Framework Document:
Pilot AMC for Pneumococcal Vaccines

9 November 2006

This document has been prepared by the World Bank and GAVI for the second Donor Working Group meeting on 9 November in London

Chapter 1
Executive Summary

I. Introduction

Advance Market Commitments are an innovative concept with the potential to save millions of lives by accelerating access to vaccines that would not otherwise be available for many years. A pilot AMC has been designed for pneumococcal vaccines to demonstrate both the feasibility of the AMC mechanism and its impact on accelerating vaccine development, production scale-up and introduction.

Experts and stakeholders have vetted the AMC concept and proposed mechanics. Vaccine development public-private partnerships have confirmed that market failures inhibit rapid product development and could be addressed through an AMC. Vaccine and biotechnology firms have reviewed the proposal and agree that it has the potential to influence their investment decisions to ensure earlier access to sustainable supply of priority vaccines. Technical, legal and economic experts have concluded that AMCs are a powerful, results-oriented and cost-effective mechanism. After careful review, an independent Expert Committee recommended pneumococcal disease as most suitable for the pilot AMC.

A pneumococcal pilot AMC has two overarching benefits: First, it will save lives quickly. Second, its success in stimulating industry investment will be measurable. The proposed pilot AMC will prevent up to an estimated 5.4 million childhood deaths by 2030. It will achieve this goal by accelerating GAVI-eligible country access to new, life-saving pneumococcal vaccines.

Pneumococcal vaccines are the right choice for the pilot AMC for a late-stage vaccine because:

- Pneumococcal vaccines that fit within existing immunization delivery systems have a proven ability to protect children and improve child survival in the same communities where the burden of disease is greatest.

- Commercial, not scientific, hurdles are major obstacles to industry decisions that will accelerate introduction of pneumococcal vaccines. AMCs are a market-based solution to a market failure, designed to address the major vaccine capacity and supply obstacles that keeps these vaccines from widespread use.

- Success can be defined by industry's willingness and commitment to build manufacturing capacity that would not otherwise have been built. This is easily measured and is expected to occur quickly.

- An AMC will provide good "value for money". Because there is a large global market for pneumococcal vaccines, the pilot AMC will leverage existing

industry investments in research and development that were driven by the high and middle-income markets – and ultimately, only pay for the incremental investment needed to supply developing countries.

This paper outlines in detail the structure, shape and implementation steps for the pilot. This chapter gives an overview of all aspects of the pilot. Chapter 2 provides details about pneumococcal disease and the status of vaccine development. Chapter 3 outlines the recommended AMC market size and price range and how this was estimated. Chapter 4 describes the institutional support to establish, implement and monitor the AMC. Chapter 5 discusses how the financial commitments for the AMC can be structured and the legal documents that will underpin the AMC. Finally, chapter 6 briefly outlines the most immediate next steps that will follow donor commitments to launch the Pneumococcal Pilot AMC at the end of 2006.

II. Pneumococcal disease and the status of vaccine development

Pneumonia is the leading infectious cause of child mortality worldwide, causing an estimated 1.9 million (or 19%) of the estimated 10 million child deaths that occur each year. [1] Pneumococcal disease is the leading cause of these child pneumonia deaths, as well as the second leading cause of childhood meningitis deaths. It kills more than 1.6 million people including 700,000 to 1 million children under age 5 every year. [2,3] It is a growing and increasingly urgent global problem. HIV/AIDS is increasing the rate of infections, with HIV-infected children 20 to 40 times more likely to get pneumococcal diseases. Growing antibiotic resistance is also making pneumococcal disease more difficult and expensive to treat. Because pneumococcal pneumonia frequently follows influenza, some experts are calling pneumococcal vaccination the "low hanging fruit of pandemic preparedness".

Weak treatment systems, antibiotic resistance, threats of influenza pandemics, and the availability of robust immunization systems in most countries combine to make vaccines the only reliable, effective way to prevent pneumococcal infections. Early vaccines and current candidate vaccines have been shown to fit within existing immunization delivery systems, and they improve child survival in the communities where the burden of disease is greatest. 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.

Demand for Pneumococcal Vaccines

High and middle-income countries, which have greater financial capacity to support pneumococcal vaccines, have extensive demand for them. In low-income developing

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[1] Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis 2002; 2:25-32.

[2] World Health Organization. Pneumococcal vaccines. Wkly Epidemiol Record 2003; 14:110-119

[3] GAVI Website accessed Feb. 17, 2006.
http://www.vaccinealliance.org/General_Information/Immunization_informa/ Diseases_Vaccines/
vaccine_preventable_deaths.php

countries, demand for pneumococcal vaccines as with most vaccines, depends on predictable and sustainable donor support and pricing. Extensive discussions by GAVI partners with decision-makers in developing countries indicate that, with acceptable financing and pricing terms, there is substantial latent demand for pneumococcal vaccines. The expected demand for the vaccine is based on high recognition of the burden of pneumonia and meningitis disease. Preliminary discussions with governments in Africa and Asia have confirmed strong interest in introducing an affordable pneumococcal vaccine if one were available.

However, while demand estimates are the best available, industry still faces considerable demand risk. The AMC mitigates the financial/market risk that the poorest developing countries will not be able to pay a reasonable price to purchase vaccines that are a priority for their national health program, but, as a market-based mechanism, it does not guarantee demand or purchase. Given significant historical levels of demand risk, there is a need for continued investment in activities to improve the quality and timeliness of pneumococcal vaccine demand forecasts in parallel with the AMC. These types of activities are complementary activities will be key to maximizing AMC impact.

Status of Vaccine Development

For developing countries, the ideal pneumococcal vaccine is one that is safe, highly efficacious (>80% efficacy) against more than 60% of pneumococcal serotypes occurring locally, can be delivered in the existing schedule (without additional visits), and comes in a presentation that is easily adapted to local systems.

Investments to develop and produce pneumococcal vaccines have been stimulated to date by large potential markets in high and middle-income countries (estimated at $5-6 billion). The pneumococcal vaccine pipeline includes one licensed product and more than 20 candidate vaccines in varying stages of development. The licensed vaccine has safely and effectively vaccinated more than 30 million children in industrial countries. Capacity is, however, inadequate and the vaccine is not considered suitable for wide spread introduction in developing countries. Two vaccines that extend protection for populations in both developing and industrial countries by adding more serotypes may be licensed by 2010. Other vaccines, including from emerging manufacturers may come to the market in the following 5 to 10 years.

III. AMC Market Analysis

Childhood pneumococcal vaccines have a large potential market in high and middle-income countries. Analyses indicate that these markets might generate annual demand of about 174 million doses. Low-income country demand is expected to be about the same, at 178 million doses a year. However, large incremental investments in capacity will be needed to meet this demand as current capacity is adequate only to serve the high and middle-income markets. Given the risks associated with low

income country markets, and the costs of scaling-up capacity, these incremental investments will not occur without financial incentives. In addition, predictable and sustainable prices and funding are needed for governments to introduce the vaccine into their national immunization programs.

The success of the AMC pilot for pneumococcal vaccines will be measured in two ways: first, its ability to influence the decisions of vaccine firms to accelerate and increase investments in the late-stage development and capacity scale-up of pneumococcal vaccines; and second, its ability to obtain more predictable and sustainable prices and supply of vaccine over the long term. In addition to these overarching goals, stakeholders have noted that the AMC should foster competition, should encourage innovation, should engage emerging as well as multinational manufacturers and, of course, should be an efficient use of donor funds.

To set appropriate AMC terms that are likely to influence industry's investments in ways that will achieve the AMC's objectives – but that also use donor funds efficiently – extensive work has been undertaken to understand how industry will likely assess the AMC proposal. The AMC market model is based on valuation methodology commonly used by the industry to compare returns across alternative investments and with the cost of capital. The analyses also consider the number of firms likely to develop a product within a reasonable AMC duration (e.g. 7 to 11 years) so that the AMC might be sized to support more than one firm and thus encourage competition.

The recommended size of the donor contribution to the AMC is $1.5 billion in nominal terms with an NPV cost of $860 million.[✦] The price per dose is to be determined but is estimated to be within the range of $5-7 per dose with developing countries responsible for an affordable co-payment per dose of roughly $1. The first payments are anticipated to begin in 2010 and last for 9 to 10 years. Once the AMC is depleted each participating firm will continue to supply the vaccine at a pre-determined low price for an established period. This AMC market amount would support the first three firms to come to the market with a pneumococcal vaccine, providing each with a neutral or positive risk-adjusted NPV.

Post-AMC terms

The post-AMC supply and price of pneumococcal vaccines is as important as the availability of vaccine during the AMC. To balance the long-term objectives of donors, governments and industry, the post-AMC price and supply are factored into the AMC negotiations. To assure predictability, each firm will be required to commit to a post-AMC price for their vaccine at the time that it qualifies for AMC funding and they sign the Supply Agreement. Each firm will have the freedom to set its post-AMC price – and this price also will also be used to determine the co-pay of countries

[✦] This assumes that the AMC Independent Assessment Committee (IAC) establishes the pneumococcal Target Product Profile (TPP) as expected to attract conjugate vaccines with efficacy in the range provided by the 10 and 13 valent candidates.

during the AMC. Market forces are thus used to determine industry pricing, as long term revenues arising from the post-AMC prices will be balanced against the more immediate impact on demand during the AMC of those predicted prices.

To assure reliable supply, firms will be required to commit to supply with specific exit conditions including volume commitments tied to previous years demand (rolling 2-year average), and conditional exit options (such as 4 to 5 years notice before exit), and sunset of the AMC agreement at an established time (e.g. 10 years after the depletion of the AMC).

Impact of Pneumococcal AMC

The additional outputs that an AMC for pneumococcal vaccines can be expected to motivate include:

- Investments by two to three multinational vaccine manufacturers in plant capacity to meet the gradually increasing demand from the low-income countries, which is anticipated to ramp up beginning in 2012;

- Accelerated introduction of pneumococcal vaccines in a group of early adopter countries by 2010. Historically, delays of 15 years have been seen, which would mean without any activities pneumococcal vaccines would not even begin to be introduced before 2020.

- At least one emerging vaccine manufacturer to take a product from early research and development through to product licensure in the next 10 years.

- Competition among manufacturers for the developing country market.

- Investment in new technologies for new and more efficient vaccine production and second generation technologies (e.g., protein vaccines) tailored to developing country markets.

- Two to three manufacturers to provide countries with an early post-AMC price that is predictable, affordable and sustainable.

Overall, the AMC will result in 70 to 100 million immunized infants over the life of the AMC. This will prevent between 500,000-700,000 deaths during the AMC itself. However, the impact of the AMC goes beyond the contract period as it assures a long-term sustainable supply and price. The impact also goes beyond the children immunized, as herd immunity will act as a multiplier, expanding the benefits of immunization to un-immunized children and older populations.

IV. Governance and Institutional Support

The Pneumococcal AMC Pilot will be established and implemented over a 13-year period from 2007 to 2020, moving through several different phases in the project's life. To best support this, the AMC functions will be split between two institutions,

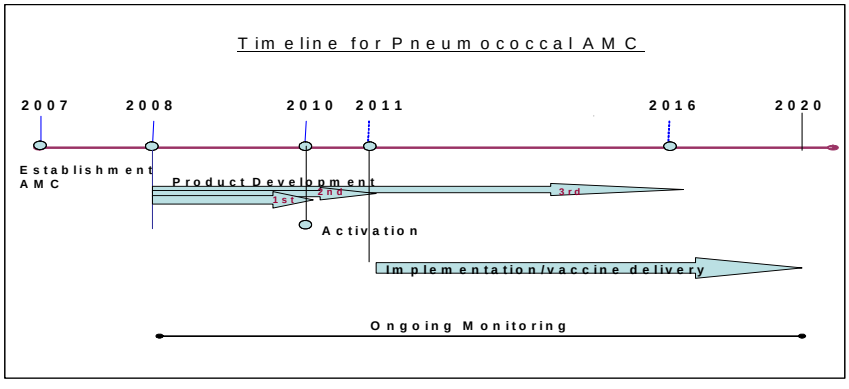
GAVI and the World Bank, each with a unique capacity to address the evolving programmatic and financial requirements of the AMC. Similarly, as the project evolves, so will the role of donors and other stakeholders. To launch the AMC pilot, donors will need to agree on the appropriate terms and processes to achieve the AMC objectives. The target outcomes, systems and procedures established at the pilot's inception, must ensure independence and credibility of AMC implementation, underpinned by transparent reporting, and accountability to all parties. The success of the AMC depends on the absolute understanding by all stakeholders that once agreed, the AMC terms and procedures will be respected, implying great attention to transparent monitoring during the implementation years.

(1) **Establishment**. The initial setting-up phase will put in place the arrangements underpinning the AMC. This will include negotiations, by and between donors, the host institution/s and industry. These negotiations will result in the Framework and Supply Agreements that provide for a specific level of funding at a specific price for pneumococcal vaccines meeting the specified Target Product Profile (TPP). The Framework will also specify the procedures and monitoring that will be followed as the AMC is implemented.

(2) **Product Development**. Once the framework agreement is signed, an interim period will follow in which the key institutional requirement will be to monitor the development and scale-up of pneumococcal vaccines to meet the AMC goals.

(3) **Activation**. The AMC is triggered when a specific manufacturer first produces a target vaccine that is determined to meet the TPP. The manufacturer then enters into a Guarantee and Supply Agreement under the framework agreement.

(4) **Implementation**. Once the Guarantee and Supply Agreement is signed, the transactions associated with the procurement and delivery of vaccines to countries and the payment to industry will be supported. Institutional responsibilities focus on efficient and timely management of these transactions.



GAVI and The World Bank would be the two entities directly responsible for supporting the programmatic and financial functions of the AMC based on their relative strengths.

- **The GAVI Alliance** is a public-private partnership focused on accelerating access to priority new vaccines. It has established processes and a credible track record in supporting the 72 poorest countries with new vaccines and funds to strengthen national immunization programs. GAVI has strong links with all the stakeholders in the immunization community including governments, donors, industry, and technical partners. The Executive Committee of the GAVI Board has indicated its commitment to host the AMC Secretariat and support the programmatic and operational functions for the AMC Pneumococcal pilot.

- **The World Bank** has the recognized financial and administrative capacity to support the establishment of a variety of donor commitments and payment structures. Assuming appropriate internal approvals are obtained, the World Bank would be responsible for providing administrative and financial services to the AMC, drawing on its established capacity for financial management, and contractual and administrative services. The World Bank will support donors in evaluating and implementing an efficient mechanism to bundle donor commitments into a single, credible commitment to industry for the full AMC amount.

In addition to the two primary implementing entities, the following stakeholders will be critical in the implementation and success of an AMC:

- **Donors** are responsible for assuring credible funding, including financing the cost of bundling varied commitments into a single financial instrument. Donors are also responsible for establishing the appropriate policies and processes to guide AMC implementation across the different phases. A **Donor Committee** will be established to allow AMC sponsors to efficiently provide input into the technical design and processes for the AMC during the establishment phase and to allow monitoring of its implementation and progress toward the AMC's objectives.

- All **pharmaceutical, vaccine and biotech firms** are eligible to participate in the AMC. They will be party to the negotiations on the Framework and Supply Agreements to ensure processes are viewed as independent and credible. Each firm will evaluate the AMC and determine the extent of its own investment in a pneumococcal vaccine to serve the target AMC countries.

- **Developing countries** are responsible for making timely, evidence-based decisions on whether introducing pneumococcal vaccines is a priority for the national health program. Developing country governments can then apply for the vaccine through the established GAVI process of national applications and requests.

- **Technical agencies** such as WHO and UNICEF are implementing partners of the GAVI Alliance who will ensure delivery of vaccine in country and that the AMC is integrated within existing processes as much as possible. WHO will provide

recommendations to the IAC through convening expert groups and using established processes such as for pre-qualification of vaccines.

- The **Independent Assessment Committee (IAC)** is the cornerstone of the proposed AMC. The IAC will oversee core parts of the AMC process, including the establishment of Target Product Profiles (TPPs) for candidate vaccines and ascertaining whether they are met. The credibility of AMCs rests largely on the perception of industry, donors and developing country governments about the independence, fairness and reliability of the IAC.

V. Financial structures

Financial commitments for AMCs must be clear, credible and legally-binding. In addition, the financing structure must be flexible enough to accommodate different donor systems and preferences as the sponsors of the AMC will have different domestic authorization and appropriation laws and procedures.

Once donors have collectively agreed their respective shares of the total AMC amount, individual donors will have three basic financing options available to them:

(i) Full up-front financing of the full amount of their share at the start of the product development phase.

(ii) Up-front commitment of the full amount of their share at the start of the product development phase with the stream of payments made on an annual basis over a period of years. Total resources would steadily build up and be available in time to meet expected disbursements.

(iii) Up-front commitment of the full amount of their share with disbursements only starting in the implementation phase and matching AMC payment needs precisely.

The key role of the financial structure is to bundle donor financing into a single financial asset that provides clear, coherent and legally-binding financial underpinnings to the legal obligations set out in the Framework Agreement. In the case of pneumococcal vaccines, the value of this financial asset needs to be US$860 million in 2006 prices in NPV terms in order to elicit the desired response from industry.

Donor commitments will be a mix of cash, together with different types of commitments. There will be no risks associated with cash financing. However, given political and budgetary realities, together with uncertainty around the timing of future AMC payments as well as variation in sovereign credit ratings, there will be some timing, collection and payment risks associated with donor financial commitments.

What this means is that, in addition to packaging multiple assets into a single instrument, the role of the intermediary financial structure will also be to ensure such risks are mitigated. If the assets of the financial structure do not equal the required market amount the response from industry will be muted.

The details of this bundling process will depend on the nature of donor pledges and the precise role of intermediary institutions and will need to be defined during the Establishment phase.

Legal structures

An AMC will be established using a framework agreement that sets out its key terms, including legal obligations of donors and the implementation details for the structure**.** The framework agreement will specify the market size of the AMC, and the price and requirements for the targeted vaccine. It will set out the underlying financial commitments, and the obligation to enter into a guarantee and supply agreement with any qualifying manufacturer whose vaccine meets the requirements. It will delineate the responsibilities and processes of the Independent Assessment Committee, as well as ongoing responsibilities after the AMC funding is exhausted.

For an AMC to alter the behavior of potential producers, the framework agreement and the guarantee and supply agreements must create contractual obligations, including with respect to financing, that are fully credible and legally binding despite the likelihood that donor commitments may be provided in different forms under different legal jurisdictions. The agreements must be capable of legal enforcement and include dispute resolution and enforcement provisions. Final agreements will depend on negotiated decisions among all parties, recording all core business requirements and procedures of the AMC.

VI. Next steps

To establish the AMC, the key stakeholders including donors, firms, GAVI, the World Bank and other technical partners must continue to work together to refine and finalize the policies, processes and AMC terms outlined in this paper.

Each donor will be responsible for structuring their pledge into a financial commitment that fulfills the objectives of the AMC. These individual pledges will need to be bundled into a single commitment that is credible to industry.

Setting in place the technical, procedural, legal and financial arrangements that will underpin the AMC will be an negotiation that will culminate in the signing of the AMC Framework Agreement and Supply and Guarantee Agreement. Negotiations will provide for a specific level of funding at a specific price for a vaccine meeting specified TPPs. The two legal agreements will codify the agreed terms, processes and roles and responsibilities.

A number of other administrative processes will take place in parallel with the negotiations, allowing the creation of the Secretariat functions as well as the IAC. GAVI will establish the AMC Secretariat that will act as the focal point to ensure all of the various start-up activities are effectively coordinated. The World Bank and

Donor Committee will agree on the systems and procedures to ensure that specific donor payments and flows are managed efficiently and support AMC payments under eligible guarantee and supply agreements. Finally, GAVI and the World Bank, in consultation with stakeholders, will be responsible for outlining and implementing the process to identify the IAC members. The IAC will have the responsibility for developing the TPP for pneumococcal vaccines through the processes outlined in this paper and reviewing the recommended AMC financial terms once the TPP is established.

Once established, the Pneumococcal AMC will support industry and governments in helping to prevent unnecessary pneumococcal deaths in the poorest countries of the world. Importantly, it will also enable stakeholders to quickly assess the impact of the AMC mechanism to determine if AMCs will be able to accelerate other health priorities such as vaccines against malaria.

Chapter 2
Pneumococcal Disease Burden and Rationale for Pneumococcal Vaccination

I. Global burden of pneumococcal disease

Streptococcus pneumoniae (S. pneumoniae) a global disease, is the most common cause of bacterial pneumonia mortality and the most severe cause of bacterial meningitis worldwide. The World Health Organization estimates that more than 1.6 million people, including >700,000 - 1 million children under age 5 years die every year of pneumococcal infections.[4,5] Although children everywhere are affected, >90% of pneumococcal deaths occur in poor countries.

The HIV/AIDS epidemic in developing countries is increasing the rate of pneumococcal infections because children with HIV/AIDS are 20- to 40-times more likely to get pneumococcal disease than children without HIV/AIDS.[6,7] Antibiotic resistance is making pneumococcal disease more difficult and expensive to treat. Finally, because influenza is so commonly followed by pneumococcal pneumonia, some experts are calling pneumococcal vaccination the "low hanging fruit of pandemic preparedness". Together these factors make pneumococcal disease a growing and urgent 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 may require them to use precious savings or borrow funds. Hospitalized children also need a parent as a 'bedside advocate' during their stay to feed and care for them. The opportunity costs during the 7-21 days of hospitalization can also significantly impact a family's economic situation.

Pneumococcal meningitis is the most severe form of the disease. It kills about one-half of the children who get it and disables many of the survivors.[8] Life-long disabilities after pneumococcal meningitis include hearing loss, learning delays, speech impediments, and paralysis. Because of these disabilities, survivors of

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[4] World Health Organization. Pneumococcal vaccines. Wkly Epidemiol Record 2003; 14:110-119

[5] GAVI Website accessed Feb. 17, 2006. http://www.vaccinealliance.org/General_Information/Immunization_informa/ Diseases_Vaccines/ vaccine_preventable_deaths.php

[6] Madhi SA, Peterson K, Madhi A, Wasas A, Klugman KP. Impact of human immunodeficiency virus type 1 on the disease spectrum of *Streptococcus pneumoniae* in South African children. Pediatr Infec Dis J 2000; 19:1141-1147.

[7] Mao C, Harper M, McIntosh K, *et.al*. Invasive pneumococcal infections in human immunodeficiency virus-infected children. J Infect Dis 1996; 173:870-876.

[8] Goetghebuer T, West TE, Wermenbol V, Cadbury AL, Milligan P, Lloyd-Evans N, Adegbola RA, Mulholland EK, Greenwood BM, Weber MW. Outcome of meningitis caused by Streptococcus pneumoniae and Haemophilus influenzae type B in children in The Gambia. Trop Med Intl Health 2000; 5:207-13.

pneumococcal disease have fewer economic and educational opportunities than their peers which significantly contribute to the vicious cycle of poverty to ill health to poverty.

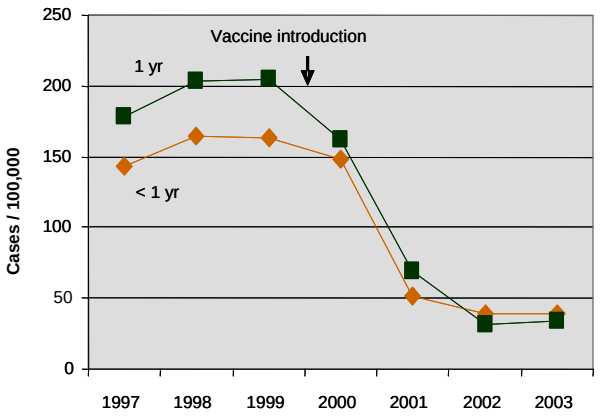
II. Pneumococcal vaccines

S. pneumoniae is a bacterium with ~90 pneumococcal variations, called "serotypes". Serotypes are determined by the sugar capsule that coats the bacterium. This sugar capsule helps the bacterium evade the immune system. Immunity to the capsule prevents disease and transmission. Pneumococcal conjugate vaccines prevent disease by stimulating immunity to the serotypes included in the vaccine.

The ranking of individual pneumococcal serotypes causing serious disease among children varies somewhat from country to country. However, the vast majority of disease in children is due to about 7-11 serotypes. Conjugate vaccines that contain 10 or more serotypes are expected to prevent 70-80% of all disease in children worldwide.[9,10,11] Vaccines that contain more serotypes will prevent more disease and help assure that one formulation protects every child, everywhere.

The significant health impact of routine vaccination has already been demonstrated in the USA with the existing 7-valent vaccine. Figure 1a show that following introduction of 7-valent pneumococcal conjugate vaccine as a routine immunization in the USA there was a dramatic decrease (69%) in the incidence of invasive pneumococcal disease in children under 2 years of age. There was also a significant decrease in disease among adults (32% in 20-39 years old; 8% in 40-64 years old; and 18% in > 65 years old). These data show that, by interrupting the transmission of pneumococcal disease, the vaccine is preventing illness among unvaccinated adults (and unvaccinated children, data not shown).[12] As shown in figure 1b, more than twice as many cases of pneumococcal disease are being prevented through the herd immunity effects of vaccination than are being directly prevented by the vaccination of

Figure 1a. Change in the rate of invasive pnuemococcal disease in infants and children



[9] WHO website, accessed Feb. 17, 2006. http://www.who.int/vaccines-diseases/research/mening.shtml

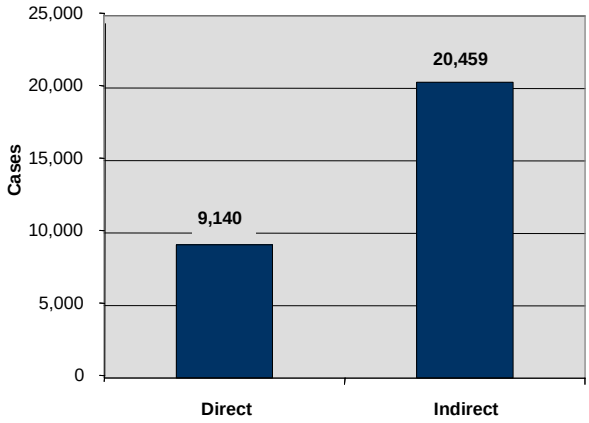
[10] Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part 2. Clin Infect Dis 2000; 30:122-40.

[11] Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part 1. Clin Infect Dis 2000; 30:100-21.

[12] Whitney CG, Farley MM, Hadler J, *et.al.* Decline in Invasive Pneumococcal Disease after the Introduction of Protein-Polysaccharide Conjugate Vaccine. New Engl J Med 2003; 348:1737-46
349:1341-8

young children.[13] This herd immunity is also expected to occur with vaccination in developing countries. As such, childhood vaccination could prevent a substantial proportion of the ~800,000 adult deaths due to pneumococcal disease each year. Increases in non-vaccine type disease (i.e., serotype replacement) have been seen but the increases have been small in relation to the overall decline in disease.

Figure 1b. Estimated no. of cases of vaccine type invasive pneumococcal disease prevented by direct and indirect effects of 7-valent vaccine



Routine vaccination has also eliminated racial disparities in disease incidence. For example in the USA, African-American and Native Alaskan/American Indian children had rates of invasive pneumococcal disease several fold higher than that of white children in the USA. Vaccination has wiped out these racial disparities and the incidence of disease is now similar in all groups.[14,15]

Vaccine trial results

Randomized clinical trials using candidate vaccines prove that pneumococcal conjugate vaccines can improve child survival and protect the most vulnerable children. Two clinical trials were conducted in Africa using a 9-valent vaccine candidate. A trial in The Gambia showed a 16% reduction in all-cause mortality in vaccinated children.[16] In other words, *~7 child deaths were prevented for every 1000 vaccinated children.* Also, this study showed that hospital admissions for any reason and x-ray confirmed pneumonia were reduced by 15% and 37%, respectively.

Preventing pneumococcal disease among HIV-infected children is imperative. In South Africa, over a 10 year period, the incidence of pneumococcal disease doubled as the prevalence of HIV infection in children rose to ~6%.[17] In Soweto, South Africa, a 9-valent pneumococcal vaccine candidate showed that the vaccine was 83%

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[13] CDC. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease, United States, 1998-2003. MMWR 2005; 54:893-7.

[14] Flannery B, Schrag S, Bennett NM, Lynfield R, Harrison LH, Reingold A, et al. Impact of childhood vaccination on racial disparities in invasive Streptococcus pneumoniae infections. JAMA 2004; 291:2253-5.

[15] Hennessy TW, Singleton RJ, Bulkow LR, Bruden DL, Hurlburt DA, Parks D, et al. Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in Alaska Natives: progress towards elimination of a health disparity. Vaccine 2005; 23:5464-73.

[16] Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, Oluwalana C, Vaughan A, Obaro SK, Leach A, McAdam KP, Biney E, Saaka M, Onwuchekwa U, Yallop F, Pierce NF, Greenwood BM, Adegbola RA; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005; 365:1139-46

[17] Karstaedt AS, Khoosal M, Crewe-Brown HH. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. Pediatr Infect Dis J 2000; 19:454-7.

effective in non HIV-infected children and 65% effective in HIV-infected children.[18] Rates of pneumococcal pneumonia are so high among HIV infected children that the vaccine prevented one episode of pneumonia for every 40 children vaccinated. Use of pneumococcal vaccines will improve the lives of HIV infected children.

Each trial used a 3 dose regimen in which children received pneumococcal vaccines on the same schedule and at the same time as other routine vaccines including DTwP, Hib, hepatitis B, and oral polio vaccines. Pneumococcal vaccination will require additional investment in cold chain capacity, training of health workers, and an additional injection but not require additional visits.

In sum, pneumococcal vaccines that fit within existing systems have a proven ability to improve child survival in the communities where the burden of disease is greatest.

III. Cost-Effectiveness Analysis

Pneumococcal conjugate vaccination in low-income countries is a very cost-effective 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 shows that pneumococcal vaccine meets established WHO criteria for a "very cost-effective" health intervention in GAVI-eligible countries.✦ The main findings of the analysis are:

1. 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 $690 per death prevented.
3. Vaccination would reduce medical expenditures by more than $558 million/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. This is well below the weighted average per capita GDP in

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[18] Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N, Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. New Engl J Med 2003;

✦ (Sinha A et al., accepted for publication, The Lancet). 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, non-medical 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. All results are presented in purchasing power parity-adjusted international dollars (2000).

❋ Disability Adjusted Life Year – quantitative indicator of burden of disease that reflects the total amount of healthy life lost, to all causes, whether from premature mortality or from some degree of disability during a period of time.

GAVI-eligible countries and meets WHO criteria for a "very cost-effective" intervention. 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. Importantly, pneumococcal vaccine is most cost-effective in countries with the highest infant mortality rates.

IV. Vaccine introduction issues

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

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 strengthening immunization delivery systems and country co-pay/co-financing. In short, introduction of this new vaccine will require a relatively small, incremental effort and resources for local institutions.

As this vaccine will be delivered through the existing immunization delivery system and during established health contacts with infants, the incremental cost for delivering pneumococcal conjugate vaccine is relatively small -- roughly $0.47 per dose. This estimate was derived from country-level data provided to GAVI in national financial sustainability plans. These costs include all non-vaccine costs (e.g., capital, transport, personnel, injection supplies, training, other) for immunizations delivered in routine immunization programs.

VI. Other interventions to address 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 may remain as high as 10% even in industrialized countries.

Supplemental zinc is being studied as a potential treatment for severe pneumonia in children in developing countries. Studies have shown that zinc supplements decrease the severity of clinically diagnosed pneumonia but it is unclear whether this impacts on bacterial pneumonias such as pneumococcal pneumonia.[19,20] Studies are ongoing

[19] Brooks WA, Yunus M, *et.al.* Zinc for severe pneumonia in very young children: Double-blind, placebo-controlled trial. Lancet 2004; 363:168

to address the potential for zinc supplements to prevent pneumonia. 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 to warrant a WHO statement for the inclusion of zinc supplement for the treatment and potentially the prevention of pneumonia. 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.

VII. Pneumococcal vaccine pipeline

For developing countries, the ideal pneumococcal vaccine is one that is safe, highly efficacious (>80% efficacy) against more than 60% of pneumococcal serotypes occurring locally, can be delivered in the existing schedule (without additional visits), and comes in a presentation that is easily adapted to local systems.

The pneumococcal vaccine pipeline includes one licensed product and more than 20 candidate vaccines in varying stages of development (Figure 2). The one licensed pneumococcal conjugate vaccine is registered in over 75 countries. This vaccine, called Prevnar™ (manufactured by Wyeth) meets some but not all of these ideal characteristics. It is safe and highly efficacious and contains 7 important serotypes. However, it lacks two serotypes that are important in many developing countries, and therefore, its impact on health will be more limited than an ideal vaccine. Also, the presentation of the vaccine (a single dose pre-filled syringe) is not optimal for use in developing country systems. Perhaps most importantly, the current vaccine supply was sized to meet high-income country demand and can only meet a small amount of developing country demand. Current capacity is completely insufficient to meet the expected growth in demand from developing countries.

Two late-stage candidate vaccines are nearing licensure. These vaccines would likely meet all of the characteristics of an ideal vaccine for developing country use. According to publicly available data from GSK, they intend to submit a license application for their 10-valent vaccine candidate to the US or European regulatory authorities, or both in 2007.[21] This makes it likely that the 10-valent vaccine will be licensed by 2008. (This vaccine includes the same serotypes as the 7-valent plus serotypes 1, 5, and 7F, which are important in developing countries). To be

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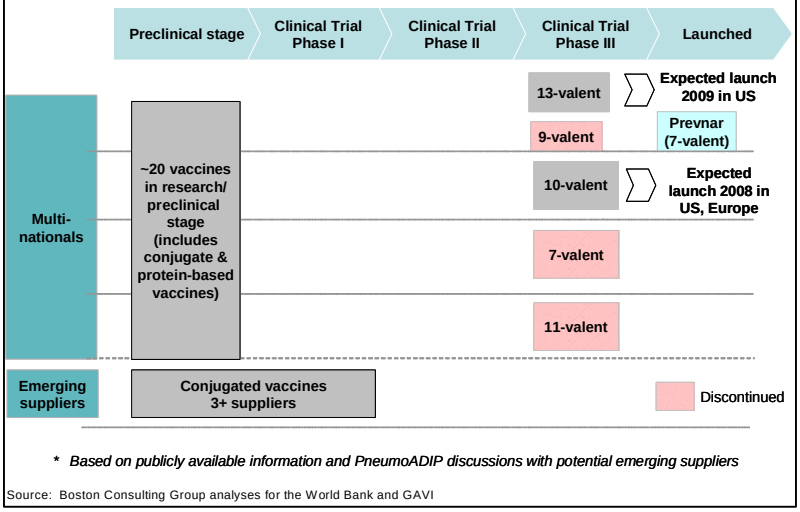
[20] Brooks WA, Santosham M, *et.al.* Effects of weekly zinc supplements on incidence of pneumonia and diarrhea in children under 2 years in an urban, low-income population in Bangladesh: Randomized controlled trial. Lancet 2005; 366:99

[21] GlaxoSmithKline website http://www.gsk.com/investors/product_pipeline/docs/pipeline.pdf

conservative, PneumoADIP, a public-private partnership for pneumococcal vaccine introduction, has predicted developing country access by 2010 but it could be as early as 2009. Wyeth's website indicates that they are in development of a 13-valent candidate and that they have stated publicly that they expect to launch that vaccine in late 2009. The 13-valent vaccine includes all the serotypes in the 10-valent vaccine plus three additional important serotypes. They plan to replace the 7-valent vaccine with the 13-valent vaccine. Thus, it seems likely that by 2010, there will be a 10-valent and a 13-valent vaccine available, and that each one will meet the needs of developing countries.

Between 2015 and 2019, several additional vaccines and manufacturers are possible. Several emerging market manufacturers are currently working on pneumococcal conjugate vaccines. Beyond conjugates, there are efforts underway to develop a "common protein" pneumococcal vaccine. The idea is that this kind of vaccine would protect against all serotypes of pneumococcal disease. Based on their current status, a successful emerging market manufacturer or protein vaccine candidate is likely to come to market between 2015 and 2019. Currently, there is about $85M of "push" funding available to accelerate the development of these products.

Figure 2. Current pipeline of potential pneumococcal vaccines



Source: Boston Consulting Group analyses for the World Bank and GAVI

Commercial, not scientific, hurdles are the largest obstacle to assuring a sustainable, affordable vaccine supply. Analyses by Mercer Management Consulting on behalf of PneumoADIP indicate that the costs of manufacturing (COGS) are not an obstacle to affordable pricing. Improvements in manufacturing efficiencies and/or reductions in labor rates have the potential to keep cost of goods low enough to support prices affordable for developing countries in the long term.

VII. Demand for pneumococcal vaccines

Demand for pneumococcal vaccines in developing countries is conditional on predictable and sustainable donor support and pricing. Extensive discussions by GAVI partners with decision-makers in developing countries indicate that, with acceptable financing and pricing terms, there is substantial latent demand for pneumococcal vaccines.

For example, in 2002, at the request of GAVI and the World Bank, McKinsey & Co. interviewed Health and Finance Ministers from a broad range of GAVI eligible countries. Representatives from Kenya, Tanzania, Ghana, Malawi, Rwanda, and Mozambique all acknowledged pneumococcal disease as a major problem and highlighted pneumococcal vaccines as a potential priority vaccine. More recently, Dr. Raj Bhan, Secretary for Science and Technology, Government of India, said on the BBC that "Pneumococcal vaccine is the no. 1 priority for introduction in India".

Developing country demand is primarily driven by strong awareness of the following:

- The burden of pneumonia and the severity of bacterial meningitis in their countries. This is especially true in sub-Saharan Africa and high mortality areas of Asia where research and surveillance consistently find the highest rates of disease and mortality.
- Clinical trial results showing 16% reduction in child mortality rates and protection of HIV-infected children.
- Herd immunity effects with the 7-valent vaccine in the USA and elsewhere.

VIII. Expected impact in countries.

Based on historical experience with Hib and hepatitis B vaccines, we can expect that if there is no AMC or other effort to finance the accelerated development, production scale-up and introduction of pneumococcal vaccines in GAVI-eligible countries essentially no pneumococcal vaccines will reach the world's poorest countries before about 2020. Global supply will be limited to the demand from high and middle-income countries, keeping prices relatively high and constraining access in GAVI eligible countries.

Chapter 3
AMC Market Analysis for Pneumococcal Pilot

I. Objectives

The success of the AMC pilot for pneumococcal vaccines will be measured in two ways: first, its ability to influence vaccine firms to accelerate and increase investments in the late stage development and capacity scale-up of pneumococcal vaccines; and second, its ability to negotiate more predictable and sustainable prices and supply of vaccine over the long term. In addition to these overarching goals, stakeholders have noted that the AMC should foster competition, should encourage innovation, should engage emerging as well as multinational manufacturers and, of course, should be an efficient use of donor funds.

To set appropriate AMC terms that are likely to influence industry's investments in ways that will achieve the AMC's objectives– but that also use donor funds efficiently (e.g. avoiding "windfalls" to pharmaceutical firms), it is necessary to understand how industry will likely evaluate the AMC proposal. The AMC terms that will be set by the donors include the market size, and price per dose or intervention, and based on these, the expected duration of the AMC. To support donors in their understanding, the World Bank commissioned Applied Strategies, a life-sciences strategy consulting firm, to develop a transparent model that offers insight into how an AMC might be valued by industry.

II. Methodology

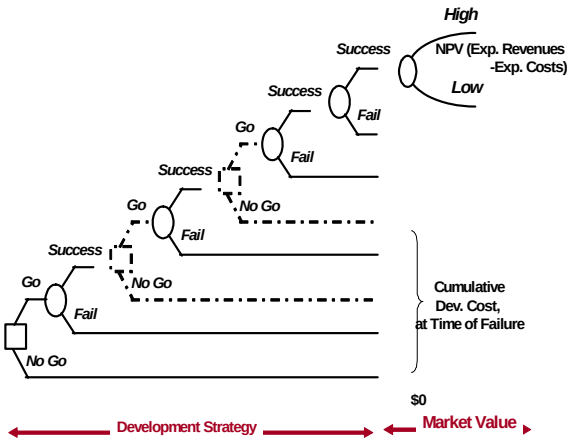
The model is based on valuation methodology commonly used by the industry to compare returns across alternative investments and with the cost of capital. If the investment under review has a positive return then it is prioritized, if not, it is more closely examined and may be dropped. The valuation methodology:

- Identifies and addresses the timing and risks of each development investment based on the scientific knowledge and likelihood of success;
- Assesses the cost of product development, manufacturing and commercialization for the target market (in this case the poorest developing countries) that is not covered by public funding (in the case of this model, only investments financed by the private sector are taken into account);
- Analyzes numerous product profiles and commercial market scenarios at every stage of development, including the likelihood and impact of competition;
- Compares each investment decision to other opportunities and the cost of capital;
- Translates estimates of investment, cost and return into expected cash flows over time (in net present value terms) and (given the inherent uncertainty of whether a candidate will succeed at each stage of development) adjusts this

cash flow for risk, (meaning the probabilities of success and failure). However, the financial return on certain life saving products may be bolstered by intangible value associated with being socially responsible.

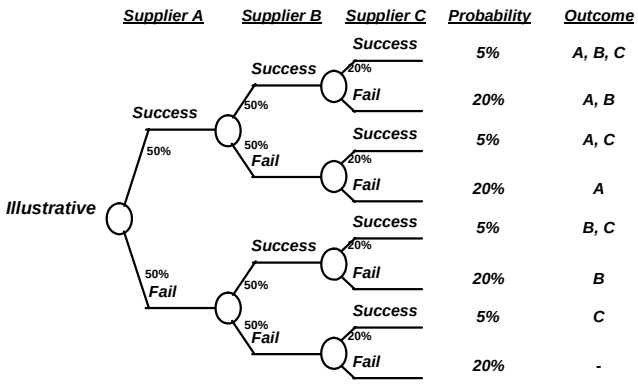
Like other investment opportunities, each supplier will evaluate an AMC based on the information available at the time of the current decision as shown in the "Go/No Go" schematic in Figure 1. The AMC modeling works on the same principle, estimating the AMC size required to provide firms with a neutral or positive return for pneumococcal vaccines. Different scenarios were run to estimate how large the AMC needed to be to meet different objectives including encouraging competition, innovation and investment in adequate capacity to serve the poorest developing countries

Figure 1: Suppliers make a Go/No Go decision at each development step based on forward looking analysis.



This Go/No Go decision tree in Figure 1, only captures part of the firm's analyses as it looks only at the probabilities of the one firm developing a product that makes it all the way to the market. Firms must then overlay a second analysis which looks at the likelihood of competitors developing a successful product which will compete for market share. Given the goal to have the AMC encourage competition and continued innovation, the analyses also need to consider the number of firms likely to develop a product within a reasonable AMC duration (e.g. 7-11 years) so that the AMC might be sized to support more than one firm.

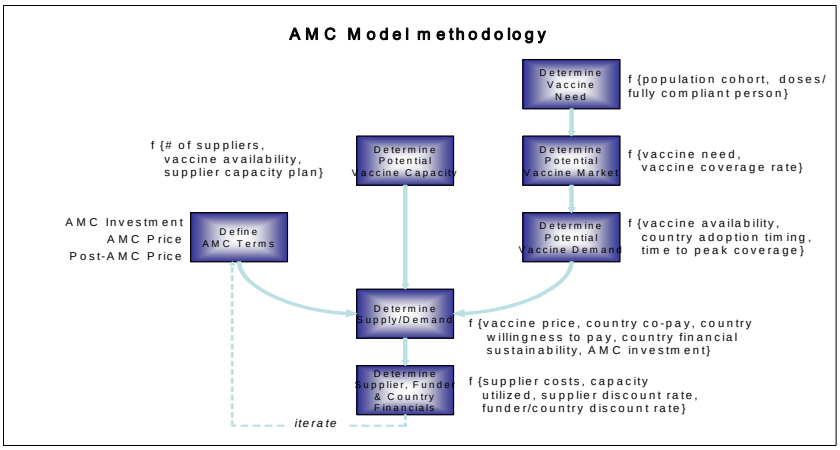
Figure 2: The AMC model is designed to explore the level of AMC funding required to provide a neutral or better return on investment given multiple supplier outcomes



Like all models, this one only offers insight into whether the AMC provides adequate economic incentives to motivate desired investments. It does not reflect other intangible motivations such as a firm's desire to be a good corporate citizen or to be

affiliated with the researchers who crack the science for a killer disease. These intangibles may provide additional motivations for firms to engage in the AMC.

The model builds on data that are critical to firms' likely response to an AMC, focusing on the demand forecast for pneumococcal vaccines, policy decisions like the likely co-pay required of governments both during and following the AMC, financial terms like the cost of capital or opportunity cost of using capital and the supply side (taking into account specific investments by firm, status of development and probabilities of success/failure, estimated cost of goods, and timing and amount of capacity). The data requirements and assumptions are outlined in more detail below. Most of the assumptions were developed by the PneumoADIP in consultation with technical experts. Building on these assumptions, the model then tests how different AMC terms (market sizes and prices) would affect both a firm's likely return and their risk-adjusted net present value return to estimate at what AMC size and price each firm can "stay whole" or make a neutral or better risk-adjusted return on its investment. The model used an opportunity cost of capital of 10% commonly used by the vaccine firms.

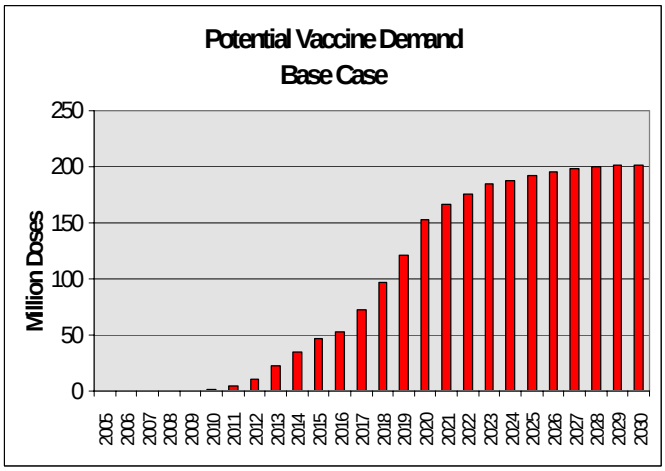


III. AMC Model inputs

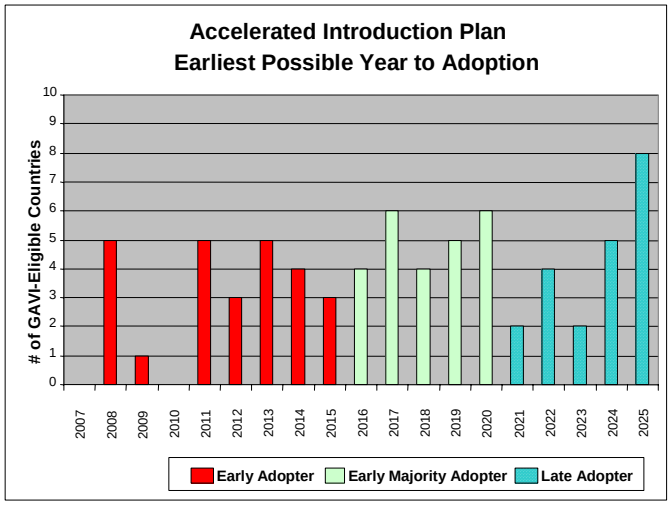
Concerns have been raised that poor information, compared to what is available to manufacturers themselves, will undermine public sector attempts to value an AMC. While there is uncertainty and asymmetric information, experience has shown that reasonably robust estimates of the critical inputs are available through data collection and analysis. For example, solid industry benchmarks exist for the time, cost and probability of success at each stage of vaccine development. These benchmarks can then be modified based on additional information on what each firm is doing. Indications of the costs of goods sold (COGS) by firm are also available in reasonable detail given that pneumococcal vaccines use a known technology

Concerns have also been raised about how AMCs will affect Intellectual Property Rights. The AMC is designed specifically to address a failure in market incentives – namely the lack of predictable and sufficient resources in developing countries to ensure a return on investments. For an AMC to be successful it should not –and does not—alter IP issues, as this would reduce predictability. In addition, the intellectual property issues around biologicals like vaccines are very different from

pharmaceutical products. "Copying" vaccines is more difficult and costly than in the case of drugs because the ability to reproduce a production process depends more on experience and tacit knowledge (for example, to assure batch consistency) than on information revealed in the patent application. In the case of pneumococcal vaccines it is worth emphasizing that these vaccines cannot be patented as a biological, though parts of the production process may be and that at least one conjugation technology, a necessary part of the production process, already exists in the public domain



- *Demand forecasting* – Reliable estimates of country demand that accurately predict uptake of a new vaccine are the basis on which industry estimates market size. Forecasts vary from disease to disease and are based on the timing of uptake (year of introduction) and volume (a function of the target population and the expected coverage levels). The model uses demand forecasts for the 72 poorest developing countries currently eligible for GAVI funding. If the forecasts are inaccurate – for example, assuming a more rapid uptake by countries than actually materializes – a vaccine firm will not receive revenues, and will be left with inventory that typically expires after 24 months. To date, forecasts of new vaccine uptake in developing countries have been quite inaccurate. This contributes to industry's unwillingness to invest in these unpredictable markets. Forecasting is difficult especially as optimistic thinking about what "should" occur has, at times, shaped forecasts more than actual country input or historical fact.



Extensive work has gone into developing a reasonable and transparent pneumococcal demand forecast based on conservative estimates of when countries are likely to consider introduction given such variables as the strength of the national immunization program and the priority of pneumococcal disease in the country. The majority of "early adopters" of pneumococcal vaccine are expected to be in countries in Africa and Asia where there is a high, well-

recognized burden of disease, moderate to strong immunization systems, and a historical willingness to uptake new vaccines. These estimates have been vetted by public health experts, industry and countries and will be continually refined as additional information is received.

Potential barriers to scaling up at the country level that were taken into consideration in the forecasting include lack of disease awareness, programmatic constraints that limit uptake of the vaccine as a separate injection, inability to sustain the financing in constrained health budgets, and political instability. Competing priorities in the early introduction years will include rotavirus, and to a lesser extent, Japanese encephalitis and malaria vaccines which share the same target population (birth cohorts) but are geographically concentrated into fewer countries. HPV vaccines will also likely become available during this period, albeit for young women, and may also impact demand.

It is extremely important to recognize that this while this forecast was developed based on the best available information, there is still risk that countries will not introduce pneumococcal vaccines on the timetable or in the amounts anticipated. This creates significant demand risk for each firm. While the AMC mitigates the financial/market risk that the poorest developing countries will not be able to pay a reasonable price to purchase vaccines that are a priority for their national health program, it does not guarantee demand or purchase. Strategies in parallel to the AMC that will mitigate demand risk must balance the importance of strengthening weak systems and poor forecasting processes, with the need to create incentives in the public sector for better forecasting while also maintaining a level of "normal" market risk associated with product introduction. The range of activities suggested for implementation by GAVI and its partners are outlined later in this paper.

Although forecasting techniques are improving most notably through greater efforts to provide national decision makers with evidence for a timely decision, they have historically been quite weak. The cost of poor forecasting is felt primarily by the vaccine firms who are left with expiring vaccine stocks or underutilized production facilities – both costly. Obviously, the public sector should not guarantee a firm that its vaccine stocks will be purchased regardless of demand or price. However, given the current level of demand risk, there is a need to invest in activities to improve the quality and timeliness of pneumococcal vaccine demand forecasts in parallel with the AMC. These types of activities are complementary to the AMC.

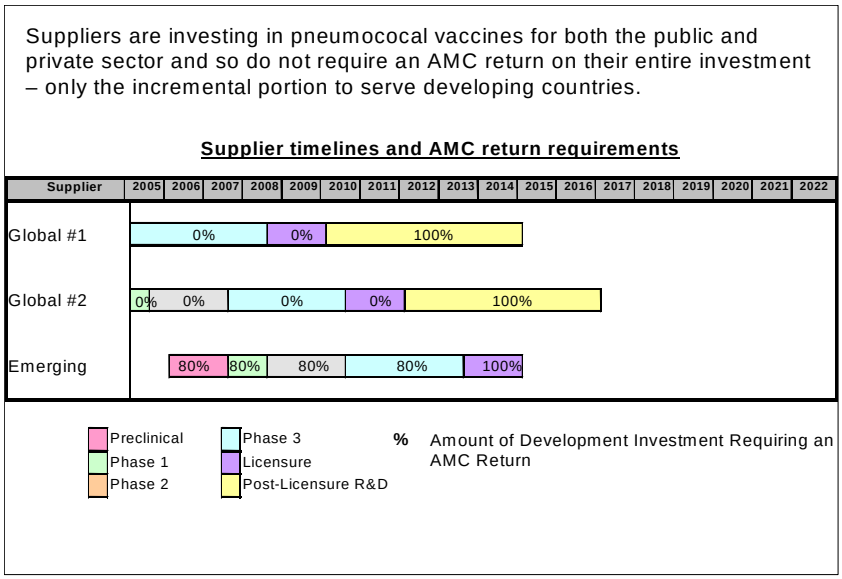
As part of its activities to accelerate access to vaccines and to strengthen immunization, GAVI and a variety of donors and technical partners have proposed to further increase investments to strengthen vaccine introduction. In the case of GAVI, activities such as the following are either already underway or will be evaluated and potentially implemented by GAVI and its partners including WHO, UNICEF, the PneumoADIP and others.

- Complementary funding to strengthen national delivery systems;
- PneumoADIP and others to aid governments to make timely, evidence-based decisions on pneumococcal vaccine introduction;
- GAVI and partners improving the transparency of forecasting systems;
- GAVI and partners improving the accuracy of forecasting through analysis to understand bottlenecks;
- Explore mechanisms such as Letters of Intent to allow governments to indicate their interest in a new vaccine in a more timely fashion;
- Explore public sector providing a take/or pay guarantee for a small amount of initial volume to share the demand risk.

Although not under the control of the AMC, the credibility and accuracy of demand forecasts will have an impact on the success of the AMC. Donors may wish to monitor efforts in this area and support efforts through GAVI and others to address these issues.

- *Status of development and capacity* – The level of scientific knowledge, the stage of development of a vaccine candidate, and predictions of whether it is likely to move successfully through each stage of the development process affects the amount and timing of investment and future revenues. Capacity decisions also are very expensive with long lead times due to the time to build, validate and obtain regulatory approval for a production facility. Pneumococcal vaccines are based on a known technology and are at a late stage of development, thus reducing the risk that unexpected technological problems will occur. Two firms have already invested in a vaccine with the primary goal of supplying industrial country markets. The AMC market size would compensate for investment dedicated to the developing world but not provide a return on investment in assets to serve the industrial country market. In addition, it is likely that an emerging country supplier will successfully develop and scale-up a pneumococcal vaccine for developing countries in the lifetime of the AMC. Thus the AMC is also sized to be attractive to a late entry emerging supplier, able to provide a return on their full costs of development and scale-up.

The AMC terms were explored to provide a return on, first, a small amount of incremental investment in studies to provide evidence of the efficacy of the vaccine in different parts of the world (such as South Asia) and, second, significant investment in incremental production capacity to serve the developing world demand.



- *Cost of goods* (COGs) – The COGs or costs of production have a tremendous impact on a firm's expected return at a given price. However, these costs cannot be known until late in the development process (once there is proof of product). The technology used to make pneumococcal vaccines is well known and costs for individual firms can be estimated with a fairly high degree of accuracy. Ultimately, the COGs will determine whether the firm will lose or gain at the AMC guaranteed price and in the post-AMC supply and price agreement. The higher the COGs, the less attractive a low AMC price becomes, up to the point where the AMC would need to be re-evaluated and possibly increased. Some of the likely pneumococcal vaccine suppliers will have low costs of goods to begin with but for those who do not, another impact of an AMC may be to motivate suppliers to make the process improvements and/or partnership deals needed to bring costs of goods in line with these prices.

- *Competition* – Although the vaccine industry is highly concentrated with 5 firms responsible for over 80% of the market, both the donors and vaccine firms believe the AMC should be structured to promote competition. The model takes into consideration that the AMC market will be split between two or more firms and so must provide each with an adequate return given its investments.

  The AMC must be large enough to support multiple suppliers to develop and produce the vaccine in order to increase competition and increase the likelihood of long-term sustainable supply at more affordable prices. Given that a proven technology exists for pneumococcal vaccines and that two manufacturers are already in late-stage development, it is likely that two and possibly three firms would enter into AMC arrangements. As such, different scenarios were run to

determine the AMC size and price needed to provide a return for a first, second and third firm to market. An AMC with a high price would provide significant returns to the first firm to enter an AMC agreement but would be depleted too quickly for 2nd and 3rd firms to enter the market. A more moderate price allowed the AMC to exist for 9-10 years, thus providing more time for firms to develop the vaccine, establish capacity and benefit from the AMC.

IV. Sensitivity Analyses

Several sensitivity analyses were run on the AMC market size and price estimates to identify the most robust AMC terms given natural uncertainty about the future. The scenarios including exploring what if demand was slower than estimates (1-3 year delays), what if COGs were higher than estimated, what if vaccines came to the market 2 years later than predicted etc. Based on these analyses, the recommended AMC terms are believed to be robust even if some of the assumptions prove to be optimistic.

Importantly, industry re-evaluates the market and its potential return before making each new investment as more accurate data on the product and market become available. Similarly, the AMC must also be periodically re-evaluated to determine if initial estimates on what constitute an adequate size and price continue to hold true. While the AMC recommendations are robust, if three or four assumptions prove to be inaccurate, the AMC may not provide adequate incentives to obtain the desired investments across three different firms.

V. Recommended AMC terms

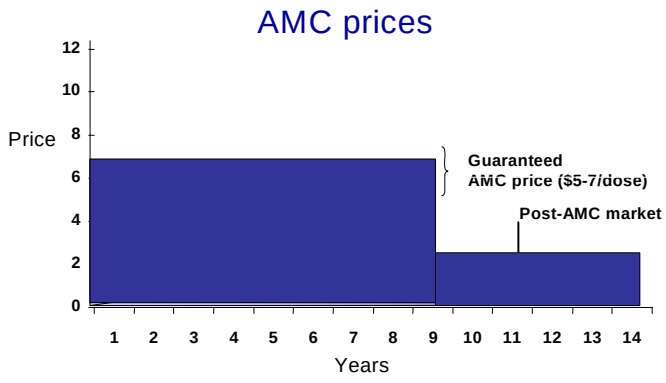
As outlined above, the status of pneumococcal vaccines that was modeled can be summarized as follows. Investments to develop and produce pneumococcal vaccines have been stimulated to date, by large potential markets in high and middle-income countries (estimated at $5-6 billion). Serving low-income countries requires additional investments in late-stage development and production capacity and a willingness to provide predictable long-term prices. The pneumococcal vaccine pipeline includes one licensed product and more than 20 candidate vaccines in varying stages of development. The licensed vaccine has safely and effectively vaccinated more than 30 million children in industrial countries. Capacity is, however, inadequate and the vaccine is not being considered suitable for widespread introduction in developing countries. Two vaccines that extend protection for populations in both developing and industrial countries by adding more serotypes may be licensed by 2010. Other vaccines, including from emerging manufacturers may come to the market in the following 5-10 years.

Assuming the IAC establishes the pneumococcal Target Product Profile (TPP) as expected to attract conjugate vaccines with efficacy in the range provided by the 10 and 13 valent candidates, the recommended size of the donor contribution to the AMC is $1.5 billion in nominal terms with an NPV cost of $860 million. The price per dose is to be determined but is estimated to be within the range of $5-7 per dose with developing countries responsible for an affordable co-payment per dose of roughly $1. The first payments are anticipated to begin in 2010 and last for 9-10 years. Once the AMC is depleted each participating firm will continue to supply the vaccine at a pre-determined low price for an established period. The success of the AMC does not depend on this exact 'business case': it is robust to variations of number of suppliers, country demand and product timing. This AMC market amount would support the first 3 firms to come to the market with a pneumococcal vaccine, all the firms would have a neutral or positive risk-adjusted NPV.

VI. Post-AMC pneumococcal vaccine supply and price

The objective of the AMC is both to allow firms to recoup a return on investment to develop and supply pneumococcal vaccines to the poorest countries and to ensure donor funds are only used if results are achieved. The post-AMC supply and price of pneumococcal vaccines is as or more important as the availability of the vaccine during the AMC. A balance is needed between the short and long term objectives of donors, developing country governments and industry.

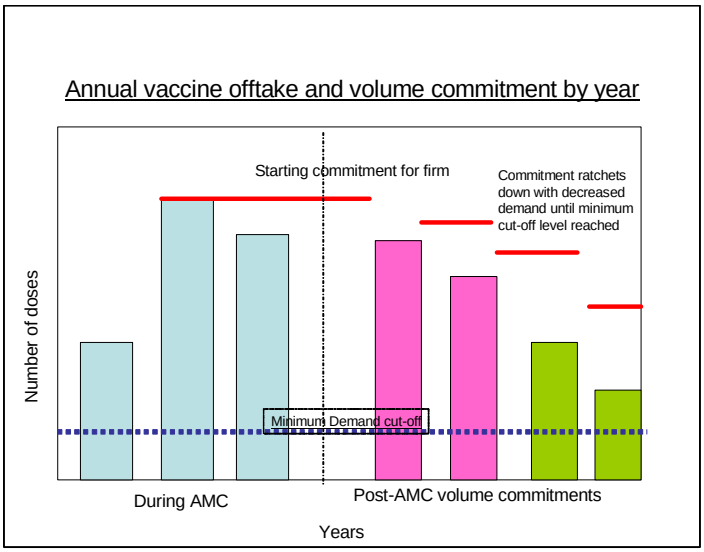
The AMC would guarantee, in advance a reasonable price for the vaccine. The donor subsidy would offset the small country co-pay and would ensure industry could make a return on investment – if they develop and supply the product.



- Donors require assurances that firms will continue to supply the vaccine at affordable prices following their guaranteed AMC funding.
- Countries require predictable pricing and reliable supply to ensure that their initial decision to introduce the vaccine is sustained once the AMC is depleted.
- Finally, firms require prices that cover their costs, continued reliable demand and time limited contractual obligations.

To balance all of these valid objectives, the post-AMC price and supply are factored into the AMC negotiations. To assure predictability, firms will be required to commit to a post-AMC price at the time that their vaccine is accepted for AMC funding and they sign the Supply Agreement. To allow firms to ensure the economic viability of

their long term price, each firm will have the freedom to set its post-AMC price, however, this price also will be used to determine the co-pay of countries during the AMC. Market forces are thus used to balance industry pricing – firms will wish to set post-AMC prices as high as possible to cover costs and make a return, however, higher prices will translate into higher co-pays for countries which if they are too high will result in lower demand. Firms are thus forced to balance the impact their post-AMC pricing has on demand during the AMC.



To assure reliable supply, firms will be required to commit to supply with specific exit conditions including volume commitments tied to previous years demand (rolling 2-year average), and conditional exit options (such as 4-5 years notice before exit, sunset of the AMC agreement at an established time (e.g. 10 years after the depletion of the AMC). The following graphic illustrates the on-going volume commitment of firm and its link to actual offtake.

VII. Impact of a Pneumococcal AMC

Pneumococcal vaccines are in late stage development, but without an AMC, it is unlikely that manufacturers will invest in capacity or test pneumococcal vaccines for the poorest developing countries. It is also highly unlikely that countries will have an affordable or sustainable price or a reliable supply on the basis of which governments can make sound and committed introduction decisions. Based on historical experience, in the absence of an AMC or other financial effort, no pneumococcal vaccines will reach the world's poorest countries before about 2020.

The additional outputs that an AMC for pneumococcal vaccines can be expected to motivate include:

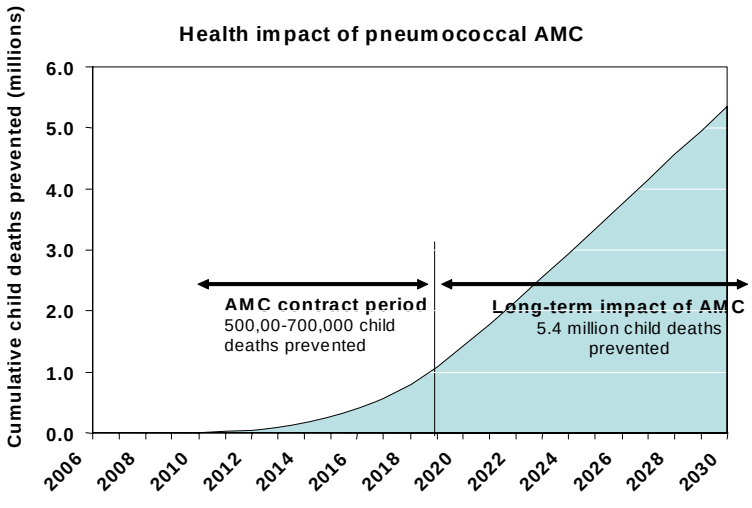
- Investments by two to three multinational vaccine manufacturers in plant capacity to meet the gradually increasing demand from the low-income countries, which is anticipated to ramp-up beginning in 2012;

- Accelerated introduction of pneumococcal vaccines in a group of early adopter countries by 2010. Historically, delays of 15 years have been seen, which would mean that, without an AMC and supporting activities, pneumococcal vaccines would not even begin to be introduced before 2020.

- At least one emerging vaccine manufacturer to take a product from early research and development through to product licensure in the next 10 years.
- Competition among manufacturers for the developing country market.
- Investment in new technologies for new and more efficient vaccine production and second generation technologies (e.g., protein vaccines) focused for developing country markets.
- Two to three manufacturers to provide countries with an early post-AMC price that is predictable, affordable and sustainable.

Overall, the AMC will contribute to the immunization of 70-100 million infants over the life of the AMC. This will prevent between 500,000-700,000 deaths during the AMC itself. However, the impact of the AMC goes beyond the contract period as it assures a long-term sustainable supply and price. The impact also goes beyond the children immunized, as herd immunity will act as a multiplier, expanding the benefits of immunization to the un-immunized and older populations.

Figure 3. Potential deaths prevented by accelerating the adoption of pneumococcal vaccines into developing countries



Chapter 4
AMC Governance and Institutional Support

I. Introduction

The Pneumococcal AMC Pilot will be established and implemented over a 13-year period from 2007 to 2020, moving through several different phases in the project's life. To best support the AMC, the functions will be split between two institutions, GAVI and the World Bank, each with a unique capacity to address the evolving programmatic and financial requirements of the AMC. Similarly, as the project evolves so will the role of donors and other stakeholders. To launch the AMC pilot, donors will need to agree on the appropriate terms and processes to achieve the AMC objectives. The target outcomes, systems and procedures established at the pilot's inception, must ensure independence and credibility of AMC implementation, underpinned by transparent reporting, and accountability to all parties. The success of the AMC depends on the absolute understanding by all stakeholders that once agreed, the AMC terms and procedures will be respected, implying great attention to transparent monitoring during the implementation years.

This paper describes the AMC process in detail, explaining how a pilot will work. It outlines the four stages of the AMC's life as well as the evolving roles of the key actors. Throughout all of these stages, the credibility of the AMC pilot and transparency of its results will depend in part on good reporting and appropriate governance.

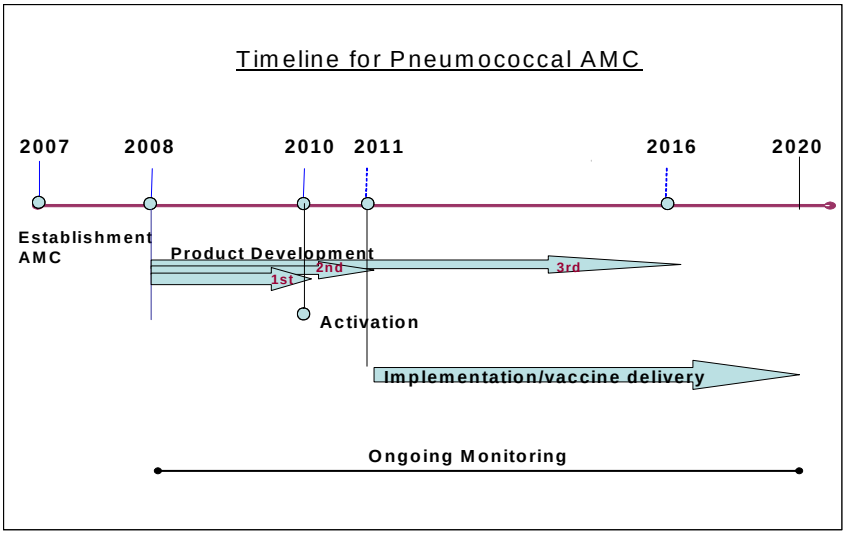
(5) **Establishment**. The initial setting-up phase will put in place the arrangements underpinning the AMC. This will include negotiations, by and between donors, the host institution/s and industry. These negotiations will result in the Framework and Supply Agreements that provide for a specific level of funding at a specific price for pneumococcal vaccines meeting the specified Target Product Profile (TPP). The Framework will also specify the procedures and monitoring that will be followed as the AMC is implemented.

(6) **Product Development**. Once the framework agreement is signed, an interim period will follow in which the key institutional requirement will be to monitor and report on the firm's activities and investments to accelerate the development and scale-up of pneumococcal vaccines to meet the AMC goals.

(7) **Activation**. The AMC is triggered when a specific manufacturer first produces a target vaccine that is determined to meet the TPP. The manufacturer then enters into a Guarantee and Supply Agreement under the framework agreement.

(8) **Implementation**. Once the Guarantee and Supply Agreement is signed, the transactions associated with the procurement and delivery of vaccines to countries and the payment to industry will be supported. Institutional

responsibilities focus on efficient and timely management of these transactions.



There are seven key actors responsible for supporting, governing and drawing on the AMC throughout the stages of its life.

GAVI and The World Bank would be the two entities directly responsible for supporting the programmatic and financial functions of the AMC based on their relative strengths.

- **The GAVI** Alliance is a public-private partnership focused on accelerating access to priority new vaccines. It has established processes and a credible track record in supporting the 72 poorest countries with new vaccines and funds to strengthen national immunization programs, including to support the forecasting and introduction of new vaccines such as pneumococcal vaccines. GAVI has strong links with all the stakeholders in the immunization community including governments, donors, industry, and technical partners. The Executive Committee of the GAVI Board has indicated its commitment to host the AMC Secretariat and support the programmatic and operational functions for the AMC Pneumococcal pilot.

- **The World Bank** has the recognized financial and administrative capacity to support the establishment of a variety of donor commitments and payment structures. Assuming appropriate internal approvals are obtained, the World Bank would be responsible for providing administrative and financial services to the AMC, drawing on its established capacity for financial management, and contractual and administrative services. The World Bank will support donors in evaluating and implementing an effective mechanism for bundling donor commitments into a single, credible instrument for the full AMC amount.

In addition to the two primary implementing entities, the following stakeholders will be critical in the implementation and success of an AMC:

- **Donors** are responsible for assuring credible funding including financing the cost to bundle the varied commitments into a single commitment. Donors are also

responsible for establishing the appropriate policies and processes ex ante to guide AMC implementation across the different phases. A **Donor Committee** will be established to allow AMC sponsors to efficiently provide input into the technical design and processes for the AMC during the establishment phase and to monitor implementation and progress toward the AMC's objectives.

- All **vaccine, pharmaceutical and biotech firms** are eligible to participate in the AMC. They will be party to the negotiations on the Framework and Supply Agreements to ensure processes are viewed as adequately independent and credible. Ultimately, each firm will be responsible for evaluating the AMC and determining their own investments in a pneumococcal vaccine to serve the target AMC countries.

- **Developing countries** have responsibility for making timely, evidence-based decisions on whether introducing pneumococcal vaccines is a priority for the national health program. Developing country governments can then apply for the vaccine through the established GAVI process of national applications and requests.

  Technical agencies such as WHO and UNICEF are implementing partners of the GAVI Alliance who will ensure delivery of vaccine in country and that the AMC is integrated within existing processes as much as possible. As detailed in the IAC section below, WHO also will support the IAC by convening an expert group to recommend a TPP for pneumococcal vaccines. Furthermore, the evaluation of a given product will be done in collaboration with WHO's pre-qualification process. UNICEF is a core GAVI partner, with offices in each of the 72 GAVI-eligible countries. In addition to acting as the current procurement agent for GAVI it is also critical in ensuring a range of in-country activities that help support demand forecasting and delivery of vaccines to the population.

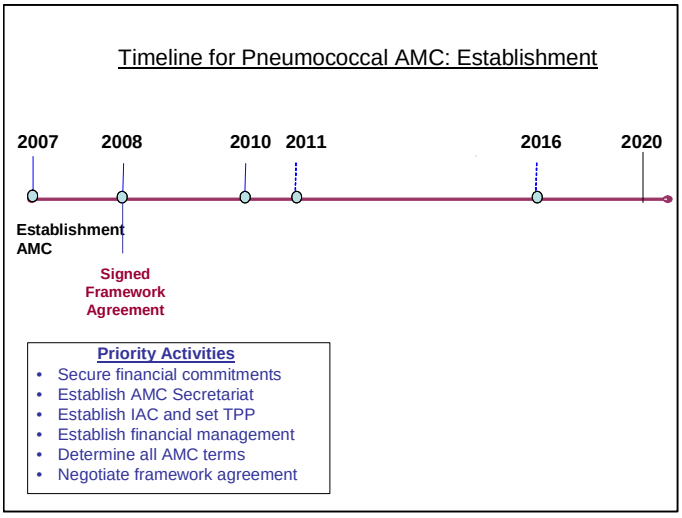
- The **Independent Assessment Committee (IAC),** detailed at the end of the paper, is the cornerstone of the proposed AMC. The IAC will oversee core parts of the AMC process, including the establishment of Target Product Profiles (TPPs) for candidate vaccines and ascertaining whether they are met. The credibility of AMCs rests largely on the perception of industry, donors and developing country governments about the independence, fairness and reliability of the IAC.

The evolving institutional support from GAVI and the World Bank and governing role of donors is mapped in detail for the four stages of the AMC life. This paper closes with a detailed review of the technical lynchpin of the AMC --- the IAC which is responsible for establishing the AMC product standards and vetting when a product meets them and is eligible for AMC funding.

II. AMC Project stages

Establishment. Setting in place the technical, procedural, legal and financial arrangements that will underpin the AMC will be a negotiation that will culminate in the signing of the AMC Framework Agreement and Supply Agreement. Negotiations will provide for a specific level of funding at a specific price for a vaccine meeting specified TPPs. During this phase, a number of processes will go on in parallel allowing the creation of the IAC, TPP and Secretariat functions while the framework agreement is being negotiated. The Framework Agreement will codify the agreed terms, processes and roles and responsibilities.

- **Providing secure financial commitments, and ensuring that they are credible to industry**: The World Bank will work with donors as requested to support them in structuring financial commitments that are at the same time consistent with national budgetary requirements, acceptable to industry, and responsive to the necessary flexibility in timing of disbursements which characterizes the AMC structure. Once donors have determined the amount and structure of their financial commitments, the World Bank will work with the Donor Committee to determine the optimal financial arrangements to bundle donor commitments into a single commitment credible to industry.



- **Supporting the administrative structure/AMC secretariat**: The AMC Secretariat will be the focal point for ensuring all of the various start-up activities are effectively coordinated. GAVI proposes to hire two staff to the AMC Secretariat to directly support the stakeholders in establishing the AMC. These staff will be responsible for circulating information, responding to comments, and implementing agreed procedures.

- **Establishing the IAC:** The World Bank and GAVI, as the AMC hosts, will be responsible for outlining and implementing the process to identify the IAC members. A widespread call for nominations will be made and donors will be encouraged to submit names. A short list of nominees will be developed by a small independent panel appointed by the GAVI Executive Secretary and the World Bank with input from stakeholders including donors, developing countries, technical agencies and industry. The final shortlist will be approved by the GAVI Alliance Board and presented to the Donor Committee. This is outlined in more detail in the IAC section of this paper.

- **Creating the TPP**: The IAC has the responsibility for developing the TPP for pneumococcal vaccines. As detailed later in the paper, the IAC would request WHO to convene an expert advisory group to develop a TPP for its review. This process builds on existing capacity in WHO and is designed to be credible to all parties. The AMC Secretariat in GAVI would provide the day-to-day support to implement the steps.

- **Finalizing key financial terms on price and market size**: The IAC is responsible for reviewing the recommended AMC financial terms once the TPP is established. The IAC will request the AMC Secretariat to convene the necessary experts if additional input is required.

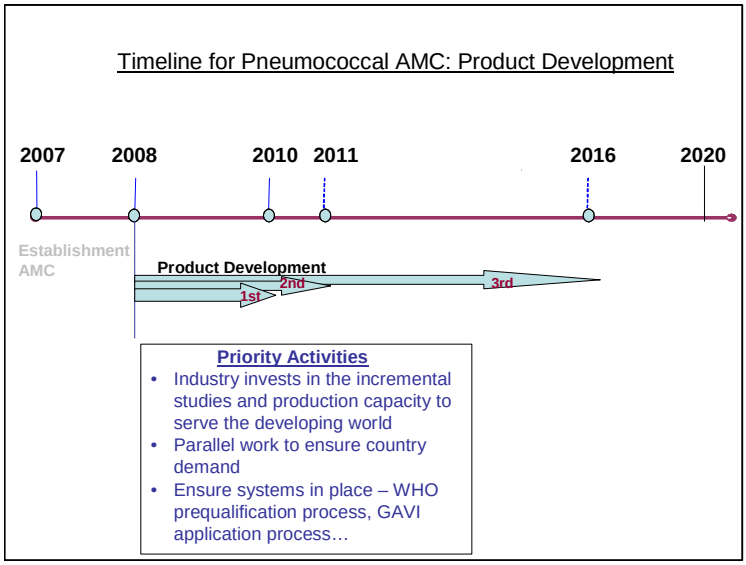
- **Establishing financial management arrangements**: The World Bank and Donor Committee will agree on the systems and procedures to ensure that specific donor payments and flows are managed efficiently and support AMC payments under eligible guarantee and supply agreements.

- **Negotiating the Framework Agreement**: The World Bank and GAVI would be responsible for working with all stakeholders to draft the Framework Agreement. The World Bank, in particular will draw on its legal staff and may require specialized external counsel. The negotiation process will provide stakeholders with the opportunity to review and comment on the detailed AMC policies, processes and data that will be codified in the Framework Agreement.

Product Development. Once the framework agreement is signed, an interim period will follow in which the key institutional requirement will be to monitor progress toward the AMC goals. Institutionally, what will be important during this period will be the confidence of all parties in the capacity of GAVI and the IAC to be diligent in:

- **Tracking and reporting AMC progress**: Annual progress reports will be prepared and provided to the donors through annual meetings. These reports will be based on each firm's activity report and will allow donors to track progress to developing AMC-credible vaccines including the product pipeline, current stage of development and anticipated licensing dates, WHO pre-qualification and availability to countries.

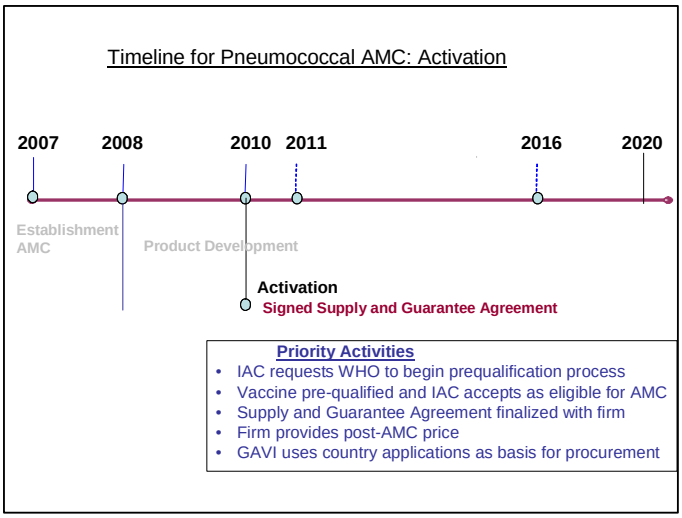
- **Supporting ongoing work to ensure country demand:** Given the need to continue efforts to improve the accuracy of demand forecasts, it is imperative that a range of parallel activities be implemented to ensure countries have the evidence to make timely decisions on vaccine introduction into national programs. This will require ensuring critical data (disease burden, vaccine efficacy etc) are available, collecting and aggregating national and sub-national vaccine demand information, and improving the quality, timeliness and transparency of the global demand forecasting. This work is being incorporated into GAVI's strategic work plan which will be funded by existing GAVI resources and will be carried out by lead technical partners such as the PneumoADIP, WHO, and UNICEF.



- **Activating the AMC at the appropriate time:** Systems must be primed to efficiently respond once a firm submits a vaccine they believe will meet the TPP requirements. Tracking and reporting on progress will help to provide some advance warning of when a product is likely to be submitted for evaluation. However, as the IAC will depend on the WHO pre-qualification process to assess the vaccine's eligibility for AMC funding, it will be imperative that this system have the capacity to immediately begin the pre-qualification process the moment the vaccine is submitted. Similarly, GAVI will ensure that countries have the necessary guidelines to submit applications for pneumococcal vaccine introduction in a timely way. Activities to prepare countries for application including inviting submission of letters of intent will also be explored.

Activation. The AMC is triggered when a specific manufacturer first produces a target vaccine that meets the TPPs. The manufacturer then enters into a Guarantee and Supply Agreement under the framework agreement. Institutional functions will include:

- **Supporting the IAC and its process of assessing whether the candidate vaccine meets the TPPs:** The process to assess a vaccine against the TPP will be based on existing regulatory oversight and WHO's pre-qualification system. This process is outlined in detail in the section on the IAC.

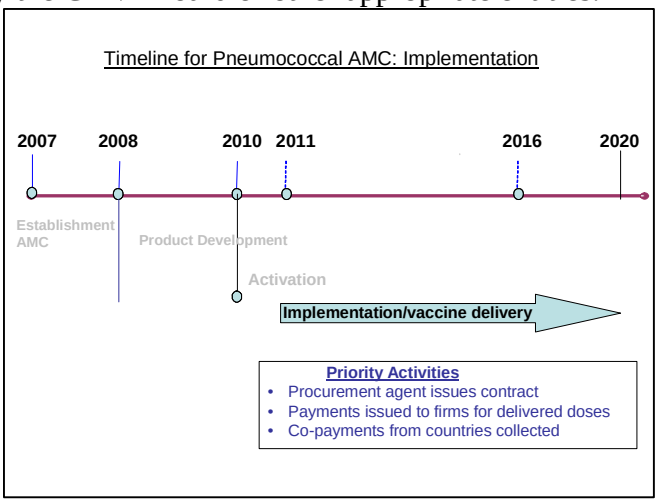


- **Finalizing the Supply and Guarantee Agreement with the manufacturer**: The Supply Agreement will have been outlined as part of the initial Framework Agreement, however, additional specificity will be outlined in the Supply Agreement. This Agreement will become the legal contract for a firm to supply the given vaccine at the agreed AMC price and the post-AMC price specified by the firm.

- **Triggering donor payments:** Donor payments will be triggered only at the point that the conditions of the TPP have been met and countries indicate demand to include pneumococcal vaccines in their national program. The World Bank will be responsible for managing the donor payments efficiently.

- **Ensuring that demand forecasts translate in product uptake in countries:** As the AMC payment will be made only on the basis of national product orders, timely receipt of governments' requests to GAVI for the vaccine will be critical. The country application will follow GAVI's existing process. Any additional financial subsidy to countries above the AMC co-payment will need to be determined and approved by the GAVI Board or other appropriate entities.

Implementation. Once a Guarantee and Supply Agreement is signed, the transactions associated with the procurement and delivery of vaccines to countries and the payment to industry must be supported. Institutional responsibilities will include efficient and timely management of these transactions, including:



- **Commissioning a procurement agent**: GAVI will be responsible for requesting its procurement agent (currently UNICEF) to issue supply contracts in accordance with AMC terms and purchase orders based on the volumes and timing indicated by each eligible country. GAVI processes are in place to closely monitor uptake and delivery of vaccine to adjust the delivery of doses as necessary.

- **Disbursing payments to firms**: The World Bank will be responsible for ensuring an efficient and timely system to make payments to firms is put in place (e.g. using the GAVI procurement account) for the volume of doses delivered to countries at the agreed AMC price.

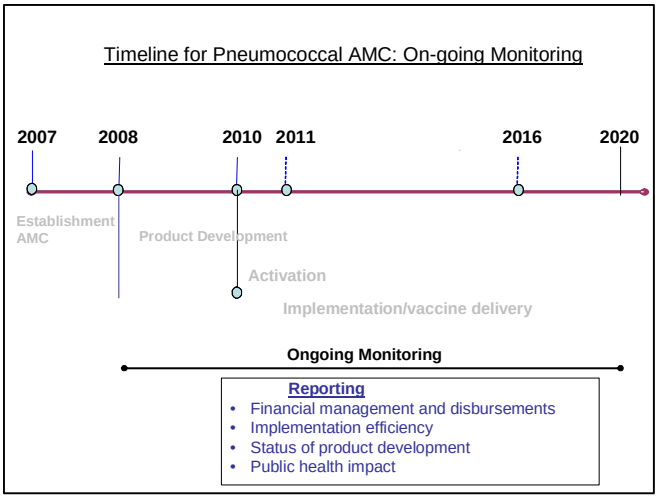
- **Collecting co-payments from national governments**: Country co-payments will be collected through existing GAVI processes. GAVI may chose to further subsidize the country co-payments, for example, reducing the agreed co-payment of $1/dose to a lower amount based on the GAVI co-financing policy.

- **Managing donor commitments and payments to match disbursement schedules:** The World Bank will be responsible for ensuring that donor payments are made consistent with disbursement needs as agreed with firms.

Throughout these stages there will be on-going monitoring and reporting by GAVI and the Bank. To ensure transparency, reporting will cover:

- **Financial management, disbursements, status of funds:** The World Bank will ensure that appropriate reporting arrangements are in place covering the financial status of the AMC, collective management of AMC donor funds and disbursements.

- **Efficiency of implementation including procurement and vaccine delivery:** GAVI will report on the programmatic implementation of pneumococcal vaccine introduction including the demand, procurement, country co-financing and vaccine delivery. AMC donors can also receive information on this through their donor representatives on the GAVI Board.



- **Continued technical progress**: Reports will share any public information on progress by firms to develop, scale-up, and deliver vaccines to serve the eligible countries. The indicators against which the success of the AMC will be monitored will be detailed in advance in the framework agreement.

- **Public health impact**: GAVI and its partners will report on the estimated public health impact of the AMC as measured by pneumococcal vaccine coverage and deaths prevented.

Finally, an ex-post evaluation of the AMC pilot and its impact will be critical for stakeholders to determine if investments in other AMCs, for example, for a malaria vaccine, is a good use of funds. Setting up a "counter-factual" or baseline of what would have occurred in the absence of the AMC will be extremely difficult. However, GAVI and the World Bank will work with partners to determine the "best" evaluation metrics and systems.

III. Oversight

As the financiers of the AMC, donors have important responsibilities particularly at the outset of the AMC when the specific results and performance triggers will be established and the implementation and monitoring functions and processes will be agreed. To this end, an AMC Donor Committee (DC) will be established to facilitate donor input into the AMC design as detailed in the Framework Agreement. Once donor decisions are embodied in the established AMC, the primary donor responsibility will be to ensure appropriate monitoring and reporting. The credibility of the AMC depends on the absolute understanding by all stakeholders that once agreed, the AMC terms and procedures will be up-held. It is proposed that the Donor Committee will meet once a year or with whatever frequency deemed appropriate, to discuss annual progress reports and other issues that may arise. At the Donors' request, the Chair of the IAC may be invited to attend such meeting.

Donors, industry, and other stakeholders will also agree on what significant events could trigger a re-assessment of the AMC itself or its conditions. If such events were to occur, as detailed in the framework agreement, donors, the IAC, or the host institutions (GAVI and the World Bank) would be able to call a special meeting of the DC to examine the change in circumstances and decide on an appropriate response. (A similar provision would allow the parties to a guarantee and supply agreement to call for a re-assessment in specified circumstances.)

The GAVI Alliance Board, as the governing Board of the host entity will have overall responsibility for implementing the programmatic part of the AMC. The GAVI Board is composed of a range of global stakeholders in immunization including OECD governments, developing countries, research institutes, the Gates Foundation, UN agencies such as WHO and UNICEF, both multinational and developing country vaccine industry and the World Bank. The GAVI Board is a body that already represents many of the AMC stakeholders. The GAVI Board is the policy making

body of the Alliance and will approve the policies and processes for the application and review of country applications for pneumococcal vaccines. Furthermore, it will determine any country co-financing policies and be ultimately responsible for complementary GAVI investments in health system strengthening, improving vaccine management in country, and strengthening demand forecasting and other activities.

IV. Independent Assessment Committee

A significant part of the value of an AMC is that it is a transparent and credible commitment for a future market. The total amount available, the price per dose and the product goals (TPP) are established in advance to encourage industry investment and to provide clear assurances of the value of the potential market. Establishing a credible and independent process to set the vaccine TPPs and to determine whether or not a vaccine meets those specifications is critical to the success of the AMC. The IAC is the cornerstone of this process and is responsible for ensuring that the TPP setting process and the decision of whether a product meets the TPP and is eligible for AMC funding, is fair, transparent and credible to all signatories of the Framework Agreement and other stakeholders.

Wherever possible, the IAC builds on and uses existing entities and processes, such as the decisions of competent regulatory authorities on product safety and efficacy. At the same time, it would ensure review of any additional information required to prove public health impact in the target developing countries. The IAC must be authoritative and independent so that its decisions are recognized as fair and justified by all the parties involved: donor governments, manufacturers, developing countries and the public health community. The IAC will be the interlocutor between pneumococcal disease and vaccine experts, industry, donors and other stakeholders. The composition of the IAC and the selection process for its members must be fair and transparent to ensure credibility of the IAC. Issues such as conflicts of interest, composition, and independence must be addressed.

AMC objectives include harmonizing with existing structures and processes, avoiding duplication and assuring consistency in AMC vaccine standards and processes with existing vaccine regulatory and qualification processes. Currently, regulatory approval and WHO prequalification of vaccines determine or greatly influence which vaccines are licensed by developing country governments and which vaccines can be procured by UN agencies or GAVI. To be effective, the IAC process has been designed to harmonize with these existing procedures to ensure that AMC eligible vaccines are also licensed in developing countries (given regulatory approval and WHO standards) and can be procured through normal channels (e.g. GAVI and UNICEF).

Finally, the AMC secretariat would ensure that open and direct communication channels remain open between the IAC and stakeholders (manufacturers, relevant public-private partnerships (e.g., PneumoADIP), Donor Committee, the client

population, etc.) to facilitate rapid response to any concerns that may arise over the life of an AMC.

The present paper describes the functions of the IAC, outlines how it would be structured to fulfill those functions and proposes an implementation plan and timetable.

Functions of the IAC

The IAC's core functions are outlined below.

i. Oversee the establishment of TPPs

Setting the vaccine TPPs for the AMC is the IAC's most important task. Although the IAC is responsible for this process, it is more practical for the IAC to exercise an independent oversight role, delegating the task of defining the TPP for the pneumococcal vaccines to an appropriately constituted scientific and technical group with in-depth knowledge about pneumococcal disease and vaccines. The TPP would determine the required public health performance standards – for example, the level of effectiveness in target populations against a certain endpoint. Other measures relevant to public health impact might also be defined such as the maximum number of doses per treatment, compatibility with available delivery systems (e.g. dosing schedule, temperature sensitivity, method of application), minimum duration of immunity, and non-interference with other public health interventions. The TPP will, of course, be based on the product quality and safety standards established by functional regulatory authorities

The following procedures for establishing TPPs were designed to bring in pneumococcal experts in an open, transparent, well understood and participative process, with firm guidelines describing how it will work. The process also harmonizes with existing procedures to set vaccine performance standards for developing countries.

TPPs would be set by the IAC first requesting the World Health Organization (WHO) to convene an expert advisory group to recommend TPP terms. This activity is within WHO's global mandate, and is already being done for licensed vaccines by WHO, through its Department on Immunization, Vaccines, and Biologicals (IVB). While precise details remain to be worked out, this expert group would present its recommendations to SAGE (an advisory group on immunizations to the WHO Director General) who would pass them to the IAC. If the recommendations were then also confirmed by SAGE, they could become official WHO policy on performance. WHO Member States have a high level of confidence in WHO policy recommendations, so this approach would ensure a wide acceptance of the TPPs. The final decision to accept a TPP rests with the IAC.

A detailed proposal prepared by WHO outlined the steps WHO would follow to provide the requested support and details how WHO would interact with the IAC.

The IAC would first, be responsible for vetting nominees who would participate in the expert meeting, and second, sit with SAGE during the final approval process. The preparation of background papers for the expert committee would also be delegated to WHO, with participation from the AMC secretariat and possibly the IAC itself. In addition, the IAC would be included as one of the liaison groups that would participate in the expert consultation, along with other members of the stakeholder community. WHO estimated that the proposed process, including the preparation of papers would take three-six months.. The value of allowing a month-long comment period between the expert consultation and the SAGE meeting to enable interested parties to comment on the proposed TPPs is being considered. Although this could lengthen the time needed to set the TPPs, it would ensure that all relevant groups consider themselves part of the process.

The IAC would have the final authority to accept, amend or reject a TPP. By delegating the expert process to others, the IAC maintains a neutral and objective position and can thus provide the stakeholders with an assurance on the fairness of the process and outcomes. In the unlikely event where the TPP would be rejected, the AMC secretariat would facilitate a mechanism to resolve the dispute possibly including a joint meeting of the IAC and the SAGE .

ii. Monitor and report scientific progress throughout the process

The IAC will review information gathered by the AMC secretariat about the AMC's influence on the development and production of pneumococcal vaccines, including progress towards a vaccine that would meet the TPP. To minimize the transaction cost of reporting while also ensuring transparency, an annual review process convened by the IAC is being considered. Manufacturers, AMC participants and interested parties would consider the science as well as complementary issues such as demand creation. The IAC would also review and approve the annual progress report to donors prepared by the host institution to ensure consistency.

iii. Modify TPPs if appropriate

Given how technically advanced the pneumococcal vaccines are, it is unlikely that the TPP or AMC prices set in the Framework agreement will need to be revised. However, a process is outlined below to avoid confusion if this improbable event arises.

A general principle of the AMC structure is that TPPs may be lowered, but, except in the event of a force majeure, never made more stringent once they are set. Even if they are lowered, this could still be disruptive for manufacturers that had invested in research and development to meet the original higher level. Therefore, modification of the TPPs will be a rare event that will be defined in the Framework Agreement. Re-setting a TPP will follow the same process as its initial establishment, with the IAC requesting WHO to convene a group of experts. The IAC is responsible for deciding if a TPP should be modified downward.

The original size and price of the AMC would be defined at the outset. In addition, the post-AMC price (the long-term, developing country "market" price of the vaccine after the AMC is depleted), would be established by each manufacturer when it signs the AMC Guarantee and Supply Agreement. This will ensure that developing country governments can make decisions on introduction of the vaccine based on predictable prices. However, an AMC price may be changed if there is a significant change in circumstances. It is proposed that the IAC would request the AMC secretariat to convene experts in the rare event that it is needed to evaluate the changed circumstances and decide whether a change in price is appropriate. Recommendations coming out of this process will then be communicated back to the IAC for decision and action.

iv. Oversee the determination of whether a product meets the TPP

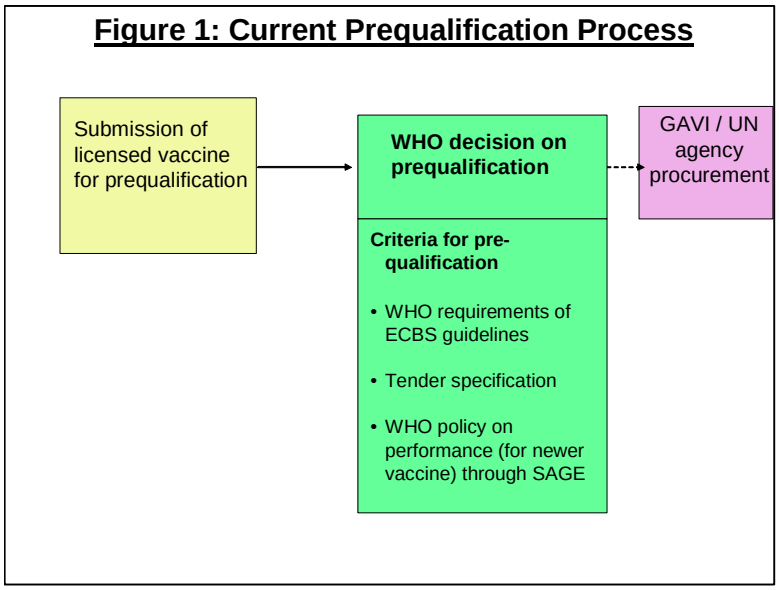
The IAC will have the final authority to decide whether a product meets the TPP, and thus is eligible for AMC funding. To meet the TPP, a product must meet certain minimum quality and safety standards and the public health performance standards set out in the TPP.

It is also important to ensure that the vaccine approved for AMC funding, can be procured through United Nations procurement agencies and GAVI as well as directly by countries. At present, all vaccines procured by UNICEF or GAVI must be WHO-prequalified. The WHO prequalification process, in effect since 1987, is a process that assures United Nations procurement agencies of the suitability of a product for global use in national immunization programs. The process is widely respected and the list of prequalified vaccines is used by many countries as a guide for fast-track licensure. Given its important role in the licensing decisions of countries and procurement processes UN agencies, AMC-eligible products will also need to be pre-qualified by WHO. To minimize duplication and ensure the consistency of decisions, the following two processes would be adopted:

(a) Assessing whether minimum quality and safety standards have been met:
Determining the quality (including purity and consistency), safety and efficacy of a vaccine is the mandate of national regulatory processes and authorities, through the licensing process. To avoid duplication and ensure consistent standards, the TPP should not have separate quality or safety standards. The IAC will accept that the vaccine meets the minimum required quality and safety standards if the vaccine has been licensed by a functional regulatory authority and is prequalified by WHO.

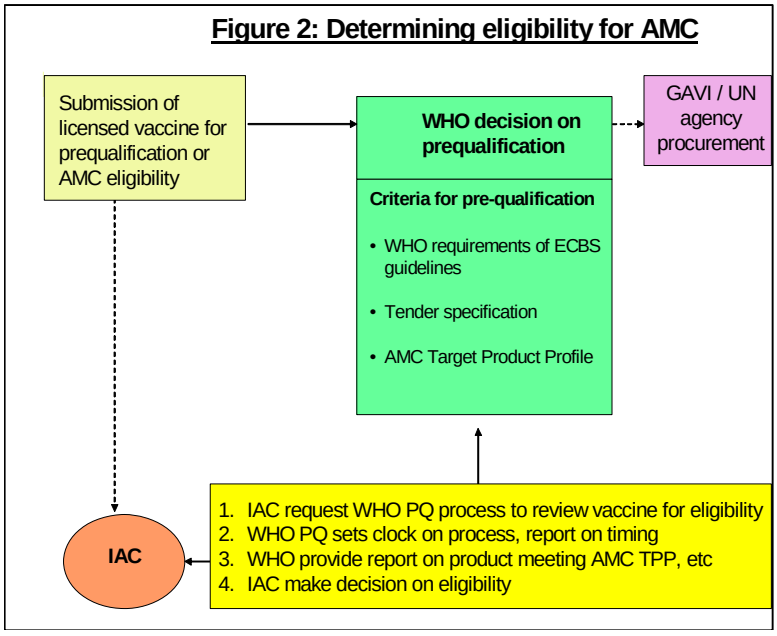
(b) Assessing whether the public health performance standards in the TPP have been met and whether the products can be procured through normal channels:
Based on a review of existing entities and processes conducting similar functions, and to minimize duplication and enhance consistency of processes and outcomes, these assessments would be made by using the WHO prequalification processes but using the established TPP standards.

Figure 1 depicts the current WHO prequalification process for any product. A product is submitted for prequalification when there is an interested UN procurement agency buyer. The product is prequalified using an established process and based on three criteria:



- meeting the specifications of the tender (packaging, thermostability, shipping criteria, presentation, etc);
- meeting the specifications of the relevant WHO "requirement" or ECBS guideline; [22]
- for newer vaccines, meeting the performance standards outlined in the WHO policy recommendation, developed generally through expert consultation and approved by the SAGE, relevant to field performance.

Figure 2 depicts how the current process will be modified to assess whether AMC-eligible products meet the public health performance standards set out in the TPP and whether the products can be procured through normal channels. For an AMC eligible product, the WHO prequalification team will assess the product against the **performance standards in the TPP** (WHO policy on performance), in addition to the two other prequalification criteria. The WHO prequalification team will report its findings to the IAC, indicating the performance of the product against each of



[22] The ECBS guideline is a guideline outlining production requirements developed through WHO's Expert Committee on Biological Standardization (ECBS).

the prequalification criteria. The IAC will decide in the light of this advice whether the product is eligible for purchase under the AMC, and report to the AMC Secretariat. WHO may also be requested by a UN agency to prequalify vaccines that have public health value for more limited use (e.g. regional), but that do not meet the AMC TPP. It is believed that the proposed system would not constrain WHO from establishing regionally appropriate performance standards and prequalifying non-AMC vaccines as required.

Thus, the IAC will make the final decision whether a product meets the TPP, and is eligible for AMC funding, based on the product being licensed and approved by a functional regulatory authority and being WHO prequalified. The precise details of this process are being developed with various experts and WHO.

v. Resolve disputes

The IAC needs the capacity to monitor and resolve disputes and complaints associated with the carrying out of the above activities, either by the IAC itself or by the organizations to which it delegated various tasks. It could act as an appeals group in case of challenges, for example, to TPPs, prices, and compliance determinations but would not interfere in the prequalification process.. The personal credibility of the IAC members and the independence and impartiality of the IAC itself will largely determine the confidence of stakeholders in the TPP and product-review processes and outcomes.

Proposed Structure of the IAC

Membership: To be efficient and functional, an IAC will comprise seven to ten members with no vested interest in the specific products under consideration. Member expertise represented will reflect the IAC's functions, and might include, besides public health expertise, understanding of health economics, vaccine business development, contract law, clinical performance and delivery systems. Members and the chair of the IAC will serve in their personal capacities, and not as representatives of any organization or group.

Chair: The chair of the IAC will be a widely respected public health expert. He or she should be able to respond to IAC needs as they arise (e.g. easily reachable and able to travel).

Selection process: The World Bank and GAVI as the AMC hosts will be responsible for outlining and implementing the process to identify the initial IAC members, as well as future IAC members should anyone need to step down for unforeseen reasons. A widespread call for nominations through all channels likely to yield names of suitable candidates will be made. Donors will be encouraged to submit names. All candidates will be contacted as to their interest and availability and be requested to submit their *curricula vitae.* A short list of nominees will be developed by a small

independent panel appointed by the GAVI Executive Director and the World Bank with input from stakeholders including donors, countries, technical agencies and industry. The final shortlist will be submitted to the GAVI Alliance Board and presented to the Donor Committee.

Secretariat support: An AMC Secretariat responsible for implementing the AMC and reporting to donors will be established in GAVI. This secretariat will provide administrative and technical support to the IAC through two staff members. The AMC secretariat will support the IAC in gathering information, organizing meetings, communicating with the client organizations (being the "face" of the IAC), and ensuring that all the administrative details of the work of the IAC, including convening meetings, recording and communicating decisions of the IAC and maintaining records of its deliberations, are handled. Other functions include reporting, communications and development of statements and drafting of papers for IAC review and approval.

Methods of work: The long-term nature of the IAC makes it essential that decisions made by the committee be recorded and respected by future committees even as membership changes. Therefore, care will go into the drafting of and agreement to its operational methods, which will be endorsed by the GAVI Alliance Board and the AMC Donor Committee. A guiding principle is that the IACs deliberations will be as open, transparent, and consultative as possible. Procedural issues will be defined including manner of decision making, handling of confidentiality and conflicts of interest, and how conflicts are resolved.

- **Handling of conflicts of interest:** The selection process for the IAC will attempt to nominate people as free of conflicts as possible. Despite this, it is unlikely that members will be totally free of bias. Many groups (including the FDA Advisory Panels, the SAGE, etc) have handled this issue by a combination of:

  - Full disclosure of financial issues.
  - Open meetings so that all can see that due process is followed in deliberations. Other participants may comment.
  - Members having a conflict on a particular issue recuse themselves during the discussion and consensus taking on that issue.
  - Members may request to go into closed session in case of confidentiality issues.

- **Terms of office and replacement of members:** Because of the long-term nature of an AMC, and thus of the responsibilities of the IAC, the World Bank and GAVI will be responsible for defining the process to ensure that terms of office are scheduled to ensure the continuity of the committee, and to replace members as necessary.

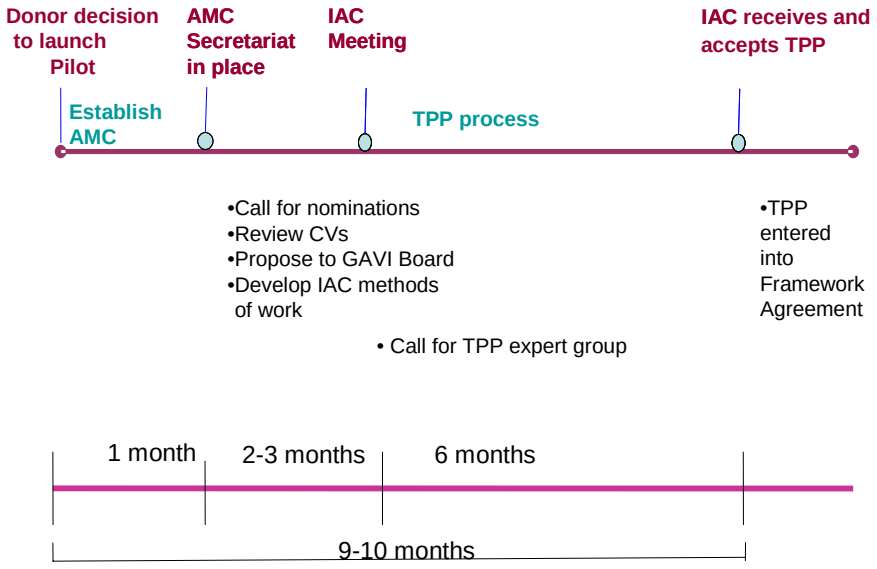
Oversight and accountability: The IAC's terms of reference arise from the AMC legal agreements. Ultimately, the IAC is accountable to the AMC donors for its specific functions. However, day-to-day engagement will be through the AMC Secretariat at GAVI.

Donors will receive annual reports on the AMC including the work of the IAC. In the event of a crisis in the workings of the IAC, donors will be able to convene a special meeting of the Donor Committee to discuss the issues and determine how to rectify the situation.

Implementation Plan

The figure below illustrates the steps to establish the IAC and develop the first TPP for pneumococcal vaccines. This projection shows up to a ten month period from the initial launch to the TPP being ready for inclusion in the Framework Agreement.

Timeline for the IAC and TPP for pneumococcal vaccines



Chapter 5

Financing Arrangements for a pilot Advance Market Commitment for Pneumococcal Vaccines

III. Introduction

As previous chapters make clear, the success of an AMC depends on strong technical, institutional and governance foundations. Weaknesses in any of these areas will undermine the potential of the mechanism to accelerate the development of Pneumococcal vaccines and their availability to the people that need them.

The same is true of the financial structure. An AMC aims to alter the R&D decision-making of vaccine producers by means of a future financial commitment. If this commitment is not properly structured then the anticipated shift in the behaviour of the private sector will not occur.

A first fundamental principle is therefore that the **financial commitments should be clear, credible and legally-binding.**

Furthermore, another key feature of the pilot AMC is that it will be financed by multiple donors. These donors will have differing domestic authorization and appropriation laws and procedures that will determine the nature and profile of the financial commitments they make. Varying political and economic contexts may also mean donors have different payment profile preferences.

This implies a second key principle that **the financing structure must be flexible enough to accommodate different donor systems and preferences**.

This chapter describes how the use of an intermediary could deliver a structure that is both sufficiently credible for industry and sufficiently flexible for donors. The precise details of the financing arrangements cannot be specified at this point since much will depend on the nature of donors' pledges. Furthermore, participating donors will want an opportunity to provide their perspectives on the appropriate structure. Once financing pledges are made, a period of detailed discussion between donors and the World Bank and GAVI will be necessary to define the structure.

Finally at the end of this chapter, there is a brief discussion of the ODA scoring issues associated with donor contributions to an AMC.

II. Functions of the Financing Structure

While it would be theoretically possible for donors to contract directly with potential producers as multiple signatories to the Framework Agreement, the challenges for donors in agreeing to a common legal framework would be significant. Furthermore, a set of multiple direct commitments with different legal foundations is not an effective way to shape industry incentives. Potential developers should not have to undertake an assessment of multiple donor commitments, and their legal foundations, in order to achieve the necessary level of assurance. Under these circumstances, the concern of industry would be that they would have to pursue multiple avenues of redress (perhaps in multiple jurisdictions) in the event that legal dispute arose over AMC disbursements. In other words, such an approach would meet the condition of flexibility for donors but would fall down against the principle of clarity and coherence for industry.

On this basis, a successful AMC demands a financing structure that will intermediate between donors and industry. Donor commitments and cash would be placed in this structure, which would be held under the management of the World Bank and GAVI. In turn, the key role of the structure would be to act as a single contact point for industry by bundling donor financing into a single financial asset that would provide clear, coherent and legally-binding financial underpinnings to the obligations set out in the Framework Agreement. In the case of the pilot AMC for pneumococcal vaccines, this means assets worth US$1.5 billion in nominal terms (or US$860 million in 2006 prices in NPV terms). During this product development phase the liquid assets in the intermediary would also need to be managed and invested appropriately.

During the implementation phase (i.e. when product procurement and payments are underway), the intermediary would translate commitments into cash as needed to pay suppliers. It would also need the capacity to smooth any timing mismatches between commitments and payments.

III. Donor Financing Options

Once donors have collectively agreed their respective shares of the total AMC amount, individual donors will have three basic financing options available to them:

(i) Full up-front financing of the full amount of their share at the start of the product development phase.

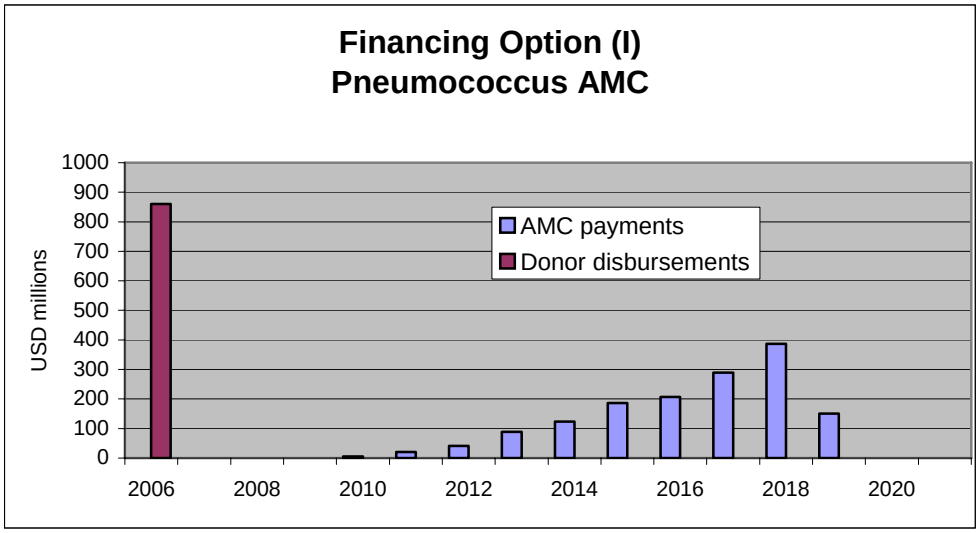
(ii) Up-front commitment of the full amount of their share at the start of the product development phase with the stream of payments made on an annual basis over a period of years. Total resources would steadily build up and be available in time to meet expected disbursements.

(iii) Up-front commitment of the full amount of their share with disbursements only starting in the implementation phase and matching AMC payment needs precisely.

The graphs and discussion on the following pages demonstrate these various options. The graphs make the simplifying assumption that all donors choose the option in question. However, in reality, as discussed above, this will not be the case. Donor financing will be a mix and the financing structure will accommodate their different preferences.

(i) Full up-front financing

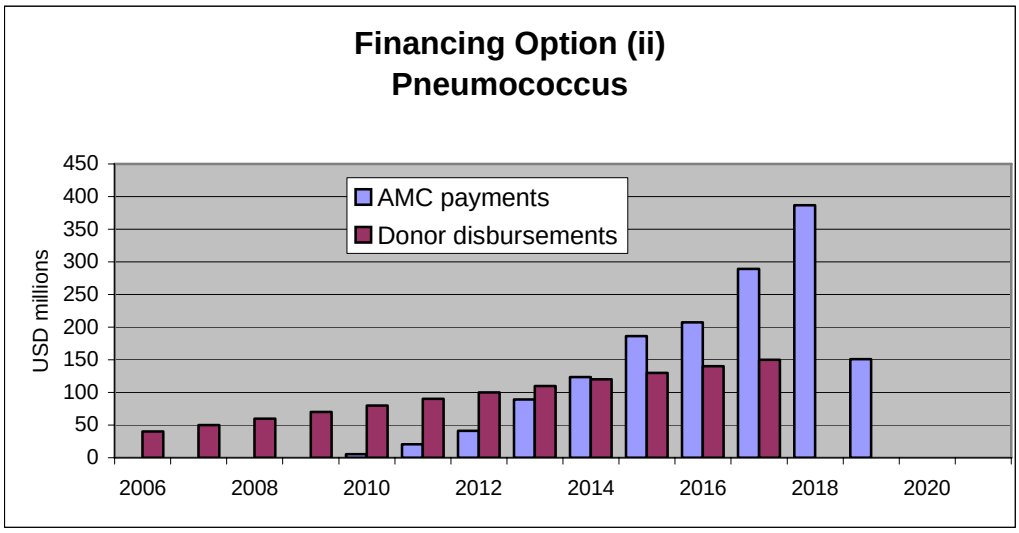
This is the financial arrangement that delivers the maximum credibility in terms of donor commitments and thus minimizes the costs and challenges associated with 'bundling' these commitments. If potential developers saw that the necessary resources to make AMC payments were already held by the intermediary, they would have an extremely high level of assurance that payments would be made in the event of the product being developed and demanded.



This level of assurance may be viewed as having a high opportunity cost, as donors would pay cash now that would be invested to supply funds as needed over the life of the AMC. This could be a cost-effective use of donor funds, taking into account the high economic and social returns to accelerating the development and availability of pneumococcal vaccines. A key element of the AMC, and a key driver of its cost-effectiveness, is the way in which future financial commitments catalyze a shift in present industry behavior. Full up-front financing would have the greatest credibility with industry. However, it may not be a viable option, politically, for many donors.

(iii) Up-front commitment of the full amount with the stream of payments made on an annual basis.

This has the potential to provide an appropriate balance between delivering credible donor commitments (which would in turn minimize 'bundling' costs) and maximizing the productivity of public expenditure. On the one hand, credibility would be supported by the legal and financial aspects of the commitments following well-established precedents for most countries (i.e. full authorization followed by annual appropriations). And, as donor disbursements accumulated, the credibility of the financing arrangements would become ever stronger. On the other hand, the issue of excessive idle cash balances is limited because donors only transfer resources on a gradual basis. This is particularly true for a vaccine in the late-stages of development like pneumococcal vaccines, where the first AMC disbursements are anticipated relatively soon, in 2010, when the first product meets the specified standards.

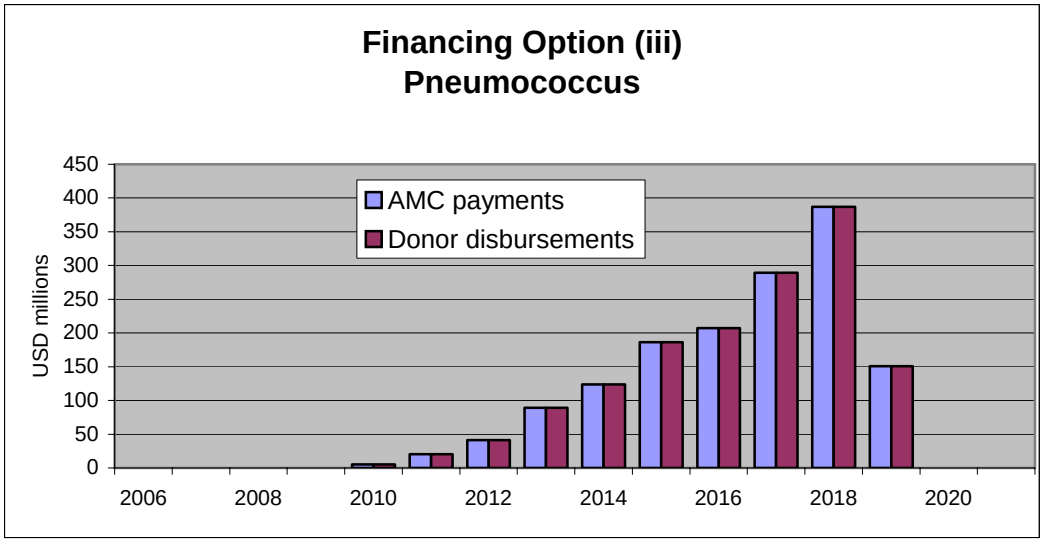


In order to minimize the opportunity costs for donors associated with early payments into the financial structure, donors could 'back-load' their annual contributions (as the graph above illustrates.) The overall attraction of this measured approach to structuring disbursements would be to ensure commitments were credible, avoid idle cash balances and enable sponsors to use relatively well-established mechanisms for their commitments.

(iii) Up-front commitment of the full amount with disbursements matching AMC payments as required.

Option (iii) would not involve any donor financing until AMC payments to suppliers begin. This has the advantage of matching donor disbursements exactly to AMC payments thereby maximizing the productivity of donor public spending

on AMCs and the cost-effectiveness of the mechanism. However, as noted above, the disadvantage may be a practical one, namely that the budgetary and accounting systems of many donors do not lend themselves to making credible and legally-sound financial commitments, contingent on a future event (the production of the specified vaccine). It is common practice for governments to make commitments to procure goods to be supplied at some time in the future. There is much less precedent where the goods in question do not yet exist and when the supplier is not defined.



For a late-stage product such as pneumococcal vaccines, the product development stage is expected to be relatively short, the additional complications associated with Option (iii) may not justify the benefits. Nevertheless, it is worth noting that, for future AMCs for 'early-stage' vaccines, where payments would be more distant, Option (iii) may have attractions for some donors. Furthermore, given that the pneumococcal AMC is intended as a pilot, donors may choose to take the opportunity to choose Option (iii) as a means of piloting the approach.

IV. Bundling the Donor Commitments

As discussed above, the key role of the intermediary is to act as the single contact point for industry by bundling donor financing into a single financial asset that provides clear, coherent and legally-binding financial underpinnings to the legal obligations set out in the Framework Agreement. In the case of pneumococcal vaccines, as the market analysis chapter set out, the value of this financial asset needs to be US$1.5 billion in nominal terms (US$860 million in 2006 prices in NPV terms) in order to elicit the desired response from industry.

Donor commitments will be a mix of cash, together with different types of commitments. There will be no risks associated with cash financing. However, given political and budgetary realities, together with uncertainty around the timing of future AMC payments as well as variation in sovereign credit ratings, there will be some timing, collection and payment risks associated with donor financial commitments.

What this means is that, in addition to packaging multiple assets into a single instrument, the role of the intermediary will also be to ensure such risks are mitigated. If the assets of the financial structure do not equal the required market amount, the response from industry will be muted.

The details of this bundling process will depend on the nature of donor pledges and the precise role of intermediary institutions. Once financing pledges are made, a period of detailed discussion between donors and the World Bank and GAVI will be necessary to define the arrangements. Nevertheless, possible elements of a solution might include:

- Third-party guarantee of the contractual obligations in the FA, to be provided by a commercial entity, or possibly an international financial institution

- The use of cash holdings by the intermediary (assuming some donors opt for up-front financing) to underwrite risks associated with the future financial commitments. Given that needed AMC disbursements to suppliers are anticipated on an annual basis over a long period (nine years), it might be possible for the cash portion of the holdings to be used to guarantee AMC payments on a rolling annual basis.

- Some donors choosing to offset risks associated with their commitments with pledges of higher face-value.

A key principle to establish is that, given the different payment profiles and risks associated with the different financing options, donor commitments would need to be converted into risk-adjusted NPV terms to determine actual donor shares.

V. Recording of AMC Commitments in Fiscal Accounts and as Oversees Development Assistance (ODA)

The issue of fiscal accounting is central to some innovative financing initiatives, for example the International Financing Facility for Immunisation (IFFIm), which uses long-term donor payment streams as legal backing for near-term issuance of AAA-rated bonds, whose proceeds finance immunization programs. AMCs, on the other hand, do not seek to transform donor commitments into cash but instead catalyze additional industry R&D investment. As a result, the issue of fiscal accounting is less difficult.

Accounting treatment across donor countries will necessarily vary, given the different accounting systems. Nevertheless, some general remarks follow:

From a fiscal accounting perspective, Option (i) is the simplest to assess. Donor contributions to the AMC would be made in a single year and would score in the fiscal accounts for that year.

For Option (ii), specific country rules and procedures will determine accounting treatment. Under some systems, the authorization of the overall donor may need to be fully accounted for up-front, even though actual appropriations will occur on an annual basis over several years. In other countries, depending on the type of instrument of commitment used, it may simply be the annual appropriations that need to be recorded.

On Option (iii), a point worth noting is that donor AMC disbursements depend on (i) a qualifying product being developed and (ii) demand from eligible countries. So, while donor AMC commitments would be legally binding, they would also be contingent. This means that donors may not have to account up-front for their AMC instrument. Again, annual donor disbursements would be accounted for as they occur.

On the question of reporting of AMC contributions as Overseas Development Assistance (ODA), the key point is that the OECD's Development Assistance Committee (DAC) currently records two flows of Overseas Development Assistance (ODA). These are (i) donor country outflows, and (ii) recipient country inflows. The ODA/GNI ratio for individual donor countries is calculated on the basis of donor country outflows. As a result, donor AMC payments would be recorded as Donor ODA (and used for the ODA/GNI calculations) at the time that financial payments are made by Donors, rather than at the time that recipient countries receive the benefits of the vaccines. So for example, with Option (i), the full donor contribution would be recorded as ODA in the first year. By contrast, for Option (ii), the annual payments would be recorded as Donor ODA. Finally, under Option (iii), in which donor payments to the AMC match supply to developing countries, ODA scoring would match the flows of vaccines to developing countries.

VI. Legal Aspects

AMCs would be effected through two types of legal contracts that delineate core undertakings of donors and vaccine suppliers:

- Framework Agreement: The Framework Agreement will set out the AMC's key terms, including legal obligations of donors and the implementation details for the structure. It will specify the market size of the AMC, and the price and requirements for the targeted vaccine. It will set out the underlying financial commitments, and the obligation to enter into a Guarantee and Supply Agreement with any qualifying manufacturer whose vaccine meets the requirements. It will delineate the responsibilities and processes of the

Independent Assessment Committee, as well as ongoing responsibilities after the AMC funding is exhausted. Suppliers would sign on to this framework agreement and assume certain reporting obligations that would assist in tracking progress toward potential target vaccines.

- Guarantee and Supply Agreement: Participating suppliers that produce a vaccine that meets the TPP would be entitled to enter into the second-stage Guarantee and Supply Agreement for their product. This Agreement would specify the more detailed terms and processes for shipment and payment of vaccines as well as the post-AMC price established by the firm.

For an AMC to alter the behavior of potential producers, the framework agreement and the guarantee and supply agreements must create contractual obligations, including with respect to financing, that are fully credible and legally binding despite the likelihood that donor commitments may be provided in different forms under different legal jurisdictions. The agreements must be capable of legal enforcement and include dispute resolution and enforcement provisions.

Chapter 6
Next Steps

Advance Market Commitments are an innovative concept with the potential to save millions of lives by accelerating access to vaccines that would not otherwise be available for many years. A great deal of work has been done to turn this concept into a practical, implementable mechanism. A pilot AMC has been designed for pneumococcal vaccines to demonstrate both the feasibility of the AMC mechanism and its impact on accelerating vaccine development, production scale-up and introduction.

To establish the AMC, the key stakeholders including donors, firms, GAVI, the World Bank and other technical partners must continue to work together to refine and finalize the policies, processes and AMC terms outlined in this paper.

Each donor will be responsible for structuring their pledge into a financial commitment that fulfills the objectives of the AMC. These individual pledges will need to be bundled into a single commitment that is credible to industry.

Setting in place the technical, procedural, legal and financial arrangements that will underpin the AMC will be an intensive negotiation that will culminate in the signing of the AMC Framework Agreement and Supply and Guarantee Agreement. Negotiations will provide for a specific level of funding at a specific price for a vaccine that meets specified TPPs. The two legal agreements will codify the agreed terms, processes and roles and responsibilities.

A number of other administrative processes will take place in parallel with the negotiations, allowing the creation of the Secretariat functions as well as the IAC. GAVI will establish the AMC Secretariat that will act as the focal point to ensure all of the various start-up activities are effectively coordinated. The World Bank and Donor Committee will agree on the systems and procedures to ensure that specific donor payments and flows are managed efficiently and support AMC payments under eligible guarantee and supply agreements. Finally, GAVI and the World Bank, in consultation with stakeholders will be responsible for outlining and implementing the process to identify the IAC members. The IAC will have the responsibility for developing the TPP for pneumococcal vaccines through the processes outlined in this paper and reviewing the recommended AMC financial terms once the TPP is established.

Once established, the Pneumococcal AMC will support industry and governments in helping to prevent unnecessary pneumococcal deaths in the poorest countries of the world. Importantly, it will also enable stakeholders to quickly assess the impact of the AMC mechanism to determine if AMCs will be able to accelerate other health priorities such as vaccines against malaria.