Enteric fever among children: 50 cases in a French tertiary care centre

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ABSTRACT

Background

Enteric fever in France is primarily travel-associated. Characteristics of paediatric cases are scarce and information from field studies in endemic countries might not be generalizable to non-endemic countries.

Methods

In this retrospective study, we reviewed all cases of typhoid and paratyphoid fever treated in a French paediatric tertiary care centre from 1993 through 2015.

Results

Fifty cases of enteric fever due to *Salmonella enterica* serovar Typhi (n=44) and Paratyphi (n=6) were identified. Sixty-one percent of the children had travelled to Africa and 34 % to the Indian subcontinent. Among travel-associated cases, eighty-five percent were visiting friends and relatives (VFR). Ninety-six percent had high fever associated with gastrointestinal symptoms. Anaemia (66%), elevated CRP (80%), transaminitis (87%) and mild hyponatremia (50%) were the main biological findings. Blood cultures were positive in 90% of cases. Twelve strains (24%) were resistant at least to one antibiotic, and all of them had been isolated since 2003, increasing the resistance rate during this last period to 43% (12/28). Ceftriaxone was administered to 71 patients for a median duration of 6 days (IQR: 4–8). The median time to apyrexia after onset of treatment was 4 days (IQR: 2–5 days). Complications occurred in 9 children with 5 (10%) presenting neurologic disorders. All 50 patients recovered.

Conclusion

In France, paediatric enteric fever is mainly a travel-associated disease and occurs in patients returning from a prolonged stay in an endemic area. Children VFR are at high risk and should

be a priority target group for pre-travel preventive measures. The increase in antibiotic resistance reflects the situation in endemic countries and is a major concern.

INTRODUCTION

Typhoid and paratyphoid fever are systemic infections caused by human-adapted pathogens: *Salmonella enterica*, including *S. enterica* serovar Typhi (*S.* Typhi) and serovar Paratyphi *(S.* Paratyphi) A, B and C. These infections remain a major public health challenge in developing countries where populations live under conditions of poor sanitation. Over 26 million cases and 200,000 deaths are annually estimated worldwide, with the highest incidence being reported in Asia (over 100 cases per 100,000 persons/year) [1,2] and the greatest burden among children aged 2-15 years.[3,4] In past decades, antimicrobial resistance sequentially emerged from resistance to first-line drugs (chloramphenicol, ampicillin and cotrimoxazole), to fluoroquinolone and very recently to cephalosporin, leading to treatment failures and therefore increasing the disease burden in endemic countries.[5,6]

In developed countries, the incidence of enteric fever has dramatically declined over the past century and has become a predominantly travel-associated disease.[7] In France, laboratory-confirmed *S.* Typhi and *S.* Paratyphi infections are notifiable conditions and epidemiological investigations are carried out by Public Health authorities to prevent secondary transmission from identified cases and identify the source of contamination for non-travel-associated cases.[8] From 1999–2015, a total of 1928 cases were reported among residents of mainland France (mean estimated incidence: 1.84 cases per million population).[9] Of those, 1577 (82%) occurred among travellers returning from endemic countries in the month prior to symptom onset, predominantly from Africa (48%), followed by Asia (46%). The risk for infection

among travellers varies with the destination and the purpose of travel.[7,8] Travellers "visiting friends and relatives" (VFR) are recognized as a high-risk group for enteric fever.[10]

Current knowledge on paediatric enteric fever is mainly provided by studies in endemic countries where children bear the highest burden in terms of incidence and complications.[3,11] Clinical features of enteric fever might differ between younger and older children and adults.[4] In France, children under 18 years account for 32% of the total number of enteric fever cases.[9]

Data describing paediatric enteric fever cases in non-endemic countries are scarce. Meanwhile, the proportion of children among travellers is increasing[12,13] and particularly among VFR travellers where infants and young children are over-represented as compared with non-VFR travellers.[14,15] Furthermore, compared with adult travellers, children are at higher risk for infectious diseases and specifically for faecal-oral infections.[16,17]

To identify demographic, clinical and microbiological features of paediatric enteric fever in a non-endemic area, we conducted a retrospective analysis of all cases of typhoid and paratyphoid fever among paediatric patients in a French tertiary health care centre.

PATIENTS AND METHODS

Study design and definitions

All cases of typhoid and paratyphoid fever among patients less than 18 years of age treated at the Robert-Debré teaching hospital in Paris, France, from July 1st 1993 through December 31st 2015 were retrospectively reviewed. Robert-Debré Hospital serves a population with low socio-economic status and a large proportion of immigrants.[18]

A case was defined, in accordance with the European and national case definition, as an "acute illness compatible with typhoid or paratyphoid fever (i.e sustained fever with headache, diarrhoea, constipation, malaise or abdominal pain…) associated with the isolation

of *S.* Typhi or *S.* Paratyphi A, B or C from blood, stool or other clinical specimens" [1]. Enteric fever was considered to be travel-associated if the patient had travelled within one month before symptoms onset, if not, cases were considered to be domestically-acquired.

Data collection

Cases were identified by querying both laboratory and hospital discharge databases using codes for *S.* Typhi, *S.* Paratyphi A, B and C and "typhoid and paratyphoid fever" according to the ICD-10.

All epidemiological, demographic, clinical, biological, radiological, antimicrobial treatment and clinical outcomes data were extracted from medical charts and collected using EpiData Software® version 3.0 (The EpiData Association, Odense, Denmark).

Laboratory methods

Salmonella species and serovars were determined using biochemical tests (API 20^{E} system bioMérieux, Marcy-l'Etoile, France) and specific immune sera. Susceptibility to antimicrobial drugs was tested by the disk diffusion method according to the French recommendations (CA-SFM 2011[2]); 32 antibiotics were tested. Minimum inhibitory concentrations (MIC) were determined using the E-test method (bioMerieux, Marcy-l'Etoile, France). We considered susceptibility to ampicillin, cotrimoxazole, ceftriaxone, nalidixic acid and ciprofloxacin; azithromycin was also considered for cases from 2009 and thereafter. Resistance to ceftriaxone was defined by a MIC above 2 mg/l. Resistance to nalidixic acid was defined by a MIC above 16 mg/l, decreased susceptibility to ciprofloxacin by a MIC between 0.5 mg/l and

[1] 2002/253/EC: Commission Decision of 19 March 2002 laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Official Journal, OJ L 86, 03.04.2002, p. 44–62

[2] http://www.sfm-microbiologie.org/UserFiles/files/casfm/casfm_2011.pdf

1 mg/l and resistance to ciprofloxacin by a MIC above 1 mg/l. A strain was considered susceptible to azithromycin if the MIC was below 16 mg/l.

Statistical analysis

Continuous variables were summarised using median and interquartile range (IQR), and categorical variables were summarised using frequencies and percentages. Continuous data were compared using the non-parametric Mann-Whitney test and rates using the Fisher exact test. Statistical significance was set at the 5% level (2-sided *P* value). Analyses were conducted using STATA software (version 11.0; StatCorp LP, College Station, TX, USA).

Ethics approval

Data collection was approved by the French National Data Protection Commission (number 1898715) and the local institutional review board approved the study. Data were de-identified, in keeping with the French legislation [3].

RESULTS

Demographics and travel history

From 1993 to 2015, 50 cases of typhoid (n=44) and paratyphoid (n=6) fever among children and adolescents were identified.

Table 1 shows the general characteristics of the 50 patients included in the study. Median age was 7 years (IQR: 3.2–10.8), and male-to-female ratio was 0.9. Patients were equally distributed among age groups.

Forty-three patients (86%) had returned from an endemic region within 1 month prior to symptoms onset. Among the 41 travel-associated infections with available information

[3] Loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés modifiée.

regarding the region visited, 25 (61%) were acquired in Africa (Table 1). The reason for travel was known for 34 (81%) of these children: 29 (85%) were VFR and 3 (9%) were expatriates living in endemic countries. For the 39 returning travellers with complete information concerning dates of travel, the median duration of stay abroad was 8 weeks (IQR: 5.6–8.9).

Seven children (14%) had no recent travel history. All those 7 non-travel-associated cases occurred over 10 years prior to our study; we were therefore not able to retrieve the results of the investigations conducted by the public health authorities since data had since been de-identified. One patient had travelled to Cameroon 2 years prior to diagnosis and no microbiological investigations had been conducted within the family. Two patients had been in contact with a family member confirmed as a *S.* Typhi asymptomatic carrier. One case in 1999 appeared to be linked to the ingestion of shellfish. For the 3 remaining cases, no information on the source of infection was available.

Information concerning vaccinations was known for 45 (90%) patients. Three had received the Typhim Vi® vaccine within the past 3 years and all had travel-associated *S.* Typhi infections. For one, a *S.* Paratyphi A co-infection was additionally confirmed.

Clinical findings

Clinical findings are summarised in table 2. Of the 36 cases for which both date of return from travel and date of symptoms onset were available, median interval between return and symptoms was 0.5 days (IQR: -7–13.5) and median interval from symptoms onset to diagnosis was 8 days (IQR: 4–12). Illness was characterised by a history of fever combined with gastrointestinal symptoms in 48 patients (96%). Constipation (6%), rose spots (6%), splenomegaly (6%) and relative bradycardia (6%) were not commonly reported.

Clinical findings were not significantly different in patients infected with *S.* Typhi compared with the patients infected with *S.* Paratyphi and (data not shown).

Laboratory and imaging features

The main laboratory findings are presented in table 2. Anaemia, according to the WHO definition[4], was present in 33 (66%) patients with 10 (31%) presenting a mild and 21 (66%) a moderate anaemia. Among them, one patient with a pre-existing chronic renal failure presented with severe anaemia requiring red blood cell transfusion. Thirty-nine (87%) patients had elevated liver enzymes of which 14 (31%) had AST and/or ALT 3-fold above normal. Of these, 5 exhibited a clinical and radiological hepatomegaly and 3 had jaundice. Twenty-four (50%) patients presented with hyponatremia at time of diagnosis. In 10 (21%), sodium level was under 130 mmol/l and in 4 (8%) under 125 mmol/l. Biologic features were not significantly different in patients infected with *S.* Typhi compared with patients infected with *S.* Paratyphi (data not shown).

Abdominal ultra-sound was performed in 24 (48%) patients, 11 (46%) were considered normal, whereas 10 (42%) showed hepatomegaly, of which 3 were combined with a splenomegaly. Splenomegaly alone was found in 2 (8%) patients, and one had gall bladder stones.

Microbiological findings

Overall, 44 (88%) *S.* Typhi and 6 (12%) *S.* Paratyphi, including 4 *S.* Paratyphi A and 2 *S.* Paratyphi B, strains were identified. Strains were isolated in blood culture (n=45; 90%), in stool culture (n=3; 6%) or in urine culture (n=2; 4%).

[4] http://www.who.int/vmnis/indicators/haemoglobin.pdf

Thirty-five (80%) *S.* Typhi and 6 (100%) *S.* Paratyphi infections were travel-associated. All *S.* Paratyphi A strains were isolated in patients returning from the Indian sub-continent.

Table 3 shows the antibiotic resistance profiles of the 12 non-fully susceptible strains, which have all been isolated since 2003. As such, since 2003, 43% (12/28) of the isolated strains showed antibiotic resistance. Eleven (79%) of the 14 strains isolated from patients returning from the Indian sub-continent and 1 (8%) of the 12 isolated from patients returning from Sub-Saharan Africa were resistant. No strain was resistant to third-generation cephalosporin, and the azithromycin MIC was below 16 mg/L for all strains.

Management and outcome

Forty-eight patients (96%) were admitted to hospital for a median duration of 7 days (IQR: 5.5–9).

A third-generation cephalosporin was administered as the first-line regimen to 47 (94%) patients, of which 46 (92%) received ceftriaxone for a median duration of 6 days (IQR: 4–8) at a median dose of 50 mg/kg/d (IQR: 50–75). Two patients received ciprofloxacin at admission, one for a urinary tract infection. Additional antibiotics were administered to 23 (46%) children, of which 13 (57%) received an aminoglycoside. Two patients were not admitted and received daily IV ceftriaxone in the outpatient department. Six patients received azithromycin during 4 to 7 days after a short course (5 days) of ceftriaxone and 6 received ciprofloxacine during 5 to 7 days.

The median time to apyrexia after onset of treatment was 4 days (IQR: 2–5).

Complications occurred in 9 (18%) patients, and 4 (8%) were admitted to a paediatric intensive care unit (PICU); 5 (10%) presented neurologic disorders such as confusion and altered consciousness. Encephalitis was diagnosed in one, who presented febrile seizures,

confusion and altered consciousness. He recovered after 48 hours of antibiotic treatment. One patient was admitted to PICU for severe dehydration. Appendicitis, syndrome of inappropriate antidiuretic hormone secretion and haemophagocytic syndrome were observed in 1 patient each. Five children had a follow-up visit with stool culture 2 weeks to one month after discharge. All 50 children fully recovered.

DISCUSSION

To our knowledge, this is the largest study of enteric fever among children in a European hospital. This study highlights the demographic, clinical and microbiologic characteristics of 50 paediatric cases. Forty-three (86%) cases were imported, of which 61% were acquired in Africa. This distribution is different from what is reported in other studies from non-endemic countries where most infections were acquired in the Indian subcontinent and South-East Asia.[13,19,20] It is however consistent with French national surveillance data from 1999–2015 which show that travel-associated enteric fever cases among persons aged under 18 are predominantly acquired in Africa (61%) followed by Asia (36%).[9] Forty-four percent of immigrants in France come from Africa, 31% from Europe and 25% from the rest of the world. The proportion of immigrants originating from Africa is even higher in Paris region, with 50% versus 3.7% from the Indian subcontinent.[18]The observed distribution might reflect the countries of origin of the immigrant population served by the Robert Debré Hospital. Furthermore, this immigrant population includes a substantial proportion of VFRs [21] and children are over represented among VFR travellers as compared to non-VFR travellers.[10,14]

In this case series, 85% of the travelling children were VFRs. The median duration of stay in an endemic region was prolonged (8 weeks). Studies have identified that length of stay, visits to rural areas, not following food and water precautions and not receiving pre-travel advice are factors associated with a higher risk for enteric fever among travellers.[22] VFR travellers

usually combine these risk factors[23]: in a study among returning travellers in Quebec, VFRs accounted for 94.4% of typhoid cases.[10] Furthermore, the majority of the children in our study had not been vaccinated, which suggests a lack of pre-travel health advice. VFR travellers face multiple barriers to accessing and/or accepting pre-travel health advices including language barriers, lack of knowledge about travel-associated health risks, and a perception of an immunity due to previous travels stay and/or birth in their country of origin [21] Therefore, children VFR should be a priority target group for preventive pre-travel measures. Increasing the awareness of healthcare professionals on travel-associated risks in this group is one key element to reduce the number of imported cases of enteric fever.[10,21]

In our study, seven (14%) cases were acquired domestically, all before 2001. Epidemiological investigations carried out by the Public Health authorities for non-travel-associated cases aim to (i) identify the source of infection and (ii) mitigate the risk for secondary transmission and outbreaks. These investigations are complex and resource intensive. They might require screening for chronic carriers, acute or convalescent patients or contaminated food and often the source is not identified. [24]

Three children above 2 years of age had a documented history of typhoid vaccination. Two types of vaccines are recommended for travellers: a live-attenuated oral vaccine (Ty21a) and a parenteral Vi polysaccharide vaccine. In France, only the typhoid Vi vaccine is available and recommended to travellers above 2 years of age.[25] The effectiveness of both vaccines is moderate and ranges from 60% to 80% and appears to be similar among travellers as among population in endemic regions. [26–28] Conflicting results have been published in children from 2 to 5 years old, effectiveness varying from 35% in Pakistan to 80% in India but was similar to adults in travellers from UK.[28] Furthermore, these vaccines are effective only against *S.* Typhi strains, yet the incidence of *S.* Paratyphi A appears to be growing, exceeding the

incidence of *S.* Typhi in certain regions.[29] These findings underline that hygiene precautions remain essential to prevent these water- and food-borne diseases.

As described in previous studies among children and adults in endemic and non-endemic countries, clinical features of enteric fever are non-specific and mimic other febrile illnesses like malaria, dengue fever or influenza, especially in younger children.[4,19,20,30,31] Fever (48–96%), asthenia (42–84%) and intestinal symptoms (e.g., diarrhoea (37–74%), vomiting (24–48%) and abdominal pain (25–50%)), were the most common findings in our case series. More specific features (e.g., rose spots, relative bradycardia) appear in the third or fourth week of evolution, which is rarely observed in European medical settings.[32] Mild anaemia elevated liver enzymes; raised CRP and mild hyponatremia were the main biological findings in our patients.. Over 80% of them exhibited elevated transaminases, and 31% had rates more than threefold above the normal range.. Typhoid hepatitis is more frequently seen in children[4] and distinguishing typhoid hepatitis from viral hepatitis can be challenging. Transaminitis is less acute and less severe in typhoid hepatitis than in other acute types of hepatitis, and the outcome is always favourable after antibiotic treatment.[33] Hyponatremia, reported in 50% of our patients, was also described in the same proportion in two adult case series.[19,30] Although the pathophysiology is unclear, one could suggest a syndrome of inappropriate antidiuretic hormone secretion or haemophagocytic syndrome.

Apyrexia was obtained in 4 days (IQR: 2–5) after onset of treatment, which is consistent with paediatric studies in endemic countries. Complications were reported in 9 (18%) children, of which 5 presented neurological disorders and 4 required a transfer to a PICU. These rates are higher than those reported in adult return travellers[20,30,31] and closer to those observed among children in endemic countries.[4] In endemic countries, neurologic complications are predominantly described in children whereas neuropsychiatric changes, delirium and insomnia are more frequent in adults.[4,34]

In this case series, since 2003, 43% of the isolated strains demonstrated resistance or reduced susceptibility to antibiotics, mostly imported from South Asia, with different resistance patterns reflecting the recent and rapid evolution of resistance mechanisms in this region.[5,6] As multidrug-resistant strains (resistant to chloramphenicol, cotrimoxazole and ampicillin) became widespread in the 1980s [6,35], fluoroquinolones have provided an effective simple oral regimen in the last two decades. However, the emergence of nalidixic acid-resistant strains with decreased susceptibility and documented resistance to ciprofloxacin [36] has been associated with prohibitive rates of treatment failure and relapse in endemic regions as well as among travellers. [37–39] These evolutions have been observed in South Asia and, in lower proportions, in Africa.[5,36,38] Thus, a 10 to 14 days course of ceftriaxone appears to be a reasonable option as first-line treatment for adults returning from the Indian sub-continent and all paediatric patients[36,37]. Although relapse rates of 5 to 15% at 1 month have been described with short-course ceftriaxone therapy[40,41], 94% of the patients in our series received a short-course of ceftriaxone (median 6 days; IQR: 4–8.5) and no relapse or treatment failure were observed. Meanwhile, as in non-Typhi *Salmonella* and *Enterobacteriaceae*, extended-spectrum beta-lactamase (ESBL)-producing *S.* Typhi and *S.* Paratyphi A isolates have recently been reported. [42]

Trials suggest short-course azithromycin (20 mg/kg/day, with a maximum dose of 1000 mg/day) as a safe therapeutic option for uncomplicated enteric fever in children and adults.[37,40,43] The once-daily administration combined with the short duration of treatment could improve compliance and therefore ease the treatment of enteric fever [37,43] Although no clinical breakpoints are available to define azithromycin susceptibility or resistance, alarming reports of strains with increasing MICs for azithromycin have been published.[44]

This descriptive analysis of 50 paediatric enteric fever cases highlights that paediatric enteric fever in France is mainly travel-associated and that children VFR are particularly at

risk. In returned travellers, high fever associated with intestinal and/or neurological symptoms, elevated CRP, mild hepatitis, hyponatremia and anaemia should alert physicians to the possibility of enteric fever, and blood cultures should be performed. The increase of antibiotic resistance of *S.* Typhi and *S.* Paratyphi isolates in travel-associated cases reflects the situation in endemic countries and is a major concern. Children VFRs bear the highest burden of infectious diseases, including enteric fever, and pre-travel health preventive programs should target this high-risk group of travellers.

Author contributions:

Virginie Pommelet designed the study, collected, analyzed the data and drafted the manuscript, which was reviewed and edited by all other authors. Patricia Mariani carried out the laboratory analysis.

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REFERENCES

1. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ*. 2004;82(5):346-353.

2. Maurice J. A first step in bringing typhoid fever out of the closet. *Lancet*. 2012;379(9817):699-700.

3. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al. A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bull World Health Organ*. 2008;86(4):260-268.

4. Britto C, Pollard AJ, Voysey M, Blohmke CJ. An Appraisal of the Clinical Features of Pediatric Enteric Fever: Systematic Review and Meta-analysis of the Age-Stratified Disease Occurrence. *Clinical Infectious Diseases*. 2017;64(11):1604-1611. doi:10.1093/cid/cix229

5. Crump JA, Mintz ED. Global Trends in Typhoid and Paratyphoid Fever. *Clinical Infectious Diseases*. 2010;50(2):241-246. doi:10.1086/649541

6. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant Salmonella typhi: a worldwide epidemic. *Clin Infect Dis*. 1997;24 Suppl 1:S106-9.

7. Connor BA, Schwartz E. Typhoid and paratyphoid fever in travellers. *Lancet Infect Dis*. 2005;5(10):623-628.

8. Delmas G, Vaillant V, Jourdan N, Le Hello S, Weill FX, de Valk H. Typhoid and paratyphoid fever in France between 2004 and 2009. *Bull Epidemiol Hebd*. 2011;2:9-12.

9. http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-declaration-obligatoire/Fievres-typhoides-et-paratyphoides/Donnees-epidemiologiques.

10. Bui Y-G, Trépanier S, Milord F, Blackburn M, Provost S, Gagnon S. Cases of Malaria, Hepatitis A, and Typhoid Fever Among VFRs, Quebec (Canada). *Journal of Travel Medicine*. 2011;18(6):373-378. doi:10.1111/j.1708-8305.2011.00556.x

11. Sinha A, Sazawal S, Kumar R, et al. Typhoid fever in children aged less than 5 years. *Lancet*. 1999;354(9180):734-737.

12. Herbinger K-H, Drerup L, Alberer M, Nothdurft H-D, Sonnenburg F von, Löscher T. Spectrum of imported infectious diseases among children and adolescents returning from the tropics and subtropics. *J Travel Med*. 2012;19(3):150-157. doi:10.1111/j.1708-8305.2011.00589.x

13. Khatami A, Khan F, Macartney KK. Enteric Fever in Children in Western Sydney, Australia, 2003-2015. *Pediatr Infect Dis J*. 2017;36(12):1124-1128. doi:10.1097/INF.0000000000001606

14. Han P, Yanni E, Jentes ES, et al. Health challenges of young travelers visiting friends and relatives compared with those traveling for other purposes. *Pediatr Infect Dis J*. 2012;31(9):915-919. doi:10.1097/INF.0b013e318259efbe

15. Hagmann S, Neugebauer R, Schwartz E, et al. Illness in children after international travel: analysis from the GeoSentinel Surveillance Network. *Pediatrics*. 2010;125(5):e1072-1080. doi:10.1542/peds.2009-1951

16. Newman-Klee C, D'Acremont V, Newman CJ, Gehri M, Genton B. Incidence and types of illness when traveling to the tropics: a prospective controlled study of children and their parents. *Am J Trop Med Hyg*. 2007;77(4):764-769.

17. Maloney SA, Weinberg M. Prevention of infectious diseases among international pediatric travelers: considerations for clinicians. *Semin Pediatr Infect Dis*. 2004;15(3):137-149.

18. https://www.insee.fr/fr/statistiques/2874036?sommaire=2874056&geo=REG-11.

19. Patel TA, Armstrong M, Morris-Jones SD, Wright SG, Doherty T. Imported enteric fever: case series from the hospital for tropical diseases, London, United Kingdom. *Am J Trop Med Hyg*. 2010;82(6):1121-1126. doi:10.4269/ajtmh.2010.10-0007

20. Dave J, Millar M, Maxeiner H, et al. East London experience with enteric fever 2007-2012. *PLoS ONE*. 2015;10(3):e0120926. doi:10.1371/journal.pone.0120926

21. Hendel-Paterson B, Swanson SJ. Pediatric travelers visiting friends and relatives (VFR) abroad: Illnesses, barriers and pre-travel recommendations. *Travel Medicine and Infectious Disease*. 2011;9(4):192-203. doi:10.1016/j.tmaid.2010.09.007

22. Steinberg EB, Bishop R, Haber P, et al. Typhoid fever in travelers: who should be targeted for prevention? *Clin Infect Dis*. 2004;39(2):186-191. doi:10.1086/421945

23. Angell SY, Cetron MS. Health disparities among travelers visiting friends and relatives abroad. *Ann Intern Med*. 2005;142(1):67-72.

24. Balasegaram S, Potter AL, Grynszpan D, et al. Guidelines for the public health management of typhoid and paratyphoid in England: practice guidelines from the

National Typhoid and Paratyphoid Reference Group. *J Infect*. 2012;65(3):197-213. doi:10.1016/j.jinf.2012.05.005

25. http://invs.santepubliquefrance.fr/Publications-et-outils/BEH-Bulletin-epidemiologique-hebdomadaire/Archives/2018/BEH-hors-serie-Recommandations-sanitaires-pour-les-voyageurs-2018.

26. Fraser A, Paul M, Goldberg E, Acosta CJ, Leibovici L. Typhoid fever vaccines: systematic review and meta-analysis of randomised controlled trials. *Vaccine*. 2007;25(45):7848-7857. doi:10.1016/j.vaccine.2007.08.027

27. Mahon BE, Newton AE, Mintz ED. Effectiveness of typhoid vaccination in US travelers. *Vaccine*. 2014;32(29):3577-3579. doi:10.1016/j.vaccine.2014.04.055

28. Wagner KS, Freedman JL, Andrews NJ, Jones JA. Effectiveness of the typhoid Vi vaccine in overseas travelers from England. *J Travel Med*. 2015;22(2):87-93. doi:10.1111/jtm.12178

29. Ochiai RL, Wang X, von Seidlein L, et al. Salmonella paratyphi A rates, Asia. *Emerg Infect Dis*. 2005;11(11):1764-1766. doi:10.3201/eid1111.050168

30. Clark TW, Daneshvar C, Pareek M, Perera N, Stephenson I. Enteric fever in a UK regional infectious diseases unit: a 10 year retrospective review. *J Infect*. 2010;60(2):91-98. doi:10.1016/j.jinf.2009.11.009

31. Caumes E, Ehya N, Nguyen J, Bricaire F. Typhoid and paratyphoid fever: a 10-year retrospective study of 41 cases in a Parisian hospital. *J Travel Med*. 2001;8(6):293-297.

32. Cunha BA. Typhoid fever: the temporal relations of key clinical diagnostic points. *Lancet Infect Dis*. 2006;6(6):318-320; author reply 320-1. doi:10.1016/S1473-3099(06)70472-8

399 33. Shetty AK, Mital SR, Bahrainwala AH, Khubchandani RP, Kumta NB. Typhoid hepatitis in
400 children. *J Trop Pediatr*. 1999;45(5):287-290.

401 34. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med*.
402 2002;347(22):1770-1782. doi:10.1056/NEJMra020201

403 35. Gupta SK, Medalla F, Omondi MW, et al. Laboratory-based surveillance of paratyphoid
404 fever in the United States: travel and antimicrobial resistance. *Clin Infect Dis*.
405 2008;46(11):1656-1663. doi:10.1086/587894

406 36. Date KA, Newton AE, Medalla F, et al. Changing Patterns in Enteric Fever Incidence and
407 Increasing Antibiotic Resistance of Enteric Fever Isolates in the United States, 2008–
408 2012. *Clinical Infectious Diseases*. 2016;63(3):322-329. doi:10.1093/cid/ciw232

409 37. Thompson CN, Karkey A, Dongol S, et al. Treatment Response in Enteric Fever in an Era
410 of Increasing Antimicrobial Resistance: An Individual Patient Data Analysis of 2092
411 Participants Enrolled into 4 Randomized, Controlled Trials in Nepal. *Clinical Infectious*
412 *Diseases*. 2017;64(11):1522-1531. doi:10.1093/cid/cix185

413 38. Crump JA, Kretsinger K, Gay K, et al. Clinical response and outcome of infection with
414 Salmonella enterica serovar Typhi with decreased susceptibility to fluoroquinolones: a
415 United States foodnet multicenter retrospective cohort study. *Antimicrob Agents*
416 *Chemother*. 2008;52(4):1278-1284. doi:10.1128/AAC.01509-07

417 39. Hume S, Schulz T, Vinton P, Korman T, Torresi J. Increasing rates and clinical
418 consequences of nalidixic acid-resistant isolates causing enteric fever in returned

travellers: an 18-year experience. *Eur J Clin Microbiol Infect Dis*. 2009;28(8):963-970. doi:10.1007/s10096-009-0732-6

40. Frenck RW Jr, Nakhla I, Sultan Y, et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clin Infect Dis*. 2000;31(5):1134-1138. doi:10.1086/317450

41. Bhutta ZA, Khan IA, Shadmani M. Failure of short-course ceftriaxone chemotherapy for multidrug-resistant typhoid fever in children: a randomized controlled trial in Pakistan. *Antimicrob Agents Chemother*. 2000;44(2):450-452.

42. Pokharel BM, Koirala J, Dahal RK, Mishra SK, Khadga PK, Tuladhar NR. Multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing Salmonella enterica (serotypes Typhi and Paratyphi A) from blood isolates in Nepal: surveillance of resistance and a search for newer alternatives. *Int J Infect Dis*. 2006;10(6):434-438. doi:10.1016/j.ijid.2006.07.001

43. Frenck RW Jr, Mansour A, Nakhla I, et al. Short-course azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. *Clin Infect Dis*. 2004;38(7):951-957.

44. Hassing R-J, Goessens WHF, van Pelt W, et al. *Salmonella* Subtypes with Increased MICs for Azithromycin in Travelers Returned to the Netherlands. *Emerging Infectious Diseases*. 2014;20(4):705-708. doi:10.3201/eid2004.131536

	No. (%) (*n=50*)
Median age, years (IQR)	7 (3.2–10.8)
Sex	
Male	22 (44%)
Female	28 (56%)
Domestically-acquired infection	7 (14%)
Travel history	43 (86%)
Reason for travel (n=34)	
VFR	29 (85%)
Tourism	2 (6%)
Other[a]	3 (9%)
Region visited (n=41)	
Sub-saharan Africa	14 (34%)
Indian Sub-continent	14 (34%)
North Africa	11 (27%)
Middle East	1 (2%)
Other[b]	1 (2%)
Median duration of stay in an endemic region, weeks (IQR)[c]	8 (5.6-8.9)

IQR: interquartile range; VFR: visiting friends and relatives

[a] 3 patients were long-term expatriates returning from endemic countries

[b] French Guiana

[c] For the 39 children who were not long-term expatriates returning from an endemic region

Table 1. General characteristics and travel history of the 50 children with enteric fever

	No. (%)
Symptoms	
Fever	48 (96 %)
High grade fever (>40°C)	24 (48 %)
Chills	24 (48 %)
Asthenia	42 (84 %)
Headache	14 (28 %)
Abdominal pain	25 (50 %)
Nausea	9 (18 %)
Vomiting	24 (48 %)
Diarrhea	37 (74 %)
Blood in stools	2 (4 %)
Constipation	3 (6 %)
Physical signs	
Tachycardia	13 (26 %)
Relative bradycardia	3 (6 %)
Dehydration	22 (44 %)
Jaundice	6 (12 %)
Rose spots	3 (6 %)
Abdominal tenderness	24 (48 %)
Hepatomegaly	13 (26 %)
Splenomegaly	3 (6 %)
Laboratory features	
Anaemia[a]	33 (66%)
Leucopenia < 4000 / mm^3	2 (4 %)
Neutropenia < 1500/mm^3	4 (11 %)[b]
Thrombopenia < 150.000 /mm^3	9 (18 %)
CRP > 10 mg/L	40 (80 %)
Elevated AST and/or ALT > 45 UI/l[c]	39 (87%)
AST and/or ALT > 3N	14 (31 %)
Hyponatremia < 134 mmol/L[d]	24 (50 %)

[a] Acording to the WHO definition of anaemia adjusted to age (http://www.who.int/vmnis/indicators/haemoglobin pdf, accessed [17th july 2016]).
[b] Out of 36; [c] out of 45; [d] out of 48

Table 2. Clinical and biological features of the 50 children with enteric fever

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	Year	*S. enterica* Serovar	Country	Antibiotic resistance profile
1	2003	Typhi	Cameroun	MDR
2	2005	Typhi	Pakistan	Nal^R
3	2006	Typhi	Pakistan	Nal^R
4	2007	Typhi	India	Nal^R
5	2007	Typhi	Bangladesh	MDR-Nal^R
6	2009	Typhi	Pakistan	MDR-Nal^R
7	2009	Typhi	Pakistan	MDR-Nal^R
8	2010	Typhi	Bangladesh	Nal^R
9	2010	Paratyphi	Bangladesh	Nal^R
10	2010	Paratyphi	Pakistan	Cip^R
11	2013	Typhi	Bangladesh	MDR-Nal^R
12	2015	Typhi	India	Nal^R

MDR: Multiple drug resistance (resistant to the traditional first-line antimicrobial agents: ampicillin, chloramphenicol and cotrimoxazole)

Nal^R: resistant to Nalidixic acid (MIC>16 mg/l) and decreased ciprofloxacin susceptibility (MIC between 0.125 and 1 mg/l)

Cip^R: Resistant to ciprofloxacin (MIC >1 mg/l)

Table 3. Antibiotic resistance profiles and geographical origin of the 12 resistant *Salmonella enterica* strains

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