

Detailed Review Paper on Pneumococcal Conjugate Vaccine - presented to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, November 2006

SAGE pneumococcal conjugate vaccine working group

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I. Introduction

Key points

1. Pneumonia due to *Streptococcus pneumoniae* contributes importantly to deaths among children under 5 years
2. A seven-valent pneumococcal conjugate vaccine (PCV7) was licensed for use in infants and children by the US FDA in 2000 and has since been registered in over 70 countries worldwide.
3. Clinical trials in industrialized and developing countries, immunogenicity studies in different populations, and post-licensure experience in North America provide an evidence base for this position statement.
4. This position paper presents recommendations on the global use of pneumococcal conjugate vaccines, with a focus on the currently licensed seven-valent conjugate vaccine and the closely related 9-valent formulation.

An estimated 10.6 million children under five years of age die each year; 90% of these deaths occur in developing countries.^{1,2} Acute respiratory infections, most notably pneumonia, are a leading cause of mortality among children in developing countries. In 2000-2003 pneumonia was the leading cause of death in the under-five age group.²

The bacterium *Streptococcus pneumoniae*, or pneumococcus, is a leading cause of pneumonia, meningitis and bloodstream infections, killing an estimated 1.6 million people each year including 700,000 to 1 million children under five.³ Children under two years of age contribute disproportionately to pneumococcal deaths. Prevention of pneumococcal mortality and morbidity through vaccination offers an important complement to other available strategies to reduce pneumonia-associated deaths such as Integrated Management of Childhood Illnesses (IMCI), micronutrient supplementation, improved nutrition, and efforts to reduce indoor air pollution.

Until recently the only pneumococcal vaccine available was the pneumococcal polysaccharide vaccine (PPV23). Pneumococcal polysaccharide vaccine has never been recommended for children less than 2 years of age because of their inability to mount the required T cell-independent immune response. For children 2 years of age and older

pneumococcal polysaccharide vaccine is only recommended for those with underlying medical conditions that increase the risk for pneumococcal disease. The efficacy of this vaccine in children has not been well characterized. Clinical trials have yielded conflicting results.⁴⁻⁷ Although one study in Papua New Guinea reported significant efficacy of a 14- and a 23-valent polysaccharide formulation against total mortality and pneumonia mortality among vaccinated children four months to four years of age, the preponderance of evidence suggests that polysaccharide formulations are not effective at preventing pneumonia in children. Observational data support PPV23 effectiveness estimates of 50 to 60% against invasive disease among children 24 to 59 months of age.⁸ Effectiveness against non-invasive disease, such as pneumonia, is less clear although there is some evidence of an impact on acute otitis media.⁹⁻¹³ However, immunity induced by these vaccines is short-lived and is not associated with induction of immunological memory, requiring periodic re-vaccination to maintain protective efficacy.

The licensure in 2000 of a seven-valent pneumococcal conjugate vaccine (PCV7) for use among infants and toddlers opens a new avenue for pediatric pneumococcal disease prevention. The last WHO pneumococcal vaccine position statement, issued in April 2003, called for data from non-industrialized countries on the efficacy of pneumococcal conjugate vaccines against invasive disease and pneumonia before recommendations for wider-spread usage of pneumococcal conjugate vaccines could be formulated. This position statement also highlighted the need for a reduced cost of PCV7 before it could become a real option for poorer countries.

Since the position paper was published, two phase III clinical trials of PCV in Africa and one in the Philippines have been completed. Two of these evaluated pneumonia as a primary endpoint. Additionally, the Global Alliance for Vaccines and Immunizations (GAVI) launched an initiative to accelerate vaccine introduction into developing countries and reduce costs of new vaccines and is considering pneumococcal conjugate vaccine as a candidate for this program.

Here, we update the WHO position on the global use of the pneumococcal conjugate vaccine to incorporate this more recent information. The statement focuses on pediatric pneumococcal disease prevention through use of the licensed PCV7 formulation. It additionally includes evidence from studies of PCV9, a closely-related investigational 9-valent formulation, manufactured by the same company. Formulations with 10 and 13 serotypes are at advanced stages of clinical development and are addressed briefly.

II. Pneumococcal Disease Burden

Key points

1. Pneumococcal infections are estimated to cause >700,000 deaths annually among children under 5 worldwide; most deaths occur in developing countries.
2. Important clinical syndromes include pneumonia, bloodstream infections, meningitis, and acute otitis media
3. Emerging antibiotic resistance increases the cost of treatment of pneumococcal infections and can result in treatment failures
4. Major risk factors for pneumococcal infection include young age (age <5; particularly age <2); underlying immunodeficiency or other underlying illnesses (particularly HIV/AIDS, sickle cell disease, nephrotic syndrome, asplenia, cancer); day care attendance; lack of breastfeeding; exposure to tobacco smoke.
5. Influenza virus infection is an important risk factor for secondary pneumococcal infections, most commonly pneumonia
6. The incidence of disease is also elevated among older adults
7. Disease occurs everywhere but incidence varies geographically; available data suggests disease incidence is higher in developing countries than among industrialized countries

8. The burden of disease among those with HIV-infection is addressed in section VIII.

Streptococcus pneumoniae is among the major pathogens causing invasive and non-invasive infections among children worldwide. The primary clinical syndromes associated with pneumococcal infections are pneumonia, meningitis, bloodstream infections and acute otitis media. A recent study in Kenya estimated an incidence of presentation to hospital with pneumococcal bacteremia of 597/100,000 children less than 5 years of age per year.¹⁴ Case fatality ratios are highest for invasive infections and range from 5-20% for bacteremia to 40-50% for meningitis. Among meningitis survivors, long-term neurologic sequelae occur in 25-56% of cases.¹⁵

Most pneumococcal infections can be treated effectively with antibiotics, although meningitis still often results in devastating outcomes. Over the last 20 years, the emergence of antimicrobial resistance among *S. pneumoniae* complicates treatment of infections. Penicillin and co-trimoxazole resistance are common in many parts of the world. Multidrug resistance has also emerged and is best documented in industrialized countries. Treatment failures due to resistance have been documented for acute otitis media, meningitis and bloodstream infections.

Major risk factors for infection include: young age (age <5; particularly age <2); underlying immunodeficiency or other underlying illnesses (particularly sickle cell disease, nephrotic syndrome, cancer); day care attendance; lack of breastfeeding; and exposure to tobacco smoke.¹⁶ Risk of infection can also vary with race. For example invasive disease rates are elevated among indigenous populations of Australia and New Zealand and among the Black, Alaska Native and American Indian populations in the United States. The incidence of disease is also elevated among the elderly; in

industrialized countries rates start to increase by age fifty. There is some evidence that adults who have frequent exposure to young children are also at elevated risk for pneumococcal infections. In developing countries age-specific incidence among adults is not well characterized. For both children and adults, preceding infections with some viruses, most notably influenza, increase the risk of secondary pneumococcal infections. Based on data from past influenza pandemics, the attack rate for secondary pneumococcal pneumonia in a pandemic setting is anticipated to range from 5 to 13%.¹⁷

Pneumococcal disease occurs everywhere but the incidence of infection varies geographically. On average, disease incidence is higher in developing countries than among industrialized countries. The pneumococcal disease burden is notably higher in countries affected by the HIV epidemic; the disease burden among children with HIV infection is addressed in more detail in section VIII.

III. The Pathogen

Key points

1. Gram positive diplococcus; reservoir is the nasopharynx
2. 90+ serotypes based on capsular polysaccharide
3. Approximately 20 serotypes account for over 70% of invasive disease; approximately 10 serotypes are commonly associated with pediatric infections
4. Serotypes, antimicrobial resistance profile, and pneumococcal molecular type (“clone”) are strongly associated
5. The global distribution of serotypes varies. From many parts of the world there are limited data. Some serotypes common in developing countries (particularly types 1 and 5) are no longer common in industrialized countries.
6. The serotypes associated with invasive infections among HIV infected children are similar to the serotypes that infect healthy children. This is discussed more in section VIII

S. pneumoniae is a gram positive, encapsulated diplococcus that is part of the normal flora of the human nasopharynx. Nasopharyngeal colonization is transient and

typically asymptomatic. It is more common and prolonged among children than among adults. In some circumstances, pneumococci from the nasopharynx enter adjacent structures (e.g. paranasal sinuses and middle ear) and can be aspirated into the lungs or enter the blood stream resulting in disease. Infection of the blood stream and subsequent infection of secondary sites is referred to as invasive disease.

The polysaccharide capsule is an important factor associated with virulence. It also is recognized as a major antigen by the human immune system. Antibodies to the capsular polysaccharide protect against pneumococcal infection. Based on differences in this polysaccharide, over 90 serotypes of *S. pneumoniae* have been identified. Approximately 20 serotypes are associated with over 70% of invasive pneumococcal disease in all age groups worldwide and approximately half that number account for the majority of pediatric infections. The distribution of serotypes associated with meningitis does not differ importantly from the serotypes associated with other invasive infections. Additionally, the serotypes associated with invasive infections among HIV-infected children are similar to the serotypes that infect HIV-uninfected children. This is discussed further in section VIII.

Based on molecular typing of multiple housekeeping genes, pneumococcal strains can be characterized into clones. While clones and serotypes do not correspond directly, there is a strong association between serotype and clones. There is also a strong association among specific clones, serotypes and antimicrobial resistance pattern. Some clones are globally disseminated. The majority of these are associated with antibiotic resistance. Strains that are penicillin-resistant are much more likely also to contain genes conferring resistance to other drug classes. High-level penicillin resistance and resistance

to the macrolides are now quite common among pneumococci in many parts of the developed world. In developing countries, intermediate levels of penicillin non-susceptibility are more common than high levels. Resistance to the fluoroquinolones is also emerging and has been detected among invasive pneumococcal isolates from adults in the United States and children in South Africa.¹⁸

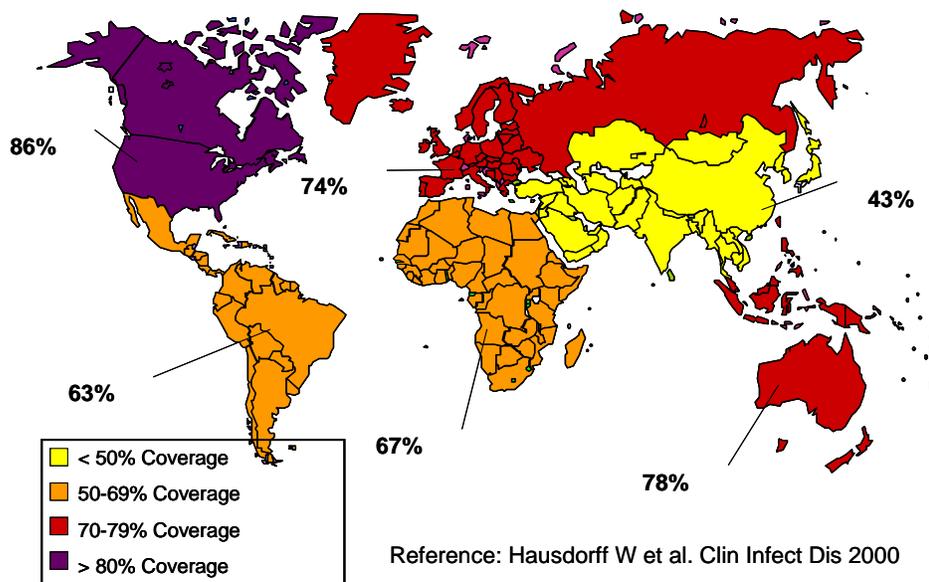
The distribution of serotypes associated with invasive pneumococcal disease varies geographically and can also vary over time, for example due to the introduction of a new clone into a population. Age-specific population-based surveillance for invasive pneumococcal disease is the best method of characterizing serotype distributions for a given population. Surveillance that captures only the most severe disease (eg, hospital-based studies or studies where blood cultures are reserved for the most ill patients) can yield distributions that are different from surveillance where blood culture is performed for all febrile children with temperature $> 39^{\circ}\text{C}$. Serotype distributions also vary by age. In addition to marked differences between children and adults, even within the under-five age group a recent study in Kenya showed that 6-29 month olds differed markedly in the serotypes causing infections compared to younger and older children (A. Scott, unpublished data). Some serotypes are associated with disease outbreaks, e.g. outbreaks of meningitis due to serotype 1 are reported from the African meningitis belt.

The serotypes included in PCV7 were selected based in part on the recent distribution of serotypes associated with invasive disease among US children. Before the vaccine was introduced into the United States in 2000, the serotypes included in the vaccine represented approximately 80% of pediatric invasive infections. In other parts of the world, the proportion of invasive disease caused by serotypes included in PCV7

varies (see **Figure for section III**). In particular, in some parts of Africa and also in some Asian and European countries, serotypes 1 and 5, two non-PCV7 serotypes, represent an important proportion of pediatric invasive infections.¹⁹ Despite being common causes of invasive pneumococcal disease, these serotypes are not often found in the nasopharynx.

Although pneumococcus is an important cause of non-invasive infections, most notably non-bacteremic pneumonia, the serotype distribution for these syndromes cannot be characterized.

Figure for Section III. Proportion of pediatric invasive pneumococcal disease due to PCV7 serotypes



IV. Pneumococcal Conjugate Vaccine

IV.1. Vaccine Composition

Key points

1. PCV7, the only currently licensed pneumococcal conjugate vaccine, includes polysaccharide from serotypes 4,6B, 9V, 14, 18C, 19F and 23F conjugated to an immunogenic mutant diphtheria toxin, CRM197
2. PCV9 is an unlicensed vaccine, developed by the same manufacturer as PCV7, that adds polysaccharide from serotypes 1 and 5 to PCV7.
3. Because PCV9 is closely related to PCV7, this report will focus on studies of both vaccines and will use immunogenicity and efficacy data from performance of the 9 valent formulation to project the expected performance of the 7-valent formulation in the same or similar populations.
4. Other vaccine formulations are under development and are discussed in section XI
5. The current formulation of PCV7 requires refrigeration and will result in a 300% increase in cold chain requirements in a programme already using combined DTP-HepB-Hib (pentavalent) vaccine. It is anticipated that vaccine presentations with lower cold chain requirements will be available in the future.

As of 2006, the only licensed pneumococcal conjugate vaccine product is PCV7 (Prevnar in US/Prevenar outside US) which includes the capsular polysaccharide of 7 serotypes (4,6B, 9V, 14, 18C, 19F, 23F), each coupled to a nontoxic variant of diphtheria toxin, CRM197. The vaccine contains 2 µg each of capsular polysaccharide from serotypes 4,9V, 14, 19F and 23F; 2 µg of oligosaccharide from 18C; 4 µg of capsular polysaccharide of 6B; 20 µg of CRM197; and 0.125 mg of aluminum/0.5 ml dose as an aluminum phosphate adjuvant.

The currently available presentation of PCV7 is single-dose, pre-filled sterile syringes and contains no thimerosal or other preservative. The vaccine is available in boxes containing a single dose or in packs of 10 doses. The latter presentation has a volume of 59.7 cm³/dose. This presentation offers some advantages in that it simplifies the management of supplies (only one item) and avoids programmatic errors associated

with the supply of separate items. However, it will result in a 300% increase in cold chain requirements in a programme already using combined DTP-HepB-Hib (pentavalent) vaccine. Such an expansion of cold chain capacity may not be immediately feasible in many developing countries and may require them to adjust their vaccine distribution schedule (more frequent supplies) to avoid expanding the cold chain immediately. It is anticipated that vaccine presentations more suitable for use in developing countries, i.e. with lower cold chain capacity requirements and with auto-disable syringes, will be available in the future.

PCV9, a closely-related but unlicensed product, contains two additional serotypes, 1 and 5 (2 µg of capsular polysaccharide of each type) also conjugated to CRM197. Other unlicensed formulations that have been evaluated or that are under development are addressed briefly in Section XI.

Because PCV9 is so closely related to PCV7, this position statement focuses on both vaccines.

IV.2. Biological basis for conjugate vaccine

Key points

1. Pneumococcal conjugate vaccines, unlike unconjugated polysaccharide vaccines, stimulate robust immune responses in infants and toddlers
2. Conjugate vaccines induce a T-cell dependent immune response, characterized by response in young infants, boosting upon re-administration and immunologic memory
3. Conjugate vaccines protect against systemic and mucosal infections and nasopharyngeal colonization

The immunological basis of pneumococcal conjugate vaccines will be discussed in detail in a WHO-commissioned report on the immunological basis of immunization,

which is currently under preparation. Briefly, pneumococcal capsular polysaccharides, the outer coat that serves as the primary pneumococcal antigens eliciting a host immune response, induce a T-cell independent immune response which does not develop in children until around two years of age. In contrast, when polysaccharides are covalently coupled to immunogenic proteins such as the mutant diphtheria toxin CRM₁₉₇ used in PCV7 and PCV9, a T cell-dependent response is elicited. This type of response is already present in infants, thus making PCV a good immunogen for infants and toddlers. Another characteristic of T-cell dependent responses is the induction of immunological memory characterized by affinity maturation and a booster response on subsequent exposure to the antigen.

Careful choice of the protein-carrier is critical because some carriers, particularly those to which individuals may already be primed, have the potential to suppress the boosting response. Multivalent coupling of polysaccharide to proteins can also result in reduced immunogenicity of one or more components. Thus, as new higher-valent formulations are developed, serotype-specific immunogenicity and efficacy is important to monitor.

In addition to eliciting T-cell dependent immune responses, conjugate vaccines can confer both systemic and mucosal immunity. Serum IgG and secretory IgA can be detected in the saliva of toddlers and infants after parenteral vaccination with PCV formulations.^{20, 21} The mucosal immune response contributes importantly to protection against respiratory tract colonization with serotypes included in the vaccine. Colonization is a precursor to infection and is also the source of person-to-person transmission. Several studies have documented the effect of pneumococcal conjugate

vaccination on nasopharyngeal carriage with the majority showing significant decreases in colonization with vaccine-included serotypes.²²

IV.3. Safety

Key points

1. Acceptable safety profile based on clinical trials of PCV7 and PCV9
2. Post-marketing surveillance of adverse events among more than 20M vaccinated children in the United States has not identified any significant serious adverse events associated with PCV7
3. Safety among HIV-infection is addressed in section VIII.

WHO commissioned an in-depth review of the safety of PCV formulations which will be presented to the WHO Global Advisory Committee on Vaccine Safety in November 2006; we briefly present the safety profile here. Data from Phase III clinical trials and smaller immunogenicity and safety studies suggest that PCV7 and PCV9 are both well-tolerated among infants and toddlers. In the major Phase III trials of PCV7 (see Table for section IV.5), over 47,000 children received at least 1 dose of PCV7. Local and minor reactions such as redness, swelling, and tenderness were within the range of what is seen for other EPI vaccines (e.g., DTP) and were generally mild and self-limiting. Fever rates in the US Kaiser trial were higher among children receiving PCV7 than among controls.²³

Overall, the rate of deaths and hospitalizations deemed possibly, probably or definitely related to vaccine did not differ between vaccine and control groups in the PCV7 pre-licensure trials. Febrile seizures were found to be more common among PCV7 recipients in the Kaiser trial; however, there was no clustering of these seizures within 3 days of vaccine receipt.²³

Post-licensure passive vaccine-associated adverse events surveillance in the United States during the first two years of routine vaccine use (corresponding to administration of an estimated 31.5 million PCV7 doses) primarily captured minor adverse events consistent with those identified from pre-licensure clinical trials.²⁴ The proportion of reports that described serious events, defined as events involving death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability, was similar to that for the aggregate of other vaccines in use in the United States (14.6% vs. 14.3%).^{24, 25}

PCV9 studies in Africa (over 57,000 children were vaccinated) suggest this formulation is also well tolerated among infants and toddlers. A subgroup of 425 children in the Gambia PCV9 trial was monitored for minor adverse events at days 2 and 7 post-vaccination. Rates or degree of swelling, tenderness or redness at the injection site after any dose did not differ between vaccine and placebo groups. Rates of reported fever were higher in the PCV group but rates of measured fever did not differ. In the Gambia trial, significantly more outpatient visits were made within the week after dose 1 among PCV recipients; this difference was not seen after subsequent doses.²⁶

Minor reactions were not measured in the South Africa PCV9 efficacy trial but an earlier double blind, placebo-controlled randomized trial of 500 children from the same Soweto population found no differences in local or systemic reactions between children who received PCV9 in addition to the standard EPI vaccines, and children who received placebo.

In the Gambia trial, the number of hospital admissions and deaths within 7 days of receiving any dose of vaccine was similar, and slightly lower in the PCV9 group. Only

1 serious adverse event (cellulitis at injection site) was judged definitely related to vaccine.²⁶ In the South Africa trial there was some suggestion that rates of viral pneumonias requiring hospitalization within the first week after vaccination were higher among PCV recipients. Asthma-related diagnoses also appeared higher among vaccinees although there was no evidence of temporal relationship with vaccine.²⁷

Fewer safety data are available for children older than 2 years at the time of vaccination and for special populations such as children with sickle cell disease. Available evidence suggests a safety profile similar to what is observed for children less than 2 years of age without underlying conditions.

Safety data for children infected with HIV are discussed in section VIII.

IV.4. Immunogenicity

Key points
1. Efficacy trials with nested immunogenicity studies provide the direct link between immunogenicity levels and efficacy against disease.
2. More than 10 immunogenicity studies of 7-valent vaccine have been conducted in 8 countries world wide. These studies have assessed the immunogenicity of several vaccine schedules, infants and children of different ages, and among children with and without underlying illnesses.
3. Immunogenicity studies in this broad range of populations and schedules consistently show that PCV7 and PCV9 elicit protective immune responses in vaccinated infants and children.
4. Immunogenicity among children infected with HIV is discussed in section VIII

Antibodies against pneumococcal capsular polysaccharides are protective against pneumococcal disease. These antibodies confer protection through opsonin-dependent phagocytosis of pneumococci. Consequently, two important measures of pneumococcal vaccine-induced immunity include quantification of pneumococcal capsular polysaccharide-specific IgG antibody concentration in vaccinated individuals and assessment of antibody opsonophagocytic activity.

Efficacy trials with nested immunogenicity studies provide the most direct link between immunogenicity levels and efficacy against disease. All Phase III trials that measured efficacy of PCV7 or PCV9 against invasive pneumococcal disease (see Table for section IV.5) included nested immunogenicity studies that measured antibody concentrations post-vaccination. Based on reverse cumulative distribution curves for antibody levels following the primary immunization series in the US and South Africa trials, a WHO expert panel determined that an antibody concentration of 0.35 mcg/ML for all vaccine-included serotypes corresponded to clinical efficacy against invasive disease due to vaccine-included serotypes. Non-inferiority in the proportion of vaccine-included serotypes with antibody levels above this concentration is recommended for evaluation of new vaccine formulations or vaccination schedules.²⁸ In addition, supporting evidence of functional activity of the antibody induced and induction of immunological memory are required for evaluation using serological criteria.

Although serotype-specific immunogenicity levels vary with some serotypes being less immunogenic than others, data from the Gambia Phase III PCV9 trial and Phase II and III trials of PCV9 in South Africa suggest that antibody concentrations were elevated among vaccinated children compared to controls, and geometric mean concentrations were above 0.35 mcg/ML for each of the serotypes included in the vaccine following a primary series of vaccination administered at 6, 10 and 14 weeks or 2, 3 and 4 months of age [Huebner et al, Vaccine, 2004; Madhi, et al. PIDJ 2005; Sakaa et al., in preparation]. In the 2 US trials of PCV7, the vaccine elicited similar, protective immune responses.²³

²⁹ Over 10 immunogenicity studies of PCV7 or PCV9 among children in more than 8 countries further support these findings (selected studies shown in Table for Section

IV.4). Because children in these studies, as well as in the Phase III trials, were vaccinated at different ages from infancy through to older childhood, immunogenicity results appear robust with respect to age, irrespective of the timing of the vaccine doses in the primary infant schedule. Evidence for the effectiveness of accelerated schedules and reduced or alternate schedules is discussed further in Section IX.

The Phase III efficacy/immunogenicity analyses of PCV9 did not evaluate populations of special interest such as those at elevated risk for pneumococcal disease due to underlying conditions. The US California Kaiser trial performed a secondary stratified analysis limited to low birth weight and preterm infants.³⁰ This evaluation found that PCV was as immunogenic in low birth weight and preterm infants as in normal birth weight and full term infants. Several studies have evaluated immunogenicity of PCV among infants with sickle cell disease and have found that in terms of antibody concentration they respond at least as well as infants without sickle cell disease.^{31,32} An immunogenicity study of PCV7 among pediatric solid organ transplant recipients from 2 to 18 years of age found significant rises in antibody concentration from pre-vaccine levels after a single dose of vaccine.³³ Immunogenicity among children with HIV infection is discussed in Section VIII. Children in regions of seasonal or endemic malaria may also have impaired immune responses although there are currently no evidence of this. Secondary analyses from the Gambia trial suggested that PCV may be less effective among children receiving all 3 doses during the malaria season; this requires further exploration.²⁶

Table for Section IV.4.: Results from select regionally representative immunogenicity studies

Trial site	Vaccine and schedule	Efficacy vs. VT-IPD	No. enrolled	Immunogenicity (post-primary series)	
				GMC	% >0.35 ug/ml
Northern California, USA ³⁴	7-valent-CRM ₁₉₇ 2,4, 6, 12-15 mo	97%	302	>1 ug/ml for all serotypes	>95% of children had >0.15 ug/ml for all ser
Navajo and Apache, USA*	7-valent-CRM ₁₉₇ 2,4, 6, 12-15 mo	77%	610	>2.4 ug/ml for all serotypes	>91% for all serotype
Soweto, South Africa ³⁵	9-valent-CRM ₁₉₇ 6, 10, 14 wks	85%	500	>2.9 ug/ml for all serotypes	Not available
The Gambia ^{36, 37}	9-valent-CRM ₁₉₇ 2, 3, 4 mo	77%	590	>1.1 ug/ml for all serotypes	Not available
United Kingdom ³⁸	9-valent-CRM ₁₉₇ 2, 4, 12 or 2,3,4,12 mo		155	>1,0 ug/ml for all serotypes, both schedules	>84% for both schedt
Taiwan ³⁹	7-valent-CRM ₁₉₇ 2,4, 6, 12-15 mo		60	Not available	>93% of children had >1 ug/ml for all seroty
Germany ⁴⁰	7-valent-CRM ₁₉₇ 2,4, 6, 12-23 mo		345	0.91 for 6B, >2.1 for all other serotypes	Not available

*K. O'Brien, unpublished data

IV.5. Efficacy

Key points (Intent-to-treat results reported throughout)

1. Invasive disease
 - a) Point estimates of vaccine efficacy against invasive pneumococcal disease due to all serotypes have been consistently over 40%, in both high and low burden settings in US (California Kaiser, US American Indian) and in Africa (South Africa, the Gambia)
 - b) Efficacy point estimates for invasive disease due to serotypes included in the vaccine have been at least 70% in all populations where it has been tested; post licensure effectiveness studies show high effectiveness for each of the serotypes included in PCV7
2. Pneumonia
 - a. The Gambia, South Africa and US California trials found significant efficacy (20-35%) against radiologically confirmed pneumonia according to the WHO definition; the US Navajo trial did not find significant efficacy against this endpoint
 - b. In both the South Africa and Gambia trials, the vaccine was also effective at preventing WHO-defined severe clinical pneumonia
3. Mortality
 - a. The Gambia trial showed a 14% efficacy of vaccine at preventing all-cause child mortality in intent-to-treat analysis
4. AOM
 - a. Efficacy against vaccine type pneumococcal otitis media of 54% from one trial (Finland); higher efficacy against more severe disease (e.g. requiring tympanostomy tube placement)
 - b. Reduction in otitis media due to vaccine serotypes was offset by increase due to other serotypes and other pathogens with no net benefit against all cause acute otitis media
 - c. Vaccine-type pneumococcal otitis media includes a majority of antibiotic resistant pneumococci; thus benefits of vaccine may derive primarily from preventing resistant infections
5. HIV-infected children: will be addressed in a separate section (section VIII)

To facilitate comparisons of results across trials, intent-to-treat (ITT) results are reported throughout, unless otherwise specified. For the endpoint of invasive pneumococcal disease due to vaccine-included serotypes, all Phase III clinical trials of PCV7 and PCV9 found significant point estimates for efficacy of 70% or higher (see Table for section IV.5). The consistency is striking given the varied study populations and settings in which the trials were conducted and the differing immunization schedules. The efficacy against overall invasive pneumococcal disease (45-55% in three trials; 89%

in the US California trial) was lower than that against serotypes included in the vaccine, but remained substantial and significant. Estimates also accord well with a US post-licensure multistate case-control evaluation of vaccine effectiveness; the overall and serotype-specific efficacies estimated from this study are almost identical to the Kaiser trial findings.⁴¹ Direct efficacy estimates against culture-confirmed meningitis are not available from the clinical trials. The US post-licensure case-control study was able to evaluate this endpoint and found an efficacy against meningitis caused by serotypes included in the vaccine of 96% (CI 83, 99%), similar to the efficacy against invasive disease overall.

The Gambia trial is the only published trial that evaluated radiologically confirmed pneumonia as a primary endpoint.²⁶ This trial found a significant vaccine efficacy of 35% with a narrow confidence interval (see Table for section IV.5). While efficacy did not vary substantially according to age, sex or season of illness, efficacy was reduced, although not to a level of statistical significance, among children who received all 3 doses in the malaria season. This warrants further exploration since the other Phase III trials were not conducted in areas with endemic malaria. The South Africa, US California, and US American Indian trials evaluated radiologically confirmed pneumonia as a secondary endpoint. Point estimates from South Africa and California were similar, but slightly lower than the efficacy reported in the Gambia. In contrast, the US American Indian trial found a negative point estimate for efficacy with a confidence interval overlapping zero (O'Brien, Unpublished). A possible reason for lack of efficacy in the American Indian trial was that pneumonia case ascertainment was purely among inpatients while the efficacy demonstrated in the California trial was predominantly in

outpatients. In population with good access to high quality care, pneumococcal pneumonia is treated early and does not require hospitalization. In such populations, the impact of pneumococcal vaccine on hospitalized pneumonia may be difficult to demonstrate.

Both the South Africa and Gambia trials also evaluated efficacy against WHO-defined clinical pneumonia as a secondary endpoint. Efficacy against severe clinical pneumonia was significant in the South Africa trial and efficacy against overall clinical pneumonia was significant in the Gambia trial. In The Gambia, efficacy was only shown against clinical pneumonia accompanied by radiographic pneumonia. There was no evidence of any protection against clinical pneumonia in the absence of radiographic consolidation or effusion. On the other hand, in South Africa there was demonstrable efficacy against pneumonia without alveolar consolidation on chest radiographs. Other trials have not reported data separately for clinical pneumonia without radiographic changes. Point estimates for clinical pneumonia endpoints are lower than for radiologically-confirmed pneumonia (see Table) in part because of the limited specificity of the case definitions. Because pneumonia is such a common clinical syndrome, even a low vaccine efficacy translates into important vaccine-attributable disease reductions. This is evident from the absolute rate and risk reductions associated with pneumonia endpoints.

All-cause mortality was not a primary endpoint in any of the trials. In the Gambia trial, the baseline mortality rates were high enough to perform a secondary analysis and a 14% (95% CI: 2-24) efficacy against all cause mortality was measured (Table for section IV.5). Prevention of pneumococcal pneumonia is likely the strongest contributor to

reductions in overall mortality. The Gambia trial also found a significant 13% (95% CI: 6-19) vaccine efficacy against all cause hospital admissions.²⁶

For acute otitis media the data are more equivocal. Only 1 trial was designed with pneumococcal AOM as a primary endpoint. This trial, conducted in Finland, found significant efficacy against culture-confirmed pneumococcal AOM infections and a higher efficacy against infections due to vaccine serotypes (Table for section VI.6). Overall efficacy against AOM due to all causes however, was much lower (6%) and not statistically significant due in part to increases in disease caused by non-vaccine serotypes (see section IX) and also to AOM caused by other pathogens. The US American Indian trial also evaluated all cause acute otitis media and found no evidence of vaccine efficacy (see Table); this trial did find a 5.1% efficacy against severe episodes of AOM, although the confidence intervals were wide and included 0. The US Kaiser trial found a small but significant reduction (7.8%) in all cause AOM visits three and half years after vaccination. This trial also found significantly reduced frequent otitis and tube placement among PCV recipients.

Although PCV may not importantly reduce overall AOM episodes, because the vaccine is effective at preventing disease due to the major pneumococcal antibiotic-resistant clones, PCV7 introduction may still significantly reduce the incidence of acute otitis media-associated treatment failures and adverse sequelae. However, there was no evidence of an impact of PCV7 on the incidence of otitis-associated tympanic membrane perforations among Australian Aboriginal children, the one setting where this endpoint has been evaluated.⁴²

Table for section IV.5. Results of randomized, controlled trial of pneumococcal conjugate vaccine efficacy (7- and 9-valent CRM₁₉₇ formulations)

Characteristic	Clinical Trial Sites				
	US Northern California Trial ^{23, 43, 44}	US Navajo and Apache Nations ⁴⁵	Soweto, South Africa ^{27, 46}	Gambia Trial ²⁶	Finland ⁴⁷
PCV vaccine formulation	PCV7	PCV7	PCV9	PCV9 (mixed with DPT/Hib)	PCV7
Control group vaccine	MenC-CRM ₁₉₇	MenC-CRM ₁₉₇	Placebo	Placebo (mixed with DPT/Hib)	Hepatitis I
Vaccine dosing schedule	2,4,6 and 12-15 months	First dose between 6 weeks and <7 months; total of 3 doses by 12 months, with interval of > 30 days between doses; booster at >12-<24 months at least 60 days after primary series	6, 10, 14 weeks	3 doses at least 25 days apart; age at first dose between 40 and 364 days	2,4,6 and
Concurrent vaccines given	As per routine childhood schedule (DTwP or DTaP; OPV or IPV; Hib, Hepatitis B, MMR; varicella)	As per routine childhood schedule (Hepatitis B, Hib, DtaP, IPV or OPV, MMR)	Hib	As per EPI schedule (oral polio, Hepatitis B)	As per rou schedule (
Proportion of IPD caused by vaccine-included serotypes at baseline, children < 5 years	89%	56% (O'Brien, unpublished)	HIV-negative: 89% (PCV9 serotypes); 68% (PCV7 serotypes) HIV-positive: 53% (PCV9 serotypes); 49% (PCV7 serotypes)	61% (PCV9 serotypes); 46% (PCV7 serotypes) [Cutts, unpublished]	58% of cu otitis medi
N	37,868	8,292	39,836	17,437	1,662

Comment [T1]:

Design	Individually randomized		Cluster randomized		Individually randomized		Individually randomized		Individual	
Planned primary endpoint	Vaccine-type invasive pneumococcal disease		Vaccine-type invasive pneumococcal disease (Direct plus indirect effects because of cluster design)		Vaccine-type invasive pneumococcal disease		Pneumonia with consolidation on chest x-ray		Vaccine-type pneumococcal pneumonia	
Participants that met the per-protocol definition	89% in both groups		82% in PCV arm; 80% in control arm		93% in both groups		94% in both groups		95% in the vaccine arm; 96% in the control arm	
Endpoints evaluated	Efficacy ⁴ (95% CI)	Absolute rate reduction ⁵	Efficacy ⁹ (95% CI)	Absolute risk reduction ⁶ (95% CI)	Efficacy (95% CI)	Absolute risk reduction ⁸ (95% CI)	Efficacy (95% CI)	Absolute rate reduction (95% CI)	Efficacy (95% CI)	
Invasive disease, vaccine serotypes ¹	94 (80, 99)	2.4	83 (21,96)	1.9 (95% CI)	HIV-: 83 (39,97) HIV+: 65 (24,86)	HIV -: 0.8 (95% CI) HIV+: 13 (95% CI)	71 (46,86)	2.0 (1.1, 2.9)	N/A	
Invasive disease, all pneumococcal types	89 (74, 96)	2.6	52 (-7,79)	2.0 (95% CI)	HIV-: 42 (-28,75) HIV+: 53 (21, 73)	HIV -: 0.4 (95% CI) HIV+: 19 (95% CI)	45 (19,62)	2.0 (0.8, 3.3)	N/A	
WHO-radiologically confirmed pneumonia ²	26 (7, 41)	1.8 ⁶	-21 (-62, 9)		HIV-: 20 (2,35) HIV+: 13 (-7, 29)	HIV -: 1.0 (95% CI) HIV+: 9.1 (95% CI)	35 (26,43)	13 (9,17)	N/A	
WHO-defined clinical pneumonia ³	N/A	N/A	N/A	N/A	HIV-: -24 (-39, -5) HIV+: -8 (-38,37)	HIV -: -1.0 (95% CI) HIV+: -1.3 (95% CI)	6 (1-11)	14 (3, 25)	N/A	

WHO-defined severe clinical pneumonia ³	N/A	N/A	N/A	N/A	HIV-: 11 (1,20) HIV+: 17 (5,28)	HIV -: 1.6 (95% CI) HIV+: 20 (95% CI)	<i>Need ITT from Felicity</i>	2.9 (-0.1, 5.8)	N/A	
Hospital admissions (all cause)	N/A	N/A	N/A?	N/A?	N/A?	N/A?	13 (6-19)	13 (6-20)	N/A	
Mortality (all cause)	N/A	N/A	N/A	N/A	HIV-: 0 (95% CI) HIV+: 6 (95% CI)	HIV-: 0 (95% CI) HIV+: 7.9 (95% CI)	14 (2-24)	4.1 (0.4-7.7)	N/A	
Vaccine type acute otitis media ⁷	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	54 (41-64)	
All cause acute otitis media ⁷	6 (4-9)	<i>Can't get from paper</i>	-5 (-25,-12)		N/A	N/A	N/A	N/A	6 (-4, 16)	

¹Vaccine-type refers to serotypes included in the vaccine. For PCV7 this includes: 4,6B, 9V, 14, 18C, 19F and 23F . For PCV9 this additionally includes serotypes 1 and 5.

²Pneumonia associated with radiograph-confirmed alveolar consolidations in accordance with WHO recommendations ⁴⁸.

³ WHO clinical pneumonia was defined as history of cough or breathing difficulty of <14 days with a raised respiratory rate for age; pneumonia was classified as severe if chest-wall indrawing was also present.

⁴Efficacy for the intent-to-treat analysis is reported throughout

⁵ per 1,000 children

⁶Per 1,000 child-years

⁷ Acute otitis media was defined as X in Kaiser; Y in Navajo; Z in Finland

⁸ All pneumonia measures are reported as risk reduction (per 1000 children enrolled in the trials); all other measures are reported as rate reduction (per 1000 child-years of follow-up)

⁹ Efficacy is reported for primary efficacy group (first vaccination at <7 months of age); because of the group randomized design, efficacy estimates include direct and indirect effects.

*per protocol efficacy

IV. 6 Extrapolating from PCV9 to PCV7

Key Points

1. Phase III trials of PCV7 with IPD/pneumonia end points were only conducted in the United States; phase II immunogenicity and safety trials have been conducted in many countries, including developing countries.
2. Phase III trials of PCV9 were conducted in two African countries, The Gambia and South Africa; immunogenicity studies were also conducted in the same areas.
3. Efficacy and immunogenicity data from these trials allow bridging of results between the two vaccine products for serotypes common to both vaccines
4. Bridging for pneumonia is more complex and requires assumptions about the distribution of serotypes causing pneumonia, which is largely unknown

Currently there are efficacy trial data from developing countries for PCV9 but not for PCV7. Phase III trials of PCV7 with invasive pneumococcal disease and pneumonia endpoints were conducted in the United States. Phase III trials of PCV9 with invasive pneumococcal disease and pneumonia endpoints were conducted in the Gambia and South Africa.

Immunogenicity data provide a useful link between the two vaccines that allows extrapolation from one to another. The investigational vaccine PCV9 was produced by the same manufacturer as PCV7 and had the same formulation except for the addition of 2 serotypes. Thus this document extrapolates from the performance of PCV9 to the performance of PCV7 on the basis of immunogenicity and efficacy trial data.

For invasive pneumococcal disease protective efficacy, these data reassuringly show that PCV9 in two African settings performed similarly to PCV7 in two US populations for the serotypes included in the 7-valent formulation. Additionally, multiple studies of conjugate vaccines suggest that higher valent formulations typically have similar or lower efficacy than lower valent formulations for the serotypes in common. Thus extrapolation from PCV9 to performance of PCV7 will likely yield conservative estimates of PCV7 performance with regards to invasive disease.

For pneumonia, and for all-cause mortality, bridging is more complex and requires assumptions about the distribution of serotypes associated with these endpoints, which is largely unknown.

IV.7 Duration of Protection

Key Points

1. Data from clinical trials on duration of protection is generally limited by the period of observation and rarely extends beyond 2-3 years following immunization.
2. Immunogenicity data suggests that PCV7 will likely provide long-lasting immunologic memory and protection as other conjugate vaccines have done..

As for many new vaccines, there are limited data currently available on duration of protection of pneumococcal conjugate vaccines. Existing data suggest that PCV7 will likely provide long-lasting immunologic memory and protection as other conjugate vaccines have done.

The US Native American trial evaluated nasopharyngeal carriage 3 years following infant vaccination. This study found that carriage of serotypes included in the vaccine was significantly less common among vaccine recipients than among controls, suggesting that protection against acquisition of vaccine-included serotypes persists for at least 3 years.⁴⁹ The South Africa trial, which did not include a booster dose of vaccine after 12 months of age, re-evaluated immunogenicity at a mean of 5.6 years after vaccination and continued blinded surveillance for invasive pneumococcal disease surveillance for a mean follow up of 6.3 years after vaccination.⁵⁰ This extended follow up found that among HIV-uninfected children antibody concentrations remained above protective levels compared to controls and vaccine efficacy remained significant against invasive pneumococcal disease (78%; 95% CI 34-92%). HIV-infected children showed some evidence of waning immunity with immunogenicity levels below 0.35 µg/ml and

not significantly different between vaccine recipients and controls for 3 of 7 serotypes evaluated. Further study of the duration of immunity in the presence and absence of a booster dose will provide additional information to inform expectations on duration of protection and policy decisions regarding the utility of booster doses.

V. Direct Effects of Vaccine: Anticipated Deaths and Disease Prevented

Key Points

1. Based on global pneumococcal disease burden, global serotype distribution, and PCV7 efficacy data, the serotypes included in PCV7 are estimated to cause 390,000 to 550,000 deaths among children <5 years old
2. This burden of vaccine preventable mortality is similar to that anticipated for several other priority vaccines
3. Incidence of preventable pneumococcal disease is the recommended indicator of anticipated PCV7 impact; the proportion of invasive disease due to serotypes included in PCV7 is not a reliable indicator when used alone
4. HIV is addressed in Section VIII

In 2000, Hausdorff systematically reviewed the available pneumococcal serotype data from surveillance worldwide.⁵¹ This analysis estimates that the serotypes included in the 7-valent vaccine account for >55% of all invasive pneumococcal disease among children <5 years old each year.

Based on current estimates of pneumococcal deaths and the Hausdorff analysis of serotypes responsible for invasive pneumococcal disease, an estimated 390,000 to 550,000 children <5 years old die each year of infections due to the serotypes included in the 7-valent vaccine (i.e., 55% of 716,000 to 1,000,000 deaths). These figures indicate that the potential health impact of 7-valent vaccine is on par with those of Hib (386,000) and rotavirus (402,000).⁵² The 7-valent serotypes also cause some serious illness and death among adults but these are not included in the estimates above.

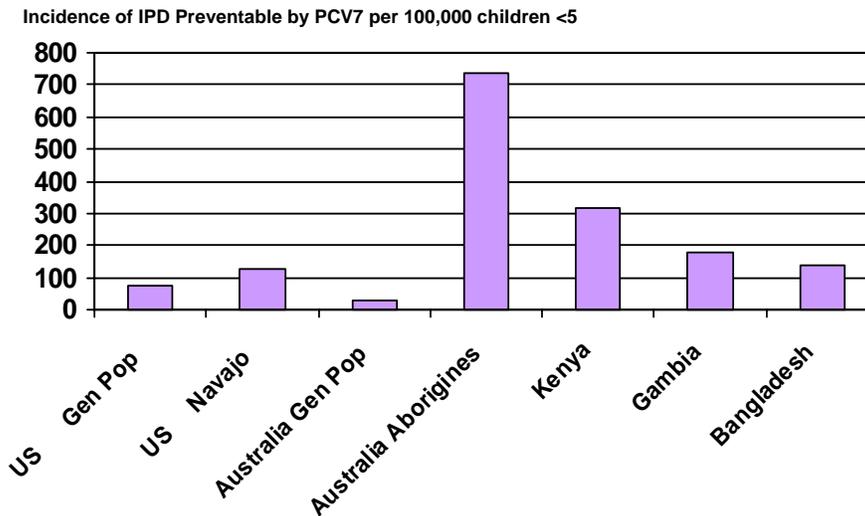
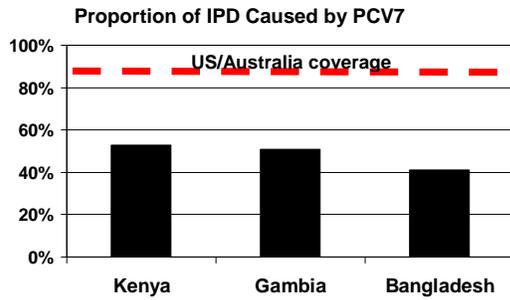
The introduction of PCV7 is expected to improve child health and survival in all countries. The greatest impact on child mortality is expected in countries with high

infant and child mortality rates (>50 deaths per 1000 births). Countries with lower child mortality rates and high quality surveillance should use these data to estimate the PCV7-preventable burden of disease and compare it with the preventable burden for other priority vaccines.

Many countries will have some local evidence of the proportion of pneumococcal disease caused by serotypes included in PCV7. While this measure can contribute importantly to country-specific estimates of the direct impact of vaccine, it is not reliable when used as the sole indicator of anticipated PCV7 impact. (see Figure for Section V). For example, in the United States, the baseline percent of invasive pneumococcal disease caused by serotypes in the 7-valent vaccine was 56% among American Indian children compared to 83% among the general US pediatric population. However, vaccine-attributable declines in invasive pneumococcal disease incidence three years after vaccine introduction were markedly higher among American Indians than among the general US population (125 cases per 100,000 among American Indian children, compared to 73 cases/100,000 among the general US population of children < 5 years of age) because of the substantially higher incidence of disease in the American Indian population before vaccine introduction.⁵³ Similarly, in Australia, the percent of invasive disease due to serotypes included in PCV7 was lower among the Australian Aboriginal population than among the general Australian population (72% vs. 92%). However, the incidence of disease due to 7-valent serotypes were among Australian aboriginal children were an order of magnitude greater than for the general population (1025 vs 32 cases per 100,000 children < 5 years of age).

These examples illustrate the benefits of using the estimated ‘incidence of preventable disease’ (i.e., the product of the serotype distribution and the rate of pneumococcal disease) as an indicator of the anticipated impact of PCV7 at the country level (see Figure for Section V). Among countries that have introduced PCV7 to date, the incidence of preventable invasive pneumococcal disease among children < 5 years of age has ranged from 29 per 100,000 (Australia) to 73 per 100,000 children (United States). Where country-specific estimates of the incidence of pneumococcal disease are not available, the preventable burden of disease may be estimated based on data from epidemiologically similar populations.

Figure for section V.2.: Proportion of IPD preventable by PCV7 vs. Incidence of IPD preventable by PCV7 in the US, Australia, and 3 Developing Countries. Data from Bangladesh are unpublished and should not be disseminated.



VI. Additional Impact of Vaccine

Key points

1. Vaccine introduction will not affect antibiotic use for acute otitis media and pneumonia but may reduce antibiotic use in settings where empiric therapy for occult bacteremia is a common practice
2. Antibiotic resistance among invasive infections will decrease, primarily due to prevention of infections due to vaccine-type serotypes
3. Indirect protection of the unvaccinated population through reduced transmission of serotypes included in the vaccine (“indirect effects” or “herd immunity”) is likely to result in significant prevention of invasive disease in adults and young infants
4. Hospitalizations for viral-associated pneumonia may decrease due to prevention of viral-associated secondary pneumococcal infections

VI. 1. Antibiotic Use

Introduction of pneumococcal conjugate vaccination may reduce antibiotic use in some settings. In a randomized, controlled trial of PCV9 in Israeli toddlers attending day care, the overall reduction in days of antibiotic use observed among vaccinees was 17%.⁵⁴ The greatest reductions were for lower respiratory infections and for children <3 years of age. Because children attending day care are at increased risk for respiratory infections, including those due to pneumococcus, they may represent a special population. A community-study of children in Anchorage Alaska found no change in prevalence of antibiotic use during the 2 years following vaccine introduction.⁵⁵

In many developing countries, a detectable impact on antibiotic use for pneumonia and acute otitis media is not anticipated, given the broad IMCI definitions for pneumonia and otitis media. In settings where empiric therapy for occult bacteremia is a common practice, PCV introduction may reduce antibiotic use because the primary objective of empiric therapy is to treat an undetected pneumococcal infection.

VI.2. Antibiotic resistance

Because the serotypes included in PCV7 are the serotypes accounting for most pneumococcal antibiotic resistance, introduction of PCV7 is anticipated to result in a reduced incidence of resistant pneumococcal infections. In populations where PCV7 introduction results in reduced antibiotic use, a reduced selective pressure for resistance may further slow the emergence and spread of resistance among predominant disease-causing serotypes.

In the South Africa PCV9 trial, the rates of invasive pneumococcal disease caused by penicillin-resistant strains and co-trimoxazole-resistant strains were reduced by 67% and 56%, respectively.²⁷ US post-introduction surveillance data showed an 81% decline in invasive pneumococcal disease caused by penicillin-resistant strains in children <2 years of age, and a 49% decline in adults >65 years of age.⁵⁶ Similarly, macrolide-resistant IPD decreased by 60% in persons of all ages in Atlanta.⁵⁷ In the US, replacement disease due to the antibiotic resistant serotype 19A may erode some of the reductions in resistance.⁵⁶ Longer-term data are needed. To determine conclusively the relationship between antibiotic use, vaccination and antibiotic resistance levels.

VI.3. Pneumococcal Disease in Other Age Groups (Indirect Effect)

Indirect protection of unvaccinated individuals (“indirect effects” or “herd immunity”) results from reduced nasopharyngeal carriage of pneumococcal serotypes among vaccinated children, which in turn decreases the opportunities for transmission of these serotypes to the rest of the population.

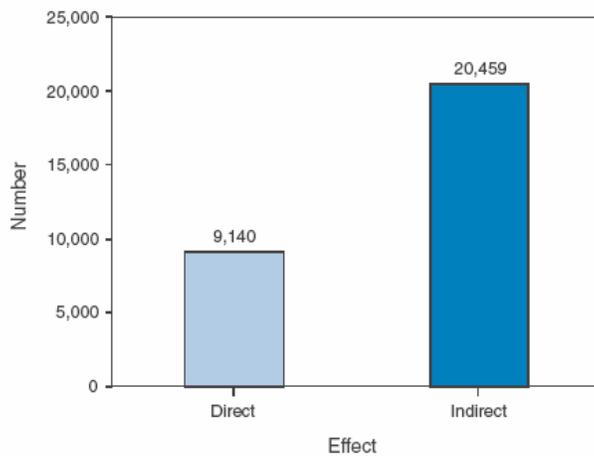
Analysis of surveillance data from the US for 4 years after vaccine introduction in 2000 indicates that the vaccine’s indirect effects surpassed its direct effects despite vaccine shortages which resulted in full vaccination of only 68% of the targeted 19-35 month age group. Invasive disease among infants 0-30 days of age decreased by 39%, with a similar reduction evident for infants 31 to 90 days of age.⁵⁸ Among persons 5 years of age and older, the incidence of invasive pneumococcal disease due to serotypes included in the vaccine decreased by 62%. The absolute rate reduction was greatest among those 65 years of age and older, at 21.7 cases per 100,000. Overall, an estimated

69% of cases of invasive disease due to vaccine included serotypes were averted through indirect effects of the vaccine.⁵⁹

Post-introduction surveillance in Canada reveals some evidence of indirect protection of age groups other than those targeted by the vaccine. In adults 65 years of age and above, there was no significant change in the incidence of invasive pneumococcal disease overall, but the incidence of invasive pneumococcal disease due to serotypes included in the vaccine was reduced by 62.7%. Rates of disease caused by serotypes included in PPV23 but not in PCV7 remained stable, whereas rates of disease caused by serotypes in neither PPV23 nor PCV7 increased by 163%, underlining the need for continued surveillance.⁶⁰

There are currently no data on indirect effects of vaccination from developing countries. Based on the North American experience, indirect protection of the unvaccinated population through reduced transmission of serotypes included in the vaccine is likely to result in prevention of invasive disease in adults and young infants. However, there is also a hypothesis that inclusion of a booster dose after the first year of life contributed importantly to indirect effects observed in North America because the mean antibody titre that protects against colonization is higher than the level required to protect against invasive disease. The extent of indirect effects of PCV that can be anticipated for developing countries and the importance of the booster dose in herd immunity are issues requiring further study, and which can only be determined with surveillance programs and in the context of routine immunization programs.

Figure for section VI.3. Direct and indirect effects of PCV7 in the US general population



* Direct VT IPD cases prevented in 2003 = 1998–1999 average number of VT IPD cases in children aged <5 years x 2003 PCV7 coverage with 3 doses (68.1%) x PCV7 effectiveness for VT IPD (93.9%).

† Indirect VT IPD cases prevented in 2003 = (1998–1999 average number of VT IPD cases across all age groups – 2003 number of VT IPD cases across all age groups) – 2003 direct VT IPD cases prevented. Calculation of indirect cases prevented does not account for replacement disease.

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VI.4. Viral-associated hospitalizations

Infections with several viruses, most notably influenza and respiratory syncytial virus, are associated with an increased risk of secondary pneumococcal pneumonia. In many instances, secondary bacterial infection contributes importantly to virus-associated pneumonia disease burden and mortality. It is thus plausible that PCV may also protect children from serious complications of common viral infections. As a secondary analysis, the South Africa Trial evaluated efficacy of PCV9 at preventing clinical pneumonia hospitalizations associated with positive laboratory tests for a range of viruses including respiratory syncytial virus, influenza A, parainfluenza viruses, and adenovirus. An intent-to-treat analysis found an efficacy of 22% (95% CI: 9,34) of PCV7 at

preventing hospitalized clinical pneumonia associated with any laboratory evidence of a virus. A higher point estimate of efficacy (41%) was reported for hospitalized clinical pneumonias associated with influenza A positive tests.⁶¹ Because this was a secondary analysis further investigation into the role of PCV7 at preventing severe viral complications among children is warranted.

VII. Unintended Consequences of Vaccine: Replacement disease

Key points

1. Vaccine-attributable increases in infections due to pneumococcal serotypes not included in the vaccine (non-vaccine types) is called “replacement disease”
2. The factors contributing to the emergence of replacement disease are varied and complex. Replacement disease is not anticipated to result in increases in the overall pneumococcal disease burden. However, it may attenuate the anticipated benefits of PCV introduction
3. Changes in incidence of non-vaccine serotypes after vaccine introduction need to be evaluated carefully to determine if they are likely attributable to vaccine, or to natural temporal changes in serotypes causing disease (for example due to regional outbreaks).
4. Complete replacement is anticipated for nasopharyngeal carriage based on robust data from multiple studies
5. Significant replacement is anticipated for acute otitis media although the vaccine is expected to reduce significantly infections due to antibiotic resistant strains
6. Some replacement will occur for invasive disease but it is not anticipated to erode vaccine benefits significantly and it will likely emerge over a period of years
7. Replacement will likely occur for pneumonia; direct measurements are not possible.
8. Replacement disease among the HIV-infected population is discussed in section VIII

VII.1 Definition and causes of Replacement Disease

Increases in pneumococcal disease caused by serotypes not included in the vaccine can occur either as a result of natural variability or pneumococcal conjugate vaccine use. The latter phenomenon is referred to as replacement disease. The driving force behind replacement disease is the effectiveness of pneumococcal conjugate vaccines in preventing acquisition of nasopharyngeal colonization with serotypes included in the vaccine. This increases the opportunity for serotypes not included in the

vaccine to colonize the upper respiratory tract of vaccinees and non vaccinees resulting in increased disease due to these types. It also confers an advantage to any serotype included in the vaccine that has an altered capsular polysaccharide no longer recognized by vaccine-induced immunity. Replacement disease is important to detect and monitor because it has the potential to reduce the prevention benefits of PCV.

The factors resulting in replacement disease are complex. Models that can reliably predict the scope of replacement disease for a given population are not yet available. Nonetheless, PCV clinical trials and the US experience with widespread PCV7 introduction provide data from which the following generalizations can be drawn.

VII.2. Distinguishing replacement disease from natural variations in pneumococcal serotype distribution

Nasopharyngeal and invasive pneumococcal serotype distributions vary naturally as a result of serotype-specific outbreaks, antibiotic-mediated selection pressure, host population changes, and introduction and loss of strains due to migration and drift. For example, in 2004 and 2005 an outbreak of serotype 1 in West Africa led to dramatic increases in meningitis due to this serotype in Northern Ghana, in the absence of any PCV7 use.⁶² Surveillance from around the world has documented many examples of serotypes becoming prevalent for a number of years and then receding in importance. Thus, not all changes in the incidence of a given serotype are due to vaccine use.

Because natural variation is difficult to distinguish from replacement disease, changes in serotype distribution and disease burden following vaccine introduction must

be evaluated carefully to assess their potential relationship to vaccine pressure. Vaccine clinical trials are one source of data on replacement disease. A benefit of trial data is the inclusion of a contemporaneous control population. A limitation is that most trials do not have the duration of follow-up or high enough population levels of vaccine coverage to characterize the extent of replacement disease adequately, particularly for invasive disease. Most data on replacement disease comes from before/after surveillance activities linked to PCV introduction. For these studies, secular trends may make it difficult to determine whether shifts in the serotypes causing pneumococcal disease are vaccine attributable. Some features suggestive of vaccine-attributable increases in a non-vaccine serotype are summarized in Box 1.

VII.3. Nasopharyngeal carriage

More than 8 controlled clinical trials using a variety of conjugate vaccine formulations, dosing schedules and study populations have evaluated the effect of PCV on NP colonization. Several observational studies have also looked at nasopharyngeal carriage before and after vaccination. These studies have consistently shown that complete replacement of serotypes included in the vaccine with serotypes not included in the vaccine will occur in the nasopharynx with no net effect on overall carriage rates.⁶³ Nasopharyngeal replacement is already detectable after the third dose of the infant series⁶⁴ and [O'Brien unpublished data] and can be sustained for at least 3 years post vaccination⁴⁹; the ultimate duration of this vaccine effect has not yet been characterized.

VII.4. Acute Otitis Media

The emergence of replacement pneumococcal otitis media also appears to be the rule rather than the exception. The phase III PCV7 trial designed to evaluate acute otitis endpoints (see Table for section IV.5) found that replacement disease occurred over a short time frame following vaccine introduction and reduced but did not eliminate the overall efficacy of the vaccine.^{47, 65} Similar results have also been found for a non-CRM197 formulation.^{66, 67}

Although replacement disease minimizes overall reductions in the incidence of pneumococcal acute otitis media, because the vaccine prevents disease due to the major pneumococcal antibiotic-resistant clones, PCV7 introduction may still significantly reduce the incidence of acute otitis media-associated treatment failures and adverse sequelae. There has been no impact of PCV7 on the incidence of severe otitis media (tympanic membrane perforations) among Australian Aboriginal children, the one setting where this has been evaluated.⁴²

VII.5. Invasive disease

None of the phase III clinical trials (see Table for section IV.5) documented replacement invasive disease although both the South Africa and the Gambia trials found a similar increase in non-vaccine type invasive disease among PCV recipients that did not achieve statistical significance. None of the pre-licensure trials, however, were designed to measure the effect of vaccination on replacement disease. In this regard, long-term post-licensure surveillance for invasive disease is a more appropriate method and allows for monitoring of replacement disease in a setting of widespread vaccine use. Although there are no direct data from non-industrialized countries, current evidence from North

American surveillance suggests that some degree of replacement invasive disease will most likely occur, that it will not result in major reductions in the overall benefits of vaccine, and that it will emerge over the course of years rather than months.

The United States was the first country to introduce PCV on a large scale and has conducted multistate, population-based invasive disease surveillance before and after vaccine introduction. The incidence of invasive disease due to serotypes not included in the vaccine and in particular, of disease caused by serotype 19A, has increased significantly among US children <5 years of age following PCV7 introduction. This increase has been seen persistently from 2001-2005, the most recent year evaluated. However, the net increase in incidence of invasive disease caused by serotypes not included in the vaccine (+12 cases /100,000 children, comparing baseline rates to the rate in 2005) is minimal compared to the large decrease in incidence of disease caused by serotypes included in the vaccine (-80/100,000 children). [ABCs, unpublished data]

Within the US, invasive pneumococcal disease surveillance is also conducted among American Indians (Navajo and Apache), and Alaska Natives, two populations at increased risk for pneumococcal disease. Among the Navajo and Apache, population-based surveillance during the pre-vaccine period and during the nine years since PCV7 was first introduced shows no increase among any age group in the overall incidence of invasive disease due to serotypes not included in the vaccine. Specific serotypes not included in the vaccine have increased in incidence while others have decreased in incidence resulting in no change overall.⁶⁸

Among Alaska Native children, the trend in invasive disease due to serotypes not included in the vaccine is different from either the Navajo or the general US pediatric

population. Before vaccine introduction, 73% of invasive pneumococcal disease among Alaska Natives was due to serotypes included in PCV7; similarly, among non-native Alaskans, 79% of invasive pneumococcal disease was due to serotypes included in PCV7. However, while the non-native Alaska population experienced a 79% overall reduction in pneumococcal disease since PCV7 vaccine introduction in 2001, the Alaska Native population has seen this effect eroded to 37% because of increases in the incidence of disease caused by serotypes not included in the vaccine.⁶⁹ The increase in incidence of serotypes not included in the vaccine occurred primarily in children less than 1 year of age, whereas replacement disease would typically be expected to be most pronounced in older children (12-59 months) that had received the full infant series. While the overall increase in incidence of disease caused by serotypes not included in the vaccine increased progressively among <1 year olds following vaccine introduction, this increase was not due to a single serotype, but to small increases in several serotypes not included in the vaccine. Serotype-specific sample sizes are too small to allow for an adequate assessment of whether the changes can be attributed to vaccine. Thus, the evidence for vaccine-attributable replacement disease among Alaska Natives is not yet conclusive, and highlights the challenges and importance of monitoring for replacement disease post introduction.

To date no developing countries have introduced PCV outside of trial or study settings. Of the populations studied in North America, the Navajo and Apache study populations are perhaps the most similar to African and Asian resource-poor, rural populations in terms of living conditions, socioeconomic status, a baseline high incidence of pneumococcal disease and a somewhat low proportion of invasive disease serotypes

covered by vaccine (56% among children under 5 years, compared to 83% in general US population).

VII.6. Pneumonia

Determining the etiology of pneumonia is difficult and, even with the most sensitive techniques, a specific etiologic cause can be documented in less than half of all pneumonia cases. Even fewer cases provide a pneumococcal isolate that could be used for serotyping. As a result, the distribution of serotypes causing pneumococcal pneumonia is largely unknown and typically the distribution of serotypes causing invasive disease is used as a surrogate. Because pneumococcal pneumonia shares some aspects of systemic infections like bacteremia and sepsis, and some aspects of mucosal disease like colonization and otitis media, there is the expectation that some serotype replacement will occur in pneumococcal pneumonia. Given the difficulties in diagnosis of pneumococcal pneumonia, it is not expected that countries will be able to directly measure serotype-specific changes in this syndrome.

Box for section VII. Features distinguishing vaccine-attributable replacement disease from natural variation in disease causing serotypes*

- A progressive or sustained increase in the incidence of disease due to a non-vaccine serotype in the years following vaccine introduction
- Increases that are more notable among children <5 years (vaccine targeted age group) or specific sentinel populations (eg, HIV infected adults)

- Increases that are more notable among populations where PCV7 was introduced than among epidemiologically and geographically similar, vaccine-naïve populations
- Increases in a strain that was common before vaccine introduction
- Molecular evidence consistent with expansion of vaccine-escape mutants

* Increases in pneumococcal disease caused by serotypes not included in the vaccine can occur either as a result of natural variability or pneumococcal conjugate vaccine use. The latter phenomenon is referred to as replacement disease. To detect and monitor replacement disease with reliability, high quality pneumococcal surveillance with a well-defined, pre-vaccine baseline is crucial. Additionally, although important for interpreting trends, evaluation of year to year variation must be considered with caution due to the potentially wide confidence intervals around point estimates based on a small number of cases.

VIII. PCV and the HIV-infected population

Key points

- HIV infected children have an elevated burden of pneumococcal disease – 9-40 times higher than uninfected children
- Serotype distribution is similar among HIV-infected & -uninfected children; HIV infected adults have a greater burden of IPD from PCV7 serotypes.
- PCV was well-tolerated, immunogenic, and efficacious in clinical trials with HIV-infected children. The immunogenicity and efficacy is lower than among HIV uninfected children.
- PCV use is expected to safely and effectively prevent disease in HIV-infected children; given the increased risk of pneumococcal disease among this group, vaccination of HIV infected children is anticipated to result in substantial absolute reduction in pneumococcal disease incidence
- PCV is complementary to ART or cotrimoxazole prophylaxis programs. It does not obviate the need for either, but can be used safely in the presence of either

- Herd immunity from routine use of PCV among infants has reduced the incidence of vaccine type disease among HIV-infected adults, however, serotype replacement has eroded some of the benefit and the extent to which this will continue remains unknown.
- To date the data on replacement disease among children with HIV infection are insufficient to allow for conclusions

VIII.1. Pneumococcal disease burden and serotype distribution

In many parts of the world, invasive pneumococcal disease is an important HIV-associated opportunistic infection. Data from 14 studies in Southern Africa and the United States in the era before widespread use of highly active antiretroviral therapy (HAART) suggest that children infected with HIV have a 9 to 40-fold risk of invasive pneumococcal infection compared to uninfected children, with incidence rates ranging from 1800 to 18500 episodes per 100,000 child years.⁷⁰ Adults infected with HIV have a similar or even higher fold increase in incidence of pneumococcal disease compared to uninfected adults. Adults treated with highly active antiretroviral therapy (HAART) are at lower risk of pneumococcal infection, although the risk remains elevated compared to the HIV-uninfected population.^{71,72} Data for children are lacking although the assumption is that HAART would have a similar effect. Invasive pneumococcal disease case fatality ratios are similar for HIV and HIV-uninfected children, based on data from the US, Jamaica and Southern Africa.⁷⁰ One study in South Africa found that children with advanced HIV disease had higher mortality than children with less advanced HIV disease.⁷³ The serotype distribution of invasive pneumococcal isolates is similar among HIV-infected and uninfected children, although data from developing countries are limited and come primarily from South Africa.⁷³⁻⁷⁷ Among adults, in contrast, several studies suggest the serotypes included in PCV7 are over-represented among the HIV-infected population.⁷⁰

VIII.2. Vaccine Safety

Three US studies of PCV7 and 1 South African trial of PCV9 (see table for section VI.6) evaluated vaccine safety among children with HIV infection.^{27, 78-80} These studies showed that PCV7 is well tolerated among HIV-infected children and that adverse events in this population did not differ significantly from those seen in the uninfected population. All of these studies were too small to detect any rare but important adverse events; such events can only be detected by post licensure surveillance. Additionally, to date no studies have evaluated the direct effect of PCV administration on CD4 count and HIV viral load among children.⁷⁰

VIII.3. Immunogenicity

The quantitative antibody response to PCV is slightly lower, but generally not statistically different from that in HIV-uninfected children based on results from 7 studies.⁷⁰ In three studies participants were receiving HAART. In five studies that assessed the relationship between immunogenicity and CD4 count, no relationship was found; in one study in South Africa, children with AIDS had lower geometric mean concentrations than other HIV infected children.⁸¹ The functional activity of pneumococcal antibodies elicited by PCV is also lower among HIV-infected than uninfected children, suggesting that the antibodies produced in response to vaccination are less functional.⁸¹ Whether HIV-infected children mount a booster response to PCV remains unclear and may depend on age at first immunization as well as severity of HIV disease; to date there are no data for children not on antiretroviral therapy.⁷⁰

VIII.4 Vaccine Efficacy and Vaccine-attributable Absolute Rate Reduction in Disease

PCV efficacy is somewhat lower in HIV-infected children but still substantial and statistically significant. The strongest data come from the South Africa Phase III trial of almost 40,000 children, approximately 6% of whom were infected with HIV.²⁷ Efficacy among this subgroup for a variety of pneumococcal endpoints is shown in Table for section IV.5. Although the efficacies are somewhat lower than among HIV-uninfected children (for example 65% efficacy against invasive disease due to vaccine included serotypes compared to 83% efficacy among HIV uninfected children), the absolute rate reduction in disease due to vaccine is an order of magnitude greater than among HIV-uninfected children because of the highly increased incidence of pneumococcal infections among HIV infected children at baseline.

At the time the South Africa vaccine trial was conducted, HIV-infected children were not receiving antiretroviral therapy. Efficacy data are not available for children on HAART. The expectation is that vaccine efficacy will be improved due to improved immune function, although the overall efficacy will still likely be lower than among uninfected children. Conversely, the absolute rate reduction in disease is expected to be lower than in the absence of HAART because the baseline pneumococcal incidence among HIV-infected children on HAART will be lower than among children not receiving antiretroviral therapy. Nonetheless the absolute rate reduction in disease is still expected to be substantially larger than among HIV-uninfected children.

VIII.5. Indirect effects

Data on indirect effects among the HIV-infected population stem primarily from one US multicenter study.⁸² In this multistate population, herd immunity from routine

use of PCV among infants reduced the incidence of vaccine type invasive pneumococcal disease by 62% and overall invasive pneumococcal disease by 19% among HIV-infected adults. However, serotype replacement has eroded some of the benefit (see section VII) and the extent to which this will continue remains unknown.

VIII.6. Replacement disease

Because impaired host immunity among HIV infected children results in a higher baseline incidence of pneumococcal disease and reduced efficacy of PCV, there is some concern that this group might be more at risk for replacement disease than the general population. Although the data are limited, available evidence suggests that among HIV infected children, replacement disease is likely to occur for all pneumococcal syndromes but the net benefits of vaccine will remain significant and absolute rate reductions in disease will likely be substantial.

During the course of the South Africa PCV9 clinical trial, serotype-specific increases in invasive pneumococcal disease among HIV positive participants did not occur.²⁷ However, the trial timeframe was short relative to the time often required for replacement disease to emerge. To date no longer term data are available regarding replacement disease among HIV-infected children. Among HIV-infected adults, US multistate population-based surveillance for invasive pneumococcal disease has documented significant replacement invasive disease, particularly among African-American women, although the net indirect effects of vaccine are still positive with a 62% reduction in invasive disease incidence due to vaccine types and 19% reduction in invasive disease due to all serotypes.⁸²

VIII.7. PCV use in settings of HAART and co-trimoxazole prophylaxis

PCV is complementary to antiretroviral therapy or co-trimoxazole prophylaxis programs and does not obviate the need for either. PCV offers direct and effective protection against pneumococcal disease due to vaccine included serotypes. Antiretroviral therapy indirectly prevents some pneumococcal disease through improved immune function among HIV-infected children. Antiretroviral therapy alone however does not bring the risk of pneumococcal infection down to the rate among HIV uninfected children, much less to the lower incidence achievable by vaccination. Co-trimoxazole prophylaxis among HIV infected children may be effective at preventing some HIV-associated opportunistic infections including pneumococcal infections, particularly in populations where co-trimoxazole resistance among pneumococci is rare. Evidence to date suggests PCV can be used safely in the presence of both or either intervention; use of all three is expected to afford the most protection to HIV-infected children.

IX. Vaccine Administration

Key Points

1. Intramuscular administration at ≥ 6 weeks of age is recommended. Infants less than 12 months old should receive 3 doses as a primary course with a minimum interval of 4 weeks between doses.
2. Existing WHO policy for contraindications should apply. Minor illnesses are not a contraindication to vaccination; delay of vaccination may be chosen for major illnesses
3. May be administered concomitantly with other EPI vaccines
4. Immunogenicity and efficacy data from 9-valent vaccine studies in South Africa show that a 6,10, 14 week schedule, as used for other EPI vaccines, can confer high levels of protective efficacy. Data from the Gambia trial with 9-valent vaccine shows that when actual vaccination begins at later than 6 weeks of age, and with greater than 4 week intervals (which is often typical in the implementation of EPI) the vaccine's protective efficacy is also high
5. Phase III trials in 2 African countries show that a 3-dose primary series confers substantial protection. There is evidence from industrialized countries that a booster dose after 12 months of age improves immune response. Ongoing

studies using alternative schedules may help in further optimizing the immunization schedule for infants in developing countries.
6. In the year of vaccine introduction, immunization of all children 12-24 months of age and children 2 to 5 years of age at high risk of infection with a single dose of vaccine will provide additional benefit.
7. Use of PPV23 after PCV is recommended for certain high risk groups (eg, children with sickle cell disease, HIV, other immune deficiencies) in industrialized countries and may be considered in some developing countries, depending on local conditions and resources.
8. Use of PPV23 before PCV has not been studied in detail. Data from adults/elderly suggests it may interfere with PCV response; simultaneous co-administration with PPV23 has not been studied
9. Incorporation of PCV into the EPI schedule will require additional cold chain facilities in the short term; planning and strategies for parental education may also be required to ensure acceptability of an additional vaccine.

IX 1. Administration

PCV 7 is administered intramuscularly as a 0.5 ml dose. It may be administered at the same time as other concomitant injections but in a separate syringe and a separate site.

IX.2. Contraindications and Precautions

Vaccination is contraindicated among persons known to have hypersensitivity to any component of the vaccine. Health care providers may choose to delay vaccination in children with moderate to severe illness. It is standing WHO policy that minor illnesses, e.g. mild upper respiratory infection with or without mild fever, are not contraindications for vaccination.

IX.3. Co-administration with other vaccines

Available data show that PCV7 can be administered at the same time but at different sites as other vaccines included in the current EPI schedule for children without adversely affecting the efficacy of PCV7 or the other co-administered vaccines. In the US trials, DTaP was the sole pertussis formulation used among the American Indian population and the primary formulation used in the California Kaiser trial. Although a reduced immunogenicity and possibly efficacy of Hib vaccine has been shown when co-administered with acellular pertussis⁸³, immunogenicity data from the American Indian trial and the California Kaiser trial, as well as the post-licensure experience from the US where DTaP is used nationally, suggest no evidence of a similar effect of acellular pertussis on PCV7.^{23, 34, 59, 84} Phase 2 clinical trials using an 11 valent formulation where pneumococcal polysaccharide was conjugated to either tetanus or diphtheria toxoid suggest the immune responses to the serotypes conjugated to tetanus toxoid were diminished when co-administered with acellular pertussis vaccine as compared to whole cell pertussis vaccines.⁸⁵ However, this formulation is currently not licensed.

A randomized, double-blind, placebo-controlled immunogenicity study of PCV9 co-administered with routine EPI vaccinations among 500 infants in South Africa at 6, 10 and 14 weeks of age and found pneumococcal immunogenicity levels above what has been seen in the US and Finland with PCV7. PCV9 recipients also had higher levels of antibody against *Haemophilus influenzae* type b (Hib) and Diphtheria than controls.³⁵ Increased antibody levels against Hib were hypothesized to result from synergy between the CRM₁₉₇ component of PCV9 and the CRM₁₉₇ component of the Hib vaccine administered. In the US American Indian trial, the Hib -meningococcal outer membrane protein complex (Hib-OMP) vaccine was used rather than a CRM₁₉₇ conjugate

formulation. Immunogenicity results for both Hib-OMP and PCV7 suggest that both vaccines perform well even when the proteins they are conjugated to do not match.⁸⁴

IX.4. Use Before or After PPV23

Use of PPV23 before PCV has not been studied in detail. Data from adults suggest that use of PPV23 before and individual receives primary immunization with PCV results in hyporesponsiveness to PCV. [O'Brien and Goldblatt, TLID, In Press?] Thus, PPV23 use before completion of primary PCV immunization is not recommended.

Use of PPV23 after PCV is routine for certain high risk groups (eg, children with sickle cell disease, HIV-infection, or belonging to groups at elevated risk for pneumococcal disease such as Australian Aborigines) in industrialized countries and may be considered in some developing countries, depending on local conditions and resources. Some studies have evaluated using PPV23 in place of a PCV booster dose between 12 and 15 months of life. Data are very limited on the long-term impact of such regimens. Some data suggest that there may be a negative impact on PCV effectiveness [Veenhoven, 2003 #581; MacKenzie?] although this has not been confirmed. The impact of PPV23 booster dose is currently being evaluated in an ongoing study in Fiji and more data are anticipated in the future.

Simultaneous co-administration with PPV23 has not been studied.

IX.5. Vaccine Schedule

The EPI childhood schedule, followed by many developing and industrialized countries, recommends a 6, 10, 14 week schedule for the primary series of DTP, polio, hepatitis B and Hib vaccine. Available evidence supports the use of PCV7 in a similar schedule. Phase III clinical trial data from South Africa provide the strongest evidence that this schedule, although accelerated compared to the US schedule of 2, 4 and 6 months of age, is effective for preventing pneumococcal disease. In this trial, children were vaccinated very close to the targeted intervals (first dose: 6.6 ± 1.2 weeks; second dose: 11.2 ± 2.5 weeks; third dose: $15.9 \pm X$ weeks) and the efficacy and immunogenicity were comparable to what was seen in the US trials (see table in section IV.5). An independent randomized double blind immunogenicity study of 500 infants in this population vaccinated at 6, 10 and 14 weeks found pneumococcal antibody concentrations higher than levels achieved in the US or in Finland following a 2,4 and 6 month schedule lending further support for the effectiveness of this accelerated primary series schedule.³⁵ The Gambia trial had less strict criteria for age at first vaccination and likely reflects the more typical range of ages at vaccination in developing countries following the EPI schedule. In this trial, the first dose of vaccine was received at a median of 10.7 weeks, with an interquartile range(IQR) from 8 to 15 weeks; the second dose was received at a median of 17.4 weeks (IQR: 13.9-23.7 weeks); and the third dose was received at a median of 24.1 weeks (IQR: 19.4-32 weeks). Despite the wide variation in the actual age at receipt of each dose in the two trials, the vaccine demonstrated protective efficacy against a range of pneumococcal disease syndromes.

Phase III trials in South Africa and the Gambia showed that a 3-dose primary series confers substantial protection. Similarly, a US PCV7 post licensure case control

study found that receipt of 3 doses at less than 7 months of age had a 95% effectiveness (95% CI: 88, 99) against invasive pneumococcal disease caused by serotypes included in the vaccine.

There is immunogenicity evidence from industrialized countries that a booster dose after 12 months of age improves immune response. The US post-licensure case-control study found that compared directly to a schedule of 3 doses given at ≤ 7 months of age, a 4-dose schedule (3 doses ≤ 7 months, 4th dose at 12 to 16 months) significantly reduced risk of disease caused by vaccine types (matched odds ratio 0, 95% CI 0, 0.87).⁴¹ The sample size of children receiving alternate schedules in this study was not sufficient to allow for a meaningful comparison of a 3 dose primary series with a 2 primary dose schedule plus a booster dose. Immunogenicity data also suggests that a schedule with 2 primary dose in infancy followed by 1 booster dose after 12 months might be more immunogenic than a 3 dose primary schedule during infancy, and would save the additional cost of requiring a 4th dose.³⁸ Some European countries have recently adopted a “2+1” PCV7 schedule based in part on these findings. The United Kingdom experience of a resurgence of Hib disease after using a schedule without a booster dose has also been interpreted as evidence of the importance of a booster dose. However, in the UK, several factors may have contributed to this resurgence⁸⁶ and a similar resurgence has not been seen in Central and South America, despite use of a 3 primary dose Hib schedule for years in some countries. To date no direct efficacy data or head-to-head comparisons of the 2+1 regimen with other regimens are available, and there are no data regarding this issue from developing countries, though trials are ongoing to evaluate similar schedules. Data on cost-effectiveness of different potential schedules

(eg, using different numbers of doses, intervals between doses, with and without boosters) should be obtained.

Immunogenicity data, and data from the US post-licensure case control study suggest a single dose for unvaccinated children 12-59 months of age at first vaccination confer protection. Though lower than in the first year of life, serious disease continues to occur at high rates in children up to 5 years of age. Investigation of the effectiveness of catch-up vaccination and optimal catch-up regimens for developing countries is another important area for research.

IX.6. Implications of incorporating an additional vaccine

Adding pneumococcal vaccine will require administering a separate, additional injection to children at the immunization visits scheduled for 6, 10 and 14 weeks (or other equivalent doses in programmes using a different schedule). This will also result in a marginal increase in the number of syringes to be disposed off (increase from 10 to 13 syringes per child).

This will require some additional equipment, training and effort for health workers who administer vaccines. One practical issue is the increase in equipment to maintain the cold chain since the current formulation of PCV7 requires refrigeration (see section IV.1)..

The addition of a vaccine may also potentially impact parental acceptability. Parental reluctance to accept an additional injection will probably be reduced by their recognition of the severity of pneumococcal diseases like meningitis and pneumonia and their desire to protect their children against these diseases. In the United States,

immunization coverage rates are at all time high levels in spite of the fact that children currently receive as many as 4-5 injections at a single visit. Parental concerns can probably be addressed but to be effective, careful planning and strategies to educate health workers and parents will be important.

X. Cost-Effectiveness Analysis

Key points

1. Economic analyses have generally found PCV cost-effective in industrialized countries. Giving PCV vaccination of children additional credit for reduced morbidity and/ or for preventing disease in adults and other age groups results in significantly better cost-effectiveness, with cost-effectiveness ratios decreasing by two to 21-fold.
 - a. At current vaccine costs, routine PCV vaccination is estimated to cost between USD 32,000 to 166,000 per life-year saved.
 - b. Studies have found break-even prices of between \$4 and \$32 per vaccine dose.
 - c. Giving PCV vaccination of children additional credit for reduced morbidity and/ or for preventing disease in adults and other age groups results in significantly better cost-effectiveness, with cost-effectiveness ratios decreasing by two to 21-fold.
2. A cost-effectiveness analysis for some of the poorest developing countries (GAVI-eligible countries) was recently developed. The analysis was not tailored to a particular vaccine formulation, but used the Gambia PCV9 trial findings as the benchmark.
3. Key findings of the developing country analysis include:
 - a. PCV use at current rates of DTP coverage could prevent ~ 470,000 deaths and 3.07 million hospitalizations per year in GAVI-eligible countries between the ages of 3 and 59 months of age.
 - b. The greatest numbers of deaths would be saved in countries with large birth cohorts and high childhood mortality.
 - c. Using a vaccine cost of \$5 per dose, vaccination would meet WHO's criteria for "very cost effective" in 70 of 72 GAVI-eligible countries.
 - d. Cost-effectiveness estimates were sensitive to vaccine cost and estimates of vaccine efficacy against all-cause mortality and were relatively insensitive to other parameters. Vaccine effectiveness was more important at higher vaccine costs.
4. Among GAVI-eligible countries, PCV7 is expected to prevent 10-30% fewer pneumococcal deaths and disease than PCV9
5. Sensitivity analyses based on the developing country model above show that even with this reduced efficacy, the cost per DALY saved would be \$33 - 56 and the vaccine would remain cost-effective.

Cost-effectiveness analyses of PCV7 in industrialized countries have found costs of PCV7 to range from US \$32 000 and 166 000 per life-year saved using the societal

perspective and have characterized circumstances under which PCV7 is cost-effective [Ray and Sinha in preparation]. Analyses that include the indirect effects of vaccine on preventing disease in other age groups, benchmarked to the US experience, find substantially reduced costs per life-year saved and substantially improved cost-effectiveness (\$7500-\$18,000 per life-year saved).⁸⁷ Key factors influencing cost-effectiveness of the vaccine include vaccine cost and pneumococcal disease burden.

A cost-effectiveness analysis for some of the poorest developing countries (GAVI-eligible countries) was recently developed⁸⁸ and enhanced [Sinha, unpublished]. The primary analysis of the enhanced model focused on deaths and disease averted by the direct effects of PCV vaccine and incorporated a modest herd immunity effect among non-vaccinated infants. Herd immunity effects among older children, adolescents and adults were not incorporated. The analysis was not tailored to a particular vaccine formulation, but used the Gambia PCV9 trial findings as the benchmark

The primary analysis assumed that vaccine was protective between the ages of 3 and 59 months and found that PCV use at current rates of DTP coverage could prevent 470,000 deaths and 3.07 million hospitalizations annually.

The greatest numbers of deaths would be saved in countries with large birth cohorts and high childhood mortality. This analysis focused strictly on effects in the targeted birth cohort. Analogous to the experience with industrialized countries⁸⁷, even more modest indirect effects than seen in the United States among older children, adolescents and adults could lead to substantially more deaths and disease prevented.

For the base analysis, at a vaccine cost of International \$5 per dose, vaccination met WHO's criteria for "very cost effective" in 70 of 72 GAVI-eligible countries.

Cost-effectiveness estimates were sensitive to vaccine cost and estimates of vaccine efficacy against all-cause mortality and were relatively insensitive to other parameters. Vaccine effectiveness was more important at higher vaccine costs.

Among GAVI-eligible countries, PCV7 is expected to prevent 10-30% fewer pneumococcal deaths and disease than PCV9. In a sensitivity analysis of the developing country model, the reduced efficacy anticipated for PCV7 resulted in a cost per DALY averted ranging from International \$33 to 56 per DALY averted and the vaccine remained cost-effective.

Table for section X. Sensitivity analysis of vaccine's effect on mortality in developing country cost-effectiveness model

Reduction in PCV7 mortality benefit, relative to PCV9	\$ per DALY averted	Net costs	DALYs averted	Deaths averted
0%	22	324,399,757	14,961,456	469,594
- 10%	33	423,061,555	12,658,928	422,635
- 30%	56	586,845,447	10,473,019	328,716

XI. Other vaccines under development

Key Points

The pneumococcal vaccine pipeline is strong

- A 10-valent conjugate formulation (includes PCV7 serotypes plus serotypes 1, 5 and 7F) is in late stage clinical trials; license application is anticipated in 2007
- A 13-valent formulation is at earlier stages in the licensure process, anticipated on the market by 2010
- Trial of an 11-valent vaccine in Philippines found efficacy against pneumonia that is comparable to the Gambia, South Africa, and US California trials
- More than 20 other conjugate and common protein formulations are in early development, some by developing country manufacturers

Support from the Global Alliance for Vaccines and Immunizations (GAVI) and efforts by organizations committed to accelerate pneumococcal conjugate vaccine introduction (eg, PneumoAdip) lay a foundation for an affordable and sustainable vaccine supply for developing countries

PCV7 is currently the only licensed pneumococcal conjugate vaccine. It is manufactured by Wyeth and licensed in ~75 countries, including 5 GAVI countries (India, Indonesia, Pakistan, Honduras, and Nicaragua). The manufacturer has begun preparing an application for WHO prequalification and is expected to submit the application in January, 2007.

The pneumococcal conjugate vaccine pipeline is strong, in part because the scientific hurdles are largely overcome and in part because there is a large global market. The next vaccine expected from the pipeline is a 10-valent conjugate vaccine that adds serotypes 1, 5, and 7F to the serotypes in the 7-valent vaccine. This vaccine is in late-stage clinical development with a target for a license application of 2007 (expected licensure date of 2008). An earlier 11 valent formulation of this vaccine was evaluated for clinical efficacy against acute otitis media in the Czech republic. The vaccine showed an 51.5% efficacy against pneumococcal otitis media and 52.6%% efficacy against vaccine type pneumococcal otitis media. Interestingly, the vaccine also showed efficacy against otitis caused by non-typeable *H. influenzae*, which is most likely related to an immune response to the protein carrier in the vaccine (protein D of *H. influenzae*). A 13-valent conjugate vaccine is also in advanced stages of clinical development; this vaccine adds serotypes 1, 3, 5, 6A, 7F, and 19A to the serotypes in the 7-valent. Licensure is forecasted for 2010. Available data on higher-valency formulations suggests they will be effective and induce serotype-specific protections similar to PCV7. This has been the case for PCV9 compared to PCV7 (see sections IV.4-6); a Phase III trial of an 11-valent formulation in the Philippines which evaluated pneumonia as the primary endpoint found efficacy results consistent with the Gambia trial findings [12th International Congress on Infectious Diseases, June 16, 2006. Lisbon, Portugal].

Emerging market manufacturers are developing multi-valent conjugate vaccines and are expected to supply them after 2015. More than 20 other conjugate and protein-based

vaccines are in early stages of product development or in research (pre-product development) phases.^{89, 90}

Support from the Global Alliance for Vaccines and Immunizations (GAVI) and efforts by organizations committed to accelerate pneumococcal conjugate vaccine introduction (eg, PneumoADIP) lay a foundation for an affordable and sustainable vaccine supply for developing countries.

Table for Section XI: Summary of Vaccine Candidates: Stage of Development and Expected Launch.

Candidate Vaccine		Stage of Development	Expected Launch
Candidates that are likely to be licensed and launched			
Wyeth	7-valent*	Licensed; launched in 2000	Registered in >70 countries
	13-valent	Product in clinical testing	2010
GSK	10-valent	Phase III completed by 2007; effectiveness study for pneumonia prevention in planning stage	2008
Candidates that will NOT be licensed or launched			
Wyeth	9-valent	Phase III in So.Africa completed; Phase III in Gambia completed.	No current plans for further development
GSK	11-valent	Phase III for otitis media successfully completed; reformulation of vaccine after Phase III OM	No current plans for further development
Aventis	11-valent	Phase III in Philippines was completed in 2006	No current plans for further development
Merck	7-valent	Completed Phase III; otitis media efficacy demonstrated	No current plans for further development

*The 7-valent vaccine is comprised of capsular components from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The 9-valent vaccine adds serotypes 1 and 5, which together account for ~10-20% of invasive pneumococcal disease in Asia and Africa. The 10-valent vaccine adds serotype 7F to the serotypes included in the 9-valent vaccine. The 11-valent adds serotypes 3 to the serotypes included in the 10-valent vaccine. The 13-valent adds 6A and 19A to the serotypes in the 11 valent.

XIII. Importance of surveillance

Baseline and post-vaccine surveillance for pneumococcal disease are encouraged for countries planning to introduce pneumococcal conjugate vaccines. Surveillance, particularly in developing countries that are among the first to introduce PCV, will help

fill gaps in our knowledge about the impact of PCV in non-industrialized settings, and will facilitate country-specific decisions to invest in PCV.

For countries with existing or planned pneumococcal surveillance, objectives worthy of focus include monitoring for vaccine-associated adverse events, vaccine-attributable replacement disease, indirect effects of vaccine (protection of age groups outside the vaccine target), and monitoring of pneumococcal invasive disease and severe clinical pneumonia trends.

Because knowledge of these issues for the HIV-infected population are particularly limited with the majority of evidence deriving from studies in the United States and South Africa in the pre-HAART era, a surveillance focus on this population holds promise to contribute to our understanding of the impact of PCV in settings where HIV is common.

Depending on surveillance objectives and settings, different surveillance methods may be appropriate. For example, monitoring for rare vaccine-associated adverse events may be accomplished adequately by passive surveillance. In contrast, monitoring for vaccine-attributable replacement disease would ideally be achieved by long term population-based surveillance for invasive pneumococcal disease, and requires a capacity to collect and serotype isolates.

XIV. References

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