Risk Factors for the Occurrence of Sporadic *Salmonella enterica* Serotype *typhimurium* Infections in Children in France: A National Case-Control Study

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To determine risk factors for the occurrence of sporadic *Salmonella typhimurium* infections among children in France, we conducted a matched case-control study. Cases were identified between 15 June and 30 September 1996. We interviewed 101 pairs of case patients and control subjects, matched for age and place of residence. The risk of illness was greater for children who ate undercooked ground beef than for those who did not (odds ratio [OR], 5.0; 95% confidence interval [CI], 1.9–13.1). Case patients were more likely than control subjects to have taken antibiotics during the month before onset of disease (OR, 2.2; 95% CI, 1.0–4.9).

Case patients <5 years of age were more likely to have been in contact with a household member with diarrhea 3–10 days before onset (*P* = .05). Consumption of undercooked ground beef is a risk factor for the sporadic occurrence of *S. typhimurium* infection among children, and antibiotics may facilitate the occurrence of illness. The possibility of person-to-person transmission among young children needs to be considered.

Nontyphoidal *Salmonella* are among the main causes of foodborne diseases in the Western world [1]. Between 1994 and 1997 the number of isolates of *Salmonella enterica* serotype *typhimurium* (*S. typhimurium*) from humans steadily increased in France, and *S. typhimurium* has become the commonest serotype isolated in human cases [2]. An increase of infections due to *S. typhimurium* definitive type (DT) 104 specifically has also been observed over recent years in other European countries [3].

Unlike *Salmonella enteritidis*, which is mainly associated with poultry and eggs, *S. typhimurium* can be found in a broad range of foodstuffs. It is the most frequent serotype among *Salmonella* isolates from beef products as well as from pork and pork products [4]. Several outbreaks of *S. typhimurium* food poisoning associated with beef have been reported [5, 6]. However, the food items implicated in outbreaks of *S. typhimurium* infections are not necessarily those responsible for sporadic cases. In response to concern about the rise in the number of isolates of *S. typhimurium* serotype, we conducted a study of sporadic cases to determine whether this increase could be related to risk factors such as the consumption of specific food items.

**Subjects and Methods**

We used a matched case-control study design. A sporadic case was defined as the occurrence (from 15 June through 30 September 1996) of fever (temperature >38°C) or diarrhea (≥3 loose stools per day for ≥1 day) in a child ≤14 years old who resided in metropolitan France (i.e., the European territory of the French republic; overseas districts and territories excluded), in association with the isolation of *S. typhimurium* from stool or blood.

Case patients were identified weekly by a review of isolates received by the National Reference Centre for *Salmonella* and *Shigella* (NRC). The NRC receives *Salmonella* isolates for serotyping from between one-third to one-half of the 4000 French microbiology laboratories. The laboratories that send *Salmonella* isolates to the NRC are equally distributed throughout the districts of France (data not shown). Case patients who were part of a recognized outbreak (defined as at least 2 cases linked to the same meal in the same household or institution) were excluded. The information routinely collected for each isolate received at the NRC allowed us to identify such outbreaks and to exclude them.

Control subjects were matched to case patients according to age (in 3 age groups: <1, 1–5, and 6–14 years) and place of residence. For each case patient, a child of the same age group and the same city or county (in rural areas) of residence who had had no gastrointestinal symptoms during the month before onset of the case patient’s illness was sought by the case patient’s physician to serve as a control subject. The physician was asked to select the first patient to meet the above-mentioned criteria. When control subjects could not be located by the physician, they were sought from the Minitel electronic telephone directory in a manner equivalent to random-digit dialing by area of residence [7].

The investigator (not blinded to the case/control status) inter-

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Consent to participate in this study was obtained from the physician and the parents of each case patient and control subject.

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viewed parents of case patients and control subjects by telephone, using a pretested, standardized questionnaire. All data were made anonymous after the completion and validation of questionnaires, before they were entered into the computer. In addition to information on symptoms and demographic characteristics, the questionnaire sought information from the month before onset of the case patient’s illness with regard to the following exposures: consumption, purchase, storage, and preparation habits for various food items such as eggs and egg products, poultry, beef (e.g., for ground beef, the extent to which it was cooked and consumed in dishes such as bolognaise and shepherd’s pie), and shellfish; contact with persons who had diarrhea (before [3–10 days before] the case patient’s date of onset or around the same time [2 days before to 2 days after onset]); and attendance at a day-care facility or nursery. Information was also collected on underlying conditions, use of medications such as antibiotics in the month before disease, and the presence of a pet at home.

In order to detect an OR of 2.5 with 25% exposure among control subjects (α, 5%; β, 80%), a sample size of 94 pairs of case patients and control subjects was required; we therefore planned to enroll 100 case patients and control subjects.

Analysis was done with Epi-Info version 6 (Centers for Disease Control and Prevention, Atlanta) for single-variable analysis. We analyzed categorical data by calculating univariate matched odds ratios and their 95% CIs. Statistical significance was assessed by McNemar’s χ² test for dichotomous variables and the matched t-test for continuous variables. Exposures found to be associated with illness by univariate analysis (P < .2) were included in a conditional logistic-regression model (EGRET statistical software;Statistic and Epidemiology Research, Seattle). The final model was obtained through stepwise deletion of variables; variables were retained in the final model on the basis of statistical and epidemiological criteria [8].

Results

Of the 497 patients age ≤14 years for whom an isolate of S. typhimurium had been recorded by the NRC during the study period, 189 were chosen at random, of which 27 were excluded for the following reasons: delay between diagnosis and serotyping of >1 month (n = 1), lack of symptoms (n = 3), residence or travel outside metropolitan France (n = 9), and physician refusal (n = 8). Of the remaining 162, 101 were enrolled, yielding a participation rate of at least 62% (101 of 166; the parents of 1 case patient refused to be interviewed, and the physician and/or case patient could not be identified or contacted in 60 case patients). Patients included in the case patient group were similar to those not included with regard to geographic distribution, age group, and hospitalization (data not shown). Case patients included were from throughout France. All except 1 of the included case patients had loose stools, 84% had a temperature >38°C, and 33% had vomiting. Diarrhea lasted 2–30 days (median, 7 days). Twenty-four (23.8%) of 101 case patients was admitted to the hospital.

Questionnaires were completed for 101 case patients and 101 control subjects. Eighty-seven control subjects were selected from among patients of the case patient physicians, and 14 were selected from the Minitel electronic telephone directory. Therefore, the analysis was done on 101 case-control pairs: 11 in the age group of <1 year, 77 in the age group of 1–5 years, and 13 in the age group of 6–14 years. Case patients and control subjects did not differ in terms of sociodemographic characteristics (rural vs. urban environments and occupations of parents [data not shown]).

Food consumption and cooking habits. Fifty-four percent of the case patients and 52% of the control subjects had meals outside their homes (P = .8). Seventy-nine percent of the case patients and 83% of the control subjects reported eating ground beef (P = .5). Among those who ate ground beef, there was a 5-fold greater risk of illness (95% CI, 1.9–13.1) from eating raw or undercooked ground beef than from eating well-done ground beef, particularly in the age group of 1–5 years (table 1). Twenty-eight percent of the case patients and 49% of the control subjects reported eating ground beef (OR, 0.3; 95% CI, 0.2–0.7). Case patients were more likely than control subjects to have consumed ground beef purchased frozen (OR, 2.3; 95% CI, 0.9–6.1).

Ninety-three percent of the case patients and 98% of the control subjects reported eating chicken (P = .2). Among children who ate chicken, there was no large difference between eating chicken that was not well done (OR, 1.5; 95% CI, 0.3–9.0; table 1) and eating chicken that was bought ready to eat (OR, 0.8; 95% CI, 0.4–1.6; table 1). In addition, 58% of the case patients and 31% of the control subjects reported eating chicken sausages (OR, 5.0; 95% CI, 1.1–22.8; table 1).

Eighty-nine case patients (88%) and 90 control subjects (89%) ate eggs (OR, 0.9; 95% CI, 0.3–2.4). As for a previous study [7], we summarized the exposure to raw eggs and to food containing raw or lightly cooked eggs as a composite, unique variable. Among case patients and control subjects who ate eggs, 24 case patients (27%) and 43 control subjects (48%) reported eating raw eggs or food containing raw or lightly cooked eggs (OR, 0.4; 95% CI, 0.2–0.8). Eleven percent of the case patients and 23% of the control subjects ate bivalve mollusks (oysters or mussels; OR, 0.4; 95% CI, 0.2–0.9). Case patients were more likely than control subjects to have eaten raw-milk Camembert (OR, 3.3; 95% CI, 0.9–12.1).

Other exposures. Case patients and control subjects did not differ with regard to underlying conditions, recent use (in the previous month) of medications such as antacids, or immunosuppressive therapy. However, case patients were more likely than control subjects to have been treated by antibiotics in the previous month (OR, 2.2; 95% CI, 1.0–4.7). The type of antibiotics was known for 23 of 26 case patients and included amoxicillin (n = 9), amoxicillin and clavulanic acid (n = 4), cephalosporin (n = 4), penicillin V (n = 2), and macrolides (n = 4). Fifty-five percent of the case patients and 50% of the control subjects had a pet at home (P = .5).

Person-to-person transmission. For 9 case and 1 control
subject, at least 1 household member or a close contact had diarrhea 3–10 days before the onset of the case patient’s symptoms (P = .03; table 2). These contacts were a family member (78%), someone at the place of care (nursery or day-care facility; 11%), or another contact (11%).

Multivariate analysis. The following variables were included in the initial model: use of antibiotics in the previous month, consumption of raw or undercooked ground beef, consumption of dishes containing thoroughly cooked ground beef, consumption of chicken sausages, consumption of raw-milk Camembert, consumption of raw eggs or food containing raw or lightly cooked eggs, and consumption of bivalve molluscs. In the final model only the consumption of raw or undercooked ground beef (OR, 3.8; 95% CI, 1.7–8.4), antibiotic use in the month before the date of onset of symptoms (OR, 2.3; 95% CI, 1.0–5.5), and consumption of foods containing thoroughly cooked ground beef (OR, 0.4; 95% CI, 0.2–0.8) remained independently associated with S. typhimurium infection.

Discussion

This is the first reported nationwide study of the risk factors associated with sporadic S. typhimurium infections in France. Very few similar studies of this emergent Salmonella serotype have been reported in the literature [9, 10]. This study showed that sporadic S. typhimurium infection was independently associated with the consumption of undercooked ground beef and that antibiotic use before the infection may facilitate such infection. Since type 104 is the S. typhimurium phage type most frequently isolated in France (~70%) [11], it is probable that most of the strains isolated from the case patients belonged to this phage type. Therefore, we assumed that our findings could be extrapolated to sporadic DT 104 S. typhimurium infection in France.

Eating raw ground beef had been implicated as the source of an outbreak in the United States [6], and in France, a community outbreak of S. typhimurium infection has also been caused by ground beef (Institut de Veille Sanitaire, Saint-Maurice, unpublished data, December 1999). Cattle are a reservoir of S. typhimurium, which is the Salmonella serotype most often recovered from beef and dairy herds [12]. Raw-milk cheese has also caused a community-wide outbreak of S. typhimurium infection in France [13]. However, a large case-control study of infection with S. typhimurium DT 104 in England and Wales did not find an association between infection and beef consumption, but methods of cooking beef at home were not recorded [10]. Another study of sporadic cases in the United States failed to demonstrate an increased risk associated with eating hamburgers but suggested the role in infection of consuming undercooked eggs [9].

The univariate analysis suggested a protective effect with regard to several exposures (consumption of raw eggs, food containing raw or lightly cooked eggs, or dishes containing thoroughly cooked ground beef). However, only thoroughly cooked dishes containing ground beef remained a statistically significant protective factor in the multivariate analysis. The negative association between consumption of raw eggs, consumption of bivalve molluscs, and S. typhimurium infection in univariate analysis may illustrate an information bias. Our experience [7] indicates that many parents are aware of the risk of gastroenteritis posed by the consumption of these foods and may answer that they did not serve these foods, even though they might have done so.

Because S. typhimurium is ubiquitous and has been isolated from domestic animal species and from their environments, it is possible that other vehicles of sporadic S. typhimurium infection were missed in our study. Indeed, S. typhimurium outbreaks have been linked with various food items such as chicken.

Table 1. Characteristics of children infected with Salmonella typhimurium and control subjects (101 matched case-control pairs) with regard to food consumption and antibiotic use in the month before onset (France, 1996).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>Matched OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken, bought ready to eat</td>
<td>17/94 (18.1)</td>
<td>21/98 (21.4)</td>
<td>0.8</td>
<td>0.4–1.6</td>
</tr>
<tr>
<td>Raw-milk Camembert cheese</td>
<td>16/55 (29.1)</td>
<td>11/63 (17.5)</td>
<td>3.3</td>
<td>0.9–12.1</td>
</tr>
<tr>
<td>Raw or undercooked ground beef</td>
<td>37/73 (50.7)</td>
<td>14/72 (19.4)</td>
<td>5.0</td>
<td>1.9–13.1</td>
</tr>
<tr>
<td>Age &lt;1 y</td>
<td>1/4 (25.0)</td>
<td>0/4 (0.0)</td>
<td>3.0</td>
<td>0.6–14.9</td>
</tr>
<tr>
<td>Age 1–5 y</td>
<td>30/57 (50.8)</td>
<td>12/58 (20.7)</td>
<td>6.3</td>
<td>1.9–21.4</td>
</tr>
<tr>
<td>Age 6–14 y</td>
<td>6/12 (50.0)</td>
<td>2/12 (20.0)</td>
<td>3.0</td>
<td>0.6–14.9</td>
</tr>
<tr>
<td>Dishes containing thoroughly cooked ground beef</td>
<td>26/92 (28.3)</td>
<td>43/87 (49.4)</td>
<td>0.3</td>
<td>0.2–0.7</td>
</tr>
<tr>
<td>Chicken sausages</td>
<td>24/41 (58.5)</td>
<td>16/51 (31.4)</td>
<td>5.0</td>
<td>1.1–22.8</td>
</tr>
<tr>
<td>Raw eggs or food containing raw or lightly cooked eggs</td>
<td>24/89 (27.0)</td>
<td>43/90 (47.8)</td>
<td>0.4</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Antibiotics taken in the previous month</td>
<td>26/101 (25.7)</td>
<td>14/101 (13.9)</td>
<td>2.2</td>
<td>1.0–4.7</td>
</tr>
</tbody>
</table>

NOTE. Data are no. of children positive/no. examined or questioned (%).

a Among the children who ate chicken (94 case patients and 98 control subjects).

b Among the children who ate Camembert (55 case patients and 64 control subjects; for 1 control subject, the type of Camembert was unknown).

c Among children who ate ground beef (73 case patients and 72 control subjects).

d Undefined.

e Among children who ate poultry (41 case patients and 51 control subjects).

f Among children who ate eggs (89 case patients and 90 control subjects).
Table 2. Onset of diarrhea in household members and/or close contacts of children infected with Salmonella typhimurium and of control subjects (France, 1996).

<table>
<thead>
<tr>
<th>Age group, onset of diarrhea in household member or close contact(s)</th>
<th>Case patients (n = 101)</th>
<th>Control subjects (n = 101)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>9 (8.9)</td>
<td>1 (1.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Same time</td>
<td>10 (9.9)</td>
<td>0 (0.0)</td>
<td>.0004</td>
</tr>
<tr>
<td>None</td>
<td>82 (81.2)</td>
<td>100 (99.0)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Same time</td>
<td>2 (18.2)</td>
<td>0</td>
<td>.5</td>
</tr>
<tr>
<td>None</td>
<td>9 (81.8)</td>
<td>11 (100.0)</td>
<td></td>
</tr>
<tr>
<td>1–5 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>8 (10.4)</td>
<td>1 (1.3)</td>
<td>.05</td>
</tr>
<tr>
<td>Same time</td>
<td>7 (9.1)</td>
<td>0</td>
<td>.02</td>
</tr>
<tr>
<td>None</td>
<td>62 (80.5)</td>
<td>76 (98.7)</td>
<td></td>
</tr>
<tr>
<td>1–14 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>1 (7.7)</td>
<td>0</td>
<td>.3</td>
</tr>
<tr>
<td>Same time</td>
<td>1 (7.7)</td>
<td>0</td>
<td>.3</td>
</tr>
<tr>
<td>None</td>
<td>11 (84.6)</td>
<td>13 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of children. Before, 3–10 days before onset of case patient’s diarrhea; same time, 2 days before to 2 days after onset of case patient’s diarrhea.

*Matched P value; McNemar χ² test.

b Reference.

bought ready to eat (in France [14]), salami (in northern Italy [15]), cold roast pork (in northern England [16]), and sliced cooked ham [17]. Exposure to some of these foods might be either very rare or very common in the general population and therefore might be difficult to detect in a case-control study in which only exposures associated with markedly elevated relative risk are sought.

Our findings also suggest that children who had used antibiotics during the month before onset were more likely to be ill than those who had not. Several mechanisms could explain this finding: antimicrobial exposure might increase the susceptibility to Salmonella by altering the colonic bacterial flora [18, 19], or receiving medications such as antibiotics might just be a marker of increased susceptibility to infections in general. A response bias is also possible: although the questionnaire addressed the use of antibiotics in the month before illness, case patients might have included in their answer the treatment prescribed for the episode of S. typhimurium infection.

Earlier case-control studies of sporadic salmonella infection did not mention the use of antibiotics as a potential risk factor [9, 10, 20–23]. These studies were mainly targeted to adults. One study of S. enteritidis sporadic infections in children that involved similar methodology and a comparable statistical power did not indicate any relation between antibiotics and S. enteritidis infection [7]; however, this serotype is not known to exhibit antimicrobial resistance. In a large milkborne outbreak of antimicrobial-resistant S. typhimurium infections, it was shown that the illness was associated with use of antimicrobials in the month before [24]. Thus, antibiotic use may facilitate salmonella infection differently, according to the serotype involved.

Our study also suggests that person-to-person transmission accounts for a subset of the youngest case patients. Person-to-person transmission of Salmonella has not been implicated often in the past and has been reported mainly with regard to nosocomial infections [25]. In another study of S. enteritidis sporadic infections in children in France, we also showed that transmission of S. enteritidis from a household member or a contact was not rare for younger children [7].

The participation rate of ~60% may have affected the representativeness of our results. Parents of case patients may better recall exposure in the month before onset than parents of control subjects, and the fact that the interviewer was not blinded to the case/control status could have contributed to an information bias. However, the questionnaire was designed to minimize this problem. Food histories assessed for the month before the onset of the case patient’s illness correspond more with food preferences than with exposure to specific foods. We preferred this approach because children’s food habits do not vary much over time. Our results cannot be extrapolated to adults, but the main objective was to assess the risk factors among children, especially young ones, who are much more susceptible than adults to salmonella infection. Some of the subgroup analyses were based on a small number of observations, resulting in a lack of statistical power, and the matched design of the study could have resulted in overmatching for some variables.

Despite these limitations, we have shown that undercooked ground beef contributes to the occurrence of sporadic S. typhimurium infection in France and that sufficient cooking of dishes containing beef reduces the risk. With the assumption that the association between consumption of ground beef and S. typhimurium infection in children is causal, the attributable fraction for ground beef in the population age group of <15 years, based on the results of our study, would be 35% (95% CI, 12–58). Since S. typhimurium is the Salmonella serotype most frequently found in humans and most commonly isolated from beef products, adequate cooking of ground beef may reduce substantially the incidence of this infection among children. Parents should therefore be reminded that ground beef should be eaten thoroughly cooked. Proper hand-washing should also be emphasized with regard to preventing this infection, as for all enteric infections. Further studies are needed to assess the role of antibiotics in the occurrence of S. typhimurium infection.

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References

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