Effectiveness of Pneumococcal Polysaccharide Vaccine for Preschool-Age Children with Chronic Disease

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Streptococcus pneumoniae is a leading cause of pneumonia, meningitis, bacteremia, and death in young children. A polysaccharide vaccine has been recommended for use in chronically ill children and adults 2 to 64 years of age, as well as all adults >65 (1). While many studies have assessed the immunogenicity of the polysaccharide vaccine, scant data exist on its effectiveness in younger children.

More than 90 serotypes of S. pneumoniae have been described (2); however, most invasive infections in the United States are caused by ≤10 serotypes (3). Pneumococcal vaccines available since 1978 consist of a mixture of capsular polysaccharides from the most common serotypes causing invasive disease. This vaccine is recommended for children ≥2 years of age with underlying diseases or immunosuppressive medical treatments that are risk factors for invasive pneumococcal disease (1,3).

Clinical trials of pneumococcal polysaccharide vaccine effectiveness in children have shown conflicting results (4-7). Vaccine failure in immunized children has been reported (8), and one study comparing immunization with antibiotic prophylaxis in children with sickle cell disease concluded that the vaccine was inferior to penicillin prophylaxis (9). Uncertainty regarding the effectiveness of vaccination may contribute to low vaccination rates among persons at risk for pneumococcal disease (1).

In indirect cohort analysis (10), the distribution of pneumococcal serotypes causing invasive disease among vaccinated and unvaccinated groups is compared. If the vaccine is effective, vaccinated persons have fewer infections with serotypes represented in the vaccine than unvaccinated persons. This method has been used to calculate an overall effectiveness of 57% in persons >5 years of age, based on serotypes of invasive isolates obtained through a national, voluntary sentinel surveillance system (11). Using data from national surveillance, we examined vaccine effectiveness for children 2 through 5 years of age.

The Study
Since 1978, a national, hospital laboratory-based surveillance system has collected data on invasive pneumococcal disease (12). Participating institutions are requested to report all pneumococcal isolates obtained from normally sterile body sites, along with information on the patient's age, sex, symptoms, underlying diseases, and vaccination history. The specifics of how demographic and vaccination information is collected are the responsibility of participating institutions. Isolates are serotyped at the

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Centers for Disease Control and Prevention on the basis of capsular swelling with serotype-specific antisera (Quellung reaction).

Children included in the analysis were 24 to 59 months of age with one or more chronic illnesses, had vaccination status and date indicated on the surveillance form, received vaccine between January 1984 and April 1996, and had onset of invasive pneumococcal disease between January 1984 and April 1996. Only isolates from cerebrospinal fluid (CSF) or blood were considered in the analysis. Information on antibiotic prophylaxis was not collected. Chronic illness was defined as an underlying illness considered a risk factor for invasive pneumococcal disease and an indication for vaccination (3).

Vaccine effectiveness was defined as the percentage of reduction in the risk for infection from serotypes included in the vaccine (vaccine-type serotypes) among vaccinated persons compared with unvaccinated persons. Infections with vaccine-related serotypes (6A, 9A, 9L, 18B, 18F, 23A) not specifically included in the vaccine were categorized as infections with nonvaccine serotypes, except where noted. Effectiveness was expressed as 1 minus the odds ratio x 100%; the 95% confidence intervals (also x 100%) were calculated by the methods of Cornfield when cell sizes were all greater than five subjects and by exact methods otherwise. Calculations were performed with Epi-Info version 6.02 (CDC/World Health Organization, Atlanta, GA) with the EXACT supplemental program (David O. Martin).

We performed a preliminary analysis of all pneumococcal isolates from children in the database to determine the proportion of vaccine-type organisms in unvaccinated persons by sex, underlying illness, or state of residence. Proportions of vaccine-type serogroups did not differ by underlying illness or by sex. Because the proportion of vaccine-type isolates from children from Alaska was 92.3%, compared with the 85.4% of isolates from children from other states (chi-square = 6.3; p <0.02), children from Alaska were excluded from the analysis.

The analysis included 173 children, 52% male, median age 3 years; 48 children (28%) had received vaccine before acquiring invasive pneumococcal disease. Isolates were obtained from blood only from 156 children (90%), from CSF only from 10 children (6%), and from both sites from 7 children (4%). The median time between date of vaccination and date of specimen collection was 338.5 days (33 days to 1,341 days), and no child had been vaccinated within 30 days of invasive pneumococcal infection. Of serotypes from the 173 invasive infections, serotypes 4, 6A, 6B, 14, 23F, 19F, 9V, and 18C accounted for 81% of the isolates (Figure 1).

Forty-six (27%) of children in the study had sickle cell disease (Figure 2). The “other” category included children with congenital anomalies such as congenital heart or lung defects, children with anatomic asplenia, and children on immunosuppressive medication regimens. Thirty-three (69%) of 48 vaccinated children had sickle cell disease.

**Figure 1.** Invasive pneumococcal infections among 173 children ages 2 through 5 years (24-59 months), by serotype. Bottom bar represents proportion of total invasive infections in the cohort caused by each serotype. Top bar depicts cumulative proportion of invasive infections caused by serotypes represented by the bars to the left. Serotypes in the “other” category included 19 serotypes with three or fewer isolates. Two isolates could not be serotyped.

**Figure 2.** Frequency of various underlying chronic illnesses among 173 children with invasive pneumococcal disease. The category “malignancy” excluded hematopoietic malignancies, which are included in the leukemia category. Organ transplant includes both solid organ and bone marrow transplants. CSF is cerebrospinal fluid.
The Table presents vaccine effectiveness estimates for the overall cohort and for children with and without sickle cell disease. For children with the disease, the lower bound of the 95% confidence interval included 0%. The estimate of vaccine effectiveness for children without sickle cell disease was higher than the estimate for children with the disease. Point estimates of effectiveness for children with nephrotic syndrome or HIV infection were 80%; however, the 95% confidence intervals included 0% (data not shown). Other chronic diseases reported in this cohort included leukemia, nonhematopoietic malignancy, and organ transplant; however, none of the children with these underlying diseases were vaccinated, and effectiveness could not be calculated.

Protein conjugate vaccines offer the advantage of being effective in the first 2 years of life, when response to polysaccharide vaccines is poor. However, the number of serotypes that can be represented in these vaccines is limited. To evaluate polysaccharide effectiveness for serotypes not represented in a protein conjugate vaccine under evaluation for license (13), we excluded children infected with serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Polysaccharide vaccine was highly effective in preventing invasive disease due to serotypes included in the polysaccharide vaccine but not in the conjugate vaccine (Table). If the 14 children with serotypes 6A, 9A, 9L, 18B, 18F, and 23A are also excluded (because of potential protection conferred by the proposed conjugate vaccine for these vaccine-related serotypes), the vaccine effectiveness estimate is 92% (exact 95% confidence intervals 17% to 100%).

Conclusions

Case-control studies have demonstrated that pneumococcal capsular polysaccharide vaccines are effective (14-16) and cost-effective (17,18) in the prevention of invasive pneumococcal disease among elderly and chronically ill adults. We used data from a national sentinel surveillance system for invasive pneumococcal disease to determine whether children ages 2 to 5 years were also protected. An overall vaccine effectiveness of 63% was demonstrated by indirect cohort analysis (15). The indirect cohort analysis presented here strengthens the case for the use of pneumococcal polysaccharide vaccine for children with underlying conditions. For children with sickle cell disease, penicillin prophylaxis remains the most effective preventive measure for reducing pneumococcal disease.

Accuracy of vaccine history is critical to this analysis and may vary between surveillance sites. To minimize inaccuracies, patients with no indication of vaccine history were excluded. For those with a reported vaccine history, misclassification due to inaccurate history should be as likely among patients with vaccine-type as among nonvaccine-type infections because the serotype of patient isolates was not known when vaccine status was determined (serotyping was done at CDC). Bias due to this nondifferential misclassification will be towards the null hypothesis (no effect of vaccination) (19).

Newly developed pneumococcal protein conjugate vaccines are safe and immunogenic for infants and young children (13,20,21). Preliminary results from a large, Phase-III trial of a heptavalent conjugate vaccine among healthy children indicate substantial efficacy in preventing invasive disease (13). However, the expense and technical difficulty of creating conjugates for each serotype will likely limit the number of serotypes represented in a polyvalent conjugate vaccine to fewer than 12. Available data suggest that polysaccharide vaccine, when administered after primary immunization with a conjugate vaccine, elicits a significant booster effect in
healthy infants (22) equivalent to the booster response engendered by a second conjugate vaccine series (23). These results and the level of effectiveness seen with pneumococcal polysaccharide vaccine in our study suggest that the polysaccharide vaccine will still be a useful adjunct to conjugate vaccine, by providing additional protection to children ≥2 years of age for whom polysaccharide vaccine is currently indicated.

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