remainder of GAVI's funding (\$40 million) would support a dedicated team, GAVI partners, and activities in countries to support the evidence-based introduction of the vaccine and assessment of the vaccine's impact in early adopter countries.

Proposed costs. Between 2007 and 2010, the accelerated introduction forecast will require the following new GAVI authorizations (Table 2):

- \$87 million to \$149 million to procure the vaccine from the manufacturer.
- \$40 million for activities and a dedicated team to provide strategic and technical support to the countries that are considering vaccine introduction and the partners involved in vaccine introduction.

Table 2. Costs in the Request for GAVI Authorization of Funds 2007-2010 (Undiscounted)

Activities	Years 2007-2010		
Vaccine investment costs	\$ 87 -\$149 million		
Strategic and technical support costs	\$ 40 million		
Total	\$127 - \$189 million		

4b. Obligations beyond 2010

GAVI's commitment to support limited use of the vaccine for introduction in the early adopter countries requires an obligation from 2011–2015 to continue the vaccination program. The extent of the obligations from 2011–2015 depend on whether GAVI limits the vaccine's use to the early adopting countries (2007-2010) that continue to uptake between 2011–2015 (Option 1), or if it allows additional countries to apply for and introduce the vaccine between 2011–2015 (Option 2) (see Table 3.). The obligations for each scenario and description of costs including assumptions used in the calculations are presented below and outlined in greater detail in Annex D.

Option 1. Continued Funding of Early Adopter Countries Only 2011-2015

If GAVI chooses not to extend support for vaccination beyond the early adopter countries that take up the vaccine in 2007–2010, then their obligations for 2011–2015 amount to a total of \$415 million for vaccine procurement and \$25 million for Strategic & Technical Support between 2011–2015. Health systems costs, presumably covered under existing health systems support, would amount to \$70 million. Vaccine financing costs, which are not borne by GAVI, are ~\$15 million during this period.

Option 2. Early Adopter & Additional Country Funding 2011-2015

If GAVI decides to expand its support for new vaccine introduction and uptake follows according to the Accelerated Introduction Forecast, then GAVI obligations between 2011–2015 are expected to amount to a total of \$926 million for vaccine procurement and \$25 million for Strategic & Technical Support between 2011–2015. Health systems costs, presumably covered under existing health systems support, would amount to \$285 million. Vaccine financing costs, which are not borne by GAVI, are estimated at \$25 million during this period.

Activities	Years 2011-2015
Option 1 – Continued Early Adopter Only Investment	\$ 415 million
Option 2 – Early Adopter & Additional Countries	\$926 million
Strategic and technical support costs	\$25 million
Total	\$440 - \$951 million

Table 3.	Estimated Range	of Costs of	GAVI Fund	ls 2011-2015
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4c. Financing. Sources of Funds and Discussion of Funding Gaps

Between 2007–2015, substantial funding gaps are not anticipated. Current GAVI resources should be adequate to cover financing between 2007–2015 for vaccine procurement and support to countries. GAVI's existing health systems strengthening resources should be adequate to cover the costs of delivering the vaccine in the limited number of countries that are expected to adopt between 2007 and 2015.

An Advance Market Commitment (AMC) for pneumococcal vaccines would complement the investments outlined in this case by supporting the funding requirements during the 2010-2015 period.

First, an AMC will be used only for future products that prevent a larger proportion of disease than that covered by the 7-valent (e.g., 10 and 13 valent vaccines). Second, an AMC is likely to begin paying for vaccines beginning ~2010, thus the time period overlaps are likely to be minimal. By using AMC funds for pneumococcal vaccine, it will also allow GAVI to use its funding to finance other priority vaccines, without interrupting pneumococcal vaccination.

In GAVI Phase 2, countries and their local partners are expected in GAVI Phase 2 to provide a co-payment for pneumococcal vaccines. On a country-by-country basis this will require efforts to obtain and sustain the financial resources to support vaccine introduction. Experience with the co-payments on pentavalent vaccine will prove useful and instructive to countries that are planning for pneumococcal (or other new) vaccine introduction.

Section 5: Financial Sustainability

Financial sustainability is an important issue for all new vaccine introductions. GAVI's current Phase 2 financing policies encourage good decision-making and begin the process of ensuring financial sustainability. By 2016, when the early adopters of pneumococcal vaccine are facing the issues of financial sustainability the experience gained with other new vaccines (e.g., hepatitis B, Hib) during the interim years will provide a useful base for planning and successful transition. For countries introducing pneumococcal vaccination, it will be important to communicate the following:

- GAVI's expectations for financial sustainability planning, including when it must begin and what levels of co-financing are expected at different points
- The value of pneumococcal vaccination. As the cost-effectiveness analysis shows, while there are costs associated with pneumococcal vaccine introduction, there are also substantial savings in terms of medical costs and DALYs.

Part II. Rationale for Investing

Section 6. The Relevance to GAVI Objectives

6a. Alignment With GAVI Strategic Goals, Principles, and Milestones

This investment case aligns with GAVI's mission of "Saving children's lives and protecting people's health by increasing access to immunization in poor countries" because without a GAVI financing commitment, another 15 years is likely to pass before these countries will have access to life-saving pneumococcal vaccines. It also contributes to GAVI's strategic goal #2: "Accelerate the uptake and use of underused and new vaccines and associated technologies and improve vaccine supply security." It aligns with GAVI's 12 principles, most notably, with these specific principles:

- Principle 1. Contribute to achieving Millennium Development Goals by preventing 117,000 child deaths annually by 2015.
- Principle 2. Promote equity by assuring children in poor countries have access to the same vaccines as children in rich countries.
- Principle 5. Focus on underused and new vaccines. Pneumococcal vaccines were identified in 2002 as one of GAVI's "high priority" new vaccines.
- Principle 7. Be coherent with GAVI partner mandates. This investment case is consistent with the goals of WHO/UNICEF Global Immunization Vision and Strategy (GIVS).

GAVI's contribution for this investment case is expected to be time-limited in the period 2007–2015, and catalytic because it will generate greater increases in manufacturing capacity and faster decreases in vaccine pricing than would have happened otherwise.

6b. Target Countries and Strategic Demand Forecast

Children in all 72 GAVI-eligible countries (and the adults in their communities) will potentially benefit from the use of pneumococcal conjugate vaccines. Realistically, however, not all countries are expected to take up the vaccine immediately even if offered for a nominal co-payment due to competing priorities or a preference for other vaccines (e.g., rotavirus, Japanese encephalitis, meningococcal), civil unrest, or economic instability.

The countries forecasted for 7-valent in this early period include those with a significant burden of pneumonia, adequate delivery systems, and evidence of a substantial burden of pneumococcal disease due to the 7-valent serotypes.

Between 2011 and 2015, the number of countries increase and the use of extended protection vaccines (with 10 and 13 serotypes) is forecasted.

Accelerated introduction forecast. The accelerated uptake scenario begins with the use of 7-valent vaccine between 2007–2010 in a limited number of countries (most likely, 4–6 countries). Forecasted demand during this period amounts to <35 million doses. The main assumptions and data used in this demand forecast and a detailed description of the methods are summarized in Annex E.

This strategic demand forecast (Figure 7.) has been shared widely with GAVI partners, including vaccine manufacturers (both multinational and emerging market), and *it has been widely regarded as both credible in its assumptions and innovative in the approach it has taken to modeling. A number of manufacturers have indicated*

that this demand forecast has helped them to "make the business case" internally for programs to develop and supply pneumococcal vaccines for GAVI-eligible countries.



Pneumococcal Accelerated Introduction Forecast, 2007-2025 **Demand Including Wastage (M Doses)**



Section 7: The Expected Incremental Impact of the Investment

7a. Description of Benefits and Beneficiaries

By 2015, the accelerated introduction of pneumococcal vaccines will:

Contribute to achieving the fourth Millennium Development Goal of reducing childhood mortality because it will:

- Prevent 446.000 cumulative child deaths by 2015:
- Prevent 117,000 child deaths in the year 2015; •
- Reduce child mortality in children aged 3 to 59 months by ~9% in the • countries where it is used.

Contribute to achieving the first Millennium Development Goal of eradicating extreme poverty and hunger because it will:

- Improve the economic conditions of poor families by reducing hospitalizations • for serious illness by 15%;
- Reduce medical expenditures by up to >\$180 million per year. •

By 2025, the accelerated introduction of pneumococcal vaccines will:

- Prevent 3.9 million child deaths overall and 453,000 per year;
- Prevent 32 million hospitalizations overall;
- Save over \$690 million per year in medical expenditures;
- Improve the lives of HIV-infected children by preventing a common, serious complication:
- Prevent additional cases of serious disease and deaths among unvaccinated children and adults through herd immunity;

7b. Burden of Disease — Baseline

Pneumococcal disease is the leading cause of vaccine-preventable mortality worldwide. In 2004, WHO estimated >700,000 children under 5 years old, and about 1.6 million persons of all ages die of pneumococcal disease each year.(1)

In The Gambia pneumococcal vaccine trial, the 9-valent vaccine prevented 16% of all child deaths among vaccinated children while preventing 50% of confirmed pneumococcal disease.(6)

WHO estimates that pneumococcal disease causes ~900,000 deaths among older children and adults each year. The available data on the serotypes causing disease among adults in GAVI-eligible countries indicates that the serotypes included in pneumococcal conjugate vaccines cause a substantial proportion of these cases. Pneumococcal conjugate vaccination of children is expected to confer some degree of herd immunity – that is, protection of unvaccinated adults.

A herd immunity reduction of just 10%–15% amounts to the potential to prevent an additional 80,000 to 120,000 deaths per year.

7c. Impact of the Investment on Burden of Disease by 2025

The impact of an investment in pneumococcal vaccination can:

- Vaccinate 535 million children against pneumococcal disease
- Prevent 3.9 million child deaths and 31.9 million hospitalizations
- Prevent pneumococcal deaths in older children and adults through herd immunity
- Save over \$5.9 billion in medical costs

7d. Contribution to Achieving Millennium Development Goal 4: Reducing Child Mortality by Two Thirds by 2015

Pneumococcal vaccination will prevent 8.9% of child deaths between 3 - 59 months, making a substantial contribution to achieving the MDGs in the countries where it is used.

7e. Opportunities for Expanding the Health Impact

The forecast for vaccine introduction (Figure 8) represents a realistic, yet ambitious improvement over previous vaccine introductions (e.g., Hib or hepatitis B).



Figure 8. Pneumococcal vaccines' accelerated introduction forecast: Annual and cumulative deaths averted, 2007–2015

Further improvements in uptake are possible but would require additional effort and/or resources. For example, pneumococcal conjugate vaccines are very heat stable and thus, are well suited to use in large-scale campaigns. The use of the vaccine in campaigns could be an excellent way to "front load" prevention. Vaccinating children ages 1 through 4 years with a single dose, for example, 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 slated for 2007–2010. These projects will provide an evidence base to determine whether wider application of a campaign policy in 2011–2015 is a good strategy to reach the MDGs for child survival.

Section 8: Constraints and Probability of Success

8a. Social and Cultural Constraints

The biggest social and/or cultural constraint for pneumococcal vaccine demand is expected to be the lack of awareness of the burden of pneumococcal disease among some key audiences. Audience research conducted by GAVI's PneumoADIP, McKinsey & Co, and others indicates that there is a widespread recognition of the burden of pneumonia and meningitis and the severity of pneumococcal disease among technical audiences (e.g., pediatricians, nurses, MoH officials). However, many politicians and the lay public may be unaware of the specific burden of pneumococcal disease in their country. Unless the evidence of the burden of disease and the value of the vaccine are communicated to them, it could constrain the demand for the vaccine.

Fortunately, the pneumococcal vaccines are not prepared in a way that makes safety risks likely to be a major constraint to uptake. Unlike some vaccines (e.g., oral polio vaccine), where there is a risk of getting the disease from the vaccine, pneumococcal conjugate vaccines are made from inactive particles of the vaccine and as such, it is not possible to get pneumococcal disease from the vaccine. In addition, the vaccine's excellent safety profile will support efforts to build demand. Nevertheless, efforts to demonstrate the vaccine's safety and value are important for ensuring acceptance.

8b. Epidemiological and Environmental Constraints

The biggest epidemiological and environmental challenge is that it is difficult to diagnose *S. pneumoniae* as the causative agent of many of the diseases that it causes. As a result, most physicians and health workers in developing countries treat patients with pneumococcal pneumonia, meningitis, and sepsis every day without knowing that the pneumococcus is responsible for the patients' illnesses. For this reason, it is a high priority to support the development of surveillance to document local evidence of the burden of pneumococcal disease in developing countries and to build tools that allow the extrapolation of data across borders and between studies. It should also be noted that in many of the countries where pneumococcal disease burden is high, there are many competing priorities (e.g., malaria, HIV, meningococcal, rotavirus disease).

8c. Technical Constraints

Technical constraints facing pneumococcal vaccines are expected to be largely the same as any other vaccine 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. The presentation of the 7-valent vaccine is a single-dose pre-filled syringe. This presentation will require substantial cold chain investments to maintain it at 2 to 8 degrees Celsius. A brief summary of the cold chain requirements for introducing 7-valent vaccine was developed for this investment case by WHO/IVB/EPI and is available as Annex L.

8d. 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. These challenges include resources (money and personnel) for immunization, national procurement of vaccines (raising foreign exchange), and country co-pay/co-financing. In short, it is important to recognize that introduction of this new vaccine will require an incremental effort and resources for local institutions but, as compared to delivery of other interventions (e.g., HIV therapy) these should be relatively easier.

Critical Risks

Risk	Risk Rating	Risk Minimization Measure
GAVI support not long enough to sustain demand until prices decline	High, but modifiable	Extend GAVI support to ensure that price declines occur
Supply interruptions	Variable, depends on supply and demand over time	Strengthening of supply chain and strategic demand forecasts and close communication between suppliers and GAVI to keep demand and supply aligned with each other
Some countries are not able to sustain vaccine financing in 2016	Variable by country, but modifiable	Possible approaches include extending GAVI financing beyond 2015, mobilizing alternative donor support after 2015, and supporting efforts to increase overall health and immunization spending between now and 2015
Supplier cannot reach acceptable terms	Moderate and modifiable by GAVI actions	A contractual agreement with suppliers to finance agreed volumes of vaccine over an extended period of time at set prices made at least 1–2 years in advance of anticipated demand
Countries and local partners unsure about the value of vaccination	Variable from low to high, depending on the country	Continued efforts to establish and communicate the value of pneumococcal vaccination in the contexts of health, development, and poverty reduction

Section 9: Economic Analysis

9a. Cost-Effectiveness and Cost Benefit Analysis

Pneumococcal conjugate vaccination in low-income countries is a good investment of health resources, and its cost-effectiveness is greatest in those countries with high infant and child mortality rates.

A recent study from Harvard University, performed for GAVI's PneumoADIP, shows that pneumococcal vaccine meets the WHO criteria for "cost-effective" or "very cost-effective" for all Vaccine Fund-eligible countries. The analysis used UNICEF estimates of child mortality and data on the incidence of pneumonia, incidence of meningitis, vaccine efficacy, vaccination coverage, direct medical costs, nonmedical direct costs, productivity costs, and costs associated with the vaccine itself and vaccine program administration. The primary analysis used a vaccine cost of \$5 per dose and a 3-dose schedule. Other key assumptions are described in Annex D. All results are presented in PPP-adjusted International \$(2000).

The main findings of the cost-effectiveness analysis were:

 Vaccination of all infants in GAVI-eligible countries at current DTP3 rates would prevent ~470,000 deaths per year among children between the ages of 3 months and 5 years.

- 2. The weighted average cost-effectiveness ratio is **\$22 per DALY averted or \$691 per death prevented**.
- 3. Vaccination would **reduce medical expenditures by more than \$558 million per year**.
- 4. The costs of procuring and delivering pneumococcal vaccine are estimated at **\$882 million dollars** annually.
- 5. The net costs of vaccination would be \$324 million dollars annually.

Pneumococcal vaccine for children is a good value. The weighted average cost per DALY saved is \$22, well below the weighted average per capita GDP in GAVIeligible countries. Herd immunity protection of older children and adults will make the vaccine even more cost-effective by preventing illnesses, deaths, and costs without requiring additional vaccination costs.

Pneumococcal vaccination is cost-saving in 3 of 72 GAVI-eligible countries and in the remaining 69 countries, the cost per DALY saved meets WHO criteria for a "very cost-effective" intervention.

In these analyses, the vaccine's impact on mortality was assumed to vary based on a country's under 5 mortality rate. The Harvard analysis assumed conservatively that the ability of pneumococcal vaccine to prevent death in vaccinated infants and children under 5 years old was equal to or less than the rate observed in the randomized trial in The Gambia, i.e., 7.4 deaths averted per 1000 children vaccinated. In countries with mortality rates lower than The Gambia, vaccine effectiveness was assumed to be proportionately lower.

In addition to its direct effects on vaccinated children, surveillance data collected in the post-vaccination era in the United States shows that pneumococcal vaccine prevents illnesses and deaths among unvaccinated children and adults through herd immunity. In the United States, more than 2 times as many pneumococcal disease cases and 10 times as many pneumococcal deaths are prevented as a result of these herd immunity effects, when compared with the cases and deaths prevented directly by vaccination.

The Harvard analysis ascribed a modest herd immunity effect in unvaccinated young children (under age 5 years) only. In these unvaccinated young children, vaccine efficacy was assumed to be one half of the efficacy level observed in vaccinated children for mortality, meningitis, and hospitalized pneumonia prevention, and one quarter of the efficacy level observed in vaccinated children for outpatient pneumonia prevention.

Although pneumococcal vaccination is expected to protect older children and adults through herd immunity, this model did not include herd immunity benefits among older children or adults.

Table 4 shows the impact of vaccine on health, in terms of lives saved, DALYs saved, and prevented hospitalizations and outpatient visits. Pneumococcal vaccine is projected to save 470,000 lives and 15 million DALYs annually in GAVI-eligible countries.

	AFRO	AMRO	EMRO	EURO	SEARO	WPRO	Total
Births (1000s)	25,846	1027	9538	1504	36,345	2594	76,855
No. immunized (1000s)	15,129	755	5888	1432	26,319	2236	51,760
Annual lives saved	194,044	3443	74,287	3980	185,102	8740	469,594
Annual hospitalizations prevented	952,397	31,716	392,634	50,447	1,520,409	79,824	3,027,426
Annual outpatient visits prevented	807,662	36,589	336,045	65,606	1,456,345	96,499	2,798,746

Table 4. Annual Health Benefits of Pneumococcal Vaccination, by WHO Region

Table 5 shows the impact of vaccination on costs. The \$862 million invested in vaccination will be offset by \$558 million in medical savings, resulting in a weighted average cost per DALY averted of \$22 and cost per life saved of \$690

 Table 5. Annual Vaccination Program Costs, Medical Costs Saved, Net Costs, and Cost-Effectiveness by WHO Region

	AFRO	AMRO	EMRO	EURO	SEARO	WPRO	Total
Births	25,846	1,027	9,538	1,504	36,345	2,594	76,855
(1000\$)							
NO.							
immunized							
(1000s)	15,129	755	5,888	1,432	26,319	2,236	51,759
Vaccination							
Costs							
(1000s)	\$251,196	\$13,091	\$99,189	\$24,929	\$455,287	\$38,370	\$882,062
Averted							
disease							
costs							
(1000s)	\$159,214	\$10,240	\$80,428	\$15,748	\$270,423	\$21,609	\$557,622
Net costs							
(1000s)	\$91,982	\$2851	\$18,761	\$9181	\$184,864	\$16,760	\$324,399
Cost per							
DALY							
averted	\$15	\$26	\$8	\$70	\$30	\$59	\$22
Cost per life							
saved	\$474	\$828	\$253	\$2307	\$999	\$1918	\$691

9b. Sensitivity and Secondary Analyses

Sensitivity analyses included one-way, two-way, and probabilistic analyses. These analyses indicate that the cost-effectiveness of pneumococcal vaccination remains robust over a wide range of assumptions. Important findings from the sensitivity analyses include:

 Vaccine price is a strong driver of the cost-effectiveness. The cost per DALY averted varies almost directly with the price of vaccine. However, vaccination remains cost-effective over the full range of vaccine prices considered and is cost-savings at dose costs below \$3 per dose (Figure 9). The costeffectiveness ratio remains ≤\$75 per DALY for vaccine prices as high as \$10. The threshold dose price is \$3, below which vaccination becomes costsaving.

2. Disease and administration costs, variations in DTP coverage, and variations in the DALYs per death prevented assumption have little impact on the cost-effectiveness.





9c. Comparability of Pneumococcal and Rotavirus Vaccine Economic Models

Overall, the rotavirus and pneumococcal vaccine cost-effectiveness models are highly similar in major assumptions and methods. Each economic team used an external expert panel to review and revise key assumptions. The models also share common sources of data.

The central assumptions driving cost-effectiveness in both models were vaccine dose cost, estimated disease burden and vaccine efficacy. Overall comparability between models depends on comparable assumptions for these aspects of the models. These critical assumptions are comparable across models, and reflect the current state of knowledge for rotavirus and pneumococcal diseases and vaccines. Annex H describes in detail the similarities and differences of each model.

9d. Market Analysis

The main characteristics of the global pneumococcal market, which provide opportunities for GAVI include:

- Strong demand exists in high-income and middle-income markets.
 - PneumoADIP's market assessment puts the potential value of the highand middle-income markets at \$5.8 billion annually.
- A strong pipeline for pneumococcal vaccines exists, largely driven by the high demand in high-margin markets of high- and middle-income countries, but also including private markets in low-income countries.

- Pipeline includes both multinationals and emerging market suppliers committed to supplying developing countries;
- High margins in the high-priced markets allow suppliers to recoup R&D costs, capital investments, and cover risks. This should enable them to price in GAVI-eligible countries without having to cover all their risks and costs;
- Wyeth revenues for Prevnar® exceeded \$500 million in the 2nd quarter of 2006.

The main characteristics of the global pneumococcal vaccine market, which provide challenges for GAVI include:

- Current capacity is sized to supply high- and middle-income countries. Existing excess capacity should allow introduction to start and grow to the levels expected in 2011. However, as long as capacity only slightly exceeds demand in high- and middle-income markets, there will be a limit to the number of countries that can introduce vaccine between 2012 and 2015.
- Capacity to supply the volumes of doses required for eventual GAVI demand will require large capital investments by industry, and these must be taken years in advance of actual demand. Decisions by manufacutrers need to be made now to meet demand estimates 2012-2015.
- GAVI markets require large volumes of doses and produce relatively small revenues, as compared to high-income markets.
 - Consider that 50 million doses per year (the target demand in 2015) at \$5 per dose amounts to \$250 million per year in revenue. When compared with the possibility for \$2.5 billion in revenue from the same volumes in high-income markets. It is clear that with GAVI's limited "pull", industry's willingness to make capacity commitments for GAVI must be motivated by factors other than revenues alone.

Supply situation. The global market for pneumococcal vaccines represents opportunities and challenges for ensuring affordable, sustainable supply of the vaccines to GAVI-eligible countries. Success requires GAVI to use its financing and alliance of partners to capitalize on the opportunities in order to address these challenges and convince suppliers to provide high-quality vaccines at sustainable, affordable prices. A detailed analysis of the supply situation is presented in Annex J.

Pricing. In building its demand forecast and pricing assumptions, GAVI's PneumoADIP aimed to find "solution space" for bringing together donors, countries, and suppliers. Solution space in pricing was defined as prices that represented a "good investment case" for donors and countries and at the same time represented a "good business case" for suppliers. Cost-effectiveness analyses indicate that at \$5 per dose, the vaccine represents a "very cost-effective" health investment for countries and donors. It is also recognized that this price point is higher than GAVI has ever paid before for a vaccine, and that if demand targets are met, it will require a large, but feasible, annual envelope of funding. See Annex K for additional detail on the rationale for the pricing assumptions used in this investment case.

Business case analyses conducted by GAVI's PneumoADIP indicate that the prices used in this investment case can support a good business case for suppliers. In other words, if the demand targets are met, these prices and volumes should motivate suppliers to get in and stay in the business of supplying GAVI markets.

GAVI's PneumoADIP approached its business case analysis from the perspective of suppliers using Net Present Value (NPV) methodology. The main findings of these business case analyses are:

- The prices and timing of revenues in the Accelerated Introduction Forecast provide a positive NPV (i.e., greater than \$0) for the period 2007–2015 for the 2 suppliers expected to serve the market.
- Prices that would be most acceptable to developing countries without GAVI support (i.e., below \$1 per dose) would not support a business case for suppliers to enter the market.
- Delays in timing of the demand represent a significant risk for the supplier's business case. For example, if demand is delayed by 3 years, then the supplier NPVs are negative (i.e., the suppliers lose money by supplying GAVI).

9e. Equity Impact

Among vaccines, pneumococcal conjugates are especially capable of reducing health inequities because they have the ability to protect both vaccinated children, and through reduced transmission, to protect unvaccinated children and adults. The experience with the 7-valent vaccine in the United States gives an indication of the potential equity impacts in developing countries. In the United States, herd immunity has been observed to occur rapidly following vaccine introduction and with vaccine coverage rates of <65% in children under 2 years old.

In the USA, the number of cases prevented by herd immunity actually exceeds the number of cases prevented in vaccinated children.

Pneumococcal conjugate vaccination has also diminished racial inequities in the risk of pneumococcal disease. Before vaccination, Alaska Native children experienced an excess risk of invasive pneumococcal disease of 170 cases per 100,000 children below age 5 years, as compared to non-Alaska Native children. After vaccination, that difference had been reduced to 5 cases per 100,000 children per year.

Part III. Monitoring and Evaluating Implementation

Section 10: Monitoring and Evaluation

Monitoring and Evaluation

This investment case is based on a strategic demand forecast that, if met, will accelerate the introduction of pneumococcal vaccines. This will lead to significant health impacts and changes in the supply environment. These changes in supply are expected to meet the projected demand from GAVI eligible countries.

The best indicators of success are to measure changes in pneumococcal disease mortality and morbidity in developing countries and changes in supplier intentions. Both of these can be difficult to measure or require a long period of observation before changes can be seen. Consequently, this case proposes some putative process and outcome indicators to help assess progress during the period 2007-2010. Based on the experience in this time period, improved indicators can be developed for the period 2011-2015.

Definition of success

- Introduction of pneumococcal vaccine into one or more GAVI-eligible countries;
- Evaluation of the impact of pneumococcal vaccination in 2 or more of the early-adopting countries;
- A healthier market and more secure supply of pneumococcal vaccine for GAVI-eligible countries;
- Capacity sufficient to meet projected demand during this period.

Milestones

- WHO pre-qualification of at least one, and preferably two, pneumococcal conjugate vaccine(s);
- Successful negotiation of an agreement with industry to supply vaccine for the period 2007-2010;
- Establishment of GAVI co-financing policy so that countries can begin making financial preparations for introduction;
- Receipt of country applications for pneumococcal vaccine introduction by the beginning of 2008;
- Inclusion of pneumococcal vaccination to the WHO/UNICEF Joint Reporting Form.
- Ongoing disease surveillance in GAVI-eligible countries likely to introduce before 2012;
- Country-level planning for financial sustainability undertaken.

Roles and responsibilities

- GAVI and its partners will need to determine the best approach to negotiating and contracting with industry;
- WHO and industry will be responsible for assuring pre-qualification progress;
- WHO and UNICEF will be responsible for reporting coverage data;
- GAVI-eligible countries and their local partners, including WHO, will need to establish surveillance prior to introduction
- GAVI-eligible countries and their local partners will need to begin planning for financial sustainability;
- GAVI and its partners will need to establish co-financing policies for pneumococcal vaccines and communicate them to countries.

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Annexes

Annex A. Global Burden of Pneumococcal Disease

Summary

Previous WHO estimates of pneumococcal disease burden have ranged as high as 1 million child deaths per year. More recent WHO provisional estimates have put the burden of pneumococcal disease at >700,000 child deaths per year, with ~900,000 deaths among older children and adults (>5 years of age). These existing global estimates are helpful for priority setting at a global level. However, they are based on a simple assumption that a proportion of all pneumonia deaths worldwide are pneumococcal in origin. As such, they are not a substitute for robust national and regional estimates based on locally available data.

On October 23–24, 2006, WHO is convening an expert group in London to review and approve estimates for the global burden of pneumococcal (and Hib) disease. These estimates will represent over 2 years of work in the systematic collection and evaluation of disease burden data, the use of advanced meta-analytic methods, and engagement of a broad range of technical experts in the process. The outcomes will include country- specific estimates of the number of cases and deaths due to pneumococcal disease, separated out into pneumonia, meningitis, and other pneumococcal disease. These estimates will strengthen the global estimates on which decisions, such as the investment case, are taken, and provide countries and regions with more robust estimates based on local evidence.

This Annex provides an overview of the process to date. It will be updated before the final submission to incorporate the global and regional disease burden estimates generated by this WHO process.

Background

Credible estimates of the global and regional burden of *Streptococcus pneumoniae* (SP) are needed to prioritize this pathogen and pneumococcal vaccines relative to other diseases and interventions of public health importance. Such estimates are critical to cost-effectiveness analyses at the country, regional, and global levels. Estimates of pneumococcal attributable deaths and the proportion of these that are potentially preventable by vaccination inform the potential of pneumococcal conjugate vaccines to contribute to the Millennium Development Goals.

Estimates of pneumococcal cases and the preventable fraction through vaccination are critical for cost-effectiveness analyses of low-, middle-, and higher-income countries. The procurement of vaccine by middle-income countries is important for the industry business case and for optimal pricing for GAVI-eligible countries.

Therefore, the specific purposes for this effort to estimate pneumococcal disease burden are to:

- a. Facilitate country-level decision-making regarding the introduction (or continued use) of SP vaccines
- b. Facilitate multilateral and bilateral agencies in prioritizing SP prevention activities relative to other interventions
- c. Guide WHO global and regional vaccination policy and strategy

d. Inform decision-making processes related to vaccine development and production

The most accurate measures of SP disease burden would be based on empirical (not modeled) data from reliable surveillance, laboratory, and/or cause-specific vital registration systems. However, given both the inadequacy of current diagnostic tools for pneumococcal disease, and the fact that such systems currently do not provide reliable and timely information in the majority of countries that comprise most of the disease burden, modeling approaches are currently used. SP disease burden estimates have been generated in the past but the methods have not been systematic, transparent, or rigorously documented to allow for auditing of the work.

Therefore, WHO, in collaboration with GAVI's PneumoADIP and Hib Initiative, have undertaken to provide updated estimates of the burden of pneumococcal (and Hib) disease among children less than 5 years. The process for generating these disease burden estimates was designed to be comprehensive, systematic, transparent, and rigorous in its documentation. Since beginning in March 2004, the project has involved:

- WHO
- GAVI's PneumoADIP at Johns Hopkins
- US Centers for Disease Control and Prevention
- London School of Tropical Medicine and Hygiene
- Over 10 scientists and 20 data abstractors
- Experts in various disciplines (epidemiology, statistics, modeling, clinical medicine, library science)

The process and assumptions have been reviewed and monitored by a WHO Expert Panel (June 2005 and October 2006). In fall 2006, the complete dataset will be subjected to an external audit.

The specific goals of the WHO pneumococcal disease burden project were to generate estimates of:

- a. Cases, deaths, and DALYs at national, regional, and global levels for SP disease (by disease syndrome) in children <5 years of age
- b. Cases, deaths, and DALYs prevented through vaccination at national, regional, and global levels for SP disease in children under 5 years of age

Methods

- a) Rigorous literature review
- b) Models developed accounting for data availability
- c) Data quality from published papers critical to model: There are many ways to fail to identify pneumococcus as the etiologic agent in surveillance studies. Previous modeling exercises have not taken this into consideration to our knowledge.

We approached the estimation procedure by developing models that would articulate the relationship between various disease parameters. There are several models that could be used to estimate the public health burden of SP. However, all models rely on the existence of data which for some settings are sparse, not easily comparable, and sometimes of low quality, leading to a degree of uncertainty or bias in the estimates. Moreover, some models are not sensitive to programmatic interventions that may rapidly affect SP disease burden. We addressed each of these issues in the modeling approach. It was recognized that there are 3 major disease syndromes caused by the pneumococcus:

- 1. Meningitis
- 2. Pneumonia
- 3. Nonmeningitis/nonpneumonia–invasive syndromes (i.e., primarily nonfocal bacteremia/sepsis). The nonpneumonia/nonmeningitis syndrome estimation is derived by knowing the relative contribution of this syndrome to meningitis and applying that to the meningitis estimates.

To identify the parameter values for the models, we undertook an extensive review of the published and unpublished literature searching for reported values for the model parameters, as well as information that would allow an assessment of the study method quality. We trained over 20 abstractors (epidemiologists and clinicians) on a standardized data abstraction tool.

The steps and output from those steps are shown in Figure A-1 and a summary of the steps are provided here.

- <u>Conduct Literature Search.</u> Librarians at WHO conducted the search using systematic approach of 6 databases. The result was 10,661 titles relevant to SP.
- <u>Screen Titles and Abstracts (where available).</u> All titles and available abstracts were screened by trained physicians or epidemiologists for papers that might be relevant. The result was 1,909* publications deemed "potentially relevant" based on the abstract or insufficient information to determine if the paper should be retrieved.
- <u>Full Article Retrieved of "Potentially Relevant" Citations</u>. Potentially relevant papers were retrieved in PDF format. Total number 1,861.*
- <u>Secondary Screening of "Potentially Relevant" Papers.</u> All "Potentially Relevant" papers were reviewed in their entirety. Some papers were found not to contain relevant information for the GDB estimation once the full paper was made available. These papers were excluded from further steps. The number of citations excluded from further steps: 985.*
- <u>Data Abstraction Form (DAF) Completed.</u> For those papers found to have relevant information, at least one trained abstractor reviewed the paper in full and recorded well-defined data elements from the paper on a DAF.
- <u>Secondary Review of Selected Papers and Data Abstraction Form</u> <u>Completion.</u> For those papers that had case fatality ratios, incidence data, or disease syndrome distribution, the paper was reviewed a second time by a different reviewer to ensure the accuracy of the data abstracted from the paper and recorded on the DAF. Total papers undergoing a second review: 402.*
- In total, there are 583* papers with a single DAF and 402* papers with 2 DAFs completed for a total of 1317* DAFs completed.

*All numbers are for SP and Hib disease burden papers combined.





Annex B. The Potential Impact of 7-Valent Pneumococcal Vaccination in GAVI-eligible countries

Global burden of disease due to 7-valent vaccine serotypes

Recent WHO estimates of pneumococcal mortality in children <5 years old range from 716,000 in 2002^{1} to ~1 million in its pneumococcal vaccines position paper in $2003.^{2}$

In 2000, Hausdorff systematically reviewed the available data from surveillance in all countries world wide.³ Based on this analysis, the serotypes included in the 7-valent vaccine are expected to account for >55% of all invasive pneumococcal disease in children <5 years old each year.

Based on the current disease burden estimates and the Hausdorff analysis, at least 394,000 to 550,000 children <5 years old die each year of infections preventable by 7-valent vaccine (i.e., 55% of 716,000 to 1,000,000 deaths). These figures indicate that the potential health impact of 7-valent vaccine is on par with those of Hib (386,000) and rotavirus (402,000).¹ The 7-valent serotypes also cause serious illness and death among adults but these are not included in the estimates above.

The analysis by Hausdorff showed that the 7-valent vaccine types caused 63-86% of pediatric pneumococcal disease in Africa, Europe, North America, Oceania, and South America (Figure B-1).³ The exception was Asia, at 43%. However, the estimate from Asia was the least precise because it had the least representative data and there were significant questions about the quality of the data.

Expected impact of the vaccine in Bangladesh, Gambia, and Kenya

In an effort to improve the evidence base on the burden of pneumococcal disease and the serotypes causing pneumococcal disease in developing countries, GAVI's PneumoADIP has invested more than \$8 million in strengthening surveillance in these countries. The results of these surveillance projects are becoming available and are showing some important differences in the epidemiology of pneumococcal disease, especially in Asia.

Recent evidence from surveillance by the ICDDR,B in Bangladesh shows that the rate of disease due to the 7-valent vaccine serotypes is similar to the rates observed in Africa (specifically, The Gambia and Kenya) (Figure B-2).⁴ It also shows that the burden of preventable disease in each of these countries is considerably greater than the rates of disease prevented by the use of the vaccine in the USA and in Australia, two of the first countries in the world to introduce the vaccine for all children.

Recent 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)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) (Figure B-3).⁶

A call to action on pneumococcal vaccination, beginning with 7-valent

In light of the proven efficacy of the vaccine and the large burden of preventable disease, a group of leading pediatricians, researchers, and public health professionals called, in *The Lancet,* for donors, suppliers, and developing country governments to take actions to commence pneumococcal vaccination this year, beginning with the 7-valent vaccine, and expanding thereafter with next generation vaccines.⁷ This call to action recognizes the importance of preventing pneumococcal

disease and the value of the 7-valent vaccine as a tool for beginning the effort against pneumococcal disease in childhood.

Figure B-1.

7-valent vaccine: Proportion of pediatric pneumococcal disease preventable by vaccination



Figure B-2. Incidence of IPD preventable by PCV7 in the US and Australia and in three developing countries in Africa and Asia, and proportion of IPD preventable by PCV7



Expected impact of 7-valent vaccine in Kenya and Gambia exceeds that in US and Australia

Annex B. The Potential Impact of 7-Valent Pneumococcal Vaccination in GAVI Countries Figure B-3. Comparison of the potential impact of 7-valent vaccine to Hib vaccine, based on data from Kenya



Cases of invasive disease prevented per 100,000 children <5 years
References to Annex B

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Annex C. Proposed Costs for Strategic & Technical Support 2008–2010

Vaccine Introduction Strategy

A 20-year strategy for GAVI to accelerate pneumococcal vaccine adoption is shown in Figure C-1. This long-term strategy is defined in 5-year periods with key objectives and potential outcomes and with an expected benefit of saving up to 3.9 million childhood lives through this accelerated vaccine introduction process. Success in each period, however, requires commitments and success in the previous periods.

The current investment case focuses on the years 2007–2010. This period, called the Launch Period, is characterized by the introduction of new vaccines into a limited number of specific developing countries. Success with the vaccine in these countries establishes the evidence base for expanded vaccination during the Expand Period, 2011-2015.

Figure C-1. Long-term strategy and potential outcomes for accelerating the adoption of pneumococcal vaccines into developing countries

	Accelerated Early Adoption Accelerated Global Disease Control							
Period	2007-2010 LAUNCH	2011 - 2015 EXPAND	2016 - 2020 COMPLETE	2021 - 2025 SUSTAIN				
Vaccine(s)	7-Valent Conjugate	>7-valent conjugates (serotypes 1 & 5)	Extended conjugates; common proteins possible	Extended conjugates; common proteins				
Objective(s)	Launch in a small number of early adopter countries	Expand coverage using extended protection vaccines	Introduce vaccines into weaker health systems; improve & maintain high coverage rates	Sustain high immunization coverage rates				
Cumulative Lives Saved	47,000	446,000	1,718,000	3,856,000				

Activities from 2008-2010 and Projected Costs of \$40 Million

Over the past 3½ years, GAVI's PneumoADIP team has focused on establishing, communicating, and delivering the value of a pneumococcal vaccine.

The activities of the next funding period will build upon this work by shifting the focus from the development of the strategic plan to actual implementation of the plan. The implementation of the strategic plan will ensure that country healthcare officials have compelling, evidence-based reasons for introducing pneumococcal vaccination, are educated and knowledgeable on the safety, efficacy, and impact of the vaccine, and have access to a sustainable vaccine supply at an affordable price.

During this period, it will be essential to support a dedicated team and activities in support of evidence-based demand and assuring the supply to meet and sustain that demand. This team will need to be funded and mandated to provide support for both demand and supply related activities. The funding estimates in this Annex are based on the experience of GAVI's PneumoADIP over the past 3.5 years.

Table C-1 shows the projected areas of activities to continue the expansion of introduction of pneumococcal vaccine, which include:

- Vaccine introduction and disease surveillance
- Social mobilization for action against pneumococcal disease
- Securing vaccine supply
- Core team

Table C-1. Accelerated Pneumococcal Vaccine Introduction Efforts , 2008-2010

Develop and prepare countries to evaluate the burden of	f pneumococcal disease and the impact of pneumococcal			
vaccines and expand the assessment of safety, immunogenicity, and efficacy and effectiveness of vaccines in				
GAVI-eligible countries				
Objectives	Activities			
Continue to establish local and global evidence of the burden of disease	Support WHO-led surveillance and national disease burden assessment			
	projects to prepare for postadinen monitoring of vaccine enectiveness			
Establish vaccine effectiveness and immunogenicity in early adopter countries	Prepare sites and conduct demonstration projects in partnership with early adopter countries			
Establish economic burden of disease and value of vaccination in geographic regions and country level in GAVI-eligible countries	Conduct cost-effectiveness projects in key countries			
Measure vaccine impact in early adopter countries, including herd immunity and serotype replacement	Monitor effectiveness of vaccine in the populations of the early adopter countries			
Social Mobilization for Action Against Pneumoo	occal Disease			
Educate and communicate the value of pneumococcal v	accination with key global partners to decision-makers			
and key stakeholders at a regional and country level	accination with key global partitions to accision makers			
Objectives	Activities			
Assess country understanding and interest, develop and implement	Conduct country consultations			
communication materials, and monitor impact of communication efforts				
Consolidate data derived from disease burden surveillance and demonstration projects	Create regional and country-level evidence-based summaries; develop printed materials and visuals			
Ensure that key decision-makers have the appropriate disease burden and value of vaccination information for evidence-based health decisions regarding pneumococcal disease	Communicate evidence to regional and country-level policy makers through regional forums and meetings			
Share key disease burden and value of vaccination information with Key Opinion Leaders	Sponsor key scientific meetings			
Securing Sustainable Vaccine Supply				
Supporting efforts by GAVI partners to ensure that there sustained by credible financing commitments	is an affordable supply of vaccine to meet demand and			
Objectives	Activities			
Increase probability of sustainable supply of affordable vaccines	Continue to develop and build relationships with suppliers			
Work with appropriate agencies to negotiate and implement supply	Begin activities for procurement of vaccine for adoption in 2010 and			
agreements	beyond			
agreements Move from strategic-based to supply-chain-based forecast	beyond Develop supply-chain forecast on an 18-month rolling basis with partners			
agreements Move from strategic-based to supply-chain-based forecast Prequalify the 10- and 13-valent vaccines	beyond Develop supply-chain forecast on an 18-month rolling basis with partners Support prequalification activities for 2010-2015 vaccines			
agreements Move from strategic-based to supply-chain-based forecast Prequalify the 10- and 13-valent vaccines Prerequisite for GAVI application process; Insight for demand forecast input refinement	beyond Develop supply-chain forecast on an 18-month rolling basis with partners Support prequalification activities for 2010-2015 vaccines Support country development of cMYPs			
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agreements Move from strategic-based to supply-chain-based forecast Prequalify the 10- and 13-valent vaccines Prerequisite for GAVI application process; Insight for demand forecast input refinement Identify country needs and facilitate proactive preparedness (e.g. technical assistance, logistics, training, infrastructure), health systems, and cold-chain planning Core Team A dedicated team of talented individuals to efficiently ma project's mission and goals Objectives To enhance the transition into the Launch period to maintain historic records and list of all transactions To follow project management structure to ensure the most efficient use of funds for the greatest effort	beyond Develop supply-chain forecast on an 18-month rolling basis with partners Support prequalification activities for 2010-2015 vaccines Support country development of cMYPs Support country preparedness through appropriate partnerships nage and direct the project's resources to achieve the Activities Prepare summary reports of all activities from the ADIP work to transition to next period Maintain all budgets; develop and map milestones to track progress of work			
agreements Move from strategic-based to supply-chain-based forecast Prequalify the 10- and 13-valent vaccines Prerequisite for GAVI application process; Insight for demand forecast input refinement Identify country needs and facilitate proactive preparedness (e.g. technical assistance, logistics, training, infrastructure), health systems, and cold-chain planning Core Team A dedicated team of talented individuals to efficiently maproject's mission and goals Objectives To enhance the transition into the Launch period to maintain historic records and list of all transactions To follow project management structure to ensure the most efficient use of funds for the greatest effort To follow project management structure to ensure the most efficient use of funds for the greatest benefit	beyond Develop supply-chain forecast on an 18-month rolling basis with partners Support prequalification activities for 2010-2015 vaccines Support country development of cMYPs Support country preparedness through appropriate partnerships nage and direct the project's resources to achieve the Activities Prepare summary reports of all activities from the ADIP work to transition to next period Maintain all budgets; develop and map milestones to track progress of work Manage all partnerships, sub-contracts and contracts to budget and milestones			

Vaccine Introduction and Disease Surveillance

With the introduction of these vaccines, post-launch activities to monitor the effectiveness of vaccination in early adopting countries become essential. To help establish compelling evidence for country decision-making, activities such as surveillance, demonstration projects, and cost-effectiveness studies must continue (Table C-1). These activities at the country level will:

- Provide disease burden and cost-effectiveness data at the country and regional levels specifically in early adopters countries, and prepare the next group of countries for adoption of a new vaccine
- Improve ability of labs to gather high-quality data
- Improve and standardize serological methods
- Identify additional markers that could improve specificity and decrease cost and time to detect and treat the disease
- Improve the ability to exchange information and technology through the development of research and surveillance tool kits for general use that include standardized protocols, standard operating procedures, and case report forms.

Social Mobilization for Action Against Pneumococcal Disease

Effective communication of key data on the value of vaccination is critical for successful acceleration of new vaccine introduction and sustaining the vaccine program subsequently.

During the Launch period, it will be important to transition from a global to a regional and country level. With more accurate and confident information on disease burden, supply, and price, it should facilitate communication at these levels.

These activities will need to continue after launch in the early adopter countries to ensure that communication of scientific and disease burden data to our defined dialogue partners on a regional and local level is consistent using effective and appropriate communication channels (Table C-1). Preparing for the next wave of country adoption is also included in Launch activities. These activities will:

- Provide consistent fact-based information to increase disease burden awareness
- Improve understanding of disease and treatment
- Increase the value assigned to immunization by policy makers in countries and donor agencies
- Raise confidence and understanding on the economic impact of pneumococcal vaccination at a country level

Securing Sustainable Vaccine Supply

Finally, to ensure accelerated adoption will require the ability to address a number of regulatory, finance, and supply issues. The activities in this area build upon lessons learned from Hep B and Hib and include supply activities such as continuing to build relationships with suppliers and creating a credible supply chain forecast on a rolling 18- month basis; regulatory activities to support prequalification of the 10-valent and 13-valent vaccines; and financing activities such as supporting countries to prepare comprehensive Multi-Year Plans (cMYPs), and in planning for financial sustainability (Table C-1).

These activities will:

- Increase the probability of securing affordable and sustainable supplies of pneumococcal vaccines through continued improvements in public-private relationships
- Support the development of credible supply-chain forecasts at the country level
- Support regulatory activities for prequalification of new vaccines
- Support country-level preparation for national vaccine introduction including cMYP, vaccine cold-chain planning, delivery, and administration

Core Team

Success in a project of this magnitude begins with supporting a talented team of individuals. To ensure their high performance and the efficient use of project resources requires project management and administration (Table C-1).

A summary of the budget breakdown by topic area is presented below in Figure C-2.

Figure C-2. Distribution of the \$40M funding for the Strategic and Technical Support team and activities, 2008–2010



Annex D.

Cost Estimates for Vaccine Purchase and Health Systems: Assumptions Used for the Pneumococcal Investment Case

This Annex provides details on the assumptions used to calculate the vaccine and health systems costs included in this investment case. Throughout the investment case, total cost estimates assume the volume and timing of demand outlined in the Accelerated Introduction Forecast (Figure D-1).

Figure D-1. Forecasted demand for pneumococcal vaccine and cumulative deaths prevented, 2007–2025.



The Request

The Board is requested to authorize GAVI financing between 2007 and 2010 to procure vaccine and for the strategic and technical activities needed to support evidence-based demand for the vaccine. The majority of the funding requested is to purchase the vaccine. In other words, the financing requested from GAVI is mainly to subsidize the cost of the vaccine to a price that allows GAVI-eligible countries the ability to demand it (see Table D-1). The range in funding requested assumes a fixed number of doses but varies depending on the price of the vaccine.

The remainder of GAVI's funding (\$40 million) would support a dedicated team, GAVI partners, and activities to support the evidence-based introduction of the vaccine and assessment of the vaccine's impact in early adopter countries (see Annex C).

Accelerating use of pneumococcal vaccination in GAVI-eligible countries will also require \$14 million from the existing commitments for strengthening health systems and \$6 million in country co-payments.

Proposed Costs

Between 2007 and 2010, the accelerated introduction forecast will require the following new GAVI authorizations:

- \$87 million to \$149 million to procure the vaccine from the manufacturer
- \$40 million for activities and a dedicated team to provide strategic and technical support to the countries that are considering vaccine introduction and the partners involved in vaccine introduction.

Table D-1. Costs in the Request for GAVI Authorization of Funds 2007-2010 (Undiscounted)

Activities	Years 2007-2010		
Vaccine investment costs	\$ 87 -\$149 million		
Strategic and technical support costs	\$ 40 million		
Total	\$127 - \$189 million		

Obligations beyond 2010

GAVI's commitment to support limited use of the vaccine for introduction in the early adopter countries requires an obligation from 2011–2015 to continue the vaccination program. The extent of the obligations from 2011–2015 depend on whether GAVI limits the vaccine's use to the early adopting countries (2007-2010) that continue to uptake between 2011–2015 (Option 1), or if it allows additional countries to apply for and introduce the vaccine between 2011–2015 (Option 2) (see Table D-2.). The obligations for each scenario and description of costs including assumptions used in the calculations are presented below and outlined in greater detail in Annex D.

Option 1. Continued Funding of Early Adopter Countries Only 2011-2015

If GAVI chooses not to extend support for vaccination beyond the early adopter countries that take up the vaccine in 2007–2010, then their obligations for 2011–2015 amount to a total of \$415 million for vaccine procurement and \$25 million for Strategic & Technical Support between 2011–2015. Health systems costs, presumably covered under existing health systems support, would amount to \$70 million. Vaccine financing costs, which are not borne by GAVI, are ~\$15 million during this period.

Option 2. Early Adopter & Additional Country Funding 2011-2015

If GAVI decides to expand its support for new vaccine introduction and uptake follows according to the Accelerated Introduction Forecast, then GAVI obligations between 2011–2015 are expected to amount to a total of \$926 million for vaccine procurement and \$25 million for Strategic & Technical Support between 2011–2015. Health systems costs, presumably covered under existing health systems support, would amount to \$285 million. Vaccine financing costs, which are not borne by GAVI, are estimated at \$25 million during this period.

Activities	Years 2011-2015
Option 1 – Continued Early Adopter Only Investment	\$ 415 million
Option 2 – Early Adopter & Additional Countries	\$926 million
Strategic and technical support costs	\$25 million
Total	\$440 - \$951 million

Table D-2. Estimated Range of Costs of GAVI Funds 2011-2015

									2011	-15	i oblig	gati	ons
		2	2007	-20	10		Opti	on	1		Opt	ion	2
		\$3	per	\$5	5 per	\$3	3 per	\$5	5 per	\$3	3 per	\$!	5 per
	Costs	d	ose	d	ose	d	ose	d	ose	d	ose	c	lose
	Vaccine purchase	\$	87	\$	149	\$	255	\$	425	\$	545	\$	926
New authorizatior request	Strategic and Technical Support	\$	40	\$	40	\$	25	\$	25	\$	25	\$	25
	New GAVI authorization total	\$	127	\$	189	\$	280	\$	450	\$	570	\$	951
Existing GAVI authorizations	Health Systems	\$	14	\$	14	\$	70	\$	70	\$	285	\$	285
financing	Country Vaccine	\$	6	\$	6	\$	15	\$	15	\$	25	\$	25
	Grand Total	\$	147	\$	209	\$	365	\$	535	\$	880	\$	1,261

Table D-3. Obligations in 2011–2015 Based on the Commitments Made in 2007–2010 for Pneumococcal Vaccine Introduction (Assumes High Vaccine Price)

Assumptions Behind the Calculation of Costs

Vaccine costs. This investment case used two prices, \$3 per dose and \$5 per dose to estimate the cost of purchasing vaccines between 2007 and 2015. To this date, no formal negotiations have been undertaken with manufacturers and no manufacturers have offered this price to GAVI. With approval of this investment case, negotiations are expected to begin shortly. The rationale for the prices used is discussed in detail in Annex K.

Country vaccine costs. The GAVI Board has made clear that in GAVI Phase 2, countries will be expected to co-finance new vaccines. At the time that these analyses were conducted (August 2006), the GAVI Board has indicated co-pay ranges for DTP-HepB-Hib pentavalent vaccine for each country from 2006–2010. These co-pay ranges are:

- "Least poor countries" co-payment equals \$0.70 to \$0.95 per dose
- "Intermediate countries" co-payment equals \$0.20 to \$0.50 per dose
- "Poorest countries" co-payment equals \$0.10 to \$0.25 per dose
- "Fragile countries" no co-payment required

For the calculations in this analysis, we ran estimates using the "Low" and "High" end of the co-payments. Each country was assigned a co-pay based on which of the 4 groups it currently belongs. Based on the demand forecast, country vaccine costs were then calculated on a country-by-country and year-by-year basis then aggregated for this analysis. This analysis was run separately for the "Low" and the "High" co-payment assumptions. The co-payment is kept constant between 2007 and 2015.

For our base-case analysis, we present the costs assuming the Low copayment scenario. This is intended to give GAVI a ceiling estimate of its commitment. If the co-payment is higher than estimated by the Low co-pay then GAVI's commitment will be lower.

In practice, because the co-pay is low relative to the GAVI subsidy, *there is little difference between the costs with the low or the high co-pay assumption.* The difference in country vaccine costs vary from \$31 million to \$71 million over the period 2007–2015, depending on co-payment assumption.

GAVI vaccine costs. The assumption in this analysis is that GAVI will significantly subsidize the costs of the vaccine to GAVI-eligible countries. Specifically, the GAVI subsidy is calculated as the Vaccine Price less the country co-payment: GAVI subsidy = (Vaccine price – Country co-payment)

Health systems costs. The demand forecast used in this investment case assumes, for the sake of calculating numbers of doses demanded, that the vaccine will be given as a 3 dose series to all infants in a country, and that vaccination will reach the same number of children as DTP3 coverage. As such, we initially estimated the health systems costs for delivering pneumococcal conjugate vaccine through routine infant immunization programs.

The characteristics of the vaccine and the epidemiology of pneumococcal disease, however, make the use of this vaccine in campaigns or other mass outreach approaches potentially attractive. Thus, to estimate the health systems costs of delivering the vaccine through campaigns we contacted WHO/IVB for estimates of these costs. WHO provided estimates for the costs of delivering measles vaccine through mass campaigns and suggested using this as the estimate for delivering pneumococcal vaccine in mass campaigns. (Data kindly provided by Lara Wolfson, WHO.)

The estimated health systems costs for delivery through routine immunization systems and through mass campaigns were strikingly similar:

- Routine immunization estimate: \$0.47 per dose
- Mass campaign estimate: \$0.49-\$0.51 per dose

For the purposes of simplicity, we used an estimate of **\$0.50 per dose** delivered as the health systems costs. This estimate should be sufficiently robust to cover the expected costs whether a country decides to deliver it through a mass campaign, or via the routine immunization system.

Annual estimated health systems costs are presented below in Table D-2.

How the Health Systems Cost Estimates Were Derived

Costs in campaigns. Based on data provided by WHO, the median and mean estimated costs of delivering a dose of measles vaccine in campaigns in 2004 were \$0.51 and 0.49 per dose, respectively. For this analysis, we used \$0.50 per dose as the estimated cost for delivering a dose of pneumococcal vaccine. This is consistent with the costs of delivering measles vaccine through campaigns.

Costs for routine infant vaccination. Individual country vaccine program costs were derived from country-level data provided to GAVI in their financial sustainability plans (FSPs). To account for data that were missed in the FSP process, the estimates from the FSP were inflated by 60%. In the FSPs from the 9 GAVI-eligible countries reviewed, the vaccine program costs ranged between \$0.27 and \$0.97 per dose delivered. These costs accounted for all nonvaccine costs (capital, transport, personnel, injection supplies, training, other) for immunizations delivered via Expanded Program on Immunization (EPI), and the 60% increase correction factor.

To develop individual country-specific vaccine program costs, we built an index based on the country's per capita Gross Domestic Product (GDP) relative to the other countries in the analysis and benchmarked on the range of per dose costs observed in the FSPs. We assigned the country with the lowest per capita GDP in our analysis the minimum program cost, \$0.27. We assigned the country with the maximum per capita GDP, the maximum program cost, \$0.97.

For every other country falling between the 2 extremes, we created a per capita GDP-based weighting term. We constructed this weighting term so that all program costs would fall between the maximum and the minimum. Furthermore, we constructed the weighting term so that the program cost assigned would also reflect a country's per capita GDP, relative to that of the difference between the minimum and the maximum GDPs in the group.

After all the country-specific program costs were estimated, we calculated a weighted average for all 72 GAVI-eligible countries where the weight for each country was the proportion of all vaccinated children in GAVI who were in each country. **The overall weighted average program cost was \$0.47 per dose.**

Equations for calculating country-specific vaccine program costs

- Weighting term = (Country K's per capita GDP Minimum country per capita GDP)/ (Maximum per capita GDP – Minimum per capita GDP)
- Range = \$0.97 \$0.27 = \$0.70
- Minimum Program Cost = \$0.27
- Per dose program cost in Country K = Minimum Program Cost + (Weighting term x Range)

Equation for calculating overall weighted average vaccine program cost Weighting term = (Number of vaccinated children in Country K / Number of vaccinated children in all 72 GAVI-eligible countries)

Annex E. Pneumococcal Vaccine Strategic Demand Forecast Analysis

Overview

In this investment case, the projections of the costs of the investment and the expected impact on mortality are based on outputs from a strategic demand forecast developed by GAVI's PneumoADIP between 2003–2005. This Annex provides an overview of the framework, assumptions, and some key outputs from the strategic demand forecast.

Estimates of the cost-effectiveness of vaccination were based on a model developed by Harvard University. The assumptions and methods for the cost-effectiveness analysis are covered in Annex G.

Demand Forecasting Background

Demand forecasting is a technique used to predict future demand based on information available today. Typically, demand forecasts are separated into 2 main types:

- Strategic demand forecasts
- Supply chain forecasts

Strategic demand forecasts are typically done early in a product's development and generally have a time horizon of 5–20 years. They are needed to support product strategy development and investment decisions. Because of the time horizon, their precision is generally better in the near term and more indicative in the medium and longer term.

Supply chain forecasts generally have a 1- to 2-year time horizon. These are typically used when a vaccine is already licensed or about to be licensed. These are rolling forecasts based on actual orders or strong indications of demand with precise volumes and timings. Supply chain forecasts are often based on a "bottom up" process from countries. UNICEF's demand forecasts for established vaccines are an example of a supply chain forecast.

The analyses in this investment case are based on a strategic demand forecast. The following sections outline how the forecast was created and the assumptions used in the model.

Strategic Demand Forecasting Model

GAVI's PneumoADIP's strategic demand forecast was developed using a software package developed for GAVI's PneumoADIP by Applied Strategies, LLC. This model is prepopulated with basic data for each GAVI country in each year from 2005 to 2025. Prepopulated data include birth and population data, DTP3 (Third dose of Diphtheria toxoid, Tetanus toxoid and Pertussis vaccine) coverage rates, and WHO regions.

The user can enter assumptions into the model such as adoption dates for each country, the country co-pay required, and the price of the vaccine, The model then generates outputs such as the projected number of infants vaccinated in each year, number of lives saved, number of doses required, and amount of financing required. The model variables are described in greater detail in the next pages.

Model Variables

Target population. Birth cohorts of the 72 countries eligible for GAVI financial support. The source of the birth cohort and other population data used in the analysis is the UN Population Data 2004 (projections through 2025). This is the same data set used by WHO and GAVI in their projections.

Introduction year. This is the first year that a pneumococcal vaccine is available to GAVI-eligible countries. Availability to GAVI-eligible countries assumes that the vaccine supplier has received prequalification from WHO. Pneumococcal vaccines projected for GAVI-eligible countries for this analysis included Prevnar (7-valent) available in 2008, 10-valent vaccine available in 2010, and 13-valent vaccine available in 2012.

Vaccination coverage rate. Estimates of DTP3 coverage for each country and each year were entered into the model. The estimates were provided by WHO: Immunization Coverage Estimates and Trajectory database (WHO ICE-T). DTP3 coverage rates were selected as a good indicator for pneumococcal vaccine coverage because the vaccine is given to infants on the same schedule as DTP vaccine.

Years to peak adoption. It was assumed that introduction of pneumococcal vaccine into a national program would require 2–4 years to reach "peak" levels of coverage. (Peak coverage was defined as DTP3 coverage in that year.) The number of years the country will take to reach its peak vaccination coverage rate varies by country segment. For early, mid, and late adopters it was assumed that 2, 3, and 4 years would be required to reach peak levels. The build-up to peak was assumed to be evenly spaced over time. For example, countries requiring 2 years would reach 50% of peak coverage in the first year and full coverage the second year.

Doses per course. Based on data from efficacy and immunogenicity trials, pneumococcal vaccination was assumed to require 3 doses given in infancy, on the same schedule as DTP vaccine.

Wastage rate. Percentage of vaccine that is likely to be rendered unusable as a result of spoilage, breakage in transit, being part of an unused open package, at the country level. Wastage was estimated at 10% according to WHO vaccine wastage rate estimates for liquid formulation in 1–2 dose vials. Demand forecasts were adjusted to account for country wastage.

Earliest time to adoption (ETA). The minimum number of years the country will take before it adopts the available vaccine, given each country's willingness and ability to adopt.

It was recognized that not all countries are equally likely to take up a pneumococcal vaccine immediately. Adoption was considered to be affected by both a willingness and an ability to adopt. Below is a description of the quantitative methods used to assess willingness and ability to adopt.

Based on the quantitative analysis, countries were allocated to 1 of 3 segments (early, mid, or late adopters) and assigned an "earliest time to adoption." The segments assigned to each of the 72 GAVI-eligible countries were reviewed and refined in consultation with WHO regional offices and other international experts from GAVI, USAID, UNICEF, and other organizations over a 2-year period.

Willingness to adopt. Disease burden was assessed by: 1) the burden of child pneumonia deaths; 2) the ability to measure pneumococcal disease within the country (e.g., disease surveillance in place); and 3) the presence or absence of competing diseases (e.g., HIV/AIDS, malaria, meningococcal disease); and 4) the country's history of adopting new vaccines (HepB and Hib).

Countries were segmented by high pneumonia deaths (\geq 10,000/yr); medium pneumonia deaths (1,000–9,999/yr); and low pneumonia deaths (<1,000/yr). Estimates of the number of child pneumonia deaths were based on calculations from a recent WHO publication on pneumonia mortality.

The ability to measure disease was either "yes" or "no" based on the presence of disease surveillance. A significant competing disease was considered a disease that was documented to have a significant impact on childhood survival and was assessed as either high (more than 1 significant competing disease), medium (1 significant competing disease), or low (no significant competing disease).

Ability to adopt. The ability to adopt was an estimate of whether a country was able to adopt a new vaccine, estimated as a function of each country's vaccination infrastructure, economic strength and stability, and the ability of a country to sustain vaccination after donor funding ends.

The vaccination coverage rate of DTP3 was used as a proxy of country vaccination infrastructure with countries segmented by high coverage rates (\geq 80%), medium coverage rates (66–79%), and low coverage rates (<65%). Country economic strength and stability was assessed by gross national income (GNI) per capita (Source: World Bank) with countries segmented by high GNI (\geq \$700), medium GNI (\leq 401–\$599), and low GNI (\leq \$400) and known political instability (e.g., civil unrest or war).

Figure E-1 shows the earliest forecasted adoption year in the model. It shows that vaccine introduction is expected to roll-out gradually over the period of the forecast.



Figure E-1. Forecasted adoption year

Maximum acceptable vaccine price. The model includes a "sustainability" assumption that assumes a country would not adopt a new pneumococcal vaccine unless it had the ability to sustain procurement of the vaccine after donor funding ended. The vaccine price each country has the ability to pay after the donor funding ends is called the Maximum Acceptable Vaccine Price (MAVP). Based on the cost-effectiveness data, the high disease burden, and the consistently high vaccine impact with pneumococcal conjugate vaccines, it was assumed that all GAVI-eligible countries, along with their local partners, would be willing to accept a price of \$2 per dose as a sustainable price.

Country co-pay. For this analysis, we ran calculations with 2 different levels of country co-pay based on the ranges set for pentavalent vaccine by the GAVI Board in its July 28, 2006 teleconference. These co-pay ranges are:

- "Least poor countries" co-payment equals \$0.70 to \$0.95 per dose
- "Intermediate countries" co-payment equals \$0.20 to \$0.50 per dose
- "Poorest countries" co-payment equals \$0.10 to \$0.25 per dose
- "Fragile countries" no co-payment required

For the calculations in this analysis, we ran estimates using the "low" and "high" end of the co-payments. Each country was assigned a co-pay based on which of the 4 groups it currently belongs to. Based on the demand forecast, country vaccine costs were then calculated on a country-by-country and year-by-year basis, then aggregated for this analysis. This analysis was run separately for the "low" and the "high" co-payment assumptions. The co-payment is kept constant between 2007 and 2015.

Health systems costs. For health systems costs, we assumed a cost of \$0.50 per dose. This cost was calculated for doses delivered, not "wastage" doses. See Annex D for more detail on how health systems costs were estimated.

Vaccine prices. The analysis assumed a constant price to GAVI of \$5 per dose until 2015. During this period it is expected that countries will make a small co-payment but that the price to countries will be highly subsidized by GAVI financing. Beyond 2015, the price to countries and their local partners is assumed to be \$2 per dose. Greater detail on the assumptions around pricing and supply are in Annex H.

Supplier, donor, and country discount rates. The discount rate used for present value calculations of suppliers (10%), donors (5%), and countries and/or country partner donors (5%) cash flows.

Results. Accelerated Introduction Demand Forecast Analysis

The main finding from GAVI's PneumoADIP's strategic demand forecast is that accelerated vaccine introduction with an affordable, sustainable vaccine supply is possible. All of the underlying data, not just the top line conclusions, was shared with the donors, suppliers and countries and the transparency of methodology and assumptions management was the key to the credibility of the forecast among these partners.

Key insights derived from the model include:

Clarity and a shared view of the objectives is needed for a credible forecast

- The partners, donors, suppliers and countries, need to be engaged early in the development
- GAVI countries are diverse in terms of disease burden, competing health needs, and distribution systems that country-by-country forecasts are the most helpful
- It is difficult to get information from one partner without having credible information about the other two, and developing world markets have significant differences in market characteristics
- Demand is not independent of price, product profile, or a country's willingness and ability to pay
- The drivers of demand for products differ at the stages from early development through licensure

Developing a strategic demand forecast for low-income countries is a complex challenge and ensuring credible demand over time is a risk that all vaccine markets face.

The Pneumococcal Accelerated Introduction Forecast for 2007 to 2025 across all GAVI-eligible countries is shown in Figure E-2. The figure illustrates that demand builds to 56 million doses by 2015. Between 2015 and 2020, the demand grows rapidly, reaching 176 million doses by 2020 and exceeding 200 million doses per year beginning in 2023.



Figure E-2. Pneumococcal accelerated introduction forecast, 2007–2025

Figure E-3 shows the pneumococcal forecast in the period 2007–2015 in relation to the actual experience with Hib vaccine between 1998 and 2006. The years of Hib uptake, 1998 to 2006 (shown in blue italics) are compared to the forecasted pneumococcal uptake between 2007 and 2015 (shown in blue). As this figure shows, the pneumococcal forecast represents a substantial improvement over the historical precedent of Hib vaccine uptake. This improvement seems possible because:

- The burden of pneumococcal disease is more widely recognized than the burden of Hib disease.
- The efforts of GAVI and PneumoADIP have helped to establish the value of vaccination over the last 3 years, making more countries aware of and ready for pneumococcal vaccine adoption.

Figure E-3. Pneumococcal accelerated introduction forecast exceeds actual Hib introduction in GAVI-eligible countries



Note: Hib demand figures were provided by Hib Initiative.

Figure E-4 shows a breakdown of the forecasted demand between 2007–2015 by WHO region. This figure shows that the vast majority of demand is expected in the regions where the burden of pneumonia and pneumococcal disease are greatest— Africa and south and southeastern Asia.





Annex F.

Calculation of the Mortality Impact of Pneumococcal Vaccination in GAVIeligible countries

Executive Summary

Projections of the mortality impact of pneumococcal vaccines for this investment case were based on the results from a randomized, controlled trial of 9-valent pneumococcal vaccine in The Gambia, a typical rural African setting. The Gambian trial results are a good benchmark for projections of vaccine mortality impact because the trial setting is representative of the health situation in many GAVI-eligible countries and because it provides a statistically significant estimate of the efficacy of pneumococcal vaccination for prevention of all-cause child mortality.

In the trial, children were vaccinated through the existing Gambian Expanded Program on Immunization (EPI) at the ages of 6, 10, and 14 weeks. Events were observed between 3 and 29 months of age. The vaccine's efficacy for preventing culture-confirmed invasive pneumococcal disease due to vaccine serotypes was 77%, and vaccine serotypes accounted for 65% of invasive pneumococcal disease in the control group. Overall, a 50% reduction in culture-proven invasive pneumococcal disease was observed. There were 330 deaths among the 8189 children randomized to receive the pneumococcal vaccine and 389 deaths among the 8151 children randomized to receive the placebo, giving an absolute reduction of 7.4 deaths prevented per 1000 vaccinated children during the period of observation. In relative terms, the observed efficacy against all-cause mortality was 16%.

The projections of mortality impact included in this investment case used 7 deaths prevented per 1000 vaccinated infants. For an individual country, serotype replacement and country-specific variations in serotype distribution might alter these estimates slightly downward (or perhaps slightly upward). *Overall, as a global aggregate, the estimates of deaths prevented are probably a conservative underestimate* of the vaccine's impact. The estimates are conservative because the estimates do not include prevention of mortality among:

- Immunized children beyond age 30 months
- Unimmunized children aged 3–59 months through herd immunity
- Neonates and children younger than 3 months through herd immunity
- Unimmunized older children and adults through herd immunity

Two other factors that would make the estimates conservative:

- The estimates do not include prevention of mortality due to serotypes included in the 10- or 13-valent vaccines that are expected to be used after 2010.
- The estimates to do not include the prevention of mortality among unvaccinated children and adults through herd immunity.

Background

Pneumococcal disease, especially pneumococcal pneumonia and meningitis, is a leading killer of children and an important cause of illness and death among adults. Because it is difficult to diagnose, observational studies of pneumococcal disease using blood and CSF cultures always underestimate the burden of pneumococcal disease and hence, the impact of vaccination. Vaccine trials that measure the effect on clinical syndromes and/or overall child mortality are the most accurate way to estimate the potential impact of pneumococcal vaccination.

Overview of The Gambia Pneumococcal Vaccine Trial

The vaccine trial site. Our projections of mortality impact of vaccination were based on the results of the pneumococcal vaccine trial conducted in The Gambia, because that study setting is the most representative of GAVI-eligible countries. For example, based on UNICEF 2000 estimates, 50 of the 72 GAVI-eligible countries had a child mortality of ≥90 child deaths per 1000 live births. In The Gambia trial site, child mortality was estimated as 99 per 1000 live births.

The trial was conducted in the eastern half of The Gambia, in the Central and Upper River Districts (see Map F-1). The setting is typical of many rural areas in less-developed countries. There is only one tarmac road, which parallels the river on the south bank. The population of the north bank is served only by dirt and gravel roads. Health services are rudimentary in the villages. There is one District hospital with a pediatrician, a laboratory, and an x-ray machine in Bansang. One other large health center in Basse has physicians, nurses, and some limited in-patient care capacity. Most preventive healthcare is provided either by mobile clinics that visit regularly (approximately once per month), or by standing clinics in some of the larger villages.

The disease and health patterns are typical of rural areas throughout Africa and other GAVI-eligible countries. There are seasonal malaria and a high overall infant and child mortality rate. Most child deaths occur at home. Under 5 mortality is approximately 99 per 1000 live births in the study area. Demographic and health surveillance conducted by the Medical Research Council has identified pneumonia as the first or second leading cause of child mortality, accounting for approximately 20% of child deaths. Malaria and diarrhea are also major killers. A large proportion of child deaths in these surveillance projects could not be attributed to any single disease. HIV seroprevalence among adults is relatively low (~1%), but sickle cell disease is not uncommon.



Map F-1. The Gambia (study setting shaded in gray)

The vaccine used. Infants in this trial were randomized to receive either 9-valent pneumococcal conjugate vaccine or placebo "cake" – i.e., a freeze-dried placebo preparation that appeared like the pneumococcal conjugate vaccine but contained no active immunization. These lyophilized formulations were reconstituted using a liquid DTP-Hib combination vaccine (Tetramune[™], Wyeth). The 9-valent vaccine included the following pneumococcal serotypes: 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F. The pneumococcal vaccine was provided by Wyeth. Each serotype was conjugated individually to a carrier protein, CRM-197, which is a nontoxic mutant of diphtheria toxoid. (Note: Wyeth's 7-valent vaccine includes all of the same serotypes, with the exception of serotypes 1 and 5, and uses the same carrier protein.)

The vaccination regimen. The EPI schedule in The Gambia calls for vaccination with oral poliovirus vaccine, DTP vaccine, Hepatitis B vaccine, and Hib conjugate vaccine at ages 6, 10, and 14 weeks. In the trial, infants received the study vaccines, along with all other regularly scheduled vaccines, at their regularly scheduled visits. In practice, children were immunized at an average age at first dose of 11 weeks, and an average age of third dose of 24 weeks. Vaccination coverage is generally high in The Gambia. Ninety-four percent of the enrolled children were vaccinated fully and according to the regimen.

Surveillance. Surveillance for child survival was maintained through home visits. Every 3 months a field worker visited every household of a participating child to observe whether the enrolled child was alive, deceased, withdrawn from the surveillance, or moved away. Clinical surveillance was conducted at Bansang Hospital and Basse Health Center. Children were followed from their first vaccination through to the age of 30 months, to death, or to the end of the study, April 30, 2004, whichever came first.

Results. There were 330 deaths among the 8189 children randomized to receive the pneumococcal vaccine and 389 deaths among the 8151 children randomized to receive the placebo, giving an absolute reduction of 7.4 deaths prevented per 1000 vaccinated children during the period of observation. In relative terms, the observed efficacy against all-cause mortality was 16% (95% CI, 3–28).

The vaccine efficacy for prevention of a first episode of radiologically confirmed pneumonia was 37% (95% CI, 27–45). The vaccine's efficacy for preventing culture-confirmed invasive pneumococcal disease due to vaccine serotypes was 77% (95% CI, 51-90). Serotypes included in the 9-valent vaccine accounted for 65% of invasive pneumococcal disease in the control group. Overall, a 50% reduction in culture-proven invasive pneumococcal disease was observed (95% CI, 21–69). The serotypes included in the 7-valent vaccine were responsible for approximately 70% of the benefit observed in the trial.

Trial sponsorship and oversight. The trial was sponsored by a large group of international organizations including the WHO, the Medical Research Council-UK, the Medical Research Council Laboratories – The Gambia, the US National Institute of Allergy and Infectious Diseases, the US Centers for Disease Control and Prevention, and the Children's Vaccine Program at PATH. Wyeth provided the pneumococcal conjugate vaccine, the placebo cake, and DTP-Hib vaccines. These vaccines were labeled by NIAID, and random assignments were generated by NIAID. The vaccine manufacturer was not involved in the analysis of the trial results. The study was reviewed and approved by ethical committees in The Gambia and the UK, and conducted under an Investigational New Drug application with the US Food and

Drug Administration and in accordance with internationally recognized Good Clinical Practices.

Calculating pneumococcal vaccine's mortality impact. The number of deaths prevented was calculated by multiplying a rate of deaths prevented by the number of infants and children vaccinated. The numbers in this calculation are outlined below (Table F-1).

- The number of vaccinated infants and children was calculated using the projections of vaccine uptake generated in the demand forecast model.
 - Estimates from the UN Population Division were used for the number of live births and children aged 1–4 years for each country and each year.
 - WHO Immunization Coverage Estimates and Trajectories (ICE-T) estimates for DTP3 coverage were used for each country and each year.
- For deaths averted per 1000 vaccinated, 2 separate estimates were used. Separate estimates were created for infants who received the 7-valent vaccine vs. those who received a later vaccine (assumed to be a 10- or 13valent vaccine). See Table F-1 below for specific estimates used.
 - Infant vaccination with 10- or 13-valent vaccine. The estimate of 7 deaths prevented per 1000 is based directly on The Gambia pneumococcal trial estimate using the 9-valent vaccine.
 - Infant vaccination with the 7-valent vaccine. The estimate of 5 deaths prevented is based on the observation that 70% of the impact of the 9valent vaccine in The Gambia was attributable to the serotypes included in the 7-valent vaccine. 70% of 7.4 deaths prevented equals 5.2 deaths prevented per 1000 vaccinated.

 Table F-1. Estimates of Deaths Prevented Used in Pneumococcal Investment Case

 Calculations

Regimen for Infants (<1 year olds)	Vaccine	Deaths Prevened Estimate		
	10- or 13-valent	7 per 1000 vaccinated		
	7-valent	5 per 1000 vaccinated		

Note: Estimates were benchmarked on The Gambia pneumococcal vaccine trial.

Annex F Reference List

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Annex G. Methods Used in the Harvard University Cost-effectiveness Analysis

Background

Cost-effectiveness analysis is a commonly used tool for evaluation of health investments. One useful way to evaluate the cost-effectiveness of an intervention is to compare its cost-effectiveness (e.g., cost per DALY averted) against a predefined benchmark for cost-effectiveness. The World Health Organization has established as benchmarks for health investments the following:

- *"Very cost-effective."* Investments with a cost per DALY saved of less than a country's per capita Gross Domestic Product (GDP). For example, all interventions with a cost per DALY saved of \$699 or less in a country with a per capita GDP of \$700 are "very cost-effective"
- *"Cost-effective."* Investments with a cost per DALY saved of less than 3 times a country's per capita GDP. For example, all interventions with a cost per DALY saved of \$2099 or less in a country with a per capita GDP of \$700 are "cost-effective"

Like nearly all vaccination programs in low-income countries, cost-effectiveness analyses show that pneumococcal vaccination is a "very cost-effective" health intervention. This Annex describes the analytic model used to calculate costeffectiveness of pneumococcal vaccines and the assumptions in the model.

Overview

We constructed a cost-effectiveness model using standard methods¹ to assess the lives saved, disability-adjusted life years (DALYs) averted, costs, and costeffectiveness of pneumococcal conjugate vaccination of infants in the world's poorest countries. These outcomes were evaluated for each of the 72 countries eligible for GAVI support. A 5-member expert panel advised us on model structure and model inputs. The members included experts in pneumonia epidemiology, disease burden modeling, cost-effectiveness, and economics.

Highlights of the Analytic Method

Highlights include:

- 1. The health benefits of vaccination included prevention of mortality and morbidity among children between the ages of 3 to 59 months (< 5 years). The effects of both direct protection and herd immunity were included.
- Vaccine efficacy against all cause mortality was assumed to be equal to or less than that observed in The Gambia vaccine trial — that is, 7.4 deaths averted per 1000 children vaccinated, even in countries with higher childhood mortality rates. For countries with child mortality rates less than that observed in The Gambia, the rate of deaths prevented by vaccination was varied downwards.
- 3. Vaccination coverage was based on WHO DTP3 coverage rates for these countries in 2003.
- 4. The analysis assumed 3.1 doses per vaccinated child to account for wastage associated with the delivery of this vaccine.
- 5. Vaccine price of \$5 per dose was assumed. The rationale behind this assumption is explained in detail in Annex D.

- Vaccination delivery costs (health systems costs) were based on data from Financial Sustainability Plans and varied by country. Typically the costs were ~\$0.50 per dose for the incremental vaccine administration and delivery costs required for pneumococcal vaccination. The derivation of these health systems costs are described in detail in Annex D.
- 7. A discount rate of 3% was used for discounting costs and benefits.

The Model Structure

The decision tree (Figure G-1) included 2 strategies: 1) Vaccine purchase and provision, in which pneumococcal vaccine was purchased and provided to countries beginning in 2006, using GAVI financial support and 2) no vaccine. "No vaccine" assumed that there would be no uptake of the vaccine, based on prior experience in GAVI-eligible countries.²

Figure G-1. Decision tree depicting the 2 policy options and subsequent health events. Circles represent chance nodes; branches that follow these nodes occur with probabilities specified in the assumptions



In the GAVI financial support strategy, each child born had probabilities of death and nonfatal disease that depended upon whether the child received the vaccine and vaccine efficacies against all-cause mortality, meningitis, and pneumonia.

A child's death resulted in the accrual of DALYs and medical costs associated with the fatal episode of pneumococcal disease. A nonfatal syndromic disease resulted in the accrual of DALYs and costs associated with the nonfatal episode. Preventing a death or nonfatal episode through vaccination averted both DALYs and illness-related costs. The vaccination program itself resulted in costs related to purchase of vaccine and to program administration.

We used vaccine efficacy vs. all-cause mortality and other clinical definitions of illness as the benchmarks for this model. We chose this model structure because data on childhood mortality and vaccination rates are available and of similar quality for all countries in this analysis. Had we chosen to build the model based on

estimates of the incidence of pneumococcal-specific infection or the distribution of pneumococcal serotypes, we would have been limited to a small number of countries and data of highly variable quality.

The results of the analysis therefore can be interpreted as the cost-effectiveness of any pneumococcal vaccine that has an impact on pneumococcal disease that is equivalent to or greater than the 50% reduction in pneumococcal disease observed in The Gambia trial. In practice, the difference between the predicted and actual impact of vaccination will depend in part on the match between the vaccine used and the local epidemiology of pneumococcal disease. For example, 10- and 13-valent vaccines may have a greater impact than that observed with the 9-valent, and the 7-valent may have a lower impact, but the extent of these differences will vary by country. Key assumptions used in the model are highlighted in Table G-1.

Region	Risk of dying between 3 and 59 months of age, %*	Vaccination coverage, %	Vaccine program cost, \$ per dose	Cost of treating fatal disease, \$
<u>AFRO</u>	13%	64%	\$0.35	\$150
AMRO	2%	91%	\$0.58	\$328
EMRO	8%	62%	\$0.45	\$197
EURO	5%	84%	\$0.45	\$264
SEARO	4%	78%	\$0.51	\$161
WPRO	4%	87%	\$0.50	\$243
Range used in sensitivity analyses	75%–125% base case value	Base case value to 100%	1–5 times base case value	0.1–10 times base case value

Table G-1. Key Assumptions Used in Cost-effectiveness Analysis. Weighted Average* Values for WHO Regions

* Weighted by country-level birth cohorts

Vaccine Efficacy

It was assumed that vaccine would be administered according to the recommended schedule for DTP-containing vaccines in GAVI-eligible countries (6, 10, and 14 weeks of age), and that vaccination rates in each country would be equal to the proportion of children reported to receive 3 doses of DTP vaccine in that country in 2003 (DTP3 rate).³

Estimates of pneumococcal vaccine efficacy were available from several large, randomized controlled trials.⁴⁻⁸ Our analyses were based on the results of the trial conducted in The Gambia,⁵ because that study setting most closely approximated that of other GAVI-eligible countries. The Gambian trial is also unique in that it provides an estimate of the efficacy of pneumococcal vaccination for prevention of all-cause child mortality.

In the trial, children were vaccinated through the existing Gambian expanded program on immunization (EPI) at the ages of 6, 10, and 14 weeks. Events were observed between 3 and 29 months of age. The vaccine's efficacy for preventing culture-confirmed invasive pneumococcal disease due to vaccine serotypes was 77%, and vaccine serotypes accounted for 65% of invasive pneumococcal disease in the control group. Overall, a 50% reduction in culture-proven invasive pneumococcal disease was observed.

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There were 330 deaths among the 8,189 children randomized to receive the pneumococcal vaccine and 389 deaths among the 8,151 children randomized to receive the placebo, giving an absolute reduction of 7.4 deaths prevented per 1000 vaccinated children during the period of observation. In relative terms, the observed efficacy against all-cause mortality was 16%.

We assumed that pneumococcal conjugate vaccine would be administered in the same schedule as that used in the trial. We assumed that vaccine would prevent death and disease between ages 3 and 59 months. For nonfatal meningitis and nonfatal pneumonia, we used the vaccine efficacies observed in the Gambian trial. Vaccine efficacy against all-cause mortality was a central estimate. Therefore, in extrapolating trial results to other countries, we assumed that vaccine efficacy against all-cause mortality would be greatest in those countries with high under-five mortality rates (U5MRs) and lowest in countries with lower U5MRs. This assumption was based on the observation that the proportion of childhood deaths caused by acute respiratory infection (ARI) increases as U5MR increases, suggesting that the burden of pneumococcal disease, a common cause of ARI, may be higher in countries with higher child mortality.⁹

In countries with U5MRs greater than that observed in the Gambian trial population (99 per 1000 live births¹⁰), we assumed that vaccine efficacy against mortality would be capped at 7.4 deaths prevented per 1000 children. In countries with very high U5MRs, this cap resulted in a relatively lower percent reduction in deaths. Conversely, the projected vaccine efficacy against mortality was adjusted downwards from 7.4 per 1000 for any country with a U5MR less than or equal to 99 per 1000, based on the ratio of the country's U5MR to that of the Gambian trial population. Unlike vaccine trials, in this analysis, variations in vaccine efficacy reflect variations in the underlying risk of pneumococcal mortality in individual countries — not inherent variations in the biological activity of the vaccine.

Pneumococcal vaccination coverage was assumed to be equivalent to DTP3 coverage. A strong and important herd immunity effect has been observed in populations vaccinated against pneumococcal disease in childhood.¹¹ Vaccination reduces transmission of pneumococcus to unvaccinated children, thereby reducing the risk that unvaccinated children will develop pneumococcal disease. These herd immunity effects can also reduce disease among older children, adolescents, and adults. We assumed that herd immunity would reduce disease among nonvaccinated members of the birth cohort. The model benchmarked the herd immunity effect to the direct vaccine efficacy effect. Specifically, for prevention of mortality, meningitis, and hospitalized pneumonia, it was assumed that the herd immunity effect would be 50% of the direct vaccine efficacy. For prevention of outpatient pneumonia, it was assumed that the herd immunity effect.

The probability of death between 3 and 59 months of age was derived from neonatal mortality data¹² and standard life tables using standard demographic methods¹³ to convert rates to probabilities using an exponential cumulative incidence function.¹⁴

Costs of Disease and Vaccination

All costs are expressed in international dollars 2000. The price at which vaccine will be made available to GAVI or to developing countries is unknown. Our base case used \$5 per vaccine dose, under the assumption that the two-tiered pricing scheme used in international public vaccine markets will apply to pneumococcal vaccine as well.^{15,16} This assumption is supported by indications from the 2 most advanced vaccine suppliers, Wyeth and GSK, in their discussions with GAVI.

Vaccine program costs were estimated under the assumption that pneumococcal vaccination would be incorporated into routine vaccine administration during infancy. Vaccine program costs were derived from country-level data provided to GAVI in their financial sustainability plans¹⁷ by 7 GAVI-eligible countries and ranged between \$0.27 and \$0.97 per dose. These costs accounted for all nonvaccine costs (capital, transport, personnel, injection supplies, training, other) for immunizations delivered via EPI.

The cost of a death preventable by pneumococcal vaccination was assumed to be equal to the cost of a case of hospitalized pneumonia. Direct medical costs included hospital days, medical personnel time, diagnostic tests, and medications. Direct non-medical costs included transportation to healthcare facilities and parent or caregiver time spent caring for a sick child. The costs of hospital days and medical personnel time were derived from a set of WHO regional standard unit costs developed by the WHO-CHOICE project,¹⁸ assuming that 85% of hospital care was delivered in secondary facilities and 15% in tertiary facilities. WHO-CHOICE costs were applied to each country based on its WHO region and adjusted by ratios of public to private healthcare payment and urban to rural population.¹⁹

The costs of diagnostic tests, medications, transportation, and parent time were derived from a detailed study of resource use in childhood pneumococcal disease conducted in India for the Children's Vaccine Initiative (Personal communication: Krishnan, A.). These costs were extrapolated to other countries, weighting costs by relative per capita GDP¹⁹ and ratios of public to private healthcare payment and urban to rural population.

Costs for meningitis and outpatient pneumonia were derived in an analogous fashion.

Health Outcomes

The base case analysis considered deaths and nonfatal disease averted by vaccination. Deaths averted were converted into years of life lost and DALYs, a standard measure used by the WHO and World Bank in quantifying societal burden of disease,²⁰ We used standard methods and assumptions, including age weighting, in estimating DALYs.^{20,21} DALYs averted were based on country-level estimates of life expectancy at age one year from standard life tables.¹³ DALYs accrued as a result of nonfatal acute illness were not captured in this analysis.

It was assumed that only nonfatal meningitis would result in permanent disability. Rates of meningitis-related permanent disability were taken from a Gambian study.²² Standard disability weights for sequelae (deafness, seizure disorder, motor deficit, and mental retardation) were applied.^{13,20} Otitis media and consequent hearing loss were not incorporated into this model.

The Primary (Base Case) Analysis and Sensitivity Analyses

The base case analysis was performed from a societal perspective, including all direct medical and nonmedical costs borne by GAVI, governments, and families. Health outcomes and costs were discounted at 3% per year. We estimated cost-effectiveness ratios (CERs) for each country based on the following formula: CER = (Vaccine program costs – Costs averted due to death and disease prevented)/ (Disability-adjusted life years averted). The CER numerator and denominator were calculated by multiplying probabilities in the decision tree by values for costs and DALYs, using standard decision analytic methods.¹

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As standards of comparison, we used the WHO's thresholds of cost-effective interventions being those whose cost-effectiveness ratios are less than 3 times per capita GDP and very cost-effective interventions being those whose cost-effectiveness ratios fall below one time per capita GDP.²³

To test the robustness of model results, we varied each assumption over a plausible range in one-way and two-way sensitivity analyses. We also varied assumptions probabilistically using second-order Monte Carlo simulation. In the probabilistic sensitivity analysis, each assumption was assigned a range of values it could take and a frequency distribution over that range. Values for each assumption were randomly drawn from their distributions, and the model run 10,000 times using these probabilistically sampled sets of assumptions.

We also conducted scenario-specific secondary analyses, including a scenario in which the risk of death and the probability of vaccination varied inversely by income strata.

Analyses were performed using DATAPro software (TreeAge Inc, Williamstown, Mass) and Microsoft Excel (Microsoft Corp, Redmond, Wash).

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Annex H. Comparability of the Rotavirus and Pneumococcal Vaccine Economic Analyses

Comparability of Rotavirus and Pneumococcal vaccine economic models

Overall, the rotavirus and pneumococcal vaccine cost-effectiveness models are highly similar in major assumptions and methods. Each economic team used an external expert panel to review and revise key assumptions. The models share common sources of data for:

- Birth cohorts (UN Population Division),
- DTP3 coverage rates (WHO ICE-T),
- Discount rates for costs and benefits (3% per annum),
- Vaccine wastage rates (10%).
- Disability weights for calculating DALYs (Disability Adjusted Life Years).

The central assumptions driving cost-effectiveness in both models were vaccine dose cost, estimated disease burden and vaccine efficacy. Overall comparability between models depends on comparable assumptions for these aspects of the models. These critical assumptions are comparable across models, and reflect the current state of knowledge for rotavirus and pneumococcal diseases and vaccines.

Vaccine dose cost. The pneumococcal vaccine model incorporates a steady state assumption for vaccine dose cost, while the rotavirus vaccine model incorporates a price erosion projection over time. The pneumococcal team is currently incorporating a price erosion projection into PCV's economic model.

Disease burden. Both models accounted for inpatient and outpatient, fatal and non-fatal disease, using best empiric estimates and expert panel validation.

Vaccine efficacy. Both models used high quality, Phase III clinical trial data as the basis for their vaccine efficacy estimates. The rotavirus model explicitly modeled delays in immunization and a resultant blunted vaccine efficacy compared with ontime immunization. The pneumococcal model accounted for this by incorporating vaccine efficacy estimates from a clinical trial in which delayed immunization occurred routinely (median, five and ten weeks delay for first and third doses), but did not model otherwise model immunization delays explicitly. The pneumococcal model incorporated both direct vaccine effect and indirect protection via herd immunity, extrapolating from the U.S. experience. As is appropriate to the current state of knowledge, the rotaviral vaccine model did not incorporate indirect effects. In a second tier are assumptions to which results from these economic models are robust but which differ between models. Because the models are robust to them, they have little potential to influence comparability, but perceived differences may influence face validity. Such assumptions include perspective and currency.

Perspective. The incorporation of transportation costs and caregiver productivity costs (i.e., societal costs) into the pneumococcal vaccine model had minimal effects on net costs. Net costs and cost-effectiveness remain comparable between models.

Currency. The bulk of net costs in both models are derived from vaccine-related costs. These costs are comparable across both models, despite being present in international dollars versus U.S. dollars. Why? Vaccine will be traded on the international market where the PPP weight is 1. On that market, one international dollar equals one U.S. dollar. Cost offsets due to averted disease-related costs will

differ according to the currency (ID versus USD) used. However, both models are robust to disease-related cost assumptions.

There are other minor differences in the models, included in the summary table below. These minor differences do not influence comparability. As an example, while methods to estimate vaccine administration costs differed between models, the RV per dose estimate of USD 0.50 and the PCV model per dose estimate (weighted average) of ID 0.47 differ trivially.

Overall comparability and implications for interpretation

While there are differences between the two models, both research teams feel that the results are generally comparable. Each model includes additional sensitivity analyses and scenarios that address key uncertainties and provide a range of estimates of impacts and cost-effectiveness that are likely to capture the actual outcomes. Although the point estimates for the two analyses differ, the ranges of estimates for the two vaccines are very similar. Both vaccines should be considered equally cost-effective and both would meet the standard of "very cost-effective" suggested by the World Health Organization.

Table H-1.	Methods used in rotavirus	vaccine and	pneumococcal	vaccine economi	С
analyses					

	ROTA	PNEUMO	COMMENTS
PERSPECTIVE	Primary perspective is health care system; Secondary is societal	Primary perspective is societal; Secondary is health care system	Societal costs, including household indirect and direct costs have a minimal impact on cost-effectiveness results.
EXPERT PANEL	Yes	Yes	Same in both models.
DISCOUNTING	SCOUNTING 3% costs and benefits 3% costs and benefits		Same in both models.
COSTS			
 Direct medical costs 	Source: WHO-CHOICE	Source: WHO-CHOICE	Same in both models.
• Vaccine administration costs	Literature review	Source: 8 Financial Sustainability Plans	Vaccination administration costs account for a small fraction of the intervention costs. The independent estimates were very similar.
• Currency	2002 USD	2000 International D (PPP-adjusted US dollars)	The difference in base year does not significantly impact values. The majority of the net cost is driven by the purchase price of the vaccine. Since the vaccine would be an internationally purchased good, the USD and International dollar price would be essentially equivalent.
• DALYs	Formula: based on life expectancy at age 1 for fatal events; standard disability weights for non-fatal cases; age- weighted and discounted at 3%	DALYs: based on life expectancy at age 1 for fatal events; standard disability weights for non- fatal cases; age-weighted and discounted at 3%	Same in both models.

	ROTA	PNEUMO	COMMENTS
VACCINE PROGRAM:			
• Doses	2	3	Intrinsic difference.
Wastage rate	10%	10%	Same in both models.
• Coverage	Base case coverage is from WHO estimates of DTP3 coverage. Accounts for delays in dose 1 and 2, as well as reduced coverage in those at high risk of mortality. Additional scenarios for on-time vaccination, delayed vaccination and theoretical best- achievable DTP3.	DTP3 for steady state based on WHO ICE-T estimates for 2003	Actual coverage levels do not impact cost-effectiveness. Base case in the pneumo model would be comparable to the 'on-time' scenario in the rota model.
• Vaccine efficacy	85% against severe disease resulting in hospitalization or mortality; 70% for other rotavirus illness; if only one dose received, efficacy is ½ two-dose efficacy	Based on Gambian trial result of 7.4 deaths averted per 1000 children (16% of all deaths) against all- cause mortality, adjusted at country-level as described above. Additional VE assumptions	Both models use the best available clinical and epidemiological data to estimate the burden and health benefit relevant for each vaccine. Differences in methods are based on differences in disease dynamics and information availability.
		 in pneumo analysis: VE against non-fatal hospitalized pneumonia 35% VE against non-fatal meningitis 22% VE against non-fatal, outpatient pneumonia 7% Herd immunity effects: Clinical pneumonia: Non-vaccinated infants received ¼ the protection afforded vaccinated infants IPD: Non-vaccinated children receive ½ the protection afforded 	

This comparison was written by the developers of the cost-effectiveness models for Rotavirus and Pneumococcal vaccines.

Annex I. Product Description and Presentation

This annex describes the only currently licensed 7-valent pneumococcal conjugate vaccine: Prevnar manufactured by Wyeth. The following Description and Dosage & Administration information is an excerpt from Wyeth's 30-page package insert for Prevnar in the U.S. market. The photographs of Prevnar in this annex (Figures I-1, I-2) are courtesy of Wyeth.

PREVNAR

(Page 1 of Wyeth's 30-page package insert for Prevnar in U.S.)

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein)

FOR PEDIATRIC USE ONLY For Intramuscular Injection Only

DESCRIPTION

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein), Prevnar®, is a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM197 protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides which are directly conjugated to the protein carrier CRM197 to form the glycoconjugate. This is effected by reductive amination. CRM197 is a nontoxic variant of diphtheria toxin isolated from cultures of Corynebacterium diphtheriae strain C7 (β 197) grown in a casamino acids and yeast extract-based medium. CRM197 is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and are analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

The individual glycoconjugates are compounded to formulate the vaccine, Prevnar® Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens, and by the saccharide to protein ratios in the individual glycoconjugates.

Prevnar® is manufactured as a liquid preparation. Each 0.5 mL dose is formulated to contain:

2 μ g of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 μ g of serotype 6B per dose (16 μ g total saccharide); approximately 20 μ g of CRM197 carrier protein; and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant.

After shaking, the vaccine is a homogeneous, white suspension.

DOSAGE AND ADMINISTRATION

(Pages 26-27 of Wyeth's 30-page package insert for Prevnar in U.S.)

For intramuscular injection only. Do not inject intravenously.

The dose is 0.5 mL to be given intramuscularly.

Since this product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension in the vaccine container. The vaccine should not be used if it cannot be resuspended.

After shaking, the vaccine is a homogeneous, white suspension.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration (see DESCRIPTION). This product should not be used if particulate matter or discoloration is found.

The vaccine should be injected intramuscularly. The preferred sites are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in toddlers and young children. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel. Before injection, the skin at the injection site should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate and wait to see if any blood appears in the syringe, which will help avoid inadvertent injection into a blood vessel. If blood appears, withdraw the needle and prepare for a new injection at another site.

Vaccine Schedule

For infants, the immunization series of Prevnar® consists of three doses of 0.5 mL each, at approximately 2-month intervals, followed by a fourth dose of 0.5 mL at 12-15 months of age. The customary age for the first dose is 2 months of age, but it can be given as young as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. The fourth dose should be administered at least 2 months after the third dose.

Previously Unvaccinated Older Infants and Children

For previously unvaccinated older infants and children, who are beyond the age of the routine infant schedule, the following schedule applies:

Age at First Dose	Total Number of 0.5 mL Doses
7-11 months of age	3*
12-23 months of age	2†
≥24 months through 9 years of age	1

* 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the

second dose by at least 2 months.

† 2 doses at least 2 months apart.

Safety and immunogenicity data are either limited or not available for children in specific high risk groups for invasive pneumococcal disease (e.g., persons with sickle cell disease, asplenia, HIV-infected).

HOW SUPPLIED Single Dose Syringe (10 per package)*

STORAGE DO NOT FREEZE. STORE REFRIGERATED, AWAY FROM FREEZER COMPARTMENT, AT 2°C TO 8°C (36°F TO 46°F).

*This information is different from the 30-page insert; information updated by GAVI's PneumoADIP for current product presentation of Prevnar.

Figure I-1. Prevnar single syringe



Figure I-2. Prevnar 10-syringe pack


Annex J. Supply Situation Analysis for Pneumococcal Vaccines

Overview

Ensuring adequate capacity to supply GAVI-eligible countries is required for accelerating vaccine introduction and for sustaining its use over the long term. This is also the biggest challenge for GAVI because current global capacity, while adequate for early introduction is insufficient to meet long-term demand in GAVI countries. A supply situation analysis is a key step in the formulation of successful strategies for assuring adequate, affordable, and sustainable vaccine supplies.

This Annex provides a current analysis of the global pneumococcal conjugate vaccine supply situation, including the key drivers of the situation and opportunities and challenges for GAVI. It provides details of the methods and assumptions of the analyses conducted by GAVI's PneumoADIP between 2003 and 2006 that underlie these findings.

Supply Situation Analysis

In 2003, GAVI's PneumoADIP convened a "Supply Strategy Working Group" to help it develop a strategy for pneumococcal vaccine supply. The Working Group included 8 experts from World Bank, Gates Foundation, GAVI Fund, WHO consultants, and USAID. They engaged in a series of strategy sessions between 2003 and 2005 that directed GAVI's PneumoADIP to conduct specific research and/or analysis aimed at better understanding the supply, price and demand environment.

The goals of the supply situation analysis included:

- To understand, from a "supplier perspective", how the potential global market for childhood pneumococcal vaccines would be viewed, including assessment of the size of the GAVI market relative to other markets.
- To determine if existing manufacturing capacity could support short and longterm demand in GAVI countries by assessing existing capacity and comparing it to projected global demand (including both GAVI and non-GAVI demand).
- To determine the size and timing of needed investments in global capacity to meet GAVI demand and the supplier perspective on those investment decisions.
- To determine whether the costs and economics of pneumococcal conjugate (and common protein) vaccine manufacturing support potentially affordable vaccine prices and to understand the key drivers of those prices.

The analyses and methods used to achieve these goals included:

- Global market assessment.
- Model-driven analysis of the costs and economics of vaccine manufacturing.
- Supply and demand forecasting. (Note: details on the strategic demand forecasting are available in Annex E.)
- Business-case analyses from a supplier perspective (i.e., NPV and other financial analyses).

This Annex reviews the assumptions and methods in these analyses and summarizes the main findings and implications for GAVI.

Global market assessment.

Assessment of the potential market size (i.e., potential revenues) is a key driver of vaccine development and supply decisions. In order to help understand the global market from a supplier's perspective, and to better understand how a supplier would view the GAVI market in the context of the global market, GAVI's PneumoADIP conducted a "global market assessment".

Data to populate the model was obtained from the WHO including the list of global countries, the ICE-T® data base for DTP3 immunization coverage rates and birth cohorts. Countries were segmented into 3 groupings (High, Middle, and Low) based on World Bank data on Gross Domestic Product per capita and using established World Bank cut-offs for these levels. Within each country, the potential vaccine market was segmented further into doses that would be sold on the private vs. public markets.

The global market assessment was vetted with experts in industry in both the multinational and emerging suppliers to confirm the number of doses and estimates of price. Multinationals generally agreed that the number of doses in the high and middle income countries are used as indicators for sizing capacity. Emerging suppliers generally agreed on the number of doses in the low income markets and contributed to estimating the size of the private market in low income countries.

The global market assessment for infant pneumococcal vaccines shows that there is a large potential value market for pneumococcal vaccines (see Table J-1).

	Low Income	Middle Income	High Income	Total
Total Vaccine Market				
(Doses in millions)	178	131	43	352
Total Vaccine Market				
(US\$ millions)	\$1,342	\$3,453	\$2,368	\$7,163

Table J-1. 2005 global vaccine market assessment

The main findings of the global market assessment include:

- High-income markets provide the greatest market revenue opportunity, even though the doses needed for high-income countries represent less than 15% of the global potential demand.
- The potential value of high-income and middle-income markets is remarkably large by vaccine market standards (~\$5.8 billion annually). This estimate is equivalent to the value of the entire vaccine market globally (all vaccines, all doses, all countries) in 1999.
- Supplying the high income markets requires only ~43M doses per year (this is the equivalent of the minimum capacity of any single manufacturing facility).
- GAVI markets require large volumes of doses and produce relatively small revenues, as compared to high-income markets. It is this disparity between revenues and demand that challenge GAVI markets with a consistent and stable supply of low priced vaccines.

 Consider that 50 million doses per year (the target demand in 2015) at \$5 per dose amounts to \$250 million per year in revenue. When compared with the possibility for \$2.5 billion in revenue from the same volumes in high-income markets.

Costs and economics of vaccine manufacturing.

In 2003 many technical experts in vaccination believed that the costs of manufacturing multi-valent pneumococcal conjugate vaccines were too high to support any potential "solution space" on pricing. That is to say, many believed that the costs of manufacturing a dose of multi-valent pneumococcal vaccine were higher than the public sector's potential willingness to pay, and hence, conjugate vaccines would never be affordable.

To determine if potentially affordable pricing was possible, GAVI's PneumoADIP commissioned Mercer Management Consulting in 2005 to conduct a study to model the costs and economic drivers of pneumococcal conjugate (and common protein) manufacturing. Mercer conducted the study by interviewing individuals familiar with the processes and steps in vaccine manufacturing but who are not currently employed by either of the leading manufacturers of pneumococcal conjugates. The costs of production and of the capital (i.e., infrastructure) needed to produce the doses were estimated to arrive at an average cost of goods (COGs).

Production costs for pneumococcal vaccine can be aggregated into 3 main cost types: 1) variable costs (such as vials, stoppers, and labeling), i.e., costs that are directly proportional to the number of doses produced, 2) semi-variable costs, i.e., costs that are fixed at the batch or lot level (such as animal testing and production labor costs) and thus the larger the batch the lower the semi-variable cost per dose, and 3) fixed overhead costs (such as quality assurance labor). Capital costs to support the build-out of manufacturing capacity can be divided into two pieces: bulk production and filling/finishing.

The Mercer model enables the user to assess the key drivers of vaccine manufacturing costs. This "key driver" analysis was useful in providing insights into potential strategic options for the public sector to use in trying to assure a sustainable, affordable vaccine supply.

The methods and results of the Mercer study were shared with GAVI's ADIP Management Committee and with a small number of experts with experience in vaccine manufacturing, including some with significant experience at executive positions in companies. The analyses were widely regarded as solid, using sound methodology, and accurate in their findings.

The main insights from the Mercer study include the following:

- Vaccine manufacturing costs for multi-valent pneumococcal conjugate vaccines are not an obstacle to sustainable, affordable pricing.
- Based on the build-up of costs and margin requirements, suppliers should be willing to sell a multivalent vaccine at affordable prices, using any of the major conjugation chemistries (currently in-use or planned).
- The supplier's willingness to sell can be influenced by GAVI. For example, committing to demand in advance reduces suppliers' risk in making upfront investments, thereby influencing their margin requirements.

- Key product and manufacturing process characteristics (e.g., conjugation chemistry used) do vary materially with respect to some of the leading candidates, driving differences in cost, capacity, and capital requirements for serving developing world demand.
- The manufacturing cost structure of many pneumococcal conjugate vaccines is heavily driven by semi-variable costs, specifically the costs of the conjugation process. This is somewhat different from other vaccines like hepatitis B vaccine, where variable and semi-variable costs are relatively low.
- Semi-variable costs are highly sensitive to the yields and process time of the conjugation step in manufacturing (i.e., lower yields and longer processing times drive up the costs of manufacturing). Thus, improvements in these two areas make a large difference in vaccine manufacturing costs.

The Mercer analysis also indicates achieving affordable pricing will be determined by several other factors:

- Number of suppliers holding all else constant, the greater the number of suppliers, the lower that pricing is likely to be; however, this effect may be discontinuous (e.g., going from 1 to 2 suppliers may have no effect, whereas adding a 3rd supplier may serve to lower pricing), and it will be in part driven by the overall global relationship between supply and demand.
- Type of suppliers the importance of GAVI demand to each supplier will influence how aggressively suppliers bid from a pricing perspective.
- Transaction terms The quantities tendered, the time period of the contract, and whether volume is committed can all impact the attractiveness of the agreement to suppliers and their resulting price positions.
- Signaling effects When negotiating pricing for a given vaccine, suppliers who sell a range of relevant products to the buyer may take into account the impact on pricing for other vaccines.
- Supplier approach to pricing No supplier will be expected to lose money by supplying GAVI. Some suppliers, especially those with large high-income markets, may however view the pricing from more of a 'humanitarian' perspective and as such be willing to accept lower prices in return for being able to fulfill this corporate social responsibility mission.

Supply forecasting.

To assess current manufacturing capacity and to forecast future capacity, GAVI's PneumoADIP interviewed suppliers and external consultants with expertise in capacity. PneumoADIP then developed annual projections of the global capacity for pneumococcal conjugate vaccine production. These projections were then compared to potential demand in high- and middle-income countries and forecasted demand in GAVI countries to determine at what point existing or projected global capacity would be inadequate to meet forecasted demand.

The key findings from this analysis include:

 Between 2008 and 2010, Wyeth has sufficient existing capacity to meet the forecasted GAVI demand and the projected demand in high- and middle-income countries.

- Beginning in 2010, Wyeth's existing capacity will effectively diminish because they will begin switching the facilities making 7-valent vaccine currently to making 13-valent vaccine because the same manufacturing sites produce roughly half as many 13-valent doses as 7-valent doses.
- With the addition of GSK as a supplier, global capacity (Wyeth and GSK combined) will be adequate to support forecasted demand out to 2012.
- Beyond 2012, forecasted demand potentially exceeds projected supply. This will make GAVI's vaccine supply vulnerable and limit the ability of countries to ramp up vaccination in an effort to meet MDGs.
- Three to five year lead times are needed to increase capacity, therefore it is critical that GAVI commit to pneumococcal vaccination now. A commitment now can help assure that vaccine uptake is not constrained by manufacturing capacity.

Business case for suppliers

Suppliers generally approach investment decisions, such as investing to assure vaccine supply at affordable prices for GAVI, by conducting a business case analysis. Working with private sector consultants from Applied Strategies Consulting (a firm with substantial experience in life sciences strategic consulting), GAVI's PneumoADIP sought to evaluate the "business case" for suppliers to enter and remain in the market for GAVI demand.

The approach used to conduct the business case analysis from the perspective of suppliers was Net Present Value (NPV) methodology. The NPV methodology for these analyses was somewhat simplified compared to what industry would use internally but captures the same main key variables.

For the NPV calculation revenues for each company in each year were calculated assuming:

- Total number and timing of doses demanded according to the Accelerated Introduction Forecast; (e.g., 17 million doses in 2010 and 56 million doses demanded in 2015)
- Equal (50/50) market share (each company supplies one half of the doses demanded) in years where there were 2 suppliers;
- Annual Revenues = (Price per dose) X (Volume of doses supplied)

For the NPV calculation, the costs of supplying the market for each company in each year were calculated accounting for:

- The marginal costs of production (i.e., cost of goods, or COGs) for each dose supplied to GAVI
- The incremental fixed costs required to supply the added demand of the GAVI market (i.e., investments to buy or build a new manufacturing plant)
- The cost of money. Costs and revenues were discounted at a rate of 10% per annum, a figure that is commonly used in life sciences industry calculations.

Sensitivity analyses around the timing of demand and its relation to supply and capacity decisions were also used to determine the potential impact of "demand risk" on the supplier's business case.

The main findings of these business case analyses are:

- The prices and timing of revenues in the Accelerated Introduction Forecast provide a "positive" NPV (i.e., greater than \$0) for the period 2008-2015 for the two suppliers expected to serve the market.
- Prices that would be most acceptable to developing countries without GAVI support (i.e., below \$1 per dose) would not support a business case for suppliers to enter the market.
- Delays in timing of the decision for funding represent a significant risk for the supplier's business case. For example, if funding is delayed by 3 years, then the supplier NPVs change from positive to negative (i.e., the suppliers lose money by supplying GAVI) considering all else remains constant. In addition delays in funding mean that the forecasted demand will exceed vaccine supply, resulting in a missed opportunity to save lives with pneumococcal vaccination.
- Capacity to supply the volumes of doses required for eventual GAVI demand will require large capital investments by industry and these must be taken years in advance of actual demand.

Overall summary of supply situation.

The GAVI market remains relatively small in terms of revenues, as compared to high-income markets, and requires large volumes of doses. Still the high revenue opportunities in high- and middle-income countries provide opportunities for stimulating vaccine development. More than 20 conjugate and protein-based vaccines are in various stages of product development, largely due to this strong "pull" from high- and middle-income countries (see Table 1 and Figure 2 in the Investment Case for more detail).

The pipeline includes multinationals and emerging market companies committed to supplying GAVI. For multinationals, the high margins in the high priced markets potentially allow suppliers to recoup R&D costs and capital investments which in turn may allow them to tier prices substantially for GAVI-eligible countries. Emerging market suppliers are committed to R&D activities to provide an affordable vaccine for their markets as well. This is a prime example of healthy markets driving supply and innovation. The key for GAVI is to leverage those private investments in R&D and to convince suppliers to add the capacity needed to supply GAVI-eligible countries.

These analyses helped GAVI's PneumoADIP find a potential 'solution space' in terms of pricing and timing of supply between donors, countries and industry. These analyses indicate that with a firm commitment from GAVI and GAVI-eligible countries, it should be possible to get early access to life-saving pneumococcal vaccines and achieve sustainable supply at affordable prices. Analyses of the manufacturing costs, paired with assumptions about expected rates of return, indicate that the pricing scenarios outlined in GAVI's PneumoADIP demand forecast (prices starting at \$5.00 per dose and decreasing over time) are possible.

Without support from GAVI and continued work with suppliers, donors and countries, the major decrease needed in vaccine price along with the significant increase in capacity needed to serve low income country demand will contribute to a substantial delay its introduction into developing countries.

Annex K. Vaccine Pricing Methodology and Insights

Overview

Vaccine pricing reflects the intersection of supply and demand. Success requires the boundaries of a buyer's "willingness to pay" and a supplier's "willingness to sell," to overlap, with the former defining the upper price boundary and the latter defining the lower price boundary. In 2003, many experts believed that it would be impossible to find prices that could satisfy vaccine manufacturers and GAVI and developing countries – i.e., that the lower price boundary for suppliers would be higher than the "willingness to pay" of GAVI and countries. Even today, the existing 7-valent vaccine is priced at \$50 per dose or higher throughout the world, and for many this skepticism continues.

GAVI's PneumoADIP approached this problem by trying to determine a "solution space" on prices, volumes, and timing of demand that would potentially bring together suppliers, GAVI and countries. This Annex summarizes the assumptions and analyses that were used in order to arrive at the prices used in this document.

The assumption that suppliers are potentially willing to sell at the price included in the strategic demand forecast is based on the following rationale and analyses:

- Tiered pricing for GAVI is acceptable. Although no price has yet been agreed with GAVI, indications from Wyeth and GSK are that the prices for GAVI-eligible countries will be tiered compared with those charged to high- and middle-income countries and to those in private markets in low-income countries. This is based on conversations with these suppliers over the past 3 years.
- Research and development costs will be allocated to high margin markets, not GAVI. The large market in industrialized countries and private markets allows the leading suppliers currently to recoup their R&D investments and other risks in these highly profitable markets, and thereby, does not require them to recoup those costs from pricing for GAVI-eligible countries. It should be noted that the same cannot be said for other suppliers who may be in earlier stages of development and for whom the donor market is a factor in the decision to conduct such a program.
- The proposed price per dose supports the costs of incremental capital investments in capacity and production costs for the doses supplied to meet GAVI demand. At this price level, if GAVI's PneumoADIP's demand forecast targets are met, then the revenue stream for industry will represent a "positive" business case for supplying GAVI-eligible countries. That is to say, the supplying of pneumococcal conjugate vaccines will be profitable, after accounting for the marginal costs of production and incremental investment in capacity needed to supply GAVI demand. The Mercer analysis of manufacturing costs indicates that this assumption is most readily met for suppliers who have efficient conjugation methods. For manufacturers with less efficient processes, it will be difficult to meet this assumption unless they can shift some manufacturing steps to an area with a lower cost of labor or improve their process efficiency.
- Manufacturers will accept a 10% per annum cost of capital. To account for the time value of capital, our analyses assumed a 10% discount rate per

annum for costs and revenues. According to consultants experienced in the life sciences industry, this is a typical assumption in business case analyses in this field. It should be noted that if suppliers view the demand risk for the GAVI market as high, then they may require a higher rate.

A healthy supply situation is one in which 2-3 suppliers are providing vaccines to GAVI. Business case analyses (see Annex J for more details on this approach) indicate that the proposed price should support 2 suppliers between 2008 and 2015, and 3 suppliers between 2016 and 2025. Alternative scenarios were run with different prices to determine the impact on expected supply behavior. For example, if prices drop too low, the business case for some suppliers changes from positive to negative and the result is a more limited supply base. This approach was also useful for determining that some prices that would be very acceptable to GAVI-eligible countries (i.e., less than \$1 per dose) would not support a successful business case for any suppliers and were therefore not proposed. Thus, the proposed price represents a potential "willingness to sell" price that should support the desired number of suppliers, each with a successful business case.

The following analyses and assumptions were considered when arriving at the proposed "willingness to pay" prices for GAVI.

Demand in GAVI (and especially by GAVI-eligible countries) is very sensitive to price. Target product profile interviews conducted by PneumoADIP in 2004-2005 show that countries see prices of \$1 per dose as a sort of "price ceiling" above which they currently cannot imagine how to raise the funds from national and local sources needed to sustain vaccine procurement. The closer that GAVI's price is to this "magic number" the easier it is for countries to imagine a long-term price that is potentially affordable from national budgets.

This price point represents a new "high" for GAVI purchase, and the amount of financing needed to support the forecast will be significant, but feasible within existing projections for GAVI resources. At \$5 per dose, the amount of financing needed to procure 50 million doses in 2015 is \$250 million.

Cost-effectiveness analyses indicate that at prices of \$5 per dose, pneumococcal vaccination represents a "very cost-effective" investment of health resources, and that at a price of \$3 per dose or lower, the vaccine is cost-saving. While cost-effectiveness analyses would also support prices as high as \$10, it was considered unlikely these prices would be viewed favorably given that in resource constrained environments, where many highly cost-effective interventions are unused or under-utilized, the "opportunity cost" of this funding would be considered too high.

Annex L.

Cold chain impact analysis of introduction of PCV-7

Note: The analyses for this annex were kindly prepared by WHO/IVB/EPI+ using the Vaccine Volume Calculator.

Characteristics of the 7-valent pneumococcal conjugate vaccine Prevnar™ /Prevenar™ (manufactured by Wyeth):

Formulation: liquid, no preservative (i.e., does not contain thiomersal)

Presentation: 10 single dose pre-filled syringes, packed volume 59.7 cm3/dose

The comparative advantages of this presentation relative to other presentations include:

- Bundled vaccine: simplifies the management of supplies (only one item) and avoids programmatic errors associated with the supply of separate items to be matched to ensure safe delivery of services.
- The packed volume of a single dose pre-filled syringe of PCV7 is less than other available vaccines in pre-filled syringe. Only Uniject presentations (HepB Uniject, TT Uniject) have less packed volume (with < 30cm3/dose).
- The unit packed volume of a pre-filled syringe of PCV7 is less than 60 cm3/dose (which is equal to the unit packed volume of one AD syringe).

One potential problem in the current presentation is that the syringe is not "autodisable." This would put it in conflict with existing WHO-UNICEF-UNFPA policy on safety of immunization.¹ This may be addressed in preparation for introduction into developing countries. The addition of a vaccine vial monitor would also be an advantage in developing countries. WHO has advised Wyeth of these issues during meetings in relation to the pre-qualification process and application.

Cold chain requirements

The analysis is based on the following assumptions:

- Developing country context with more or less cold chain infrastructure, where
 vaccines are distributed from the national to intermediate (provincial, district)
 to peripheral/service delivery levels.
- 10 single-dose pre-filled syringe presentation will be used, since multi-dose presentation is not yet available.
- The introduction of PCV-7 is likely to be made after a country has introduced HepB and/or Hib in some combination and presentation.
- The baseline immunization schedule used for analysis will combine the traditional vaccines (BCG, OPV, DTP, Measles, TT and YF) with one of the DTP-HepB-Hib combinations in 10-dose presentations. DTP-HepB-Hib combinations in single dose pre-filled syringe presentations are excluded.
- The PCV7 is stored at +2°C to +8°C at all levels of the cold chain.
- Wastage factor of 10% (same as for syringes).

• Diluents for freeze dried vaccines are stored in the cold chain with their vaccines at service delivery level. At national and intermediate stores, diluents are stored at ambient, if not packed together with the vaccines.

The results from estimations are presented in Figure L-1 below. The introduction a three doses schedule of this vaccine in a national immunization programme will have a substantial impact on the cold chain storage requirement. The total net volume of this vaccine alone is 199 cm3 per child. That represents:

- 500% increase for a national immunization programme using only traditional vaccines.
- 300% increase if the programme is already using combined DTP-HepB-Hib (pentavalent), in addition.

Such an expansion of cold chain capacity may not be immediately feasible in many developing countries. This may require them to adjust their vaccine distribution schedule (more frequent supplies) to avoid expanding the cold chain immediately.





Analysis of dry storage requirements and waste management issues

Additional analysis made to assess the dry storage requirement and the waste management issues show relatively little impact.

For dry storage, the impact remains marginal with the introduction of the vaccine (Figure L-2). An increase of 24% compared to the traditional vaccines and less than 5% if pentavalent is already introduced is expected. The slight increase is due to the volume of the additional safety boxes needed for safe disposal of used syringes.

Figure L-2. Dry storage requirements estimations



The impact on the waste management is reasonable (Figure L-3). The total number of syringes and needles required per child (for injection and reconstitution) will increase from 9.8 to 12.8 syringes and needles to be disposed of. This increase is mainly due to the number of injections required per child rather than the vaccine presentation.





Reference for Annex L

¹ WHO-UNICEF-UNFPA joint statement* on the use of auto-disable syringes in immunization services. <u>http://www.who.int/injection_safety/toolbox/en/Bundling.pdf</u>