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Prevalence and factors associated with extended-spectrum beta-lactamase bacterial isolates among term neonates with sepsis at Dodoma Regional Referral and Benjamin Mkapa Hospitals

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Abstract

Background

Extended spectrum beta lactamase (ESBL) producing bacteria, significantly lower the effectiveness of treatment of neonatal sepsis which accounts for 15-20% of death globally. There is limited data on prevalence and determinants of associated factors, hence highlighting the need of conducting this study at university of Dodoma teaching hospitals in Dodoma.

Methods

A cross-sectional study enrolled 300 term neonates with sign and symptoms of sepsis treated at Benjamin Mkapa and Dodoma Regional Referral Hospital. Data collection began from 01/09/2024 to 30/06/2025 and medical records were accessed on the same dates. A consecutive sampling was conducted until sample size was reached. Data was collected through structured questionnaires. Double disc synergistic test was done for detection of ESBL producing bacterial isolates and antimicrobial susceptibility test conducted as per CLSI.Data analysis was done using SPSS version 26. Descriptive statistics was computed and logistic regression models were used to identify factors associated with ESBL production. A p value<0.05 and 95% CI was considered statistically significant.

The study protocol was reviewed and approved by the Institution Research Review Ethical Committee (IRREC) at the University of Dodoma (UDOM). The approval number to conduct this research at Benjamin Mkapa Hospital was AB.150/293/01/"A"/241 and Dodoma Regional Referral Hospital was PB.22/1307/02/86. Written informed consent to participate was obtained from the parent or legal guardian of each neonate prior to enrollment. Parents/guardians received a full explanation of the study aims, procedures, potential benefits and risks, and the voluntary nature of participation. They were informed that refusal or withdrawal at any time would not affect the clinical care their child received. Study data and bacterial isolates were anonymized and stored securely; only the study team

had access to identifiable information. Permission to publish anonymized group-level results was obtained as part of the consent process.

Clinical trial number: not applicable

Results

Among 300 neonates, 114/300(38%) yielded culture positive and 49/114 (43%) were gram negative. ESBL producing bacteria accounted for 14.7%(44/300) and significant associated factors were caesarean delivery [p value=0.005, AOR= 5.22, 95% CI(1.66-16.40)], PROM [p value<0.001, AOR=21.54, 95% CI(5.53- 83.97)], maternal febrile condition [p value<0.001, AOR= 20.71, 95% CI(5.17- 82.89)], elevated CRP (10-49mg/L) [p value=0.033, AOR=4.97, 95% CI(1.14- 21.68)], and invasive procedure [p value=0.046, AOR=3.10, 1.02- 9.38)].The common isolate were *Klebsiella aeruginosa* 15/49(30.6%) and *Escherichia coli* 12/49(24.5%) with meropenem sensitivity of 93.3% and 91.7%, resistance to Ampicillin at 93% and 100%, Ceftriaxone resistance 73% and 66.7% respectively.

Conclusion

The prevalence of ESBL was found to be considerable burden in term neonate with sepsis. Neonates born through caesarean section, with maternal febrile conditions, and PROM should be considered high risk of acquiring ESBL. There was multiple resistance to first- and second-line antibiotics as recommended by WHO in treatment of neonatal sepsis hence further review needed on antibiotic of choice used according WHO and Tanzania standard treatment guideline.

Extended-spectrum beta-lactamase**,** resistance**,** term neonates**,** neonatal sepsis**,** prevalence, and associated factors.

Background

Neonatal sepsis is a condition affecting newborns within the first 28 days of life, which is associated with high morbidity and mortality rates, ranking among the top three causes of infant mortality globally (Dolma et al., 2018; Marando et al., 2018a; Tumuhamye et al., 2020). It is a systemic infection caused by bacteria, fungi, or viruses resulting in widespread inflammation and potential organ failure (Attia Hussein Mahmoud et al., 2023; Sands et al., 2022; Vincent, 2023). Neonatal sepsis is linked to vertical transmission from the mother, which occurs within the first 72 hours of life

and is classified into early-onset neonatal sepsis (EONS), whereas late-onset neonatal sepsis (LONS) is typically associated with environmental exposure or hospital-acquired infections (Celik et al., 2022; Sofouli et al., 2023). The incidence rates of neonatal sepsis are low in High-income countries (HIC), typically ranging between 1 and 5 cases per 1,000 live births. At the same time, it is substantialy higher in low- and middle-income countries(LMIC), ranging between 10 to 50 cases per 1,000 live births (Fleischmann et al., 2021; Sands et al., 2022; World Health Organisation, 2020).

Globally, neonatal sepsis contributes to approximately 15–20% of all neonatal deaths as it is significantly related to 2.4 million neonatal deaths annually, as reported by the World Health Organization (Muganza et al., 2021; World Health Organisation, 2020). Mortality rates are substantialy higher in LMICs, accounting for more than 30%, and lower in HICs, accounting for below 10%; the difference is primarily due to delayed diagnosis and limited access to effective antibiotics in LMICs (Adonis Muganza et al., 2021; Fleischmann et al., 2021). Neonatal sepsis is highly associated long-term complications, including developmental delays, chronic health conditions, and neurological impairments (Bakhuizen et al., 2014; Pek et al., 2020; Rath et al., 2022; Stoll et al., 2004). Furthermore, neonatal sepsis imposes a heavy economic burden on individuals and the public health system as a reason for extended hospital stays, intensive medical care, and treatment of complications (Watson et al., 2024).

The growing antibiotic resistance exhibited by bacteria causing neonatal sepsis has emerged as a significant concern that significantly reduce treatment effectiveness and infant outcomes. This clinical implication is even more complex in Bacteria that produces Extended Spectrum Beta-Lactamases (ESBLs) which hydrolyzes and cause resistance to various β-lactam antibiotics (Goltz et al., 2024; Kagia et al., 2019). The bacteria producing ESBL demonstrate resistance to several broad-spectrum antibiotics, including penicillin, third-generation cephalosporins like cefotaxime, ceftriaxone, and ceftazidime, and monobactams like aztreonam (Dolma et al., 2018; He et al., 2024).

The prevalence of Bacteria producing ESBL- in term neonates with sepsis is steadily rising globally and tends to vary significantly across different regions (He et al., 2024; Peirovifar et al., 2014; Shakil et al., 2009). In HICs, the prevalence of Bacteria producing ESBL- in neonates with sepsis has been rising steadily, reaching 10-30% of

neonatal sepsis, whereas in LMICs, there are significantly higher rates, accounting for more than 50% (Badakali et al., 2022; Marando et al., 2018; Sands et al., 2022; World Health Organisation, 2020). A meta-analysis study reported the pooled prevalence to be 15% in Africa, 12% in South America, 11% in India, 7% in the rest of Asia, and 4% in Europe (Flokas et al., 2017). In Kilifi District, Kenya, the prevalence was estimated to be around 10% (Kagia et al., 2019), while in Mwanza, Tanzania, it was found to be 10.5% among 304 newborns (Marando et al., 2018).

Gram-negative bacteria producing ESBL, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter spp*, are the most common causative organisms of especially in LMICs (Herindrainy et al., 2018; Kagia et al., 2019; Zhu et al., 2023). *E. coli* is the most frequently identified pathogen for community-acquired and hospital-acquired neonatal infections, while *Klebsiella pneumonia* is associated with hospital-acquired infections, especially in NICUs (He et al., 2024). Less common bacteria include *Enterobacter spp*, *Proteus spp*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Dolma et al., 2018; Tumuhamye et al., 2020).

Studies have reported various factors significantly associated with ESBL neonatal sepsis, ranging from maternal, neonatal, and healthcare-related factors. Such factors include UTI during pregnancy, prolonged rupture of membranes, intrapartum use of broad-spectrum antibiotics, chorioamnionitis,, invasive procedures, mechanical ventilation, overcrowded NICUs, prolonged or inappropriate antibiotic use, and inter-facility transfers (Dolma et al., 2018; Goltz et al., 2024; Harimanana et al., 2022; Zhu et al., 2023).

The WHO and Tanzania standard treatment guideline recommends combining Ampicillin, Cloxacillin, and Gentamycin as the first line and ceftriaxone as the second line for treating neonatal sepsis(Ababneh et al., 2022; United Republic of Tanzania, 2019). However, mortality rate is still high mainly due to resistance to this medication. Carbapenems which are effective alternative in treating neonatal sepsis caused by ESBL are not readily available and expensive to be afforded (Ababneh et al., 2022). Also, there is limited published data on the Prevalence and factors associated with ESBL neonatal sepsis, which creates more challenges in its management. This study is important in addressing this gap as it will contribute to the early detection and effective management of ESBL neonatal sepsis.

Materials and methods

Study Design and Area

This was the quantitative analytical cross-sectional study design which was conducted at two teaching hospitals of the University of Dodoma which are Dodoma Regional Referral Hospital (DRRH) and Benjamin Mkapa Hospital (BMH) due to their large number of patient with Neonatal sepsis also received term neonate with sepsis whom are inadequate diagnose with poor response to treatment due to over use and inadequate antibiotics from referred center.

Both hospitals serve all districts within the Dodoma region along with several districts from neighboring regions like Singida, Iringa, and Morogoro. Both hospitals are designated teaching hospitals for the University of Dodoma, encompassing undergraduate and post-graduate levels. The department had a Neonatal ICU that takes care of severely sick neonates and unstable premature neonates, a Kangaroo mother care service, and a surgical Neonatal ICU for neonates with surgical conditions.

Study Population

The study enrolled term neonates aged 0 to 28 days of life with one or more signs or symptoms suggestive of neonatal sepsis who were receiving care in the neonatal care unit at DRRH and BMH during the study period. The study included all Term neonates with two or more of the following signs and symptoms; axillary temperature (with >37.5°C or <36.5 °C), Difficulty in breathing with lower chest wall indrawing, grunting, bluish discoloration (Cyanosis), hypoxia (<90%). Vomiting, inability to feed, redness of umbilicus and skin infection pulse rate (>160 or <100 beat per min) and respiratory rate (>60 or <30 breaths per minute). Excluded term neonate with Low birth weight (<2.5kg)

Sample Size

The estimated prevalence of ESBL of 25.4% from a previous relevant study (Nelson et al., 2014) was utilized to obtain the study's sample size. Kish and Leslie's 1965 formula was used to calculate sample size (Charan & Biswas, 2013) formula as follows: $n = \frac{Z^2P(1-P)}{d^2}$. Where; Z a standard normal variate equal to 1.96 at type

1 error and 95% confidence interval p = proportion in population based on the previous relevant study, which was 25.4% from the study done in Mwanza, Tanzania (Nelson et al., 2014). d= absolute error, which is equal to 0.05 at a 95% confidence interval n = Estimated sample size $n = \frac{1.96^2 * 0.254(1-0.254)}{0.05^2} = 291$ Neonatal sepsis patients. Based on the prevalence of 25.4% from Nelson et al. (2014), a minimum of 291 neonates was required. To account for non-response or incomplete data, 300 were enrolled.

.**Sampling technique**

A simple random consecutive sampling technique was employed, and all term neonates with sepsis had an equal chance and participated in this study. The lottery method for simple random selection was achieved on consecutive day by assigning a unique number for each eligible neonate on separate pieces of paper. These pieces of paper were thoroughly mixed in a container to randomize their order. Once well mixed, the required number of identifiers was drawn from the container one at a time without replacement. The neonates corresponding to the drawn identifiers were enrolled in the study.

Data Collection Tools and Procedure

Data was collected for a period of 10 months from 01/09/2024 to 30/06/2025. A pre-tested structured questionnaire was used to collect data through face-to-face interviews, and medical records. Data collected through interview were socio-demographics such as age, sex, residence, weight, gestational age. A structured checklist for clinical assessment included a thorough history taking involving maternal risk factors such as Maternal febrile condition, chorioamnionitis, PROM, delivery method. Also, neonatal factors such as resuscitation, intervention and invasive procedure, long hospital stay was recorded accordingly. Physical examination aimed at assessing neonatal sepsis symptoms and signs such as fever, hypothermia, convulsion, difficulty in breathing, vomiting, jaundiced, redness of umbilicus, abdominal distension, respiratory distress with Fast breathing (tachypnea <20cpm or >60cpm), grunting and lower chest wall in drawing and tachycardia with duration of symptoms. Laboratory investigation was microbiological (identification of specific ESBL producing pathogen, antimicrobial susceptibility pattern); Hematological

finding was (Full blood picture, & C-reactive protein). All information required from medical records were accessed during the same period of the study (01/09/2024 to 30/06/2025).

Vital Signs: Upon admission, the axillary body temperature were assessed using an Omron digital thermometer from China. Following each use, the thermometer was sanitized using cotton wool and 70% alcohol to prevent contamination. A Masimo radical pulse oximeter manufactured in India was recording heart rate and oxygen saturation from the neonate's thumb or fingers. Respiratory rate was recorded manually by counting chest movement in a full minute.

Laboratory procedures; Blood collection, Transportation and Handling

The laboratory assessment involved various tests, including a Full blood picture, CRP, Blood culture, and antimicrobial susceptibility test. The laboratory request form was completed and included the date, time, and patient number. Hands were washed with soap and water and then disinfected with alcohol hand disinfectant, Sterile gloves were donned, the sterile blood culture pack was opened onto the trolley. Povidone iodine was poured into the fluid recess on the blood culture tray/pack. The needle and syringe were dropped onto the sterile field. The selected venipuncture site was cleaned with 10% povidone iodine in a circular motion outward using an aseptic technique. Then, 1- 2 minutes was allowed for disinfectant to dry. A venipuncture was done; blood was collected from the dorsal hand vein, antecubital vein, or scalp veins. The sterile needle with a 5ml syringe was used to collect the blood sample. After blood collection, the needle was removed, and gentle pressure applied. Then 3mls of blood sample was put into a labeled bottle and sent to laboratory for culture and sensitivity and 2ml of blood was collected into EDTA tube for FBC. All collected blood samples were transported within 1hour to laboratory for clinical microbiology and Hematology investigations.

Blood Culture

The vials of collected blood sample were delivered to the Clinical microbiology section for incubation using the BD BACTEC FX 40 (BD Bectron,Dickinson and Company,Maryland,USA) blood culture system. At the laboratory incubated at 35C aerobically for 5 days. A flashing red and green light was indication of a positive and

negative blood culture respectively. All positive blood cultures were further sub-cultured on two chocolate agars, two blood agar and MacConkey agar plates. One inoculated blood agar and one inoculated chocolate agar plates were incubated under microaerophilic environment in a candle jar at 37°C for 24 hours and the remaining inoculated plates were incubated at 37°C aerobically for 24 hours.

Bacteria Identification

Pure bacterial colonies were obtained and isolated bacteria were identified by their morphological characteristics on the culture media. Glass slide was labelled and one bacteria colony was spread on the slide to make a smear for gram stain. The stained bacteria were examined under light microscope at 100X magnification. Biochemical identification tests were used for further bacteria identification in which, for gram positive bacteria, catalase and coagulase tests were used. Moreover, triple sugar iron, Sulphur indole motility, indole, urea, lysine and citrate tests were used for biochemical identification of gram-negative bacteria.

ESBL detection and Antibiotic susceptibility testing

As per the recommendation of the Clinical and Laboratory Standards Institute, the antibiotic susceptibility testing was performed using the Modified Kirby-Bauer Disk Diffusion Method were Ampicillin, Gentamicin, Ciprofloxacin, Ceftriaxone, Amoxiclav, Meropenem and Cefotaxime were used. Two to five bacterial colonies were dissolved into cryovial tube containing 2mls of 0.9% saline solution to make a suspension at a concentration equivalent to 0.5 MacFarland solution turbidity for antibiotic susceptibility testing. After the turbidity match, the suspension was inoculated on Muller Hinton agar (MHA) and the plates was left at room temperature for 5-10 minutes to dry and 7 antibiotic discs as mentioned above were placed on MHA plate at least 24mm from center to center of adjacent discs. Inoculated MHA plates with antibiotic discs were incubated at 37°C for 24 hours. Diameters of the zone of inhibition of the incorporated discs was measured according to break points by the CLSI (2025). The susceptibility of tested drugs was examined by measuring zone of inhibition around antibiotic discs and identified which drugs were sensitive, intermediate or resistant to isolated bacteria. Isolates with zone of inhibition <27mm for cefotaxime (30µg) was identified as suspicious for ESBL production and were

further processed for their antibiotic susceptibility in double disc diffusion test. In the double disc diffusion test, two antibiotic discs, cefotaxime (30µg) disc and cefotaxime (30µg) plus clavulanic acid were placed 30mm apart on MHA plate inoculated with bacteria suspension equivalent to 0.5 MacFarland solution turbidity, then incubated aerobically at 37°C for 24 hours. ESBL production was inferred when the zone of was increased by >5mm by the clavulanic acid.

Complete Blood Picture (FBP)

In the laboratory for analysis, the Ruby system hematological analyzer machine manufactured in the United States of America was utilized (Abbot,CELL-DYN Ruby from the United States of America). This machine employs cytometric techniques to assess various blood components, including white blood cells, platelets, red blood cells, and hemoglobin levels. The outcomes displayed on the screen for review and printed out for documentation. The reference values which were adapted from Al-Marzoki et al (2012), was the average Hemoglobin g/dL range was 11-17.3 with SD 1.46, WBC x109 range 9-30.1 with SD 2.8, Neutrophil count (2.7-13x10*9/l) SD 11.2, Lymphocyte % 15-75 SD 10.7, Platelet count X 109/L 150-450 SD 10

C - reactive protein

This was done by using the Dade Behring Nephelometer II analyzer system (Siemens BN II, Utah in USA DBNII) with a 3-channel, 3valve dilute with 2500-ul syringes,840nm+-25 wavelength analyzer, and terminal equipped with power Mac Cintosh 7200/72 computer. Quantification was made by latex-enhanced nephelometry. The test sample was diluted and combined with latex particles coated in mouse monoclonal anti-CRP antibodies. A calibration curve was determining the CRP levels in the tested sample, creating an antigen-antibody combination with adhesive particles. In this study, the cut-off values were greater than 8.7gm/dl which indicated abnormalities in CRP showing the presence of bacteria, where values less than 1gm/dl indicated normal CRP.

Data processing and analysis

Data entry and cleaning were conducted using Microsoft Excel computer software. Then, the cleaned data were exported to IBM-SPSS software for Windows version 27

for analysis. Analysis was performed for summary statistics, and the results were shown using tables and charts. Frequencies and percentages for categorical variables was observed. Continuous variables were assessed using statistical measures such as median, and interquartile range. A chi-square test was used to assess the association between independent and dependent variables. The factors significantly associated with ESBL resistance among neonatal sepsis patients was analyzed using Univariate and multivariable logistic regression and determined the crude odds ratios (COR) and adjusted odds ratios (AOR); a significance level of p-value less than 0.05 was considered statistically significant at a 95% confidence interval.

Results

Socio-Demographic and Clinical Characteristics of ESBL producing bacterial isolate among term neonates with sepsis at DRRH and BMH

Majority accounting 231(77.0%) of neonates with sepsis were aged seven days and below with the median age of 5 days and interquartile range of 6 (to 2 to 8) days of life. There was almost equal distribution between female and male being 156(52.0%) and 144(48.0%) respectively. Total of 285(95.0%) were hospital deliveries and 92(30.7%) were referrals. Regarding clinical characteristics of neonate with sepsis, 202(67.3%) were delivered through spontaneous vertex delivery whereas 98(32.7%) were through cesarean delivery. About 66(22.0%) were born by mothers with PROM and 46 (15.3%) their mothers had febrile condition prior to delivery (Table 4.1).

Prevalence of Extended-Spectrum Beta-Lactamase (ESBL) producing bacterial isolates among Term neonates with Sepsis at DRRH and BMH

Out of all 300 neonates with sepsis at the University of Dodoma teaching hospitals, 144 had positive blood culture,49 (43%) were gram-negative isolates. Among them, 44(89.8%) had ESBL-producing bacteria, making the prevalence of 14.7% out of all 300 neonates with sepsis (Figure 1). The most common isolated bacteria were *Klebsiella aeruginosa* 15(30.6%), followed by *Escherichia coli* 12(24.5%), *Klebsiella pneumonia* 7(14.3%) and pseudomonas *spp* 5(10.2%) figure2.

Factors associated with ESBL producing bacterial isolates among Term neonates with sepsis at DRRH and BMH.

In chi square test, several variables were statistically significantly associated with ESBL neonatal sepsis. Such factors include delivery method (p value<0.001), PROM, and maternal febrile condition, each with p value<0.001. also, invasion procedures, c-reacting protein, platelet count and resuscitation were significantly associated with ESBL neonatal sepsis with p value <0.05 (table 4.3.)

In multivariate logistic regression, various maternal factors shown significant association with ESBL neonatal sepsis. Such maternal factor included mode of delivery, history of PROM and maternal febrile condition. Neonates born through caesarean section were five-fold more likely to have ESBL compared to those born through SVD [p-value= 0.005, AOR=5.22, 95% CI (1.66-16.40)]. Also, neonates born from mothers with PROM were about 22-fold more likely to have ESBL compared to their counterpart [p value<0.001, AOR=21.54, 95% CI (5.53-83.97)] and those born by mothers with intrapartum febrile illness were about 21-times more likely to have ESBL compared to their counterpart [<0.001, AOR=20.71, 95% CI (5.17-82.89)].

Regarding neonatal factors, neonates with elevated C-reactive protein were statistically significantly associated with ESBL neonatal sepsis in such a way that those with high CRP count being about fivefold more likely [p value=0.033, AOR=4.97, 95% CI (1.14- 21.68)], and those with very high CRP being 61-fold [p value<0.001, AOR= 61.44, 95% CI (7.94-475.78)]. Neonates who underwent an invasive procedure were about threefold more likely to have ESBL compared to those with no invasive procedure [p value=0.046, AOR=3.10, 95% CI (1.02-9.38)].

The findings in Table 4.4, the univariate analysis showed gestational age was statistically significant associated with ESBL neonatal sepsis (p=0.030). Early term neonates had 4.57 times higher odds of developing ESBL sepsis compared to post-term neonates [COR=4.57, 95% CI:1.09-19.13]. However, in a multivariable regression model, early term neonates had 78% lower odds of developing ESBL sepsis compared to post-term neonates [AOR=0.22, 95% CI: 0.05-0.92, p=0.037]. Although full-term neonates also showed reduced odds [AOR=0.36, 95% CI: 0.10-01.26], this was not statistically significant (p=0.110)

Antimicrobial Susceptibility of Common Bacterial Isolates producing ESBL among Term Neonates with Sepsis at DRRH and BMH

The finding (Table 4.5) reveals that ampicillin, gentamicin, and ceftriaxone showed high resistance rates among isolates, particularly at DRRH. For ampicillin, resistance was observed in 1 (100%) of the isolates at DRRH, while sensitivity was found in 1(10%) at BMH and 44 (97.8%) at DRRH. Similarly, gentamicin showed resistance in 1 (10%) at BMH and 9 (90%) at DRRH, with only a small proportion being sensitive. Ceftriaxone also exhibited considerable resistance, with 1 (9.1%) at BMH and 10 (90.9%) at DRRH. Regarding antimicrobial susceptibility, *Klebsiella aeruginosa* showed resistance to the majority of medications, including ampicillin (93,3%), gentamycin (86.7%), ceftriaxone (73.3%), and amoxicillin-clavulanic (84.6%) except for meropenem (6.7%) and Amikacin (40.0%). *Escherichia coli* was resistant to ampicillin (100%), ceftriaxone (66.7%), and amoxicillin-clavulanic (66.7%), and was sensitive to meropenem (91.7%). (Table 4.6)

Discussion

In this study, a large proportion of term neonates were within the first seven days of life which highlights the burden of early-onset sepsis being critical concern in our settings.Current study reveal prevalence of 14.7% ESBL bacterial isolate among 114 term neonate with culture positive with 89.4% of ESBL producer among gram negative bacteria isolates. The high level of prevalence of ESBL on current study differ from other study due to method of isolation of organisms used, where in this study was phenotypically done, differences in geographical locations influenced by local antibiotic usage, hospital infection control practices, and circulating bacterial strains. Factors associated were Cesarean delivery, Rupture of membrane, maternal febrile conditions, Gestational age, CRP, Invasive procedures. This finding is similar to the studies from LMICs, where early neonatal sepsis is often high due to perinatal transmission along with limited intrapartum infection prevention (Sands et al., 2022). The almost equal male to female sex distribution in this study highlights no strong sex-based predisposition to neonatal sepsis which aligns with other studies from different regions (Marando et al., 2018; Mhada et al., 2012). Clinically, 67.3% of neonates were delivered via spontaneous vertex delivery (SVD), while 32.7% were born through cesarean section (CS). It is evident that the rate of CS is raising in Africa as seen in

several other studies however it is highly associated with increased risk of neonatal infections due to prolonged hospital stay and possible breaches in aseptic techniques (Kagia et al., 2019). The high prevalence of ESBL-producing bacterial isolate from this study limits the effectiveness of common first-line and second line antibiotics, such as third-generation cephalosporins, however the antibiotic of choice for treatment of ESBL neonatal sepsis are carbapenems which are not easly available however when irrational used increases the risk of broader carbapenem resistance, a major public health threat. The findings attained, will emphasize need for robust laboratory protocols that involves routinely screen for ESBL production in all gram-negative bacteria isolated from neonatal cultures. Standard empirical antibiotic regimens for neonatal sepsis should be reviewed and potentially updated to account for the local prevalence of ESBL. In our setting, a combination therapy or the use of carbapenems might be necessary for initial treatment of high-risk term neonates. This ensures that appropriate, targeted antibiotic therapy can be initiated promptly which are standard empirical treatment for neonatal sepsis. The identified factors related to delivery mode, membrane rupture, invasive procedures, CRP and maternal febrile conditions highlight the need for improving infection control measures. Therefore, there must be i improved hand hygiene, proper care for invasive lines, and surveillance in high-risk areas like the neonatal intensive care unit (NICU).This study will provide a crucial local awareness of antibiotic resistance, which can assist in improving the development of a antimicrobial stewardship program. This ensures control and careful use of antibiotics to preserve their effectiveness and prevent further resistance. This study identified factors associated with ESBL prevalence, did not establish a direct causal link. Further research would be needed to determine definitive causation. It is recommended that advanced techniques like whole-genome sequencing to understand the transmission dynamics and spread of specific ESBL strains within the hospital and community and rapid diagnostic tests to identify ESBL-producing bacteria earlier and guide targeted therapy.

Prevalence of Extended Spectrum Beta Lactamase (ESBL) Causing Neonatal Sepsis

The prevalence of Extended Spectrum Beta Lactamase ESBL-producing bacteria among neonates with sepsis in this study was 14.7%. the findings was similar to the study done in Zanzibar 13.4% however there was difference in studied

population(Omar et al., 2024), it was relatively high compared to 10% observed in Kenya, although 10% was during admission and after a follow-up there was very high accounting to 21.4% acquisition per day during the hospital stay (Kagia et al., 2019). Another lower prevalence was reported in the study in Mwanza, Tanzania, was 10.5% (Marando et al., 2018a), however in 2014 at Mwanza the prevalence was higher to our study which accounted for 25.4% and the acquisition rate was 60.0% on day 1, 25.7% on day 3, and 14.3% on day 7 (Nelson et al., 2014). However, this differed from the studies may be attributed to different methodology, sample size and population.

This high prevalence of ESBL-producing neonatal sepsis is scientifically plausible in LMICs because of the overuse of broad-spectrum antibiotics in maternal care peripartum and neonatal care (Cantey, 2016; Manandhar et al., 2021; Romandini et al., 2021). The prevalence of ESBL producing pathogens is unexpectedly high even in countries with advanced technology and economy like China.However the study assessed the and trends of ESBL-producing EKP (Enterobacteriaceae, *Klebsiella pneumoniae*, and *Escherichia coli*) UTIs in a pediatric cohort over five years not neonates as per our study (He et al., 2024b). Another study in China reported 233 cases of gram-negative bacterial neonatal sepsis whereby 60.5% of cases were confirmed as *E. coli* and 69 being ESBL-producing. The proportion of ESBL-producing *E. coli* strains over the years was as low as 31.6% in 2019, followed by a steady increase to 66.7% by 2021 (Zhu et al., 2023). This study shows that the prevalence of ESBL-producing E. coli steadily increases in developed countries like China, reaching twice only in three years; this could probably be due to the widely spread use of antibiotics.

Successful control of ESBL producing neonatal sepsis was reported in some developed countries like Italy, with the use of meropenem, surveillance cultures for all neonates, improvement of NICU environments, and medical devices, together with extended use of contact precautions (Priante et al., 2022). Same findings were reported in Korea to successfully address the outbreak whereby the healthcare-associated infection rate decreased from 6.0 to 0.0 per 1000 patient-days after implementing the enhanced IC procedures. Also, active surveillance cultures revealed that 31.9% of the screened neonates were colonized with ESBL-KPN due to Contaminated NICU environments and medical devices, as well as transmission by medical personnel (Baek et al., 2020). Therefore, monitoring the NICU environment, devices and practice is great hit on preventing ESBL producing bacteria among neonates.

Factors Associated with ESBL Causing Neonatal Sepsis

In this study, several factors were found to be significant predictors of ESBL-producing sepsis among neonates. Such factors include cesarean delivery, premature rupture of membrane, maternal febrile conditions, elevated C-reactive protein (CRP) and invasive procedure.

In this study Cesarean section were found to have a 5-fold increased likelihood of ESBL infection compared to those born through spontaneous vaginal delivery. This finding aligns with evidence from a study done in Kenya which reported that CS was about four-time high risk of ESBL producing bacteria (Kagia et al., 2019) and the study done in Uganda (Tumuhamye et al., 2020). The study done in Madagascar reported the cesarean delivery to be three times more likely to acquire ESBL producing organisms among Neonates (Herindrainy et al., 2018) similar to the study done in China (Li et al., 2017).

Cesarean delivery tend to disrupt gut microbiota and impair immune function by causing a Th1/Th2 cell imbalance, as metabolic pathway analysis revealed a three significantly upregulated intestinal microbial pathways, along with reduced serum IgG and IL-12p70 levels and IFN-γ/IL-4 ratio was notably lower (Buffington et al., 2023; Lai et al., 2024). The bypass of maternal vaginal microbiota, exposes neonates delivered by cesarean section to skin contamination and hospital acquired microbials which are resistant to antibiotics (Article et al., 2021; Jaspan et al., 2023; Reznik et al., 2024). Mothers undergoing cesarean delivery are routinely given prophylactic antibiotics to prevent surgical site infections which exposes neonates to transmission of resistant bacteria such as ESBL-producing *K. pneumoniae* (Diniz et al., 2021; Inchingolo et al., 2024a; Pivrncova et al., 2022).

In this study, neonates whose mothers experienced PROM were over 21 times more likely to develop ESBL- producing bacteria causing neonatal sepsis. This finding is supported by the study done in Indonesia which reported History of PROM as independent risk factor for ESBL-producing bacteria causing neonatal sepsis (Andini et al., 2023; Rathore et al., 2020). A meta-analysis of Sub-Saharan African data found that neonates born to mothers with PROM had an almost two-fold increased risk of sepsis (AOR = 1.95) (Bech et al., 2022). Another meta-analysis study done in East

Africa showed the similar pattern with PROM associated with a markedly elevated risk of neonatal sepsis (Abate et al., 2020).

Premature rupture of membranes is associated with early and prolonged exposure of the fetus to potentially resistant vaginal and enteric bacteria by breaching the sterile amniotic environment (Bech et al., 2022; Olita et al., 2019; Rathore et al., 2020; Zhu et al., 2023). The prolonged PROM exceeding 18 hours markedly increases the risk of ascending infection with ESBL-producing organisms like *E. coli* and *Klebsiella pneumoniae* (Merenstein & Weisman, 2005; Tsehaynesh et al., 2017; Wolf et al., 2021; Zhu et al., 2023). Also, tendence of using broad spectrum antibiotics increases the likelihood of vertical transmission of ESBL strains due to existing prolonged rupture of membrane (Abate et al., 2020; Andini et al., 2023; Chen et al., 2017.; Tumuhamye et al., 2020).

Gestational age was significantly associated with ESBL producing neonatal sepsis. Un variate analysis showed that early term neonates had higher odds of developing ESBL sepsis compared to post term neonates. However, after adjusting for confounding factors, early term neonates had lower odds of ESBL sepsis that post term neonates. Full term neonates also showed reduced odds through not statistically significant. These findings suggest that post term neonates are more vulnerable to ESBL infections, possibly due to placental insufficiency, reduced immune protection and delivery complications. Similar results were reported in studies from Ethiopia, India and Kenya which found increased sepsis risk among preterm and post term neonates due to immature or compromised immune system (Belachew & Tewabe, 2020; Kagia et al., 2019)

In this study, neonates born by mothers with intrapartum febrile illness had increased risk of ESBL-producing neonatal sepsis. This finding is contrary to the study done in Mwanza, Tanzania which reported no association between maternal fever and neonatal sepsis (Marando et al., 2018). Some other studies like one done in Nigeria have reported that intrapartum febrile illnesses like rectal-vaginal colonization was about 18 times and maternal ESBL-E colonization were about 14-times more likely increased risk of ESBL neonatal sepsis (Neemann et al., 2020). This may be attributed to various facts like vertical transitions of bacteria from mothers with tendency of using broad-spectrum antibiotics to manage maternal infections may alter the vaginal

flora, promoting colonization with multidrug-resistant organisms such as ESBL-producing *E. coli* and *Klebsiella* species (Bulabula et al., 2017; Jeon et al., 2014; Neemann et al., 2020). These organisms can ascend into the amniotic fluid or be transferred during passage through the birth canal, especially in the context of prolonged rupture of membranes or invasive procedures (Bulabula et al., 2017; Ganesan et al., 2016; Jaspan et al., 2023; Neemann et al., 2020; Olita et al., 2019).

Regarding neonatal perspective this study found that elevated C-reactive protein (CRP) levels is significantly associated with ESBL-producing bacteria in such a way that neonates with moderately high CRP were nearly five times more likely while those with very high CRP showed an astonishing 61-fold increased risk. These results correspond with several studies which emphasized CRP as a biomarker, noting that elevated CRP in febrile neonates significantly correlates with ESBL sepsis which is severe and hard to manage (Cao & Lippmann, 2022; Dhamsaniya et al., 2025; Eichberger et al., 2022). Although limited African data report CRP associations quantitatively, several studies acknowledge CRP as a useful marker for neonatal sepsis diagnosis.

C-reactive protein (CRP) is one of potent blood biomarker which is acute-phase protein synthesized by the liver in response to pro-inflammatory cytokines especially IL-6 as response of bacterial invasion (Ganesan et al., 2016; Singhal et al., 2021). In clinical practice CRP concentrations above 10 mg/L are suggestive of infection, but in ESBL sepsis the values are soaring well above 100 mg/L. Because CRP rises rapidly within 6–12 hours of infection onset very high CRP levels become a useful biomarker to flag neonatal sepsis due to ESBL organisms early, guide urgent escalation of antimicrobial therapy (Cao & Lippmann, 2022; Singhal et al., 2021).

Also, in this study, invasive procedures like intravenous line insertions and mechanical ventilation were associated with a threefold increase in ESBL neonatal sepsis risk. The findings is supported by a systematic review in sub-Saharan Africa which found neonatal resuscitation at birth increased the risk of sepsis by three-fold times (Bech et al., 2022). Several other studies from different countries including Kenya, Ethiopia, Uganda, Nigeria and Madagascar have reported invasive procedure including parenteral feeding, frequent blood sampling, and catheterization as independent factor for neonatal sepsis caused by ESBL-producing organisms like *E. colli*, and *klebsiella*

(Abate et al., 2020; Bech et al., 2022; Inchingolo et al., 2024; Lai et al., 2024; Raquel et al., 2016; Song et al., 2022; Yirga et al., 2020).

Invasive procedures including endotracheal intubation, umbilical or peripheral intravenous lines, arterial catheterization, and lumbar puncture are associated with ESBL invasion as they breach the neonate's natural skin and mucosal defenses which creates direct entry points for bacteria (Badakali et al., 2022; Belachew & Tewabe, 2020; Marando et al., 2018; Ratridewi et al., 2011). Also, in neonatal intensive care units, devices like canula or catheterization often remain in place for extended periods and may become colonized by multidrug-resistant organisms, including ESBL-producing *E. coli* or *Klebsiella pneumoniae* (Song et al., 2022; Yirga et al., 2020).

Antimicrobial Susceptibility of Common Bacterial Isolate among Neonates with ESBL Neonatal Sepsis

In this study total positive blood culture accounted for 38.0% whereby gram-negative bacteria were accounted for 43.0% and the most common isolated bacteria were *Klebsiella aeruginosa* 30.6%, *Escherichia coli* 24.5%, *klebsiella pneumonia* 14.3% and pseudomonas *spp* 10.2%. this was similar to most of studies from different regions especially in Africa where *Klebsiella pneumoniae*, *E. coli, Enterobacter cloacae*, and *K. oxytoca* were common in Kenya (Kagia et al., 2019). In Mwanza , Tanzania the most common was *Klebsiella pneumoniae* ST45, which contributed significantly to neonatal sepsis and mortality (Marando et al., 2018). These isolate are wide reported in Africa and are highly contributing to ESBL neonatal sepsis as reported in numerous studies (Peirovifar et al., 2014; Wolf et al., 2021; Yirga et al., 2020). These bacteria have high capacity for rapid horizontal gene transfer, persistence in hospital environments, and colonization of neonatal gut and skin surfaces all explaining their outsized contribution to ESBL neonatal sepsis (Cao & Lippmann, 2022; Sharma et al., 2016; Wolf et al., 2021).

The antimicrobial resistance patterns observed in *Klebsiella aerogenes* and *Escherichia coli* in this study closely align with findings from several global and regional studies. In this study *Klebsiella aeruginosa* shown resistance to majority of medication being ampicillin (93,3%), gentamycin (86.7%), ceftriaxone (73.3%) and amoxiclav (84.6%) except for meropenem (6.7%) and Amikacin (40.0%). *Escherichia*

coli was resistant to ampicillin (100%), ceftriaxone (66.7%), amoxiclav (66.7%) and was sensitive to meropenem (91.7%). These findings are supported by a study from Korea and Italy, which showed *Klebsiella spp* had high resistance to cephalosporins but were controlled by meropenem (Baek et al., 2020; Priante et al., 2022). Similarly, in Ethiopia, isolates from urinary tract infections exhibited complete resistance to ampicillin and amoxicillin-clavulanate, while showing low resistance to meropenem and aminoglycosides, reinforcing current findings (Dinagde et al., 2009; Tsehaynesh et al., 2017).

Similarly, our data showed *Escherichia coli* had 100% resistance to ampicillin, and 66.7% resistance to both ceftriaxone and amoxicillin-clavulanate, but retained high sensitivity to meropenem (91.7%). This is consistent with a multicenter study done in Egypt where *E. coli* isolates showed over 80% resistance to ampicillin and 62% to ceftriaxone, while maintaining over 99% susceptibility to meropenem and other carbapenems(Hassuna et al., 2020). A similar pattern was observed in Bangladesh, where *E. coli* showed 86.5% resistance to ampicillin and 54% resistance to ceftriaxone, while meropenem susceptibility remained above 94% (Rahman et al., 2024). Furthermore, a study conducted in Ghana reported resistance to ceftriaxone, supporting the continued use of meropenem against *E. coli and Klebsiella spp* despite widespread resistance to beta-lactam antibiotics (Acheampong et al., 2022).

In this study, despite the high resistance profile of isolates, meropenem stands out as the most effective antibiotic against *K. pneumoniae*, showing more than 71.4% sensitivity almost in all isolates and 28.6% intermediate resistance with no full resistance. This aligns with global patterns where carbapenems remain among the few reliably effective agents against ESBL-producing *Klebsiella* strains (Rahman et al., 2024).

The high resistance of *Klebsiella aerogenes* and *Escherichia coli* to commonly used antibiotics in developing countries is a multifaceted problem influenced by various systemic, behavioral, and environmental factors. One of the most significant contributors is the inappropriate use of antibiotics, including overuse, under-dosing, and use without proper medical supervision (Dolma et al., 2018; Marando et al., 2018; World Health Organisation, 2020). In many low- and middle-income countries (LMICs), antibiotics are readily available over the counter without prescription,

leading to self-medication and misuse (Harimanana et al., 2022; Kagia et al., 2019; Marando et al., 2018; Zhu et al., 2023).

Conclusion

The findings of this study highlight a concerning prevalence of ESBL-producing bacteria among neonates with sepsis.

The predominant Gram-negative organisms were *Klebsiella aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli*.

The common isolated pathogens demonstrated very high resistance to antibiotics like ampicillin, gentamicin, ceftriaxone, and amoxicillin-clavulanic acid which are commonly used in our settings.

These pathogens demonstrated high susceptibility to meropenem and amikacin whereby meropenem covered all pathogens except Acinetobacter spp which was not common isolate and amikacin covered majority of pathogens except for *Escherichia coli*, *pseudomonas spp* and *Klebsiella pneumoniae*.

Maternal factors such as caesarean delivery, prolonged rupture of membranes (PROM), maternal febrile conditions as well as neonatal factors like elevated C-reactive protein (CRP) levels and exposure to invasive procedures, were significantly associated with ESBL-producing bacteria among neonates with sepsis.

Recommendation

There is a need for those with blood culture positive gram negative to screened for ESBL as majority of gram-negative organism were ESBL producer, furthermore majority had Multi antimicrobial resistance therefore there is need to review on empirical antibiotic used according to WHO and Tanzania standard treatment guidelines. In settings where blood culture and sensitivity are not available, Its recommended further studies on association between CRP as biomarker for detection ESBL neonatal sepsis

Ethical Consideration

The Institution Research Review Ethical Committee (IRREC) at the University of Dodoma (UDOM) offered ethical clearance for conducting this study. Permission to

conduct the study was provided by the Medical Officer of Dodoma Municipal Council (DMC) to the respective hospital administrations. The study had adhered to all ethical requirements, including getting signed informed permission from each participant, especially the parents or caregivers on behalf of the newborns who agreed to participate in the research. The goal, potential risks, and incentives of the research were detailed in the permission form. The consent clarified, and those harmed occurred were handled effectively. Informed consent forms were prepared in English and translated into Kiswahili for easy comprehension. Written informed consent to participate was obtained from the parent or legal guardian of each neonate prior to enrollment. Parents/guardians received a full explanation of the study aims, procedures, potential benefits and risks, and the voluntary nature of participation. They were informed that refusal or withdrawal at any time would not affect the clinical care their child received. Study data and bacterial isolates were anonymized and stored securely; only the study team had access to identifiable information. Permission to publish anonymized group-level results was obtained as part of the consent process. In addition, participants were free to leave the research at any time without incurring any fees. The study was conducted in accordance with the guidelines and regulations of the Declaration of Helsinki.

List of Abbreviations

AOR	Adjusted Odds Ratios
BMH	Benjamin Mkapa Hospital
BSI	Bloodstream Infection
C/S	Cesarean Section
CRP	C - reactive protein
DBNII	Dade Behring Nephelometer II
DMC	Dodoma Municipal Council
DPCH	Department of Pediatrics and Children Health
DRRH	Dodoma Regional Referral Hospital
EDTA	Ethylene Diamine Tetra-acetic Acid
ENT	Ear Nose Throat
EOS	Early Onset Sepsis
ESBL	Extended Spectrum of Beta-Lactamase

ESBL-E	Extended-Spectrum Beta-Lactamase-Enterobacteriaceae
ESBL-PE	Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae
FBP	Full Blood Picture
FI	Feeding Intolerance
GA	Gestational Age
GNB	Gram-Negative Bacteria
GPB	Gram-Positive Bacteria
HALOS	Hospital-Acquired Late-Onset Sepsis
IBM	International Business Machine
LMICs	Low- and Middle-Income Countries
MDR	Multi-Drug-Resistant
MDRB	Multi- Drug-Resistant Bacteria
MNH	Muhimbili National Hospital
MUHC	Makole Urban Health Center
NICU	Neonatal Intensive Care Unit
PI	Principal Investigator
RPC	Research and Publication Committee
SVD	Spontaneous Vaginal Delivery
TMD	Transient Myeloproliferative Disorder
TZS	Tanzania Shillings
UDOM	University of Dodoma
UIN	Unique Identification Number
VLBW	Very Low Birth Weight
WBC	White Blood Cell
WHO	World Health Organization

Consent for publication

Not applicable.

Availability of data and materials

The dataset analyzed during this study contains sensitive patient information and is therefore subject to restrictions imposed by the Ethical Research Committee of the University of Dodoma. Access to the data can be granted upon reasonable request by

contacting the Directorate of Research, Publication, and Consultancy at the University of Dodoma, P.O. Box 259, Dodoma, Tanzania (email: drpc@udom.ac.tz).

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict

Conflict of interest: None to be declared.

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Authors' contributions

S.J and **D.M** conceptualized the study and developed the methodology. **M.L.M** and **S.W.M** supervised **S.J** during data collection and led the data analysis. **D.G.I** drafted the initial manuscript. **D.M, M.L.M** and **S.J** contributed to data interpretation and critically reviewed and edited the manuscript. All authors contributed to review the final version, and approved it for submission.

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Table 1. Socio-demographic characteristics of ESBL producing bacterial isolates among term neonates with sepsis at DRRH and BMH (N=300)

Variable	Frequency (n)	Percentage (%)
Age of the neonate		
7 days and below	231	77.0
>7 days of life	69	23.0
Gestational age (Weeks)		
Early term (37-38)	215	71.7
Full term (39-40)	73	24.3
Post term (≥41)	12	4
Sex		
Female	156	52.0
Male	144	48.0
Residence		
Urban	222	74.0
Rural	78	26.0
Place of delivery		
Hospital	285	95.0
Home	15	5.0
Referral patient		
Yes	92	30.7
No	208	69.3
Mothers education level		
Non- formal education	17	5.7
Primary education	156	52.0
Secondary education	98	32.6
College or higher	29	9.7
Occupation of the mother		
Unemployed	79	26.3
Self employed	186	62.0
Employed	35	11.7

Table 2. Clinical characteristics of ESBL producing bacterial isolate among term neonates with sepsis at DRRH and BMH (N=300)

Variable	Frequency (n)	Percentage (%)
Types of birth		
Multiple pregnancy	26	8.7
Single tone	274	91.3
Delivery method		
SVD	202	67.3
C/S	98	32.7
PROM (>18hrs)		
Yes	66	22.0
No	234	78.0
Maternal febrile condition		
Yes	46	15.3
No	254	84.7
Apgar score at 1min and 5min		
Low Apgar	72	24.0
High score	228	76.0
Neonatal inability to breastfeed		
Yes	131	43.7
No	169	56.3
Neonatal Convulsion		
Yes	50	16.7
No	250	83.3
Neonatal Vomiting		
Yes	49	16.3
No	251	83.7
Redness of umbilicus		
Yes	16	5.3
No	284	94.7
Neonatal abdominal distention		
Yes	34	11.3
No	266	88.7

Neonatal Jaundice		
Yes	116	38.7
No	184	61.3
Neonatal Fever or Hypothermia (>37.5 or < 36.5)		
Yes	173	57.7
No	127	42.3
Neonatal difficulty in breathing		
Yes	135	45.0
No	165	55.0
Excessive crying		
Yes	21	7.0
No	279	93.0
Congenital malformation		
Yes	33	11.0
No	267	89.0
Anaemia (<10g/dl)		
Yes	24	8.0
No	276	92.0
Chest retractions		
Yes	103	34.3
No	197	65.7
Grunting		
Yes	70	23.3
No	230	76.7
Platelets Status (150-450x10*9/l)		
Normal counts	226	75.3
Mild thrombocytopenia	40	13.3
Moderate thrombocytopenia	16	5.3
Severe thrombocytopenia	18	6.1
CRP		
Normal (<10 mg/l)	253	84.3

elevated (10-49 mg/l)	31	10.3
Very high (>50 mg/l)	16	5.4
Neonatal invasive procedure		
Yes	90	30.0
No	210	70.0
Resuscitation		
Yes	60	20.0
No	240	80.0
WBC count (3.1-21.6x10*9/l)		
Normal counts	242	80.7
Leukopenia	22	7.3
Leukocytosis	36	12.0
Neutrophils (1500-78000 cells/microliter)		
Normal counts	242	80.7
Neutropenia	22	7.3
High counts	36	12.0
Lymphocyte (15-75x10*9/l)		
Normal counts	167	55.7
Low counts	9	3.0
High counts	124	41.3

Table 3. Chi-square test of factors associated with ESBL-producing organisms among term neonates with sepsis at DRRH and BMH. (N=300)

Variable	ESBL neonatal sepsis		Pearson's chi value	P value
	No (%)	Yes (%)		
Sex				
Female	138(88.5)	18(11.5)	2.541	0.111
Male	118(81.9)	26(18.1)		
Residence				
Urban	188(84.7)	34(15.3)	0.287	0.711*
Rural	68(87.2)	10(12.8)		
Place of delivery				
Hospital	245(86.0)	40(14.0)	1.817	0.249*
Home	11(73.3)	4(26.7)		
Referral patient				
Yes	78(84.8)	14(15.2)	0.032	0.861
No	178(85.6)	30(14.4)		
Mother's education level				
Non-formal	13(76.5)	4(23.5)	5.404	0.144*
Primary	140(89.7)	16(10.3)		
Secondary	80(81.6)	18(18.4)		
College / higher	23(79.3)	6(20.7)		
Maternal factor				
Multiple pregnancy	23(88.5)	3(11.5)	0.223	0.779*
Single tone	233(85.0)	41(15.0)		
Type of birth				
SVD	186(92.1)	16(7.9)	22.484	**< 0.001**
C/S	70(71.4)	28(28.6)		
PROM (>18hrs)				
Yes	36(54.5)	30(45.5)	64.085	**< 0.001**
No	220(94.0)	14(6.0)		

Variable	ESBL neonatal sepsis		Pearson's chi value	P value
	No (%)	Yes (%)		
Maternal Febrile conditions prior delivery				
Yes	20(43.5)	26(56.5)	76.049	**< 0.001**
No	236(92.9)	18(7.1)		
APGAR 1 min				
Low Apgar	59(81.9)	13(18.1)	0.869	0.445
High score	197(86.4)	31(13.6)		
APGAR 5 min				
Low Apgar	19(76.0)	6(24.0)	1.898	0.231
High score	237(86.2)	38(13.8)		
Gestational age (Weeks)				
Early term	33(15.2)	184(84.8)	4.703	0.095*
Full term	7(9.9)	64(90.1)		
Post term	4(33.3)	8(66.7)		
Platelets status (150-450x10*9/l)				
Normal count	202(89.4)	24(10.6)	14.722	**0.003***
Mild thrombocytopenia	31(77.5)	9(22.5)		
Moderate thrombocytopenia	12(75.0)	4(25.0)		
Severe thrombocytopenia	11(61.1)	7(38.9)		
CRP				
Normal (<10 mg/l)	232(91.7)	21(8.3)	55.861	**< 0.001**
Elevated (10-49 mg/l)	18(58.1)	13(41.9)		
Very high (> 50 mg/l)	6(37.5)	10(62.5)		
Invasive procedure				
Yes	60(66.7)	30(33.3)	35.795	**< 0.001**
No	196(93.3)	14(6.7)		
Resuscitation				

Variable	ESBL neonatal sepsis		Pearson's	P value
	No (%)	Yes (%)	chi value	
Yes	34(56.7)	26(43.3)	49.245	**< 0.001**
No	222(92.5)	18(7.5)		
Hb status (<10g/dl)				
Low Hb count	18(85.7)	3(14.3)	0.003	1.000*
Normal Hb count	238(85.3)	41(14.7)		
Total WBC count (3.1-21.6x10*9/l)				
Normal counts	170(87.6)	24(12.4)	2.522	0.307*
Leukopenia	26(78.8)	7(21.2)		
Leucocytosis	60(82.2)	13(17.8)		
Neutrophils (1500-7800 cells/microliter)				
Normal counts	209(86.4)	33(13.6)	1.079	0.640*
Neutropenia	18(81.8)	4(18.2)		
Neutrophilia	29(80.6)	7(19.4		
Lymphocyte (15-75x10*9/l)				
Normal count	145(86.8)	22(13.2)	0.920	0.615*
Low counts	7(77.8)	2(22.2)		
High count	104(83.9)	20(16.1)		

Table 4. Univariate and Multivariable binary logistic regression of factors associated with ESBL producing organism among Term neonate with sepsis at DRRH and BMH.

Variable	ESBL		Univariate regression		Multivariable regression	
	No (%)	Yes (%)	P value	COR (95% CI)	P value	AOR (95% CI)
Sex						
Female	138(88.5)	18(11.5)	Ref			
Male	118(81.9)	26(18.1)	0.113	1.69(0.88-3.23)		
Type of birth						
SVD	186(92.1)	16(7.9)	Ref			
C/S	70(71.4)	28(28.6)	**<0.001**	4.65(2.37-9.11)	**0.005**	5.22(1.66-16.40)
PROM (>18hrs)						
Yes	36(54.5)	30(45.5)	**<0.001**	13.10(6.34-27.06)	**<0.001**	21.54(5.53-83.97)
No	220(94.0)	14(6.0)	Ref			
Maternal Febrile prior delivery						
Yes	20(43.5)	26(56.5)	**<0.001**	17.04(9.01-36.25)	**<0.001**	20.71(5.17-82.89)
No	236(92.9)	18(7.1)	Ref			
Platelets count (150-450x10*9/l)						

Variable	ESBL		Univariate regression		Multivariable regression	
	No (%)	Yes (%)	P value	COR (95% CI)	P value	AOR (95% CI)
Normal count	202(89.4)	24(10.6)	Ref			
Mild thrombocytopenia	31(77.5)	9(22.5)	**0.040**	2.44(1.04-5.74)	0.242	0.35(0.60-2.03)
Moderate thrombocytopenia	12(75.0)	4(25.0)	0.094	2.81(0.84-9.39)	0.821	1.32(0.12-14.39)
Severe thrombocytopenia	11(61.1)	7(38.9)	**0.002**	5.36(1.90-15.12)	0.286	2.60(0.44-15.08)
CRP						
Normal (<10 mg/l)	232(91.7)	21(8.3)	Ref			
Elevated (10-49 mg/l)	18(58.1)	13(41.9)	**<0.001**	7.98(3.44-18.51)	**0.033**	4.97(1.14-21.68)
Very high (> 50 mg/l)	6(37.5)	10(62.5)	**<0.001**	18.41(6.09-55.66)	**<0.001**	61.44(7.94-475.78)
Invasive procedure						
Yes	60(66.7)	30(33.3)	**<0.001**	7.00(3.48-14.06)	**0.046**	3.10(1.02-9.38)
No	196(93.3)	14(6.7)	Ref			
Resuscitation						
Yes	34(56.7)	26(43.3)	**<0.001**	9.43(4.68-19.01)		
No	222(92.5)	18(7.5)	Ref			

Variable	ESBL		Univariate regression		Multivariable regression	
	No (%)	Yes (%)	P value	COR (95% CI)	P value	AOR (95% CI)
Gestational age (Weeks)						
Early term	33(15.2)	184(84.8)	**<0.030**	4.57(1.09-19.13)	**0.037**	0.22(0.05-0.92)
Full term	7(9.9)	64(90.1)	0.262	1.64(0.69-3.89)	0.110	0.36(0.10-1.26)
Post term	4(33.3)	8(66.7)	Ref			

Table 5. Antimicrobial Susceptibility of Drugs at the BMH and DRRH

		Facility of the patient admitted	
		BMH	DRRH
Ampicillin	Sensitive	1(2.2%)	44(97.8%)
	Intermediate	0	3(100%)
	Resistance	0	1(100%)
Gentamicin	Sensitive	1(2.7%)	36(97.3%)
	Intermediate	0	2(100%)
	Resistance	1(10%)	9(90%)
Ceftriaxone	Sensitive	1(2.6%)	37(97.4%)
	Resistance	1(9.1%)	10(90.9%)
Meropenum	Sensitive	0	6(100%)
	Intermediate	0	2(100%)
	Resistance	2(4.9%)	39(95.1%)
Cefotaxime	Sensitive	1(2.6%)	37(97.4%)
	Intermediate	0	2(100%)
	Resistance	1(11.1%)	8(88.9)
Amoxyclav	Sensitive	0	30(100%)
	Intermediate	0	8(100%)
	Resistance	1(9.1%)	10(90.9%)
Ciprofloxine	Sensitive	1(3.8%))	25(96.2%)
	Intermediate	1(33.3%)	2(66.7%)
	Resistance	0	20(100%)
Amikacin	Sensitive	1(5.9%)	16(94.1%)
	Intermediate	1(25%)	3(75%)
	Resistance	0	28(100%)

Table 6. Antimicrobial Susceptibility of Common Bacterial Isolate producing ESBL among Term Neonates with Sepsis at DRRH and BMH (N=49)

Isolates	Antimicrobial							
	Amp n (%)	Gent n (%)	Ceft n (%)	Mero n (%)	Cefo n (%)	Amox cl n (%)	Cipro n (%)	Amik n (%)
Klebsiella aeruginosa								
Sensitive	0(0.0)	2(13.3)	4(26.7)	14(93.3)	3(20.0)	1(7.7)	6(42.8)	9(60.0)
Intermediate	1(6.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(7.7)	0(0.0)	0(0.0)
Resistance	14(93.3)	13(86.7)	11(73.3)	1(6.7)	12(80.0)	11(84.6)	8(57.2)	6(40.0)
Escherichia coli								
Sensitive	0(0.0)	4(33.3)	4(33.3)	11(91.7)	3(25.0)	4(33.3)	3(30.0)	3(25.0)
Intermediate	0(0.0)	1(8.3)	0(0.0)	0(0.0)	2(16.7)	0(0.0)	2(20.0)	2(16.7)
Resistance	12(100.0)	7(58.4)	8(66.7)	1(8.3)	7(58.3)	8(66.7)	5(50.0)	7(58.3)
Enterobacter spp								
Sensitive	0(0.0)	0(0.0)	0(0.0)	1(50)	0(0.0)	1(50)	1(50.0)	2(100.0)
Intermediate	1(50.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Resistance	1(50.0)	2(100.0)	2(100.0)	1(50.0)	2(100.0)	1(50.0)	1(50.0)	0(0.0)
Enterococcus								
Sensitive	0(0.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	1(50.)	0(0.0)	1(50.0)

Intermediate	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	0(0.0)	1(50.0)
Resistance	1(100.0)	2(100.0)	2(100.0)	0(0.0)	2(100.0)	0(0.0)	2(100.0)	0(0.0)
Klebsiella pneumonia								
Sensitive	1(14.3)	0(0.0)	0(0.0)	5(71.4)	0(0.0)	5(71.4)	6(85.7)	1(16.7)
Intermediate	0(0.0)	0(0.0)	0(0.0)	2(28.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Resistance	6(85.7)	7(100.0)	7(100.0)	0(0.0)	7(100.0)	2(28.6)	1(14.3)	5(83.3)
Morganel morgan								
Sensitive	0(0.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)
Intermediate	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)
Resistance	1(100.0)	0(0.0)	1(100.0)	0(0.0)	1(100.0)	0(0.0)	1(100.0)	0(0.0)
Providential spp								
Sensitive	0(0.0)	1(100.0)	0(0.0)	1(100.0)	1(100.0)	0(0.0)	1(100.0)	1(100.0)
Intermediate	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Resistance	1(100.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)
Serratia spp								
Sensitive	0(0.0)	1(33.3)	1(33.3)	2(66.7)	1(33.3)	1(33.3)	1(50.0)	3(100.0)
Intermediate	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(33.4)	0(0.0)	0(0.0)
Resistance	3(100.0)	2(66.7)	2(66.7)	1(33.3)	2(66.7)	1(33.3)	1(50.0)	0(0.0)
Pseudomonas								
Sensitive	0(0.0)	2(40.0)		4(80.0)	1(20.0)	1(25.0)	1(20.0)	2(40.0)

Intermediate	1(20.0)	0(0.0)		0(0.0)	0(0.0)	0(0.0)	1(20.0)	1(20.0)
Resistance	4(80.0)	3(60.0)		1(20.0)	4(80.0)	3(75.0)	3(60.0)	2(40.0)
Acinetobacter								
Sensitive	0(0.0)	0(0.0)	1(20.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	1(100.0)
Intermediate	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Resistance	1(100.0)	1(100.0)	4(80.0)	1(100.0)	1(100.0)	0(0.0)	1(100.0)	0(0.0)

CONSENT FORM

ID No. of the participant: _____

Introduction

I, **Dennis Greyson Idinga**, from the University of Dodoma. I am researching **"the prevalence and factors associated with extended-spectrum of beta-lactamase bacterial isolates among term neonates with sepsis at DRRH and BMH in Tanzania."**

How to participate in this study

I am kindly asking you to participate in this study because you are among many patients admitted to neonatal unit. After your willingness to participate in the study, you will be interviewed using a questionnaire.

Confidentiality

Everything will remain confidential and will be used only for research purposes. The principal investigator (PI) will write a report that will contain the information you provided.

Risks

I do not expect any harm will happen to you as a result of participating in the study.

Rights to join in the study

Taking part in this study is completely your choice and willingness, you have the right to participate or decide otherwise without giving any reason. Once you have decided to participate you are also free to terminate your participation at any time.

Benefits of participating in this study

If you agree to participate in this study you will help the Hospital and country in general to know the incidence of the condition and establish proper management plans and the laboratory results will be made available to manage the neonates' condition.

Who to contact?

If you have any question about this study you are free to contact the principal investigator, **Dennis Greyson Idinga,** mobile phone number is **+255 757 556 832.**

If you agree to this interview please sign this consent form

I have read and understood the contents of this consent form and my questions have been sufficiently answered. Therefore, I agree to participate in this study.

Signature of the interviewee: _____ Date: _____

Signature of the interviewer: _____ Date: _____

Mobile phone number of the participant: _____

Mobile phone number of the next of kin to the participant: _____

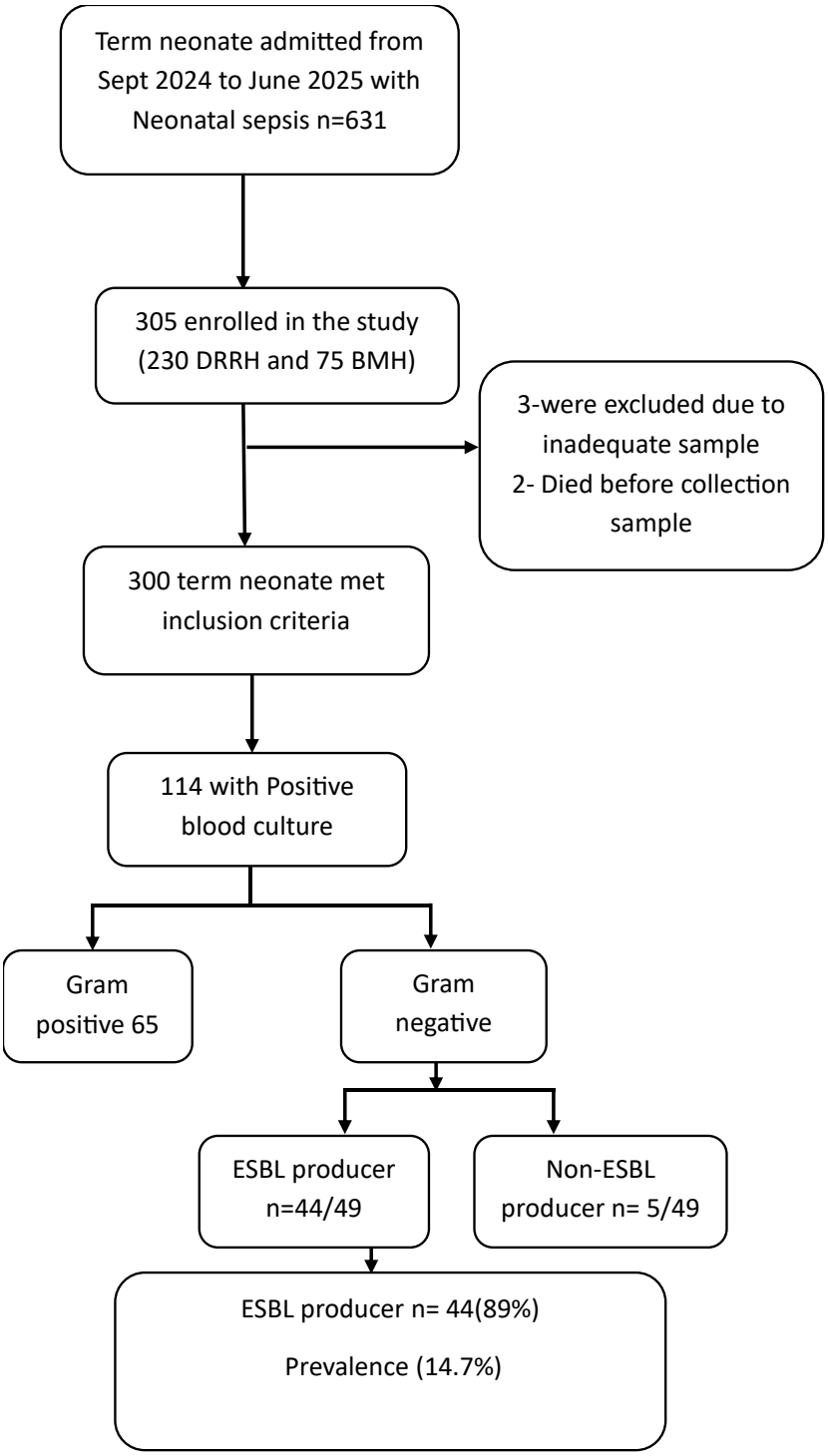


Figure 1: Flowchart

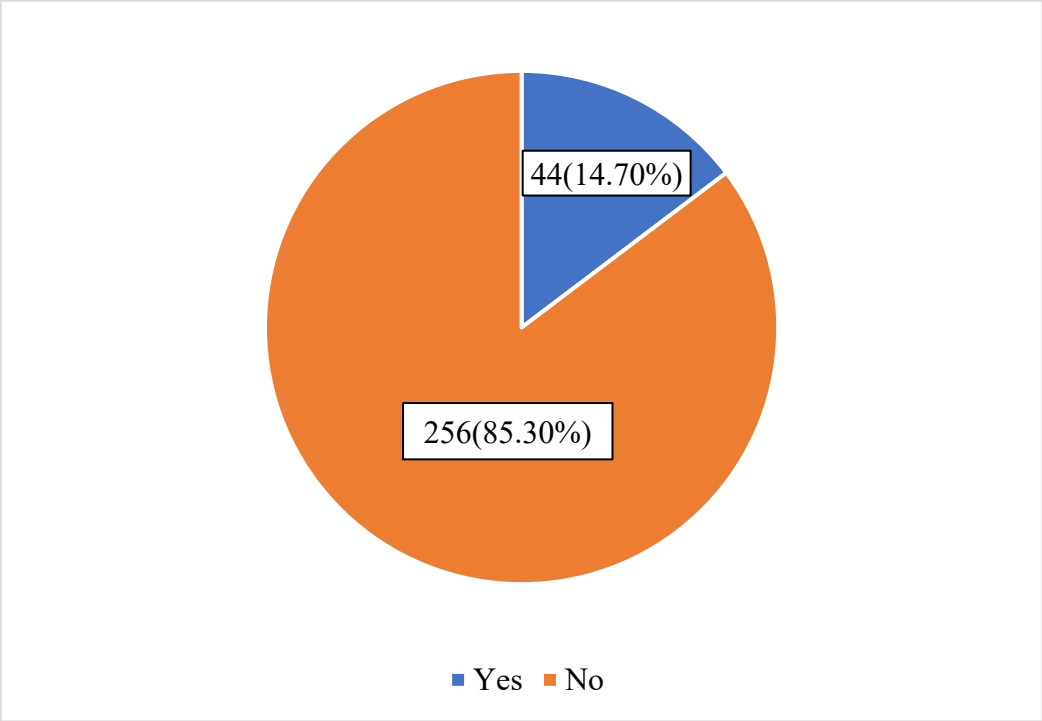


Figure 1: Figure 4:2: Prevalence of Extended Spectrum Beta Lactamase (ESBL) producing organisms among Term neonates with Sepsis at DRRH and BMH. (N=300)

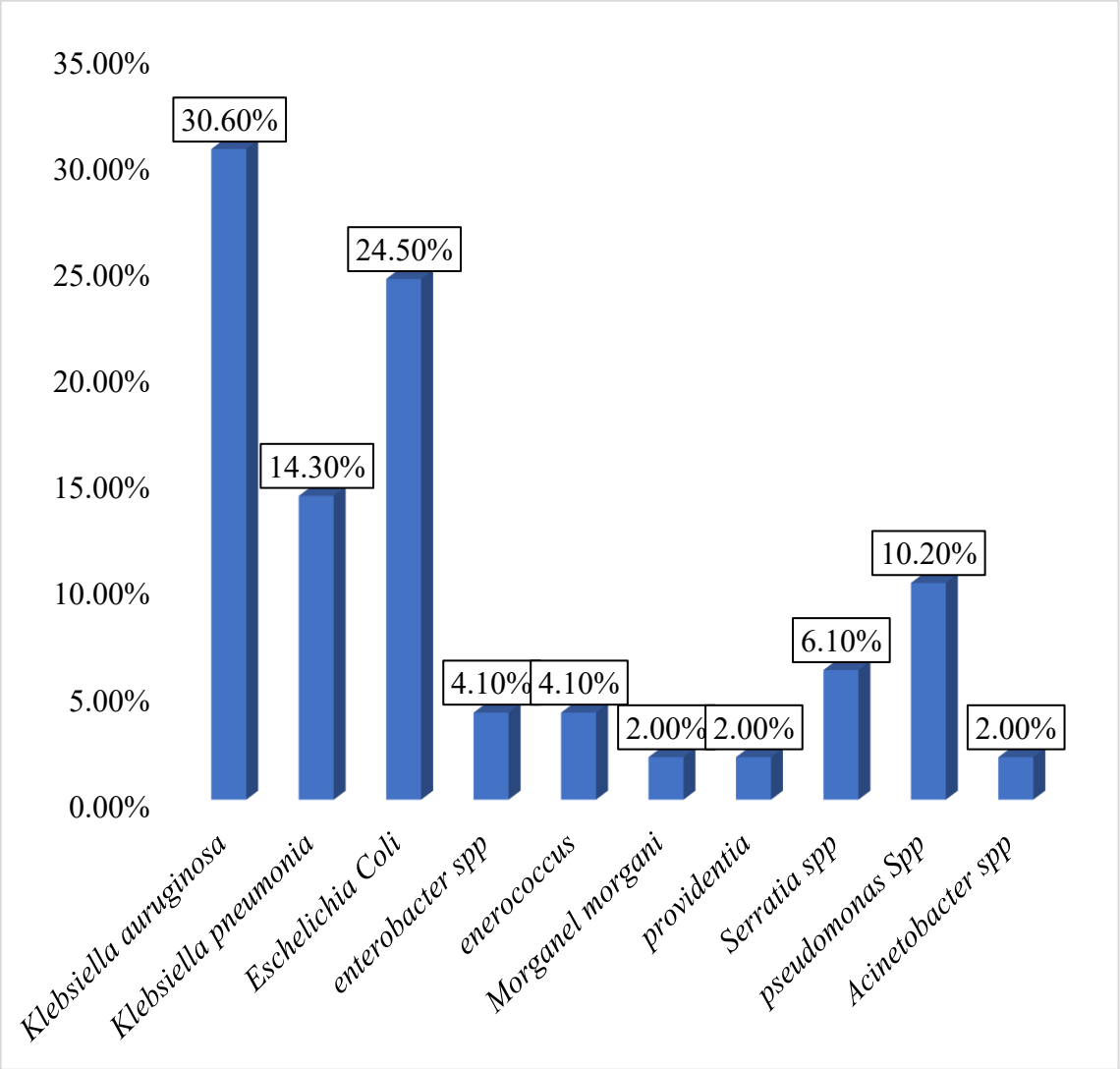


Figure 2: Figure 4:3: Gram-negative isolates among term neonates with sepsis at DRRH and BMH (N=49)