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Prospective antimicrobial stewardship interventions by multidisciplinary teams to reduce neonatal antibiotic use in South Africa: The Neonatal Antimicrobial Stewardship (NeoAMS) study

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Abbreviations: AMR, Antimicrobial resistance; AMS, Antimicrobial stewardship; BSI, Bloodstream infection; CRP, C-reactive protein; EONS, Early-onset neonatal sepsis; FBC, Full blood count; IQR, Interquartile range; LMIC, low-middle income country; LOT, length of therapy; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NNU, neonatal unit; TDM, therapeutic drug monitoring.

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ABSTRACT

Background: Hospitalized neonates are vulnerable to infection and have high rates of antibiotic utilization.

Methods: Fourteen South African neonatal units (seven public, seven private sector) assembled multidisciplinary teams involving neonatologists, microbiologists, pharmacists, and nurses to implement prospective audit and feedback neonatal antimicrobial stewardship (NeoAMS) interventions. The teams attended seven online training sessions. Pharmacists conducted weekday antibiotic prescription reviews in the neonatal intensive care unit and/or neonatal wards providing feedback to the clinical teams. Anonymized demographic and NeoAMS interventions data were aggregated for descriptive purposes and statistical analysis.

Findings: During the 20-week NeoAMS intervention in 2022, 565 neonates were enrolled. Pharmacists evaluated seven hundred antibiotic prescription episodes; rule-out sepsis (180; 26%) and culture-negative sepsis (138; 20%) were the most frequent indications for antibiotic prescription. For infection episodes with an identified pathogen, only 51% (116/229) of empiric treatments provided adequate antimicrobial coverage. Pharmacists recommended 437 NeoAMS interventions (0·6 per antibiotic prescription episode), with antibiotic discontinuation (42%), therapeutic drug monitoring (17%), and dosing (15%) recommendations most frequent. Neonatal clinicians' acceptance rates for AMS recommendations were high (338; 77%). Mean antibiotic length of therapy decreased by 24% from 9·1 to 6·9 days (0·1 day decrease per intervention week; $P = 0·001$), with the greatest decline in length of therapy for culture-negative sepsis (8·2 days (95% CI 5·7-11·7) to 5·9 days (95% CI 4·6-7·5); $P = 0·032$).

Interpretation: This neonatal AMS programme was successfully implemented in heterogenous and resource-limited settings. Pharmacist-recommended AMS interventions had high rates of clinician acceptance. The NeoAMS intervention significantly reduced neonatal antibiotic use, particularly for culture-negative sepsis.

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Introduction

Hospitalized neonates are at considerable risk of infection with bacterial and fungal pathogens due to their immature immune systems, prolonged hospital stays, and frequent exposure to invasive devices [1]. Sick and preterm neonates are particularly impacted, with difficulty distinguishing infectious from non-infectious illnesses compounding the problem of high antibiotic utilization rates [2].

In both high and low-middle income countries (LMIC), there is substantial variability in neonatal antibiotic utilization rates ranging from 2% to 97%, suggesting that antibiotics may be overused in neonatal care globally [3,4]. Most neonatal antibiotic prescriptions are empiric, with six to sixteen times more neonates receiving therapy for an episode of culture-negative sepsis than for laboratory-confirmed infection [5,6].

Given the challenges in early diagnosis of neonatal infection and the adverse health outcomes of prolonged antibiotic use, many neonatal units have implemented antimicrobial stewardship (AMS) programmes [7-9]. These programmes aim to optimize infection outcomes, minimize antibiotic toxicity, and reduce the selection of antimicrobial resistant (AMR) pathogens. Neonatal-specific AMS programmes are associated with lower antibiotic utilization rates, with successful strategies including automatic stop dates, audit and feedback, sepsis risk calculators, biomarker-guided therapy, and treatment guideline implementation [8,10]. In the Surveillance and Correction of Unnecessary Antibiotic Therapy (SCOUT) study, standardizing treatment duration for common neonatal bacterial infections reduced antibiotic utilization by 27% with no adverse impact on neonatal outcomes [11].

The contribution of pharmacists in reducing neonatal antibiotic utilization is well documented in high-income settings. A meta-analysis of 19 studies involving pharmacists in neonatal ASP showed an overall 23% reduction in antibiotic use and a 15% decline in antibiotic length of therapy (LOT) [12]. Similar reductions have been achieved in three LMIC single-center neonatal studies using daily AMS rounds by pharmacists, treatment algorithms, stop orders, and antibiotic restriction policies [13-15]. There is a lack of published data on multidisciplinary AMS programme implementation and impact in African neonatal units [16].

The first South African population level estimates (2014-2019) of early-onset and healthcare-associated sepsis (days 0-2 and 3-27 of life) were 1·1 and 4.9 per 1000 livebirths respectively. The BabyGERMS study also documented the predominance of AMR gram negative pathogens in neonatal sepsis with declining antibiotic susceptibility rates [17]. In response to these findings, the National Neonatal Sepsis Task Force (NNSTF) was launched to support infection prevention and surveillance, outbreak investigation and antimicrobial stewardship in neonatal units in South Africa [18]. Given the need for further evidence on AMS implementation in LMIC, we implemented the first national neonatal antimicrobial stewardship (NeoAMS) intervention using a multidisciplinary team

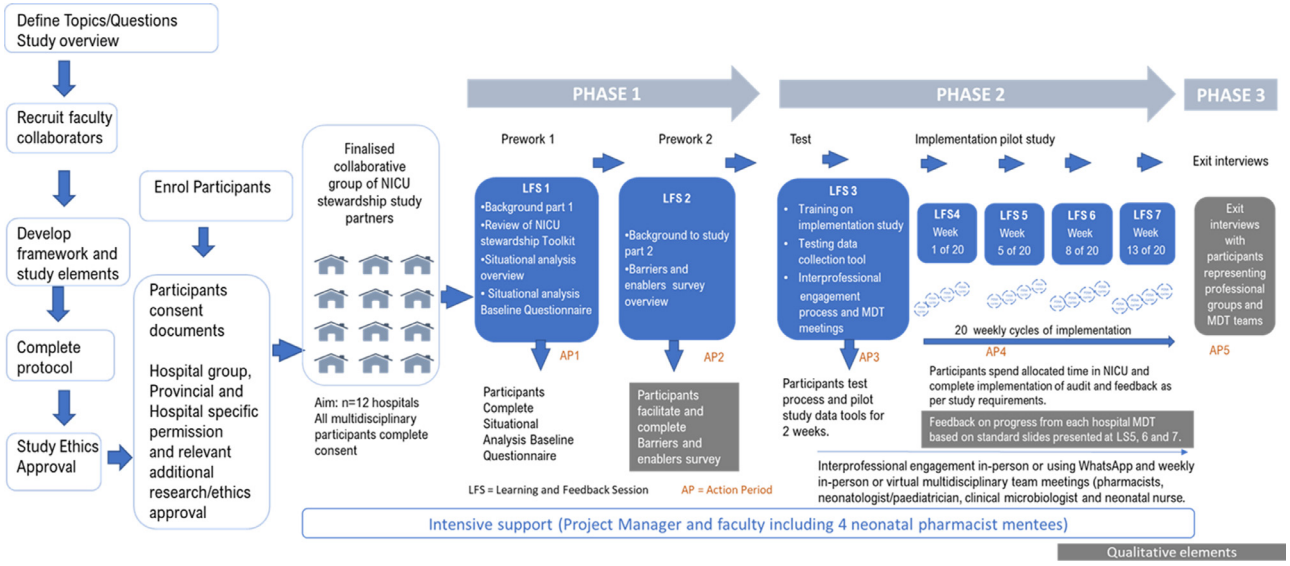

Figure 1. NeoAMS study procedures using the Breakthrough Series Collaborative Study Design.

approach, with the hypothesis that NeoAMS would promote rational antibiotic use in public and private hospital neonatal units in South Africa.

Methods

Study design and population

In the NeoAMS study, we tested a multidisciplinary AMS intervention in 14 neonatal admission units (neonatal intensive care units and neonatal wards) at seven public and seven private sector hospitals in six of the nine South African provinces.

This prospective, mixed-methods interventional study was conducted in three phases from February to July 2022. The phases included: (1) a pre-intervention situational analysis of existing AMS resources, capacity, a survey of contextual barriers, enablers, and drivers for implementation of neonatal AMS; (2) an AMS intervention using a multidisciplinary collaborative method known as the Breakthrough Series (Figure 1) [19] incorporating seven online AMS real-time training and progress feedback sessions using standardized templates, weekday pharmacist audit of neonatal antibiotic prescriptions with real-time, face-to-face feedback and AMS recommendations given to the treating clinician and the multidisciplinary team; and (3) a post-intervention qualitative exploration of the multidisciplinary teams' experiences and learnings (phases 1 and 3 reported in separate publications). Ethical approval was obtained from the University of Cape Town Human Research and Ethics Committee (UCT HREC: Ref 446/2021) and reciprocal approval was obtained from the relevant HREC at each participating site. All data collected from patient records were anonymized at the point of collection.

Role of the funding source

Merck had no role in the study design, data collection, analysis, data interpretation, or drafting of the manuscript.

Study setting and site selection

The NeoAMS lead investigators recruited study faculty members including specialist neonatologists and clinical microbiologists from the SA National Neonatal Sepsis Task Force (NNSTF), pharmacists, and professional nurses at public and private sector hospitals in South Africa, in collaboration with four international advisors with expertise in AMS programmes, neonatal infections, and qualitative research. The NeoAMS faculty collaboratively designed the study protocol, surveys, data collection tools, and assisted with neonatal unit recruitment through email and telephonic circulation of an open "call to participate" in the study. The study faculty used their wide professional network to identify hospitals and associated health professionals that were invited to participate in the study and supported to complete hospital specific ethics and research approval.

The NeoAMS intervention

Recognizing that sustainable and effective AMS programmes depend on multiple health professionals and teamwork to identify and implement interventions, the NeoAMS faculty facilitated the creation of a designated NeoAMS team at each site. To participate in the intervention, each site had to recruit at least one member from the designated groups including pharmacists, neonatologists/pediatricians, microbiologists, and neonatal nurses. These teams were crucial in introducing, guiding, and supporting the NeoAMS pharmacists during the study, given the specialized nature of neonatal care and gaps in neonatal infectious disease knowledge of non-infectious diseases trained pharmacists. Each team was provided with a previously validated neonatal AMS training toolkit developed by the study faculty. The toolkit aimed to provide non-specialized pharmacists with essential skills and tools for neonatal AMS, including primers on neonatal sepsis, culture-negative sepsis, and recommended duration of antibiotic therapy. Weekly NeoAMS study team meetings were held, with completion of a site baseline survey and participation in several interactive, online learning sessions (see Supplementary Table 2). Study pharmacists were required to spend at least one hour each weekday auditing antibiotic prescriptions and providing feedback on AMS recommendations to the treating clinician/s in the neonatal wards and/or neonatal intensive care unit (NICU), collectively referred to as the neonatal unit (Figure 1). Pharmacists, nurses and neonatologists identified eligible patients in the wards and where appropriate pharmacists made AMS recommendations to the prescribers, e.g., to stop antibiotics for culture-negative sepsis after five days,

improve hangtime, make dose/dosing frequency changes, perform therapeutic drug monitoring, change therapy for bug-drug mismatch, or de-escalate to a narrow spectrum antibiotic agent. All NeoAMS team members participated in interdisciplinary discussions regarding antibiotic use and microbiology reports. The site microbiologist and neonatologists supported the AMS training of the pharmacists, most of whom had no prior neonatal infectious diseases experience. When encountering difficult AMS cases or in cases of disagreement on AMS recommendations, the site microbiologist was consulted to provide guidance on stopping, switching, de-escalating or escalating antibiotic therapy.

Data sources and collection

Pharmacists identified neonates with suspected or confirmed infection during weekday neonatal unit visits. Neonates with active antibiotic prescriptions were identified by convenience sampling during in-person pharmacist visits and/or by targeted sampling using electronic/verbal notifications of new antibiotic prescriptions from the neonatal unit. The time available to pharmacists to conduct NeoAMS activities (prescription audits, data collection, and AMS feedback) varied by hospital, at the discretion of the local pharmacy supervisor. Anonymized data from the neonatal medical records, laboratory results, and antibiotic prescription charts were recorded daily by pharmacists on standardized paper case report forms and later transcribed into a REDCap database hosted on the University of Pretoria, South Africa server.

Variables and outcomes of interest

Data was collected on neonatal unit characteristics, neonatal, and maternal demographics, indication for antibiotic prescription, type of antibiotic prescribed, diagnostic tests used for investigation of infection episodes, microbiology culture and susceptibility tests, and antibiotic length of therapy (LOT). We described both process and outcome measures of interest in neonatal AMS. These included the number and type of interventions recommended by pharmacists, acceptance rate of AMS recommendations, time spent by the pharmacist per neonate on audit and feedback, and changes in the antibiotic LOT during the study.

Study definitions

All neonates hospitalized in any ward designated as part of the neonatal unit and receiving one or more antibiotics were eligible for participation, including those in NICU, neonatal high care, neonatal low care, neonatal isolation, and/or neonatal kangaroo mother care wards. NICU and high care wards included sick neonates with medical/surgical conditions receiving additional supportive care, e.g., invasive/non-invasive ventilation, inotropes, total parenteral nutrition etc. General neonatal wards (low care, isolation, kangaroo mother care) included babies requiring minimal supportive care, e.g., nasal cannula oxygen, nasogastric tube feeds, and intravenous medication or fluids. Early-onset neonatal sepsis was defined as signs and symptoms of infection presenting within the first 72 h of life, whereas hospital-acquired infection was diagnosed beyond 72 h of life/hospital stay. Preterm neonates were defined as those born before 37 weeks' gestation. Public hospitals include government funded facilities that offer free healthcare to pregnant women and children under five years of age. Private hospitals use a fee-for-service model, usually funded through the purchase of private healthcare insurance. Rule-out sepsis was diagnosed in neonates commenced on empiric antibiotic therapy for signs and/or symptoms suggesting sepsis but in whom blood cultures were not significant, and inflammatory markers were low and/or an alternative explanation was found, allowing antibiotics to be discontinued within 24-72 h of initiation. Culture-negative sepsis was defined as a neonate evaluated for suspected infection whose bacterial blood or other cultures were sterile, but who had symptoms, and/or signs of infection, and/or elevated inflammatory markers that led to prescription of a treatment course of >4 days of antibiotic therapy. Prophylaxis included antibiotics administered peri–operatively (e.g., cefazolin), for tuberculosis exposure (e.g., isoniazid), and as a prokinetic agent (e.g., erythromycin). Discordant empiric antimicrobial therapy was defined for culture-positive infection episodes as instances where the pathogen cultured was not susceptible to the empiric antimicrobial agents prescribed. LOT was defined as the number of calendar days of antibiotic therapy regardless of the number of agents used. Antibiotic hangtime was defined as the time between antibiotic prescription and administration.

Statistical analysis

Study variables were summarized with median and interquartile range for asymmetric continuous variables, mean and standard deviation for symmetric continuous variables and count and percent for categorical variables. Variables were compared for public and private hospitals using the chi-square test for categorical variables and Wilcoxon Rank Sum test for continuous variables. The change in key metrics (antibiotic LOT, number of AMS interventions per infection episode, and proportion of interventions accepted by study week) was assessed by regression analysis, controlling for hospital. Log-transformation was applied to LOT before linear regression. Trends in number of interventions and intervention acceptance rate by study week was analyzed by Poisson regression and linear regression respectively. The antibiotic therapy start date for each infection episode was regarded as Day 1 of intervention. The therapy start dates were used to group interventions for each hospital by study week, allowing all hospitals to be brought to a common start date irrespective of when each multidisciplinary NeoAMS team commenced activities. For calculating the proportion of AMS interventions accepted, the denominator was the number of interventions recommended, sub-analyzed by recommendation type. Data analysis was carried out using SAS (Statistical Analysis System) version 9·4 for Windows, SAS Institute Inc., Cary, NC, USA: SAS Institute Inc. (2002-2010).

Results

Neonatal unit characteristics and baseline AMS practices

A total of 14 neonatal units (seven public, seven private) in six of the nine South African provinces participated in the NeoAMS study. Each hospital met or exceeded the minimum composition of the MDT comprising of 89 health professionals (27 pharmacists, 18 neonatal nurses, 28 neonatologists, 16 clinical microbiologists). Most private sector neonatal units were small (<20 beds) whereas most public sector units were large (>70 beds); all units included NICU beds. Although most units reported availability of antibiotic prescribing guidelines (11, 79%) and hospital AMS programmes (9, 64%), none involved multi-disciplinary NICU teams, only 5 had NICU pharmacist involvement, and few had data on NICU antimicrobial utilisation (3, 21%). Existing hospital-wide AMS activities/resources included dedicated antibiotic prescription charts (11, 79%), institution-specific antibiotic restriction policies (7, 50%), policies to guide antibiotic LOT (6, 43%), and biomarker-guided antimicrobial therapy (6, 43%) (Supplementary Table 1).

Neonatal patient characteristics

A total of 565 neonates were enrolled during the 20-week intervention period, 205 (36·3%) from private and 360 (63·7%) from

Table 1
Demographic profile of neonates enrolled in the neoAMS study[a] ($N = 565$).

	Total neonates $n = 565$ (%)
Place of delivery,[b] *n* (%)	
Hospital	537 (95·0)
Home	18 (3·2)
Unknown	10 (1·8)
Mode of delivery,[b] *n* (%)	
Vaginal delivery	195 (34·5)
Caesarean section	345 (61·1)
Unknown	25 (4·4)
Maternal age in years (median, IQR)	30 (24-34)
Sex (male), *n* (%)	313 (55·6)
Birth weight in grams (median, IQR)	1880 (1140-2675)
Gestational age in weeks (median, IQR)	33 (29-37)
Total neonatal infection episodes (*n*)	753
Indwelling device/s at infection onset,[c] *n* (%)	
Central line[d]	272 (36·1)
Peripheral line	292 (38·8)
Endotracheal tube	131 (17·4)
Urinary catheter	20 (2·7)
Naso/orogastric tube	275 (36·5)
Ventriculoperitoneal shunt	4 (0·5)
No devices	167 (22·2)

[a] Values expressed as median (IQR = interquartile range), all others as numbers (percentage).
[b] Comparative analysis excluded missing data.
[c] The denominator for indwelling devices at infection onset was the total infection episodes.
[d] Central line (included umbilical venous catheters, umbilical arterial catheters subclavian/internal jugular catheters, and peripherally inserted central catheters).

public hospital neonatal units (Table 1). The median maternal age was 30 years, and rate of delivery via caesarean section was 61.1%. Neonates' median gestational age was 33 weeks and birth weight 1880 gs.

Indications for antibiotics

The 565 enrolled neonates received antibiotic therapy for 753 infection episodes. After excluding infection episodes with missing LOT data, 700 antibiotic prescription events in 526 patients with ≥1 infection episode/s remained (Table 2). Most neonates were hospitalized in the NICU at the time of infection onset (569/700; 81·3%). Blood cultures were sent prior to antibiotic initiation in 72·7% of infection episodes (See Supplementary Table 3 for pathogen spectrum).

C-reactive protein (CRP) was a frequently used diagnostic test for infection in both public and private units, whereas procalcitonin was seldom used in public hospitals. The median (IQR) day of life at infection episode onset was 1 (1-11) day. The most frequent indication for empiric antibiotic therapy was to rule out early-onset sepsis (290/700; 41·4%), followed by therapy for suspected hospital-acquired sepsis (183/700; 26·1%). Median antibiotic LOT was longest for hospital-acquired BSI (9 days), pneumonia (8 days), and necrotizing enterocolitis (8 days). The crude neonatal mortality rate during antibiotic therapy was 16/700 (2·3%) amongst the 16 neonates who died, hospital-acquired BSI was the most frequent infection episode type (6; 37·5%).

Antibiotic use

A median of 2 (IQR 1-2) empiric antibiotic agents were initiated for infection episodes, with almost two-thirds (909/1418; 64·1%) being "access" antibiotics as defined by the AWaRe classification (Table 3 and Supplementary Table 4). The majority (427/447; 95·5%) of empiric antibiotics prescribed in public hospital neonatal units were in accordance with local hospital recommendations. Prescribing guidelines were lacking in 185/700; 26.4% (Table 3). Antibiotic hangtime was under 60 min for 65.7% of prescriptions.

Pharmacist-recommended ams interventions

Pharmacists made 437 AMS interventions in the 700 infection episodes, with the most frequent being, "stop antibiotic" "perform therapeutic drug monitoring" (TDM), and "change antibiotic dose/dose frequency" (Table 3). Neonatal unit clinicians accepted 77% of the suggested AMS interventions, with higher acceptance rates in public versus private hospital neonatal units 83·5% vs. 72·7%; $P = 0.004$). Hangtime, TDM, and de-escalation of antibiotics were the most frequently accepted AMS recommendations. Stop antibiotic recommendations were accepted in 69% of cases. The acceptance rate of interventions did not vary over the study period ($P = 0.75$) or by infection diagnosis (see Supplementary Figure 1).

Impact of the intervention

Overall mean antibiotic LOT was assessed using regression analysis by study intervention week. LOT declined by 24% overall at a rate of 0·1 day per study week from 9·1 to 6·9 days ($P = 0.001$). In a sub-analysis of antibiotic LOT by final infection diagnosis, the most substantial decline was observed in the treatment of culture-negative sepsis from 8·2 days (95% CI 5·7-11·7) to 5·9 days (95% CI 4·6-7·5); $P = 0.032$. There was no evidence of changes in antibiotic LOT for culture-confirmed bloodstream infection ($P = 0.690$), pneumonia ($P = 0.291$), or necrotizing enterocolitis ($P = 0.370$).

Discussion

This multidisciplinary AMS intervention at 14 neonatal units in South Africa (NeoAMS) significantly reduced the antibiotic LOT in neonates with culture-negative sepsis from 8·2 to 5·9 days and overall LOT by 24%. The 20-week intervention elicited a large volume of pharmacist-initiated AMS recommendations, with high rates of neonatal clinician acceptance. This study adds to the limited evidence base for neonatal AMS in Africa and demonstrates the positive impact of multidisciplinary team-led AMS. These findings confirm that successful AMS initiatives are possible in resource-limited neonatal settings.

In developing the NeoAMS intervention, we recognized that sustainable and effective AMS programmes depend on teamwork and collaboration from multiple health care professionals to identify and implement interventions. We utilized a multidisciplinary collaborative method known as the Breakthrough Series [19] to assemble NeoAMS teams, facilitated interactive online real-time AMS training and feedback, and regular interactions between site team members. Previous AMS intervention studies in South African adult populations have also illustrated the critical role of pharmacist-driven AMS process improvement [20]. Given the limited clinical exposure to neonatal infectious diseases amongst non-specialized pharmacists in South Africa, we adopted a multidisciplinary AMS approach to facilitate pharmacists' introduction to the neonatal unit. Furthermore, recognizing pharmacists' heavy workloads, the NeoAMS intervention allowed flexibility in the timing and frequency of pharmacists' visits to the neonatal unit to audit antibiotics.

Neonatal and maternal demographic characteristics varied significantly between public and private sector hospitals, with more infection episodes in the public neonatal units, attributable to higher rates of preterm birth, overcrowding, and lower staff to patient ratios in the public sector. Surprisingly, blood cultures were obtained before initiation of antibiotic therapy in just 73% of infection episodes.

Table 2
Investigation and management of neonatal infection episodes ($N = 700$).

	Total infection episodes $n = 700$ (%)
Day of life at infection onset (median, IQR)	2 (1-11)
Location at time of infection onset, *n* (%)	
Neonatal ICU	569 (81·3)
High care	85 (12·1)
Neonatal ward	27 (3·9)
Other	19 (2·7)
Indication for empiric antibiotic, *n* (%)	
Rule-out early-onset sepsis	290 (41·4)
Rule-out hospital-acquired sepsis	183 (26·1)
Pneumonia	76 (10·9)
Necrotizing enterocolitis	32 (4·6)
Prophylaxis	59 (8·4)
Urinary tract infection	4 (0·6)
Skin-soft tissue/cellulitis	4 (0·6)
Not documented	52 (7·4)
One/more blood cultures collected prior to commencing antibiotics, *n* (%)	509 (72·7)
Microbiology specimens submitted, *n* (%)	
Blood culture	606 (86·6)
CSF culture	59 (8·4)
Urine culture	58 (8·3)
Respiratory culture	22 (3·1)
None	75 (9·9)
Proportion of specimens positive, *n* (%)	
Blood culture	107/606 (17·7)
Cerebrospinal fluid culture	1/59 (1·7)
Urine culture	9/58 (15·5)
Respiratory specimen culture	11/22 (50·0)
Sepsis biomarkers sent, *n* (%)	
C-reactive protein	647 (92·4)
Procalcitonin	127 (18·1)
C-reactive protein[a] in mg/L (median, IQR)	3 (1-17)
Procalcitonin value in ng/L[b] (median, IQR)	1·1 (0·3-7·5)
Final infection episode diagnosis, *n* (%)	
Rule out sepsis	180 (25·7)
Culture-negative sepsis	138 (19·7)
Pneumonia	98 (14·0)
Prophylaxis	77 (11·0)
Hospital-acquired BSI	71 (10·1)
Early-onset BSI	26 (3·7)
Necrotizing enterocolitis	25 (3·6)
Urinary tract infection	7 (1·0)
Skin-soft tissue/cellulitis	2 (0·3)
Not documented	76 (10·9)
Crude neonatal mortality during antibiotic therapy, *n* (%)	16 (2·3)
Relative contribution to overall mortality by infection category, *n* (%)	
Rule out sepsis	1 (6·3)
Culture negative sepsis	3 (18·8)
Prophylaxis	1 (6·3)
Hospital-acquired BSI	6 (37·5)
Early-onset BSI	2 (12·5)
Necrotizing enterocolitis	1 (6·3)
Not documented	2 (12·5)
Overall length of antibiotic therapy by final infection category in days, median (IQR)	
Rule out sepsis	3 (3-4)
Culture negative sepsis	7 (5-9)
Pneumonia	8 (6-11)
Prophylaxis	6 (4-7)
Hospital-acquired BSI	9 (6-12)
Early-onset BSI	6 (3-9)
Necrotizing enterocolitis	8 (6-10)
[c]Urinary tract infection	.
[c]Skin and soft tissue infection	.
Not documented	7 (6-13)

Note: A total of 753 infection episodes were recorded but 53 had missing antibiotic end dates and were deleted, leaving 700 episodes in a corresponding 526 of the original total 565 patients. IQR = interquartile range; BSI = bloodstream infection.

[a] $n = 640$.

[b] $n = 127$.

[c] Median LOT not calculated for these infections as there were <10 episodes.

Table 3
Antibiotic utilization and pharmacist-recommended stewardship interventions.

	Total infection episodes n = 700 (%)
Antibiotics prescribed per infection episode (median, IQR)	2 (1-2)
AWaRe classification of antibiotics, *n* (%)	
Total agents	1418 (100)
Access	909 (64·1)
Watch	481 (33·9)
Reserve	28 (2·0)
Empiric prescription guideline compliance, *n* (%)	
Compliant	488 (69·7)
Non-compliant	16 (2·3)
Not recorded	6 (0·9)
No local guidelines	185 (26·4)
Antibiotic hangtime, *n* (%)	
<60 min	460 (65·7)
>60 min	93 (13·3)
No time indicated	147 (21·0)
Infection episodes pharmacists identified for AMS interventions, *n* (%)	263 (37·6)
Total AMS interventions recommended by pharmacists, *n*	437
Mean AMS interventions recommended per infection episode	0·62
Minutes (median, IQR) spent by pharmacist per patient per day	10 (10-30)
Type of AMS interventions recommended, *n* (%)	
Stop antibiotic/s	185 (42·3)
Therapeutic drug monitoring intervention	75 (17·2)
Change in antibiotic dose/dosing frequency	64 (14·6)
De-escalate or change antibiotic[a]	21 (4·8)
Hang time recommendation	19 (4·3)
Loading dose recommendation	16 (3·7)
Initiate antibiotic/s	13 (3·0)
Other[b]	44 (10·1)
AMS interventions accepted by clinicians/total pharmacist-recommended interventions, *n* (%)	338/437 (77·3)
Intervention acceptance rate[c] by type, *n* (%)	
Stop antibiotic/s	128 (69·2)
Therapeutic drug monitoring	70 (93·3)
Change in antibiotic dose frequency	43 (67·2)
De-escalate or change antibiotic[a]	14 (67·7)
Hang time recommendation	17 (89·5)
Loading dose recommendation	16 (100)
Initiate antibiotic/s	11 (84·6)
Other[b]	39 (88·6)

Note: A total of 753 infection episodes were recorded but 53 had missing antibiotic end dates and were deleted, leaving 700 episodes in a corresponding 526 of the original total 565 patients. AWaRe: World Health Organisation access, watch, reserve, classification of antibiotics for evaluation, and monitoring of use (2021); AMS = antimicrobial stewardship; ^calculated only for infection episodes with an identified pathogen.

[a] After receipt of culture results.

[b] Other = duplicate antibiotic spectrum, antibiotic selection based on guideline, adverse antibiotic drug reaction, antibiotic drug interaction, obtain or repeat cultures, source control recommended.

[c] Intervention acceptance rate – calculated as number of clinician-accepted interventions divided by the total pharmacist-recommended interventions for each intervention type, *n* (%).

Previous studies identified continuation of empiric therapy >48 h for rule-out sepsis and culture-negative sepsis, as important AMS targets [3,11,21]. In NeoAMS, the most frequent final infection diagnoses were rule-out sepsis, culture-negative sepsis, and pneumonia, confirming the validity of these AMS targets in hospitalized South African neonates. During the intervention, the overall antibiotic LOT decreased significantly, specifically for culture-negative sepsis but not for bloodstream infection, pneumonia, or necrotizing enterocolitis. This finding confirms the importance of culture-negative sepsis as an AMS target for resource-limited neonatal units, achieving comparable reductions in antibiotic use to the SCOUT study (27%) [11]. The lack of impact on LOT in bloodstream infections and necrotizing enterocolitis is not surprising, as clinicians are less likely to accept recommendations to stop antibiotics in critically ill neonates. However, neonatal pneumonia treatment courses of five days have been shown to be safe and effective [11,22] highlighting another potential AMS target for South African neonatal units. Identifying strategies to safely reduce antibiotic LOT is critical, especially in preterm neonates where each additional day of antibiotic use is associated with 5% increased odds of death or major morbidity [23,24]. Given the high rates of healthcare-associated sepsis in South African neonatal units [17], interventions to strengthen infection prevention and control (IPC) programmes and involve IPC practitioners in neonatal AMS should be prioritized (Fig. 2).

The proportion of “access” antibiotics documented in the present study (64%) was very similar to that reported from South African neonatal units in a global antimicrobial use point prevalence survey [25]. Overall ampicillin, gentamicin, piperacillin-tazobactam, amikacin, and meropenem were the most commonly prescribed agents, in keeping with the South African Standard Treatment Guidelines for neonatal sepsis [26]. Although most public sector neonatal units had access to and complied with the national or institutional guidelines, almost three-quarters of private hospital neonatal units lacked prescribing guidelines for neonatal sepsis, highlighting an important potential AMS intervention in those facilities. Whereas most private neonatal units achieved antibiotic hangtime <60 min, only half of the public neonatal units achieved this target, although there was substantial missing data on hangtime in these units. Delayed hangtime (median

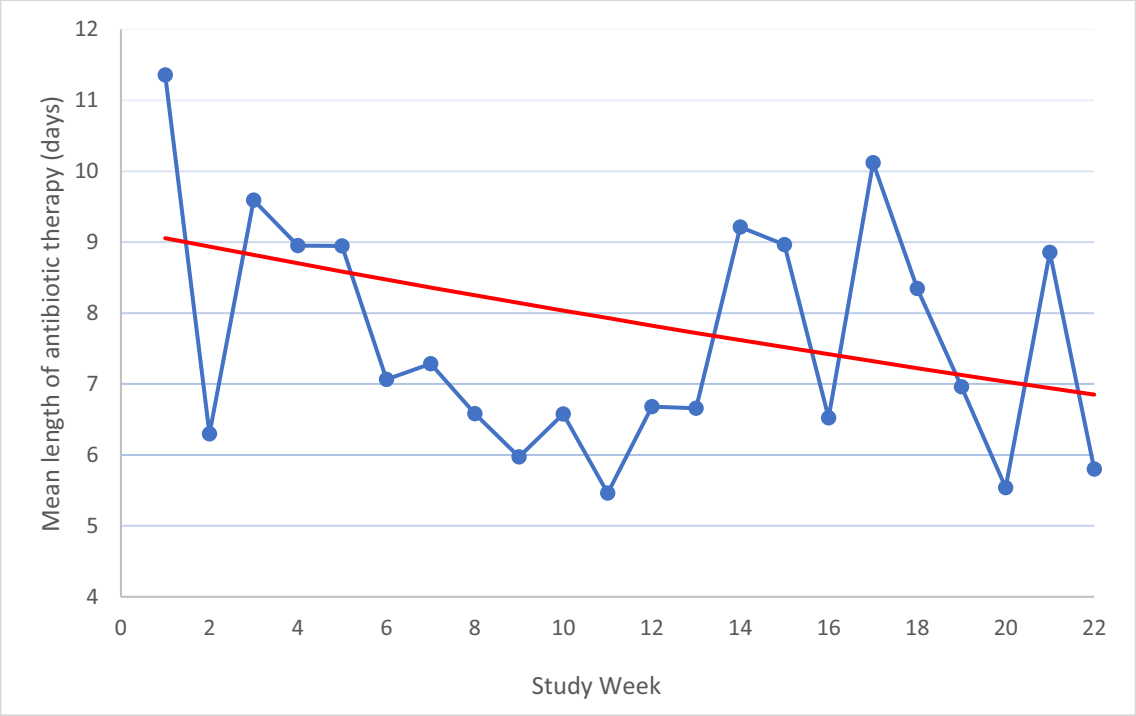

Figure 2. Mean antibiotic length of therapy for infection episodes by study week.
Note: A total of 753 infection episodes were recorded but 53 had missing antibiotic end dates, leaving 700 complete infection episodes in a corresponding 526 patients. Mean length of therapy (LOT) was plotted by study intervention week using linear regression analysis. Overall, there was a significant decrease in LOT over the study period corresponding to an estimated decrease of 0·1 LOT days per study week (P = 0·001), illustrated in the plot (blue = mean LOT per week; red = estimated LOT from regression).

2 h) has been reported from an audit of antibiotics prescribed for laboratory-confirmed sepsis at a large public sector neonatal unit in South Africa and independently predicted mortality [27]. Consequently, improving hangtime should be an AMS intervention priority in South African neonatal units, although improvement may be hampered by high patient-to-nurse ratios and delays in antibiotic dispensing.

Although surveys and studies have documented high neonatal unit antibiotic utilization rates globally [3-6], almost all published neonatal AMS intervention data were generated in high-income settings [12,16]. Even less data exist on the contribution of pharmacists to reducing neonatal antibiotic utilization in LMIC [12-15], with a single publication describing the development of a neonatal AMS programme for pharmacists in South Africa [28]. In a survey on AMR/AMS at six South African hospitals, most pharmacists (80%) felt that they were not supported to implement AMS and 45% felt uncomfortable recommending treatment changes to clinicians [29]. In our study ongoing pharmacist support by the multidisciplinary team members led to high acceptance of pharmacist recommendations.

Three previous single-center interventional neonatal AMS studies achieved reduced antibiotic LOT using daily pharmacist AMS rounds, treatment algorithms, routine stop orders, and antimicrobial restriction policies [13-15]. In the NeoAMS study, we used interactive online training to improve identification and acceptance of neonatal AMS opportunities, including de-escalation/discontinuation, optimized antibiotic dosing, and enhanced monitoring with TDM, blood cultures, and biomarkers. Similar AMS recommendations resulted in reduced antibiotic usage in Indian, Australian, and Chinese NICU's [14,15,30,31], with rates of clinician acceptance similar to that found in the present study (77%) [30,31]. In the NeoAMS study, pharmacists recommended 0·6 AMS interventions per antibiotic prescription episode with a relatively short time (10 min/patient) needed to review prescriptions and make AMS recommendations, suggesting that the intervention may be feasible even in high volume neonatal units.

The NeoAMS study had several limitations, including the convenience sampling method, variability in pharmacists' time available for neonatal unit AMS activities, use of reported indications for antibiotic use, exclusion of antiviral and antifungal medications in the AMS intervention, lack of final clinical outcome data and the possibility of unmeasured confounding in between group comparisons. Blood culture isolates were reported as received and did not differentiate between presumed contaminants and pathogens. The generalizability and sustainability of the NeoAMS programme is also unknown. Strengths of the study include representation of multiple neonatal units from geographically disparate public and private sector hospitals across South Africa, the large number of antibiotic prescriptions evaluated, and the use of both process (number of AMS interventions) and outcome (length of therapy) AMS measures. In addition, the study identified opportunities for quality improvement such as obtaining cultures prior to antibiotic administration. Future research on AMS programmes in resource-limited neonatal units should incorporate involvement of infection prevention practitioners, investigation of the barriers and facilitators to AMS implementation, and the behavioral determinants of antibiotic prescribing in neonatal units.

In conclusion, this first national prospective multidisciplinary AMS implementation and intervention in South African neonatal units enabled many pharmacist-initiated AMS interventions with high clinician acceptance rates and significantly reduced antibiotic LOT in neonates with culture-negative sepsis. The NeoAMS intervention highlights the potential positive impact of neonatal AMS interventions led by multidisciplinary teams in resource-limited settings.

Data sharing

De-identified participant data, the study protocol, and data dictionary are available from the corresponding author on reasonable request following publication, with completion of a signed data sharing agreement.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

Primary ethical approval was obtained from the University of Cape Town Human Research and Ethics Committee (UCT HREC): HREC Ref 446/2021 with reciprocal approval obtained from the relevant REC at each of the other 13 participating sites. All data collected from patient records was anonymized at the point of collection.

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Author contributions

All 38 authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted. The remaining 51 collaborators are listed in the NeoAMS study group. Dr. Prusakov completed the work for this research while an employee of Nationwide Children's Hospital, Columbus, OH. Dr. Prusakov is currently an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107158.

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