MAJOR ARTICLES

Seroepidemiology and Chemoprophylaxis of Disease Due to Sulfonamide-Resistant Neisseria meningitidis in a Civilian Population

Allen B. Kaiser, Charles H. Hennekens, Milton S. Saslaw, Peggy S. Hayes, and John V. Bennett

An epidemic caused by group C sulfonamide-resistant Neisseria meningitidis occurred during an eight-month period in two lower socioeconomic communities in Dade County, Florida. Five of 85 close contacts of patients (5.9%) contracted meningococcal disease. Nasopharyngeal carriage and serologic evidence of meningococcal infection were significantly more frequent among close contacts than among controls in the neighborhood. The risk of meningococcal infection was found to be significantly greater for persons who shared five-person bedrooms than for those who slept in less crowded bedrooms. A trial was conducted with rifampin among close contacts of patients. Rifampin eradicated meningococcal carriage in 92% of the treated group, and rifampin-resistant strains did not emerge. The data indicate the need for chemoprophylaxis of all close contacts of persons with meningococcal disease without regard for the results of nasopharyngeal cultures. Casual acquaintances (such as schoolmates) were not found to need prophylactic therapy.

Neisseria meningitidis possesses the ability to cause outbreaks of life-threatening illness in otherwise healthy individuals [1-5]. Because of the dramatic swiftness with which meningitis or meningococcemia due to N. meningitidis can develop, considerable effort has been expended in development of preventive measures. Recently, the problem of prophylaxis has been complicated by the increase in prevalence of sulfonamide-resistant strains of N. meningitidis [6-8]. Studies in which serologic techniques have been used for identification of individuals susceptible to disease [9-13] and in which antibiotics and vaccines have been evaluated during meningococcal outbreaks [14-16] have involved military populations almost exclusively. However, an outbreak of disease caused by group C, sulfonamide-resistant N. meningitidis in two lower socioeconomic populations in Dade County, Fla. afforded the opportunity to study this disease in a civilian population. The susceptible population was delineated by epidemiologic and serologic means, and the prophylactic use of rifampin to eliminate carriage of sulfonamide-resistant strains during an epidemic in civilians was studied.

During the eight months from August 1, 1969 through April 1, 1970, 30 cases of meningococcal disease were reported in Dade County, Fla. Only 16 cases were expected for that period of time, based on the average reported attack rate of meningococcal disease in Dade County for the preceding 10 years. Seven of the nine isolates of blood or cerebrospinal fluid from the outbreak were identified at the Center for Disease Control as group C N. meningitidis and were resistant to $\geq 10 \mu g$ of sulfadiazine/ml. Fifteen of the 30
cases occurred in two widely separated, well-circumscribed, predominantly black, lower socioeconomic communities that comprised only 9% of the total population of the county. The cases outside of these two communities were widely scattered geographically, and no epidemiologic associations could be established among them. These cases were not included in the investigation of the outbreak involving the two communities.

The overall rate of attack for the two communities was 13 per 100,000, which was significantly higher than the overall attack rate for Dade County of 2.4 per 100,000 ($P < 0.01$). The case-fatality ratio was 33% (five of 15). The meningococcal etiology was confirmed in 12 patients by a positive culture of blood and/or cerebrospinal fluid. One patient had negative cultures, but intracellular gram-negative cocci were identified in the cerebrospinal fluid. The remaining two patients presented with the Waterhouse-Friderichsen syndrome, and each had one or more family members from whom group C $N. meningitidis$ was isolated on nasopharyngeal culture.

Individuals who frequently slept and ate in the same dwelling with index cases were defined as close contacts; all other acquaintances, such as schoolmates, neighbors, or relatives, were defined as community controls. Eighty-five close contacts were identified; 14 attended a day-care nursery, and 71 were household members of 11 families. A secondary case was defined as the onset of disease following known close contact with a person who was ill with meningococcal disease or who subsequently became ill. There was one secondary case in a day-care nursery contact, and four secondary cases occurred in members of three households. The rate of secondary attack among close contacts (5.9%) was significantly higher than the overall attack rate for the two communities (0.013%) and varied inversely with age, ranging from 25% for children less than one year old to 3.6% for children 10–19 years old (table 1). The high secondary attack rates and case-fatality ratios in the two communities prompted the intensive investigation described below.

### Materials and Methods

**Bacteriologic surveys.** Nasopharyngeal cultures were obtained from all available members of the 11 households and the day-care nursery (close contact cultures). Cultures were obtained in late February 1970, during the third week in March, weekly in April, and monthly thereafter through August 1970. In all, 80 close contacts and 10 convalescing patients within the two communities were cultured at least once, and the majority were cultured eight times.

During the third week in March, nasopharyngeal cultures were obtained from 267 students and six teachers at each of three grammar schools in the two communities. All available students and teachers from one classroom of the kindergarten, second, fourth, and sixth grades from the three schools were cultured. Of the 12 classrooms from which children and teachers were cultured, three were classrooms of patients, and one was the classroom of a household contact of a patient.

A day-care nursery with no cases of $N. meningitidis$ disease was located in one of the communities; nasopharyngeal cultures were obtained from seven members in March 1970.

Members of five households that were in the affected communities but had no cases of $N. meningitidis$ disease were also cultured. These households were all large and were located in close proximity to households with cases of meningitis and/or meningococcemia, and the children were frequent playmates of patients or close contacts of patients. Nasopharyngeal cultures of 36 members of these households were obtained at least once in April. The schoolmates, the members of the day-care nursery, and the members of the five neighborhood households constituted the 316 community controls.

All nasopharyngeal specimens were obtained orally with a bent cotton swab. The swabs were

### Table 1. Age-specific attack rates of secondary cases of disease caused by group C $N. meningitidis$ among close contacts in lower socioeconomic communities of Dade County, Florida (August 1, 1969–April 1, 1970).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. at risk</th>
<th>Cases</th>
<th>Secondary attack rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 1$</td>
<td>4</td>
<td>1</td>
<td>25.0</td>
</tr>
<tr>
<td>1–4</td>
<td>17</td>
<td>2</td>
<td>11.8</td>
</tr>
<tr>
<td>5–9</td>
<td>15</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>10–19</td>
<td>28</td>
<td>1</td>
<td>3.6</td>
</tr>
<tr>
<td>$\geq 20$</td>
<td>21</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>5</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Table 2. Results of initial nasopharyngeal cultures for group C Neisseria meningitidis in close contacts of patients with meningococcal disease and in community controls.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. close contacts cultured/no. positive (%)</th>
<th>No. controls cultured/no. positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–19</td>
<td>59/25 (42)</td>
<td>299/3 (1.0)</td>
</tr>
<tr>
<td>≥ 20</td>
<td>21/3 (14)</td>
<td>17/0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>80/28 (35)</td>
<td>316/3 (1.0)</td>
</tr>
</tbody>
</table>

Serologic studies. In early April 1970, sera for serologic testing were obtained from 107 persons: 49 community controls (14 members of the five neighborhood houses and 35 sixth graders at one of the grammar schools) and 58 close contacts. Additional sera were obtained from 43 close contacts in February, March, and late April. Sera were stored at −20°C for 30 min before testing. The indirect HA antibody test was performed by a previously described method [20]. Antigen of group C N. meningitidis was supplied by Dr. Malcolm S. Artenstein, Walter Reed Army Institute of Research. Hyperimmune group C antiserum and a known negative human serum were used as controls.

Results

Nasopharyngeal cultures. Of 80 close contacts of patients, 35% yielded group C N. meningitidis from the initial nasopharyngeal culture (table 2). In contrast, only three of 316 community controls (1.0%) had positive cultures. This difference was highly significant (P < 0.0001).

Because of the sampling difference between close contacts and community controls (an average of 6.3 vs. 1.1 cultures per person, respec-
Figure 1. Incidence and distribution of titers of hemagglutinating antibody to antigens of group C Neisseria meningitidis.

The close contacts of cases had titers $\geq 1:16$, whereas significant titers occurred in only 6.1% of the community controls ($P < 0.0005$). Although the numbers were small, the frequency of significant titers was higher in persons less than 20 years of age.

Only one of the three children under the age of five who were close contacts had a titer of $<1:16$ against group C N. meningitidis. This child had a negative nasopharyngeal culture and no detectable HA antibody during the initial survey of the community. Four weeks after the survey, she developed fulminant meningococcemia and died shortly after admission to a general hospital. Other siblings in the household had positive nasopharyngeal cultures during this interval.

Sleeping arrangements and meningococcal infection. The bacteriologic and serologic evidence of high infection rates among the close contacts compared with the rates among community controls prompted a retrospective analysis of the role of sleeping arrangements. Two questions were asked: (1) Were the rates of infection among close contacts associated with the presence of persons who developed meningococcal disease in the same bedroom? (2) Were the rates of infection related to the number of persons sleeping in a bedroom? There were 28 bedrooms in the 11 households of patients. One to five persons slept in each bedroom (average, three persons per room). In members of households in which the index case of disease occurred early in the epidemic, the frequency of positive cultures or significant titers was apparently not different from these values in others studied.

A person was judged to have been infected with group C N. meningitidis if (1) a nasopharyngeal culture was positive at any time for group C N. meningitidis, (2) a single sample of serum had a titer against group C of $\geq 1:16$, or (3) the person had had a proven case of disease due to group C N. meningitidis. Of the 82 household members present before the onset of the epidemic, a judgment could be made in 81; 44 of these 81 household members (54%) were found to have been infected.

The importance of sleeping in the same bedroom with one of the 11 index cases of disease was analyzed. Twenty-six persons routinely slept in the same bedrooms as the index cases; only 15 of these persons (58%) had evidence of meningococcal infection. This percentage was not significantly different from the infection rate of 41% among the 44 persons who did not sleep in the same bedrooms as the index cases ($P > 0.2$).

A significant association was noted, however, between the number of occupants of bedrooms ("crowding") and the proportion of persons infected (table 4). None of those sleeping alone was infected. Rates of infection increased with the increase in number of occupants of one bed-

### Table 3. Titers of hemagglutinating antibody to group C Neisseria meningitidis in close contacts of patients with meningococcal disease and in community controls.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. close contacts/ no. with titer of $\geq 1:16$ (%)</th>
<th>No. controls/ no. with titer of $\geq 1:16$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>38/20 (53)</td>
<td>47/3 (6.3)</td>
</tr>
<tr>
<td>$\geq 20$</td>
<td>20/3 (15)</td>
<td>2/0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>58/23 (40)</td>
<td>49/3 (6.1)</td>
</tr>
</tbody>
</table>
Table 4. Relationship of household sleeping arrangements and infection with *Neisseria meningitidis* in two lower socioeconomic communities of Dade County, Florida (August 1, 1969–April 1, 1970).

<table>
<thead>
<tr>
<th>No. of occupants per bedroom</th>
<th>All bedrooms</th>
<th>Bedrooms with occupants &lt; 20 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. occupants/ % infected (median age)</td>
<td>No. occupants/ % infected (median age)</td>
</tr>
<tr>
<td>1</td>
<td>2/0.0 (55)</td>
<td>0/ ...</td>
</tr>
<tr>
<td>2</td>
<td>11 22/36.4 (16)</td>
<td>9 12/58.3 (13)</td>
</tr>
<tr>
<td>3</td>
<td>6 18/38.8 (14)</td>
<td>6 12/50.0 (10)</td>
</tr>
<tr>
<td>4</td>
<td>5 19*/57.8 (9)</td>
<td>5 17/58.8 (7)</td>
</tr>
<tr>
<td>5</td>
<td>4 20/90.0 (11)</td>
<td>4 19/89.4 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>28 81*/53.1 (13)</td>
<td>24 60/66.7 (10.5)</td>
</tr>
</tbody>
</table>

* One person is omitted since insufficient data were available to determine whether he had been infected.

As noted earlier, the older close contacts were less likely to have titers \( \geq 1:16 \) and had a lower rate of positive cultures. Because adults in these households usually slept alone or in pairs, sleeping arrangements were analyzed for persons less than 20 years of age (table 4). In this younger group, a significant difference was noted only when bedrooms containing five persons were compared with those containing fewer than five. Seventeen of 19 persons less than 20 years of age (89.4%) in the five-person bedrooms were infected, but only 23 of 41 persons (56.1%) in smaller bedrooms were infected (\( P < 0.01 \)).

Information on which persons occupied the same bed was available for only 75% of the close contacts, so that the importance of bed occupancy could not be statistically tested. However, among the close contacts for whom data were available, infection rates varied from 31% among persons sleeping alone to 56% among persons sleeping two or more to a bed. More than 25% of the close contacts slept in beds with three or more occupants.

*Rifampin drug trial.* As a result of the high attack rate, excessive mortality, and the predominance of sulfonamide-resistant strains in the two communities, a trial with rifampin was initiated among 54 close contacts from the 11 households in April 1970. Close contacts over five years of age, excluding pregnant women, were considered eligible for participation in the drug trial. Thirty-five close contacts were randomly assigned by dice throw to a therapy category, and 19 were assigned to a control category. After culture of the nasopharynx, rifampin was given daily for four days in the fasting state under the direct supervision of a physician or nurse. Persons weighing \( \geq 66 \) lb received 600 mg/day, and persons weighing \( < 66 \) lb received 300 mg/day.

Nineteen persons in the study had positive nasopharyngeal cultures before institution of therapy (figure 2). After 27 days all of the six untreated carriers continued to have nasopharyngeal cultures positive for *N. meningitidis*. In contrast, 12 of 13 treated carriers were negative on the first culture (day 6) after therapy (eradication rate, 92%, \( P < 0.0005 \)). The one patient who, despite therapy, still had a positive culture on the sixth day, continued to yield group C *N. meningitidis* through the 27th day. His isolates, before and after therapy, were sensitive to \( < 0.12 \) µg of rifampin/ml, and all strains isolated during the study were sensitive to \( < 0.5 \) µg/ml. During the study 11 of the 13 treated carriers were at risk of reinfection from a household contact who had a positive nasopharyngeal culture. After completion of the drug trial, no additional cases of disease were reported in 1970 among the 36 “susceptible” (titers \( < 1:16 \)) close contacts of cases.

**Discussion**

Identification of contacts at high risk has proven difficult in outbreaks of meningococcal disease among civilians, although numerous studies, including this one, have stressed the high rate of secondary attack among household members, especially the younger members. From 0.7% to 16% of members of households with one index case have developed meningococcal meningitis and/or meningococcemia [4, 21–24]. However, secondary attack rates among contacts outside of the household have been less completely studied. The importance of day-care nurseries is apparent from these data, and day-care nurseries have been noted previously to be a significant source of spread [25]. The rate of nasopharyngeal carriage by members of the involved nursery approximated the rate of carriage by household contacts of cases.

In contrast to these findings within the nursery, a remarkably low carriage rate was found among grammar school contacts, including the kinder-
Figure 2. Effect of rifampin on carriage of Neisseria meningitidis on various days after treatment. All patients except no. 68 and 109 were exposed to at least one persistent household carrier of group C N. meningitidis during the period of study. (□) = negative culture; □ = positive culture; □ = no culture; ◊ = N. meningitidis of a different strain from that originally carried.

garten contacts. One previous study of nasopharyngeal carriers within public schools also revealed a low carriage rate (6%) among schoolmates of a case [3]. Similarly, casual contacts, such as neighborhood playmates, did not experience secondary disease or high carriage rates in either this study or a previous one [25]. In addition, a study of the transmission of disease within a hospital revealed that hospital contacts had no increased carriage of the infecting strain [26].

The information currently available suggests that all household contacts of cases and all other individuals experiencing prolonged intimate contact with cases should be considered to be at increased risk of disease. Primary attention should be directed towards the younger contacts. On the other hand the data presented here suggest that, for other casual contacts within the community, such as schoolmates or playmates, chemoprophylaxis is not warranted.

Crowding within the sleeping quarters of close contacts was associated with increased carrier rates, when crowding was defined in terms of number of persons per bedroom. Although room measurements were not available and thus crowding could not be defined in terms of cubic feet of space per person, it was apparent that severe spatial crowding did exist in many of these lower socioeconomic houses. Four or five persons often occupied the same bedroom, and 25% of the close contacts slept three or more to a bed. It is probable that the primary mode of transmission of N. meningitidis is contact spread, such as by large drops that travel less than three feet through the air and by direct person-to-person contact [16, 27, 28]. The severe degree of crowding noted
Civilian Meningococcal Disease among the close contacts may have been important in facilitating such contact spread of *N. meningitidis*. Severe crowding was also of significance in the epidemic of meningococcal disease in Chile in 1941 [22] and among British troops during World War I [29]. In the latter study, meningococcal carrier rates in the crowded sleeping quarters approached those of our study only when the British soldiers slept on cots 2.5 feet wide and less than 9 inches apart. Although the authors of several studies among American military populations concluded that there was no correlation between crowding of sleeping quarters and carrier rates, severe crowding (sufficient to provide contact spread) was not present in these studies [16, 30]. In regard to sleeping arrangements, it was of interest that the presence of a case vs. a carrier in a bedroom did not increase the probability of infection among other persons in that room. This is at variance with the previous finding of a higher infectivity rate for cases vs. carriers [31].

In this study of the efficacy of rifampin in eliminating the carrier state, a success rate of 92% was noted, and resistant strains could not be isolated, even from the single treatment failure. However, rifampin-resistant strains have been isolated from carriers within military populations, and resistant strains might be expected to appear during chemoprophylaxis among civilians if this drug is more widely used [32–34].

In considering the high correlation between positive nasopharyngeal cultures and titers \( \geq 1:16 \), the close contact whose cultures are negative may be the person at highest risk in the household. The fulminating course of the young close contact with negative cultures and a titer of \( < 1:16 \) illustrates the point. Culture of close contacts seems to be of little value in routine prophylaxis, and chemotherapy should therefore be aimed at all close contacts of cases.

References


