MAJOR ARTICLE

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

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(See the Editorial Commentary by MacLennan on pages 648–50.)

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

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Africa [5–7]. Malaria epidemiology in Africa is heterogenous, 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 northern 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 ≥37.5°C, or a rectal temperature of ≥38.0°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.

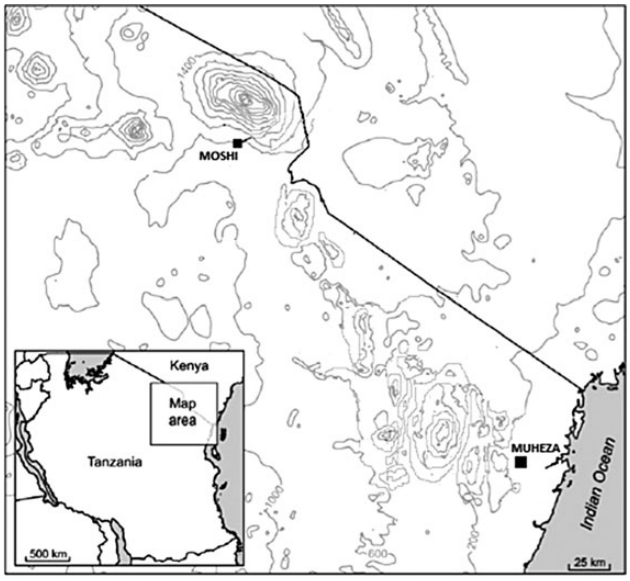

Figure 1. Map of study sites at Teule Hospital, Muheza, and Kilimanjaro Christian Medical Centre, Moshi, Tanzania.

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 ≥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 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,

15]; 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 χ^2 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 1. Demographic Characteristics of Participants, Teule Hospital and Kilimanjaro Christian Medical Centre, Tanzania

Characteristic	Teule (n = 3639), no./No. (%)	KCMC (n = 467), no./No. (%)	*P* Value
Age, y, median (range)	1.57 (0.2–13.0)	1.43 (0.2–13.5)	.319
Female	1669/3639 (45.9)	200/467 (42.8)	.215
Mother's highest level of education			
None	511/3582 (14.3)	29/451 (6.4)	<.001
Less than Standard 7	573/3582 (16.0)	34/451 (7.5)	<.001
Standard 7	2395/3582 (66.9)	250/451 (55.4)	<.001
Higher	103/3582 (2.9)	138/451 (30.6)	<.001
Referred from another inpatient facility	151/3635 (4.2)	178/464 (38.4)	<.001
Residence[a]			
Rural	2805/3633 (77.2)	168/392 (42.9)	<.001
Urban	433/3633 (11.9)	200/392 (51.0)	<.001
Mixed urban/rural	395/3633 (10.9)	24/392 (6.1)	.003

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].

Table 2. Clinical and Laboratory Characteristics of Participants on Admission, Teule Hospital and Kilimanjaro Christian Medical Centre, Tanzania

Characteristic	Teule (n = 3639), no./No. (%)	KCMC (n = 467), no./No. (%)	OR (95% CI)	*P* Value
Reported history				
Antibacterial use in past 48 h	450/3600 (12.5)	210/398 (52.8)	0.13 (.10–.16)	<.001
Antimalarial (oral or parenteral) use in past 48 h	1308/3166 (41.3)	143/408 (35.1)	1.30 (1.05–1.63)	.015
Duration of illness, d, median (range)	3 (0–92)	4 (1–90)	NA	<.001
Clinical findings				
Temperature, °C, median (IQR)	37.9 (37.1–38.7)	38.2 (37.8–39)	NA	<.001
Prostration[a]	410/3625 (11.3)	73/459 (15.9)	0.67 (.51–.90)	.004
Lethargy	508/3637 (14.0)	88/466 (18.9)	0.70 (.54–.91)	.005
Severe pallor	812/3638 (22.3)	33/466 (7.1)	3.77 (2.62–5.59)	<.001
Splenomegaly[b]	703/3597 (19.5)	6/463 (1.3)	18.50 (8.38–50.88)	<.001
Capillary refill >3 s	41/3638 (1.1)	16/467 (3.4)	0.32 (.17–.62)	<.001
Skin pinch >2 s	43/3638 (1.2)	29/465 (6.2)	0.18 (.11–.30)	<.001
Core to peripheral temperature difference	146/3630 (4.0)	25/449 (5.6)	0.71 (.46–1.15)	.123
Hypoxia[c]	78/3574 (2.2)	59/448 (13.2)	0.15 (.10–.21)	<.001
Blantyre coma score ≤2	116/3606 (3.2)	9/461 (2.0)	1.67 (.84–3.77)	.153
Severe acute malnutrition[d]	146/3193 (4.6)	69/370 (18.7)	0.21 (.15–.29)	<.001
Aged 6 mo to <5 y	123/2921 (4.2)	54/297 (18.2)	0.20 (.14–.29)	<.001
Aged 5–13 y	23/272 (8.5)	15/73 (20.6)	0.36 (.17–.079)	.003
Laboratory findings				
Glucose, mg/dL, median (IQR)	109.9 (88.3, 129.7)	115.3 (100.9, 131.5)	NA	<.001
Hypoglycemia, glucose <45 mg/dL	113/3631 (3.1)	3/463 (0.6)	4.93 (1.63–24.33)	.001
Lactate, mmol/L, median (IQR)	2.4 (1.8–3.6)	2.3 (1.8–3.2)	NA	.133
Hyperlactatemia, lactate >5 mmol/L	429/3248 (13.2)	35/459 (7.6)	1.84 (1.28–2.72)	.001
Hemoglobin, g/dL, median (IQR)	8.1 (5.9–9.8)	9.6 (7.9–11.2)	NA	<.001
Severe anemia, hemoglobin <5 g/dL	595/3632 (16.4)	20/459 (4.4)	4.30 (2.72–7.17)	<.001

Abbreviations: CI, confidence interval; IQR, interquartile range; KCMC, Kilimanjaro Christian Medical Centre; NA, not applicable; OR, odds ratio.

[a] Prostration defined as inability to sit unsupported if >9 months or, if age ≥9 months, inability to drink.

[b] Splenomegaly defined as palpable spleen >2 cm below the costal margin.

[c] Hypoxia defined as oxygen saturation <90% as measured by pulse oximetry.

[d] Participants aged <6 months and those with *z* score outliers excluded from analysis.

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, 8.18–118.26) (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 2*A*). 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–.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 2*B*).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

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

Infection	Teule (n = 3639), no./No. (%)	KCMC (n = 467), no./No. (%)	OR (95% CI)	*P* Value
Malaria	2195/3639 (60.3)	11/460 (2.4)	62.05 (34.16–125.56)	<.001
Recent malaria	501/3639 (13.8)	3/458 (0.6)	24.21 (8.18–118.26)	<.001
HIV	142/3639 (3.9)	60/445 (13.2)	0.27 (.19–.37)	<.001
Bacteremia	336/3639 (9.2)	20/463 (4.3)	2.25 (1.42–3.77)	<.001
Nontyphoidal *Salmonella*	162/3639 (4.5)	1/463 (0.2)	21.53 (3.79–857.09)	<.001
NTS associated with malaria	53/162 (37.7)	0/1 (0)	NA	NA
NTS associated with recent malaria	67/162 (41.4)	0/1 (0)	NA	NA
NTS associated with HIV	8/162 (4.9)	1/1 (100.0)	NA	NA
Bacteremia if NTS excluded[a]	175/3478 (5.0)	19/462 (4.1)	1.24 (.76–2.12)	.391
Bacteremia if NTS associated with malaria or recent malaria excluded	216/3519 (6.1)	20/463 (4.3)	1.45 (.90–2.44)	.119
Salmonella Typhi	11/3639 (0.3)	6/463 (1.3)	0.23 (.08–.76)	.008
Escherichia coli	23/3639 (0.6)	3/463 (0.7)	0.98 (.29–5.09)	1.000
Streptococcus pneumoniae	54/3639 (1.5)	6/463 (1.3)	1.15 (.49–3.28)	1.000
Blood culture contaminants[b]	252/3639 (6.9)	27/463 (5.8)	1.20 (.79–1.88)	.379

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

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

[b] 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.

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,

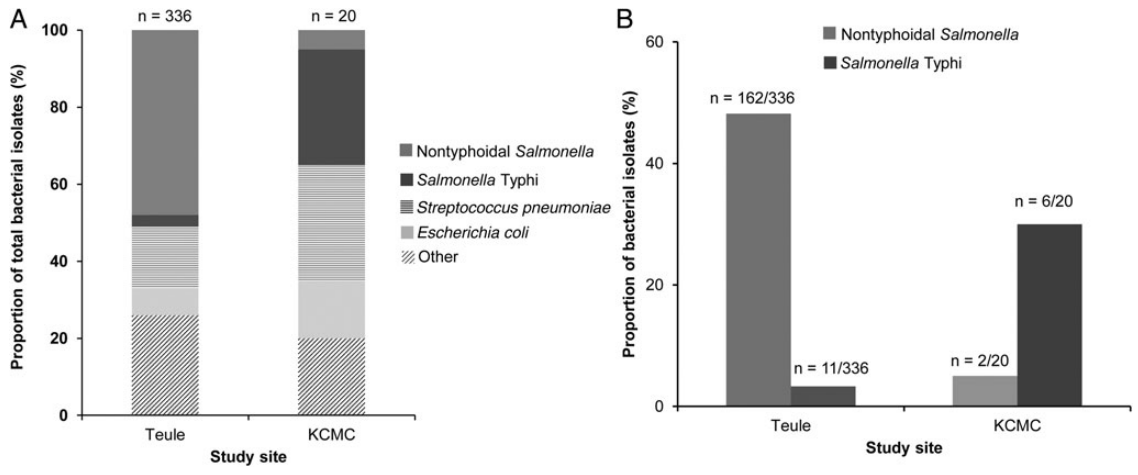

Figure 2. *A*, Bloodstream isolates, as proportion of total, among participants at Teule Hospital and Kilimanjaro Christian Medical Centre (KCMC). *B*, Nontyphoidal *Salmonella* and *Salmonella* Typhi bloodstream isolates, as proportion of total isolates, among participants at Teule Hospital and KCMC.

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

	Univariate Analysis				Multivariate Analysis	
Risk Factor	NTS (n = 163), no./No. (%)	No NTS (n = 3939), no./No. (%)	OR (95% CI)	*P* Value	AOR (95% CI)[a]	*P* Value
Age, y, median (range)[b]	1.25 (0.3–9.0)	1.57 (0.16–13.5)	0.84 (.76–.94)	.001	0.79 (.70–.90)	<.001
Rural ward residence	133/146 (91.1)	2836/3453 (82.1)	2.23 (1.25–3.96)	.006	NA	NA
Antibacterial preexposure[c]	19/157 (12.1)	639/3838 (16.7)	0.69 (.42–1.12)	.134	NA	NA
Antimalarial preexposure, oral[c]	56/146 (39.0)	1126/3430 (32.8)	1.31 (.93–1.84)	.118	NA	NA
Antimalarial preexposure, parenteral[c]	19/147 (12.9)	285/3413 (8.4)	1.63 (.99–2.68)	.052	NA	NA
Current malaria	53 (32.5)	2153/3933 (54.7)	0.40 (.29–.56)	<.001	0.68 (.43–1.08)	.100
Recent malaria	67 (41.1)	437/3930 (11.1)	5.58 (4.02–7.74)	<.001	4.13 (2.66–6.44)	<.001
Severe acute malnutrition	17/149 (11.4)	198/3410 (5.8)	2.09 (1.24–3.53)	.005	2.01 (1.15–3.52)	.014
HIV infection	9 (5.5)	193/3927 (4.9)	1.13 (.57–2.25)	.711	NA	NA
Severe anemia	47 (28.8)	568/3925 (14.5)	2.39 (1.67–3.40)	<.001	2.19 (1.48–3.23)	<.001

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.

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

	Univariate Analysis				Multivariate Analysis	
Risk Factor	*Salmonella* Typhi (n = 17), no./No. (%)	No *Salmonella* Typhi (n = 4085), no./No. (%)	OR (95% CI)	*P* Value	AOR (95% CI)[a]	*P* Value
Age, y, median (range)[b]	5.83 (0.3–13.5)	1.56 (0.2–13.4)	1.41 (1.26–1.58)	<.001	1.35 (1.21–1.51)	<.001
Rural ward residence	10/12 (83.3)	2963/3592 (82.5)	1.06 (.23–9.86)	.939	NA	NA
Antibacterial preexposure[c]	6/17 (35.3)	652/3978 (16.4)	2.78 (1.03–7.55)	.045	NA	NA
Antimalarial preexposure, oral[c]	9/16 (56.3)	1174/3560 (33.0)	2.61 (.97–7.03)	.057	NA	NA
Antimalarial preexposure, parenteral[c]	3/15 (20.0)	301/3545 (8.5)	2.69 (.76–9.60)	.126	NA	NA
Current malaria	2/17 (11.8)	2204/4079 (54.0)	0.11 (.03–.50)	.004	0.14 (.03–.64)	.011
Recent malaria	0/17 (0.0)	504/4076 (12.4)	. . .	.254	NA	NA
Severe acute malnutrition	4/15 (26.7)	211/3544 (5.6)	5.74 (1.81–18.19)	.003	NA	NA
HIV infection	0/17 (0.0)	202/4073 (5.0)	. . .	1.000	NA	NA
Severe anemia	1/17 (5.9)	614/4071 (15.1)	0.35 (.05–2.66)	.311	NA	NA

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, .81–2.13), whereas the odds of NTS bacteremia in those with high mean parasite density were 0.22 (95% CI, .14–.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, .03–.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 observed at a site of high malaria endemicity that iNTS was a common cause of bacteremia and *Salmonella* Typhi was uncommon, 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 *Salmonella* 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 hospitalized 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 significant 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 bacteremia, 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 increased 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 infection. 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 infection 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 infection, 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.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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