EPIDEMOLOGY AND CLINICAL ASPECTS OF ENTERIC FEVER IN ISRAEL

EYAL MELTZER, ORIT YOSEPPOSITCH, CHANTAL SADIK, MICHAEL DAN, AND ELI SCHWARTZ*
Center for Geographic Medicine and Department of Medicine C, Sheba Medical Center, Tel Hashomer, Israel; Infectious Disease Unit, E. Wolfson Medical Center, Holon, Israel; Faculty of Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; Epidemiology Department, Ministry of Health, Jerusalem, Israel

Abstract. Enteric fever decreased in Israel in the last 50 years, but its current epidemiology is unknown. In a nationwide study, we evaluated all cases of enteric fever from 1995 to 2003. On hundred thirty-six cases met the case definition. During the period studied, the incidence of enteric fever decreased from 0.42 to 0.23/100,000. A total of 57.4% of the cases were acquired abroad. The incidence of endemic enteric fever was 2.7 times higher in Arabs than in Jews. In Arabs, Salmonella Typhi was the causative agent in all cases, and almost all cases were endemic. In Jews, most cases were imported, with a decrease in imported S. typhi, cases and an increase in imported S. Paratyphi A cases. Salmonella Paratyphi B was endemic, and restricted to the Jewish population. The reasons for the difference in causative agents along ethnic lines need further evaluation. A more efficient vaccine for travelers that includes S. Paratyphi A is needed.

INTRODUCTION

Enteric fever was previously endemic in Israel, with several epidemics documented in the 1920–1940s. Improved sanitation and water quality have led to a marked decrease in incidence rates of the disease, and the last reported outbreak of enteric fever occurred in 1985. Although no outbreaks have since been documented, the current epidemiology of the disease is not known. The last two decades have seen several demographic changes in Israel that may have had an effect on the occurrence of enteric fever: a massive influx of immigrants and of foreign workers arriving from disease-endemic countries, and a significant increase in Israeli travelers to disease-endemic countries. The aim of the present study was to evaluate the current epidemiology of enteric fever in Israel.

METHODS

Israeli health regulations mandate the reporting of all cases of enteric fever or isolation of its causative organisms: Salmonella enterica serovars Typhi and Paratyphi A and B to the Ministry of Health (MOH). In addition to these reports, cases are investigated by epidemiology nurses of the MOH. The data presented here originate from reports forwarded to the MOH from 1995 to 2003. The study was reviewed and approved by the by the Ethical Review Board of Sheba Medical Center (review board document no. 3193/2004). Informed consent was not required for this study.

A case of enteric fever was defined as isolation of S. enterica serovars Typhi and Paratyphi A and B from a blood culture, or the isolation of these organisms from the stool in a patient hospitalized with clinical features compatible with enteric fever. Other patients, e.g., those from whom these organisms were isolated from stool or bile without a compatible clinical setting were considered carried and excluded from the current evaluation. All cases that occurred following recent (eight weeks) travel outside the state of Israel were considered imported cases. All others were regarded as endemic cases. Travel data were available for all cases.

From the epidemiologic investigation, demographic, clinical, and microbiologic data were gathered. Additional data on laboratory studies, therapy, and outcome were obtained from the hospital discharge letter that was available in most cases.

Statistical analysis. Chi-square and Student’s t-tests were used to analyze qualitative and quantitative variables, respectively.

RESULTS

From 1995 to 2003, 136 cases met the case definition and were included in the analysis. Of these cases, 58 (42.6%) were apparently endemic, and 78 cases (57.4%) were acquired abroad. The number of cases of enteric fever decreased during the study period (Figure 1). The overall prevalence of enteric fever in Israeli citizens was 0.24/100,000, and the yearly incidence between 1995 and 2003 decreased from 0.42/100.00 to 0.23/100,000.

Most cases were sporadic, and no outbreaks of enteric fever were recorded. There were four episodes involving pairs of patients: two imported case-pairs, where both spouses were ill simultaneously, and two endemic case-pairs involving a mother and her son.

Endemic cases. Fifty-eight cases (42.6%) were acquired in Israel. Among them, 34 (58.6%) occurred in Jews, 22 (37.9%) in Arabs, and 2 (3.4%) were in migrant workers. The overall incidence of endemic enteric fever in Israel was 0.1/100,000.

Endemic enteric fever and ethnic groups. The incidence of endemic enteric fever in Arabs was 2.7 times higher than in Jews (0.21 and 0.078/100,000 respectively; P = 0.016). The incidence of enteric fever among Jews was low and virtually unchanged during the study period, but it decreased among Arabs. The apparent trend is towards a similar incidence (Figure 2). Infection with S. Typhi occurred at a higher mean ± SD age among Jews than among Arabs: 35.4 ± 27.8 (median = 34) years versus 20.9 ± 13.3 (median = 24.5) years, respectively (P = 0.04). The percentage of children ≤ 10 years of age was similar, on the other hand six cases occurred in Jewish patients > 50 years of age, but none occurred in Arabs (P = 0.007). The male:female ratio was 0.93, and did not differ significantly between Jews and Arabs.

Geographic distribution. Patients were distributed in all parts of the country. However, 25.8% of the cases were in residents of Jerusalem (comprising only 10% of the country’s population). The prevalence of cases was 0.15/100,000 in Jews living in Jerusalem compared with 0.49/100,000 in Arabs (P < 0.05) (Figure 3).
**Imported cases.** Seventy-eight (57.4%) cases were imported. The male:female ratio and mean age were not significantly different between endemic and imported cases, but imported cases occurred less frequently in children and the elderly (Table 1).

Seventy three imported cases were in travelers and five were in immigrants or their family members. Imported cases originated from several regions, but the majority (74.4%) of the cases was acquired in the Indian subcontinent (Table 2). The number of imported cases decreased during the study period. This was largely due to a decrease in S. Typhi infections, which was partially offset by an increase in S. Paratyphi infections (Figure 1).

**Migrants.** Eight cases (5.9%) of typhoid occurred in immigrants: one in a newly arrived immigrant from Ethiopia and seven in migrant workers. Six were imported cases: four newly arrived and two returning from a visit abroad. The remaining two cases were contracted in Israel, possibly through residing in crowded conditions with other workers. However, a detailed epidemiologic evaluation was not available.

In three endemic cases among Israelis, contact with a migrant worker was suggested as a possible source of infection. All three cases involved migrant workers from disease-endemic countries (India and the Philippines) who were caring for either a child or an elderly patient. However, a defini-
tive link was not established because in all three cases the workers left their households during hospitalization and were not available for assessment.

**Bacteriologic analysis.** One hundred ten cases were caused by *S. Typhi* (80.9%), 17 (12.5%) by *S. Paratyphi A*, and 9 (6.6%) by *S. Paratyphi B*. All but one of the cases infected with *S. Paratyphi A* were imported, mostly from the Indian subcontinent. All cases of infection with *S. Paratyphi B* were endemic, and occurred exclusively in Jews.

**Outcome.** The outcome was favorable in most patients. There were two deaths (1.5%) that were not related directly to the infection. One was due to toxic epidermal necrolysis, a complication that was attributed to the antibiotic therapy. The other was an elderly patient terminally ill with leukemia who appeared to be recovering uneventfully from infection with *S. Paratyphi B*, but died of sepsis and pneumonia approximately two weeks after her discharge from a hospital.

Relapse or complications were observed in 11 other patients (8.1%). Three had relapses, two had endocarditis, two had splenic abscesses, one had jaundice (due to quinolones or enteric fever), one had an intestinal perforation, one had hemolytic anemia, and one had reactive arthritis. Clinical parameters and rates of complications were similar in endemic and imported cases.

Most clinical and laboratory findings were similar in those infected with *S. Typhi* or *S. Paratyphi A*. However, in those infected with *S. Paratyphi A*, the rate of complications was higher than in those infected with *S. Typhi* (24% versus 6%, respectively; *P* = 0.02) (Table 3). *Salmonella Paratyphi B* appeared to have a different clinical spectrum. It was associated with disease in children; on three occasions it caused a self-limited disease that subsided within a few days without antibiotic treatment. Laboratory findings were also different from classical enteric fever in that patients usually had leukocytosis, a higher level of platelets, and normal liver function test results (Table 3).

**DISCUSSION**

Enteric fever was prevalent worldwide until early in the 20th century. Better water quality and sanitation have led to a marked change in the epidemiology of the disease in developed countries. The two major changes occurring in the pattern of disease were a marked decrease in total incidence in the past 50 years, and a trend of becoming associated with travel.

In Israel, enteric fever was endemic and epidemics occurred in the past. Since the establishment of the state of

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**Table 1.** Comparison of endemic and imported enteric fever*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All cases (n = 136)</th>
<th>Endemic (n = 58)</th>
<th>Imported (n = 78)</th>
<th><em>P</em></th>
<th>Jews (n = 34)</th>
<th>Arabs (n = 22)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age, years</td>
<td>27.20 ± 17.58</td>
<td>27.24 ± 23.64</td>
<td>27.15 ± 10.64</td>
<td>NS</td>
<td>31.39 ± 28.12</td>
<td>20.88 ± 13.34</td>
<td>NS</td>
</tr>
<tr>
<td>Age 0–10 years</td>
<td>23</td>
<td>19</td>
<td>4</td>
<td>&lt; 0.001</td>
<td>12</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Age ≥ 50 years</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td>0.04</td>
<td>9</td>
<td>0</td>
<td>0.007</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>1.09</td>
<td>0.93</td>
<td>1.21</td>
<td>NS</td>
<td>0.89</td>
<td>0.83</td>
<td>NS</td>
</tr>
<tr>
<td><em>Salmonella Typhi</em></td>
<td>111</td>
<td>50</td>
<td>62</td>
<td>NS</td>
<td>26</td>
<td>22</td>
<td>≤ 0.01</td>
</tr>
<tr>
<td><em>S. Paratyphi B</em></td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>&lt; 0.001</td>
<td>9</td>
<td>0</td>
<td>≤ 0.01</td>
</tr>
<tr>
<td><em>S. Paratyphi A</em></td>
<td>16</td>
<td>1</td>
<td>15</td>
<td>≤ 0.002</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS = not significant.
Israel, the incidence of enteric fever decreased from approximately 90/100,000 in early 1950s to 0.24/100,000 during the study period (Figure 4). Both incidence and sources of infection are similar to those reported from other developed nations. Most (57.4%) cases are now being imported from other parts of the world, mainly from the Indian subcontinent. In the United States, cases from southern Asia are now more common than cases from Latin America.

During the last two decades, Israel absorbed several waves of immigrants, mainly from Ethiopia and the former USSR. In addition, a large community of migrant workers (estimated to be approximately 200,000) became established in Israel. It has previously been shown that a large influx of immigrants from Ethiopia, a country with a high incidence of enteric fever, did not have a significant effect on incidence rates of enteric fever in Israel. Similarly, our data show that migrant workers had little effect on the incidence of enteric fever. There were three cases in which contact with a migrant worker was considered a possible source of infection in an endemic case. All three involved a setting where a migrant worker was involved in caring for an elderly person or a child. However, these cases lack definitive culture evidence for transmission, since none of the workers (who were staying in the country illegally) were available for testing.

Only seven cases (5.1%) of enteric fever occurred in migrant workers. Migrant workers in Israel are mainly young adults from countries where enteric fever is endemic (e.g., Thailand, the Philippines and sub-Saharan Africa). They have been shown to have a more restricted access to health care in Israel, as in other Western countries. High mobility and avoidance of contact with authorities may cause the incidence of enteric fever in this community to be underreported.

The difference in the age distribution and etiology of endemic typhoid between the Jewish and Arab populations deserves particular attention. Typhoid caused by S. Paratyphi B was restricted to the Jewish community. It is known that the d-tartrate-positive (dT+) strain of S. Paratyphi B (i.e., serovar Java) can be transmitted to humans from animal reservoirs, especially poultry. However, the cases in our series were not caused by the Java serovar and were therefore associated with human-to-human transmission. It is suggested that the restriction of bacteria along ethnic lines might reflect a low level of close human contact between these communities. Salmonella Paratyphi B is known to be endemic in several Middle Eastern countries, and outbreaks of imported cases among European travelers have been reported. In the United States, differences in the incidence of various food-borne salmonellae among ethnic groups are known to exist, but they are mostly associated with travel or consumption of certain foods (i.e., pork consumption among Asians). We are unaware of other reports in which a restricted human pathogen was endemic to an ethnic group and not to an area.

From a clinical viewpoint, paratyphoid fever is commonly perceived to be a milder condition compared with enteric fever, but there are few studies that compared these two fevers. Our study shows that this may be true for infection with S. Paratyphi B. In our series, S. Paratyphi B was typically found among children, and was frequently associated with a gastroenteritis-like, self-limited disease in some cases who also had different laboratory parameters (Table 3). This is consistent with findings from England and France, where in a large outbreak of S. Paratyphi B, most patients had a gastroenteritis-like illness, but only a few were bacteremic. Conversely, we found that S. Paratyphi A infection was associated with a more severe clinical outcome, as demonstrated by the higher rate of complications (Table 3).

The occurrence of enteric fever in the elderly was also restricted to the Jewish population. All five elderly Israelis with enteric fever were debilitated, either living with nursing attendants at home or in a nursing home. Close contact with nursing attendants might be a key factor in acquiring typhoid in these cases because it was the main and closest human contact.

The incidence of enteric fever caused by S. Typhi was 3.8 times higher in the Arab population than in the Jewish population in Israel. During the study period, the incidence of enteric fever in the Arab population decreased (Figure 2). The difference in prevalence might have been due to a lower socioeconomic status and suboptimal infrastructure in the Arab communities. However, these factors are improving.

It should be noted that contact with the Palestinian population in the West Bank and Gaza Strip was not routinely assessed by MOH staff. Data from the Palestinian Authority Health Ministry and Bureau of Statistics show the incidence of enteric fever in the West Bank and Gaza Strip to be approximately 17 cases/100,000, which is 150-fold greater than the Israeli rate. Contact with residents of the West Bank, travel to this region, and consumption of food produced there are probably much higher among the Arab population in Israel. In this regard, a case in point is the data from Jerusalem, where the largest Jewish and Palestinian communities in Israel live side by side, and with East Jerusalem in an

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indian subcontinent</td>
<td>58 (74.4)</td>
</tr>
<tr>
<td>Far East</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Africa</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Middle East</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>South America</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Total</td>
<td>78 (100)</td>
</tr>
</tbody>
</table>

**Table 2. Sources of imported enteric fever**

**Table 3.** Clinical and demographic parameters of patients infected with Salmonella typhi versus those infected with S. paratyphi

<table>
<thead>
<tr>
<th>Parameter</th>
<th>S. Typhi (n = 110)</th>
<th>S. Paratyphi B (n = 9)</th>
<th>S. Paratyphi A (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>27.9 ± 18</td>
<td>15.8 ± 29</td>
<td>25.3 ± 41</td>
<td>0.053†</td>
</tr>
<tr>
<td>Age 0–10 years</td>
<td>16</td>
<td>7</td>
<td>0</td>
<td>≤ 0.0001†</td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Relapse/ complications</td>
<td>6%</td>
<td>0%</td>
<td>24%</td>
<td>0.02‡</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81%</td>
<td>87%</td>
<td>79%</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>77%</td>
<td>75%</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>37%</td>
<td>0%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.9 ± 1.7</td>
<td>12.1 ± 2.2</td>
<td>12.7 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocytes × 10³</td>
<td>5.9 ± 3.3</td>
<td>14 ± 7.6</td>
<td>5.7 ± 2.2</td>
<td>0.02†</td>
</tr>
<tr>
<td>Thrombocytes × 10³</td>
<td>201 ± 94</td>
<td>268 ± 120</td>
<td>201 ± 49</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (units)</td>
<td>104 ± 98</td>
<td>24 ± 4</td>
<td>89 ± 111</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values, where indicated, are mean ± SD. Hb = hemoglobin; ALT = alanine aminotransferase.
† For comparison between S. Typhi and S. Paratyphi B.
‡ For comparison between S. Typhi and S. Paratyphi A.*
intermediary position between Israel and the West Bank. Although the ratio of enteric fever between Arabs and Jews is approximately three, the overall prevalence was twice that in the rest of Israel (Figure 3). Thus, improvement in public health in Palestine may have a beneficial effect on the incidence of enteric fever in Israel. Prospective epidemiologic analysis with molecular biology tools can help answer these questions.

Enteric fever, a disease of epidemic proportions 80 years ago, is now uncommon in Israel, and mostly imported via international travel. The presence of a large community of migrant workers in Israel had a small impact on the incidence of enteric fever. However, some concern about the transmission of infection from foreign-born nursing attendants to elderly patients is warranted. There are differences in the incidence of enteric fever between Jews and Arabs in Israel. It is suggested that close proximity and contact with the Palestinian population may contribute to this finding.

Paratyphoid fever is not a homogenous disease. Infection with S. Paratyphi B is endemic in this region and frequently a mild disease, often affecting children. Infection with S. Paratyphi A is usually imported from the Indian subcontinent, is as severe as infection with S. Typhi, and occurs largely in vaccinated travelers.

Further reinforcement of hygiene among travelers to disease-endemic countries and a vaccine with improved coverage for both S. Typhi and S. Paratyphi A are urgently required. These data show how the incidence of enteric fever, a common measure of national public health, is dependent on regional and global factors. Thus in Israel as elsewhere, health interventions outside the borders may have a beneficial effect on further decreasing enteric fever.

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Authors’ addresses: Eyal Meltzer and Eli Schwartz, Center for Geographic Medicine and Department of Medicine C, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel; Telephone: 972-54-472-8552 and 972-52-666-6132, Fax: 972-3-530-3501 and 972-3-350-2011; E-mails: emeltzer@post.tau.ac.il and elischwa@post.tau.ac.il. Orit Yossepowitch and Michael Dan, Infectious Disease Unit, E. Wolfson Medical Center, P.O. Box 5, Holon 58100, Israel; Telephone: 972-3-502-8729, Fax: 972-3-501-6126; E-mails: yossepowitch@netvision .net.il and midan@post.tau.ac.il. Chantal Sadik, Epidemiology Department, Ministry of Health, P.O. Box 1176, Jerusalem 91010, Israel; Telephone: 972-2-670-6814, Fax: 972-2-670-6876. E-mail: chantal_sadik@moh.health.gov.il.

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