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Title: Pre-traveller Typhoid vaccinations for Australian children visiting friends and relatives (VFR) overseas. A call to (inject) arms.

Instructive Case

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Conflict of Interest

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Abstract and key words

- Not applicable for Instructive Case

Text

Introduction

Vaccine-preventable diseases (VPDs) in international travellers cause a significant burden on health services at an individual and societal level[1]. One of the most common VPDs globally in travellers, is typhoid and paratyphoid fever, collectively referred to as 'enteric fever'[2]. Enteric fever is a potentially life-threatening acute febrile illness, with a global burden of disease disproportionally affecting children. It is characterised by bacteraemic febrile illnesses caused by *Salmonella enterica*, subsp. *enterica* serotype Typhi *(S. typhi)* or serotype *Paratyphi A, B or C (S. paratyphi)* with children typically presenting with prolonged fever, malaise and abdominal pain[2]. Global estimates demonstrate that the incidence, mortality and morbidity of enteric fever was highest among children <15 years, peaking in the 5-9 year age group[3]. It is common for foreign-born Australian residents and their children to travel to their country of origin for the purpose of 'visiting friends and relatives' (VFR)[1]. VFR travellers are less likely to seek pre-travel advice or vaccination, despite their accompanying children comprising the largest risk group of paediatric typhoid cases presenting in Australia[4,5]. This travel is often to areas endemic of enteric fever such as South Asia, South-East Asia, Sub-Saharan Africa, East Asia and Oceania[3].

This case series raises the opportunity to strengthen preventative measures including vaccination and general pre-travel advice for individuals visiting endemic areas. Prevention of enteric fever in returning travels will relieve the public health burden of this infectious disease on our health care services.

Materials and Methods

We undertook a retrospective, descriptive study of confirmed cases of typhoid and paratyphoid fever presenting to a major tertiary paediatric hospital in Victoria between February and March, 2019. Clinical and microbiological data was collected for each case from medical and laboratory records. A positive case was defined as isolation of *S.* typhi or *S.* paratyphi on blood culture (and in one case, positive on stool culture where the sibling was blood culture positive) with associated clinical features suggestive of enteric fever.

Results

In 2019, nine previously well children presented to the emergency department of a major tertiary hospital upon returning from overseas travel (see Table 1). Nine culture-positive cases of enteric fever were confirmed between February to March with eight cases being attributed to *S. typhi* (with one case having confirmed extensively drug resistant (XDR) *S. typhi*) and one attributed to *S. paratyphi* (see Table 2). Eight isolates were from positive blood cultures and one was from stool only. The case whose stool was positive for *S. typhi* was the sibling of a case with a confirmed positive blood culture. Of the eight children who had bacteraemia, five (63%) cases had more than one positive blood culture taken at least 24 hours apart. All cases were negative for malaria on thick and thin films and no other organisms were isolated.

The age range of cases were 4-15 years of age. All were Australian residents of parents born overseas. The majority (n=8) were VFR in their parent's country of origin. Countries visited by these children and their families included endemic areas such as India (n=5), Pakistan (n=1) and Indonesia (n=2) as well as Cambodia (n=1). The case from Cambodia was culture positive for *S. paratyphi*.

The duration of travel ranged between 9 to 74 days with the mean duration of 38.6 days. The extended duration of stay for most cases was reflective of prolonged planned visits to friends and relatives. Six (67%) cases became unwell with symptoms whilst overseas with four (44%) receiving oral antimicrobial therapy. The most commonly reported symptoms were fever (100%), diarrhoea (78%), abdominal pain (78%), and nausea and vomiting (44%). There were no deaths. The case with XDR typhoid experienced life-threatening septic shock, complicated by hyponatraemia, thrombocytopaenia and microcytic anaemia. This resulted in a 7-day admission to the Paediatric Intensive Care Unit and a total hospital admission duration of 12 days. Antimicrobial therapy for *S. typhi* or *S. paratyphi* involved at least one day of intravenous ceftriaxone (range 1-6 days) followed by a seven-day course of oral azithromycin. Upon acquiring sensitivities to the confirmed XDR *S. typhi* case, who had recently returned from Pakistan, the case completed a total of 10 days of intravenous meropenem and 18 days of oral azithromycin. This azithromycin duration included a further 7 day course of azithromycin upon discharge, given that the case had had 7 positive blood cultures whilst on treatment.

None of the cases had received typhoid vaccination or any other travel vaccines or chemoprophylaxis. All children were aged two years or older, thus eligible for the parenteral typhoid vaccine available in Australia. Only one case had received pre-travel advice from their general practitioner who had not recommended any pre-travel vaccines or chemoprophylaxis. All cases were notified to the Department of Health and Human Services.

Discussion

The prevention of typhoid fever in children visiting friends and relatives (VFR) in endemic areas has received limited attention. A 2016 review of notified cases of typhoid in two Australia jurisdictions noted almost all paediatric typhoid cases were VFR (31 of 32, 97%)[5]. Our experience highlights the importance of pre-travel advice and vaccination for children who fit in this category of 'high-risk' populations. This population has a higher proportion of travel-related infections compared to those who travel for other purposes, such as work or tourism[1]. Prior research demonstrates that VFR travellers are less likely to seek pre-travel advice, spend longer time in endemic areas, and are more likely to engage in activities that increase their chance of contracting typhoid (e.g. eating locally prepared food, drinking local water and travel to rural areas with poor sanitation)[6]. Another study reported that those who had not sought pre-travel medical advice were ten times more likely to contract typhoid fever[7]. A 28-year Canadian review found that 89% of children with typhoid fever fit into the VFR category[8].

Four of the nine cases sought medical treatment for symptoms whilst overseas and were reportedly treated with oral antimicrobial therapy (of which the exact antimicrobials are unknown). This may impact diagnostic capabilities and severity of illness upon return to Australia. It was hypothesised that the siblings who were positive for *S. typhi* were both bacteraemic at some time point, despite one sibling having no growth in blood cultures and only a positive faecal PCR for S. *typhi*. This may have been secondary to incomplete treatment with antibiotics whilst still overseas.

Almost all cases did not consult travel advice from a medical practitioner before departure and therefore, did not receive pre-travel vaccinations. One case had sought pre-travel advice however despite being of an eligible age, they did not receive any travel vaccines or chemoprophylaxis. This reinforces the importance of developing effective interventions for improving community awareness and understanding of travel-related infection risks. Ensuring effective and accurate

pre-travel public health messaging around travel advice, including risk assessment and tailored recommendations regarding vaccinations, education around hygiene, and food and water precautions provides an opportunity to reduce the incidence of infection. Current recommendations advise that administration of the typhoid vaccine should be completed at least 2 weeks prior to travel to endemic areas[9]. All children older than two years of age should be offered the typhoid vaccine when travelling to endemic areas[9]. Children ≥ 2 years can receive 1 dose of the parenteral typhoid vaccine and are recommended to receive a repeat parenteral dose every 3 years if ongoing travel is anticipated[9]. Children ≥ 6 years can receive 3 doses of the oral typhoid vaccine[9]. Repeat vaccination is suggested after 3 to 7 years. A single dose of the combined hepatitis A/typhoid vaccine is currently recommended for people ≥ 16 years who are travelling to countries where both diseases are present. There is evidence that this combined vaccine has been demonstrated to be well tolerated in children as young as 2 years old[10]. Previously infected travellers should be informed that natural infection does not provide complete protection against recurrent illness and vaccination is recommended if re-exposure is expected. Typhoid vaccines can be safely given with other travel vaccines, however, the oral typhoid vaccine should be administered separately from the oral cholera vaccine as well as certain antimalarias (particularly mefloquine)[9]. Improving community awareness for this population group through effective, culturally-appropriate interventions may increase engagement with health practitioners prior to travel. Many VFR families travel for the longest duration (with resultant increased risk of acquiring enteric fever) during the summer school holidays, which raises the opportunity to target awareness campaigns towards the end of the school year and each school term.

Conclusion

International travel to visit friends and relatives remains a popular phenomenon for Australian families. Travellers who visit relatives from a parent's country of origin are a 'high risk' population who may underestimate the risk of VPD's and are less likely to seek pre-travel advice

and vaccinations to prevent typhoid fever. Children who are VFR or visiting endemic areas should be offered the typhoid vaccine prior to travel. Improving public health measures through increasing community awareness and clinician knowledge around travel health advice are imperative to preventing infection with typhoid fever.

Learning Points

- Vaccine-preventable diseases (VPDs) in international travellers cause a significant burden on health services at an individual and societal level
- Travellers who visit relatives from a parent's country of origin are less likely to seek pre-travel advice or vaccination, despite their accompanying children comprising the largest risk group of paediatric typhoid cases presenting in Australia
- Foreign-born Australian residents and their children often travel to their country of origin for the purpose of 'visiting friends and relatives' (VFR) during the summer school holidays, which raises the opportunity to target awareness campaigns towards the end of the school year and each school term
- Medical professionals should provide appropriate pre-travel advice and offer vaccination to such 'high risk' patients older than 2 years of age and their families to reduce the risk of enteric fever and its associated complications

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Tables

Table 1. Characteristics of nine case-patients confirmed with enteric fever February - March, 2019.

Characteristic	***n* (total = 9)**	**%**
Sex		
Male	7	78
Female	2	22
Age		
2-4	2	22
5-9	3	33
15-19	4	45
Country of birth		
Australia	5	56
Typhoid-endemic country	4	44
Country of travel		
Cambodia	1	11
India	5	56
Indonesia	2	22
Pakistan	1	11
Reason for travel		
Visiting friends or relatives (VFR)	8	89
Holiday	1	11
Duration of travel (weeks)		
1-2	2	22
3-4	2	22
>/= 5	5	56

Pre-travel advice sought from general practitioner, travel physician or paediatrician	1	11
Received pre-travel vaccinations or chemoprophylaxis	0	0
Received any form of the Typhoid Vaccine	0	0
Development of symptoms whilst overseas	6	67
Required oral antimicrobial treatment for illness overseas	4	44
Symptoms		
Fever	9	100
Diarrhoea	7	78
Nausea and vomiting	4	44
Abdominal pain	7	78
Headache	1	11
Clinical sign		
Fever	9	100
Tachycardia	2	22
Relative bradycardia	1	11
Organism		
S. typhi	8	89
S. paratyphi A	1	11
Follow Up		
Paediatric Infectious Diseases Outpatient Clinic	1	11
General Paediatrics Outpatient Clinic	2	22
General Practitioner	6	67

Table 2. Susceptibility of *S. typhi* and *S. paratyphi* in cases

Isolate	**Country of Travel**	**Organism Sensitivities**	**Organism Resistance**
1. *S. paratyphi A*	Cambodia	Amoxycillin, ceftriaxone, co-trimoxazole, azithromycin (MIC 8)	Gentamicin
2. *S. typhi*	India	Amoxycillin, ceftriaxone, co-trimoxazole, azithromycin (MIC 2)	Gentamicin
3. *S. typhi*	India	Amoxycillin, ceftriaxone, co-trimoxazole, azithromycin (MIC 6)	Gentamicin
4. *S. typhi*	India	Amoxycillin, ceftriaxone, cotrimoxazole, azithromycin (MIC 6)	Ciprofloxacin, gentamicin
5. *S. typhi*	India	Amoxycillin, ceftriaxone, co-trimoxazole, azithromycin (MIC 4)	Ciprofloxacin, gentamicin
6. *S. typhi*	India	*confirmed on stool culture, no sensitivities available	

7. *S. typhi*	Indonesia	Amoxycillin, ceftriaxone, co-trimoxazole, ciprofloxacin	Azithromycin
8. *S. typhi*	Indonesia	Amoxycillin, ceftriaxone, co-trimoxazole, azithromycin (MIC 2)	Gentamicin
9. *S. typhi*	Pakistan	XDR *S. typhi* Meropenem, azithromycin (MIC 2)	Ceftriaxone, amoxycillin, ciprofloxacin, co-trimoxazole, gentamicin

*MIC – Minimum inhibitory concentration.

Figure legends

- None