Effect of Community-Wide Conjugate Pneumococcal Vaccine Use in Infancy on Nasopharyngeal Carriage through 3 Years of Age: A Cross-Sectional Study in a High-Risk Population

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Background. A 7-valent pneumococcal conjugate vaccine (PnCRM7) has been shown to be highly effective in preventing invasive pneumococcal disease. Pneumococcal conjugate vaccines also protect against nasopharyngeal carriage of vaccine serotypes, but the duration of protection against nasopharyngeal carriage is not known.

Methods. A group-randomized efficacy trial of PnCRM7 (vaccine serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) was conducted on the Navajo and White Mountain Apache reservations from April 1997 to October 2000. A group C meningococcal conjugate vaccine was used as the control vaccine. Infants enrolled between 6 weeks and 7 months of age received 3 doses of vaccine 2 months apart and a fourth dose at 12–15 months of age. Vaccinees were enrolled in a nasopharyngeal carriage study from February 2001 to January 2002 to assess the duration of protection against pneumococcal carriage induced by PnCRM7.

Results. We included 749 children in the analysis, including 468 children vaccinated with PnCRM7 and 281 children vaccinated with group C meningococcal conjugate vaccine. The median age was 3.3 years (range, 1–7 years), and the median time since last dose of study vaccine was 27 months (range, 12–48 months). Frequencies of overall pneumococcal carriage were similar among PnCRM7 and group C meningococcal conjugate vaccine recipients (63.9% vs. 60.5%, respectively). The absolute frequency of vaccine-type pneumococcal carriage was lower among PnCRM7 recipients (10.3%) than among controls (17.1%; \( P = .01 \)). This reduction was offset by an increase of nonvaccine-type pneumococcal carriage among PnCRM7 recipients (39.2% vs. 29.8%; \( P = .01 \)).

Conclusion. Community-wide PnCRM7 vaccination in infancy reduces the prevalence of vaccine-type carriage and increases the prevalence of nonvaccine-type carriage through at least 3 years of age.

Pneumococcus is a leading cause of invasive and non-invasive disease among children. The importance of pneumococcal infections is highlighted by an increasing prevalence of drug-resistant strains, which may complicate treatment options and, in some cases, lead to treatment failure [1–3]. Children <2 years of age are at highest risk for pneumococcal infection. Until recently, disease prevention strategies for this age group have been limited.

The efficacy of a 7-valent pneumococcal conjugate vaccine (PnCRM7; Wyeth Vaccines) against invasive disease was evaluated among children in northern California and among American Indian children in the southwest United States [4, 5]. Both trials demonstrated that PnCRM7 was highly efficacious against vaccine-type (VT) invasive disease when given as a 4-dose series at 2, 4, 6, and 12–15 months of age. In February 2000, PnCRM7 was licensed in the United States for children up to 9 years of age and is routinely recommended for children <2 years of age [6].

Prelicensure and postlicensure studies have shown that pneumococcal conjugate vaccines protect against nasopharyngeal (NP) carriage of VT pneumococci [7–11]. Numerous studies have shown that conjugate vac-
cines protect against VT carriage in the months immediately after vaccination [8, 9, 11, 12]. However, very minimal data are available on the persistence of this effect 2–3 years after vaccination [13, 14]. The duration of protection against carriage is of particular importance, because it is this effect that confers indirect protection against disease among unimmunized contacts. None of the studies have evaluated the duration of protection in populations at high risk for pneumococcal carriage and disease, for whom indirect effects may be particularly important.

The American Indian efficacy trial used a group-randomized design, which permits an evaluation of the total effect of vaccination, including the direct effect conferred to individuals by vaccination and the indirect effect conferred to unvaccinated individuals by interrupted transmission of the organism [15]. A carriage study was nested in the trial to evaluate the impact of PnCRM7 on carriage among vaccinees and their younger siblings [16]. After the trial was unblinded, we conducted a follow-up carriage study among American Indian trial participants, vaccinated during infancy, to assess the duration of protection against carriage induced by PnCRM7. It is this latter follow-up carriage study that we report here.

MATERIALS AND METHODS

A group-randomized, controlled efficacy trial of PnCRM7 was conducted on the Navajo and White Mountain Apache (WMA) reservations in the southwest United States from April 1997 to October 2000. Descriptions of the study area and population, as well as of the randomization procedures for the trial, have been described elsewhere [5, 15]. In brief, randomization units on the Navajo and WMA reservations were defined by geography and population size, so as to group communities with significant social interactions of adults and children into the same randomization unit and to separate communities with minimal social interactions into different randomization units.

On the basis of the randomization unit in which the child lived, each study participant received either PnCRM7 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 vaccine also contained 0.5 mg of aluminum phosphate as an adjuvant.

Infants enrolled between 6 weeks and 7 months of age 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 carriage study was conducted during the trial to evaluate the impact of PnCRM7 on carriage among vaccinees and their unvaccinated household members. After the trial was unblinded, we recruited trial participants for a follow-up carriage study from February 2001 through January 2002. Among the pool of subjects who were enrolled in both the parent efficacy and carriage studies (550 subjects), we attempted to contact those families whose homes were less than a 1-h drive from the respective field offices. We also approached families who participated in the parent efficacy trial but did not participate in the NP study, either because they were at a study site that had not participated in the parent NP study or because they were simply not recruited into the NP study at a participating site. Children with congenital abnormalities of the nasopharynx were excluded. We included in the analysis only those children whose NP specimens were collected at least 12 months after the last dose of study vaccine was administered.

A single nasal swab sample was collected from each participant by trained nurses and field workers using a small, flexible aluminum shaft swab. The swabs were inoculated into skim milk tryptone-glucose-glycerin transport media [17], frozen at −70°C, and transported to the Centers for Disease Control and Prevention (Atlanta, GA) for culture, isolation, and serotyping. Specimens were streaked onto gentamicin-tryptose soy agar 5% sheep blood agar plates (Becton Dickinson) and incubated overnight at 37°C in 5% CO2. Phenotypic characteristics (determined by morphological analysis and α-hemolysis) were used for presumptive identification of pneumococci. Pneumococci were confirmed by optochin susceptibility and bile solubility assays. A single colony was selected from each plate and serotyped by Quellung reaction. Serotypes were categorized into 1 of 3 mutually exclusive categories: VT included types 4, 6B, 9V, 14, 18C, 19F, and 23F; vaccine-associated (VA) types included types in groups 6, 9, 18, 19, or 23 that were not VTs; and nonvaccine types (NVT) were all types that were not VT or VA types. Nontypeable isolates were excluded from analysis. The parent or guardian of the study child was interviewed for the number of children <5 years of age in the household, antibiotic use, day care attendance, and other known risk factors for carriage.

To interpret the carriage findings in PnCRM7- and MnCC-randomized communities, we estimated PnCRM7 coverage rates among Navajo and WMA children during and after the efficacy trial. From April 1998 to October 2000 (the period of the trial), the only doses of PnCRM7 available in the community were those administered in the context of the study. Subsequent to October 2000, PnCRM7 was available through the Indian Health Service as an open-label, licensed product (Prevnar; Wyeth Vaccines). All doses administered during the course of the trial were documented as part of the study. Subsequent to the trial, in October 2000, immunization records at Indian Health Service facilities on the Navajo and WMA res-
Table 1. Characteristics of Navajo and White Mountain Apache children enrolled in a study of nasopharyngeal carriage.

| Characteristic                              | PnCRM7 group | Control group | Excluded from analysis |
|---------------------------------------------|--------------|---------------|------------------------|
|                                             | (n = 468)    | (n = 281)     | (n = 257)              |
| Age, years                                  |              |               |                        |
| 0–2                                         | 202 (41.1)   | 87 (30.5)     | 141 (54.9)             |
| 3–4                                         | 269 (54.7)   | 182 (63.9)    | 108 (42.0)             |
| 5–6                                         | 21 (4.3)     | 16 (5.6)      | 8 (3.1)                |
| Median age, years                           | 3.4          | 3.5           | 2.8                    |
| Male sex                                    | 242 (51.7)   | 135 (48)      | 135 (52.5)             |
| Tribe                                       |              |               |                        |
| Navajo                                      | 388 (82.9)   | 213 (75.8)    | 229 (89.1)             |
| White Mountain Apache/other                 | 80 (17.1)    | 68 (24.2)     | 28 (10.9)              |
| Mean interval since last dose of study vaccine, months (range) | 27 (12–48)   | 28 (13–48)    | ...                    |
| Received antibiotic within 1 month          | 26 (5.6)     | 20 (7.1)      | 23 (8.9)               |
| Attended day care within 1 month            | 49 (10.5)    | 44 (15.7)     | 33 (12.8)              |
| Median no. in household                     | 6            | 6             | 5                      |
| Median no. of children <5 years old living in household | 2            | 2             | 2                      |
| Smoker living in household                  | 119 (25.4)   | 64 (22.8)     | 48 (18.7)              |
| Used wood/coal-burning stove within 1 month | 142 (30.3)   | 92 (32.7)     | 60 (23.4)              |

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

a Control subjects received MnCC.
b Children who received MnCC and were excluded from carriage analysis, because they received open-label PnCRM7 (Prevnar; Wyeth Pharmaceuticals) after the trial was unblinded but before collection of nasopharyngeal swab samples.

Observations were used to document all children (study participants as well as nonparticipants) who received open-label PnCRM7 as part of the routine childhood immunization schedule. Annual age-specific user population statistics from the Indian Health Service were used in the estimation of PnCRM7 coverage.

Analysis was conducted using SAS software, version 8.0 (SAS). Proportions were compared using \( \chi^2 \) or Fisher’s exact test where appropriate. Results were considered to be statistically significant if the 2-tailed \( P \) value was <.05.

The study was approved by the institutional review boards of the Johns Hopkins Bloomberg School of Public Health, the Centers for Disease Control and Prevention, the Navajo Nation, the Phoenix Area Indian Health Service, and the National Indian Health Service. Tribal approval was given by the Navajo Nation and the WMA tribes. Parents or guardians provided written, informed consent for their child to participate.

RESULTS

A total of 1042 trial participants were enrolled in the follow-up carriage study; of these enrollees, 190 (18.2%) were enrolled in the initial carriage study. Two hundred fifty-seven children who received MnCC had received PnCRM7 after the trial was unblinded but before collection of NP swab samples and were thus excluded from further analysis. Of the remaining 785 participants, 8 (<1%) had pneumococcal isolates that could not be serotyped (i.e., isolates that were nonviable or missing). These subjects were excluded from analysis. Lastly, 28 children (4 in the MnCC group and 24 in the PnCRM7 group) had swab samples collected <12 months after their last dose of study vaccine was administered and were excluded from analysis.

The median age of the 749 participants was 3.3 years (range, 1–7 years). PnCRM7 and MnCC recipients were similar in age, antibiotic use, day care attendance, number of siblings, and other risk factors for carriage (table 1). The 257 excluded MnCC recipients were younger, but they did not significantly differ from either group with regard to other risk factors (table 1).

The majority (83%) of subjects had received 4 doses of study vaccine before collection of NP swab samples. Of those who received 4 doses, the median age at each vaccination was 2.1, 4.6, 6.9, and 12.5 months of age. The mean time since last vaccination was 27 months (range, 12–48 months) and did not differ between PnCRM7 and MnCC recipients (table 1).

The prevalence of overall pneumococcal carriage was similar between PnCRM7 recipients and control subjects (63.9% vs. 60.5%, respectively) (table 2). However, the prevalence of VT
Table 2. Frequency of pneumococcal nasopharyngeal carriage among American Indian study children 1–7 years of age.

| Pneumococcal carriage | PnCRM7 group (n = 468) | Control groupa (n = 281) |
|------------------------|------------------------|--------------------------|
|                        | No. of subjects | Percentage of subjects (95% CI) | No. of subjects | Percentage of subjects (95% CI) | P | OR (95% CI) |
| All types              | 299            | 63.89 (59.35–68.25)            | 170            | 60.50 (54.52–66.25)            | NS | 1.15 (0.85–1.57) |
| VT                     |                |                              |                |                              |    |               |
| Overall                | 48             | 10.26 (7.65–13.37)            | 48             | 17.08 (12.87–22.00)           | .01 | 0.55 (0.36–0.85) |
| 4                      | 3              | 0.64 (0.13–1.86)             | 1              | 0.36 (0.009–1.96)            | .60 | 1.81 (0.19–17.45) |
| 6B                     | 6              | 1.28 (0.47–2.76)             | 13             | 4.63 (2.49–7.78)            | .01 | 0.27 (0.10–0.71) |
| 9V                     | 3              | 0.64 (0.13–1.86)             | 3              | 1.07 (0.22–3.09)            | .53 | 0.60 (0.12–2.98) |
| 14                     | 3              | 0.64 (0.13–1.86)             | 3              | 1.07 (0.22–3.09)            | .53 | 0.60 (0.12–2.98) |
| 18C                    | 3              | 0.64 (0.13–1.86)             | 6              | 2.14 (0.79–4.59)            | .07 | 1.81 (0.19–17.45) |
| 19F                    | 24             | 5.13 (3.31–7.53)             | 16             | 5.69 (3.29–9.08)            | .74 | 0.89 (0.47–1.72) |
|                          | 6              | 1.28 (0.47–2.76)             | 6              | 2.14 (0.79–4.59)            | .37 | 0.59 (0.19–1.86) |
| VA                     |                |                              |                |                              |    |               |
| Overall                | 68             | 14.53 (11.46–18.05)          | 41             | 14.59 (10.68–19.27)         | NS  | 0.99 (0.65–1.51) |
| 6A                     | 37             | 7.91 (5.62–10.73)            | 11             | 3.91 (1.97–6.89)            | .03 | 2.10 (1.06–4.20) |
| 19A                    | 12             | 2.56 (1.33–4.44)             | 10             | 3.56 (1.72–6.45)            | .44 | 0.71 (0.30–1.67) |
| Other                  | 19             | 4.53 (2.46–6.27)             | 20             | 7.69 (4.40–10.78)           | .09 | 0.57 (0.29–1.09) |
| NVT                    | 184            | 39.32 (34.86–43.90)          | 84             | 29.89 (24.60–35.62)         | .01 | 1.52 (1.11–2.08) |

NOTE. NS, not significant; NVT, nonvaccine type; PnCRM7, 7-valent pneumococcal conjugate vaccine; VA, vaccine-associated type; VT, vaccine type.

a Control subjects received Neisseria meningitidis group C protein conjugate vaccine.

The frequency of pneumococcal nasopharyngeal carriage was lower among the 493 PnCRM7 recipients (10.3%) than among the control subjects (17.1%; P = .01). Among PnCRM7 recipients who were colonized, a significant reduction in serotype-specific carriage was observed for type 6B (2.0% vs. 7.7%; P = .003). Reductions in VT carriage among PnCRM7 recipients were similar when stratified by time since the last dose of study vaccine was administered (table 3).

The prevalence of NVT carriage was higher among PnCRM7 recipients (39.3%) than among control subjects (29.9%; P = .01). Among PnCRM7 recipients who were colonized, significant increases in serotype-specific carriage were observed for types 6A (12.4% vs. 6.5%; P = .04), 11A (5.7% vs. 1.2%; P = .02), 17F (4.7% vs. 1.2%; P = .04), and 22F (7.7% vs. 2.4%; P = .02). Among PnCRM7 recipients, the most commonly carried nonvaccine serotypes were 6A, 35B, and 22F. Among MnCC recipients, the most commonly carried nonvaccine serotypes were 6B, 6A, and 19A.

Among WMA, the prevalence of VT carriage among PnCRM7 and MnCC vaccinees was 8.8% and 23.5%, respectively (P < .05). Among Navajo, the prevalence of VT carriage was lower among PnCRM7 vaccinees than among control subjects (10.6% vs. 15%; P = .11), but was not statistically significant. Increases in NVT carriage were observed among recipients of PnCRM7 in both WMA (50% vs. 32.4%; P = .03) and Navajo (37.1% vs. 29.1%; P = .05) tribes.

The long-term impact of PnCRM7 on carriage should be interpreted in the context of overall vaccine coverage; thus, we also evaluated PnCRM7 coverage during the period of this cross-sectional study. Among children aged 19–35 months living in PnCRM7-randomized communities, rates of PnCRM7 coverage (i.e., receipt of at least 3 doses) increased from <5% in June 1998 to 59% among Navajos and 80% among WMA in December 2000, just prior to the initiation of the carriage study (figure 1). Coverage with PnCRM7 remained 52%–58% among Navajo and 66%–75% among WMA through the carriage study period ending in January 2002. Among 19–35-month-old subjects living in MnCC-randomized communities, PnCRM7 vaccine coverage rates in December 2000, just before the initiation of the carriage study, were <1%, and they increased to 20% by January 2002 in both Navajo and WMA populations.

**DISCUSSION**

This study documents that protection against VT pneumococcal carriage induced by PnCRM7 vaccination during infancy extends well beyond the immediate vaccination period and persists until at least 3 years of age. Before routine use of PnCRM7 in these communities, the prevalence of VT pneumococci among PnCRM7 vaccinees 7–18 months of age who...
were colonized was 24% [16]. In the current study, this proportion was 16%; however, these children were 1–7 years of age. The prevalence of overall pneumococcal carriage among our study population (~60%) is 2–3-fold higher than that among similarly aged children in the general US population and in Europe [13, 14, 18]; among MnCC recipients who were colonized, ~28% carried VT pneumococci (for an absolute VT carriage rate of 17.1% among these children). These data demonstrate the ability of PnCRM7, even at moderate levels of immunization coverage, to sustain reductions in carriage of VT pneumococci in populations with a high burden of invasive disease and early, intense pneumococcal carriage [19, 20].

Similar studies involving older European children have yielded mixed results. A reduction in VT carriage 3–4 years after a 4-dose PnCRM7 vaccination series was reported among Finnish children [14], whereas no significant difference in VT carriage was found for 2–4-year-old British children who had received 3 doses of PnCRM7 in infancy and a booster of 23-valent polysaccharide pneumococcal vaccine at 13 months of age [13].

The underlying NP exposure among these European children is significantly less intense than the NP exposure among the American Indian children that we studied. Thus, part of the ongoing protection against carriage may relate to boosting of the vaccine-induced immune response from ongoing exposure to VT strains and maintenance of antibody concentrations within the range that is required for protection against pneumococcal acquisition. Another hypothesis is that use of a booster dose of PnCRM7 following the primary series may provide a more sustained or more robust immune response to pneumococcal NP challenges and, therefore, be an important contributor to long-term protection against VT carriage.

The immunologic mechanisms by which conjugate vaccines directly protect against carriage are not fully understood. Data exist supporting the notion that vaccine protects against acquisition of new strains, rather than acting to terminate existing carriage [8, 12, 21], and recent data suggest that naturally acquired or vaccine-induced circulating serotype-specific antibody in high concentrations are correlated with protection from strain acquisition [22, 23].

In addition to the epidemiologic differences in pneumococcal exposure within the community, this study differs significantly from others insofar as the PnCRM7-vaccinated children lived in communities where PnCRM7 coverage was ~50%, and the unvaccinated children lived in communities where the PnCRM7 coverage was 0%-10%. Thus, the group-randomized design provided a unique opportunity to evaluate the total effect (i.e., direct and indirect effects) of vaccination on duration of carriage protection. The reduced prevalence of VT carriage observed beyond 3 years of age was likely achieved by a combination of individual protection conferred by PnCRM7 and reduced pneumococcal exposure conferred by living in a community where a significant proportion of the children have been vaccinated (i.e., indirect effect).

The degree to which exposure is reduced likely depends on the prevalence of VT carriage and the level of immunization coverage in the community. From the conclusion of the trial through the duration of the carriage study, PnCRM7 coverage among Navajo and WMA children in PnCRM7-randomized communities ranged from 50% to 80% (figure 1). The magnitude of the indirect effect, as well as the correlation between community-wide vaccination and reductions in carriage, is not completely understood. It may be that there is a window of coverage that is ideal for promoting an indirect effect; coverage below that level may be insufficient to induce an indirect effect, and coverage above that level might lead to a shorter duration of protection against carriage in the absence of boosting from natural exposure. Longer-term observational and modeling studies will be needed to further disentangle these possibly competing effects.

This study provides evidence that NVT carriage prevalence among PnCRM7 recipients is higher not only immediately following vaccination [24] but also well beyond that time period [9, 10, 25]. Of these NVT isolates, the serotype-specific pre-

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**Table 3.** Frequency of vaccine-type pneumococcal carriage among Navajo and White Mountain Apache study children by time since last dose of study vaccine.

| Time since last dose, months | PnCRM7 group (n = 468) | Control group (n = 281) |
|-----------------------------|------------------------|------------------------|
|                             | No. of subjects | Percentage of subjects (95% CI) | No. of subjects | Percentage of subjects (95% CI) | P |
| 12–23 months                | 19 | 9.6 (5.91–14.65) | 16 | 16 (9.43–24.68) | .10 |
| >24 months                  | 29 | 10.7 (7.28–15.01) | 32 | 17.7 (12.42–24.03) | .03 |

**NOTE.** Mean ages of PnCRM7 recipients were 2.7 years for those with 12–23 months since last dose and 3.8 years for those with >24 months since last dose. PnCRM7, 7-valent pneumococcal conjugate vaccine.
Figure 1. Proportion of Navajo and White Mountain Apache (WMA) children 19–35 months of age who had received at least 3 doses of pneumococcal conjugate vaccine (PCV), December 1997–January 2001. MnCC, group C meningococcal conjugate vaccine.

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mechanisms of protection against carriage, of how vaccine alters pneumococcal transmission, and ultimately of how vaccines contribute to the prevention of pneumococcal disease in the community as a whole will inform the long-term strategy and uses of pneumococcal vaccines.

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