BACTERIA AETIOLOGY, ANTIMICROBIAL SUSCEPTIBILITY AND OUTCOME OF CHILDRENAGED 2 MONTHS TO 15 YEARS WITH SEPSIS ADMITTED AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM.

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By

Evance K Godfrey

A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree of Master of Medicine (Paediatrics and Child Health) of

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled **‘‘Bacteria aetiology, antimicrobial susceptibility and outcome of children aged 2 months to 15years with sepsis admitted at Muhimbili National Hospital, Dar es salaam i**n (partial) fulfilment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Evance Kisheo Godfrey,** I declare that this **dissertation** is my original work and it has not been presented and shall not be presented to any other University for a similar or any other degree award.

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DEDICATION

This work is dedicated to my mum Catherine Shanua, my wife Epifania Shirima and my sons Ivan, John and Johnson.

ABSTRACT

Sepsis is defined as a systemic inflammatory host response syndrome (SIRS) to infection, commonly bacterial. The global prevalence of sepsis is 8.2% with a mortality rate of 25%, whilst in Tanzania the prevalence is 6.6%. Treatment of sepsis involves early initiation of antibiotics based on local sensitivity patterns. However, there is an increase in antimicrobial resistance to commonly used antibiotics, hence the need to learn the local susceptibility patterns so as to promote rational use of antibiotics.

Objective

To determine the bacteria aetiology, antimicrobial susceptibility and outcome of children aged 2 months to 15 years with sepsis admitted at Muhimbili National Hospital (MNH), Dar es Salaam.

Methodology

A hospital based cross sectional study was conducted at MNH, among 245 participants who were consecutively recruited. A standardized structured questionnaire was used to collect information, Blood cultures and complete blood counts were done. Antimicrobial susceptibility was done using disc diffusion method (Kirby-bauer) and sensitivity was based on clinical and laboratory standard institute system. Data were analyzed using SPSS version 20. Continuous variables were analyzed using mean, median, range and interquartile range while categorical variables using frequencies and proportions. Measure of association was done using Student's T test, for continuous variables whilst Chi square and Fisher's exact test was used for categorical variables. A P value of 0.05 or less was considered to be statistically significant.

Result

There was predominance of male study participant's 161/345 (67.5%) the median age was 2 years with interquatile range (IQR) 10 month – 4 years. Culture positive bacteria sepsis was 29.8%, common bacteria isolates were *S.aureus* (39.7%) *Coagulase Negative Staphylococcus* (CoNS) (35.6%) *E coli* (12.3%) *Klebsiella spp* (6.8%) *and Pseudomonas aeruginosa* (5.5%). All bacteria showed higher resistance to ampicillin (80%- 100%) followed by ceftriaxone (40 -

70%). All *Pseudomonas aeruginosa* were 100% resistant to ampicillin gentamycin and cefriaxone and were sensitive to amikacin. There was less than 40% resistance to amoxiclav, meropenem, ciprofloxacin, amikacin, and clindamycin. The overall mortality rate from sepsis was 9.4%. Among children discharged 59.3% had prolonged hospital stay of more than 7 days. Age group 1 to 5years, prior use of antibiotics, tachycardia, and leukocytosis were significantly associated with high mortality.

Conclusion

Bacterial sepsis is prevalent at Muhimbili National Hospital contributing to a high mortality of 9.4% and a prolonged hospital stay of more than 7 days in 59.3% of the children. In this study population gram positive bacteria were found to be predominant. Both groups of bacteria had a high resistance to first and second line antimicrobials including: ampicillin, gentamycin, and ceftriaxone.

Recommendations

Blood culture should be done once sepsis is suspected, and antimicrobial with good sensitivity pattern should be reserved for severe infection not responding to conventional antibiotics, children at risk of dying should be cared at intensive care unit.

LIST OF ACRONYMS

CoNS	Coagulase Negative Staphylococcal aureus
EMD	Emergency Medicine Department
ESBL	Extended Spectrum Beta Lactamase
IRB	Institutional Review Board
MIC	Minimal Inhibitory Concentration
MNH	Muhimbili National Hospital
MRSA	Methicilin Resistance Staphylococcal Aureus
MUAC	Mid Upper Arm Circumference
MUHAS	Muhimbili University of Health and Allied Science
NPC	New Pediatric Complex
NTS	Non Typhi Salmonella
POPC	Paediatric Overall Performance Category
SAM	Severe Acute Malnutrition
SIRS	Systemic Inflammatory Response Syndrome
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Sepsis: In this study bacteria sepsis was defined as any child presenting with fever/hypothermia and age specific tachycardia/bradycardia or tachypnoea/bradypnoea(1).

Minimum Inhibitory Concentration:

It is the lowest concentration of antibiotics required to inhibit visible growth of bacteria.

Susceptibility: This is where an infection due to an isolate may be appropriately treated with the dosage regimen of an antimicrobial agent recommended for that type of infection and infecting species with good response.

Resistant: Isolates are not inhibited by the usually achievable concentrations of the antimicrobial agent with normal dosage schedules.

Caregiver: Is a biological parent or close relative or guardian who is taking care of the child and able to provide written informed consent for the child.

Severe Acute Malnutrition (SAM): A child with a mid upper arm circumference (MUAC) of less than 11.5cm or weight for length Z score of less than -3SD with or without edema

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1.0 INTRODUCTION

1.1Background

Sepsis is defined as a life threatening organ dysfunction caused by a deregulated host response to infection (2). Systemic inflammatory host response (SIRS) is a widespread inflammatory host response to infection manifested by fever, and changes in heart rate or respiratory rate. Sepsis is also defined as SIRS with documented infection (3).

1.1.1 Epidemiology

According to Weiss *et al* in the sepsis prevalence and outcome study (SPROUT), the global prevalence of sepsis was found to be 8.2% with a 2 times higher prevalence in South America 16.3% and Asia 15.3%, whilst the prevalence was found to be 3 times higher in Africa (23.1%), Tanzania which is among the African countries, reported a prevalence of 6.6% in 2013 (4,5).

Globally, more than 5.8 million children die annually, 1.7 million occur in Asia,2.4 million in Western and Eastern Sub-Saharan Africa (6). Sepsis and sepsis related deaths account for more than 50% of these deaths (7). Comparatively, the hospital mortality rate due to sepsis is 25% in developed and developing countries (4). The burden is even higher in Tanzania, where every year 154,000 children die before reaching their 5^{th} birthday and 71% are due to sepsis related deaths (8). Therefore, towards attaining sustainable development goal number three, which aims at reducing under five mortality to 25 per 1000 children by 2030, efforts must be made to reduce sepsis related mortality which contributes to about 50% of all under five deaths (9).

1.1.2 Causes of Sepsis in Children

Sepsis can be caused by bacteria, fungi, virus and protozoa. Bacteria are the main cause of sepsis. The types of bacteria causing sepsis include: gram positive organism such as *Staphylococcal aureus, Streptococcal spp,* and gram negative bacteria which are *Klebsiella pneumoniae, E coli, Pseudomonas spp, H. influenza* and *Campylobacter spp* (5,10)

1.1.3 Sensitivity patterns

Antimicrobial susceptibility test is a method used by microbiologist to direct therapy based on minimum inhibitory concentration (MIC). MIC is lowest concentration of a drug required to inhibit visible growth of microorganisms after overnight incubation (12). Various methods have been used for sensitivity testing. In disc diffusion method bacterial inoculum of approximately 1–CFU/mL is applied to the surface of a large (150 mm diameter) Mueller-Hinton agar plate. A fixed concentration, paper antibiotic disks are placed on the inoculated agar surface. These are then incubated for 16–24 hours prior to determination of results. The zones of growth inhibition around each of the antibiotic disks are measured to the nearest millimeter. The diameter of the zone is related to the susceptibility of the isolate and to the diffusion rate of the drug through the agar medium. The zone diameters of each drug are interpreted using the criteria published by the Clinical and Laboratory Standards Institute (CLSI).Interpretation can be susceptible, resistant or intermediate resistant (13,14).

1.1.4 Treatment of sepsis

Early recognition of sepsis and initiation of antibiotics is important because a delay is associated with high mortality. Due to emergence of resistance, the choice of antimicrobials should be guided by local sensitivity pattern of microorganisms, as we need to start empirical treatment based on bacterial epidemiology and susceptibility pattern of antimicrobials prior to receiving laboratory confirmed results (15).

Due to seasonal variation of bacteria causing sepsis, emergence of multi-drug resistant bacteria and changes in antimicrobial susceptibility, this study aimed at assessing current trends of bacteria causing sepsis and antimicrobial susceptibility so as to build a current antimicrobial treatment protocol for sepsis in our setting.

1.2 Problem statement

Sepsis is still a leading cause of morbidity and mortality in Tanzania despite various interventions like exclusive breastfeeding, immunization, early detection of infections and treatment. Primary prevention of sepsis by immunization would be the ideal measure;

however, it is also difficult to have vaccine coverage for all bacterial isolates.

At MNH, we adopt the WHO guideline on antibiotic choice for treatment of sepsis. However, it is also suggested that antibiotic used should be according to the local epidemiology and sensitivity pattern of bacterial isolates. Locally, there is limited data on the epidemiology and sensitivity pattern of bacterial isolates in paediatric patients. This contributes to frequent changes in antibiotics which increase the burden on patients due to drug interaction, cost of buying new drugs and prolonged hospital stay.

Studies have shown that there is poor response to first line antibiotics and hence the need for paediatricians to shift to second and third line antibiotics, which could be due emergence of antibiotics resistance. Studies done at MNH amongst neonates with sepsis showed a high level of resistance to first line and second line antibiotics (16,17). This might reflect the same resistance pattern amongst older children with bacterial sepsis.

The ideal approach would be to utilize blood culture results as the gold standard for detection of sepsis and sensitivity patterns. However, result from blood culture can only be available within 48 hours. Due to the clinical severity of sepsis at presentation amongst admitted children, empirical treatment needs to be initiated.

1.3 Conceptual framework

Once a diagnosis of sepsis is made in settings where the local epidemiology pattern and susceptibility is unknown, it may lead to incorrect choice of antibiotics and subsequently progression to multiple organ failure (MOF) and death or prolonged hospital stay. In order to prevent this, we need to intervene by taking blood cultures and start antibiotics based on known local susceptibility patterns.

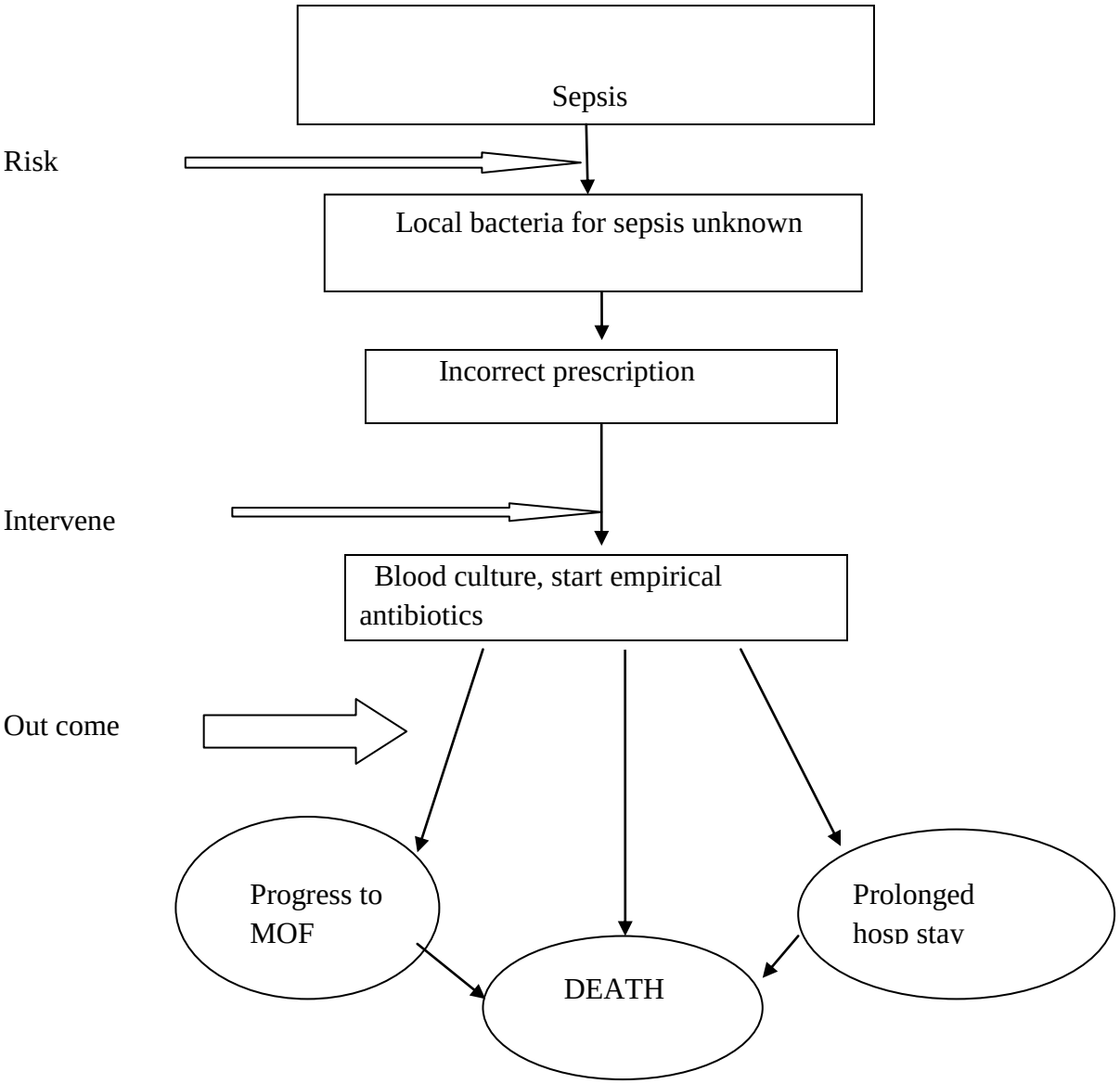

Figure 1: The conceptual framework of sepsis and its outcome

1.4 Rationale

The findings from this study will help to identify common bacterial isolates causing sepsis among children aged 2 months to 15 years admitted at MNH. The sensitivity patterns will also shed some light on the best antimicrobial combinations for empirical treatment of sepsis in children in our setting. This may help in reducing sepsis related morbidity and mortality and will also reduce the duration of hospital stay if children are treated early with the most appropriate antibiotics. The findings will also contribute to the revision of MNH paediatric guidelines on antibiotic choices for management of sepsis; hence lead to the reduction of frequent changes and irrational use of antibiotics.

1.5 Research questions

1 What are the common bacterial organisms causing sepsis in children admitted at MNH?

2 What is the sensitivity pattern of bacteria causing sepsis in children admitted at MNH?

3 What is the immediate outcome of treatment of children with sepsis admitted in MNH?

1.6 Objectives

1.6.1 Broad objective

To determine the bacterial aetiology, antimicrobial susceptibility, and immediate outcome of children aged 2 months to 15 years with sepsis admitted at Muhimbili National Hospital.

1.6.2 Specific objective

1 To identify common bacterial isolates causing sepsis in children aged 2 months to 15 year admitted at Muhimbili National Hospital.

2 To determine the sensitivity patterns of bacterial isolates causing sepsis in children aged 2 months to 15 years admitted at Muhimbili National Hospital.

3 To describe the immediate outcome of children aged 2 months to 15 years admitted with bacterial sepsis at Muhimbili National Hospital.

2.0 LITERATURE REVIEW

2.1 Pathogens causing bacterial sepsis in children

Pathogens causing bacteria sepsis in children aged 2 months to 15years are commonly gram positive organisms like *S pneumoniae*, *Staphylococcal aureus*, Methicillin resistant staphylococcal aureus MRSA and gram negative organisms like *E coli*, *Klebsiella spp*, *Pseudomonas spp, Neisseria meningitidis* and *Enterobactericeae* (12, 15). In developed countries including: United States of America (USA), Europe, Australia and New Zealand studies done between 2012 and 2014 showed the common bacterial isolates causing childhood sepsis are: *E coli, S aureus, Klebsiella spp* and *Pseudomonals spp*. However, few studies isolated other bacteria which are *Neisseria meningitides, Enterobacter spp, MRSA, Streptococcal pneumoniae* and *Group A streptoccal spp* (18–21).

In a meta analysis of studies done in Asia and sub-Saharan Africa in 2011, *Streptococcal pneumoniae* were the leading isolate in Sub-Saharan Africa while *Salmonella typhi* was the leading isolates in Asia, followed by *E coli, Klebsiella spp and S aureus* (12). Another study which was done five years later in 2016, in South East Asia, showing the leading bacterial isolates to be: *Ecoli, Klebsiella pneumoniae, S aureus.* Other isolates were *Acinobacter* and *Enterobacter spp S pneumoniae, Streptococcus suis* and *Beta Haemolytic Streptococcus* (22). Similarly in India, there was a predominance of gram negative bacteria with leading isolates such as *Klebsiella pneumoniae, Enterococcus*, and *E.coli* as well as gram positive *S aureus* (23). Likewise, in Africa, studies done in Malawi, Ethiopia, Nigeria, South Africa and Kenya between 2013 and 2017 revealed almost similar pattern of bacterial isolates with predominance of *S aureus, Coagulase Negative Staphylococcal, E coli, Klebsiella pneumoniae, and Pseudomonas species*. However, in the Malawi and Kenyan studies, isolates also included Non-Typhoid *Salmonella spp* and *Salmonella spp in* up to *83%* of the children with sepsis (24–28). In Northern and Eastern Tanzania, *E coli* and *Klebsiella pneumoniae* were the leading isolates found in studies done between 2013and2015. Other isolates found were *Citrobacter, Enterobacter, Proteus, Salmonella and S aureus*(5,29). Studies done in MNH between 2007 and 2012 similar organisms including: *Klebsiella, Salmonella, E coli, Enterococci and S aureus* were isolated. However, there was predominance of gram positive

bacteria in 2010, *whereby Coagulase Negative S aureus* was the predominant isolate found and which was highly prevalent in children with severe acute malnutrition in 2012 (5, 27,28–30,).

Evidence from these studies showed that *S aureus, E coli and Klebsiella pneumoniae* were the predominant isolates both in developed and developing countries, but there was also a high occurrence of *Salmonella spp* especially in developing countries.

2.2 Sensitivity pattern of pathogens causing bacterial sepsis in children

According to the WHO, there is a global increase in antimicrobial resistance among common bacteria causing sepsis in children with a high resistance to 3rd generation cephalosporins by *K pneumonia* and *E coli.* Similarly, a high level of Methicilin Resistance *Staphylococcal aureus* has been reported. There is also a reduction in susceptibility to penicillin by *S. pneumoniae*(10). In USA, Extended Spectrum Beta Lactamase (ESBL) producing bacteria were found to be susceptible to ceftriaxone, meropenem but less susceptible to ampicillin(33).

A systematic review of antibiotic resistance among gram negative bacteria in children with sepsis in resource limited countries in 2014 showed a high resistance of *Klebsiella pneumonia and E coli* to gentamycin and ceftriaxone between 50% and 100%; with 100% resistance to ampicillin both in Asia and Africa (34). Similarly in Mozambique, Malawi and Ethiopia, studies done between 1998 and 2017 found that isolated bacteria were resistant to ampicillin and gentamycin between 50 and 100%. Additionally *Klebsiella spp* and *Salmonella spp* were resistant to ceftriaxone with a linear increase in resistance from 2001 to 2006. This is contrary to a study from Nigeria in 2013 in which the isolated gram positive bacteria showed less than 30% resistance to amoxiclavulinic acid and gentamycin (25–27,35).

On the east coast of Tanzania, in a study done in Zanzibar, isolated bacteria were found to be resistance to third generation cephalosporins but sensitive to carbapenems. However, in Northern Tanzania, 80% of the bacteria isolated were resistant to ampicillin and gentamycin, but sensitive to ceftriaxone (5,29). Similarly, in our centre, at the MNH bacteria isolated in children with severe acute malnutrition(SAM) and children with no malnutrition were found to be resistant to penicillin and gentamycin up to 50%(30,31). In the study by Blomberg in 2007

at MNH, bacteria were isolated and were found to be 100% sensitive to vancomycin, meropenem and erythromycin (32).

Therefore, antimicrobial resistant patterns are variable by region, with some similarities but are also changing with time. These can be contributed by microbial related factors or prescription practices in the respective regions.

2.3 Outcome of children with sepsis

The primary outcome of children with sepsis is often categorized as either survival or progression to multiple organ failure and death. However, among the survivors, there may be impaired physical and mental function which can be measured by the paediatric overall performance category (POPC). POPC will depend on the duration of hospital stay among other factors (36). Though this has not been studied in detail and in this study it was not used.

In 2016 reported hospital mortality rate from childhood sepsis was 10% in USA, 17% in the United Kingdom and >50% in developing countries in 2016. In India specifically, mortality rate from childhood sepsis was found to be 32.7% (23). Similarly in 2017, in Tanzania, it was shown that hospital mortality of children with sepsis was 14.2% with a 1.5% deaths occurring at the Emergency Medicine Department even prior to admission in the paediatrics wards. Their median time to death was 3 days with a mean hospital duration of stay of 6 days (37). Likewise, in Australia, the median length of hospital stay of children with sepsis was reported to be 7 days (19).

3.0 METHODOLOGY

3.1 Study design

A hospital based cross sectional study with longitudinal follow up.

3.2 Study duration

The study was conducted over 7-month period from September 2018 to March2019

3.3 Study area

The study was conducted in paediatric wards located in new pediatric complex (NPC) at Muhimbili National Hospital. MNH is the National Referral and University Teaching Hospital with approximately 1500 beds capacity, and attending1,000 to 1200 outpatients per day and approximately 1200 admissions per week. The paediatric ward has a bed capacity of 127 with approximately 20 admissions per day. A mini survey done in one of the general paediatric wards between 2014 to 2015 reported a total of 1891 admissions, amongst which sepsis contributed to 26% of the reasons for admissions. The overall mortality rate in this ward was 4.2% and 59% of these deaths were due to sepsis. In the acute pediatric care unit, sepsis was found to contribute up to 72% of all the admissions and 44% of the deaths. In the malnutrition ward, the total number of admission in 2017 were 272 with an average of 1 admission per day

3.4 Study population

All children aged 2 months to 15 years admitted in the pediatrics wards during the study period from September 2018 to March 2019 were eligible.

3.4.1 Inclusion criteria

All children who met the criteria for sepsis(1) which included:

Axilla Temperature <36.5℃ or>39℃ or

Tachypnea Age specific respiratory rate from

2 to 11months ≥50/min

1year to 5years ≥ 40/min

>5 years 24/min

Children who were mechanically ventilated for an acute pulmonary process

Tachycardia or bradycardia with

Age specific pulse rate

2 months to <2 years <100 or >160b/m

2 to 10 years <60 or >90b/m

>10yrs <50 or >90b/min

Children admitted with severe acute malnutrition because children with SAM are presumed to have severe bacterial infection even without signs and symptoms like fever tachycardia/bradycardia or tachpynoea.

3.4.2 Exclusion criteria

Children whose parent/ caregiver declined to give consent

Children confirmed to have malignancy because they may have fever, leukocytosis or leukopenia as a natural history of their disease and not merely due to sepsis.

3.5 Sample size

Sample size was calculated from the following formula(38)

$$n = \frac{z^2 p(100-p)}{\varepsilon^2}$$

Where

z= level of confidence (1.96 for 95% confidence level)

p = expected proportion = 6.6% This is the estimated prevalence of culture positive sepsis in Tanzania according to study done by Christopher *et al* in Mwanza in 2013 (5)

ε = margin of error = 3.3%

n= (1.96x1.96x6.6x93.4)/10.89

n = 217

Addition of 10% non-response rate 22 children

217 +22= 239

Minimal sample size was estimated be 239 children

3.6 Sampling procedure

Study participants were enrolled consecutively until the required minimum sample size was attained.

3.7 Data collection

3.7.1 Demographic and clinical information

Demographic and clinical information were obtained by interviewing the caregiver and from the patient's case notes and laboratory results in their medical file. This information was documented in a standardized structured questionnaire. The participant's outcome was recorded as either discharge or death or prolonged hospital stay if she/he stayed for more than 7 days.

3.7.2 Anthropometric measurements

Length/height (cm), weight (kg) and mid-upper arm circumference (cm) were measured. The child's weight was taken with child in light clothing and shoes removed using a SECA® scale to the nearest 100 grams. Height for children >24 months and length for children ≤24 months or those unable to stand was measured to the nearest 0.1 centimeter using a portable stadiometer and length board respectively. The mid-upper arm circumference (MUAC) was measured using the World Health Organization (WHO) standard MUAC tape.

The mid-point of the upper arm between the shoulder and elbow was first identified. The MUAC was then measured with the arm extended and hanging alongside the body. Caution was taken to ensure that the MUAC tape neither pinched the body nor was it left loose. The measurement was read through a window to the nearest 0.1centimeter. The WHO standard growth charts published in 2016 were used to assess the nutritional status (39) and the data were recorded as severe acute malnutrition (SAM) if he/she meet criteria.

3.7.3 Blood culture

After location of the antecubital or femoral vein in some cases, the venopuncture site was cleaned with a cotton swab soaked in 70% alcohol (spirit) for a minimum of 30 seconds, Iodine solution (10% Povidone Iodine) was then applied for another 30 seconds in a concentric circle away from the puncture site covering a circular area. The puncture site was left to air dry for one minute before venopuncture to give time for complete disinfection. A sterile needle and syringe were used to draw 5 milliliters (mls) of blood. The protective flip top over cap of the sample collection bottle was removed, the rubber stopper was cleansed by a cotton swab soaked in 70% alcohol or iodine solution and allowed to dry for 1 minute before inoculation. The needle used to draw the blood from the vein was discarded, a new needle was fixed to the syringe outlet, then using the syringe markings as a guide for correct volume, 3mls of blood was inoculated in to the BacT/Alert PF (Pediatric) bottle, and the remaining 1 ml was put in a plain 5ml vacutainer for complete blood count and remaining 1 ml was taken for other blood investigation which includes renal and liver function tests and electrolyte if indicated.

The culture bottles were labeled with participants name, medical record number, date, and time of specimen collection. Care was taken not to cover the bottles barcode labels and lot numbers. Bottles were sent to the laboratory immediately, then sub cultured on MacConkey solid agar plate, blood and chocolate plate for 48hrs then readings was done, for those plates which grew microorganisms. Further tests were done which included: gram staining and biochemical testing to classify bacteria to species level. Blood cultures were regarded as negative if there was no bacteria growth after 72hours. Blood culture with the following bacteria growth were regarded as contaminants *Micrococcus spp, Corynebacteriumspp, Propionibacterium and Bacillus spp* (40).

3.7.4 Antimicrobial susceptibility test

This was done for first second and third line antibiotics used in treatment of sepsis in our setting as dictated by the Tanzanian national treatment guidelines. First line antimicrobial include: ampicillin and gentamycin whilst the second line antimicrobials include: ceftriaxone, vancomycin and amoxi clavulinic acid. The third line antimicrobial tested was meropenem. In addition, for cultures which isolated *Enterobactericiae spp* the following antibiotics were

added: amikacin 30µgm, ciprofloxacin 5µgm and piperacillin tazobactam 100µgm/10µgm whilst for *Staphylococcal spp* addition of erythromycin 15µgm and clindamycin 2µgm was done to meet the Clinical Laboratory Standard Institute (CSLI) guideline. Drug concentrations used included; Ampicillin 10µg, gentamicin 10µg ceftriaxone 30µg, vancomycin 30µg amoxi clavulinic acid 30µgm and meropenem 10µgm. Sensitivity was tested using disc diffusion method (Kirby- bauer) and sensitivity was based on the clinical and laboratory standard institute system (CLSI). The result was then recorded as sensitive or resistant, if the zone of growth inhibition was less than what was expected from the disc diffusion for the particular tested antimicrobial.

3.7.5 Complete blood count

A complete blood count was also performed using *Abbott Cell-Dyn 3700 Haematology analyzer*, (Abbott Diagnostics, USA), an automated analyzer that generates haematologic measurements including white blood cells, red blood cells, hemoglobin concentration, MCV and MCH from EDTA-anticoagulated whole blood. This was done to detect the presence of leukocytosis or leucopenia as sepsis marker.

3.7.6 Data collection tools

The following tools were used: 5 ml syringes for drawing blood samples, pediatrics blood culture bottles for storage and transportation of blood samples, clinical case notes for documentation, and structured questionnaires for collection of demographic and clinical information

3.8 Data analysis

Data cleaning was done to ensure quality and consistent, Data were then entered into the statistical package for social science (SPSS) version 20. For continuous variable mean, median, standard deviation and interquartile range were used. Student T test was used to compare means (SD) of data which were normally distributed and Mann-Whitney U test was used to compare medians (IQR) for skewed data. Categorical variable were summarized using frequencies and proportions. The differences in proportions were tested using Chi square test or Fisher's exact test. The respective 95% confidence intervals were determined and a p-value equal or less than 0.05 was considered statistically significant.

3.9 Ethical consideration

Ethical clearance was sought from the MUHAS Institution Review Board (IRB) and permission to conduct this study was obtained from Directorate of Research, Training and Consultancy at MNH. Caregivers were informed about the study, the importance of doing it, the procedures which will be done; if they understood and accepted to participate, they were requested to sign a written informed consent before enrollment. Children above 7 years were required to sign an assent form if they accepted to participate in the study and their caregivers concurrently signed a written consent form.

Strict confidentiality was maintained by use of a study identification number assigned to each participant. All children received the best standard of care offered at MNH regardless of whether they accepted to participate in the study or not**.** For those children whose blood culture showed bacteria growth, clinical assessment was done and those with good response were continued with the same prescribed antibiotics whilst those with poor response, antibiotics were changed according to the susceptibility result.

4.0 RESULTS

Flow diagram

A total of 1672 infants and children were admitted between September 2018 and March 2019. Of these 264 met the inclusion criteria. About a quarter 68 (25.8%) presented with SAM and whilst most 196 (74.2%) had SIRS. Of these participants, 8 deaths occurred before taking blood culture samples, because they were critical on admission and died during resuscitation. Three blood cultures grew *Micrococcus* and *Bacillus* considered to be contaminants and were discarded. Therefore only 245 samples were analyzed. (Figure2).

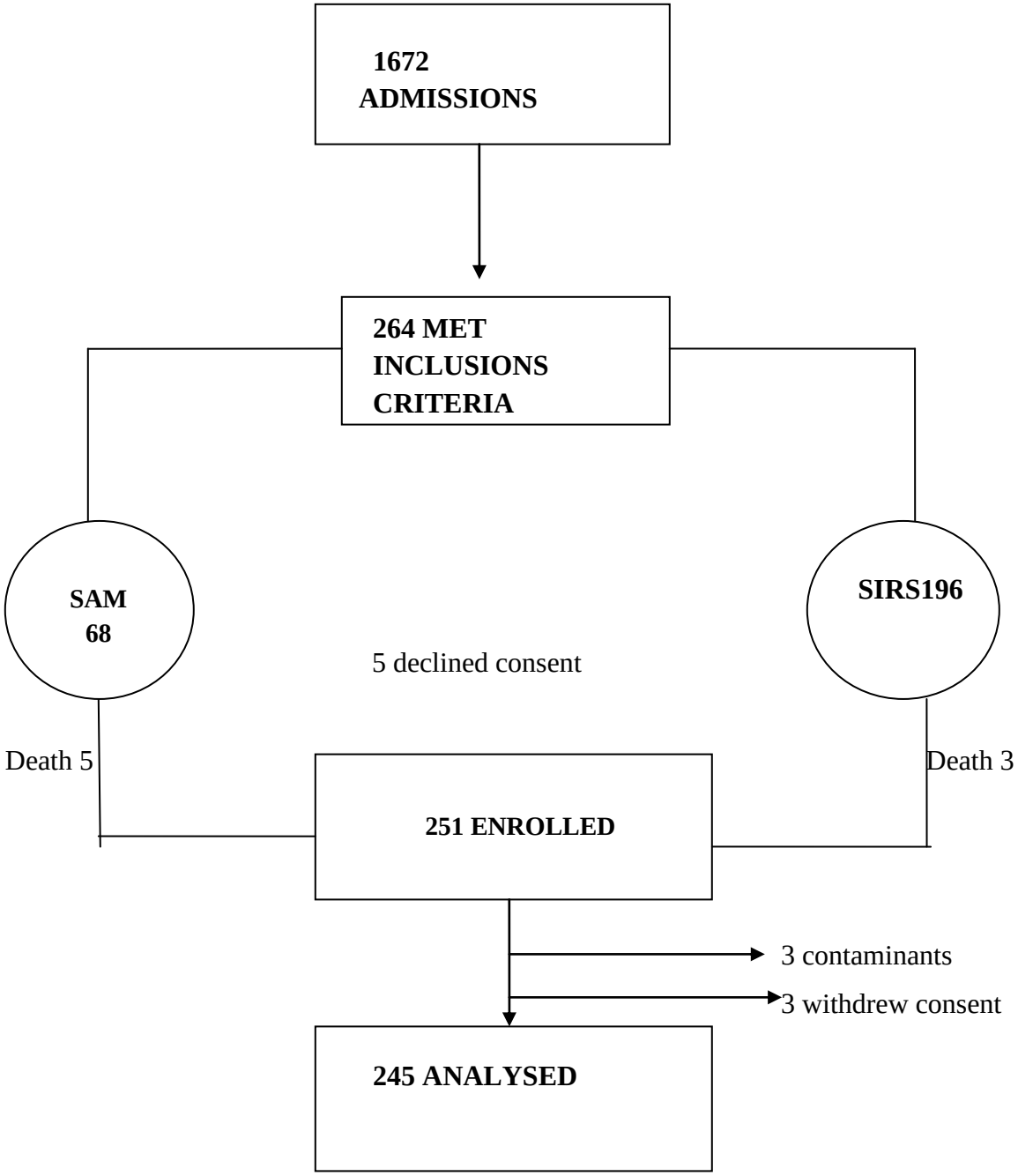

Figure 2: Flow diagram showing recruitment of study participants

4.1 Demographic and clinical characteristics of study participants

A total of 245 children met the inclusion criteria with 161 (65.7%) male predominance and 84 (34.3%) female. Majority of children (79.6%) were less than 5 years of age. The median age of these were 2 years with interquatile (IQR) 10 month to 4 years. Most children 92.6% were having temperature>39.c at presentation and 45.7% had leukocytosis. About half of children (44.5%) used antibiotics for more than 3 days prior (45.9%), commonly ceftriaxone (45.9%), the same antibiotics ceftriaxone (59.6%) was prescribed on admission. Few children 22.9% changed to another antibiotic during hospital stay. One hundred and ninety nine blood cultures were taken within 24 hours (Table no1).

Regarding the caregivers, most of the children were cared for by biological parents whose age ranged between 20 to 40 years (81.2%); with median age of 34 years and an IQR (28to 38years). Majority (92.7) were married with (52.7%) having primary level of education. Few (3.7%) attained university level of education, and (45.3%) were self employed as shown in table 2

Table 1: Demographic and clinical characteristics of children admitted at MNH (N=245)

Variable	Category	n (%)	Variable	Category	n (%)
Child age (years)			**White blood cells**	<4k/µl	31(12.7)
	<1	72(29.4)		4k-11k/µl	102(41.6)
	1-5	123(50.2)		>11k/µl	112(45.7)
	>5	50(20.4)			
	Median (IQR)	2(0.8,4)	**Antibiotic use, before**	Yes	109(44.5)
				No	136(55.5)
Child sex					
	Male	161(65.7)	**Antibiotic used**	Amoxicillin	3(2.7)
	Female	84(34.3)		Ampicillin	32(29.4)
				Gentamycin	32(29.4)
Temperature (^{o}C)	<36.5	11(4.5)		Ceftriaxone	50(45.9)
	36.5-38	7(2.9)		Amoxiclav	4(3.7)
	>39	227(92.6)		Ampiclox	12(11.0)
Respiratory rate(c/min)	<24	1(0.4)	**Duration for taking Antibiotic (hours)**	<24hrs	11(10.1)
	24-39	92(37.5)		24-72	48(44.0)
	40-49	92(37.5)		>72	50(45.9)
	50-59	34(13.9)			
	>60	26(10.6)	**Antibiotics used on admission**	Ampicillin	35(14.3)
				Gentamycin	28(11.4)
Pulse rate(b/m)	<60	3(1.2)		Ceftriaxone	146(59.6)
	60-120	4(1.6)		Amoxiclav	20(8.2)
	>120-160	130(53.1)		Meropenem	30(12.2)
	>160	108(44.1)		Others	18(7.3)
			Change in antibiotics	Yes	56(22.9)
				No	189(77.1)
			Blood culture 24hrs	Yes	199(81.2)
				No	46(18.8)

Table 2: Socio-demographic characteristics of parents/caregivers of children admitted at MNH

Variable	Category	N (%)
Informant		
	Parent	232(94.5)
	Caretaker	13(5.3)
Informant age (years)		
	<20	5(2.0)
	20-40	199(81.2)
	>40	41(16.7)
	Median (IQR)	34(28,38)
Informant sex		
	Male	22(9.0)
	Female	223(91.0)
Marital status		
	Single	3(1.2)
	Married	227(92.7)
	Widow	4(1.6)
	Divorced	11(4.5)
Level of education		
	No formal education	11(4.5)
	Primary education	129(52.7)
	Secondary education	59(24.1)
	College	37(15.1)
	University	9(3.7)
Occupation		
	Self employed	111(45.3)
	Employed	63(25.7)
	Unemployed	58(23.7)
	Peasant	13(5.3)

4.2 Blood culture result

The overall prevalence of culture positive sepsis among the participant was 29.8 % (73/245) as shown in Figure 2. Fifty one of the cultures positive were from male and 22(30.1%) were from female, and majority of blood culture positive were between 1 and 5 years , However, there was no significant association between child's age and sex with respect to blood culture results. Positive cultures were more likely to be found in children aged 1-5 years who were predominantly male, however, this difference was not found to be statistically significant as shown in Table 3.

About half of the bacterial isolates were gram positive 55(75.3%) with predominance of *S. aureus* 29 (39.7%), *Coagulase Negative Staphylococcus* (CoNS) 26 (35.6%); whilst the gram negative bacteria included: *E coli* 9(12.3%), *Klebsiella spp* 5(6.8%) *and Pseudomonas aeruginosa* 4 (5.5%). As shown in Figure 3. Table 4 shows the distribution of bacterial isolates causing sepsis in different age groups whereby *S aureus* and CoNS were more common in children aged 1 to 5 years, while *E coli* was predominant in children above 5 years and this was statistically significant with a p value 0.001.

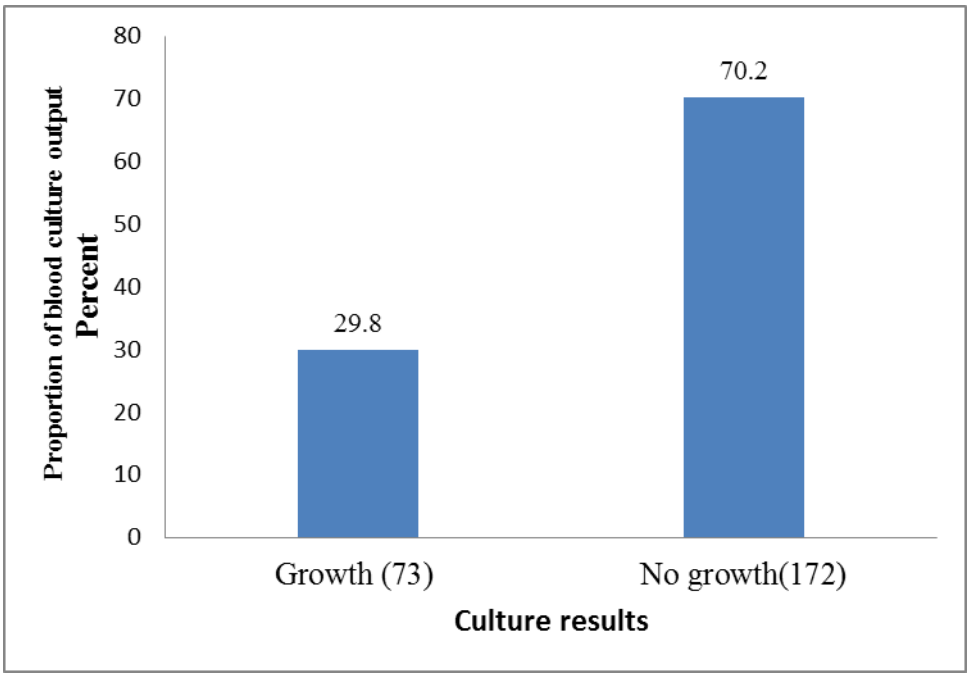

Figure 3: Blood culture results amongst children with sepsis admitted at MNH

Table 3: Blood culture results by demographic characteristics (N=245)

Variable	Culture results			
	Growth (N=73)	No growth(N=172)	Total (N=245)	P-value
Child Sex				
Male	51(69.9)	110(64.0)	161(67.5)	
Female	22(30.1)	62(36.0)	84(34.3)	**P=0.373**
Age in years				
<1	19(26.0)	53(30.8)	72(29.4)	
1-5	42(57.5)	81(47.1)	123(50.2)	**P=0.314**
>5	12(16.4)	38(22.1)	50(20.4)	

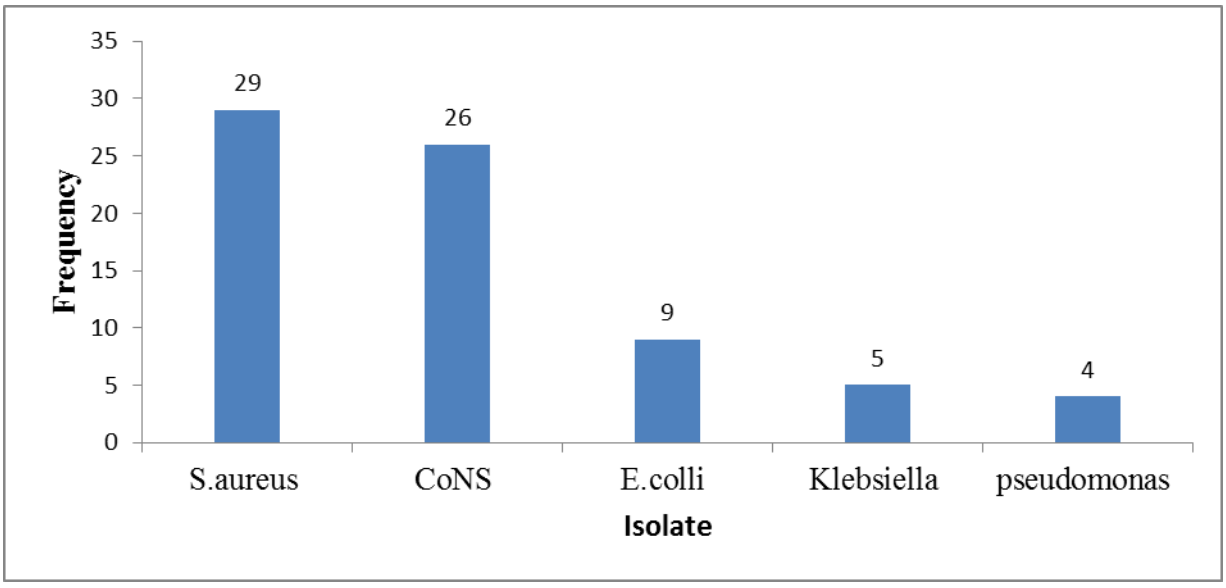

Figure 4: Common bacterial isolates causing sepsis in children aged 2 months to 15 year admitted at Muhimbili National Hospital

Table 4: Bacteria isolates by demographic characteristics (N=245)

Variable	Bacteria Isolated						P-value
	E coli	S aureus	Klebsiella	Cons	Pseudomonas	Total	
Child age (years)							
<1	0(0.0)	8(27.6)	2(40.0)	9(34.6	0(0.0)	19(26.0)	
1-5	3(33.3)	18(62.1)	1(20.0)	16(61.5)	4(100)	42(57.5)	****P=0.002**
>5	6(66.7)	3(10.3)	2(40.0)	1(3.9)	0(0.0)	12(16.4)	
Sex							
Male	7(77.8)	21(72.4)	3(60.0)	17(65.4)	3(75.0)	51(69.9)	
Female	2(22.2)	8(27.6)	2(40.0)	9(34.6)	1(25.0)	22(30.1)	***P=0.929**

*** Indicates that Fisher's exact test was used to determine the association**

**** indicates that Fisher's exact test was used to determine the association and the association was significant**

4.3 Antibiotics susceptibility pattern of bacteria isolates.

Resistance to antimicrobial agents amongst both gram positive and negative bacteria was ranging from 5% to 100% as shown in Table 5. There was a notably higher level of resistance to first line antibiotics such as ampicillin (80-100%) and second line antibiotics such as ceftriaxone (40-70%) among all bacterial isolates. The *S aureus* isolates in this study showed good sensitivity of about 80% and above to a clindamycin, meropenem, amoxiclav and ciprofloxacin but had a high resistance to ampicillin (83%), ceftriaxone (69%) erythromycin (62%) and vancomycin (44.8%). Similar findings were observed for CoNS which showed up to 96.2% of the bacterial isolates to be resistant to ampicillin 57.7% resistant to ceftriaxone, vancomycin and erythromycin. The CoNS had moderate susceptibility to gentamycin 61.5% ciprofloxacin 65.5% amoxclav77% and meropenem 69.2%, but were most sensitive to clindamycin (80.6%). Among the gram negative bacteria, *E coli* isolates were found to be 100% sensitive to amikacin and piperacillin-tazobactam but were resistant to gentamycin 22.2%, meropenem 33.3% amoxclav and ciprofloxacin 44.4%. On the other hand *Ecoli* illustrated a marked resistance to ceftriaxone 66.7% and ampicillin 89% respectively. Other gram negative bacteria such as *Klebsiella spp* also showed good response to meropenem

(80%), piperacillin-tazobactam (80%) and 100% sensitivity to amikacin. Like *E.coli*, the *Klebsiella spp* also had a similar resistance pattern of (80%) to ampicillin, 60% to amoxclav and gentamycin and 40% to ceftriaxone and ciprofloxacin respectively. All *Pseudomonas aeruginosa* isolates were resistant to ampicillin gentamycin and ceftriaxone and but 75% were sensitive to amikacin.

Table 5: Bacteria isolated and antimicrobial sensitivity pattern among children admitted at MNH.

Bacteria	**AMP S (%)**	**GEN S (%)**	**CEF S (%)**	**AM0 S (%)**	**VAN S (%)**	**CL S (%)**	**ME S (%)**	**TA S (%)**	**ER S (%)**	**CI S (%)**	**AM S (%)**	**N**
aureus	5 (17)	24 (82.8)	9 (31)	22 (75.9)	16 (55.2)	24 (82.8)	24 (82.8)	NA	11 (38)	22 (75.9)	NA	29
E coli	1 (11)	7 (77.8)	3 (33.3)	5 (55.6)	NA	NA	6 (66.7)	9 (100)	NA	5 (55.6)	9 (100)	9
Klebsiella	1 (20%)	2 (40)	3 (60)	2 (40)	NA	NA	4 (80)	4 (80)	NA	3 (60)	5 (100)	5
CoNS	1 (3.8)	16 (61.5)	11 (42.3)	20 (77)	11 (42.3)	21 (80.6)	18 (69.2)	NA	11 (42.3)	19 (65.5)	NA	26
Pseudomonas	0	0	0	1 (25)	NA	NA	1 (25)	1 (25)	NA	1 (25)	3 (75)	4

S Sensitive AMP Ampicillin GEN Gentamycin CEF Cefriaxone AMO Amoxiclav CL Clindamycin ME Meropenem TA Piperacillin Tazobactam ER Erythromycin CI Ciprofloxacin AM Amikacin NA Not applicable

4.4 Clinical outcome of study participants

The proportion of children dying from sepsis at MNH was 9.4% (Figure4). More deaths occurred in children aged between 1 and 5 years and the difference was found to be statistically significant (P= 0.035). It was also found that significantly more deaths occurred in children who had prior antibiotic use (73.9%) (P value 0.003), those presenting with a pulse rate of more than 160 beats/minute (p value 0.003) and those with leukocytosis of >11 (p value 0.002). Similarly, more deaths occurred in children found to be infected with *E coli* and CoNS bacteria however, this was not statistically significant (Table 6). Among the children who survived and were discharged home, 59.3% had prolonged hospital stay of more than 7days.

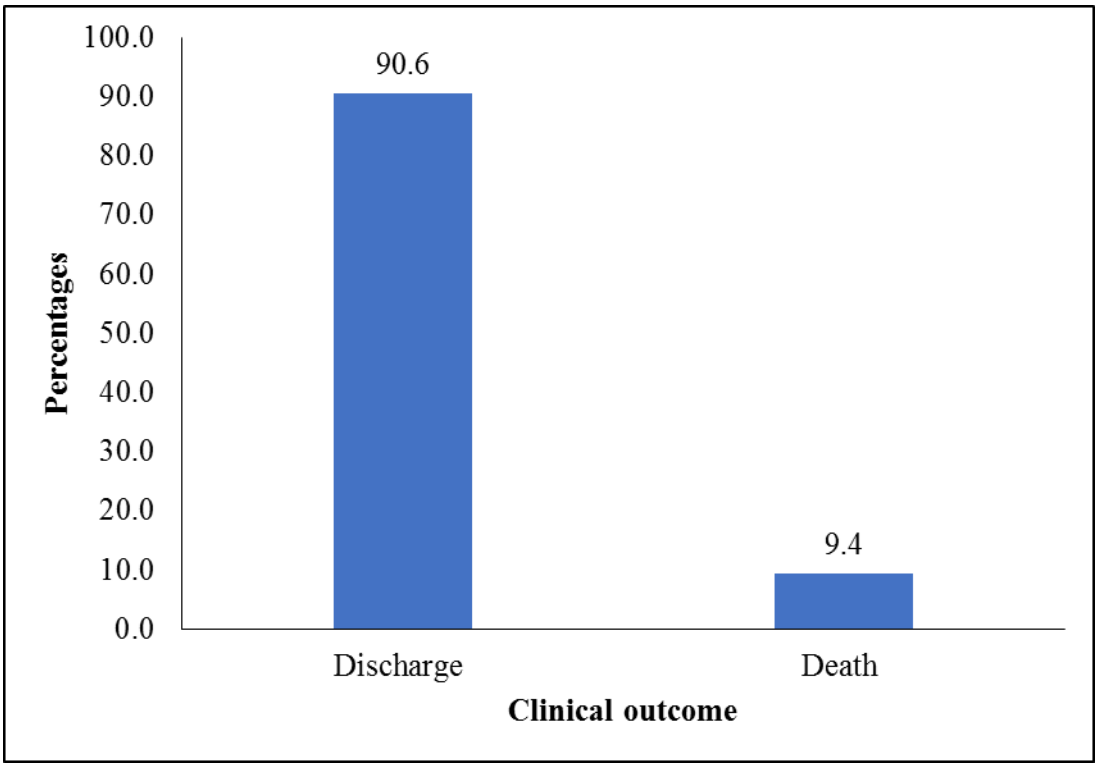

Figure 5: Clinical outcome of children aged 2months to 15years admitted with bacterial sepsis at Muhimbili National Hospital n=245

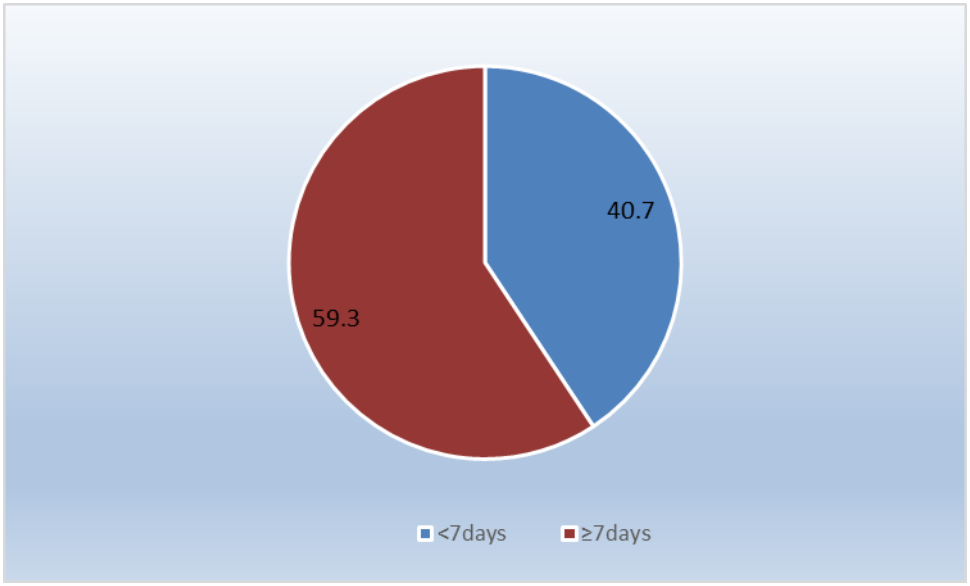

Figure 5 Duration of hospital stay among children with sepsis admitted at MNH N=222

Table 6: Clinical outcome and social demographic and clinical characteristics

Variable	Clinical outcome		
	Discharge (n=222)	Death (n=23)	P-value
Child age (years)			
<1	69(31.1)	3(13.0)	
1-5	112(50.4)	11(47.8)	**P= 0.039
>5	41(18.5)	9(39.1)	
Child Sex			
Male	147(66.2)	14(60.9)	X^2= 0.264
Female	75(33.8)	9(39.1)	P= 0.607
Bacterial Isolate			
S.aureus	27(43.6)	2(18.2)	
E.Colli	6(9.7)	3(27.3)	*P= 0.06
Klebsiella	4(6.4)	1(9.1)	
CoNS	23(37.1)	3(27.3)	
Pseudomonas	2(3.2)	2(18.2)	
Used Antibiotic before			
Yes	92(41.4)	17(73.9)	X^2= 8.898
No	130(58.6)	6(26.1)	**P= 0.003
Temperature C			
<36.5	8(3.6)	3(13.0)	
36.5-38	6(2.7)	1(4.3)	
>39	208(93.7)	19(82.6)	*P=0.081
Pulse rate b/m			
<60	1(0.5)	2(8.7)	
60-120	3(1.3)	1(4.4)	
>120-160	121(54.5)	9(39.1)	
>160	97(43.7)	11(47.8)	**P=0.017
Wbc			
<4k/µl	23(10.4)	8(34.8)	
4k-11k/µl	97(43.7)	5(21.7)	X^2 12.2647
>11k/µl	102(45.9)	10(43.5)	P=0.002
Change of Antibiotics			
Yes	48(21.6)	8(34.8)	X^2 2.0473
No	174(78.4)	15(65.2)	P=0.152

*** Indicates that Fisher's exact test was used to determine the association**

**** indicates that Fisher's exact test was used to determine the association and the association was significant**

5.0 DISCUSSION

The results of this study showed bacterial isolates in children with sepsis and their antimicrobial susceptibility pattern towards first, second and third line antibiotics used for treatment of sepsis at MNH.

5.1 Common bacteria causing sepsis in children at MNH

In this study culture positive bacteria sepsis was 29.8%. This finding is higher than what has been reported in Iran 9.1%, Ethiopia 18.2%, Kenya 6.4% and previous studies done in Tanzania and Zanzibar which has positive culture results in 6.6%-14% of the children. However, it is lower than blood culture yields reported in Nigeria 35% and Zimbabwe 37.1% respectively. These discrepancies can be due to: study design, difference in blood culture system, seasonal variation, varying levels of infection control methods and nature of participants selected (24–29,32,35,41,42).

In this study, the common bacteria isolated were *S aureus*, *E coli*, *Klebsiella spp*, and *Pseudomonas aeruginosa*. This was comparable to bacteria isolated in studies done in developed countries, although other bacteria like *Acinobacter*, *Neissseria meningitidis and Streptococcal pneumonia* predominated (18–21,31). Similarly, in a meta-analysis done in Africa in 2011, similar bacteria were isolated but there was predominance of *S pneumonia* isolates in children with *sepsis* (12). This difference in bacterial isolates can be due epidemiological and geographical distribution of bacteria, seasonal variation S*treptococcal pneumonia* were the leading isolates found in sub-Saharan countries in 2011 (12), however, there has been a decline in *S pneumonia* related sepsis since the introduction of the pneumococcal conjugate vaccine (PCV) globally (43) and in Tanzania since 2012 (44,45). The low prevalence of *Streptococcal* isolates could also be contributed by the prior use of antibiotics reported among 44.4% of the participants. The most commonly used antibiotics in our setting are the penicillin group which could either have been self-medicated or prescribed at lower level health facilities. In this study CoNS were the second common bacteria isolated contrary to studies in developed countries were no such isolates have been reported. Early in the 1970s CoNS were regarded as contaminants but several studies has reported an increased

incidence of CoNS in children with sepsis (17,25,26,30,31,42,46). In Ethiopia, it showed higher rate ranging from 26.1% to 43.3% similar higher rate was observed in Tanzania as it was the second common isolate between 2010 to 2012 compared to these findings (30,31). CoNS are common in children who are immunocompromised and those with advanced medical care such as mechanical ventilation and, central line catheterization. The isolation of CoNS among such patients reflects CoNS as a true pathogen and not a contaminant. In this study, some children underwent central line catheterization and about 27.8% had severe acute malnutrition which is state of immune suppression.

Notably, in this study there was a predominance of gram positive bacteria contrary to studies done in India, Kenya, Malawi and South Africa where gram negative bacteria predominated. In Tanzania, at MNH there has been a shift from gram negative to gram positive bacteria since 2007 (23,24,27,28,30–32). This can possibly be due to seasonal variation in patterns of organism causing sepsis or differences in the study population because these studies involved neonates who are normally infected by gram negative bacteria.

5.2 Antibiotic susceptibility pattern for bacteria isolates

There was an increased resistance to the commonly used antibiotics which are: ampicillin, ceftriaxone, vancomycin, erythromycin, amoxiclavullinic acid, gentamycin and ciprofloxacin. This was similar to what has been observed in several studies in developed and developing countries (5,12,21,27,32,34,47–49). However, there was less resistance to gentamycin and amoxiclav compared to a previous study in Bugando in Western Tanzania (5). The same resistance pattern has also been reported among neonates with sepsis admitted at MNH (16,17), implying that antibiotic resistance is a burden in all age groups.

There was notably an increase in resistance to ceftriaxone up to 50% compared to previous studies which reported up to 40% (30,32). This is possibly due to over prescription of the drug since more than 50% of the participants used ceftriaxone. This trend of increased resistance was also noted with meropenem whereby previous studies had reported a 100% sensitivity (29,32). There is increased prescription of meropenem, most children admitted at MNH have

already used cephalosporins. This provides the attending pediatricians with no choice than to use meropenem as a third line antimicrobial; with the consequence of increased resistance.

From this study ciprofloxacin showed good sensitivity to both gram positive and negative bacteria. Previously ciprofloxacin was not prescribed in children due to the fact that it cause arthropathy from animal studies however studies done in children showed it is reversible arthropathy (50). It has been recommended by WHO to use for septicemia non responding to other medication (51,52) From this study ciprofloxacin can be recommended as an alternative to non response to 1st and 2nd line antibiotics.

The *Staphylococcal spp* isolated showed good sensitivity to Clindamycin. This antimicrobial is rarely prescribed in our setting because it not a stock item. However it can be reserved for severe *Staphylococcal* infections which are not responding to the conventional antimicrobials stipulated in the MNH treatment guideline. On the contrary, *Pseudomonas aeruginosa* isolates showed a high resistant pattern to most antibiotics used at MNH. This could be because it is a common cause of a hospital acquired infection. Several studies have also reported an increase in antimicrobial resistance in children with hospital acquired infections (32,53–55). This poses a challenge on the choice of antimicrobials to treat sepsis.

5.3 Clinical outcome of children with sepsis admitted at MNH

The mortality rate from sepsis in this study was 9.4% which is lower than the rate documents in India 32.7% (23). It is equally lower than previous findings in Tanzania, from a 2018 unpublished report from Damian *et al* which showed an overall mortality from sepsis of 13.1% in 2018 which was lower than the rate reported in 2017 which showed a rate of 14.2% (37,56). There is significant decrease in childhood mortality due to sepsis from 14.2% in 2017 to 9.4% at MNH. The mortality rate reported in this study is higher than the average national mortality rate of 6.7% as reported by the Tanzania Demographic and Health Survey of 2015-16 (58), in this study there was high mortality compared to developed countries with mortality rate of 5.6% (20), The observed difference can be due to seasonal variation in the occurrence of sepsis. It can also reflect the level of care between developed and developing countries, whereby all children with sepsis were admitted in ICU in developed countries compared to

sub-Saharan countries. More than half of survivors had a prolonged hospital stay of > 7days contrary to a report from other studies which showed a hospital stay of 4 to 6 days (23,37). This can be due to the severity of sepsis at the time of admission leading to delayed discharge. It was observed that more deaths occurred in age between 1 to 5 years, those who have used antibiotics prior having tachycardia and leukocytosis possibly they had been sick for long time.

5.4 Strength of the study

The study employed the SIRS criteria for diagnosis of sepsis which is more accurate compared to the use of any fever as proxy to sepsis.

Children with severe acute malnutrition were also included in this study as a representative sub-population at high risk of sepsis and sepsis related complications, hence this enhanced culture yield as this group may be missed using SIRS criteria for sepsis.

5.5 Study limitation

1. Up to forty percent of the children referred to MNH were already on antibiotics; which could have resulted into culture negative sepsis and /or a low yield for some of the bacterial isolates.
2. This was a hospital based single centre study hence the result cannot be generalized

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Bacterial sepsis is prevalent at Muhimbili National Hospital contributing to a high mortality of 9.4% and a prolonged hospital stay of more than 7 days in 59.3% of the children. Gram positive and gram negative bacteria were isolated in children with sepsis. In this study population gram positive bacteria were found to be predominant. Both groups of bacteria had a high resistance to first and second line antimicrobials including: ampicillin, gentamycin, and ceftriaxone.

6.2 Recommendations

1 Antibiotics prescription for treatment of sepsis in children needs to be revised based on current sensitivity patterns and there is need for constant antimicrobial surveillance studies.

2. Antimicrobials with good sensitivity pattern like clindamycin and ciprofloxacin should be reserved for severe infections which do not respond to convectional antibiotics.
3. Children with sepsis aged between1 and 5 years presenting with prior antibiotics use, having tachycardia and leukocytosis should be considered critical and receive intensive care to reduce their risk of dying.

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APPENDICES

Appendix 1 English questionnaire

Aetiology, antimicrobial susceptibility and clinical outcome of children with sepsis admitted in the paediatric wards at MNH

Date …….. Study ID…….

(A) DEMOGRAPHIC CHARACTERISTICS

1. Age of the child? ……
2. Gender of the child (a) M (b) F
3. Who is taking care of the child? (a) Biological Parents……. (b) Others ……
4. Age of caregiver ……..
5. Gender of caregiver (a) M (b) F
6. Marital status…….. (a) Single
   (b) Married
   (c) Cohabiting
   (d) Widow
   (e) Divorce
7. Level of education……

(a) No formal education
   (b) Primary
   (c) Secondary
   (d) College
   (d) University level

8. Occupation of caregiver.
   (a) Self employed
   (b) Employed
   (c) Unemployed
   (d) Peasant

B Clinical characteristics

9. Temperature…..(a)<36.5 (b)37.5-38 (c) >38.5

10. Respiratory rate…(a)< 24 (b) 24- 39 (c) 40-49 (d) 50-59 (e)≥60

11. Pulse rate ……(a) < 60b/min (b)60-120 (c) >120-160 (e) > 160

12. Nutritional status weight …… length …… MUAC ….(A) SAM (b) normal

13. FBP findings WBC (a)<4k/µl (b)>4 -11 k/µl (c)>11k/µ

14.Was the child use antibiotics prior? (a) Yes (b) No

15 If yes, mention the antibiotics used …..(a) Amoxicillin (b) Ampicillin (c) Gentamycin (d) (e) Ceftriaxone (f) Amoxiclav (g) others……

16 How long has she/he been on antibiotics?……(a)≤ 24hrs (b) 24 -≤72HRS (c)72hrs

17 Antibiotics prescribed on admission day ……, (a) Ampicillin (b) Gentamycin (c) Ceftriaxone (d) Amoxiclav (e) Meropenem (f) Others……..

18. Was there any change in antibiotics during hospital stay at MNH? (a)Yes …. (b)No

19. When was the blood culture taken? (a) Within 24hrs or (b) 48hrs(C) Not taken

20. Result of the blood culture……(a)*S aureus* (b)*E coli* (c)*Klebsiella* (d)MRSA(e) Others…….,……..

21. Sensitivity pattern …… refer to table No1

22. Clinical outcomes …….(a) Discharge (b) Death

23. Duration of hospital stay before discharge … (a) ≤7days (b) >7days

24. Duration of hospital stay before death …….(a) <24hrs (b)24 to 72hrs (c) >72hrs

Table 1 Types of bacteria isolated and their antibiotic susceptibility patterns

Antibiotics	**E coli**	**Saureus**	**Klebsiella**	**CoNS**	**MRSA**	**Acinobacter**	**Others**
Ampicillin							
Gentamycin							
Ceftriaxone							
Amoxclav							
Meropenem							
Clindamycin							
Ciprofloxacin							
Erythromycin							
PTazobactam							
Vancomycin							
Amikacin							

Appendix 2 Dodoso ya kiswahili

Kichwa cha habari. Bakteria wanaosababisha maambukizi kwenye damu, antibiotiki zinazoweza kuwakabili na matokeo ya matibabu kwa watoto wanaotibiwa Hospitali yaTaifa Muhimbili

Tarehe…….. Number ya dodoso……..

1 Umri wa mtoto…….

2 Jinsia …….. (a) kiume (b) kike

3 Nani anamhudumia mtoto..(a) Mzazi (b) Mlezi

4 Umri wa mlezi/mzazi …….

5 Jinsia…….. (a)Me (b) ke

6 Hali ya ndoa……. (a) Sijaolewa

(b) Nimeoa/olewa

(c) Tunaishiwote

(d) Mjane

(e) Nimeachika

7 Kiwango cha elimu… (a) Sijasoma

b) Elimu ya msingi

(c) Sekondari

(d) Chuo

(e) Chuo kikuu

8 Kazi ……(a) Mjasiriamali

(b) Nimeajiriwa

(c) Sinakazi

(d) Mkulima

Appendix 3 Consent form

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES (MUHAS)

An informed consent form for a study on aetiology antimicrobial susceptibility and outcome of children with sepsis admitted at Muhimbili National Hospital

INTRODUCTION

My name is Dr. Evance Godfrey a resident at Muhimbili University of Health and Allied Sciences, Dar es Salaam. I'm doing a research on bacterial aetiology, antimicrobial susceptibility and outcome of sepsis in children admitted at MNH. I am going to give you information and invite you to be part of this research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. If you have questions, please ask me or the doctor/nurse.

Purpose of the research

The purpose of this research is to determine bacterial aetiology antimicrobial susceptibility and clinical outcome of children admitted at MNH with sepsis, so as to know the best antibiotics to use during management of bacterial sepsis in children before blood culture result are out. This will help in reducing morbidity and risk of mortality due to sepsis.

What does participation involves?

This research will involve a questionnaire which will assess the child if she/he qualifies to be enrolled in to the study. You sign this consent form and answer the questions in the questionnaire as well as you can. It will take approximately 3 minutes.

We are inviting all children together with parents/caregivers who admitted to MNH to participate.

Your participation in this research is entirely voluntary. Whether you choose to participate or not, all the services you receive at this hospital will continue and nothing will change. You may change your mind later and stop participating even if you agreed earlier.

CONFIDENTIALITY

Information about you that will be collected during the research will be kept confidential and only the researchers will be able to see it. We will not be sharing the identity of those participating in the research. We will disclose blood culture result to you and the attending pediatrician so that he/she can prescribe antibiotics to which the microorganisms are sensitive to.

RISKS

By participating in this research you will serious harm only minor pain during blood collection

BENEFITS

This will help us to t review the guideline of treatment of sepsis

CERTIFICATE OF CONSENT

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions and any questions that I have asked have been answered to my satisfaction. I voluntarily give consent for my child to participate as a participant in this research.

Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If A CAREGIVER IS ILLITERATE

A literate witness must sign (if possible, this person should be selected by the participant and should have no connection with the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the participant has had the opportunity to ask questions. I confirm that the participant has given consent freely.

Name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

Appendix 4 Fomu ya ridhaa kwa mzazi

Namba ya utambulisho----------

KICHWA CHA HABARI: UTAFITI KUHUSU BAKTERIA WANAOSABABISHA MAAMBUKI KWENYE DAMU, ANTIBIOTIKI ZINAZOWEZA KUWAKABILI NA MATOKEO YA MATIBABU KWA WATOTO WANAOTIBIWA HOSPITALI YA TAIFA MUHIMBILI.

Utangulizi:

Habari, naitwaDkrEvance K Godfrey, mwanafunzi wa shahada ya uzamili ya udaktari wa watoto katika Chuo cha Sayansi Shirikishi cha Muhimbili.

Tunafanya Utafiti kuangalia aina ya bacteria wanaosababisha maambukizi kwenye damu, antibiotiki zinazoweza kuwakabili na matokeo ya matibabu kwa watoto wanaotibiwa hospitali ya taifa Muhimbili. Nitakupa maelezo na kukualika kushiriki katika Utafiti huu, kabla ya kuamua unaweza kuongea na mtu yeyote kupata maelezo ya kutosha, kama kuna maneno hujaelewa vizuri unaweza kumwuliza daktari au muuguzi yeyote.

Lengo la huu utafiti Lengo lake nikutambua aina ya bacteria wanaosababisha maambukizi kwenye damu, antibiotiki zinazoweza kuwakabili na matokeo ya matibabu kwa watoto wanotibiwa Hospitali ya Taifa Muhimbili. Hii itasaidia kujua antibiotic nzuri itakayoweza kuwatibu watoto wenye maambukizi kabla ya kupata majibu ya damu ya kuotesha, na itasaidia kupunguza matumizi yasiyo sahihi ya antibiotiki.

Kushirikikutahusishanini:

Kama unakubali mwanao ashiriki katika Utafiti huu, tutakuuliza maswali kuhusu mwanao nafamiliayako. Mwanao atafanyiwa uchunguzi wa kumpima joto la mwili, hali ya upumuaji na kuchukuliwa vipimo vya damu ya kuotesha ambayo ni sehemu ya matibabu anayostahili,

Kushiriki kwako ni kwa hiari na mwanao atapata huduma zote stahiki hata kama hutashiriki kwenye utafiti, pia kama baadae ukiamua kujitoa kwenye Utafiti mwanao ataendelea kuhudumiwa vilevile.

Usiri wa taarifa: Taarifa zote zitakazopatikana katika Utafiti huu zitabaki kuwa ni siri. Tutatumia namba ya hospitali na namba ya utambulisho ya Utafiti kwaajili yakuwatambua washiriki wa utafiti, hakuna majina yatakayotumika katika Utafiti huu au katika machapisho yoyote ya kiutafiti yatakayotokana na Utafiti huu hapo baadaye. Majina yataonekana kwenye hii fomu ya ridhaa tu, ambayo itatunzwa na mtafiti, mbali na fomu nyingine za washiriki.
Majibu ya damu ya kuotesha yakiwa tayari tutamtaarifu daktari wako na wewe ili kuweza kubadilisha antibiotiki kama itaonekana inafaa zaidi

Madhara ya kushiriki

Kwakushiriki kwenye Utafiti huu hautapata madhara yeyote.

Je, nitalipwa kwakushiki? Kushiki kwenye Utafiti ni hiari. Hakutakuwa na malipo kwakushiki kwako kwenye utafiti. Pia hautahitajika kulipia chochote ili mwanao ashiriki katika utafiti

Tamko la ridhaa

Mimi …… nimesoma yaliyomo kwenye hii fomu ya ridhaa, au nimesomewa yaliyomo kwenye hii fomu ya ridhaa. Maswali yangu yote yamejibiwa na nimepewa nakala ya hii fomu ya ridhaa. Ninakubali kwa hiari yangu mwenyewe kuruhusu mwanagu ashiriki katika Utafiti huu

Saini ya mzami/mlezi ……. Tarehe: …….

Tamko la shahidiwamzazi/mleziasiyejuakusoma au kuandika

Mimi……nimeshuhudia mzazi/mlezi wa mtoto akisomewa fomu hii ya ridhaa kwa usahihi. Mzazi/mlezi wa mtoto alipata nafasi ya kuuliza maswali ambayo yote yalijibiwa. Ninathibitisha kuwamzazi/mlezi wa motto ameruhusu kwa hiari yake mwanae ashiriki katika utafiti.

Saini ya shahidi …….……. Tarehe:…….

Dole gumba la mzazi/mlezi

Appendix 5 Assent form in English

Title: A**etiology, antimicrobial susceptibility and clinical outcome of children with sepsis admitted at MNH**

Hello, I am Evance Godfrey, a resident in Paediatrics and Child Health conducting a research on aetiology, antimicrobial susceptibility and clinical outcome of sepsis children admitted at MNH

A research is a way to learn about people and if you decide you want to be a part of this study, you and/or your caregiver will be asked a few questions. You may also need to undergo some blood investigations. If you do not want to be in this research study, you will continue to receive the treatment and care you will need.

The reports and documents will not have your identity on it and whatever information you give us will be kept confidential.

You do not have to be in this study if you do not want to. If you decide to stop after we begin, that's okay too.

If you decide you want to be in this study, please sign your name.

I, ---------- want to be in this research study.

---------- ----------

Sign your name here Date

Appendix 6: Fomu ya ridhaa kwa mtoto

Namba ya utambulisho----------

KICHWA CHA HABARI. BAKTERIA WANAOSABABISHA MAAMBUKIZI KWENYE DAMU, ANTIBIOTIKI ZINAZOWEZA KUWAKABILI NA MATOKEO YA MATIBABU KWA WATOTO WANAOTIBIWA HOSPITALI YA TAIFA MUHIMBILI.

Habari, naitwa Dkr Evance K Godfrey, mwanafunzi wa shahada ya uzamili ya udaktari wa watoto katika Chuo cha Sayansi Shirikishi cha Muhimbili.

Tunafanya Utafiti kuangalia aina ya bakteria wanaosababisha maambukizi kwenye damu, antibiotiki zinazoweza kuwakabili na matokeo ya matibabu kwa watoto wanotibiwa hospitali ya taifa muhimbili. Nitakupa maelezo na kukualika kushiriki katika utafiti huu, kabla ya kuamua unaweza kuongea na mtu yeyote kupata maelezo ya kutosha, kama kuna maneno hujaelewa vizuri unaweza kumwuliza daktari au muuguzi yeyote.

Utafiti ni njia ya kujifunza juu ya watu na ikiwa unaamua unataka kuwa sehemu ya utafiti huu, wewe na/au mlezi wako ataulizwa maswali machache. Unaweza pia kuhitaji vipimo vya damu kuotesha bacteria na kuangalia dawa ambayo inaweza kuwakabili hao bacteria watakaoota

Ikiwa hutaki kuwa katika utafiti huu, utaendelea kupata matibabu na huduma unayohitaji. Ripoti na nyaraka hazitakuwa na utambulisho wako juu yake na taarifa yoyote unayoyotoa itachukuliwa siri. Huna lazima kuwa katika utafiti huu ikiwa hutaki. Ikiwa utaamua kuacha baada ya kuanza, hiyo ni sawa pia.

Ikiwa unaamua unataka kuwa katika utafiti huu tafadhali saini jina lako.

Mimi, ---------- nataka kuwa katika utafiti huu.

---------- ----------

Andika jina lako hapa Tarehe