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Case Reports and Series

Enteric fever in a non-endemic setting: Review of cases over a 12-year period at University hospitals Birmingham, UK

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A B S T R A C T

Objectives: Enteric fever remains a common diagnosis in returned travellers to the UK, the majority of which require hospital admission. Increased resistance to antibiotics has complicated the management and rates of vaccine uptake remain unclear.
Methods: We performed a retrospective study of culture-confirmed cases of enteric fever from blood samples in patients admitted to University Hospitals Birmingham, UK, between January 2010 and June 2022 to assess antimicrobial susceptibility, treatment outcomes and vaccination uptake.
Results: In total, 108 patients were identified during the time period (*S.typhi* n = 57 [53 %]; *S.paratyphi* n = 51 [47 %]). Nearly all (93 % [100/108]) had returned from South Asia. There was no evidence of typhoid vaccination pre-travel for most patients (n = 96 [89 %]) in both groups. Over half of patients with *S.typhi* had microbiologically positive stool samples compared to just over 20 % of the *S. paratyphi* group (20/36 [55 %] vs 5/23 [22 %], p = 0.015). Three cases of ceftriaxone resistant enteric fever occurred.
Conclusion: Enteric fever remains a frequent presentation to a non-endemic setting with close links to high-endemic regions such as South Asia. Vaccination uptake among local populations could be improved. Few cases of ceftriaxone-resistant enteric fever were seen which is a consideration for improved antimicrobial stewardship.

Introduction

Enteric fever is the collective term for typhoid and paratyphoid infection, caused by *Salmonella typhi* or *Salmonella paratyphi* (A-C) (respectively). It remains a major global public health concern with an estimated 14.3 million cases annually, resulting in 135,000 deaths in 2017 (Stanaway et al., 2019). The populations most at risk are those in areas without access to clean water and adequate sanitation. In the UK, nearly all cases of enteric fever are associated with overseas travel, with a sharp decline in endemic cases of 1000 per year in the late 1930 s to 200 cases per year by the 1980 s, likely due to improved sanitation (Galbraith et al., 1987). The last decade has seen around 300–500 cases per year (mainly linked to travel to South Asia) in England, Wales and Northern Ireland, with a drop during the SARS-CoV-2 pandemic (UK Health Security Agency. Enteric fever (typhoid and paratyphoid) England, Wales and Northern Ireland:, 2021). The UK rate is more than any other country in the European region (European Centre for Disease Prevention and Control. Typhoid and paratyphoid fever Annual Epidemiological Report for, 2019).

Although enteric fever can usually be successfully treated with antibiotics there is a worrying trend in antimicrobial resistance, with extensively drug resistant (XDR) strains (resistant to first line agents, fluoroquinolones and third generation cephalosporins) seen in Pakistan over the last few years, with the first UK case reported in 2017 (Godbole et al., 2018). The British Infection Association (BIA) guidelines recommend empiric treatment with combined meropenem and azithromycin in patients with suspected enteric fever returning from Pakistan (Nabarro et al., 2022), although this has to be balanced with antimicrobial stewardship and the risk of morbidity associated with delayed effective treatment. The rate of XDR cases in the UK is 10 %, of which 94 % returned from Pakistan (Chattaway et al., 2021).

Prevention of enteric fever in travellers through the consumption of safe drinking water and food is advised but difficult to guarantee. Vaccination is recommended by the World Health Organisation (WHO) to control enteric fever in endemic and epidemic settings, particularly in travellers to Pakistan (Nabarro et al., 2022; Health Security, 2022), and is currently freely available from the NHS. In the UK there are currently two types of vaccine available for *S.typhi;* an injectable which utilises the

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capsular polysaccharide Vi and an oral vaccine based on a live, attenuated strain. There are no available vaccines for S.*paratyphi* and due it's absence of Vi, there is no cross-protection with the *S.typhi* vaccine. Early studies of the injectable Vi polysaccharide vaccine showed efficacy in Nepal and South Africa ranging between 55–75 % (Acharya et al., 1987; Klugman et al., 1987). Peak antibody response occurs approximately 4 weeks post vaccination and persists for 36 months (Keitel et al., 1994; Tacket et al., 2004). The uptake of vaccine in at-risk travellers from low-to-high endemic regions is unclear as well as the post infection travel advice from centres that manage cases.

University Hospitals Birmingham (UHB), UK, is one of the largest hospital trusts in the country, caring for a diverse population of over a million people of which 51 % identify as coming from a non-white background (Office for National Statistics. How the population changed in Birmingham: Census, 2021). Many residents frequently visit friends and family overseas in high-endemic areas and we see a relatively large number of cases, with the West Midlands being the third highest region of reported cases (https://www.gov.uk/government/publications/typhoid-and-paratyphoid-laboratory-confirmed-cases-in-england-wales-and-northern-ireland/enteric-fever-typhoid-and-paratyphoid-england-wales-and-northern-ireland-, 2024). This retrospective study aimed to identify all microbiologically confirmed cases of enteric fever in patients admitted to UHB over the last 12-years to assess the clinical presentation and treatment, anti-microbial resistance (AMR), documentation of vaccination status and clinical outcome.

Materials and methods

Study design

We conducted a retrospective descriptive study of all blood culture positive isolates of *S.typhi* and *S.paratyphi A, B or C* admitted to any hospitals within UHB NHS Trust over a 12-year period from 2010 to 2022. A case note review (where available) was then undertaken for each patient using either paper notes or an electronic patient record system (PICS). Data on patient demographics, epidemiology, clinical, laboratory and microbiological criteria were retrospectively collected. In contrast to a previous study in the Midlands region, we only included cases identified from blood cultures but also collected data on stool culture results where available for these patients (Clark et al., 2010). Following identification of cases, we collected: age, gender, country visited, vaccination status pre-travel, vaccination discussed during admission or follow-up, duration of symptoms pre-admission and length of admission. Information on symptoms and signs, biochemistry, haematology, radiology and stool culture were also collected. Antibiotic treatment and duration were recorded along with treatment outcomes. Fever clearance was defined as having a sustained temperature $<$ 37.5 °C for at least 48 h. Relapse was defined as a temperature of $\geq$ 37.5 °C after fever clearance with or without a new positive culture result (Clark et al., 2010; Thompson et al., 2017). This study was registered with the University Hospitals Birmingham Clinical Audit Department.

Microbiology

Samples were processed at either the Queen Elizabeth Hospital microbiology laboratory or the Birmingham UKHSA (United Kingdom Health Security Agency) laboratory according to BSAC (pre-2016) and EUCAST (2016 onwards) standards. Using the local laboratory information management system we were able to identify blood culture isolates, antimicrobial susceptibility data and assess corresponding stool culture results. All suspected case samples were managed in a Containment Level 3 (CL3) laboratory and presumptive identification performed using API 20E kits (Biomerieux) and latex agglutination kits. Samples were then sent to the Gastrointestinal Bacterial Reference Unit (GBRU) at Colindale, UK, for identity confirmation via biochemical and serological tests or real time PCR. Numerous typing methods were used at GBRU over the period including phage typing, pulse-field gel electrophoresis, multilocus variable tandem repeats analysis (MVLA), multilocus sequence typing (MSLT) and whole genome sequencing (WGS). Susceptibility testing was performed using disc diffusion for amoxicillin, azithromycin, co-trimoxazole, chloramphenicol, ceftriaxone and meropenem. Liofilchem® MIC Test strips and Biomerieux ETESTs® were used to test azithromycin, ceftriaxone and ciprofloxacin minimum inhibitory concentrations (MIC).

Statistical analysis

Statistical analyses were performed using GraphPad Prism (v10.2.0). For categorial variables, differences between two groups (individuals with *S.typhi* or *S.paratyphi*) were analysed using the two-tailed Fisher's exact. For continuous variables, the D'Agnostino-Pearson omnibus test was used to assess data normality. Parametric data comparing the two groups were analysed using the unpaired *t*-test and non-parametric data were analysed using the Mann-Whitney test.

Results

In total, 108 patients were identified during the time period, 57 (53 %) with *S.typhi* and 51 (47 %) with *S.paratyphi* (all serovar A). Baseline data showed little difference between those who had acquired *S.typhi* or *S.paratyphi*, with similar total numbers, distribution across hospital sites and countries visited (Table 1). Nearly all (93 % [100/108]) had returned from South Asia with the majority having visited Pakistan (69 % [69/100]). Length of symptoms before admission (median *S.typhi* = 8 [IQR 5, 14] vs *S.paratyphi* = 9 [IQR 5, 14] days) and duration of admission (*S.typhi* = 6 [IQR 4, 8] vs *S.paratyphi* = 5 [IQR 3, 7] days) were very similar between the two groups. Patients with *S.typhi* were significantly younger and had a higher male patient ratio compared to the *S.paratyphi* group (67 % vs 59 %). There was no evidence of typhoid vaccination pre-travel for most patients (n = 96 [89 %]) in either group and few cases had documented evidence of a recommendation to seek vaccination for future travel (n = 9 [8 %]).

Symptoms at presentation were similar except for vomiting which was present on admission in twice as many patients with *S.typhi* (n = 39 [68 %] vs n = 19 [37 %], p = 0.002), who also were also more likely to present with hypotension (n = 17 [30 %] vs n = 6 [12 %], p = 0.033) (Table 2). Renal impairment was more common in the *S.typhi* group, reflected by a reduced median eGFR compared to the *S.paratyphi* group, although not statistically significant (median *S.typhi* = 76 [IQR 71, 82] vs *S.paratyphi* = 90 [IQR 78, 90]). Over half the patients with *S.typhi* had positive stool samples compared to just over 20 % among those with *S.*

Table 1
Demographics of patients with blood culture-positive enteric fever.

	Typhi (*n*=57)	Paratyphi A (n=51)
Age	23 [17, 31]	29 [20, 39]
Gender		
Male	38	30
Female	19	21
Country visited		
India	11	11
Pakistan	35	34
Bangladesh	5	4
Other	3	1
Not mentioned	3	1
Vaccinated pre-travel	8	4
Vaccination discussed	4	5
Length of symptoms* (pre admission)	8 [5, 14]	9 [5, 14]
Length of admission	6 [4, 8]	5 [3, 7]

*Excludes 4 Typhi and 3 Paratyphi cases with incomplete data.
ns = not significant (p > 0.05).

Table 2
Symptoms, signs, and investigation findings for patients with blood culture positive-enteric fever at hospital admission.

N	*S.typhi* 57 (%)	*S.paratyphi* 51 (%)	p
Symptoms			
Fever	54 (95)	50 (98)	ns
Sweats	15 (26)	17 (33)	ns
Abdominal pain	21 (37)	20 (39)	ns
Diarrhoea	21 (37)	23 (45)	ns
Vomiting	39 (68)	19 (37)	0.002
Headache	22 (39)	20 (39)	ns
Myalgia	18 (32)	18 (35)	ns
Cough	12 (21)	13 (25)	ns
Signs			
Bradycardia	2 (4)	4 (8)	ns
Tachycardia	44 (77)	34 (67)	ns
Hypotension	17 (30)	6 (12)	0.033
Rash	0	0	ns
Abdominal tenderness	18 (32)	15 (29)	ns
Organomegaly	2 (4)	1 (2)	ns
Laboratory results			
WCC	7 [5, 9]	7 [6, 9]	ns
Neutrophil count	5 [4, 7]	5 [4, 6]	ns
Haemoglobin	125 [108, 138]	130 [119, 146]	ns
Platelets	213 [163, 251]	235 [197, 264]	ns
eGFR*	76 [71, 82]	90 [78, 90]	ns
ALT	63 [36, 105]	55 [37, 86]	ns
Alkaline phosphatase	117 [79, 152]	96 [80, 149]	ns
Bilirubin	11 [8, 21]	10 [8, 21]	ns
CRP	115 [68, 171]	76 [38, 116]	0.004
Abdominal radiology			
X-ray	8 (14)	5 (10)	ns
Ultrasound	28 (49)	18 (35)	ns
CT	8 (14)	9 (18)	ns
Microbiology			
Stool sample sent	36 (63)	23 (45)	ns
Stool sample positive	20 (56)	5 (22)	0.015

*14 S.typhi and 7 S.paratyphi cases had no eGFR due to paediatric reference range but all creatinine.
Values within normal range except 1 S.typhi case.
Median [interquartile range].
ns = not significant (p > 0.05).

paratyphi (20/36 [55 %] vs 5/23 [22 %], p = 0.015).

There were notable differences in antimicrobial susceptibilities across the two groups (Table 3). Approximately half of the isolates from patients with *S.typhi* were resistant to chloramphenicol (21/37 [57 %] vs 0/28, p = 0.001) and co-trimoxazole (24/50 [48 %] vs 0/40, p = 0.001) as opposed to none in the *S.paratyphi* group. All three cases of ceftriaxone resistant enteric fever were seen in the S.*typhi* group, while the azithromycin resistance rates (*S.typhi* n = 9/52 [17 %] vs S.paratyphi n = 11/48 [23 %]) and azithromycin MICs (median *S.typhi* 6 mg/L [IQR 4, 12] vs *S.paratyphi* 12 mg/L [IQR 8, 17], p = 0.009) was higher in the S.*paratyphi* group.

Table 3
Antimicrobial resistance results.

N	*S.typhi* 57	*S.paratyphi* 51	p
Ciprofloxacin	75% (43/57)	90% (46/51)	ns
Ceftriaxone	5% (3/57)	0 (0/51)	ns
Chloramphenicol	57% (21/37)	0 (0/28)	0.0001
Amoxicillin	48% (23/48)	33% (13/40)	ns
Co-trimoxazole	48% (24/50)	0 (0/40)	0.0001
Azithromycin	17% (9/52)	23% (11/48)	ns
Meropenem	0 (0/19)	0 (0/10)	ns
Ciprofloxacin MIC	0.25mg/L [0.25, 0.38]	0.5mg/L [0.5, 0.75]	<0.0001
Azithromycin MIC	6mg/L [4, 12]	12mg/L [8, 16]	0.01

Median [interquartile range].
ns = not significant (p > 0.05).
MIC=minimum inhibitory concentration

Antimicrobial management was similar across the groups (Table 4). Initial antibiotic treatment was with ceftriaxone in 81 % (88/108) of cases with a median duration of 7 days [IQR 5, 14] in the *S.typhi* group and 6 days [IQR 4, 14] in the *S.paratyphi* group. The three patients with a ceftriaxone resistant strain were subsequently prescribed meropenem. Most patients in both groups were prescribed azithromycin as an oral step-down treatment (*S.typhi* 88 % [29/33] vs *S.paratyphi* 69 % [20/29], p = 0.25) with a limited number of other oral antibiotics used. The median duration of antibiotic treatment was 14 days, the same in each group.

In terms of treatment outcomes (Table 5), the median fever clearance time was longer in the *S.typhi* compared to *S.paratyphi* group (7 [IQR 4, 8] vs 5 [IQR 4, 7] days). There were six cases of relapse. Four were seen in the *S.paratyphi* group which included two readmissions who received further antibiotic treatment (although both were culture negative at re-presentation). There were no cases of intestinal perforation in either group, there were a limited number of radiological abnormalities seen. In addition to three cases of cholecystitis across groups, two patients in the *S.typhi* group had features of colitis on abdominal X-ray imaging and one patient in the *S.paratyphi* group had caecal thickening and inflammation seen on CT imaging.

The number of cases over time is shown in Fig. 1. After a peak of ten cases of S.typhi in 2018 and eight S.paratyphi in 2019, there was a steep drop in 2020–2021.

Discussion

In this retrospective cohort study we identified similar numbers of patients diagnosed with microbiologically-confirmed enteric fever due to *S.typhi* and *S.paratyphi A* in our hospitals over a 12 year period. No cases of S.*paratyphi B* or *C* were detected in our cohort. As these are more commonly seen in travellers returning from South America and the Middle East and few of our patients had been to these regions, this is perhaps unsurprising (Herdman et al., 2021).

The largest number (63 %) of cases presented to Heartlands Hospital serving the population in the east of the city which reflects the ethnic

Table 4
Antibiotic treatment.

N	*S.typhi* 57	*S.paratyphi* 51	p
Initial agent			
Ceftriaxone*	47 (82)	41 (80)	ns
Cefixime	1 (2)	0	ns
Meropenem	1 (2)	1 (2)	ns
Co-amoxiclav	0	1 (2)	ns
Azithromycin	0	2 (4)	ns
Not clear	8 (14)	7 (14)	ns
Duration (days)			
Ceftriaxone	7 [5, 14]	6 [4, 14]	ns
Oral step-down agent			
Azithromycin	29 (51)	20 (39)	ns
Amoxicillin	0	1 (2)	ns
Co-trimoxazole	1 (2)	4 (8)	ns
Cefixime	1 (2)	4 (8)	ns
Ciprofloxacin	1 (2)	0	ns
Clarithromycin	1 (2)	0	ns
Total treatment duration (days)	14 [12 ,14]	14 [12, 14]	ns

Median [interquartile range].
ns = not significant (p > 0.05).

Table 5
Clinical outcomes.

	S.typhi	*S.paratyphi*	p
N	57	51	
Fever clearance (days)*	7 [4, 8]	5 [4, 7]	ns
Relapse	4 (7)	2 (4)	ns
Cholecystitis	2 (4)	1 (2)	ns
Intestinal perforation	0	0	ns

*Data available for 29 S. typhi and 24 S. paratyphi cases.
Median [interquartile range].
ns = not significant ($p > 0.05$).

demographic in this area. Pakistan was the most frequent country visited for patients returning with enteric fever (64 %). This may be a concern given the rise in XDR cases reported here (Godbole et al., 2018; Nabarro et al., 2022). Few cases had documented evidence of having received a typhoid vaccination before travel and there was little evidence that this was either discussed and recommended during the admission or at discharge or follow-up. Vaccination is a well recognised public health intervention recommended by several groups including the WHO, the US Centers for Disease Control and Prevention (CDC) and UKHSA and is also available freely from the UKs NHS (Health Security, 2022; World Health Organisation. Typhoid vaccines: WHO position paper – March 2018). Anecdotally, the reasons given among our cohort for not receiving pre-travel vaccinations include a lack of awareness and having to travel at short notice for events such as funerals. It is unclear what the vaccination uptake is nationally and among patients admitted with enteric fever to other UK hospitals. We aim to focus our future strategy on improving awareness among our local cohort.

In general, patients were symptomatic for over a week before presenting to hospital, although this may be due to delays in travel back to the UK and at least 12 patients sought healthcare during their time abroad, receiving antibiotic treatment which may have attenuated their illness. There was little difference in the length of patient admission between the *S.typhi* and *S.paratyphi* groups, with a median of a week, consistent with previous data from another UK setting (Clark et al., 2010; Dave et al., 2015). Enteric fever remains a significant health problem in returning travellers to non-endemic settings with an associated financial impact. A retrospective case review of enteric fever in East London over six years calculated a cost of £454,000 for 908 hospital bed days in 105 patient episodes (Dave et al., 2015).

Nearly all patients presented with fever but fewer than half also had gastrointestinal symptoms. Interestingly, significantly more patients with *S.typhi* had vomiting that those with *S.paratyphi*. Relative bradycardia in association with fever is consider a classic symptom of enteric fever although it was uncommon in our cohort (Ye et al., 2018). The other symptoms and signs were consistent with the existing literature. There was a clear difference between the groups with respect to culture positive stool (56 % vs 22 %, *S.typhi* vs *S.paratyphi*). These results are not in keeping with previous reviews of UK cases (Clark et al., 2010; Dave et al., 2015) and the cause for this difference is unclear.

In common with many other bacterial pathogens, antimicrobial resistance among *S.typhi* and *S.paratyphi* isolates has evolved over time. Initially, chloramphenicol was the treatment of choice but the emergence of resistance prompted use of amoxicillin and co-trimoxazole. These agents gradually lost susceptibility resulting in multi-drug resistant typhoid in the late 1980 s (Rowe and Ward, 1978; Threlfall et al., 1992). The development of fluoroquinolone resistance (particularly in South Asia) led to ceftriaxone being used as first line therapy for many years from the turn of the century. The first cases of XDR typhoid started to emerge in Pakistan in 2016 which has subsequently resulted in the loss of ceftriaxone as an effective agent (Godbole et al., 2018; Aslam et al., 2021). This prompted the BIA to recommend empiric dual therapy with meropenem and azithromycin in patients returning from Pakistan (Nabarro et al., 2022). Our data support the existing literature with most cases being resistant to ciprofloxacin. There were some notable differences in susceptibility between the groups such as chloramphenicol or co-trimoxazole resistance which may have implications when choosing an oral step-down agent and outpatient management of patients with *S. paratyphi A*. Given the need to preserve the efficacy of azithromycin, alternatives such as chloramphenicol or co-trimoxazole may be viable options (although the higher MIC for azithromycin in the S.*paratyphi* group should be noted). The use of ceftriaxone followed by azithromycin in most cases was reflective of national guidance (Nabarro et al., 2022; McCann et al., 2022), although the median duration of 14 days treatment in each group could potentially have been shortened.

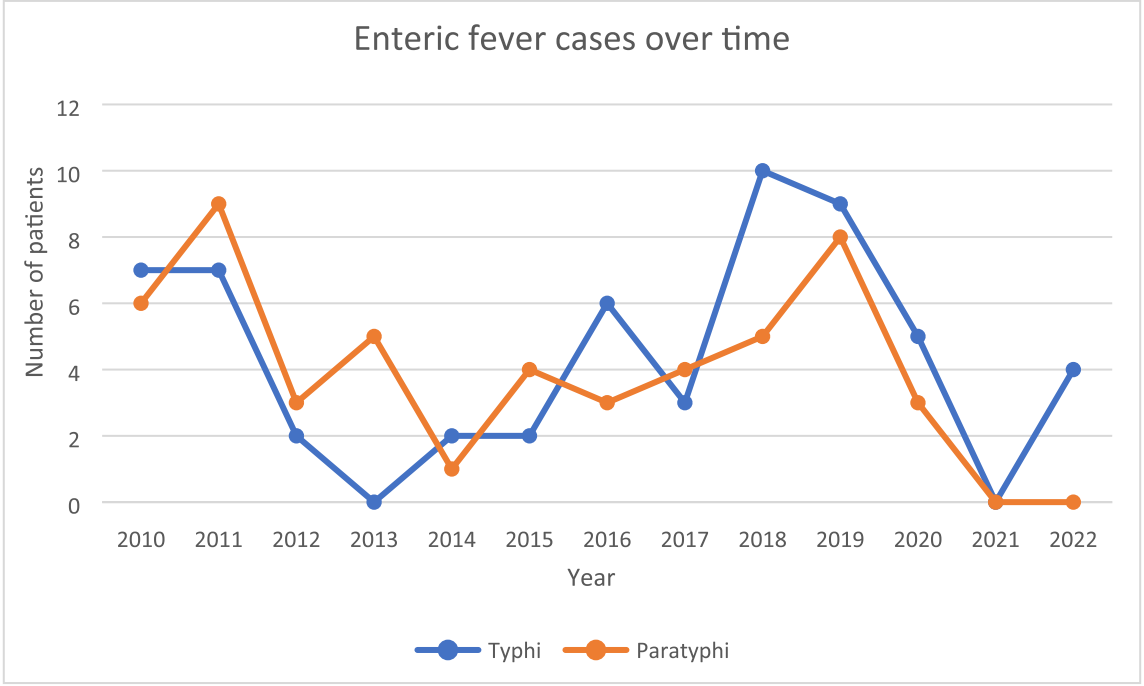

Fig. 1. Enteric fever cases over time.

When the BIA guidance was published in 2022 there were no azithromycin resistant strains reported by the UK national reference laboratory (Nabarro et al., 2022). We identified 16 isolates with a MIC>16 mg/L, the EUCAST breakpoint, including one isolate with an MIC>256 mg/L (EUCAST, 2024). While this is of concern given the lack of alternatives beyond the carbapenems, it is unclear if this represents true resistance. Discordance in azithromycin susceptibility between diagnostic laboratories and reference laboratories has previously been reported and has not been supported by whole genome sequencing of the suspected resistant isolates (Goldblatt et al., 2020).

Our review included the significant reduction in travel during the SARS-CoV-2 pandemic. The sharp drop in cases between 2020–2021 is likely explained by the travel restrictions in place at the time. As most of our patients had travelled to Pakistan during the study period, with many doing so post 2016, it was perhaps surprising that we saw so few cases of XDR enteric fever. In fact, a recent review from Pakistan found around half the cases presenting to a hospital in Lahore to be ceftriaxone resistant (Aslam et al., 2021). The three cases we identified were all in the *S.typhi* group and all confirmed as cefpodoxime resistant. As many suspected cases returning now from Pakistan are given empiric meropenem, this is a consideration if the low rates of XDR isolates persist (Chattaway et al., 2021).

Few complications were seen in our cohort. The fever clearance time of up to 7 days is typical and none of the relapse cases were culture positive with the same organism. There were three cases in which acquisition of enteric fever occurred without a recent travel history. One patient had not travelled overseas for eight years but had attended a large religious gathering in Birmingham. Their stool culture was negative, although a relative had recently returned from Bangladesh. The second case had not travelled but worked in a restaurant locally and had a positive stool sample. The third case was a student who again had a positive stool sample. As enteric fever is a notifiable illness, these cases were discussed with the local health protection team, who screened household contacts and found no other cases. It was noted however that the isolate from the restaurant worker was genotypically similar to a cluster of five other cases seen nationally.

This study had several strengths. We present one of the largest case series from a non-endemic setting in one of the largest NHS trusts in the UK. In addition to baseline demographics, clinical investigative results and antimicrobial resistance, we have recorded vaccination status and whether discussion was recorded regarding a recommendation of vaccination before future travel. There were some limitations to this study. Missing data (due to limited availability of clinical notes) mainly affected assessment of treatment outcome. We also have limited data on typing which may have been able to link some of these cases, particularly if family members or friends had travelled together. Whilst our hospitals trust is the largest in the region, there were likely many additional cases who presented to other hospitals in Birmingham and the wider area with enteric fever and were therefore not captured in our data set.

Conclusion

Our study shows that enteric fever remains a relatively frequent presentation to a non-endemic setting following travel to high-endemic regions such as South Asia. The difference in stool shedding between *S. typhi* and *S.paratyphi* infections was unexpected. Evidence of vaccination pre-travel and discussion post-acquisition was poor and is a potential area for infection and public health specialists to target. Key differences in AMR patterns between groups and few cases of XDR enteric fever may offer an area for improved stewardship. Finally, we found several cases of azithromycin resistance amongst our isolates which is a concern and will need close surveillance.

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