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Short Communication

Salmonella Typhi and Paratyphi A infections in Cambodian children, 2012–2016

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ABSTRACT

Objectives: Enteric fever remains an important diagnostic and treatment challenge in febrile children living in the tropics. In the context of a national *Salmonella enterica* serovar Paratyphi A outbreak, the objective of this retrospective study was to compare features of *S.* Typhi and *S.* Paratyphi A infections in Cambodian children.
Methods: Clinical and laboratory features were reviewed for 192 blood culture-confirmed children with *S.* Typhi and *S.* Paratyphi A infections presenting to a paediatric referral hospital in Siem Reap, 2012–2016.
Results: Children with *S.* Typhi infections were younger, were more likely to have chills and/or diarrhoea, and were more frequently hospitalized than those with *S.* Paratyphi A infections. Over three quarters (88.3%) of *S.* Typhi isolates were multidrug-resistant, compared to none of the *S.* Paratyphi A.
Conclusions: In this small study of Cambodian children, *S.* Typhi infections were more severe than *S.* Paratyphi A infections. Antibiotic resistance limits treatment options for enteric fever in this population.

Enteric fever, caused by infection with *Salmonella enterica* serovar Typhi (*S.* Typhi) or serovar Paratyphi A/B/C (*S.* Paratyphi), remains a significant cause of morbidity and mortality globally (GBD, 2017 Typhoid and Paratyphoid Collaborators, 2019). The non-specific clinical presentation and rising rates of antimicrobial resistance make empiric treatment challenging (Gibani et al., 2018). In Cambodia, a recent national outbreak of *S.* Paratyphi A was identified initially in returning European tourists (Vlieghe et al., 2013; Kuijpers et al., 2017). Since comparative data on *S.* Typhi and *S.* Paratyphi A infections in paediatrics are scarce, this outbreak afforded a review of clinical presentation, treatment, and outcomes in Cambodian children.

Clinical and laboratory data were reviewed from blood culture-confirmed cases of *S.* Typhi and *S.* Paratyphi A infection at Angkor Hospital for Children, a paediatric referral hospital in Siem Reap, between January 1, 2012 and December 31, 2016. Over this time period, it was normal clinical practice for febrile children to have blood cultures on hospital admission, as described previously (Fox-Lewis et al., 2018). Data were analysed using R (v3.4.0); comparisons between groups were made using the Wilcoxon rank sum test, Chi-square test, or Fisher's exact test, as appropriate.

Clinical notes from 192/224 (85.7%) cases could be reviewed. *S.* Typhi predominated in 2012–2013 (100/106; 94.3%) and 2015–2016 (38/45; 84.4%). In 2014, almost 61.0% of infections (25/41) were caused by *S.* Paratyphi A (Fig. 1). Relevant clinical features are summarized in Table 1.

On univariable analysis, *S.* Paratyphi A infected older children compared to *S.* Typhi: median age 10.2 years (range 2.7–15.5 years) and 7.2 years (range 1.2–15.2 years), respectively ($p < 0.001$). Chills (20.8% vs. 0%; $p < 0.001$) and diarrhoea (24.0% vs. 7.9%; $p = 0.03$) were more common in children with *S.* Typhi infection, whereas headache was more common in those with *S.* Paratyphi A (30.5% vs. 50.0%; $p = 0.04$). There were no significant differences in clinical examination or white blood cell count results between the two groups. Children with *S.* Typhi infection had slightly lower haemoglobin values than those with *S.* Paratyphi A: median 105 g/l versus 115 g/l ($p < 0.001$). Children with *S.* Typhi were more likely to be admitted than those with *S.* Paratyphi A: 61.0% versus 42.1% ($p = 0.05$); they also had longer hospitalization duration and fever clearance times (Table 1).

In a multivariable logistic regression model, younger age (odds ratio 0.79, 95% confidence interval 0.67–0.91; $p = 0.002$) and longer

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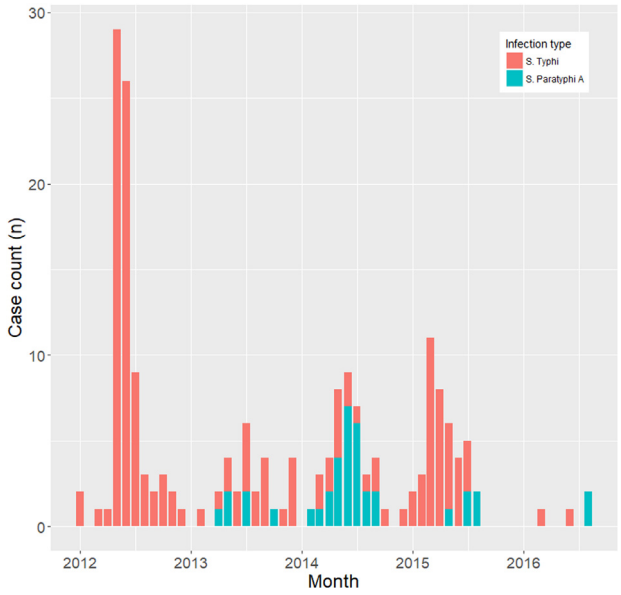

Fig. 1. *Salmonella enterica* serovar Typhi and *S. enterica* serovar Paratyphi A monthly case counts, January 2012–December 2016.

duration of fever at presentation (odds ratio 1.20, 95% confidence interval 1.03–1.46; $p = 0.03$) remained associated significantly with *S.* Typhi infection, controlling for the other factors (Table 2).

Almost all (136/154; 88.3%) of the *S.* Typhi isolates were multidrug-resistant (resistant to ampicillin, chloramphenicol, co-trimoxazole) and 98.1% (151/154) were non-susceptible to ciprofloxacin. None of the *S.* Paratyphi A were multidrug-resistant and only 15.8% (6/38) were non-susceptible to ciprofloxacin. A total of 124 isolates (64.5%) were tested against ceftriaxone and all were susceptible. Azithromycin and ceftriaxone were the most commonly prescribed drugs both before and after culture confirmation: azithromycin in 87/192 (45.3%) before and 113/192 (58.9%) after culture confirmation; ceftriaxone in 90/192 (46.9%) before and 116/192 (60.4%) after.

There were no clear clinical or basic laboratory differences between *S.* Typhi and *S.* Paratyphi A infections in Cambodian children. However, *S.* Paratyphi A infections were less severe, requiring less frequent and shorter durations of hospitalization. These findings are similar to those noted in an urban paediatric population in Bangladesh (Naheed et al., 2010). Interestingly, no differences in presentation and outcomes were found in Cambodian adults hospitalized in Phnom Penh with *S.* Typhi and *S.* Paratyphi A infections over the same time period (Kuijpers et al., 2017).

Table 1
Univariable comparisons of clinical and laboratory features of children with *Salmonella enterica* serovar Typhi or *S. enterica* serovar Paratyphi A infection.

Variable	Overall (n = 192)	*S.* Typhi (n = 154)	*S.* Paratyphi A (n = 38)	p-Value
History				
Age (years), median (range)	7.8 (1.2–15.5)	7.2 (1.2–15.4)	10.2 (2.7–15.5)	<0.001
Sex, *n* (%)				
Female	103 (53.6)	85 (55.2)	18 (47.4)	0.5
Male	89 (46.4)	69 (44.8)	20 (52.6)	
Fever, *n* (%)	192 (100)	154 (100)	38 (100)	NA
Duration of fever at presentation (days), median (range)	5 (1–26)	5 (1–26)	4 (1–10)	0.07
Cough, *n* (%)	64 (33.3)	51 (33.1)	13 (34.2)	1
Chills, *n* (%)	32 (16.7)	32 (20.8)	0 (0)	<0.001
Abdominal pain, *n* (%)	102 (53.1)	84 (54.5)	18 (47.4)	0.5
Diarrhoea, *n* (%)	40 (20.8)	37 (24.0)	3 (7.9)	0.03
Vomiting, *n* (%)	53 (27.6)	43 (27.9)	10 (26.3)	1
Constipation, *n* (%)	13 (6.7)	13 (8.4)	0 (0)	0.08
Headache, *n* (%)	66 (34.4)	47 (30.5)	19 (50.0)	0.04
Physical examination on admission				
Temperature (°C), median (range)	38.6 (35.8–40.8)	38.7 (35.8–40.8)	38.5 (36.5–40.2)	1
Abdominal tenderness, *n* (%)	36 (18.8)	30 (19.5)	6 (15.8)	0.8
Abdomen soft, *n* (%)	161 (83.9)	130 (84.4)	31 (81.6)	0.9
Rose spot, *n* (%)	0 (0)	0 (0)	0 (0)	NA
Splenomegaly, *n* (%)	4 (2.1)	3 (1.9)	1 (2.6)	1
Hepatomegaly, *n* (%)	32 (16.7)	29 (18.8)	3 (7.9)	0.1
Coated tongue, *n* (%)	1 (0.5)	1 (0.6)	0 (0)	1
Abnormal lung sounds, *n* (%)	8 (4.2)	6 (3.9)	2 (5.3)	0.7
Haematology results on admission				
Haemoglobin (g/l), median (range)	107 (46–189)	105 (50–189)	115 (46–150)	<0.001
White blood cell count ($\times 10^9$/l), median (range)	7.4 (1.5–16.6)	7.6 (1.5–16.6)	7.0 (3.1–11.4)	0.1
Neutrophil count ($\times 10^9$/l), median (range)	4.5 (0.8–12.6)	4.6 (0.8–12.6)	3.9 (1.7–8)	0.07
Platelet count ($\times$109/l), median (range)	250 (30–762)	251 (30–762)	238 (118–664)	0.7
Admission and outcome				
Admission, *n* (%)	110 (57.3)	94 (61.0)	16 (42.1)	0.05
Duration of hospitalization (days), median (range)	8 (1–24)	9 (1–24)	6.5 (2–10)	0.002
Duration of fever during hospitalization[a] (days), median (range)	6 (0–21)	7 (0–21)	4 (0–9)	<0.001
Intensive care unit admission, *n* (%)	2 (0.5)	2 (1.3)	0 (0)	1
Discharge status				
Well, *n* (%)	104 (94.5)	88 (93.6)	16 (100)	0.6
Left against medical advice, *n* (%)	6 (5.5)	6 (6.5)	0 (0)	
Died, *n* (%)	0 (0)	0 (0)	(0)	

[a] Days until temperature consistently <37.5 °C.

Table 2
Results of a multivariable logistic regression model of clinical and laboratory features of children with *Salmonella enterica* serovar Typhi or *S. enterica* serovar Paratyphi A infection. The model included 189 children (three children with missing blood count data excluded). With the exception of 'chills' (which was associated completely with *S.* Typhi infection), all clinical and laboratory features with univariable *p*-values of <0.1 were included in the model, with infection category (*S.* Typhi versus *S.* Paratyphi) as the dependent variable.

Variable	OR (95% CI)[a]	*p*-Value
Age (years)	0.79 (0.67–0.91)	0.002
Duration of fever at presentation (days)	1.20 (1.03–1.46)	0.03
Diarrhoea	4.95 (1.17–35.76)	0.06
Constipation	1.67×10^{7} (8.49×10^{-24} to ∞)	1.0
Headache	0.96 (0.39–2.45)	0.9
Haemoglobin (g/l)	0.98 (0.96–1.01)	0.2
Neutrophil count ($\times$109/l)	1.18 (0.94–1.52)	0.2
Managed as outpatient	0.48 (0.20–1.13)	0.1

OR, odds ratio; CI, confidence interval.
[a] An OR of >1 indicates a feature is associated with infection by *S.* Typhi rather than *S.* Paratyphi A.

A limitation of the study was that 32 infections could not be included in the analyses due to missing medical notes: 28 *S.* Typhi and four *S.* Paratyphi A. To assess for potential bias, the date of birth for these children was retrieved from the hospital microbiology laboratory database. Whilst these 32 children were older than those included in the study (median age 12.3 versus 7.8 years; $p < 0.001$), including these children in the comparison of age and infecting serovar did not alter the association noted above (*S.* Paratyphi A 10.2 years (interquartile range 7.7–11.8 years) vs. *S.* Typhi 7.9 years (interquartile range 5.5–11.1 years); $p = 0.005$).

Antimicrobial resistance is a significant problem for *S.* Typhi in Cambodia, and is known to be due to the globally dominant H58 clade (Emary et al., 2012; Wong et al., 2015). For the time being, azithromycin is the only acceptable oral treatment for *S.* Typhi infection. For hospitalized patients, ceftriaxone remains effective, but if extended-spectrum beta-lactamase-producing strains emerge, as they have elsewhere in Asia (Klemm et al., 2018), then carbapenem antibiotics will be the only treatment choice for severe disease. The deployment of newly developed typhoid conjugate vaccines in high-burden countries will be critically important to prevent the emergence and spread of such strains (Shakya et al., 2019).

In conclusion, enteric fever remains a clinical diagnostic challenge in Cambodian children, and antibiotic resistance limits treatment options.

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Ethical approval

The study protocol was approved by the Institutional Review Board of Angkor Hospital for Children.

Conflicts of interest

The authors have no conflicts of interest to declare.

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