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Community-acquired bacteremia among HIV-infected and HIV-exposed uninfected children hospitalized with fever in Mozambique

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Abstract

Background: Bacteremia is a major cause of morbidity and mortality worldwide. Children infected with HIV present with patterns of bacteremia generally associated with poor prognosis. In Mozambique, data on bacteremia are sparce.

Methods: We conducted an observational study of HIV-infected and HIV-exposed uninfected children, aged 0–59 months, hospitalized with fever between April 1, 2016 and February 28, 2019. A single bacterial culture was collected at admission. Descriptive statistics were used to summarize microorganisms detected and antibiotic susceptibility testing.

Results: A total of 808 HIV-infected (90%) and HIV-exposed uninfected (10%) children were enrolled. Blood culture positivity was 12% (95% CI: 9.9%–14.4%). Five organisms accounted for most cases: *Staphylococcus Aureus* (37%), *Klebsiella spp* (11%), *Salmonella spp* (11%), *Escherichia Coli* (9%) and *Micrococcus* (7%). Antibiotic resistance was common. Nearly 70% of *Staphylococcus Aureus* were methicillin-resistant and roughly 50% of *Klebsiella* had ESBL production.

Conclusion: Community-acquired bacteremia was common in HIV-infected and HIV-exposed uninfected children hospitalized in Mozambique with a febrile illness. High rates of MRSA and

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ESBL producing organisms has implications for empiric antibiotics utilized in Mozambique. Longitudinal data on the prevalence and antimicrobial resistance patterns of important pathogens are badly needed to guide policy for drug formulary expansion and antibiotic prescription guidelines.

Keywords

Bacteremia; HIV; pediatrics; antibiotic sensitivity; Mozambique

INTRODUCTION

Bacteremia is a major cause of morbidity and mortality worldwide, with a high disease burden in developing countries and among children under 5 years old (Crichton et al., 2018). Children infected with HIV present with patterns of bacteremia that are different in severity and frequency and are generally associated with poor prognosis (Jaspen et al., 2008; Kolo et al., 2015; Musiime et al., 2013). The World Health Organization (WHO) has classified recurrent severe bacterial infection as a stage IV pediatric AIDS-defining condition (World Health Organization 2007).

Studies suggest that bacteremia in hospitalized African children exceeds that of high-income countries and that gram-negative organisms, in particular, non-typhoidal Salmonella, are among the most common isolates, especially where the prevalence of HIV and malaria is high (Reddy et al., 2010; Feasey et al., 2012; Mandomando et al., 2009). Other common causes of reported bacteremia in HIV-infected children have included *Streptococcus pneumonia, Staphylococcus aureus* and Enterobacteriaceae (Crichton et al., 2018; Hill et al., 2007). However, existing estimates of the burden of most pathogenic bacterial infections in sub-Saharan Africa are predominantly limited to urban areas. Thus, the impact of bacteremia in children under 5 is largely unknown, as many people live in rural areas (Reddy et al., 2010; Berkley et al., 2005; Sigaúque et al., 2009).

Children with invasive bacterial infections usually present with fever, which is a common symptom for seeking medical attention (Popoola et al., 2019; Reddy et al., 2010). HIV infection, malaria, and malnutrition increase the incidence and severity of invasive bacterial infections, especially pneumococcal infections (Sigaúque et al., 2009; Onchiri et al., 2016).

Access to a microbiology laboratory is limited in many developing countries (Reddy et al., 2010). In Mozambique, blood culture capacity is currently only available at referral hospitals or research centers with little direct impact on patient care (Duffy et al., 2020; Moon et al., 2020; Moon et al., 2013). Consequently, health professionals must rely on empirical approaches oriented towards syndromic treatment, risking an unsatisfactory clinical outcome and potentially promoting antimicrobial resistance (Reddy et al., 2010; Moon et al., 2013; Duffy et al., 2020; Moon et al., 2020).

The increase in antibiotic resistance rates in bacteria such as *Escherichia coli*, with resistance to third-generation cephalosporins and fluoroquinolones, is particularly problematic because cephalosporins are the basis of empiric therapy in many developing countries (Droz et al., 2019). The prevalence of extended-spectrum beta-lactamase-

producing (ESBL) Enterobacteriaceae in Asia and sub-Saharan Africa has been estimated to be 60%–90%, increasing the growing challenge of treating bloodstream infections (Musiime et al., 2013).

Current WHO guidelines recommend the combination of ampicillin and gentamicin for empiric treatment of pediatric bacteremia, with a third-generation cephalosporin recommended as second-line therapy when staphylococcal infection is suspected (World Health Organization 2013). Despite these recommendations, many low- and middle-income countries use third-generation cephalosporins as the first-line treatment for suspected bacteremia due to their widespread availability (Downie et al., 2013).

In Mozambique, data on bacteremia are limited, and the few studies describing the epidemiology and etiologies of pediatric bacteremia are limited to patients near the capital city of Maputo, in the south (Sigaúque et al., 2009; Mandomando et al., 2010). In this study, we aimed to estimate the prevalence of laboratory-confirmed bacteremia among HIV-infected and HIV-exposed uninfected children at the time of hospitalization in Mozambique and to describe their antibiotic susceptibility profile and clinical correlates.

MATERIALS AND METHODS

Study design and population

We conducted an observational study of HIV-infected and HIV-exposed uninfected children in the cities of Maputo and Quelimane, Mozambique, who were prospectively followed from hospital admission. Inclusion criteria included all HIV-infected and HIV exposed-uninfected children, aged 0–59 months, with a documented axillary temperature of ≥37.5 °C or rectal temperature ≥38.0 °C, or a history of fever within 24 hours before hospitalization, between April 1, 2016, and February 28, 2019. Patients who did not meet the above criteria were excluded from participation. Patients were recruited from the pediatric urgent care departments of 3 hospitals in Maputo and 2 in Quelimane. The recruiting hospitals in Maputo generally serve urban catchments areas, while the recruiting hospitals in Quelimane serve predominantly rural catchment areas. All are tertiary referral hospitals supported by the National Health System (Figure 1).

Definitions

Because Mozambique is one of the countries most severely affected by HIV, national protocols obligate routine HIV testing of children at most entry portals into the health system, including pediatric urgent care at hospitals. A child was considered HIV-positive if they had documented proof of HIV infection by polymerase chain reaction (PCR) or HIV rapid antibody test. Children with no documented history of HIV but with reported maternal HIV exposure were offered a PCR test (if < 9 months old) using the Amplicor HIV-1 DNA-PCR kit (Roche Diagnostics, USA) or an HIV rapid antibody test (if ≥9 months old) using the Determine HIV-1/2 Rapid Test (Abbott Laboratories, USA) and the confirmatory Uni-Gold Rapid Test (Trinity Biotech Co., Ireland). Those with negative test results were considered HIV-exposed uninfected. A febrile child admitted with no documented history of

HIV and no maternal HIV exposure, with high clinical suspicion of HIV, were enrolled and offered HIV testing per the above.

Severe anemia was defined as a hemoglobin (Hb) concentration of < 7 g/dl, moderate anemia as a Hb 7–9.9 g/dl, mild anemia as a Hb 10–10.9 g/dl, and no anemia as Hb ≥11 g/dl. All patients were followed until the end of their hospital stay. Final disposition status was discharged, died during hospitalization, or abandoned treatment, meaning they left the hospital against the wishes of the treating clinician.

Data collection

Data were collected by study clinicians utilizing a paper-based study instrument and then uploaded into a password-protected, tablet-based, online database maintained by the Research Electronic Data Capture consortium (www.project-redcap.org). This method allowed for the recording of demographic information, medical and medication history, and information on clinical course while hospitalized.

Laboratory Procedures

For all eligible patients, study staff collected a single blood specimen for bacterial culture before initiation of antibiotics. Additional diagnostic testing was performed if there was clinical suspicion based on history or signs/symptoms. Readily available tests included: complete blood count, blood chemistries, dipstick urinalysis, chest x-ray, lumbar puncture for chemistries and bacterial culture, stool culture, stool ova and parasites, HIV rapid antibody testing or DNA-PCR, and malaria antigen rapid testing.

Blood culture organism determination

Under aseptic conditions, 1–5 mL of whole blood (depending on age) was collected through a single venipuncture using a butterfly needle with vacuum tubing connected directly to a BACTEC blood culture bottle and transported to the laboratory within 5 hours at room temperature. At the laboratory, samples were loaded into an automated system for 5 days (BACTEC 9050 Becton-Dickinson, NJ, USA). Positive samples were examined by gram stain and subcultured on solid culture media according to standard laboratory procedures.

The plates were analyzed for bacterial growth after 24 hours, and the colony characteristics were used in combination with the gram stain result for presumptive identification. Staphylococci were identified by the catalase and coagulase tests and then further differentiated using the API-Staph test system (bioMerieux). Streptococci were identified by the optochin and bile solubility tests (alpha-hemolytic) or by the Streptococci agglutination kit (Bio-Rad) to differentiate between beta- and non-hemolytic Streptococci and Enterococci. Enterobacteriaceae and related bacteria were identified by the oxidase test and then further differentiated using the API 20E test system (bioMerieux). Pseudomonas were identified by the oxidase test and then further differentiated using the API 20NE test system (bioMerieux).

Antibiotic Susceptibility Determination

Antibiotic susceptibility testing was performed using the Kirby-Bauer antibiotic testing method (KB testing or disk diffusion) (Hudzicki, 2009). Isolates were classified as susceptible, intermediate, or resistant according to the Clinical Laboratory Standards Institute guidelines (Performance standards for antimicrobial disk susceptibility tests; approved standard - 12th ed., 2018). Per these guidelines, ESBL production was assumed for *Klebsiella* spp, *E coli*, and *Proteus mirabilis* if isolates were reported as resistant to all penicillins and cephalosporins, apart from cefoxitin. Finally, methicillin-resistant *S aureus* (MRSA) was deduced based on reported resistance to cefoxitin.

Once a month, 3 vials inoculated with a 0.5 McFarland suspension of *S aureus* and *E coli* (both, American Type Culture Collection) and a negative vial (inoculated with normal saline) were introduced into the BACTEC 9050. Quality controls were determined successful if the vials inoculated with the bacteria suspension became positive within 24–72 hours, while the non-inoculated vial remained negative after 5 days. Quality control for antibiotic susceptibility testing was done once a month according to Clinical Laboratory Standards Institute guidelines (Clinical and Laboratory Standards Institute 2018).

Statistical Analysis

Patient demographic and clinical characteristics were summarized by recruitment hospital region using median (interquartile range [IQR]) or frequency (proportion) and compared using Chi-squared or Wilcoxon rank-sum tests, as appropriate. Descriptive statistics were used to summarize blood microorganisms detected per age grouping and the results of antibiotic susceptibility testing. The 95% CI for prevalence was constructed using the Wilson method developed for a binomial probability (Wilson, 1927). All analyses were completed using R statistical software (version 3.6.3; www.r-project.org).

Ethical Considerations

The Mozambican National Bioethics Committee for Health (Comité Nacional de Bioética para Saúde, CNBS) (404/CNBS/14) and the Institutional Review Board of Vanderbilt University Medical Center (IRB#141167) approved this analysis. Informed consent was obtained from the parent or legal guardian of all children enrolled in the study.

RESULTS

A total of 808 HIV-infected (90%) and HIV-exposed uninfected (10%) children aged 0–59 months were enrolled in our study; 57% were male, and 40% were 0–12 months old (Table 1). There were 426 children (53%) recruited from hospitals in Quelimane and 382 (47%) from hospitals in Maputo. A higher proportion of children aged 0–12 months were enrolled in Quelimane compared with Maputo (58% vs 40%; $P < 0.001$). Of 799 children with a documented temperature at admission, 63% had a temperature of ≥38.5 °C; for the children from Quelimane this was 58% (median 39 °C [IQR 38,39]) compared with only 14% of children from Maputo (median 38 °C [IQR 37,38]) ($P < 0.001$). Overall, most children (72%) had a reported fever for < 7 days before admission, with a slight increase in fever

days before admission for children enrolled from Quelimane (median 5 days [IQR 3,7]) compared with Maputo (median 4 days [IQR 2,7]) ($P < 0.001$).

Of the children from Maputo 72% were on antiretroviral therapy (ART) before admission compared with only 47% from Quelimane ($P < 0.001$). A total of 611 (76%) children were anemic at admission (Hb ≤11.0 g/dL). The majority (44%) of children were classified as having moderate anemia (Hb 7–9.9 g/dl) and the median Hb was 9.2 g/dL (IQR: 7.7, 10.4). The 5 most common diagnoses associated with hospital admission included acute respiratory infection (50%), malnutrition (40%), gastroenteritis/diarrhea (24%), malaria (14%), and bacteremia (12%). Overall, 61 children (8%) in the cohort died during hospitalization.

In total, 243 children recruited into this study had a positive blood culture result, of which 138 were ultimately classified as coagulase-negative Staphylococcus and 8 as Diphtheroids and considered contaminants (60%). The culture positivity rate for our patient population (97/808 blood cultures) was thus considered to be 12% (95% CI: 9.9%–14.4%). Because cultures were drawn at hospital admission, all positive blood culture results were determined to represent community-acquired bacteremia. We limited the remainder of our analysis to the 97 children determined to have bacteremia, of which 53 (55%) were recruited from Quelimane and 44 (45%) from Maputo (Table 2). There was no statistical difference in age categories between geographic regions, with 8% of children overall being < 3 months of age, 39% 3–12 months, and 53% 13–59 months. Most children with bacteremia (62%) reported fever for < 7 days before admission, though a higher proportion of children from Quelimane had a documented temperature of ≥38.5 °C (60% vs 16%, $P < 0.001$). Overall, 49% percent of children with bacteremia were on ART at admission, with a higher proportion of children from Maputo compared with those from Quelimane (68% vs 36%, $P=0.002$). Frequently, children were documented as having multiple diagnoses for their hospital stay. For children with bacteremia, 46% were also diagnosed with a concomitant acute respiratory infection, 47% with malnutrition, 35% with gastroenteritis/diarrhea, and 12% with malaria. Nineteen percent of children with community-acquired bacteremia died during their hospitalization.

There was an equal distribution between gram-negative (49.5%) and gram-positive (49.5%) organisms in blood culture organisms identified, with identification of only one (1%) fungal organism (Table 3). In children < 3 months old, gram-negative organisms pre-dominated (88%), with *Klebsiella* spp being the most frequent organism (4/8, 50%), followed by *Listeria* spp (1/8, 12.5%), *P mirabilis* (1/8,12.5%), *Salmonella* spp (1/8,12.5%), and *S aureus* (1/8,12.5%). Among children 3–59 months of age, the most common organisms were *S aureus* (35/89, 39%), *Salmonella* spp (10/89, 11%), and *E coli* (9/89, 10%).

The antibiotic susceptibility patterns of the different organisms are shown in Table 4. Among gram-negative organisms, there was a low level of susceptibility to penicillin (3/38, 8%), amoxicillin/clavulanate (11/44, 25%), and cotrimoxazole (12/33, 36%); all frequently used first-line oral antibiotics in Mozambique. Additionally, there was a low level of susceptibility to ampicillin (6/43, 14%), a common first-line intravenous antibiotic for children suspected of having a bloodstream infection. In contrast, there was a relatively high level of susceptibility to gentamicin (31/44, 70%) and ceftriaxone (28/43, 65%), also common first-line intravenous antibiotic options. The majority of Enterobacteriaceae

were highly resistant. Among *Klebsiella* isolates, 2/3 (66%) of *Klebsiella pneumoniae* and 3/8 (38%) *Klebsiella* spp were ESBL-producing. Further, among *P mirabilis* isolates, 1/2 isolates (50%) was an ESBL producer. There were no ESBL producers among *E coli* isolates. *Salmonella* spp were > 88% resistant to penicillin, ampicillin, and amoxicillin/clavulanate and 60% resistant to cotrimoxazole.

Among gram-positive organisms, 100% of *S pneumoniae*, Group A Streptococcus, Group C Streptococcus, and Enterococcus isolates were susceptible to either penicillin, ampicillin, or amoxicillin/clavulanate. However, of *S aureus* isolates, approximately 69% (25/36 resistant to cefoxitin) were considered methicillin-resistant, and only 26% (9/34) were susceptible to cotrimoxazole.

DISCUSSION

Overall, 12% (97/808) of the HIV-infected and HIV-exposed uninfected children enrolled in this study were subsequently diagnosed with community-acquired bloodstream infection at hospitalization. Furthermore, we found in-hospital mortality of 19% for those children later found to have bacteremia. This finding is consistent with other reports across sub-Saharan Africa in which community-acquired bacteremia was identified in 7%–19% of children hospitalized with a febrile illness, underscoring the importance of bacterial bloodstream infections as a cause of morbidity and mortality in this population (Popoola et al., 2019; Hill et al., 2007; Berkley et al., 2005).

Maputo is the nation's capital, with most of the population residing in an urban setting. Quelimane, the capital city of Zambézia Province, represents a catchment population that is much more likely to reside in a rural setting. Despite this urban-rural contrast, we found no statistical difference in bacteremia or death outcomes during hospitalization between febrile children admitted to hospitals in Maputo compared with Quelimane. However, HIV-infected children enrolled from Maputo were significantly more likely to be on ART at admission than their counterparts from Quelimane, which is interesting because other studies have reported decreased incidence of bacteremia in HIV-infected children once established on ART (Kapogiannis et al., 2008; le Roux et al., 2011).

In Mozambique, the country's Expanded Program on Immunization has been working since 1979 to increase vaccine coverage (Shemwell et al., 2017). With support from GAVI since 2001, the program has been able to gradually introduce new vaccines, including Hepatitis B and Haemophilus Influenza B in 2008, followed by the pneumococcal conjugate vaccine (PCV-10) in 2013 (Cassocera et al., 2020).

Five organisms accounted for 76% of all bacteremia in this study, with *S aureus* most common (37%), followed by *Klebsiella* spp (11%), then *Salmonella* spp (11%), *E coli* (9%) and Micrococcus (7%). Antibiotic resistance was common. Nearly 70% of *S aureus* isolates were methicillin-resistant, and roughly 50% of *Klebsiella* isolates had ESBL production. High prevalence of antibiotic-resistant organisms has already been reported for HIV-infected children, with speculation that many were colonized with resistant organisms before hospitalization (le Roux et al., 2011; Cotton et al., 2008; Groome et al., 2012).

As our blood cultures were collected at the time of hospital admission, this seems also to be plausible in our population. Mozambique is one of the high prevalence countries for HIV and tuberculosis (Moon et al., 2013; Duffy et al., 2020; Moon et al., 2020). As such, the bacteria in the country are under direct pressure with a large proportion of the general population taking prophylactic cotrimoxazole. This is highlighted by the fact that 4/5 of the most common bacteria identified in our cohort were predominantly resistant to cotrimoxazole: *S aureus* (74%), *Klebsiella* spp (86%), *Salmonella* spp (60%), and *E coli* (62%). Among study participants with a positive blood culture, only one was positive for *S pneumoniae*, which is much lower than would typically be expected in this age group. Mozambique's strong immunization program, which includes the PCV-10 vaccine, could contribute to reductions in infections with *S pneumoniae*; however, it is unlikely to be the sole reason. Future studies should explore this in greater detail. Antibiotics are readily available and accessible without a prescription at pharmacies across Mozambique. The true extent of antibiotic usage in febrile children under 5 years before being seen at a health facility has not fully been elucidated. However, in one study, Mozambique reported private pharmacies as the first point of contact for antibiotics in only approximately 5% of cases, compared with 40%–90% in some southeast-Asian countries and 51% in Ghana (Do et al., 2021).

Invasive community-acquired MRSA infections in children, especially among those with HIV infection, are being reported with increasing frequency (Groome et al., 2012; Kateete et al., 2019). In addition to antimicrobial pressure resulting from high cotrimoxazole usage, this increase is potentially being driven by algorithm-based clinical management tools such as the WHO Integrated Management of Childhood Illnesses, which promotes the empiric use of antibiotics in febrile children, before the etiologic diagnosis of the cause of the fever (World Health Organization).

Data on ESBL in Mozambique remains scarce. However, one report from the country's central region found a high rate of ESBL *Klebsiella* and *E coli* in urinary tract infections among hospitalized children. Another study from Mozambique's southern region found high rates of presumed community-acquired ESBL *Klebsiella* bacteremia and urinary tract infections in children upon admission to hospital (van der Meeren et al., 2013; Pons et al., 2015). While numerous reports show an increasing trend of community-acquired ESBL infections in adults, this has been less documented in children (Cotton et al., 2008). However, the addition of our findings to the other studies of ESBL in children in Mozambique should raise a red flag in the growing concern of ESBL infection in the country.

Our study has several limitations. First, our inclusion criteria were based on a documented fever or history of fever in the pre-ceding 24 hours. Bacterial bloodstream infections can present with hypothermia and not fever, such that our inclusion criteria could have resulted in an underestimation of the true prevalence of bacteremia in this population. Next, the definitions and diagnostic testing utilized for determining HIV status are based on Mozambican national protocols. However, it should be recognized that some children > 9 months old with a positive HIV rapid test could represent an HIV-exposed uninfected child with continued presence of maternal HIV antibodies. Nonetheless, the likelihood

of this is very low to none. Further, documentation of prior hospitalizations was limited in our cohort, limiting our ability to more thoroughly evaluate if bacterial bloodstream infections identified represented community or hospital-acquired infections. Mozambique's HIV care and treatment program functions through specific outpatient clinics across the country. Despite electronic medical records at these clinics, this data is not readily accessible to clinicians in in-patient settings. As a result, our study clinicians had little access to patient information regarding ART duration, viral suppression, or other management data such as CD4 cell counts. Another limitation of this study is that we are unable to access data on total under-5 hospital admissions across the 5 recruiting hospitals during the study period. Access to this information would provide greater clarity on the extent to which our results are generalizable within the Mozambican local context. Finally, our regional focus on Zambézia and Maputo Provinces does not allow us to make inferences for other regions of Mozambique. Larger sample sizes and a wider catchment area of study cohorts are required to provide a more in-depth understanding of the organisms causing community-acquired bacteremia across Mozambique and their antibiotic susceptibility patterns.

CONCLUSION

Community-acquired bacteremia was common in HIV-infected and HIV-exposed uninfected children hospitalized in Mozambique with a febrile illness. The high rate of documented MRSA and ESBL-producing organisms has implications for the empiric antibiotic choices utilized in Mozambique when a sick child presents at the hospital with a fever. Our findings demonstrate a pressing need for expanding local microbiology capacity. Longitudinal data on the prevalence and antimicrobial resistance patterns of important pathogens are urgently needed to guide national policy for drug formulary expansion and antibiotic prescription guidelines.

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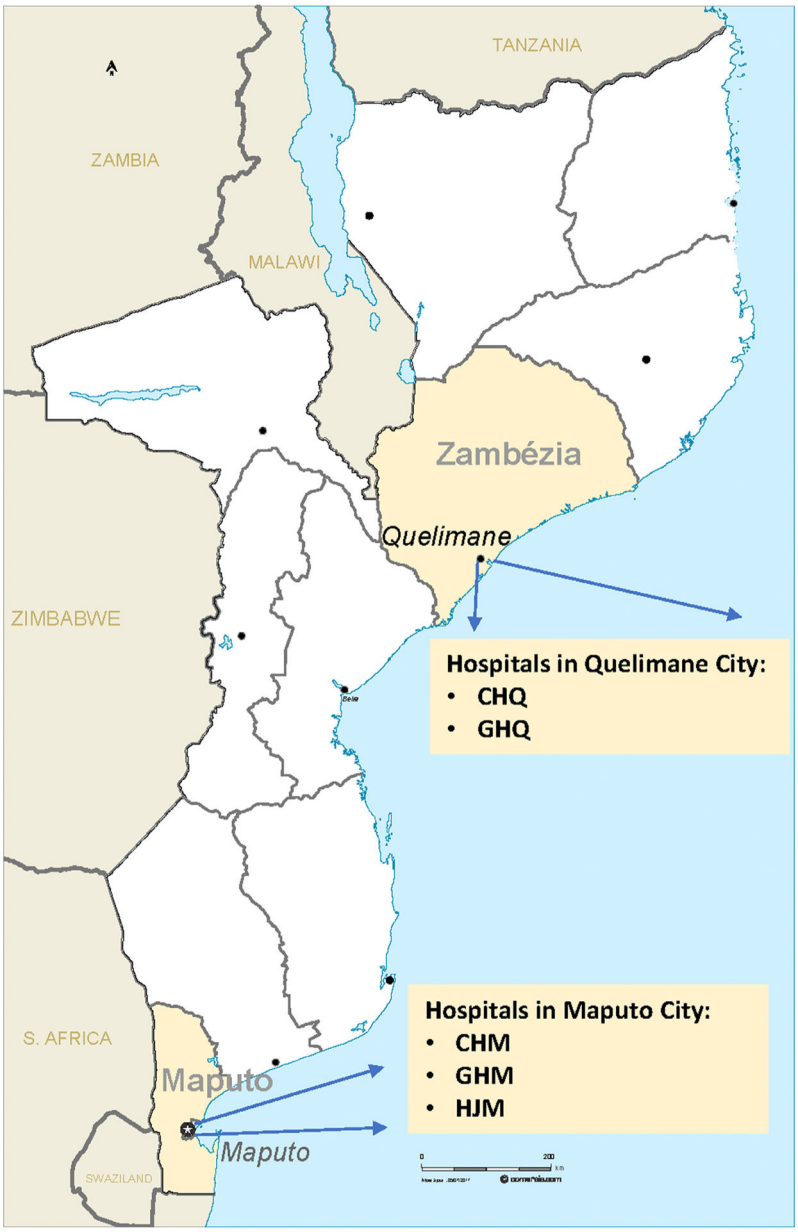

Figure 1. Map of Mozambique with study hospitals identified in Maputo and Quelimane.
CHQ = Central Hospital Quelimane; GHQ = General Hospital Quelimane
CHM = Central Hospital Maputo; GHM = General Hospital Mavalane; HJM = Hospital Jose Macamo

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Table 1

Clinical characteristics of HIV-infected and HIV-exposed children aged 0–59 months, hospitalized in Mozambique with fever or history of fever

Characteristics N (%)	**Maputo**[a] **(n = 382)**	**Quelimane**[b] **(n = 426)**	**Combined (n = 808)**	***P*-value** [†]
Age				< 0.001
< 3 months	31 (8)	52 (12)	83 (10)	
3–12 months	124 (32)	198 (46)	322 (40)	
13–24 months	127 (33)	107 (25)	234 (29)	
25–59 months	100 (27)	69 (16)	169 (21)	
Sex (n = 807)				0.270
Male	210 (55)	250 (59)	460 (57)	
Female	172 (45)	175 (41)	347 (43)	
Temperature °C on admission (n = 799)				< 0.001
< 38.5	328 (86)	176 (42)	504 (63)	
≥38.5	53 (14)	242 (58)	295 (37)	
Temperature °C [median, IQR]	37 [37,38]	39 [38,39]	38 [37,39]	< 0.001
Fever duration at admission (n = 756)				0.350
< 7 days	244 (70)	297 (73)	541 (72)	
≥7 days	105 (30)	110 (27)	215 (28)	
Fever duration in days at admission [median, IQR]	4 [2,7]	5 [3,7]	4 [3,7]	< 0.001
HIV status				0.650
Positive	347 (91)	383 (90)	730 (90)	
HIV-exposed uninfected	35 (9)	43 (10)	78 (10)	
On antiretroviral therapy[&] (n = 788)	272 (72)	193 (47)	465 (59)	< 0.001
Anemia Status				< 0.001
Non-anemic (Hb ≥11 g/dl)	34 (9)	114 (27)	148 (18)	
Mild anemia (Hb 10–10.9 g/dl)	52 (14)	68 (16)	120 (15)	
Moderate anemia (Hb 7–9.9 g/dl)	207 (54)	150 (35)	357 (44)	
Severe anemia (Hb < 7 g/dl)	68 (18)	66 (15)	134 (17)	
Missing	21 (5)	28 (7)	49 (6)	
Hemoglobin level (g/dl) Median [IQR] (n = 759)	8.7 [7.5,9.9]	9.6 [8.0,11.1]	9.2 [7.7,10.4]	< 0.001

Characteristics N (%)	Maputo[a] (n = 382)	Quelimane[b] (n = 426)	Combined (n = 808)	*P*-value †
Hospital Diagnosis $				
Acute respiratory infection	228 (60)	180 (42)	408 (50)	< 0.001
Malnutrition	169 (44)	156 (37)	325 (40)	0.027
Gastroenteritis/diarrhea	94 (25)	96 (23)	190 (24)	0.490
Malaria *	35 (9)	78 (18)	113 (14)	< 0.001
Bacteremia *	44 (12)	53 (12)	97 (12)	0.690
Tuberculosis	26 (7)	29 (7)	55 (7)	0.100
Helminth infection	8 (2)	1 (< 1)	9 (1)	0.012
Dermatitis	5 (1)	10 (2)	15 (2)	0.280
Seizures	8 (2)	10 (2)	18 (2)	0.820
Other	99 (26)	104 (24)	203 (25)	0.620
Length of Hospital Stay (N = 782)				0.690
< 7 days	147 (40)	172 (41)	319 (41)	
≥7 days	220 (60)	243 (59)	463 (59)	
Death during hospitalization	31 (8)	30 (7)	61 (8)	0.560

[a] Maputo = participants recruited from General Hospital Mavalane, Hospital Jose Macamo, or Central Hospital Maputo

[b] Quelimane = participants recruited from either General Hospital Quelimane or Central Hospital Quelimane

& On antiretroviral therapy refers to HIV-infected children in treatment and HIV-exposed uninfected children receiving antiretroviral therapy prophylaxis.

* Laboratory confirmed diagnosis

$ Values could add up to more than 100%g/dl = grams per deciliter

Table 2

Clinical characteristics of HIV-infected children aged 0–59 months, hospitalized in Mozambique in a subset with positive blood culture result at admission

Characteristics (n = 97)	**Maputo[a] (n = 44)**	**Quelimane[b] (n = 53)**	***P*-value [†]**
Age			0.110
< 3 months	2 (4)	6 (11)	
3–12 months	13 (30)	25 (47)	
13–24 months	21 (48)	15 (29)	
25–59 months	8 (18)	7 (13)	
Sex			0.450
Male	29 (66)	31 (58)	
Female	15 (34)	22 (42)	
Temperature °C on admission (n = 96)			
< 38.5	37 (84)	21 (40)	< 0.001
≥38.5	7 (16)	31 (60)	
Temperature °C [median, IQR]	37 [37,38]	39 [38,39]	< 0.001
Fever duration at admission (n = 88)			0.900
< 7 days	27 (68)	33 (69)	
≥7 days	13 (32)	15 (31)	
Fever duration in days at admission [median, IQR]	4 [3,7]	5 [4,8]	0.074
HIV status			0.720
Positive	40 (91)	47 (89)	
HIV-exposed uninfected	4 (9)	6 (11)	
On antiretroviral therapy[&](n = 94)	30 (68)	18 (36)	0.002
Anemia Status			0.038
Non-anemic (Hb ≥11 g/dl)	4 (9)	11 (21)	
Mild anemia (Hb 10–10.9 g/dl)	5 (11)	10 (19)	
Moderate anemia (Hb 7–9.9 g/dl)	25 (57)	14 (26)	
Severe anemia (Hb < 7 g/dl)	9 (21)	14 (26)	
Missing	1 (2)	4 (8)	
Hemoglobin level (g/dl) Median [IQR]	8.2 [7.1, 9.8]	9.5 [6.4, 10.7]	0.310

Characteristics (n = 97)	Maputo[a] (n = 44)	Quelimane[b] (n = 53)	*P*-value †
Concomitant Hospital Diagnosis $			
Acute respiratory infection	26 (59)	19 (36)	0.022
Malnutrition	25 (57)	21 (40)	0.091
Gastroenteritis/diarrhea	16 (36)	18 (34)	0.810
Malaria *	2 (5)	10 (19)	0.033
Tuberculosis	3 (7)	5 (9)	0.640
Helminth infection	1 (2)	0 (0)	0.270
Dermatitis	0 (0)	1 (2)	0.360
Seizures	0 (0)	1 (2)	0.360
Other	10 (23)	11 (21)	0.810
Length of Hospital Stay (n = 94)			0.270
< 7 days	17 (39)	25 (50)	
≥7 days	27 (61)	25 (50)	
Death during hospitalization	10 (23)	8 (15)	0.340

[a]Maputo = participants recruited from General Hospital Mavalane, Hospital Jose Macamo, or Central Hospital Maputo

[b]Quelimane = participants recruited from either General Hospital Quelimane or Central Hospital Quelimane

&Being on antiretroviral therapy refers to HIV-infected children in treatment and HIV-exposed uninfected children receiving antiretroviral therapy prophylaxis.

*Laboratory confirmed diagnosis

$Values could add up to more than 100%g/dl = grams per deciliter

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Table 3

Microorganisms identified by age group

N (%)	Age in Months				
	<3 mths 8 (8)	**3–12 mths 38 (39)**	**13–24 mths 36 (35)**	**25–59 mths 15 (15)**	**Total (n=97)**
Gram-negative bacteria	**7 (88)**	**17 (44)**	**18 (50)**	**6 (40)**	**48 (49.5)**
Acinetobacter baumannii	–	–	1	–	1 (1)
Cronobacter spp	–	–	1	–	1 (1)
Escherichia coli	–	2	6	1	9 (9)
Enterobacter spp	–	2	–	–	2 (2)
Haemophilus influenzae	–	1	–	–	1 (1)
Klebsiella spp *	4	5	1	1	11 (11)
Listeria spp	1	–	–	–	1 (1)
Neisseria meningitidis	–	1	–	–	1 (1)
Proteus mirabilis	1	–	–	1	2 (2)
Pseudomonas aeruginosa	–	1	3	1	5 (5)
Salmonella spp	1	3	5	2	11 (11)
Serratia marcescens	–	1	1	–	2 (1)
Shigella spp	–	1	–	–	1 (1)
Gram-positive bacteria	**1 (12)**	**20 (53)**	**18 (50)**	**9 (60)**	**48 (49.5)**
Enterococcus	–	1	–	–	1 (1)
Group A streptococcus	–	1	1	–	2 (2)
Group C streptococcus	–	–	1	–	1 (1)
Micrococcus spp	–	3	–	4	7 (7)
Staphylococcus aureus	1	15	15	5	36 (37)
Streptococcus pneumoniae	–	–	1	–	1 (1)
Other	–	**1 (3)**	–	–	**1 (1)**
Candida albicans	–	1	–	–	1 (1)

* *Klebsiella* spp = includes 3 isolates identified as *Klebsiella pneumoniae*

Table 4

Antibiotic susceptibility of isolated microorganisms: number of samples tested and percent susceptible

	Acinetobacter baumannii	*Cronobacter*	*E coli*	*Enterobacter* spp	*Haemophilus influenzae*	*Klebsiella* spp	*Listeria* spp
Ampicillin	–	0/1 (0)	2/9 (22)	0/2 (0)	0/1 (0)	1/11 (9)	–
Amox/clav	–	0/1 (0)	2/9 (22)	0/2 (0)	–	0/11 (0)	1/1 (100)
Cefotaxime	0/1 (0)	–	5/6 (83)	0/2 (0)	–	3/7 (43)	–
Cefoxitin	0/1 (0)	0/1 (0)	6/7 (86)	–	–	4/7 (57)	0/1 (0)
Ceftriaxone	0/1 (0)	0/1 (0)	8/9 (89)	0/2 (0)	1/1 (100)	4/9 (44)	–
Ciprofloxacin	1/1 (100)	0/1 (0)	6/9 (67)	0/2 (0)	0/1 (0)	8/9 (89)	1/1 (100)
	–	1/1 (100)	5/9 (56)	0/2 (0)	0/1 (0)	1/11 (9)	0/1 (0)
Chloramphenicol							
Cotrimoxazole	1/1 (100)	0/1 (0)	3/8 (38)	0/1 (0)	0/1 (0)	1/7 (14)	0/1 (0)
Erythromycin	–	0/1 (0)	0/4 (0)	0/2 (0)	–	0/3 (0)	–
Gentamicin	1/1 (100)	0/1 (0)	6/9 (67)	0/2 (0)	–	5/9 (56)	1/1 (100)
Penicillin	–	0/1 (0)	2/8 (25)	0/2 (0)	0/1 (0)	0/11 (0)	0/1 (0)
Tetracycline	1 (100)	1/1 (100)	5/8 (63)	0/2 (0)	–	5/9 (56)	–
Tobramycin	0/1 (0)	0/1 (0)	4/5 (80)	0/1 (0)	–	1/3 (33)	1/1 (100)
	Neisseria meningitidis	***Proteus mirabilis***	***Pseudomonas aeruginosa***	***Salmonella* spp**	***Serratia marcescens***	***Shigella* spp**	
Ampicillin	–	0/1 (0)	1/4 (25)	2/11 (18)	0/2 (0)	0/1 (0)	
Amox/clav	–	0/2 (0)	2/4 (50)	6/11 (55)	0/2 (0)	0/1 (0)	
Cefotaxime	0/1 (0)	1/1 (100)	1/2 (50)	8/11 (73)	1/1 (100)	–	
Cefoxitin	–	–	1/3 (33)	4/4 (100)	0/2 (0)	–	
Ceftriaxone	0/1 (0)	1/2 (50)	1/3 (33)	10/11 (91)	2/2 (100)	1/1 (100)	
Ciprofloxacin	–	2/2 (100)	4/5 (80)	11/11 (100)	2/2 (100)	1/1 (100)	
	–	0/1 (0)	1/4 (25)	6/11 (55)	2/2 (100)	1/1 (100)	
Chloramphenicol							
Cotrimoxazole	–	1/2 (50)	1/4 (25)	3/5 (60)	2/2 (100)	–	
Erythromycin	–	–	0/3 (0)	0/8 (0)	0/2 (0)	–	
Gentamicin	–	2/2 (100)	4/5 (80)	11/11 (100)	1/2 (50)	0/1 (0)	
Penicillin	1/1 (100)	0/1 (0)	0/2 (0)	0/8 (0)	0/2 (0)	–	
Tetracycline	0/1 (0)	0/2 (0)	1/4 (25)	7/11 (64)	0/2 (0)	–	

Tobramycin	–	–	0/3 (0)	6/8 (75)	–	–
	Enterococcus	**Grp A streptococcus**	**Grp C streptococcus**	***Micrococcus* spp**	***Staphylococcus aureus***	***Streptococcus pneumoniae***
Ampicillin	0/1 (0)	0/2 (0)	1/1 (100)	3/4 (75)	11/36 (31)	1/1 (100)
Amox/clav	–	–	–	1/2 (50)	11/36 (31)	1/1 (100)
Cefotaxime	–	0/2 (0)	0/1 (0)	0/1 (0)	10/36 (28)	–
Cefoxitin	–	0/1 (0)	–	0/3 (0)	11/36 (31)	–
Ceftriaxone	–	0/1 (0)	0/1 (0)	1/2 (50)	13/36 (36)	1/1 (100)
Ciprofloxacin	1/1 (100)	–	–	7/7 (100)	24/36 (67)	1/1 (100)
Chloramphenicol	0/1 (0)	0/2 (0)	–	6/7 (86)	29/36 (81)	1/1 (100)
Cotrimoxazole	–	–	–	1/7 (14)	9/34 (26)	0/1 (0)
Erythromycin	1/1 (100)	1/2 (50)	1/1 (100)	2/7 (28)	8/35 (23)	0/1 (0)
Gentamicin	–	–	0/1 (0)	4/6 (67)	18/36 (50)	–
Penicillin	1/1 (100)	2/2 (100)	1/1 (100)	2/6 (33)	11/36 (31)	–
Tetracycline	1/1 (100)	1/2 (50)	1/1 (100)	4/7 (57)	16/36 (44)	–
Tobramycin	–	–	–	–	3/30 (10)	–

spp = species