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CAUSES OF COMMUNITY-ACQUIRED BACTEREMIA AND PATTERNS OF ANTIMICROBIAL RESISTANCE IN VIENTIANE, LAOS

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Abstract

There is no published information on the causes of bacteremia in the Lao PDR (Laos). Between 2000 and 2004, 4512 blood culture pairs were taken from patients admitted to Mahosot Hospital, Vientiane, Laos, with suspected community-acquired bacteremia; 483 (10.7%) cultures grew a clinically significant community-acquired organism, most commonly *Salmonella enterica* serovar typhi (50.9%), *Staphylococcus aureus* (19.0%), and *Escherichia coli* (12.4%). *S. aureus* bacteremia was common among infants (69.2%), while children 1–5 years had a high frequency of typhoid (44%). Multi-drug-resistant *S. Typhi* was rare (6%). On multiple logistic regression analysis, typhoid was associated with younger age, longer illness, diarrhea, higher admission temperature, and lower peripheral white blood cell count than non-typhoidal bacteremia. Empirical parenteral ampicillin and gentamicin would have some activity against ~ 88% of clinically significant isolates at a cost of US \$1.4/day, an important exception being *B. pseudomallei*. Bacteremic infants in this setting require an anti-staphylococcal antibiotic.

INTRODUCTION

Despite being a major cause of hospital admission and mortality, there is relatively little information available on community-acquired bacteremia in the tropics.¹⁻¹⁰ The Lao PDR (Laos) is mostly situated between the Mekong River and the Annamite Mountains, the majority of the population of 5.2 million people are rural rice farmers, the per capita income is U.S. \$304/year and life expectancy is 54 years.¹¹ In comparison to wealthier countries in Asia, there is minimal information on the epidemiology of bacterial disease in Laos.¹²⁻¹⁶ There has been no accessible blood culture service and hence no information on the causes of blood stream bacterial infections, nor information on the drug sensitivity patterns of pathogenic organisms or evidence-based antibiotic treatment guidelines.

In 2000 we began the provision of the first routine, freely available inpatient blood culture service in Laos and describe the microbiological and clinical features of community-acquired bacteremia among patients admitted to Mahosot Hospital, the main internal medicine primary-tertiary hospital in Vientiane, the capital city.

PATIENTS AND METHODS

Study site

The study was conducted between February 2000 and 2004 among inpatients on all wards at Mahosot Hospital, Vientiane, a 365-bed hospital with approximately 1200 admissions/month.¹⁵ Peritoneal and hemodialysis, cancer and antiretroviral therapy, and central venous catheterization were not available. Ethical clearance was granted by the Ethical Review Committee of the Faculty of Medical Sciences, National University of Laos.

Clinical procedures and sampling

We recruited all patients admitted with suspected community-acquired bacteremia if they gave informed verbal consent. No formal definition was used and recruitment was at the discretion of the responsible physician. History and clinical examination were recorded on standard forms. A venous blood sample was drawn aseptically for 2 blood cultures (based on tryptic hydrolysate of casein and soy peptone) (Pharmaceutical Factory No 2, Vientiane). The volume of blood taken was 5 mL/bottle for adults (> 15 years), 2 mL/bottle for children > 1 year, and 1 mL/bottle for infants. The ratio of blood to media was 1:10.

Microbiological procedures and definitions

Vented blood culture bottles were incubated in air at 37°C for 7 days. All bottles were examined daily and if turbid were subcultured onto blood and chocolate agar. 'Blind' subculture was performed on day 7 post-inoculation. Bacteria and fungi isolated were identified using standard biochemical tests.^{17,18} Goat blood was used for blood agars.¹⁹ Antibiotic susceptibilities were determined by the Kirby-Bauer disk diffusion method using antibiotic impregnated disks (Oxoid, Basingstoke, UK),²⁰ and minimum inhibitory concentrations (MICs) using standard broth dilution methods or Etests™ (AB Biodisk, Solna, Sweden). Methicillin susceptibility testing of *S. aureus* was performed only during the last 6 months of the study.

True bacteremia, hospital-acquired bacteremia, and blood culture contaminants were defined using conventional criteria.^{6,21} Community-acquired bacteremia was defined as clinically relevant positive blood cultures taken within 48 hours of hospital admission, or if the blood culture was drawn after 48 hours and the clinical presentation and identified pathogen were consistent with community-acquired disease. A single episode was recorded when the same organism was isolated from multiple blood culture sets during the same hospital admission.

Statistical analysis

Analysis was performed using STATA v8 (Stata Corporation, College Station, TX). Categorical variables were compared with χ^2 and Fisher's exact test and continuous variables by the Student's *t* test, ANOVA, Mann-Whitney U, and Kruskal-Wallis tests as appropriate. Multiple logistic regression analysis (backward) was used to examine relationships between culture results and clinical details and the predictive value of the model was measured using the area under the receiver operating characteristic curve (AUROCC). Continuous variables entered in multiple logistic regressions were categorized into clinically meaningful categories and their relationship with outcome was examined using both continuous and categorical representations. None of the variables showed evidence for non-linear relationships with the outcome, so they were modeled as continuous variables.

RESULTS

Of the ~57,000 admissions during the 4 years, a total of 4512 blood culture pairs from 4460 patients were taken; 754 (16.7%) yielded an organism, of which 483 (10.7%) were considered clinically significant community-acquired organisms, 4 (0.1%) were significant hospital-acquired organisms, and 267 (5.9%) yielded an organism that was classified as a contaminant (Table 1). The mean (95%CI) monthly percentage of patients admitted who had a blood culture drawn was 7.6% (6.9–8.3), of which 0.9% (0.7–1.1) had a clinically significant positive culture; 2772 (61%) blood cultures were taken from adults, and 1740 (39%) were from children (age < 15 years) including 341 (7.6%) from infants (< 1 year). In an analysis performed after organisms were classified according to clinical significance, an organism was cultured in both bottles for 343 of 449 patients with clinically significant bacteremia (76%) and for 157 of 246 patients with an organism regarded as a contaminant (64%) ($P < 0.001$). Of 782 blood cultures taken more than 2 days after admission, 40 (5.1%) grew a clinically significant organism, in comparison to 3515 taken within 2 days of admission of which 425 (12.1%) grew a clinically significant organism. The estimated minimum incidence of community-acquired bacteremia in the catchment area was 4.5 of 100,000 people/year and 8.4 of 1000 admissions/year. This assumes a catchment population of 900,000 and that Mahosot Hospital contains 30% of hospital beds in Vientiane. The mean (95%CI; range) number of clinically significant pathogenic species isolated per month was 3.8 (3.3–4.3; 1–8).

Blood culture isolates

Clinically significant isolates were obtained from 11.2% of adults, 9.9% of children, and 8.2% of infants (see Table 1). Of the clinically significant organisms grown from patients with community-acquired bacteremia, 373 (77%) were Gram-negative, 109 (23%) were Gram-positive, and 1 patient had cryptococemia. Of these, 23 were isolated more than 2 days after admission (*Salmonella enterica* serovar typhi (*S. Typhi*) ($N=16$) and *B. pseudomallei* ($N=7$)). Overall, 3 pathogens made up 80% of all isolates, with *S. Typhi* being the most frequent isolate (50.9%) followed by *S. aureus* (19.0%) and *E. coli* (12.4%). Four *Klebsiella pneumoniae* infections were thought to be hospital acquired. There were no significant differences in the spectrum of bacteria isolated from children (< 15 years) and adults ($P > 0.02$). The organisms most commonly isolated from children aged 1–5 years were *S. Typhi* (44%), *S. aureus* (17.7%), and *E. coli* (17.7%). For children aged < 1 year, the common species isolated were *S. aureus* (69.2%), *E. coli* (7.7%), and *K. pneumoniae* (7.7%) with no *S. Typhi* isolated. The frequency of *S. Typhi* was lower ($P < 0.0001$) and the frequency of *S. aureus* higher ($P < 0.0001$) in those < 1 year old in comparison to those 1–5 years old.

None of the 7 patients with *Ps. fluorescens* cultured had received a blood transfusion, 22 and none of 10 patients with *Acinetobacter* species cultured had pneumonia. 23 Ten patients < 1 week old had blood cultures positive for coagulase-negative staphylococci, but none of these infants were premature and these were considered to be contaminants.

Clinical features

Comparison of patients with Gram-positive, non-typhoidal Gram-negative and *S. Typhi* bacteremia suggested that the 3 groups differed significantly ($P < 0.02$) for 23 variables (Table 2). Subsequent paired analysis suggested that patients with *S. Typhi* bacteremia differed significantly from those with Gram-positive and non-typhoidal Gram-negative bacteremia for 16 and 18 variables, respectively (see Table 2).

In comparison to patients with typhoid, patients with Gram-positive bacteremia were ill for fewer days, were less likely to have abdominal pain or diarrhea and more likely to have used steroids or have had dyspnea, rash, meningism, septic arthritis, abscess or renal calculi, had a higher pulse rate, respiratory rate, peripheral white count and percentage of neutrophils, and lower admission temperature (see Table 2). In comparison to patients with typhoid, those with non-*S. Typhi* Gram-negative bacteremia were older, ill for fewer days, and less commonly had diarrhea, but more commonly had dyspnea, jaundice, meningism, septic arthritis, or abscesses and a history of diabetes, chronic renal failure, systemic lupus, renal calculi, to have used steroids or to be a smoker, and to have a higher systolic blood pressure and percentage of neutrophils in the peripheral white count.

Of 18 infants with *S. aureus* bacteremia, 13 (72%) were neonates, 9 were dyspneic, 7 were jaundiced, 4 had diarrhea, and 1 had a cutaneous abscess. None had scabies. Blood cultures from a 31-year-old fisherman admitted with fever and jaundice, with a history of cholecystectomy and postoperative biliary tract obstruction, grew *Edwardsiella tarda*. A 67-year-old housewife, with diabetes and using steroids, was admitted with 5 days of diarrhea and fever. *Shigella flexneri* was grown from her blood cultures and she deteriorated and was taken home moribund. *B. pseudomallei* was isolated from the blood of 14 (3%) patients; 6 had pneumonia, 2 had septic arthritis, and 5 had diabetes.

Antimicrobial susceptibility patterns

Antibiotic disk diffusion susceptibility testing of 226 *S. Typhi* isolates demonstrated that 12% were resistant to ampicillin, 11% resistant to co-trimoxazole, and 12% resistant to

chloramphenicol, while none were resistant to nalidixic acid; 6% were multi-drug resistant (resistant to ampicillin, co-trimoxazole, and chloramphenicol; MDR) (Table 3). No methicillin-resistant *S. aureus* were identified. Two of four *S. pneumoniae* tested were resistant to oxacillin by disc diffusion (penicillin MICs were determined for 2 isolates to be 0.032 (sensitive) and 1.0 µg/mL (intermediately resistant)). The mean (95%CI) co-trimoxazole E-test MIC for *B. pseudomallei* was 0.20 (0.12–0.28) µg/mL; all were sensitive.

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Predictors of all-cause bacteremia and *S.Typhi* bacteremia

Univariate analysis indicated that abdominal pain ($P < 0.001$), vomiting ($P = 0.01$), diarrhea ($P < 0.001$), a history of diabetes mellitus ($P < 0.001$), an axillary temperature ($P < 0.0001$), and the presence of an abscess ($P = 0.009$) were associated with a positive clinically significant community-acquired bacteremia among those who had a blood culture drawn (see Table 2). Multiple logistic regression, with these variables as a starting set, identified all variables as independent predictors of a positive blood culture (Table 4).

The mean (95%CI) ratio of admission pulse to temperature was lower in those with *S.Typhi* (2.53 (2.48–2.58) $\text{min}^{-1}/^{\circ}\text{C}$) than those with non-typhoidal bacteremia (2.76 (2.68–2.84) $\text{min}^{-1}/^{\circ}\text{C}$) ($P < 0.0001$). AUROCC (95%CI) for the pulse: temperature ratio as predictive of *S.Typhi* bacteremia was 0.386 (0.333–0.439).

Multiple logistic regression was performed to identify independent clinical and laboratory features predicting the diagnosis of *S.Typhi* bacteremia versus non-*S.Typhi* bacteremia with the 20 variables significant ($P < 0.02$) on univariate analysis (see Table 2) included. Typhoid was associated with a lower peripheral white count, higher admission temperature, a longer duration of illness, the presence of diarrhea, and a younger age (see Table 4).

Outcome

Data on outcome were available for 3909 patients (87%), of whom 16 were transferred, 189 are known to have died, and 163 were taken from the hospital to die at home, giving an overall mortality of 9.0%. Patients taken home to die were moribund, received no further known effective medical care, and the overwhelming majority are expected to have died. Of 483 patients whose blood grew a clinically significant community-acquired organism, outcome is known for 420 of whom 31 (7.4%) are known to have died, 3 were transferred, and 15 were taken home to die. The overall mortality for patients with a clinically significant blood culture was therefore 11.0%. The mortalities in those with Gram-positive and Gram-negative sepsis were 18.4 and 8.4%, respectively ($P = 0.006$). The mortality of non-typhoidal Gram-negative sepsis was 23%. The organism specific mortalities (including patients taken home to die) were 1.4% for *S.Typhi*, 12% for *E.coli*, 17% for *S.aureus*, 18% for *K. pneumoniae*, and 60% for *B. pseudomallei*. Twenty-one patients who had an axillary temperature $< 37.5^{\circ}\text{C}$ on admission and discharge information grew an organism thought to represent community-acquired bacteremia and 6 of 21 (29%) died. In contrast, only 37 of 373 (9.9%) of those admitted with a temperature $\geq 37.5^{\circ}\text{C}$ died ($P = 0.018$). Four of 16 infants (25%) with *S. aureus* bacteremia and outcome data died or were taken home moribund.

Univariate comparison of the variables in Table 2 between those with community-acquired bacteremia who lived and died gave significant ($P < 0.02$) differences for 5 variables. The median (range) number of days of illness for those who died was 7 (1–120) days and for those who lived 3.5 (1–60) days ($P = 0.005$). Dyspnea was recorded for 73 of 356 (21%) of survivors and 17 of 44 (39%) for those who died ($P = 0.007$). Mean (95%CI) admission temperature was lower in those who died (38.6 (38.2–38.9) $^{\circ}\text{C}$) than in those who survived

(39.0 (38.9–39.1)°C) ($P=0.008$). Mean (95% CI) admission pulse was higher in those who died (111.2 (103.2–119.2)/min) than in those who survived (101.3 (99.3–103.3)/min) ($P=0.002$). The median (range) percentage of neutrophils in the peripheral blood of those who lived and died were 69% (2–94) and 79% (35–93), respectively ($P=0.01$). Multiple logistic regression, using the above 5 variables, identified admission temperature, pulse, and neutrophil % as independently associated with death (see Table 4).

DISCUSSION

S.Typhi was the predominant organism isolated from blood cultures among patients presenting with community-acquired bacteremia to a hospital in Vientiane. This is similar to the situation in southern Vietnam, where 67% of clinically significant bacteria cultured from patients admitted with community-acquired bacteremia were *S.Typhi*.⁸ Typhoid is considered rare in southern Laos, an impression supported by the paucity of reports of intestinal perforation from hospitals in this area. In adjoining northeast Thailand typhoid is extremely rare,^{4,5} emphasizing the heterogeneity of typhoid epidemiology in southeast Asia. Study limitations include the lack of information on antibiotic treatment before and after discharge and detailed information on co-morbidity. The decision as to whether a blood culture should be drawn was the responsibility of a diversity of doctors and some septic patients may not have had cultures taken. Only 11% of the Lao population lives in the relatively urbanized areas of Vientiane City, and the results of this study may not be generalizable to the rest of the country. In Vientiane a considerable percentage (25–50%) of patients admitted with fever had taken prior antibiotics, usually ampicillin or co-trimoxazole, and this will have reduced our probability of growing clinically significant organisms, especially *S. pneumoniae* (Khennavong M and others, unpublished data).

The admission pulse:temperature ratio was significantly lower in those with *S.Typhi* in comparison to those with other causes of community-acquired bacteremia, consistent with the finding of relative bradycardia in typhoid. However, the difference is insufficient to be clinically useful and will be confounded by relative bradycardia associated with other clinically similar diseases such as scrub typhus,²⁵ which is also common in Vientiane.¹⁵

The *S.Typhi* isolated from patients in Vientiane had a relatively low MDR frequency. This contrasts with findings from the Indian subcontinent, Burma, and Vietnam, where multi-drug resistance has spread widely. In Rangoon 86–93% of *S.Typhi* isolates were MDR.¹⁰ As first-line drugs have become ineffective, there has been an increase in community use of fluoroquinolones, to which *Salmonellae* were originally exquisitely sensitive.²⁶ Resistance has followed rapidly. In this series all isolates were sensitive to nalidixic acid. This contrasts with India and southern Vietnam, where the majority of isolates are both MDR and moderately resistant to fluoroquinolones.²⁶ The relative susceptibility of *S.Typhi* in Laos probably relates to limited population movement and extreme poverty limiting the use of anti-infective medicines. However, in May 2004 a 20-year-old rice farmer from the Plain of Jars (Xieng Khuang Province) was admitted with blood cultures growing MDR *S.Typhi* also resistant to nalidixic acid. She is not known to have visited Vietnam.

H. influenzae, *S. pneumoniae*, and *N. meningitidis* were either very rarely isolated or not found in this series, in contrast to the situation in Europe and North America, but similar to previous reports from Asia,^{5,7,8} although the relative unimportance of *H. influenzae* in southeast Asia has been questioned.²⁸ *E. tarda* bacteremia has been described in 4 Thai patients,^{29,30} and is a Mekong River fish pathogen. Fishing is a very important source of food in rural Laos and that organisms derived from fish and freshwater may be common is also suggested by the isolation of *A. hydrophilia* from 3 patients. Thirteen patients with *P. aeruginosa* bacteremia were identified in this series. Community-acquired *P. aeruginosa*

bacteremia has been described among otherwise healthy children in Taiwan.³¹ In our series, 9 were children and the median (range) number of days between admission before blood culture was 0 (0–4), 3 had diarrhea, and 3 died. Whether the patients in our series had genuine community-acquired *P. aeruginosa* bacteremia was difficult to determine with certainty, although no other cause was found to account for their illness.

S. Typhi was the commonest pathogen cultured from children as well as from adults. In children aged 1–5 years typhoid was responsible for 44% of community-acquired bacteremias. In contrast, among 19,339 Kenyan children (< 13 years) only 1 child had *S. Typhi* bacteremia; the organisms isolated most commonly were *S. pneumoniae* and non-typhoidal *Salmonella*.³ The high proportion of Lao infants with *S. aureus* bacteremia (69%) is higher than in most previous reports.^{3,32,33} As 72% of these infants were neonates, at least some of these infections may have been hospital acquired. Of 43 Kenyan infants with *S. aureus* bacteremia, 25 (58%) had no identifiable focus and presented with pneumonia and gastroenteritis.³³ Absence of a focus was associated with high mortality perhaps because they tended not to be treated with a specific anti-staphylococcal antibiotic. With a mortality of 25% in this Lao series, anti-staphylococcal antibiotic therapy should be considered in infants, especially neonates, irrespective as to whether they have a potential infected focus.^{33,34}

No *S. Paratyphi* were cultured in the 4 years of this study, in striking contrast to the situation in Nepal and India.³⁵ Non-typhoidal salmonellae were rare causes of bacteremia in Vientiane. The prevalence of HIV infection in Laos is lower than in adjoining countries, with a 1.1% prevalence of HIV antibodies among ‘women working in bars, night clubs, and guesthouses’ in Vientiane in 2001.³⁶ As it is likely that the HIV prevalence in Laos will rise, the incidence of non-typhoidal *Salmonella* and *Cryptococcus* bacteremia may also increase.⁵

To estimate the necessary duration of a study to determine the main causes of community-acquired bacteremia, the cumulative number of clinically significant taxa isolated is plotted against study duration in Figure 1. The number of taxa did not reach an asymptote after 4 years and the first year of the study would have identified only 12 (52%) of the total taxa that were identified in 4 years. However, in one year the main causes of bacteremia, responsible for 97% of the cases during the 4 years, would have been identified.

Public health measures, such as improved sanitation and vaccination, to reduce the incidence of typhoid, may have a significant impact on morbidity and mortality in northern Laos, as it appears to have done in Thailand.³⁷ However, vaccination is relatively expensive in Laos costing ~US \$8/dose. With improved trans-border road communications the prevalence of MDR and nalidixic acid resistant typhoid may increase in Laos.

Antibiotic guidelines have recently been introduced for typhoid and melioidosis. For community-acquired bacteremia, empirical therapy with parenteral ampicillin and gentamicin would have some activity against ~88% of clinically significant organisms identified at a local cost of ~ US \$1.4/day in adults. This regimen would not benefit patients with melioidosis, which is difficult to diagnose clinically and has a very high mortality. Ceftriaxone would have activity against a broader range of organisms and is likely to have some benefit in patients with melioidosis (although it is inferior to ceftazidime),³⁸ but the local daily drug cost would be higher at ~US \$3.0/day. Intravenous cloxacillin is not widely available and is also relatively expensive at ~US \$3.6/day.

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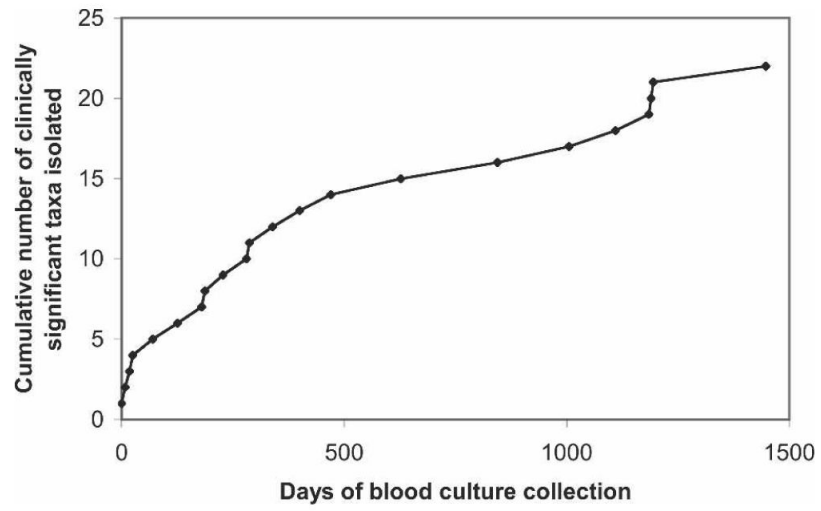


Figure 1. Cumulative number of bacterial and fungal taxa cultured during the 4 years of the bacteremia study.

Table 1

Organisms isolated from blood cultures, interpreted as community acquired and as contaminants, from 4,512 blood culture pairs at Mahosot Hospital, Vientiane, Laos, 2000–2004

Organism	Clinically significant											
	All		Adults		Children 1–15		Infants		Probable contaminants			
	N	%	N	%	N	%	N	%	N	%		
All organisms	483	10.7	311	11.2	146	10.0	26	9.1	267	5.9		
Gram-negative organisms	373	77.2	253	81.4	114	78.1	6	23.1	102	38.2		
<i>Salmonella enterica</i> serovar typhi	246	50.9	159	51.1	87	59.6	0	0	0	0		
<i>Escherichia coli</i>	60	12.4	48	15.4	10	6.8	2	7.7	0	0		
<i>Klebsiella pneumoniae</i> *	20	4.1	15	4.8	3	2.1	2	7.7	12	4.5		
<i>Burkholderia pseudomallei</i>	14	2.9	12	3.9	2	1.4	0	0	0	0		
<i>Pseudomonas aeruginosa</i>	13	2.7	4	1.3	8	5.5	1	3.8	0	0		
<i>Salmonella</i> species	9	1.9	6	1.9	3	2.1	0	0	0	0		
<i>Salmonella choleraesuis</i>	3	0.6	3	1.0	0	0	0	0	0	0		
<i>Aeromonas hydrophila</i>	3	0.6	2	0.6	1	0.7	0	0	0	0		
<i>Edwardsiella tarda</i>	1	0.2	1	0.3	0	0	0	0	0	0		
<i>Proteus vulgaris</i>	1	0.2	1	0.3	0	0	0	0	0	0		
<i>Citrobacter freundii</i>	1	0.2	1	0.3	0	0	0	0	0	0		
<i>Shigella flexneri</i>	1	0.2	1	0.3	0	0	0	0	0	0		
<i>Haemophilus influenzae</i>	1	0.2	0	0	0	0	1	3.8	0	0		
<i>Enterobacter</i> species	0	0	0	0	0	0	0	0	26	9.7		
<i>Pseudomonas</i> species †	0	0	0	0	0	0	0	0	18	6.7		
<i>Acinetobacter</i> species	0	0	0	0	0	0	0	0	10	3.7		
<i>Burkholderia cepacia</i>	0	0	0	0	0	0	0	0	8	2.9		
<i>Klebsiella</i> species	0	0	0	0	0	0	0	0	6	2.2		
<i>Ochrobacterium anthropi</i>	0	0	0	0	0	0	0	0	1	0.4		
Others ‡	0	0	0	0	0	0	0	0	21	7.9		
Gram-positive organisms	109	22.6	57	18.3	32	21.9	20	76.9	163	61.0		
<i>Staphylococcus aureus</i>	92	19.0	49	15.8	25	17.1	18	69.2	0	0		
<i>Streptococcus pneumoniae</i>	6	1.2	3	1.0	3	2.1	0	0	0	0		

Organism	Clinically significant											
	All		Adults		Children 1–15		Infants		Probable contaminants			
	N	%	N	%	N	%	N	%	N	%		
<i>Streptococcus</i> Group C	3	0.6	0	0	2	1.4	1	3.8	0	0		
Unspecified viridans streptococci	2	0.4	1	0.3	1	0.7	0	0	0	0		
<i>Streptococcus</i> species	2	0.4	1	0.3	1	0.7	0	0	5	1.9		
<i>Streptococcus</i> Group B	1	0.2	1	0.3	0	0	0	0	0	0		
<i>Streptococcus</i> Group G	1	0.2	0	0	0	0	1	3.8	0	0		
<i>Streptococcus milleri</i>	1	0.2	1	0.3	0	0	0	0	0	0		
<i>Streptococcus bovis</i>	1	0.2	1	0.3	0	0	0	0	0	0		
Coagulase negative <i>Staphylococcus</i>	0	0	0	0	0	0	0	0	95	35.6		
<i>Enterococcus</i> species	0	0	0	0	0	0	0	0	9	3.4		
<i>Aerococcus viridans</i>	0	0	0	0	0	0	0	0	3	1.1		
Others [§]	0	0	0	0	0	0	0	0	51	19.1		
Fungi	1	0.2	0	0	0	0	0	0	2	0.8		
<i>Candida</i> species	0	0	0	0	0	0	0	0	2	0.8		
<i>Cryptococcus neoformans</i>	1	0.2	0	0	0	0	0	0	0	0		

* An additional 4 *Klebsiella pneumoniae* isolates were thought to have been hospital-acquired.

[†] Unidentified *Pseudomonas* spp. (6), *Ps. fluorescens* (7), *Ps. putida* (1), *Ps. stutzeri* (3), *Ps. [Chryseomonas] luteola* (1).

[‡] Unidentified Gram-negative organisms (8), *Pantoea* spp. (6), *Serratia* spp. (3), *Morganella* sp. (1), *Flavimonas* sp. (1), *Agrobacterium* sp. (1), *Alcaligenes* sp. (1).

[§] Unidentified Gram-positive organisms (10), *Micrococcus* sp. (1), *Staphylococcus* species of uncertain identity (36), *Corynebacterium* spp. (4).

Table 2

Clinical features of patients with and without clinically significant blood culture isolates, Gram-negative non-typhoidal bacteremia, Gram-positive bacteremia and with *S. Typhi* bacteremia

Variable*	Blood cultures judged clinically			Community-acquired bacteremia			<i>P</i> [§]
	Negative or not significant	Significant [†]	<i>P</i>	Non-typhoidal Gram-negative bacteremia	Gram-positive bacteremia	<i>S. Typhi</i> [‡]	
N	4029	483		127	109	246	
Age, years [¶]	20 (0–100) ³⁹⁸¹	22 (0–95) ⁴⁸⁰	0.1	37 (0–95) ¹²⁷	15 (0–90) ¹⁰⁸	20 (1–74) ²⁴⁴	0.0001
Age (% < 15 years)	1568/4029 (39)	172/483 (35)	0.2	33/127 (26)	52/109 (48)	87/246 (35)	0.002
Sex (% male)	2331/3995 (58)	265/483 (55)	0.1	60/127 (47)	66/109 (61)	138/246 (56)	0.1
Non-days ill ^{¶¶}	–	6 (1–180) ³⁵⁷	–	4 (1–60) ⁷⁸	4 (1–120) ⁷⁹	7 (1–180) ²⁰⁰	0.0001
Headache	2667/3843 (70)	306/461 (66)	0.2	79/119 (66)	56/101 (56)	170/240 (71)	0.02
Abdominal pain	1320/3812 (35)	202/460 (45)	< 0.001	50/119 (42)	31/101 (31)	121/239 (51)	0.003
Diarrhea	1060/3801 (28)	171/463 (37)	< 0.001	28/119 (24)	27/103 (27)	116/240 (48)	< 0.001
Vomiting	1198/3810 (31)	118/343 (34)	0.01	29/119 (25)	23/101 (23)	66/242 (27)	0.8
Dyspnea	839/3769 (22)	107/463 (23)	0.7	39/120 (33)	33/102 (33)	34/240 (14)	< 0.001
Diabetes mellitus	134/3746 (4)	48/452 (10)	< 0.001	25/115 (22)	12/101 (12)	11/235 (5)	< 0.001
Chronic renal failure	54/3736 (1)	11/448 (3)	0.1	7/114 (6)	3/98 (3)	1/235 (0.4)	0.005
Systemic lupus	80/3688 (2)	5/440 (1)	0.2	4/111 (4)	1/196 (0.5)	0/232	0.01
Renal calculi	77/3752 (2)	11/451 (3)	0.6	6/112 (6)	4/100 (4)	1/238 (0.4)	0.01
Solid use	106/3747 (3)	20/454 (4)	0.06	10/115 (9)	7/100 (7)	3/238 (1)	0.002
Smoker	539/3713 (15)	73/454 (16)	0.4	30/116 (26)	17/97 (18)	25/240 (10)	0.001
Temperature, °C ^{¶¶}	38.7 (38.6–38.7) ³⁸³¹	39.0 (38.9–39.0) ⁴⁵⁵	< 0.0001	38.9 (38.8–39.1) ¹²²	38.7 (38.4–38.9) ¹⁰²	39.1 (39.0–39.2) ²³⁰	0.0002
Pulse/minute ^{¶¶}	101.7 (101.1–102.3) ³⁸⁴²	102.2 (100.4–104.1) ⁴⁵⁷	0.6	103.7 (100.2–107.1) ¹¹⁸	109.8 (104.5–115.0) ¹⁰³	98.2 (96.3–100.2) ²³⁵	< 0.0001
BP systolic mm Hg ^{¶¶}	104.9 (104.4–105.5) ³³⁰⁴	104.1 (102.4–105.8) ⁴⁰²	0.3	108.4 (104.0–112.9) ¹⁰⁴	105.7 (100.6–110.7) ⁷⁵	101.6 (100.0–103.1) ²²³	0.003
BP diastolic mm Hg ^{¶¶}	67.2 (66.8–67.6) ³²⁹⁴	66.1 (65.0–67.1) ³⁹⁹	0.06	68.4 (65.5–70.6) ¹⁰³	66.0 (63.5–68.4) ⁷⁴	65.2 (64.0–66.4) ²²²	0.07
Respiratory rate/min ^{¶¶}	25 (10–140) ³⁴⁰³	25 (10–100) ³⁷⁶	0.5	24 (10–100) ¹⁰⁸	28 (18–90) ⁸¹	25 (18–90) ¹⁸⁶	0.006
Jaundiced	728/3695 (20)	91/439 (21)	0.6	34/116 (29)	24/93 (26)	33/229 (14)	0.002
Hepatomegaly	599/3684 (16)	80/442 (18)	0.3	28/115 (24)	15/95 (16)	37/231 (16)	0.1
Splenomegaly	190/3651 (5)	30/441 (7)	0.2	11/115 (10)	8/94 (9)	11/231 (5)	0.2
Rash	355/3642 (10)	37/436 (9)	0.4	6/115 (5)	21/94 (22)	9/226 (4)	< 0.001

Variable*	Blood cultures judged clinically			Community-acquired bacteremia				P [§]	
	Negative or not significant	Significant [†]	P	Non-typhoidal Gram-negative bacteria	P [‡]	Gram-positive bacteria	P [‡]		S. Typhi [†]
Meningism	263/3646 (7)	21/440 (5)	0.06	8/114 (7)	0.01	9/97 (9)	0.002	4/228 (2)	0.006
Septic arthritis	139/3638 (4)	19/432 (4)	0.6	8/113 (7)	0.004	8/89 (9)	<0.001	3/229 (1)	0.003
Abscess	89/3597 (3)	20/431 (5)	0.009	7/113 (6)	<0.01	10/93 (11)	<0.001	3/224 (1)	0.001
White cell count 10 ⁹ /L	–	10.8 (1.2–61.8) ³³³	–	12.7 (2.2–39.3) ⁷⁴	<0.0001	13.0 (1.3–44.2) ⁷²	<0.0001	9.2 (2.3–38.6) ¹⁸⁷	0.0001
Neutrophils%	–	69 (2–94) ³³²	–	78 (2–94) ⁷³	<0.0001	75 (10–93) ⁷²	0.004	67 (35–94) ¹⁸⁷	0.0001
Mortality	306/3489 (9)	46/420 (11)	0.1	24/103 (23)	<0.001	18/98 (18)	<0.001	3/218 (1)	<0.001

NOTE:

[§] P value for ANOVA, Kruskal-Wallis, test or χ^2 test—if $P < 0.02$.

[†] P value for comparison with S. Typhi bacteremia given (Sceffe test if ANOVA performed). Superscript numbers refer to the sample size for that category.

^{*} There were no significant differences ($P > 0.02$) for all comparisons for the following variables that are not shown in the table: nausea, vomiting, cough, sputum, dysuria, arthralgia, sore throat, alcohol excess, illicit IV drug use, level of consciousness, hematocrit and platelet count.

[‡] Comparison of those with non-typhoidal bacteremia and S. Typhi bacteremia suggested that S. Typhi patients were younger ($P = 0.003$), ill for longer ($P < 0.0001$), had a higher frequency of abdominal pain ($P = 0.003$) and diarrhea ($P < 0.001$), lower frequency of dyspnea ($P < 0.001$), diabetes ($P < 0.001$), chronic renal failure ($P = 0.004$), renal calculi ($P = 0.003$), steroid use ($P = 0.001$), smoking ($P = 0.001$), jaundice ($P = 0.001$), rash ($P < 0.001$), meningism ($P = 0.002$), septic arthritis ($P = 0.001$) and abscess(es) ($P = 0.001$), higher admission temperature ($P = 0.003$), lower admission pulse ($P < 0.0001$), systolic blood pressure ($P = 0.001$), peripheral white count ($P < 0.001$) and neutrophil percentage ($P < 0.0001$).

^{||} Mean (range)

[¶] Mean (95% CI).

Table 3
Percentage of isolates susceptible to selected antibiotics for organisms isolated from blood cultures

Organism	Ampicillin	Co-trimoxazole	Chloramphenicol	Ceftriaxone	Nalidixic acid	Gentamicin	Penicillin	Erythromycin
<i>Salmonella enterica</i> serovar typhi* [‡]	198/226 (88%)	197/221 (89%)	199/225 (88%)	50/50 [‡]	168/168	–	–	–
<i>Salmonella choleraesuis</i>	2/2	2/2	2/2	–	1/1	–	–	–
<i>Salmonella</i> species	7/8 (88%)	7/8 (88%)	6/7 (86%)	3/3	7/7	–	–	–
<i>Edwardsiella tarda</i>	0/1	1/1	0/1	1/1	1/1	–	–	–
<i>Escherichia coli</i>	13/51 (25%)	17/47 (36%)	34/55 (62%)	23/25 (92%)	39/45 (87%)	11/12 (92%)	–	–
<i>Klebsiella pneumoniae</i>	1/18 (6%)	12/17 (71%)	12/18 (67%)	6/6	15/18 (83%)	9/9	–	–
<i>Aeromonas hydrophilia</i>	0/1	3/3	3/3	1/1	2/2	–	–	–
<i>Burkholderia pseudomallei</i>	–	10/10 [‡]	11/12 (92%)	–	–	–	–	–
<i>Staphylococcus aureus</i>	–	58/74 (78%)	63/80 (79%)	–	–	66/67 (99%)	9/72 (13%)	32/78 (41%)
<i>Streptococcus pneumoniae</i>	–	1/5 (20%)	4/4	–	–	–	2/4 [‡] (50%)	2/5 (40%)

MIC = minimum inhibitory concentrations.

* MICs were determined for 163 *S.*Typhi isolates; 50 by broth dilution and 113 by E test. 19/163 (11.7%) and 2/163 (1.5%) were resistant or had intermediate resistance to co-trimoxazole, 19/163 (11.7%) and 1/163 (0.6%) were resistant or had intermediate resistance to chloramphenicol, 19/161 (11.8%) and 1/161 (0.6%) were resistant or had intermediate resistance to ampicillin. 18/161 (11.2%) were MDR. None were resistant to nalidixic acid (N = 163), ofloxacin (N = 135), and ceftriaxone (N = 50). The median (range) MICs (µg/mL) were co-trimoxazole 0.03 (0.016– > 512), chloramphenicol 4 (0.15– > 256), ampicillin 0.5 (0.05– > 512), ceftriaxone 0.03 (0.015–0.125), nalidixic acid 1.5 (1–8) and ofloxacin 0.06 (0.015–1.0).

[‡]As determined from oxacillin disc diffusion testing.

[‡]Disk diffusion technique, except[†] by E test. No *S. aureus* isolates were methicillin resistant.

Table 4

Multiple Logistic Regression of variables predictive of *S. Typhi* bacteremia, community-acquired bacteremia and mortality

Variable	OR	95% CI	P
Predictive of blood cultures growing <i>S. Typhi</i> versus a non- <i>S. Typhi</i> clinically significant cause of community-acquired bacteremia AUROCC (95%CI) = 0.809 (0.760–0.857)			
Age/years	0.95	0.93–0.97	< 0.001
Days ill	1.04	1.00–1.08	< 0.001
Diarrhea	3.56	1.63–7.83	0.001
Axillary temperature °C	1.94	1.20–3.12	0.007
Peripheral white count 10 ⁹ /L	0.88	0.83–0.94	< 0.001
Predictive of blood cultures growing or not growing a clinically significant cause of community-acquired bacteremia AUROCC (95%CI) = 0.645 (0.615–0.674)			
Abdominal pain	1.40	1.09–1.79	0.007
Vomiting	0.74	0.58–0.95	0.018
Diarrhea	1.44	1.12–1.86	0.005
Diabetes mellitus	3.16	2.16–4.62	<0.001
Abscess	2.29	1.33–3.94	0.003
Axillary temperature °C	1.45	1.28–1.65	< 0.001
Predictive of death among patients with community-acquired bacteremia AUROCC (95%CI) = 0.738 (0.643–0.833)			
Axillary temperature °C	0.47	0.30–0.76	0.002
Neutrophils%	1.06	1.02–1.10	0.005
Pulse/minute	1.02	1.00–1.04	0.041

AUROCC (95%CI) = area under the receiver operating characteristic curve with 95% confidence interval.