**Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: a systematic review and meta-analysis in line with the STROBE-NI reporting guidelines**

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## Summary

**Background:** Aetiological data for neonatal infections are essential to inform policies and programme strategies at various levels, but such data are scarce from sub-Saharan Africa. We therefore conducted a systematic review and meta-analysis of available data from the African continent since 1980, with a focus on regional differences in aetiology and antimicrobial resistance (AMR) in the last decade (2008 – 2018).

**Methods:** We included data for microbiologically confirmed invasive bacterial infection including meningitis and AMR among neonates in sub-Saharan Africa and assessed the quality of scientific reporting according to Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) checklist. We calculated pooled proportions for reported bacterial isolates and AMR.

**Findings:** We included 151 studies comprising data from 84534 neonates from 26 countries, almost all of which were hospital-based. Of the 82 studies published between 2008 and 2018, insufficient details were reported regarding most STROBE-NI items. Regarding culture positive bacteraemia/sepsis, *S aureus*, *Klebsiella* spp and *E coli* accounted for 25% (95% CI 21 – 29%) 21%, (16 – 27%) and 10% (8 – 10%) respectively. For meningitis, the predominant identified causes were Group B *streptococcus* 25% (16 – 33%), *S pneumoniae* 17% (9 – 26%), and *S aureus* 12% (3 – 25%). Resistance to WHO recommended β-lactams was reported in >68% of 904 cases and to aminoglycosides in 27% of 1176 cases.

**Interpretation:** Hospital-acquired neonatal infections and AMR are a major burden in Africa, and improved surveillance is required. More population-based neonatal infection studies are also needed, and all studies should be reported according to standardised reporting guidelines, such as STROBE-NI to aid comparability and reduce research wastage.

**Funding**: Uduak Okomo was supported by a Medical Research Council PhD Studentship

## Introduction

An estimated 2.5 million neonatal deaths (deaths in the first 28 days after birth) occur each year, representing almost half (47%) of all under-five deaths globally.1 Despite the continued global decline in neonatal mortality levels, marked disparities in neonatal mortality exist across world regions and countries. The burden is highest in sub-Saharan Africa with 39% of all newborn deaths and neonatal mortality rate (NMR) of 27 deaths per 1000 livebirths.1 Within sub-Saharan Africa, the burden of newborn deaths and NMRs are unevenly distributed geographically.2 Overall progress towards achieving the Sustainable Development Goals’ (SDGs) NMR target of <12 deaths per 1000 livebirths by 2030 within the region is slow; however, West and Central Africa have the highest proportion of countries requiring major shifts in their mortality rate reduction to achieve this target.3,4

Bacterial infections are a leading cause of global neonatal deaths with a high burden of cases in sub-Saharan Africa and a higher cause-specific mortality risk,5 yet there is a significant gap in aetiology-specific data from the region, with no published trends regarding causative organisms. Across the region, geographical differences in causal pathogens may also exist, particularly given the diverse prevalence of maternal risk factors (HIV, UTI and other antenatal infections), neonatal risk factors (preterm birth, low birth weight), and varying health system contexts, including differential rates of facility birth rates.6 The WHO guidelines for management of suspected neonatal infections recommend empirical treatment with benzylpenicillin or ampicillin and gentamicin as first-line therapy, with a third-generation cephalosporin as second-line for non-responders or patients in whom drug-susceptibility testing of bacterial isolates indicates resistance to first-line therapy.7 These guidelines do not take into account the timing of infection (early vs late) or infants returning for admission from home. The rise and spread of antimicrobial resistance (AMR) threatens treatment of neonatal infection, with the potential to erode the recent gains in neonatal survival.8 In sub-Saharan Africa, resistance to recommended empirical therapies among neonatal pathogens has previously been reported;9-12 however, regional differences in the use of antibiotics and prevalence of resistance has not been explored.

Neonatal infection aetiology and AMR data are essential to inform policies and appropriate management strategies, yet remain a “*black box*” in sub-Saharan Africa.13 Much of the African biomedical research are published in local rather than international journals that are not included in the leading international research databases and thus are missed by reviews using only these databases.14-19 In 2016, the Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) checklist20 was developed to improve scientific reporting of neonatal infection studies and facilitate reliable comparison of infection data across settings. STROBE-NI is an extension of the 2007 22-item STROBE21 checklist with 28 additional elements specifically relating to neonatal infection. The impact of STROBE-NI on the quality of reporting has not yet been assessed. We therefore applied STROBE-NI criteria retrospectively in our systematic review of serious bacterial neonatal infection aetiology and antimicrobial resistance in sub-Saharan Africa, focusing on regional differences in order to increase the knowledge base and inform research priorities in the region.

## Methods

#### Search strategy and selection criteria

In this systematic review and meta-analysis, we searched MEDLINE, Embase, Global Health, PubMed, Africa Wide Information, and African Index Medicus to identify studies from sub-Saharan Africa published from January 1, 1980 to June 6, 2018 (date of last search), which reported aetiology of invasive bacterial infections (bacteraemia/sepsis/septicaemia, meningitis), specified neonatal data (or clearly delineated neonatal data from other age groups). Each database was searched using terms identified from Medical Subject Headings (MeSH) related to age, clinical infectious syndromes, and geographical descriptors, as well as terms used for systematic reviews on similar topics in various combinations as follows: “neonatal”, “newborn”, “infant”, “sepsis”, “infection”, “pathogen”, “bacteria”, “virus”, “aetiology”, “Africa”, “sub-Saharan” (webappendix tables 1 – 3). There were no language restrictions on the search.

Studies were excluded if they (i) presented data aggregated with regions beyond sub-Saharan Africa; (ii) reported on a single pathogen (as this might lead to a biased estimate of the significance of that pathogen), solely high-risk subpopulations (such as very low birth-weight, extremely premature, encephalopathy), or only newborns with potentially confounding comorbidities (malaria, tetanus, syphilis, tuberculosis or HIV); (iii) contained erroneous, incomplete, or internally inconsistent data; or (iv) assessed the diagnostic accuracy of any test using only positive samples and not in the clinical context of suspected neonatal infection. Preterm and low birth weight infants are a unique and high-risk group for many morbidities including hospital-acquired infections. The prevalence of HIV infection also varies across sub-Saharan Africa and influences the risk of neonatal GBS sepsis in high-prevalence settings but not to other pathogens. Including studies that reported only these ‘high-risk’ groups could possibly bias the significance of the aetiology results.

Abstracts and titles were compiled into Endnote (Thomson Reuters), de-duplicated, and reviewed individually by two investigators (UAO and ENKA) to identify potentially eligible articles. All such identified articles were retrieved in full text (where available) and their reference lists were again independently assessed by both reviewers through PubMed and African Journals Online (AOL) to obtain relevant abstracts as needed. Articles identified by this process as potentially eligible for inclusion were also retrieved as full text. French articles were read by both UO and ENKA. We made every attempt to contact the authors for copies of full text articles not available in the public domain. Where the full text could not be retrieved but enough detail was presented in the abstract, we used data from the abstract. We also included grey literature (theses and dissertations). Disagreements over inclusion were resolved by consensus.

#### Data analysis

Information was independently extracted from selected articles by two investigators (UAO and ENKA) and entered into a spreadsheet, including country and region of sub-Saharan Africa (Central, Eastern, Southern or West Africa as defined by the African Union),22 study year, publication year, location, setting, case ascertainment, and microbiological techniques, number of neonates investigated, sample volume, number of cultures carried out and the proportion that were positive, number of invasive bacterial isolates and where available, antimicrobial susceptibility testing. Previous reviews excluded coagulase-negative *Staphylococci* (CoNS), which are potentially pathogenic in very preterm neonates in intensive care with ventilator support and in-dwelling devices, not frequently used in many sub-Saharan African settings.23,24 We therefore excluded data for CoNS from summary tables. Inconsistencies between investigators in data extracted were resolved by further review of the original papers.

Data reporting completeness was assessed by applying the STROBE-NI checklist (webappendix table 4) for studies published after 2007 which is when the STROBE checklist was published. Each study was assessed independently by two investigators (UAO and ENKA), and item reporting classified as “‘not reported/unclear” or “some information mentioned but insufficient” or “clear and detailed information provided”.

To analyse the aetiology data, studies were grouped according to the year of publication: 1980 – 2007 and 2008 – 2018. Data on invasive bacterial infections (bacteraemia/sepsis and meningitis) were collated for each period. However, to assess current aetiology and AMR analysis was restricted to studies published between 2008 and 2018. We calculated pooled proportions per pathogen for bacteraemia and meningitis using random effects meta-analysis of binominal data, applying the Freeman-Tukey Double Arcsine Transformation to stabilize variances.25,26 We used random effects models to allow for inter-study heterogeneity.27 We also did post-hoc subgroup analyses by country in each region, and other study characteristics in countries with more than 10 studies and high heterogeneity. We used Stata (version 13) for all statistical analyses.

## Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Our systematic review identified 16059 records (Figure 1), from which we identified 150 eligible studies (including nine theses/dissertations28-36) meeting our inclusion criteria. For 23 potentially eligible studies, we were unable to obtain the full text (webappendix table 5). Fifty percent (75/150) of included studies were identified only in African databases. One study37 reported data from two West African countries and was counted as two separate studies, resulting in a total of 151 included studies (webappendix tables 6 - 8). Eleven studies29,32,37-45 were in French and the rest in English; no studies in Portuguese or any African language were identified. The total study population included 84534 neonates from 26 sub-Saharan African nations (Figure 2), one-third (33%, 49/151) from Nigeria.

132 studies investigated only neonatal patient populations, and from the other 19 studies40,45-62 we extracted neonatal data from mixed age-group datasets. All studies were hospital-based except for one community- (home-based surveillance) study from Madagascar.63 Hospital-based studies were mostly tertiary referral facilities (university or large national hospitals), and only 23 from district or secondary referral hospitals.34,48,51,54,59-62,64-78 139 studies were in urban settings while five from Kenya,54,61,64,65,68 three from Mozambique,59,72,73 two from Nigeria,79,80 and one from Cameroon77 reported data from predominantly rural populations. Eighty-eight studies involved prospective data collection, 61 were retrospective reviews (26 laboratory-based surveillance of aetiology data), and two studies had both retrospective and prospective components. There was one randomised-controlled trial,28 one before-and-after study81, three case-control studies42,78,82, six observational cohort studies;38,48,63,83-85 and the remaining 139 studies were cross-sectional designs.

#### Assessment of reporting completeness and quality according to STROBE-NI criteria

Sixty-nine studies were published between 1980 and 2007, with the remaining 82 studies published between 2008 and 2018. Figure 3 summarises the completeness of reporting from 81 observational studies (excluding 1 RCT) published after 2007, as outlined in the STROBE-NI checklist. Case ascertainment by physician diagnosis was reported in 54% (44/81) studies, 26 of which documented the individual clinical signs used for the diagnosis of neonatal sepsis and/or meningitis. Only seven studies36,63,74,86-89 reported using the WHO/IMCI clinical algorithm, two studies90,91used the French National Agency for Accreditation and Health clinical diagnostic criteria,92 and one Ugandan study93 reported using criteria adopted from International Paediatric Sepsis Consensus94 and Indian Academy of Paediatrics.95 One-third of studies (37%; 30/81) reported microbiological and/or laboratory criteria for diagnosis of neonatal infection syndromes (sepsis, meningitis), and 69% (56/81) described microbiological sample type and sampling strategy (clinical indication vs. routine) as well as number of newborns sampled. Sixty studies reported only blood culture data, 11 studies reported only CSF data, and 10 studies reported both blood and CSF data of which only 8 reported disaggregated data.

Of 70 studies that reported blood culture data, 13 were retrospective reviews of laboratory data and did not report the number of culture samples per infant. Nine studies88,89,93,96-101 reported submission of two blood cultures from each neonate while all others reported collection of a single sample. Across these studies, a total of 31 564 blood cultures were collected of which 7856 (25%) were positive for a bacterial pathogen (webappendix Table 9). Few studies (21%; 15/70) reported the timing of sampling in relation to antimicrobial administration. Blood volume for culture was reported by 36 (51%) studies, ranging from 0.4 mL – 5mL. Over 80% of studies included data on number (and proportion) of blood samples cultured, number (and proportion) that were positive, as well as the number of pathogens isolated. Although 53 (76%) of these studies also described blood culture methods used, culture media and methods of identification of organisms varied between studies. More studies (n = 28) used manual blood culture methods than automated techniques (n=24) (webappendix Table 9), and one study reported using both. Between 8 and 44% of cultures were positive among studies using automated techniques, and 14 - 87% among studies using manual methods.

Among 19 studies reporting disaggregated CSF culture data, only eleven31,48,63,68,73,89,90,102-105 reported on both number of lumbar punctures (LPs) carried out and number positive. Across these studies, 1738 LPs were reported of which 135 (8%) were positive, with positivity rates ranging from 0 – 100% (webappendix Table 10).

Forty-one (51%) studies clearly described antimicrobial susceptibility tests used, the most widely reported method being the Kirby-Bauer disc diffusion method. Only four studies reported use of Etest72,73,106,107 or Microdilution59 on all or some isolates. Several established guidelines for resistance interpretation were referenced; Clinical and Laboratory Standards Institute (CLSI; 36 studies), EUCAST,107 British Society for Antimicrobial Therapy,60,61,71,97 and French Society of Microbiology.91

Only 12 (15%) studies provided context by describing the pathway of neonatal presentation. Most described the neonatal population according to place of birth as either “inborn” or “outborn”, and only one study34 mentioned all neonatal presentations to the neonatal unit. Important neonatal characteristics such as gestational age and birthweight were each reported by less than half (47%; 38/81) of the studies, most of which presented data in discrete categories with summary statistics (medians and ranges). Data on comorbidities (e.g. encephalopathy) and feeding were rarely reported, and only 6 of the included studies reported neonatal HIV exposure/testing.

Most studies did not report the level/type of neonatal care (webappendix Figure 1), with the context poorly described across all studies, regarding basic neonatal care (resuscitation, breastfeeding), intensive neonatal care (oxygen supplementation, invasive and non-invasive respiratory support, indwelling devices), nurse-to-patient ratio, and non-microbiological investigations. Only 31% (25/81) of studies reported the antimicrobial guidelines used for empiric management of neonatal sepsis (webappendix Table 11).

Description of microbiological laboratory context was also poor across all studies, regarding facilities, sample types, and capacity for conventional or molecular microbiology. Most of the studies reported selected pathogens and did not provide full data of all organisms. Only one South African study108 and two Nigerian studies88,89 stated criteria used to determine the clinical significance of detected organisms. Few studies listed pathogens excluded as contaminants. Although often reported as contaminants, several studies reported coagulase-negative staphylococci (CoNS),24,34,38,55,71,74,86-89,96,98,103,106,108-123 Viridians streptococci,61,85 *Staphylococcus epidermidis*,84,99,124-126 *Bacillus* spp106,121 and *Micrococcus* spp127 as neonatal pathogens. However, only few studies24,36,122,123,127,128 described the rationale for determining the clinical significance of CoNS. Four studies 36,60,107,125 cited laboratory quality control measures, and only one study 107 sent samples to an external laboratory for confirmation.

#### Aetiology of bacteraemia/sepsis

Between 1980 and 2007, *Staphylococcus aureus*, *Klebsiella* spp (mostly *Klebsiella pneumoniae*) and *Escherichia coli* accounted for 25% (95% CI 19 – 31%), 15% (95% CI 11 – 20%) and 10% (95% CI 8 – 13%) of all reported cases of neonatal bacteraemia/sepsis, respectively (Table 1a). These three pathogens, plus unidentified Gram-negative organisms, accounted for more than two-thirds of all reported causes of bacteraemia/sepsis. We observed similar distributions between 2008 and 2018, with *S. aureus* (25%, 95% CI 21 – 29%) *Klebsiella* spp (21%, 95% CI 16 – 27%) and *E coli* (10%, 95% CI 8 – 10%) (table 2).

Only one paper129 delineated hospital-acquired and community-acquired pathogens, with a higher prevalence of *Klebsiella* spp among neonates with hospital-acquired infection [31% (10/32) *vs*. 17% (8/48); p=0.126] and a slightly higher prevalence of *S aureus* among those with community-acquired infection (17% (8/48) *vs*. 13% (4/32); p=0.609). Three studies61,63,72 specifically examined community-acquired infections, and two studies24,81 reported only hospital-acquired infections; the remaining studies did not analyse pathogens by place of acquisition. We were unable to carry out post-hoc analysis of differences in aetiology by gestational age, birth weight, and HIV status due to the poor reporting of these data across the studies.

Table 2a shows the regional distribution of reported causes of neonatal bacteraemia/sepsis. In Central and Southern Africa, *Klebsiella* spp was the predominant isolate representing 38% (95% CI 19 – 54%) and 25% (95% CI 10 – 41%) of bacteraemic infections respectively; whereas in East and West Africa *S aureus* was the most common isolate accounting for 20% (95% CI 14 – 28%) and 32% (95% CI 25 – 39%) of cases respectively (see the appendix for this meta-analysis). We observed much intra- and inter-regional heterogeneity in all our meta-analyses (*I*2 range 56 - 98%), both overall and in subgroups defined by region (figure 3 and webappendix figure 2). Further sensitivity analyses stratifying for important study characteristics showed significant differences in the prevalence of *S aureus* bacteraemia between countries in each region (webappendix figure 4). Most (80%, 1020/1282) of *S. aureus* isolates in West Africa were reported from Nigerian studies. Among these, the prevalence of *S aureus* bacteraemia was higher among retrospective studies compared to prospective studies (47% *vs* 30%, p=0.043), and among studies reported from tertiary healthcare facilities compared to those from secondary facilities and (36% *vs* 23%; p=0.020) (webappendix figure 5).

#### Aetiology of meningitis

Table 1b shows pooled pathogen prevalence associated with neonatal meningitis by time period. Group B *Streptococcus* (GBS)(26%, 95% CI 18 – 35%) was the most commonly reported cause between 1980 and 2007, followed by *S. aureus* (18%, 95% CI 7 – 32%), *S pneumoniae* (15%, 95 % CI 11 – 21%), *Klebsiella* spp (15%, 95% CI 9 – 21%), and *E. coli* (15%, 95% CI 10 – 20%). Between 2008 and 2018 GBS, *S pneumoniae*, and *S aureus* remained the major reported causes (Table 2b). GBS predominated in East (19%, 95% CI 11 – 28%) and Southern Africa (31%, 95% CI 21 – 41%); although most of the data were from South Africa. We observed variable heterogeneity (0 – 87%) in the aetiology of neonatal meningitis between regions (figure 4 and webappendix figure 3).

#### Antimicrobial resistance

Sixty-three studies (78%) reported in vitro antibiotic susceptibility data but only 29 studies specified individual pathogens and isolates numbers tested. No study reported minimum inhibitory concentrations (MIC) to the antibiotics reported, making it difficult to assess intermediate or decreased susceptibility. Table 3 presents findings for the most prevalent isolates.

22 studies36,63,74,79,84,86,88,91,93,97,98,106,108,110,112,113,118,123,128,130-132 reported resistance among *Klebsiella* spp (predominantly *K pneumoniae,* with few cases of *K oxytoca*), documenting non-susceptibility to gentamicin of 66% (95% CI 47% – 83%), ceftriaxone 49% (95% CI 28 – 71%), and cefotaxime 78% (95% CI 55 – 95%). Reported resistance to amikacin, an alternative to gentamicin was low (14%, 95% CI 7 – 23%).63,108,113,123,128,131,132 High frequencies of extended spectrum β-lactamase (ESBL)-producing *K pneumoniae* spp were reported from South Africa (range 41 – 97%),24,63,108,122,123 Tanzania (49%, 24/50),86 and Botswana (60%, 16/27).128 In one South African study,108 resistance to piperacillin/tazobactam, was higher among ESBL-producing *K pneumoniae* isolates (90%, 9/10) compared to the non-ESBL producing isolates (43%, 3/7). Non-susceptibility to carbapenems was reported in at least once country in each region,63,86,88,91,106,108,123,132 with low resistance rates (4%, 95% CI 1 – 10%).

Pooled prevalence of non-susceptibility of *E. coli* isolates to ampicillin63,74,79,84,86,88,98,106,110,112,113,118,123,128,131,132 and gentamicin63,74,79,84,86,88,91,97,98,106,108,110,113,118,123,128,130-132 was 89% (95% CI 77 – 97%), and 47% (95% CI 25 – 69%) respectively. One-third of *E coli* isolates were resistant to ceftriaxone.74,79,84,86,88,97,98,106,110,112,113,118,131 The reported prevalence of ESBL-producing *E coli* isolatesranged from 12% (7/58) in South Africa24 to 46% (10/22) in Tanzania.86 Resistance to piperacillin/tazobactam was also low (7% , 95% CI 0 – 27%).63,123,128,132 Only two studies reported carbapenem resistant isolates; one each from Tanzania86 and South Africa.108

For *S aureus* infection, WHO recommends first-line treatment with cloxacillin and gentamicin to which the pooled resistance was 40% (95% CI 8 – 79%)79,84,93,97,98,110,130,131 and 27% (95% CI 14 – 41%)63,79,84,88,93,97,98,106,110,111,113,118,128,130,131 respectively. Methicillin resistance was reported by eight studies,24,86,108,112,118,122,125,133 (only one from Nigeria) with 50% (95% CI 30 – 70%) of isolates non-susceptible. Resistance to cefoxitin, the recommended antibiotic to determine methicillin resistant *S aureus* strains (MRSA) when using the disk diffusion method,134 was reported in 27% (13/49) of isolates in an Ethiopian study,113 and 26% (6/23) of isolates in a Nigerian study.88 None of the two studies that analysed susceptibility patterns of GBS documented non-susceptibility to any antibiotic. 128,131

## Discussion

This is the largest systematic review of neonatal infection aetiology and AMR from sub-Saharan Africa, and a strength is the assessment of reporting quality using STROBE-NI.20 The inclusion of African regional research databases in our search strategy resulted in the identification of 75 relevant studies compared to those identified through the usual major databases, although Central Africa is still poorly represented. Our review represents a significant increase in studies from the continent compared with previous reviews in which the number of included sub-Saharan African studies ranged from 7 - 23.9,14-19 We highlight the variability in recording and reporting, across and within manuscript sections which impede comparability of results and utility of available data. No single STROBE-NI item was adequately addressed across all manuscripts, and although this could be improved with wider use of STROBE-NI guidelines, this review could therefore not distinguish between infections that were maternally, community or hospital-acquired.

## Research in context

#### Evidence before this study

Neonatal deaths account for 47% of under-five deaths globally and infections are one of the leading causes of mortality. Linked to Sustainable Development Goals, there has been a strong emphasis on promotion of institutional delivery for all births with the aim of improving maternal and neonatal outcomes. In sub-Saharan Africa where more than half of the 36 million annual births now occur in health facilities, many hospital environments have sub-optimal hygiene, placing mothers and newborns at risk of hospital-acquired infections with associated morbidity, mortality and cost. WHO recommends ampicillin (or penicillin) plus gentamicin as treatment for serious infections in newborns and infants younger than 2 months of age. Antimicrobial resistance is an increasing global threat leading to poor treatment outcomes and the potential to erode the gains in neonatal survival of the last few decades. Aetiology-specific data for neonatal infections in the African continent are scarce, but available data suggest that Gram-negative organisms are the predominant cause of early-onset sepsis, with a high prevalence of extended-spectrum β-lactamase-producing organisms.

#### Added value of this study

This is the first systematic review of neonatal infection aetiology in sub-Saharan Africa, with extensive inputs from >16,000 initial hits. Our review addresses the knowledge gap about causes of invasive bacterial infection and antimicrobial resistance, assessing regional differences in pathogen dominance and resistance patterns. An added strength is that we assessed the quality of scientific reporting by applying the Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) checklist.

**Implications of all the available evidence**

The reporting quality was poor across all studies with many items from STROBE-NI not described, thereby making the data challenging to combine and interpret. There is a stark lack of population-based studies investigating neonatal infection aetiology yet clearly a huge burden of infection among neonates in hospitals, including hospital-acquired infections. *Staphylococcus aureus* and *Klebsiella* spp and *Escherichia coli* were the leading reported causes of bacteraemia/sepsis supporting the view that lack of appropriate hygiene during labour, delivery and postnatal care are major contributors in the development of neonatal bloodstream infections. For reported causes of neonatal meningitis, Group B *streptococcus* and *Streptococcus* *pneumoniae* dominate andpresent specific opportunities for prevention i through maternal immunisation. The limited antimicrobial resistance data suggests resistance to WHO recommended first-line antibiotics occurs in more than 27% of cases and resistance to second-line antibiotics in more than 18% of cases.

 The use of standardised reporting guidelines such as STROBE-NI is strongly recommended for future neonatal infection studies. There also is need for strengthening of capacity for microbiological diagnosis, and innovations in diagnostics, particularly for “high risk” pathogens. Geographical variation of pathogens and resistance underscore the need for active surveillance and to inform region-specific therapeutic guidelines for empirical treatment of infections. Infection control policies to combat hospital-acquired infections is an urgent imperative.

In many sub-Saharan African hospitals, sick newborns do not routinely undergo microbiological investigations.124,135 Considering that the annual need-to-treat population for pSBI in sub-Saharan Africa is 2.6 million, with around ten cases of pSBI diagnosed for each associated neonatal death,136 the 31, 874 blood cultures and 1742 LPs reported in the studies identified in this review (of which 25% and 8% respectively were culture-positive) reveal the paucity of published data for such a large population at risk. A published audit of almost 5000 neonates admitted in the main hospital in The Gambia found that 94% received antibiotics, but only 26 neonates had a blood culture sample taken (of which 6 had a result), and even fewer had a LP result.135 An LP is part of the diagnostic work-up for all sick newborns with pSBI in order to identify meningitis and give the most appropriate antibiotic for the correct time period. Routine investigations for neonates such as blood cultures and LPs need to be instated as standard of care, but requires investments in clinical care workers, commodities and laboratories.

Nearly a decade ago, in a review of studies published between 1980 and 2007, Zaidi and colleagues15 reported GBS, *S pneumoniae*, *Salmonella* spp, and *S aureus,* as dominant pathogens associated with invasive bacterial infection in African newborns. However, this study did not distinguish between causes of bacteraemia/sepsis and meningitis or assess sub-regional differences in pathogen distribution. In our review, *S aureus* was a more important cause of bacteraemia/sepsis over the same period (1980 – 2007), while GBS and *S pneumoniae* accounted for over one-third of neonatal meningitis infections for which a pathogen could be isolated. Our results show that since 2008, *S aureus* has remained an important cause of bacteraemia/sepsis, especially in hospital settings, while GBS and *S pneumoniae* are important causes of neonatal meningitis with differences in pathogen distribution between and within regions. GBS and *S pneumoniae* present specific opportunities for interventions, for example by maternal immunisation.137-139

Our results show sub-regional geographical variation in the distribution of specific bacterial pathogens between and within regions (Table 2). One key finding was the higher number of studies from Southern Africa reporting GBS infections compared to other regions, although the prevalence of infections did not differ significantly across regions. Most data are from South Africa and, as noted by other reviews of aetiology and antimicrobial data in sub-Saharan Africa,9,140 a specific focus on GBS research in South Africa may have led to geographical publication bias. In spite of this, true geographic differences in disease epidemiology or regional differences in virulence and host susceptibility cannot be ruled out.137,141 Variability in GBS disease may also reflect differences in case ascertainment (especially amongst home births), prior antibiotic treatment, blood culture or LP practices, variability in laboratory capacity, and the quality of microbiological investigations.141 A South African study, reported significant variation in neonatal invasive GBS disease incidence by province with differential access to healthcare, poor laboratory capacity and varying diagnostic procedures.142 Because early-onset GBS disease usually occurs within the first 24 hours of life, with the majority presenting within hours of being born,143 those born at home or with limited access to healthcare are missed as they die at home.144

Another notable finding was the difference in the prevalence of *S aureus* bacteraemia/sepsis between regions, which was significantly higher in West Africa compared to Southern Africa. Most of the West African studies were from Nigeria where the prevalence of S *aureus* bacteraemia/sepsis differed significantly according to method of data collection and level of healthcare facility. Potential explanations for the higher prevalence of infection among retrospective compared to prospective studies include variability in what is defined as clinically significant and failure to collect certain data at study design or recognise the significance of reporting certain data. The higher prevalence of *S aureus* bacteraemia/sepsis among studies from tertiary facilities could be explained by the fact that these facilities receive patients from a wider geographical area, usually the sickest infants who might have already received care from one or more referral facilities and acquired pathogens from the hospital environment. *S aureus* is an important cause of neonatal hospital-acquired infections,145,146 and nosocomial outbreaks may go unrecognised.

*Klebsiella* spp and *E coli* normally colonise the maternal genital tract and can cause early-onset neonatal infections.147 However, multi-drug resistant ESBL-producing organisms observed in several studies are usually acquired from contaminated hospital environments,148 with increased risk of mortality, especially among preterm babies.149 In Mali, typing of ESBL *Enterobacteriaceae* among bacteraemic children and adults from two referral hospitals showed a high rate of cross transmission between patients and spread of strains from one hospital to another due to patient transfers.150 This underlines the crucial need for improved infection prevention measures particularly in congested neonatal units, with high antimicrobial exposure, and poor infection control.14,81,146,151

We identified a high prevalence of resistance to recommended empirical therapies, in keeping with reports from older paediatric and adult populations in Africa.9,152,153 Similarly high resistance rates have been reported among South Asian neonates, including India where an excess of 80000 neonates die each year from resistance-attributable neonatal sepsis deaths.8,154 Alternative therapeutic options such as fluoroquinolones, carbapenems and piperacillin/tazobactam are limited, expensive, inappropriate for use in community settings, and therefore considered antibiotics of last resort.11,155 Low to moderate rates of resistance to these antimicrobials were observed in studies in this review. Our high reported rates of MRSA are in keeping with a previous review MRSA in Africa,156 and suggest that treatment for suspected or confirmed *S aureus* infection must rely on second-line drugs such as vancomycin, which are expensive and can have severe side-effects.157 Our finding of reduced susceptibility to amoxicillin among *S aureus* is particularly worrisome given that it is the only WHO-recommended oral antibiotic for outpatient treatment of possible serious bacterial infection in infants whose families do not accept or cannot access hospital-based care.158 The emergence of resistance to this simple option is likely to result in more deaths.

Our findings have some limitations. First, although our search generated many results, some potentially eligible studies were excluded for not providing separate neonatal aetiology data. Included studies were mostly from West Africa, with a third of studies from Nigeria, and there was little or no data for other countries with comparable neonatal mortality levels, particularly conflict and post-conflict countries. Second, there was significantly high heterogeneity between studies, although this was expected due to the differences in case ascertainment, microbiological methods, and data collection methods between the various included studies. Thirdly, because most of the studies reported collection of only one sample, it was difficult to determine in some instances whether a specific organism should be considered a contaminant or not, particularly CoNS which we excluded. It is therefore possible that some real pathogens were missed, or some contaminants were included.

Nevertheless, these data provide useful insights into the pathogens associated with neonatal invasive bacterial infection in sub-Saharan Africa and the status of AMR. Interventions that focus on hospital-based care around the time of birth could prevent millions of neonatal and maternal deaths, and stillbirths as well as disability.159 Yet with poor quality care is where the dangers of infection transmission and AMR threaten the gains of neonatal survival. Reducing the burden of neonatal infection mortality and morbidity requires a multi-pronged approach. Infection prevention and surveillance of hospital-acquired infections is critical as well as expanded and improved clinical microbiology services for detection and optimum treatment. Tailored local antimicrobial guidelines, implementation of antimicrobial stewardship policies, and effective AMR surveillance are necessary strategies to tackle AMR.9 Innovative point of care diagnostics would be transformative. Although there is potential for maternal vaccines against GBS and *S pneumoniae*, the value proposition of new vaccines should be based on sound data. Differences in geographical distribution of specific bacterial serotypes needs to be determined to guide optimal selection of vaccine targets.

Despite marked increases in facility births, almost half of the 36 million annual births in sub-Saharan Africa still occur at home, many of whom never receive treatment when sick.6 The scarcity of aetiology and AMR data from community-based studies poses a critical gap in the knowledge of pathogens causing infections in babies born and dying at home. The Aetiology of Neonatal Infections in South Asia (ANISA), an observational cohort study, identified atypical bacteria and respiratory syncytial virus infection as the predominant causes of community-acquired serious infections among infants in that region.144 No such study has been conducted in Africa where rates of infection and pathogens seen are likely different from Asia.

Our findings also underscore the current “research wastage” for reported data on neonatal infection aetiology, antimicrobial sensitivity and outcomes.20 Application of the STROBE-NI checklist could improve scientific reporting, increase comparability, and reduce this wastage of precious data in high-burden regions.20 However, while unified reporting standards and more studies are needed, the burden of neonatal infections will only be reduced if these data are available and used locally by public health leaders and programme managers, and implemented within local healthcare systems, whilst respecting local contexts.13

**Contributors**

UO and JEL conceived the idea for this study. UO developed the checklist of inclusion and exclusion criteria, and together with ENKA carried out the literature search, reviewed published papers, and made the primary selection of eligible papers. UO compiled the data, designed Figures 1 and 2 and wrote the first draft of the paper. UO and AJ analysed and interpreted the data with the support of JEL, SC, KL and BK. AR and MS provided guidance on the analysis and interpretation of antimicrobial resistance data. UO had full access to all the data in the study. UO, JEL and BK had final responsibility for the decision to submit for publication. All authors provided input to the overall direction and content of the paper, reviewed each draft of the paper, and have seen and approved the final version.

**Conflicts of interests**

We declare that we have no conflicts of interest.

**Acknowledgements**

UO was supported by a Medical Research Council PhD Studentship. The authors gratefully acknowledge Professor Martin Meremikwu and Dr Henry J. Lawson for their insights.

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**Table 1. Pooled pathogen prevalence estimates serious bacterial neonatal infections in sub-Saharan Africa from meta-analyses, by period of publication**

|  |  |  |  |
| --- | --- | --- | --- |
| **A) Bacteraemia/Sepsis** | **1980 – 2007****(43 studies)** |  | **2008 – 2018****(71 studies)** |
| **Number of isolates** | **Proportion****(95% CI)** |  | **Number of isolates** | **Proportion****(95% CI)** |
| **Gram-positive** |  |  |  |  |  |
| *Staphylococcus aureus* | 912 | 0.25 (0.19 – 0.31) |  | 2080 | 0.25 (0.21 – 0.29) |
| Streptococcus pyogenes | 75 | 0.04 (0.02 – 0.08) |  | 117 | 0.04 (0.02 – 0.07) |
| Group B *Streptococci* | 213 | 0.07 (0.03 – 0.12) |  | 342 | 0.06 (0.03 – 0.10) |
| Group D *Streptococci*/ *Enterococcus* | 139 | 0.05 (0.03 – 0.07) |  | 449 | 0.05 (0.04 – 0.07) |
| *Streptococcus pneumoniae* | 72 | 0.04 (0.02 – 0.08) |  | 114 | 0.02 (0.01 – 0.04) |
| Viridians streptococci | 7 | 0.01 (0.00 – 0.05) |  | 71 | 0.03 (0.01 – 0.05) |
| Other *Streptococcus* species/unspecified | 63 | 0.03 (0.01 – 0.05) |  | 209 | 0.05 (0.03 – 0.07) |
| Other/ unspecified Gram-positives | 87  | 0.04 (0.01 – 0.08) |  | 155 | 0.06 (0.03 – 0.09) |
| **Gram-negative** |  |  |  |  |  |
| *Klebsiella* species | 644 | 0.15 (0.11 – 0.20) |  | 1730 | 0.21 (0.16 – 0.27) |
| *Escherichia coli* | 377 | 0.10 (0.08 – 0.13) |  | 856 | 0.10 (0.08 – 0.13) |
| *Pseudomonas* species | 146 | 0.04 (0.02 – 0.05) |  | 189 | 0.03 (0.02 – 0.04) |
| *Enterobacter* species | 270 | 0.08 (0.03 – 0.13) |  | 263 | 0.04 (0.03 – 0.05) |
| *Serratia* species | 0 |  |  | 129 | 0.03 (0.01 – 0.07) |
| *Proteus* species | 54 | 0.02 (0.01 – 0.04) |  | 126 | 0.03 (0.02 – 0.04) |
| *Salmonella* species | 162 | 0.03 (0.02 – 0.05) |  | 176 | 0.04 (0.02 – 0.06) |
| *Citrobacter* species | 61 | 0.04 (0.01 – 0.07) |  | 122 | 0.02 (0.02 – 0.04) |
| *Haemophilus influenzae* | 11 | 0.01 (0.00 – 0.02) |  | 10 | 0.01 (0.00 – 0.03) |
| *Neisseria meningitidis* | 0 |  |  | 17 | 0.03 (0.00 – 0.08) |
| *Acinetobacter* species | 94 | 0.05 (0.02 – 0.07) |  | 299 | 0.05 (0.03 – 0.07) |
| Other/unspecified Gram-negatives | 522 | 0.20 (0.14 – 0.27) |  | 508 | 0.10 (0.06 – 0.14) |
| **Other pathogens** | 14 | **0.05 (0.02 – 0.07)** |  | **9** | **-** |
| **Total** | **3832** |  |  | **7971** |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| **B) Meningitis** | **1980 – 2007****(38 studies)** |  | **2008 – 2018****(19 studies)** |
| **Number of isolates** | **Proportion****(95% CI)** |  | **Number of isolates** | **Proportion****(95% CI)** |
| **Gram-positive** |  |  |  |  |  |
| *Staphylococcus aureus* | 77 | 0.18 (0.07 – 0.32) |  | 92 | 0.12 (0.03 – 0.25) |
| Streptococcus pyogenes | 10 | 0.01 (0.00 – 0.03) |  | 8 | 0.07 (0.03 – 0.12) |
| Group B *Streptococci* | 297 | 0.26 (0.18 – 0.35) |  | 416 | 0.24 (0.16 – 0.33) |
| Group D *Streptococci*/ *Enterococcus* | 8 | 0.03 (0.00 – 0.07) |  | 68 | 0.03 (0.01 – 0.06) |
| *Streptococcus pneumoniae* | 210 | 0.15 (0.11 – 0.21) |  | 157 | 0.17 (0.09 – 0.26) |
| Viridians streptococci | 0 |  |  | 13 | 0.01 (0.00 – 0.03) |
| Other *Streptococcus* species/unspecified | 36 | 0.06 (0.02 – 0.11) |  | 37 | 0.03 (0.02 – 0.04) |
| Other/ unspecified Gram-positives | 23 | 0.04 (0.02 – 0.07) |  | 12 | 0.00 (0.00 – 0.01) |
| **Gram-negative** |  |  |  |  |  |
| *Klebsiella* species | 150 | 0.15 (0.09 – 0.21) |  | 39 | 0.10 (0.04 – 0.18) |
| *Escherichia coli* | 170 | 0.15 (0.10 – 0.20) |  | 45 | 0.11 (0.06 – 0.18) |
| *Pseudomonas* species | 21 | 0.04 (0.02 – 0.08) |  | 6 | 0.03 (0.00 – 0.08) |
| *Enterobacter* species | 29 | 0.07 (0.03 – 0.13) |  | 15 | 0.06 (0.02 – 0.11) |
| *Serratia* species | 11 | 0.05 (0.02 – 0.10) |  | 3 | 0.08 (0.01 – 0.20) |
| *Proteus* species | 19 | 0.03 (0.01 – 0.05) |  | 2 | 0.01 (0.00 – 0.06) |
| *Salmonella* species | 68 | 0.06 (0.03 – 0.10) |  | 19 | 0.08 (0.05 – 0.13) |
| *Citrobacter* species | 12 | 0.07 (0.02 – 0.14) |  | 3 | 0.04 (0.00 – 0.11) |
| *Haemophilus influenzae* | 36 | 0.04 (0.02 – 0.07) |  | 10 | 0.01 (0.00 – 0.04) |
| *Neisseria meningitidis* | 25 | 0.02 (0.00 – 0.08) |  | 20 | 0.04 (0.00 – 0.10) |
| *Acinetobacter* species | 9 | 0.04 (0.01 – 0.08) |  | 9 | 0.10 (0.04 – 0.17) |
| Other/unspecified Gram-negatives | 114 | 0.11 (0.07 – 0.15) |  | 394 | 0.12 (0.02 – 0.25) |
| **Other pathogens** | 80 | **0.24 (0.17 – 0.32)** |  | **11** | **0.01 (0.00 – 0.02)** |
| **Total** | **1405** |  |  | **1381** |  |

**Table 2. Regional distribution of pathogens causing serious bacterial neonatal infections between 2008 – 2018.\***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **A) Causes of bacteraemia/sepsis** | **Central Africa** | **Eastern Africa** | **Southern Africa** | **West Africa** | **All regions** |
| **(4 studies)** | **(17 studies)** | **(13 studies)** | **(37 studies)** | **(71 studies)** |
| **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** |
| **All Gram positives** | **22** |  | **546** |  | **1306** |  | **1663** |  | **3537** |  |
| *Staphylococcus aureus* | 13 | 0.26 (0.14 – 0.40) | 296 | 0.20 (0.14 – 0.28) | 489 | 0.12 (0.07 – 0.19) | 1282 | 0.32 (0.25 – 0.39) | 2080 | 0.25 (0.21 – 0.29) |
| *Streptococcus* pyogenes | 2 | 0.04 (0.00 – 0.11) | 46 | 0.06 (0.05 – 0.08) | 50 | 0.04 (0.03 – 0.05) | 19 | 0.03 (0.00 – 0.09) | 117 | 0.04 (0.02 – 0.07) |
| Group B *Streptococci* | 2 | 0.08 (0.02 – 0.24) | 35 | 0.02 (0.00 – 0.06) | 290 | 0.10 (0.05 – 0.17) | 15 | 0.05 (0.00 – 0.27) | 342 | 0.06 (0.03 – 0.10) |
| Group D *Streptococci*/ *Enterococcus* | 1 | 0.04 (0.01 – 0.19) | 71 | 0.06 (0.05 – 0.08) | 242 | 0.08 (0.06 – 0.10) | 135 | 0.04 (0.02 – 0.06) | 449 | 0.05 (0.04 – 0.07) |
| *Streptococcus pneumoniae* | 0 |  | 31 | 0.03 (0.01 – 0.06) | 59 | 0.04 (0.03 – 0.05) | 24 | 0.01 (0.00 – 0.03) | 114 | 0.02 (0.01 – 0.04) |
| *Viridians streptococci* | 0 |  | 15 | 0.04 (0.02 – 0.06) | 17 | 0.06 (0.03 – 0.09) | 39 | 0.00 (0.00 0 0.01) | 71 | 0.03 (0.01 – 0.05) |
| Other *Streptococcus* species/unspecified | 4 | 0.07 (0.01 – 0.16) | 22 | 0.03 (0.01 – 0.06) | 72 | 0.04 (0.00 – 0.11) | 111 | 0.06 (0.03 – 0.10) | 209 | 0.05 (0.03 – 0.07) |
| Other/ unspecified Gram positives | - |  | 30 | 0.14 (0.00 – 0.43) | 87 | 0.03 (0.00 – 0.07) | 38 | 0.07 (0.01 – 0.18) | 155 | 0.06 (0.03 – 0.09) |
| **All Gram negatives** | **68** |  | **766** |  | **1603** |  | **1988** |  | **4425** |  |
| *Klebsiella* species | 38 | 0.34 (0.15 – 0.56) | 299 | 0.19 (0.13 – 0.25) | 732 | 0.25 (0.10 – 0.41) | 641 | 0.21 (0.14 – 0.28) | 1730 | 0.21 (0.16 – 0.27) |
| *Escherichia coli* | 17 | 0.17 (0.07 – 0.29) | 146 | 0.10 (0.07 – 0.14) | 241 | 0.08 (0.06 – 0.10) | 452 | 0.11 (0.06 – 0.16) | 856 | 0.10 (0.08 – 0.13) |
| *Pseudomonas* species | 0 |  | 15 | 0.01 (0.01 – 0.03) | 42 | 0.01 (0.01 – 0.02) | 132 | 0.05 (0.03 – 0.06) | 189 | 0.03 (0.02 – 0.04) |
| *Enterobacter* species | 4 | 0.07 (0.01 – 0.06) | 88 | 0.07 (0.03 – 0.12) | 79 | 0.02 (0.01 – 0.04) | 92 | 0.03 (0.02 – 0.05) | 263 | 0.04 (0.03 – 0.05) |
| *Serratia* species | 0 |  | 26 | 0.04 (0.01 – 0.09) | 86 | 0.04 (0.00 – 0.13) | 17 | 0.02 (0.00 – 0.06) | 129 | 0.03 (0.01 – 0.07) |
| *Proteus* species | 1 | 0.04 (0.01 – 0.09) | 9 | 0.02 (0.01 – 0.03) | 3 | 0.01 (0.00 – 0.04) | 113 | 0.04 (0.02 – 0.05) | 126 | 0.03 (0.02 – 0.04) |
| *Salmonella* species | 0 |  | 29 | 0.04 (0.02 – 0.06) | 98 | 0.07 (0.04 – 0.11) | 49 | 0.03 (0.01 – 0.05) | 176 | 0.04 (0.02 – 0.06) |
| *Citrobacter* species | 1 | 0.04 (0.01 – 0.19) | 11 | 0.07 (0.03 – 0.12) | 23 | 0.02 (0.01 – 0.03) | 87 | 0.03 (0.02 – 0.04) | 122 | 0.02 (0.02 – 0.04) |
| *Haemophilus influenzae* | 0 |  | 4 | 0.00 (0.00 – 0.01) | 2 | 0.00 (0.00 – 0.01) | 4 | 0.04 (0.01 – 0.09) | 10 | 0.01 (0.00 – 0.03) |
| *Neisseria meningitidis* | 0 |  | 12 | 0.01 (0.00 – 0.02) | 3 | 0.01 (0.00 – 0.02) | 2 | 0.04 (0.01 – 0.13) | 17 | 0.03 (0.00 – 0.08) |
| *Acinetobacter* species | 6 | 0.11 (0.03 – 0.21) | 54 | 0.05 (0.01 – 0.09) | 156 | 0.07 (0.03 – 0.11) | 83 | 0.02 (0.02 – 0.03) | 299 | 0.05 (0.03 – 0.07) |
| Other/unspecified Gram negatives | 1 | 0.04 (0.01 – 0.19) | 73 | 0.09 (0.03 – 0.17) | 118 | 0.04 (0.02 – 0.06) | 316 | 0.14 (0.07 – 0.23) | 508 | 0.10 (0.06 – 0.14) |
| Other pathogens | 0 |  | 9 | N/a (only 1 study) | 0 |  | 0 |  | **9** | **-** |
| **Total** | **90** |  | **1321** |  | **2909** |  | **3651** |  | **7971** |  |

 **Table 2 (continued). Regional distribution of pathogens causing serious bacterial neonatal infections between 2008 – 2018.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **B) Causes of meningitis** | **Central Africa** | **Eastern Africa** | **Southern Africa** | **West Africa** | **All regions** |
| **(2 studies)** | **(6 studies)** | **(5 studies)** | **(6 studies)** | **19 studies** |
| **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** | **N** | **Proportion (95% CI)** |
| **All Gram positives** | **1** |  | **67** |  | **845** |  | **40** |  |  |  |
| *Staphylococcus aureus* | 0 |  | 4 | 0.05 (0.01 – 0.12) | 71 | 0.02 (0.01 – 0.03) | 17 | 0.29 (0.17 – 0.42) | 92 | 0.12 (0.03 – 0.25) |
| *Streptococcus pyogenes* | 0 |  | 8 | 0.07 (0.03 – 0.12) | 0 |  | 0 |  | 8 | 0.07 (0.03 – 0.12) |
| Group B *Streptococci* | 1 | 0.50 (0.09 – 0.91) | 16 | 0.19 (0.11 – 0.28) | 394 | 0.31 (0.21 – 0.41) | 5 | 0.21 (0.01 – 0.52) | 416 | 0.24 (0.16 – 0.33) |
| Group D *Streptococci*/ *Enterococcus* | 0 |  | 3 | 0.03 (0.00 – 0.08) | 60 | 0.05 (0.03 – 0.06) | 5 | 0.08 (0.00 – 0.25) | 68 | 0.03 (0.01 – 0.06) |
| *Streptococcus pneumoniae* | 0 |  | 31 | 0.18 (0.08 – 0.30) | 113 | 0.12 (0.04 – 0.24) | 13 | 0.07 (0.00 – 0.70) | 157 | 0.17 (0.09 – 0.26) |
| *Viridians streptococci* | 0 |  | 2 | 0.02 (0.00 – 0.07) | 11 | 0.01 (0.01 – 0.02) | 0 |  | 13 | 0.01 (0.00 – 0.03) |
| Other *Streptococcus* species/unspecified | 0 |  | 2 | 0.04 (0.01 – 0.12) | 35 | 0.03 (0.02 – 0.04) | 0 |  | 37 | 0.03 (0.02 – 0.04) |
| Other/ unspecified Gram positives | 0 |  | 1 | 0.05 (0.01 – 0.24) | 13 | 0.01 (0.01 – 0.02) | 0 |  | 12 | 0.00 (0.00 – 0.01) |
| **All Gram negatives** | **3** |  | **83** |  | **431** |  | 48 |  |  |  |
| *Klebsiella* species | 1 | 0.50 (0.09 – 0.91) | 10 | 0.07 (0.03 – 0.12) | 18 | 0.22 (0.02 – 0.51) | 10 | 0.10 (0.03 – 0.19) | 39 | 0.10 (0.04 – 0.18) |
| *Escherichia coli* | 1 | 0.50 (0.09 – 0.91) | 16 | 0.11 (0.06 – 0.17) | 8 | 0.06 (0.02 – 0.13) | 20 | 0.22 (0.08 – 0.38) | 45 | 0.11 (0.06 – 0.18) |
| *Pseudomonas* species | 0 |  | 2 | 0.06 (0.00 – 0.20) | 1 | 0.02 (0.00 – 0.09) | 3 | 0.03 (0.00 – 0.10) | 6 | 0.03 (0.00 – 0.08) |
| *Enterobacter* species | 1 | 0.50 (0.09 – 0.91) | 9 | 0.10 (0.04 – 0.18) | 4 | 0.07 (0.03 – 0.16) | 1 | 0.07 (0.01 – 0.30) | 15 | 0.06 (0.02 – 0.11) |
| *Serratia* species | 0 |  | 0 |  | 3 | 0.08 (0.03 – 0.22) | 0 |  | 3 | 0.08 (0.01 – 0.20) |
| *Proteus* species | 0 |  | 2 | 0.01 (0.00 – 0.06) | 0 |  | 0 |  | 2 | 0.01 (0.00 – 0.06) |
| *Salmonella* species | 0 |  | 10 | 0.08 (0.03 – 0.13) | 7 | 0.12 (0.06 – 0.22)) | 2 | 0.06 (0.00 – 0.19) | 19 | 0.08 (0.05 – 0.13) |
| *Citrobacter* species | 0 |  | 1 | 0.11 (0.02 – 0.43) | 0 |  | 2 | 0.04 (0.01 – 0.13) | 3 | 0.04 (0.00 – 0.11) |
| *Haemophilus influenzae* | 0 |  | 2 | 0.02 (0.00 – 0.07) | 6 | 0.00 (0.00 – 0.01) | 2 | 0.04 (0.01 – 0.13) | 10 | 0.01 (0.00 – 0.04) |
| *Neisseria meningitidis* | 0 |  | 7 | 0.04 (0.00 – 0.13) | 9 | 0.02 (0.00 – 0.14) | 4 | 0.04 (0.00 – 0.11) | 20 | 0.04 (0.00 – 0.10) |
| *Acinetobacter* species | 0 |  | 9 | 0.10 (0.04 – 0.17) | 0 |  | 0 |  | 9 | 0.10 (0.04 – 0.17) |
| Other/unspecified Gram negatives | 0 |  | 15 | 0.06 (0.00 – 0.20) | 375 | 0.31 (0.28 – 0.33) | 4 | 0.06 (0.01 – 0.13) | 394 | 0.12 (0.02 – 0.25) |
| Other pathogens | 0 |  | 0 |  | 11 |  | 0 |  | **11** | **0.01 (0.00 – 0.02)** |
| **Total** | **4** |  | **150** |  | **1139** |  | **88** |  | **1381** |  |

\*The extracted culture data were baseline data expect for an intervention study from Senegal,81 where blood culture data were extracted before and after the intervention

**Table 3. Antimicrobial resistance in organisms causing serious bacterial neonatal infections across29 studies from sub-Saharan Africa, 2008 - 2018**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Central Africa** | **East Africa** | **Southern Africa** | **West Africa** | **All sub-regions** |
| **Antimicrobial** | **Number of isolates\*** | **% Resistance****(95% CI)** | **Number of isolates\*** | **% Resistance****(95% CI)** | **Number of isolates\*** | **% Resistance****(95% CI)** | **Number of isolates\*** | **% Resistance****(95% CI)** | **Number of isolates\*** | **% Resistance****(95% CI)** |
| ***Staphylococcus aureus*** |
| Cloxacillin36,79,84,93,97,98,110,130,131 | ND |  | 39 | 52% (36 – 68%) | ND |  | 227 | 41% (8 – 79%) | 266 | 40% (8 – 79%) |
| Oxacillin63,86,88,106,113,128 | ND |  | 82 |  | 11 |  | 23 |  | 116 |  |
| Gentamicin36,63,79,84,88,93,97,98,106,110,111,113,118,128,130,131 | ND |  | 119 | 21% (2 – 47%) | 8 | 63% (24 – 95%) | 279 | 26% (11 – 44%) | 406 | 27% (14 – 41%) |
| Methicillin24,86,108,112,118,122,125,133 | ND |  | 120 | 35% (13 – 62%) | 140 | 73% (57% - 86%) | 13 | 31% (13 – 58%) | 273 | 50% (30 – 70%) |
| Cefoxitin36,88,113 | ND |  | 49 | 27% (16 – 40%) | ND |  | 35 | 14% (3 – 28%) | 84 | 16% (3 – 37%) |
| Ciprofloxacin36,79,86,88,97,106,112,113,130 | ND |  | 98 | 26% (9 – 47%) | 3 | 0 (0 – 56%) | 172 | 13% (3 – 27%) | 273 | 16% (6 – 27%) |
| Vancomycin63,86,88,108,112 | ND |  | 50 | 0 (0 – 12%) | 5 | 0 (0 – 43%) | 23 | 35% (19 – 55%) | 78 | 5% (0 – 24%) |
| ***Klebsiella spp*** |
| Gentamicin63,74,79,84,86,88,91,97,98,106,108,110,113,118,123,128,130-132 | 28 | 86% (70 – 97%) | 150 | 71% (33 – 97%) | 188 | 83% (57 – 99%) | 211 | 47% (26 – 69%) | 577 | 66% (47 – 83%) |
| Cefotaxime36,63,86,88,91,98,106,123,128,132 | 28 | 98% (87 – 100%) | 56 | 52% (38 – 66%) | 176 | 89% (57 – 100%) | 49 | 54% (11 – 93%) | 309 | 78% (55 – 95%) |
| Ceftazidime36,74,86,88,91,97,98,106,110,113,123 | 12 | 92% (65 – 99%) | 69 | 36% (25 – 48%) | 130 | 96% (92 – 99%) | 139 | 44% (11 – 80%) | 350 | 58% (28 – 86%) |
| Ceftriaxone36,74,79,84,86,88,97,98,106,110,112,113,118,131 | ND |  | 160 | 53% (34 – 71%) | 51 | 94% (84 – 98%) | 186 | 38% (13 – 66%) | 397 | 49% (28 – 71%) |
| Ciprofloxacin36,63,79,86,91,97,106,112,113,118,128,130 | 12 | 92% (65 – 99%) | 144 | 14% (3 – 30%) | 98 | 58% (48 – 68%) | 135 | 26% (1 – 66%) | 389 | 30% (12 – 53%) |
| Amikacin63,108,113,123,128,131,132 | 16 | 19% (7 – 43%) | 47 | 5% (0 – 15%) | 110 | 21% (8 – 38%) | ND |  | 173 | 14% (7 – 23%) |
| Carbapenem†63,86,88,91,106,108,123,132 | 28 | 11% (1 – 26%) | 56 | 0 (0 – 6%) | 154 | 3% (0 – 11%) | 24 | 17% (1 – 10%) | 238 | 4% (1 – 10%) |
| Piperacillin tazobactam63,108,123,128,132 | 16 | 44% (23 – 67%) | 5 | 0 (0 – 43%) | 103 | 44% (22 – 67%) | ND |  | 124 | 37% (19 – 57%) |
| ***Escherichia* *coli* 36,63,74,79,84,86,88,91,93,97,98,106,108,110,112,113,118,123,128,130-132** |
| Ampicillin | 4 | 100% (51 – 100%) | 66 | 93% (75 – 100%) | 28 | 84% (67 – 97%) | 51 | 78% (55 – 96%) | 149 | 89% (77 – 97%) |
| Amoxycillin | 6 | 72% (24 – 100%) | 46 | 52% (13 – 90%) | 9 | 19% (0 – 57%) | 94 | 39% (11 – 71%) | 155 | 45% (24 – 66%) |
| Cefotaxime | 6 | 55% (10 – 96%) | 24 | 44% (21 – 68%) | 29 | 34% (12 – 69%) | 15 | 39% (12 – 69%) | 74 | 37% (12 – 66%) |
| Ceftazidime | 2 | 100% (34 – 100%) | 34 | 33% (18 – 51%) | 19 | 68% (43 – 88%) | 63 | 41% (10 – 76%) | 118 | 48% (26 – 72%) |
| Ceftriaxone | ND |  | 64 | 40% (18 – 63%) | 5 | 100% (57 – 100%) | 64 | 24% (4 – 50%) | 133 | 38% (19 – 58%) |
| Ciprofloxacin | ND |  | 40 | 4% (0 – 16%) | 8 | 64% (24 – 96%) | 52 | 13% (0 – 34%) | 100 | 14% (3 – 30%) |
| Gentamicin | 6 | 26% (0 – 74%) | 60 | 43% (13 – 75%) | 29 | 48% (9 – 88%) | 98 | 52% (13 – 90%) | 193 | 47% (25 – 69%) |
| Amikacin | 4 | 0 (0 – 49%) | 16 | 0 (0 – 7%) | 23 | 8% (0 – 34%) | ND |  | 43 | 1% (0 - 11%) |
| Carbapenem† | 6 | 0 (0 – 30%) | 24 | 0 (0 – 13%) | 21 | 1% (0 – 28%) | 8 | 0 (0 – 32%) | 59 | 0 (0 – 5%) |
| Piperacillin tazobactam | 4 | 25% (5 – 70%) | 1 | 0 (0 – 79%) | 18 | 9% (0 – 30%) | ND |  | 23 | 7% (0 – 27%) |

ND = no data. \*Cumulative number of isolates tested across cited studies with susceptibilities reported; not all studies tested susceptibilities to all listed antibiotics

†Includes Imipenem and Meropenem.