Household Outbreaks among Culture-confirmed Cases of Bacterial Gastrointestinal Disease

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To examine the general frequency of household outbreaks, the authors performed a retrospective search among cases of the five most frequent gastrointestinal bacterial pathogens in Denmark, a country of 5.3 million inhabitants. This was done for 57,667 cases registered from 1991 to 2001 by finding all cases that shared addresses and became infected within 3 weeks of one another. The percentage of cases that were part of household outbreaks was found to be 3.2% for Campylobacter, 13.3% for Salmonella serotype Enteritidis, 5.6% for Salmonella serotype Typhimurium, 2.0% for Yersinia enterocolitica, and 10.4% for Shigella sonnei. The vast majority of the outbreaks had not previously been registered. The wide variation in the ability to cause household outbreaks among the different types of bacteria reflects differences in their epidemiology and most likely also mirrors their overall outbreak potential. Differences in the time occurring between infections of household members may also indicate differences in the importance of person-to-person transmission for the different types of bacteria. The fact that household outbreaks occur with a relatively high frequency may be utilized in future analyses of sources of infection, in particular of Campylobacter, for which more household outbreaks than expected were identified.

Campylobacter coli; Campylobacter jejuni; diarrhea; gastroenteritis; Salmonella enterica; Shigella sonnei; Yersinia enterocolitica

Food-borne bacterial gastrointestinal disease has been recognized as an increasing public health problem in most Western countries throughout the last two decades. The incidence of Salmonella and Campylobacter infections, in particular, has increased severalfold in many countries, prompting research into the epidemiology of these bacteria (1–3). The investigation of outbreaks has been pivotal to understanding the routes of infection of gastrointestinal bacteria. This has been the case with Salmonella, in particular, because outbreaks occur frequently and because outbreak strains are readily distinguishable by sero-, phage-, or other subtyping methods. In the case of Campylobacter infections, relatively few outbreaks are known. Indeed, the great majority of cases are believed to be sporadic (4) and, if outbreaks occur, they are difficult to identify because simple, discriminatory, and cost-efficient subtyping methods for Campylobacter are not available.

Because outbreaks are typically discovered through their size, small outbreaks tend not to be noted, and to what extent they occur is not well known. Theoretically, however, small outbreaks are likely to occur more frequently than outbreaks involving a large number of persons. Such outbreaks would be expected to be especially prolific in families or among other groups of people living together because they would often be exposed to the same risk factors. Although of less epidemiologic value than large-size outbreaks, the registration of household outbreaks is still of importance. They may, if they occur frequently, point to the sources of infection or they may sometimes reveal larger outbreaks.

In Denmark, over the past decade, the five most frequent bacterial agents of gastrointestinal disease were Campylobacter, Salmonella serotype Enteritidis, Salmonella serotype Typhimurium, Yersinia enterocolitica, and Shigella sonnei. Campylobacteriosis has quadrupled since 1992 to an incidence of 87 per 100,000 inhabitants in 2001 (5, 6) and has been the leading cause of bacterial gastroenteritis since 1999. Consumption of poultry is a principal source of these infections, but other sources probably also contribute (4, 6). S. Enteritidis with chicken eggs and S. Typhimurium with poultry and pork meat as the primary sources of infections

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have to a large degree been controlled through intervention strategies to reduce the prevalence of salmonella in broilers, pigs, and laying hens (7). Human salmonellosis has been declining for several years, and the incidence in 2001 was 27 cases per 100,000 persons for S. Enteritidis and 11 per 100,000 for S. Typhimurium (6). The incidence of Y. enterocolitica has fallen steadily throughout the period and was five cases per 100,000 persons in 2001. The primary source of these infections is believed to be pork, but the reasons for the decline in the number of cases are not well understood (6). Finally, Sh. sonnei gave rise to three cases per 100,000 persons in 2001. Cases are primarily travel related or linked to food imported from tropical regions (5).

In the present study, we determine the proportion of shared addresses among persons with bacterial gastrointestinal infection and estimate the number of household outbreaks. We used cases registered from January 1991 to May 2002 of the five most frequent bacterial causes of gastrointestinal disease in Denmark. The number of outbreaks found differed widely among the different types of bacteria, reflecting the differences in epidemiology of these pathogens.

MATERIALS AND METHODS

Bacterial isolation and typing

From 1991 to 2002, the diagnosis of enteric bacterial pathogens in Denmark was performed at the Statens Serum Institut or at 10 regional clinical microbiology laboratories (8). Campylobacter isolates were identified to the genus level only (9). They were almost exclusively Campylobacter jejuni and Campylobacter coli, with C. jejuni comprising about 94 percent (10). Salmonella isolates were serotyped according to the Kauffmann-White serotyping scheme (11). In addition, phage typing (12, 13) was carried out on all isolates of S. Typhimurium from 1998 to 2002 and on 25 percent of S. Enteritidis isolates from 1998 and 1999 and 50 percent of S. Enteritidis isolates from 2000 to 2002. Yersinia and Shigella isolates were serotyped as described by Denka Seiken Co., Ltd. (Tokyo, Japan).

Registration of cases

Since 1991, cases of laboratory-confirmed bacterial gastrointestinal disease in Denmark have been registered in a central database at the Department of Gastrointestinal Infections, Statens Serum Institut. Cases are listed by their Civil Registration System number (Central Person Registration number). This is a unique identifier assigned to all Danish residents (14). Furthermore, cases are recorded as episodes; the same person positive for a particular pathogen will be registered only once within a 180-day period.

Register of addresses

All addresses in Denmark are given a unique code, the address identification code. It consists of a number identifying the municipality, a number identifying the street name, the street number, and a code identifying the individual compartments in multistory buildings. The address identification code is linked to the Central Person Registration numbers of the residents in the Civil Registration System. All Danish residents are required by law to notify the Civil Registration System of their address within 5 days of changing it.

In the study period, the number of Danish residents varied between 5.1 and 5.4 million (15). As an example of the distribution of household sizes, an inquiry into the Civil Registration System revealed that on January 1, 2000, there were 5,349,991 registered Danish residents occupying 2,445,724 registered addresses. At 99 percent of these addresses, the household consisted of eight or fewer persons. At 17 percent of the addresses there was only one occupant; at 30 percent, two occupants; at 17 percent, three occupants; at 22 percent, four occupants; at 9 percent, five occupants; at 3 percent, six occupants; and at 0.8 percent and 0.4 percent, seven and eight occupants, respectively.

Linkage of address codes to the registered patient episodes

Between January 1, 1991, and May 31, 2002, a total of 58,759 registered episodes of Campylobacter (26,781 episodes), S. Enteritidis (17,301 episodes), S. Typhimurium (8,325 episodes), Y. enterocolitica serotype O3 (4,798 episodes), and Sh. sonnei (1,440 episodes) were recorded. Of these, 58,645 (99.8 percent) contained a full Central Person Registration number, and address identification codes were successfully ascribed to 57,667 (98.3 percent). Addresses were sought at the time of infection, defined as the date 14 days prior to the date of receiving the sample in the laboratory.

Statistical analyses

Estimates of the probability of selecting the same address more than once when randomly picking a given number of Danish residents were obtained empirically. This was done by random selection of persons from the Civil Registration System at a fixed date. For each round of selection, the number of times any address was hit two times or more was registered. The selection did not take account of the age distribution or other demographic parameters of the population. The number of persons selected was the number of eligible cases for each of the bacteria types, and the date used was January 1, 2000. The selection process was iterated 1,000 times for each of the five types of bacteria. Further iterations did not change the estimates. All analyses were done using statistical software from the SAS Institute, Inc. (Cary, North Carolina).

RESULTS

Table 1 details the number of cases with known addresses and the percentage thereof that shared addresses with one or more other cases. The cases sharing addresses are divided into groups depending on the time between the dates of infection (at any time relative to each other, within 6 weeks, 3 weeks, or on the same day). The proportion of cases that shared addresses and became infected within 3 weeks of one another
TABLE 1. Percentage of cases that shared an address with one or more other cases, Denmark, 1991–2001

<table>
<thead>
<tr>
<th>Bacteria type</th>
<th>Total no. of cases</th>
<th>% of cases sharing addresses divided into time between submission of the positive samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>At any time*</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>26,479</td>
<td>4.8</td>
</tr>
<tr>
<td>Salmonella Enteritidis</td>
<td>16,955</td>
<td>14.2</td>
</tr>
<tr>
<td>Salmonella Typhimurium</td>
<td>8,158</td>
<td>7.2</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>4,682</td>
<td>3.0</td>
</tr>
<tr>
<td>Shigella sonnei</td>
<td>1,393</td>
<td>11.9</td>
</tr>
</tbody>
</table>

* Pairs of cases who shared an address but not at the time of infection, as well as persons who were infected more than once and lived at the same address, are not included.

The majority of cases sharing households and their relation to outbreaks

As table 1 shows, the majority of cases that shared households submitted the positive sample for bacteriologic examination within a few weeks of one another and, in fact, many of these submitted the sample on the same day. This strongly indicates that these cases were part of household outbreaks, that is, became infected from the same source.

The clustering in time may be seen more clearly from table 2. Here, the percentage of cases sharing households is broken down into ten time windows of 1 week each, depending on the time between infection dates of the cases. The table shows that the number of cases that shared households went down steeply as the time separating infection dates increased. The clustering of cases at the same addresses was most pronounced within the first week and almost absent after 3 weeks. However, this varied among the different types of bacteria. There was generally a longer time separating the infection dates of S. Typhimurium cases than of S. Enteritidis cases. Thus, for cases that shared households and became infected within 6 weeks of one another, the median number of days between submissions was 0 days for S. Enteritidis cases and 7 days for S. Typhimurium cases. Likewise, a relatively large proportion of Sh. sonnei cases submitted samples with a separation in time of 2 weeks or more, and the median number of days was 6 days within the 6-week window. The relative distribution per week of cases that shared households and became infected within 6 weeks of one another is shown in table 3.

To further corroborate the idea that cases registered within a narrow time span and sharing addresses were part of household outbreaks, salmonella subtyping data were compared. We examined the instances in which cases belonged to the same household and became infected within 6 weeks of one another, and in which the phage type information was available for the Salmonella isolates. Phage types of S. Typhimurium could be compared for 77 households and were identical for 74 of these. Phage types of S. Enteritidis could be compared for 80 households and were identical for 78. In the five instances where the phage types did not match, the typing procedure was repeated with the same result. Direct interviews of the cases were then undertaken. These indicated that the cases belonging to the same households had been infected on the same occasions (data not shown). Therefore, the different phage types most likely resulted from mixed infections with different Salmonella types.

Finally, the number of occupants living at the addresses shared by cases infected within 6 weeks of each other was determined. This was done by looking up each of the addresses in the Civil Registration System. Hereby, it was shown that there was not an overrepresentation of rare households with an atypically high number of occupants among these addresses (data not shown).

TABLE 2. Percentage of cases that shared addresses divided into the number of weeks between submitting the positive sample of any two cases, Denmark, 1991–2001

<table>
<thead>
<tr>
<th>Bacteria type</th>
<th>&lt;1 week</th>
<th>1–2 weeks</th>
<th>2–3 weeks</th>
<th>3–4 weeks</th>
<th>4–5 weeks</th>
<th>5–6 weeks</th>
<th>6–7 weeks</th>
<th>7–8 weeks</th>
<th>8–9 weeks</th>
<th>9–10 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>2.53</td>
<td>0.46</td>
<td>0.20</td>
<td>0.11</td>
<td>0.08</td>
<td>0.04</td>
<td>0.02</td>
<td>0.02</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Salmonella Enteritidis</td>
<td>10.27</td>
<td>2.20</td>
<td>0.78</td>
<td>0.17</td>
<td>0.07</td>
<td>0.08</td>
<td>0.04</td>
<td>0.04</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Salmonella Typhimurium</td>
<td>2.94</td>
<td>1.95</td>
<td>0.74</td>
<td>0.43</td>
<td>0.34</td>
<td>0.05</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>1.41</td>
<td>0.47</td>
<td>0.13</td>
<td>0.13</td>
<td>0.00</td>
<td>0.04</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Shigella sonnei</td>
<td>6.10</td>
<td>2.94</td>
<td>1.36</td>
<td>0.36</td>
<td>0.43</td>
<td>0.43</td>
<td>0.14</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
In table 4, the data are arranged by clustering addresses rather than patients. It shows the number of addresses where two or more different cases lived, divided into groups depending on the time between the dates of infection. Within the 3-week window, the number of address clusters almost exclusively denotes household outbreaks. In contrast, the majority of address clusters consisting of cases who were infected more than 6 months apart may be expected to have arisen by chance.

Estimates for how often cases would share an address assuming they were sporadic and all fell ill on the same day were obtained via the Civil Register by repeatedly looking up a random subset of persons corresponding to the number of cases. The estimates and their 95 percent confidence intervals are also shown in table 4. For *Sh. sonnei* and both *Salmonella* serotypes, these estimates are consistent with the idea that infections separated by more than 6 months at the same address occurred simply by chance. However, in the cases of *Campylobacter* and *Y. enterocolitica*, there was more than the expected number of addresses shared by cases infected more than 6 months apart.

### Yearly number of household outbreaks

Finally, figure 1 compares the total number of patient episodes having known addresses with the number of household outbreaks each year for each type of bacterium. The outbreaks are calculated as addresses shared by cases registered within 3 weeks of one another. As seen from the figure, the number of cases of household outbreaks was more or less proportional to the total number of cases. During most years, *S. Enteritidis* accounted for more outbreaks than the other four types in combination, but it was surpassed by *Campylobacter* in the years 2000 and 2001.

### DISCUSSION

Using a simple but novel approach we have estimated the number of household outbreaks occurring among laboratory-confirmed cases of the most frequent agents of bacterial gastroenteritis in Denmark. This was done by determining all the addresses of the cases and by identifying the households in which more than one person lived. For the majority of cases who shared households, the dates of infection were separated by only a small number of days. This fact strongly indicates that these cases were part of household outbreaks, since it is highly unlikely that they shared households by coincidence.

A surprisingly large number of household outbreaks were identified, of which the majority had not previously been noticed. For example, for the years 2000 and 2001, we uncovered 168 *Campylobacter* household outbreaks (data not shown), while only eight outbreaks were reported to the

### TABLE 3. Distribution in percentage of cases per week that shared addresses and submitted a positive sample within 6 weeks of one another, Denmark, 1991–2001

<table>
<thead>
<tr>
<th>Bacteria type</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>74.0</td>
<td>13.5</td>
<td>5.8</td>
<td>3.1</td>
<td>2.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Salmonella Enteritidis</td>
<td>75.7</td>
<td>16.2</td>
<td>5.8</td>
<td>1.2</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Salmonella Typhimurium</td>
<td>45.6</td>
<td>30.2</td>
<td>11.4</td>
<td>6.7</td>
<td>5.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>64.7</td>
<td>21.6</td>
<td>5.9</td>
<td>5.9</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Shigella sonnei</td>
<td>52.5</td>
<td>25.3</td>
<td>11.7</td>
<td>3.1</td>
<td>3.7</td>
<td>3.7</td>
</tr>
</tbody>
</table>

### TABLE 4. Number of address clusters within different time windows, Denmark, 1991–2001

<table>
<thead>
<tr>
<th>Bacteria type</th>
<th>No. of address clusters divided into time periods separating infection of cases</th>
<th>Expected no. of random clusters*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 0–3 weeks Within 4–6 weeks Within 7 weeks–6 months Within 7 months–11.4 years</td>
<td>No. 95% CI†</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>412 30 30 234 (134)‡</td>
<td>140 117, 163</td>
</tr>
<tr>
<td>Salmonella Enteritidis</td>
<td>991 22 23 43 (29)</td>
<td>54 41, 68</td>
</tr>
<tr>
<td>Salmonella Typhimurium</td>
<td>216 33 11 22 (26)</td>
<td>14 8, 22</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>47 4 3 17 (3)</td>
<td>6 2, 11</td>
</tr>
<tr>
<td>Shigella sonnei</td>
<td>65 8 1 2 (0)</td>
<td>0 0, 2</td>
</tr>
</tbody>
</table>
Veterinary and Food Administration in this period (6, 16). Similarly, for S. Enteritidis, S. Typhimurium, Y. enterocolitica, and Sh. sonnei, this analysis identified 110, 34, four, and eight household outbreaks, respectively, in these 2 years. Of these, only three of the S. Enteritidis outbreaks were registered (6, 16). Thus, this study shows that family or household outbreaks are frequently occurring phenomena and much more frequent than indicated by the reported number of household outbreaks. This may well be the situation in many other countries in addition to Denmark and, in fact, this analysis is likely to underestimate the real percentage of cases that are part of household outbreaks. The number of registered laboratory-confirmed cases has been found to be severalfold lower than the number of actual cases of bacterial gastroenteritis in the community (17, 18), and the less cases registered the lower is the chance that more than one case in a household outbreak will be registered.

The fraction of cases that were part of household outbreaks varied widely among the different types of bacteria. The tendency to cause household outbreaks was low for Campylobacter and in particular for Y. enterocolitica, while it was intermediate for S. Typhimurium and high for Sh. sonnei and S. Enteritidis. This tendency remained fairly stable from year to year even though the overall incidence of the bacteria changed. The different tendencies to cause household outbreaks reflect differences in the epidemiology of the bacteria, such as differences in the sources and vehicles of infection. Most likely they also mirror the overall outbreak potential, that is, the tendency to cause larger outbreaks as well.

In the case of Campylobacter this may be of interest. We found that more than 3 percent of the registered Campylobacter cases were part of household outbreaks. Although 3 percent may sound modest, Campylobacter accounted for more household outbreaks than did S. Enteritidis in 2000 and 2001 because of the relatively high overall incidence of Campylobacter in these years. Assuming that household outbreaks and large outbreaks share common causes and that these causes are behind the increase in household outbreaks, we anticipate that more large-size outbreaks than expected may also occur. Moreover, household outbreaks may sometimes be part of other larger outbreaks, for instance, outbreaks at social gatherings or general outbreaks. Setting up an early warning system based on tight clustering of cases in geography and time may help to identify larger outbreaks that otherwise would not be noticed and that, in turn, may help to cast light on the routes of infection of this pathogen. To set up such systems would be feasible in countries where surveillance for campylobacteriosis includes timely information on single cases and their addresses. In addition, the household outbreaks could be investigated as soon as they occur. Although standard analytical epidemiologic methods such as case-control and cohort investigations have limited statistical power in these situations, a series of structured interviews of members of families where two or more persons have been ill may reveal information on relevant exposures.

The different tendencies to cause household outbreaks were most pronounced in the case of the two different Salmonella serotypes. S. Enteritidis gave rise to a substantial number of household outbreaks, more than the four other types of bacteria combined, and more than twice as many S. Enteritidis cases as S. Typhimurium cases were involved in household outbreaks. This corresponds well with the gener-
ally known high outbreak potential of *S.* Enteritidis. For instance, in the United States from 1988 to 1996, *S.* Enteritidis accounted for a little more than half of all *Salmonella* outbreaks but only one fifth of the number of registered cases, a little fewer than for *S.* Typhimurium (19). The difference in the number of household outbreaks may be explained by the different sources of infection of the two serotypes. The major source of *S.* Enteritidis infections is chicken eggs (20), whereas the sources of *S.* Typhimurium infections in Denmark were primarily pork and poultry (6). Many dishes in the Danish cuisine contain raw or undercooked eggs but not undercooked pork or poultry meat. In addition, *S.* Enteritidis may multiply in many of the dishes containing raw or undercooked eggs, and by pooling eggs, several people may be infected from a single contaminated egg.

Another aspect concerns the time separating the infection dates of cases in a household outbreak. These periods of time varied among the different types of bacteria and, in the case of *Sh. sonnei* and *S.* Typhimurium, relatively more household outbreaks took place in which the cases submitted the positive sample more than 1 week apart from each other. As for *Sh. sonnei*, it seems likely that this is due to person-to-person spread. Unlike that of the other pathogens we studied, secondary transmission of *Sh. sonnei* is thought to occur frequently because of its relatively low infectious dose. More surprisingly, the data may also indicate that person-to-person spread plays an important role in the transmission of *S.* Typhimurium, as has also previously been suggested (21). Alternatively, though probably less likely, such cases may be part of larger general outbreaks and, although infected from the same source (e.g., contaminated pork), not infected at the exact same occasion and time.

For both *Campylobacter* and *Y. enterocolitica*, more cases than expected acquired the infection while living at the same address as another case but with the infections separated in time by more than 6 months. In addition, a relatively high number of *Campylobacter* cases became infected twice while living at the same address. This raises the possibility that some addresses may constitute or be part of geographic areas carrying an increased risk for infections with *Campylobacter or Y. enterocolitica*, as would be the case if the infections were transmitted through the environment, for example, through drinking water or pet animals. However, several other possible explanations also exist. Some households may be more at risk than others as a result of underlying illness, dietary habits, or poor kitchen hygiene. In addition, a past episode of a diagnosed gastrointestinal infection in a family may well increase the likelihood of seeing a physician if a member of the same family develops similar symptoms. Which of these explanations are more likely remains to be investigated.

In summary, this analysis identified a large number of hitherto overlooked household outbreaks among registered cases of the most frequent pathogenic gastrointestinal bacteria. The degree to which the different types of bacteria caused household outbreaks varied widely, reflecting differences in the routes of infection and possibly in the overall outbreak potential. In addition, the time occurring between the infection dates of the cases who were part of household outbreaks indicated varying levels of importance of person-to-person transmission among the different types of bacteria. The existence of these many small outbreaks may be used in future outbreak analyses.

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