Invasive Salmonella Infections in Areas of High and Low Malaria Transmission Intensity in Tanzania

Holly M. Biggs, Rebecca Lester, Behzad Nadjm, George Mtowe, Jim E. Todd, Grace D. Kinabo, Rune Philemon, Ben Amos, Anne B. Morrissey, Hugh Reyburn, and John A. Crump

Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, North Carolina; London School of Hygiene and Tropical Medicine, United Kingdom; Oxford University Clinical Research Unit, Hanoi, Vietnam; National Institute for Medical Research–Amani Centre, Tanga, Joint Malaria Programme, Moshi, Kilimanjaro Christian Medical Centre, Moshi, Kilimanjaro Christian Medical University College, Moshi, and Teule Hospital, Muheza, United Republic of Tanzania; Duke Global Health Institute, Duke University, Durham, North Carolina; and Centre for International Health, University of Otago, Dunedin, New Zealand

Background. The epidemiology of Salmonella Typhi and invasive nontyphoidal Salmonella (NTS) differs, and prevalence of these pathogens among children in sub-Saharan Africa may vary in relation to malaria transmission intensity.

Methods. We compared the prevalence of bacteremia among febrile pediatric inpatients aged 2 months to 13 years recruited at sites of high and low malaria endemicity in Tanzania. Enrollment at Teule Hospital, the high malaria transmission site, was from June 2006 through May 2007, and at Kilimanjaro Christian Medical Centre (KCMC), the low malaria transmission site, from September 2007 through August 2008. Automated blood culture, malaria microscopy with Giemsa-stained blood films, and human immunodeficiency virus testing were performed.

Results. At Teule, 3639 children were enrolled compared to 467 at KCMC. Smear-positive malaria was detected in 2195 of 3639 (60.3%) children at Teule and 11 of 460 (2.4%) at KCMC (P < .001). Bacteremia was present in 336 of 3639 (9.2%) children at Teule and 20 of 463 (4.3%) at KCMC (P < .001). NTS was isolated in 162 of 3639 (4.5%) children at Teule and 1 of 463 (0.2%) at KCMC (P < .001). Salmonella Typhi was isolated from 11 (0.3%) children at Teule and 6 (1.3%) at KCMC (P = .008). With NTS excluded, the prevalence of bacteremia at Teule was 5.0% and at KCMC 4.1% (P = .391).

Conclusions. Where malaria transmission was intense, invasive NTS was common and Salmonella Typhi was uncommon, whereas the inverse was observed at a low malaria transmission site. The relationship between these pathogens, the environment, and the host is a compelling area for further research.

Keywords. typhoid fever; Salmonella; sub-Saharan Africa; malaria.

Salmonella enterica is a major cause of community-acquired bloodstream infection and death among children across sub-Saharan Africa [1, 2]. However, the proportion of disease caused by infection with Salmonella enterica serovars Typhi and Paratyphi (typhoidal Salmonella) vs nontyphoidal S. enterica serovars (NTS), shows considerable temporal and geographic variation. The epidemiology of typhoidal Salmonella appears to be driven by environmental risk factors including overcrowding, poor sanitation, and unsafe food and water [3]. By contrast, hospital-based studies of invasive NTS (iNTS) among African children and adults implicate host-associated risk factors including human immunodeficiency virus (HIV)–related immunosuppression, malaria, anemia, and malnutrition [4].

The association of malaria with bacteremia, particularly NTS, has been documented at multiple locations in...
Malaria epidemiology in Africa is heterogeneous, and in northeast Tanzania malaria transmission rates vary geographically from intense and perennial in coastal areas, to low or absent in the highland areas of the Kilimanjaro Region [8]. In this study we compare the prevalence of malaria and bacteremia, focusing on NTS and *Salmonella* Typhi, among febrile hospitalized children at 2 sites of different malaria transmission in Tanzania.

**METHODS**

**Study Sites**

The study was conducted in 2 locations 258 km apart in northeastern Tanzania: Moshi in the Kilimanjaro Region and Muheza in the Tanga Region (Figure 1). Moshi is situated at 890 m above sea level, and Muheza is 96 m above sea level. The climate in both locations is characterized by short and long rainy periods. In Moshi, *Plasmodium falciparum* malaria transmission is low and seasonal [9], whereas in Muheza malaria transmission at the time of the study was intense and perennial, with 2 seasonal peaks corresponding with the end of the rainy seasons [8]. In Moshi, the study was conducted at Kilimanjaro Christian Medical Centre (KCMC), a 458-bed referral hospital serving several regions in northern Tanzania. In Muheza, the study was conducted at Teule Hospital (Teule), a 330-bed district hospital serving the Tanga Region of northeastern Tanzania.

**Participants**

At both study sites, as described in detail elsewhere [10, 11], pediatric inpatients aged 2 months to 13 years admitted within the past 24 hours were eligible for enrollment if they had a history of fever in the past 48 hours, an axillary temperature \( \geq 37.5^\circ C \), or a rectal temperature of \( \geq 38.0^\circ C \). Patients were excluded if they had known malignancy, renal or hepatic failure, bone marrow aplasia, trauma, or surgery. Participants were prospectively enrolled 5 days a week; study enrollment occurred at Teule from 1 June 2006 through 31 May 2007 and at KCMC from 17 September 2007 through 31 August 2008.

**Data Collection**

Case report forms, including clinical history, physical examination, and demographics, were standardized between the study sites and completed by trained clinical officers who were study team members. Blood was drawn using aseptic technique for aerobic blood culture, blood parasite examination, and HIV testing. Additionally, point-of-care tests for hemoglobin, glucose, and serum lactate and a rapid diagnostic test for *P. falciparum* malaria were performed.

**Laboratory Methods**

Blood culture was performed using BacT/ALERT pediatric fan bottles that were loaded into the BacT/ALERT 3D Microbial Detection System (bioMérieux, Durham, North Carolina), where they were incubated for 5 days. Standard methods were used for identifying bloodstream isolates. Giemsa-stained blood films were examined for blood parasites by oil immersion microscopy. Slides were independently double-read and discrepancies resolved by an independent third reader. HIV antibody testing was performed using a previously described algorithm [10]. Point-of-care testing was performed for hemoglobin and glucose using Hemocue (Angelholm, Sweden), and for lactate using Lactate-Pro (Arkray, Kyoto, Japan). A histidine-rich protein 2 (HRP-2)–based rapid diagnostic test for *P. falciparum* was done using site-validated Paracheck (Orchid Biomedical, Mumbai, India).

**Study Definitions**

Malaria was defined as *P. falciparum* asexual parasitemia of any density on microscopy. Recent malaria was defined as negative for *P. falciparum* asexual parasites by microscopy with a positive HRP-2–based rapid diagnostic test. This definition is based on the persistence of detectable HRP-2 for \( \geq 1 \) month after clearance of parasites [12, 13]. Parasite densities were calculated from the geometric mean of the 2 closest counts of asexual parasites per 200 white blood cells and the actual white blood cell count or, if missing, 8000 cells/µL. Severe anemia was defined as a hemoglobin level <5 g/dL. Hypoglycemia was defined as a glucose level of <45 mg/dL [14]. Severe acute malnutrition was defined for children aged 6 months to <60 months as mid-upper arm circumference <115 mm, weight-for-height z score less than -3, or presence of bilateral pitting pedal edema [14].
for children ≥60 months, severe malnutrition was defined as body mass index-for-age z score less than −3 or presence of bilateral pitting pedal edema [16, 17]. Participant residence was classified as rural, urban, or mixed based on the 2002 Tanzania Population and Housing Census [18].

Statistical Analysis
Data were entered using the Cardiff Teleform system (Cardiff, Inc, Vista, California) into an Access database (Microsoft Corporation, Redmond, Washington). Descriptive statistics are presented as proportions, medians, ranges, and interquartile ranges. The Pearson χ² test was used to compare categorical data; Fisher exact test was used when any cell contained <10 observations. Wilcoxon rank-sum was used to compare categorical and nonparametric continuous data. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated when appropriate. All P values are 2 sided and evaluated for statistical significance at the .05 significance level.

Backward multivariable logistic regression was performed to assess risk factors for NTS and Salmonella Typhi bacteremia. Populations from Teule and KCMC were combined for analysis. Variable selection for logistic regression was decided by the authors on the basis of theoretical and empirical findings. Collinearity testing was performed for selected variables. Likelihood ratios were used to compare iterations of the models. Presented P values are based on Wald tests.

World Health Organization (WHO) Anthro version 3.2.2 macros for Stata were used to calculate nutritional z scores using WHO Child Growth Standards [15] for children aged 6 months to <60 months and WHO Reference 2007 [16] for children aged ≥60 months. Participants with z score outliers (less than −5 or >5) were excluded from analysis. All analyses were performed using Stata software, version 12 (StataCorp, College Station, Texas).

Research Ethics
This study was approved by the KCMC Research Ethics Committee, the Tanzania National Institutes for Medical Research National Research Ethics Coordinating Committee, and the institutional review boards of Duke University Medical Center and the London School of Hygiene and Tropical Medicine.

RESULTS
At Teule, 4334 pediatric admissions were screened for enrollment over the study period, 3766 were eligible, and 3639 were enrolled and had sufficient data for study inclusion. At KCMC, 1154 pediatric inpatients were screened, 644 were eligible, and 467 were enrolled. Participant demographics for each site are displayed in Table 1. Median age and sex were not statistically different between the sites. At Teule, more participants reported rural residence, participants’ mothers had completed fewer overall years of formal education, and fewer were referred from another inpatient facility compared to those at KCMC. Antibacterial use in the 48 hours before admission was reported by 450 of 3600 (12.5%) children at Teule compared to 210 of 398 (52.8%) at KCMC (P < .001). Antimalarial use before admission was reported by 1308 of 3166 (41.3%) participants at Teule compared to 143 of 408 (35.1%) at KCMC (P = .015).

Clinical Presentation
Clinical and laboratory features of participants by site are shown in Table 2. Compared with those at Teule, on admission, KCMC participants had a longer median duration of illness, and more frequently had lethargy, prostration, delayed capillary

<table>
<thead>
<tr>
<th>Table 1. Demographic Characteristics of Participants, Teule Hospital and Kilimanjaro Christian Medical Centre, Tanzania</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Age, y, median (range)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Mother’s highest level of education</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Less than Standard 7</td>
</tr>
<tr>
<td>Standard 7</td>
</tr>
<tr>
<td>Higher</td>
</tr>
<tr>
<td>Referred from another inpatient facility</td>
</tr>
<tr>
<td>Residencea</td>
</tr>
<tr>
<td>Rural</td>
</tr>
<tr>
<td>Urban</td>
</tr>
<tr>
<td>Mixed urban/rural</td>
</tr>
</tbody>
</table>

Abbreviation: KCMC, Kilimanjaro Christian Medical Centre.

a Residence was classified as rural, urban, or mixed based on the 2002 Tanzania Population and Housing Census [18].
refill, prolonged skin pinch, and acute malnutrition. Compared with those at KCMC, on admission Teule participants were significantly more likely to have severe pallor, splenomegaly, hypoglycemia, and severe anemia.

Malaria, Bacteremia, and HIV Infection
Smear-positive *P. falciparum* malaria was detected in 2195 of 3639 (60.3%) children enrolled at Teule compared to 11 of 460 (2.4%) at KCMC (OR, 62.05; 95% CI, 34.16–125.56); evidence of recent malaria was found in 501 of 3639 (13.8%) children at Teule compared to 3 of 458 (0.6%) at KCMC (OR, 24.21; 95% CI, 8.18–73.92) (Table 3). Bacteremia was present in 336 of 3639 (9.2%) children at Teule compared to 20 of 463 (4.3%) children at KCMC (OR, 2.25; 95% CI, 1.42–3.77). There was no difference in bacteremia prevalence between patients who reported or denied prior antibacterial use (OR, 0.95; 95% CI, .69–1.29).

NTS was the isolated pathogen in 162 of 336 (48.2%) bacteremia cases at Teule, whereas at KCMC 1 of 20 (5.0%) bacteremia cases was due to NTS (OR, 17.69; 95% CI, 2.74–739.32) (Figure 2A). The overall prevalence of NTS bacteremia at Teule was 4.5% compared to 0.2% at KCMC (OR, 21.53; 95% CI, 3.79–857.09). When NTS was excluded from the bacteremia figures, bacteremia prevalence at Teule was 175 of 3478 (5.0%) and at KCMC 19 of 462 (4.1%; OR, 1.24; 95% CI, .76–2.12).

Salmonella Typhi was isolated in 11 of 3639 (0.3%) patients at Teule compared to 6 of 463 (1.3%) at KCMC (OR, 0.23; 95% CI, .08–0.76). The ratio of NTS to Salmonella Typhi was 162:11 (14.7:1) at Teule compared to 1:6 (0.2:1) at KCMC (Figure 2B). There was no significant difference in *Streptococcus pneumoniae* or *Escherichia coli* bacteremia prevalence between the sites (OR, 1.15; 95% CI, .49–3.28 and OR, 0.98; 95% CI, .29–5.09, respectively). HIV prevalence
among children at Teule was 142 of 3639 (3.9%) compared to 60 of 445 (13.2%) at KCMC (OR, 0.27; 95% CI, .19–.37). Of NTS cases at Teule, 119 of 160 (74.4%) were associated with malaria or recent malaria and 8 of 160 (5.0%) were associated with HIV infection. The sole case of NTS at KCMC was associated with HIV infection.

### Risk Factors for NTS and *Salmonella Typhi* Bacteremia

Results of univariate and multivariate analysis of risk factors for NTS and *Salmonella Typhi* bacteremia are presented in Tables 4 and 5, respectively. In multivariate analysis, iNTS was associated with younger age (adjusted OR [AOR], 0.79; 95% CI, .70–.90; per each 1-year increase in age), recent malaria (AOR, .79; 95% CI, .65–.95).

Table 3. Malaria, HIV Infection, Bacteremia, and Associated Mortality, Teule Hospital and Kilimanjaro Christian Medical Centre, Tanzania

<table>
<thead>
<tr>
<th>Infection</th>
<th>Teule (n = 3639), no./No. (%)</th>
<th>KCMC (n = 467), no./No. (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>2195/3639 (60.3)</td>
<td>11/460 (2.4)</td>
<td>62.05 (34.16–125.56)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recent malaria</td>
<td>501/3639 (13.8)</td>
<td>3/458 (0.6)</td>
<td>24.21 (8.18–118.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIV</td>
<td>142/3639 (3.9)</td>
<td>60/445 (13.2)</td>
<td>0.27 (.19–.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>336/3639 (9.2)</td>
<td>20/463 (4.3)</td>
<td>2.25 (1.42–3.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nontyphoidal <em>Salmonella</em></td>
<td>162/3639 (4.5)</td>
<td>1/463 (0.2)</td>
<td>21.53 (3.79–857.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NTS associated with malaria</td>
<td>53/162 (32.7)</td>
<td>0/28 (0.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NTS associated with recent malaria</td>
<td>67/162 (41.4)</td>
<td>0/1 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NTS associated with HIV</td>
<td>8/162 (4.9)</td>
<td>1/1 (100.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bacteremia if NTS excluded*</td>
<td>175/3478 (5.0)</td>
<td>19/462 (4.1)</td>
<td>1.24 (.76–2.12)</td>
<td>.391</td>
</tr>
<tr>
<td>Bacteremia if NTS associated with malaria or recent malaria excluded</td>
<td>216/3519 (6.1)</td>
<td>20/463 (4.3)</td>
<td>1.45 (.90–2.44)</td>
<td>.119</td>
</tr>
<tr>
<td><em>Salmonella Typhi</em></td>
<td>11/3639 (0.3)</td>
<td>6/463 (1.3)</td>
<td>0.23 (.08–.76)</td>
<td>.008</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>23/3639 (0.6)</td>
<td>3/463 (0.7)</td>
<td>0.98 (.29–5.09)</td>
<td>1.000</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>54/3639 (1.5)</td>
<td>6/463 (1.3)</td>
<td>1.15 (.49–3.28)</td>
<td>1.000</td>
</tr>
<tr>
<td>Blood culture contaminantsb</td>
<td>252/3639 (6.9)</td>
<td>27/463 (5.8)</td>
<td>1.20 (.79–1.88)</td>
<td>.379</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; KCMC, Kilimanjaro Christian Medical Centre; NTS, nontyphoidal Salmonella; NA, not applicable; OR, odds ratio.

* One of 162 patients from Teule with NTS also had a second pathogenic organism isolated.

* Any of the following isolates in the absence of a concurrent pathogenic organism: coagulase-negative *Staphylococcus*, *Micrococcus*, *Corynebacterium*, *Bacillus* species, viridans group *Streptococcus*, and non-*Cryptococcus* and non-*Candida* yeasts.

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Figure 2.  
A, Bloodstream isolates, as proportion of total, among participants at Teule Hospital and Kilimanjaro Christian Medical Centre (KCMC).  
B, Nontyphoidal *Salmonella* and *Salmonella Typhi* bloodstream isolates, as proportion of total isolates, among participants at Teule Hospital and KCMC.
4.13; 95% CI, 2.66–6.44), severe anemia (AOR, 2.19; 95% CI, 1.48–3.23), and severe acute malnutrition (AOR, 2.01; 95% CI, 1.15–3.52). A negative association with current P. falciparum parasitemia that did not reach statistical significance was observed (AOR, 0.68; 95% CI, .43–1.08).

To further explore the relationship between current malaria and iNTS, malaria parasitemia at Teule was categorized by mean parasite density as low (1 to <5000 parasites/µL) or high (≥5000 to >50 000 parasites/µL). Low mean parasite density was present in 405 of 2195 (18.5%) of those with current

### Table 4. Univariate and Multivariate Analysis for Risk Factors Associated With Nontyphoidal Salmonella Bacteremia, Combined Data From Kilimanjaro Medical Centre and Teule Hospital, Tanzania

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTS (n = 163), no./No. (%)</td>
<td>No NTS (n = 3939), no./No. (%)</td>
</tr>
<tr>
<td>Age, y, median (range)b</td>
<td>1.25 (0.3–9.0)</td>
<td>1.57 (0.16–13.5)</td>
</tr>
<tr>
<td>Rural ward residence</td>
<td>133/146 (91.1)</td>
<td>2836/3453 (82.1)</td>
</tr>
<tr>
<td>Antibacterial preexposure c</td>
<td>19/157 (12.1)</td>
<td>639/3838 (16.7)</td>
</tr>
<tr>
<td>Antimalarial preexposure, oral c</td>
<td>56/146 (39.0)</td>
<td>1126/3430 (32.8)</td>
</tr>
<tr>
<td>Antimalarial preexposure, parenteral c</td>
<td>19/147 (12.9)</td>
<td>285/3413 (8.4)</td>
</tr>
<tr>
<td>Current malaria</td>
<td>53 (32.5)</td>
<td>2153/3933 (54.7)</td>
</tr>
<tr>
<td>Recent malaria</td>
<td>67 (41.1)</td>
<td>437/3930 (11.1)</td>
</tr>
<tr>
<td>Severe acute malnutrition</td>
<td>17/149 (11.4)</td>
<td>198/3410 (5.8)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>9 (5.5)</td>
<td>193/3927 (4.9)</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>47 (28.8)</td>
<td>568/3925 (14.5)</td>
</tr>
</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; NA, not applicable; NTS, nontyphoidal Salmonella; OR, odds ratio.

a AOR and P values presented for multivariable analysis are the values of the most simplified/best fit model. AOR and P values for variables dropped from the final model due to nonsignificance are not presented.

b Modeled as continuous variable (OR represents the reduced odds of infection per year of age).

c Exposure to antibacterial or antimalarial in the 48 hours preceding hospital admission.

### Table 5. Univariate and Multivariate Analysis for Risk Factors Associated With Salmonella Typhi Bacteremia, Combined Data From Kilimanjaro Medical Centre and Teule Hospital, Tanzania

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Salmonella Typhi (n = 17), no./No. (%)</td>
<td>No Salmonella Typhi (n = 4085), no./No. (%)</td>
</tr>
<tr>
<td>Age, y, median (range)b</td>
<td>5.83 (0.3–13.5)</td>
<td>1.56 (0.2–13.4)</td>
</tr>
<tr>
<td>Rural ward residence</td>
<td>10/12 (83.3)</td>
<td>2963/3592 (82.5)</td>
</tr>
<tr>
<td>Antibacterial preexposure c</td>
<td>6/17 (35.3)</td>
<td>652/3978 (16.4)</td>
</tr>
<tr>
<td>Antimalarial preexposure, oral c</td>
<td>9/16 (56.3)</td>
<td>1174/3560 (33.0)</td>
</tr>
<tr>
<td>Antimalarial preexposure, parenteral c</td>
<td>3/15 (20.0)</td>
<td>301/3545 (8.5)</td>
</tr>
<tr>
<td>Current malaria</td>
<td>2/17 (11.8)</td>
<td>2204/4079 (54.0)</td>
</tr>
<tr>
<td>Recent malaria</td>
<td>0/17 (0.0)</td>
<td>504/4076 (12.4)</td>
</tr>
<tr>
<td>Severe acute malnutrition</td>
<td>4/15 (26.7)</td>
<td>211/3544 (5.6)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>0/17 (0.0)</td>
<td>202/4073 (5.0)</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>1/17 (5.9)</td>
<td>614/4071 (15.1)</td>
</tr>
</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; NA, not applicable; OR, odds ratio.

a AOR and P values presented for multivariable analysis are the values of the most simplified/best fit model. AOR and P values for variables dropped from the final model due to nonsignificance are not presented.

b Modeled as continuous variable (OR represents the increased odds of infection per year of age).

c Exposure to antibacterial or antimalarial in the 48 hours preceding hospital admission.
malaria, whereas high mean parasite density was present in
1790 of 2195 (81.5%). Those with low mean parasite density
had 3.53 times the odds of developing NTS bacteremia
compared to those with high mean parasite density (95% CI, 1.93–6.36). Among the entire Teule study population, the odds
of NTS bacteremia in those with low mean parasite density
were 1.34 (95% CI, 0.81–2.13), whereas the odds of NTS bacte-
rima in those with high mean parasite density were 0.22 (95% CI, 1.14–3.33).

Salmonella Typhi was associated, in multivariate analysis,
with older age (AOR, 1.35; 95% CI, 1.21–1.51 per each 1-year
increase in age) and negatively associated with current malaria
(AOR, 0.14; 95% CI, 0.03–0.64). No patients with Salmonella
Typhi had HIV infection or recent malaria, so these variables
were not included in the logistic regression model.

DISCUSSION

Among pediatric inpatients recruited under similar protocols
during comparable enrollment periods in Tanzania, we ob-
served at a site of high malaria endemicity that iNTS was a
common cause of bacteremia and Salmonella Typhi was un-
common, whereas the inverse was true in an area of low
malaria endemicity. A similar observation has been made in
Kenya, where in a rural area holoendemic for malaria, there
was a high ratio of iNTS to Salmonella Typhi infection among
adults and children, whereas in an urban informal settlement
where malaria is sporadic, Salmonella Typhi bacteremia
predominated [19]. Other studies of bacteremia in malaria
endemic areas of sub-Saharan Africa have noted that Salmonel-
la Typhi may be rare or absent in settings where iNTS and
malaria are prevalent [5, 6, 20, 21]. A recent study comparing
bacteremia incidence over time at Teule showed that as malaria
and iNTS incidence declined, incidence of Salmonella Typhi
rose [22]. Additionally, recently presented data from Malawi
showed that, during the past 2 years, following a decade-long
decline in iNTS, a sustained outbreak of Salmonella Typhi has
occurred [23].

The relationship between malaria and bacteremia has been
well documented in sub-Saharan Africa [7, 24–26]. We found a
higher overall prevalence of bacteremia among febrile hospital-
ized children at a site with high malaria transmission compared
to a site with low malaria transmission. The difference in
the prevalence of bacteremia between the 2 sites was driven largely
by NTS. The prevalence of Streptococcus pneumoniae and
Escherichia coli, the other most common bacterial isolates in
children in sub-Saharan Africa [2], was no different between
the sites.

The association between iNTS and malaria in sub-Saharan
Africa was observed initially as a temporal association between
NTS bacteremia and the rainy season in a malaria-endemic
area [7]. Subsequently, declining NTS bacteremia following
reduced malaria prevalence has been observed at a number of
African sites [22, 25, 26]. Among African children, iNTS has
been described as being associated with malaria parasitemia
[6, 21, 27], recent malaria [5], anemia [5], and severe malarial
anemia [28]. In multivariable analysis, we demonstrated signifi-
cant associations between iNTS and severe anemia and between
iNTS and recent malaria, but not current malaria. In univariate
analysis, iNTS was positively but not significantly associated
with mean malaria parasite density <5000 parasites/µL, but was
significantly negatively associated with mean malaria parasite
density 5000 to >50 000 parasites/µL. Other studies in Africa
have shown that, although malaria is a risk factor for bacte-
rima, the risk is inversely related to malaria parasite density [7,
20, 29]. Additionally, although other studies have shown an
association between current malaria and NTS bacteremia [6, 21,
27] a study of Kenyan children also found a negative association
with current malaria, but a positive association with recent
malaria [5].

Recent evidence suggests that malaria may predispose to
iNTS via to changes in iron storage metabolism as a result of
malarial hemolysis, causing neutrophil dysfunction and in-
creased susceptibility [30, 31]. Additionally, mouse models have
suggested that malaria parasite–specific factors, such parasite-
induced reductions in levels of interleukin 12, may increase
susceptibility to iNTS [32]. Other potential mechanisms for the
increased risk of iNTS in malaria include translocation of gut
microflora across a disordered gut barrier, caused by malarial
sequestration of parasitized red blood cells in the intestine [33–
35], and increased free iron from hemolysis promoting survival
of Salmonella [4].

Other reported risk factors for iNTS in children in sub-Saharan
Africa include malnutrition [6] and HIV infection [1, 36]. We
found an independent association between iNTS and severe
acute malnutrition, but no significant association with HIV infec-
tion. The association between iNTS and HIV infection has been
more frequently reported among adults than children [36, 37],
and has been linked to level of immunosuppression [38]. We
were unable to assess iNTS risk in relation to level of HIV-related
immunosuppression as CD4-positive T-lymphocyte counts were
unavailable for more than half of HIV-infected participants at
Teule. Additionally, all iNTS cases but one were from Teule,
where HIV prevalence was relatively low, compared to some
studies in which an association between iNTS and HIV infec-
tion has been described [5]. This could have affected our ability
to detect an association between iNTS and HIV. Although a
significantly greater proportion of participants at the low
malaria-endemicity site had severe acute malnutrition or HIV
infection, iNTS was rare at this site. This finding adds weight to
the role of malaria and anemia in host susceptibility to iNTS infec-
tion, and raises the possibility that, in this particular setting
in sub-Saharan Africa, these host risk factors may be among the most important contributors to iNTS infection.

Case numbers for *Salmonella* Typhi were small, but multivariate analysis showed that children of older age were at increased risk. Similar to iNTS, current malaria was negatively associated with *Salmonella* Typhi. However, in contrast to iNTS, no child with *Salmonella* Typhi had HIV infection or recent malaria, and only one had severe anemia. It is well described that iNTS and *Salmonella* Typhi have different risk factors and pathogenesis, so these findings are not surprising. Past studies, including a study of adult inpatients at KCMC, have noted that HIV-infected persons appear to have lower odds for clinical typhoid fever than HIV-uninfected persons [2, 39]. One proposed mechanism for this finding is a dampened cell-mediated immune response in patients with HIV infection affecting the clinical manifestations of *Salmonella* Typhi bacteremia [40]. We did not measure variables such as sanitation and hygiene, consumption of unsafe food and water, and crowding, that are commonly associated with typhoid fever. Although more participants reported urban residence at the site where *Salmonella* Typhi was more common, urban residence was not independently associated with infection with typhoidal Salmonella. Overall, although malaria endemicity likely accounts for differences in iNTS prevalence between the sites, our data cannot account for the differences in *Salmonella* Typhi prevalence. Other, unmeasured factors, including differences in environmental reservoirs and exposures, the occurrence of geographically localized epidemics, and potential interactions between the pathogens, may play a role in the differing epidemiology.

This study has a number of potential limitations. Although the study protocol was similar at both sites, different proportions of eligible children and different absolute numbers of children were enrolled at each site. Our analyses are hospital-based, and we were unable to compare community-level incidence, which may be a better way to describe the relative pathogen prevalence between communities. Additionally, there were differences in the referral levels and patient populations of the 2 hospitals. We collected only inpatient data, and it is possible that data could be biased by differences in admission practices between the sites. Many clinical features that have been shown to be predictors of pediatric mortality in low malaria endemicity areas [41] were more frequent at KCMC, a referral hospital. However, some predictors of pediatric mortality often associated with malaria, such as hypoglycemia and hyperlactatemia [42], were more common at Teule. Markers of disease severity and mortality among hospitalized children may differ between malarious vs nonmalarious areas, making comparisons of these features between the sites challenging. Children at Teule came from more rural areas and had mothers with fewer years of formal education than those at KCMC. Differences in socioeconomic status and in environmental exposures related to rurality, which we did not explore but may be risk factors for invasive salmonellosis, could have contributed to invasive salmonellosis differences between sites.

Self-reported use of antibacterials before admission was common, which could have resulted in reduced blood culture yield. Patients at KCMC were significantly more likely to have reported prior antibacterial use, which could have led to an underestimate of bacteremia at the low malaria transmission site. However, self-report reliability is questionable, as supported by a lack of statistical difference in bacteremia prevalence between those reporting and denying prior antibacterial use in this study.

### CONCLUSIONS

Our comparisons between sites of high and low malaria endemicity in Tanzania add weight to the growing body of evidence that recent malaria infection and anemia are risk factors for iNTS and raise the possibility that NTS and *Salmonella* Typhi may compete in as yet unknown ways. It is possible that other undetermined factors such as *Salmonella* serovar–specific immune responses, interactions with coinfections, the gut microflora, and environmental reservoirs may provide venues for competition and replacement of these pathogens. The interaction between these pathogens, the environment, and the host requires further elucidation and is a compelling area for future research.

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