Could a single dose of pneumococcal conjugate vaccine in children be effective? Modeling the optimal age of vaccination[☆]

Ezra J. Barzilay [a], Katherine L. O'Brien [b], Yeong S. Kwok [c], Robert M. Hoekstra [d], Elizabeth R. Zell [d], Raymond Reid [b], Mathuram Santosham [b], Cynthia G. Whitney [e,*], Daniel R. Feikin [e]

[a] *Emory University School of Medicine, Department of Pediatrics, Atlanta, GA, USA*
[b] *Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*
[c] *University of Michigan Medical School, Department of Internal Medicine, Ann Arbor, MI, USA*
[d] *Biostatistics Information Management Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA*
[e] *Respiratory Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Disease, Centers for Disease Control and Prevention, 1600 Clifton Road NE Mailstop C23, Atlanta, GA 30333, USA*

Abstract

Using incidence rates from CDC's Active Bacterial Core surveillance and immunogenicity data from the Navajo/Apache trial of pneumococcal conjugate vaccine (PCV), we used Markov modeling to predict the optimal age to give a single dose of PCV. Antibody concentration thresholds of 0.35 and 1.0 mcg/ml were considered protective. Our outcome was vaccine serotype-specific invasive pneumococcal disease (IPD) incidence at 24 months. The models predicted the optimal age to vaccinate is 5–7 months with vaccine-induced immunologic memory and 8–10 months without memory. IPD reduction ranged from 15 to 62%, depending on model parameters. A single PCV dose in infants could prevent substantial IPD.
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1. Introduction

Streptococcus pneumoniae, the leading etiologic agent of bacterial pneumonia, causes over 1 million deaths annually in children worldwide [1], though the majority of these deaths occur in developing countries. An effective and safe vaccine against pediatric pneumococcal disease now exists. Since 2000, when the heptavalent pneumococcal conjugate vaccine (PCV7) was introduced into the United States, a significant reduction in invasive pneumococcal disease in children has occurred [2]. The current cost of pneumococcal conjugate vaccines, however, is a significant barrier to vaccine use in developing countries; a delay of almost 10 years occurred between the introduction into the United States of the conjugate vaccine for *Haemophilus influenzae* type b (Hib) and Hib's introduction into the first African country, in large part due to the vaccine's cost. PCV7, at $50–60 a dose, [3] is several times more expensive than the Hib conjugate vaccine was at the time of its licensure.

One strategy to lower the cost of pneumococcal conjugate vaccine (PCV) regimen is to reduce the number of doses administered to a child. The recommended regimen in the United States is a three-dose primary series at 2, 4, and 6

months with a booster dose at 12–15 months [4]. However, there are reasons to believe that a single dose of PCV might be an effective strategy for the prevention of invasive pneumococcal disease, although not necessarily non-bacteremic pneumococcal pneumonia. The protective level of antibodies required to prevent invasive pneumococcal disease might be low enough [5–7] that a single dose could achieve such concentrations. A single dose of conjugate vaccine might be capable of eliciting immunologic memory and reducing transmission (i.e., herd immunity) [8]. Lastly, preliminary evidence from the United States after introduction of PCV7 suggests that regimens of fewer than 3–4 vaccine doses might offer significant protection against invasive pneumococcal disease [9].

We sought to assess the optimal age for administration of a single dose of PCV7 in the first 2 years of life, and the amount of invasive pneumococcal disease that could be prevented by such a vaccine strategy. The timing of a single dose for optimal individual protection is a balance of two major factors: the age-specific incidence of pneumococcal disease and the ability of the immune system to respond to the vaccine. We created a mathematical model that incorporated these two factors to predict the optimal age of administration of a single PCV7 dose.

2. Methods

2.1. Surveillance data

Surveillance for invasive disease (i.e., from blood, cerebrospinal fluid, or other normally sterile sites) caused by *Streptococcus pneumoniae* is conducted as part of the Active Bacterial Core surveillance (ABCs), part of CDC's Emerging Infections Program Network, as has been described elsewhere [2,10]. We used ABC data collected from 1998 to 1999, before the introduction of PCV7 into the routine immunization program. The participating surveillance sites during this time included all or part of the states of California, Connecticut, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee for an approximate surveillance population of 15 million people. Serotyping was performed either by CDC's streptococcal lab or the Minnesota Health Department using the quelling reaction.

2.2. Age-specific incidence rates of invasive pneumococcal disease

Rates of vaccine-type invasive pneumococcal disease (VT-IPD) among the ABCs' population were calculated using 1999 U.S. Census Bureau population estimates. National projections of cases were estimated by applying race-specific rates for the aggregate surveillance areas to the racial distribution of the U.S. population. Incidence rates were calculated in 3-month intervals from 0 to 23 months of age, the denomina-
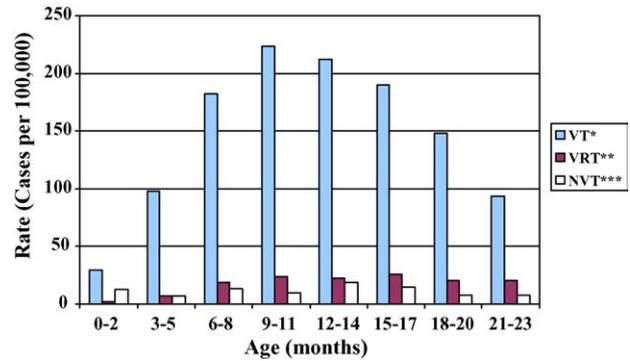
Fig. 1. Incidence rates of pneumococcal serotypes during 3 month intervals in the first 2 years of life, ABCs, 1998–1999. ([*]VT is vaccine types (4, 6B, 9V, 14, 18C, 19F, 23F); [**]VRT is vaccine-related type (6A, 9A, 9N, 18A, 18B, 18F, 19A, 19C, 23A, 23B); [***]NVT is non-vaccine type.).

tor being the census population of children aged 0–11 months or 12–23 months, divided by 4. Rates were calculated for individual serotypes and the cumulative of the seven serotypes in PCV7. The cumulative incidence of VT-IPD using ABCs data was highest at 224 cases per 100,000 children in the 9–11 month age group (Fig. 1). The serotype with the highest rate in this age group (97 cases per 100,000 children) was serotype 14.

2.3. Immunogenicity data

We used immunogenicity data from a randomized controlled trial of PCV7 among Navajo and White Mountain Apache (Apache) children [11,12]. In this study, a community randomization scheme was used, in which all children less than 2 years of age from a given community whose parents consented to participate in the trial were administered either PCV7 or control vaccine (group C meningococcal conjugate vaccine). Therefore, children less than 24 months were vaccinated with PCV7 at various ages, rather than being vaccinated only according to the routine childhood immunization schedule. For a subset of enrolled children, sera were collected 1 month after the first PCV7 dose. The geometric mean concentration (GMC) of serotype-specific antibody and the percentage of children with antibody concentrations above critical threshold concentrations were available for all seven serotypes in PCV7 (Table 1). For age intervals where no immunogenicity data was available (i.e., 5–7 and 8–10 months of age), the GMC and percentage of children with antibody concentrations above thresholds were linearly interpolated from the adjacent age intervals.

2.4. Protective concentrations of serotype-specific antibodies

In a recent WHO meeting it was concluded that an antibody concentration of 0.35 mcg/ml correlates with

Table 1
Immunogenicity data after a single dose of pneumococcal conjugate vaccine by serotype, Navajo and White Mountain Apache children

	Age at time of vaccination (months)								
	0–1 N = 143[a]	2–4 N = 72[a]	5–7 _[b]	8–10 _[b]	11–13 N = 43[a]	14–16 N = 47[a]	17–19 N = 28[a]	20–22 N = 22[a]	23 N = 12[a]
Serotype 4									
GMC[c]	0.89	1.33	2.10	2.62	3.65	2.36	2.31	3 23	3.54
% >0.35	81.9	83.8	89.2	94.6	100.0	93.6	100.0	100.0	100.0
% >1.0	49.3	59.6	70.0	80.4	90.9	83.0	72.4	78.3	100.0
Serotype 6B									
GMC	0.27	0.20	0.32	0.45	0.57	0.55	0.86	0.97	0.85
% >0.35	35.9	26.7	41.3	55.9	70.5	61.7	72.4	73.9	75.0
% >1.0	13.8	4.0	11.0	18.0	25.0	38.3	41.4	56.5	41.7
Serotype 9V									
GMC	0.38	0.47	0.65	0.82	1.00	0.94	0.57	1.06	2.12
% >0.35	50.3	62.5	68.0	73.6	79.1	83.0	62.1	86.4	100.0
% >1.0	17.5	26.4	33.9	41.3	48.8	55.3	31.0	63.6	75.0
Serotype 14									
GMC	0.67	0.79	0.96	1.14	1.31	0.94	0.84	0.88	1.03
% >0.35	69.9	68.1	76.4	84.7	93.0	80.9	78.6	81.8	75.0
% >1.0	37.8	50.0	53.5	57.0	60.5	51.1	42.9	45.5	50.0
Serotype 18C									
GMC	0.47	0.64	0.92	1.20	1.48	1.32	1.18	1.39	1.71
% >0.35	592	73.3	79.1	84.9	90.7	85.1	86.2	95.2	91.7
% >1.0	26.1	37.8	50.0	60.0	69.8	61.7	65.5	61.9	75.0
Serotype 19F									
GMC	0.60	0.64	0.84	1.03	1.23	1.05	1.10	1.12	1.35
% >0.35	71.3	71.6	77.3	82.9	88.6	83.0	93.1	82.6	83.3
% >1.0	28.7	32.4	39.0	45.7	52.3	46.8	51.7	56.5	58.3
Serotype 23F									
GMC	0.20	0.21	0.36	0.56	0.72	0.64	1.24	1.12	1.55
% >0.35	20.0	22.7	38.1	53.6	69.0	59.6	93.1	78.3	91.7
% >1.0	6.21	13.3	23.2	33.0	42.9	34.8	34.5	60.9	75.0

Sera measuring antibody concentrations were collected 1 month after vaccination. All antibody concentrations are in mcg/ml.

[a] The N varies slightly by serotype due to laboratory variability in running sera. N's given here are for serotype 14.

[b] GMC and % above thresholds were obtained by linear extrapolation from adjacent values because no children in these age groups received PCV7.

[c] GMC is the geometric mean concentration.

efficacy in preventing VT-IPD. The data used to come to this conclusion came from the Kaiser Permanente efficacy trial in Northern California [13] the American Indian efficacy trial, [11,12] and the South African efficacy trial [14]. It should be noted that this 0.35 mcg/ml was determined from a pooled analysis of theses trials to be the best correlate of protection against VT-IPD to be used in comparing non-inferiority of vaccines for regulatory purposes, and does not necessarily assure protection in an individual. Since studies of Hib conjugate vaccine showed that long-term protection against invasive disease is conferred at a higher serum antibody concentration than that required for short-term protection against invasive disease, we also used a second, more conservative threshold of protection arbitrarily selected as 1.0 mcg/ml in our models [15]. We did not model antibody levels required to prevent acquisition of pneumococcal colonization, non-bacteremic pneumonia or acute otitis media.

2.5. Models of vaccine impact

The primary endpoint of our models was the cumulative incidence of VT-IPD at 24 months of age. We modeled the effects of a single dose of PCV7 given at eight different ages (0–2, 3–5, 6–8, 9–11, 12–14, 15–17, 18–20, and 21–23 months) on the cumulative incidence of VT-IPD at 24 months of age (Table 2). All models used a Markov modeling technique, whereby the rate of VT-IPD at each 3-month age interval was applied to the number of children who had not yet had VT-IPD to arrive at the cumulative incidence at 24 months of age. We assumed that a child could only have one episode of VT-IPD. The baseline rate of VT-IPD at each age interval was reduced by the proportion of children who had antibody concentrations above the indicated threshold after a single dose of PCV7. We evaluated the sensitivity of our model by changing the rates of VT-IPD (R_{ij} in Table 2) or the proportions of children protected after vaccination (T_{ij}

Table 2

Formulae used for Markov modeling of cumulative incidence rates of vaccine-serotype invasive pneumococcal disease at 24 months of age when given a single those of PCV7

Calculation	Formula
No vaccination	$\sum_{j=1}^{7} \left(1 - \prod_{i=1}^{8} (1 - R_{ij}) \right)$ where j is the serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F); i is the age group (1 = 0–2 months, 2 = 3–5 months, 3 = 6–8 months, 4 = 9–11 months, 5 = 12–14 months, 6 = 15–17, months, 7 = 18–20 months, 8 = 21–23 months); R_i is the rate of invasive pneumococcal disease in age group i for serotype j
Single dose of PCV7	$\sum_{j=1}^{7} \left(1 - \prod_{i=1}^{8} (1 - (1 - T_{ij}) R_{ij}) \right)$ where j is the Serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F); i is the age group (1 = 0–2 months, 2 = 3–5 months, 3 = 6–8 months, 4 = 9–11 months, 5 = 12–14 months, 6 = 15–17 months, 7 = 18–20 months, 8 = 21–23 months); R_{ij} is the rate of invasive pneumococcal disease in age group i for serotype j. T is the proportion of children above threshold of protection. The addition of the factor $(1 - T_{ij})$ adjusts for the effect of staggered vaccination time.

$\sum$ (sigma): summation notation, where $\sum_{i=1}^{5} i = 1 + 2 + 3 + 4 + 5$, $\prod$ (Pi) : product notation, where $\prod_{i=1}^{5} i = 1 \times 2 \times 3 \times 4 \times 5$.

in Table 2) according to the variations in model parameters described below.

2.6. Models

2.6.1. Basic model

We used U.S. incidence rates of VT-IPD from ABCs from 1998 to 1999, before the introduction of PCV7 into the routine immunization program. The post-vaccination immune response did not wane over time, assuming there was immunologic memory after a single dose of vaccination. As a result, the percentage of children that reached protective thresholds of 0.35 and 1.0 mcg/ml 1 month after vaccination remained constant in all subsequent age intervals up to 24 months. Maternally acquired or naturally occurring antibodies were not subtracted out.

2.6.2. Subtracting maternally acquired and naturally occurring immunity

In this model we attempted to distinguish vaccine-derived antibodies from maternally acquired and naturally occurring antibodies. Maternal antibodies are passed on to the fetus transplacentally and decay over the first few months of life, resulting in an increasing rate of colonization and infection with pneumococci over the first 6 months of life [16,17]. The proportion of children vaccinated in the first few months of life that reaches the thresholds of protection might appear falsely high due to these maternal antibodies, making it seem that the impact of vaccination was higher than it actually was. Through a literature review of PCV immunogenicity studies from the pre-vaccine era, or from randomized control trials of PCV versus placebo, we obtained maternally acquired and naturally occurring antibody concentrations for PCV7 serotypes [6,11,18–30]. This was done for the same 3-month age intervals from birth to 24 months as described above. Data on naturally occurring antibody concentrations was found for all age intervals except the following: 9–11 month group for all seven serotypes, 18–20 month group for serotypes 4, 6B,

and 9V and 21–23 month group for serotypes 4 and 9V. When no data were available, antibody concentrations for that age interval were obtained by making a linear interpolation from the GMCs in the adjacent age groups. If no data were available from an adjacent age group (i.e., 21–23 month interval), the last available GMCs were used. The 95% confidence intervals around each study's GMC were used to calculate the standard deviation of the GMCs. This standard deviation was then used to calculate the percentage of study children that had antibody concentrations above the 0.35 and 1.0 mcg/ml. The weighted average of the percent of children above each threshold of protection was calculated from all available studies. In the last step, the weighted average of the percent of children with antibody concentrations above the thresholds of protection from maternally acquired and naturally occurring antibodies was subtracted from the observed percentages after single vaccination in the Navajo/Apache study for each age group. The resulting percentages were applied in this model as the percentages of children with vaccine-derived antibody concentrations above the thresholds of protection.

2.6.3. Waning of the post-vaccination immune response

Because it is unknown whether a single dose of PCV7 will confer immunologic memory, we also ran the model assuming lack of immunologic memory. To estimate the waning of antibodies after vaccination, we used data from three PCV7 immunogenicity studies that gave a primary series at 2, 4, and 6 months followed by a booster dose in the second year of life [20,23,24]. We calculated the weighted average of the antibody concentrations 1 month following the third dose of the primary series at 7 months of age and immediately prior to administering the booster dose at 12–15 months of age. We then constructed a decay curve using an exponential decay of antibodies over time. We applied the slope constant of this exponential decay curve to each of the post single-dose GMCs from the Navajo/Apache study to determine the decayed GMCs at each subsequent

Table 3
Distribution by age of invasive pneumococcal disease in children under the age of 2 years in the United States (ABCs' data) and developing countries [31–34]

Age in months	Developing countries	United States	Ratio of developing countries to US
<6	26%	11%	2.35
6–11	33%	34%	0.98
12–23	41%	55%	0.75

3-month interval after vaccination. To calculate the percentage of children with antibody thresholds above 0.35 and 1.0 mcg/ml at each of these intervals, we used the standard deviation reported for GMCs from the Navajo/Apache study. The resulting percentages were applied in this model.

2.6.4. Developing country incidence rates of VT-IPD

Data was not available from developing country settings on the incidence rates of VT-IPD at 3-month intervals from birth to 24 months of age. Therefore, to determine developing country rates, we reviewed three studies from developing countries and one from Alaska Natives in which the distribution of invasive pneumococcal disease in children under 2 years in three age groups was available: 0–5 months, 6–11 months and 12–23 months [31–34]. The percentages of all IPD occurring in each age group were averaged for the four studies (Table 4). The percentage of disease in American children under the age of 2 years using ABCs was also calculated for the same three age groups. The ratio of the percentages of IPD in developing countries to those in the United States for the three age groups was determined. The distribution of pneumococcal disease in developing countries was shifted to younger infants compared with the distribution in the United States (Table 3). Using these ratios, the incidence rates obtained from ABCs were adjusted to more closely resemble a developing country distribution. It should be noted that though the incidence rates used in this model were not those of developing countries,

the distribution of VT-IPD over the first 2 years of life was.

2.7. Statistical analysis

Age-specific, race-adjusted incidence rates of VT-IPD were calculated from ABCs using SAS for Windows (version 9.1, SAS Institute, Cary, NC). Modeling was done in Excel for Windows (version 10.0, Microsoft Corporation, Redmond, WA).

3. Results

We ran 16 models. An example of the model output in Table 4 shows the basic model using 0.35 mcg/ml as the threshold of protective immunity. In this model, the cumulative incidence of VT-IPD at 24 months of age was lowest when the vaccine was given at 5–7 months, yielding a 62% reduction in VT-IPD, compared with when no vaccination was given. Fig. 2 shows the cumulative incidence of VT-IPD at 24 months of age when the vaccine was given at different ages for the eight models using a threshold of 0.35 mcg/ml. The models using a threshold of 1.0 mcg/ml showed less reduction in VT-IPD but had a similar pattern for all eight models. In summary, the models suggest that the optimal age to vaccinate with a single dose of PCV7 is between 5–7 months if there is immunologic memory and 8–10 months if there is waning immunity after vaccination (Table 5). The exception to these findings is in the basic model for developing countries, where VT-IPD rates are higher at younger ages, in which vaccination before 5 months of age was optimal. The amount of VT-IPD prevented by a single dose varied by model (Table 5). The greatest reduction in VT-IPD occurred in the basic models using the 0.35 mcg/ml threshold (62% reduction using U.S. rates (Fig. 2a) and 60% using developing country rates (Fig. 2e), and the least reduction in VT-IPD occurred in the models that assumed no immunologic memory and subtracted out maternally acquired and naturally occurring

Table 4
Incidence of VT-IPD due to each serotype and cumulative for all seven serotypes at 24 months of age when a single-dose of PCV7 is given at different ages in the basic model (which assumes immunologic memory, using a protective threshold of 0.35 mcg/ml)

Age at vaccination	Serotype							Cumulative
	4	6B	9V	14	18C	19F	23F	
No vaccination	107.7	155.3	67.1	476.4	108.5	164.1	95.8	1175.0
0–1 months	19.5	99.6	33.4	143.6	44.3	47.1	76.6	464.1
2–4 months	19.8	114.6	25.2	160.5	31.7	50.6	74.5	476.9
5–7 months	16.4	98.5	24.4	153.8	29.8	54.4	64.6	442.0
8–10 months	30.1	90.7	30.7	184.7	33.8	64.6	60.0	494.8
11–13 months	50.3	91.7	40.5	246.2	48.5	78.7	60.6	616.4
14–16 months	67.3	120.7	45.1	338.4	72.1	116.8	75.5	836.0
17–19 months	77.8	133.2	59.9	406.7	86.1	129.9	79.8	973.4
20–22 months	100.6	142.9	66.4	447.5	96.7	150.9	92.3	1097.2

Rates are number of cases per 100,000 children annually.
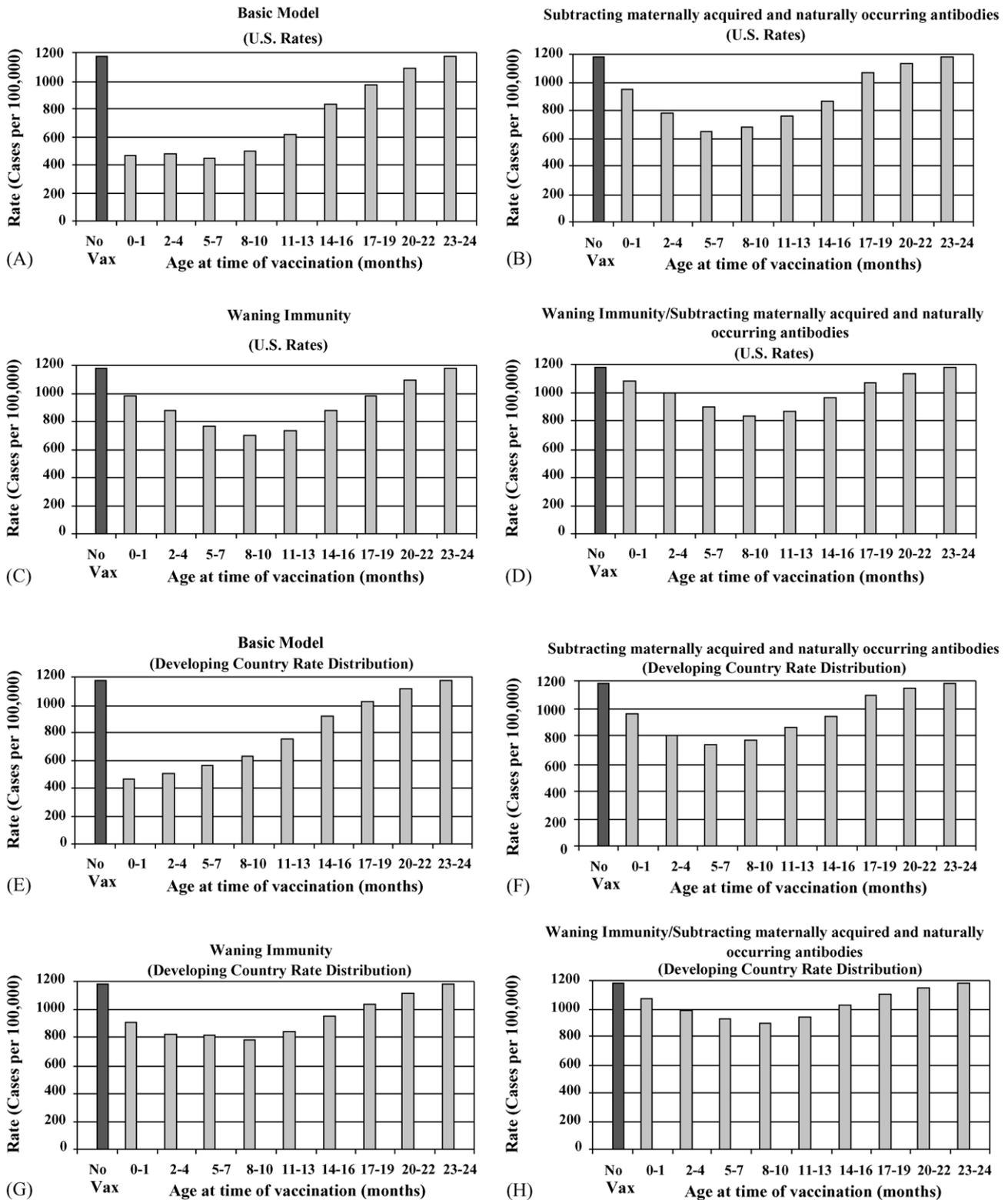
Fig. 2. Cumulative incidence of VT-IPD at 24 months of age when PCV7 is given at different ages, using various model parameters: (A) Basic model, U.S. rates, 0.35 mcg/ml threshold of protection; (B) subtracting maternally acquired/naturally occurring antibodies, U.S. rates, 0.35 mcg/ml threshold of protection; (C) waning immunity, U.S. rates, 0.35 mcg/ml threshold of protection; (D) waning immunity and subtracting maternally acquired/naturally occurring antibodies, U.S. rates, 0.35 mcg/ml threshold of protection; (E) basic model, developing country rate distribution, 0.35 mcg/ml threshold of protection; (F) subtracting maternally acquired/naturally occurring antibodies, developing country rate distribution, 0.35 mcg/ml threshold of protection; (G) waning immunity, developing country rate distribution, 0.35 mcg/ml threshold of protection; (H) waning immunity and subtracting maternally acquired/naturally occurring antibodies, developing country rate distribution, 0.35 mcg/ml threshold of protection.

Table 5
Summary of models predicting optimal age to administer single dose of PCV7 to children less than 2 years of age to reduce incidence of VT-IPD at 24 months

| | Threshold of protection | | | |
| | 0.35 mcg/ml | | 1.0 mcg/ml | |
	Optimal age	VT-IPD prevented	Optimal age	VT-IPD prevented
US Distribution of VT-IPD				
Basic model	5–7 months	62%	5–7 months	36%
Subtracting maternally acquired/naturally occurring Ab[a]	5–7 months	45%	5–7 months	35%
Waning immunity not subtracting maternally acquired/naturally occurring Ab	8–10 months	40%	8–10 months	20%
Waning immunity, subtracting maternally acquired/naturally occurring Ab	8–10 months	29%	8–13 months[b]	17%
Developing country distribution of VT-IPD				
Basic model	<2 months	60%	2–4 months	34%
Subtracting maternally acquired/naturally occurring Ab	5–7 months	37%	5–7 months	29%
Waning immunity not subtracting maternally acquired/naturally occurring Ab	8–10 months	34%	8–10 months	17%
Waning immunity, subtracting maternally acquired/naturally occurring Ab	8–10 months	23%	8–10 months	15%

[a] Ab is antibodies.

[b] The reductions in VT-IPD in this model were equivalent for children vaccinated at 8–10 months and 11–13 months.

antibodies using the 1.0 mcg/ml threshold (18% using the U.S. rates and 15% using the developing country rates).

4. Discussion

Our models predicted that a single dose of PCV7 administered to infants could prevent a significant amount of vaccine-serotype specific invasive pneumococcal disease. With the exception of the basic model using developing country incidence rates, all of the models predicted that a dose given between 5 and 10 months of age would yield the greatest reduction in VT-IPD. In the models in which immunologic memory from a single dose was assumed, the optimal age tended to be earlier (i.e., 5–7 months). In the models without immunologic memory, the optimal time was slightly later (i.e., 8–10 months), overlapping with the time of peak incidence of VT-IPD.

According to the models, a single dose of PCV7 does not prevent as much disease as three- or four-dose regimens. Results of efficacy trials of pneumococcal conjugate vaccines showed efficacies against VT-IPD of 83% among Navajo and Apache children, [12] 97% among children at Northern California Kaiser hospitals, [13] and 83% among South African children [14]. In our model, the amount of VT-IPD prevented was as high as 62%. While not equivalent to the full-dose regimens, the amount of VT-IPD prevented by a single dose could still be substantial.

There are several reasons to consider a single dose of pneumococcal conjugate vaccine. The first is the high price of these vaccines. At its current market price (approximately $50–$60 per dose), [3] PCV7 is unlikely to be introduced into developing countries. This is particularly true for three- or four-dose regimens. While the cost of a single dose is currently prohibitive, as the price of the vaccine drops, as it should with time and increased use, the cost of a single dose might fall into the range of financial feasibility for some countries. Programmatically, a dose of PCV given to chil-

dren 5–10 months of age might be problematic since it does not coincide with the primary series of routine immunization schedules in most developing countries (i.e., 6, 10, and 14 weeks). In many countries, however, measles vaccine is given early at 9 months of age; PCV could also be given at that visit.

The second reason to consider a single dose of PCV is that there is some evidence that a single dose might be effective. Since its introduction into the United States in 2000, there have been extended time periods when vaccine supply has been inadequate. So the supply of vaccine could reach the most children during these times of shortage, ACIP recommended deferring the 12–15 month booster dose, and when needed the 6-month dose [35]. Despite the shortage of PCV7, the reduction in invasive pneumococcal disease in the United States since 2000 among vaccinated children has been impressive.

Among children under the age of 2 years, there was a 78% reduction in VT-IPD between 1998/1999 and 2001 [2]. Such decreases in VT-IPD have continued into 2002–2003, [36] despite the PCV7 supply shortage that prevented most children from receiving the full vaccine series. Moreover, preliminary findings of a case-control study of vaccine effectiveness done by CDC suggested that one dose of PCV7 had an efficacy of 67% (95% confidence intervals 28–85%) [9]. However, it should be noted that the effectiveness of a single dose in the post-licensure period in the U.S. needs to be interpreted in light of the herd immunity induced on the population from children who may have received more than one dose. The effectiveness of a single-dose only regimen could be reduced without herd immunity.

Third, as previously mentioned an antibody concentration as low as 0.35 mcg/ml appears to correlate with efficacy in preventing VT-IPD [7]. This concentration might be achievable by a single dose of PCV. A study in South Africa showed that after the first dose of a nine-valent conjugate vaccine given at 6 weeks of age, more than 60% of children had IgG concentrations >0.5 mcg/ml, except for serotypes 6B and 23F

[6]. Geometric mean concentrations after the first dose for five of the nine serotypes were >1.0 mcg/ml. It should be noted, however, that maternally-acquired antibodies were not subtracted out in this study, which would serve to overestimate the immune response to a single dose. In a study in the Philippines using a different PCV formulation, a single dose given at 18 weeks of age yielded equivalent or higher antibody concentrations at 9 months of age to 10 of 11 serotypes compared with the standard 3-dose regimen given at 6, 10, and 14 weeks [37]. Several other studies have shown that two doses of PCV can elicit significant increases in antibody concentrations [21,24]. Moreover, the high rates of early pneumococcal colonization in developing countries might prime them to respond more vigorously to a single dose of vaccine given at 5–10 months of age [21,25,38].

Fourth, it might be possible that a single dose of PCV could produce immunologic memory. Despite low circulating concentrations of antibodies, children might still be protected against IPD if their immune systems have been primed and are able to respond vigorously when presented with pneumococci. Immunologic memory might be one of the reasons why the effectiveness of PCV7 against VT-IPD has been high even in times of vaccine shortage [9]. Some evidence exists from other conjugate vaccines that immunologic memory might occur with reduced doses. A study in Niger showed that children who received a single dose of meningococcal A/C conjugate vaccine at 14 weeks or 9 months had a vigorous anamnestic response to a challenge dose of meningococcal polysaccharide at 24 months, producing high concentrations of antibodies to meningococcal polysaccharides A and C with significant increases in serum bactericidal activity [39]. Studies are necessary to determine if a single dose of PCV, given at any age, will lead to immunologic memory.

Our model had certain limitations. First, we used immunogenicity data as a proxy for efficacy data. The immunologic correlates of protection used are estimates. The lower threshold of 0.35 mcg/ml is based on review of available data from randomized controlled trials and post-marketing effectiveness [5]. Because this threshold seemed quite low, we also used a more conservative threshold of 1.0 mcg/ml based on the supposed level for long-term protection of the PRP antibody after Hib conjugate vaccine [15]. The fact that the optimal age to vaccinate did not change when using the higher threshold suggested the model's findings are robust. It should also be pointed out that we used the 0.35 mcg/ml threshold for all serotypes. This might not be appropriate for some serotypes (i.e. 19F) and could have led to the model overestimating effectiveness for these serotypes. Second, the immunogenicity data we used came from a single study among Native American children [11,12]. Differences in the magnitude or timing of the antibody response to vaccination might have yielded estimates of disease reduction that were unrepresentative of the general population. However, the efficacy of PCV7 in this population was similar to that in South African children and only slightly lower than

in children in Northern California, which suggests similar immunogenicity [12–14]. Furthermore, the actual immunogenicity data from American Indian children and the general U.S. population do not differ significantly [40]. Third, we had to make several assumptions in the model that might not be uniformly true. We used a linear interpolation between adjacent available data to obtain missing immunogenicity values, a statistical assumption that might not accurately reflect the true immunogenicity. Another assumption was that children only get invasive pneumococcal disease once, which is not true for children with underlying illness that predisposes them to pneumococcal disease. This, however, would cause little error since such children account for a small proportion of disease episodes. A fourth limitation of this study is that the 0.35 mcg/ml threshold used was based on studies of efficacy against IPD. The threshold of protection against non-bacteremic pneumococcal pneumonia, the most common manifestation of pneumococcal disease in developing countries, might be higher, thereby making our estimated levels of protection against VT-IPD an overestimate for pneumococcal pneumonia. In addition, the antibody threshold considered in this model may not be applicable in high-burden HIV areas; a recent study showed that antibody induced by PCV has been found to be less functional in HIV infected lhan uninfected children [41].

A last, significant limitation of our model was that we did not include the herd effect of vaccination in the model. The herd effect is clearly important for conjugate vaccines. The rate of invasive Hib disease in infants in the United States began to decline when Hib conjugate vaccine was introduced for toddlers [42]. Since the introduction of PCV7 for children in 2000, VT-IPD has also declined among adults, suggesting a strong herd effect of reduced transmission [2]. It should be noted however, that in order to reduce VT pneumococcal colonization of the nasopharynx, a key to eliciting a herd effect, a higher antibody concentration might be needed than what is needed to protect against IPD. This has been shown with Hib vaccine [43]. A single dose of PCV given at certain young ages might not be able to produce high enough levels of antibodies to prevent colonization. Additionally, use of PCV7 results in near-complete replacement colonization with non-vaccine serotypes of pneumococci, [8,38] and likely some replacement IPD, albeit at rates that are much lower than the reduction in rates of VT-IPD [44].

In conclusion, a single dose of pneumococcal conjugate vaccine has the potential to prevent a significant amount of invasive pneumococcal disease in children. Our model predicted that the optimal time to give a single dose of PCV7 was 5–7 months if immunologic memory occurred and 6–8 months if it did not. The model also predicted that a single dose could result in up to a 62% reduction in VT-IPD. Because of many assumptions inherent in modeling, immunogenicity trials of a single dose of PCV are needed to verify our findings and if those yield positive results, further studies of the effectiveness of a single dose of PCV would be warranted.

References

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

[2] Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. New Engl J Med 2003;348(18):1737–46.

[3] Centers for Disease Control and Prevention. Vaccines for Children vaccine price list; 2005. Last accessed on 5 July 2005, http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm.

[4] Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2000;49(RR-9);1–35.

[5] Jodar L, Butler J, Carlone G, Dagan R, Goldblatt D, Kayhty H, et al. Serological criteria for evaluation and licensure of newpneumococcal conjugate vaccine formulations foruse in infants. Vaccine 2003;21(23):3265–72.

[6] Huebner RE, Mbelle N, Forrest B, Madore DV, Klugman KP. Immunogenicity after one, two or three doses and impact on the antibody response to coadministered antigens of a nonavalent pneumococcal conjugate vaccine in infants of Soweto South Africa. Pediatric Infect Dis J 2002;21(11):1004–7.

[7] WHO Expert Committee on Biological Standardization. Recommendations for the Production & Control of Pneumococcal Conjugate Vaccines. WHO Technical Report Series (2003). Draft recommendations adopted by the 54th meeting of the WHO Expert Committee on Biological Standardization, 17–21 November 2003. Last Accessed on 27 June 2005, http://www.who.int/biologicals/publications/Pneumococcal%20Conjugate%20Vaccines_Recomm%20for%20the%20production%20&%20control%20of_ECBS%2054th%2017_21%20Nov%202003.pdf.

[8] Dagan R, Givon-Lavi N, Zamir O, Sikuler-Cohen M, Guy L, Janco J, et al. Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. J Infect Dis 2002;185(7):927–36.

[9] Pilishvili T, Farley M, Vazquez M, Reingold A, Nyquist A, Stefanek K, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children. In: Proceedings of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy Abstracts. Chicago, IL: American Society for Microbiology; 2003. p. 285.

[10] Schuchat A, Hilger T, Zell E, Farley MM, Reingold A, Harrison L, et al. Active bacterial core surveillance of the emerging infections program network. Emerg Infect Dis 2001;7(1):92–9.

[11] O'Brien KL, Swift AJ, Winkelstein JA, Santosham M, Stover B, Luddy R, et al., Pneumococcal Conjugate Vaccine Study Group. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM(197) among infants with sickle cell disease. Pediatrics 2000;106(5):965–72.

[12] O'Brien KL, Moulton LH, Reid R, Weatherholtz R, Oski I, Brown L, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003;362(9381):355–61.

[13] Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al., Northern California Kaiser Permanente Vaccine Study Center Group. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatric Infect Dis J 2000;19(3):187–95.

[14] Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. New Engl J Med 2003;349(14):1341–8.

[15] Levine OS, Schwartz B, Pierce N, Kane M. Development, evaluation and implementation of Haemophilus influenzae type b vaccines for young children in developing countries: current status and priority actions. Pediatric Infect Dis J 1998;17(9 Suppl):S95–113.

[16] Gray BM, Converse III GM, Dillon Jr HC. Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. J Infect Dis 1980;142(6):923–33.

[17] Shahid NS, Steinhoff MC, Hoque SS, Begum T, Thompson C, Siber GR. Serum, breast milk, and infant antibody after maternal immunisation with pneumococcal vaccine. Lancet 1995;346(8985):1252–7.

[18] Dagan R, Melamed R, Muallem M, Piglansky L, Greenberg D, Abramson O, et al. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. J Infect Dis 1996;174(6):1271–8.

[19] Dagan R, Melamed R, Zamir O, Leroy O. Safety and immunogenicity of tetravalent pneumococcal vaccines containing 6B 14 19F and 23F polysaccharides conjugated to either tetanus toxoid or diphtheria toxoid in young infants and their boosterability by native polysaccharide antigens. Pediatric Infect Dis J 1997;16(11):1053–9.

[20] Shinefield HR, Black S, Ray P, Chang I, Lewis N, Fireman B, et al. Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. Pediatric Infect Dis J 1999;18(9):757–63.

[21] Leach A, Ceesay SJ, Banya WA, Greenwood BM. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. Pediatric Infect Dis J 1996;15(4):333–9.

[22] Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. J Pediatrics 1996;128(5 Pt 1):649–53.

[23] Miernyk KM, Parkinson AJ, Rudolph KM, Petersen KM, Bulkow LR, Greenberg DP, et al. Immunogenicity of a heptavalent pneumococcal conjugate vaccine in Apache and Navajo Indian, Alaska native and non-native American children aged <2 years. Clin Infect Dis 2000;31(1):34–41.

[24] Rennels MB, Edwards KM, Keyserling HL, Reisinger KS, Hogerman DA, Madore DV, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. Pediatrics 1998;101(4 Pt 1):604–11.

[25] Obaro SK, Adegbola RA, Chang I, Banya WA, Jaffar S, McAdam KW, et al. Safety and immunogenicity of anonavalent pneumococcal vaccine conjugated to CRM197 administered simultaneously but in a separate syringe with diphtheria, tetanus and pertussis vaccines in Gambian infants. Pediatric Infect Dis J 2000;19(5):463–9.

[26] King Jr JC, Vink PE, Farley JJ, Smilie M, Parks M, Lichenstein R. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. Pediatrics 1997;99(4):575–80.

[27] Choo S, Seymour L, Morris R, Quataert S, Lockhart S, Cartwright K, et al. Immuno genie ity and reactogenicity of a pneumococcal conjugate vaccine administered combined with ahaemophilus influenzae type b conjugate vaccine in United Kingdom infants. Pediatric Infect Dis J 2000;19(9):854–62.

[28] Daum RS, Hogerman D, Rennels MB, Bewley K, Malinoski F, Rothstein E, et al. Infant immunization with pneumococcal CRM197 vaccines: effect of saccharide size on immunogenicity and interactions with simultaneously administered vaccines. J Infect Dis 1997;176(2):445–55.

[29] Ahman H, Kayhty H, Tamminen P, Vuorela A, Malinoski F, Eskola J. Pentavalent pneumococcal oligosaccharide conjugate vaccine PncCRM is well-to lerated and able to induce an antibody response in infants. Pediatric Infect Dis J 1996;15(2):134–9.

[30] Ahman H, Kayhty H, Lehtonen H, Leroy O, Froeschle J, Eskola J. *Streptococcus pneumoniae* capsular polysaccharide-diphtheria toxoid conjugate vaccine is immunogenic in early infancy and able to induce immunologic memory. Pediatric Infect Dis J 1998;17(3):211–6.

[31] Davidson M, Parkinson AJ, Bulkow LR, Fitzgerald MA, Peters HV, Parks DJ. The epidemiology of invasive pneumococcal disease in

Alaska 1990—ethnic differences and opportunities for prevention. Journal of Infect Dis 1994;170(2):368–76.

[32] Kertesz DA, Di Fabio JL, de Cunto Brandileone MC, Castaneda E, Echaniz-Aviles G, Heitmann I, et al. Invasive *Streptococcus pneumoniae* infection in Latin American children: results of the Pan American Health Organization Surveillance Study. Clin Infect Dis 1998;26(6):1355–61.

[33] Lagos R, Munoz A, Valenzuela MT, Heitmann I, Levine MM. Population-based surveillance for hospitalized and ambulatory pediatric invasive pneumococcal disease in Santiago. Chile Pediatric Infect Dis J 2002;21(12):1115–23.

[34] O'Dempsey TJ, McArdle TF, Lloyd-Evans N, Baldeh I, Lawrence BE, Secka O, et al. Pneumococcal disease among children in a rural area of west Africa. Pediatric Infect Dis J 1996;15(5):431–7.

[35] From the Centers for Disease Control Prevention. Updated recommendations on the use of pneumococcal conjugate vaccine in a setting of vaccine shortage—Advisory Committee on Immunization Practices. JAMA 2002;287(7):833–4.

[36] Flannery B, Schrag S, Bennett NM, Lynfield R, Harrison LH, Reingold A, et al. Impact of childhood vaccination on racial disparities in invasive *Streptococcus pneumoniae* infections. JAMA 2004;291(18):2197–203.

[37] Lucero MG, Puumalainen T, Ugpo JM, Williams G, Kayhty H, Nohynek H. Similar antibody concentratens in Filipino infants at age 9 months, after 1 or 3 doses of an adjuvanted, 11-valent pneumococcal Diphtheria-Tetanus conjugated vaccine: a randomized controlled trial. J Infect Dis 2004;189(11):2077–84.

[38] Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999;180(4):1171–6.

[39] Chippaux IP, Garba A, Ethevenaux C, Campagne G, de Chabalier F, Djibo S, et al. Immunogenicity, safety, and memory of different schedules of *Neisseria* meningitidis A/C-diphtheria toxoid conjugate vaccine in infants in Niger. Vaccine 2004;22(25–26):3303–11.

[40] O'Brien KL [personal communication].

[41] Madhi SA, Kuwanda L, Cutland C, Holm A, Kayhty H, Klugman KP. Quantitative and qualitative antibody response to pneumococcal conjugate vaccine among African human immunodeficiency virus-infected and uninfected children. Pediatric Infect Dis J 2005;24(5):410–6.

[42] Adams WG, Deaver KA, Cochi SL, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood Haemophilus influenzae type b (Hib) disease in the Hib vaccine era. JAMA 1993;269(2):221–6.

[43] Fernandez J, Levine OS, Sanchez I, Balter S, LaClaire L, Feris I, et al. Prevention of *Haemophilus* influenzae type b colonization by vaccination: correlation with serum anticapsular IgG concentration. J Infect Dis 2000;182(5):1553–6.

[44] O'Brien KL, Dagan R. The potential indirect effect of conjugate pneumococcal vaccines. Vaccine 2003;21(17–18):1815–25.