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EPIDEMIOLOGY AND SURVEILLANCE

Epidemiological and Clinical Characteristics of International Travelers with Enteric Fever and Antibiotic Resistance Profiles of Their Isolates: a GeoSentinel Analysis

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Citation Hagmann SHF, Angelo KM, Huits R, Plewes K, Eperon G, Grobusch MP, McCarthy A, Libman M, Caumes E, Leung DT, Asgeirsson H, Jensenius M, Schwartz E, Sánchez-Montalvá A, Kelly P, Pandey P, Leder K, Bourque DL, Yoshimura Y, Mockenhaupt FP, van Genderen PJJ, Odolini S, Schlagenhauf P, Connor BA, Hamer DH. 2020. Epidemiological and clinical characteristics of international travelers with enteric fever and antibiotic resistance profiles of their isolates: a GeoSentinel analysis. Antimicrob Agents Chemother 64:e01084-20. https://doi.org/10.1128/AAC.01084-20.

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Received 28 May 2020
Returned for modification 30 July 2020
Accepted 11 August 2020
Accepted manuscript posted online 17 August 2020
Published 20 October 2020

ABSTRACT Enteric fever, caused by *Salmonella enterica* serovar Typhi (*S.* Typhi) and *S. enterica* serovar Paratyphi (*S.* Paratyphi), is a common travel-related illness. Limited data are available on the antimicrobial resistance (AMR) patterns of these serovars among travelers. Records of travelers with a culture-confirmed diagnosis seen during or after travel from January 2007 to December 2018 were obtained from GeoSentinel. Traveler demographics and antimicrobial susceptibility data were analyzed. Isolates were classified as nonsusceptible if intermediate or resistant or as susceptible in accordance with the participating site's national guidelines. A total of 889 travelers (*S.* Typhi infections, $n = 474$; *S.* Paratyphi infections, $n = 414$; coinfection, $n = 1$) were included; 114 (13%) were children of <18 years old. Most individuals (41%) traveled to visit friends and relatives (VFRs) and acquired the infection in South Asia (71%). Child travelers with *S.* Typhi infection were most frequently VFRs (77%). The median trip duration was 31 days (interquartile range, 18 to 61 days), and 448 of 691 travelers (65%) had no pretravel consultation. Of 143 *S.* Typhi and 75 *S.* Paratyphi isolates for which there were susceptibility data, nonsusceptibility to antibiotics varied (fluoroquinolones, 65% and 56%, respectively; co-trimoxazole, 13% and 0%; macrolides, 8% and 16%). Two *S.* Typhi isolates (1.5%) from India were nonsusceptible to third-generation cephalosporins. *S.* Typhi fluoroquinolone nonsusceptibility was highest when infection was acquired in South Asia (70 of 90 isolates; 78%) and sub-Saharan Africa (6 of 10 isolates; 60%). Enteric fever is an important travel-associated illness complicated by AMR. Our data contribute to a better understanding of region-specific AMR, helping to inform empirical treatment options. Prevention measures need to focus on high-risk travelers including VFRs and children.

KEYWORDS antimicrobial resistance, enteric fever, paratyphoid, travel, typhoid

Infections with *Salmonella enterica* serovar Typhi (*S.* Typhi) or *S. enterica* serovar Paratyphi A, B, or C (*S.* Paratyphi), referred to, respectively, as typhoid fever and paratyphoid fever and collectively as enteric fever, are important causes of morbidity and mortality among international travelers (1). Typhoid fever and paratyphoid fever are common in many resource-limited countries, with an estimated global burden of 10.9 million cases (116,800 deaths) and 3.4 million cases (19,100 deaths), respectively, in 2017 (2).

Despite improvements in global control since the 1990s, enteric fever remains a major challenge to health systems, affecting predominantly young children in countries of endemicity in Asia and Africa. The recent development of new-generation typhoid conjugate vaccines (TCVs) that will allow effective immunization of infants (>6 months of age) and young children led the World Health Organization (WHO) to recommend typhoid vaccination program implementation in countries with a high disease burden (3).

Enteric fever in high-income countries is largely related to international travel (>85% of cases), with most cases imported from South Asia by travelers who visited friends or relatives (VFRs) (1, 4, 5). The parenteral Vi-polysaccharide (Vi-PS) or oral attenuated Ty21a vaccine is recommended for travelers to countries where typhoid fever is endemic (6). The protective efficacy against typhoid fever has been estimated to be 50 to 80%; while there is no vaccine for paratyphoid fever, Ty21a may have some protective efficacy against *S.* Paratyphi B (6–8).

Effective antimicrobial therapy, since its first use in 1940s, has been undermined by the emergence of antimicrobial resistance (AMR) (9). Resistance to chloramphenicol among enteric fever isolates was soon followed by the identification of multidrug-resistant (MDR) strains that were additionally resistant to ampicillin and co-trimoxazole, rendering fluoroquinolones as an effective and commonly used alternative (10). Subsequently, fluoroquinolone-resistant infections appeared and became widespread especially in South Asia, leaving macrolides and third-generation cephalosporins as the preferred options for therapy. Most recently, the appearance and international spread of extensively drug-resistant (XDR) strains that are MDR but also carry resistance to third-generation cephalosporins and fluoroquinolones have been reported (11–14). *S.*

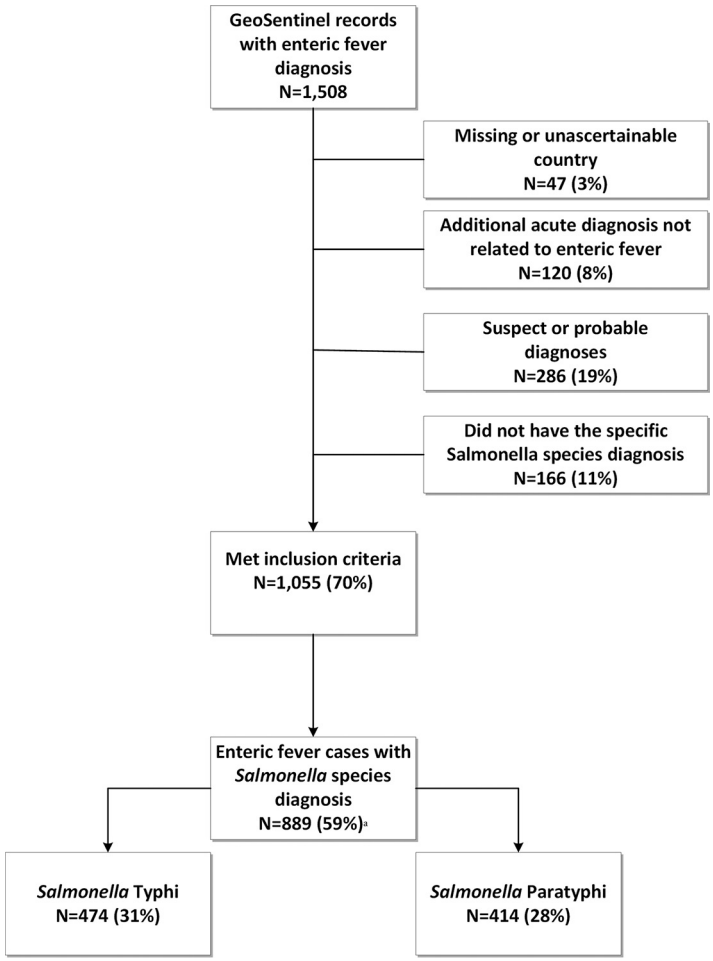

FIG 1 Number of enteric fever records from GeoSentinel that meet the exclusion and inclusion criteria and species diagnoses for included cases, January 2007 to December 2018. [a], among the 889 cases of *Salmonella* species infection, a single coinfection was not counted in the species-specific data.

Typhi- and *S.* Paratyphi-relevant antibiotic susceptibility profiles and genomic characteristics conferring resistance have been shown to vary geographically (15, 16); hence, the study of international travelers with enteric fever is valuable for sentinel surveillance and for informing the clinical management of cases.

The objective of this global multisite cross-sectional analysis was to describe the demographic and clinical characteristics of international travelers with enteric fever, in addition to their isolate's antimicrobial susceptibility information, using data from the GeoSentinel Surveillance Network.

RESULTS

Travelers diagnosed with enteric fever. From 2007 to 2018, 889 travelers (including 17 migrants) (*S.* Typhi, $n = 474$ infections; *S.* Paratyphi, $n = 414$ infections; coinfection, $n = 1$) were included in the study (Fig. 1). Among 179 patient records with available information, culture was performed on blood (150; 84%) or stool (54; 30%). The median age of travelers was 28 years (range, 0 to 79 years), and 58% were male (Table 1). Many travelers (448 of 691; 65%) did not have a pretravel consultation with a health care provider. Among travelers with *S.* Typhi infection and available information, 7 of 70 (10%) had been vaccinated with a typhoid fever vaccine.

Almost three-quarters of travelers (71%) were exposed to enteric fever in South Asia, and most infections were acquired in India (41%), Nepal (12%), Bangladesh (9%), or Pakistan (9%) (Table 1). In the Western Hemisphere, most typhoid and paratyphoid

TABLE 1 Characteristics of travelers with enteric fever reported to GeoSentinel, 2007 to 2018

Characteristic[k]	Value for the group		
	All ($n = 889$)	With *S.* Typhi infection ($n = 474$)[a]	With *S.* Paratyphi infection ($n = 414$)
Median age (yr [range])[b]	28 (0–79)	27 (0–79)	29 (2–75)
No. (%) of male travelers[c]	512 (58)	276 (58)	236 (57)
No. (%) of travelers with pretravel consultation[d]	448 (65)	299 (80)	148 (47)
Reason for travel (no. of travelers [%])[e]			
VFR	366 (41)	250 (53)	116 (28)
Tourism	308 (35)	133 (28)	174 (42)
Business	118 (13)	45 (10)	73 (18)
Missionary[f]	52 (6)	20 (4)	32 (8)
Student	22 (3)	11 (2)	11 (3)
Migration	18 (2)	10 (2)	8 (2)
Migrant worker	3 (<1)	3 (1)	0
Research	1 (<1)	1 (<1)	0
Region of exposure (no. of travelers [%])[g]			
South Asia	631 (71)	319 (67)	311 (75)
Southeast Asia	104 (12)	43 (9)	61 (15)
Sub-Saharan Africa	48 (5)	39 (8)	9 (2)
Central America[h]	31 (4)	30 (6)	1 (<1)
South America	28 (3)	13 (3)	15 (4)
North Africa	12 (1)	8 (2)	4 (1)
Caribbean	10 (1)	7 (2)	3 (1)
Middle East	8 (1)	2 (<1)	6 (2)
Northeast Asia	7 (1)	5 (1)	2 (1)
Western Europe	5 (1)	3 (1)	2 (1)
Oceania	4 (1)	4 (1)	0
North America	1 (<1)	1 (<1)	0
Median trip duration (days [IQR])[i]	31 (18–61)	31 (19–61)	30 (18–61)
Median duration of time between return and presenting to a site (days [IQR])[j]	9 (6–21)	6 (3–8)	9 (5–21)
No. (%) of hospitalized travelers[e]	522 (59)	289 (61)	232 (56)

[a]One record described a tourist traveler to South Asia (India) with coinfection; information on this traveler was not included in the species-specific columns.
[b]Data were not available for 5 travelers ($n = 2$ with *S.* Typhi infection; $n = 3$ with *S.* Paratyphi infection).
[c]Data were not available for 2 travelers ($n = 2$ with *S.* Paratyphi infection).
[d]Data were not available for 198 travelers ($n = 98$ with *S.* Typhi infection; $n = 100$ with *S.* Paratyphi infection).
[e]Data were not available for 1 traveler (*S.* Typhi infection).
[f]Includes missionaries, humanitarians, volunteers, and aid workers.
[g]Exposure to enteric fever was reported from 64 countries; the top three countries of exposure were India ($n = 203$), Bangladesh ($n = 52$), and Pakistan ($n = 43$) among *S.* Typhi cases and India ($n = 149$), Nepal ($n = 93$), and Pakistan ($n = 33$) among *S.* Paratyphi cases.
[h]Central America included cases reported from Mexico ($n = 16$).
[i]Data were not available for 61 travelers ($n = 35$ with *S.* Typhi infection; $n = 25$ with *S.* Paratyphi infection; $n = 1$ with a dual diagnosis).
[j]Data were not available for 531 travelers ($n = 245$ with *S.* Typhi infection; $n = 286$ with *S.* Paratyphi infectction).
[k]VFR, visiting friends and relatives; IQR, interquartile range.

infections were acquired in Mexico ($n = 16$) and Bolivia ($n = 9$). The median trip duration was 31 days (interquartile range [IQR], 18 to 61 days); 56 of 828 (7%) travelers traveled for <7 days, and 154 (19%) traveled for <14 days. The top symptoms among 237 travelers for whom information was available were fever (73%), any gastrointestinal complaint (49%), headache (28%), fatigue (24%), or myalgia (11%). Fifty-nine percent of travelers (522 of 888) were hospitalized.

While 65% of all travelers did not have a pretravel consultation, 80% (299 of 376) of travelers with *S.* Typhi infection did not have a pretravel consultation with a health care provider. Travelers with *S.* Typhi infection most frequently traveled as VFRs (53%) or for tourism (28%). In contrast, travelers with *S.* Paratyphi infection most frequently traveled for tourism (42%); VFR and business travel accounted for 28% and 18%, respectively (Table 1). The traveler with the *S.* Typhi and *S.* Paratyphi coinfection confirmed by blood culture was a tourist to India and was hospitalized after travel.

Of the 889 travelers, 114 (13%) were children of <18 years of age. The median age was 8 years (range, 0 to 17 years), and 55% were male (Table 2). Over two-thirds of

TABLE 2 Characteristics of children of <18 years of age with enteric fever reported to GeoSentinel, 2007 to 2018

Characteristic[e]	Value for the group			
	All ($n = 114$)	Aged 0–5 yr ($n = 36$)	Aged 6–11 yr ($n = 37$)	Aged 12–17 yr ($n = 41$)
Salmonella species infections (no. [%])				
S. Typhi	73 (64)	29 (81)	22 (59)	22 (54)
S. Paratyphi	41 (36)	7 (19)	15 (41)	19 (46)
Median age (yr [range])	8 (0–17)	3 (0–5)	8 (6–11)	15 (12–17)
No. (%) of male children	63 (55)	15 (42)	22 (59%)	26 (63%)
No. (%) of children with pretravel consultation[a]	56 (71)	20 (77)	18 (67)	18 (69)
Reason for travel (no. of children [%])				
VFR	88 (77)	30 (83)	31 (84)	27 (66)
Tourism	16 (14)	5 (14)	3 (8)	8 (20)
Business	6 (5)	1 (3)	2 (5)	3 (7)
Migration	2 (3)	0	1 (3)	1 (2)
Student	1 (1)	0	0	1 (2)
Missionary	1 (1)	0	0	1 (2)
Region (no. of children [%])				
South Asia[b]	102 (90)	32 (89)	33 (89)	37 (90)
Southeast Asia	6 (5)	1 (3)	2 (5)	2 (5)
Middle East	3 (3)	2 (6)	1 (3)	0
Central America	2 (2)	1 (3)	0	1 (2)
South America	2 (2)	0	1 (3)	1 (2)
Median trip duration (days [IQR])[c]	36 (27–59)[c]	39 (31–48)	37 (28–53)	31 (18–62)
Median duration of time between return and presenting to a site (days [IQR])[d]	9 (6–19)	9 (6–15)	10 (7–28)	7 (5–16)
No. (%) of hospitalized children	69 (61)	23 (64)	21 (57)	25 (61)

[a]Data were not available for 35 children ($n = 10$ children 0 to 5 years of age; $n = 10$ children 6 to 11 years of age; and $n = 14$ children 12 to 17 years of age).
[b]Top three countries of exposure in all three age categories were India ($n = 36$), Pakistan ($n = 34$), and Bangladesh ($n = 20$).
[c]Data were not available for 7 travelers ($n = 1$ among children 0 to 5 years of age; $n = 2$ among children 6 to 11 years of age; and $n = 4$ among children 12 to 17 years of age).
[d]Data were not available for 60 travelers ($n = 19$ among children 0 to 5 years of age; $n = 16$ among children 6 to 11 years of age; and $n = 25$ among children 12 to 17 years of age).
[e]VFR, visiting friends and relatives; IQR, interquartile range.

children in all age groups (56 of 79 travelers) did not have a pretravel consultation with a health care provider. Only one child, a teenager, reported receiving a typhoid fever vaccination. Children most frequently traveled as VFRs (77%); those aged 12 to 17 years more frequently traveled for tourism (20%) than children in the younger age groups (Table 2). Children most frequently acquired enteric fever in South Asia. Sixty-one percent were hospitalized.

Antibiotic susceptibility findings. Overall, antibiotic susceptibility data were available for 218 travelers (*S.* Typhi, $n = 143$ infections; *S.* Paratyphi infections, $n = 75$) (Table 3). Among *S.* Typhi isolates, 65% (87 of 133), 50% (4 of 8), 13% (16 of 121), and 8% (4 of 50) were nonsusceptible to fluoroquinolones, ampicillin, co-trimoxazole, and macrolides, respectively. Only 2 of 137 (1.5%) isolates were nonsusceptible to third-generation cephalosporins; all were susceptible to carbapenems. Among *S.* Paratyphi isolates, 100% (2 of 2), 56% (40 of 72), and 16% (5 of 31) were nonsusceptible to ampicillin, fluoroquinolones, and macrolides, respectively; all isolates tested were susceptible to co-trimoxazole, third-generation cephalosporins, and carbapenems (Table 3).

Fluoroquinolone nonsusceptibility among *S.* Typhi isolates was highest among travelers to South Asia (70 of 90; 78%) and sub-Saharan Africa (6 of 10; 60%) (Table 3). *S.* Typhi macrolide and co-trimoxazole nonsusceptibility was found only among isolates from travelers to sub-Saharan Africa (1 of 5 [20%] and 3 of 6 [50%], respectively) and South Asia (3 of 36 [8%] and 13 of 87 [15%], respectively). Third-generation cephalosporin-nonsusceptible isolates ($n = 2$) were reported from two travelers to India with a resistance profile different from the recently observed

TABLE 3 Proportion of nonsusceptible *Salmonella* Typhi and *Salmonella* Paratyphi isolates in international travelers overall and by geographic regions presenting to GeoSentinel sites, 2015 to 2018[a]

Drug or class	No. (%) of isolates by group or region[b]									
	All		South Central Asia[c]		Southeast Asia		Sub-Saharan Africa		Central America	
	S. Typhi (*n* = 143)	*S.* Paratyphi (*n* = 75)	*S.* Typhi (*n* = 99)	*S.* Paratyphi (*n* = 55)	*S.* Typhi (*n* = 14)	*S.* Paratyphi (*n* = 14)	*S.* Typhi (*n* = 10)	*S.* Paratyphi (*n* = 1)	*S.* Typhi (*n* = 12)	*S.* Paratyphi (*n* = 0)
Fluoroquinolones	87/133 (65)	40/72 (56)	70/90 (78)	32/52 (62)	5/14 (36)	8/8 (100)	6/10 (60)	0/1 (0)	4/11 (36)	NA
Ampicillin	4/8 (50)	2/2 (100)	3/6 (50)	1/1 (100)	1/2 (50)	1/1 (100)	NA	NA	NA	NA
Co-trimoxazole	16/121 (13)	0/63 (0)	13/87 (15)	0/48 (0)	0/9 (0)	0/9 (0)	3/6 (50)	0/1 (0)	0/12 (0)	NA
Macrolides	4/50 (8)	5/31 (16)	3/36 (8)	5/22 (23)	0/3 (0)	0/7 (0)	1/5 (20)	NA	0/2 (0)	NA
Third-generation cephalosporins	2/137 (2)	0/72 (0)	2/96 (2)	0/53 (0)	0/53 (0)	0/14 (0)	0/10 (0)	0/1 (0)	0/11 (0)	NA
Carbapenems	0/63 (0)	0/31 (0)	0/43 (0)	0/21 (0)	0/5 (0)	0/6 (0)	0/5 (0)	0/1 (0)	0/4 (0)	NA

[a]Isolates were classified as nonsusceptible if intermediate or resistant or as susceptible according to participating sites' national guidelines.
[b]Antibiotic susceptibility testing protocols varied across clinic sites; hence, a variable number of *S.* Typhi and *S.* Paratyphi strains were tested for each class of enteric fever-relevant antibiotic. NA, not available.
[c]Only regions with at least 10 isolates with susceptibility testing results available are shown; regions not shown are the Caribbean (2 *S.* Typhi isolates and 1 *S.* Paratyphi isolate), Middle East (2 *S.* Typhi and 1 *S.* Paratyphi isolates), North Africa (2 *S.* Typhi isolates), South America (1 *S.* Typhi isolate and 4 *S.* Paratyphi isolates), and Western Europe (1 *S.* Typhi isolate).

XDR outbreak strain (11). *S.* Paratyphi fluoroquinolone nonsusceptibility was noted among all isolates (8 of 8) and 62% (32 of 52) of isolates from travelers to Southeast Asia and South Asia, respectively. *S.* Paratyphi macrolide-nonsusceptible isolates were all from travelers to South Asia (5 of 22; 23%).

DISCUSSION

This retrospective analysis of travel-associated enteric fever reported from 68 global clinical sites between 2007 and 2018 indicates that typhoid and paratyphoid fever still represent significant health risks to travelers. Global travel-related typhoid and paratyphoid fever surveillance is instrumental to improving travelers' health as well as international control efforts.

Primarily typhoid fever and, to a lesser degree, paratyphoid fever have long been recognized as important febrile illness etiologies in travelers, especially among those who travel to Asia (17, 18). About half of cases were due to *S.* Paratyphi infection. Similarly, approximately 50% of reported enteric fever cases in the United Kingdom between 2008 and 2017 were paratyphoid fever while this infection accounts for about 20% or less of reported enteric fever cases in the United States (19, 20). However, an increasing proportion of travel-associated paratyphoid fever, primarily caused by *S.* Paratyphi A acquired in southern Asia, has been recently noted in national surveillance programs (4). This increase may be partially due to typhoid fever vaccines' protective effects against infection with *S.* Typhi, or it may reflect actual increases in *S.* Paratyphi A infection prevalence that has been reported in some Asian countries (21). Enteric fever transmission remains heavily concentrated in countries in South Asia, including Bangladesh, India, Nepal, and Pakistan (22, 23), where most travelers in this analysis acquired their infections. More travelers will be at risk for exposure to enteric fever as the strongest growth in tourist arrivals over the next decade has been estimated for countries in South Asia, Southeast Asia, and the Pacific region (24).

Symptoms in travelers with enteric fever were nonspecific and aligned well with the results of a recent enteric fever systematic review (25). Frequently, the clinical presentation may mimic other febrile illnesses like malaria, dengue fever, or influenza, which may cause a delay in establishing the diagnosis and rapidly initiating presumptive treatment (26). GeoSentinel does not collect data on clinical complications, yet the similar proportion of hospitalizations for typhoid and paratyphoid fever in this analysis suggests that paratyphoid has a comparable potential for severe illness (21).

Travelers with typhoid fever differed in some important respects from those with paratyphoid infections. While typhoid fever was more frequent in VFRs and while most travelers with typhoid fever did not have a pretravel consultation, paratyphoid fever

was more commonly diagnosed in tourists, and about half traveled without a pretravel consultation. This difference possibly reflects the impact of the pretravel consultation on typhoid fever vaccine use. While many international travelers to high-risk regions do not seek travel health advice before departure (18, 27), VFRs, in particular, are even less likely than other travelers to do so (28–31). Lack of risk awareness, financial barriers to pretravel care including typhoid vaccine, cultural and language barriers to access health care, and often departure on short notice may explain this behavior (31). Consequently, traveler health outreach and education programs, especially programs tailored for VFRs, are urgently needed.

Enteric fever primarily infects children in regions of endemicity but may also affect children traveling internationally to areas where enteric fever is endemic. In one U.S. study based on national surveillance data, up to 41% of infections were among children of $<$18 years of age (1), emphasizing that pediatric travelers may carry a disproportionate risk of enteric fever during international travel to high-risk regions (32). In this analysis, pediatric travelers with enteric fever, and especially those $\leq$5 years of age, were more frequently diagnosed with typhoid, were VFRs, and had not received a pretravel consultation in comparison to the entire cohort of cases analyzed. On the other hand, more teenage travelers with enteric fever traveled for tourism. This finding is in line with results from the Global TravEpiNet analysis on pediatric international travelers' pretravel health preparation (33). In this multicenter U.S. study, young children ($\leq$5 years old) seeking pretravel health care were disproportionally VFRs who traveled for long periods ($>$28 days) to high-risk regions in Africa and Asia, a type of travel that possesses recognized factors associated with increased risk for travel-associated illnesses, including enteric fever (33). Consequently, children and, in particular, child VFRs are an important target group for prevention efforts (32). Children frequently see primary pediatric heath care providers for routine care; therefore, training and educating pediatric providers may help identify children with travel plans and improve access to prevention counseling and typhoid vaccine usage.

Data on typhoid vaccination were limited, but the proportion of travelers vaccinated was low, comparable to rates described in U.S. surveillance data of typhoid cases from 2011 to 2015 (2.8 to 5.3%) (19). While currently available typhoid vaccines have been shown to provide moderate protection to travelers to regions of endemicity, efforts to increase vaccination rates among travelers to areas of endemicity are still recommended to help reduce travel-associated typhoid fever (7). As almost 1 in 5 typhoid fever cases in this analysis had traveled for less than 2 weeks, short-term travelers to high-risk destinations are likely to benefit from vaccination as well. However, young children are inadequately covered by the current vaccines: the Vi-PS vaccine is indicated for use in children from the age of 2 years (as it is poorly immunogenic in children under 2 years of age), and the oral Ty21a vaccine is indicated for use in children from the age of 5 years (as capsules are difficult to swallow for young children). The next-generation conjugated typhoid vaccines promise to be more efficacious and allow infant immunization between the age of 6 months and 2 years (34, 35). The programmatic introduction of the typhoid conjugate vaccine in regions of endemicity in Africa and Asia is under way, but its availability to international travelers will require more study and time (36). Moreover, an effective vaccine against paratyphoid is needed, given its increasing epidemiologic significance among persons living in regions of endemicity in Asia and in travelers alike (21).

Successful patient management with suspected enteric fever depends on the early empirical initiation of effective antibiotic therapy. These data confirm previous findings that fluoroquinolones should be clearly avoided in this context as nonsusceptibility to this drug class was frequently observed in travelers with typhoid and paratyphoid fever acquired in diverse geographic regions, including South Asia, Southeast Asia, sub-Saharan Africa, and Central America (15). Genomic studies have shown that the currently predominant *S.* Typhi genotype H58, associated with MDR and fluoroquinolone resistance mutations, has spread from South Asia and the Middle East to many African regions except West Africa (15, 37). Antimicrobial

susceptibility testing (AST) data were consistent with those of a recent U.S. surveillance study which demonstrated infrequent MDR isolates among travelers with typhoid fever and none among those with paratyphoid fever (4). In contrast, a recent U.K. *S.* Typhi genomic surveillance study found that one in four isolates was MDR, but the rates varied greatly by region (15). While no typhoid cases in this cohort were XDR and third-generation cephalosporins appear to be a reasonable empirical antimicrobial choice, it should be noted that travelers with XDR *S.* Typhi infections have been recently reported (11–14). Resistance to macrolides, which have been hailed as an inexpensive alternative in the face of mounting antimicrobial resistance, was noted at rates similar to those of previous studies in returning travelers and of culture surveillance in Asia (22, 38), while a recent study raised concerns about delayed treatment responses to azithromycin (39). Carbapenems may therefore be an appropriate alternative when empirical antimicrobial treatment for enteric fever is started, particularly in severe disease acquired in a region where XDR *S.* Typhi has been reported (12).

This report of travel-associated typhoid and paratyphoid cases has several limitations. GeoSentinel sites are specialized tropical and travel health clinics, and reported cases are not representative of all travel-associated enteric fever cases. Moreover, these data are not population based, lack denominator data, and hence cannot provide rates or incidence estimates. Second, beyond limited demographic information (e.g., age and sex), other variables are not specific to a given diagnosis (e.g., country of exposure or hospitalization); thus, records with another acute infectious disease diagnosis in addition to *S.* Typhi or *S.* Paratyphi infection were excluded to ensure that the data provided were specific to the diagnoses of interest. Clinical (including vaccination information) and antibiotic resistance data were collected only since 2015. In addition, AST protocols varied across clinical sites. While most reported AST results were for clinically relevant antimicrobials (e.g., fluoroquinolones and third-generation cephalosporins), less frequently reported AST results (e.g., ampicillin) may not be as reliable.

Conclusions. Although recent estimates indicate a reduction in the global burden, enteric fever continues to cause serious illness in international travelers. In ill travelers it often remains a challenge to diagnose and manage enteric fever due to nonspecific clinical characteristics and rising AMR. Our data may contribute to a better understanding of region-specific AMR, thus helping to inform clinicians' empirical treatment choices. High-risk travelers, including VFRs and children, should be actively screened for future travel during routine health care encounters, ensuring timely access to appropriate preventive measures, including typhoid vaccination.

MATERIALS AND METHODS

Data source. GeoSentinel is a global clinician-based sentinel surveillance system of 68 specialized travel and tropical medicine sites in 28 countries that monitor travel-related illnesses among international travelers and migrants (www.istm.org/geosentinel). It was established in 1995 as a collaboration between the U.S. Centers for Disease Control and Prevention (CDC) and the International Society of Travel Medicine (ISTM). All sites have experience diagnosing travel-related infectious diseases and use the best diagnostic methods available in their respective countries. GeoSentinel diagnosis codes have standardized case definitions and are entered into the database by site clinicians. Treatment and clinical outcomes are not routinely reported. GeoSentinel's data collection protocol has been reviewed by the CDC's National Center for Emerging and Zoonotic Infectious Diseases and is classified as public health surveillance and not human subject research. In addition, local institutional review boards of participating sites reviewed and approved participation. For sites located in countries where national regulations required it, patient informed consent was obtained.

Inclusion and exclusion criteria. Records with a culture-confirmed diagnosis of travel-related *S.* Typhi or *S.* Paratyphi infection reported to GeoSentinel from 2007 through 2018 were included. Records were excluded if there was a nonascertainable region of exposure, more than one region of exposure, or an additional acute infectious disease diagnosis not related to enteric fever (e.g., dengue fever).

Data extraction. Data were extracted on traveler demographics (e.g., age and sex), trip details (e.g., travel duration, travel reason, and receipt of a pretravel consultation with a health care provider), clinical visit information (e.g., presentation date to the GeoSentinel site, hospitalization, diagnostic specimens and methods, and antimicrobial susceptibility testing [AST] results), disease attributes (e.g., region and country of acquisition and typhoid vaccination history), and clinical presentation (e.g., illness onset data and symptoms). GeoSentinel began systematically collecting symptom data in 2014. Starting in 2015, vaccination information, AST results, diagnostic specimens, and diagnostic methods were collected.

Isolates that undergo AST at GeoSentinel sites are subject to site- and country-specific testing methods. Isolates were classified as nonsusceptible if intermediate or resistant or as susceptible in accordance with participating site's national guidelines.

Statistical analysis. Data were managed with Microsoft Access (Redmond, WA, USA). All analyses were descriptive and performed using SAS, version 9.4 (Cary, NC, USA).

ACKNOWLEDGMENTS

We thank Aisha Rizwan for her assistance with project coordination.

GeoSentinel, the Global Surveillance Network of the International Society of Travel Medicine (ISTM), is supported by a Cooperative Agreement (U50CK00189) from the Centers for Disease Control and Prevention (CDC), as well as by funding from the ISTM and the Public Health Agency of Canada. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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