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Effectiveness of Antimicrobial Stewardship Program in the Neonatal Intensive Care Unit at Tikur Anbesa Specialized Hospital, Ethiopia

By: Elias Adugna (B.Pharm)

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By: Elias Adugna (B.Pharm)

Advisor: Mr. Getachew Alemkere (B.Pharm, MSc, Assist. professor)

Co-advisors:-

Dr. Minyahil Alebachew (B.Pharm, MSc, PhD, and Assistant Professor)

Dr. Asrat Dimtse (MD, Pediatrics and Child health senior consultant and Neonatologist)

Dr. Elham Sani (MD, Pediatrics and Child health senior consultant and Infectious disease specialist)

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Addis Ababa University

School of Graduate Studies

This is to certify that the thesis prepared by Elias Adugna entitled **"**Effectiveness of antimicrobial stewardship program in the Neonatal Intensive Care Unit of Tikur Anbesa Specialized Hospital**."** and submitted in partial fulfillment of the requirements for the degree of Master of Pharmacy in Clinical Pharmacy complies with the regulations of the university and meets the accepted standard concerning originality and quality.

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External Examiner	Signature	Date
Getachew Alemker Assist Professor)	_____	_____
Major Advisor	Signature	Date
Minyahil Alebachew (PhD)	_____	_____
Co-Advisor	Signature	Date
Asrat Dimtse (MD, Pediatrics, Neonatologist)	_____	_____
Co-Advisor	Signature	Date
Elham Sani (MD, Infectious disease specialist)	_____	_____
Co-Advisor	Signature	Date

'Chair of Department or Graduate program coordinator'

Abstract

Background: Antimicrobial stewardship programs are multifaceted interventions aimed at optimizing antibiotic use, combating antimicrobial resistance and improving patient outcomes including length of stay and mortality. Tikur Anbessa Specialized Hospital (TASH) implemented an AMS in its Neonatal Intensive Care Unit (NICU) on 3 April 2022.

Objective: To evaluate the impact of Antimicrobial stewardship interventions in the Neonatal Intensive Care Unit at Tikur Anbessa Specialized Hospital, Ethiopia.

Methods: A retrospective cross-sectional chart review (1, April 2021–31, March 2024) categorized into pre-intervention (1, April 2021–3, April 2022), intervention (3, April 2022–27, March 2023), and post-intervention (28, March 2023–31, March 2024) periods was conducted. Neonates treated with antibiotics for infectious diseases were included. Data on demographics, diagnostics, and antibiotic regimens were collected. Analyses included descriptive statistics, chi-square, ANOVA with Tukey post hoc tests, logistic regression (mortality predictors), and linear regression (LOS predictors), with significance set at $P < 0.05$.

Result: A total of 763 neonates were enrolled (260 pre-AMS, 253 during AMS, 250 post-AMS). During the intervention, mean antibiotic duration decreased by 29.3% (from 10.98 ± 7.03 to 7.76 ± 6.08 days; $P < 0.001$), with a notable shift from broad-spectrum antibiotics (Cefotaxime, Meropenem, Cefepime, Vancomycin) to Ampicillin–Gentamicin. LOS declined by 29% (18.2 to 12.9 days; $P = 0.004$), and mortality halved (15.0% to 7.5%; AOR = 0.43; $P = 0.011$). AMS recommendations prompted discontinuation in nearly half of cases, with 94.5% acceptance. Low birth weight (<2.5 kg) doubled mortality risk (AOR = 2.01; 95% CI, 1.15–3.53; $P = 0.014$). Following AMS cessation, antibiotic duration rebounded by 55.4% (+5.3 days), LOS increased by 19.5% (+2.68 days), and mortality rose to 14.4%, indicating a reversion toward pre-intervention practices.

Conclusion: AMS implementation in the NICU significantly optimized antibiotic use and improved clinical outcomes, reducing reliance on broad-spectrum agents, LOS, and mortality. However, cessation led to regression toward prior prescribing behavior, underscoring the necessity for sustained stewardship interventions.

Key words: Antimicrobial stewardship, AMS, Antimicrobial resistance, AMR, Neonatal Intensive Care Unit, NICU, Ethiopia.

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List of Abbreviations and Acronym

AAU	Addis Ababa University
AMR	Antimicrobial Resistance
AMS	Antimicrobial stewardship programs
CDC	Centers for Disease Control and Prevention
ESBL	Extended-Spectrum Beta-Lactamase
FMOH	Federal Ministry of Health
HAIs	Hospital-Acquired Infections
ICU	Intensive Care Unit
IDS	Infectious Disease specialist
IDSA	Infectious Disease society of America
LMICs	Low and middle income countries
MDR	Multi-drug resistant
MRSA	Methicillin-Resistant Staphylococcus Aureus
NICUs	Infants in Neonatal Intensive Care Units
SHEA	Society for Healthcare Epidemiology of America
TASH	Tikur Anbesa Specialized Hospital
WHO	World Health Organization
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
NS-AMS	Neonatal specific antimicrobial stewardship program

1. INTRODUCTION

1.1 Background of the study

Antimicrobial resistance (AMR) signifies a phenomenon that has been recognized even before the widespread application of the first antibiotic intended for human use, specifically penicillin (1). AMR is a naturally occurring and disseminable adaptive mechanism within bacterial communities; thus, the widespread use of antibiotics accelerates a rapid increase in the global prevalence of AMR, consequently undermining the therapeutic effectiveness of these drugs (2).

Infants in Neonatal Intensive Care Units (NICUs) constitute a population with notably high worldwide levels of antimicrobial resistance (AMR) (3). The use of antimicrobials is a key driver for AMR, with antibiotics representing the most frequently prescribed pharmacological agents within the NICU environment (4, 5). In contrast to older children and adults, neonates frequently present with nonspecific clinical manifestations and laboratory findings, complicating the differentiation of infections from other pathophysiological conditions (6, 7). Furthermore, it is estimated that nearly fifty percent of the antimicrobial agents administered in hospital environments may be deemed inappropriate (8). Although timely interventions for a true infection are critical, repeated and unwarranted exposures to broad-spectrum antibiotics have been directly correlated with detrimental outcomes in the NICU, encompassing the emergence of extensively drug-resistant organisms, heightened incidences of fungal infections, necrotizing enterocolitis, prolonged hospital stays, and increased mortality rates (9-11).

Antimicrobial stewardship (AMS) are ideally structured to deliver multidisciplinary interventions (e.g., infectious diseases, microbiology, and pharmacy) that aim to ensure the appropriate selection of antibiotics, including the correct dosage and duration of treatment (12, 13). AMS used to optimize antimicrobial use and potentially extend the effective lifespan of these agents, while new antibiotics are in development. The core components of an AMS can vary across different healthcare institutions; however, at a minimum, they should encompass (1) surveillance of antibiotic prescribing practices, (2) monitoring of AMR trends, and (3) post-prescription evaluations (14). Additional advantages of AMS programs include the provision of education and dissemination of information that empower healthcare professionals to curtail unnecessary antibiotic utilization (15).

AMS program implementation in the NICUs is important, owing to long hospital stays and the increased risk of hospital-acquired infections (HAIs) in this vulnerable demographic, particularly among preterm and low birth weight infants. Often, the pathogen responsible for clinical bacterial infections in neonates remain unidentified, which subsequently limit targeted therapeutic interventions; as a result, the prevalence of antibiotic prescriptions for clinical sepsis or presumed bacterial infections in neonates tends to be often high (16).

AMS strategies NICUs must be tailored to the specific practices and challenges of each institution. Evaluating local antibiotic use is essential to identifying stewardship targets and designing effective interventions (17). Core strategies include infection prevention, dissemination of evidence-based guidelines on antibiotic indications, empiric and targeted therapy choices, treatment duration for both culture-positive and culture-negative sepsis, and differentiation between colonization and true infection. Additional approaches such as formulary restriction, pre-authorization for selected antimicrobials, prospective audit and feedback, and therapeutic drug monitoring are also integral (18). Pre-authorization requirements for select broad-spectrum antibiotics help prevent inappropriate use (19), while Audit-feedback interventions involve a review of antibiotic prescriptions with feedback given to the prescribers in real-time, which facilitates discussion of recommendations. Audit-feedback strategies have been shown to improve antibiotic prescribing practices in general pediatric wards (20). There is clearly a need for effective AMS strategies to minimize the risk of AMR associated with inappropriate use of antimicrobials in NICU (21, 22).

AMS programs employ specific metrics to evaluate and enhance antibiotic use, aiming to improve patient outcomes and mitigate resistance. Key measurements include adherence to clinical guidelines, ensuring appropriate drug selection, dosing, and treatment duration—and tracking antibiotic consumption through metrics like DOT per 1,000 patient-days. Monitoring antibiotic-free days provides insight into periods without antibiotic exposure, reflecting stewardship effectiveness. Microbiological data, particularly resistance patterns, are essential for guiding empirical therapy and updating treatment protocols. Clinical outcomes, such as the incidence of late-onset sepsis, necrotizing entercolitis, and mortality rates, are assessed to ensure AMS interventions do not compromise patient safety. Additionally, cost analyses evaluate the economic impact of antibiotic use, aiming to reduce unnecessary expenditures while maintaining

high-quality care. Collectively, these measurements offer a comprehensive framework for assessing the efficacy of AMS initiatives (23).

To increase the appropriate prescription and utilization of antimicrobials the Federal Ministry of Health (FMOH) has developed and revised an AMS guide to support the implementation of AMS program (29). In response to this, TASH implement AMS in neonate intensive care unit since 3,April, 2022. Our aim was to investigate the impact of AMS in reducing antibiotic use, and improving clinical outcome in neonates, for maintaining and expanding this stewardship program at other wards of TASH and other health care institutions of the country.

1.2 Statement of the problem

Neonatal mortality remains a major global health challenge. Among the 2.5 million neonates who die within the first four weeks of life annually, approximately 23% die due to infectious diseases, including sepsis and pneumonia (30). While advances in neonatal care have reduced overall child mortality, neonatal deaths now account for 47% of under-five mortality (31). In high-burden regions, infections contribute to up to 50% of neonatal deaths (30). with sepsis ranking as the third leading cause of neonatal mortality worldwide (32). More than half of sepsis-related deaths occur in developing countries (33). In Ethiopia, one neonate dies for every 35 children in the first month of life ((34), with life-threatening infections representing the most common clinical diagnosis and the second leading cause of NICU admission (35).

Although antimicrobial agents have saved millions of lives since their discovery, inappropriate and excessive use has driven the emergence of AMR. After more than 75 years of widespread use, many antimicrobials now show diminished efficacy (36). The World Health Organization predicts that by 2050, up to 13 million deaths could be attributed to infectious diseases if AMR remains uncontrolled (37). Multidrug-resistant (MDR) bacterial infections now represent a critical global health threat, accounting for nearly 30% of mortality associated with severe infections (38). Neonates in NICUs are particularly vulnerable due to prematurity, invasive procedures, and frequent antibiotic exposure (39). Studies show increasing neonatal colonization with MDR Gram-negative organisms, frequent outbreaks, and limited treatment options ((40) (41).

In LMICs, access to effective antibiotics for MDR infections is severely restricted (38). The burden of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae is especially high. Studies from Asia and Africa report alarming prevalence: up to 87% of *E. coli* and 95% of *Klebsiella* isolates among septic neonates have been identified as ESBL producers (42) (43), with associated higher mortality rates and prolonged hospital stays (44). Systematic reviews indicate that nearly 50% of neonatal pathogens in LMICs are resistant to WHO-recommended first- and second-line regimens (38,45). In Ethiopia, pooled prevalence of MDR organisms is 70.5% (46). Studies at St. Paul's Hospital and Asella Teaching Hospital revealed over 80–90% resistance rates among *Klebsiella*, *Acinetobacter*, and *E. coli* isolates, underscoring the urgent need for AMS interventions (47) (48).

The principal driver of AMR is inappropriate antimicrobial use worldwide, with misuse more prevalent in LMICs (49-51). Globally, an estimated 50% of hospital prescriptions are inappropriate (51, 52). Similar findings have been reported in Ethiopia, where nearly half of antimicrobial prescriptions are judged inappropriate (53-55). In NICUs, more than one-quarter of neonates receive antibiotics, often for prolonged empiric therapy without microbiological confirmation (56). By contrast, NICUs with AMS programs report significantly lower antibiotic utilization rates compared to those without stewardship interventions.

AMS programs are globally recognized as effective strategies to optimize antibiotic use, improve diagnostic practices, reduce resistance, and enhance patient outcomes. Studies in LMICs show that models using non-specialized healthcare professionals, such as clinical pharmacists, can significantly decrease antimicrobial use (24-26). In Ethiopia, evidence is limited but promising. At Tikur Anbessa Specialized Hospital (TASH), cessation of a pharmacist-led AMS intervention was associated with increases in antimicrobial use, mean duration of therapy, hospital stay, and mortality (27). Other studies also indicate reductions in antibiotic costs with AMS interventions (28). Despite these findings, there is still a lack of robust data assessing impact of AMS interventions specifically in NICUs in Ethiopia, where the burden of neonatal sepsis, AMR, and inappropriate antibiotic use is high.

Therefore, evaluating the impact of an Antimicrobial Stewardship Program in the NICU of TASH is critical to generate local evidence on its effectiveness in improving antibiotic use, diagnostic yield, and neonatal outcomes, and to inform the scaling up of stewardship interventions to other wards and hospitals in Ethiopia.

1.3 Significance of the study

Despite high prevalence of inappropriate antimicrobial use, MDR strains, and high mortality rate of neonate due to infectious disease occurring in the Ethiopia, AMS is not fully implemented in most health care institutions of the country. Therefore, the finding of this study might help to:

- To understand changes in antibiotic use patterns, in the patient hospital stay and mortality due to the introduction of an AMS. Provide insightful information about impact of antibiotic stewardship program on antibiotic use, and in-hospital length of stay and mortality in the TASH ICU. The size and scope may well vary with their efficacy in meeting basic goals of optimizing anti-infective utilization, antibiotic resistance changes and patient outcomes.
- Important for community patients to ensuring optimal antibiotics use, reducing unnecessary exposure to antibiotic, preventing the emergency of resistant organisms, and improving patient outcomes through targeted therapy,
- It enables health care providers to optimize antimicrobial use, leading to improved patient care, reduced health care costs, and minimize risks of antimicrobial resistance.
- Researcher in these areas provides valuable insights into infectiveness of AMS intervention in NICU, contributing to the development of evidence based guidelines and protocols.
- Finding from such studies inform health care policies and guidelines, guiding decision-making processes aimed at improving AMS practices in NICUs, ultimately benefiting public health initiatives and healthcare resource allocation.
- Primarily important for utilizing in the ongoing justification for maintaining and expanding this stewardship program at other wards of TASH and other health care institutions of the country.

2. LITERATURE REVIEW

2.1 Antimicrobial Resistance

Antimicrobials are an extremely valuable resource across the spectrum of modern medicine to treat and prevent infectious diseases. Their development has been associated with dramatic reductions in communicable disease mortality and has facilitated technological advances in cancer therapy, transplantation, and surgery (57). Even though, antimicrobial resistance is a natural phenomenon that occurs spontaneously as microbes evolve, human activities have accelerated the pace at which microorganisms develop and disseminate resistance. The indiscriminate and excessive usage of antimicrobial drugs without treatment indication appears to be the most significant factor associated with the emergence and fast spread of resistant microorganisms in recent years (58).

Moreover, antibiotic consumption has increased by 36% in the past decade; no new classes of these drugs have been discovered since the 1980s to solve the currently prevailing problems. For instance, when we see respiratory tract infections, it is mostly considered as self-limiting viral origin, such as common colds, viral sore throats and bronchitis which, antibiotic treatment has limited effect on symptoms. However, it accounts the most commonly treated acute problems in the primary care in Europe. Both the upper and lower respiratory tract infections account for 57% and 30% of antibiotics used respectively (59). As CDC estimated that, 47 million unnecessary antibiotics were prescribed by United States of America Doctors' more than 100 million worldwide with offices and emergency departments each year. Around 50% of these unnecessary antibiotics are prescribed for acute respiratory infections. Likewise, 75% of antibiotics prescribed incorrectly in nursing homes. The two extremes ages, children under 2 and 65 and above older adults receives most of the antibiotic prescriptions (60).

The most common associated problems are wrong antibiotic usage, incorrect dose or duration, patient non adherence to the treatment regime. This may lead harmful side effects, allergic reactions, *Clostrdium difficile*, fungal antibiotic-resistant organism infections (58). A bloodstream associated bacteriemia such as, isolates of *Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa* and Proteus spp., causes the majority of HAI and successfully "escape" the effects of antibacterial drugs (61). Rates of antimicrobial resistance among hospital and community pathogens have

increased considerably. This is especially more common in clinic settings in which resistant strains are frequently found before they spread to the community (62). The increasing prevalence of hospital and community-acquired infections caused by MDR bacterial pathogens is the limiting option for effective antibiotic therapy. Moreover, this alarming spread of antimicrobial resistance has not been paralleled by the development of novel antimicrobials (63).

The issue has received high attention from various organizations, including WHO, Infectious Diseases Society of America, who recognized AMR as one of the greatest threats to human health worldwide. Methicillin-resistant *Staphylococcus aureus* (MRSA) alone is the significant cause of death each year in Americans than combinations of emphysema, HIV/AIDS, Parkinson's disease and homicide (64). In 2012 the European population-weighted mean percentage of carbapenem resistance was 6.2% the highest burden of carbapenem resistance *K. Pneumoniae* (28.8%) was seen in Greece, followed by Italy nearly 19%, this might be associated with the highest rate of antibiotic consumption, which is much higher than other European countries like Sweden around 1% (65). Apart from spreading resistance, an alarming pattern of multi and pan-drug resistant Gram-negative bacteria are currently emerging; multi-resistant *Enterobacteriaceae* is an increasing major concern worldwide (66).

Generally, antibiotic resistance, with the current rising up rates of antimicrobial resistance, insufficient research and development activities; irrational use of antibiotics for humans and food animals; and uncoordinated overall international technical and nontechnical efforts, could result in a time in which treatment of many of the infections is impossible (67). Thus, in order to address the impact of antimicrobial resistance on medical, social, and economical burdens, real and unreserved global coordinated efforts, paralleled with antimicrobial stewardship programs Implementation and evaluation, led by the health professionals have to be taken.

2.2 Antimicrobial stewardship

Antimicrobial stewardship is characterized as "a systematic or institution-wide strategy aimed at promoting and overseeing the prudent utilization of antimicrobials to safeguard their efficacy (68). The principle of AMS was advocated by the IDSA in the year 2007. It was initially delineated as coordinated interventions predicated on the objective of enhancing antimicrobial usage through the selection of suitable agents, the appropriate dosage, the correct administration route, and the duration of therapy, all while ensuring that patient outcomes remain

uncompromised(69, 70). AMS denotes a comprehensive array of systematically organized strategies aimed at (i) enhancing patient care and clinical outcomes through the administration of optimal therapeutic interventions; (ii) mitigating collateral damage by minimizing the utilization of antimicrobial agents (thereby reducing the incidence of resistance), and (iii) curtailing the financial burden associated with antibiotic procurement (71). These methodologies possess the potential for global application to aid in the regulation of AMR by fostering public awareness and instructing healthcare professionals on the judicious application of antimicrobials within the framework of an antimicrobial stewardship program. In summary, AMR ought to be regarded as an imperative global concern, necessitating that all nations and organizations engage in coordinated initiatives to develop and implement novel policies and research pertaining to antimicrobial stewardship.

2.2.1 History of Antimicrobial Stewardship

The origins of AMS trace back to Sir Alexander Fleming's warnings in the 1940s regarding the emergence of antibiotic resistance, which manifested within a decade due to widespread drug misuse (72). Despite subsequent efforts by infectious disease organizations in the mid-20th century—including educational initiatives, quality management protocols, and clinical guidelines—these measures proved largely ineffective in curbing resistance. A pivotal shift occurred in 1996 when McGowan and Gerding conceptualized the term "Antimicrobial Stewardship," asserting its necessity as a core component of all antimicrobial decision-making (73). This framework was formally integrated into clinical guidelines by the Society for Healthcare Epidemiology of America (SHEA) and the IDSA in 1997 (74). By 2007, AMS evolved into a structured programmatic strategy endorsed by these organizations. Concurrently, European scientists Ian Gould and Jos van der Meer advanced its global adoption through the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Antimicrobial Stewardship in 1999, solidifying AMS as a cornerstone of antimicrobial resistance mitigation worldwide (75).

In the United States, the CDC initiated its inaugural educational campaign in 2009 to promote judicious antibiotic use in acute-care settings, later formalizing enhanced antibiotic stewardship as a strategic priority in 2013 (76). Accrediting bodies subsequently underscored the critical role

of AMS Program in clinical practice (77), though a 2014 study revealed only 39% of healthcare facilities had adopted such programs (78). By 2017, federal mandates required all hospitals to integrate AMS Program into institutional frameworks (79). In Europe, numerous nations implemented cost-efficient national or regional ASPs to improve prescribing practices, strengthen surveillance, and foster stewardship awareness. The European Commission reinforced these efforts in 2017 by issuing guidelines on responsible antimicrobial use (79) and publishing progress reports on AMS advancements (80). Concurrently, the WHO European Region evaluated public awareness initiatives to optimize antimicrobial stewardship strategies globally (81).

AMS initiatives have been demonstrated to enhance the utilization of antibiotics within developed nations; however, the strategies aimed at mitigating AMR are not effectively operationalized in developing nations (82) , resulting in a pressing need to establish, implement, and assess efficacious AMS programs in these regions (83). In response to this critical situation, the (82) WHO and the United Nations General Assembly endorsed the global and institutional-level execution of AMS programs in 2016. Recently, the WHO disseminated an AMS toolkit specifically tailored for developing countries, underscoring the significance of local contextual factors in the formulation and execution of AMS initiatives (84).

AMS programs, by promoting evidence-based prescribing practices, directly address the global health crisis posed by AMR, which threatens patient safety, escalates healthcare costs, and undermines therapeutic efficacy (76). These initiatives enhance patient outcomes by reducing adverse drug events and treatment failures linked to inappropriate antimicrobial use, while concurrently delivering cost savings through minimized unnecessary prescriptions and hospitalizations(85). Core components of effective AMS include continuous clinician education to align prescribing with current guidelines, robust surveillance systems to monitor antimicrobial consumption and resistance trends, and interdisciplinary collaboration among healthcare providers, microbiologists, and public health experts (86).

1. *Impact on Antimicrobial Utilization*

AMS intervention significantly improves antimicrobial utilization particularly within high-risk environments such as NICUs, which related to the emergence of antimicrobial resistance by

reducing broad-spectrum antibiotic prescriptions and shortening treatment durations across various healthcare settings globally. In high-income countries, such as the United States, AMS Program implementation in Memphis (2010–2013) led to a 54% reduction in broad-spectrum antibiotic use for early-onset sepsis (86), while a meta-analysis involving over 350,000 neonates showed a 19% reduction in antimicrobial initiation and a 20% decrease in treatment duration following AMS implementation (87, 88). Similarly, in Cork, Ireland (2016–2017), the incorporation of electronic prescribing and audits led to a remarkable 91% reduction in prolonged broad-spectrum antibiotic use (greater than 36 hours), decreasing from 82 to 7.5 days of therapy per 1,000 patient days (88).

In Vancouver, Canada (2010–2015), there was a significant reduction in the inappropriate use of Vancomycin and Cefotaxime (risk ratios of 0.37 and 0.49, respectively), while the misuse of Meropenem remained constant (89). while study done in Mount Sinai Hospital Toronto Canada reveal that Overall antibiotic use decreased to 339 days of therapy per 1000 patient-days from 395 (14%, $P < 0.001$), without an increase in mortality (90). Similarly the study carried out at the NICU of the University Hospital of Modena, Italy reveal that in the "intervention period", there was a 29% reduction in both DOT/1000 PD and AUR/1000 PD (91). Systematic review of AMS interventions in pediatric healthcare settings in LMIC shows that any type of AMS intervention can reduce antibiotic consumption, with more consistent reduction resulting from clinical decision tools and enabling strategies than guideline implementation alone. AMS interventions resulted in significantly decreased clinical infections (4/4 studies) and clinical failure (2/2) and reduced MDR organism colonization rate (4/4). There was no concomitant increase in mortality (4/4 studies) or length of stay (2/2) (92). Other similar Systematic review study in LMICs also show that, AMS intervention had significantly reduce in the use of antibiotics overall and broad-spectrum/ restricted antibiotics in NICU (93).

In China, AMS programs resulted in a marked improvement in treatment efficiency, with a significant increase in very low birth weight infants receiving antibiotics for ≤3 days (94), and a reduction in total antibiotic use from 182.2 to 31.6 days per 1000 patient-days (95). In middle-income settings, such as Lebanon, demonstrated sustained effectiveness, with initial antimicrobial use falling by 35% and a median decrease of 63% over five years; notably, ampicillin and gentamicin use decreased by 63% and 79%, respectively (96). Systematic reviews across eight African nations further support the role of AMS in enhancing adherence to

evidence-based guidelines and curtailing unnecessary antibiotic treatments (97). In Ethiopia, The study done at TASH show that, once a pharmacist-led AMS intervention ceased, total antimicrobial use increased by 51.6% and mean duration of treatment by 4.1 days/patient. Mean length of stay as well as crude mortality also increased significantly in the post-intervention phase (length of stay: 24.1 days vs. 19.8 days; in hospital death 14.7 vs. 6.9%) (27).

Collectively, these findings underscore the global impact of AMS intervention in improving antibiotic utilization, regardless of income level, through interventions such as audit-feedback mechanisms, early-onset sepsis risk calculators, and microbiologically guided de-escalation strategies and implementation of guideline.

2. *Impact on length of hospital stay*

AMS intervention in NICUs has been shown to not only reduce unnecessary antibiotic exposure but also improve clinical outcomes, notably by shortening the LOS. Contrary to concerns that reduced antibiotic use could harm patient outcomes, evidence supports the safety and efficacy of AMS intervention. Systematic reviews demonstrate that these programs significantly decrease the duration of antimicrobial therapy, leading to shorter hospital stays without increasing sepsis-related mortality (88, 98). The study done in Children's Mercy Kansas City in USA reveal those patients with an AMS program review and agreed recommendations had a reduced LOS by 22.7% (10.2 days vs. 13.2 days) and other study in USA show that Acceptance of AMS program interventions by prescribers was linked to a shorter hospital LOS (6.5 days vs. 7 days) and a reduced duration of antimicrobial therapy (99). Consistently the studies done in developing country show that AMS intervention can reduce length of hospital.

In Iran a median length of hospital stay that was significantly reduced post AMS intervention from 11 days to 7 days, 36.3% ($P<0.01$) (100), in Palestine ,a study specifically addressing Meropenem and Vancomycin use in Pediatrics ICU with a much higher baseline length of stay of 23 days, showed a significant reduction to 16 days ($P = 0.02$) (101) and in Cairo, Egypt at Cairo University specialized pediatric hospital on surgical NICU patients show that, average length of staying hospital decreased in the AMS period by a mean difference of 2.5 days ($P= 0.027$) (102).

In china also optimizing antibiotics use can reduce both length of stay at hospital and lower rate of complication related to hospital stay such as nosocomial infection and late onset sepsis (94) In

very-low-birth-weight infants, reduced antibiotic use has been associated with improved short-term outcomes (94) (103). Studies consistently show that optimized antibiotic strategies through AMS intervention contribute to decreased LOS and lower rates of complications such as nosocomial infections, intraventricular hemorrhage, and late-onset sepsis (94). Time series analyses and quality improvement projects, including those conducted in rural NICU settings, have reinforced these findings, showing reductions in LOS and antimicrobial exposure with no adverse impact on sepsis or mortality rates (104). AMS Programs achieve these results by implementing protocols that enable early discontinuation of antibiotics when cultures are negative or clinical symptoms resolve, and by minimizing the use of broad-spectrum antibiotics which are linked to hospital-acquired infections (89) Additionally, diagnostic tools such as the Neonatal Sepsis Risk Calculator help identify low-risk infants, avoiding unnecessary treatment and associated hospital stays (103).

3. *Impact on mortality rates*

AMS intervention in NICUs has been associated with either a reduction or no significant change in mortality rates, highlighting their safety and potential benefits in improving neonatal outcomes. A retrospective cohort study involving 1,580 neonates demonstrated that AMS programs effectively reduced antibiotic use without increasing mortality or adverse clinical outcomes (98). Similarly, an observational study conducted in a level III NICU reported a decline in all-cause mortality following the initiation of an AMS program (104). Meta-analysis demonstrated a 35% relative risk reduction in mortality when guideline-directed empiric antimicrobials were prescribed (105).

The study done in developing country at NICU and pediatric ICU show that, implementation of an AMS bundle resulted in a reduction of mortality from 10% to 8% ($P < 0.05$), most likely related to a reduction in HAI (106). Study in Iran also show that audit and feedback reduced all-cause mortality from 28% to 6% ($P = 0.001$) (101), Additionally, A study from India and Egypt can also show significant reduction of mortality rate from 25% to 16% and from 14.1% to 9.5% respectively (104) (107). Similarly, an observational study conducted in a level III NICU reported a decline in all-cause mortality following the initiation of an AMS program, suggesting that prudent antibiotic use may contribute to improved survival rates (108). Recommendations to discontinue unnecessary antibiotics in both NICU and PICU settings were not associated with

increased mortality, further supporting the safety of AMS program-guided interventions (109). These findings demonstrate that AMS Programs can lead to significant reductions in mortality rates in NICUs. Several mechanisms may explain these outcomes, including the avoidance of adverse effects linked to excessive antibiotic use—such as necrotizing enter colitis and bronchopulmonary dysplasia—through the careful reduction of antimicrobial exposure (91). AMS programs also encourage the use of narrow-spectrum antibiotics and individualized therapy adjustments based on culture results, thus minimizing the risks associated with broad-spectrum overtreatment (110). Moreover, standardized protocols for sepsis evaluation and timely treatment ensure that neonates with confirmed infections receive appropriate and effective care, which is crucial for enhancing survival (103). Overall, the evidence underscores that AMS program can play a vital role in improving neonatal care without compromising patient safety, particularly in terms of mortality outcomes.

4. *Impact on Antimicrobial Resistance (AMR)*

AMS are often a key strategy among action plans against antimicrobial resistance (111). The importance of such a program cannot be over-emphasized as it ultimately may help to decrease antimicrobial resistance in NICUs worldwide (55, 89, 112-117). AMS comprise a set of multidisciplinary activities focusing on proper antibiotic use, including implementing interventions for antibiotic prescription, monitoring of antibiotic usage and resistance patterns, regular reporting information on antibiotic use and resistance to medical staff, and educating clinicians about resistance and optimal prescription (118). Evidence indicates that healthcare facilities implementing AMS Programs experience lower rates of MDRO infections, largely due to the prudent and targeted use of antibiotics which decreases the selective pressure that drives resistance. A systematic review of 12 studies conducted between 2015 and 2024 found that AMS program contributed to a reduction in the incidence of MDROs in NICUs, although further long-term research on AMR outcomes remains necessary (119). Similarly, a 12-year longitudinal study reported no increase in resistant pathogens following AMS program implementation (112), while data from a rural Indian NICU documented a decline in culture-positive sepsis rates from 18% to 11.56% post- AMS program (112). Effective AMS program strategies include prioritizing the use of narrow-spectrum antibiotics, de-escalating therapy based on culture results, and conducting ongoing resistance surveillance to ensure adaptive treatment approaches (120). These

findings underscore the capacity of AMS program to mitigate AMR in neonatal settings while preserving the clinical effectiveness of antimicrobial therapies.

3. OBJECTIVES

3.1 General Objective

- To evaluate the effectiveness of Antimicrobial stewardship (AMS) interventions in the Neonatal Intensive Care Unit at Tikur Anbessa Specialized Hospital, Ethiopia from July to September 30/2024.

3.2 Specific Objectives

- Assess the effect of AMS interventions on antibiotic use.
- Compare microbiology testing or utilization practice before, during and after the intervention.
- Assess the effect of AMS interventions on clinical outcomes including length of stay and mortality.
- Identify factors contributing to poor clinical outcomes in the before, during and-after intervention phases.

4. METHODS

4.1 Study setting

The study was conducted in the TASH NICU. TASH was established in 1972. The hospital is located in Lideta Sub-City, Addis Ababa, Ethiopia. It is the largest teaching hospital affiliated with the College of Health Sciences, Addis Ababa University, and serves as a training center for undergraduate and postgraduate medical, pharmacy, and other health science students. The hospital serves more than 500,000 patients per year in its 20 outpatient specialty clinics, inpatient, and emergency departments. The TASH NICU is selected purposely due to the presence of an AMS program.

The first AMS program in TASH was a pharmacist-led, microbiology backed program started by support of the McGill University lasting from November 2017 to August 2018. Based on this program, AMS program resulted in implementation. However, the AMS program did not persist after the project and the practice returned to the old mantra (27). After this AMS committee was revitalized in 2019 until the COVID-19 pandemic disrupted it. On the post-COVID-19 period the AMS interventions were kept minimal. Recently, there is AMS program in the oncologic unit. The NICU AMS program was started April, 2022 year.

4.1.1 TASH context during the pre-intervention, intervention and post-intervention periods

1. Context in the pre-intervention periods (1, April, 2021 to 3, April, 2022)

During this period there was not active AMS program in the NICU. However, an AMS program has been undergoing in the pediatric oncology unit since 2023 and ongoing to this period.

2. Interventions (3, April 2022 to 27, March 2023)

On the April of 2022 the TASH NICU team has established an AMS program involving a pharmacist lead AMS audit that is presented and discussed in the biweekly AMS round in the presence of an ID physician. Below described are the details of the AMS program in the NICU running from 3, April 2022 to 27, March 2023:

1. Prospective audit and feedback

A multidisciplinary team was formed with one neonatologist, seven to ten pediatricians, two neonatologist fellows, three to five residents, one clinical pharmacist and a neonatal nurse. The AMS program in the NICU is led by infectious disease specialist and clinical pharmacist, backed microbiologist and has 15 to 20 members.

The role of the team was to implement a neonatal specific antimicrobial stewardship program (NS-AMS) program and monitor antibiotic usage. Educational sessions to faculty and staff on the benefit of NS-AMS program and harm of antibiotic overuse were also delivered at the beginning of the project. Topics included in the sessions were etiologies of neonatal sepsis based on newborn's age, the adverse effects of antimicrobial overuse, and the increased incidence of multi-drug resistance.

The NS-AMS program team performed biweekly audit and feedback rounds on patients taking antibiotics, and a neonatal clinical pharmacist rounded daily with the clinical team and inquired about the need and duration of antimicrobial therapy. The clinical pharmacist would give a recommendation to the clinical team and left the final decision to the attending physician.

During audit day, Pharmacist members of the AMS team approached treating teams to identify patients receiving any of the targeted antibiotics. through chart reviews supplemented with information from treating teams, they prepared a narrative summary of the case for discussion with the AMS team, focusing on the start date of therapy, indication for therapy, whether the patients had microbiological workup, and results of testing.

Each case presentation was followed by a short team discussion, centered on findings of the diagnostic workup and on acceptable duration of therapy. Members of the treating team were invited to contribute to the discussion. After reaching a consensus, the AMS team issued a recommendation which was transmitted verbally to the treating team and also documented on a structured form attached to the patient chart. When consensus could not be reached, the recommendation of the Infectious disease specialist physician prevailed. Recommendations were broadly categorized into: discontinue antibiotic, change (dose, duration, route and/or antibiotic type), and continue with specified duration.

2. Implementation of Algorithm for Early-Onset Sepsis in Preterm Neonates

To address variability in antimicrobial prescribing among neonatologists, an AMS intervention was implemented algorism for the management of early-onset neonatal sepsis in infants with a gestational age of less than 34 weeks. The intervention involved the development of standardized treatment algorithms based on international guidelines, including those from the American Academy of Pediatrics and the WHO, and was adapted to local antimicrobial resistance patterns, formulary constraints, and expert opinion. They recommend that those premature infants born to mothers with lower risk factors for EOS may not need empirical antibiotics at admission, discontinue empirical antibiotics if the blood culture remains negative after 48 h and the child's clinical presentation does not indicate ongoing infection (121), which demonstrate that a reduction in antibiotic use in VLBW infant NICU through quality improvement study in both LMICs and HICs (122) (123). Algorithms, exemplified in (Figure 1), were integrated into routine AMS rounds to guide clinical decision-making and reinforce consistent, evidence-based prescribing practices.

3. Department policy plan for starting antibiotics

The team had formulated a policy plan for rational antibiotic usage under the guidance of the visiting neonatologist. Broad-spectrum antibiotics like ampicillin, or Cefotaxime and gentamicin were standardized for empirical antimicrobial treatment for all admissions. Criteria for starting antibiotic, dose, dosing interval and duration were clearly mentioned. Meropenem, Cefepime, Ceftazidime, Vancomycin and Amikacin were standardized as second-line antimicrobial regime for sick babies. Preauthorization was made mandatory for residents before starting second-line antimicrobial regime in order to stop the empirical antibiotic treatment policy. The team circulated this policy to all residents and consultants managing NICU.

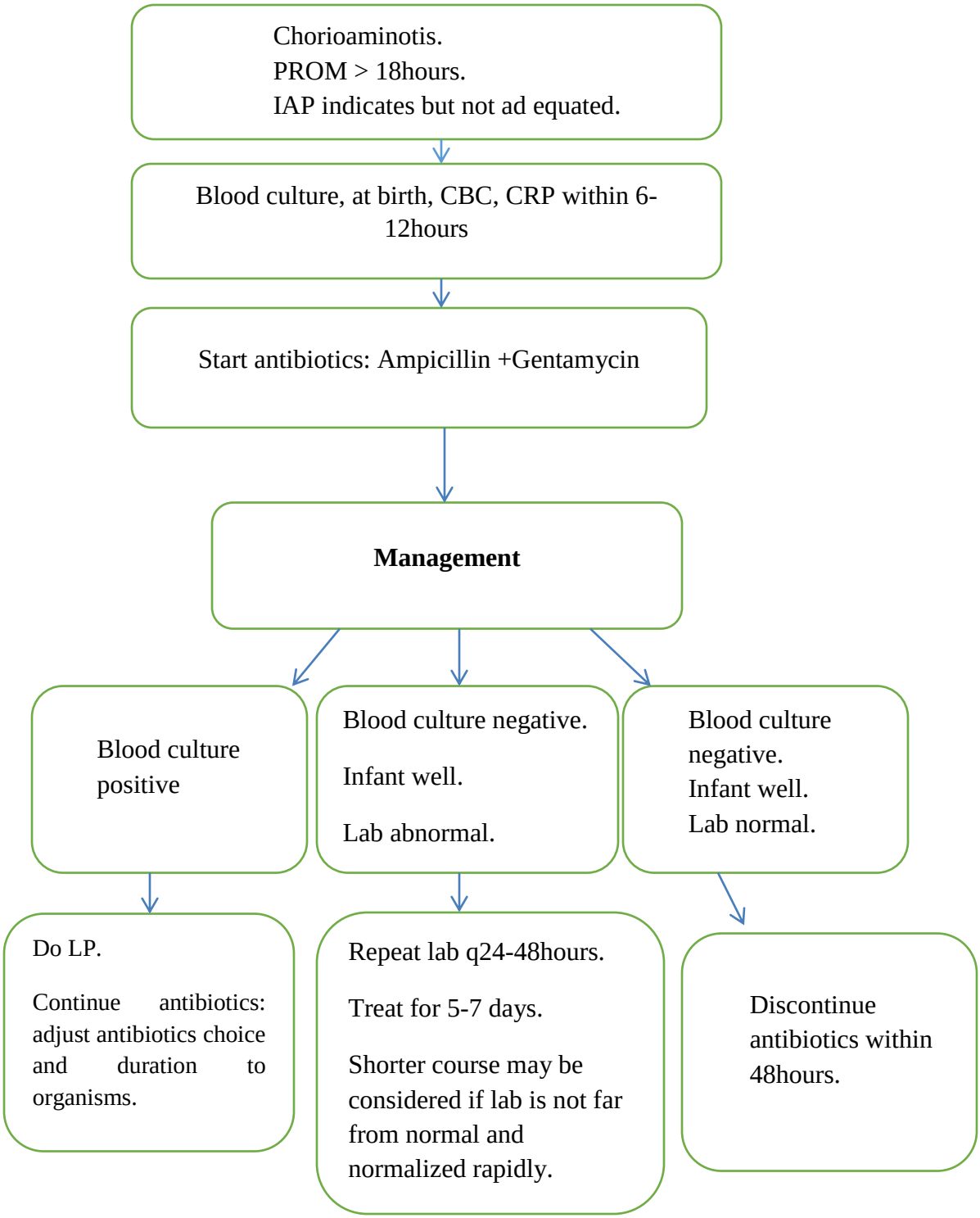

Figure 1: Evaluation of asymptomatic infant with <=34 gestations with risk factor of sepsis

4. Adaptation of universal aseptic precautionary measures

In order to address the issue of cross-infection, the investigative team conducted inquiries with both the residents and nursing personnel regarding the aseptic protocols that were being implemented. The team observed a deficiency in the adherence to aseptic protocols by the nursing staff. To ensure rigorous implementation of universal aseptic precautionary measures, including frequent sanitization, minimal handling, and the utilization of nursing barriers, the team sought the expertise of the infection control committee within the microbiology department. At the request of the department head, an infection control nurse was appointed for the NICU. His responsibilities encompassed the facilitation of hand washing drills, the collection of swabs from the hands of personnel and equipment, as well as monitoring compliance with aseptic protocols during various procedures. She conducted hand washing drills each morning, subsequently requesting random demonstrations from staff members in front of the entire NICU team. Additionally, a manual detailing the steps for proper hand washing was affixed above each washing station for the purpose of reinforcement.

The entire NICU personnel commenced to rigorously adhere to aseptic protocols, driven by the concern of obtaining positive swab outcomes. Support and guidance were provided, and in instances of any lapses in compliance, fellow staff members promptly reminded the individual in question. Furthermore, hand washing techniques were also disseminated to mothers visiting their infants in the NICU. The team expressed satisfaction with the performance and self-regulation exhibited by all operational units. Although the infection control nurse was present during morning shifts, these practices were sustained throughout subsequent shifts as well.

5. *Post-intervention phase Context (28, March, 2023 to 31, March, 2024)*

The post intervention phase was from 28, March 2023 to 31, March 2024. During this period, The clinical pharmacist, who is member of the AMS team conducts seven days rounds is not present and the biweekly audit and feedback rounds is not performed by NS-AMS program team and there is no Educational sessions for staff. The collected data is not audited and provide structured feedback to prescribers. If microbiology laboratory results were not known, the auditors did not make specific efforts to collect results from the laboratory. Only data available on the medical chart was collected by data collector. While prescribers continued to have access to treatment algorism for EOS/risk factor for EOS in preterm neonate, the cumulative

antibiogram, follow department policy plan for starting antibiotics and there are universal aseptic precautionary measures.

4.2 Study design and Period

A retrospective cross-sectional chart review was carried out in the NICU between Julys to September 30/2024. The chart review was carried out for the NICU TASH records of 12, April, 2021 to 31, March, 2024. The chart review was carried out in the pre-intervention (from 1, April, 2021 to 3, April, 2022), intervention periods (from 3, April, 2022 to 27, March, 2023) and post-intervention periods (from 28, March, 2023 to 31, March, 2024). The rationale of choosing retrospective cross-sectional chart review method include: a relatively inexpensive ability to research the rich readily accessible existing data; and we can examine patient data over an extended period, enabling us to asses' trends and changes in antibiotics use and patient outcome before and after implementation of the stewardship program, this method can yield large sample size, enhancing stastical power and allowing for most robust analysis, and also retrospective chart review feasible were resource for data collection and intervention implementation limited.

4.3 *Populations*

4.3.1 Source population

All neonates admitted to TASH with infectious disease.

4.3.2 Study population

All neonates admitted to neonate intensive care unit of TASH with a diagnosis of infectious disease and received antibiotics during the study period and fulfilled eligibility criteria.

4.4 Sampling and sample size determination

4.4.1 Sample size determination

The sample size for this study was determined based on the total number of eligible neonates admitted to the NICU during the study period, rather than through formal statistical calculation. Of the 2,362 neonates admitted across all phases which obtained from the hospital's i-CARE dashboard system of TASH, 763 met the inclusion criteria and were enrolled in the analysis. These included 260 neonates from the pre-intervention phase, 253 from the intervention phase, and 250 from the post-intervention phase.

4.5 *Sampling Technique*

All Individual patients who fulfill the inclusion criteria were included in the study.

4.6 Inclusion and Exclusion criteria

4.6.1 Inclusion criteria

All neonate (aged <28 days) patients admitted to the NICU, having suspected or confirmed infectious diagnosis and received antibiotics.

Neonate include in study are:-

- Neonate which diagnosed with infectious disease.
- Neonate received antibiotic therapy during ICU stay.
- Neonate which were hospitalized for >24hours.
- Neonate with complete medical record.

4.6.2 Exclusion criteria

- Neonate with incomplete information.
- Neonate patients whose hospital stay was less than 24 hours.

4.7 Study variables

4.7.1 Independent variables

Patient related factors

- Age
- Sex
- Gestational age
- Birth weight

Disease related factors

- Clinical features at presentation
- Presence of co-morbidities
- Suspected or confirmed bacteriological Dx before initiation of antibiotics
- Presence of complication
- Indication of antibiotics

4.7.2 Dependent variables

- Clinical outcome Metrics:
  - Average length of stay in the NICU
  - Mortality rate among NICU patients
- Antimicrobial use Metrics:
  - Duration of antibiotic therapy per patient

4.8 Data collection and analysis

4.8.1 Data collection instrument

The data was collected using a data abstraction sheet prepared by reviewing different literatures and guidelines (124). Data was collected on patient demographics and clinical characteristics (patient ID, age at admission, gender, gestational age, birth weight and diagnosis at admission), antimicrobial usage (antimicrobial agent(s) used, dosage, duration of therapy ,reason for initiation, primary indication for admission), investigation (including culture and susceptibility data) and diagnosis related information(types of infection), indication for antibiotics(empiric; for suspected infection presumed or unknown source, definitive; based on positive culture and molecular test or, prophylaxis) appropriateness of antibiotic regimens, AMS recommendations (nature of intervention like, de-escalation, discontinuation, change (dose, duration, route and/or antibiotic type) continue with specified duration) and patient clinical outcome related information(clinical response to antimicrobial therapy, resolution of infection, length of hospital stay, mortality rate, need for intensive care intervention like ventilator and respiratory support). Data regarding antimicrobial use was reported as average duration of therapy and days of therapy per 1000 patient-days. All neonates receiving antibiotics had their history and course of the disease, laboratory and microbiological findings, indications, and drug choices evaluated during the rounds. Laboratory and microbiological findings was obtained to detect preliminary and final microbiologic culture results, that guiding the selection of definitive therapy.

4.8.2 Pilot testing of the data collection tool

The data collection format was pre-tested on a representative sample (5%) to ensure clarity, lack of ambiguity, comprehensiveness, and content uniformity. Based on the pre-test results, necessary modifications were made to the format.

4.8.3 Data quality Assurance

The collected data was checked for completeness and validity on the day of collection and before data entry. This includes direct supervision and review by the advisor to ensure reliability.

4.8.4 Study Outcomes

The primary outcomes were antimicrobial average duration of therapy per patient and days of therapy (DOTs) per 1000 patient days. The secondary outcomes include length of stay at hospital and in-hospital mortality.

4.8.5 Data collection

1. Retrospective chart review pre-intervention phase (1, April 2021 – 3, April 2022).

To understand the baseline usage of antibiotics in our NICU, a retrospective review of charts of all neonates who received antibiotics from 1, April 2021 till 3, April 2022, was performed. The duration of 13 months was chosen to account for seasonal variation and differences in practice among the three neonatologists at that time. The range of data was 1 years prior to the interventional initiation for review for this study. Neonate were included if they were admitted to the NICU and received intravenous or intramuscular antimicrobials during their hospitalization.

In pre-intervention period Aggregate data collected from the microbiology laboratory over the preceding year were used to develop NICU cumulative antibiogram and the developed antibiogram manual was pasted on wall of NICU ward building for memorization by treating team and also Prescribers and pharmacists were given access to this tool on their mobile devices for longer than the duration of the study.

Chart review was validated by having two independent reviewers collecting the baseline data separately and comparing findings. Data collected also included gestational age, sex, age at antibiotic initiation, birth weight, gestational age, previous antibiotics, previous admission, on antimicrobials including antibiotic(s) used, dosage, start and end dates, and dosing intervals duration of use, documented indication/justification of use, and laboratory workup including blood, urine, and cerebrospinal fluid, complete blood count, C - reactive protein and image finding.

2. Retrospective chart review of the intervention phase (3, April 2022 – 27, March 2023)

In interventional phase retrospective chart review was conducted from 3, April 2022 – 27, March 2023, to evaluate the impact of AMS intervention in the NICU. Patient medical records, microbiology logs, pharmacy dispensing data, and stewardship team documentation were systematically reviewed. Data collection focused on neonates admitted during intervention who received intravenous/intramuscular antimicrobial therapy. Data extracted included gestational age, sex, age at antibiotic initiation, birth weight, gestational age, previous antibiotics, previous admission, on antimicrobials including antibiotic(s) used, dosage, start and end dates, and dosing intervals duration of use, documented indication/justification of use, and laboratory workup including blood, urine, and cerebrospinal fluid, complete blood count, C - reactive protein and image finding. Antimicrobial utilization metrics, such as average duration and days of therapy, were calculated per 1,000 patient-days. The chart review also included documentation of clinical outcomes, including mortality and LOS. Data were abstracted by two independent reviewers using a structured tool, ensuring consistency and minimizing bias in retrospective extraction.

3. Retrospective chart review of the post intervention phase (28, March 2023 – 31, March 2024)

A retrospective chart review was executed for the post-intervention phase, encompassing the duration from 28, March 2023 – 31, March 2024, with the objective of assessing the efficacy of the antimicrobial stewardship (AMS) intervention within the neonatal intensive care unit (NICU). Patient medical records, microbiology logs, and pharmacy dispensing data were meticulously examined. The data collected pertained to neonates admitted during this timeframe who underwent systemic antimicrobial therapy. The information extracted comprised demographic characteristics such as birth weight, gestational age, sex, history of prior admissions, previous antibiotic treatments, infection diagnoses, comorbidities, justifications for antibiotic usage, as well as microbiologic results including complete blood count (CBC) with differential, culture positivity, C-reactive protein (CRP) levels, imaging studies, antibiotics administered, along with their initiation and cessation dates, and respective dosages. The chart review additionally encompassed the documentation of clinical outcomes, specifically mortality rates and LOS. Data abstraction was performed by trained personnel utilizing a structured tool, thereby ensuring uniformity and reducing bias in the retrospective data extraction process.

4.8.6 Data analysis

The collected data was analyzed using SPSS version 26. Descriptive statistics was used to summarize socio-demographic and clinical characteristics For categorical data, such as birth weight category and type of infection, were described using frequencies and percentages, and continuous data, such as the antibiotic duration and length of stay at hospital, were given as the mean ± standard deviation when normally distributed or the median with the interquartile range (IQR) when not normally distributed. Comparisons between the pre-intervention, during active stewardship periods and post-intervention periods was performed using Pearson's chi-square test For categorical data, For continuous data, the one-way ANOVA analysis was used or Kruskal-Wallis tests, as appropriate. Significant differences were assessed by Tukey's tests of post hoc contrasts. The predictors of neonatal mortality (alive and dead) were estimated using binary logistic regression with adjustments for potential confounders such as birth weight, gestational age, and others. Multiple linear regressions was used to identify predictors of LOS, incorporating variables such as intervention period, birth weight, infection category, comorbid conditions, and timing of microbiologic sample collection. Interaction terms were included in logistic models to examine subgroup effects (e.g., birth weight). Variables were classified as categorical, binary, or continuous, as appropriate. Statistical significance was determined using a two-sided p - value < 0.05. Model fit was evaluated using the Hosmer-Lemeshow test for logistic regression and adjusted R^2 with F-statistics for linear regression.

4.9 Ethical consideration

Ethical approval was obtained from the School of Pharmacy (of Addis Ababa University) Ethical Review Committee through the letter number ERB/SOP/568/15/2024 and permission to conduct the study was obtained from TASH administration. During data collection the name and other identifiers of the patient was not recorded in the data collection checklist to ensure confidentiality.

1. RESULT

5.1 Socio - demographic characteristics

A total of 763 neonates charts were reviewed in this study across three phases: 260 neonate charts from pre-intervention phases, 253 during the intervention, and 250 post-intervention. The demographic characteristics of study population remained largely consistent over phases in terms of gestational age, age of neonate, and birth weight, which support comparability among the study populations. The mean age at admission and birth weight were approximately normally distributed across groups and showed no significant variations with p-value of 0.957, and 0.079 respectively. While gestational age was not normally distributed, particularly due to left-skewed values from early gestational ages; however, no statistically significant difference in its distribution was detected ($p = 0.101$, Kruskal–Wallis test $p = 0.562$). The proportions of neonates born at less than 37 weeks and those with birth weights below 2.5 kg also did not differ significantly across periods, further evidencing demographic similarities.

Clinically, a significant reduction in average length of hospital stay was observed during the intervention phase (12.92 ± 2.75 days, $p = 0.007$) compared to the pre-intervention phase (17.95 ± 14.12 days). Infection rates remained consistently high (~92%) throughout all phases, highlighting an ongoing challenge in infection management. Surgical admissions among infected infants dropped post-intervention, though this change was not statistically significant. Comorbidities such as cardiovascular, renal and other diseases were reported more frequently during and after the intervention, potentially due to improved screening or documentation. Overall, the intervention demonstrated a transient reduction in length of hospital stay, but did not significantly impact infection rates or other clinical outcomes, underscoring the need for further strategies to address these persistent issues and sustain improvements in neonatal care (***Table 1***).

Table 1: Demographic and Clinical Characteristics of study participants, TASH, NICU Ethiopia

Variable	**Pre-Intervention (n=260)**	**During Intervention (n=253)**	**Post-Intervention (n=250)**	***p*-value**
Age (days)	4.64 ± 3.46	4.46 ± 3.17	4.22 ± 3.64	0.957
Gestational age (weeks)	36.83 ± 3.32	36.90 ± 3.25	36.96 ± 2.86	0.101
Birth weight (kg)	2.53 ± 0.79	2.68 ± 0.72	2.60 ± 0.74	0.079
Gestational age <37w	104 (40.0%)	107 (42.3%)	94 (37.6%)	0.562
Gestational age ≥37w	156 (60.0%)	146 (57.7%)	156 (62.4%)	0.562
Birth weight <2.5 kg	119 (45.8%)	120 (47.4%)	106 (42.4%)	0.513
Birth weight ≥2.5 kg	141 (54.2%)	133 (52.6%)	144 (57.6%)	0.513
Length of stay (days)	17.95 ± 14.12	12.92 ± 2.75	15.60 ± 7.00	0.007*
Presumed infection – Yes	240 (92.3%)	233 (92.1%)	232 (92.8%)	0.954
Surgical admission (of infected)	15 (75.0%)	15 (75.0%)	9 (50.0%)	0.198
Medical admission (of infected)	5 (25.0%)	5 (25.0%)	9 (50.0%)	0.172
Previous admission >2 days – Yes	59 (22.7%)	47 (18.6%)	67 (26.8%)	0.083
Comorbidities				
-Cardiovascular Disease	5 (1.9%)	14 (5.5%)	7 (2.8%)	0.064
- Renal Disease	4 (1.5%)	10 (4.0%)	10 (4.0%)	0.188
– Others (HIV or Liver disease)	2 (0.8%)	7 (2.8%)	9 (3.6%)	0.095

5.2Antibiotic Indications and Prescribing Patterns

Among the 763 neonates enrolled across the study phases, early-onset neonatal sepsis emerged as the most commonly reported indications for antibiotics, consistently affecting more than 60% of patients in all three periods, demonstrating consistent prevalence without significant variation. Hospital-acquired infections were the second most common, followed by respiratory and skin/soft tissue infections (**Table 2**).

Table 2: Indications of Antibiotics, TASH, NICU Ethiopia

Infection Type	**Pre-Intervention (n=260)**	**During Intervention (n=253)**	**Post-Intervention (n=250)**
Early-onset neonatal sepsis	172 (66.2%)	167 (66.0%)	159 (63.6%)
Hospital-acquired infection	50 (19.2%)	40 (15.8%)	52 (20.8%)
Respiratory infection	22 (8.5%)	21 (8.3%)	26 (10.4%)
Skin/soft tissue infection	18 (6.9%)	31 (12.3%)	18 (7.2%)
Neurologic infection	18 (6.9%)	12 (4.7%)	15 (6.0%)
Late-onset neonatal sepsis	10 (3.8%)	13 (5.1%)	14 (5.6%)
Cardiovascular infection	3 (1.2%)	4 (1.6%)	6 (2.4%)
Genitourinary infection	4 (1.5%)	3 (1.2%)	5 (2.0%)
Gastrointestinal infection	4 (1.5%)	2 (0.8%)	3 (1.2%)
Surgical site infection	0 (0.0%)	4 (1.6%)	4 (1.6%)
Febrile neutropenia	0 (0.0%)	0 (0.0%)	1 (0.4%)

5.2.1 Antibiotic Prescribing Patterns

While empirical therapy remained the dominant approach, it declined from 93.5% pre-intervention to 88.1% during intervention before slightly rebounding to 90.4% post-intervention, indicating modest but inconsistent change in prescribing patterns. Most impressively, definitive (culture-guided) therapy saw a six-fold increase—from 1.2% pre-intervention to 7.5% during AMS intervention (**Table 3**). This pattern suggests an ongoing need for AMS programs to further optimize antibiotic utilization in the NICU setting.

Table 3: Antibiotics Prescribing Patterns

Prescribing Category	Pre-Intervention (n=260)	During Intervention (n=253)	Post-Intervention (n=250)
Prophylactic use	14 (5.4%)	11 (4.3%)	9 (3.6%)
Empirical therapy	243 (93.5%)	223 (88.1%)	226 (90.4%)
Definitive therapy	3 (1.2%)	19 (7.5%)	15 6.0%)

5.3 Diagnostic Testing Practices

From diagnostic test C-reactive protein (CRP) testing shows the most remarkable improvement, increasing from 219 cases (84.2%) pre-intervention to (252 cases, 99.6%) during the intervention, with consistence high utilization post-intervention (240 cases, 96.0%; $p<0.001$). Complete blood count with differential analysis remained similarly high across all periods, performed 100% in both pre-intervention and during intervention phases, with only a minimal decrease to 99.2% post-intervention ($p = 0.128$). Imaging findings showed a distinct temporal pattern, with positive results two times fold during the intervention period (106 cases, 41.9%) compared to pre-intervention (52 cases, 20.0%), before returning to baseline in post-intervention period (45 cases, 18.0%; $p < 0.001$) (***Table 4***).

Table 4: Utilization of Diagnostic Tests

Diagnostic Test	**Pre-intervention (n=260)**	**During intervention (n=253)**	**Post-intervention (n=250)**	***p*-value**
C-reactive protein	219 (84.2%)	252 (99.6%)	240 (96.0%)	<0.001*
WBC with differentials	260 (100%)	253 (100%)	248 (99.2%)	0.128
Imaging findings	52 (20.0%)	106 (41.9%)	45 (18.0%)	<0.001*

5.4Microbiology Testing Practices

The result revealed a significant increase in test ordering frequency (77.8%), escalating from 103 tests (39.6%) in the pre-intervention period to 175 tests (70.4%) post-intervention ($\chi^2 = 49.386$, $p < 0.001$). This remarkable growth was accompanied by important qualitative shifts in testing patterns. The timing of specimen collection differ significantly ($\chi^2 = 30.215$, $p < 0.001$), with post-antibiotic collection becoming high (83.0% post-intervention vs. 56.3% pre-intervention). Blood cultures remained the most specimen source across all periods, with no significant change in source distribution ($p = 0.168$). Even though the overall diagnostic yield showed non-significant change across study periods ($p = 0.189$), further examination show that culture positivity result was significantly affected by collection timing. The Chi-square analysis revealed a higher positivity rate with pre-antibiotic collection (26.9%) compared to post-antibiotic

collection (10.5%; $p < 0.001$), also logistic regression confirmed that post-antibiotic collection significantly reduced the odds of pathogen recovery (B = -1.139, $p < 0.001$). These findings highlight the critical importance of pre-antibiotic specimen collection for increasing diagnostic yield, even within improved testing practices under AMS intervention.

A significant transformation was under goes with microbiology workup patterns ($p < 0.001$), with culture-plus-susceptibility testing predominating during the intervention period (82.4% vs. 14.3% pre-intervention), then transitioning to predominantly culture-only testing post-intervention (79.4%) (***Table 5***).

Table 5: Microbiology Testing Practices

Variable	**Pre-intervention n/N (%)**	**During intervention n/N (%)**	**Post-intervention n/N (%)**	***p*-value**
Microbiology tests ordered	103/260 (39.6%)	145/253 (57.3%)	175/250 (70.4%)	<0.001*
Timing of specimen collection				<0.001*
- Before antibiotics	45/103 (43.7%)	60/148 (41.4%)	30/175 (17.0%)	
- After antibiotics	58/103 (56.3%)	86/148 (58.6%)	146/175 (83.0%)	
Specimen source				0.168
- Blood	91/103 (89.2%)	125/148 (84.5%)	161/175 (92.0%)	(0.168)
- Urine	5/103 (4.9%)	10/148 (6.8%)	3/175 (1.7%)	
- CSF	6/103 (5.9%)	13/148 (8.8%)	11/175 (6.3%)	
Microbiology workup				<0.001*
- Gram stain only	41/103 (39.0%)	6/148 (4.1%)	6/175 (3.4%)	<0.001*
- Culture only	49/103 (46.7%)	20/148 (13.5%)	139/175 (79.4%)	
-Culture with susceptibilities	15/103 (14.3%)	122/148 (82.4%)	30/175 (17.1%)	
Positive culture results	18/103 (17.5%)	27/148 (18.1%)	20/175 (11.4%)	0.189

5.5 Results of Antimicrobial Stewardship intervention in NICU

Across study period a total of 2,027 antibiotic prescriptions were issued to neonate. During pre-intervention phase 721 (35.6%) is prescribed which decline to 640 (31.6%) during the intervention, reflecting an 11.2% reduction. However, in post-intervention antibiotic prescription increased to 666 (32.9%) marking a 4.1% increase compared to during active AMS intervention. From 640 antibiotic prescriptions audited during intervention period nearly half (49.5%) were recommended to discontinue antimicrobial, while 44.7% were continued as prescribed and 4.5 % required to change dose, frequency, or route. 94.5% underscores high acceptance for its clinical relevance and feasibility of the antimicrobial stewardship intervention. The most common reasons for discontinuation included investigations unsupported diagnosis/source (36.9%), treatment duration completed (30.3%), and inappropriate spectrum coverage (13.2%) (***Table 6***).

Table 6: AMS Recommendations and Intervention Rationales

Category	**Detail**	**N, (%)**
Recommendations	Discontinue current antibiotic	317 (49.5%)
(N=640 prescriptions)	Continue current antibiotic	286 (44.7%)
	Change current antibiotic (dose/frequency/route)	29 (4.5%)
	Consult ID	8 (1.25%)
Discontinuation Reasons	Investigations unsupported diagnosis/source	117 (36.9%)
(N=317 discontinued)	Treatment duration sufficient	96 (30.3%)
	Spectrum inappropriate	42 (13.2%)
	Indication/source unclear	12 (3.8%)
Change Reasons	Dosing/route inappropriate	18/29(62.1%)

Category	Detail	N, (%)
(N=29 changes)	Safety considerations	11/29 (37.9%)
Acceptance	Overall acceptance (*n* = 649)	605(94.5)
Reasons for non-acceptance (n = 35)	Patient nearing the end of planned therapy) Suspicion of antibiotic resistance	19(2.96%)
	Suspicion of an additional focus or pathogen	13(2.03%)
	Suspicion of antibiotic resistance	3(0.46)

Table 7: Antibiotic Prescription Patterns and Discontinuation Recommendations (n, %)

	Pre-Intervention (n=721)	**Intervention Phase (n=649)**		**Post-Intervention (n=666)**
Name of Antibiotic	**Total prescriptions (n=721); (%)**	**Total prescriptions (n=640); (%)**	**Recommendation to discontinue (n=317); (%)**	**Total prescriptions (n=666); (%)**
Ampicillin	225 (31.2%)	226 (34.8%)	136 (42.9%)	233 (35.0%)
Gentamycin	142 (19.7%)	164 (25.3%)	119 (37.5%)	162 (24.3%)
Cefotaxime	90 (12.5%)	53 (8.2%)	23 (7.3%)	49 (7.4%)
Metronidazole	56 (7.8%)	39 (6.0%)	0 (0.0%)	35 (5.3%)
Cefepime	71 (9.8%)	46 (7.1%)	14 (4.4%)	60 (9.0%)
Meropenem	78 (10.8%)	52 (8.0%)	9 (2.8%)	61 (9.2%)
Vancomycin	54 (7.5%)	26 (4.0%)	14 (4.4%)	40 (6.0%)
Pepracillin-Tazobactam	1 (0.1%)	3 (0.5%)	0 (0.0%)	6 (0.9%)
Ceftazidime	3 (0.4%)	1 (0.15%)	0 (0.0%)	1 (0.2%)
Cloxacillin	1 (0.1%)	1 (0.15%)	0 (0.0%)	1 (0.2%)
Amikacin	0 (0.0%)	29 (4.5%)	0 (0.0%)	18 2.7%)

5.6 Primary Outcome: Impact of AMS on Antibiotic Use

5.6.1 Antibiotic use patterns

The use of first line antibiotics like ampicillin and gentamycin increase significantly (from 86.5% to 93.2%; $p = 0.047$, 54.6% to 64.8%; $p = 0.023$), reflecting a shift toward narrower-spectrum antibiotics encouraged by AMS protocols. In contrast, broad-spectrum antibiotics such as Cefotaxime showed a marked and significant reduction (from 34.6% to 19.6%; $p < 0.001$), Meropenem from 30.0 % to 20.6% during intervention to 24.4 % post intervention period ($p = 0.046$), Cefepime from 27.3 % to 18.2% during intervention then to post intervention period 24.0% ($p = 0.047$), and Vancomycin from 20.8 % to 10.3 % then 16.0% post intervention period ($p = 0.005$) usage. Although Metronidazole use declined, the change was not statistically significant ($p = 0.054$). Importantly, the use of Amikacin which not recorded pre- intervention period was introduced and increased during stewardship intervention significantly ($p < 0.001$) (***Table 8***).

Table 8: Antibiotics Use Patterns

Antibiotic	**Pre-intervention (%)**	**Intervention (%)**	**Post-intervention (%)**	***p*-value**
Ampicillin	86.5 (225)	89.3 (226)	93.2 (233)	0.047
Gentamycin	54.6 (142)	64.8 (164)	64.8 (162)	0.023
Cefotaxime	34.6 (90)	20.9 (53)	19.6 (49)	<0.001
Metronidazole	21.5 (56)	15.4 (39)	14.0 (35)	0.054
Cefepime	27.3 (71)	18.2 (46)	24.0 (60)	0.047
Meropenem	30.0 (78)	20.6 (52)	24.4 (61)	0.046
Vancomycin	20.8 (54)	10.3 (26)	16.0 (40)	0.005
Piperacillin-Tazobactam	0.4 (1)	1.2 (3)	2.4 (6)	0.262
Ceftazidime	1.2 (3)	0.4 (1)	0.4 (1)	0.474
Cloxacillin	0.4 (1)	0.4 (1)	0.4 (1)	1.000
Amikacin	0.0 (0)	11.5 (29)	7.2 (18)	<0.001

5.6.2 Average Duration of Antibiotic Treatment (Days)

Both total average duration and specific antibiotics duration therapy were significantly differing across interventional phase ($p < 0.001$, ANOVA). With a significantly shorter total average duration (7.76 days, SD = 6.08) during interventional period compared to both the pre-intervention (10.98 days, SD = 7.03) and post-intervention phases (12.06 days, SD = 4.41), confirming with post hoc Tukey tests ($p < 0.001$). Notably, the longest average duration therapy of antibiotics in post-intervention phase, indicating a rebound effect following the withdrawal of AMS intervention activities. similarly evident for broad-spectrum antibiotics, with Vancomycin increasing from 9.0 to 17.3 days, metronidazole from 8.3 to 13.9 days, and Cefotaxime from 6.9 to 11.4 days. Even though first line antibiotics—such as ampicillin decreasing from 10.9 ± 6.3 to 6.5 ± 5.9 days ($p < 0.001$), and gentamicin from 9.6 ± 4.4 to 5.2 ± 3.7 days ($p < 0.001$) reductions were observed during the intervention remarkably —these gains were not consisted (***Table 9***).

Table 9: Average Duration of Antibiotic Therapy

Antibiotic	Pre-Intervention (Mean ± SD)	Interventional (Mean ± SD)	Post-Intervention (Mean ± SD)	*p*-value (ANOVA)
Total Average	10.98 ± 7.03	7.76 ± 6.08	12.06 ± 4.41	<0.001
Ampicillin	10.95 ± 6.29	6.46 ± 5.86	11.13 ± 4.69	<0.001*
Gentamycin	9.61 ± 4.43	5.16 ± 3.67	9.53 ± 3.68	<0.001*
Metronidazole	9.72 ± 6.84	8.28 ± 6.03	13.89 ± 5.27	<0.001*
Cefotaxime	8.61 ± 5.64	6.91 ± 4.68	11.39 ± 5.09	<0.001*
Cefepime	12.14 ± 11.29	11.47 ± 6.89	15.52 ± 6.43	0.036*
Meropenem	17.62 ± 9.02	14.10 ± 8.53	17.10 ± 6.32	0.044*
Vancomycin	15.06 ± 10.47	9.00 ± 5.15	17.28 ± 7.34	0.002*
Pepracillin-Tazobactam	4.00 ± 0.00	10.33 ± 8.50	15.83 ± 5.78	0.252
Ceftazidime	16.67 ± 11.02	4.00 ± 0.00	13.00 ± 0.00	0.414
Cloxacillin	10.00 ± 0.00	14.00 ± 0.00	15.00 ± 0.00	N/A

Amikacin	N/A	16.24 ± 7.66	12.82 ± 4.50	0.101

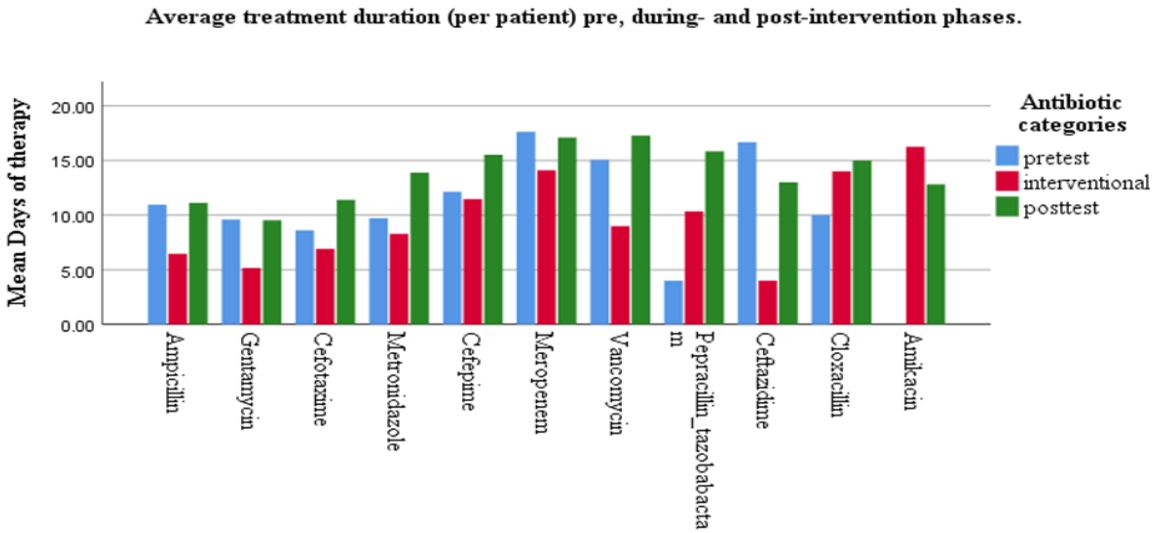

Figure 2: Average treatment duration (per patient) pre, during and post intervention phases

5.6.3 Days of Antibiotic Therapy (DOT) (DOT/1000 Patient-Days)

This study demonstrated statistically significant reductions in mean DOT in overall antibiotic consumption, quantified at 34% throughout the intervention period (20,925 to 13,779 days of therapy per 1,000 patient-days; $p < 0.001$). The AMS intervention was particularly effective in diminishing the usage of high-frequency antibiotics, with ampicillin and gentamicin experiencing a 50% reduction, Vancomycin showing a 78% decline, and Cefotaxime reflecting a 44% decrease. Nonetheless, the subsequent cessation of the intervention led to an alarming 96% increase in antibiotic usage (27,051 days of therapy), surpassing pre-intervention levels by 30%, which was marked by significant escalations in ampicillin utilization of 160%, gentamicin at 179%, and Cefepime at an increase of 114%, in addition to a 114-fold rise in Pepracillin-tazobactam ($p = 0.022$), indicative of compensatory broad-spectrum antibiotic prescribing practices. Although amikacin was incorporated during the intervention period (2,340 days of therapy), it experienced a notable decline of 69% post-intervention, whereas Ceftazidime and Cloxacillin demonstrated statistically insignificant changes ($p \geq 0.05$), emphasizing the ephemeral nature of stewardship efficacy and underscoring the imperative for ongoing interventions to avert the resurgence of antibiotic resistance (**Table 10**).

Table 10: Days of antibiotics therapy (DOT/1000 Patient-Days)

Antibiotic	**Pre-intervention (Mean ± SD)**	**During Intervention (Mean ± SD)**	**Post-intervention (Mean ± SD)**	**ANOVA *p*-value**
Total Antibiotics	20,925.0 ± 16,486.0	13,778.6 ± 14,590.0	27,050.9 ± 16,820.4	**<0.001**
Ampicillin	5,771.27 ± 4,151.36	2,857.77 ± 2,932.83	7,430.22 ± 3,779.20	**<0.001**
Meropenem	4,982.69 ± 9,075.91	3,160.98 ± 7,503.50	4,498.62 ± 8,702.20	**0.042**
Gentamycin	2,712.16 ± 3,056.45	1,361.18 ± 1,541.36	3,793.94 ± 3,315.89	**<0.001**
Vancomycin	2,537.74 ± 6,347.22	569.94 ± 2,094.22	3,060.78 ± 7,729.36	**<0.001**
Cefepime	2,271.23 ± 5,385.27	1,729.19 ± 4,570.98	3,704.11 ± 7,301.59	**0.001**
Cefotaxime	1,392.46 ± 2,481.45	773.22 ± 1,885.68	1,629.33 ± 3,687.12	**0.002**
Metronidazole	1,056.95 ± 2,656.04	818.38 ± 2,437.82	1,730.37 ± 4,633.47	**0.007**
Amikacin	0.00 ± 0.00	2,340.24 ± 7,263.83	716.80 ± 2,819.75	**<0.001**
Ceftazidime	176.01 ± 1,857.15	9.79 ± 109.89	43.33 ± 685.16	0.226
Cloxacillin	21.12 ± 340.57	59.96 ± 953.75	57.69 ± 912.20	0.819

This chart shows monthly Days of Therapy (DOT) for each antibiotic as a grouped bar graph, and it also includes a line representing the average treatment duration across all antibiotics per patient. The x-axis uses abbreviated month labels for clarity (Figure *3*).

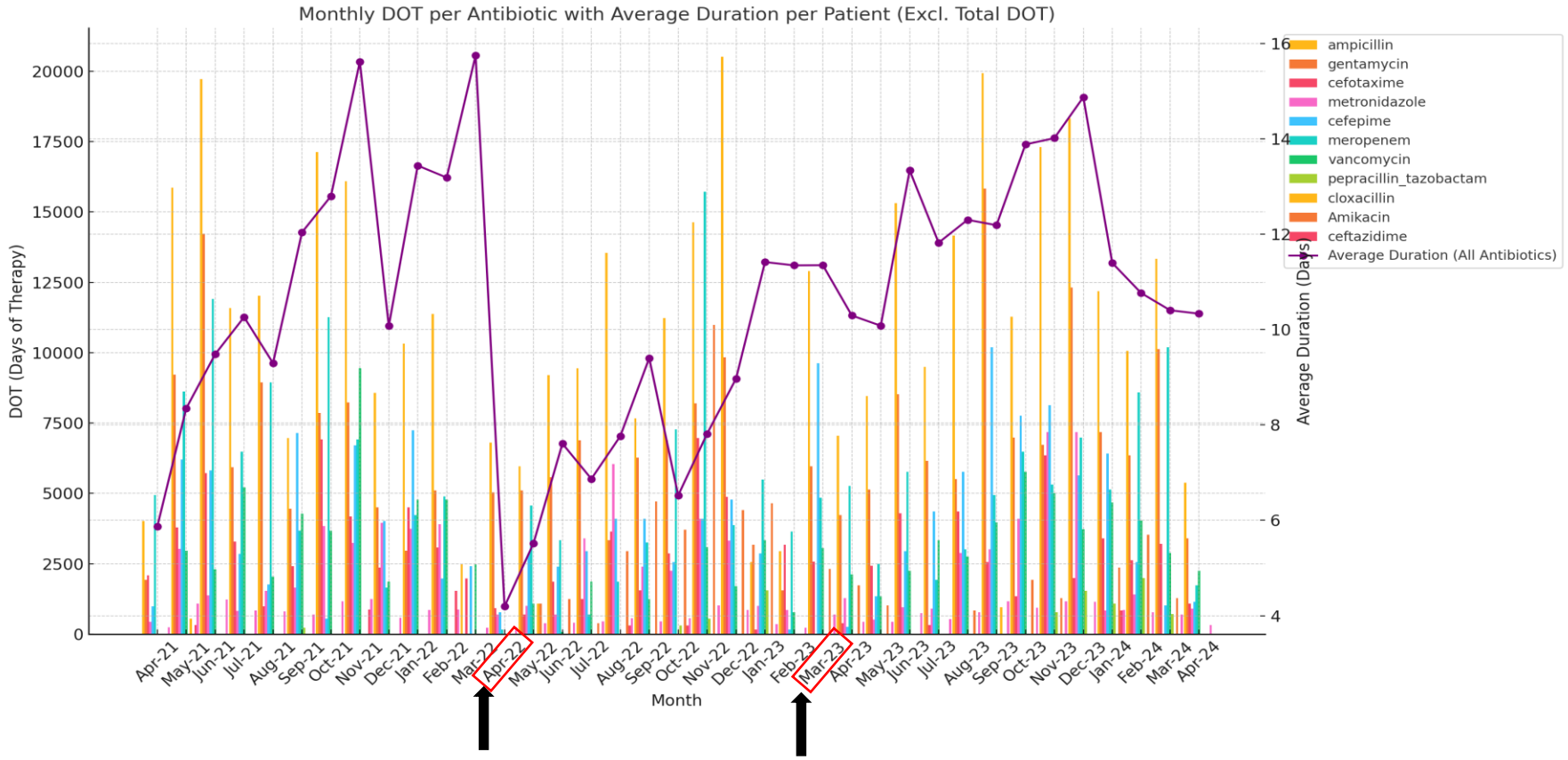

Figure 3: Monthly Antibiotic DOT (Excl. Total DOT) with Average Duration

5.7 Secondary Outcomes: Impact of Antimicrobial Stewardship on Clinical Outcomes

AMS intervention demonstrated significant, but time-limited improvements in neonatal clinical outcomes. A significant reduction in LOS, were observed during the active intervention phase 29% (12.92 days, 95% CI [9.61, 16.24]) compared to the pre-intervention period (18.22 days, 95% CI [16.51, 19.92]; $p = 0.002$), though this benefit was not sustained post-intervention (15.60 days, $p = 0.225$). Similarly, mortality decreased significantly by 57% during intervention (AOR 0.40, 95% CI 0.21-0.75, $p = 0.004$), then rebounded to baseline levels in post-intervention period (AOR 0.98, p=0.936).

5.7.1 Impact of AMS Intervention by Birth Weight Group

In LBW neonates <2.5 kg Stratified analysis show that antibiotic duration therapy significantly decreased during the intervention phase (mean = 8.33 ± 5.83 days) compared to pre-intervention (10.84 ± 7.67 days; $p = 0.006$), followed by a significant retaining in post-intervention period (12.85 ± 4.63 days; $p < 0.001$), across birth weight groups. Mortality also reduced substantially during the intervention (8.3%) relative to pre-intervention (23.5%), before increasing again post-intervention (18.9%), with a statistically significant overall trend ($\chi^2 = 16.59$, $p = 0.002$). Length of stay decreased modestly during the intervention but did not reach statistical significance (p = 0.450).in normal birth weight neonates' ≥2.5 kg, antibiotic duration therapy and LOS similarly reduced during the intervention with both $p < 0.001$. But, changes in mortality were not statistically significant in this group ($\chi^2 = 3.18$, $p = 0.204$).

Post-intervention mortality was significantly dominant than during the intervention period in LBW neonates (B = 0.939, p = 0.023; OR = 2.56), and no significant variation was observed in the normal weight group (B = 0.553, p = 0.166) which confirmed by Logistic regression incorporating an interaction term (Phase × Birth Weight Group) (**Table 11**).

Table 11: AMS Impact by Birth Weight Group

Outcome	**Birth Weight Group**	**Pre-Intervention**	**Intervention**	**Post-Intervention**	**p-value (ANOVA/ Chi²)**	**Regression(B, *p*-value)**
Antibiotic Duration (Mean ± SD)	LBW (<2.5 kg)	10.84 ± 7.67	8.33 ± 5.83	12.85 ± 4.63	$p < 0.001$	—
Antibiotic Duration (Mean ± SD)	Normal (≥2.5 kg)	11.10 ± 6.47	7.26 ± 6.28	11.48 ± 4.16	$p < 0.001$	—
Length of Stay (Mean ± SD)	LBW (<2.5 kg)	18.6 ± 15.7	14.7 ± 36.9	17.0 ± 7.5	$p = 0.450$	—
Length of Stay (Mean ± SD)	Normal (≥2.5 kg)	17.9 ± 12.4	11.3 ± 11.5	14.5 ± 6.4	$p < 0.001$	—
Mortality Rate (%)	LBW (<2.5 kg)	23.5%	8.3%	18.9%	$\chi^2 = 16.59$, $p = 0.002$	*B*=0.93, *p*= 0.023
Mortality Rate (%)	Normal (≥2.5 kg)	7.8%	6.8%	12.5%	$\chi^2 = 3.18$, $p = 0.204$	B=0.553 *p*= 0.166
Mortality Interaction Term	Overall	—	—	—	—	*P*=0.166

5.7.2 Neonatal Mortality and Risk Factors

Of the 763 neonates included in study, 667 survived and 96 died. Birth weight <2.5 kg remained a significant predictor (AOR = 2.07, p = 0.009), and associated with lower odds of death in the intervention phase was (AOR = 0.43, p = 0.011). Otherwise there is no association between gestational age, intervention phase, infection categories, and comorbidities statistically with mortality after adjustment and assessed by a binary logistic regression model (***Table 12***).

Table 12: Neonatal Mortality, Alive/Dead Counts and Odds Ratios

Variable	**Alive (n)**	**Dead (n)**	**COR (95% CI)**	**AOR (95% CI)**	**p-value for AOR**
Birth weight <2.5 kg	287	58	2.46(1.39-4.35)	2.07 (1.20–3.56)	0.009
Gestational age <37 wks	169	25	1.19 (0.72–1.96)	1.17 (0.43–3.13)	0.788
Pre-intervention	221	39	Ref	Ref	—
During intervention	234	19	0.44 (0.24–0.80)	0.43 (0.22–0.83)	0.011
Post-intervention	212	38	0.99 (0.60–1.62)	1.07 (0.64–1.78)	0.800
Early onset sepsis	58	9	0.87 (0.40–1.85)	0.86 (0.40–1.85)	0.717
Late onset sepsis	53	10	0.83 (0.39–1.78)	0.61 (0.18–2.03)	0.388
Hospital-acquired infection	40	8	0.79 (0.37–1.66)	0.85 (0.40–1.78)	0.644
Respiratory infection	51	9	0.81 (0.38–1.72)	0.81 (0.38–1.72)	0.608
Neurologic infection	19	7	1.93 (0.77–4.86)	0.42 (0.16–1.14)	0.071
Genitourinary infection	10	2	1.21 (0.26–5.68)	1.34 (0.23–7.66)	0.784
Gastrointestinal infection	15	3	1.24 (0.35–4.42)	1.06 (0.31–3.60)	0.960

Skin/soft tissue infection	26	5	1.37 (0.52–3.59)	1.36 (0.51–3.66)	0.553
Surgical site infection	7	1	0.85 (0.10–7.39)	0.61 (0.07–5.32)	0.661
Cardiovascular infection	14	3	1.65 (0.45–6.08)	0.46 (0.11–1.94)	0.274
Febrile neutropenia	5	1	1.59(0.18–14.23)	—	1.000
Renal disease	17	3	1.52 (0.44–5.22)	1.06 (0.30–3.76)	0.928
Cardiovascular disease	24	4	1.10 (0.38–3.18)	0.71 (0.23–2.23)	0.509
Other comorbidities	3	1	1.91(0.18–19.95)	1.01 (0.04–24.1)	0.998

5.7.3 Length of Stay and Associated Factors

The overall model was statistically significant ($F = 2.05$, $p = 0.008$, $R^2 = 0.045$).During intervention (B = -1.87, p = 0.039), Genitourinary infection (B = 21.62, $p < 0.001$) and cardiovascular disease complication (B = 7.32, $p = 0.041$) were significantly associated with increased LOS and however other predictors were not statistically significant after a multiple linear regression model conducted (***Table 13***).

Table 13: Linear Regressions Results for Length of Stay

Variable	**B (Unstd.)**	***p*-value**
Birth weight <2.5 kg	-1.605	0.335
Gestational age <37 weeks	-0.870	0.606
Before intervention (Ref)	—	—
During intervention	-1.87	0.039
After intervention	-0.83	0.391
Early onset sepsis	-0.01	0.998
Late onset sepsis	-0.12	0.974
Hospital-acquired infection	1.40	0.511
Respiratory infection	1.68	0.519
Neurologic infection	-0.24	0.941
Genitourinary infection	21.62	<0.001
Gastrointestinal infection	-2.65	0.666
Skin/soft tissue infection	-2.13	0.450
Surgical site infection	-3.99	0.546
Cardiovascular infection	-0.64	0.901
Febrile neutropenia	0.77	0.966
Renal disease	6.21	0.097
Cardiovascular disease	7.32	0.041
Other comorbidities	8.17	0.057

6. DISCUSSION

AMS programs are important in NICU, particularly in low and middle income country like Ethiopia, where antibiotic overuse and MDR infections are prevalent (5, 9-11). AMS intervention have proven effective in mitigating these risks by optimizing antibiotic use which includes reducing inappropriate broad-spectrum prescriptions, shortening treatment durations, and improving neonatal outcomes across diverse healthcare settings globally (69, 125).

The finding of this study conducted in the NICU of TASH, Ethiopia demonstrate transformative potential and implementation challenges of AMS program in resource limited settings. This study show a 29.3% reduction in antibiotic duration during the intervention period ($p < 0.001$), which aligns with AMS outcomes from similar studies: Lebanon reported 56 - 77% reduction in antibiotic duration for early onset and late onset neonatal sepsis (96), while china achieved 30% reduction in duration of therapy (94). These improvements surpass those seen in high income setting like 20% antibiotic use duration reduction in USA reported from meta-analysis of 70 studies involving over 350,000 neonates (87, 88), Italy (29%) (91), and Mount Sinai Hospital Toronto Canada (14% reduction) (90), suggesting that resource limited NICUs may have greater baseline overuse and thus more room for improvement.

AMS intervention can also improve clinical outcome by shortening length of stay (LOS) in hospital. Contrary to concerns that reduced antibiotic use could harm patient outcomes, evidence supports the safety and efficacy of AMS program. In this study setting most notably, the 29% (5.3days) reduction in LOS (18.2 to 12.9 days, p =0.004 which was comparable with study from low and middle income country. In Iran a median length of hospital stay that was significantly reduced post AMS from 11 days to 7days, 36.3% (p <0.01) (100), in Palestine a study specifically addressing Meropenem and Vancomycin use in Pediatrics ICU with a much higher baseline length of stay of 23 days, showed a significant reduction to 16 days 30.4% (P = 0.02) (101), and in Cairo, Egypt, at Cairo University specialized pediatric hospital on surgical NICU patients show that, average length of staying hospital decreased in the AMS period by a mean difference of 2.5 days (p = 0.027) (102). In china also optimizing antibiotics use can reduce both length of stay at hospital and lower rate of complication related to hospital stay such as nosocomial infection and late onset sepsis (94, 95). The consistency across these settings implies that LOS reductions may be more achievable in developing country NICUs where baseline stays

are often prolonged. However, the 20% LOS rebound post-intervention highlights a key difference from high-income programs - where electronic prescribing and permanent AMS teams typically sustain gains (88, 91), revealing the vulnerability of manual, personnel-dependent stewardship in our context.

Moreover, systematic review study demonstrates that AMS intervention can significantly change duration of therapy which led to shorter LOS without increasing adverse clinical outcome and mortality. The study done in Children's Mercy Kansas City in USA reveal those patients with an AMS intervention review and agreed recommendations had a reduced LOS by 22.7% (10.2 days vs. 13.2 days) and other study in USA show that Acceptance of AMS interventions by prescribers was linked to a shorter hospital LOS (6.5 days vs. 7 days) and a reduced duration of antimicrobial therapy (99).

AMS interventions in NICUs have been associated with a reduction in mortality rates, highlighting their safety and potential benefits in improving neonatal outcomes. In TASH study setting we observed a 50% reduction in mortality (15.0% to 7.5%, AOR=0.43, p =0.011) outperformed when compared to other developing countries. Similar AMS initiatives in Egypt NICUs achieved a 32% mortality reduction (from 14.1% to 9.5%) (110), while India reported 36% decreases (from 25% to 16%) (108). Additionally, a study done in Indonesia at NICU and pediatric ICU show that, implementation of an AMS bundle resulted 23% reduction of mortality (from 10.4% to 8%, $p < 0.05$) (106).

A study in Iran also show that audit and feedback reduced all-cause mortality from 28% to 6% ($p = 0.001$) (126). This TASH improvement may reflects the presence of high baseline mortality in our setting (15%) compared to those studies (6-25%), emphasizing how AMS can have disproportionate benefits in higher risk environments. However, the rebound effect post intervention phase, where LOS increased to 15.60 days and mortality returned to baseline levels (14,4%; AOR 0.98, p = 0.936), mirrors challenges observed in Canadian NICUs (88, 91). This temporal association show that close relation between optimized antibiotic use and improved LOS and mortality, and the dependence of these outcomes on sustained stewardship efforts. Furthermore, a retrospective cohort study involving 1,580 neonates demonstrated that AMS Programs effectively reduced antibiotic use without increasing mortality or adverse clinical outcomes (90). An observational study conducted in a level III NICU reported a decline in all-

cause mortality following the initiation of an AMS Program (108). Meta-analysis demonstrated a 35% relative risk reduction in mortality when guideline-directed empiric antimicrobials were prescribed (100).

Regarding antimicrobial utilization patterns our finding reduced broad spectrum antibiotics use during intervention phase compared to pre and post intervention period (Cefotaxime decreased from 34.6% to 20.9% (p = 0.001), Meropenem from 30.0 % to 20.6% (p = 0.046), Cefepime from 27.3 % to 18.2% (p = 0.047), and Vancomycin from 20.8 % to 10.3 % (p = 0.005), with increased first-line empirical therapy ampicillin and gentamicin use by 55-56%. This study are parallel with outcome of study from high income country in Memphis USA (2010-2013) after AMS guideline for early onset sepsis implementation, which led to 54% reduction in targeted broad-spectrum antibiotic use (86). Similarly, in Cork, Ireland (2016–2017), the integration of electronic prescribing and audits reduced prolonged broad-spectrum antibiotic use by 91% (88) and targeted AMS intervention in Canada also reduce the use of broad spectrum antibiotics like Cefotaxime and Vancomycin significantly (RR 0.37 and 0.49, respectively) (89). This likely reflects our higher baseline reliance on broad-spectrum antibiotics (85% of neonates receiving antibiotics daily) compared to high-income NICUs (26-40%) (5). The post-intervention resurgence of meropenem/cefotaxime use (18-64% increases) has been similarly documented in Lebanon (96) and Egypt (110), suggesting this may be a characteristic challenge for LMIC NICUs where antibiograms show high resistance to first-line agents.

Generally this study demonstrate that AMS intervention can achieve rapid improvements comparable to high in come country even in resource-limited country where diagnostic limitations necessitate more empirical treatment and their long term effect of these intervention can depend on maintaining core AMS intervention component. Because the discontinuations prospective audit and feedback including AMS round, and education session, led to decrease microbiologic follow up, compliance with treatment protocol of early onset neonatal sepsis algorism and department based pre-authorization policy result in rebound day therapy of antibiotics in post-intervention phases by 55.3%, significantly (p < 0.001), with remarkable increase use of broad spectrum antibiotics like Cefotaxime, Meropenem, Vancomycin, Cefepime, by, 64%, 18.4% ,31.8% and 55.3% respectively. These indicate that neonatologist and resident in NICU understand that the burden of AMR and through access of antibiogram they

acquired knowledge of NICU environment which demonstrated that gram negative bacteria is resistance to first line antibiotics (ampicillin/gentamycin) and third generation cephalosporin they put neonate on reserved antibiotics. Without prospective audit and feedback, AMS round, and education session, the neonate stay for long period of time on broad-spectrum antibiotics which increase length of stay in hospital and potential adverse effect of antibiotics including mortality. Furthermore there is post-antibiotic sample collection which reduced pathogen recovery, limiting opportunities for targeted de-escalation and extends duration of empiric broad spectrum antibiotics therapy in post intervention phase which confirmed by regression, mirroring limitation that found in other study (127).

The stratified AMS intervention by birth weight provide important insights among LBW infants at TASH NICU, average antibiotic use duration therapy decreased by 23.1% (10.84±7.67 to 8.33±5.83 days, p =0.006) and mortality reduced by 64.7% (23.5% to 8.3%, χ^2=16.59, p =0.002) during active AMS intervention, outcomes surpasses Egypt's 33% mortality decline (110), but showed substantially reversed post-intervention (mortality OR=2.56, p =0.023), these can explain that LBW group's unique vulnerability to AMS intervention discontinuation. In contrast, normal birth weight (≥2.5 kg) neonates exhibited more stable improvements, with sustained 34.6% antibiotic use duration (11.10±6.47 to 7.26±6.28 days, p < 0.001) and no significant variation in mortality (χ^2=3.18, p =0.204), mirroring durable outcomes seen in high-income programs (128, 129).

These findings suggest that while AMS intervention benefit all neonates, LBW infants require targeted strategies: (1) mandatory 48-hour antibiotic reviews with microbiologic verification (adopting China's model for VLBW infants (122),dedicated pharmacist-led weekly audits (addressing our observed 72% vs. 85% discontinuation rates in LMIC vs. HIC settings (91) (130)), and (3) bundled diagnostics (CRP + cultures) to offset LMIC-specific challenges like post-antibiotic yield reduction (10.5% vs. 26.9%, p < 0.001). The intervention's differential efficacy with LBW infants deriving greater absolute benefits but requiring more intensive sustainment calls for risk-adapted AMS frameworks in resource-limited NICUs, where 20–30% of stewardship resources should be allocated to LBW-specific protections to maintain mortality reductions estimated at 18–22% above regional baselines (109, 131).

The structured AMS program at TASH NICU demonstrated significant reductions in both neonatal mortality and LOS, with key predictors aligning with global evidence while highlighting the intervention's direct impact on care efficiency. Neonatal mortality was strongly predicted by low birth weight (<2.5 kg; AOR=2.07, p = 0.009), consistent with studies identifying LBW as a universal risk factor for neonatal death. However, participation in the AMS intervention phase independently reduced mortality odds by 57% (AOR=0.43, p = 0.011), paralleling mortality declines reported in Egypt (33%) (107) and India (36%) (109), and surpassing the 19–20% mortality reductions seen in high-income AMS program meta-analyses (90, 132). This protective effect likely reflects the intervention's success in mitigating LBW-specific risks through protocolized sepsis management (55–56% increased ampicillin/gentamicin use) and enhanced diagnostics (77.8% more cultures with susceptibility testing), which reduced delays in appropriate therapy—a critical factor for vulnerable neonates (133).

For LOS, the intervention phase was significantly associated with reduced hospitalization duration (β=-1.87, p = 0.039), corroborating the program's overall 29% LOS reduction (18.2 to 12.9 days, p=0.004). This aligns with global evidence that AMS programs shorten LOS by reducing unnecessary antibiotic exposure and complications (104, 127, 134). However, genitourinary infections (β=21.62, p < 0.001) and cardiovascular disease (β=7.32, p = 0.041) remained independent predictors of prolonged hospitalization, reflecting the persistent burden of nosocomial infections and which considered as complicated infection and need long period of treatment and congenital anomalies in LMIC settings (95, 132). The direct LOS reduction during the intervention phase (−1.87 days) underscores the program's efficacy in streamlining care, likely through early antibiotic discontinuation (72% in culture-negative cases) and reduced empiric broad-spectrum use. These findings mirror successes in high-income settings, such as Ireland's 91% decline in prolonged antibiotic use(88) and U.S. programs achieving 15–20% LOS reductions (132), while surpassing LMIC benchmarks like Lebanon's 3.5-day decrease (132).

7. STERENGTH AND LIMITATION OF THE STUDY

7.1 Strength of the study

The study utilized a well-structured which is enabling robust comparisons and assessment of both immediate and sustained effects of the AMS program. The interventional phase was extensive, incorporating multiple strategies aimed at diverse facets of stewardship, including prescribing practices, microbiological utilization, and diagnostic accuracy, adherence to policy, and infection control, which permitted real-time modifications and enhanced clinical involvement. Furthermore, the study integrated both clinical outcomes (such as mortality and length of stay) and diagnostic variables, including culture and susceptibility results, C-reactive protein testing, imaging studies, and complete blood counts with differential, thereby enabling a more nuanced assessment of diagnostic stewardship and its influence on antimicrobial decision-making.

7.2 Limitations

1. **Retrospective collection of data and documentation bias**

The retrospective review of chart may have resulted in the acquisition of inconsistent and incomplete data, particularly pertaining to clinical reasoning, the timing of interventions, and microbiological outcomes. Moreover, the absence of documentation or inadequate recording of certain pertinent variables, such as the justification for antibiotic selection or the exact timing of cultures, poses a significant risk for information bias.

2. **Inability to Control for Confounding Variables**

As a non-randomized cross-sectional design, this investigation is susceptible to confounding factors arising from unmeasured variables (for instance, staff experience, seasonal infection patterns, and fluctuations in patient acuity). These factors may have independently affected both antibiotic prescribing practices and clinical outcomes, irrespective of the Antimicrobial Stewardship (AMS) intervention.

3. **Lack of Real-Time Stewardship in post-intervention period**

The cessation of prospective auditing and feedback during the post-intervention phase, the study cannot fully extract the effects of earlier stewardship education from the absence of ongoing support, limiting the interpretation of sustained outcomes.

4. **Cross-Sectional review Limit Temporal Inference**

Data analyzed in period-specific cross-sections rather than continuously over time, while the study included three time points. This limits the ability to assess gradual change or long-term durability of intervention effects and may unclear seasonal or temporal variations in practice.

5. **Single-Center Study Limits Generalizability**

The study findings are based on data collected from a single NICU setting, which may limit external validity, which may differ in other setting regards to institutional policies, microbiologic practices, and staffing models and affecting the transferability of results.

8. CONCLUSION

This study demonstrates that a well-executed antimicrobial stewardship program in a neonatal intensive care unit leads to significant clinical improvements across evaluated domains. The intervention was associated with one-third reduction in length of stay and duration of antibiotic therapy, while mortality rate decreased by nearly half during the active intervention period. These outcomes were achieved through optimized prescribing patterns, including an increased use of narrow-spectrum antibiotics, and better adherence to first-line treatment protocols. Enhanced diagnostic stewardship played a crucial role by enabling more targeted antimicrobial use, without compromising patient safety. Notably, the intervention particularly benefited high-risk groups, such as low birth weight infants, emphasizing the value of tailored approaches. The observed reversal of gains following the program's discontinuation highlights the direct impact of the antimicrobial stewardship program and underscores the necessity for sustainable, ongoing institutional support. Overall, this study supports the feasibility and effectiveness of antimicrobial stewardship in resource-limited neonatal settings, aligning with global evidence that such programs can safely reduce antibiotic exposure and improve outcomes without increasing adverse events.

9. RECOMMENDATIONS

Based on the finding of this study, the following recommendations are forwarded; proposed to enhance antimicrobial stewardship practices in neonatal intensive care units (NICUs):

1. **To Hospitals and Health Workers**

1. Institutionalize Continuous Stewardship Activities

To maintain the benefits observed during the intervention period, AMS programs should be formally integrated into routine NICU operations. This includes maintaining prospective audit and feedback rounds, involving clinical pharmacists, and ensuring consistent multidisciplinary collaboration.

2. Strengthen Microbiologic Support and Diagnostic Stewardship

Complete and timely microbiologic testing, particularly culture collection before antibiotic initiation, should be prioritized. Strengthening microbiologic and diagnostic utilization through routine availability and timely processing of microbiologic investigations, including culture and susceptibility testing. To ensure pre-antibiotic sampling can significantly enhance diagnostic precision and support more targeted therapy.

3. Develop Sustainable Policies and Clinical Algorithms

The adoption of standardized treatment algorithms and departmental policies should be maintained beyond the active intervention period. These tools empower clinicians to make evidence-based decisions and reduce unnecessary antibiotic exposure, especially for suspected early-onset sepsis.

4. Expand AMS Programs to Include Education and Feedback Loops

Provide ongoing training, awareness sessions, and feedback mechanisms should be provided for healthcare providers to reinforce stewardship principles and adapt to evolving resistance patterns.

2. **To Policymakers**

Establish and enforce national AMS policies and clinical guidelines tailored for neonatal and pediatric populations and allocate resources for building laboratory infrastructure to support microbiologic testing and real-time diagnostic feedback in NICUs. To promote compliance and

sustainability, integrate AMS program indicators into national health quality metrics and hospital performance assessments to promote compliance and sustainability.

3. **To Federal ministry of Health**

Adapt AMS frameworks for resource-limited settings:- since the feasibility and success of this intervention in a limited-resource context, similar programs should be adapted and scaled to other NICUs and other setting with appropriate modifications based on local needs and capacities.

4. **To Researchers**

Conduct multi-center, longitudinal studies to evaluate the long-term effects of AMS interventions on antimicrobial resistance, patient outcomes, and cost-effectiveness and investigate the potential of rapid diagnostics and digital health tools to enhance real-time decision-making and improve AMS effectiveness. Explore context-specific barriers and enablers to sustained AMS implementation, particularly in resource-constrained healthcare settings.

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Annex

AMS DATA EXTRACTION SHEET

1. Patient demographic and clinical information			
Date of Admission:	Department:	Ward:	
Patient name (ID):	Gestational age (In weeks)……	Birth weight (in Kgs):_____	Sex: Male ☐ or Female ☐
Chart Number:		Allergies:	
Previous admission history for >2 days		Yes ☐ No ☐	
Previous antibiotic use	Yes ☐ No ☐, If yes specify antibiotic_____		
Does the neonate on respiratory support? (if yes, which respiratory support…….) Does neonate on Circulatory support? A. Yes, (if yes, which circulatory support…….) From where the neonate transferred/admitted to ICU a) Another hospital/clinic (specific name_____) b) TASH Emergency department c) TASH neonatal/pediatric wards (specify the ward_____) d) From the community		Yes ☐ No ☐	
Presumed infection at admission?	Yes ☐ No ☐, If yes, Source/origin of infection A) community B) Hospital If no, Indication for ICU admission_____		
Discharge date dd……mm…..yyyy…..	If death during hospitalization, date of death; dd….mm…yyyy….		

2. antibiotic prescribed for specified indication (see below)

Antibiotics prescribed	**Dose (mg)**	**Route**	**Interval**	**Start date**	**End date (if recorded)**

3. Indication for antibiotic treatment

Indication	S. Prophylaxis ☐	Empirical ☐	Definitive ☐	
Diagnosis (it might be more than one)	Urinary tract infection ☐	Gastrointestinal Infection ☐	Bloodstream Infection ☐	
	Pneumonia ☐	CNS / meningitis ☐	Skin infection ☐	Bone infection ☐
	Other (specify): _____			
Comorbidities/other diagnosis	_____			
Diagnostic workups done	Fever recorded			
	WBC with differentials			
	Imaging findings			
	Cultures	Microbiology specimens collected? ☐ Date: _____	Microbiology results received? ☐ Date: _____	Microbiology results acted upon? ☐ Comment: _____
		Sent before antibiotics ☐	Sent after antibiotics ☐	Not sent ☐
	If sent, the culture specimen source	Blood ☐ Urine ☐	Sputum ☐ CSF ☐	Other (specify): _____
	Microbiology specimens collected? ☐ Date:	Microbiology results received? ☐ Date:	Microbiology results acted upon? ☐ Comment: _____	

	_____	_____	

4. Initial review of antibiotic treatment

Is the indication for antibiotic treatment documented?	Is antibiotic treatment prescribed according to recommended guidelines?	Comments
Yes ☐ No ☐	Yes ☐ No ☐ Why not? Comment → No guideline is available ☐	

Correct dose (considering prescribed dose OR frequency)?	Appropriate route?	Treatment duration or review date stated?
Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Overall appropriateness	Yes ☐ (if all the indication, guideline, dose, route, and duration is Yes) No ☐ (if at least one is No)

5. AMS auditor/reviewer comments or recommendations

Is antibiotic treatment reviewed? Yes ☐ No ☐

If yes, what action?	Escalate ☐	Continue ☐	De-escalate ☐	Stop ☐	Adjust ☐	IV-oral switch ☐
	Setting duration ☐			Outpatient parenteral antibiotic therapy ☐		
Justification for the action						

6. Specific audit recommendation/s:

_____

_____

7. Actions based on comments/recommendation/s

Fully accepted ☐	Partially accepted ☐	Not accepted ☐

If not accepted,

Reasons:_____

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