SUPPLEMENT ARTICLE

Bloodstream Infections and Frequency of Pretreatment Associated With Age and Hospitalization Status in Sub-Saharan Africa

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Background. The clinical diagnosis of bacterial bloodstream infections (BSIs) in sub-Saharan Africa is routinely confused with malaria due to overlapping symptoms. The Typhoid Surveillance in Africa Program (TSAP) recruited febrile inpatients and outpatients of all ages using identical study procedures and enrollment criteria, thus providing an opportunity to assess disease etiology and pretreatment patterns among children and adults.

Methods. Inpatients and outpatients of all ages with tympanic or axillary temperatures of ≥38.0 or ≥37.5°C, respectively, and inpatients only reporting fever within the previous 72 hours were eligible for recruitment. All recruited patients had one blood sample drawn and cultured for microorganisms. Data from 11 TSAP surveillance sites in nine different countries were used in the analysis. Bivariate analysis was used to compare frequencies of pretreatment and BSIs in febrile children (<15 years old) and adults (≥15 years old) in each country. Pooled Cochran Mantel–Haenszel odds ratios (ORs) were calculated for overall trends.

Results. There was no significant difference in the odds of a culture-proven BSI between children and adults among inpatients or outpatients. Among both inpatients and outpatients, children had significantly higher odds of having a contaminated blood culture compared with adults. Using country-pooled data, child outpatients had 66% higher odds of having *Salmonella* Typhi in their bloodstream than adults (OR, 1.66; 95% confidence interval [CI], 1.01–2.73). Overall, inpatient children had 59% higher odds of pretreatment with analgesics in comparison to inpatient adults (OR, 1.59; 95% CI, 1.28–1.97).

Conclusions. The proportion of patients with culture-proven BSIs in children compared with adults was similar across the TSAP study population; however, outpatient children were more likely to have *Salmonella* Typhi infections than outpatient adults. This finding points to the importance of including outpatient facilities in surveillance efforts, particularly for the surveillance of typhoid fever. Strategies to reduce contamination among pediatric blood cultures are needed across the continent to prevent the misdiagnosis of BSI cases in children.

Keywords. bloodstream infections; hospitalization; pretreatment; sub-Saharan Africa.

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Bacterial bloodstream infections (BSIs) are a common cause of febrile illness in children and adults in sub-Saharan Africa [1–3] (Marks et al, unpublished data). Healthcare providers in many locations in sub-Saharan Africa often rely on clinical observations and symptoms for diagnosis due to the general lack of diagnostic laboratory facilities [4]. BSIs are often misdiagnosed as malaria due to the similarities in their clinical presentation [1, 5], which can result in inappropriate treatment, treatment delays, and an increased risk of poorer outcomes for the patient [6–9]. Children in sub-Saharan Africa experience higher rates of febrile disease caused by malaria than adults [10], which can increase the difficulty of obtaining an accurate BSI diagnosis in children. BSIs have been reported to carry a higher case fatality rate than malaria [6, 11, 12], and many deaths, particularly among children, occur within 48 hours of admission, adding to the imperative for improvements in diagnostic methods and treatment regimens [11, 13].

The use of medication, such as antimicrobials and antimalarials, prior to visiting healthcare providers is frequently reported in sub-Saharan Africa [14, 15]. This is problematic as the use of these medications without supervision may delay appropriate treatment and influence health-seeking behaviors of the catchment populations at surveillance sites [15]. Furthermore, the sensitivity of blood culture for *Salmonella* Typhi has been shown to decrease with increasing duration of illness [16]. Furthermore, use of antimicrobials prior to blood culture has been shown in some cases to reduce the sensitivity of blood culture, which can hamper surveillance efforts [11, 17].

Several studies conducted in Africa have attempted to assess the risk factors and incidence of BSIs in order to add to local epidemiological knowledge and improve health infection outcomes for children and adults. However, many studies are limited to 1 surveillance site and frequently examine exclusively inpatient or outpatient populations [5, 6, 11, 13, 18, 19]. The Typhoid Surveillance in Africa Program (TSAP) established 13 surveillance sites in 10 countries across sub-Saharan Africa to estimate the incidences of typhoid fever, invasive nontyphoidal *Salmonella* (iNTS) disease, and other BSIs [20]. TSAP recruited inpatients and outpatients of all ages using the same study procedures and enrollment criteria, providing a prime opportunity to assess febrile disease etiology and pretreatment patterns among children and adults from inpatient and outpatient populations.

METHODS

TSAP established a surveillance network for BSIs that encompassed 13 sentinel sites in 10 different countries in sub-Saharan Africa. These sites were Pietermaritzburg, South Africa; Asante Akim North, Ghana; Moshi Urban and Rural Districts, Tanzania; Kibera, Kenya; Polesgo and Nioko, Burkina Faso; Butajira, Ethiopia; Bandim, Guinea-Bissau; Isotry and Imerintsiatosika, Madagascar; Pikine, Senegal; and East Wad Medani, Sudan. The sites generally followed a standardized protocol [20] and used the same enrollment criteria to allow comparability of results; the site in Ghana and 1 clinic at the site in Guinea-Bissau recruited only children, and were excluded from this analysis. Inpatients and outpatients of all ages with tympanic or axillary temperatures of ≥38.0 or ≥37.5°C, respectively, were eligible for enrollment; additionally, inpatients with a reported fever within the previous 72 hours were also eligible. Inpatients were recruited upon admission. All recruited patients had a single blood draw, which was incubated to isolate infecting microorganisms (1 aerobic bottle taken per patient). *Salmonella* identification was confirmed at the Bernhard Nocht Institute of Tropical Medicine and Hygiene in Hamburg, Germany. Blood cultures were considered contaminated if nonpathogenic organisms or normal skin flora were cultured, including coagulase-negative staphylococci, *Bacillus* species, and *Micrococcus* species; contaminated blood cultures were excluded from the analysis of all-cause BSI, *Salmonella* Typhi, and iNTS. All pretreatment medication variables were self-reported by the patients (or a parent or guardian in the case of children) through direct inquiries of a study investigator.

Statistical Analysis

Bivariate analyses were conducted to compare the odds of reported pretreatment with antimicrobials, antimalarials, and analgesics as well as bacterial blood culture results between febrile children (<15 years old) and adults (≥15 years old) recruited during TSAP surveillance. Separate analyses were conducted for all outpatient children and adults and all inpatient children and adults. Countries containing sites that recruited outpatients included Burkina Faso, Ethiopia, Kenya, Madagascar, Senegal, Sudan, and Tanzania. Countries containing sites that recruited inpatients included Burkina Faso, Guinea-Bissau, Ethiopia, Senegal, South Africa, and Tanzania. Country-specific Cochran–Mantel–Haenszel odds ratios (ORs) were calculated; logit-estimated ORs using a correction of 0.5 in cells containing zeros were also used as appropriate. Pooled Cochran–Mantel–Haenszel ORs were calculated from the country-specific ORs of each variable examined to report an overall trend, and the Breslow–Day test for homogeneity was used to determine significant variation between country-specific ORs. SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all analyses.

RESULTS

Etiology of BSI and Pretreatment in TSAP Outpatients

Data from 4037 child and 3879 adult outpatients meeting the TSAP eligibility criteria were available for analysis. The median age of the outpatient population was 14 years (interquartile range [IQR], 5–28 years). However, the median age varied by

site, ranging from 4 years in Burkina Faso and Tanzania to 26 years in Madagascar (Table 1). Among the recruited children, 47.8% (1928/4037) were female, compared with 61.7% (2392/3879) of the adults; the proportion of females recruited was varied between study sites.

The odds of antimicrobial or antimalarial pretreatment between children and adults were not significantly different at any of the study sites (Table 2), and the odds of analgesic pretreatment did not differ between children and adults in most countries. However, among outpatients recruited in Burkina Faso, children had 44% higher odds of prior analgesic use than adults (OR, 1.44 [95% confidence interval {CI}, 1.13–1.83]), whereas children in Ethiopia were 58% less likely to have been pretreated with analgesics than adults (OR, 0.42 [95% CI, .29–.62]).

With the exception of Kenya and Ethiopia, a contaminant bacterium was significantly more likely to be isolated from blood cultures performed on children's samples than adult blood samples at all study sites. The odds of a contaminated blood culture among children compared with adults ranged from 1.73 (95% CI, 1.06–2.81) in Senegal to 4.83 (95% CI, 1.01–21.15) in Tanzania. There was no significant difference in the odds of all-cause BSI between children and adults at any of the TSAP sites. However, with the exception of Ethiopia and Sudan, a higher proportion of children than adults were blood culture positive for *Salmonella* Typhi. Notably, children in Madagascar were significantly more likely than adults to have *Salmonella* Typhi cultured from their bloodstream (OR, 5.71 [95% CI, 1.42–22.89]). The odds of iNTS infection were not statistically different between children and adults at any of the study sites.

Among outpatients, the country-pooled ORs (combined data from all locations) showed no significant difference in the likelihood of pretreatment with antimicrobials or analgesics in children vs adults (Table 3); however, there was significant variation in pretreatment with antimicrobials and analgesics between countries ($P < .0001$; Breslow–Day test). The country-pooled OR for pretreatment with antimalarials indicated that children were approximately 23% less likely to have received antimalarials than adults (OR, 0.77 [95% CI, .62–.94]). From the combined blood culture results, the country-pooled data found that children were twice as likely of having a contaminated blood culture than adults (OR, 2.06 [95% CI, 1.68–2.52]); this was also significantly variable between sites and countries ($P = .0096$; Breslow–Day test). The pooled-country OR for all-cause BSI showed no difference in odds of BSI, or iNTS-induced BSI, between children and adults. However, children had overall 66% higher odds of infection with *Salmonella* Typhi compared with adults (OR, 1.66 [95% CI, 1.01–2.73]).

Etiology of BSI and Pretreatment in TSAP Inpatients

Data from 1565 child and 951 adult inpatients meeting the TSAP inclusion criteria were available for analysis. The median age of the inpatient study population was 5 years (IQR, 1–29 years) and varied across study sites (Table 1), from age 2 years in Burkina Faso and South Africa, to age 28 years in Senegal. Of the recruited children, 43.8% (686/1565) were female vs 59.2% of adults (563/951).

Inpatient children in South Africa were more than twice as likely as adults to report pretreatment with antimicrobials (OR, 2.33 [95% CI, 1.12–4.85]; Table 4). The odds of antimicrobial use before hospital admission between child and adult inpatients were not significantly different at other sites, although the proportion of children reporting pretreatment was generally higher than adults in all locations apart from Guinea-Bissau. In Ethiopia and South Africa, pretreatment with antimalarial drugs was rarely reported. Outpatient children enrolled at sites in Burkina Faso, Guinea-Bissau, and Senegal reported pretreatment with antimalarials more frequently than adults; only in Guinea-Bissau were the odds of antimalarial use in inpatient children significantly higher than in adults (OR, 2.20 [95% CI, 1.08–4.55]). In all sites except Ethiopia, more children than adults reported pretreatment with analgesics, although only inpatient children enrolled in South Africa had significantly higher odds of analgesic pretreatment compared with adults (OR, 1.75 [95% CI, 1.29–2.36]).

In all countries, except for Senegal, inpatient children had higher odds of having a contaminated blood culture than adults; however, this difference was only statistically significant in South Africa (OR, 1.74 [95% CI, 1.24–2.45]). There was no significant difference in the country-specific odds of infection with *Salmonella* Typhi or iNTS in inpatient children compared with inpatient adults despite iNTS infections occurring more frequently among children.

Among inpatients, the country-pooled ORs for pretreatment with antimicrobials and antimalarials did not indicate any significant difference between children and adults (Table 3). However, inpatient children had 59% higher odds of pretreatment with analgesics compared to inpatient adults (OR, 1.59 [95% CI, 1.28–1.97]). In addition, children had overall higher odds of having a contaminated blood culture than adults (OR, 1.48; [95% CI, 1.12–2.00]). However, the country-pooled ORs for all-cause BSI, *S.* Typhi, and iNTS infection were not significantly different.

DISCUSSION

Our findings from this analysis of the TSAP data suggest that all-cause BSIs occur at a similar frequency in both outpatient and inpatient children and adult populations at the various study sites. A meta-analysis by Reddy and coworkers estimated 40% lower odds of BSI among inpatient children compared with adults in sub-Saharan Africa [21]; however, we found no significant difference in the odds of all-cause BSI between children and adults at any of the TSAP sites, nor was the overall trend

Table 1. Description of Surveillance Sites and Recruited Patients

Country	Burkina Faso		Ethiopia	Guinea Bissau	Kenya[a]	Madagascar		Senegal	South Africa	Sudan	Tanzania	
City	Ouagadougou[b]		Butajira[c]	Bissau[d]	Nairobi[e]	Imerintsiatosika[f]	Antananarivo[f]	Dakar[g]	Pietermaritzburg[h]	Wad Medani[i]	Moshi[j]	
Site	Nioko	Polesgo	Butajira	Bandim	Kibera	Imerintsiatosika	Isotry	Pikine	Pietermaritzburg	East Wad Medani	Moshi Urban	Moshi Rural
Surveillance period[k], (mo)	Apr 2012–Sep 2013 (18)		May 2012–Jan 2014 (21)	Dec 2011–Apr 2013 (17)	Jan 2012–Dec 2013 (24)	Nov 2011–June 2013 (20)	Feb 2012–May 2013 (16)	Dec 2011–Apr 2013 (17)	Feb 2012–Jan 2014 (24)	Jul 2012–Jul 2013 (13)	Sep 2011–May 2013 (21)	
Type of healthcare facility (IPD/OPD)	1 H (IPD/OPD)	1 HCC (OPD)	1 H, 3 HCC (IPD/OPD)	1 H (IPD)	1 HCC (OPD)	1 HCC (OPD)	1 HCC (OPD)	1 H, 3 HCC (IPD/OPD)	1 H (IPD)	3 HCC (OPD)	1 H (IPD/OPD)	
Patients recruited/eligible patients, no./No. (%)												
Children	710/3445 (21.0)	518/1452 (36.0)	501/NA	567/1369 (41.4)	953/953 (100)	342/442 (77.4)	309/367 (84.2)	288/NA	731/NA	191/427 (45.0)[l]	363/NA (79.0)[m]	
Adults	208/759 (27.0)	238/629 (38.0)	346/NA	106/163 (65.0)	298/298 (100)	634/919 (69.0)	1192/1421 (83.9)	770/NA	397/NA	131/147 (89.0)[l]	318/NA (79.0)[m]	
Outpatients recruited, No. (% of patients recruited by age)												
Children	658 (92.7)	518 (100)	480 (95.8)	. . .	953 (100)	342 (100)	309 (100)	250 (86.8)	. . .	321 (100)	132 (56.9)	74 (56.9)
Adults	194 (93.3)	238 (100)	336 (97.1)		298 (100)	634 (100)	1192 (100)	567 (73.6)	. . .	323 (100)	53 (30.5)	44 (30.6)
Female, No. (%)												
Children	308 (46.8)	241 (46.5)	216 (45.0)	. . .	457 (48.0)	182 (53.2)	155 (50.2)	113 (45.2)	. . .	160 (49.8)	62 (47.7)	33 (44.6)
Adults	125 (64.4)	163 (68.5)	200 (59.5)	. . .	165 (55.4)	388 (61.2)	842 (70.6)	262 (46.2)	. . .	188 (58.2)	32 (60.4)	27 (61.4)
Median age, y (IQR)	4 (1–12)	7 (3–21)	11 (5–25)	. . .	7 (3–14)	20 (9–32)	26 (16–40)	20 (13–29)	. . .	15 (9–32)	5 (1–19)	4 (1–34)
Inpatients recruited, No. (% of patients recruited by age)												
Children	52 (7.3)	. . .	21 (4.2)	567 (100)	. . .	. . .	. . .	38 (13.2)	731 (100)	. . .	100 (43.1)	56 (43.1)
Adults	14 (6.7)	. . .	10 (2.9)	106 (100)	. . .	. . .	. . .	203 (26.4)	397 (100)	. . .	121 (69.5)	100 (69.4)
Female, No. (%)												
Children	25 (48.1)	. . .	11 (52.4)	242 (42.7)	. . .	. . .	. . .	12 (31.6)	322 (44.1)	. . .	47 (47.0)	27 (48.2)
Adults	9 (64.3)	. . .	6 (60.0)	72 (67.9)	. . .	. . .	. . .	81 (39.9)	264 (66.5)	. . .	69 (57.0)	62 (62.0)
Median age, y (IQR)	2 (1–9)	. . .	3 (<1–22)	4 (1–9)	. . .	. . .	. . .	28 (19–40)	2 (<1–29)	. . .	20 (1–36)	26 (3–41)

Abbreviations: H, hospital; HCC, healthcare center; IPD, inpatient department; IQR, interquartile range; NA, not available; OPD, outpatient department.

[a] In Kibera, active population mobilization was conducted in addition to passive surveillance.

[b] University of Ouagadougou.

[c] Armauer Hansen Research Institute.

[d] Bandim Health Project.

[e] US Centers for Disease Control and Prevention/Kenya Medical Research Institute.

[f] University of Antananarivo.

[g] Institute Pasteur du Senegal.

[h] National Institute for Communicable Diseases.

[i] University of Gezira.

[j] Kilimanjaro Christian Medical Center/Duke University Medical Center.

[k] Surveillance activities were scheduled for 12 months in Burkina Faso, Guinea-Bissau, Senegal, Sudan, Ethiopia, and Madagascar and for 24 months in Kenya, South Africa, and Tanzania. If funds allowed, the scheduled period was extended.

[l] Health facility records used to estimate eligible patients do not correspond to entire surveillance period. Study database records matching the health facility records were used to estimate proportion.

[m] Health facility records were not categorized by age or location and numbers are not specific to study area. Study records not specific to study area were used to estimate the proportion.

Table 2. Frequencies and Odds of Pretreatment and Blood Culture Results in Outpatient Children Versus Outpatient Adults

Study Site	Burkina Faso	Ethiopia	Kenya	Madagascar	Senegal	Sudan	Tanzania
Pretreatment antibiotics, OR (95% CI)	0.93 (.59–1.45)	0.86 (.50–1.51)	0.83 (.22–3.16)	0.94 (.73–1.21)	1.03 (.50–2.13)	1.26 (.83–1.90)	0.79 (.48–1.30)
Children	71/1162 (6.1)	30/480 (6.3)	8/953 (0.8)	104/532 (19.6)	11/248 (4.4)	60/318 (18.9)	71/205 (34.6)
Adults	28/426 (6.6)	24/335 (7.2)	3/298 (1.0)	266/1295 (20.5)	24/556 (4.3)	49/314 (15.6)	39/97 (40.2)
Antimalarials, OR (95% CI)	0.91 (.67–1.24)	0.69 (.33–1.44)	1.04 (.29–3.81)	0.76 (.32–1.80)	0.59 (.25–1.39)	0.58 (.37–0.91)	0.77 (.43–1.39)
Children	164/1164 (14.1)	15/473 (3.2)	10/954 (1.1)	7/484 (1.5)	7/248 (2.8)	36/319 (11.3)[a]	38/206 (18.5)
Adults	65/426 (15.3)	15/332 (4.5)	3/298 (1.0)	22/1168 (1.9)	26/558 (4.7)	57/317 (18.9)	22/97 (22.7)
Analgesics, OR (95% CI)	1.44 (1.13–1.83)	0.42 (.29–.62)	0.96 (.64–1.44)	1.01 (.83–1.24)	0.97 (.71–1.32)	0.82 (.60–1.13)	1.91 (.97–3.75)
Children	876/1165 (75.2)[a]	52/477 (10.9)[a]	108/952 (11.3)	232/539 (43.0)	153/248 (61.7)	185/319 (58.0)	184/206 (89.3)
Adults	289/426 (67.8)	75/335 (22.4)	35/298 (11.7)	615/1439 (42.7)	348/557 (62.5)	200/319 (62.6)	79/97 (81.4)
Blood culture results							
Contamination, OR (95% CI)	2.95 (2.12–4.09)	1.14 (.74–1.76)	0.87 (.31–2.45)	2.57 (1.09–6.09)	1.73 (1.06–2.81)	1.91 (1.01–3.58)	4.83 (1.01–21.15)
Children	311/1176 (26.5)[a]	61/480 (12.7)	14/953 (1.5)	10/651 (1.5)[a]	31/250 (12.4)[a]	29/321 (9.0)[a]	19/206 (9.2)[a]
Adults	47/432 (10.9)	38/336 (11.3)	5/298 (1.7)	11/1826 (0.6)	43/567 (7.6)	16/323 (5.0)	2/97 (2.1)
All-cause BSI, OR (95% CI)	1.91 (.98–3.73)	0.95 (.33–2.76)	0.74 (.48–1.15)	1.78 (.80–3.95)	1.09 (.37–3.17)	1.05 (.30–3.67)	1.28 (.24–6.71)
Children	46/865 (5.3)	8/419 (1.9)	76/939 (8.1)	10/641 (1.6)	5/219 (2.3)	5/292 (1.7)	5/187 (2.7)
Adults	11/385 (2.9)	6/298 (2.0)	31/293 (10.6)	16/1815 (0.9)	11/524 (2.1)	5/307 (1.6)	2/95 (2.1)
Salmonella Typhi, OR (95% CI)	3.61 (.83–15.77)	0.35 (.03–3.92)	1.10 (.57–2.11)	5.71 (1.42–22.89)	2.42 (.60–9.76)[b]	NA	1.02 (.09–11.35)
Children	16/865 (1.9)	1/419 (0.2)	42/939 (4.5)	6/641 (0.9)[a]	4/219 (1.8)	0/292 (0)	2/187 (1.1)
Adults	2/385 (0.5)	2/298 (0.7)	12/293 (4.1)	3/1812 (0.2)	4/524 (0.8)	0/307 (0)	1/95 (1.1)
iNTS, OR (95% CI)	4.04 (.51–31.97)	NA	0.31 (.06–1.54)	8.50 (.35–209.00)	NA	NA	NA
Children	9/865 (1.0)	0/419 (0)	3/939 (0.3)	1/641 (0.2)	0/219 (0)	0/292 (0)	0/187 (0)
Adults	1/385 (0.3)	0/298 (0)	3/293 (1.0)	0/1815 (0)	0/524 (0)	0/307 (0)	0/95 (0)

Data are presented as no./No. unless otherwise specified.

Abbreviations: BSI, bloodstream infection; CI, confidence interval; iNTS, invasive nontyphoidal *Salmonella*; NA, not available; OR, odds ratio.

[a] Indicates a significant difference between the proportion of children compared with adults at $\alpha \leq .05$ by the χ^2 test of proportions.

[b] One child and two adults cases included in the *Salmonella* Typhi group had *Salmonella* Paratyphi A.

Table 3. Country-Pooled Odds Ratios of Children Compared With Adults

	Outpatients		Inpatients	
Study Site	Pooled OR[a] (95% CI)	Breslow–Day *P* Value	Pooled OR[a] (95% CI)	Breslow–Day *P* Value
Pretreatment				
Antibiotics	0.96 (.81–1.13)	.8671	1.37 (.99–1.87)	.4160
Antimalarials	0.77 (.62–.94)	.7705	1.13 (.83–1.55)	.0258
Analgesics	0.99 (.88–1.11)	.0001	1.59 (1.28–1.97)	.5934
Blood culture results				
Contamination	2.06 (1.68–2.52)	.0096	1.49 (1.12–2.00)	.3190
All-cause BSI	1.11 (.83–1.49)	.2944	0.98 (.62–1.54)	.6567
Salmonella Typhi	42 (.48–4.20)	.0269	0.52 (.15–1.80)	.2454
iNTS	1.91 (.57–6.44)	.1874	3.88 (.32–46.57)	.6498

Abbreviations: BSI, bloodstream infection; CI, confidence interval; iNTS, invasive nontyphoidal *Salmonella*; OR, odds ratio.

[a] The pooled Cochran–Mantel–Haenszel OR is adjusted for country by pooling the country-specific ORs into 1 summary measure.

Table 4. Frequencies and Odds of Pretreatment and Blood Culture Results in Inpatient Children Compared to Inpatient Adults

Study Site	Burkina Faso	Guinea-Bissau	Ethiopia	Senegal	South Africa	Tanzania
Pretreatment antibiotics, OR (95% CI)	2.43 (.48–12.20)	0.66 (.18–2.42)	1.60 (.26–9.83)	1.55 (.58–4.15)	2.33 (1.12–4.85)	1.10 (.72–1.66)
Children	15/52 (28.9)	11/564 (2.0)	6/21 (28.6)	6/36 (16.7)	42/637 (6.6)[a]	67/153 (43.8)
Adults	2/14 (14.3)	3/103 (2.9)	2/10 (20.0)	22/193 (11.4)	9/306 (2.9)	91/219 (41.6)
Antimalarials, OR (95% CI)	1.54 (.44–5.36)	2.2 (1.08–4.55)	1.54 (.06–41.08)	1.92 (.85–, 4.35)	0.15 (.01–3.62)	0.71 (.45–1.10)
Children	24/49 (49.0)	99/565 (17.5)[a]	1/21 (4.8)	10/37 (27.0)	0/558 (0)	45/153 (29.4)
Adults	5/13 (38.5)	9/103 (8.7)	0/10 (0)	32/198 (16.2)	1/247 (0.4)	82/221 (37.1)
Analgesics, OR (95% CI)	2.20 (.55–8.77)	1.52 (1.00–2.31)	0.41 (.07–2.56)	1.10 (.49–2.49)	1.75 (1.29–2.36)	1.59 (.84–3.00)
Children	44/52 (84.6)	338/565 (59.8)[a]	3/17 (15.0)	28/37 (75.7)	320/558 (57.4)[a]	140/156 (89.7)
Adults	10.14 (71.4)	51/103 (49.5)	3/10 (30.0)	147/199 (73.9)	107/246 (43.5)	187/221 (84.6)
Blood culture results						
Contamination, OR (95% CI)	1.08 (.11–10.54)	1.14 (.58–2.23)	NA	0.28 (.04–2.15)	1.74 (1.24–2.45)	1.42 (.09–22.87)
Children	4/52 (7.7)	66/567 (11.6)	0/21 (0)	1/37 (2.6)	152/731 (20.8)[a]	1/156 (0.6)
Adults	1/14 (7.1)	11/106 (10.4)	0/10 (0)	18/203 (8.9)	52/397 (13.1)	1/221 (0.5)
All-cause BSI, OR (95% CI)	0.85 (.03–22.15)	0.85 (.28–2.56)	0.45 (.03–8.03)	2.12 (.63–7.17)	1.07 (.55–2.08)	0.58 (.20–1.67)
Children	1/48 (2.1)	18/483 (3.6)	1/21 (4.8)	4/37 (10.8)	25/579 (4.3)	5/155 (3.2)
Adults	0/13 (0)	4/95 (4.2)	1/10 (10.0)	10/185 (5.4)	14/345 (4.1)	12/220 (5.5)
Salmonella Typhi, OR (95% CI)	NA	0.19 (.01–3.03)	NA	0.98 (.05–20.80)	0.12 (.01–.48)	1.43 (.28–7.17)
Children	0/48 (0)	1/501 (0.2)	0/21 (0)	0/37 (0)	0/579 (0)	3/155 (1.9)
Adults	0/13 (0)	1/95 (1.1)	0/10 (0)	2/185	2/345 (0.6)	3/220 (1.4)
iNTS, OR (95% CI)	0.85 (.03–22.15)	2.12 (.12–38.58)	NA	NA	NA	1.42 (.09–22.21)
Children	1/48 (2.1)	5/501 (1.0)	0/21 (0)	0/37 (0)	0/579 (0)	1/155 (0.7)
Adults	0/13 (0)	0/95 (0)	0/10 (0)	0/185 (0)	0/345 (0)	1/220 (0.5)

Data are presented as no./No. unless otherwise specified.

Abbreviations: BSI, bloodstream infection; CI, confidence interval; iNTS, invasive nontyphoidal *Salmonella*; NA, not available; OR, odds ratio.

[a] Indicates a significant difference between the proportion of children compared to adults at $\alpha \leq .05$ by the χ^2 test of proportions.

indicative of a significant difference, regardless of inpatient or outpatient setting. This difference in findings may be in part due to the countries included in these analyses, as Kenya, Sudan, and Tanzania were the only countries TSAP and the Reddy meta-analysis shared in common. In addition, 53.5% of adults and 13.5% of children included in the Reddy analysis were human immunodeficiency virus (HIV) seropositive [21]. This may account for the overall lower prevalence of BSI observed in the TSAP study, particularly among adults, if the populations included had lower HIV seroprevalence or better treatment coverage; however, HIV serostatus was not determined as part of TSAP surveillance.

The overall small number of infections caused by *Salmonella* Typhi and iNTS at the various study sites limited the overall power in this analysis. Despite most TSAP sites having a higher frequency of *Salmonella* Typhi infections in children than adults, this was only statistically significant in outpatients in Madagascar. These data support the findings from other studies in other developing regions, where the mean age of typhoid fever patients was reported to be between 8 and 12 years [22]. The country-pooled OR for TSAP sites indicated an overall significant trend of higher odds of *Salmonella* Typhi infection in children compared with adults in outpatients, whereas the country-pooled OR did not indicate significantly different odds between inpatient children and adults. Consequently, the use of only inpatient study sites may underestimate the overall prevalence of typhoid fever in pediatric patients relative to adults; future studies with more power are required to clarify this association.

In general, children had significantly higher odds of having a contaminated blood culture than adults among both inpatients and outpatients. Similarly, Reddy et al also observed an overall contamination rate of 13.1% among inpatient children and nearly 4 times the odds of blood culture contamination from children's blood samples than adult blood samples [21]. A higher frequency of contamination of pediatric blood cultures is likely to result in an underdetection of BSI and may hamper surveillance efforts. It is critical that future surveillance projects take steps to implement interventions aimed at lowering the contamination rate of pediatric blood samples to reduce the number of missed cases among children. This may be accomplished through specialized training, dedicated phlebotomy personnel, and appropriate use of antiseptics prior to blood draw [23].

There was no significant difference in the odds of reported pretreatment with antimicrobials between children and adults, which has been shown to reduce the ability of blood culture to detect bacterial pathogens [16, 17, 24]. We are unable to report whether the medications patients reported taking prior to recruitment were prescribed by a healthcare professional, but it is common for people in sub-Saharan Africa to buy antimicrobials from pharmacies without a prescription or obtain them from friends and family [14, 25] (Pach et al, unpublished data). Notably, the overall odds of analgesic use prior to recruitment were higher in hospitalized children compared to adults. This is important to consider as analgesics suppress fever and can lead to missed cases in children if they do not meet the temperature cutoffs often used as inclusion criteria in BSI surveillance, particularly at sites recruiting inpatients.

There are several limitations to this study that should be considered when interpreting these results. Data collection was not complete for all of the pretreatment variables examined, which may induce bias. Additionally, pretreatment was reported by the patient or the child's guardian, which is less accurate than assaying for the presence of antimicrobials in urine [26]; however, direct questioning about medication, as was used in TSAP, has been shown to be more reliable than open-ended questioning [27, 28]. Several factors may result in an underestimation of the true proportion of BSI-positive blood cultures in the TSAP populations: Blood culture volumes in this study were not assessed at all sites and were not considered in this analysis, although it is known to impact detection of BSI, particularly in children [11]; in addition, only 1 blood culture per patient was performed due to resource limitations, though it is recommended to perform this test in sets of 3 to maximize sensitivity [29]. Additionally, the age distribution of recruited patients varied by site, and may have impacted the calculated odds of BSI in children compared to adults. Finally, few of the TSAP surveillance centers were tertiary care centers to which many patients with severe BSI may be referred from smaller primary and secondary care centers, thus possibly resulting in lower detection of BSI in the studied populations.

CONCLUSIONS

The relative proportion of patients testing positive for BSIs in febrile children compared to febrile adults in sub-Saharan Africa appears to be similar in the TSAP study populations for both inpatients and outpatients; however, outpatient children had a higher risk of *Salmonella* Typhi infections compared with outpatient adults. This finding points to the importance of including outpatient facilities in surveillance efforts, particularly for surveillance of typhoid fever. In addition, strategies to reduce contamination among pediatric blood cultures are greatly needed across the continent to decrease missed BSI cases in children. Local trends in the usage of certain medications prior to visiting healthcare centers should be considered for their effect on study inclusion criteria and blood culture sensitivity.

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