Salmonella Paratyphi B, Public Health and Parental Choice: When to treat asymptomatic carriers of infection

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Structured ABSTRACT

Background: Salmonella Paratyphi B (Paratyphoid B) is a rare infection and a notifiable disease in England. Disease is typically mild, and chronic carriage in children has been described in endemic countries. Almost all cases in England are imported, with very few cases of community transmission reported.

Methods: The aim of this work was to describe an unusual cluster of Paratyphoid B cases transmitted within England, examining clinical, epidemiologic and microbiologic data. Detailed phylogenetic analysis is presented to corroborate public health epidemiologic links between cases.

Results: One child had recently returned from an endemic area and had mild gastrointestinal symptoms. One year later, 2 other children with no travel history developed invasive disease requiring hospitalization. Epidemiologic links confirmed person-to-person spread between these three cases. All isolates of S. Paratyphi B (n = 93) received by the Gastrointestinal Bacteria Reference Unit between 2014 and 2019 were typed using whole genome sequencing. Three cases of Paratyphoid B were identified in the same geographical location over a 2-year period. S. Paratyphi B strains isolated from the stool and blood of the three cases were closely linked (0–5 single-nucleotide polymorphisms) using whole genome sequencing.

Conclusions: This case series highlights the potential public health risks of paratyphoid B and the range of pediatric complications associated with this illness, especially in younger children. Although rare, chronic carriage of Paratyphoid B can lead to transmission in nonendemic areas and should be considered in all children presenting with signs of enteric fever even where there is no history of foreign travel.

Key Words: Salmonella Paratyphi B, enteric fever, paratyphoid, child, public health
Background

Globally, there are an estimated 26 million new cases of typhoid fever and 5 million cases of paratyphoid fever every year with 215,000 deaths.\(^1\) Salmonella enterica, subspecies enterica, serovar Paratyphi B infection (paratyphoid B) is one of the rarer causes of enteric fever and is a notifiable disease in the United Kingdom. In England, Wales and Northern Ireland, approximately 300 cases of enteric fever are reported annually with the majority (99%) associated with recent travel to endemic countries.\(^2\) S. Typhi contributes to approximately 60% of the cases, and the remaining cases are caused by S. Paratyphi A (35%–40%) or rarely S. Paratyphi B (2%–5%). There have been 93 cases of paratyphoid B infection reported between January 1, 2014, and December 31, 2019, in England and Wales, 30% of which were in children 1–14 years of age. Most imported cases of paratyphoid B in England are seen in travelers returning from South America and the Middle East.\(^2\) To date, there have been few other cases described of paratyphoid B acquired in England and only a couple of case series from Wales\(^3\) and Scotland.\(^4\)

Disease is typically described as being milder and of shorter duration than infections caused by other host-adapted enteric fever serovars like S. Typhi and S. Paratyphi A. Acute mortality is reduced by treating with antibiotics at this stage.\(^5\) The majority of infections are cleared, with fecal shedding occurring in convalescent carriers for 3 weeks to 3 months post-infection and temporary carriers for between 3 and 12 months. Chronic carriage of paratyphoid B with excretion for over 1 year is uncommon, occurring in less than 5%.\(^6,7\) Risk factors for chronic carriage include female sex, older age, the presence of gallstones and inadequate acute treatment courses.\(^5\) Treatment of carriers early on with antibiotics is controversial with some concerns it may prolong carriage; however, once chronic carriage is established, prolonged treatment with a fluoroquinolone may be the best option.\(^7\) Chronic carriage may be a cause or consequence of gallstones, and eradication may be difficult without cholecystectomy. Detection of chronic carriage is vital to reduce individual risk of gallbladder cancer and public health risk of ongoing transmission in the community.\(^8\)

This case series presents one of the first clusters of community transmission of paratyphoid B in England, resulting in 2 children developing severe invasive paratyphoid B requiring hospitalization, having acquired the infection from an asymptomatic carrier. Phylogenetic analysis is presented to corroborate public health epidemiological links between cases. This case series highlights the potential public health risks of paratyphoid B and a range of pediatric complications associated with this illness.

Materials and Methods:

Epidemiology:

Hospital case notes of individual patients were reviewed by the clinical team. Patient travel and clinical information were obtained by Public Health England (PHE) using an enhanced surveillance questionnaire and parent interviews. No specific consent was required from the patients whose data were used in this analysis as PHE has authority to handle patient data for public health monitoring and infection control under section 251 of the UK National Health Service Act of 2006.

Microbiology and Typing:
Blood and stool isolates grew non–lactose-fermenting colonies on MacConkey agar, identified as Salmonella species by matrix-assisted laser desorption ionization time-of-flight mass spectrometry in the local hospital diagnostic laboratory.

Presumptive isolates of S. Paratyphi B from blood of the two patients acutely unwell in England and stool from all three cases were sent to the PHE Gastrointestinal Bacteria Reference Unit for confirmation and further characterization using whole genome sequencing (WGS) as previously described.\(^9\) *Salmonella* serovar determination was predicted based on the *Salmonella* eBURST group and sequence type and checked against a validated PHE database [strain differentiation was achieved by utilizing single-nucleotide polymorphisms (SNPs) using SnapperDB v2.6.0].\(^10\)

All isolates since 2014 of S. Paratyphi B (n = 93) were prospectively sequenced in the Gastrointestinal Bacteria Reference Unit and were characterized using pairwise SNP analysis (single-linkage hierarchical clustering). To put the three cases in the context of the S. Paratyphi B population structure seen in England and Wales, we undertook phylogenetic analysis of 72/93 of these isolates. A soft-core alignment was generated of 72 genomes using SnapperDB v2.6.0.\(^10\) Recombination was detected and masked in the alignment using Gubbins v2.0.0 before being used to construct a maximum-likelihood phylogenetic tree using RAxML v2.8.2.\(^11,12\) PHE also makes validated FASTQ sequences publically available by routinely uploading *Salmonella* sequence data to National Center for Biotechnology Information, BioProject PRJNA248792 (https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA248792).

Antimicrobial susceptibility testing was undertaken by GRBU using agar dilution and interpreted using mean inhibitory concentration breakpoints according to the European Committee of Antimicrobial Susceptibility Testing. In addition, the antimicrobial resistance, determinants were sought from the WGS using GeneFinder as previously described.\(^13\)

Results:

Cases

Case 1:

A 4-year-old boy, resident of England, developed fever and diarrhea for 1 week while travelling in Bolivia. His symptoms resolved without treatment, and he was well on return to the United Kingdom. Weeks later, he presented to primary care with intermittent mild abdominal discomfort and a few days of mild loose stool. S. Paratyphi type B was identified on stool cultures, and he was treated with oral azithromycin for 1 week. Strict hygiene procedures were put in place, and he was excluded from nursery according to the national public health operational guidelines for prevention of enteric fever in England.\(^14\) Repeated monthly stool cultures remained positive, and he was allowed to commence primary school with strict infection control measures, supervised toileting and hand hygiene as long as he remained asymptomatic. Prolonged antibiotic treatment with ciprofloxacin was considered after referral to a pediatric center but agreed to be postponed as the child was asymptomatic, not yet a chronic carrier and there were concerns regarding prolonged use of this class of antibiotic.

Approximately 1 year after the initial diagnosis, stool cultures remained positive. Immunodeficiency was ruled out, but an abdominal ultrasound revealed 2 gallstones. Four weeks of oral ciprofloxacin treatment was commenced and the possibility of cholecystectomy discussed. This was not required
as the infection cleared and gallstones slowly reduced in size on serial ultrasound. Infection clearance was confirmed on 2 sets of 3 stool cultures a few months apart. He remains well at follow-up 1 year later.

Case 2:

A year after Salmonella Paratyphi B was first detected in the index case, a 3-year-old girl attended the emergency department unwell with high fever, diarrhea, significant right iliac fossa pain and tenderness and an elevated C-reactive protein of 166mg/dL. She underwent a diagnostic laparoscopy, which showed a macroscopically normal appendix. Serial blood and stool cultures were subsequently positive for S. Paratyphi B. She was treated with intravenous ceftriaxone followed by oral azithromycin, and PHE was notified. She had not traveled outside of the United Kingdom but, it was later revealed, had shared a bath with the index case on one playdate. She made a full recovery and was discharged home. Strict hygiene measures were implemented for her and reemphasized to the parent of the index case. Stool excretion was negative by 3 months post-infection, and she was well at follow-up 1 year later.

Case 3:

Two months after case 2, a 5-year-old boy with no history of foreign travel presented with a high fever, diarrhea and vomiting. He was dehydrated, hyponatremic (Na 131) and hypokalemic (K 2.5) requiring admission for intravenous fluid replacement and ceftriaxone for presumed sepsis. Blood and stool cultures were subsequently positive for S. Paratyphi B. Further public health investigations revealed he was a school friend of the index case, and they had playdates together outside of school prior to admission, where they had shared finger food and used the same toilet facilities. He was treated with intravenous ceftriaxone followed by oral azithromycin and made a full clinical recovery but continued to be a convalescent carrier 2 months later. After discussion with family, he was treated with an extended course of 4 weeks of ciprofloxacin following which he cleared the infection. He was excluded from school at diagnosis until he had microbiological clearance, to the significant detriment of both the patient and his family. He was well at follow-up 1 year after diagnosis.

Following this third confirmed case, all children in the same school class as the index case and case 3 were offered testing for S. Paratyphi B as part of a risk assessment. Nineteen of 30 children submitted a stool sample, and none were positive.

Microbiology, Reference Laboratory and Public Health Investigations:

Public health investigations, including parent interviews and questionnaires, confirmed person-to-person spread between the three cases in the community including the two who had not traveled to endemic countries. Isolates from the three cases were identified by genomic sequencing as S. Paratyphi B, sequence type 86, eBURST group 5 with the SNP address 2.2.78.94.98.129.. Fig. 1 shows the maximum-likelihood phylogenetic tree of 72 of the closest matching isolates; 24/72 had traveled to South America (the three clinical cases mentioned above are highlighted in red). The strains isolated from blood and stool samples from the three cases were very closely related (SNP difference, 0–5). Isolates from blood and/or stool from all three cases were fully sensitive to amoxicillin, ceftriaxone, cefazidime, ertapenem, ciprofloxacin and azithromycin on phenotypic testing.
Discussion:

Paratyphoid B is thought to cause a milder and shorter illness compared with enteric fever and predominantly presents as a nonspecific febrile illness with gastrointestinal symptoms. This case series, however, illustrates the varied presentations and complications of this disease including sepsis, electrolyte disturbances, severe abdominal pain mimicking appendicitis, choledolithiasis and chronic carriage in young children in a developed country.

The global burden of infection, complications and outcomes is not as well defined for paratyphoid B as it is for the other serotypes causing enteric fever. Although outbreaks of S. Paratyphi B have been described worldwide, none have been reported in England in the last 3 decades. Most cases in England are imported from South America and the Middle East, and diagnosis can be confirmed if blood and stools are appropriately cultured. However, mild cases without a history of travel to an endemic area are difficult to detect and can be mistaken for self-limiting viral or bacterial gastroenteritis. Severe cases, such as cases 2 and 3 described here, may be ill enough to present to hospital, but with no travel history, “possible enteric fever” is unlikely to be in the differential diagnosis or put on microbiological request forms. This is important as identification of S. Paratyphi B is not straightforward in diagnostic laboratories as other zoonotic serotypes like S. enterica Paratyphi B variant Java have an identical serological profile (somatic and flagellar antigens) making it difficult to identify the true pathogen. Culture-positive cases need confirmation by reference laboratory methods such as D-tartarate utilization and/or polymerase chain reaction. Increasingly highly discriminatory methods such as WGS are being used to differentiate between various sub-lineages with identical serological profiles.

PHE operational guidelines define carriage slightly differently to Gunn et al. A convalescent carrier is defined as a case who continues to excrete S. Paratyphi B in the stool, or rarely the urine, after 2 courses of appropriate antibiotic treatment for up to 12 months; and a chronic carrier is a case who excretes beyond 12 months after onset. Although uncommon in developed countries, children can become chronic carriers of S. Paratyphi B infection. Strains of S. typhi and S. Paratyphi A and B have an affinity for the gall bladder and form biofilms that contribute to chronic colonization of the host. Gallstones may be a risk factor for or a consequence of infection, and chronic carriers should be screened for gall stones and other metastatic foci. As chronic carriage is associated with an increased risk of cholangiocarcinoma, over and above the known risk associated with gallstones, eradication treatment should be considered in cases of prolonged carriage for the individual as well as for public health.

Currently, PHE guidance recommends further testing of confirmed cases of enteric fever aged 5 years and under (high risk group), UNTIL 3 negative stool samples taken 48 hours apart are obtained, starting at least 1 week after completion of acute treatment. However older children are not screened, and antibiotic guidance for those with nonacute disease is limited. This case series highlights the need to reevaluate this approach for chronic carriage 1 year after completion of treatment, to enhance case finding and reduce complications in older children and adults. New molecular tests have greater sensitivity and high negative predictive value for detection of gastrointestinal bacteria, and Salmonella polymerase chain reaction stool screening testing would be useful to rule out chronic carriage.

With increasing antimicrobial resistance to Salmonellae, worldwide treatment may become difficult. Most strains of Para-typhi B in the United Kingdom are imported from South America, Middle East and Pakistan (Fig. 1), and the vast majority are still sensitive to first-line antibiotics for enteric fever,
although multi-drug resistance has been described in other countries.\textsuperscript{16} Currently, eradication of carriage entails prolonged antibiotic therapy, with quinolones being the most effective agents used for this purpose due to the high antibiotic concentration achieved in bile, provided the strain is sensitive.\textsuperscript{24,25} However, patients do need to be counselled of the risks associated with this class of antimicrobial and a risk assessment made on a case-by-case basis. Other invasive interventions like cholecystectomy have been described with variable outcomes.\textsuperscript{26}

This case series demonstrates the public health risk of transmission of paratyphoid B infection in children under 5 years of age through direct contact or sharing of toilet facilities in the community, in a developed country like England with good food and water hygiene and sanitation services. Although school was notified and strict public health measures put in place, onward transmission still occurred in susceptible hosts with no prior immunity to this infection, especially when agreed hygiene measures were not followed. Isolation of children with convalescent or chronic carriage from the nursery or school has a detrimental impact on their social development and education and puts a strain on the household having to provide childcare for prolonged periods.

WGS is a highly discriminatory typing method for \textit{Salmonella} spp., and these cases demonstrate the use of SNP typing to confirm links between cases.\textsuperscript{20} Strain relatedness derived from WGS and SNP typing can demonstrate that a single clone lineage can be dominant in an endemic country, and travel cases returning to the United Kingdom from said endemic countries can be closely linked. This can be clearly visualized in Fig. 1, where travel cases share the same clades of cases from the same endemic country/continent. To strengthen the impact of strain resolution and outbreak detection, it is paramount that epidemiological data are also obtained to provide important additional context.

This case series highlights the complications and management of chronic carriage of \textit{S. Paratyphoid} B in this age group. Further awareness needs to be raised among pediatricians and general practitioners in England to facilitate early diagnosis and public health notification to prevent the morbidity associated with this illness and outbreaks such as this.

Figure legend

Figure1: Maximum-likelihood phylogenetic tree of Paratyphi B strains available (n=72) from the reference laboratory.

Conflicts of interest: Nil to declare

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