Low Bacteremia Prevalence Among Febrile Children in Areas of Differing Malaria Transmission in Rural Kenya: A Cross-Sectional Study

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Background. With malaria declining, other causes of fever may account for a substantial portion of severe childhood illness in sub-Saharan Africa. We determined prevalence, etiologies, and correlates of bacteremia among children in Western Kenya.

Methods. In a cross-sectional study, febrile children aged 6 months to 15 years presenting to Kisii (low malaria endemicity) and Homabay (high malaria endemicity) Hospitals were enrolled and screened for malaria, human immunodeficiency virus (HIV) infection and bacteremia. Correlates of bacteremia were evaluated using logistic regression.

Results. Among 1476 children enrolled, 48 (3.3%) had bacteremia (23 of 734, 3.1% in Kisii and 25 of 734, 3.4% in Homabay). *Salmonella* spp (19 typhi and 21 nontyphoidal salmonella) accounted for 83% (40 of 48) of isolates. The distribution of *Salmonella* spp was similar between sites. Bacteremia was associated with incomplete vaccination (adjusted odds ratio [aOR] = 2.1; 95% confidence interval [CI], 1.1–4.1), before treatment with antimalarials (aOR = 2.7; 95% CI, 1.4–4.1), having sought care elsewhere (aOR = 2.2; 95% CI, 1.2–4.0) and lower education of caregiver (aOR = 2.5; 95% CI, 1.1–4.8). Nontyphoidal salmonella bacteremia was associated with HIV (aOR = 6.8; 95% CI, 1.1–35.1) and anemia (hemoglobin <8 g/dL) (aOR = 5.2; 95% CI, 1.4–18.9).

Conclusions. Bacteremia was relatively uncommon, but children with HIV, anemia, incomplete vaccination, and/or persistent fever despite malaria treatment may have higher risk and may benefit from targeted bacterial culture and/or empiric antibiotic therapy.

Key words. Africa; bacteremia; children; fever; malaria.

Febrile illness is a leading cause of morbidity and mortality among children in sub-Saharan Africa (SSA) [1]. Historically, a large proportion of febrile illness in SSA was due to malaria [2]. However, malaria incidence has declined in many regions over the past decade [2, 3]. In addition, because malaria rapid diagnostic tests are increasingly available in many settings, malaria is more easily excluded as a cause of fever [4]. Community-acquired bacteremia is an important cause of febrile illness among African children, with case-fatality exceeding 40% when not treated [5–8]. Despite this high fatality rate, the majority of hospitals in rural areas of SSA have limited laboratory capacity to diagnose bacteremia or other alternative causes of fever [9].

Malaria has been associated with the risk of childhood bacteremia, and rates of bacteremia may be expected to decline concurrently with reductions in malaria [2, 4, 10–12]. As a result, the proportion of febrile illness due to bacteremia may have changed in recent years following declines in malaria prevalence. Moreover, pathogen distribution and antibiotic susceptibility profiles may also have changed following widespread introduction of *Haemophilus influenzae* type b and pneumococcal vaccines, and the

growing population of human immunodeficiency virus (HIV)-infected individuals receiving antiretroviral therapy and/or prophylactic cotrimoxazole [13].

Many studies assessing bacteremia as a cause of acute pediatric fever have focused primarily on children admitted to urban referral hospitals or established research facilities [6, 9, 14]. Given regional and rural-urban differences in rates and etiologies of bacteremia [4, 15], and differences in prevalence of potential correlates of bacteremia (including HIV, malnutrition, and malaria), these data may not be generalizable to children in other areas. We determined the prevalence and correlates of bacteremia due to any pathogen and to specific bacterial pathogens in consecutive febrile children presenting to 2 regional rural hospitals with differing malaria transmission intensity in Western Kenya.

MATERIALS AND METHODS

Study Sites and Settings

The study was conducted at Kisii Provincial and Homa Bay District Hospitals in rural Western Kenya. These hospitals serve regions that are geographically and demographically distinct, with significant differences in the prevalence of HIV and malnutrition [16–18]. Kisii has low, seasonal malaria transmission with an annual entomological inoculation rate (EIR) of 0.4–1.5 infectious mosquito bites per person per year [19, 20]. Homa Bay historically has experienced intense perennial malaria transmission [21], although reports indicate declining transmission from an EIR of >300 in 2004 [22] to an EIR of 24 infectious mosquito bites per person per year in 2008 [23]. Human immunodeficiency virus prevalence among antenatal care clients in Homa Bay is 28% (among the highest in Kenya), and it is 4.6% in Kisii [24].

Immunization Schedule During Study Period

During the study period, the immunization schedule in place per the Kenya National Expanded Program of Immunization (KEPI) included Bacillus Calmette-Guérin vaccine and oral poliovirus vaccine (OPV) at birth; subsequent OPV, and pentavalent diphtheria-pertussis-tetanus-hepatitis B, *H influenzae* type b vaccine (Penta) at 6, 10, and 14 weeks of age; and measles and yellow fever vaccines at age 9 months of age. Routine immunization of all children under 12 months of age with pneumococcal conjugate vaccine (PCV 10) was introduced in Kenya in February 2011.

Study Design, Population, and Eligibility

This was a cross-sectional study of pediatric febrile illnesses. Over 2 years (April 2012 to March 2014), children aged 6 months to 15 years presenting with an axillary temperature of ≥37.5°C to outpatient clinics at study sites were approached consecutively for enrollment. Children were eligible to participate in the study if they could provide a blood sample, had not used antibiotics in the last 24 hours (excluding prophylactic antibiotics, such as cotrimoxazole for HIV infection or exposure), and their parents or guardians were willing to provide consent to participate in the study and agreed to attend directed HIV counseling and testing. Assent was obtained from children ≥13 years old. Children were excluded if they were unaccompanied by parents, were hospitalized due to trauma, surgery, or known malignancy, and/or if the parents/guardians did not consent to HIV testing of the child. The study was approved by the Research Ethics Committees at the University of Washington and the Kenya Medical Research Institute.

Data Collection

Study staff administered standardized questionnaires that assessed sociodemographic information, presenting symptoms, medical history, and physical examination findings. All children were assessed using Integrated Management of Childhood Illness (IMCI) guidelines, and those with 1 or more of the IMCI danger signs (unable to drink or breastfeed, convulsions, continuous vomiting, lethargy, and/or unconsciousness) were classified as having severe febrile illness [25]. Blood was collected for complete blood count, malaria, HIV, and bacterial culture testing; and children were managed according to standard of care at the hospitals. Children with suspected bacteremia received empiric antibiotic treatment immediately after blood collection according to Kenya Ministry of Health guidelines [26]. Community-acquired bacteremia was defined as a positive blood culture due to a bacterial pathogen within the first 48 hours of hospital presentation from a child with no history of previous hospitalization.

Laboratory Data Collection

Blood Cultures and Identification of Isolates. Up to 3 mL venous blood specimens were collected by a trained phlebotomist using standard BACTEC Peds blood culture bottles and shipped to the US Army Medical Research Unit-Kenya Microbiology Hub in Kericho, Kenya, within 24 hours of collection. Cultures were incubated in a BD BACTEC 9050 automated blood culture system. Bottles were considered negative if they did not signal within 5 days of incubation at 35°C and were discarded. Blood cultures flagged as positive were Gram stained and subcultured onto appropriate media; blood and nutrient agars for Gram-positive bacteria, and Chocolate, MacConkey, Sorbital-MacConkey, Hektoen enteric agars for Gram-negative bacteria. Subcultured isolates were immediately incubated for 24–48 hours to obtain pure

bacteria colonies that were subjected to bacterial identification and antibiotic susceptibility testing using a Microscan Walkaway40 plus system. Positive blood cultures were classified as probable pathogens, possible pathogens, or likely contaminants [27] by infectious disease specialists at the University of Washington. When culture test results became available, usually after 24–48 hours, patients with positive blood cultures who were not admitted to hospital wards were immediately recalled for appropriate antimicrobial therapy if deemed necessary by the study clinicians.

Human Immunodeficiency Virus Testing. Per Kenya Ministry of Health guidelines, all enrolled children >18 months old were tested for HIV using Abbott Determine rapid test and confirmed using Uni-Gold if positive. Children <18 months were tested using RNA polymerase chain reaction.

Malaria Diagnosis. Blood was evaluated for malaria using both thin and thick smear microscopy and histidine-rich protein 2-based malaria rapid diagnostic tests (RDTs) (Orchid Biomedical Services, India). Malaria was defined as a positive smear microscopy or RDT.

Statistical Analysis

Sociodemographic, clinical, and laboratory characteristics were summarized and compared between study sites. Continuous variables were summarized using mean and standard deviation and compared using the 2-sample *t* test. Categorical variables were summarized using counts and proportions and compared between study sites using Pearson's χ^2 tests or Fisher's exact tests.

Height-for-age z-score (HAZ), weight-for-height z-score (WHZ), and weight-for-age z-score (WAZ) were calculated using the 2006 and 2007 World Health Organization's (WHO) reference populations for children aged 6 months to <5 and children ≥5, respectively [28,29]. Stunting, wasting, and underweight were defined as HAZ ≤2, WHZ ≤2, and WAZ ≤2, respectively. A child classified as either wasted, underweight or stunted, or having a mid-upper arm circumference (MUAC) <12.5 cm, was considered malnourished.

We determined the prevalence of bacteremia after considering potential contaminants as negative cultures. Based on a thorough literature review and biological plausibility, we selected a priori, demographic, host and environmental variables for assessment of their association with bacteremia. These included HIV, malaria, severe or moderate anemia (hemoglobin <8 g/dL), malnutrition, prior treatment with antimalarials or antibiotics, high or prolonged fever, presence of IMCI danger signs, completeness of age-appropriate vaccination (per KEPI), contact with animals, overcrowded living (>2 persons/room), consumption of unsafe water, and caregiver's education [5–7, 10, 30–33]. We evaluated these cofactors in all children, and in subgroups of febrile children that were <5 years old, and malaria-negative using logistic regression models. In bivariate analyses, we evaluated unadjusted associations between bacteremia and several a priori-defined predictors. To identify independent predictors of bacteremia, we adjusted for the after a priori-selected confounders in the multivariate logistic regression; child's age, sex, and study site. We retained in multivariate analyses correlates that have strong plausible theoretical and clinical link with bacteremia even if they were not significant in bivariate analysis. Analyses were conducted using Stata 13.1 (Stata Corp., College Station, TX), and statistical significance was set at $P < .05$.

RESULTS

Between April 2012 and March 2014, we screened for eligibility 1605 children, and we enrolled 1476 (Figure 1). Sociodemographic and clinical characteristics of enrolled children by site are presented in Table 1. Compared with children from Kisii, children from Homa Bay were significantly younger (mean age: 33.9 vs 36.8 months; $P = .014$), more likely to be female ($P = .05$), have primary caregivers with low education levels ($P < .001$), live in lower-income households (<5000 Kenya shillings/month) ($P = <.001$), live in crowded households ($P < .001$), consume unsafe water ($P < .001$), and were more likely to have travelled for ≥30 minutes to hospital ($P < .001$). Children from Homa Bay were also less likely to have received all the age-appropriate vaccinations (34.6% vs 12.0%; $P < .001$).

Children in Homa Bay were more severely ill based on the presence of ≥1 IMCI danger signs (51.5% vs 16.9%; $P < .001$) and more likely to be malaria-infected (49.2% vs 8.6%; $P < .001$), HIV-infected (4.5% vs 1.2% $P < .001$), or have a HIV-infected biological mother (19.3% vs 3.4%; $P < .001$) than children from Kisii. In addition, children from Homa Bay were less likely to have previously sought healthcare elsewhere for their current illness (24.3% vs 34.7%; $P = .001$).

Overall, 94 (6.4%) of 1476 children enrolled had a positive blood culture (Table 2). Of these, 46 isolates were determined to be likely contaminants (overall contamination rate of 3.1%; Kisii 4.8% (35 of 734) and Homa Bay 1.5% (11 of 742; $P < .001$). Considering contaminants as negative blood cultures, the prevalence of bacteremia was 3.3% (48 of 1476) and did not differ by site (Kisii 3.1% [23 of 734] and Homa Bay 3.4% [25 of 742]; $P = 0.799$) but differed by age; the prevalence of bacteremia was 3.7% (19 of 508) in children <2 years old, 2.4%

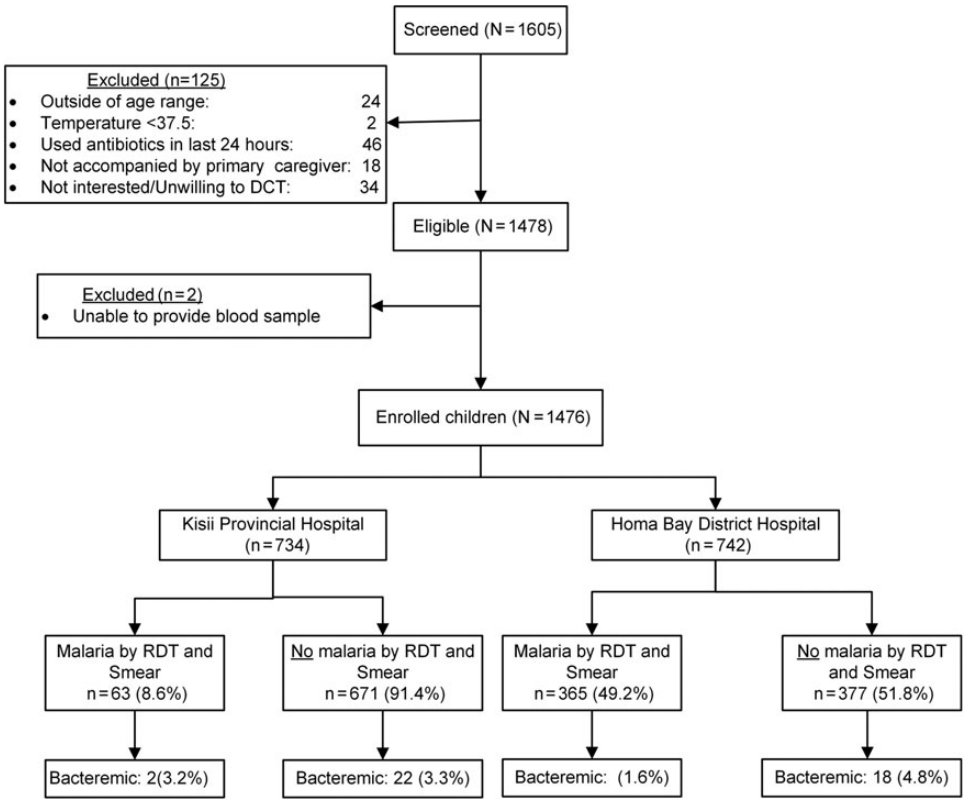

Figure 1. Flow chart summarizing the number of children enrolled during the study period by study site and laboratory diagnosis of malaria and bacteremia.

(20 of 825) in children 2 to <5 years, and 6.3% (9 of 143) in children ≥5 years old ($P = 0.04$). *Salmonella* species (19 nontyphoidal *Salmonella* [NTS] and 21 *Salmonella* typhi) accounted for 83.3% (40 of 48) of all bacterial isolates (Table 2). *Streptococcus* species (2 *Streptococcus pneumoniae* and 1 *Streptococcus pyogenes*) were the second most common isolates identified. The distribution of pathogens did not differ between sites or age groups.

Bacteremia was more common among febrile malaria-negative children than in those with malaria (3.8% vs 1.9%; $P = 0.05$), and dual infections with malaria and bacteremia were rare; 28.5% of children had malaria only, 2.7% had bacteremia only, and <0.5% children had both confirmed malaria and bacteremia. Over two thirds (68.4%) of enrolled children had fever that was due to infections other than malaria or bacteremia. Although antibiotics were frequently given to children with confirmed malaria (55.7%), antibiotics were presumptively prescribed more frequently (93.1%) to children without malaria; $P < .001$. Overall, despite the low prevalence of bacteremia, antibiotics were prescribed to 82.2% of the children.

Results of bivariate and multivariate analyses of correlates of bacteremia due to any pathogen are presented in Table 3. In bivariate analysis, bacteremia was positively associated with prior treatment with antimalarials (crude odds ratio [cOR] = 3.0; 95% confidence interval [CI], 1.6–5.6), having previously sought care elsewhere (OR = 2.3; 95% CI, 1.3–4.0), and lower education (≤primary level) of caregiver (cOR = 2.4; 95% CI, 1.2–4.6). Bacteremia was negatively associated with malaria parasitemia (cOR = 0.5; 95% CI, 0.2–0.9). In multivariate analysis, bacteremia was significantly associated with not receiving all required age-appropriate vaccinations (adjusted odds ratio [aOR] = 2.1; 95% CI, 1.1–4.1), prior treatment with antimalarials at home (aOR = 2.5; 95% CI, 1.4–4.8), having sought healthcare elsewhere (aOR = 2.2; 95% CI, 1.2–4.0), and lower education of caregiver (≤primary level) (aOR = 2.3; 95% CI, 1.1–4.8). Odds of bacteremia were lower for malaria-infected children (aOR = 0.4; 95% CI, 0.2–0.8) and prolonged fever lasting at least a week (aOR = 0.4; 95% CI, 0.2–0.9). No association was seen between bacteremia and HIV, malnutrition, consumption of unsafe water, contact with farm animals, overcrowding, or severe febrile illness. These results were the same for children <5 years old (Supplementary Table 1).

When analysis was restricted to children without malaria, prior treatment with antimalarials a week before hospitalization (aOR = 2.9; 95% CI, 1.4–5.8), having sought

Table 1. Demographic and Clinical Variables of Study Children and Caregivers by Site

Variable	Study Site		*P* Value
	Kisii (n = 734) n %	Homa Bay (n = 742) n %	
Female sex	330 (45.0)	371 (50.0)	.053
Age in months (mean ± SD) (median)[i]	36.8 ± 24.6 (35.0)	33.9 ± 18.6 (33.0)	.014
Child has visible severe wasting?	10 (1.4)	21 (2.8)	.04
Consumption of water from unimproved sources	28 (3.8)	162 (21.8)	<.001
Exposed/in close contact with farm animals	550 (74.9)	588 (79.2)	.049
Overcrowding living (>2 persons/room)	158 (21.5)	382 (51.5)	<.001
Did not receive all age-appropriate vaccines	88 (12.0)	257 (34.6)	<.001
Travel time to the hospital ≥30 minutes	347 (47.3)	445 (60.0)	<.001
Caregiver's Demographic Characteristics			
Primary caregiver			.152
Biological mother	672 (91.6)	700 (94.5)	
Biological father	34 (4.6)	23 (3.1)	
Legal guardian	28 (3.8)	18 (2.4)	
Marital status			.151
Single	41 (5.6)	59 (8.0)	
Married	657 (89.5)	653 (88.0)	
Widowed/Divorced	36 (4.9)	30 (4.0)	
Has up to primary level of education only	326 (44.4)	511 (68.9)	<.001
Household income <Ksh. 5000 (USD <60)	199 (27.1)	402 (54.2)	<.001
Medical History/Clinical Characteristics			
Malnutrition indicators			
MUAC <12.5 cm[ii]	16 (2.2)	26 (3.5)	<.049
Wasting (WHZ ≤2)[iii]	122 (19.1)	84 (12.1)	<.001
Stunted (HAZ ≤2)[iv]	91 (13.8)	106 (15.1)	.478
Underweight (WAZ ≤2)	55 (8.3)	79 (11.3)	.068
Mother infected with HIV[v]	24 (3.4)	140 (19.3)	<.001
Child infected with HIV[vi]	9 (1.2)	31 (4.2)	<.001
High grade fever (>39°C)	226 (30.8)	289 (39.0)	<.001
Fever for ≥7 days	273 (37.2)	90 (12.1)	<.001
Used antimalarials in past 7days	92 (12.5)	112 (15.1)	.154
Used antibiotics in past 7days	60 (8.2)	40 (5.4)	.033
WHO/IMCI[vii]-defined pneumonia	9 (1.2)	242 (32.6)	<.001
Any IMCI danger sign present	124 (16.9)	382 (51.5)	<.001
Unable to drink/breastfeed	14 (1.9)	186 (25.1)	
Vomits everything	68 (9.3)	232 (31.3)	
Convulsions	34 (4.6)	53 (7.5)	
Lethargic/unconscious	49 (6.7)	71 (9.6)	
Where care was sought, prior to hospital visit	255 (34.7)	180 (24.3)	<.001
Traditional healer	9 (3.5)	3 (1.7)	
Chemist	112 (43.9)	88 (48.9)	
Health Centre/dispensary/clinic	134 (52.6)	89 (49.4)	
White blood cells ($\times 10^3/\mu L$) (median; IQR)	10.7 (8-14.6)	10.1 (6.3-13.8)	.510[viii]
Red blood cells ($\times 10^6/\mu L$) (median; IQR)	4.7 (4.2-5.1)	4.3 (3.8-5.1)	.127[viii]
Severe/moderate anemia (hemoglobin <8 g/dL)	19 (2.6)	30 (4.0)	.119
Has chronic disease (sickle-cell/heart disease)	3 (0.4)	19 (2.6)	.001
Malaria by RDT and/or Smear[ix]	63 (8.6)	365 (49.2)	<.001

Abbreviations: HAZ, height-for-age z-score; HIV, human immunodeficiency virus; HRP-2, histidine-rich protein 2; IMCI, Integrated Management of Childhood Illness; IQR, interquartile range; MUAC, mid-upper arm circumference; RDT, rapid diagnostic test; SD, standard deviation; WAZ, weight-for-age z-score; WHO, World Health Organization; WHZ, weight-for-height z-score.

[i] Data are presented as No. (%) or mean (SD) or median (IQR).

[ii] Data missing for 8 children from Kisii and 26 children from Homa Bay.

[iii] Data missing for 49 children from Kisii and 15 children from Homabay.

[iv] Data missing for 1 child from Kisii and 2 children from Homabay.

[v] Data missing for 26 children from Kisii and 3 from Homabay.

[vi] Data missing for 14 children from Kisii.

[vii] WHO Integrated Management of Childhood Illness.

[viii] *P* value by Mann-Whitney *U* test.

[ix] Malaria diagnosed using both smear and HRP-2-based RDT. Those positive on smear alone were 4, RDT 10, both smear and RDT 414.

care elsewhere (aOR = 3.2; 95% CI, 1.7–6.1), and low education of caregiver (aOR = 2.7; 95% CI, 1.2–5.6) were significantly associated with bacteremia.

We evaluated NTS and *Salmonella* typhi bacteremia separately, because they differ in terms of cofactors and pathogenesis [30]. The limited prevalence of NTS (1.4%; 20 of 1476) and of *Salmonella typhi* (1.3%; 19 of 1478) precluded an exhaustive analysis of risk factors for bacteremia. However, in bivariate analysis (NTS bacteremia vs negative blood culture results), NTS bacteremia was

Table 2. Prevalence of Bacteremia and Relative Importance of Causative Agents

		Kisii n = 734	Homa Bay n = 742	All Sites n = 1476
Any Pathogenic Bacteremia		23 (3.1%)	25 (3.4%)	48 (3.3%)
Causative Organisms	Serotype			
Salmonella		16	24	40
	NTS	8	11	19
	typhi	8	13	21
Staphylococcus		2	0	2
	aureus	2	0	2
Streptococcus		2	0	3
	pneumoniae	2	0	2
	pyogenes	0	1	1
Escherichia coli		2	0	2
Haemophilus	Unspecified	1	0	0
Potential Contaminants		35 (4.8%)	11 (1.5%)	46 (3.1%)
Micrococcus		7	5	12
Staphylococcus	*epidermidis*	3	0	3
	hominis	3	1	4
	auricularis	2	0	2
	capitis	1	0	1
	sciuri	1	1	2
	intermedius	0	1	1
Streptococcus	*anginosus*	1	0	1
	bovis	4	1	5
	parasanguis	1	0	1
	mutans	0	1	1
Acinetobacter lwoffii		0	1	1
Gram-positive rods	Unspecified	9	0	9
Gram-negative rods		1	0	1
Gram-variable rods		1	0	1
Pleomorphic bacilii		1	0	1

Abbreviations: NTS, nontyphoidal salmonella.

associated with not receiving of all vaccines (cOR = 3.0; 95% CI, 1.2–7.5), anemia (cOR = 5.8; 95% CI, 1.6–20.4), low household income (cOR = 3.2; 95% CI, 1.2–8.5), and HIV infection (cOR = 4.1; 95% CI, 0.9–18.3). In analyses adjusting for age, sex, and site, NTS was significantly associated with HIV infection (aOR = 6.8; 95% CI, 1.2–38.8) and anemia (aOR = 5.2; 95% CI, 1.4–18.9). These results were the same for under-5 children (Supplementary Table 2). When compared with other bacteremias, NTS was strongly associated with malaria parasitemia (aOR = 7.8; 95% CI, 1.4–42.6) and overcrowded living (aOR = 6.5; 95% CI, 1.0–41.9).

In both bivariate and multivariate analyses (*Salmonella* typhi bacteremia vs negative blood culture results), bacteremia due to *Salmonella* typhi was strongly associated with recent treatment with antimalarials (bivariate cOR = 4.7; 95% CI, 1.9–11.8 and multivariate aOR = 3.3; 95% CI, 1.2–8.8) and contact with cows (bivariate cOR = 2.7; 95% CI, 1.1–6.8 and multivariate aOR = 2.6; 95% CI, 1.0–6.7).

DISCUSSION

We determined the prevalence and correlates of bacteremia in febrile children presenting to hospitals in settings of differing malaria transmission in rural Western Kenya. In this cohort, bacteremia was relatively uncommon; only 3.3% of enrolled children had a pathogen isolated from blood culture. *Salmonella* spp (including NTS and *Salmonella* typhi) were predominant causes of bacteremia in this study.

Bacteremia prevalence in this study was similar to that reported in Tanzania, although lower than has been reported in other African studies, particularly those in malaria-endemic areas, which have reported prevalence as high as 15% [8, 9, 30, 34–36]. Our finding is supported by the observed declining incidence of bacteremia, especially NTS bacteremia as malaria incidence also declines [10, 37]. For example, between 2006 and 2010, declines in malaria incidence among Tanzanian children <15 years old, from 504 to 106 per 100 000 children, were associated with reductions in NTS bacteremia incidence from 82 to 7 per 100 000 children [37]. In Kenya, pediatric hospitalizations for bacteremia have declined since 1999, paralleling declines in malaria [10]. As bacteremia declines, other pathogens are increasingly identified as important causes of fever in African children. For instance, in a cohort of Tanzanian pediatric outpatients with inclusion criteria similar to ours, viral infections were responsible for a larger

Table 3. Bivariate and Multivariate Analyses of Correlates of Bacteremia

Variable	Bacteremia Present		cOR (95% CI)	aOR (95%CI)*
	No (n = 1428)	Yes (n = 48)		
Child HIV-Infected				
No	1375 (97.4)	43 (93.5)	1	1
Yes	37 (2.6)	3 (6.5)	2.6 (0.8–8.7)	2.8 (0.7–11.3)
Malnutrition Indicators				
MUAC <12.5 cm	40 (2.8)	2 (4.2)	1.5 (0.4–6.4)	1.9 (0.4–8.6)
Stunted (HAZ ≤2)	188 (14.3)	9 (22.0)	1.7 (0.8–3.6)	1.7 (0.8–3.6)
Wasting (WHZ ≤2)	201 (15.6)	5 (12.2)	0.8 (0.3–1.9)	0.8 (0.3–2.2)
Underweight (WAZ ≤2)	130 (9.9)	4 (9.8)	1.0 (0.3–2.8)	1.0 (0.3–2.8)
Contact with Animals				
No	325 (22.8)	13 (27.1)	1	1
Yes	1103 (77.2)	35 (72.9)	0.8 (0.4–1.5)	0.7 (0.4–1.4)
Sources of Drinking Water				
Improved source	184 (12.9)	6 (12.5)	1	1
Unimproved source	1244 (87.1)	42 (87.5)	1.0 (0.4–2.3)	0.9 (0.4–2.3)
Overcrowded Living (>2 persons/room)				
No overcrowded	908 (63.6)	28 (58.3)	1	1
Overcrowded	520 (36.4)	20 (41.7)	1.2 (0.7–2.2)	1.2 (0.7–2.3)
Received All Age-Appropriate Vaccines				
Yes	1098 (76.9)	33 (68.8)	1	1
No	330 (23.1)	15 (31.2)	1.5 (0.8–2.8)	**2.1 (1.1–4.1)**
High Grade Fever (>39°C)				
Temperature <39°C	932 (65.3)	29 (60.4)	1	1
Temperature >39°C	496 (34.7)	19 (39.6)	1.2 (0.7–2.2)	1.2 (0.8–2.5)
Fever for 7 or more days				
Fever for <7 days	1071 (75.0)	42 (87.5)	1	1
Fever for ≥7 days	357 (25.0)	6 (12.5)	**0.4 (0.2–1.0)**	**0.4 (0.2–0.9)**
Used antimalarial in past 7days				
No	1238 (86.7)	34 (70.8)	1	1
Yes	190 (13.3)	14 (29.2)	**2.7 (1.4–5.1)**	**2.5 (1.3–4.8)**
Used antibiotics in past 7 days				
No	1331 (93.4)	45 (93.8)	1	1
Yes	97 (6.8)	3 (6.3)	0.9 (0.3–3.0)	0.9 (0.3–3.1)
Any IMCI danger sign				
Absent	939 (65.8)	31 (64.6)	1	1
Present	489 (34.2)	17 (35.4)	1.1 (0.6–1.9)	1.0 (0.6–2.0)
Sought care elsewhere				
No	1015 (71.1)	26 (54.2)	1	1
Yes	413 (28.9)	22 (45.8)	**2.1 (1.2–3.7)**	**2.2 (1.2–4.0)**
Malaria-infected (any test)				
Negative	1008 (70.6)	40 (83.3)		1
Positive (any test)	420 (29.4)	8 (16.7)	**0.5 (0.2–0.9)**	**0.4 (0.2–0.8)**
Severe or moderate anemia				
No (hemoglobin ≥8 g/dL)	1382 (96.8)	45 (93.8)	1	1
Yes (hemoglobin <8 g/dL)	46 (3.22)	3 (6.3)	2.0 (0.6–6.7)	2.4 (0.7–8.1)
Education				
≥Secondary	627 (43.9)	12 (25.0)	1	1
Primary	801 (56.1)	36 (75.0)	**2.3 (1.2–4.6)**	**2.5 (1.2–4.8)**
Income				
≥Ksh. 5000 (USD ≥60)	851 (59.7)	24 (50.0)	1	1
<Ksh. 5000 (USD <60)	575 (40.3)	24 (50.0)	1.5 (0.8–2.6)	1.7 (0.9–3.1)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio; HAZ, height-for-age z-score; HIV, human immunodeficiency virus; IMCI, Integrated Management of Childhood Illness; MUAC, mid-upper arm circumference; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score.
Odds ratios in bold text are statistically significant ($p < 0.05$).
*Adjusted for age, sex, and study site.

proportion of febrile illness than bacteremia or malaria [38]. Our results, taken together with existing studies [36, 38], provide further evidence that community-acquired bacteremia may be an uncommon cause of fever in African children.

Bacteremia in this cohort was associated with incomplete vaccination, having previously sought healthcare, prior treatment with antimalarials, and low education of the primary caregiver. These factors suggest that the risk of bacteremia may be associated with poor engagement with the healthcare system. Incomplete vaccination may be a proxy for limited healthcare exposure, and less educated caregivers may be more likely to delay seeking care, choosing to first manage fever at home. The association of bacteremia with use of antimalarials in the week preceding hospitalization also likely reflects inappropriate home

treatment of bacteremic children. We found that caregivers with low education were more likely to have administered antimalarials to their febrile children prior to hospitalization. These findings suggest a need for targeted educational programs to improve care-seeking behavior for sick children, particularly among parents with low education.

Consistent with other studies, we found HIV-infected children had nearly a 7-fold increased odds of NTS bacteremia [5, 39, 40] compared with those not infected, and NTS bacteremia was strongly associated with malaria parasitemia and anemia [31, 41]. Unlike in previous studies [5, 33], we found no associations between NTS bacteremia and malnutrition, consumption of unsafe water, incomplete vaccination, or more severe illness. However, with only 20 NTS-infected children, we were underpowered to detect associations of NTS with many of these cofactors.

More than two thirds of the children in this study had fever attributable to causes other than malaria or bacteremia. In absence of clear guidelines for the management of febrile malaria-negative children, prescription of antibiotics and/or antimalarials remains common [36]. We observed that (1) even when microscopic and malaria rapid diagnosis was readily available and (2) test results were given to clinicians within 20–30 minutes, clinicians seemed to ignore the results. Clinicians also treated many febrile children with antimalarial despite negative microscopy and rapid diagnostic test more frequently, especially in Homa Bay, which is historically known to be malaria endemic. We recently we published a paper [42] from this same population of children highlighting the challenges of implementing the new WHO malaria diagnosis and treatment guidelines that emphasize universal parasitological testing of all suspected cases of malaria and treatment with antimalarial only in patients with confirmed positive malaria test.

Findings from the current study suggest that in the absence of signs of severe illness or important comorbidities, and also in the presence of a negative malaria test, many febrile outpatient children may not benefit from antibiotic therapy [24]. Despite the low bacteremia prevalence, >80% of the children were presumptively prescribed antibiotics. Although some of these children may have had focal bacterial infections such as pneumonia, the apparent overtreatment of many children without bacterial infection is likely to contribute to the emergence of antimicrobial resistance.

This study had several strengths, notably the inclusion of rural sites with distinct prevalence of HIV and malaria and the careful assessment of multiple cofactors for childhood bacteremia. In addition, identification of causative organisms and antimicrobial susceptibility testing was performed using standard culture techniques in a high-quality laboratory. Another strength of this study was that the observed contamination rate (2.9%) was lower than reported in previous studies (14.3%) in Kenya [5] or elsewhere in Africa [43]. However, there were also some important limitations. Although few caregivers reported recent use of antibiotics (~7%), self-reported history may not have reliably captured all antibiotic use. In addition, although bacterial cultures and malaria testing were performed, viral testing was not performed, and the cause of fever, which was undiagnosed in over two thirds of the children, could have been viral in origin. Finally, the low rate of bacteremia limited the statistical power to conclusively determine cofactors of specific bacterial pathogens. With only 48 children with bacteremia, respectively, the power to detect important associations (odds ratios $\geq$2) was limited (46%). We may have detected only the risk factors that are associated with largest odds of bacteremia.

CONCLUSIONS

The association between malaria and bacteremia has been well established [10, 37], and bacteremia in sub-Sahara Africa has been reported to be twice as common in an area of high malaria transmission intensity as in an area of low endemicity [30]. However, despite declining malaria, and marked differences in malaria and HIV endemicity at the study sites, we found bacteremia to be uncommon at both sites. Although bacteremia in this study was generally uncommon, important subgroups of children including those presenting with severe illness, those with persistent fever despite prior use of antimalarials, those incompletely vaccinated, those with HIV infection, those with anemia, and those whose caregivers have lower education may be at higher risk. Interventions such as focused education to improve early care-seeking, targeted microbiologic assessment, and empiric therapy with antibiotics may be beneficial in these high-risk children, particularly given the significant mortality associated with bacteremia [5, 6]. Finally, we found that in settings of high malaria transmission, bacteremia was more than 3 times as common in children without malaria compared with those children with malaria (5.0% vs 1.6%; $P < .001$). Improved management guidelines focused on subgroups of children at higher risk of bacteremia are needed to reduce mortality and morbidity while limiting the overuse of antimalarials and antibiotics in many low-resource settings.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

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Author contributions. F. M. O. conceived the research idea, assembled the data, performed the analysis, interpreted the analysis results, and wrote and reviewed the paper with contributions from all the coauthors. P. B. P. participated in the data collection and management, analysis and interpretation, writing, critical review, and revision of the paper. B. S. O. and J. N. M. participated in study implementation, data collection, and clinical management of the children and reviewed the paper. B. A. R. and C. F. participated in the conception of the research idea and supervised its analysis and interpretation, and they also critically reviewed and revised the paper. G. J.-S. and J. L. W. conceived, designed, and supervised the study implementation and participated extensively in the writing and the review of this paper. All authors discussed the results and commented on the manuscript at all stages and gave final approval of the version to be published. The corresponding author had full access to all the study data and had final responsibility for the decision to submit manuscript for publication.

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