Anticapsular Serum Antibody Concentration and Protection against Pneumococcal Colonization among Children Vaccinated with 7-Valent Pneumococcal Conjugate Vaccine

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Background. Pneumococcal conjugate vaccines prevent invasive and noninvasive disease due to infection with vaccine serotypes. Pneumococcal conjugate vaccines also prevent nasopharyngeal acquisition of vaccine serotypes, although the mechanism is incompletely understood.

Methods. An efficacy trial of a 7-valent pneumococcal conjugate vaccine was conducted on the Navajo and White Mountain Apache reservations, located in the Southwestern United States; group C meningococcal conjugate vaccine was the control vaccine. Infants were randomized to receive 7-valent pneumococcal conjugate vaccine or group C meningococcal conjugate vaccine at 2, 4, 6, and 12 months of age. Immunogenicity and nasopharyngeal colonization studies were nested in the efficacy trial. We analyzed the correlation between serotype-specific serum IgG concentration at 7 and 13 months of age and nasopharyngeal acquisition of disease at 12 and 18 months of age, respectively. We adjusted for potential confounders using multivariate logistic regression.

Results. Among 203 subjects, we observed 60 acquisitions of vaccine-type pneumococci, including 19 acquisitions of serotype 19F (31.7%), and 17 acquisitions of serotype 23F (28.3%). Among recipients of 7-valent pneumococcal conjugate vaccine, increased serotype-specific serum IgG was associated with a reduction in nasopharyngeal acquisition of serotype 23F (relative risk, 0.53; 95% confidence interval, 0.31–0.93) but was not associated with a reduction in acquisition of serotype 19F (relative risk, 1.07; 95% confidence interval, 0.57–2.03). Among group C meningococcal conjugate vaccine recipients, serotype-specific serum IgG was not associated with a reduction in nasopharyngeal acquisition for either serotype.

Conclusion. An increase in serum antibody concentration was associated with reduced acquisition of serotype 23F pneumococcus (but not with reduced acquisition of serotype 19F pneumococcus) among recipients of 7-valent pneumococcal conjugate vaccine. Differences in antibody concentration, in the functional characteristics of antibody, or in antibody kinetics during infancy may account for differences in carriage protection.

Pneumococcus is a leading cause of serious infection among children worldwide. A 7-valent pneumococcal conjugate vaccine (PnCRM7; Prevnar [Wyeth Vaccines]) is efficacious against vaccine-type (VT; serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) invasive pneumococcal disease when given as a 3-dose primary series with a booster [1–3] and has somewhat reduced efficacy when given in abbreviated regimens [4, 5].

Conjugate pneumococcal vaccines also reduce nasopharyngeal carriage of VT pneumococci [6–10]. Conjugate vaccines are thought to reduce VT pneumococcal carriage by preventing new acquisition, rather than by terminating existing carriage episodes [11–14]. Reductions in VT pneumococcal carriage may prevent disease among unvaccinated individuals by decreasing the transmission of these serotypes in the community (i.e., by providing herd immunity) [15–17].

The mechanisms of carriage protection are not understood. Conjugate vaccines elicit anticapsular IgA and IgG in saliva, suggesting a role for mucosal (i.e., local)...
immunity [18–20]. Systemic immune factors, namely anticapsular serum IgG, may prevent acquisition by leaking onto the nasopharyngeal mucosa [11, 13, 21, 22]. Serum and saliva IgG concentrations are positively correlated [18, 19, 21] and, unlike IgA, IgG is not susceptible to bacterial proteases in saliva [23]. Among adults, serum IgG concentrations ≥5 μg/mL prevented acquisition of serotype 14 pneumococcus [24]. To date, only 2 studies have evaluated serum IgG concentration and pneumococcal acquisition in children [14, 25].

During an efficacy trial of PnCRM7 [3], we conducted nested immunogenicity and nasopharyngeal carriage studies. The former was to assess the immunogenicity of PnCRM7 in the study population, and the latter was to evaluate the impact of PnCRM7 on pneumococcal carriage among vaccinees and their younger siblings. Some children were enrolled in both the immunogenicity and the carriage substudies. The objective of this report is to examine the association between vaccine-induced and naturally acquired IgG concentration and protection against VT pneumococcal acquisition among children.

MATERIALS AND METHODS

Study population. A group-randomized, controlled efficacy trial of PnCRM7 was conducted on the Navajo and White Mountain Apache Indian reservations in the Southwestern United States from April 1997 to October 2000 [3]. Descriptions of the study area, the population, and the randomization procedures for the trial have been reported elsewhere [26]. In brief, randomization units on the Navajo and Apache reservations were defined by geography and population size to minimize the social interactions of adults and children in a given randomization unit with those of others in a different randomization unit during the course of the trial.

Vaccines. Depending on the randomization unit in which the child lived, enrolled children received either PnCRM7 vaccine or Neisseria meningitidis group C protein conjugate vaccine (MnCC; Wyeth Vaccines) as a control vaccine. PnCRM7 contains 2 μg each of serotypes 4, 9V, 14, 19F, and 23F polysaccharides, 2 μg of serotype 18C oligosaccharide, and 4 μg of serotype 6B polysaccharide, each individually conjugated to the protein CRM197, a nontoxic variant of diphtheria toxin. MnCC contains group C oligosaccharides coupled to CRM197 by reductive amination. Each dose of study vaccine also contained 0.5 mg of aluminum phosphate as an adjuvant.

Visit schedule. Infants enrolled in the study who were between 6 weeks and 7 months of age (the primary efficacy group) received 3 doses of vaccine 2 months apart (a minimum of 4 weeks apart) and a booster dose at 12–15 months of age (at least 2 months after the third dose). A subset of these infants were enrolled in the immunogenicity study; blood samples were obtained at the time of each dose of study vaccine, 1 month after the third and fourth doses, and 9–12 months after the fourth dose (figure 1). Serum IgG concentrations were determined by ELISA at Wyeth Vaccines (Rochester, NY) [27].

A subset of efficacy trial participants and their household members ≤6 years of age were concurrently enrolled in a carriage study to evaluate the impact of PnCRM7 on carriage among vaccinees and their unvaccinated siblings. Nasopharyngeal swab samples were collected from efficacy trial participants at ∼7, 12–15, and 18–24 months of age (figure 1). The carriage study was performed between February 1998 and May 2000.

Nasopharyngeal specimen collection. Trained personnel collected nasopharyngeal specimens. A small, flexible calcium alginate swab was inserted through the nostril until resistance was encountered. If the insertion depth was approximately the distance from the tip of the nose to the ear, the swab was assumed to have reached the posterior nasopharynx. If the swab could not be passed to this depth it was withdrawn and passed through the other nostril. The swabs were inoculated into skim milk, tryptone, glucose, and glycercin transport media [28], frozen at −70°C, and transported to the Centers for Disease Control and Prevention (Atlanta, GA) for pneumococcal culture, isolation, and serotyping.

Specimens were streaked onto gentamicin–trypticase soy agar 5% sheep blood agar plates (Becton Dickinson) and were incubated overnight at 37°C in 5% CO2. Phenotypic characteristics (morphological characteristics and α-hemolysis findings) were used for the presumptive identification of pneumococci. Pneumococcal identification was confirmed by optochin susceptibility and bile solubility assays. Pneumococci were serotyped by a novel immunoblot method to detect multiple pneumococcal serotypes in nasopharyngeal specimens [29].

Subject interview. During each carriage study visit, the following information was collected by interview of the parent or guardian: the number of children in the household who were ≤6 years old, presence of a cigarette smoker, presence of a wood- or coal-burning stove, whether the child was currently...
breastfeeding or was ever breastfed, whether the child was currently receiving antibiotics or had received antibiotics in the previous month, whether the child had attended day care in the previous month, and whether the child had been hospitalized or had an episode of otitis media in the previous month. Day care was defined as any place where the child spent at least 3 days per week for a minimum of 4 h per day and where ≥5 children were present.

Analysis. Differences between study groups with respect to potential risk factors for carriage were assessed by χ² test. We defined new acquisitions as the carriage of a VT pneumococcus not previously isolated from the individual during the scheduled carriage study visits at ∼7 and/or 12–18 months of age. The correlation between postprimary (i.e., at ∼7 months of age) and postbooster (i.e., at ∼13 months of age) serum IgG concentration (e.g., age, antibiotic use at the time of nasopharyngeal swabbing) were assessed by univariate logistic regression. Potential confounders of the association between acquisition and serum IgG concentration (e.g., age, antibiotic use at the time of nasopharyngeal swabbing) were assessed by univariate logistic regression; variables with P values <.10 in the univariate model were included in the final model. Generalized estimating equations [30] were used to account for within-subject and within-community correlation between study observations. Separate models were constructed for each VT pneumococcal acquisition. PnCRM7 and MnCC vaccine recipients were analyzed separately. Analysis was conducted with SAS software, version 9.0 (SAS).

Study approvals. Approvals from the institutional review boards of the Johns Hopkins School of Medicine, the Centers for Disease Control and Prevention, the Navajo Nation, the Phoenix Area Indian Health Service, and the National Indian Health Service were obtained. Tribal approval was given by the Navajo Nation and the White Mountain Apache tribe. Parents or guardians signed a written informed consent document.

RESULTS

Characteristics of the 203 children enrolled in the immunogenicity and carriage study are shown in table 1. Of these children, 113 received PnCRM7, and 90 received MnCC vaccine. The groups were similar with respect to day care attendance, antibiotic use, reported episodes of otitis media, and other potential risk factors for carriage. The proportion of male subjects was higher among the PnCRM7 study children (53.9% vs. 38.5%; P = .03).

All study participants received 4 doses of study vaccine. The median age at receipt of each dose of study vaccine was 1.8 months, 4.2 months, 6.4 months, and 12.3 months. The median ages at which blood samples were obtained were 7.5 months and 13.5 months. Nasopharyngeal swab samples were collected at 7.5 months, 12.3 months, and 18.6 months of age. A mean of 2.9 nasopharyngeal specimens per child were obtained. Groups were similar with respect to age at vaccination, at collection of blood samples, and at collection of nasopharyngeal specimen (data not shown).

A total of 592 nasopharyngeal specimens (326 from the PnCRM7 group and 266 from the MnCC group) were collected. The overall prevalence of carriage at each visit was >60% and did not differ between groups (data not shown). The impact of PnCRM7 on VT and non-VT pneumococcal carriage is not presented here, because it is the subject of a forthcoming report. We observed 60 new acquisitions of VT pneumococci; 24 (7.4%) of the PnCRM7 recipients and 36 (13.5%) of the MnCC recipients acquired VT pneumococci (P < .05; table 2). By se-

Table 1. Demographic characteristics of Native American children enrolled in the immunogenicity and nasopharyngeal carriage study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PnCRM7 cohort (n = 113)</th>
<th>MnCC cohort (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navajo</td>
<td>78 (69)</td>
<td>64 (71.1)</td>
</tr>
<tr>
<td>Male sex</td>
<td>61 (53.9)</td>
<td>35 (38.9)</td>
</tr>
<tr>
<td>Age at first nasopharyngeal visit, median months (range)</td>
<td>7.5 (5.9–11.3)</td>
<td>7.5 (5.6–11.9)</td>
</tr>
<tr>
<td>Experienced an episode of otitis media in the previous month</td>
<td>20 (17.7)</td>
<td>21 (23.9)</td>
</tr>
<tr>
<td>Attended day care in the previous month</td>
<td>7 (6.2)</td>
<td>7 (7.8)</td>
</tr>
<tr>
<td>Children ≤6 years old in household, median no. of children (range)</td>
<td>2 (1–5)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Smoker living in household</td>
<td>30 (26.6)</td>
<td>15 (16.7)</td>
</tr>
<tr>
<td>Wood- and/or coal-burning stove in household</td>
<td>68 (60.2)</td>
<td>60 (66.7)</td>
</tr>
<tr>
<td>Nasopharyngeal specimens obtained, mean no. of specimens obtained per child</td>
<td>2.89</td>
<td>2.96</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of subjects, unless otherwise indicated. MnCC, Neisseria meningitidis group C protein conjugate vaccine; PnCRM7, 7-valent pneumococcal conjugate vaccine.

a P < .05.
b P < .001.
Table 2. New acquisition of vaccine-type (VT) pneumococcus among recipients of 7-valent pneumococcal conjugate vaccine (PnCRM7) and Neisseria meningitidis group C protein conjugate vaccine (MnCC) enrolled in the immunogenicity and nasopharyngeal carriage study

<table>
<thead>
<tr>
<th>Serotype</th>
<th>PnCRM7 cohort (n = 326)</th>
<th>MnCC cohort (n = 266)</th>
<th>All subjects (n = 592)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>3 (1.1)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>6B</td>
<td>1 (0.3)</td>
<td>4 (1.5)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>9V</td>
<td>2 (0.6)</td>
<td>6 (2.3)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>14</td>
<td>3 (0.9)</td>
<td>3 (1.1)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>18C</td>
<td>1 (0.3)</td>
<td>1 (0.4)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>19F</td>
<td>12 (3.7)</td>
<td>7 (2.6)</td>
<td>19 (3.2)</td>
</tr>
<tr>
<td>23F</td>
<td>5 (1.5)</td>
<td>12 (4.5)^a</td>
<td>17 (2.9)</td>
</tr>
<tr>
<td>Total</td>
<td>24 (7.4)</td>
<td>36 (13.5)^a</td>
<td>60 (10.1)</td>
</tr>
</tbody>
</table>

* P < .05.

For each serotype, the distribution of VT pneumococcal acquisitions was as follows: serotype 4, 3 acquisitions; serotype 6B, 5 acquisitions; serotype 9V, 8 acquisitions; serotype 14, 6 acquisitions; serotype 18C, 2 acquisitions; serotype 19F, 19 acquisitions; and serotype 23F, 17 acquisitions. The frequency of serotype 23F acquisition was significantly lower among PnCRM7 recipients than among control subjects (1.5% vs. 4.5%, respectively; P < .05); for the remaining VT pneumococci, differences between groups in the frequency of acquisition were not statistically significant. Only serotypes 19F and 23F were acquired with sufficient frequency to be included in the final analyses; the other VT pneumococci were excluded.

There were 51 acquisitions of vaccine-associated pneumococci; 26 (8%) of the PnCRM7 recipients and 25 (9.4%) of the MnCC recipients acquired vaccine-associated pneumococci. By serotype, the distribution of vaccine-associated acquisitions was as follows: serotype 6A, 23 acquisitions; serotype 19A, 18 acquisitions; serotype 23A, 5 acquisitions; serotype 23B, 3 acquisitions; and serotype 9A, 2 acquisitions. Differences between PnCRM7 and MnCC groups with respect to vaccine-associated acquisition were significant for serotype 6A only (2.2% vs. 6%, respectively; P = .02).

Geometric mean concentrations (GMCs) of serotype 19F and serotype 23F serum IgG are shown in figure 2. After a third dose of study vaccine, the proportion of subjects achieving serotype 19F IgG concentration ≥14 μg/mL was higher among PnCRM7 recipients than among control subjects (22.9% vs. 14.4%, respectively; P < .0001). Similarly, the proportion of subjects achieving a serotype 23F IgG concentration ≥14 μg/mL was higher among PnCRM7 recipients (30.2% vs. 20.4%; P < .0001). After the booster dose, the proportion achieving IgG concentrations ≥14 μg/mL for serotypes 19F and 23F were again significantly higher among PnCRM7 recipients than among control subjects (serotype 19F, 42.9% vs. 8.1%; P < .0001; serotype 23F, 53.9% vs. 2.9%; P < .0001).

In the univariate models, age and serum IgG concentration were significantly associated with risk of acquisition among PnCRM7 recipients. Sex, antibiotic use at the time of swabbing, and antibiotic use in the month before swabbing were not associated with reduced acquisition of serotypes 19F or 23F in the univariate model and, therefore, were not included in the final model.

Among PnCRM7 recipients, neither age (relative risk [RR], 1.11; 95% CI, 0.97–1.28) nor serotype 19F IgG concentration (RR, 1.07; 95% CI, 0.57–2.03) were associated with reduced acquisition of serotype 19F (table 3). In the serotype 23F model, age (RR, 0.99; 95% CI, 0.78–1.28) was not significantly associated with reduced acquisition of serotype 23F, but increased serotype 23F IgG concentration was associated with reduced acquisition of serotype 23F (RR, 0.53; 95% CI, 0.31–0.93). The GMC of serotype 23F antibody was higher among those who did not acquire serotype 23F pneumococcus than among those who did (GMC, 4.35 μg/mL vs. 1.40 μg/mL; P < .05). Among those who acquired serotype 23F, none had achieved serotype 23F IgG concentrations of >4 μg/mL before acquisition.

Neither age nor IgG concentration was associated with reduced acquisition among MnCC recipients. Increased serotype 6B IgG concentration was not associated with reduced acquisition of serotype 6A pneumococcus among those who did (GMC, 4.35 μg/mL vs. 1.40 μg/mL; P < .05). Among those who acquired serotype 23F, none had achieved serotype 23F IgG concentrations of >4 μg/mL before acquisition.

We analyzed postacquisition GMCs among those who had acquired serotypes 19F or 23F. For serotype 19F, GMCs were higher among those who acquired this serotype than among those who did not acquire this serotype, but these differences were not statistically significant (GMC, 1.99 μg/mL vs. 0.97 μg/mL; P = .16). For serotype 23F, GMCs were also higher among those who acquired this serotype than among those who did not...
not acquire this serotype; these differences were not statistically significant (GMC, 0.64 μg/mL vs. 0.36 μg/mL; P = .42).

**DISCUSSION**

This study demonstrates that increased concentrations of serotype 23F serum IgG were associated with reduced nasopharyngeal acquisition of serotype 23F among recipients of PnCRM7 vaccine. Among patients who acquired serotype 23F, none had achieved serotype 23F IgG concentrations >4 μg/mL before acquisition. This association was not observed for serotype 19F IgG concentration or for subsequent acquisition of serotype 19F. Because the number of children acquiring other VT pneumococcal serotypes was small, we only evaluated this association for serotypes 23F and 19F.

Only 2 other studies have evaluated the correlation between serum IgG concentration and nasopharyngeal acquisition of pneumococcus among recipients of conjugate pneumococcal vaccine [14, 25]. Filipino infants received 3 doses of a mixed-carrier diphtheria toxoid or tetanus protein–conjugated vaccine (11PncTD; Aventis Pasteur) or control vaccine at 6, 10, and 18 weeks of age. Regardless of vaccination status, none of the PnCRM7 subjects who acquired serotype 23F had IgG concentrations >4 μg/mL at 7 months of age were associated with reduced H. influenzae serotype b carriage at 9 months of age [31].

The mechanisms of protection against carriage are not understood. Measurable concentrations of anticapsular antibodies have been found in the saliva of conjugate vaccine recipients in 2 studies [18, 19]. In both studies [18, 19], salivary IgG concentrations correlated with serum IgG concentrations, suggesting that IgG diffused from serum. Salivary IgA responses were also observed, but the role of IgA in carriage protection is unclear.

**Table 3. Multivariate analyses of serum IgG concentration and risk of acquisition of serotypes 19F and 23F pneumococci among 7-valent pneumococcal conjugate vaccine (PnCRM7) and Neisseria meningitidis group C protein conjugate vaccine (MnCC) recipients.**

<table>
<thead>
<tr>
<th>Serotype, variable</th>
<th>PnCRM7 cohort RR (95% CI)</th>
<th>PnCRM7 cohort P</th>
<th>MnCC cohort RR (95% CI)</th>
<th>MnCC cohort P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype 19F</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, months</td>
<td>1.11 (0.97–1.28)</td>
<td>.14</td>
<td>0.89 (0.71–1.13)</td>
<td>.34</td>
</tr>
<tr>
<td>Serum IgG concentration, log_{10} μg/mL</td>
<td>1.07 (0.57–2.03)</td>
<td>.83</td>
<td>0.99 (0.59–1.66)</td>
<td>.96</td>
</tr>
<tr>
<td>Serotype 23F</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, months</td>
<td>0.99 (0.78–1.28)</td>
<td>.99</td>
<td>0.97 (0.67–1.40)</td>
<td>.88</td>
</tr>
<tr>
<td>Serum IgG concentration, log_{10} μg/mL</td>
<td>0.53 (0.31–0.93)</td>
<td>.02</td>
<td>1.02 (0.62–1.68)</td>
<td>.93</td>
</tr>
</tbody>
</table>

**NOTE.** RR, relative risk.

for serotypes 14 and 19F only. Furthermore, increased serotype 6B IgG was associated with reduced acquisition of the cross-reacting serotype 6A.

Data from other studies provide additional evidence for the role of vaccine-induced or passively administered serum IgG in protection against nasopharyngeal acquisition [11, 13, 31]. In an infant rat model, passive immunization with bacterial polysaccharide immunoglobulin prior to challenge with homotypic pneumococci prevented acquisition of serotypes 3 and 19F [13]. Studies of *Haemophilus influenzae* serotype b carriage had similar results [11]. Among recipients of *H. influenzae* serotype b vaccine, high concentrations (i.e., concentration ≥5 μg/mL) of serum IgG at 7 months of age were associated with reduced *H. influenzae* serotype b carriage at 9 months of age [31].
influenzae serotype b in children [31]. The protective concentrations are likely to differ by serotype, because studies of conjugate vaccine have demonstrated differences in immunogenicity, as well as in efficacy, by serotype [34, 35].

Whether the protective correlates induced by vaccination are the same correlates induced by natural exposure to pneumococcus is not clear. The failure to see a correlation between naturally acquired IgG and protection against acquisition of serotypes 19F or 23F may reflect one or more of several phenomena. First, most children did not have significant concentrations of naturally acquired serotype 19F or serotype 23F antibody. Thus, the failure to see a correlation may simply reflect that, overall, these children had antibody concentrations that were lower than the protective level. Very few children had antibody concentrations >5 μg/mL, even at 18 months of age. Alternatively, the observed variability in carriage among these children may reflect variability in their exposure to these serotypes, rather than variability in protective antibody distribution.

Second, the mechanism of natural protection may differ from that induced by vaccination. Mouse models have shown that carriage protection is not necessarily serotype-specific and is not dependent on the ability to produce antibodies [36]. Furthermore, some have hypothesized that observed decreases in the incidence of pneumococcal disease with age for many different pneumococcal serotypes, combined with the relatively slow acquisition of serotype-specific antibody, argue for protective mechanisms beyond serotype-specific antibody [37]. Thus, the failure to observe a correlation between IgG concentration and carriage protection among children who are not vaccinated with PnCRM7 may indicate that anticapsular antibody is not the primary mechanism of natural protection at this early age.

Because of the schedule of nasopharyngeal specimen collection, we may have missed carriage episodes. As a result, IgG concentrations among uncolonized children may reflect systemic responses to recent exposure, rather than the concentrations required to prevent acquisition. A greater impact on carriage might have been observed had more nasopharyngeal specimens been collected or had more subjects been enrolled. Because the number of VT pneumococcal acquisitions was small, we were not able to evaluate the association between IgG concentration and acquisition for all serotypes in the PnCRM7 vaccine. Lastly, we did not test any carriage isolates for antibiotic resistance; it is possible that acquisition and carriage of antibiotic-resistant pneumococci—many of which are VT pneumococci—may have affected the observed outcomes.

Identifying correlates of protection against carriage is important in the evaluation of new conjugate vaccines or alternative vaccination regimens, particularly when considering their potential impact on transmission and herd immunity [31]. This study underscores the need to more closely examine local and systemic responses to carriage among recipients of conjugate vaccines. Furthermore, the properties and functional characteristics (e.g., subclass distribution, avidity, and opsonophagocytic activity) of serum and salivary antibodies elicited by vaccination need to be explored [18], because these may contribute to protection against acquisition. Lastly, because routine use of conjugate vaccines is expected to dramatically alter the ecology of carriage, further investigation is warranted regarding the importance of natural exposure to VT pneumococci in priming the immune system and contributing to long-term immunity against invasive disease, especially among populations with high carriage prevalence.

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References

10. O’Brien KL, Bromson MA, Carlone GM, et al. Effect of a 7-valent pneumococcal conjugate vaccine on nasopharyngeal (NP) carriage among Navajo and White Mountain Apache (N/WMA) infants [ab-