Space-time cluster analysis of invasive Meningococcal disease
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Clusters are recognized when meningococcal cases of the same phenotypic strain (markers: serogroup, serotype, and subtype) occur in spatial and temporal proximity. The incidence of such clusters was compared to the incidence that would be expected by chance by using space-time nearest-neighbor analysis of 4,887 confirmed invasive meningococcal cases identified in the 9-year surveillance period 1993–2001 in the Netherlands. Clustering beyond chance only occurred among the closest neighboring cases (comparable to secondary cases) and was small (3.1%, 95% confidence interval 2.1%–4.1%).

An outbreak of invasive meningococcal disease is a public health emergency because of the disease’s unpredictability, sudden lethality, and serious sequelae. Although risk factors are known, the reasons for developing invasive disease are not fully understood. Most persons, when colonized with Neisseria meningitidis, become asymptomatic carriers and are sources for further transmission. The apparently sporadic occurrence of invasive disease reflects invisible transmission chains of circulating strains, since invasive disease develops in only a small proportion of those infected. The precise mechanisms generating clusters or outbreaks puzzle public health workers, epidemiologists, and microbiologists (1,2).

During the 9-year period 1993–2001, the Netherlands had a population between 15.3 and 16 million and encompassed 33,900 km². Most of the 500 annual reports of meningococcal disease were sporadic cases, and serogroup B is the most common. From 1993 to 2001, the number of reported cases was from 422 to 770 per year; the peak occurred in 2001 as a result of an increase in serogroup C meningococcal cases. The mean incidence, based on reports of =3.4 per 100,000 per year, is comparable to that in England and Wales (3.7) (3) but three times higher than in the United States (1.1) (4). The Dutch policy for preventing secondary cases compares to the policy in most Western countries and is based on identifying and prophylactically treating close contacts. When two or more possibly related cases (secondary case or cluster) are identified, group contacts in an educational institution (daycare center or primary school) also receive prophylaxis with rifampicin. In the Netherlands, routine vaccination of children for serogroup C meningococcal disease was implemented in September 2002. Furthermore, from June to October 2002, a vaccination campaign was carried out for all 1- to 18-year-olds in response to the increase of serogroup C cases in 2001 and 2002.

Outbreaks are recognized when place (e.g., an educational institution like a primary school), time (e.g., within 1 month), and conventional phenotypic markers (same serogroup, serotype, and subtype) make a connection likely (field cluster) or when an excess of incidence (e.g., 20x normal) is noticed in a retrospectively specified geographic or population area within a chosen period (community outbreak). Field clusters and community outbreaks are rarely seen in the Netherlands, possibly because of underreporting. A group of unrelated cases that occur in temporal and spatial proximity may be misinterpreted as a cluster or outbreak, but these cases would not justify additional public health measures, except perhaps to reassure the public. In a real cluster, cases of the same strain occur in temporal and spatial proximity at a higher frequency than by chance. The objective of our study was to explore the phenomenon of meningococcal clustering in a more objective way by using a nearest-neighbor analysis in space and time that compares the actual occurrence of clusters with their background incidence.

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¹Deceased January 24, 2004.
Patients and Methods

Data Collection

We used data collected from two surveillance sources: mandatory reports from January 1993 through May 2001 and reports of laboratory-confirmed N. meningitidis isolates collected by the Netherlands Reference Laboratory for Bacterial Meningitis in the same period. Additionally, reports of field clusters occurring during the same time were collected as reference.

Reported Cases

Report data were obtained from the Inspectorate of Health Care. According to the Communicable Disease Act, physicians must report cases of meningococcal disease to their Municipal Public Health Service. The case definition for report includes clinical meningococcal disease in combination with microbiologic confirmation: N. meningitidis isolated from blood or cerebrospinal fluid (CSF); meningococcal antigen or DNA detected in cerebrospinal fluid by latex agglutination or polymerase chain reaction; or gram-negative diplococci detected in cerebrospinal fluid, blood, or skin biopsy. The following information was available on an individual level: date of birth, gender, initials, postal code, municipality, date of report, date of first symptoms, date of diagnosis, and age at notification.

Laboratory Isolates

The reference laboratory collects meningococcal strains from patients with meningitis or septicemia, isolated from blood or CSF. Strains are sent on a voluntary basis to the reference laboratory by all clinical microbiologic laboratories throughout the country. A strain is defined as an isolate of N. meningitidis from a patient. When two strains have the same phenotypic markers (serogroup, serotype, and subtype), these are considered to be identical and to belong to one serosubtype. The following information was available for individual patients: date of birth, gender, initials, municipality, date of sample collection, submitting laboratory, date of receipt of strain, date of blood culture, date of lumbar puncture, source of isolate (blood or CSF), serogroup, serotype, and subtype.

Record Linkage

Records between these two sources were linked (case ascertainment) by using SAS version 8.1 (SAS Institute Inc., Cary, NC). First, records were linked by date of birth, gender, and initials. Records remaining unlinked were then linked by combinations of two variables. The links in the first step were considered correct, while all further links were checked manually for consistency in data fields, spelling mistakes in initials, date of birth, and municipality. In Table 1, we provide an overview of the number of cases and serogroup profile of the data used in our analysis.

Field Cluster

After notification of meningococcal disease, the Municipal Public Health Service considers taking public

| Table 1: Overview of meningococcal disease cases and serogroup profile of cases included for analysis, 1993–2001 |
|----------------------------------|------|------|------|------|------|------|------|------|------|------|------|
| Reported cases (per 100,000 pop) | 563  | 422  | 460  | 482  | 491  | 505  | 531  | 516  | 770  | 4,740 |
| Case-ascertainment (per 100,000 pop) | 753  | 571  | 689  | 659  | 658  | 704  | 597  | 532  | 396  | 5,559 |
| Nonconfirmed cases               | 115  | 91   | 88   | 94   | 103  | 86   | 44   | 1    | 41   | 663   |
| Meningococcal cases included for analysis | 638  | 480  | 601  | 565  | 555  | 619  | 553  | 354  | 4,886 |

Serogroup profile

A (%) 3 2 2 0 2 0 2 0 2 0 7
B (%) 524 399 527 498 458 536 455 413 229 4,039
(82) (83) (88) (88) (83) (87) (82) (78) (65) (82)
C (%) 101 65 57 57 81 72 79 103 114 729
W135 (%) 4 (1) 5 (1) 7 (1) 3 (1) 6 (1) 4 (1) 12 (2) 12 (2) 7 (2) 60 (1)
X 1 0 0 1 1 2 1 1 1 0 7
Y 4 5 5 6 2 5 6 3 39
Z 0 0 1 0 0 0 0 0 0 2 3
29E 0 0 2 0 1 0 1 0 0 0 4
Not serogroupable 1 2 2 0 0 2 1 0 0 8

*Case-ascertainment (number of cases after linking procedure) was hampered due to lack of identifying variables from April 1, 1999, when the new Dutch Communicable Disease Act was introduced.

Laboratory data included from January 1993 to May 2001; during the year 2001, the surveillance was more active because of the increase in serogroup C cases.

After linking the reported cases with the laboratory cases, no strain was available for these cases.

Of 4,896 confirmed cases, 9 could not be used in the analysis because of recording errors: 2 serogroup A cases, 4 serogroup B cases, 1 serogroup C, 1 serogroup W135, and 1 serogroup Y.
Cluster Analysis of Invasive Meningococcal Disease

Results

During the 9-year surveillance period, 4,896 confirmed cases were noted. Of these, nine cases could not be used because of recording errors (Table 1). The dataset was made up of 250 different meningococcal serosubtypes, of which 42 were seen in 20 or more cases (4,189/4,887 = 86% of all strains), while 99 serosubtypes were only connected to one case (Appendix online, available from http://www.cdc.gov/ncidod/eid/vol10no9/03-0992_app.htm).
The observed background value of cases in temporal and spatial proximity to an index case being of the same serosubtype is 12.0%. When random labeling was used, this percentage was 9.7%. We observed that 15.1% of the first nearest-neighbors were of the same serosubtype, an excess probability or secondary case percentage of 3.1% (CI 2.1%-4.1%). As most nearest-neighbors are coincidental, little difference was seen in the mean temporal and spatial distance between nearest-neighbors of the same serosubtype (6.1 km [range 0-44 km] and 13.2 days [range 0-63 days]) and those of different serosubtype (7.6 km [range 0-49 km] and 14.3 days [range 0-380 days]). The probability of the second, third, fourth, and fifth nearest-neighbors being of the same serosubtype did not differ significantly from background values (this difference was 0.6%, 0.3%, 0.8%, and 0.4%, respectively). For serogroup B, the excess probability was 3.1% (CI 2.0%-4.3%, n = 4,035) for the first nearest-neighbor. For serogroup C, the excess probability was 3.5% (CI 1.6%-5.3%; n = 728), and for serogroup W135 no excess probability was found (n = 59). Seven different serosubtypes, accounting for 14% (694/4,887) of all cases, showed significant excess probability (Table 2): B:1:P1.4 (12%), B:1:P1.16 (10%), B:4:P1.5 (20%), B:4:P1.10 (5%), B:nt:P1.nt (11%), B:15:P1.7 (11%), and B:15:P1.7,16 (7%).

The Municipal Public Health Services identified 40 field clusters involving 21 different serosubtypes: 11 primary school clusters (range 2-5 cases), 7 daycare center clusters (2-3 cases), 1 swimming pool cluster (4 cases), and 21 household clusters (2-3 cases). The cases all occurred within 21 days from the first case, and 78% (32/41) occurred within 8 days.

Six serosubtypes were identified by both methods as serosubtypes with clustering, 15 were identified only in field clusters, and 1 in statistical clustering only. Most field clusters consisted of only two cases (75%); this result is consistent with the results of our statistical approach.

**Discussion**

Our results suggest that in the context of current public health efforts, clustering of meningococcal disease is rare in the Netherlands and other Western countries. Our nearest-neighbor analysis provided a useful method of assessing the phenomenon of meningococcal clustering by taking random variance into account. Cases of the same serosubtype appeared beyond the expected background rate and were only seen in the first nearest-neighbor, which implies that only secondary cases occur in excess of chance (3.1%). Connections of more than two cases could not be demonstrated beyond chance. Throughout the year, invasive disease appears mostly as isolated cases. This limited clustering may reflect the positive effect of the prophylactic rifampicin policy; however, household field clusters are still reported, which possibly shows the constraints of this prevention policy. This paucity of real secondary cases is consistent with findings from other studies. A Belgian study found 4.4% secondary cases (range 2.0%-5.2%) in 1,913 cases of invasive meningococcal disease from 1971 through 1976 (7). In France, 37 (4.5%) co-primary and secondary cases were found in 814 reported cases from 1997 to 1988 (8). A Dutch study reported 1.4% co-primary and secondary cases among 507 cases from 1989 to 1990 (9). In England and Wales, 17 (0.5%) secondary cases were found among 3,256 cases from 1984 through 1987 (10). In a Danish study published in 2000, 1.2% secondary cases were observed in 172 cases of meningococcal disease (11).

Apart from proper prophylactic treatment, no additional measures could prevent further cases, since excess clustering only occurs in the first nearest-neighbors, while a cluster is only identified after at least two connected cases. The field cluster analysis confirms this assessment, since most new cases occur within a short period (78% within 8 days), occur geographically close to each other (patients are in the same household, daycare center, or primary school), and occur mostly in pairs (75%). These findings are consistent with observations in field cluster studies showing that secondary invasive disease most likely occurs nearby, within the next few days. In a Belgian study, 83% of 63 secondary cases occurred within 8 days of identifying the index case (7); in a French study, 31
Table 2. Clustering of meningococcal disease cases by serosubtype (serogroup, serotype, and subtype)*

<table>
<thead>
<tr>
<th>Serosubtypes (phenotype)</th>
<th>Field clusters</th>
<th>Cases/cluster</th>
<th>% excess probability</th>
<th>95% CI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>B:1:P1.4</td>
<td>1 Primary school</td>
<td>3</td>
<td>12.0</td>
<td>4.2%—19.7%</td>
<td>87</td>
</tr>
<tr>
<td>B:1:P1.14</td>
<td>1 Swimming pool</td>
<td>3</td>
<td>7.2</td>
<td>NS (−0.4% to 22.4%)</td>
<td>25</td>
</tr>
<tr>
<td>B:1:P1.16</td>
<td>1 Primary school</td>
<td>2</td>
<td>10.0</td>
<td>2.4%—17.8%</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>1 Daycare center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 Household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:4:P1.2,5</td>
<td>1 Household</td>
<td>2</td>
<td>1.9</td>
<td>NS (−3.8% to 7.7%)</td>
<td>52</td>
</tr>
<tr>
<td>B:4:P1.4</td>
<td>2 Primary schools</td>
<td>3 and 5</td>
<td>2.0</td>
<td>NS (−0.7% to 4.6%)</td>
<td>1,376</td>
</tr>
<tr>
<td></td>
<td>4 Primary schools</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Daycare centers</td>
<td>2 and 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 Households</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:4:P1.5</td>
<td>1 Daycare center</td>
<td>2</td>
<td>20.0</td>
<td>3.2%—36.9%</td>
<td>25</td>
</tr>
<tr>
<td>B:4:P1.7</td>
<td>NFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:4:P1.9</td>
<td>1 Primary school</td>
<td>2</td>
<td>7.2</td>
<td>NS (−8.0% to 22.4%)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>NFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:4:P1.14</td>
<td>1 Household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:4:P1.15</td>
<td>NFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:4:P1.16</td>
<td>1 Household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:4:P1 NT</td>
<td>1 Primary school</td>
<td>2</td>
<td>2.2</td>
<td>NS (−2.4% to 6.8%)</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>1 Daycare center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 Household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:NT:P1.14</td>
<td>2 Households</td>
<td>2 and 3</td>
<td>13.0</td>
<td>NS (−19.9% to 27.9%)</td>
<td>23</td>
</tr>
<tr>
<td>B:NT:P1.15</td>
<td>1 Household</td>
<td></td>
<td>7.2</td>
<td>NS (−17.7% to 16.0%)</td>
<td>39</td>
</tr>
<tr>
<td>B:NT:P1.16</td>
<td>1 Household</td>
<td></td>
<td>10.0</td>
<td>NS (−4.4% to 24.4%)</td>
<td>20</td>
</tr>
<tr>
<td>B:NT:P1 NT</td>
<td>1 Household</td>
<td></td>
<td>10.7</td>
<td>4.7%—16.8%</td>
<td>123</td>
</tr>
<tr>
<td>B:14:P1.4</td>
<td>1 Daycare center</td>
<td></td>
<td>0.9</td>
<td>NS (1.4% to 12.2%)</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>1 Household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:15:P1.7</td>
<td>NFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B:15:P1.7,16</td>
<td>1 Primary school</td>
<td>2</td>
<td>6.8</td>
<td>1.4%—12.2%</td>
<td>109</td>
</tr>
<tr>
<td>B:15:P1.9</td>
<td>1 Household</td>
<td>2</td>
<td>10.0</td>
<td>NS (−14.4% to 21.4%)</td>
<td>30</td>
</tr>
<tr>
<td>B:16:P1.14</td>
<td>1 Household</td>
<td>2</td>
<td>—</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>B:16:P1.2,5</td>
<td>1 Daycare center</td>
<td></td>
<td>13.6</td>
<td>NS (−1.9% to 29.2%)</td>
<td>22</td>
</tr>
<tr>
<td>C:2a:P1.2,5</td>
<td>1 Household</td>
<td>2</td>
<td>−1.0</td>
<td>NS (−5.4% to 3.4%)</td>
<td>164</td>
</tr>
<tr>
<td>C:NT:P1.5</td>
<td>NFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C:14:P1 NT</td>
<td>1 Household</td>
<td>2</td>
<td>10.0</td>
<td>NS (−4.4% to 24.4%)</td>
<td>20</td>
</tr>
</tbody>
</table>

*The following results are shown: serosubtypes with reported field clusters, serosubtypes with significant excess probability for clustering by nearest-neighbor analysis, and serosubtypes with nonsignificant excess probability of more than 3% (bold: percentages significant).

†Cl. confidence interval; NT, not typable; NS, not significant.

‡NFC, no field cluster was reported for this serotype.

§Calculating excess probability not possible because n is too small.

(82%) of 38 secondary cases occurred within 8 days (8). Almost all (94%, 29/31) of the secondary cases occurred within 8 days in a study in the United States from 1980 to 1993 with eight school and university clusters (12). Five secondary cases occurred within 8 days in a school outbreak of six cases with serogroup B meningococcal disease in the United States (13).

Space-time clustering methods, e.g., those using the spatial scan-statistic (14–17), have been used for surveillance purposes with the objective of identifying outbreaks. However, to our knowledge, such methods have not been used to explore the existence of, and quantify, the phenomenon of clustering in a specific infectious disease. For this purpose the Ederer-Myers-Mantel procedure has been used (18,19); however, since this method requires separating space and time (e.g., into provinces and years), we considered it inappropriate for our purposes. Instead, we adapted the concept of nearest-neighborship to the two dimensions of space and time simultaneously (5,6).

Our study has several constraints. As many serosubtypes were rare, their individual clustering behavior could not be fully ascertained. We used place of residence as our geographic parameter, which could underestimate clustering, since transmission might occur at locations outside place of residence (such as work, school, and sport clubs). Most cases are found in children, who often spend time in daycare centers, schools, and other places outside the home. Since these places tend to be located in the same area as their homes, this factor likely did not affect our results. The extent of clustering was possibly overestimated because of imprecise geographic coordinates since our statistical method used the center of the municipality or postal code...
area, but no more precise alternative is available. Since only phenotypic strain typing was conducted (serogroup, serotype, and subtype) and not the more sensitive porA-
genotyping method that would have identified spurious
clusters, background rates of clustering may have been
overestimated. However, this method is unlikely to have
affected the excess probability (3.1%) of clustering, since
this rate is probably a result of direct transmission. Our
method for calculating background value was chosen to be
as realistic as possible; however, our results do not appear
to be sensitive to the choice of 6th to 10th nearest-neigh-
bors as a reference. For instance, results from 3rd to 10th
nearest-neighbor or 7th to 10th nearest-neighbor, as a refer-
cence, were virtually identical.

We believe that our low observed incidence of second-
ary cases partly reflects the general inability to link cases
connected by chains of transmission. As disease develops
in only a few of the links in a chain of transmission, con-
nected cases are unlikely to be still temporally and spatial-
ly close, which obviates detection. Not surprisingly, we
found three times as many serosubtypes among reported
field clusters (21 serosubtypes) than assessed with nearest-
neighborship analysis (7 serosubtypes), which confirms
that field clusters may be spurious. Although field clusters
have low specificity, their sensitivity is presumably high.
Genotyping can identify those clusters brought about by
direct transmission; nevertheless, the value of cluster sur-
veillance as a means of prevention is uncertain. Apparent
clusters are not valuable to guide additional intervention
efforts, since these would prevent few additional cases.
Our method of space-time nearest-neighbor analysis
provides a sensitive novel approach to the epidemiology of
meningococcal disease and possibly even other infectious
diseases.

Dr. Hoebe is a consultant on communicable disease control
and a member of the National Working Party for Infectious
diseases, the Netherlands. His research interests focus on out-
break investigation.

References


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