

A prospective study of the importance of enteric fever as a cause of non-malarial febrile illness in patients admitted to Chittagong Medical College Hospital, Bangladesh

Short title: Enteric fever in hospitalized patients in Bangladesh

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Abstract

Background: Fever is a common cause of admission to hospital in Bangladesh but causative agents, other than malaria are, not routinely investigated; enteric fever is thought to be common.

Methods: Adults and children admitted to Chittagong Medical College Hospital with a temperature of $\geq 38.0^{\circ}\text{C}$ were investigated in detail using a blood smear for malaria, a blood culture, real-time PCR to detect *Salmonella* Typhi, *S. Paratyphi* A and other pathogens in blood and CSF and NS1 antigen dengue ELISA.

Results: We enrolled 300 patients with fever that were malaria smear negative between January and June 2012: 156 children (aged ≤ 15 years) and 144 adults with a median (interquartile range) age of 13 (5-31) years and median (IQR) duration of illness before admission of five (2-8) days. Clinical syndromes included: enteric fever in 52 patients (17.3%), lower respiratory tract infection in 48 patients (16.0%), non-specific febrile illness in 48 patients (16.0%), a CNS infection in 37 patients (12.3%), urinary sepsis in 23 patients (7.7%), an upper respiratory tract infection in 21 patients (7.0%), and diarrhea or dysentery in 21 patients (7.0%). Despite a negative microscopy malaria was still suspected in seven patients. *S. Typhi* was detected in blood by culture or PCR in 34/56 (65.4%) of patients in which typhoid was suspected. *Rickettsia typhi* and *Orientia tsutsugamushi* were detected by PCR in two and one patient respectively and two patients were dengue NS1 antigen positive. Twenty-nine (9%) patients died during their hospital admission: 15/160 (9.4%) of children and 14/144 (9.7%) adults; 2/56 (3.6%) patients with enteric fever, 5/48 (10.4%) patients with lower respiratory tract infections, and 12/36 (33.3%) patients with encephalitis/meningitis.

Conclusion: Enteric fever was responsible for nearly one in five admissions to this hospital in Chittagong, Bangladesh with non-malaria fever with the diagnosis confirmed in two thirds. Lower respiratory tract infections and CNS infections were also common. The etiology of

70 CNS infections in this location merits more detailed study due to the high mortality rate.

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Introduction

The infectious causes of febrile illness remain poorly characterized in many parts of the world; this is largely due to limited diagnostic microbiology facilities. Hospital-based studies performed over defined periods of time have provided useful clinical and public health information in countries that lack the resources for routine diagnostic testing [1]. This approach has been used in many developing countries to determine the relative importance and antimicrobial susceptibility patterns of common pathogens and to provide clinical predictors in well-defined populations [2-4]. Moreover, the application of these methods has resulted in the identification of emerging pathogens, or re-emergence of previously recognized pathogens, among the same populations [5,6]

In Chittagong, Bangladesh, febrile illness is a common reason for seeking medical advice and hospital admission. Malaria is an important cause of febrile disease and is generally diagnosed using a malaria blood smear and/or a rapid diagnostic test [7]. For patients in whom malaria has been excluded there is limited information concerning the etiology of other febrile illnesses as standard microbiological investigations, such as blood culture, are not routinely performed. Enteric fever is believed to be common and dominated by antimicrobial resistant organisms but the burden of typhoidal pathogens has not been assessed [8-14]. The importance of other diseases, such as melioidosis, rickettsiosis and leptospirosis, are also not well defined, as data tends to be associated with localized areas where research has been conducted [15]. There is serological evidence of exposure to *Burkholderia pseudomallei* (causative agent of melioidosis), *Orientia tsutsugumushi* and *Rickettsia typhi* (the causative agent of rickettsiosis) but very few reports of confirmed illness [16,17]. The provision of accurate epidemiological data for common pathogens enables clinicians and policy makers to direct limited resources.

We conducted a prospective study to assess the etiology of non-malarial febrile illness in adults and children admitted to Chittagong Medical College Hospital, a 1,000-bed regional teaching hospital. We aimed to determine the proportion of patients with enteric fever and with other clinical syndromes, causative agents and to document patient outcomes.

Materials and Methods

Ethical Statement

Patients and parents of all children recruited to the study gave witnessed, informed and written consent before study enrolment. The Bangladesh National Research Ethical Committee (BMRC/NREC/2010-2013/1543), the Oxford Tropical Research Ethics Committee (Oxtrec 53-09) and CMCH Ethics Committee approved the study protocol.

Study site and population

Chittagong Medical College Hospital (CMCH) is a 1,000-bed teaching hospital in Chittagong Division of Bangladesh. It provides inpatient and outpatient medical, surgical, pediatric and gynecology services. Each year there are approximately 700,000 outpatient visits, 700,000 emergency department visits and 600,000 admissions (500,000 adults and 100,000 children). Bed occupancy for medical wards runs at more than 100% with extra beds provided on daily basis.

Chittagong is the second largest city of Bangladesh. It is located in southeastern Bangladesh with a population in the metropolitan area of over 6.5 million people. Chittagong has a tropical monsoon climate with average temperatures ranging between 21.6°C and 30.2°C and

average humidity of 78%. The climate varies from tropical monsoon climate from March to November and cool and dry winters from December to February [18].

Patients and Clinical Methods

Patients admitted to CMCH between 15th January 2012 and 5th July 2012 were considered for enrollment. Eligibility criteria were age more than six months, documented axillary temperature $\geq 38^{\circ}\text{C}$, a reported history of fever less than two weeks, a negative malaria smear and written informed consent given by patient or by the parents or caregiver if a child (age < 16 years). Demographic and clinical information was recorded on a case record form at the time of admission and during the course of hospitalization.

A final diagnosis was made by the study team based on clinical presentation, basic laboratory results and microbiology results. A diagnosis of enteric fever was considered if the clinical features included some (but not necessarily all) of the following: a febrile illness of > 3 days duration, the presence of abdominal symptoms (abdominal pain, diarrhea or constipation), a documented fever of $\geq 39^{\circ}\text{C}$; hepatomegaly and/or splenomegaly; a low or normal white cell count; elevation of liver enzymes (aspartate transaminase, alanine transaminase) 2-3 times above the normal range; a slow defervescence with ceftriaxone treatment (the standard antibiotic used for hospital admitted febrile patients with suspected enteric fever); no alternative confirmed diagnosis established.

Laboratory Methods

Blood was taken for complete blood count, urea and creatinine, aspartate transaminase (AST), alanine transaminase (ALT), malaria smear, a single BactAlert® blood culture, and a sample for real time PCR assays and serology. In addition, feces and urine was collected for typhoid diagnostic tests. Cerebrospinal fluid was taken at the discretion of the responsible

physician in suspected central nervous system infection. EDTA whole blood, serum, feces, urine and any residual CSF were stored at -20°C for later analysis by PCR and serology at the Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Vietnam

Bacterial culture

Blood was taken for culture within 24 hours of admission, when possible before antimicrobial therapy was started in hospital. A volume of blood, 5-12 mL in adults and 1-12 mL for children, was inoculated into an adult or pediatric BactAlert® blood culture bottle. They were incubated aerobically in a BactAlert® automated system (bioMérieux, Marcy l'Etoile, France) at 37°C for 5 days. A Gram stained smear was prepared from the broth of bottles that were positive and which was also sub-cultured onto 5% sheep blood agar and chocolate agar (Oxoid, Basingstoke, UK) incubated in a candle jar and MacConkey agar (Oxoid, Basingstoke, UK) incubated in air for 48 hours. Bacterial isolates were identified by standard methods including biochemical test using API test strips (bioMérieux, Marcy l'Etoile, France) and agglutination with specific antisera (Biorad, Hertfordshire, UK) [19].

Antimicrobial susceptibility tests were determined using disc diffusion with results interpreted according to Clinical Laboratory Standards Institute (CLSI) guidelines (20). Isolates of *Salmonella* were tested with chloramphenicol (30µg), ampicillin (10µg), trimethoprim-sulphamethoxazole (1.25/23.75µg), ceftriaxone (30µg), ciprofloxacin (5µg), and nalidixic acid (30µg). The minimum inhibitory concentration (MIC) was determined by E- test according to the manufacturer's guidelines (AB Biodisk, Solna, Sweden) against ciprofloxacin, ceftriaxone and azithromycin. Breakpoints for ciprofloxacin were: susceptible ≤ 0.06 µg/mL; intermediate $> 0.06 - \leq 0.5$ µg/mL; and resistant ≥ 1.0 µg/mL. A cut-off for susceptibility of ≤ 16 µg/mL was used for azithromycin. Other Enterobacteriaceae were tested

against ampicillin (10µg), trimethoprim-sulphamethoxazole (1.25/23.75µg), ceftriaxone (30µg), ceftazidime (30µg), ciprofloxacin (5µg) and gentamicin (10µg). Isolates non-susceptible to ceftriaxone or ceftazidime were tested for extended spectrum beta-lactamase (ESBL) activity by comparing inhibition zone sizes of cefpodoxime, ceftriaxone and ceftazidime with and without clavulanic acid with a difference of 5mm or more indicating ESBL activity. *Staphylococcus aureus* was tested with penicillin (10U), cefoxitin (30µg) (resistance indicating meticillin resistance) and erythromycin (15µg). *Escherichia coli* ATCC® 25922 and *Staphylococcus aureus* ATCC® 25923 were used as control strains for these assays. All media and tests were subject to regular internal quality assessment. Bacterial isolates were stored on beads in glycerol at -80°C and later transferred to the OUCRU, Vietnam for re-confirmation of their identification and susceptibility results.

Serology

The admission serum was analysed by ELISA for dengue NS1 antigen using a PanBio Kit (PanBio, Australia) according to the manufacturer's instructions.

Nucleic Acid Amplification Tests

DNA was extracted from the stored whole blood samples with a QIAmp DNA mini kit (Qiagen, UK). A real-time PCR for *S.enterica* Typhi and *S.enterica* Paratyphi was performed using 25µL reactions containing 5µL of extracted DNA targeting *STY0201* (Putative fimbrial adhesion in *S. Typhi* CT18) or *SSPA2308* (hypothetical protein in SPA AKU-12601) as previously described [21]. Probe-based real-time PCR was also performed on the DNA extracted from blood to detect *Leptospira* spp, *R.typhi* and *O.tsustugamushi* [22-24]. Low-positive plasmid controls determined adequate detection limits of each assay.

Total nucleic acid was isolated from 100 µL of CSF specimens using the automated easyMAG[®] system (bioMérieux), and diagnostic NAATs were performed [25]. Four rPCR protocols were used for detection of *S pneumoniae*, *H influenzae* type B, *Neisseria meningitidis*, and *Streptococcus suis*. rRT-PCRs were used to detect herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), enteroviruses (generic and 71-specific) [26], and human parechoviruses (generic).

Analysis

This was an observational study intended to serve as the basis for future studies with larger sample sizes and/or interventions. The true incidence of patients presenting with enteric fever in the CMCH is unknown. With a sample of at least 250 patients we would be able to estimate a disease prevalence of 5% with a confidence interval (CI) of $\pm 2.8\%$.

Demographic and clinical features were described for the whole cohort and within the stratified age categories of < 5 years, 5-15 years and ≥ 16 years. Continuous data was described using median and inter-quartile range and compared using the Mann Whitney U-test. Proportions were compared with the Chi-squared test or the Fisher's exact test as appropriate. Age, sex, duration of illness prior to admission to hospital, and the clinical syndrome were evaluated for association with in-hospital death through a univariate analysis. A multivariate logistic regression model controlling simultaneously for the effects of confounding included variables associated with the outcome of death ($p < 0.10$) as well as *a priori* factors age, sex and duration of illness prior to admission. Analysis was performed using SPSS version 21 (SPSS inc, Chicago, USA).

Results

Demographics and clinical features

We enrolled 304 eligible febrile patients in this study. It was not possible to take blood from one patient and in three patients, who were blood culture negative, there was insufficient blood for PCR amplification. These four patients were excluded from this analysis. Of the 300 patients analyzed 156 were children (age ≤ 15 years) and 144 were adults. The median (interquartile range, range) age was 13.5 (5.0-31.0, 0.5-89) years and the median duration of illness before admission was five (IQR, 2-8; range, 1-14) days. A history of prior antimicrobial therapy was reported in 185 (61.7%) of patients including 96 (61.5%) of children and 89 (61.8%) of adults.

A final diagnosis of enteric fever was made in 52 (17.3%; 95% Confidence Interval 13.5-22.0%) patients. Other common clinical syndromes diagnosed included: lower respiratory tract infection in 48 patients (16.0%), non-specific febrile illness in 48 patients (16.0%), a CNS infection in 37 patients (12.3%), urinary sepsis in 23 patients (7.7%), upper respiratory tract infection in 21 patients (7.0%), and diarrhea or dysentery in 21 patients (7.0%). Malaria was still clinically suspected in seven patients, despite a negative malaria smear, although all had received prior anti-malarial treatment. Two subsequently had a malaria positive rapid diagnostic test result. The demographic features and clinical syndromes diagnosed in the patients according to age ranges are shown in Table 1.

Microbiological diagnoses

A microbiological diagnosis was confirmed in 58 (19.1%) patients as outlined in Table 2. *Salmonella* Typhi was most prevalent organism detected in this study and accounted for 34 cases (11.3%; 95%CI 8.2-15.5%) with a positive blood culture for *S. Typhi* in 19 (6.3%) and

15 (5.0%) with a negative blood culture but PCR amplification positive for *S. Typhi* in blood. The diagnosis was therefore confirmed in 34/52 (65.4%) of patients in whom the diagnosis was suspected. No patient was positive for *Salmonella* Paratyphi A by blood culture or by PCR. A Gram-negative bacillus was found in the culture of a patient clinically diagnosed as enteric fever and a Gram positive diplococcus was observed in the culture of an adult with pneumonia but neither was isolated or identified on sub-culture. All of the positive blood cultures grew just one organism. The tested *S. Typhi* isolates (n=18) all had intermediate susceptibility to ciprofloxacin; six were multidrug-resistant strains (MDR) exhibiting resistance to chloramphenicol, ampicillin and co-trimoxazole; all were susceptible to ceftriaxone and azithromycin. One *S. aureus* was meticillin resistant and one *E.coli* and one *K.pneumoniae* were resistant to ceftriaxone and Extended Spectrum Beta Lactamase (ESBL) positive. Two adults were PCR amplification positive for *Rickettsia typhi* and one was PCR amplification positive for *Orientia tsutsugamushi*. All patients were PCR amplification negative for *Leptospirosis*. A further two adults were positive for dengue NS1 antigen in the admission serum sample.

In the 37 patients with a CNS infection there was sufficient CSF sample available for further examination in twelve. These were positive in four children: by PCR for *Neisseria meningitidis* in two, *Streptococcus pneumoniae* in one and one was IgM positive for Japanese encephalitis virus.

Outcome

Empirical antimicrobials commonly employed for treatment were ceftriaxone, ciprofloxacin, azithromycin, cefixime, metronidazole and cefuroxime. Most patients diagnosed with enteric fever syndrome were initially treated with ceftriaxone with a step down to oral azithromycin.

The median duration of hospital stay was four (IQR 2-7, range 0-29) days.

A total of 29 (9.7%) patients died during their hospital admission: 15/156 (9.6%) of the children and 14/144 (9.7%) adults. The mortality was 2/52 (3.8%) patients with enteric fever; 5/48 (10.4%) patients with lower respiratory tract infection; and 12/37 (32.4%) patients with encephalitis/meningitis. There was no association with a history of antimicrobial use before hospital admission and mortality ($p>0.5$). The association of age, sex, duration of illness before admission and the diagnosis of the four commonest clinical syndromes with fatal outcome are shown in Table 3. In a multivariate analysis including all of these variables a diagnosis of a CNS infection was independently associated with a fatal outcome (OR 7.28 (95% CI 2.96-17.92; $p<0.001$). Of the 12 patients with a CNS infection who died, CSF was available for pathogen detection in only two one of which was positive for *S. pneumoniae*.

Discussion

In this study of febrile adults and children admitted to hospital in Chittagong enteric fever was identified as the most common clinical syndrome responsible for nearly one in five admissions. The diagnosis was confirmed by isolation of *S. Typhi* in blood culture and/or by real time PCR amplification from blood for *S. Typhi* in two thirds of suspected cases. Enteric fever was most commonly diagnosed in school aged children and young adults in this group of hospitalized patients. There was only one case in a child aged <5 years. This is a lower proportion than has been observed in community-based studies in other sites in Bangladesh [8-10]. In community studies most cases are not admitted to hospital, suggesting that more severe disease which requires hospital admission occurs in older age groups. Of the eighteen tested *S. Typhi* isolates all demonstrated intermediate susceptibility to ciprofloxacin and one third were multidrug resistant. This is consistent with other studies originating in Bangladesh

[11,12]. Ceftriaxone and azithromycin remained active and were used for treatment. There were no isolates resistant to ceftriaxone or ciprofloxacin ($\text{MIC} \geq 1.0 \mu\text{g/mL}$) [13,14]. The mortality in the confirmed enteric fever cases at 3.8% was comparable with other studies of hospitalized patients [27-30]. We did not identify enteric fever caused by *S. Paratyphi A* in this group of patients, however this organism been isolated from other patients with enteric fever in Chittagong and at other sites in Bangladesh [10]. Enteric fever caused by *S. Paratyphi A* may be less severe than the disease caused by *S. Typhi* in this setting and less likely to result in hospital admission, although observations across other parts of South Asia suggest that typhoid and paratyphoid may be equally clinically severe [31].

Lower respiratory tract infections were the second most common clinical syndrome and had a corresponding mortality of 10.4%. A further 15% of patients presented with non-specific febrile illness and there were no deaths in this group. CNS infections accounted for nearly 12% of admissions and were responsible for >40% of deaths. The etiology of these cases was undetermined in most patients mainly because insufficient CSF was available for further analysis. Other identified organisms causing bacteremia included *Staphylococcus aureus*, *Streptococcus pneumoniae*, *E.coli*, *Enterobacter cloacae* and *Klebsiella pneumoniae*; these are typical causes of bacteremia in Asia [32]. The presence of meticillin resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* illustrates the importance of resistance surveillance against commonly used antimicrobials in this region [33]. In Bangladesh, antimicrobials can be easily purchased in the community and most patients use them prior to seeking medical attention. More than half of patients in this study consumed one or more antimicrobial prior to a blood draw for microbiological culture, pretreatment with antimicrobials will clearly impinge on the yield of bacterial pathogens detected in blood and other clinical specimens. The three cases of

324 *Burkholderia cepacia* bacteremias in children under the age of five years were unexpected.
325 This organism may be associated with environmental contamination of blood cultures, but in
326 each case here was associated with signs of severe sepsis and required additional work.
327
328 The detection of two cases of *Rickettsia typhi* (murine typhus) and one case of *Orientia*
329 *tsutsugamushi* (scrub typhus) emphasizes the occurrence of these under-recognized
330 pathogens in this area [34]. A case series in Mymensingh in the north of Bangladesh reported
331 40 *Rickettsia* infections, this study included 24 patients (60%) positive for scrub typhus, by
332 the Weil-Felix test [35]. A further case series described seven Bangladeshi nationals in
333 Singapore with murine typhus [36]. In a recent prospective seroepidemiologic survey across
334 six major teaching hospitals in Bangladesh, including CMCH, an IgM enzyme-linked
335 immunosorbent assay was used to detect recent exposure to *Rickettsia typhi* and *Orientia*
336 *tsutsugamushi*. The results indicated that 805 of 1,209 (66.6%) subjects were seropositive for
337 *Rickettsia typhi* and 287 of 1,209 (23.7%) were seropositive for *Orientia tsutsugamushi* [17]
338 suggesting that these pathogens may be an important and under-reported cause of febrile
339 illness in Bangladesh.
340
341 There were no confirmed cases of *Burkholderia pseudomallei* bacteremia despite previous
342 reports of indigenous cases and in returning travelers [37,38]. In a recent seroepidemiologic
343 survey of six hospitals across Bangladesh, 359 of 1,244 (28.9%) of patients were seropositive
344 for *B.pseudomallei* by indirect hemagglutination assay suggesting that many people are
345 exposed to the organism [16]. Also notable by its absence was Leptospirosis despite
346 serological evidence that it is cause of febrile illnesses in this area [39,40]. The absence of
347 these infections in this study may be because our surveillance of febrile patients was not
348 conducted throughout the entirety of the monsoon season, which may correspond with peaks

in these infections. Further limitations of this study are the small sample size and the range of diagnostic testing performed in this study. The microbiological culture, molecular and serological methods used for the detection of pathogens would not have detected all disease episodes; a panel of assays for each disease agent would have increased sensitivity. The lack of CSF samples for further testing was a particular gap as they were associated with the highest mortality. Future studies should incorporate a wider panel of diagnostic methods for relevant pathogens and a minimum of a year-long recruitment period to encompass all potential seasonal variation.

Conclusions

Enteric fever, caused by *S. Typhi*, was a common cause of a non-malaria febrile illness in patients admitted to hospital in Chittagong. All isolated *S. Typhi* exhibited intermediate susceptibility to ciprofloxacin and many were MDR. Infection with *O. tsutsugamushi* and *R. typhi* were additionally confirmed in this setting. Lower respiratory tract and CNS infections were also common and CNS infections had a particularly high mortality rate with more than one third of patients dying during their hospital stay. The etiology of the CNS infections in this setting and requires further study.

Competing interests

The authors have no conflict of interest to declare

Author's contributions

RRM, AG, RS, HKdJ, LW, MF, MUH, MAH, MRK, HRvD, RJM, Tvdp, WJW, NPD, AMD, SB, CMP, MAF conceived and designed the study. RRM, HKdJ, LW, MF, AAS, SvE, SP, ASMZ, WR, RK, RI, TTND, HTT, PHA, JIC, CMP participated in data collection and the analysis and interpretation of data. RRM, HKdJ, SB, CMP, MAF wrote the first draft of the paper. All authors contributed to revising the draft, had full access to all the data and read and approved the final manuscript.

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Table 1 Demographic features and clinical syndromes of 304 adults and children admitted to CMCH with fever divided by age range (results are number (%) or median (IQR))

Variable	All	<5 years	5-15 years	>15 years
Duration of illness before admission (median (IQR) days)	5 (2-8)	2 (1-5)	5 (3-10)	5 (3-8)
Male	176 (58.1)	39 (54.2)	57 (65.5)	80 (55.6)
Clinical syndrome:				
Enteric fever	56 (18.5)	1 (1.4)	20 (23.0)	35 (24.3)
Lower respiratory tract infection	48 (15.8)	13 (18.1)	5 (5.7)	30 (20.8)
Non-specific febrile illness	47 (15.5)	10 (13.9)	19 (21.8)	18 (12.5)
Central nervous system infection	36 (11.9)	11 (15.3)	13 (14.9)	12(8.3)
Upper respiratory tract infection	25 (8.3)	15 (20.8)	8 (9.2)	2 (1.4)
Urinary tract infection	23 (7.6)	2 (2.8)	3 (3.4)	23 (7.6)
Diarrhea or dysentery	22 (7.2)	17 (23.3)	4 (4.6)	1 (0.7)
Malaria	7 (2.3)	0 (0)	3 (3.4)	4 (2.8)
Hepatobiliary	7 2.3)	0 (0)	4 (4.6)	3 (2.1)
Duration of admission (median (IQR) days)	4 (2-7)	3 (2-5)	5 (3-8)	4 (2-5)
Mortality (Number (%))	29 (9.6)	8 (11.1)	14 (9.7)	29 (9.6)

Table 2 Pathogens detected in 304 adults and children admitted to CMCH with fever divided by age range by age range

Pathogens	All	<5 years	5-15 years	>15 years
<i>Staphylococcus aureus</i>	2	1	1	0
<i>Streptococcus pneumoniae</i>	1	0	1	0
<i>Streptococcus acidominimus</i>	1	0	0	1
<i>Enterococcus spp.</i>	1	0	0	1
<i>Escherichia coli</i>	2	0	0	2
<i>Enterobacter cloacae</i>	2	0	0	2
<i>Klebsiella pneumoniae</i>	1	0	0	1
<i>Salmonella enterica</i> serotype Typhi				
Blood culture	19	0	8	11
PCR	20	1	2	17
<i>Burkholderia cepacia</i>	3	3	0	0
<i>Acinetobacter spp.</i>	1	0	1	0
<i>Rickettsia typhi</i>	2	0	0	2
<i>Orientia tsutsugamushi</i>	1	0	0	1
Dengue	2	0	0	2
Total	58/304 (19)	5/73 (7)	13/87 (15)	40/144 (28)

Table 3 Univariate analysis of factors associated with a fatal outcome

Covariate	Died n=29	Survived n=275	p
Age (years) ¹	13 (4-45)	13 (5-30)	0.645
Male ²	15 (51.7)	161 (58.5)	0.554
Days ill prior to admission ¹	4 (3-6)	5 (2-8)	0.758
Enteric fever ²	2 (6.9)	54 (19.6)	0.129
Lower respiratory tract infection ²	5 (17.2)	43 (15.6)	0.791
Non-specific febrile illness ²	0 (0)	47 (17.1)	0.012
Central nervous system infection ²	12 (41.4)	24 (8.7)	<0.001

1. Median (Inter-quartile range)

2. Number (%)