ANTIMICROBIAL PRESCRIPTION PRACTICES AND MORTALITY IN NEONATES ADMITTED WITH SUSPECTED NEONATAL SEPSIS AT THE MBOPPI AND BONABERI BAPTIST HOSPITALS, DOUALA, CAMEROON. A CROSS-SECTIONAL DESCRPTIVE STUDY

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Declaration

This dissertation research is my original work and has not been presented for the award of a degree in any other university.

Signature:  **Date:**20th January 2023....

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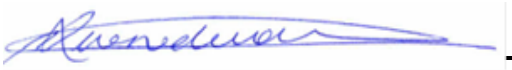
SUPERVISORS' APPROVAL

This dissertation proposal has been presented with our full approval as supervisors:

Signature:  **Date:**20th January 2023

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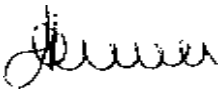
Signature:  **Date:**20th January 2023

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To my family thank you for all the support.

Dedication

To God almighty who made it possible

I dedicate this work to my dad and husband who have supported me all along the way.

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Abbreviations

BBH: Bonaberi Baptist Hospital

CRP: C Reactive Protein

CSF: Cerebrospinal

CPAP: Continuous Positive Airway Pressure

EONS: Early Onset Neonatal Sepsis

GBS: Group B Streptococcus

LBW: Low Birth Weight

LONS: Late Onset Neonatal Sepsis

MBH: Mboppi Baptist Hospital

MDG: Millennium Development Goals

NBU: New Born Unit

NICU: Neonatal Intensive Care Unit

SDG: Sustainable Development Goals

WHO: World Health Organization

Case Definitions and Operational Terms

1. **Antimicrobial resistance**: Resistance of a microorganism to an antimicrobial drug that was initially effective for treatment of infections caused by it.
2. **Apnoea**: Cessation of breathing for more than 20 seconds accompanied by bradycardia.
3. **Appropriate antimicrobial prescription**: selection of a targeted spectrum antibiotic, as well as the right dose, route of administration, frequency and duration.
4. **At-Risk Neonates**: Neonate born that have perinatal risk factors.
5. **Early Onset Neonatal Sepsis**: A clinical syndrome of bacteraemia with systemic signs and symptoms of infection in the first 72 hours of life
6. **Empirical Antibiotic Therapy**: The early and appropriate initiation of antimicrobial agents in high- risk neonates before the result of blood culture susceptibility is defined as "empirical antibiotic therapy."
7. **Late Onset Neonatal Sepsis**: An infection occurring at more than 72 hours of age after birth.
8. **Neonate**: An individual of age between 0 days to 28 days.
9. **Neonatal Sepsis**: Clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteraemia in a neonate.
10. **Proven Sepsis**: A positive blood, CSF or urine culture in the presence of clinical signs and symptoms of infection.
11. **Probable Sepsis**: Presence of signs and symptoms of infection and at least two abnormal haematological findings when blood culture is negative.
12. **Possible Sepsis**: Presence of clinical signs and symptoms of infection plus raised CRP level when blood culture is negative
13. **Preterm**: Neonate delivered before 37 weeks gestation.
14. **Tachypnoea**: It is a respiratory rate $\geq$ 60 breaths/minute in neonates.
15. **Term New-Born**: A baby born after 37 completed weeks of gestation.

Abstract

Background

Neonatal sepsis is a significant contributor to morbidity and mortality globally. Neonates usually present with nonspecific signs, hence requires a high index of suspicion (1). For this reason, clinicians start empiric antibiotics in an attempt to improve outcomes. This has led to the misuse of antibiotics and under treatment in some cases of neonates with neonatal sepsis. Cameroon's neonatal mortality rate is 26.2/1000 live births, with neonatal sepsis contributing 1/3rd to this mortality, no information exists on current practices in early-onset neonatal sepsis. These guidelines are non-existent, hence the need for our study.

Objective:

Our study's primary objective was to determine the proportion of neonates with EONS having appropriate antibiotic prescriptions at admission at two hospitals. As secondary objectives, we evaluated risk factors associated with appropriate prescription, Described the pattern of antimicrobial prescription based on the WHO classification of antimicrobials (AWaRe) and to Determine the in-hospital mortality in EONS.

Study Design

This was a cross-sectional descriptive study carried out at two hospitals: Mboppi and Bonaberi Baptist Hospitals in Cameroon from October 2021-febuary 2022.

Methodology

All records of neonates hospitalized during the study period were reviewed, an exit interview of mothers in postnatal and pediatric wards was undertaken, and those eligible for the study identified. Consent was obtained, and the neonate was enrolled in the study. Study identity number, age, sex, gestational age and birth weight were all noted in the demographic data. Data was extracted from patient files using a data abstraction tool. The participants were then monitored for 5 days to see any changes in the antibiotic. Results were recorded as alive or dead on the seventh day.

Data analysis

Data was cleaned and entered into an excel spreadsheet and transferred to SPSS version 22 for all statistical analysis**.**

Results

33% of neonates had appropriate antimicrobial prescription on admission, the odds of getting an appropriate prescription were 1.5 higher in those who had chorioamnionitis .20% of neonates had been prescribed antibiotics in the reserve group and the in-hospital case fatality was 12%.

Chapter 1: Introduction

1.1 Global Burden of neonatal mortality.

Worldwide, neonatal mortality contributes significantly to under five mortality. Sub-Saharan Africa and Asia have the highest-burden of neonatal mortality with over 90% of all new born deaths and neonatal mortality rates ranging from 40 death per 1000 live births to 18 deaths per 1000 life birth (1). Three quarters of all new born deaths occurs within the first seven days and about 1/3rd dying within first 24 hours of a neonate"s life (2)

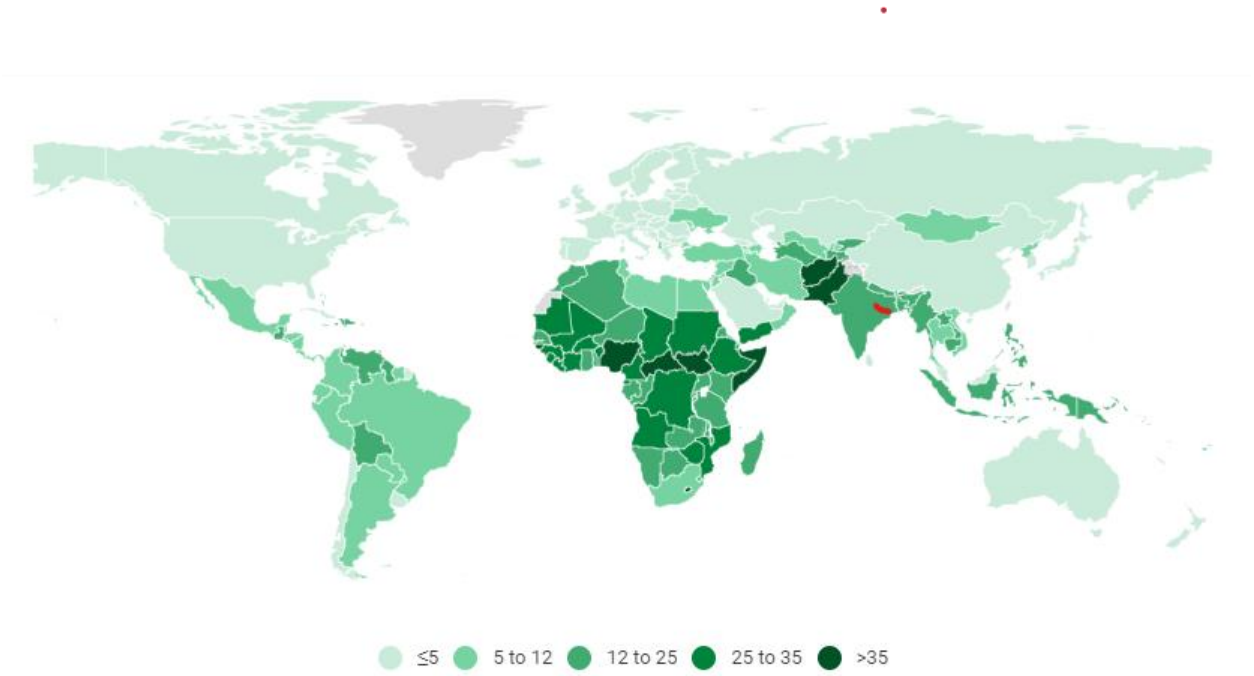


Figure 1: Burden of neonatal mortality globally (2).

Source: UN inter-agency group for child mortality estimation (UNICEF, WHO, World Bank, UN DESA population division).

The fourth millennium development goal (MDG) aimed for a 2/3rds reduction in under-5 mortality by 2015. Cameroon failed to meet this goal with a mere 10% reduction over a 10-year period (3). Cameroon's progress is among the slowest in Africa. Progress is similarly lagging with regard to the Sustainable Development Goals (SDGs) which targets 12 death /1000 live deaths or fewer by 2030 within our region (2). In Cameroon, lots of efforts have been made, which have yielded a slow decline in neonatal mortality rate, as depicted in the figure 2 below.

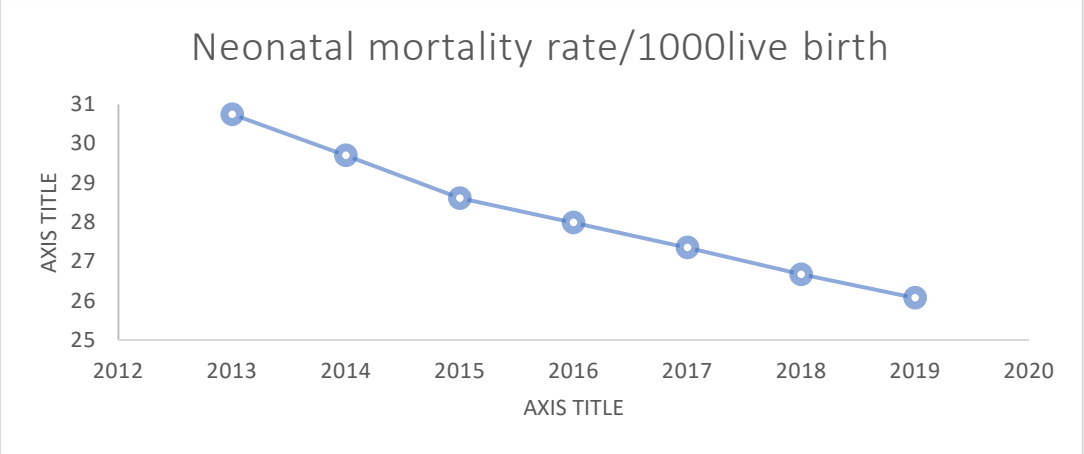


Figure 2: Neonatal mortality trends in Cameroon (4)

Source. Cameroon demographic survey. Cameroon (CMR) - Demographics, Health & Infant Mortality [Internet]. UNICEF DATA. [cited 2021 Jan 13]. Available from: https://data.unicef.org/country/cmr/

1.2 Background-Contribution of Neonatal Sepsis to Neonatal Mortality Rate.

Prematurity, difficulties during childbirth, and newborn sepsis are the main causes of neonatal mortality, with neonatal sepsis accounting for one-third of cases worldwide (2). As seen in the table below, previous research from urban Cameroon identified infections, preterm birth problems, birth asphyxia, and congenital deformities as the leading causes of neonatal hospital mortality (4).

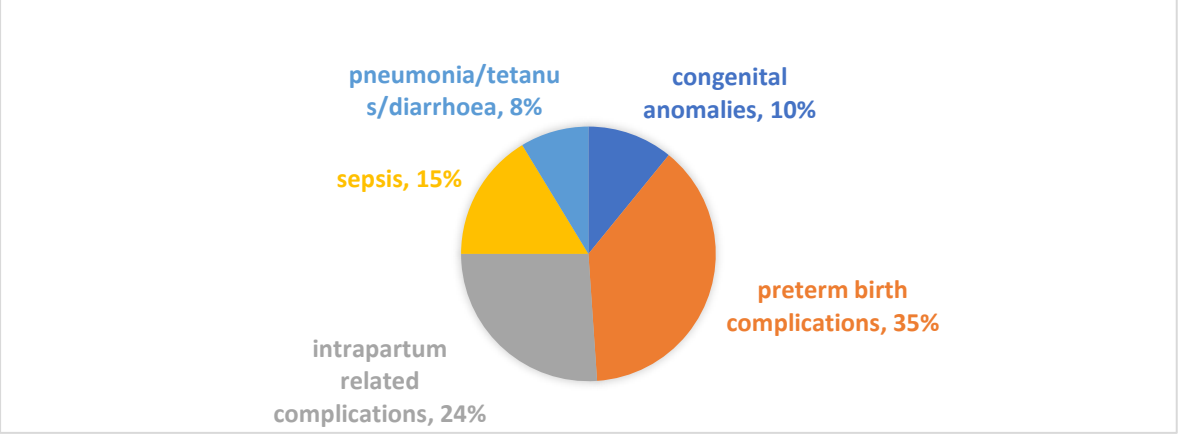


Figure 3: Causes of neonatal mortality Cameroon

Source : Ndombo PK, Ekei QM, Tochie JN, Temgoua MN, Angong FTE, Ntock FN, et al. A cohort analysis of neonatal hospital mortality rate and predictors of neonatal mortality in a sub-urban hospital of Cameroon. Ital J Pediatr. 2017 Jun 5;43 (1):52.

Neonatal sepsis is a systemic illness occurring within the first month of life. It is one of the most common causes of mortality among neonates, accounting for 225 000 mortality globally every year (5).

According to a study by Fleischmann-Struzek and colleagues (2018), middle-income nations had twice the death rates of high-income countries and a 40 times higher prevalence of newborn sepsis. Neonatal sepsis is more common in South Asia and Sub-Saharan Africa (SSA), according to global statistics (6). In 2013, South Asia was the region where sepsis-related newborn deaths occurred in 38.9% of cases.

Ranjeva and colleagues discovered that infant sepsis has a significant detrimental influence on the public health of the area as well as its economy in research on the economic repercussions of the illness in sub-Saharan Africa. They found that infant sepsis costs the Social Security Administration (SSA) 5.29 to 8.73 million disability-adjusted life years (DALYs) annually (7) Newborn hospitalizations are accounted for by sepsis alone in more over one-third (33%) of cases, according to a systematic study of neonatal sepsis conducted in Ethiopia. According to research conducted in Kenya by Ng'anga and colleagues, 58% of newborns in the postnatal unit had suspected sepsis, and 12% of them had proved sepsis. According to 2020 research by Helgera and colleagues, newborns who get treatment for neonatal sepsis are more likely to experience long-term neurodevelopmental damage, necrotizing enterocolitis, and bronchopulmonary dysplasia (9). This emphasizes the true cost of newborn sepsis worldwide, especially in SSA. Studies reveal that despite the enormous burden of newborn mortality associated with neonatal sepsis, sepsis receives less international funding as a public health priority as compared to other neonatal primary illnesses (7).

1.3 Problem Statement

With a prevalence incidence of 37.9%, neonatal sepsis is one of the main causes of newborn death in Cameroon (10). Clinical algorithms have been created in the majority of countries to help detect and treat neonates at risk of neonatal sepsis using an integrated management guide for common illnesses that WHO issued to aid low-income nations with limited access to experts. These regulations have not been country-adapted. There are no unified national rules in Cameroon as of 2021 for supporting and caring for these already vulnerable newborns.

There has been a propensity to swiftly switch antibiotics from first-, second-, and third-line regimens, respectively, without culture findings, according to anecdotal observation and research done at Lacquinti Douala hospital (11). Neonates are empirically initiated on

antibiotics because of restricted access to resources like blood cultures due to cost and availability. Additionally, there is considerable practice variation in the selection of antibiotics, their modification, and the length of therapy, which also leads to improper antimicrobial practices.

Chapter 2: Literature Review

2.1.1: Aetiology and Risk Factors

Neonatal sepsis is classified according to the time of onset as early or late. In general, early neonatal sepsis is considered when the clinical condition appears within the first 72 h of life. Late neonatal sepsis is that which starts after 72 hours of life (13) .

Early onset neonatal sepsis is developed in the peripartum phase. Consequently, the bacteria are typically from the genitourinary tract of the mother. Group B streptococcus (GBS), Escherichia coli, coagulase-negative Staphylococcus, Haemophilus influenza, and Listeria monocytogenes are typical bacterial infections causing EOS (14).

Late neonatal sepsis often develops as a result of infections being transferred from the environment after birth, such as through interaction with caregivers or healthcare professionals. Newborns that require lengthy hospitalization and invasive treatments, such as preterm or full-term infants, are more susceptible to the condition (14). About 50% of newborns with late neonatal sepsis have bacteria that are Gram positive, such as coagulase-negative staphylococcus (15). This is consistent with findings from a meta-analysis on positive culture bacteremia and sepsis done in SSA by Okomo and colleagues where Staphylococcus aureus, Klebsiella spp., and E coli were discovered to be the most prevalent microorganisms, accounting for 25%, 21%, and 10% of cases, respectively (1).

The following, among others, are some of the contributing factors most frequently linked to early-onset neonatal sepsis: Maternal urinary tract infection (UTI), chorioamnionitis, premature birth, maternal fever higher than 38°C (100.4°F), maternal GBS colonization (especially in the presence of insufficient prophylactic treatment), premature rupture of membranes (PROM), preterm rupture of membranes, prolonged rupture of membranes, and a preterm birth (16).

Table 1: Causative agents and risk factors of neonatal sepsis

Neonatal sepsis	Causative agents	Risk factors
Early-onset	-GBS E-COLI coagulase-negative Staphylococcus, Haemophilus influenza, Listeria monocytogenes	Maternal GBS PROM Prolonged rupture of membranes Prematurity Maternal UTI Maternal fever during labour Chorioamnionitis

2.1.2: Diagnosis

Clinical symptoms, nonspecific indicators including C-reactive protein and procalcitonin (when available), blood cultures, and molecular techniques are all used to make the diagnosis of new born sepsis (6).

Clinical diagnosis

The clinical presentations due to immature immune system of neonates are nonspecific and include the following:

- refusal to breastfeed
- irritability
- lethargy
- hypothermia or hyperthermia
- tachypnea
- severe chest wall in drawing
- convulsions

Paraclinical Diagnosis

Laboratory diagnosis of neonatal sepsis can be divided into direct and indirect methods.

Direct Method

This entails the identification and separation of microbes from body fluids such as blood, CSF, urine, pleural fluid, and other sites.

The gold standard for the diagnosis of neonatal sepsis is blood culture. The Sensitivity of one blood culture to detect bacteraemia is approximately 90% (6). However, there is an important time lag between collection of sample and availability of results, and blood cultures may lead to false-negative results in about 10 per cent of septic cases. In the light of this, neonates who are significantly at risk for sepsis are identified through clinical evaluation and laboratory testing, and empiric antibiotic therapy is started while waiting for the findings of blood cultures (5).

Indirect Method

Other laboratory tests that are surrogate measures of sepsis include complete blood count, CRP and a micro-Erythrocyte Sedimentation Rate (ESR) (17).

A Complete Blood Count, if obtained within the first 24 hours, may be helpful in the diagnosis of EOS. The limitation of these tests is that the wide range of normal levels reduces their positive predictive value, especially in asymptomatic patients (17).

CRP, an acute-phase reactant, increases in inflammatory conditions, including sepsis. Serial CRP has been found helpful in diagnosis of early neonatal sepsis. It can be positive as early as six hours post-infection. A study done in Kenya by Kumar et al in 2006 showed serum CRP was an accurate indicator of neonatal sepsis with high sensitivity (88.9%), specificity (82.5%) and negative predictive value (96.6%), at the standard cut-off of 5mg/dl (18).Note that CRP may also be elevated in some non-infectious conditions such as foetal distress, stressful delivery, perinatal asphyxia, meconium aspiration, and intraventricular haemorrhage (19).

2.1.3: Management

According to WHO guidelines, newborns at risk for neonatal sepsis should begin empirical therapy with a penicillin and aminoglycoside for 48 hours before reevaluating their condition. Only when sepsis symptoms are present or blood cultures are positive should treatment be maintained (6), and newborn sepsis patients should get the appropriate care. See table 2 below.

The American Academy of Pediatrics advises proper diagnosis and intrapartum ampicillin prophylaxis for mothers who present with risk factors for newborn sepsis. This covers all pregnant women who have GBS infections (20).

Giving the appropriate colloids, maintaining enough enteral feeds, preventing hyper- or hypothermia, monitoring oxygen saturation, and ensuring that it remains optimal are all examples of supportive care (20).

The only effective treatment is appropriate antibiotic medication. In lower-income countries, antibiotics should be started if there is a suspicion of Early Onset Neonatal Sepsis while awaiting culture results, according to WHO recommendations and other guidelines (NICE, AAP) (5).

The choice of antibiotics and regimen is seen in the table 2 below

Table 2. Current international guidelines for the empirical treatment of suspected sepsis or blood infection

Source: Fuchs, A., Bielicki, J., Mathur, S., Sharland, M., & Van Den Anker, J. N. (2018). Reviewing the WHO guidelines for antibiotic use for sepsis in neonates and children. Paediatrics and international child health, 38(sup1), S3–S15. https://doi.org/10.1080/20469047.2017.1408738

INTERNATIONAL GUIDELINE	YEAR	Regimen for at risk of neonatal sepsis	REGIMEN for early onset neonatal sepsis
WHO	2016	IV antibiotherapy with benzyl penicillin and gentamicin for 48 hours and reassess for signs of sepsis. If non ,stop antibiotics	-First line- M or IV gentamicin and benzyl penicillin or ampicillin for at least 7–10 days - Second line-3rd generation cephalosporin - Third line- Meropenem, aztreonam- usually depending on the culture results
NICE	2016	IV antibiotherapy with benzyl penicillin and gentamycin for 36 hours and reassess for sign of sepsis if non, stop antibiotics.	IV benzylpenicillin 25 mg/kg twice daily (increase to 3 times daily if clinically concerned) and gentamicin (starting dose 5 mg/kg every 36 h). Minimum 7-day course of IV antibiotics for strong suspicion of sepsis or a positive blood culture
AAP	2015	Combination of IV ampicillin and gentamicin. To be discontinued 36 Hours after sterile blood cultures	Broad spectrum antimicrobial agents [ampicillin 150 mg/kg per dose intravenously (IV) every 12 h and an aminoglycoside (usually gentamicin 4 mg/kg per dose IV every 24 h)]. Once a pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed) ◦ Third-generation cephalosporins (e.g. cefotaxime) represent a reasonable alternative to an aminoglycoside. Bacteraemia without an identifiable focus of infection is generally treated for 10 days

WHO-WORLD HEALTH ORGANISATION**. NICE**- NATIONAL INSTITUTE FOR HEALTH AND CARE 2 EXCELLENCE.**AAP**-AMERICAN ACADEMY OF PAEDIATRICS

2.2.4: Complications of neonatal sepsis

Neonatal sepsis has significant complications ranging from mortality to neurodevelopmental deficits (1). For those who survive sepsis long term morbidity such as cerebral palsy, cognitive

and psychomotor delay, auditory and visual impairment and even bronchopulmonary dysplasia have been identified hence reducing their quality of life thereafter (21).

To prevent these consequences, empiric antibiotics are routinely begun immediately there is a suspicion of sepsis in newborns awaiting culture findings. This has led to the widespread and continued use of broad-spectrum antibiotics in infants, particularly 3rd generation cephalosporins (1) Particularly problematic prescribing practices include giving antibiotics for illnesses that are not bacterial, using broad-spectrum antibiotics excessively or pointlessly, and choosing the wrong antibiotic or treating a pathogen for an inappropriate length of time. These are frequently observed in the neonatal population (22).

2.2 Antimicrobial Prescription Patterns

Antibiotics are essential medicines for treating and preventing bacterial infections, but their efficacy is increasingly threatened by the growth of antimicrobial resistance (23). Ideally, one should compare patient's profile to existing prescription guidelines to assess antibiotic prescription appropriateness. However, this is difficult as many patients' disease symptom and severity that inform prescribing, are not looked for or un documented in-hospital care databases. In the case of Cameroon, no local prescription guidelines are available (23).

Undertreatment of neonatal sepsis is of equal concern without clear guidelines. Inappropriate antibiotic choice, antibiotic resistance, and insufficient duration are all problems leading to increased morbidity and mortality. In survivors, morbidity often takes the form of neurologic sequelae such as cerebral palsy (24). Antibiotic use differs between countries. But it has been observed that consumption is higher in low- and middle-income nations. Presently, it is discovered that many microorganisms have developed resistance to the most widely used and efficient first-line antibiotics, primarily as a result of improper prescription practices (25). Our study's objective is to examine how often these prescriptions are given to newborns who may have early-onset neonatal sepsis.

We used electronic searches on PubMed, the Cochrane library, and Google Scholar to find articles on antibiotic prescribing practices, AMR, and in-hospital infant death. Antibiotic prescribing practices and antimicrobial resistance in neonates with early onset neonatal sepsis were the main search terms we used. After searching through 224 papers, we included neonatal studies that had been conducted internationally within the previous 15 years.

Studies conducted more than 15 years ago, on adults over 65, and studies addressing general sepsis in pediatrics were all disqualified. Thirty-six research—systematic reviews, retrospective studies, and prospective studies—met the standards for the study and were thus included in the review. Neonatal patients hospitalized for suspected neonatal sepsis made up the research population. Table 3 lists major findings from the included studies.

Table 3: Summary of studies found

Author/Year	Country	Type of Study	Study population and size	Key Findings
Ollandzobo et al/2021(26)	congo	Multi centre Cross sectional	2077 neonates	47 % of neonates had a poor quality of prescription (choice dosage)
Tank et al/2019 (27)	Kenya	Cross-sectional prospective audit	320 neonates over a 2-month period at NBU	The continuation of antibiotics was inappropriate. Overall mortality was high, especially in the first 48 hours of admission
Oluwatoyin et al/2020 (28)	Nigeria	Retrospective	Referred out born neonates with neonatal sepsis n=127	6.8% had no indication for empirical treatment. 16.1 % had irregular administrations. Conclusion: Inappropriate use of antibiotics in terms of initiation of empiric treatment, choice of drugs and failure to investigate as necessary was common
Schelleck et al/2011 (29)	South Africa	Prospective	Selective randomised sample of 100 neonates admitted for suspected neonatal sepsis	The average duration of use for all antibiotics was longer than recommended
Borade et al/2014 (24)	India	Cross-sectional	Neonates admitted in NICU with antibiotics prescriptions n-118	44% were treated inappropriately. This was attributed to the inappropriate dose and frequency of drugs given
Awan et al/2014 (30)	Pakistan	Retrospective	Neonates being treated for suspected neonatal sepsis n=50	High usage of three combination antimicrobials with high potency
Harridan et al (31)	Caribbean	Prospective	Neonates with suspected EONS n=353	19 different antimicrobials used based on empirical judgment and not cultures, thus there is need for guidelines

A cross-sectional retrospective study conducted by Oluwatoyin and colleagues in Nigeria on description of antibiotic prescriptions in neonates in a tertiary hospital where there were no written guidelines found out that 91%of their neonates received antibiotics without any laboratory investigations prior to starting antibiotics. They proposed lack of funds and laboratory logistic problems as reasons for those neonates not ever getting any laboratory investigations. More than half of the neonates had no cultures until discharge ,16.1% had irregular administration of antibiotics in terms of frequency, and they finally concluded there was irrational and injudicious use of antibiotics in their study. In their study appropriate use was defined in terms of clinical signs and symptoms ,laboratory investigations guiding the choice of antibiotics, regular administration and duration of administration for antibiotics for neonatal sepsis (28).

Borade and associates in India evaluated neonatal antibiotic prescription trends using a cross-sectional approach. Out of 118 newborns, 44% had improper care, as shown by the use of medicines at the wrong doses and frequencies. Most often given drugs were cefotaxime (35.6%), amikacin (18.1%), piperacillin (12.3%), and meropenem (7.4%). The length of therapy was not included in their investigation since there were no established standards. In order to encourage judicious prescription, their study recommended that an antimicrobial agent (AMA) prescribing policy be developed (24).

A retrospective study was done by Bukhsish and colleagues at the newborn intensive care unit of a public sector tertiary care hospital in Lahore, Pakistan, to assess the use of antibiotics in 50 cases of neonatal sepsis. The frequency of administering various antibiotic combinations was assessed in their study. Amikacin, ampicillin, and cefotaxime were the most typical combinations (48%) followed by amikacin, ampicillin, and cefotaxime (30%) and vancomycin and meropenem (22%). They came to the conclusion that high strength antibiotics were often utilized and that definitive therapy selection was less dependent on the results of culture testing (30).

In south west Ethiopia, a retrospective study was carried on antimicrobial prescribing, using WHO guidelines as reference. The showed that majority of antibiotics were prescribed with antimicrobial profile and thus there was excess prescription and deviation from WHO guidelines (32).

In Kenya an audit was carried out by Tank and colleagues where they reviewed record of 320 neonates in the KNH newborn unit. They looked at prescription patterns in terms of patient's clinical presentation, investigations, choice, route of administration, dosage, frequency and duration of treatment for neonates with neonatal sepsis and compared to the national Kenyan guidelines being followed in the unit. They concluded that though the choice of antibiotics as per guidelines was right in 91% of the population, there was still poor documentation of risk factors, poor investigations to confirm sepsis as only 13% had blood cultures done and there was no adherence to duration of antibiotics used for treatment (27). This goes to show that even with guidelines in place, there is a need to assess the effectiveness and implementation of these guidelines if we want to curb the emergence of AMR and improve care for our neonates.

An investigation of antibiotic prescription practices versus the current antibiotic policy was done in prospective research in a NICU in South Africa. There were 19 distinct antibiotics administered, and the antibiotic policy lists 11 of the 19 medications. With the exception of Cefepime and ceftriaxone, all antibiotics had an average length of usage that was greater than seven days. Although the majority of patients received antibiotics in accordance with the ward protocol, there were some exceptions that were related to the clinical state of the patients or the outcomes of blood cultures. They came to the conclusion that an antibiotic policy might be effective for directing and monitoring the proper antibiotic treatment in a NICU (29).

An antibiotic policy should enhance prescribing practices and shorten the course of antibiotic therapy, according to a Cochrane analysis that was done to discover treatments to improve antibiotic prescription in hospital inpatients. The necessity for our study stemmed from the fact that programs that gave physicians feedback or advise were more successful in enhancing prescription habits than those that did not do so (33).

The gap from the research previously mentioned demonstrated that newborn sepsis continues to be a burden in both SSA and internationally. There is evidence to suggest that antibiotics are still incorrectly prescribed on a worldwide scale, without regard for the findings of culture tests. It is necessary to provide Standard treatment guidelines (STG) and antibiotic prescribing policy where it is lacking.

2.3 Antimicrobial Resistance

Neonatal sepsis though among top three leading causes of neonatal mortality, many challenges remain in its diagnosis and management. This is because the diagnosis of sepsis is complicated

by the frequent presence of non-infections conditions that resemble sepsis, especially in preterm (17). Moreover, due to immaturity of the immune system especially in preterm, signs and symptoms can be nonspecific and subtle. With lack of optimal diagnostic tests, this had made diagnosis and optimal management a problem. Clinicians may tend to over-treat in that case leading to antibiotic abuse and resistance, or under treat the infections, which can in the end contribute to complications associated with neonatal sepsis such as meningitis and neurodevelopmental sequelae such as cerebral palsy, and death thereby contributing to raising the neonatal mortality rates (21).

With increasing challenges in the diagnosis of neonatal sepsis, there have been high antibiotic resistance rates against commonest bacterial pathogens. Okomo and colleagues in a systematic review carried out among 151 studies from 26 countries worldwide, showed there was a growing resistance to WHO recommended b lactams in 68% of cases and aminoglycosides in 26% of cases (1). Below (table 4) is a summary of some studies carried on antimicrobial resistance.

Table 4: Review of studies carried out on antimicrobial resistance in EONS

Author/year	country	Type of study	Study population	Key findings
Uduak Okomo et al /2019 (1)	26 countries from Sub-Saharan Africa	Systematic review and meta-analysis	available data from the African continent since 1980, with a focus on regional differences in aetiology and antimicrobial resistance (AMR) in the past decade (2008–18)	Resistance to WHO recommended β-lactams was reported in 614 (68%) of 904 cases and resistance to aminoglycosides in 317 (27%) of 1176 cases
Mohsen et al/2017 (34)	Egypt	prospective	314 neonates admitted with neonatal sepsis	Multidrug resistance was detected in 92 (38%) cultures, mainly among gram-negative isolates. increasing resistance to b lactamases antibiotics
Grace li et al/2019 (35)	12 countries (LMIC) amongst which Nigeria, Uganda and south Africa from 4 continents	Web base design cohort observational	39 new born units	Resistance in gram-negative pathogens to cephalosporin rates ranged from 26-82%, carbapenems 8%.
Mhada et al/2012 (36)	Tanzania	Prospective Cross-sectional	330 neonates with neonatal sepsis	. More than 80%and 90% of staph aureus and klebsiella identified and resistant to ampicillin, aminoglycosides.
Pokhrel et al/2018(37)	Nepal	Retrospective cross sectional	336 neonates with neonatal sepsis	A significant proportion of the isolates were multidrug-resistant strains. High resistance (90%) of klebsiella to cefotaxime

2.4 Factors associated with antibiotic prescription

In accordance with WHO recommendations, the existence of the perinatal and maternal risk factors stated earlier, as well as two or more clinical features and sequential biomarkers, must all be taken into account when making a diagnosis of EOS. These are the primary elements that determine an appropriate antibiotic prescription (5).

In Bangladesh, an observational birth cohort study on the antibiotic prescription during new born hospital stay was conducted. They discovered that other issues like laboratory operations,

a lack of guidelines, and cost restrictions might all contribute to the prescribing of antibiotics (22).

In the retrospective study in Pakistan carried out by Awan on colleagues on prescription trends of antibiotics in NICU, they found out that presence of clinical characteristic such as fever, refusal to feed, vomiting and seizures were present in 52%,42%,40 % and 15% respectively of neonates with EOS and started on empirical treatment which is still in line with recommendations by WHO for antibiotic prescribing in neonatal sepsis(30).

A prospective analytic study was conducted in Cameroon over a 6-month period in a tertiary hospital with the goal of identifying the clinical and biological profile of early-onset newborn sepsis. Of the 218 neonates hospitalized for the condition, they discovered that. Fever (44.9%), feeding refusal/irritability (32%), and respiratory distress/cough were the most prevalent symptoms. The most prevalent risk factors were premature birth and protracted membrane rupture (11).

Given the restricted availability of conventional blood cultures in the majority of low-income nations, which includes most of Sub-Saharan Africa, additional biochemical lab tests that have been found to have good sensitivity for sepsis include CRPs and complete blood counts (38). A study conducted in Kenya, Kumar and colleagues discovered a substantial correlation between early-onset new born sepsis and CRP levels more than 5mg/dl (18).

We will thus be evaluating the reported clinical symptoms, maternal, perinatal risk factors, and their correlation to the prescription of antibiotics based on the aforementioned research and WHO recommendations

2.5 WHO AWaRe Antibiotics Classification

Due to antimicrobial overuse and abuse, WHO developed AWaRe (Access Watch Reserve) in 2017 as a tool to categorize antibiotics and direct their usage in diverse circumstances (39).

The watch group includes antibiotics with a higher potential for resistance, while the reserve group consists of antibiotics to be used as a last resort and typically following culture results. The access group includes antibiotics that have activity against a wide range of frequently encountered pathogens (39).

The common antibiotics are described in several categories in the examples below. The entire group is included in the appendix 5.

Table 5. Antibiotics on WHO AWaRe classification

Source: WHO | WHO releases the 2019 AWaRe Classification Antibiotics

ACCESS	WATCH	RESERVE
Amikacin	Azithromycin	Aztreonam
Amoxicillin	Cefepime	Ceftolozane-Tazobactam
Amoxicillin/clavulanic Acid	Cefixime	Fosfomycin (IV)
Ampicillin	Cefotaxime	Linezolid
Ampicillin/sulbactam	Cefotetan	Meropenem-Vaborbactam
Benzathine benzylpenicillin	Cefpodoxime proxetil	Minocycline (IV)
Benzylpenicillin	Cefprozil	Polymyxin B
Cefacetrile	Ceftazidime	Tigecycline
Chloramphenicol	Cefteram pivoxil	
Clindamycin	Ceftriaxone	
Cloxacillin	Cefuroxime	
Doxycycline	Ciprofloxacin	
Flucloxacillin	Clarithromycin	
Gentamicin	Imipenem/cilastatin	
Metronidazole (IV)	Levofloxacin	
Metronidazole (oral)	Meropenem	
	Neomycin	
	Ofloxacin	
	Vancomycin (IV)	
	Vancomycin (oral)	

Boone and colleagues conducted an observational birth cohort research across 39 neonatal facilities in 12 nations using this categorization. They demonstrated that the WHO-recommended antibiotic regimen was used in 68% of cases of newborn sepsis. However, only 58% of antibiotics used overall were in the access group, whereas 1/3 were in the monitor group. They emphasized the requirement for a paediatric antimicrobial stewardship program in Bangladesh as a result. They also identified some prescription practices that lead to AMR, such as the excessive and unnecessary use of broad-spectrum antibiotics, as well as the improper selection of antibiotics or duration for the treatment of known pathogens, which may help to explain the watch group's high antibiotic usage (22).

An observational cohort research conducted by Li and colleagues among 39 neonatal units in 12 different countries revealed a rise in the use of antibiotics as first-line treatment for newborn sepsis in the reserve group, particularly in nations with lax regulations like Bangladesh and India; 29 of the 39 units have local EOS regulations. Broad-spectrum penicillin and aminoglycoside were utilized as the first line of empirical therapy in 24 centers. Out of the remaining centers, 17 units, predominantly in China and India, used "reserve" groups as an empirical choice in their Eos recommendations. This already suggests that newborn patients utilize a lot of reserve antibiotics. Overall, 43% of empirical antibiotics were utilized in the access group, 37% in the watch group, and up to 20% in the reserve group, with 4% of this reserve being used empirically in EOS (35).

Therefore, it will be fascinating to learn how antibiotics are used in our environment according to the AWaRe tool. This would make it easier for us to comprehend the causes of the antimicrobial profiles and antibiotic resistance we are now observing in neonates with neonatal sepsis and to determine the potential need for an antibiotic stewardship program.

2.6 Neonatal in-hospital mortality.

Despite the fact that all children are born equally, where they are born in the world affects their chances of surviving (40). Due to a lack of adequate facilities and human resources, children in sub-Saharan Africa have a mortality rate that is ten times higher than that of children in other nations. This is further demonstrated by the most recent SGD data, which shows that in 2018 SSA had the greatest NMR (28/100 Live birth), followed by central and southern Asia (41). Prematurity, LBW, and infections are among the most prevalent reasons of death in SSA, as previously mentioned. Infections pose a serious problem for us, especially if they are not promptly recognized and treated. This worsens the numbers for infant death.

Barsa and colleagues carried a review on neonatal survival in Kenya and South Africa. They showed that, although Kenya had been experiencing a decline in NMR from 35.4/1000 live births in 1975 to 19.6/1000 live births in 2019, it still had a long way to go in order to achieve the below 12/1000 live births target set in the SDGs. South Africa on the other hand had already achieved the target where in 2019 had a Neonatal mortality rate of 10.7%. This may be attributed to their high quality of care and development of infrastructure (42). Below is a summary of studies we reviewed and their in-hospital neonatal mortality rates

Table 6: Summary of studies showing in hospital neonatal mortality

Author/year	country	Study population	Type of study	Results (NMR)
Masaba et al/2020 (42)	Kenya and South Africa	Literature review, include 27 articles	Cross-sectional	19.6%
Tank et al/2018 /(27)	Kenya	320 neonates with sepsis	Cross-sectional hospital based	25%
Koki et al/2017 (4)	Cameroon	322 neonates with sepsis	Prospective cohort	15.7%
Mehkar et al /2017(43)	India	2073 neonates with sepsis	Prospective	36.1%
Koum et al /2016 (44)	Cameroon	350 neonates with sepsis	Prospective cohort	20.3%
Mahad et al/2010 (36)	Tanzania	330 neonates with neonatal sepsis	Cross-sectional hospital based	13.9%

2.7: Conceptual framework

The framework that follows demonstrates how incorrect antimicrobial prescriptions in EONS increase neonatal mortality and morbidity, have cost ramifications for the caregiver and society, and play a part in the development of antibiotic resistance. The sections before this one previously covered factor that may lead to incorrect prescriptions.

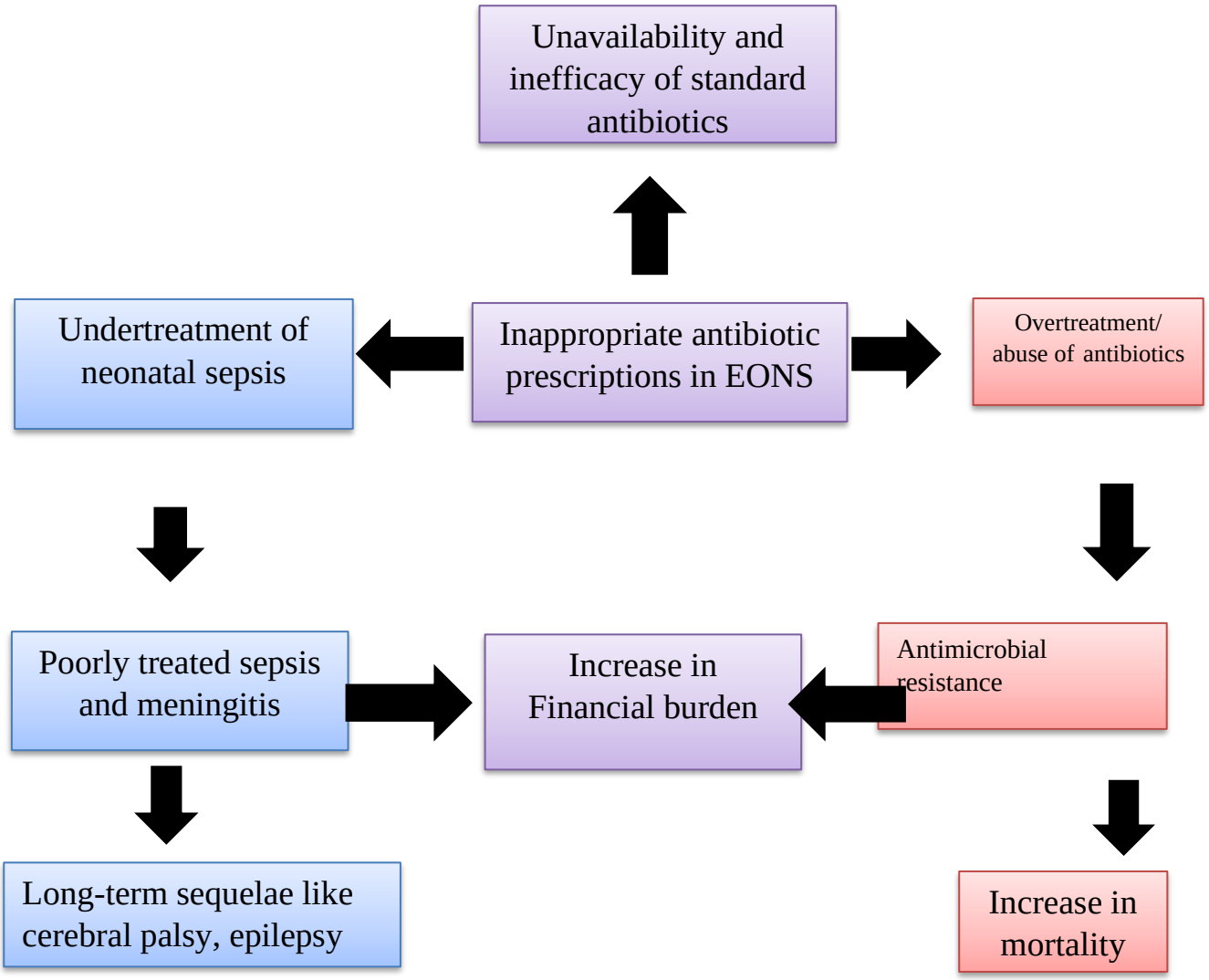


Figure 4: Relationship between prescription patterns and effects on outcome of neonates and care.

2.8 Justification of study

In Cameroon, neonatal death makes up 41% of the under-five mortality rate (10). Newborn sepsis is to blame for one-third of neonatal fatalities. Some of the reported mortality may be explained by the inappropriate prescription of antibiotics in the context of newborn sepsis. In addition, overusing antibiotics can result in the development of antibiotic resistance, which can be avoided by limiting the use of unnecessary antibiotics. In order to enforce antibiotic regulations that assist avoid incorrect or illogical use of antibiotics and maximize therapy, antibiotic stewardship programs are frequently implemented. Programs for the stewardship of

antibiotics have been found to reduce the use of antibiotics, enhance patient outcomes, and prevent the introduction of resistant strains. It's critical to assess the data on antibiotic prescription trends in newborns arriving to the Neonatal Unit in order to develop such a policy for the management of infections in the Neonatal unit.

Our research aims to provide light on the patterns of antibiotic prescription for neonates with suspected neonatal sepsis. The results will be used to help develop hospital treatment guidelines or protocols that will improve care and outcomes for neonates with neonatal sepsis both locally and nationally, combat inappropriate prescribing, and lessen the burden of cerebral palsy brought on by poorly treated neonatal sepsis (in particular, meningitis).

This study will enable us to recognize our usage of antibiotics, advance our understanding, and pinpoint frequent mistakes. We anticipate that Results from our study will also serve as first step towards creating an antibiotic stewardship program for these two hospitals.

Research question

What are the antimicrobial prescription practices and mortality rates in neonates admitted with suspected early-onset neonatal sepsis at the Bonaberi and Mboppi Baptist Hospitals Douala, Cameroon?

2.9 Objectives

2.9.1: Main objective

1. To determine the proportion of neonates with suspected EONS or at risk of neonatal sepsis based on perinatal risk factors with appropriate antibiotic (based on WHO guidelines, those needing antibiotics, type, dose, route and duration.) prescriptions at admission at the two hospitals

2.9.2: Secondary objectives

2. Evaluate factors associated with appropriate prescription –perinatal risk factors, hospital, patient signs and symptoms at presentation

3. Describe the pattern of antimicrobial prescription based on the WHO classification of antimicrobials (AWaRe)

4. Determine the case fatality amongst those with EONS recruited into the study.

Chapter 3: Methodology

This was a cross-sectional descriptive study at the paediatric ward and postnatal ward.

3.1 Study Location

Cameroon is located in Central Africa Region, located in the Gulf of Guinea with a total surface area of 475650km2 and about 26million inhabitants (45). It is shares borders with

Nigeria to the West, Chad to the North East, Central African Republic to the East, Congo, Gabon and Equatorial Guinea to the South, and to the South-West by the Atlantic Ocean.

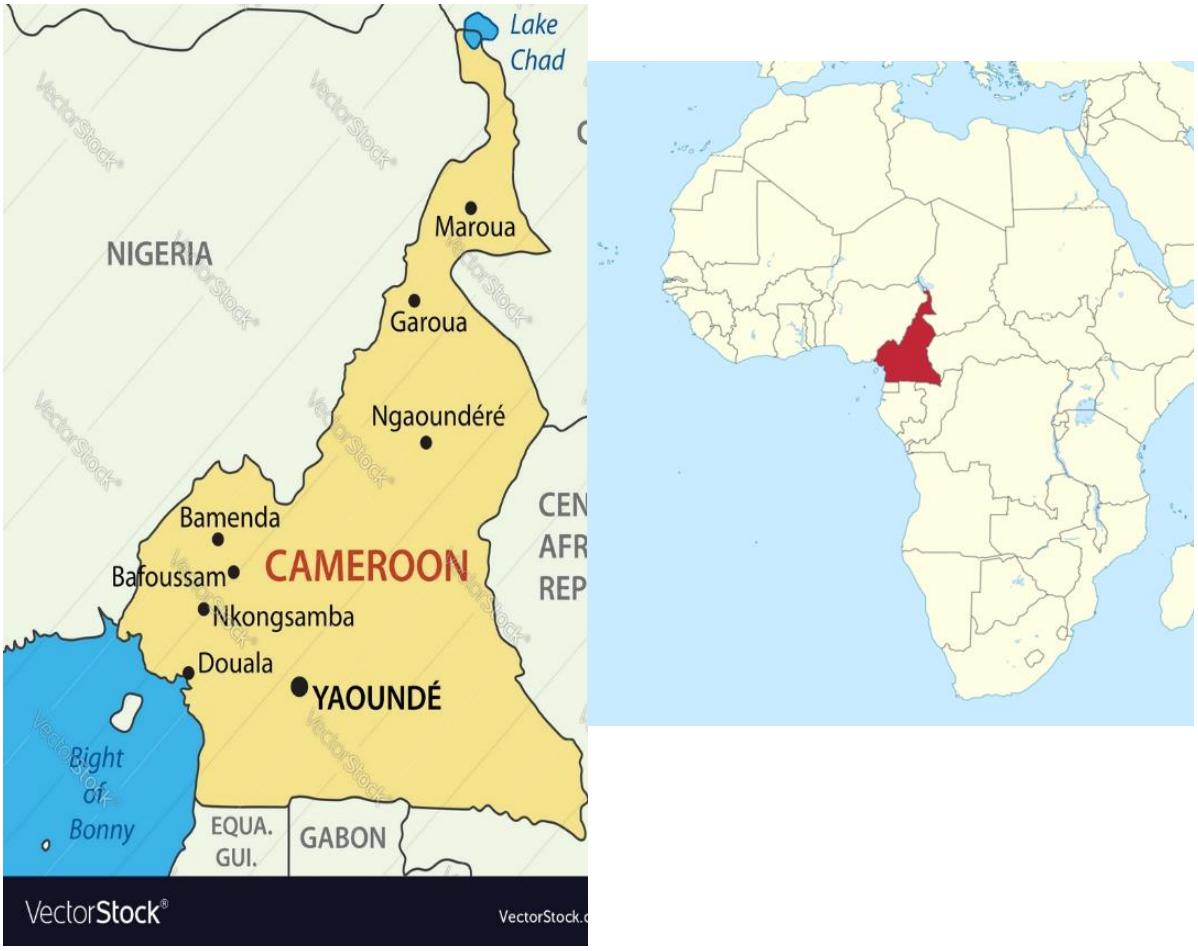


Figure 5: Map of Cameroon showing regions and Borders

Cameroon is divided into ten regions, each headed by a Governor appointed by the head of state, and has as political capital Yaoundé in the centre region. Douala where our study will be carried out is found in the littoral region and is the country's economic capital.it has two national languages; English and French. The Northwest and Southwest regions were once part of British Cameroon; the other eight regions were in French Cameroon. The regions consist of

58 divisions, each of which is ruled by a divisional officer appointed by presidential decree and performing at a lower level the governor’s duty. The divisions are further subdivided into subdivisions, each ruled by an assistant divisional officer. The subdivisions can be further split into districts, which are the smallest administrative units led by district heads (46)**.**

The national health system in Cameroon is pyramidal in setup comprising administrative and/or management structures and healthcare structures. In terms of organisation, it is organised into three levels: The Central or Strategic level is made up of the Ministry of Public Health and national hospitals' central services, charged with formulating the country's health policy. The Intermediate level or Technical Support level comprises regional delegations of public health and regional and related hospitals, tasked with the programming and supervision of activities in the field and provision of technical support.

The Peripheral level or level of Operationalisation of program activities comprises district health services, district hospitals, sub-divisional medical centers and integrated health centers. The health center is the first level of contact for the population, and offers a minimum package of activities; this level constitutes the interface between the health care services and beneficiary communities (45) **.**

Cameroon's national health system is made of public and private entities, institutions and organisations that provide health services, under the regulation of the Ministry of Public Health (47). The principal provider of health care in Cameroon is the public sector, followed by faith-based organisations. The Cameroon Baptist Convention Health Services is one of the faith-based organisations that provides healthcare in six out of Cameroon's ten regions. It has 7 hospitals, 30 integrated health centers staffed by nurses, and more than 50 primary health centers—the 4 largest hospitals (Banso Baptist Hospital, Mbingo Baptist Hospital and Mboppi Baptist Hospital).

Table 7: Organization of government health sector

Organisational Level	Administrative Structure	Service Delivery
Central Level	Ministry of Public Health	National Hospitals
Intermediate level	Regional Delegations of Public Health	Regional Hospitals
Peripheral level	District Health Services	District Hospitals - Sub-divisional Medical Centres - Integrated Health Centres

Study Hospitals

The patients were recruited from 2 hospitals in Douala, (intermediate level hospitals) the 2nd largest city in Cameroon, Mboppi Baptist Hospital and Bonaberi Baptist Hospital. Table 8 highlights the characteristics of the two facilities. MBHD has an average of 275 deliveries per month and 60 neonatal admission per month while BBHCD has an average of 120 deliveries per month and 30 neonatal admission per month.

Table 8: Description of MBHD and BBHCD

	Mboppi Baptist Hospital	**Bonaberi Baptist hospital**
Location	Douala (Economic capital of Cameroon)	
Target population	1.3 million	
Level of facility	Tertiary referral Hospital	
Bed capacity	140 beds	
Daily number of patients	1000/day	350 /day
Staff Establishment	500 includes [17 Medical Officers, 9 consultants	10 medical officers, 3 Consultants, and 6 nurse practitioners,
Maternity	2 obstetrician/gynaecologists 45 nurse-midwives 275 deliveries / month	**1 gynaecologist, 20 nurses.** **120 deliveries /month**
Paediatric ward	2 Paediatricians 35 beds – has a section for neonates that serves the whole hospital [8 incubators and 12 cots for care of preterms.]	1 Paediatrician 25 beds
ICU	None – ventilatory support not available	None – ventilatory support not available
Neonatal admission	60/month	30/month

Both are general hospital offering general consultation, emergency care, dental services, eye care, treatment and injections, clinical imaging, pharmacy, HIV and AIDS work, laboratory services, physiotherapy, antenatal care services, women health program, Tuberculosis, diabetes clinic, inpatient services**.**

In both hospitals, the following basic tools available include: blood pressure machines, feto-stethoscopes, partographs, delivery sets, vacuum extractors, caesarean section sets and newborn resuscitation equipment. In addition, there is a functional theatre with anaesthetists available throughout the week and weekends.

Both hospitals have a paediatric unit where neonates and other paediatric patients are admitted together with the primary caregivers, there is no new born unit, and babies born in the maternity ward stay together with their mothers in the same room. Mboppi Baptist hospital however has a nursery where preterms requiring specialised care such as an incubator are admitted by the paediatrician. Generally, the hospital has a high turnover of medical officers who attend to neonates both in the outpatient and the maternity in patient unit. They admit them to the paediatric postnatal wards, document the signs and symptoms, make the diagnosis and prescribe treatment for the neonates. Those neonates in the maternity ward who are suspected to have EONS or EONS are admitted to the paediatric post-natal ward together with the mothers. The nurses then are responsible for administering and documenting the given treatment.

Currently in these hospitals, the first line treatment for neonatal sepsis involves a cephalosporin, aminoglycoside and ampicillin.

3.2: Study Design

This was a cross-sectional descriptive study at the paediatric ward and postnatal ward.

3.3: Study Population

Study population consisted of all new-borns aged 0-72 hours born at MBHD or BBHCD and newborns admitted for suspected EONS or those at risk of neonatal sepsis at paediatric and postnatal wards of Bonaberi and Mboppi Baptist hospitals

Inclusion Criteria

- Neonates who met the clinical criteria for suspected EONS or at risk of EONS admitted at these hospitals at the time of data collection.

Exclusion Criteria

- Neonates who were admitted after 72 hours of life. This is because after 72 hours it is classified as late-onset neonatal sepsis and not the focus of our study.

- Referral from other hospitals because this could influence the practice patterns of clinicians at the study hospital.
- Neonates whose parents declined to consent.

3.4: Case definitions

- **Neonatal sepsis** is a blood infection that occurs in an infant younger than 28 days old (6). The presence of any one of the following clinical features is suggestive of neonatal sepsis.

❖ Refusal to breastfeed or feeding intolerance
❖ Fever -axilla temp>37.5℃
❖ Lethargy or change in level of activity
❖ Convulsions
❖ Bulging fontanel
❖ Hypothermia or hyperthermia
❖ Apnoea
❖ Signs of respiratory distress (severe chest wall in drawing, tachypnoea or fast breathing, grunting, cyanosis or decreased oxygen saturation)
❖ Jaundice within 24hrs of birth
❖ Pallor
❖ tachycardia

- **Early-onset neonatal sepsis**: occurring within 72 hours of life
- **Appropriate drug use**: Appropriate use of medicines requires that "patients receive medications appropriate to their clinical needs (based on criteria for sepsis and WHO recommended guidelines), in doses that meet their requirements, for adequate period of time (see table 2) (5).
- **Perinatal risk factors for early-onset sepsis:** Appearance of any of the following perinatal **risk factors is associated with the development of EONS.**

❖ **Maternal fever during labour and delivery ≥38ºC (100.4º)**
❖ **Prolonged rupture of membranes (> 18 hours)**
❖ **Foul smelling liquor**
❖ **Chorioamnionitis**
❖ **Maternal Group B Streptococcus colonization**
❖ **Low birth weight (< 2500g)**

❖ **Intrapartum maternal sepsis**

- **Early in-hospital mortality:** mortality within first 7 days of admission amongst those admitted for suspected early-onset neonatal sepsis.
- **Appropriate prescription:** First line antibiotherapy drugs prescribed at the right dose (according to WHO standard dosing guide), route, frequency and duration.

3.5: Study period

Study ran for a 5-month period from October 2021-febuary 2022.

3.6: Sample size determination

The following assumption was made,

- 95% confidence level.
- The prevalence of 50%. In our study, the primary outcome was the prevalence of inappropriate antibiotic practices. We assumed a prevalence of 50% as no relevant study to estimate our sample size was found, and this provides the largest sample size.
- Precision of ± 5%,

The sample size was calculated as follows using the Fischer formula for infinite population

$$n = \frac{Z^2P\,(100-P)}{e^2}$$

Where n is the sample size

P is the prevalence 50% and

Z (1.96) is the area under the curve for a confidence level of 95%

e is the marginal error which is 5 in this case.

n= (1.96) ×0.5(0.5)/0.25=383 participants

Sampling method: Proportionate consecutive sampling was used until the sample size was achieved.

Given that we were using two facilities who received different number of patients on a monthly basis, this number was split as 2/3rd from Mboppi and 1/3rd Bonaberi (see table 8). Thus, a sample of 255 from Mboppi and 128 from Bonaberi was recruited.

Study outcome variables

Table 9: Main study variables and scales of measurements

Independent variable	Scales of measurement	Dependent variable
Age in days	Continuous	Prescribing pattern
Sex	Categorical	
Dose (correctly indicated)	Categorical	
Frequency	Categorical	
Antibiotics prescribed	Categorical	
Duration of treatment	Continuous	

3.7: Study Tools

A structured questionnaire was used to collect data from participants (see appendix 3). The questionnaire included patient demographic data (age, sex, gestational age, birthweight, place of delivery). The next part included maternal and neonatal history, clinical details of the patient (signs and symptoms at presentation, risk factors for EONNS, laboratory investigations requested and those carried out, diagnosis.) We then had section on the choice of antibiotics, doses, frequency and duration prescribed at admission and tracked any changes made within 5 days of admission.

Study procedure

1.An exit interview of mothers was done for all neonates at the pediatric and postnatal wards to identify those who at risk of EONS and those with EONS. All records of neonates admitted at the postnatal and pediatric wards during the study period, were reviewed by the principal investigator and research assistants daily. Those eligible for the study were identified

2. Written consent in English or French were then obtained from the parents or guardians after proper explanation of the study to them. And neonate enrolled into the study.

3. A Study identity number was assigned to enrolled participants. Demographic data as age, sex, gestational age, birthweight, place of delivery was extracted from the file

4. Files were examined for documented maternal and neonatal history (risk factors), clinical signs at presentation, investigations requested, diagnosis, and antibiotics prescribed, duration, dose, frequency by using the assessment tool.

5. Files were reviewed by the 5th day of admission to see if any change in antibiotics and reason.

6. Outcome at 7th day was noted as either alive or dead. The above procedure is shown in figure 6 below

7. Data collection was carried out by the principal investigator and her research assistant (a nurse working in the same hospital facility who was trained on data collection prior to study).

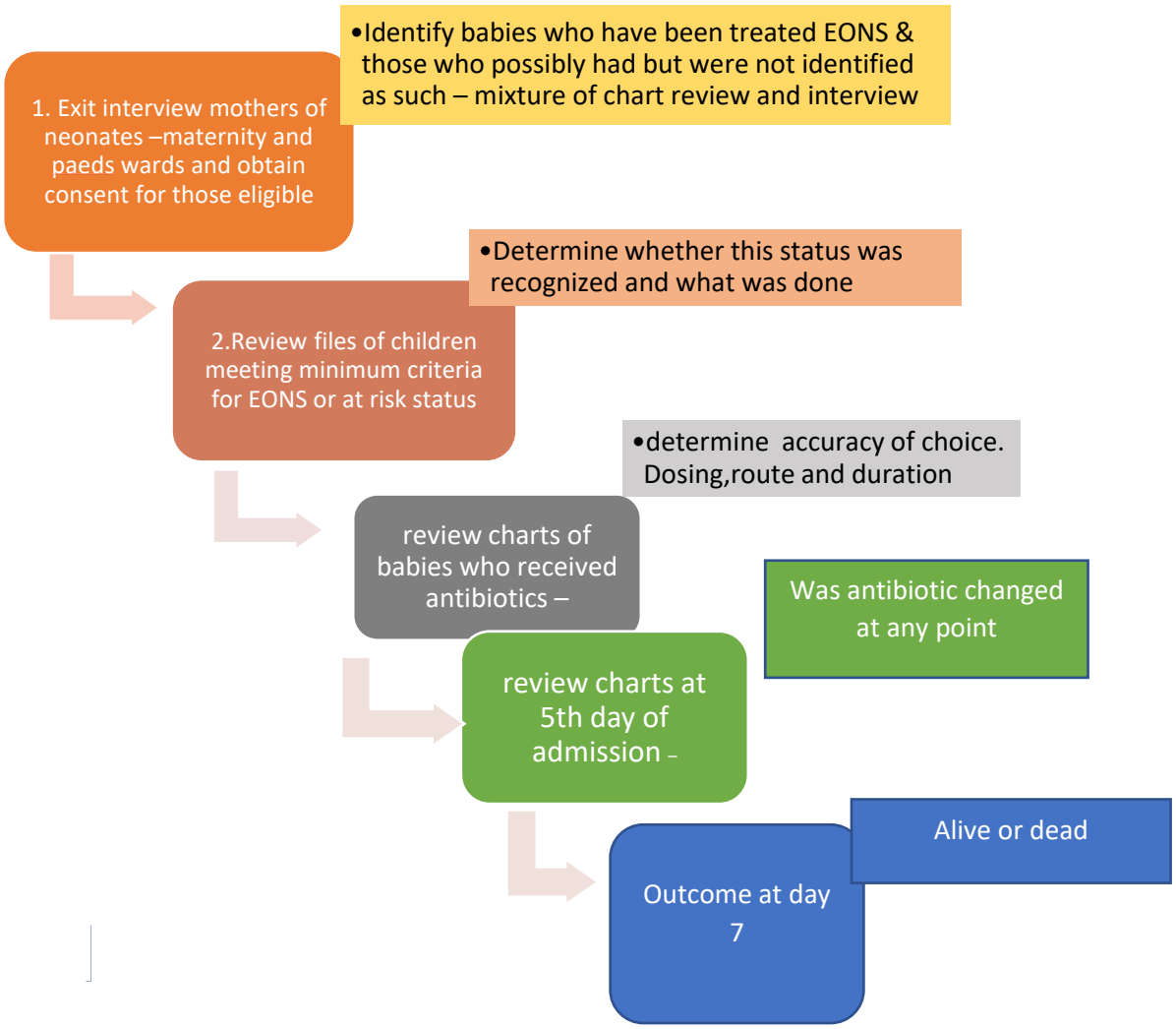


Figure 6: Flow Chart of Study procedure and expected outcome at each stage.

3.8: Data Management and Analysis

Data was entered into an excel spread sheet then cleaned and transferred to SPSS version 22 software for analysis**.** Prior to entry into SPSS, data forms were reviewed for validity and completeness by the statistician; this will ensure double entry and verification

Data Analyses

During descriptive analysis, continuous variables (like age) were described in the form of mean and standard deviation, while categorical variables were summarised using proportions and frequency tables. To determine the proportion of EONS with appropriate antibiotic (based on WHO guidelines type, dose and duration as shown in table 2) prescriptions at admission at the two hospitals, the proportion of neonates with appropriate prescription was calculated and expressed as a percentage using the formula:

(Number with appropriate prescription ÷ total number of neonates with EONS) ×100.

In our study, despite the fact there were no local guidelines, the common antibiotics used as first line was used and correct dosing, frequency, route, duration was assessed with the WHO recommended dosing, route and duration as reference.

To determine the 7 day in-hospital case fatality amongst those with EONS in our study, The mortality was calculated using the formula: number of neonates with EONS who died over 7-day period/total number of neonates in our study *100.

Data was presented using pie charts, bar charts and tables**.**

Control of error and biases

Completeness:

1. Avoiding missing files: Forms were kept in duplicate after data from original file had been extracted into the forms.

2. The research assistant were trained and provided with standard definitions of terminologies used in the questionnaire to ensure uniform interpretation of the terms.

3. Database technology was put in place to detect missing data fields and thus prompt quick appropriate action.

4. Monthly meetings with the research team was done to identify and solve any problems with the study.

Accuracy/Correctness

1. Double entry of data was done to increase accuracy and a third part review of all data sets done**.**

Data Verification and Audit Procedures

1. Monthly audits to monitor missing, inaccurate data and clarify any data collection issue was done.

2. Randomly selection of about 10% of the data was done for source verification.

Validity

In order to eliminate insensitive measure bias and guarantee that the questions were sensitive enough to identify what could be significant variations in the variables of interest, the questionnaire was pretested on a sample population.

Dissemination of results

The UON faculty was given a presentation of the study's findings. The Cameroon Baptist Convention Health Services Board, the University of Nairobi Paediatrics Department, and the University of Nairobi library will all receive copies of the thesis. The management of the Mboppi and Bonaberi Baptist Hospitals in Douala, Cameroon will be given access to the findings, and policymakers will also be informed through presentations made at conferences and publications.

ETHICAL CONSIDERATION

Authorization to conduct the study

The Kenyatta Hospital-University of Nairobi Ethics and Research Committee ((KNH-ERC/A/324)) was consulted for permission.Additionally, approval was received from the hospitals where the study was done, the Institutional Review Board, and the Cameroon Baptist Convention Health Services (CBS).

Autonomy

The study was carried out after approved consent from the participants. the participants who refused to participate had no influence on their care the received.

Beneficence and Non maleficence

There were no gains, risks or influence on care to participants who consented or refused to take part in the study. Their choice to participate in the study in no way affected their safety or care

they received while at the hospital. Identified cases of neonatal sepsis on exit were brought to the attention of the primary care doctor for further action. No experimental medicines were used.

Justice

There was equality and fairness to all participants in the study.

Confidentiality

Throughout the entire study period, strict privacy was upheld. No personal information identifying the research participants was collected; instead, they were given study identification numbers.

Chapter 4: Results

4.1: Characteristics of the study population

A total of 400neonates were identified and 383 ended up being included in the study. Figure 7 below depicts the recruitment process all through to data analysis

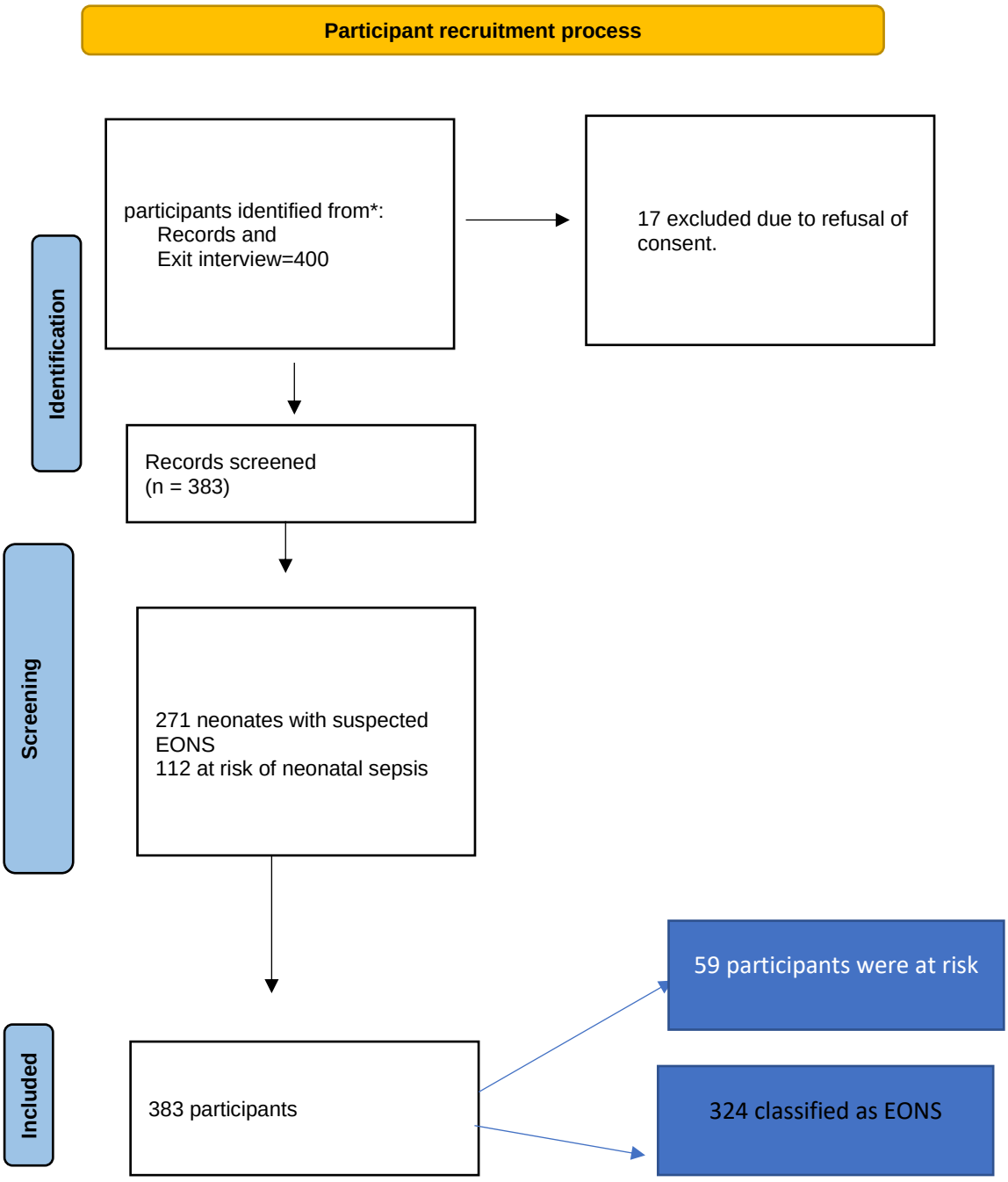


Figure 7:Participant recruitment

4.1.1: Base Line Characteristics of the Study Participants

383 participants were recruited into the study, mean age of participants was 2.3 days±1.0 days and median of 1.0 days. More than half (72.3%) were born at term (GA 37-40 weeks) and the lowest gestation was 28 weeks. 84.6% were hospital births. Males accounted for 56% As shown in the table 10 below.

Table 10 baseline characteristics of study participants

Variable	Characteristics	Frequency (n=383)	Percentage (%)
Gestational age	28 – <32	21	5.5
	32 - <37	46	12.0
	37- 40	277	72.3
	>42	39	10.2
Sex	Male	218	56.9
	Female	165	43.1
Admission weight	1000 - <1500	13	3.4
	1500 - <2500	54	14.1
	2500 - <4000	256	66.8
	≥4000	60	15.7
Place of delivery	health centre	7	1.8
	home	10	2.6
	Hospital	324	84.6
	Referral	18	4.7
	traditional birth	5	1.3
	None	19	5
Mode of delivery	SVD	268	69.9
	electives cs	5	1.3
	emergency CS	91	23.7
	no information	19	5

4.1.2: Clinical characteristics of our participants.

Of all the babies enrolled with at risk or suspected EONS, the most frequent presenting sign was fever defined by core temperature of above 37.5℃ and tachycardia which was found in 74.6 % and 78.3% respectively of the total study population. Table 11 below shows the various clinical characteristics identified while table 12 shows the proportion of neonates with at risk factors (perinatal risk factors). A total of 59 neonates were identified to be at risk

of neonatal sepsis based on the perinatal risk factors at exit however didn't present any signs and symptoms and they were monitored for any sign and symptoms by the clinicians.

Table 11: Clinical characteristics of study participants

Clinical feature	**N =383)**	**(%)**	**Clinical Feature**	**N = 383**	**%**
Fever	286	74.6%	Apnea	38	9.9%
tachycardia	300	78.3%	Tachypnoea or fast breathing	140	36.5%
Lethargy or change in level of activity	84	21.9%	Severe chest wall indrawing	100	26.1%
History of convulsions	16	4.1%	Grunting	80	20.8%
Bulging fontanel	8	2.0%	hypoxia	76	19.8%
Apnoea	38	9.9%	Jaundice within 24hrs of Birth	152	39.6%
Pallor	48	12.5%	Refusal to breastfeed	96	25.0%
Non sign or symptoms	59	15.4%			

Table 12: Perinatal risk factors

factor	N= 383	%	Not documented	%
Maternal fever	76	19.8	16	4.9
Chorioamnionitis	16	4.1	36	9.3
Vaginal discharge	72	18.7	36	9.3
Premature rupture of membrane	40	10.4	32	9.9
Difficult labor	56	14.6	24	6.3
Intrapartum antibiotics	32	8.3	24	6.3
Low birth weight	108	28.1	00	
Infant with any at risk criteria	112	56.1	00	

4.1.3: Baseline investigations requested within first 24 hours of admission:

For most patients admitted to the units, a full haemogram and CRP were requested. for patients presenting with sign and symptoms of meningitis such as convulsions, lethargy, a lumbar puncture was done for some patients. However, for blood cultures, they were not systematic performed as these are paid upfront. No patient had any urinalysis done within first 24 hours of admission

Also, basic metabolic panel (renal function and liver function test) was requested. Below (table 13) is a summary of investigations done.

Table 13:Investigations done at admission

Test	Test done	No information
CBC	292 (90.1%)	4 (1.2%)
CRP	312(96.3%)	12 (3.7%)
Blood culture	8 (2.5%)	12 (3.7%)
Lumbar puncture	104 (32.1%)	16 (4.9%)
Blood sugar	20 (6.2%)	20 (6.2%)

4.2: Proportion of Neonates with Appropriate Antimicrobial Prescription At Admission:

As first line for treatment of EONS, WHO recommends a penicillin and aminoglycoside(gentamicin). We found out that none had an appropriate prescription as per WHO recommendations. The first line therapy prescribed was a 3rd generation cephalosporin plus ampicillin and an aminoglycoside. However, we went ahead to analyze whether local prescriptions were appropriate in terms of dosing route and frequency. the proportion of neonates who had an appropriate dosing, route and frequency of the ampicillin, cefotaxime and gentamicin was 33.3% as summarized in table 14 below

Table 14 Proportion of neonates with appropriate prescription

Prescription	N(324)	%
Correct choice of antibiotics as per WHO guidelines	0	
1. Correct choice (Ampicillin cefotaxime and Gentamicin)	178	55%
2. Correct dose of ampicillin, gentamicin and cefotaxime	148	45.7%
3. Correct frequency of ampicillin and gent and cephalosporin	294	90%
4. Overall appropriate prescription (i.e. 1,2 and 3 correct)	108	33.3%

In figure 8 we show the general antibiotics pattern of antibiotic use in the hospitals within the first 24 hours of admission. the most frequent combination was a cephalosporin, aminoglycoside and ampicillin.

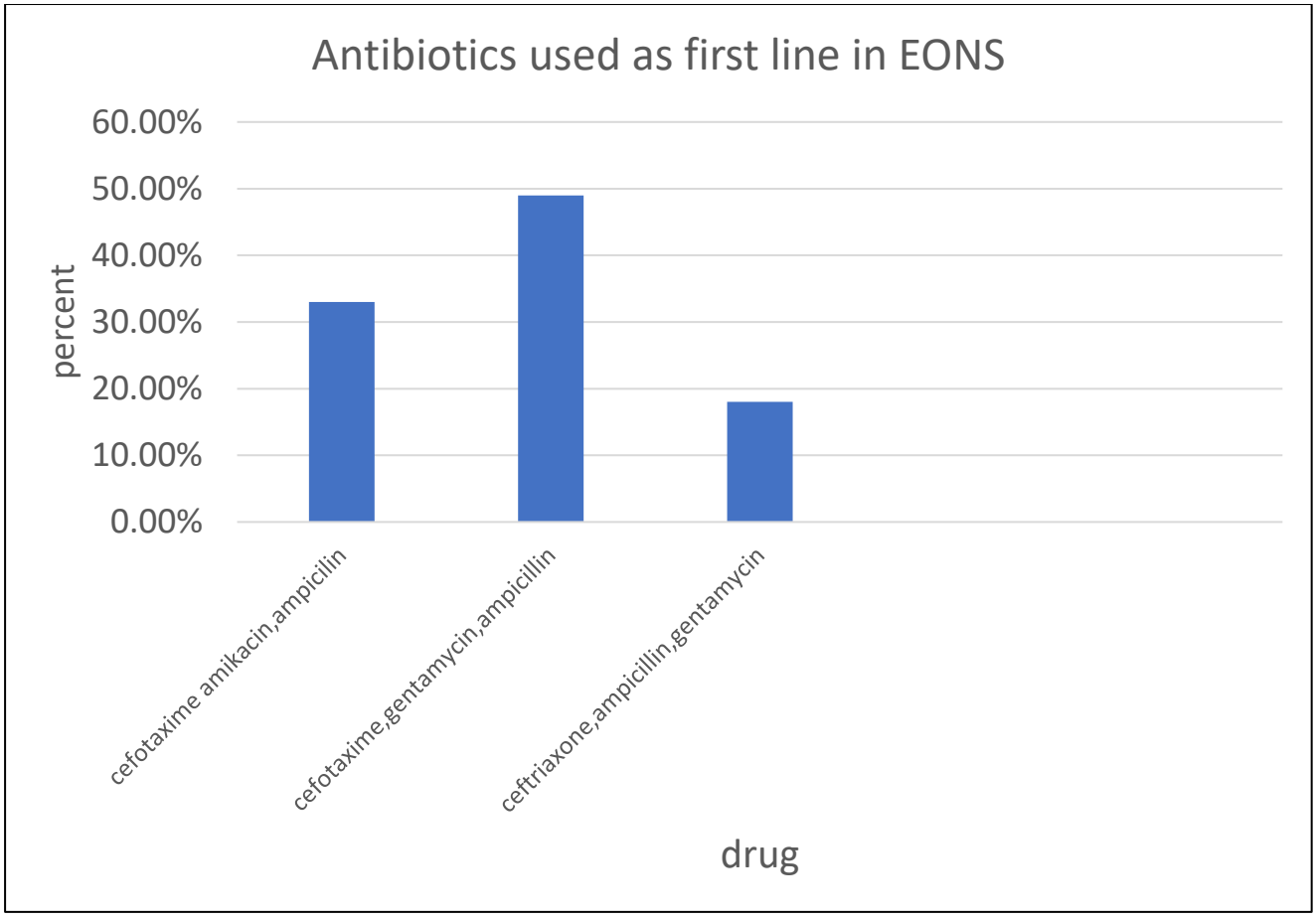


Figure 8:antibiotic prescription at admission

We then went ahead to describe the choice of antibiotics used, the dosage and route used .it was observed that all antibiotic prescribed were appropriately prescribed in terms of route and all neonates got the prescribed number of doses within the first 24 hours of admission, there was however a little percentage (10%) of neonates who didn't get their second prescribed dose of amikacin as this was not available in this hospital. It was noticed the most poorly prescribed antimicrobial were the aminoglycosides the general dose range of gentamycin was between 2.0 -7 mg /kg per dose, with most having > 5mg/kg dose irrespective of gestational age or birthweight or kidney function while amikacin was noted to be prescribed at a higher end of 20mg/kg per day in two divided doses as seen in table 15 below

Table 15:antimicrobial prescription, dose, route, frequency

	Cefotaxime N = 286	**Ampicillin N= 324**	**Gentamycin N=216**	**Amikacin N=108**	**Cefriaxone N= 38**
Correct dose mg/kg/dose WHO (5)	50	50	5-7.5	15	50
Dosing					
Appropriate dosing	272 (84.0%)	316 (97.5%)	96 (44.4%)	12(12.0%)	38(100%)
Under-dose	0	0	120(55.5%)	0	0
Over dose	8 (2.5%)	8	0	96(88.9%)	0
Recommended route – I/V	100%	100%	100%	100%	100%
Recommended doses in first 24 hours	2	2	1	1 dose	2 doses
number of doses received in first 24 hours	100%	100%	100%	11.1% - 1dose 88.9%-2 doses	100%
Duration of antibiotics					
< 7 days	53 (16.4%)	124 (38.2%)	216(66.7%)	108(33.3%)	20(6.1%)
7 days	200(69.9%)	200(61.7%)	0	0	18(47.4%
> 7 days	33	0	0	0	0

4.3: Factors associated with appropriate prescription

To assess factors associated with appropriate prescription, we assessed both clinical and perinatal factors for those who had been documented. The appropriate prescription (which was thus defined as the correct dose, frequency and route of the antibiotic chosen) was the common prescription on admission which was a combination of cefotaxime, ampicillin and gentamycin at the recommended dose.

The odds of getting an appropriate prescription were about 1.5 times higher amongst those who had chorioamnionitis, difficult labor and convulsions than those who did not have. However, this was not statistically significant as Seen in table 16 below.

Table 16: Factors associated with appropriate prescription

characteristics	Categories	Appropriate	Inappropriate	Missing values (%)	COR(CI)	AOR(CI)	P value
Maternal fever (n=299)	Present	25(33.8%)	142(63.1%)	25(7.7%)	0.10(0.06-0.18)	0.91(0.48-1.75)	0.78
	Absent	83(36.9%)	49(66.2%)				
Chorioamnionitis(n=279)	Present	93(35.4%)	70(64.6%)	45(13.9%)	0.18(0.02-1.57)	1.55(0.72-3.35)	0.82
	Absent	7(43.8%)	1(53.6%)				
Vaginal discharge (n=280)	Present	73(34.9%)	136(65.1%)	44(13.6%)	2.20(1.04-4.64)	0.74(0.36-1.52)	0.42
	Absent	10(42.3%)	41(57.7%)				
Prom (n=285)	Present	93(37.8%)	153(62.2%)	39(12.0%)	1.37(0.61-2.83)	0.9(0.51-1.61)	0.72
	Absent	12(30.8%)	27(69.2%)				
Difficult labor(n=292)	Present	92(38.8%)	145(61.2%)	32(9.9%)	1.42(0.72-2.66)	1.41(0.75-3.65)	0.29
	Absent	17(30.9%)	38(69.1%)				
Low BW(n=314)	Present	79(37.4%)	132(62.6%)	10(3.1%)	1.11(0.68-1.82)	1.07(0.52-2.20)	0.86
	Absent	36(35.0%)	67(65.0%)				
Refusal to feed(n=294)	No	74(37.0%)	126(63.0%)	30(9.3%)	0.60(0.60-1.64)	1.02(0.58-1.78)	0.95
	Yes	35(37.2%)	59(62.8%)				
Lethargy (n=295)	No	76(36.0%)	135(64.0%)	29(9.0%)	1.03(0.61-1.75)	0.92(0.49-1.74)	0.80
	Yes	31(36.9%)	53(63.1%)				
Fever (n=314)	No	73(35. %)	130(65.5%)	0			
	Yes	42(33.1%)	69(62.9%)	10(3.1%)	0.23(0.13-0.37)	0.91(0.42-2.3)	0.80
Convulsions(n=307)	No	109(37.5%)	182(62.5%)	17(5.2%)	0.75(0.25-2.24)	1.31(0.36-4.73)	0.69
	Yes	5(31.3%)	11(68.8%)				
Tachypnea(n=311)	No	68(39.3%)	105(60.7%)	13(4.0%)	0.79(0.50-1.27)	0.95(0.47-1.93)	0.89
	Yes	47(34.1%)	91(65.9%)				
Chest wall indrawing (n=303)	No	80(39.2%)	124(60.8%)	21(6.5%)	0.81(0.49-1.34)	1.14(0.46-2.84)	0.77
	Yes	34(34.3%)	65(65.7%)				
Grunting (n=307)	No	85(37.3%)	143(62.7%)	17(5.2%)	0.99(0.57-1.65)	1.00(0.42-2.39)	0.99
	Yes	29(36.7%)	50(63.3%)				
Hypoxia (n=306)	No	89(38.4%)	143(61.6%)	18(5.6%)	0.77(0.44-1.34)	1.02(0.47-2.21)	0.96
	Yes	24(32.4%)	50(67.6%)				
Jaundice (n=314)	No	64(38.3%)	103(61.7%)	10(3.1%)	0.85(0.53-1.36)	1.06(.53-2.13)	0.87
	Yes	51(34.7%)	96(65.3%)				
Pallor (n=314)	No	96(35.6%)	174(64.4%)	10(3.1%)	1.37(0.72-2.62)	0.58(0.25-1.33)	0.20
	Yes	19(43.2%)	25(56.8%)				

4.4: Pattern of antimicrobial prescription based on the WHO classification of antimicrobials (AWaRe)

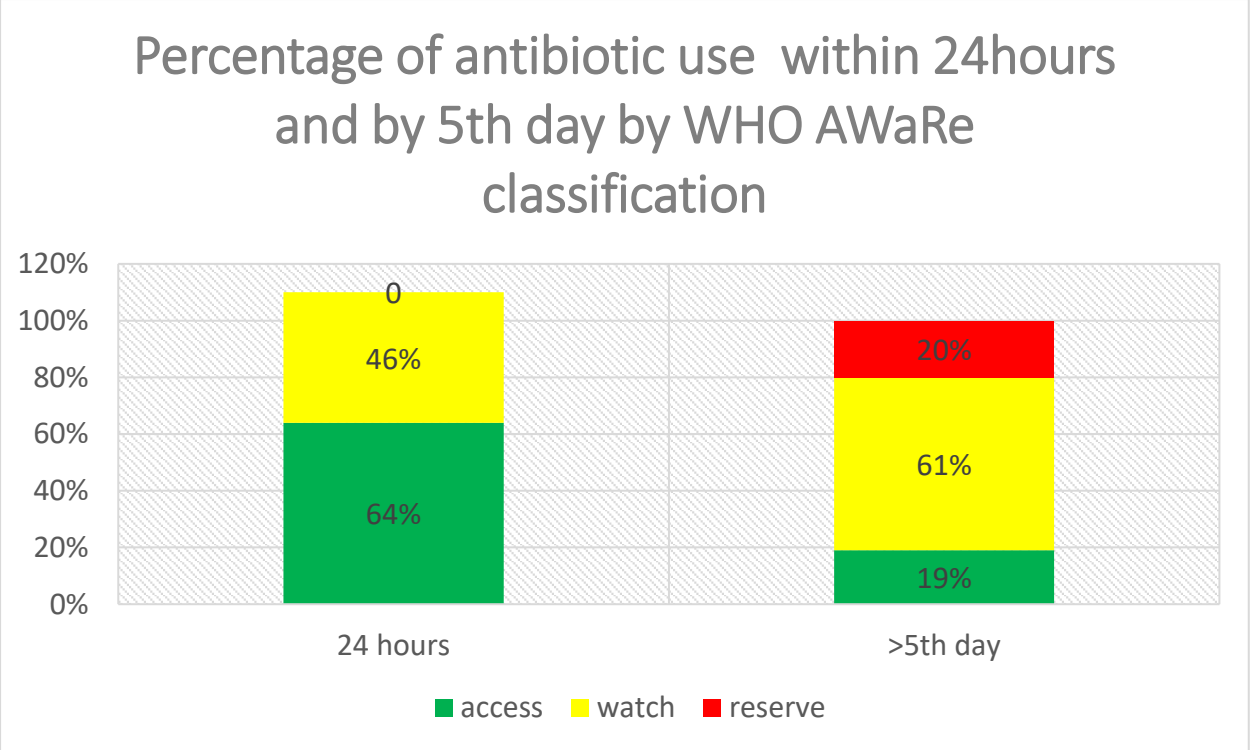
4.5.1: General antibiotic use

Antimicrobial prescriptions on admission included a cephalosporin, penicillin and gentamycin which are part of the WHO Access group and watch group however as we audited on the 5th day, we noticed that the second line antibiotics were more in the reserve group, 20% of antibiotic prescribed were in the reserve group as shown in table 17 and figure 4 below

Table 17: Antimicrobial use during the 5th day of stay

Group	Antibiotics	Frequency	Percentage use
Access	ampicillin	324	100%
	amikacin	108	33.3%
	gentamycin	216	66.7%
Watch	ceftazidime	272	84%
	cefotaxime	275	85.2%
	ciprofloxacin	272	84%
	ceftriaxone	61	18.8%
	Imipenem/cilastine	65	20.1%
	vancomycin	97	30%
Reserve	Aztreonam	65	20%

Figure 9: Percentage of antibiotic use within 24hours and by 5th day by WHO AWaRe classification



4.5: In hospital mortality:

Out of the 383 neonates who participated in our study,39 died. The total in hospital mortality during out study was 12% (CI 9.6-11.3) distributed as shown in table 18 below

Table 18: In hospital case fatality

Days	N=39	%
24 hours	14	35.9
24-72 hours	20	51.3
>72 hours-7th day	5	12.8

Chapter 5: Discussion

The aim of our study was to assess the appropriateness of antimicrobial prescriptions practices ,comparing to WHO, in neonates with early onset neonatal sepsis or at risk in two Baptist hospitals in Cameroon.

We found out that the prescriptions differed from the WHO recommended guidelines. The most used antibiotics were a combination of a 3rd generation cephalosporin, ampicillin and an aminoglycoside. Based on this combination, the proportion of neonates with appropriate antimicrobial prescription with respect to choice (cefotaxime, ampicillin and aminoglycoside), dose, route and frequency was 33%. This is similar to results obtained by Patel and colleagues where they found a high rate of inappropriate use of antimicrobials in terms of choice and also duration comparing it to the CDC 12 step guideline for antimicrobial use (48). Ollandzobo and colleagues, Congo Brazzaville also found a 47.3% rate of poor antimicrobial prescription in their study and attributed this to the lack of guidelines for physicians to follow when diagnosing and treating for sepsis (26). This could potentially pose a threat in terms of quality of care offered to the neonates contributing to their safety, recovery and even identification and prevention of complications that neonates with EONS face. Furthermore, this shows there is an impending threat for antimicrobial resistance. Therefore, an assessment of local bacteriological profile so as to establish antibiotic guidelines is needed as part of antibiotic stewardship. Our findings were much lower than 77% reported by Schellack in South Africa (29) and 97.8% in Kenya by Tank and colleagues. This difference may be due to the fact that they compared the prescription to the existing local guidelines which were widely being followed. There is evidence that quality of care tend to be better when there is a guide to follow hence one of the strategies for antimicrobial stewardship (27). Furthermore, their study sites were well structured and in a facility with pediatrician and local guidelines, therefore there was tendency to adhere to the guidelines and prescription dosages as opposed to our study site which consist of a myriad of practitioners, medical doctors and nurse practitioners from different areas with different principles hence there was a disharmony in practice methods.

According to WHO guidelines first line empiric antibiotic therapy for early onset sepsis include Gentamicin and B lactam antibiotic. We observed in this study three combinations of antibiotics were being frequently used; Combination of Aminoglycoside, Ampicillin & C3 antibiotic as first line treatment for EONS. Similar trends have been reported in some regions where antimicrobial profile have been found to be resistant to the penicillin and aminoglycosides (30) (49) ,(50) ,(51) and in areas with limited access to investigations such as

CSF analysis. The aim behind this is to empirically cover for possible bacterial meningitis and to avoid undertreating neonatal sepsis. However, this defeats the purpose when the duration of antimicrobial is not established due to lack of investigations to guide this decision-making process. In addition, this practice has been found to be associated with increase NEC, candidiasis sepsis and death. Clark and colleague carried out a multicenter retrospective cohort study of neonates receiving empirical treatment for EONS and found out that those who had received a combination of cefotaxime and ampicillin had increase likelihood of death as composed to those receiving ampicillin and gentamycin (52). This makes us wonder what could be the likely impact of that in Cameroon's setting not only the clinical aspects but the financial implication too as these drugs are not cheap and the patients have to pay upfront for those drugs. We observed the most wrongly prescribed drug was the aminoglycoside with 88% over dosages. A drug with a lot of toxicity and even more in neonates who have not yet had fully function renal system hence potential to cause kidney injury in neonates is high.

Our second objective was to assess factors associated with appropriate antimicrobial prescription. The odds of having an appropriate prescription were 1.5 times higher in those who had chorioamnionitis, difficult labor and convulsions ((1.5 95% CI 0.72-3.35, RR 1.4 95%CI0.75-2.65, RR1.3195%CI0.36-4.73) as opposed to those who did not. However, this was not statistically significant. This may be because of the fact that these usually are glaring signs and physicians tend to pay more attention in managing neonates who have the above risk factors. Also, the maternity staff in the unit undergo frequent refresher courses on management of various cases during labour and have many protocols pasted. This helps the staff quickly identify these cases or alarm signs and take action where needed.

Moreover, convulsion in a neonate is usually a danger sign and associated with meningitis Those who had fever were more likely to get an appropriate prescription (RR 0.7 95% CI-0.4-1.33). In Ollandzobo 's study, prematurity and prescriber were found to be associated with poor prescriptions. Fever usually is a less subtle sign which usually when present physicians may be become more confident in their diagnosis and hence seek appropriate treatment as compared to the other signs. Another reason for difference in factors identified maybe the fact that since our study had a myriad of practitioners with different criteria of diagnosis, documentation and treatment, many signs could have been missed or undocumented and we didn't also take into account practitioner's role as an independent factor associated with antimicrobial prescription.

Our third objective was to describe the pattern of antimicrobial use according to WHO AWaRe classification. The WHO "AWaRe" group classification of antimicrobials is to ensure more responsible prescribing with increased use of recommended antibiotics on the Access list, and reducing the use of antibiotics on the Watch and Reserve lists. Within the first 24 hours, 64% of antibiotics were in the "Access" and there was no use of "Reserve" antibiotic. while by the 5th day there was a 26 percent use of antibiotics reserve group. In our study, the drugs ampicillin and gentamicin (Access GROUP) where drugs found in the hospital and did not need to be paid for upfront hence could be the reason why there was such a high user rate of these drugs. Antibiotics on the watch criteria are guided by culture results and for the reserve by culture results and are kept for critically ill babies and as a last resort. This is similar to trends reported by Li and colleagues where they saw a 20% use of antibiotics in the reserve group (35). This shows there is growing use of reserve antibiotics and hence antibiotic stewardship programs are needed to guide the use of these. Without the presence of culture results to guide choice of antibiotics, there is tendency to misuse antibiotics and thereby creating or contributing to the already existing threat of antimicrobial resistance the world is facing. In addition to these, poor antibiotic stewardship at the end negatively impacts the health of the neonate by altering their microbiome. These drugs are expensive most of the time and, in a system, where there is no Universal health coverage and patients have to pay out of pocket and upfront, this causes a heavy financial burden on the parents of the affected neonates.

The case fatality was 12 % CI 9.6-11.3 .This is much lower than 15.7% reported by Koki and colleagues in Cameroon(44) and finding reported by Mhada and colleagues in Tanzania (36) This may be attributed to the fact that their hospitals were referral hospitals and included referred cases in their studies which tend to be very sick and have poorer prognosis hence higher likelihood of death. Moreover, our study was focused on EONS. Though this value may seem low yet more can be done to bring it much lower zero deaths bearing in mind that 95% of neonatal deaths are preventable.

Limitations

Data was abstracted from files hence tendency to get incomplete data. We tried overcoming this by sensitizing the physicians on the importance of good documentation.

Sampling was limited to faith- based hospitals and may not be representative of other hospitals

Strengths

This is the First study to look at prescription patterns in neonatal sepsis in Cameroon

Conclusion

1. Antimicrobial prescriptions differ from the WHO recommended guideline and there is a high level of inappropriate prescription amongst neonates at risk or with EONS at these hospitals

2. Neonates who had a history of difficult labour, chorioamnionitis and convulsions had 1.5 times higher odds of getting an appropriate prescription

3.There was a significant use of antibiotics in the Access criteria within the first 24 hours of admission.

4.Mortality was higher in the first 48 hours of admission

Recommendation

- Based on findings we recommend the need for harmonized protocols across Baptist hospitals which can guide clinicians on management of some common conditions especially in the absence of specialist care. These protocols should also be adapted to reflect the microbiology profile of the region so they can be applicable.
- Establishment of a record sheet is needed to help clinicians identify, assess and treat neonates with EONS so as to ease and harmonise documentation, help in correct identification and prompt treatment of the neonates
- Further studies are needed to study the antimicrobial resistance pattern in Cameroon, this will inform in antibiotic choice and guidelines.

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APPENDICES

Appendix 1: Time frame

Activity/motn	Jan/2020	feb	mar	apr	may	jun	jul	aug	sept	oct	Nov-feb	Mar 2022		Apr-nov	dec
Concept development															
Concept presentation															
Proposal submission to ethihc board															
Testing of questionaire															
Data collection															
Data analysis															
Thesis write up															
Thesis submission															

Appendix 2: Budget

Item	**quantity**	**Unit cost**	**Unit Cost (KShs)**	**Total (KShs)**
Proposal Development draft	1000 pages	10/page	10 000	10,000
Proposal Copies	10 copies	600	6,000	6000
KNH/UON ERC	1	2000	2,000	2000
Stationery (pens, notebooks)	10 packs	100	1,000	1000
Printing Questionnaires (50)	500 copies	10	5,000	5000
Security cabinet	1	5,000	5,000	5000
Training research assistant	1 day	1,500	4500	4500
3 Research assistants	12 weeks	15000	45000	45000
Airtime	-	Monthly bundle	3,000	3000
Data Analysis /statiscian	1	30000	30,000	30000
Computer Services		5,000		5000
Printing thesis drafts	1000 pages	10	10,000	10000
Printing Thesis	10 copies	600	6,000	6000
Transport	Return ticket (Nairobi Douala)	-	-	100,000
Contingency funds	30,000			30000
Total				235000

Appendix 3: Assessment tool

1. ADMISSION NOTES

Instructions: Tick/circle appropriately as required and fill in the details or measured values where applicable.

Neonate demographic information

1. Study No:_____ 2. Date of data collection: _____

3. Date of admission: _____

4. Time of admission:_____AM / PM (circle the appropriate)

5. Date of birth: _____

6. Sex: Male Female

Gestational age (weeks): _____8. Postnatal age (days): _____

9. Birth weight (grams): _____ 10.Admission weight (grams):

11. Date of birth: _____

12. Date of discharge/Death: _____

13. Outcome: Discharged Died Continued treatment

14. Place of delivery: Hospital Home

Other facility (specify)_____ No information

15. Mode of delivery: SVD Breech Emergency C/S Elective C/S No

information

16. Apgar score:_____ No information

17. Mother's age (years):_____ 18. Parity: _____

Diagnosis made: _____

Perinatal risk factors for neonatal sepsis: Maternal and Foetal Whether following risk factors for neonatal sepsis were noted by clinician or not?

Maternal fever (> 38 degrees C)	Present	Absent	No information
Foul smelling liquor	Present	Absent	No information
Chorioamnionitis	Present	Absent	No information
Discharge per vagina	Present	Absent	No information
Prolonged rupture of membranes (>18 hours)	Present	Absent	No information
Difficult or prolonged labour (>10hours primiparous, >8 hours multiparous)	Present	Absent	No information
Received intrapartum antibiotics	Present	Absent	No information
Low birth weight <2500g	Present	Absent	No information

Clinical features (signs and symptoms) of neonatal sepsis:

Whether following clinical features for neonatal sepsis were noted by clinician or not?

Temperature( )	_____		No information
Pulse rate(beats/min)	_____		No information
Respiratory rate(breaths/min)	_____		No information
Refusal to breastfeed or feeding intolerance	Yes	No	No information
Lethargy or change in level of activity	Yes	No	No information
History of convulsions	Yes	No	No information
Bulging fontanel	Yes	No	No information
Apnoea	Yes	No	No information
Tachypnoea or fast breathing	Yes	No	No information
Severe chest wall indrawing	Yes	No	No information
Grunting	Yes	No	No information
Cyanosis	Yes	No	No information
Decreased oxygen saturation	Yes	No	No information
Jaundice within 24hrs of Birth	Yes	No	No information
Pallor	Yes	No	No information

Laboratory Investigations

Were the following tests ordered?			
Complete blood count	Yes	No	No information
C reactive protein	Yes	No	No information
Blood culture	Yes	No	No information
Lumbar puncture	Yes	No	No information
Blood sugar	Yes	No	No information

Other Investigations (specify): 1. 2. 3.			

Treatment given at admission

Antibiotic choice	**Dose/kg/dose**	**Frequency/24hours**	**Route**	**Number of doses in 1st 24 hours**
Penicillin				
Gentamicin				
Ceftriaxone				
Amikacin				
ceftazidime				
ampicillin				
Other drugs				
1.				
2.				
3.				

Audit at 5th day

Antibiotic choice	**Dose/kg/dose**	**Frequency/24hours**	**Route**
Penicillin			
Gentamicin			
Ceftriaxone			
Amikacin			
ceftazidime			
ampicillin			

Other drugs			
1.			
2.			
3.			

OUTCOME OF NEONATAL SEPSIS IN 7 DAYS (tick appropriate)

1) Alive_____
2) Dead_____

i.≤24 hours_____

ii. >24 hours - ≤ 48 hours_____ iii.>48 hours – 7 days_____

iv. > cause of death

Appendix 4: PARENTAL CONSENT FORM

Consent information document in English Date:

Study Title: ANTIMICROBIAL PRESCRIPTION PRACTICES AND MORTALITY IN NEONATES ADMITTED WITH SUSPECTED NEONATAL SEPSIS AT THE MBOPPI AND BONABERI BAPTIST HOSPITALS, DOUALA, CAMEROON

Investigator: Dr Chifor Mfu Theresia

Paediatric resident, University of Nairobi P. O. Box 46657-00100, Nairobi.
Mobile:+254746393720/+237670051189

Email: chifor.terry@gmail.com

Supervisors:

1) Professor Ruth Nduati

Professor, Department of Paediatrics and Child Health, University of Nairobi, P.O. Box 49872.
Mobile number: +254 722235323
Email;ruth_nduati@yaho o.com

2) Dr. Aluvaala J

Lecturer, Department of Paediatrics and Child Health, University of Nairobi, P.O. Box 49872.
Mobile number: +254 722217034
Email: jaluvaaala@uonbi.ac.ke

Kenyatta National hospital/ University of Nairobi - Ethics and Research Committee College of Health Sciences
Telephone: (+254-020) 2726300-9, extension 44355

P.O. Box 19676-00202,
Nairobi. Email:
uonknh_erc@uonbi.ac.
ke

Introduction:

I am a postgraduate(doctor studying to better take care of babies) student at the University of Nairobi, studies leading to specialisation in Paediatrics and Child Health. I wish to request for your permission, for your baby to participate in a study that will form part of my degree work. The study will involve evaluation of files for documentation and antibiotic prescription. This will be recorded and analysed for research purposes only.

Purpose of the study:

The purpose of this study is to evaluate the antibiotic(drugs that killgerms) prescribing practices for newborns with infections called sepsis. It will provide information on the current management of sepsis and the steps that can be taken to improve management of sepsis. The information gathered will help in improving knowledge and correct errors on use and misuse of antibiotics.

Background:

Babies who get sick with first 28days of life is a major cause of illness and deaths all over the world. Early diagnosis (identifying this illness early and treating it can help the baby get well quicker. However prolonged unnecessary use of antibiotics is associated with bad consequences. Appropriate antibiotic use will improve newborn health and prevent antibiotic misuse and hence resistance.

Study Procedures:

Neonates aged 0 day to 28 days being admitted to paediatric unit, mboppi and bonaberi Baptist hospitals will be included in the study. Files of the enrolled participant will be evaluated for

neonatal assessment, investigations requested and antibiotic prescription after obtaining an informed consent o. Review of the files will be done at every day for 5 days. The data will be filled in the questionnaire. The outcome of the patient will be recorded within 7 days.

Benefits:

The results of this study will inform clinicians on use and misuse of antibiotics. It will also provide information on the current management of neonatal sepsis. The results of the research will also help clinicians to stop unnecessary use of antibiotics.

Risks:

There will be no harm or risks anticipated to your baby during the study. There will be no procedures that require pricking baby or using babys samples.no procedure will carried out in the study that may harm your baby.

Voluntariness:

The study will be fully voluntary. There will be no financial (money) rewards to your baby for participating in this study. One is free to participate or withdraw from the study at any point. Refusal to participate will not affect the management of your baby in any way.

Confidentiality:

The information obtained about your baby will be kept in strict confidence. No specific information regarding your baby will be released to any person without your written permission. We will, however, discuss general overall findings regarding all babies assessed but nothing specific will be discussed regarding your baby's condition. Your baby's study identity number will be used for follow up in the paediatric unit for 7 days and will not be revealed to anyone.

Problems or Questions:

If you ever have any questions about the study or about the use of the results you can contact

the principal investigator, Dr.Chifor Mfu, by calling on 670051189.

If you have any questions on your rights as a research participant you can contact the

The chairman of the Cameroon Baptist Convention health services ethics committee using the phone number 677633403.

Kenyatta National Hospital Ethics and Research Committee by calling 2726300, extension 44355

Consent form

Investigator: Dr Chifor Mfu Theresia
Paediatric resident, University of Nairobi P. O.
Box 46657-00100, Nairobi.
Mobile:0746393720/+237670051189
Email:chifor.terry@gmail com
Supervisors: 1) Professor Ruth Nduati
Professor, Department of Paediatrics and Child Health, University of
Nairobi, P.O. Box 49872.
Mobile number: +254 722235323
Email;ruth_nduati@yahoo.com
2) Dr. Aluvaala J
Lecturer, Department of Paediatrics and Child Health,
University of Nairobi, P.O. Box 49872.
Mobile number: +254 722217034
Email: jaluvaaala@uonbi.ac.ke
Kenyatta National hospital/ University of Nairobi - Ethics and Research
Committee College of Health Sciences
Telephone: (+254-020) 2726300-9, extension 44355
P.O. Box 19676-00202, Nairobi. Email: uonknh_erc@uonbi.ac.ke

I_____having received adequate information regarding the study research, benefits and risks hereby AGREE / DISAGREE (Cross out the appropriate) to participate in the study with my child. I understand that our participation is fully voluntary and that I am free to withdraw at any time. I have been given adequate opportunity to ask questions and seek clarification on the study and these have been addressed satisfactorily.

Parents/Guardian's Signature:_____

Date

I_____declare that I have adequately explained

to the above participant; the study procedure, benefits and risks and given him /her time to ask questions and seek clarification regarding the study. I have answered all the questions raised to the best of my ability.

Investigator's Signature_____

Date_____

Document d'informations aux fins de consentement

Date: _

Sujet de l'étude : PRATIQUES DE PRESCRIPTION D'ANTI-INFECTIEUX ET MORTALITÉ CHEZ LES NOUVEAU-NÉS HOSPITALISÉS POUR SEPSIS NÉONATAL SUSPECTÉ DANS LES HÔPITAUX BAPTISTES DE MBOPPI ET DE BONABERI, DOUALA, CAMEROUN

Enquêtrice : Dr Chifor Mfu Theresia

Interne en pédiatrie, Université de Nairobi B.P. 46657-00100, Nairobi.

Portable : +254746393720/+237670051189

E-mail : chifor.terry@gmail.com Superviseurs : Prof. Ruth Nduati

Professeure, département de pédiatrie et de santé de l'enfant, Université de Nairobi, B.P. 49872

Portable : +254 722235323

E-mail: ruth_nduati@yahoo.com

Dr Aluvaala J

Chargé d'enseignement, département de pédiatrie et de santé de l'enfant, Université de Nairobi, B.P. 49872

Portable : +254 722217034

E-mail : jaluvaaala@uonbi.ac.ke

Kenyatta National Hospital / Université de Nairobi - Comité d'éthique et de recherche Faculté des sciences de la santé

Téléphone : (+254-020) 2726300-9, extension 44355

B.P. 19676-00202, Nairobi.

E-mail : uonknh_erc@uonbi.ac.ke

Introduction :

Je suis étudiante en troisième cycle à l'Université de Nairobi, dans un cursus de spécialisation en pédiatrie et en santé de l'enfant. Je viens solliciter auprès de vous la permission de faire participer votre bébé à une étude qui sera une partie intégrante des travaux nécessaires pour l'obtention de mon diplôme. Cette étude nécessitera un examen des dossiers en vue d'évaluer la documentation et la prescription d'antibiotiques. Ces données seront enregistrées et analysées uniquement pour des fins de recherche.

Objectif de l'étude :

L'objectif de cette étude est l'évaluation des pratiques de prescription d'antibiotiques pour le sepsis néonatal. Elle apportera des informations sur l'état actuel de la prise en charge des cas de sepsis et proposera des mesures possibles pour l'amélioration de ladite prise en charge. Les informations recueillies serviront au renforcement des connaissances et à la correction des erreurs concernant l'utilisation des antibiotiques.

Mise en contexte :

Le sepsis néonatal est l'une des causes majeures de morbidité et de mortalité dans le monde. Il a été démontré qu'un diagnostic et un traitement précoces conduisent à une amélioration des résultats. Cependant, l'utilisation prolongée et inappropriée des antibiotiques s'accompagne d'effets pervers. Ainsi, utiliser les antibiotiques de manière appropriée améliorera les résultats et empêchera leur utilisation abusive et, par conséquent, la résistance à ceux-ci.

Procédures :

L'étude bénéficiera de la participation des nouveau-nés âgés de 0 à 28 jours hospitalisés dans les unités de pédiatrie des hôpitaux baptistes de Mboppi et de Bonabéri. Après obtention du consentement éclairé ou de l'assentiment, le dossier de chaque participant retenu sera étudié en vue d'évaluer l'examen clinique du nouveau-né, les examens complémentaires prescrits et la prescription d'antibiotiques. L'examen des dossiers aura lieu chaque jour pendant 5 jours.

Les données recueillies seront renseignées dans un questionnaire et les informations sur l'état de santé du patient après la prise en charge seront enregistrées dans un délai de 7 jours.

Utilité :

Les résultats de cette étude serviront de source d'informations pour les cliniciens sur l'utilisation appropriée et l'utilisation abusive des antibiotiques. En outre, ils apporteront des informations sur l'état actuel de la prise en charge des cas de sepsis néonatal. Ces résultats contribueront également à pousser les cliniciens à en finir avec l'utilisation inappropriée des antibiotiques.

Risques :

Votre bébé n'est exposé à aucun danger ni à aucun risque durant cette étude. Votre bébé ne subira aucune procédure invasive susceptible de lui nuire, dans le cadre de cette étude.

Volontariat :

La participation à cette étude est entièrement volontaire. Aucune compensation financière ne sera versée à votre bébé pour sa participation. Chaque personne contactée est libre de participer à cette étude ou de se retirer à n'importe quel moment et le refus de participer n'aura aucune conséquence sur la prise en charge de votre bébé.

Confidentialité :

Les informations obtenues sur votre bébé seront conservées en toute confidentialité. Aucune information spécifique concernant votre bébé ne sera divulguée sans votre autorisation écrite. Cependant, les conclusions générales concernant tous les nouveau-nés étudiés feront l'objet de discussions, mais rien de spécifique concernant l'état de santé de votre enfant ne sera abordé. Dans le cadre de l'étude, votre bébé se verra attribuer un numéro d'identifiant qui servira pour le suivi à l'unité de pédiatrie pendant 7 jours ; cet identifiant ne sera divulgué à personne.

Problèmes ou questions :

Si jamais vous avez des questions concernant cette étude ou l'utilisation des résultats, n'hésitez

pas à contacter l'enquêtrice principale, Dr Chifor Mfu, au 670051189.

Si vous avez des questions concernant vos droits en tant que participant à une recherche, n'hésitez pas à contacter le comité d'éthique et de recherche de Kenyatta National Hospital au (+254-020) 2726300, extension 44355.

Formulaire de consentement

Enquêtrice : Dr Chifor Mfu Theresia

Interne en pédiatrie, Université de Nairobi B.P. 46657-00100, Nairobi.

Portable : +254746393720/+237670051189

E-mail : chifor.terry@gmail.com

Superviseurs : Prof. Ruth Nduati

Téléphone : (+254-020) 2726300-9, extension 44355

B.P. 19676-

est entièrement volontaire et que je suis libre de me retirer, moi et mon enfant, à n'importe quel moment. L'occasion de poser des questions et de demander des éclaircissements sur l'étude m'a amplement été donnée et les réponses que j'ai reçues sont satisfaisantes.

Signature du parent / tuteur : _____Date : _____

Je soussigné(e), _____, déclare avoir expliqué au participant / à la participante cité(e) plus haut, de manière adéquate, la procédure, l'utilité et les risques de l'étude et lui ai donné le temps de poser des questions et de demander des éclaircissements concernant ladite étude. J'ai répondu aux questions soulevées au mieux de mes capacités.

Signature de l'enquêteur(trice) : _____Date :_____

Appendix 5.WHO Aware classification tool

ACESS	WATCH	RESERVE
Amikacin	Arbekacin	Aztreonam
Amoxicillin	Azithromycin	Ceftaroline fosamil
Amoxicillin/clavulanic Acid	Azlocillin	Ceftazidime-avibactam
Ampicillin	Biapenem	Ceftobiprole medocaril
Ampicillin/sulbactam	Carbenicillin	Ceftolozane-tazobactam
Bacampicillin	Cefaclor	Colistin
Benzathine benzylpenicillin	Cefamandole	Dalbavancin
Benzylpenicillin	Cefbuperazone	Dalfopristin-quinupristin
Cefacetrile	Cefcapene pivoxil	Daptomycin
Cefadroxil	Cefdinir	Eravacycline
Cefalexin	Cefditoren pivoxil	Faropenem
Cefalotin	Cefepime	Fosfomycin (IV)
Cefapirin	Cefetamet pivoxil	Linezolid
Cefatrizine	Cefixime	Meropenem-vaborbactam
Cefazedone	Cefmenoxime	Minocycline (IV)
Cefazolin	Cefmetazole	Omadacycline
Cefradine	Cefminox	Oritavancin
Cefroxadine	Cefodizime	Plazomicin
Ceftezole	Cefonicid	Polymyxin B
Chloramphenicol	Cefoperazone	Tedizolid
Clindamycin	Ceforanide	Telavancin
Clometocillin	Cefoselis	Tigecycline
Cloxacillin	Cefotaxime	
Dicloxacillin	Cefotetan	
Doxycycline	Cefotiam	
Flucloxacillin	Cefotiam hexetil	
Gentamicin	Cefoxitin	
Mecillinam	Cefozopran	
Metronidazole (IV)	Cefpiramide	

Metronidazole (oral)
Nafcillin
Nitrofurantoin
Oxacillin
Penamecillin
Phenoxymethylpenicillin
Pivampicillin
Pivmecillinam
Procaine benzylpenicillin
Spectinomycin
Sulfadiazine/trimethoprim
Sulfamethizole/trimethoprim
Sulfamethoxazole/trimethoprim
Sulfametrole/trimethoprim
Sulfamoxole/trimethoprim
Sultamicillin
Tetracycline
Thiamphenicol
Trimethoprim

Cefpirome
Cefpodoxime proxetil
Cefprozil
Ceftazidime
Cefteram pivoxil
Ceftibuten
Ceftizoxime
Ceftriaxone
Cefuroxime
Chlortetracycline
Ciprofloxacin
Clarithromycin
Clofoctol
Delafloxacin
Dibekacin
Dirithromycin
Doripenem
Enoxacin
Ertapenem
Erythromycin
Fleroxacin
Flomoxef
Flumequine
Fosfomycin (oral)
Fusidic Acid
Garenoxacin
Gatifloxacin
Gemifloxacin
Imipenem/cilastatin
Isepamicin
Josamycin

Kanamycin

Latamoxef

Levofloxacin

Lincomycin

Lomefloxacin

Lymecycline

Meropenem

Metacycline

Mezlocillin

Micronomicin

Midecamycin

Minocycline (oral)

Moxifloxacin

Neomycin

Netilmicin

Norfloxacin

Ofloxacin

Oleandomycin

Oxytetracycline

Panipenem

Pazufloxacin

Pefloxacin

Pheneticillin

Piperacillin

Piperacillin/tazobactam

Pristinamycin

Prulifloxacin

Ribostamycin

Rifabutin

Rifampicin

Rifamycin

Rifaximin

Roxithromycin

Rufloxacin

Sisomicin

Sitafloxacin

Sparfloxacin

Spiramycin

Spiramycin/metronidazole

Streptomycin

Sulbenicillin

Tebipenem

Teicoplanin

Telithromycin

Temocillin

Ticarcillin

Tobramycin

Tosufloxacin

Vancomycin (IV)

Vancomycin (oral)

Appendix 6: Ethical Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 17 SEP 2021 P.O. Box 20723 - 00202 NAIROBI KNH/UoN-ERC

Ref: KNH-ERC/A/324

17th September, 2021

Dr. Chifor M. Theresia
Reg. No.H58/34589/2019
Dept. of Paediatrics and Child Health
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Chifor

RESEARCH PROPOSAL: ANTIMICROBIAL PRESCRIPTION PRACTICES AND MORTALITY IN NEONATES ADMITTED WITH SUSPECTED NEONATAL SEPSIS AT THE MBOPI AND BONABERI BAPTIST HOSPITALS, DOULA, CAMEROON (P233/04/2021)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 17th September 2021 – 16th September 2022.

This approval is subject to compliance with the following requirements:

i. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
ii. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
iii. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from KNH- UoNERC for each batch of shipment.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal).
vii. Submission of an executive summary report within 90 days upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M.L CHINDIA
SECRETARY, KNH- UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chair, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Paediatrics and Child Health, UoN
Supervisors: Dr. Aluvaala Jalemba, Dept.of Paediatrics and Child Health, UoN
Prof. Ruth Nduati, Dept.of Paediatrics and Child Health, UoN

CAMEROON BAPTIST CONVENTION HEALTH BOARD
INSTITUTIONAL REVIEW BOARD

Baptist Centre, Nkwen, P.O. Box 1, Bamenda, Northwest Region

October 28, 2021

Chifor Mfu Theresia, MD
Paediatric resident
Department of Pediatrics and Child Health
University of Nairobi
Chifor.terry@gmail.com

IRB study number: IRB2021-63
Title of Protocol: **Antimicrobial Prescription Practices and Mortality in Neonates Admitted with Suspected Neonatal Sepsis at the Mboppi and Bonaberi Baptist Hospitals, Douala, Cameroon**

IRB approval date: October 28, 2021
IRB expiration date October 28, 2022

Dear Dr. Chifor,

Your proposed research seeks to determine the proportion of neonates with suspected EONS or at risk of neonatal sepsis based on perinatal risk factors with appropriate antibiotic (based on WHO guidelines, those needing antibiotics, type, dose, route and duration.) prescriptions at admission at the two hospitals.

Your study protocol was reviewed by members of the CBC Health Board IRB and presented to the entire Board on October 22, 2021. The Board deliberated on your protocol and the Board grants approval for your study.

Please understand that this is the ethical and safety approval for your study. You must present this IRB approval letter to the Hospital Administrator and Chief Medical Officer to carry out the study in the institution(s).

If you make any changes in the research protocol, please immediately send the IRB an amendment specifying the changes proposed.

The Board grants approval for this study for a one-year time period. Thereafter, before October 26, 2022, you will please complete our renewal form/final report which will be attached to an email and return it to me. The completed form must be reviewed and approved by the Institutional Review Board prior to the expiration date of the current approval period. The fee to renew a study protocol is 10,000 cfa.

Your protocol has been assigned the above reference IRB protocol number. All correspondence to us should include:

1. The IRB protocol number,
2. Name of the principal investigator and,
3. full title of the study.

Finally, all abstracts, manuscripts, posters and presentations pertaining to the above protocol, must be submitted to the IRB for pre-publication approval. This approval is for academic research purpose only. If you will like to publish this in future, a CBC Health Service staff of the Department where the study was conducted must be Co-Principal Investigator.

Please feel free to contact me with any questions and/or concerns regarding the above. Copies of all correspondence regarding this proposal should be sent to me and to Zita Acha secretary, e-mail cbchlirb@gmail.com.

Sincerely,

Samuel Ngum, PGDip, MSc., (I H), PhDc