Efficacy of Meningococcal Vaccine and Barriers to Vaccination

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Context.—Use of the quadrivalent meningococcal vaccine for control of outbreaks has increased in recent years, but the efficacy of meningococcal vaccine during mass vaccination campaigns in US civilian populations has not been assessed.

Objectives.—To evaluate the efficacy of the quadrivalent meningococcal vaccine against serogroup C meningococcal disease in a community outbreak setting and to evaluate potentially modifiable barriers to vaccination in an area with persistent meningococcal disease following immunization.

Design.—Matched case-control study of vaccine efficacy using cases of serogroup C meningococcal disease in persons eligible for vaccination during mass vaccination campaigns. Control patients were matched by neighborhood and age. The control group was used to identify possible barriers to vaccination.

Setting.—Gregg County, Texas, population 106,076, from 1993 to 1995.

Participants.—A total of 17 case patients with serogroup C meningococcal disease eligible for vaccine and 84 control patients.

Main Outcome Measures.—Vaccine efficacy and risk factors associated with nonvaccination.

Results.—Vaccine efficacy among 2- to 29-year-olds was 85% (95% confidence interval, 27%-97%) and did not change in bivariate analyses with other risk factors that were significant in univariate analysis. Among control patients, older age was strongly associated with nonvaccination; vaccination rates for 2- to 4-year-olds, 5- to 18-year-olds, and 19- to 29-year-olds were 67%, 48%, and 20%, respectively ($\chi^2$ for linear trend, $P=.01$).

Conclusions.—The meningococcal polysaccharide vaccine was effective against serogroup C meningococcal disease in this community outbreak. Although specific barriers to vaccination were not identified, older age was a risk factor for nonvaccination in the target population of 2- to 29-year-olds. In future outbreaks, emphasis should be placed on achieving high vaccination coverage, with special efforts to vaccinate young adults.

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In February 1994, an increase in the number of cases of SCMD was recognized in Gregg County, Texas (population 106,076). In a county this size, only 1 case of SCMD per year would be expected annually; however, over the 3-month period from December 1993 through February 1994, 4 cases of SCMD occurred in children younger than 10 years. The Texas Department of Health (TDH) conducted a county-wide vaccination campaign among residents aged 2 to 10 years, which was then expanded to residents aged 2 to 29 years as additional cases occurred over a 12-month period. Ultimately, approximately 36,000 people were vaccinated in 30 clinics. The steps taken by TDH were in accordance with the current Advisory Committee on Immunization Practices (ACIP) recommendations for evaluation and management of suspected community-based SCMD outbreaks. Despite the enormous public health effort undertaken by TDH, cases continued to occur. By September 1995, 39 cases of meningococcal disease had been identified, 2 of which were reported to have occurred in persons who had been vaccinated. Either meningococcal vaccine was not sufficiently efficacious or vaccine coverage was not high enough to stop the outbreak, despite multiple vaccination campaigns. To evaluate both of these potential explanations, we investigated both vaccine efficacy and barriers to vaccination.

METHODS

We identified all cases of meningococcal disease that occurred in Gregg County from December 1993 through September 1995 by reviewing surveillance records of
ties among the electrophoretic types were at each of the 24 enzyme loci, and similarity defined as an electrophoretic type. An inability, and each unique set of alleles was identified by the Centers for Disease Control and Prevention, Atlanta, Ga., confirmed the identification and serogroup of N meningitidis isolated. Blood and cerebrospinal isolates, if available, were collected from each identified patient. The TDH provided information about the time and location of each vaccination campaign and the number of vaccine doses given.

Laboratory Testing
For each available isolate from a patient identified by surveillance, laboratories at the Centers for Disease Control and Prevention, Atlanta, Ga., confirmed the identification and serogroup and performed multilocus enzyme electrophoresis with 24 enzymes. Numbers were assigned to enzyme alleles on the basis of enzyme mobilities, and each unique set of alleles was defined as an electrophoretic type. An index of genetic relatedness was determined by weighing the degree of diversity at each of the 24 enzyme loci, and similarities among the electrophoretic types were assessed by dendrogram analysis.

Case-Control Study
We performed a matched case-control study to estimate the efficacy of the quadrivalent meningococcal polysaccharide vaccine against SCMD. For purposes of case-control study enrollment, a case patient was defined as a resident of Gregg County for at least 1 year, with SCMD confirmed by isolation of N meningitidis serogroup C from blood or cerebrospinal fluid or detection of N meningitidis serogroup C antigens by latex agglutination in cerebrospinal fluid.

Only case patients who were in an age group to which vaccination was offered were eligible for enrollment. This included all children aged 2 to 10 years after March 3, 1994, when vaccination campaigns targeting 2- to 10-year-olds were begun, as well as all persons aged 2 to 29 years after February 19, 1995, when vaccine was offered to 2- to 29-year-olds. The study was conducted during September 1995.

An eligible control patient was defined as a resident of Gregg County for at least 1 year who lived in the same neighborhood as the case patient and was appropriately age-matched to the patient. The control had to have lived in that neighborhood at least 1 month before the onset of disease in the patient and had to have been of the appropriate age to be eligible for vaccination during at least 1 of the vaccination campaigns. Time of residence in Gregg County was included as a requirement to provide an opportunity for case patients and control patients to become integrated into the community, learn of the outbreak, and be vaccinated. Control patients were matched to case patients using the following age groupings: 2- to 5-year-olds, 6- to 11-year-olds, 12- to 17-year-olds, and 18- to 29-year-olds.

We systematically selected control patients by identifying the residence of the case patient and then starting 3 houses to the right, asking if any of those household members were in the age range of the case patient. If 5 control patients could not be identified on the same block as the case patient's residence, investigators went from house to house in neighboring blocks. If the end of the neighborhood was reached before 5 control patients were identified, no further control patients were collected. If a potential control patient was identified but not enrolled on the initial visit, the household was revisited.

After obtaining informed consent, we interviewed each case patient and control patient (if younger than 18 years, a parent or guardian was interviewed) using a standard questionnaire. When a reference period was needed, we asked about the month preceding the onset of illness for case patients and about the same calendar month of illness in the matched control patients. To adjust for potential confounders of vaccine efficacy and to identify other potential risk factors for meningococcal disease, data were collected about age, sex, residence, family characteristics, medical history, active and passive smoke exposure, and exposures to large groups of people.

For purposes of estimating vaccine efficacy, we defined a vaccinated person as one who had received vaccine at least 2 weeks before the onset of illness in the case patient and a nonvaccinated person as one who either had not been vaccinated or who had received vaccine less than 2 weeks before the onset of illness. Vaccination status for all persons who reported being vaccinated was confirmed by (1) seeing the person's copy of the meningococcal vaccination consent form; (2) finding the person's name in the TDH vaccine campaign electronic database; (3) finding the TDH's copy of the consent form; or (4) contacting the private physician if the person said that they had been vaccinated by their physician. If none of these methods were successful, then the person was considered to have an unconfirmed vaccination status.

Barriers to Vaccination
Subjects enrolled in the control group for the vaccine efficacy study were used as a convenience sample of a population at high risk of disease to investigate potentially modifiable barriers to vaccination. In addition to information collected for the case-control vaccine efficacy study, control patients were asked about the meningococcal disease outbreak and vaccination campaigns, access to vaccination clinics, and perceptions about SCMD, issues that could affect vaccine coverage in the target population (Table 1).

Statistical Analysis
For measuring associations in univariate analyses to determine categorical variables, χ² or Fisher exact tests (when expected values in any cell were ≤5) were used. Continuous variables were separated into dichotomous categories on their median or a biologically relevant threshold level. Matched odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated using the proportional hazards regression procedure in SAS, version 6.11 (SAS Institute, Cary, NC). All test statistics were 2-tailed.

Matched ORs for the association of SCMD and vaccination with quadrivalent meningococcal vaccine were calculated using the methods described above. Vaccine efficacy was calculated by using the following equation: 1−(matched OR for vaccination). Adjusted vaccine efficacy estimates were calculated by creating separate bivariate models adding potential confounders and effect modifiers of the association between SCMD and vaccination and looking for meaningful changes in risk estimates. Potential confounders and effect modifiers included variables that were associated with SCMD or vaccination in univariate analyses and factors identified as confounders or effect modifiers in previous studies.

To identify risk factors for failure to receive meningococcal vaccine, the general-
RESULTS

Descriptive Epidemiology

Among Gregg County residents, 39 cases of meningooccal disease were identified between December 1993 and September 1995. In 31 cases, *N meningitidis* serogroup C was isolated from blood or cerebrospinal fluid; in 1 case, serogroup C antigens were detected by latex agglutination. Seven (22%) of the 32 case patients diagnosed as having SCMD died. *N meningitidis* serogroup B was isolated from 2 case patients, isolates from 3 case patients were not serogrouped, and 2 case patients were diagnosed by clinical syndrome alone.

The Figure shows the number of confirmed SCMD cases (n=32) by month of onset. From December 1993 to February 1994, 4 cases of SCMD occurred in children younger than 10 years. Based on 1993 US census data, the attack rate was estimated to be 21 cases per 100 000 children younger than 10 years, more than 40 times the endemic SCMD rate of 0.5 cases per 100 000 population per year. Because the quadrivalent meningooccal polysaccharide vaccine, Menomune (Connaught Laboratories, Swiftwater, Pa), has been shown to be less immunogenic in children younger than 2 years, the TDH began a vaccination campaign targeting children aged 2 to 10 years. Approximately 9600 children were vaccinated in 10 vaccination clinics in March and April 1994.

For a few months, the number of new cases decreased, but in late 1994 additional cases of SCMD occurred among children, adolescents, and young adults. As a result, in February 1995 a second vaccination campaign was initiated. This time the target age group was expanded to include 11- to 29-year-olds, among whom 15% of cases had occurred. By September 1995, despite vaccination of a total of 36 602 to 29-year-olds, 11 new cases had occurred in that age group since March 1995.

The 5 months preceding the first vaccination campaign (December 1993-April 1994), 5 (72%) of 7 cases occurred among 2- to 10-year-olds, and 1 (14%) of 7 occurred among 11- to 29-year-olds. In the 10 months between vaccination campaigns (April 1994-February 1995), 5 (42%) of 12 cases occurred among 2- to 10-year-olds, and 3 (25%) of 12 occurred among 11- to 29-year-olds. In the 7 months after the onset of the second vaccination campaign, 4 (31%) of 13 cases occurred among 2- to 10-year-olds, and 7 (54%) of 13 occurred among 11- to 29-year-olds.

In mid September 1995, after the conclusion of the case-control study, a third vaccination campaign was initiated; by December 1996, a total of 364 000 (>100% of the estimated target population) 2- to 29-year-olds were vaccinated. However, by December 1996, an additional 5 cases of SCMD occurred, suggesting that disease pressure persisted. Of these 5 case patients, 3 were in the vaccination target group, and 1, a 30-year-old, had been in the target group during the second vaccination campaign. None had been vaccinated.

Laboratory Results

A total of 24 of 29 SCMD isolates identified between December 1993 and September 1995 were electrophoretic type 24; the others were 2 subtypes identified as closely related to electrophoretic type 24, which is identical to the strain that caused outbreaks in Carroll County, Georgia, and eastern Canada. It is also responsible for approximately one half of 1996 serogroup C cases detected in active, population-based surveillance (Centers for Disease Control and Prevention, unpublished data, March 1997).

Case-Control Study of Vaccine Efficacy

Of the 32 persons identified with SCMD between December 1993 and September 1995, 5 were excluded from our analysis because they became ill before the first vaccination campaign and were, therefore, not eligible for vaccine. Of the remaining 27, 10 were not eligible because they were younger than 10 years (or 29 years) or younger than 2 years at the time of illness. The remaining 17 case patients (53%) who were eligible for vaccine at the onset of illness were enrolled along with 84 matched control patients (a mean of 5 control patients per case patient).

## Case Patients Aged 2-29 y

## Case Patients Aged <2 y and >29 y

Meningococcal serogroup C cases, by month of onset, Gregg County, Texas, from December 1993 to December 1996. The asterisk indicates a case patient aged 20 years.

Case patients did not differ significantly from control patients by age, sex, race, or income (Table 2). Two control patients reported taking antimicrobial chemoprophylaxis. Two case patients, aged 5 and 6 years, reported being vaccinated 15 and 14 months, respectively, before their illness, when they were aged 3 years 11 months and 5 years 4 months; in both instances, vaccination status was confirmed. Vaccination status was confirmed for 28 of the 36 control patients who reported being vaccinated.

In univariate matched analysis, maternal education of less than high school was a risk factor for SCMD. Of several behaviors that would expose an individual to large groups of people, none were associated with increased risk of SCMD. Both church attendance and day care attendance were protective. Church attendance was inversely related to socioeconomic status and smoking, although not significantly (data not shown).

The estimated vaccine efficacy among 2- to 29-year-olds was 85% (95% CI, 27%-97%). Among preschoolers aged 2 to 5 years, estimated vaccine efficacy was 93% (95% CI, 16%-99%). Our point estimate of vaccine efficacy did not change when adjusted for factors that were significant in univariate analysis, including maternal education of less than high school, passive smoke exposure, day care attendance, church attendance, or other variables that have been previously shown to be risk factors for meningooccal disease, including income, crowding, and underlying illness. Point estimates of vaccine efficacy were not substantially altered when the subjects whose vaccination status was not confirmed but who reported being vaccinated were excluded (vaccine efficacy, 82%; 95% CI, 0%-96%) or when the subjects who reported taking chemoprophylaxis were excluded (vaccine efficacy, 86%; 95% CI, 34%-97%).

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Table 3.—Characteristics of Nonvaccinated and Vaccinated Control Patients, Adjusted for Age*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nonvaccinated (n=17)</th>
<th>Vaccinated (n=23)</th>
<th>Matched Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5 (29)</td>
<td>12 (52)</td>
<td>0.6 (0.2-1.6)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (18)</td>
<td>10 (43)</td>
<td>0.9 (0.3-2.2)</td>
</tr>
<tr>
<td>Patients with income ≤$30,000 y</td>
<td>7 (41)</td>
<td>10 (43)</td>
<td>1.4 (0.6-3.0)</td>
</tr>
<tr>
<td>Households with ≥2 person sleeping in same room</td>
<td>5 (31)</td>
<td>25 (109)</td>
<td>1.0 (0.2-3.9)</td>
</tr>
<tr>
<td>Patients who were exposed to passive smoke‡§</td>
<td>5 (29)</td>
<td>14 (57)</td>
<td>1.0 (0.4-2.4)</td>
</tr>
<tr>
<td>Mothers who attended church or religious services‡</td>
<td>4 (24)</td>
<td>14 (57)</td>
<td>0.9 (0.4-2.1)</td>
</tr>
<tr>
<td>Mothers with education less than high school§</td>
<td>5 (29)</td>
<td>23 (51)</td>
<td>1.1 (0.4-3.1)</td>
</tr>
<tr>
<td>Patients who were aged 2-17 y: nonvaccinated, n=24; vaccinated, n=30.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients aged 2-17 y who were vaccinated‡¶</td>
<td>1 (6)</td>
<td>25 (64)</td>
<td>0.1 (0.0-1.2)</td>
</tr>
<tr>
<td>Patients who attended day care‡¶</td>
<td>2 (12)</td>
<td>36 (43)</td>
<td>0.2 (0.0-0.7)</td>
</tr>
<tr>
<td>Patients who lived in Gregg County, Texas, ≥2 y</td>
<td>2 (12)</td>
<td>36 (43)</td>
<td>0.2 (0.0-0.7)</td>
</tr>
<tr>
<td>Patients who hold a full-time job‡</td>
<td>4 (24)</td>
<td>14 (57)</td>
<td>0.9 (0.4-2.1)</td>
</tr>
<tr>
<td>Patients who watched television news once per week or less‡</td>
<td>2 (12)</td>
<td>36 (43)</td>
<td>0.2 (0.0-0.7)</td>
</tr>
<tr>
<td>Patients who were exposed to cigarette smoke§§</td>
<td>2 (12)</td>
<td>36 (43)</td>
<td>0.2 (0.0-0.7)</td>
</tr>
<tr>
<td>Patients who were aged 2-5 y who were vaccinated‡¶</td>
<td>1 (6)</td>
<td>25 (64)</td>
<td>0.1 (0.0-1.2)</td>
</tr>
<tr>
<td>Patients who received antimicrobial chemoprophylaxis</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0.0 (0-1.0)</td>
</tr>
</tbody>
</table>
| Patients who watched television news once per week or less‡ can be examined. A recently introduced polysaccharide-protein conjugate vaccine for Haemophilus influenzae type b eliminated carriage of the organism, reducing

Barriers to Vaccination

Age was strongly related to vaccine coverage. Among the 84 subjects, older age was strongly associated with nonvaccination. Vaccination rates among 2- to 4-year-olds, 5- to 18-year-olds, and 19- to 29-year-olds were 67%, 48%, and 20%, respectively (χ² for linear trend, P=.01).

Table 3 shows several potential barriers to vaccination, analyzed in bivariate analysis with age. Watching television news once per week or less was significantly associated with nonvaccination (OR, 5.3; 95% CI, 1.2-24.5), although 73% of nonvaccinated people did watch television. For children aged 2 to 17 years, a risk factor for nonvaccination was maternal education level of high school or higher (OR, 7.3; 95% CI, 1.0-56.2); maternal education of less than high school has previously been shown to be a risk factor for meningococcal disease.11,12 Access to vaccine, as indicated by the work schedule of the individual or the primary caretaker and distance to the vaccination center, was not associated with nonvaccination. Believe among case patients and primary caretakers that mortality from meningococcal meningitis was less than 15% as well as their beliefs about the protective efficacy and adverse effects of vaccine were not significantly associated with nonvaccination.
exposure of the at-risk population and “protecting” unimmunized persons (ie, herd immunity). In contrast, although 2 studies conducted among US Army recruits demonstrated decreased meningococcal carriage after group C vaccination,17,18 numerous other studies have failed to show a lasting effect of meningococcal polysaccharide vaccines on carriage.20-22 Furthermore, during recent outbreaks, the rate of carriage of the responsible strain was low.23 The invasive potential of the electrophoretic type 24 strain may result from enhanced ability to penetrate mucosal surfaces and invade the bloodstream rather than more efficient person-to-person transmission or increased mucosal colonization. The possible implication of this for vaccine use is not clear, but even a vaccine that could alter carriage might not offer a great advantage in control of outbreaks caused by this strain.

Serogroup C meningococcal conjugate vaccines that might provide herd immunity and prolonged protection for infants and children are currently undergoing ongoing human clinical trials.20 These vaccines may be incorporated into routine childhood immunization programs, changing the characteristics of SCMD outbreaks and altering our approach to their control. However, until that time, management of outbreaks should involve use of the currently available polysaccharide vaccine with the goal of vaccinating every person in the at-risk population.

To determine why cases continued to occur in Gregg County despite mass vaccination campaigns with an efficacious vaccine, we looked for factors predictive of nonvaccination. To investigate this, we used the control patients from the vaccine efficacy study who had been matched to case patients by age and neighborhood. Although not representative of the entire population, this group was considered to be at high risk for meningococcal disease. In the target population of 2- to 29-year-olds, older age was a risk factor for nonvaccination. Late cases tended to occur among the older age groups, who had lower vaccination coverage. During the Canadian mass immunization campaign in 1992, vaccination coverage was also lower among young adults: among 20- to 29-year-olds, coverage was 38%; among children aged 5 to 14 years, coverage was greater than 90%.17 In our study, other than the differences in vaccination rates by age, the nonvaccinated group was very similar to the vaccinated group. Although the methods of addressing these issues are not well standardized, we found that factors traditionally considered to be important programmatic concerns (eg, perception of disease and concern about adverse effects) were not significantly associated with vaccination. In contrast, a study in a university campus population in which a meningococcal vaccination campaign took place identified lower vaccination rates among older students. The study also found that both the perception of poor access to vaccination centers and the belief that the individual was at low or no risk of contracting meningitis were associated with nonvaccination.27 Further studies should focus on identifying the specific reasons why adolescents and young adults are less likely to get vaccinated to have more effective vaccination campaigns. Communicating information about high vaccine efficacy and the necessity for high vaccination coverage to stop outbreaks may gain additional support from health care workers, public health officials, and the public for vaccination campaigns. Estimating not only overall community vaccine rates but also age-specific rates may help to ensure that all targeted age groups are being reached.

Our study demonstrated that the currently available meningococcal polysaccharide vaccine provides a high level of protection in those immunized and is an effective public health tool for use in SCMD outbreaks. However, achieving optimal coverage in older age groups was problematic. When adolescents and young adults are within the target group for vaccination, special emphasis aimed at ensuring their participation is needed.

The authors thank Paul K. McEachin, DO, MPH, Harold Higgins, MS, Marietta Crowder, MD, and Jack Frost (all from Public Health Region 4/5 North, Texas Department of Health, Tyler); Diane Simons, PhD, Beverly Ray, RN, CSC, Kate Hendricks, MD, MPH, TM, Marvi Van Egdom (Texas Department of Health, Austin); Minda Weldon, PhD, Michael W. Reeves, PhD, and Gloria W. Ajello, MD (Centers for Disease Control and Prevention, Atlanta, Ga) for their assistance in planning and implementing this investigation, and Anne Schu- chat, MD (Centers for Disease Control and Prevention, Atlanta, Ga) for her thoughtful review of the manuscript.

References


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Meningococcal Vaccine—Rosenstein et al

JAMA, February 11, 1998—Vol 279, No. 6

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