A Large Outbreak of *Salmonella* Paratyphi A Infection Among Israeli Travelers to Nepal

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**Background.** In Asia, *Salmonella* Paratyphi A is an emerging infection, and travelers are increasingly at risk. During October 2009–November 2009, an outbreak in S. Paratyphi A infection was noted in Israeli travelers returning from Nepal.

**Methods.** An outbreak investigation included a standardized exposure questionnaire admitted to all patients and medical chart abstraction. Isolates were tested for antimicrobial susceptibility and pulsed-field gel electrophoresis (PFGE).

**Results.** During 1 October 2009–30 November 2009, 37 Israeli travelers returning from Nepal were diagnosed with S. Paratyphi A bacteremia. All 37 case isolates had an identical pattern on PFGE, and all were nalidixic acid resistant. Only 1 food venue was frequented by all the outbreak cases, with the largest number of exposures occurring around the Jewish New Year. All patients recovered without complications. Time to defervescence in 17 patients treated with ceftriaxone and azithromycin combination was 3.2 days (±1.7), whereas in 13 cases treated with ceftriaxone monotherapy, the time to defervescence was 6.6 days (±1.8; *P* < .001).

**Conclusions.** A point-source, "Paratyphoid Mary"–like outbreak was identified among Israeli travelers to Nepal. Combination Ceftriaxone-Azithromycin therapy may provide a therapeutic advantage over monotherapy, and merits further clinical trials.

**Keywords.** *Salmonella* Paratyphi A; enteric fever; disease outbreaks; foodborne diseases; travel.

Enteric fever (EF) is a systemic febrile illness that is caused by infection with *Salmonella enterica* serovars Typhi or Paratyphi A, B, and C. Most cases worldwide are attributed to S. Typhi. However, in Asia, infection with S. Paratyphi A is increasing and, in some regions (such as southern China), it is now the main cause of EF [1].

EF is a fecal–oral transmissible disease that is usually transmitted via contaminated food and water, with an incubation period of up to 1 month [2]. Most cases of EF manifest as a severe, prolonged febrile disease. In some cases, the disease results in a prolonged, asymptomatic carrier state that, in a food handler, may result in a foodborne outbreak. These asymptomatic food handlers are colloquially known as “Typhoid Mary.” It should be noted that without appropriate treatment, EF is associated with significant morbidity and mortality and that the clinical syndromes caused by S. Typhi and S. Paratyphi A are clinically indistinguishable, with similar rates of complications [3].

In light of its fecal–oral transmission, EF is endemic in countries with poor sanitation. The highest incidence of EF is reported on the Indian subcontinent, with disease prevalence estimated to be >270/100 000 [4]. In resource-poor areas (eg, Kolkata), the annual incidence may approach 1% [5]. The asymmetric global burden of EF is also reflected by the high rate of EF acquired by travelers to South and Southeast Asia compared with the other endemic regions [6].

Outbreaks of EF in travelers have rarely been described. With a few exceptions [7], most outbreaks were small clusters that, in most instances, affected very few cases [8–11]. Here we describe a large point-source outbreak of S. Paratyphi A among 37 Israeli travelers who...
contracted the disease in Nepal where S. Paratyphi A is endemic. This outbreak of travel-related S. Paratyphi A infection is the largest ever recorded. The patients were febrile, bacteremic, Israeli returnees who were diagnosed and treated in Israeli hospitals. This has provided a unique opportunity of assessing the effects of different therapeutic regimens for this pathogen.

**METHODS**

**Outbreak Investigation**

Concern about a possible outbreak of EF was raised on 6 and 7 October 2009, when 4 cases of EF were recognized in 2 medical centers in Israel. All cases involved Israeli travelers returning from Nepal and all involved Orthodox Jews. Following identification of additional cases, a media announcement was made on 10 October in order to increase awareness among febrile returning travelers from Nepal and to alert primary care physicians and emergency rooms in Israel. Infectious disease units in Israeli hospitals were contacted and the Ministry of Health was informed. The outbreak investigation included an exposure questionnaire administered to all S. Paratyphi A patients diagnosed starting on 1 October 2009 and medical chart abstraction. Open-ended questioning identified 2 food venues that were visited by >20% of travelers in Pokhara and 2 in Kathmandu (the 2 most commonly visited sites by patients). A standardized exposure questionnaire was used to gather general demographic data as well as information about the timing, location, and activities conducted in Nepal that focused on timing of food venue exposure. The questionnaire was used to investigate patients during hospitalization or soon after discharge.

**Case Definition**

Outbreak cases were defined as any patient who returned from travel to Nepal during 1 October 2009–30 November 2009 and who was diagnosed with EF by identification of the outbreak strain of S. Paratyphi A in a blood culture.

**Clinical Data Evaluation**

Patients were treated in different hospitals in Israel, and the therapeutic regimen differed according to institutional policy. Clinical and laboratory data from all units that treated the patients were available to the investigators and were retrospective analyzed. Data included antimicrobial regimen used, clinical course including temperature measurements, and outcome including complications, relapse of fever and bacteremia, and disposition (discharged, transferred, died). To compare response to different regimens, the relapse rate and the time to defervescence were used as parameters for clinical response.

The χ² test was used for analysis of nonparametric data. Continuous data were described as mean ± standard deviation. Student t test was used for comparisons of means. The difference between time to defervescence of antibiotic therapy modes was assessed by both the Student t test and by the Kaplan–Meier survival curves. All P value calculations were 2-tailed, and P ≤ .05 was considered statistically significant. Data were maintained using Microsoft Access (Microsoft, Redmond, WA). Statistical analysis was conducted by IBM SPSS Statistics, version 19 (Chicago, IL).

**Microbiological Assessment**

Isolates from positive blood cultures were evaluated for antimicrobial sensitivity at each hospital using sensitivity cutoffs according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Because EF is a notifiable disease in Israel, all cases of EF are reported to the ministry of health, and all Salmonella isolates are sent to a central reference laboratory. Pulsed-field gel electrophoresis (PFGE) of all strains was performed, as described elsewhere [12].

The institutional review board of the Sheba Medical Center approved the study.

**RESULTS**

**Outbreak Investigation**

During 1 October 2009–30 November 2009, 37 travelers were hospitalized in 7 hospitals in Israel with the diagnosis of EF caused by the epidemic S. Paratyphi A strain, proven by positive blood culture.

Travelers’ characteristics are described in Table 1. Thirty-five travelers (95%) had visited a travel clinic for pretravel consultation. All 35 received a pretravel Vi typhoid vaccine and were educated regarding foodborne precautions. Seventy-one percent of cases were Orthodox Jews and declared that they followed kosher food consumption practices. Epidemiological questionnaires revealed that 100% of the travelers had stayed in Pokhara, Nepal, some time during 31 August 2009–30 September 2009. Of 6 food venues frequented by more than 1 traveler in Pokhara, only 1 was used by all those infected by the epidemic strain: kosher venue 1 (KV1). This venue was an Orthodox Jewish religious establishment that provided religious services and meals to travelers. Meals were consumed at KV1 by the outbreak cases during September 2009–October 2009, with the largest number of exposures occurring in the third week of September, which coincided with the Jewish New Year (Figure 1).

No single meal or particular food item was shared by all the travelers. Among 11 travelers who frequented KV1 only once, the incubation period was 22 ± 5.4 days (mean ± standard deviation, range 17–37 days). Among the additional 5 food venues frequented by outbreak cases in Pokhara, the percentage of travelers exposed to each venue ranged from 5% to 48%.
Enquiries regarding EF among other tourist groups in Nepal were made at this time through communications with the CIWEC Clinic Kathmandu (a healthcare facility that provides care for many ill travelers in Nepal; Eli Schwartz, personal communication) and the GeoSentinel Network (the largest network that accumulates data on ill-returning travelers; Eli Schwartz, personal communication) and were negative for an outbreak of EF among non-Israeli travelers.

We were unable to evaluate local conditions at KV1 (ie, carriage among staff and local, temporary hired food handlers) due to a lack of cooperation at the locale, which has ceased operation and its staff has dispersed.

**Microbiological Data**

The antimicrobial sensitivity pattern of all isolates showed a similar pattern—all were sensitive to ciprofloxacin but were resistant to nalidixic acid. All strains were sensitive in vitro to ceftriaxone, ampicillin, and trimethoprim–sulfamethoxazole. PFGE was performed on all samples and showed an identical pattern in 37 cases. In addition to these 37 travelers, a case of

### Table 1. Clinical Parameters of Patients With Salmonella Paratyphi A Bacteremia According to Treatment Group

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>All Patients (N = 37)a</th>
<th>Ceftriaxone Monotherapy Group (N = 13)</th>
<th>Ceftriaxone–Azithromycin Combination Group (N = 17)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>24.8 ± 4.4</td>
<td>25.8 ± 6.7</td>
<td>24.2 ± 4</td>
<td>.754</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>1.05</td>
<td>1.16</td>
<td>1.12</td>
<td>.7518</td>
</tr>
<tr>
<td>Time from fever onset to initiation of antibiotic therapy, d (mean ± SD)</td>
<td>5.2 ± 4.7</td>
<td>4.5 ± 3.8</td>
<td>5.4 ± 5.9</td>
<td>.51</td>
</tr>
<tr>
<td>Time to defervescence, d (mean ± SD)</td>
<td>4.8 ± 2.4</td>
<td>6.6 ± 1.8</td>
<td>3.2 ± 1.7</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

a Thirty-seven cases associated with the kosher venue 1 Pokhara outbreak.

b For comparison between antimicrobial treatment groups. Student t test and χ² test used for continuous and noncontinuous parameters, respectively.
S. Paratyphi A bacteremia developed in a microbiologist who handled multiple blood cultures taken from ill travelers at the time. Clinical data from this case were included in the therapeutic analyses of this outbreak.

**Treatment and Outcome**

Overall, outcome was favorable, with no fatalities and no cases of severe complications (such as intestinal perforation, intestinal bleeding, or encephalopathy). There was only 1 case of EF relapse; this occurred in a traveler who presented initially in Thailand, where she traveled after leaving Nepal. There, she was hospitalized, diagnosed with S. Paratyphi A bacteremia, and treated with ciprofloxacin. After her return to Israel, fever relapsed, she was again found to be bactereemic with S. Paratyphi A that was identical to the other isolates, and recovered uneventfully with appropriate antimicrobial therapy.

The antibiotic regimen used was not uniform and differed according to each hospital’s policy. Two regimens were used for treating the majority of cases: 17 travelers were treated with a combination of intravenous ceftriaxone 2 g daily for 14 days, with oral azithromycin 500 mg daily for the first 7 days (Sheba Medical Center Policy [13]), while 13 cases (in other medical centers) were treated with ceftriaxone 2 g daily for 14 days. One patient was treated with azithromycin monotherapy. In 8 cases, treatment was switched during the course, and data for these cases were not included in the analysis.

Time to defervescence was significantly shorter in cases treated with combination ceftriaxone and azithromycin than for patients treated with ceftriaxone monotherapy: 3.2 ± 1.7 days and 6.6 ± 1.8 days, respectively (P < .0001; Figure 2).

**DISCUSSION**

This is the largest outbreak of travel-related S. Paratyphi A infection on record. It should be noted that the usual annual number of EF cases in Israel is <10 [14].

An identical isolate occurred in all cases, with the same antimicrobial sensitivity and the same PFGE pattern. All outbreak cases had travelled to Pokhara, Nepal, where a single kosher food venue was frequented by all cases. These facts suggest that this was a point-source outbreak caused by a S. Paratyphi A carrier. The purported “Paratyphoid Mary” was in all likelihood a food handler at the KV1 in Pokhara. We could not pinpoint a single meal or a single dish that all travellers had eaten, but we could demonstrate a distinct period of time during which people who ate at this venue became infected (Figure 1). The magnitude of the current outbreak suggests a significant, prolonged breach of food hygiene at the venue; some travellers recalled having eaten at the venue only once. Paradoxically, many travelers dined preferentially at KV1 with the supposition that the kosher food served there was safe.

That this was a point-source outbreak, rather than sewage contamination of food or water, is further confirmed by the absence of a concomitant massive occurrence of other, more contagious fecal-oral infections in the study population. The absence of
reports of an upsurge in S. Paratyphi A infection among non-Israeli travelers in Nepal also supports this conclusion.

EF has declined dramatically in most developed countries but remains an important health issue in many developing nations. Until recently, paratyphoid fever probably accounted for a fifth of all world cases of EF [15]. However, recent data show that S. Paratyphi A accounts for an increasing proportion of cases and should be regarded as an emerging infection [2]. In some regions, such as southern China, S. Paratyphi A actually accounts for more than 80% of all cases of EF [1]. Most significantly, no vaccine currently exists to protect against S. Paratyphi A. In fact, 95% of the travelers in this study were up to date with their typhoid vaccine (the Vi vaccine, which is the only one available in Israel, does not confer any protection against S. Paratyphi A, which lacks the Vi antigen) [3].

The increased incidence of S. Paratyphi A is reflected in statistics of travel-related EF. Case registries from several countries have consistently shown an increase in the importance of S. Paratyphi A [3, 16–18]. This increase may, in part, be due to the partial protection against S. Typhi offered by vaccines or it may reflect the increase in S. Paratyphi A infection seen in many parts of Asia [19].

Treatment of EF has been complicated in recent decades by the rise of multidrug-resistant strains including quinolone/nalidixic acid–resistant Salmonella (NARS). Currently, the preferred regimen for NARS is a 10- to 14-day course of intravenous ceftriaxone [2]. However, apart from the need for parenteral administration with the entailed risks and costs, response to ceftriaxone is slow, with a median time to defervescence that in some reports was more than 10 days [10]. This means that some patients will still be febrile after a week of adequate therapy, often leading to multiple (mostly negative) diagnostic studies to rule out complications. The delayed response to ceftriaxone may reflect the intracellular location of Salmonella, where ceftriaxone is less active. Azithromycin is a relatively new agent that has been shown to be as effective as ceftriaxone in the treatment of EF [20]. However, these studies were largely limited to children infected with S. Typhi, and there is minimal data regarding its efficacy among travelers. In addition, azithromycin is rapidly cleared from the circulation; in some studies, time to clearance of bacteremia was actually longer with azithromycin [21].

A novel approach that was proposed recently is to combine intravenous ceftriaxone for 2 weeks together with oral azithromycin for the first week. The rationale of combining both agents was that since their maximal effects are in different tissue compartments—ceftriaxone in the extracellular compartment and azithromycin in the intracellular compartment—the combination may confer a clinical benefit [13]. The combination of these 2 drugs became the standard approach for treating typhoid patients at the Sheba Medical Center, Israel.

This outbreak provided a unique opportunity to compare treatment regimens for S. Paratyphi A. Because the pathogen was a single bacterial strain, the question of pathogen variability in the response to antimicrobials was eliminated. The patients formed a homogenous group of healthy, young adults, with a similar male/female ratio and an absence of confounding medical conditions. They presented to medical institutions according to areas of residence and were therefore allocated to specific regimens in the absence of selection bias.

Mortality and severe complications of EF, such as intestinal perforation and hemorrhage, are very rare in patients treated in developed countries; therefore, time to defervescence was used as a surrogate for clinical response, as it has been in most recent EF trials. The much shorter time to defervescence in the patients treated with the ceftriaxone–azithromycin combination (3.2 ± 1.7 days compared with 6.6 ± 1.8 days in the ceftriaxone monotherapy group) appears to support the suggestion that combined therapy is better than either monotherapy.

Our study has several limitations. Since only patients presenting in Israel were included, some cases presenting abroad may have been missed. Also, because only bacteremic cases were included, milder cases in which no cultures were performed may have gone unnoticed. However, these qualifications may only have led to an underestimation of the outbreak, which our results already show to be unusual.

A further limitation is our inability to provide a “smoking gun,” that is, a culture-proven carrier of the epidemic strain in the venue’s local staff. The nature of the outbreak precluded performance of a case control study, and a direct microbiological evaluation of the KV1 venue and its staff was not possible. However, the fact that 100% of outbreak cases ate at KV1 compared with 48% at the second most common venue and the fact that most outbreak cases maintained kosher food precautions and did not eat at nonkosher restaurants strongly suggest that this point-source outbreak originated at the KV1 venue.

While our comparison of treatment regimens for S. Paratyphi A was based on a nonrandomized study, patients had exposure and characteristics that were similar to those in the compared treatment groups. Further randomized controlled trials are recommended to confirm our findings. However, such studies seem to be unfeasible among travelers since the EF attack rate is on the order of 1:10 000 [3]. Randomized trials, especially those that involve intravenous medication and hospitalization, are costly and difficult to conduct in developing countries—the only place where local incidence makes such studies feasible. Furthermore, generalizing from young children—the age group most affected by EF in hyperendemic Asian nations—to adults may not be appropriate.

This outbreak illustrates the inadequate protection offered by dietary precautions against travel-related foodborne infections [22]. In a country such as Nepal, which is hyperendemic for EF,
and even in an establishment that is perceived to be safe by travelers, kosher food does not necessarily equal safe food.

A vaccine against S. Paratyphi A, the only true solution for this common pathogen, is urgently needed. This mantra has been repeated in many EF publications over the last 20 years [23]; however, such a vaccine is still years from clinical application. For the time being, our study suggests that until further data from controlled trials are available, adding oral azithromycin to parenteral ceftriaxone may hasten clinical response to therapy in S. Paratyphi A infection and is therefore worthwhile.

A large point-source, probably Typhoid Mary-type, outbreak of S. Paratyphi A among Israeli travelers to Nepal who ate at a kosher venue has been described. Combination therapy with ceftriaxone and azithromycin may provide a more rapid clinical response than ceftriaxone monotherapy, nearly halving the time to defervescence, and should be further explored in prospective, randomized trials.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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