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Epidemiology of bacterial Septicemia among children under five in Mbita Subcounty, South Nyanza, Kenya

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ABSTRACT

Background: Septicaemia is a major cause of mortality and morbidity, especially in sub-Saharan Africa leading to complications marked by bodily inflammation referred as sepsis. This is a systemic disease associated with presence of pathogenic microorganisms (viral, parasitic and bacterial) or their toxins in the blood. Bacterial septicaemia is the most fatal and prevalent in hospitalised cases. Globally, 76% of children under five years die due to septicaemia. In East Africa a mortality rate of 40% have been reported. In Kenya, South Nyanza regions have reported higher morbidity and mortality cases among children. We hypothesis that apart from immunosuppressive diseases, septicaemia could contribute significantly to this prevalence in the region.

Methods: Blood samples were obtained from 248 children whose guardian consented and a detailed sociodemographic questionnaire was administered. Bacterial isolation and characterization were done using the automated BACTEC 9240 system.

Results: The mean age of the participants was 27.9 (SD ±20.7) months. The majority (30.6%) were aged between 1 to 12 months, 50.8% were males, 58.9% had body temperatures above 37.6 ^{O}C while only 8.1% were HIV seropositive. The mean white blood cells (WBC) of the participants were 17720.9 (SD 8929.1) cells/ml with 5.2% had leucopenia. A total of 84 of the 248 (33.9%) of the children had septicaemia with the majority (28.6%) caused by *Staphylococcus epidermidis* followed by *Staphylococcus aureus* and *Escherichia coli* each at 13.1%. Bacteria that were reported singly included *Salmonella Paratyphi* B, *Citrobacter freundii*, *Gemella morbillorum*, *Klebsiella pneumoniae*, *Lactococcus lactis cremoris*, *Pantoea* spp, and *Pseudomonas putida*. In multivariate regression analysis, female gender (OR 0.6; 95% confidence interval (CI) 0.4 to 0.9), co-infection with malaria (OR 2.7; 95% CI 1.1 to 6.7) and
gastrointestinal disorders (OR 2.9, 95% CI 1.3 – 7.3) were independently associated with bacterial septicemia infection.

Conclusion: Significantly higher proportion of the children in this region are infected with septicaemia. Majority of the cases were caused by Gram positive bacteria. Age and other c-infection contribute significantly to septicaemia infection in this region. Rapid testing and etiological characterisation of children with suspected symptoms of septicaemia is key in this region in order to institute appropriate treatment and management.

Keywords: bacterial Septicemia, Epidemiology, Children under five, South Nyanza, Kenya
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BACKGROUND

Sepsis is one of the greatest world health problems with the prevalence and death rates increasing every year despite the achievements of intensive care, vaccination, and the abilities of antibacterial therapy (Randolph and McCulloh, 2014). Being the most vulnerable part of the population, paediatric patients require special attention given that sepsis is one of the most common causes of children's death due to infection (Kissoon *et al.,*2011). Previous estimates, shows a range of 380 000–2 000 000 annual cases of neonatal sepsis in sub-Saharan Africa

and 270 000 annual associated deaths, highlight the substantial burden of disease (Seale et al.,2010; Sepsis Alliance, 2016).

Viral, bacterial and parasitological septicemias are the commonest causes of the febrile illness in developing countries (Heffner *et al.,*2010). Invasive bacteria are important etiologies of septicemia in African children and population (Brent *et al.,*2006; Ikumapayi *et al.,*2007; Jacob *et al.,*2009). In infant, sepsis in early stages of life is conventionally regarded as maternally-acquired, and majorly caused by *Escherichia coli* and Group B *Streptococcus* found in the maternal genital tract, whereas late onset sepsis is considered environmental in origin either hospital or community acquired (Zaidi *et al.,*2009). Common causes of hospital acquired septicemia infections are coagulase-negative staphylococci, *Staphylococcus aureus*, and Gram-negative organisms such as *Klebsiella* and *Pseudomonas* species (Stoll, 2004). Varying prevalence of bacterial septicemia have been reported in sub-Saharan Africa. Previously in the Coastal Kenya, high prevalence of community acquired were due to *Streptococcus pneumonia* and *Staphylococcus aureus* (Berkley *et al.,*2005). In Tanzania 40% of child mortality were due to bacterial septicaemia. In Ethiopia, the most common etiology of neonatal sepsis was Klebsiella spp. (39.2%) and Staphylococcus aureus (22.2%) (Shitaye et al.,2010). In Uganda the *Mycobacterium tuberculosis* (21%) and *Streptococcus pneumoniae* (9%) were common etiological agents of sepsis identified (Moore et al.,2019).

The most commonly identified risk factor for septicemia include prematurity, low birth weight, abnormal WBC count (high and low), hematologic-oncologic diagnosis, and use of steroids for adults (Barry et al.,2005; Shitaye et al.,2010).

Sepsis survival depends on timely, appropriate, and optimal antibacterial treatment (Khilnani *et al.,*2008). It is known that a delay in the first antibiotic administration is associated with increased morbidity and mortality (Ferrer *et al.,*2014). This study was therefore designed to investigate the prevalence, etiology and factors associated with septicemia among children visiting Mbita District Hospital, one of the regions marked with high prevalence of HIV infection in Kenya.

METHODOLOGY

Study setting and design

This was a descriptive hospital based cross-sectional study conducted between 2019 and 2020 among children presenting with symptoms suggestive of septicemia as described by the WHO (Bataar *et al.,*2010), attending Mbita District Hospital in Nyanza Kenya. These included: Body temp <36˚C >38˚C; heart rate above 100 beats/minute, Respiratory rate above 20 per minute; and WBC count < 4000 > 12000/mm^3. Applying the formula for estimating the population proportion with specified relative precision described by Lemeshow et al (1990) setting the α at 0.05, and septicemia prevalence rate 76% (WHO, 2014), a total of 281 patients were recruited to achieve 0.95 power.

Recruitment and ethical approvals

Patients were recruited if they met the following Inclusion criteria: 1. Any patient with clinical symptoms suggestive of septicemia as defined by the WHO. 2. Attending/admitted at Mbita District Hospital. 2. Age between 1 day to 120 months. 3. Parents/guardian providing informed consent. Recruitment of the desired number of patients meeting the inclusion criteria was done using the purposive sampling method. The patients provided blood samples while the parents/guardian underwent a brief face to face interview to gather relevant study related information. Additional, hospital records were reviewed to gather clinical information about the enrolled patients. This study was approved by Ethical Review Committee of Kenyatta University before commencing to field activities. Each participant signed a form of informed consent

Laboratory analysis

Blood sample collection and transportation*:* From each of the participants enrolled, about 2-5ml (children) blood samples were collected aseptically in aerobic and anaerobic blood culture bottles BD (Becton Dickinson, US). The sampling bottles were appropriately labelled in line with pathological/request forms details i.e. name, sample code, date, time and location of the hospital and patients. The blood samples collected aseptically into appropriate blood culture tubes were packed in primary cases and secondary cases according to the WHO guideline for transporting infectious materials. The samples were maintained in upright position in a cooler box and transported to NUITM-KEMRI Biosafety level 2 laboratory at Mbita for processing.

Microbiological analysis

Samples were incubated at 37^0C for at least 3 weeks in the BACTEC 9270 (Becton Dickinson, US) automated machine. Generally, the BACTEC indicates signals for any positive culture wells. All positive culture bottle was taken to the Biosafety level III laboratory where they were sub cultured using sterile and disposable loops on basic, differential, selective media (Oxoid type) and other appropriate media like blood agar, chocolate blood agar (CBA), Xylose lysine deoxycholate (XLD), DHL, Salmonella–Shigella agar (SS), and Bromol thymol blue (BTB) for other etiological agents. All plates were incubated at 37°C for 18-24hrs. Blood agar, Brucella agar and CBA were incubated in the presence of 5-10% CO2. The suspected colonies were examined and characterized by their morphology, Gram stain, biochemical identification (Sahin, *et al.,*2008). All the identified and clinically significant isolates were purified, accurately labelled and stored in 15-40% glycerol, at -80^0c for any future work or references.

Data Analysis

The qualitative and laboratory parameters were described using frequencies (%), standard deviation, mean, and medians (interquartile ranges at 25% and 27%). Test for significance was done using Fisher's exact test or Chi-square, where applicable. In bivariate analyses, odds ratios (OR) and 95% confidence intervals (CI) for the association between bacterial septicemia infection and socio-demographic and clinical variables were calculated using Poisson regression. In multivariate analyses, a manual backward elimination approach was used to reach the most parsimonious model, including factors that were associated with bacterial septicemia infection at the significance level of P 0.05. All statistical analyses were performed using STATA v 13 (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of study patients

Table 1 summarizes the characteristics of the study population. A total of 21 children met the recruitment criteria but analyzable data were available for 248 patients recruited. The mean (± standard deviation - SD) age of the participants was 27.93 (±20.6) months with 30.6% of them aged between 1 to 12 months. The majority of the patients 50.8% were males, 48% from Rusinga locality and 91.9% HIV negative.

Clinical presentation of the study patients

The mean body temperature for the patients 38^{O}C (± 20.5) ranging between 37 to 40^{O}C. There were 58.9% patients with body temperatures above 37.6 ^{O}C. The mean WBC of the patients was 17720.9 Cells/ml (± 8929.1) Cells/ml ranging between 12075 to 22450 Cells/ml. about 25.4% of them had WBC above the normal levels of 10501 cells/ml. The mean respiratory rate (RR) of the patients was 30.6 (± 10.6) breaths/min ranging between 18 to 96 breaths/min with 71.4% having RR between 20 and 30 breaths/min. The mean heart rates (HR) of the patients was 111.7 (±12.2) beats/min ranging between 29 - 138 beats/min with 34.3% of the patients having heart rate between 101 and 110 beat/min. Co-infection/complications among the study patients included: malaria reported in 83 (33.5%) of the patients followed by respiratory illnesses 33 (13.3%), Hematologic diseases 31(12.5%), Gastrointestinal disorders 27(10.9%), malnutrition and meningitis in 9 (3.6%) each. There were 6 (2.4%) patients who had Nervous system diseases, 5(2.1%) with Ear nose and throat infections and 2 (0.8%) with HIV. There were 20 (8.1%) patients who reported no other co-infection.

Table 1: Baseline characteristics of the study population

Variable	Unit	Frequency No	Percentage %
Locality	Rusinga	119	48
Gender	Male	126	50.8
Age (Months)	Mean (± SD)	27.9	(± 20.7)
	Range	118	(2-120)
	1-12	76	30.6
Temperature (C^0)	Mean (± SD)	38.1	(± 0.5)
	Range	3	(37-40)
	>37.6	146	58.9
WBC (Cells/ml)	Mean (± SD)	17720.9	(± 8929.1)
	Range	45000	(-120)
	10501	63	25.4
Respiratory rate (Breaths/min)	Mean (± SD)	17720.9	(± 8929.1)
	Range	45000	(1-45000)
	20-30	177	71.4
Heart rate (Beat/min)	Mean (± SD)	111.7	(± 12.2)
	Range	109	(29-138)
	101-110	85	34.3
HIV status	Positive	20	8.1
Co-infections	Ear nose and throat	5	2.0
	Gastrointestinal disorders	27	10.9
	Hematologic diseases	31	12.5
	Malaria	83	33.5
	Malnutrition	9	3.6
	Meningitis	9	3.6
	Nervous system diseases	6	2.4
	Respiratory Illnesses	33	13.3

Prevalence and aetiology of septicaemia among study patients

A total of 84 of the 248 (33.9%) children had septicemia. A total of 18 different etiological agents were identified in this study. The most common causative agent of septicemia was *Staphylococcus epidermidis* (28.6%) followed by *S. aureus* and *E. coli* each at 13.1%. Others included *P. aeroginosa (*10.7%), *S. typhimurium (*8.3%), *S. hemolyticus* (4.8%) among others (Figure 1).

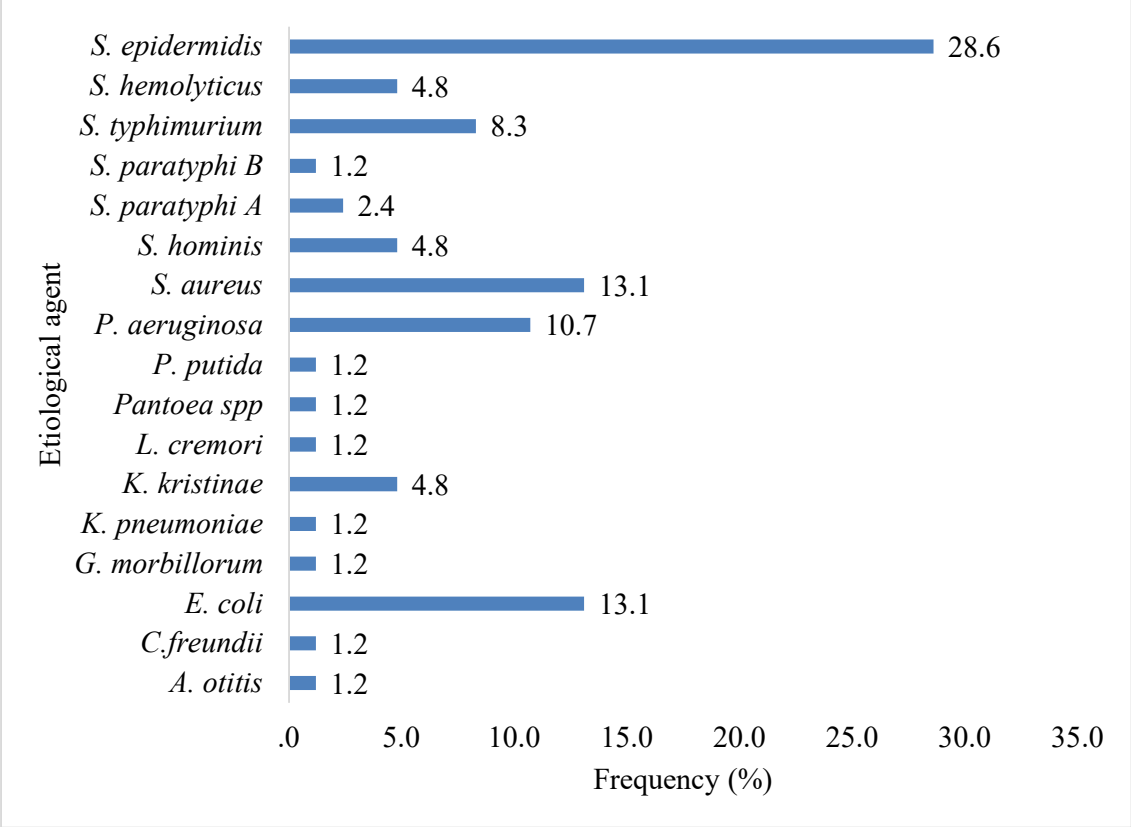

Figure 1: Frequency of etiological agents of septicemia among the study patients

Factors associated with bacteria septicemia among study patients

Table 2 summarizes the both bivariate and multivariate analysis of factors associated with septicemia infection among study patients. After adjusting for confounders; female were 70% less likely to be infected by septicemia compared to male patients (OR 0.7, 95% CI 0.4 – 0.9). Patients co-infected with malaria were less likely to be infected with septicemia compared to patients not co-infected with any other disease or condition (OR 0.2, 95% CI 0.05 – 0.9). Lastly, patients co-infected with gastrointestinal disorders were more likely to be infected with septicemia compared to patients not co-infected with any other disease or condition (OR 2.9, 95% CI 1.3 – 7.3).

Table 2. Unadjusted and adjusted factors associated with septicemia infection

Variables	Total	Sepicemia infection %	Bivariate uOR (95% CI)	Multivariate aOR (95% CI)
Locality				
Gembe	107	37.1	1.1 (0.7 - 1.7)	1.0 (0.7 - 1.6)
Lambwe	4	25	0.7(0.1 - 5.4)	0.7(0.09 - 5.3)
Mfangano	18	16.7	0.5(0.2 - 1.6)	0.4(0.1 - 1.4)
Rusinga	119	33.9	Referent	Referent
Gender				
Female	122	27.1	0.6(0.4-0.9)	0.7(0.4-0.9)
Male	126	40.5	Referent	Referent
HIV status				
Positive	20	50	1.5(0.8 - 2.9)	1.6(0.7 - 3.6)
Negative	228	32.5	Referent	Referent
Age (Months)				
1-12	76	32.9	0.8(0.3 - 2.4)	0.9(0.3 - 2.5)
13-24	72	30.6	0.8(0.3 - 2.2)	0.8(0.3 - 2.3)
25-36	27	51.8	1.2(0.4 - 3.9)	1.4(5 - 4.3)
37-48	43	37.2	0.9(0.3 - 2.7)	0.9(0.3 - 3.1)
49-60	20	15	0.4(0.08 - 1.7)	0.3(0.09 - 1.8)
>61	10	40	Referent	Referent
Temperature (^{O}C)				
36.5-37.5	11	54.6	1.9(0.8 - 4.8)	1.5(0.5 - 4.4)
>37.6	146	36.3	Referent	Referent
WBC (Cells/ml)				
<3500	2	0	ND	ND
3500-10500	11	36.4	1.1(0.4 - 3.1)	1.2(0.4 - 3.4)
10501	63	36.5	Referent	Referent
Respiratory rate (Breaths/min)				
20-30	177	37.1	1.3(0.5- 3.1)	1.4(0.5- 3.9)
31-40	37	18.4	0.6(0.2 - 1.9)	0.7(0.2 - 2.5)
41-50	11	41.7	1.4(0.4- 4.8)	1.4(0.4- 5.2)
>51	14	29.4	Referent	Referent
Heart rate (Beat/min)				
<70	3	66.7	2.1(0.5 - 8.9)	0.9(0.2 - 5.1)
80-120	150	31.3	0.9(0.6 - 1.6)	0.8(0.4 - 1.8)
>121	22	54.6	Referent	Referent
Co-infections				
Ear nose and throat infections	5	60	1.9(0.5 - 7.9)	0.7(0.1 - 4.3)
Gastrointestinal disorders	27	81.5	2.7(1.1 - 6.7)	2.9(1.3 - 7.3)
Hematologic diseases	31	32.3	1.1(0.4 - 2.9)	0.3(0.7 - 1.6)
HIV	2	100	3.3(0.7 - 16.5)	3.3(0.7 - 16.5)
Malaria	83	21.7	0.2(0.05 - 0.9)	0.2(0.04 - 0.9)
Malnutrition	9	22.2	0.2(0.03 - 1.6)	0.2(0.02 - 1.5)
Meningitis	9	0	ND	ND
Nervous system diseases	6	66.7	0.7(0.1 - 3.6)	0.5(0.09 - 3.2)
Respiratory Illnesses	33	36.4	0.4(0.08 - 1.6)	0.4(0.08 - 2.1)
None	20	30	Referent	Referent

OR -Odds ratio; CI – Confidence interval; % - Percentage; ND – Not done; u – Unadjusted OR; a – adjusted OR

Discussion

Epidemiological studies are essential in preventing and managing any disease/condition. This study, the first of its kind in Nyanza region is a buildup of growing need for data on septicemia infection among children given that just like in other developing nations, majority of babies here are born at home, and only visit hospitals mostly when the child's condition is critical. The lack of septicemia etiological data both from hospital and community

settings are numerous and include the lack of laboratory and culture facilities in most primary and secondary health facilities and rural areas, as well as delays in, and reluctance of families to seek care—resulting in most babies succumbing to serious infections within their homes without (Zaidi et al.,2009). This study is therefore critical given that sepsis survival depends on timely, appropriate, and optimal antibacterial treatment (Khilnani *et al.,*2008).

Prevalence of septicaemia

The prevalence of community acquired septicemia among the study patients was 33.9%. This prevalence was lower than that reported in Norway by Mehl *et al.,* (2017) who reported a prevalence of 39.4% of community acquired septicemia. The current prevalence was however higher than reports of other settings: In Paraguay, Guillén *et al.,* (2016) reported a prevalence of 20% of community acquired septicemia among children. In a prospective, multicenter, hospital-based study in Italy Azzari *et al.,* (2015) reported a diagnosis of sepsis in 5.3% of the children aged less than five years with fever. In Vietnam in a multi-centre point prevalence survey, Le *et al.,* (2016) reported a septicemia in 26.4% of pediatric admitted at the Vietnamese pediatric ICUs. In Zanzibar, pathogenic bacteria were recovered from the blood of 14% of the patients (Onken *et al.,*2015). In Lithuania, septicemia was diagnosed in 4% of all the patients in the pediatric ICU and was responsible for 32% of deaths (Bobelytė *et al.,*2017). In Western Cape region of South Africa, Buys *et al.,* 2016 reported a prevalence of 5% of community-acquired septicemia. Further, in Tygerberg Children's Hospital in Cape Town, South Africa, Dramowski *et al.,* (2015) reported a 6.6% prevalence of septicemia. Such variations could be attributed to heterogeneity of community set up in different regions.

Etiological agents causing septicaemia

The current study showed that *Staphylococcus epidermidis, E. coli* and *S. aureus* were the major etiology of septicemia among pediatrics in Mbita county hospital. Others included *P. aeruginosa*, *S. typhimurium*, *S. hemolyticus, K. kristinae, S. paratyphi A, S. paratyphi B, A. otitis, C. freundii, G. morbillorum, K. pneumonia, L. cremori, Pantoea spp, and P. putida.* This was different from those reported in other studies (e.g. Huynh *et al.,*2015) where the three most common isolates in neonatal sepsis were *Klebsiella, E. coli*, and *S. aureus*. In Kilifi District Hospital on the Kenyan coast Talbert *et al.,* (2010) reported Group A and Group B *Streptococcus, Streptococcus pneumoniae, Escherichia coli, Staphylococcus aureus, Klebsiella* spp., and *Acinetobacter* spp., *as the* commonest organisms causing sepsis. In South Africa Dramowski *et al.,* (2015) reported *K. pneumonia, S. aureus* and *E. coli* as the most prevalent etiology of septicemia. Evaluating bacteremia and invasive diseases in children aged less than five years with fever in Italy, Azzari *et al.,* (2015) reported *H. influenzae* and *S. pneumoniae* as the most frequently detected bacteria causing septicemia. At the pediatric intensive care unit of the Children's Hospital, an affiliate of Vilnius University Hospital Santariškių klinikos in Lithuania, Bobelytė, (2017) reported *N. meningitidis* and *Staphylococcus* spp causing sepsis. In Vietnam, a study evaluating the causative agent of septicemia showed *K. pneumoniae*, *P. aeruginosa, Acinetobacter baumannii*, and S. *aureus* were the major causes (Le *et al.,*2016). In Turkey Teke *et al.,* (2017) reported *Pseudomonas* spp as the major causative agent of septicemia in a tertiary paediatric hospital. In Pakistan, Mir *et al.,* (2011) reported *S. aureus* as the most common pathogens causing sepsis others pathogens included *Streptococcus pyogenes* (18%); Group B *beta-hemolytic streptococci* (10 %); *Pseudomonas* spp., (8.9 %); *Aeromonas* spp. (3.2%); and *Klebsiella* spp. (2%) in that order. The results of our study together with these others show that the epidemiology of pathogenic microbes causing septicemia is divergent (changing over the years), however, the incidence of Gram-negative organisms shows a marked increase in majority of the cases (Mu˜noz *et al.,*2008; Luzzaro *et al.,*2011). This realization calls for prompt and appropriate identification in order that appropriate management is instituted so as to eliminate mortality and morbidity.

Factors associated with septicemia infection

In this study, septicemia infection was influenced by gender with female being less likely to be infected by septicemia compared to male patients. Studies investigating the prevalence and role of the gender/age in the immuno-inflammatory responses provoked by septic events remains controversial (Drechsler *et al.,* 2012). Female gender (independent of age) was associated with lower risk for multi organ dysfunction syndrome and nosocomial infections (43% and 23%) after injury and hemorrhagic shock (Sperry *et al.,* 2008). Frink *et al.,* (2007) demonstrated a reduction of lower risk for multi organ dysfunction syndrome and sepsis incidence in females (predominantly premenopausal) compared to age-matched males. In contrast, Rappold *et al.,* (2002) reported no difference in gender and the incidence of sepsis and mortality. Nachtigall *et al*., (2011) on the other hand reported a 10% increase of mortality in septic women compared to septic men. Male and female patients demonstrate different sex steroid hormone responses to infection (Robert *et al.,* 2005). Drechsler *et al.,* (2009) observed high

estrogen levels in males and females with sepsis and septic shock. Nachtigall *et al.,* (2011) demonstrated that male patients had consistently lower testosterone levels than controls, and that postmenopausal female patients had higher estradiol levels than expected. Owing to the previously demonstrated immunosuppressive characteristics of androgens, several researchers have hypothesized that differences in sex steroid hormone concentrations in patients with sepsis might represent a mechanism by which male patients may have higher mortality in sepsis (Drechsler *et al.,* 2009).

Other underlying conditions and co-infections such as malaria and gastrointestinal disorders were associated with septicemia infection in our study. Paediatric studies on community- and hospital-acquired sepsis or bloodstream infection shows that the prevalence and etiology depend on the rates of underlying diseases. These underlying diseases vary depending on the population of each health-care facility and commonly include organ transplantation, preterm delivery, congenital heart disease, cancer, hydrocephaly, malnutrition, convulsive diseases, etc. (Stoesser *et al.,* 2011).

Although we did not show association between age and septicemia infection, existing reports show that the annual age and gender adjusted incidence of sepsis in the USA was 0.56/1000 in all pediatric cases, and the highest age-adjusted incidence was in infants (5.16/1000), which decreased to 0.20/100 in patients aged 10—14 years (Kaplan *et al.,* 2014). In a population-based study, 56 children were identified with gram negative bacteria caused sepsis, and the annual gender-adjusted incidence rate of gram-negative bacteria caused sepsis per 100,000 persons was 129.7 in infants; this rate significantly decreased to 14.6 and 7.6 in children aged 1-4 and 5-18 years, respectively (Al-Hasan *et al.,* 2011).

This study had some challenges and limitations including the cross-sectional nature of this study we were not able to provide a causal conclusion. This and other limitations notwithstanding, our findings provided the much-needed gathered facts about the burden of bacteremia among children <5 years of age with fever ≥39 °C seeking hospital care in Mbita – Suba County, a county currently faced with one of the highest prevalence of HIV in Kenya. Thirty-nine percent cases of septicemia among children with the aforementioned kind of fever were detected through cultural methods. Such an approach is imperative for the diagnosis of bacteremia and should be implemented among children represented by the study population. The proportion of children with septicemia in this region is likely an underestimation of what is expected in the entire population. This is because, not all patients at the hospital were included in the study.

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Competing interests

The authors declare no competing interests.

Authors' contributions

This work was part of Master of Science degree for GHS in infectious diseases of Kenyatta University. GHS, GG, YI and MK conceived the study. MON and EO participated in the laboratory assays while MON analyzed the data and prepared the draft manuscript. GHS, GG, YI and MK provided guidance and mentorship during the implementation of the study. All authors reviewed and approved the final manuscript.

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