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Challenges and opportunities in neonatal sepsis management: insights from a survey among clinicians in 25 Sub-Saharan African countries

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ABSTRACT

Background Neonatal sepsis (NS) is a global health issue, particularly in Sub-Saharan Africa, where it accounts for a substantial portion of neonatal morbimortality. This multicountry survey aimed to elucidate current practices, challenges and case definitions in managing NS among clinicians in Sub-Saharan Africa.

Methods The survey targeted physicians and medical practitioners working in neonatal care who participated in a Self-Administered Web Questionnaire. The main objective was to understand NS and infection case definitions and management from the clinician's point of view and to identify challenges and opportunities in sepsis management. Participants were queried on demographics, definitions and diagnostic criteria, treatment approaches, and infection prevention and control (IPC) measures. A total of 136 participants from 86 healthcare structures responded, providing valuable insights into NS management practices.

Results From May to July 2022 across 25 Sub-Saharan African countries, 136 neonatal clinicians with an average from 86 structures with on average 10-year experience took the survey. NS ranked highest among prevalent neonatal conditions. Diagnostic case definitions between sepsis and infection were attributed to clinical signs, anamnesis, C reactive protein, white blood cll count and blood cultures with no statistically significant differences. Early-onset sepsis was defined within 72 hours by 48%, while late-onset varied. Antibiotics were likely on admission (86.4%) and during the stay (82.2%). Treatment abandonment was reported unlikely. The preferred antibiotic regimen for early-onset sepsis was intravenous amoxicillin (or ampicillin), gentamycin and cefotaxime. Blood culture availability and IPC protocols were reported as limited, particularly concerning patient environment, pharmacy protocols and clean–dirty circuits.

Conclusions This NS survey emphasises clinicians' challenges due to limited access to diagnostic tools and raises concerns about antimicrobial overexposure. IPC also seem limited, according to participants. Addressing these challenges can enhance diagnostic practices, antibiotic stewardship and infection control in the region.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neonatal sepsis (NS) significantly impacts Sub-Saharan Africa's neonatal mortality, lacking consensus in case definitions and diagnostic tools, notably in low-resource settings.

WHAT THIS STUDY ADDS

⇒ Clinicians shared a unified case definition for NS and infection, emphasising challenges such as limited access to blood cultures, prolonged broad-spectrum antibiotic use in neonatal units and limited infection prevention and control (IPC) implementation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study unveils opportunities for implementation research, focusing on antimicrobial stewardship and improving IPC. The findings advocate for guidelines on antibiotic usage, policy changes to enhance laboratory facilities and standardised protocols for infection prevention in neonatal care.

BACKGROUND

Neonatal health is a critical global health issue, with 2.3 million neonatal deaths occurring in 2021, accounting for 47% of all paediatric under-5 deaths.[1] Neonatal infection is one of the leading causes of neonatal mortality, affecting nearly 3.9 million neonates and accounting for up to 900 000 deaths annually.[2–4] Moreover, neonates that survive sepsis have a higher risk of developmental impairment.[2 3] Sub-Saharan Africa carries almost half of the global neonatal mortality, and it is estimated that, in the region, every year, up to 8.75 million Disability-Adjusted Life Years (DALYs) are lost to neonatal sepsis (NS).[1 5]

There is no consensus on the definition of NS, nor is there a specific differentiation between NS and infection. However, it is generally accepted to classify infection in a neonate into early-onset neonatal sepsis (EOS) and late-onset neonatal sepsis (LOS). EOS is related to maternal colonisation, infection and chorioamnionitis, while LOS is mostly caused by community or nosocomial pathogens.[2 6] Regardless of classification,

NS can evolve rapidly into a life-threatening condition, necessitating a high index of suspicion and rapid empiric antibiotic treatment.[2]

Diagnosing NS can be challenging, as there is no reasonably sensitive test on clinical presentation, and blood cultures, the gold standard, may take up to 48 hours to show positivity.[7 8] Meanwhile, the diagnostic process is based on anamnestic, clinical and laboratory factors. However, since the clinical symptoms of NS are non-specific, empiric antibiotic therapy is often initiated, particularly when no other diagnostic tools exist. Repeated clinical assessments and laboratory investigations may help rule out infection and avoid unnecessary antibiotic treatment,[2 9 10] but they are often unfeasible in low-resource settings. Unnecessary antibiotic exposure in neonates increases the risk of rising drug resistance and may have a long-lasting individual impact, contributing to adult diabetes, obesity, inflammatory bowel disease, asthma and allergies.[11 12]

Understanding how clinicians in low-income and middle-income countries (LMICs) approach sepsis and infection can help identify tools to improve neonatal health in these contexts. Therefore, we propose a questionnaire to medical practitioners in Sub-Saharan Africa to map, analyse and better understand local practices, challenges and case definitions.

METHODS

Study design

We proposed an open survey through a Self-Administered Web Questionnaire (Lime Survey). The questionnaire was developed by FR-M and MD and tested for content and usability of the platform and questions format by REP, NW and LMM in several rounds.

The survey comprised 28 questions, primarily closed-ended items, grouped into 5 sections: demographic information, case definitions, treatment, laboratory tests and hospital-acquired infection. Most questions (18) used a 5-point Likert scale for importance, frequency or likelihood (available in the online supplemental materials). Respondents could not review answers once validated. Question items were randomised to prevent biases, and adaptative where possible, to reduce number and complexity of questions. The survey was available in both English and French.

The target population consisted of physicians (general practitioners, paediatricians and neonatologists) and other medical practitioners (ie, clinical health officers) who worked recently or directly with neonates and are legally authorised to prescribe antibiotics in Sub-Saharan Africa. Sub-Saharan African countries were defined as per World Bank's classification.[13] Recruitment was performed using a purposive and snowballing approach through personal email invitation, personalised messages and a network announcement on LinkedIn; all including the survey background and the investigators' presentation.

Participants received information on study goals, questionnaire length, confidentiality and data storage in a first mandatory webpage of the survey. The questionnaire was completed voluntarily and anonymously, IP addresses and cookies were not used. No incentives were offered to participate. We aimed to recruit a minimal sample of 50 participants to detect at least medium-to-large paired-sample differences (d>0.4) with a 5% threshold for type 1 error and a statistical power of 80%.

This paper follows the Checklist for Reporting Results of Internet E-Surveys statement.[14]

Patient and public involvement were not applicable in this study as it focused on surveying healthcare professionals directly involved in neonatal care. This study was approved by the Geneva University Ethics Committee (CUREG) under number CUREG-2022-04-39.

Objectives

Our main objective was to compare the work definitions of NS and neonatal infection used by different practitioners according to the importance of four case arguments: (1) C reactive protein (CRP) and white blood cell (WBC) count, (2) anamnesis (ie, maternal and birth risk factors, neonatal history), (3) clinical evocative signs and (4) blood cultures in different centres across Sub-Saharan Africa.

Other objectives were the temporal definition of EOS and LOS, antibiotic approach (main used treatments), perceived prevalence of NS in sick neonates, usual duration and frequency of treatment (antibiotic exposure), available laboratory investigations and actual practices, central catheter usage, catheter-associated infections and infection prevention and control (IPC) protocols.

Statistical analysis

The recorded answers were exported from the platform for data cleaning onto Microsoft Excel (V.16.66.1), and statistical analyses were performed on R studio (V.2023.12.1+402). All completed responses were treated, including those of incomplete questionnaires if questions concerning the primary outcome were completed. The time to complete the questionnaire was not an exclusion criterion.

We treated the Likert scales responses as continuous variables to assess dimensions such as importance (1=not important, 5=very important), likelihood (1=unlikely, 5=almost certain) and frequency (1=never, 5=always) and provide a more nuanced understanding of the respondents' attitudes and opinions.[15 16]

Our primary statistical method was descriptive analysis. This involved summarising the survey data in terms of frequencies (percentages) for categorical responses and calculating means (M) and SD for continuous responses. Additionally, we employed paired samples t-tests to compare the mean scores of related items, particularly where a direct comparison between two related concepts or practices was necessary.

Map based on Longitude (generated) and Latitude (generated). Size shows sum of Count. Details are shown for Country. The view is filtered on Country, which keeps 25 of 35 members.

Figure 1 Geographical distribution of participants according to centres.

RESULTS

From May to July 2022, 213 accesses to the survey were recorded, and 136 participants answered the forms, and of those, 108 forms met the analytical criteria. Clinicians were mostly of tertiary (65) or secondary level (38) of care, representing 83 facilities in 25 Sub-Saharan countries (figure 1). Most of the respondents were paediatricians or neonatologists (70%), followed by general practitioners (15%) and clinical officers (4%), with an average of 10 (0.5–32) years of experience in neonatal care.

Participants ranked NS or infection as the most prevalent condition in their ward with 42% (44/104) of answers, followed by prematurity at 37% (38/104), birth asphyxia at 14% (15/104) and hypothermia at 5% (5/104).

Case definition

For the case definitions, all arguments proposed were considered very important or important for diagnosing neonatal infection and sepsis. For neonatal infection, the ranking ranged from clinical signs (M: 4.75, SD: 0.51) to anamnestic arguments (M: 4.66, SD: 0.64), CRP and WBC (M: 4.33, SD: 0.84) to blood cultures (M: 4.24, SD: 1.13). For NS, the ranking was very similar, with the highest ranking for clinical signs (M: 4.72, SD:0.56), followed by anamnestic arguments (M: 4.59, SD: 0.63), blood cultures (M: 4.37, SD: 1.06) and CRP and WBC (M: 4.28, SD: 0.97).

The mean differences with a 95% CI were not statistically significant for any argument. Anamnesis had the largest mean difference of 0.06 (p=0.179) and positive blood cultures the smallest −0.13 (p=0.09) (table 1).

EOS was defined as occurring within the first 72 hours of life by 48% (52/108), and LOS as occurring after the first 72 hours of life by 46% (50/108) or after 7 days by 39% (42/108) of respondents.

Antibiotic use

Participants reported a high likelihood that any neonate would receive antibiotics on admission (M: 4.32, SD: 0.88) with at least one full course of antibiotics during a hospital stay (M: 4.11, SD: 1.1). A second full course of antibiotics was less likely reported (M: 3.13, SD: 1.3).

Table 1 Diagnostic argument importance in neonatal infection and sepsis

Diagnostic_Argument	Mean_Infection	Mean_Sepsis	Paired differences, mean, 95% CI	Two-sided p value
CRP, white blood count	4.33	4.28	0.06 (−0.08 to 0.19)	0.417
Anamnestic argument	4.66	4.59	0.06 (−0.03 to 0.16)	0.179
Clinical evocative signs	4.75	4.72	0.03 (−0.07 to 0.13)	0.592
Positive blood culture	4.24	4.37	−0.13 (−0.28 to 0.02)	0.094

This refers to questions B1 and B2: "In your practice, what is the importance of the following arguments to make a case diagnosis of neonatal infection?" and "In your practice, what is the importance of the following arguments to make a case diagnosis of neonatal sepsis?". This table compares the statistical significance of various diagnostic arguments in defining cases of neonatal infection (Mean_Infection) and neonatal sepsis (Mean_Sepsis). Mean scores (rated on a Likert scale of 1–5) for each diagnostic argument's importance, along with paired differences mean, at a 95% CI, and two-sided p values are presented.
CRP, C reactive protein.

Indicating in percentages, a likelihood of 86.4% for receiving antibiotics on admission and 82.2% for a full course during a hospital stay.

Abandoned treatment was reportedly unlikely (M: 1.94, SD: 1.0) and financial reasons were the leading cause of treatment discontinuation (see figure 2).

Regarding antibiotic duration, 380 responses were registered from 95 clinicians on when to stop antibiotics based on clinical and laboratory arguments. In 57.6% (219/380) of cases, a 5–7 day antibiotic regimen was chosen, with negative blood cultures (27.3%) or the absence of blood cultures (32.4%) being the primary reasons for administering an entire course of treatment to patients who had improved.

In 40% (154/380) of cases, clinicians discontinued antibiotics within 3 days. The main criteria used for early discontinuation were negative CRP levels, WBC count and clinical improvement (38.5%) (see figure 3).

The most reported antibiotics out of 211 responses for EOS were amoxicillin (41.7%), gentamycin (33.6%) and cefotaxime (15.2%). These antibiotics were primarily used in combined dual or triple therapy. For first-line treatment of EOS, the most frequently reported regimen was amoxicillin and gentamicin (53%), followed by amoxicillin, cefotaxime and gentamycin (16.6%) and gentamycin and cefotaxime (10%).

Out of 96 responses regarding first-line therapy for LOS, the most reported antibiotics were amoxicillin

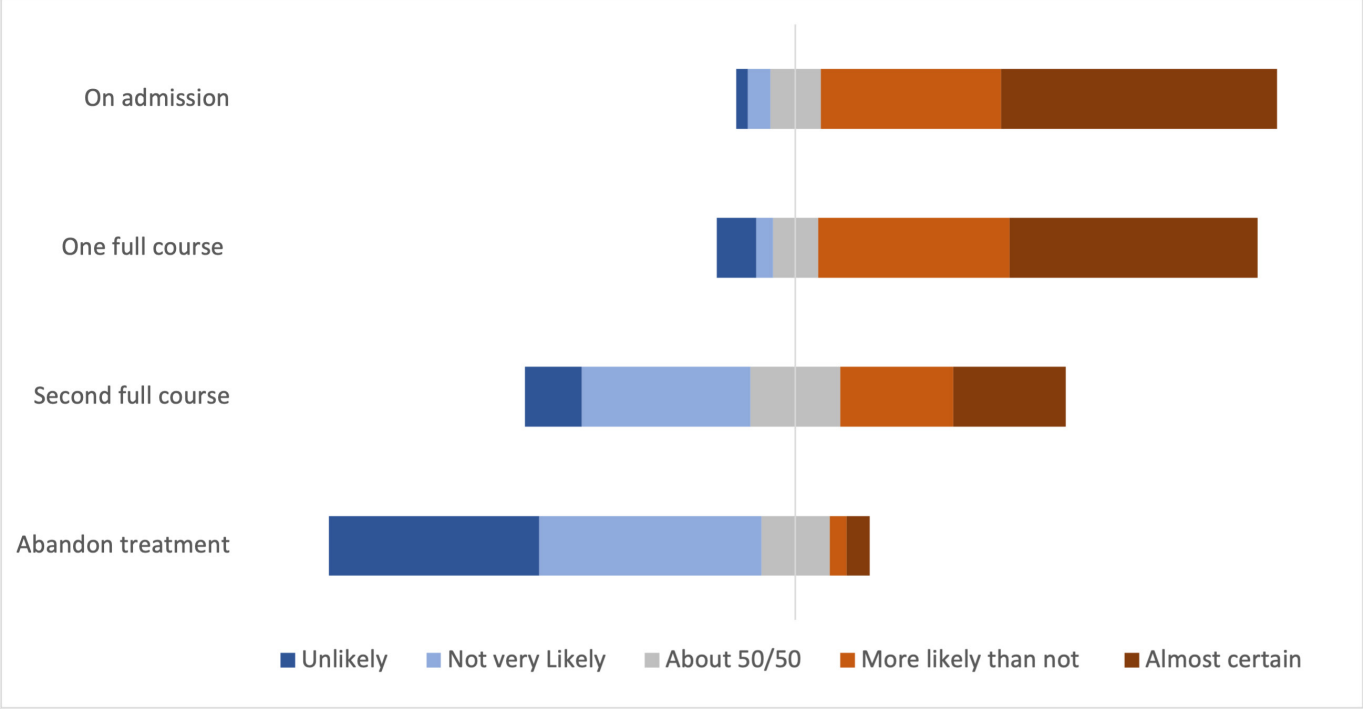

Figure 2 Likelihood of antibiotic treatment. The graphic representation of the questions C1 and C7 on a 5-point Likert likelihood scale: "In your hospital, what is the probability that a neonate receives antibiotics immediately after admission? "and "In your practice, how likely is a neonate admitted to the hospital would not receive at least five consecutive days of antibiotic treatment due to parental or caretaker refusal because of socioeconomic or cultural reasons?".

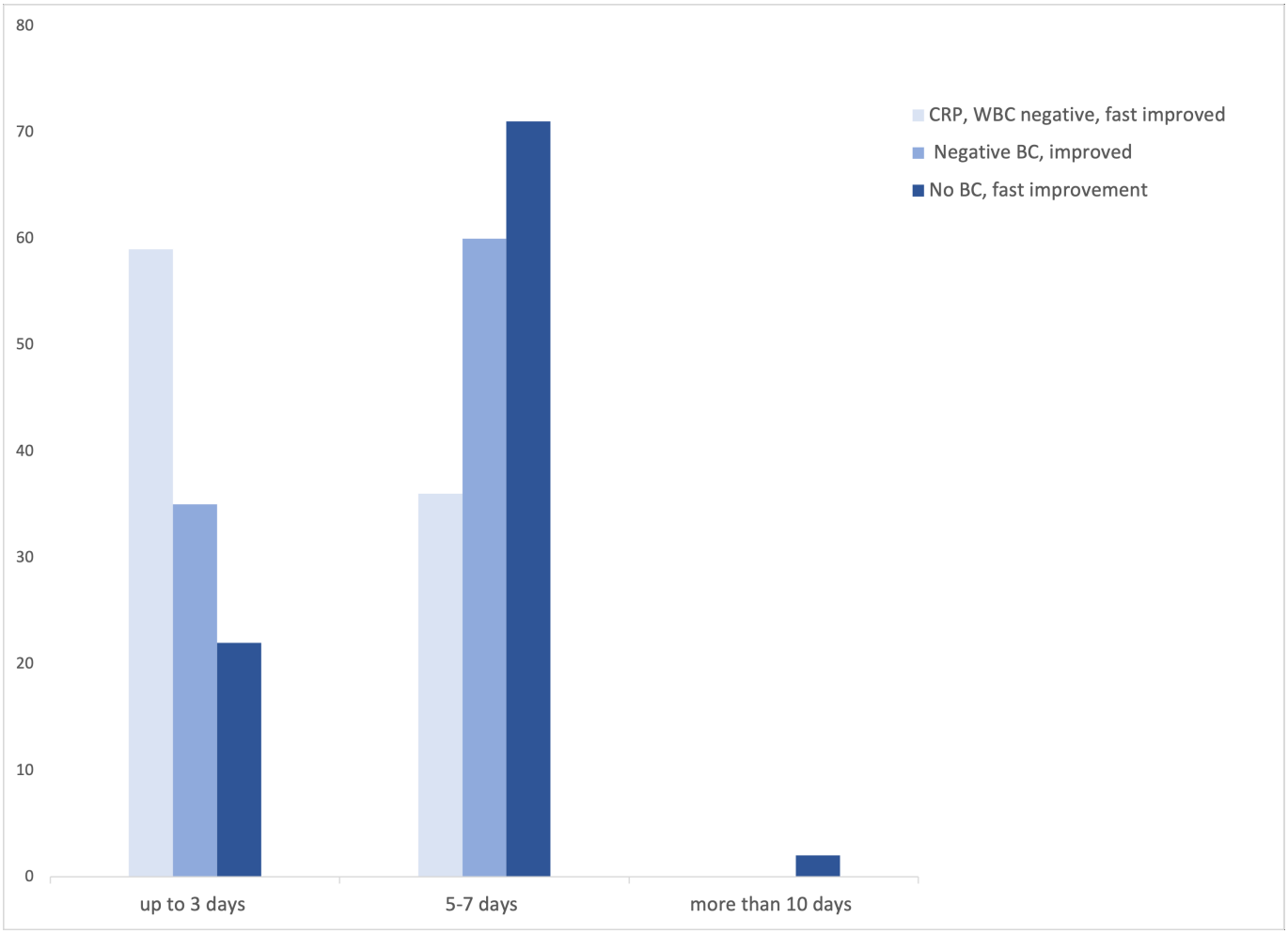

Figure 3 Antibiotic duration according to available laboratory tests. Question C9: " If you start antibiotics, you give at least…". In the graphic, the y-axis represents the number of answers and the x-axis represents the number of antibiotic treatment days according to the options in the legend. BC: blood cultures; CRP: C reactive protein; WBC: white blood cell count.

and gentamicin (33%), followed by amoxicillin, ceftriaxone and gentamycin (10%), with a total of 19 different antibiotic combinations reported. For second-line LOS treatment, out of 60 responses, the main antibiotics choices were meropenem (7%) and ceftriaxone (7%) when used alone and the combination of vancomycin and meropenem (7%).

Laboratory tests

The absence of any laboratory tests was rare (M: 1.47, SD: 0.98). WBC availability was very high (M: 4.73, SD: 0.8), followed by CRP (M: 3.98, SD: 1.4). Bacteriological tests were poorly available: Blood culture M: 2.38, (SD: 1.3) and Gram stain M: 2.38 (SD: 1.4).

Hospital-acquired infection

Overall, 43% (39/91) of the clinicians stated using central catheters, and 66.7% said limiting catheter duration in time. On a 5-point scale, the perceived risk of developing a central line-associated infection was average (M: 2.93, SD: 0.9).

For IPC, the availability of a standardised protocol for hand hygiene (HH) was 89% (81/91), and for the patient environment (beds, sinks, monitors, machines), 58.9% (52/91). The use of a pharmacy protocol (preparation of fluids, parenteral nutrition, drugs) was reported by 40.6% (37/91), a clean–dirty circuit protocol was known by 57.1% (52/91) of participants, and waste management used by 69.2% (63/91) of participants (figure 4).

DISCUSSION

In this multicentre NS survey of neonatology clinicians working in Sub-Saharan Africa, practitioners reported that NS and infection are the most prevalent conditions in the surveyed wards. According to the participants, there is no difference in a case diagnosis between NS and infection based on the proposed diagnostic arguments, and the most important arguments for clinicians were anamnesis and clinical signs.

Clinicians reported that negative CRP and WBC values, along with clinical improvement, were useful for stopping antibiotics within 3 days. Although WBC cannot be considered specific to exclude neonatal infection,[9 17 18] negative CRP values have a high negative predictive value

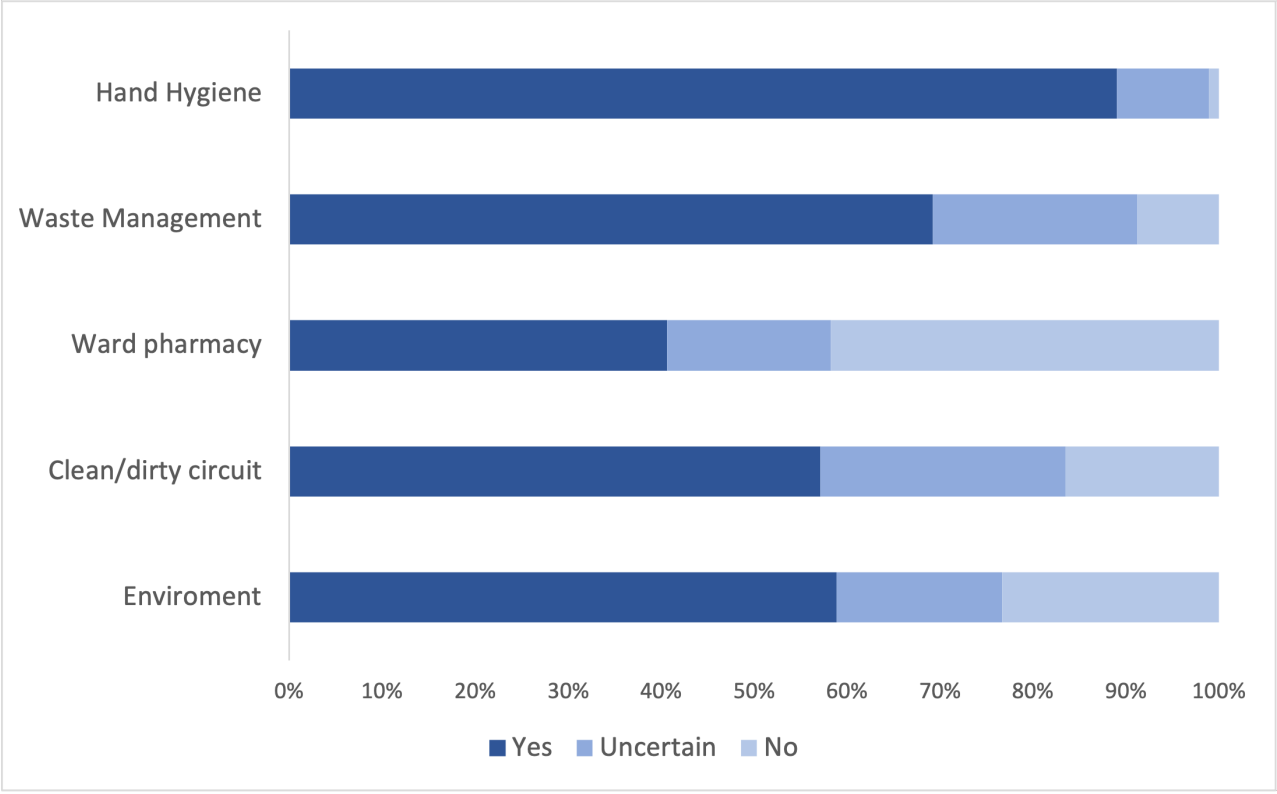

Figure 4 Availability of a standardised infection prevention and control protocol. Question A6: "Is there a standardised infection control protocol in your hospital concerning the following items?"

for sepsis, which has been confirmed by previous studies in high[9 19] and low-resource settings,[20 21] supporting this practice further.

Conversely, unavailable or negative blood cultures motivate prolonged 5–7 days of treatment. In the first case, clinicians may administer antibiotics to clinically improved neonates, assuming the improvement is due to the antibiotics when, in fact, this could be due to several neonatal conditions NS may mimic. In the latter, completing a full course of antibiotics might be justified based on the patient's improvement and the fact that culture-negative sepsis is a usual diagnosis in neonatal wards, even in high-income countries.[22–24] Nevertheless, the reported proportion of patients that might receive at least one course of antibiotics seems disproportionate to the reported incidence of confirmed NS in Sub-Saharan African countries to be 40/1000 live births.[25]

The main reported antibiotic regimens for EOS and LOS were the WHO's recommended ampicillin and gentamicin, followed by combinations with third-generation cephalosporins. Meropenem and ceftriaxone were the most reported antibiotics used as second-line therapy for LOS. More importantly, a high likelihood of antibiotic treatment at admission was reported, and at least one entire course of antibiotics was very likely for any admitted neonate. This practice might translate into high and prolonged antibiotic exposure in non-infected patients. Furthermore, possibly ineffective standard treatments were administered in most centres due to the unavailability of blood cultures and bacteriological profiles. This hypothesis is supported by data from the Burden of Antibiotic Resistance in Neonates from Developing Societies study (BARNARDS) that reported 67% resistance to at least one beta-lactam and 1 aminoglycoside out of 885 gram-negative isolates from NS. In this report, many isolates were also resistant to a third-generation cephalosporin.[26]

HH protocols were reported to be widely available, but unfortunately, we could not evaluate compliance. In a recent study from South Africa, Dramowski *et al* implemented a bundle to improve HH in the neonatal unit but could not demonstrate a change in compliance or hospital-acquired infection rates. Other studies in general medicine have shown that although HH awareness exists, compliance is low.[27–31] New strategies to strengthen HH compliance, including implementation science and behavioural modification adapted to context, could be part of the solution.[32] The other IPC components explored: pharmacy management protocols, patient environment, clean dirty circuit protocol and waste management, declared present in 40%–70% of structures, could be a target for improvement. According to WHO, these items are minimum requirements for IPC at any health structure; their implementation and monitoring should be expected in all hospitals.[33]

Our investigation suggests that using central catheters in newborns in the investigated structures is rare. Central catheters are associated with a perceived risk of

catheter-related infections affecting approximately 50% of the patients. However, it is essential to note that there is a lack of comprehensive data on neonatal catheter-associated infections in Sub-Saharan Africa. One study from a South African tertiary hospital reported an incidence of central line-associated infection of 5.9/1000 catheter days,[34] and pooled data from LMIC seem comparable. [34] Still, additional research on catheter-associated infections in the region is necessary to draw conclusive findings concerning other countries in Sub-Saharan Africa.

This study has limitations, particularly concerning the use of a survey as a data collection method. One significant limitation is the limited generalisability of the findings to the district or community-level care, as most respondents were experienced paediatricians from referral centres. Therefore, interpreting the results for other settings should be cautiously approached. Furthermore, relying on internet access and devices for questionnaire completion may introduce a selection bias. Moreover, we acknowledge that exploring site-specific infection such as neonatal meningitis was not considered at this time for feasibility reasons, but this is a subject to be further explored.

Although the number of participants was limited, the study's strength lies in the fact that it gathered many specialised clinicians with an average of 10 years of experience in neonatology. As experts in the field working in referral centres, they care for the most complex patients funnelled from a much larger catchment area. Therefore, their expertise and experience have enhanced the data quality with valuable insights into the research question.

CONCLUSION

For the neonatal clinicians who participated in the survey, sepsis management primarily relies on clinical judgement, anamnesis and clinical signs and laboratory tests to confirm or exclude sepsis are limited. This survey highlights possible high exposure to antibiotics, disproportionate to the sepsis incidence in the region and how the lack of blood cultures might result in prolonged treatment, potentially ineffective standard regimens, adding concerns about antibiotic resistance. It also emphasises the need for strategies to address broader IPC implementation. While acknowledging limitations, this study could be a step in improving neonatal healthcare in Sub-Saharan Africa, with a call for further implementation research to allow local surveillance, targeted antimicrobial usage and IPC.

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Contributors FR-M: study design, questionnaire development, questionnaire deployment, data analysis, writing. MD: design, questionnaire development and testing, manuscript edition. JED: questionnaire deployment, manuscript edition. LMM: questionnaire testing, validation and deployment, manuscript edition. NW: questionnaire testing and validation, expert scientific advice, manuscript edition. REP: design, questionnaire development, testing, validation, data analysis and manuscript edition. FR-M: Guarantor.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The Geneva University Ethics Commission approved this study under the number CUREG-2022-04-39. Participants gave informed consent to participate in the study before taking part.

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