Proposal to Host GAVI's Pneumococcal Vaccine Accelerated Development and Introduction Plan (ADIP) at Johns Hopkins Bloomberg School of Public Health

Proposed Executive Director:
Orin S. Levine, Ph.D.
Department of International Health
615 N. Wolfe St., Room E8136
Baltimore, MD 21205
Office telephone: +1 (410) 955-3952 Mobile: +1 (443) 794-3810
Email: olevine@jhsph.edu

Duration: 4 years; March 1, 2003 – December 31, 2006 (renewable)

Amount: $29,999,891

Outline of the proposal

This proposal is organized into the following sections:

I. **The investment case for pneumococcal conjugate vaccination and current status of disease burden and vaccine research.** This section summarizes the investment case for pneumococcal conjugate vaccination and highlights the key areas of uncertainty. It then summarizes existing evidence that pneumococcal infections are a major cause of infant and child mortality in developing countries and the status of research on infant pneumococcal vaccination. It includes a summary of key areas of uncertainty and research issues that must be addressed.

II. **Vision for the pneumococcal Accelerated Development and Introduction Plan (PneumoADIP).** This section describes the goals, objectives and scope of the PneumoADIP and the underlying principles and key characteristics of the proposed strategy, including analyses to support Go/No Go decisions. It includes a rationale for a single group – the PneumoADIP team – to coordinate both demand and supply issues and the reasons for undertaking key communication and supply activities in parallel with late-stage vaccine research.

III. **ADIP activities and deliverables**. This section describes the 3 main areas of focus for the ADIP, and the process by which the ADIP team will prioritize activities and determine timelines and budgets. It outlines how the PneumoADIP team will engage with and work through key external partners and existing GAVI structures including the Task Forces, the Secretariat, and the RotavirusADIP team.

IV. **Management and reporting.** This section includes the proposed management and reporting structure with an emphasis on the role of the GAVI Steering Committee and the flexibility of the ADIP team provided by the Johns Hopkins structures.

V. **The PneumoADIP team.** This section describes the organization of the proposed ADIP Team, including a brief description of the technical expertise and experience of the proposed team members.

VI. **Johns Hopkins Bloomberg School of Public Health (JHSPH): Host institution**. This section describes the key features that make the School an excellent host institution for the PneumoADIP. It briefly summarizes the resources available to the PneumoADIP team at the school. It also covers the issues of hiring personnel, issuing sub-contracts, and human subjects approvals.

VII. **Budget 2003-2006 and justifications**. This section describes the proposed 4-year budget and includes a rationale for each line item. [OMITTED]

Annexes. The Annexes include supporting documents such as a detailed budget, list of deliverables, organizational diagrams, C.V. for team members, letters of support from key partners and references for the Executive Director.

I. THE INVESTMENT CASE FOR PNEUMOCOCCAL CONJUGATE VACCINATION AND CURRENT STATUS OF DISEASE BURDEN AND VACCINE RESEARCH

The investment case for pneumococcal conjugate vaccination: Summary of McKinsey & Co. analyses

On behalf of GAVI, McKinsey & Co. conducted an independent preliminary assessment of the 'investment case' for pneumococcal vaccination – that is, *the expected value of using GAVI/VF resources* to accelerate the development and uptake of pneumococcal vaccination in VF-eligible countries. Their analysis included projections of likely national demand by countries, assessments of the supply situation, willingness of donors and the VF to support procurement, the likelihood that an coordinated effort could establish evidence for national demand, interviews with industry to determine a possible range of vaccine prices, and a cost-effectiveness analysis of the impact of vaccination. The results of this analysis were part of the basis for the GAVI Board decision to commit $30M to support the ADIP teams and process between 2003-06. (Note: McKinsey & Co. estimated that the ADIPs would need $50M between 2003-06.)

This preliminary 'investment case' for pneumococcal vaccine supported the development of an ADIP for pneumococcal vaccination on the basis of several demand and supply side factors (Figure 1). From the demand side, interviews with health officials in developing countries and international donors indicated that pneumococcal disease, especially pneumonia is recognized as a major health problem and that there is interest in a vaccine to prevent it. The analysis also showed that the preliminary cost-effectiveness analyses are competitive with other health interventions, and on the part of donors, there is an indication of willingness to help finance pneumococcal vaccination. On the supply side, there is a high likelihood of a steady supply of a safe and effective vaccine by 2007, and based on McKinsey analyses, a realistic possibility of obtaining vaccine at a price that is feasible for the VF to support (i.e., in the range of $3-8/dose).

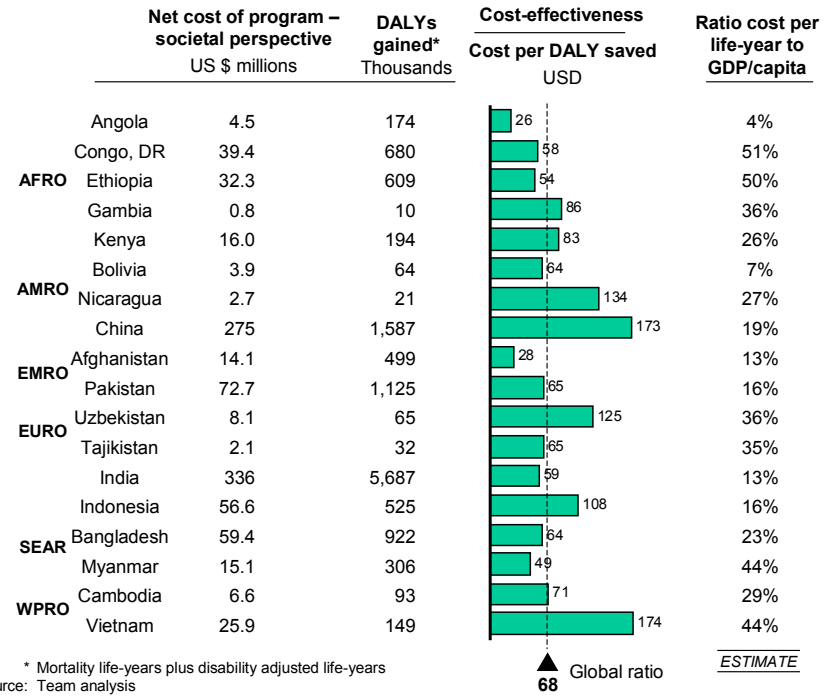
Figure 1. Summary: McKinsey & Co. analysis of the investment case for pneumococcal vaccination

* ADIP ** Assumes countries procure vaccine after 5 years of free supply
Source: McKinsey & Co. team analysis

McKinsey & Co.'s analysis of the "investment case" for pneumococcal vaccination included a preliminary cost-effectiveness analysis to assess the potential

attractiveness of pneumococcal vaccination as an investment for Vaccine Fund resources. The base-case analysis indicated that pneumococcal vaccine was a relatively attractive health investment with a cost per disability adjusted life year (DALY) saved of $68 (Figure 2). (Note: as a rule of thumb, the World Bank defines a "best investment" in health as any investment that has a cost per DALY saved less than the per capita GDP – e.g., in a country where the GDP per capita is ~$350 a "best investment" would have a cost per DALY saved less than $350.) The results of this analysis were consistent with those from two other published cost-effectiveness studies. In 1995, Shepard et al. (Vaccine 1995) and in 2000, Miller and McCann (Health Economics 2000) estimated the cost per DALY saved at $57 and $20-39, respectively.

Figure 2. Summary: McKinsey & Co. cost-effectiveness analysis for pneumococcal vaccination. All countries have costs per life-year gained below GDP/capita



Cost-effectiveness studies use different methods and estimates for key parameters, and thus, it is difficult to compare cost-effectiveness ratios across studies. From the perspective of the ADIP, it is more helpful to look at the key uncertainties in the models and sensitivity analyses that show which parameters have the greatest influence on the results. This type of analysis can help the ADIP to focus its research on improving the estimates of parameters that most significantly effect the cost-effectiveness ratios. In the McKinsey analyses, the cost-effectiveness of vaccination was influenced most by the price per dose, the DTP coverage rate in country, and the actual disease burden. Vaccine efficacy/effectiveness was also important but a less influential factor than the previous three factors. Thus, one of the values of this analysis is to direct the focus of PneumoADIP activities to the factors that potentially have a high influence on the health economics argument.

<u>The burden of pneumococcal disease in developing countries</u>

The rationale for considering pneumococcal vaccination is that it may significantly improve infant and child mortality in developing countries. There are various

estimates of the annual number of infant and child deaths but in 1999 WHO estimated that each year pneumococcal infections were responsible for up to 1 million infant and child deaths each year (WHO. Wkly Epidemiol Rec 1999). While these estimates are based on the best available data, it is quite difficult to measure the true burden of pneumococcal disease, and thus, these estimates are based on several key assumptions and extrapolations. Below, we analyze the bases for these global burden estimates and consider how the evidence base may be improved, particularly as it relates to country-level decisions on introduction of pneumococcal vaccine.

In broad terms the case for pneumococcal vaccination is based on the following general observations:

1) Acute respiratory infections (ARI) are the first or second leading cause of under 5 mortality in developing countries, accounting for an estimated 1.9 million childhood deaths in 2000, 70% of them in Africa and south and southeast Asia (Table 1) (Williams BG, et al. Lancet ID 2002). Equally important is the observation that the proportion of overall deaths due to ARI increases as overall under-5 mortality rates increase. For example, southeast Asia and Africa have the highest rates of under-5 mortality in the world and in these regions ARI is estimated to account for 19-22% of all deaths in this age group. By contrast, the European region (EUR) has the lowest under 5 mortality rate and also the lowest proportion of deaths (11%) due to ARI.

Table 1. WHO estimates of annual ARI deaths in children <5 years old, by region (Williams B et al. Lancet ID 2002)

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

Key areas of uncertainty: There are at least two key assumptions that introduce uncertainty into the estimated number of ARI deaths. First, the verbal autopsy method used to assign a probable cause of death has limited specificity for differentiating ARI deaths from deaths due to other conditions, especially in neonates. This lack of specificity introduces some inherent uncertainty into the estimates. Second, the estimates published by Williams include data from 22 countries but extrapolate to the world. Thus, the data on which the estimates are made are the best available but perhaps not equally representative of all populations.

2) Most ARI deaths are believed to be due to bacterial pneumonia. When referring to childhood mortality, the term ARI is used to cover a wide range of lower respiratory tract infections including bronchiolitis, pertussis, and pneumonia, and in some cases, measles-associated illnesses. Most experts consider that the vast majority of ARI deaths are likely due to bacterial pneumonia (probably 50-80%). This assumption is based on several observations. First, hospital based studies have generally shown that the case-fatality rate in bacterial pneumonia is several times higher than it is for viral pneumonia (Shann F. Pediatr Infect Dis J 1986). For example, in 9 studies in

which the case-fatality rate could be determined for either bacterial and viral pneumonia, the median case-fatality rate of bacterial pneumonia is ~4 times greater than the rate for viral pneumonia (medians, 11.3% for bacterial and 2.9% for viral) (Table 2).

Table 2. Case fatality rates for bacterial and viral acute lower respiratory illness.

Study (Journal Yr.)	Case-fatality rate (%)	
	Bacterial	Viral
Tupasi (Rev Infect Dis 1990)	18.8%	7.1%
Huq (Rev Infect Dis 1990)	---	4.8%
Hortal (Rev Infect Dis 1990)	7.5%	1.6%
Ruutu (J Infect Dis 1990)	---	4.8%
Weissenbacher (Rev Infect Dis 1990)	11.3%	2.9%
Shann (Lancet 1984)	15.0%	---*
Forgie (Pediatr Infect Dis J 1992)	6.5%	2.4%
Escobar (Peds 1976)	5.7%	0
Barker (J Infect Dis 1989)	17.0%	---
Range	6.5-18.8%	0-7.1%
Median	11.3%	2.9%

Supporting evidence of the importance of bacterial pneumonia comes from controlled trials of WHO's ARI case-management algorithm – in which children with cough or difficulty breathing and signs of pneumonia are given antibiotics. A meta-analysis of several studies of this strategy showed that implementation reduced overall infant and child mortality by 20-25% (Sazawal S et al. Lancet 1992). Because antibiotics are effective for treatment of bacterial, but not viral, pneumonia, these results also support the assumption that most ARI deaths are due to bacterial pneumonia. If these infections had been viral in origin, one would not have expected antibiotic therapy to have had an impact.

Key areas of uncertainty: The assumption that most ARI deaths are bacterial in origin is based on at least two key assumptions. First, most deaths from ARI occur in communities where children with symptoms receive little or no treatment, and where there are no diagnostic facilities. Thus, in general, we must assume that hospital- or clinic-based data are representative of the cases occurring in the community and extrapolate from one to the other. Second, the geographic representation of the evidence to support this assumption is quite limited and may not accurately reflect the heterogeneity of settings in the developing world.

3) Pneumococcus is the most common cause of bacterial pneumonia in infants and young children. In studies of patients with pneumonia, *S. pneumoniae* is consistently

the most commonly identified bacterial agent from either lung aspirates or blood cultures (Shann F. Pediatr Infect Dis J 1986). For example, in a review of 9 studies that used lung aspiration techniques, a median of 34% of patients had *S. pneumoniae* identified, more than any other bacterial agent, and in children with no history of antibiotic use, the media proportion bacterial was 44% (Table 3). Bacteria are generally found 2-3 times more often than viruses in lung aspirate studies of children with pneumonia who have not been treated with antibiotics (Shann F. Pediatr Infect Dis J 1986).

Key areas of uncertainty: Although the data are fairly consistent across studies, the assumption that *S. pneumoniae* accounts for the majority of bacterial pneumonia deaths has several shortcomings. First, as was the case with bacterial pneumonia in general, the etiology of pneumonia occurring in the community is generally extrapolated from cases that are seen in hospitals, clinics, or special research settings. The cases evaluated in published studies, however, may not be representative of the entire universe of ARI cases. Furthermore, the most sensitive diagnostic technique, lung aspiration, is only possible on a small sub-sample of cases where a large, peripheral consolidation can be reached with a needle, and thus, these cases are not necessarily representative of all cases of non-bacteremic pneumonia. Second, laboratory diagnosis of the etiology of pneumonia is inherently difficult. Blood cultures are highly specific but not very sensitive (i.e., they do not detect many cases of pneumonia due bacteria). Cultures of lung taps are highly sensitive, but the procedure is associated with a risk of complications (specifically, pneumothorax) that limits its use to a handful of research settings and can only be performed on a sub-set of pneumonia cases. Antigen detection tests are easy to use but have poor specificity (i.e., they yield a high number of 'false positive' results). Serologic diagnoses based on comparison of acute and convalescent titers can help with diagnosis but is again only used in research settings and will underrepresent patients who die and therefore, cannot contribute a convalescent serum sample.

Finally, because the etiology of most cases of pneumonia is unknown, estimates of the etiology of pneumonia episodes generally extrapolate from the cases of known etiology to the cases of unknown etiology in equal proportion. This may not be accurate and may overestimate the proportion of cases due to known etiologies. Newer, as yet unrecognized agents (e.g. metapneumoviruses), may actually account for a large proportion of these infections. Also, some etiologies are more difficult to detect and require more laboratory resources.

Table 3. Results of 9 lung puncture studies conducted in infants and young children with pneumonia (SP = *S. pneumoniae*, HI = *H. influenzae*, SA = *S. aureus*)

Study	N	% Bact	Etiology			
			SP	HI	SA	Other
Wall Bull WHO 1986*	51#	71%	51%	24%	2%	4%
Ikeogu Arch Dis Child 1988*	40	33%	18%	8%	10%	0
Silverman Arch Dis Child 1977*	88	79%	49%	11%	11%	31%
Mimica Am J Dis Child 1971@	530	44%	2%	2%	27%	15%
Hughes Peds 1969	18	28%	11%	22%	0	0
Riley Ped Res 1983*	18	44%	39%	6%	0	0
Escobar Peds 1976	102	19%	5%	4%	8%	2%
Shann Lancet 1984	83	61%	34%	40%	0	28%
Forgie (1-9y) Pediatr Infect Dis J 1991**	29	48%	34%	3%	10%	0
Range - All	959	19-79%	2-51%	2-40%	0-27%	0-31%
Median - All	959	44%	34%	8%	8%	2%
Range - No abx	197	33-79%	18-51%	6-24%	0-11%	0-31%
Median - No abx	197	58%	44%	10%	6%	2%

* No children with reported prior antibiotic use. # Includes only children <10 years old.
@ Only 160 children without prior antibiotics, no data on specific bacterial etiology for this subgroup.
** These patients represent a subgroup of all patients included in the study.
Source: B. Schwartz, unpublished.

In short, if these estimates are correct and ARI accounts for 20% of all childhood deaths, and most ARI deaths (75%) are due to bacterial pneumonia and most of those are due to *S. pneumoniae* (70%), it is conceivable that **pneumococcal infections may account for up to 10% of all deaths in children <5 years old in developing**

countries (20% x 75% x 70% = 10%). However, as is illustrated above, the estimates are based on a number of extrapolations and assumptions that introduce uncertainty into the final estimates.

Local evidence of pneumococcal disease

Global estimates of disease burden are important for discussions of global priorities but for national decision-makers, local evidence of disease burden is more important and meaningful. Experience and research have shown that 'medical need or merit' is the first issue of importance to countries in evaluating the importance of introducing a new vaccine. We expect that all countries will want to have at least some local or regional data for each of the following:

a) Evidence that *S. pneumoniae* causes severe disease in children. It will be important to show that pneumococci can be isolated from children with pneumonia, meningitis and sepsis, and perhaps most importantly to determine the proportion of pneumonia caused by *S. pneumoniae*.
b) Data on the most common pneumococcal serotypes in their country or region. Because pneumococcal conjugate vaccines are going to be restricted to 9- or 11-serotypes, this will be a natural question for decision-makers to ask. Existing data suggest, for example, that there are important geographic variations in serotype distributions. South and East Asia are particular areas where additional data on the serotype distribution is needed. For example, the existing 7-valent vaccine would only cover approximately 34% of the serogroups causing invasive disease in Asia, and the 9-valent vaccine that includes serogroups 1 and 5 would only increase coverage to ~55% (Table 4). However, the data on which these estimates are based are relatively more limited than the data from Africa or Latin America, for instance.
c) Data on the prevalence of antibiotic resistance among pneumococci. Because antibiotic resistance can interfere with effective treatment, we expect many decision-makers to be interested in antibiotic resistance rates in their areas.

Each of these types of data can be gathered by studies that use good microbiologic methods to isolate bacteria from patients with pneumonia, sepsis, and meningitis.

Table 4. The seven pneumococcal serogroups most frequently causing invasive disease among young children, by region. Serogroups included in the currently licensed 7-valent Pnc-CRM_{197} are in bold. Numbers in parentheses are proportion of all sterile site isolates for each serogroup. (Adapted from Hausdorff CID 2000; 30:100-121.)

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

d) Evidence of the importance of pneumonia as a cause of child morbidity and mortality. Preliminary discussions with Ministers of Health suggest that pneumonia is already recognized as an important illness of children. Additional work will likely be needed. This data may be generated by hospital or population-based studies.
e) Estimates of the costs of pneumococcal illnesses such as pneumonia, meningitis, and sepsis. The importance of pharmacoeconomic studies is increasing as countries are more often asked to rationalize health investments in economic terms. Cost of illness data can be incorporated into studies of the cost-effectiveness of intervention strategies including pneumococcal vaccination.

The PneumoADIP team at Johns Hopkins will work closely with partners in developing countries to help them design and conduct the surveillance and research needed to address these issues and to support a rational evidence-based decision on the value of pneumococcal vaccine introduction.

Status of pneumococcal vaccine development (infants and children)

Pneumococcal vaccines for infant immunization.

Three main approaches have been used to develop vaccines to prevent pneumococcal disease in infants. The polysaccharide capsule of pneumococci has long been recognized as a major virulence factor for the bacterium. Likewise, researchers have long known that anti-capsular immunity can prevent serious disease. The first pneumococcal vaccines were designed to stimulate anti-capsular immunity. These vaccines are an assortment of purified capsular polysaccharides to a wide range of important pneumococcal serotypes. As with nearly all polysaccharide vaccines, however, most of the serotypes are poorly immunogenic in infants and children <18 months of age and they elicit a T-independent immune response. One significant

shortcoming of the T-independent immune response is that the vaccine fails to induce long-lasting immune memory, a characteristic important for infant immunization. A 23-valent pneumococcal vaccine is currently licensed for use in adults and in children ≥ 2 years of age. In the 1980s in the highlands of Papua New Guinea, Ian Riley and colleagues conducted a series of controlled studies of 14- and 23-valent polysaccharide vaccines their efficacy for prevention of pneumonia and pneumonia mortality in children (Riley I et al. Lancet 1986). Estimates of the vaccine's efficacy for preventing pneumonia-associated death were 31% in infants <6 months of age, 50% in children <24 months of age, and 59% in children under age 5 years (Riley I et al. Lancet 1986). However, there were serious concerns about the applicability of the study's findings to populations outside of PNG and the study design and methods. Ultimately, further studies of the vaccine's efficacy were never undertaken. Because of its shortcomings (and now the existence of efficacious conjugate vaccines), the 23-valent is not considered a serious candidate for global use as a routine infant vaccine.

Pneumococcal conjugate vaccines are an improvement on plain polysaccharide vaccines. By linking a polysaccharide to a carrier protein these vaccines are highly immunogenic in young infants and induce a T-dependent immune response, and with it long-lasting immune memory. By 2005, at least five candidate conjugate vaccines will have gone through phase 3 trials (Table 5). One vaccine, a 7-valent pneumococcal conjugate (trade name Prevnar®, manufactured by Wyeth), was licensed for routine infant immunization in the United States and Europe in 2000. The American Academy of Pediatrics and the US Advisory Committee on Immunization Practices have recommended routine infant immunization since February 2000, and in that time >8 million infants in the USA have been vaccinated. Prevnar is now licensed in 49 countries, but almost none are developing countries.

Two other pneumococcal conjugate vaccine candidates are in advanced stages of development – a 9-valent vaccine from Wyeth and an 11-valent vaccine from GSK. Licensure and launch of these vaccines are expected by 2006 or 2007. The 9- and 11-valent vaccines include serotypes 1 and 5, which account for 10-20% invasive pneumococcal disease in Africa, Asia and other regions.

Two other vaccine candidates, an 11-valent vaccine developed by Aventis and a 7-valent vaccine developed by Merck, reached the stage of phase 3 trials, but for commercial reasons, each company has ceased investment and decided not to pursue licensure or launch of the vaccine.

Table 5. Summary of vaccine candidates: Stage of development & expected launch

	Candidate vaccine	Stage of development	Expected launch
Candidates that are or likely to be licensed and launched			
Wyeth	7-valent	Licensed; launched in 2000	
	9-valent	Phase III in So. Africa completed; Phase III in Gambia completed by 2005	2006
GSK	11-valent	Phase III for otitis media prevention; no invasive or pneumonia efficacy trial underway	2006?
Candidates that will NOT be licensed and launched			
Aventis	11-valent	Phase III in Philippines will be completed in 2005	No further investment by Aventis; will not be commercialized
Merck	7-valent	Completed Phase III; efficacy vs. otitis media demonstrated;	Company ceased efforts to license and launch; no plans for commercialization

Pneumococcal conjugate vaccines have several strengths but also some key limitations. They have a high efficacy for prevention of invasive disease against the serotypes included in the vaccine, and demonstrated (but lower) efficacy for prevention of mucosal infections including otitis media, nasopharyngeal colonization, and pneumonia. Preliminary data also indicates that vaccination reduces transmission of vaccine serotypes from immunized to unimmunized individuals. The vaccines though are limited in the number of serotypes that they include and thus there will always be some disease due to non-vaccine serotypes that is not covered. This restriction of serotypes also raises the possibility that the overall effect of vaccination will be attenuated by an increase in disease due to non-vaccine serotypes.

A third approach to immunization is the utilization of protein antigens found on the surface of the protein, antigens which may be involved in adherence or invasion or both. Several candidate vaccines based on alternative antigens are in the early stages of clinical development. Aventis, for example, is developing a vaccine candidate based on two surface proteins, PspA and PsaA, that are found on all pneumococci. Because these proteins are relatively less diverse than capsular types, it might be possible for a vaccine containing just a few proteins to provide some degree of immunity to nearly all pneumococci, regardless of serotype. The first phase 1 study in adult volunteers is underway. This candidate has not yet been evaluated in children or infants for safety or immunogenicity. Based on conversations with each of the manufacturers, McKinsey & Co. estimated that a protein-based vaccine may be ready for global launch by ~2011 at the earliest. Other companies are also investigating protein-based approaches to pneumococcal vaccination but the timeframes for these vaccines are equal to or later than 2011.

In sum, conjugate vaccines are the only vaccines that one can confidently expect to be licensed and supplied between 2006-12. While protein vaccines represent an exciting alternative possibility, they are not likely to be available before 2011 and there is still a significant risk that they will not be commercialized at all. Thus, the PneumoADIP will focus its initial vaccine research activities on determining the potential value of pneumococcal conjugate vaccination. As additional data become available on conjugate and protein vaccines, the PneumoADIP will reassess its focus. For example, if protein vaccines successfully pass through more clinical testing, so that the probability of their

licensure increases, and the limitations of conjugate vaccines grow, then the PneumoADIP might put additional emphasis on protein-based vaccines. At this time it seems appropriate to focus on conjugate vaccines because they have been used in millions of infants and passed through 4 large efficacy trials (northern California, American Indian, Finland, and South Africa), and protein vaccines have not yet been tested in infants.

Efficacy/effectiveness trials of pneumococcal conjugate vaccination of infants.

To this point, 3 large-scale field trials have evaluated the efficacy of pneumococcal conjugate vaccines for prevention of invasive pneumococcal disease, x-ray pneumonia, or both (Table 6). One other trial, conducted in Finland, evaluated the efficacy of two separate 7-valent vaccines for prevention of otitis media.

Because the endpoints of most significance to developing countries are likely to be invasive disease and pneumonia, the following section will review the 3 trials that have evaluated these endpoints. These trials were conducted in northern California, American Indians, and South Africa. The ongoing trials of 9- and 11-valent vaccine candidates in The Gambia and the Philippines are also described.

Studies using 7-valent Pnc-CRM197.

Kaiser Permanente, northern California.

This individually randomized, controlled, double-blinded trial of efficacy served as the pivotal trial for licensure of the 7-valent vaccine (manufactured by Wyeth) (Black S et al. Pediatr Infect Dis J 2000). The study was conducted among children enrolled in a large managed care plan, the Northern California Kaiser Permanente group, under the direction of Black and Shinefield, who previously conducted pivotal trials for licensure of other vaccines including the successful Hib conjugate vaccine, HibTiter™ (Wyeth Lederle Vaccines) (Black SB et al. Pediatr Infect Dis J 1991). The trial was designed to assess the efficacy of a 4-dose regimen for prevention of culture-proven invasive pneumococcal disease in young children. The trial enrolled 37,868 infants who were randomly assigned to receive either Pnc-7 CRM197 or an investigational meningococcal serogroup C conjugate vaccine containing CRM197 at ages 2, 4, 6 and 12 to 15 months. Children with sickle cell disease, known immunodeficiency, serious chronic illness, a history of seizures or of proven pneumococcal or meningococcal vaccine were excluded.

Infants were enrolled and followed in blinded fashion for a period of 3.5 years. In the intention to treat analysis, 49 cases of culture confirmed invasive pneumococcal disease due to vaccine serotypes were observed among the control vaccine recipients versus 3 cases among the pneumococcal conjugate vaccine recipients for an efficacy of 93.9% (95% C.I. 79.6, 98.5). The per protocol analysis showed that only one of 40 cases occurred among recipients of the pneumococcal conjugate vaccine, giving a higher efficacy point estimate, 97.4% (95% C.I. 82.7, 99.9). Subsequent analyses showed that partially vaccinated children (e.g. <3 doses of vaccine) were significantly protected against invasive disease.

There were sufficient cases observed in this study to determine serotype-specific protective efficacy estimates for four of the seven serotypes included in the vaccine. Serotype specific efficacy was 100% for the serotype 14, 18C, and 23F components, and 84.6% for serotype 19F. There were too few cases to assess the efficacy against serotypes 6B (seven cases in controls and one in a vaccinee) and 9V (three cases, all in control vaccinees) and no cases of serotype 4 disease were observed. Data were not sufficient to determine whether there was any cross-protection against other serotypes in the same serogroup (e.g., 6B vaccination providing protection against 6A disease).

However, the overall efficacy of the vaccine against any invasive pneumococcal infection, regardless of serotype was 89.1% (95% C.I., 73.7, 95.8).

The majority of invasive pneumococcal disease detected during this trial was bacteremia without an obvious focus (30 of 52 cases detected). There were 5 cases of pneumococcal meningitis and six cases of sepsis in control vaccine recipients, with no cases of meningitis and one case of sepsis among the pneumococcal vaccine recipients. These results are encouraging but effectiveness against the most severe manifestations of pneumococcal disease will most likely be documented through post-licensure surveillance studies.

American Indian study conducted in the Navajo and Apache populations.

In this high incidence population, Drs. Mathu Santosham and Kate O'Brien from Johns Hopkins University directed a uniquely designed efficacy trial (Moulton LH et al. Controlled Clin Trial 2001). Unlike the other trials, where individual infants were randomized to a vaccine group, this study randomized on the basis of community units on two Indian reservations. This community randomized trial of the efficacy of a 4-dose regimen of the 7-valent Pnc-CRM197 conjugate vaccine was unique among the trials with this vaccine in its ability to measure the indirect (i.e., herd immunity) effects of vaccination (O'Brien KL et al. European Soc Pediatr Infect Dis Conference Istanbul:2001). The control communities received the investigational meningococcal C conjugate vaccine; all participants and investigators were blinded to vaccine group allocations. The study's primary objective was to measure the effectiveness of community-wide vaccination for prevention of invasive pneumococcal disease. Secondary objectives included assessment of the impact of vaccination on pneumococcal carriage among vaccines, the impact on transmission in households, and efficacy for prevention of pneumonia and clinically diagnosed otitis media.

The trial enrolled 8,292 infants from the 38 randomization units. Enrollment and surveillance were truncated by the licensure of Prevnar in the USA. In the per protocol analysis, there were 8 cases of vaccine type invasive disease among control vaccinees and 2 cases among pneumococcal conjugate vaccinees (VE=76.8%; 95% CI, -9, 95); the intention to treat analysis included 3 additional cases in the control group for a vaccine efficacy estimate of 82.6% (95% CI, 21, 96). Preliminary analysis of the efficacy of the vaccine for prevention of pneumonia indicated no significant difference in incidence between vaccinees and non-vaccinees (VE –3%; 95% C.I., -60, 33). However, these data are considered preliminary and analyses are ongoing to determine whether the community randomization process may have led to unbalanced groups which may have biased the efficacy estimate.

<u>Studies using 9-valent Pnc-CRM197.</u>

South Africa. A randomized, placebo-controlled efficacy study was conducted in Soweto, an urban area near Johannesburg, South Africa. The trial was designed to assess the efficacy of a 3-dose, accelerated regimen of vaccination (ages 2, 3, and 4 months) for prevention of invasive disease and x-ray confirmed pneumonia in HIV-positive and HIV-negative infants and children. The preliminary results of the study were presented in May 2002 at the International Symposium on Pneumococci and Pneumococcal Diseases in Anchorage, Alaska.

In HIV infected children, the vaccine provided 58% efficacy versus invasive pneumococcal disease of vaccine serotypes (per protocol analysis, 95% CI, -1, 84). The vaccine did not show a significant reduction in the incidence of pneumonia with consolidation (VE=6%; 95% CI, -21, 27), but this finding is not surprising considering the

substantial role of *Pneumocystis carinii* and other organisms as agents of pneumonia in HIV infected children.

In HIV uninfected children, the vaccine demonstrated highly significant efficacy against invasive pneumococcal disease due to vaccine serotypes (VE=85%, 95% CI, 32, 98). Against pneumonia with x-ray evidence of alveolar consolidation, the vaccine efficacy estimate was 22% (95% CI, 0.1, 40) and just reached statistical significance (P=0.049). Of more relevance for public health purposes, in the per protocol analysis, the vaccine prevented 3 times as many cases of x-ray pneumonia with consolidation (33 cases) as it did culture-confirmed invasive pneumococcal disease (11 cases), indicating that most of the case of pneumococcal disease prevented by this vaccine will be undetected by routine culture methods.

The Gambia. A randomized, placebo-controlled trial design is being used to determine the efficacy of the 9-valent pneumococcal conjugate vaccine for prevention of severe pneumococcal disease including culture-confirmed invasive disease and x-ray confirmed pneumonia. The trial population includes infants born in two rural divisions of The Gambia. With a per capita GNP of $300, a high infant mortality rate (~80/1000 live births), endemic malaria transmission, and limited health care access, the situation is typical of much of rural Africa. Enrollment is expected to be completed by February 2003, follow up should be completed by March 2005.

Study using 11-valent Pnc-D/T

Bohol, Philippines.

This trial is designed to evaluate the efficacy of Aventis' 11-valent pneumococcal conjugate vaccine for prevention of radiographic pneumonia in an urban area of the Philippines on the island of Bohol. This vaccine is manufactured by linking pneumococcal polysaccharides with either diphteria or tetanus toxoids. This randomized controlled trial aims to enroll ~12,000 infants. It is anticipated that the results of this trial will be available in 2005. Aventis does not plan to proceed with licensure and commercialization of this pneumococcal vaccine. Nevertheless, the trial will provide important information on the burden of pneumococcal pneumonia and the value of pneumococcal vaccination in the Philippines and other similar parts of Asia.

Table 6. Results of randomized, controlled trials of pneumococcal conjugate vaccine efficacy against invasive disease and/or radiographic pneumonia.

	Vaccine		Endpoint	
Trial site	Pneumococcal	No. enrolled	Vaccine type pneumococcal invasive disease	Radiographic pneumonia with consolidation
Northern California, USA	7-valent-CRM_{197}	37,868	97% (83, 100)	19% (6, 30)
Navajo and Apache Nations, USA	7-valent-CRM_{197}	8,292	77% (-9, 95); 83% (21, 96)* *intention-to-treat	-3% (-60, 33)*
South Africa	9-valent-CRM_{197}	~40,000	HIV negative: 85% (32, 98) HIV positive: 58% (-1, 84)	HIV negative: 22% (0, 40) HIV positive: 6% (-21, 27)

*Preliminary results pending further analysis to determine if the community randomization may have led to unbalanced risk groups.

Summary of efficacy/effectiveness versus invasive pneumococcal disease

The efficacy of the vaccines for prevention of culture-confirmed pneumococcal invasive disease due to vaccine serotypes is consistently observed to be 83-97% in HIV seronegative children. As one would expect, the efficacy was significantly lower in HIV infected infants (58%).

Summary of efficacy/effectiveness versus radiographic pneumonia with consolidation

Pneumonia is the most common manifestation of severe pneumococcal disease in developing countries and thus, any recommendation for the use of pneumococcal vaccines will be driven largely by its ability to prevent pneumonia. Assessing the efficacy of vaccines for prevention of pneumonia, however, is substantially more difficult than assessing their efficacy for prevention of invasive disease. As an endpoint, invasive pneumococcal disease is advantageous because it is 100% specific to *S. pneumoniae* and a highly objective outcome - either there are *S. pneumoniae* in a culture or there are not; there is little room for individual variation or interpretation. Pneumonia, on the other hand, has none of these features. In clinical trials, the diagnosis of pneumonia is based on a chest x-ray finding. Many pathogens, in addition to *S. pneumoniae*, can cause x-ray confirmed pneumonia, so the endpoint is not specific to pneumococcal infections. Furthermore, the interpretation of chest x-rays itself is subjective and prone to variations between readers. While WHO has made great strides to reduce inter-reader variability in x-ray interpretation, the process will always remain inherently more subjective than the definition of invasive disease.

Currently, estimates of the efficacy of the vaccines for prevention of pneumonia are available from the American Indian, northern California, and South African trials. Preliminary results from the American Indian trial showed no significant protection against radiographic pneumonia. However, a more detailed re-analysis of the data has shown significant protection against chest x-ray pneumonia (K. O'Brien, personal communication). Interpretation of these results is complicated however as the enrollment into this trial was terminated prematurely by the licensure of the 7-valent vaccine in the USA. Further analyses are underway to understand better the findings on pneumonia efficacy and to explore further the possibility of any residual confounding that may have been introduced through the community randomized design. The northern California and South Africa trials showed significant protection versus radiographic pneumonia, with individual estimates of efficacy between 19-22% (Black SB et al. Pediatr Infect Dis J 2002; Klugman K et al. ISPPD 2002 [abstract]). Though these results seem quite consistent it is important to bear in mind that the definition of pneumonia with consolidation used in each of these trials was slightly different. The South African trial used the WHO standardized case definition while the northern California trial did not.

Interpretation of the South Africa trial results

To date, only one efficacy study of a pneumococcal conjugate vaccine has been conducted in a developing country population and that one – South Africa – was carried out in the most developed part of the continent in a population that shares few characteristics with the rural and underdeveloped areas of sub-Saharan Africa where pneumonia mortality is high. Of the three completed efficacy studies (i.e., No. California, American Indian, and So. African), the results of the South Africa trial, however, are likely to be the most applicable to VF-eligible countries, and thus, should be considered in greater detail.

Prior to announcement of the results of the South African trial, most researchers probably would have expected the vaccine to reduce pneumonia with consolidation by 30-40%. This assumption was that if Hib vaccine reduced pneumonia with consolidation in the Gambia by 20%, then pneumococcal vaccine should have an effect 1.5 to 2 times as great. As a consequence, some pneumococcal researchers viewed the 22% efficacy estimate as "disappointing". On the other hand, in HIV uninfected infants, the vaccine prevented 3 times as many cases of x-ray pneumonia as it did cases of culture-confirmed invasive pneumococcal disease (33 cases prevented vs. 11 cases prevented) indicating that most of the effect of this vaccine for prevention of illness will go undetected by routine culture methods.

If we take a less emotional perspective, the South African trial is highly instructive and highlights several possible explanations for the pneumonia efficacy data – each of which will require further research. Possible explanations include:

1) The case definition for x-ray confirmed pneumonia used in the South African trial was less specific than the one used in the Gambia Hib trial. The definitions of pneumonia used in the trials were not standardized, thus it is very difficult to base expectations for one trial on the results from another trial. If the definition of pneumonia used in the Gambia Hib trial was more specific than the one used in the South African pneumococcal trial, then this could explain the difference. It would suggest that application of the Gambia Hib trial definition to the South African x-rays might increase the observed efficacy in the South African trial (i.e., efficacy might increase to 30% or more) and remove the feeling of 'disappointment' that some researchers have had.

2) Pneumococci account for less pneumonia with consolidation than previously expected. It is conceivable that fewer of the pneumonias with consolidation are due to pneumococci, or at least vaccine serotype pneumococci, than expected before the trial. Because it is difficult to establish the etiology of non-bacteremic pneumonia, it is possible that extrapolations from lung aspirate and blood culture studies are inaccurate, and that *S. pneumoniae* are less frequently a cause of x-ray confirmed pneumonia with consolidation than expected. Alternatively, pneumococci may still be causing much of the disease but it may be due more often to serotypes not included in the vaccine. Serotype replacement could also produce this effect by increasing the relative contribution of non-vaccine serotype pneumonia among vaccinated children and thereby reducing the overall difference in pneumonia incidence. Further research is needed to determine which, if any, of these explanations is contributing to the observed results.

3) The vaccine is less effective against non-bacteremic pneumonia than it is against invasive disease. It is already known that the efficacy of the vaccine is lower against mucosal infections such as otitis media and nasopharyngeal colonization (50-60%) than it is against invasive infections such as bacteremia and meningitis (>80%). If the efficacy versus non-bacteremic pneumonia is more like otitis media than bacteremia, it could explain the efficacy rate observed. For example, if vaccine serotype pneumococci actually do cause 45% of non-bacteremic x-ray pneumonia with consolidation, a 22% efficacy vs. x-ray confirmed pneumonia could be explained by the vaccine having only a 50% efficacy versus these non-bacteremic pneumonias (i.e., 45% x 50%=22.5%). Alternatively, in the same situation if the vaccine had an efficacy of 85% vs. these infections, the observed efficacy would have been 38% (i.e., 45% x 85%=38.3%).

Each of these possible explanations has a different but substantial implication for the PneumoADIP, and for the "investment case" for pneumococcal vaccine. If it turns out that pneumococci are less important as a cause of pneumonia than presumed previously, then this will have implications on the priority assigned to pneumococcal disease prevention in countries. Alternatively, if vaccine serotype pneumococci are less important as causes of pneumonia or the efficacy of the vaccine against non-bacteremic pneumonia is relatively low, then this makes investigation of alternative approaches to vaccination relatively more important and will effect the price that the VF and countries would be willing to pay for current vaccines. At this time, the relative contribution of each of these explanations is unclear. **A major focus of the PneumoADIP will be research aimed at clarifying the effectiveness of these vaccines for prevention of pneumonia.** WHO has initiated efforts to resolve issues with the definition of pneumonia episodes and the PneumoADIP will work closely with WHO to support its efforts in this area.

Serotype replacement

There are over 90 known pneumococcal serotypes. Pneumococcal conjugate vaccines generate immunity and reduce disease due to serotypes included in the vaccine (vaccine serotypes), and to some degree, protection against cross-reacting serotypes (vaccine-related serotypes) – e.g., 6B vaccine provides some protection against 6A disease. There is the possibility, however, that when conjugate vaccines protect against the acquisition of a vaccine serotype in the nasopharynx that another non-vaccine serotype will simply replace it (an effect referred to as "serotype

replacement"). If serotype replacement occurs it will attenuate the overall impact of pneumococcal vaccination because the reduction in vaccine type disease will be associated with some increase in non-vaccine type disease.

Several studies have shown that pneumococcal conjugate immunization is associated with serotype replacement in nasopharyngeal colonization of pneumococci (Klugman Lancet ID 2001). In other words, when compared to unimmunized infants, those who receive pneumococcal conjugate vaccines are significantly less likely to be colonized with vaccine serotypes but significantly more likely to be colonized with non-vaccine serotypes. Not surprisingly, the Finnish efficacy trial also showed a significant increase in otitis media due to non-vaccine serotype pneumococci among children who had received a 7-valent pneumococcal conjugate vaccine (Eskola J N Engl J Med 2001).

While serotype replacement has been shown to occur for colonization and otitis media, no significant increase in invasive disease due to non-vaccine serotypes (i.e., serotype replacement disease) has been observed in any of the large-scale efficacy trials. While these results are encouraging, the issue of serotype replacement from invasive disease is far from settled. Post-licensure surveillance studies that include a large number of immunized infants will likely provide the most robust indication of whether serotype replacement in invasive disease occurs, and if so, an indication of the magnitude of that effect.

Herd immunity effects from pneumococcal conjugate vaccination

The value of pneumococcal conjugate vaccination would be greatly enhanced if it were shown to interrupt transmission of pneumococci and result in "herd immunity" – i.e., indirect protection of unvaccinated populations. This is a particularly important issue for developing countries where coverage rates are often in the 50-70% range. If immunizing 60% of a population could reduce transmission and effectively reduce disease incidence by 80% this would be like essentially getting a 25% bonus effect from the vaccine's use. Herd immunity may also provide 'indirect' protection of very young infants – those too young to be immunized – by reducing transmission from their older siblings and family members.

Mass immunization with Hib conjugate vaccines has led to reduced transmission of Hib organisms and herd immunity in a wide range of settings (Barbour ML Emerg Infect Dis 1996; Levine OS et al Pediatr Infect Dis J 1998). Although Hib and pneumococcal vaccines and infections share many similar characteristics, there are significant differences between the two that make it difficult to predict reliably whether, and under what circumstances, pneumococcal conjugate vaccination will lead to herd immunity. For example, Hib colonization is relatively less prevalent and generally more restricted by age than pneumococcal colonization. Early data are promising though that routine pneumococcal immunization may reduce transmission. Like Hib conjugates, pneumococcal conjugate vaccines significantly reduce colonization with vaccine-type pneumococci (Klugman KP. Lancet ID 2002). Also, results from the American Indian trial with 7-valent vaccine indicates that vaccination reduces transmission of vaccine-type pneumococci from immunized infants to older siblings, younger siblings, and other adults in the household (K. O'Brien, JHU, personal communication).

Finally, data from CDC's active bacterial core surveillance indicates that the infant immunization program in the USA has led to a significant reduction of invasive disease due to vaccine serotypes in adults aged 20-39 and >65 years (i.e., the age groups that include parents and grandparents) (C.Whitney, ICAAC 2002) (Table 7). Further studies in developing country populations – where the dynamics of transmission are different and where the vaccine programs are more marginal – are needed to be able to reliably predict the effect of mass vaccination in these populations.

Table 7. Change in Invasive Pneumococcal Disease Incidence, by Serotype and Age Group USA, CDC surveillance 1998-2001

Age group	Serotype	Cases/100,000 pop		Percent change	95% CI
		98/99 Ave	2001		
65+	Vaccine	34	24	-29	-36, -20
	Related	8.4	6.5	-22	-38, -4
	Nonvaccine	18	19	+5	-8, +20
20-39	Vaccine	6.6	4.0	-40	-49, -29
	Related	1.4	1.1	-22	-44, +7
	Nonvaccine	3.2	2.6	-20	-35, -1

Source: C. Whitney, CDC. Presented at ICAAC 2002

II. VISION FOR THE ADIP

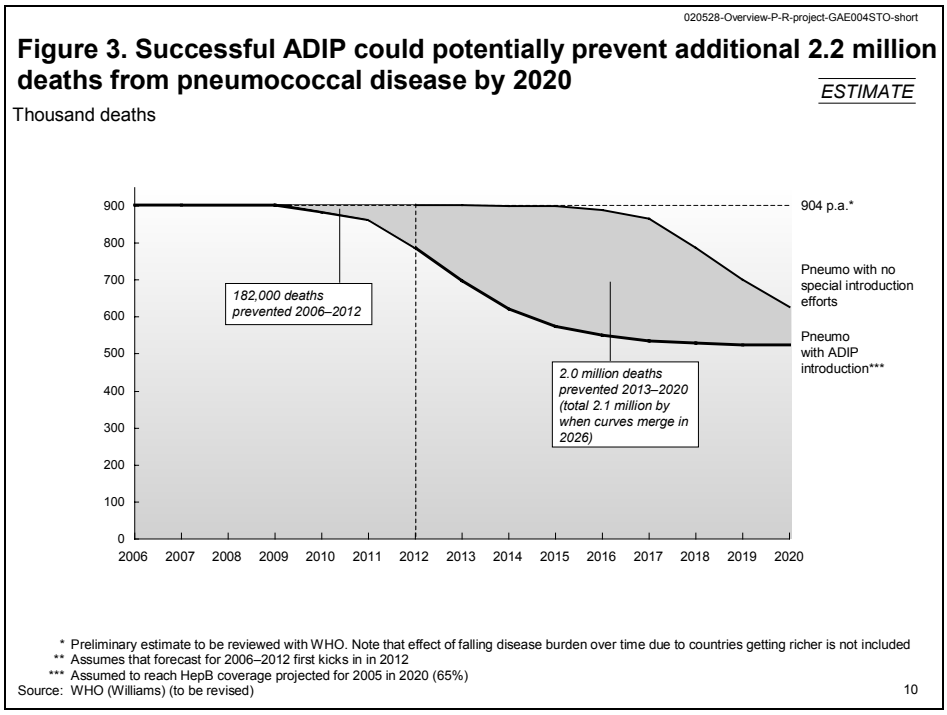
Goals of the Pneumococcal ADIP

The pneumococcal ADIP team at Johns Hopkins will aim to provide the GAVI Board, international donors, and decision-makers in developing countries with the evidence required to decide on a country or regional level whether to incorporate pneumococcal conjugate vaccination into national immunization programs. To achieve this goal, the ADIP team will build on the existing efforts of local and international partners to:

- determine the local burden of pneumococcal disease,
- evaluate the safety, immunogenicity, and effectiveness of the vaccine,
- understand local perceptions of pneumococcal diseases, including pneumonia, and meningitis, and the attractiveness of a vaccine to prevent them,
- assess the cost-effectiveness of the investment,
- communicate this information to key decision-makers,
- assure that systems are in place to deliver the vaccine if it is used,
- and work with existing and potential manufacturers to assure an adequate, sustainable, affordable supply of quality vaccine.

It is important to recognize that the ADIP concept is a departure from past efforts to introduce newly developed vaccines worldwide. Past experience has shown that demonstrating a vaccine's efficacy is necessary, but not itself sufficient, to assure introduction of the vaccine. Furthermore, presentation of technical information (e.g., disease burden and vaccine efficacy data) to the western scientific community through symposia and journal articles, but not in forums that are attended by decision-makers in developing countries, does not meet the needs of local policy-makers. As a result, previous efforts led to a situation with lots of research evidence but very little policy action. Therefore the ADIP proposed here aims to redefine the paradigm within which information is gathered, packaged and disseminated. The reason for the paradigm shift is very basic: it is simply unacceptable that >15 years after their launch in rich countries, only 10% of the world's infants in developing countries are routinely receiving Hib and hepatitis B vaccines. The PneumoADIP is an effort to develop a more successful paradigm for introduction, based on the experience from Hib and hepatitis B.

Based on preliminary analyses done by McKinsey & Co. using existing data, a successful ADIP effort could accelerate the use of pneumococcal vaccine in VF-eligible countries and ultimately prevent nearly 2.2 million child deaths between 2006 and 2020 (Figure 3). Interim projections suggest national demand may amount to >10 million vaccinated children and 180,000 deaths prevented between 2006-2012. Success of the ADIP, however, cannot be measured simply by doses delivered or deaths prevented. As an effort to help countries establish rational health priorities, a country that uses a solid evidence base and decides not to make pneumococcal conjugate vaccine introduction a priority should also be considered a success for the ADIP effort.



The ADIP project aims to achieve several important milestones over a 4 year time period (2003 - 2006) with a budget of ~$30,000,000. In project management style, the proposal includes deliverables and targets against which the project's progress can be measured.

Go/No Go decisions

The PneumoADIP team recognizes that no financial commitment has yet been made to procure pneumococcal conjugate vaccines through the Vaccine Fund, that the PneumoADIP will be monitored closely by a Steering Committee on behalf of the GAVI Board and that the Board will make "Go/No Go decisions" between 2003-2006. The role of the team will be to undertake critical analyses, and on the basis of the analyses, to provide the GAVI and VF Boards with a series of strategic options to consider and act on. The aim of the team will be to provide the highest quality analyses in order to help the Board make the most rational decisions.

The ADIP team recognizes the Board may decide that pneumococcal vaccine procurement is a "NO GO" – that is that they may either recommend the VF not use its resources to procure pneumococcal conjugate vaccines or that the PneumoADIP not be renewed after 3 years. The ADIP team also realizes that it is important to stress this point in discussions with countries so that we do not build false expectations.

Overlap with Hib vaccine activities and other ARI prevention efforts

Much of the PneumoADIP team's work will focus on supporting the collection of data to measure both the burden of pneumonia and meningitis in developing countries and the value of preventing it through vaccination. Clearly, the overlap of these activities with those that would go into Hib introduction are striking. Furthermore, country decisions to uptake Hib vaccine will influence decisions on uptake of pneumococcal vaccine. If chosen, the PneumoADIP team at Johns Hopkins would be willing to undertake the additional tasks needed to help GAVI achieve its milestones for Hib. The proposed Executive Director, Dr. Orin Levine, is an established leader in the global effort

to accelerate Hib vaccine introduction in developing countries and would be committed to seeing this succeed. Some additional resources would be needed to undertake the key Hib activities, but given the substantial overlap with pneumococcal activities, this would likely require only a small outlay relative to the benefits gained by using the PneumoADIP infrastructure.

Key characteristics of the pneumococcal ADIP strategy

Looking ahead to 2007 with or without a successful ADIP

Many GAVI partners are interested in accelerating the development and use of pneumococcal vaccines in developing countries and in some cases, their efforts to achieve this aim date back nearly 20 years. For example, NIAID supported the first efforts to develop a pneumococcal conjugate vaccine candidate in the early 1980s and required the grantee to include serotypes of importance to children all over the world, not just in the United States. WHO, USAID, CDC, and NIAID also collaborated on a global effort to determine optimal serotype formulations for global vaccine use in the late 1980s, and together with MRC/UK and PATH, have invested heavily in research in The Gambia on the burden of pneumococcal disease and the safety and efficacy of candidate pneumococcal conjugate vaccines. Another example is the ARIVAC Consortium that includes Finnish Public Health Institute (KTL), University of Queensland, Australia, and partner organizations in the Philippines, which has long been involved in studies to define the burden of pneumococcal disease in developing countries and to establish the efficacy of pneumococcal vaccines.

The ongoing efforts of GAVI partners are essential and will contribute greatly towards establishing the value of vaccination. Experience with Hib and hepatitis B vaccines, however, indicates that loosely coordinated efforts will not assure that the benefits of vaccination are available to the world's poorest countries *at the earliest point possible*. For example, >15 years after licensure in the USA, <10% of infants in VF-eligible countries were routinely vaccinated with Hib or hepatitis B vaccines. *The uptake of these two vaccines was slowed considerably because there was no coordinated effort to work on both the supply and demand factors* and because many key activities were undertaken *in sequence rather than in parallel*. While the public sector often sponsored research and surveillance that demonstrated disease burden or vaccine effectiveness, there was no coordinated effort to generate awareness of the vaccine's value on the basis of the data and to create national demand based on these data. Equally important, efforts to work on demand and supply issues were undertaken only after the vaccine's safety and efficacy were established. This sequential process reduced the risk that the public sector might spend money on efforts for a vaccine that did not prove to be sufficiently efficacious or safe to be demanded by countries. *However, the price of this sequential effort was a delay in introduction of the vaccine- a delay that can be measured in child deaths that might have been prevented.* When public sector did make an effort to partner with industry on supply issues, it was rarely willing to assume any of the risks and therefore, the partnerships did not yield any significant progress on vaccine price or capacity.

To understand the impact a successful ADIP can have it is important to anticipate the likely scenario in 2007. In particular, it is important to predict the impact of current efforts to improve the demand and supply situation globally and in VF-eligible countries. By 2007, at a minimum, we can expect the following:

Demand factors

- **The results of the Gambia and Philippines pneumococcal conjugate vaccine trials will be available (in addition to the results from the South Africa trial).** We expect that at least two of phase 3 field trials (So. Africa AND

either Gambia or Philippines) will show that 9- and/or 11-valent conjugate vaccine provides significant protection against invasive pneumococcal disease and x-ray confirmed pneumonia. The South Africa trial has already shown a 22% reduction in pneumonia with consolidation. It is difficult to predict the degree of protection that will be seen in the Gambia and Philippines trials and how the observed efficacy will impact demand. The additional data, however, will improve our ability to quantify more accurately the potential impact of vaccination. If the Gambian trial shows significant efficacy versus x-ray pneumonia, this will create a situation where 2 independent field trials with the 9-valent vaccine have shown efficacy against this important endpoint in diverse African settings. This is likely to convince at least some individuals and institutions that pneumococcal conjugate vaccine is indicated for use in Africa.

- **>25 Million infants and children in the United States and Europe will have been vaccinated with pneumococcal conjugate vaccines** and post-licensure surveillance studies will demonstrate the effect of the vaccine for reducing vaccine type invasive disease and also, potentially, serotype replacement disease and/or herd immunity. In fact, the herd immunity effect of infant immunization is already being seen in the United States, where preliminary surveillance data indicate that invasive disease due to vaccine serotypes has declined significantly in adults aged 20-39 and greater than 65 years (the age group most likely to have children and grandchildren of vaccine-eligible ages) (C. Whitney et al. ICAAC 2002). Based on the clinical trial and routine use data, we can reliably expect that there will be individuals and institutions advocating for routine infant pneumococcal vaccination in the poorest countries, where pneumococcal disease is a major cause of child mortality. Arguments will likely characterize the situation as a 'social injustice' if the benefits of vaccination continue to accrue in richer countries, where ~10% of pneumococcal deaths occur, and not in poorer countries where ~90% of pneumococcal deaths occur.

Supply factors

- **At least one, and most likely two, newer pneumococcal conjugate vaccines will be licensed and commercially available.** These vaccines will include at least two additional serotypes, 1 and 5, that are important causes of severe disease in developing countries (accounting for 10-20% of all cases). A 9-valent pneumococcal conjugate vaccine (combined serogroup C meningococcal conjugate), manufactured by Wyeth, is targeted for launch in 2006, and an 11-valent conjugate vaccine from GSK may be licensed even before 2006 if the FDA accepts immunologic correlates of protection and licenses on the basis of immunogenicity data.
- **Wyeth and GSK will expand capacity to supply the high-profit margin markets of industrialized countries**, and the private sectors of middle and low income countries. *In the absence of a coordinated ADIP effort by GAVI, it is unlikely that industry will scale up production capacity to meet demand in VF-eligible countries* between 2006-2010. If there is any demand for the vaccine in VF-eligible countries, the result will be a situation where supply is insufficient to meet demand and thus, prices stay high.
- **Even in the event of competition between GSK and Wyeth, the price of pneumococcal conjugate vaccines for industrialized countries is likely to remain in the range of $30-50 per dose through 2009.** Prices for middle income countries maybe reduced below this point, but it is unlikely that they will be in the $3-8 range that would be expected for VF-eligible countries in the

event that the ADIP is successful. **As stressed by the McKinsey & Co. analysis, the public sector's best approach to assuring an affordable supply of vaccine is to reduce the uncertainty of demand in VF-eligible countries.**

The PneumoADIP must learn from the experience with Hib and hepatitis B, anticipate the situation that will emerge in the absence of a coordinated effort, and provide the framework and activities that will result in evidence based decisions to use or not use pneumococcal conjugate vaccines. By doing so, we can structure our activities and efforts to eliminate the delays in uptake of new vaccines. However*, in order to avoid the 15-year time lag, the PneumoADIP and its stakeholders must be willing to assume some risks.* Much of the necessary research to establish the potential benefit (and risks) of pneumococcal conjugate vaccination is ongoing, but results will not be available until at least mid-2005. The results of these ongoing studies may indicate that further efforts to introduce pneumococcal conjugate vaccines in developing countries are not warranted. However, **starting to engage and communicate with national and international decision-makers now, rather than waiting until the research is completed, is a necessary risk to assure that time is not lost in the event that the research does support the use of these vaccines.**

Focus on reducing demand uncertainty

Analysis undertaken on behalf of GAVI by McKinsey & Co. shows that 'reducing demand uncertainty' is the key lever that the public sector can apply to help reach GAVI's supply and price goals for pneumococcal vaccine for VF-eligible countries (Figure 4). Through its interactions with industry, McKinsey & Co. presented an analysis with at least two important lessons for public sector representatives wishing to partner with industry. First, in the mind of industry, *demand for a vaccine does not equal need for the vaccine.* In other words, although public sector researchers often show convincing data that there is a major need for a vaccine in Africa, the expressed national demand to introduce that vaccine is much, much lower. In other words, what industry wants to see is an analysis of how many doses will be used in any given year in developing countries. They also stressed that demand has to be backed by credible financing.

Second, the McKinsey analyses show that the price of a vaccine does not equal the cost of the vaccine. The cost of goods that go into manufacturing a single dose of the vaccine (i.e., the marginal costs of production) are only a small part of the price of a dose of vaccine. Pricing is largely determined by the risks that industry takes in the development and launch of a vaccine. From the perspective of industry, one of the biggest risks that they face when they make decisions about launching a vaccine is the uncertainty of demand. What if they build a manufacturing plant sized to supply the developing world with 150M doses per year but then the developing world only demands 5M doses? In their discussions with McKinsey & Co. and GAVI, *industry representatives indicated that if the public sector (through a coordinated ADIP effort) can reduce demand uncertainty, and hence reduce the risks to them, then they are prepared to discuss reducing the cost of the vaccine and making the investments in capacity that would be needed to supply the VF-eligible countries.*

The ADIP strategy is designed to develop the evidence of disease burden and vaccine safety and effectiveness needed by countries to generate national demand and credible financing and to match the demand with a reliable and adequate supply of affordable, high-quality pneumococcal vaccines.

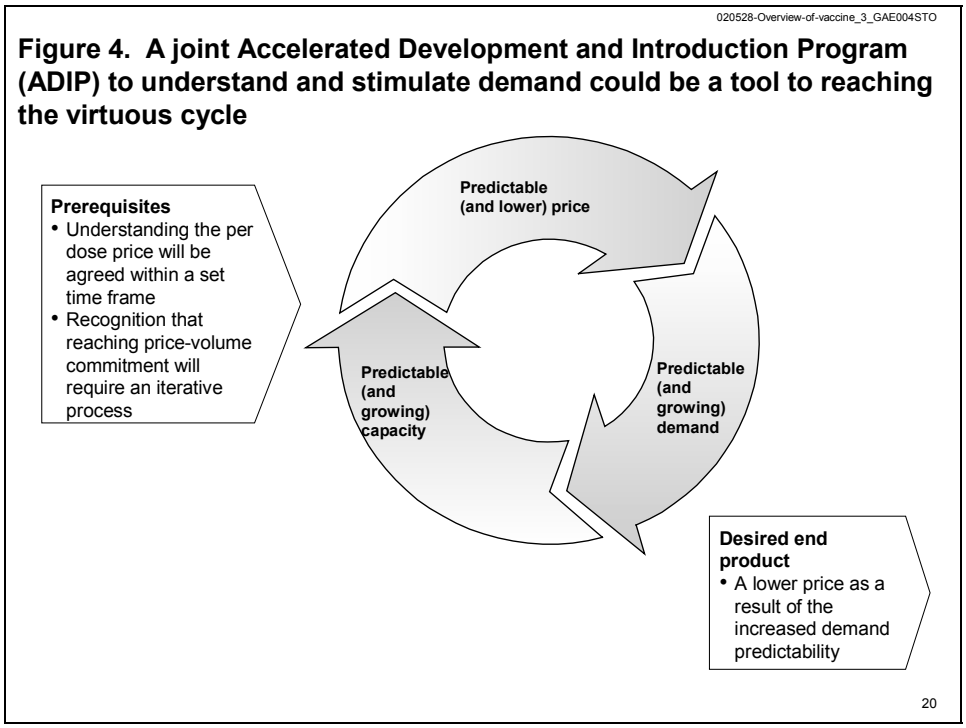


Figure 4. A joint Accelerated Development and Introduction Program (ADIP) to understand and stimulate demand could be a tool to reaching the virtuous cycle

Providing the Board with analyses that can be used to determine the 'investment case' for pneumococcal vaccine

On behalf of GAVI, McKinsey & Co. conducted an independent preliminary assessment of the 'investment case' for pneumococcal vaccination – that is, the expected value of using GAVI/VF resources to accelerate the development and uptake of pneumococcal vaccination in VF-eligible countries. Preliminary analyses by McKinsey & Co. suggest that pneumococcal conjugate vaccination is likely to be an attractive health investment for VF eligible countries, provided that the vaccine can be procured at a sharply reduced price (range $3-8 per dose). However, the 'investment case' for use of the national and VF resources must be continually re-assessed as new data on the vaccine's effectiveness and the disease burden become available, and as national demand becomes clearer. The PneumoADIP team at Johns Hopkins will provide the GAVI and VF Board with a series of rigorous analyses to assess and re-assess the attractiveness of investing in pneumococcal vaccination. These analyses will incorporate the findings from economic, financial, epidemiologic, clinical and audience research.

Examples of the types of analyses that the team will provide to the GAVI Board include:

- *Summary of vaccine safety and effectiveness for prevention of key outcomes.* The ADIP team will provide the Board with regular updates on the status of pneumococcal vaccine research including summaries on vaccine safety and effectiveness. Clearly, the vaccine must be safe and efficacious in order for GAVI to propose supporting its use in VF-eligible countries. **In particular, the effectiveness of the vaccine for prevention of pneumonia hospitalizations and deaths will be essential information**.
- *Country- and region-specific estimates of the burden of pneumococcal disease and cost-effectiveness of vaccination.* The first step in discussing the introduction of a new vaccine is to understand the local disease burden. In its

initial phases, the PneumoADIP will emphasize activities that help developing countries to estimate their local burden of pneumococcal disease. This information can then be used to develop cost-effectiveness analyses. For the GAVI Board and for local decision-makers, this information will be useful in gauging the priority for pneumococcal vaccination relative to other potential investments. Estimates, including a description of the uncertainties in each estimate, will be presented.

- *Cost-effectiveness analyses, from the perspective of the Vaccine Fund, for supporting pneumococcal conjugate vaccine use between 2007-12.* This analysis will provide the Board with an assessment of the attractiveness of investing in pneumococcal immunization and provide a basis for comparison to other possible investments.
- *Demand forecasts (i.e., projected number of doses demanded by country each year) and projected resource requirements for national governments, international donors, and the Vaccine Fund.* This analysis will provide governments, the Board and the Vaccine Fund an indication of the financing that will be required each year in order to support the procurement of vaccine for VF-eligible countries. The Vaccine Fund can use this information in its strategic planning process.
- *Financial analysis of the costs and risks involved in investing in alternative supply sources such as emerging market suppliers.* On the supply side, emerging market suppliers may provide an alternative to multinational firms but technology transfer would be required. This analysis will seek to quantify the costs, risks, benefits, and timing of technology transfer. This information will be useful to the Board when they consider alternative strategies for assuring a sustainable, affordable supply of pneumococcal vaccines.
- *Analysis of the costs of delivering pneumococcal vaccine in the context of local immunization programs.* In addition to the costs of the vaccine itself, introduction of the vaccine into national programs will also have cost implications. It will be important for national governments and the Board to see an analysis of the costs of introduction at the local level, and to consider these costs in the decision about whether to support introduction through the Vaccine Fund.
- *Systematic surveys of local and international decision-makers attitudes towards the attractiveness of pneumococcal vaccine.* The Board will want to consider the issue of sustainability of the vaccine's use and so information will be presented on the attitudes of key decision-makers towards the attractiveness of pneumococcal vaccination. This important political element will need to be considered in any decision on whether to procure the vaccine on behalf of VF-eligible countries.

We recognize that while preliminary analyses indicate the potential attractiveness of investment in pneumococcal vaccination, there are substantial uncertainties requiring additional refinements as new data become available. With the concerted ADIP effort outlined in this proposal, we believe that we can provide a broader, more rigorous analytic basis to re-assess the case for investment in pneumococcal vaccination.

<u>PneumoADIP activities support all pneumonia and meningitis prevention efforts, not just vaccination</u>

A major initial priority for the PneumoADIP team will be to support activities to define better the local burden of pneumococcal disease – including pneumonia,

meningitis, and antibiotic resistance – and to communicate these findings to key decision-makers. In this respect, the efforts of the PneumoADIP will support all efforts to improve child health through prevention and treatment of pneumonia and meningitis, not just vaccination. Efforts to improve health systems and treatment effectiveness should also be strengthened by improving the evidence base on pneumonia and meningitis burden. Furthermore, if vaccination is considered, the data generated by the PneumoADIP will be valuable to all vaccine approaches, not just conjugate vaccines.

Succeeding through partnership

The PneumoADIP team intends to meet its goals by engaging a variety of partners to undertake the necessary activities. The small team itself will act as a 'spider in the web' where the PneumoADIP is the spider and the web includes the many partners currently and potentially engaged. The challenge will be to leverage the investments of partners by coordinating and supporting ongoing and future efforts by partners.

We aim to build partnerships on several levels and through a variety of methods. In the initial phase of the ADIP, the team will seek to partner with manufacturers having products in late-stage development and to identify emerging market manufacturers who may be important sources of supply in the future. We intend to meet individually with industry to communicate the specific aims of the ADIP, establish relationships between ADIP team members and key corporate counterparts, and to explore areas for collaboration in the areas of research and communications.

We intend to work with the GAVI Task Forces – Advocacy (ATF), Financing (FTF), Implementation (ITF), and Research and Development (TF R&D) – , the GAVI Secretariat, and the Regional Working Groups (RWGs) to assure that our efforts are coordinated with their workplans. We will share our plans with the Task Forces as they are developed and make our staff available to the Task Forces for ease of communication. Dr. Levine has worked closely and effectively with the Secretariat, the TF R&D and FTF on the development of the ADIP strategy over the past 2 years, and in June 2002, Dr. Levine presented the ADIP concept to the Asia-Pacific RWG in Bangkok.

Success will depend on productive working relationships with international agencies and national counterparts in research and implementation. The proposed Executive Director, Orin Levine, has a long and successful history of collaboration with many of the leading agencies and institutions in the field of international vaccination and pneumococcal disease, and in collaboration with industry. He has worked in a range of capacities for a number of leading agencies including CDC, NIAID, WHO, and on behalf of GAVI. He has also worked collaboratively with leading researchers at a large number of international research groups including the UK Medical Research Council, the International Vaccine Institute, the London School of Hygiene and Tropical Medicine, and the Finnish Public Health Institute (KTL) to name a few, and has served on pneumococcal vaccine advisory boards for Aventis and Wyeth.

Dr. Levine is regarded as a trusted partner by many of the major constituencies who play important parts in bringing pneumococcal vaccines to children in developing countries. In addition to an understanding of research and science, he has a unique understanding of the broader issues of international donors, national decision-makers, and commercial business perspectives. Annex A includes letters of support and reference from WHO, IVI, and KTL and letters of reference for Dr. Levine from Prof. Keith McAdam, Director, MRC Laboratories – Gambia, and Prof. Yang Yong-Hong, Deputy Director, Beijing Children's Hospital, China.

Industry will be a critical partner. The PneumoADIP team will include members with substantial experience in industry to facilitate this partnership. The proposed

Director, Communication Strategy brings strong insight from her 15+ years working in the commercial operations of pharmaceutical companies. The Directors for Vaccine Research and Vaccine Supply & Financing will further strengthen these connections.

Collaborating with the Rotavirus ADIP team

We would welcome the opportunity to collaborate with our counterparts in the Rotavirus ADIP team. We expect that there will be activities, meetings, and other opportunities to share resources and experiences. For example, we could share a strategic advisory group or pool our resources on common activities like audience research that apply to each effort. (Note: Dr. Levine and Dr. Joe Bresee, RotaADIP have developed jointly an RFP for audience research and have an agreement to co-fund the project.) Frequent communication will be important, and we would be eager to establish a regular line of communication, such as a monthly conference call with the Rotavirus team.

PneumoADIP priority activities in the area of disease burden and vaccine research

On behalf of the GAVI Task Force on Research and Development, Dr. Levine – together with Drs. Thomas Cherian and Jay Wenger at WHO – convened a meeting of more than 40 experts in the area of pneumococcal disease and vaccination to outline priority activities needed to accelerate the uptake of pneumococcal vaccines in developing countries. The list of activities was prioritized by a transparent ranking approach with highest priority given to those activities that were both important and urgently needed. The list of activities was then posted on the Internet and circulated by e-mail for comments to over 300 individuals in the field, and revised based on these comments. The result was a list of 7 'highest priority activities' and 17 priority activities over all.

The efforts of the PneumoADIP team at Johns Hopkins will reflect the recommendations and priorities established by this group. The priority assigned to individual activities, though, will be re-assessed based on the input of regional PneumoADIP advisory boards (more detail on regional advisory boards and the interaction of the PneumoADIP with external structures are included in section III, Management and Reporting and Annex E) and updated to include more recent developments and new data.

Priority Research and Development Activities Necessary to Accelerate the Introduction of Pneumococcal Conjugate Vaccines in Developing Countries

From a GAVI Task Force on R&D-sponsored meeting, April 19-20, 2001

The meeting identified 18 priority activities, with 7 highest priority activities highlighted as both very important to meeting GAVI's objective and urgently needed.

Very important and urgently needed

- Developing a range of methods to assess key disease burden measures in different settings
- Standardizing interpretation of chest x-ray pneumonia
- Expanding surveillance for laboratory confirmed pneumococcal disease
- Measuring the burden of pneumonia
- Continuing evaluation of the impact of immunization in efficacy populations and high-risk populations of industrialized countries
- Generating more local advocacy and ownership from existing and future research efforts
- Develop regulatory pathways to allow licensing and release of pneumococcal vaccines for use in developing countries

Important but can begin in the next 12-18 months

- Evaluating the key disease burden outcomes in each region
- Establishing the economic impact of pneumococcal disease and the potential cost-effectiveness of immunization
- Establishing the efficacy/effectiveness of pneumococcal conjugate vaccination against key endpoints in developing countries
- Evaluating the herd immunity effects of routine infant immunization on young infants
- Evaluating the safety and immunogenicity of neonatal immunization schedules
- Evaluating 1 or 2 dose regimens of pneumococcal conjugate vaccination
- Establish and reinforce immunization practices advisory committees at the country level

Important activities whose conduct is influenced by the results of antecedent activities

- Evaluating the safety and immunogenicity of maternal immunization
- Evaluating the safety, immunogenicity, and efficacy of pneumococcal conjugate vaccination in HIV infected children
- Evaluating mixed regimens of pneumococcal conjugate and polysaccharide vaccine
- Develop standard materials and methods to license and release pneumococcal conjugate vaccines

In project-management style, we have proposed a series of specific deliverables and targets against which the project's performance can be measured. The specific targets for the PneumoADIP team are outlined in the table below. We will begin our efforts by developing and reinforcing 3-5 regional/sub-regional networks of sites to establish the burden of invasive pneumococcal disease between 2003-2006. This surveillance will help to provide evidence of pneumococci as a cause of serious illness, data on the serotypes causing disease locally, and estimates of antibiotic resistance in the community. We expect that these networks will include between 10-30 VF-eligible countries and at least 4-6 countries that are likely to be 'early adoptors' if vaccine becomes available as early as 2007.

Early feedback suggests that this approach will be highly successful. As Directors of the "interim" ADIP project, Drs. Levine and Cherian developed and circulated an RFA for networks to conduct surveillance for laboratory-confirmed invasive pneumococcal disease. The RFA required a relatively swift response (~6 weeks) and had a relatively most funding limit of $600,000 over 3 years. Nevertheless, the response to the RFA was outstanding, with 13 proposals submitted with proposals from all regions of the world. A technical review group is meeting in Geneva on Jan. 20/21 to review the proposals. At this point, GAVI has only committed to fund up to 3 projects. If all of these proposals were considered fundable, >$10,000,000 would be needed over 3 years. While it is unlikely that all of the proposals will be worthy of funding, it seems plausible to assume that the ADIP could fund strong proposals amounting to at least $5M over 3 years. Given this strong response to the initial RFA, we believe that the regional/sub-regional networks for surveillance approach will be successful.

Once these networks are in place, we will build on the infrastructure to identify a sub-set of sites for studies of pneumonia incidence, costs of illness, and perhaps, a large-scale vaccine effectiveness study if needed. Also, if a pneumococcal vaccine is introduced ultimately, the baseline data established through these surveillance networks will be useful for monitoring the impact of routine vaccination. We believe that working through networks is more valuable than working through individual sites because it helps to assure a standardization of data quality and case definitions and assures that the data collected and lessons learned at one site reach the other sites.

We expect that additional large-scale studies of the effectiveness of pneumococcal conjugate vaccines for prevention of pneumonia will be needed. Specifically, we expect that South Asia, China, and central Asia, may require data from their own region/sub-region regarding the potential impact of pneumococcal conjugate vaccines on pneumonia incidence. By 2006, at least 2 large efficacy/effectiveness trials in Africa will have been completed, and one in SE Asia; and perhaps one will be underway in Latin America. Meanwhile, India or China, which represent nearly ½ of the world's birth cohort, will have had no efficacy or effectiveness trials conducted in their region. Given that these are the same regions where there are questions about the serotype coverage afforded by a 9- or 11-valent vaccine, the lack of vaccine effectiveness data is likely to be a major impediment to informed decision-making on the value of the vaccine in these regions.

While the exact details of a trial's design and outcomes need to be discussed with representatives of the country in which it will be undertaken, we can expect that these trials will likely need to be powered to detect a significant reduction in pneumonia (e.g., hospitalizations, x-ray confirmed cases). It may also be difficult to conduct the trial as a traditional double-blind, placebo-controlled design and may require some alternative approach such as a stepped-wedge or before-after design. The details will

be determined by the interplay of several factors including the timing of the trial, the vaccine used, the country where it is undertaken, and the outcome of interest.

It is likely that countries and donors will want to see evidence that pneumococcal vaccine reduces pneumonia mortality in high-mortality settings. Unfortunately, it is impossible to imagine a prospective, double-blinded, placebo controlled trial to evaluate this endpoint. The Gambia pneumococcal vaccine trial was originally designed to measure the vaccine's impact on child survival but for a variety of reasons, the trial's endpoint was modified to x-ray proven pneumonia. One possible alternative would be to conduct a multi-center study in 2-3 separate but similar trial sites where each site is powered to assess independently the vaccine's effectiveness against pneumonia hospitalizations or cases. These sites would also collect information on child survival as a routine part of the safety follow up. The impact on mortality might be assessed by a 'meta-analysis' that combines the data from each site into a single analysis.

Evaluation of alternative vaccination regimens and the herd immunity effects of routine vaccination are important areas for further research. To this point, the studies of pneumococcal conjugate vaccine efficacy have used a vaccination regimen that parallels that of DTP vaccine (e.g., 3 doses at approximately 2, 3, and 4 months). However, there is a high burden of pneumonia among infants younger than 3 months, and thus, studies evaluating the safety, immunogenicity, and perhaps, effectiveness, of neonatal immunization are needed. If pneumococcal conjugate vaccination can be given safely at birth, and if it provides significant protection against pneumonia, it may significantly increase the value of the vaccine by increasing the total proportion of cases prevented by vaccination. Alternatively, routine vaccination of infants might also prevent cases among infants too young to be vaccinated by reducing transmission and creating a herd immunity effect. This too would increase the value of vaccination by leading to additional prevented cases without requiring additional vaccine to be procured.

III. ADIP ACTIVITIES AND DELIVERABLES

The following section summarizes how the PneumoADIP team at Johns Hopkins will prioritize the ADIP activities to be undertaken and how that process will engage partners and leverage ongoing efforts. It also outlines a series of deliverables for which the team will be accountable to the GAVI SC.

ADIP is structured around 3 main areas

The ADIP is a target-driven project with its activities structured into 3 main areas. These areas are designed to 1) establish the value, 2) communicate the value, and 3) deliver the value of the vaccine.

Establishing the value of pneumococcal vaccination involves assessing the local burden of pneumococcal disease in VF-eligible countries and assessing the impact of the vaccine for its prevention. The types of activities required to establish the burden of pneumococcal disease include surveillance for invasive pneumococcal disease and pneumonia, determining the prevalence of antibiotic resistance and the local distribution of pneumococcal serotypes and cost of illness studies. Studies of vaccine safety, immunogenicity, and efficacy/effectiveness will be needed to evaluate the potential value of the vaccine in these countries. These studies will need to be adapted to local programmatic conditions (e.g. using local schedules) and be designed to assess efficacy against the outcomes that are locally considered to be most important for introduction.

PneumoADIP TARGETS FOR LOCAL DISEASE BURDEN DATA

Target (No. or % of VF-eligible countries)	Key activities
Establish local evidence of pneumococcal disease, including pneumococcal serotype distribution and antimicrobial resistance levels, in at least: 20% of countries by 2004 30% of countries by 2005 45% of countries by 2006 60% of countries by 2007	Networks of sites to conduct lab-based surveillance for invasive pneumococcal disease; Pneumonia/meningitis etiology studies; Vaccine effectiveness trials; Nasopharyngeal colonization studies; Rapid assessments using local data.
Establish pneumonia incidence in at least: 2 countries by 2004 3 countries by 2005 6 countries by 2006 12 countries by 2007	Pneumonia surveillance/cohort studies; Vaccine effectiveness trials; Rapid assessments using local data
Determine cost of pneumococcal disease and/or vaccine cost-effectiveness using local data in at least: 10% of countries by 2004 20% of countries by 2005 30% of countries by 2006 45% of countries by 2007	Cost of illness and cost-effectiveness studies.

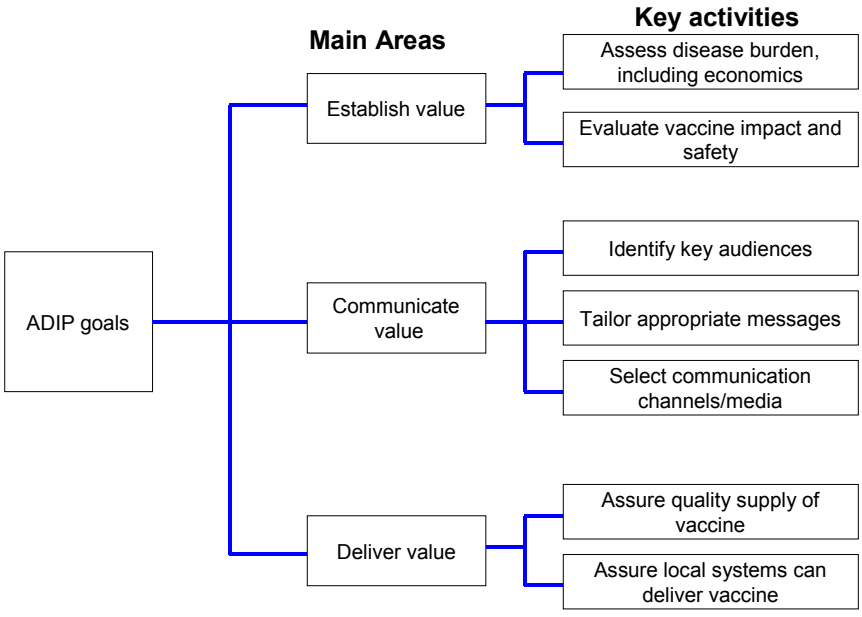
PneumoADIP TARGETS FOR VACCINE EFFECTIVENESS RESEARCH

Target (No. or % of VF-eligible countries)	Key activities
Establish safety and effectiveness of at least one vaccine candidate in at least: 3 sub-regions by 2006 4 sub-regions by 2008 5 sub-regions by 2009	Vaccine effectiveness or demonstration trials; Safety/immunogenicity trials
Determine safety/immunogenicity of candidate vaccine regimens in at least: 4 sub-regions by 2005 6 sub-regions by 2006 7 sub-regions by 2007	Pneumonia surveillance/cohort studies; Vaccine effectiveness trials; Rapid assessments using local data
Evaluate the impact of pneumococcal vaccine introduction on existing vaccine program in at least: 2 early-adopting countries by 2007	Programmatic evaluation studies
Establish surveillance infrastructure to monitor the impact of routine vaccination on the incidence of pneumonia and/or invasive disease in at least: 2 early-adopting countries by 2007	Networks of sites to conduct lab-based surveillance for invasive pneumococcal disease and/or pneumonia incidence;

Communicating the value of the vaccine means making sure that research findings reach the right decision-makers through effective channels and in a manner that addresses their key concerns or issues. We must do more than publish the results of research in peer-reviewed journals if we want to be sure that our research influences policy. Our communication strategy will assure that the evidence of disease burden and vaccine effectiveness the evidence generated by rigorous research is communicated to decision-makers. A comprehensive communication strategy will be developed in which we identify key stakeholders/audiences, outline their needs/concerns, map their communication channels, and tailor evidence-based messages to each one. The development and implementation of this strategy will be supported by activities such as audience research, conjoint analyses, convening of workshops and advisory boards, and development of forums for developing country representatives to express their needs.

Delivering the value of the vaccine means assuring an adequate, affordable, sustainable and predictable supply of quality vaccine and taking the steps to make sure that the country level systems are in place to deliver the vaccine to the children who need it. This will involve activities such as creating demand forecasts and discussing them with industry, countries, and donors, and improving our understanding of the country-level requirements for introducing pneumococcal vaccine and assuring that steps are undertaken to meet those needs.

Figure 3. ADIP activities organized around 3 main areas



Prioritizing ADIP activities

In its first few months the ADIP team's work will focus on refining targets and milestones and on prioritizing the activities (and their associated timelines and budgets) needed to achieve the targets. The team intends to build on the substantial work already undertaken in the preparatory ADIP period by McKinsey & Co. and the pneumococcal team. In its current state, the establish value activities are the most developed, but these will need to be refined further and integrated with the communication and vaccine supply and financing strategies.

Clearly, with the budget and human resource capacity available, the ADIP team will need to clarify targets and prioritize efforts carefully. In general, we expect to concentrate most of our investments in a few countries but to put smaller investments in many countries. The first step in prioritization will be to review existing demand forecasts. Next, we will group all VF eligible countries into regions/sub-regions and describe them along several dimensions including likely timing of vaccine uptake (based on demand forecasts), size of the country, existing evidence base on pneumococcal disease or vaccine and status of ongoing activities, existing communications networks/efforts, likelihood that they will influence other countries in the region, audience research feedback (if available) and other factors that might make it more or less likely that investments in this country will help to meet the ADIP targets.

Through this process, we will identify 3-4 countries where the most intensive efforts (and resources) will be invested to establish and communicate the value of the vaccine. In these 'high effort' countries, we might undertake the full range of activities to establish the value of the vaccine including disease burden studies (surveillance for invasive disease and pneumonia), cost-effectiveness studies, and vaccine trials, and undertake an intensive communication effort with a wide range of audiences targeted and a broad variety of activities. In the majority of countries, we will make smaller investments aimed at utilizing existing disease burden data or collecting minimal amounts of new data, and at increasing awareness of regional data – in this way we leverage our investments in our 'high effort' countries. In each region/sub-region there will be an effort to share data and engage multiple governments in an effort to minimize the need to repeat studies in each country.

Having developed an initial priority list, the team will work with a small group of key partners in each sub-region to solicit their input on the strategy and priorities and engage their support. These regional advisory groups will serve several key purposes. First, these groups will provide a forum for us to introduce the overall ADIP concept and the ADIP team to a broad range of partners early in the process. This advice will prove invaluable in steering us away from unforeseen problem areas and toward unexpected opportunities. Second, these meetings are the forum for national and international partners to review and comment on the strategy, targets and priorities and help to align the strategy with the current realities in each country. Third, it will allow us to begin to establish relationships between the ADIP team members and key partners that will be instrumental in achieving our targets.

Putting the analyses to work

The ADIP is a 'living document' that requires continuous updating. Ongoing analytic work by the ADIP team and its partners will be used to monitor the effectiveness of ADIP activities. For example, an early activity of the ADIP team will be to use a survey research firm to conduct audience research – i.e., in-depth interviews of country-level decision-makers of their knowledge and attitudes towards pneumonia, meningitis, and pneumococcal vaccines and the attractiveness of pneumococcal vaccination. The results of this activity will be used by all members of the ADIP team: the Director, Vaccine Research, will use it to refine the 'establish value' activity plans to assure that the research addresses the health outcomes of interest to local decision-makers; the Director, Communication Strategy, will use the information to target appropriate messages to each key audience and to define the type of educational initiatives and local support needed to affect change; and the Director, Vaccine supply and financing, will incorporate the data into the latest demand forecasts, which will then be shared with industry to assure that national demand can be matched to supply and capacity.

ADIP deliverables

A draft outline of ADIP deliverables is included as Annex B. This outline indicates what deliverables will be provided to the GAVI Steering Committee at various timepoints. It does not outline the activities that lead up to the deliverables. Once in place, the ADIP team will develop detailed activity timelines and budgets to assure that each deliverable is available on time and within budget. At each meeting of the GAVI Steering Committee, the ADIP Executive Director will present an update on progress. Any modifications to deliverables or targets will be explained in detail and an assessment of the implications for the project in terms of resources, timing, and outcomes will be provided. A budget will be presented annually for GAVI Steering Committee approval.

Annex B shows the deliverables that the ADIP team will provide at each semi-annual GAVI SC meeting. The deliverables are organized to correspond to the general areas of establish value, communicate value, and deliver value.

In 2003, the deliverables promised are primarily focused on providing detailed plans with activities, timelines, and budgets linked to each target. This process will require substantial effort to engage partners already working in these areas. In the area of establish value activities, the initial activities in defining disease burden will be primarily in the area of surveillance for lab-confirmed pneumococcal disease and cost-effective analyses. We will aim to have support to the ongoing clinical trials in The Gambia and The Philippines by the end of the year, and at least 3 networks for invasive pneumococcal disease surveillance in 10-15 countries. In communicate value, the initial focus will be on defining key audiences and opinion leaders, determining baseline attitudes and effective communication channels, and in refining a broad communication strategy. In the area of vaccine supply and financing, substantial effort will be devoted to refining the demand forecasts and in understanding industry's reaction to them. Investigations of regulatory issues will also be undertaken to assess implications on supply of vaccines for VF-eligible countries.

In 2004, in the establish value area, we will focus on sustaining and possibly expanding surveillance and pharmacoeconomic studies and start some clinical research with the vaccines. We expect to assure surveillance for invasive disease in at least 20-25 different countries by the end of the year and to generate preliminary detailed disease burden estimates for at least 6 key countries. Clinical research activities will be gearing up this year. Studies of vaccine immunogenicity, including alternative vaccination schedules, will be initiated. Planning for any large-scale clinical trials in regions such as south Asia and China (if needed) will be a major focus in this year. The team will be assessing the existing infrastructure in countries for conducting these large studies in order to determine if there are any existing sites capable of conducting these studies. In the communicate value area, we will be kicking off our communication strategy with the help of a public relations/media agency and/or consultants who can develop effective and even innovative approaches to develop local opinion leader and community interest and involvement. We will also continue our audience research to monitor and further refine our strategies to build awareness. In the deliver value area, our Director, Vaccine Supply and Financing, will be evaluating work already done in the area of pharmacoeconomics, determining its application to target countries, coordinating studies to quantify the costs of supplying the vaccine to specific countries and quantifying the economic implications of vaccine introduction, including any product modifications required (e.g., getting manufacturer to vial in multi-dose vials rather than single-dose vials).

The team will also work closely with industry/supplier contacts to share progress and jointly develop options to help assure consistent vaccine supply at a reasonable

cost. To do this, the team will need to fully incorporate the concerns of industry and articulate the benefits in terms of potential revenues and profits as well as appealing to the desire to fulfill a common mission of making the world a healthier place.

In 2005, we will provide a list of strategic options for the GAVI Board to consider, including a draft price/volume agreement with industry for supplying the VF-eligible countries. In the establish value area, we will also provide detailed country-by-country assessments of the disease burden and the value of the vaccine for consideration by the Board and other key donors. Our clinical research efforts will be in full swing. Preliminary data on safety and immunogenicity should be available and detailed plans for large-scale studies, including primary outcomes, timelines, budgets and potential sites will be developed. If possible, we should be prepared to start at least one large-scale trial in 2006 (if needed). Our communication strategy will be fully operational with the expectation that some countries may be ready to make a decision on pneumococcal vaccine by as early as 2006 (for introduction that year or in 2007). In the deliver value area, we will deliver a full analysis of the cost implications of introduction.

In 2006, if funded, the ADIP will be focusing on large-scale research studies evaluating the effectiveness of the vaccine for prevention of pneumonia in sub-regions/regions where the lack of data is an obstacle to informed decision-making about the value of vaccination. In the area of communicate value, the activities will be aimed at preparing for vaccination introduction. The focus of the activities will expand to try and include any consumer groups in early-adopting countries. The activities will be aimed at understanding their current perceptions of pneumonia, meningitis, and the vaccine and at designing a communication strategy that addresses their issues. In the area of deliver value, the focus will be on assuring vaccine supply and that early adopting countries have introduction plans for vaccination and the funding to support its uptake. The ADIP will also provide a detailed budget for the period of 2007-09 for the GAVI SC to review.

III. MANAGEMENT AND REPORTING

Management structure

The proposed management structure is designed to make the ADIP team accountable to the GAVI Steering Committee while allowing it to operate effectively within the Johns Hopkins system that houses it. In the proposed structure, the Executive Director will report directly to the GAVI SC and within Johns Hopkins to the Head, Health Systems Program, Department of International Health. Annexes C-E include 3 graphics to illustrate the relationship of the ADIP team to the GAVI SC, the Johns Hopkins system, and in relation to key external partners and structures.

Annex C illustrates the proposed responsibilities for the ADIP team in relationship to the GAVI Steering Committee. It is proposed that the GAVI SC meet every 6 months to review progress on the ADIP. Each January, the Executive Director will provide a detailed annual report on progress and a proposed budget for the next year to the GAVI SC for approval. At the mid-year meeting, the Executive Director will provide a summary of recent progress including results of any recent analyses and any proposed changes to the budget or strategy requiring immediate SC approval. The GAVI SC will have the responsibility for approving the strategic plan of the ADIP team, their budget, and the selection of ADIP team members.

Annex D shows the structure of the ADIP team and its relationship to the Department of International Health. Within the Johns Hopkins system, the Executive Director will report to Prof. Mathuram Santosham, Head, Health Systesm Program (HSP) on the performance and progress of each team member. The Head, HSP will be responsible for assuring that the team members receive the appropriate evaluations. He will make recommendations to the Chair of the Department regarding raises, or in the instance of an under-performing team member, will help with the process of replacing the individual. The Head, HSP is also responsible for assuring that the space needs of the team are adequately met. Over the course of the year, Prof. Santosham will offer feedback and advice on the team's activities to help assure that the greatest level of success is achieved.

Prof. Santosham has a long history of involvement in the areas of Hib and pneumococcal disease and their prevention by vaccination. He is a pediatrician who has been the Principal Investigator on pivotal phase 3 trials of the efficacy of Hib and pneumococcal vaccines. More recently he has worked in India and Bangladesh on studies to define the epidemiology of pneumonia in children and to define strategies for its prevention. His personal commitment to advancing prevention of pneumonia and meningitis by vaccination are reflected in his commitment to helping the ADIP team at Johns Hopkins succeed.

There are no additional structures or systems at the School that will in anyway interfere with the ability of the ADIP team to undertake its mission successfully.

Annex E shows the 'spider in a web' relationship of the PneumoADIP to 3 major external structures. Regional advisory groups will be used to help review targets and suggested activities. GAVI Task Forces and the Secretariat are important partners for assuring that the efforts of the ADIP are coordinated within GAVI itself and to avoid unnecessary duplication of efforts. The regional advisory groups and the GAVI Task Forces are important mechanisms for engaging and working through existing partners such as WHO, UNICEF, academia, industry, and others. Technical review groups will be convened as needed to score and rank proposals.

Regional advisory boards

Regional advisory boards will be a key component of the PneumoADIP approach. These boards will be compromised of key leaders from governments,

international institutions, and research. The regional advisory boards are expected to help with a range of strategic planning activities including demand forecasting, defining key areas of uncertainties in information, identifying opportunities for collaboration with ongoing efforts to establish or communicate value, and in determining research priorities.

Strategic advisory group

Many innovative public-private partnerships, such as the International AIDS Vaccine Initiative or the Malaria Vaccine Initiative, benefit from having a small external group of strategic advisors to periodically provide advice. We propose to convene a strategic advisory group of five to seven individuals with experience in areas relevant to the PneumoADIP, including public-private partnerships. The nominees will be carefully chosen to represent a range of expertise but with a few common characteristics, namely, a proven ability to think strategically and a willingness to speak openly and critically. The group's recommendations would be seriously considered by the team but non-binding.

We would be willing to submit a list of nominees to the GAVI SC for their approval. Furthermore, we would be willing to share a strategic advisory group with the eventual RotavirusADIP, if the GAVI SC thought that would be a more efficient use of resources.

IV. THE PneumoADIP TEAM

In response to suggestions from the review committee that we increase our capacity in the area of establish value, we have expanded the proposed PneumoADIP team at Johns Hopkins from 4 to 4.25 scientific faculty with the addition of Dr. Kate O'Brien (25% effort) as Assistant Director, Research Strategy. The administrative staff size remains the same at 3.5 FTE. The RFP suggests that the ADIP team members should correspond to the establish, communicate, and deliver value functions of the ADIP. The 4.25 proposed professional staff correspond largely to these functions with the exception that, at this time, the 'programmatic' manager is substituted by a 'vaccine supply and financing' director. Also, in response to the review committee's suggestions, we have delayed the hiring of this individual until the 4th quarter of 2003 and moved much of the budget for these activities until later years. This individual's responsibilities and activities will cover much of the 'deliver value' activities, but given that introduction of vaccine is not likely before 2007 and that programmatic input can be acquired as needed from key partners such as WHO, UNICEF, and GAVI, the proposed ADIP team for 2003-05 does not include a 'program' director. It is conceivable that as 2007 approaches an individual with these skills may need to be added to the team.

The 3.5 administrative staff are essential to the project's success. The funds to support their salaries represent 2% of the annual budget, but their functions assure that the funds are rigorously accounted and that agreements with partners are well-designed and monitored. By providing travel, meeting and administrative support they assure that the Directors can work efficiently and focus on refining and implementing the strategy.

Description of team – roles, responsibilities, and technical expertise

The structure of the ADIP team will be flat and lean. To be successful, each member of the team must work as a team player interacting with other team members and with key partners in other organizations. Narrowly defined job descriptions cannot apply to this group. While individuals will be responsible for each deliverable, all team members will be expected to do whatever it takes to meet the ADIP targets. At times the team will need to come together to solve a problem collectively. Flexibility, problem solving skills, and the ability to work on multiple tasks simultaneously will be essential.

The proposed ADIP team will include individuals with recognized expertise and leadership experience in a broad range of areas in both the public and private sector. This mix of backgrounds will result in the ability to leverage experience and best practices from each and assure a better understanding of the needs of all stakeholders. Each position and its responsibilities are outlined below and followed by a description of the technical expertise of the proposed Executive Director and Director, Communication Strategy (qualified candidate identified). For the unnamed Directors of Vaccine supply and financing and Vaccine Research, a description of their responsibilities and the desired technical expertise are included.

Annex F includes *curriculum vitae* for Dr. Levine and Dr. O'Brien.

Descriptions of the Directors, their responsibilities, and background and expertise

***Executive Director* – Orin S. Levine, Ph.D.**

Responsibilities: Overall team and project management; Relationships with key stakeholders; Communication of ADIP strategy and vision to international partners; Strategic planning; Design of analyses to support GAVI decision-making; Reporting to GAVI SC; Contribute to the establish value strategy in the areas of surveillance and vaccine trial design.

Technical expertise: The proposed Executive Director, Orin Levine, is a recognized expert in the area of Hib and pneumococcal disease and its prevention by vaccination. His academic background includes a B.A. degree in Management from Gettysburg College and a Ph.D. in Epidemiology from Johns Hopkins Bloomberg School of Public Health. He has published over 45 articles in the past 10 years on infectious diseases, and particularly pneumonia, meningitis, and their control by vaccination. As an investigator, his research has focused on providing developing countries with the information they need to make informed decisions about the introduction of new vaccines, primarily Hib and pneumococcal vaccines. His work runs the spectrum of vaccine-related research and includes epidemiologic studies, cost-effectiveness studies, and colonization studies; and clinical trials of vaccine safety, immunogenicity, and efficacy. Most recently, he has served as the NIAID coordinator of a large-scale, randomized-, double-blinded phase 3 trial of a candidate 9-valent pneumococcal conjugate vaccine in The Gambia, West Africa. His leadership on the trial in times of crisis have been instrumental to the success of the project.

Dr. Levine is recognized for his innovative work in several areas of epidemiology and vaccine research. He has conducted landmark studies in the area of Hib vaccines and colonization. In 1996, he conducted a study showing that the re-emergence of Hib disease in a high-risk population was due in part to continued transmission of Hib organisms. This was the first study to show continued Hib colonization in a population in spite of high vaccine coverage. He and his colleagues in the Dominican Republic were the first to establish a serologic correlate of the concentration of serum IgG required to confer protection against colonization. In China, he and his colleagues were able to demonstrate that Hib and pneumococcal colonization were associated with radiologic pneumonia in children. In the mid-1990s, there were concerns that combining whole-cell pertussis vaccine with Hib vaccine would reduce the effectiveness of the pertussis vacicnes. He and his colleagues in Chile showed that there was no observable difference in the incidence of pertussis among children who received combined DTwP-Hib vaccine as compared to those who received DTwP alone. His analysis of the efficacy of Hib vaccination in Chile for prevention of radiographic pneumonia is one of only two studies of its kind and serves as a centerpiece of the evidence base for using Hib vaccine in developing countries, and an example of the 'vaccine probe' approach.

One of Dr. Levine's personal areas of interest is developing standard methods to define the burden of Hib disease in developing countries. In 1996, at the request of the WHO, he wrote a generic protocol for surveillance to define the local burden of Hib meningitis. The protocol was the basis for 5 WHO sponsored meningitis surveillance studies in the late 1990s. The protocol has been translated into French, Russian, Bulgarian, Spanish, and Arabic and >3000 copies have been distributed. More recently, Dr. Levine, in a collaboration between WHO and CDC, developed a Hib Rapid Assessment Tool, that has been used in more than 13 countries to estimate the local burden of Hib disease using as much existing, local data as possible. Unlike the surveillance protocol that requires >1 year to complete, an advantage of this tool is that it requires only 7-10 days to complete. The tool has been useful to many of these countries in helping them to see the value of Hib vaccination.

Dr. Levine's leadership skills are well recognized in the field. For his leadership and productivity, he was awarded the CDC's Iain Hardy Award for Outstanding Contributions to Control of Vaccine-Preventable Diseases in 2000. He is a frequent invited speaker at international meetings on Hib and pneumococcal vaccines. His leadership in global efforts to accelerate the evaluation and introduction of Hib and pneumococcal vaccines goes back to 1996, when he began working with WHO and CDC on an 'agenda' of activities needed to assure uptake of the vaccine in developing

countries. In 1996, Dr. Levine, with colleagues from CDC and WHO, drafted the first version of this agenda, and subsequently refined it through the incorporation of comments from a wide range of groups and annual meetings with global leaders. In January 2001, GAVI asked Dr. Levine, Jay Wenger, WHO, and Thomas Cherian to continue this process on their behalf, focusing on pneumococcal vaccines. In this capacity, Drs. Levine and Cherian organized a meeting of international experts on pneumococcal disease, under the auspices of the Task Force on R&D, to draft an agenda of the R&D activities essential to achieving this goal, and later an international meeting on common protein vaccines. In this capacity, Dr. Levine (and Dr. Cherian) worked with consultants from McKinsey and Co. to develop and elaborate the ADIP framework.

Dr. Levine has a proven track record of working with international partners in public and private sectors. In addition to multiple successful collaborations with WHO, he has organized international meetings including two GAVI Task Force on R&D co-sponsored meetings on pneumococcal vaccines in 2001, and with Mathu Santosham, Johns Hopkins, a major international meeting on Hib control strategies in which more than 30 different countries were represented and all the major vaccine manufacturers were involved. He has also served on pneumococcal vaccine Advisory Boards for Wyeth and Aventis, and has worked with each of these companies in clinical research studies.

Dr. Levine has committed over 10 years of his career to accelerating the introduction of new vaccines against meningitis and pneumonia and is committed to continuing this effort for as long as is needed.

***Director, Vaccine Research* – To be named later**

Responsibilities: Overall strategy for establishing the burden of pneumococcal disease and the value of vaccination for its prevention; Develop "establish value" plans for countries and regions, including activities, timelines, budgets; Coordinate partnerships to meet activity targets and leverage ADIP investments; Monitor and revise plans as new evidence becomes available; Serve as liaison to Task Force on R&D and Implementation Task Force.

Technical expertise desired: Background in epidemiology and/or clinical research with experience in the areas of surveillance and clinical trials essential; Experience with pharmacoeconomic analyses highly desirable; International health experience necessary; Experience in design and conduct of surveillance projects and clinical studies in developing countries is necessary; Excellent communication skills required.

***Assistant Director, Research Strategy* - Katherine O'Brien, M.D., M.P.H.**

Responsibilities: Contribute to development of ADIP strategy for establishing the burden of pneumococcal disease and the value of vaccination for its prevention; Assist with scientific review of proposals and oversight of funded research; Conduct field visits to review study progress and assure a high standard of quality in ADIP sponsored research; Provide analyses of the status of vaccine and epidemiologic research to support the ADIP and the GAVI Board.

Technical expertise: Kate O'Brien is a recognized expert in the area of pneumococcal disease epidemiology and pneumococcal vaccination. Most recently, Dr. O'Brien served as the co-prinicipal investigator on a pre-licensure, large-scale, double-blinded, phase 3 efficacy of 7-valent pneumococcal conjugate vaccine in two American Indian populations. Dr. O'Brien has a strong interest in understanding the effects of vaccination

on transmission and herd immunity, and the efficacy trial that she led was unique among the current field trials in that the unit of randomization was community, not individual. She is a pediatrician with board certification in infectious diseases, and an Assistant Research Professor in the Department of International Health at Johns Hopkins Bloomberg School of Public Health. She is an alumnus of the EIS program at CDC where she worked with Anne Schuchat's Respiratory Diseases Branch and the author of over 25 peer-reviewed publications.

Director, Communications Strategy* – Qualified candidate identified

Responsibilities: Assess baseline needs for communications; Develop and oversee implementation of a broad communication strategy; Work with industry and other partners to identify possible areas for collaboration on communication efforts; Monitor effectiveness of strategy and revise as needed; Serve as liaison to GAVI's Advocacy Task Force.

Technical expertise:

The candidate possesses a good understanding of key technical aspects of vaccine development, manufacturing, distribution and the health care and payer environments in which decisions must be made. Working with colleagues and outside experts, he/she has been able to gain support from senior management in his/her company to pursue development of demand in certain developing countries. The candidate has demonstrated expertise in market research, understanding needs of health care providers, parents and payers in a variety of countries, and in utilizing epidemiology and disease burden information and recommending studies where information is needed for decision-making. The candidate has partnered with experts, care givers, NGOs and decision makers and has developed strategies to disseminate information and establish need through the use of educational initiatives, public relations efforts, publications, grass-roots efforts (e.g. establishing non-profit foundations dedicated to preventing the disease) and through leveraging the efforts of already existing initiatives. The candidate has also been involved in the review of pharmacoeconomic analyses and assembling expert panels to adapt studies using local data.

The candidate brings over 15 years of industry experience, mainly in pharmaceutical and vaccines, and a good understanding of the needs of the public sector.

***Director, Vaccine Supply & Financing* – To be named later (several qualified potential applicants contacted)**

Responsibilities: Demand forecasting – collect the data needed to refine the estimates and continuously re-assess forecasts based on most accurate, recent data; Communicate with industry to review demand forecasts and explore other partnerships; Supply forecasting; Develop draft price/volume agreements with industry that can be presented to GAVI and VF boards for decision; Help develop clinical trials agreements; Analyze costs, risks, and timelines for any potential modifications in product

* He/she is prepared to join the ADIP team in March 2003 if the proposal is successful and a fair compensation package can be agreed upon. The candidate's employer is currently unaware of his/her interest in this position. Thus, in order to protect this person in the event that the proposal is unsuccessful, we have not included his/her name. The description provided above summarizes his/her expertise and experiences. If needed, we could confidentially discuss the person with the committee and share a resume.

specifications (e.g., switch from single to multi-dose vials; from lyophilized to liquid presentation); Analyze costs, risks, and timelines for developing suppliers of pneumococcal conjugate vaccines in emerging market economies; Evaluate potential impact of regulatory obstacles to sustainable supply of pneumococcal vaccines; Serve as liaison to GAVI's Financing Task Force.

Technical expertise desired: Experience working on business development in the pharmaceutical or biotech industry (may include experience consulting to these sectors); Strong analytical skills required, particularly in the area of financial analysis of business investments; Experience with the organization of product launches helpful, particularly in international markets; Experience in the design of agreements for product development or procurement; Experience working internationally required; Excellent communication skills; Familiarity with international public health and research agencies highly desirable.

Administrative staff to the PneumoADIP

The team of ADIP directors will initially be supported by a small administrative staff of 3 persons, with a 4th person coming on at 50% effort in the second half of 2003. The roles of these administrative staff include managing the project's grants, budgets, agreements, travel, meetings, and administration. The importance of these administrative staff cannot be overestimated. The success of the ADIP will depend on freeing up the professional staff to do what they are uniquely qualified to do – the directors should not have to spend valuable time keeping the books or arranging their own travel or typing invoices. Also, given the demanding travel schedules of the directors, it will be important to have administrative staff in the office every day to make sure that projects move ahead as fast as possible.

The budget justification section includes a more detailed description of, and rationale for, the individual positions.

Approval of ADIP team members

We propose to involve the GAVI SC in the selection of team members in the following manner. The Executive Director (with the involvement of the Head, Health Systems Program [HSP], JHU) will recruit appropriately qualified individuals and after reviewing the candidates, the Executive Director will make a recommendation to the GAVI SC for final approval. By involving the Head, HSP in the selection process, we can be sure that any candidate approved by the SC will be acceptable to the Johns Hopkins system. Recruitment and recommendations will be made on a rolling basis – that is, as each qualified person is found, they will be forwarded to the GAVI SC for approval – so that we can establish the full-time team as quickly as possible.

The proposed Executive Director has made informal contacts with a number of potential candidates for the Director positions and with individuals who may help to locate potential candidates. Initial feedback shows a high degree of enthusiasm among potential candidates for the positions. The individual's contacted were excited about the concept of the ADIP, about the proposed organization of the team, the project management approach, and about working at the School. A list of potential candidates and key contacts can be provided on request.

Process for hiring ADIP team members

Each Director position will be hired as a 'Research Associate' – a non-tenure track post in the school. We can hire and have a person on the Johns Hopkins payroll within 2-4 weeks of identifying a candidate that meets the approval of the GAVI SC. Non-tenure track personnel are full members of the faculty, enjoying the same generous

fringe benefits as those in the more well-known 'tenure track' (i.e., tenured professors). However, unlike the 'tenure track' positions, Research Associates are not evaluated on their record of bringing in grant money, publishing papers, or teaching and mentoring students. Research Associates are judged only on their performance in achieving the goals of a particular project. Furthermore, the salary structure is flexible and at the discretion of the Department Chair.

By 15 March 2003, we expect to have the Executive Director and Director, Communication Strategy on the payroll and working. By 30 April 2003, we expect to have the remaining 2 Director positions filled, and our administrative assistant and budget analyst hired. By 15 May 2003 we expect to have the entire team hired and operational.

V. JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH: HOST INSTITUTION

As the largest, oldest and most respected school of public health in the world, the Johns Hopkins School of Public Health can provide technical expertise and support to the PneumoADIP team that rivals that of any institution. The School's nine academic departments include:

- Biochemistry and Molecular Biology
- Biostatistics
- Environmental Health Sciences
- Epidemiology
- Health Policy & Management
- International Health
- Mental Hygiene
- Molecular Biology and Immunology
- Population & Family Health Sciences

The School receives 23% of all federal research funds awarded to the 28 schools of public health in the country, and is consistently ranked as the number one school of public health in the United States by *US News and World Report*. The School has historically been at the forefront in addressing issues of International Health: the first Department of International Health was established at Johns Hopkins in 1961. The program grew out of long-standing interests at the School of Public Health in the health problems of developing countries and the consequent support given to research and program management within international agencies and national governments. The School and the Department of International Health have achieved a global leadership role in research, policy analysis, and program implementation through development of a large multidisciplinary faculty. It has the largest enrollment of international students of any school in the country. Researchers and alumni from the JHSPH live and work around the world providing a valuable network in research and policy. The School's alumni are recognized as health policy leaders, serving in government as ministers and program managers, as important members of multilateral health organizations and as leaders in research. The School has experience collaborating with US agencies, international governments, multilateral agencies, and the private sector, including corporations and NGOs. It has funding support both from the public sector and private sectors, and is experienced in adapting to donor needs.

<u>Institutional commitment</u>

The institutional commitment within Johns Hopkins Bloomberg School of Public Health reaches the very highest levels. Letters of commitment from the following individuals testify to the commitment of the administration to help the ADIP team successfully meet its objectives (see Annex G for copies of the letters):

- Al Sommer, Dean, Johns Hopkins Bloomberg School of Public Health
- Robert Black Chair, Department of International Health
- Mathuram Santosham, Head, Health Systems Program, Dept. of International Health
- Donna Helm, Associate Dean for Research Administration, Johns Hopkins Bloomberg School of Public Health
- Jane Bertrand, Director. JHU Center for Communications Programs.

Department of International Health

The Department of International Health, where the PneumoADIP team will be situated, provides a particularly rich environment. The Department includes 93 full-time faculty with experience in international health, vaccine research, pharmacoeconomics, epidemiology, and health communications. Among the faculty are recognized international leaders in the areas of immunization research, vaccine safety, pneumonia epidemiology, health communication, and cost-effectiveness studies. Some of the resources in the Department of International Health are briefly described below:

- Center for American Indian Health. Director: Mathuram Santosham, M.D. – The School, through the CAIH, has successfully worked with the Navajo and Apache nations for 30 years on a wide range of health studies. Under Prof. Santosham's leadership, the CAIH has conducted pivotal large-scale trials of Hib and pneumococcal vaccines and numerous epidemiologic studies to determine optimal preventive strategies to prevent pneumonia, meningitis, and diarrhea in these high-incidence communities.
- Center for Immunization Research. Director: Don Burke, M.D. – The CIR includes 47 full time staff and faculty with >15 years of experience in the evaluation of vaccine safety and immunogenicity including numerous phase 1 and phase 2 trials of respiratory vaccine candidates.
- Institute for Vaccine Safety. Director: Neal Halsey, M.D. – The IVS was established to address and investigate vaccine safety issues as well as provide timely and objective information for pediatricians, journalists and parents. IVS works to correct disinformation and misunderstandings that could lead to harmful choices regarding immunization. The Director, Dr. Halsey, is a recognized expert in vaccine research, with >7 years experience working with WHO in vaccine research and development, and >10 years as a member of the leading immunization advisory committees in the United States.
- Institute for International Programs. Director: Robert Black, M.D. – The IIP supports research and training in areas of international health, including substantial work on the control and prevention of pneumonia mortality in children. Many international health leaders in developing countries have been trained through the programs run by the IIP, providing a valuable link between the ADIP team at Johns Hopkins and key opinion leaders in many countries.

Johns Hopkins University Center for Communications Programs

The JHU Center for Communications Programs (JHU/CCP) represents an important potential resource to the ADIP team at Johns Hopkins. The JHU/CCP faculty are acknowledged for their expertise in the development of communication strategies to achieve public health goals, evaluation and research to assess the impact of communication efforts, and with more than 25 field stations abroad, JHU/CCP has in-country experience in many of the VF-eligible countries. The experience available in JHU/CCP makes it a uniquely valuable resource to the PneumoADIP team at Johns Hopkins that may contribute to the development of communication strategy and to its implementation with country-level partners. Also, JHU/CCP works closely with USAID, which has played a major role in establishing and supporting GAVI and its objectives.

The Center was established in 1988 to focus attention on the central role of communication in health behavior and to provide leadership in the field of health communication. The operations of the JHU/CCP are undertaken through several major USAID-funded component programs. Of the 9 major programs, the most relevant to the PneumoADIP include the Population Communication Services project (PCS, started in

1982) and the Health Communication Partnership (awarded 2002). Through these and other privately and publicly funded projects, JHU/CCP has set international standards for health communication.

The Population Communication Services (JHU/PCS) project is currently active in 25 countries across five regions. The project involves four subcontractors with complementary assets in each. The confidence of USAID in PCS' management and technical skill is demonstrated by its growth from a $2 million annual budget in 1982 to nearly $24 million in 2001.

Over 20 years PCS has grown from a small project to a comprehensive program internationally recognized for the extent and quality of its work and for its experience in managing large national and regional IEC projects. JHU/CCP has recently been awarded the Health Communication Partnership project, which has a much broader scope than did PCS. PCS' focus had been on population, reproductive health, and family planning. During the last PCS project, USAID field offices asked JHU/CCP more and more for technical assistance in strategic behavior change communication beyond family planning and reproductive health and into areas such as immunization and child survival.

JHU/CCP has developed and managed some 300 IEC projects and subcontracts in some 65 countries involving over 200 organizations and subcontractors. These have included ministries of health, ministries of information, government health education units, local government units, academic institutions, family planning associations, and other private family planning service organizations, associations of health care professionals, womens' groups, and media organizations.

JHU/CCP management reviews by USAID and external evaluations are consistently excellent. The recent PCS evaluation noted "that JHU/PCS's 18 years of stewardship of the project has contributed not only to lasting, beneficial changes in health-related behaviors around the world, but also to significant advances in the science and practice of development communication."

JHU/CCP specializes in the several areas of communication that are relevant to the PneumoADIP including, generating demand for quality health services and products, implementing national and regional behavior change projects, the Enter-Educate approach and the use of mass media, community mobilization, research and evaluation, and women's and community empowerment.

Known for pioneering the use of entertainment for health education -- the "enter-educate" approach – JHU/CCP has developed award-winning films, music videos, songs, dramas, and radio and television programs and short spots. Many of these projects have received international prizes in recognition of their excellence.

Issuing grants and contracts on behalf of the PneumoADIP

Administrative capacity

Administrative arrangements at the School are flexible and adaptable to a wide range of purposes. For example, there are no 'travel approval' processes such as those at most government or UN agencies. Similarly there are no 'meeting approval' forms or processes that require sign-offs from officials. In short, if the money is available for the travel or meeting, and the personnel at hand to arrange it, the administrative environment does not interfere in any way.

Contracting

The Johns Hopkins system for contracting is highly flexible. As a private academic institution, there are no institutional barriers to working with industry, private foundations or public sector. Quite to the contrary, Johns Hopkins has extensive experience in working with all of these sectors in a wide range of capacities.

The Office of Research Administration (ORA) in the Bloomberg School of Public Health has extensive experience in issuing contracts, subcontracts, and a wide variety of legal agreements. The ORA employs 4 specialists, who handled $224,089,757 in awards for fiscal year 2002.These awards were from a variety of funding sources which included pharmaceutical companies, other private sector firms, foundations, non-governmental organizations, and governmental agencies. Of the $224,089,757 received in awards, approximately 15% or $34,488,979 was issued to the private and public sector as sub-contracts/awards.

ORA has developed a semi-automated system for generating contract agreements that requires only a minimum of input from the ADIP team to output a draft agreement. Through dialogue between the contract specialists in ORA and the ADIP team, these draft agreements can be further adapted to suit the specific aims of the ADIP as needed. This semi-electronic system enables the ORA to generate draft agreements quickly. In general, 7-30 days are required to issue a draft agreement (i.e., one that is ready to be sent to the subcontractor). The amount of time required to fully execute the agreement depends upon the complexity of the negotiations with the subcontractor.

Annex H illustrates the speed and flexibility of ORA for developing sub-contract/award agreements with private and public sector partners. It summarizes the activity of 2 major projects at the School with a sampling of subcontracts/awards issued by ORA. These projects are related to immunization research, surveillance, or communications and provide examples that are appropriate to the ADIP. The tables in Annex H show 13 representative sub-contract agreements, of which 3 went to "public sector" institutions and 10 went to private sector organizations or non-governmental organizations. The size of the agreements varied from $11,075 to $5,807,167. The speed of ORA's processing is measured by the interval between the date that the department submitted a request and the date a contract was issued by ORA. This interval varied from 2 to 18 days. At this point, ORA issues the draft agreement to the sub-contractor for their review and approval. This step usually takes longer because sub-contractors often take much longer to review and respond than ORA took to generate the agreement. The interval between the date the contract was issued by ORA and the date the contract was fully executed generally took about 2-6 weeks with some taking longer and a few only a week to complete.

Technical review

All contracts and grants issued by the PneumoADIP at Johns Hopkins will be reviewed for technical merit before any award is made. The degree of technical review will vary based on the type of activity being undertaken, the timeframe required for getting started, and the size, scope and complexity of the activity. For example, an open 'request for proposals' (RFP) process will be used for some larger projects where there is less urgency to start immediately and there are many potential applicants (example: the current RFP for networks to conduct lab-based surveillance for invasive pneumococcal disease). In these instances, an *ad hoc* technical review group (TRG) will be formed to assess the technical merits of each proposal and to score/rank the proposals based on defined scoring criteria. The ADIP team will then use these technical scores in helping to make award decisions. In other instances, particularly where speed is essential or where there a few potentially qualified applicants, the ADIP team may directly solicit proposals from one or a few known potential sources, and then select 1 or 2 external technical reviewers to provide technical feedback on the merits of the proposal. Again, the ADIP team will have the final say on what agreements are made.

When *ad hoc* technical review groups are used, a 'Terms of Reference' will be developed in advance of the meeting that outlines the responsibilities of the TRG and of the ADIP team, and specifically dictates the issues of confidentiality, conflict of interest, and the criteria for reviewing the proposals. Because TRGs may be needed for a wide range of different activities, there will be no standing TRG. Each TRG will be composed of experts appropriate to the specific proposals that they are required to review. The first criteria for membership on the TRG will be appropriate technical expertise to review the proposals, but in composing the overall TRG, efforts will be made to assure diversity amongst the panelists and to minimize any obvious conflicts of interest. Each Technical Review Group will include a liaison from a relevant GAVI Task Force.

Dr. Levine, working in collaboration with Dr. Cherian at WHO, has experience with allocating funds in this manner. Within 3 weeks of the GAVI Board's decision to approve the opening of Window 3 for 'preparatory' ADIP activities, Drs. Levine and Cherian drafted 2 RFPs (one for surveillance and one for audience research), advertised them in international journals and on the web, selected TRG committee members appropriate to each RFA, drafted Terms of Reference appropriate to each TRG, sent invitations to each TRG member (see the GAVI website for the announcements and full RFA or RFP), and organized the TRG meeting.

Human subjects issues

The PneumoADIP team and JHSPH are committed to supporting ethical research on humans or animals. Any contract or grant issued from Johns Hopkins that includes human or animal research will include language requiring the research proposal to be approved and monitored by an appropriately constituted ethical review committee. Review by the JHSPH ethical committee is not required if the research does not include a JHSPH staff or faculty as a co-investigator, even if JHSPH issues the grant or contract. Thus, the JHSPH ethical review committee will not delay the issuing of funds for research activities supported by the PneumoADIP team.

VII. ANNEXES

A. Letters of support from WHO, IVI, KTL and reference from Prof. Yang Yong-Hong, Beijing Children's Hospital, China. (3 pages) [Omitted]
B. ADIP Deliverables timeline (7 pages)
C-E. Graphics to illustrate management and reporting structures (3 pages)
F. *Curriculum vitae* for Dr. Levine and Dr. O'Brien (37 pages total)
G. Letters of commitment from Johns Hopkins administration including Dean Sommer, Prof. Robert Black, Prof. Mathuram Santosham, Prof. Jane Bertrand, and Donna Helm (5 pages) [Omitted]
H. Example of Office of Research Administration Contracting Experience (1 page) [Omitted]
I. Budget summary [Omitted]
J. Detailed budget for core team (2 pages) [Omitted]