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, but such data are scarce from sub-Saharan Africa. We therefore completed 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 past decade (2008–18).**

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 84 534 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 or sepsis, *Staphylococcus aureus*, *Klebsiella* spp, and *Escherichia 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), *Streptococcus pneumoniae* 17% (9–6), and *S aureus* 12% (3–25). Resistance to WHO recommended β-lactams was reported in 614 (68%) of 904 cases and resistance to aminoglycosides in 317 (27%) of 1176 cases.**

Interpretation **Hospital-acquired neonatal infections and AMR are a major burden in Africa. More population-based neonatal infection studies and improved routine surveillance are needed to improve clinical care, plan health systems approaches, and address AMR. Future studies should be reported according to standardised reporting guidelines, such as STROBE-NI, to aid comparability and reduce research waste.**

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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 deaths in children younger than 5 years globally.[1] 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 of 27 deaths per 1000 livebirths.[1] Within sub-Saharan Africa, the burden of newborn deaths and neonatal mortality has an uneven geographical distribution.[2] Overall progress towards achieving the Sustainable Development Goals' (SDGs) target of 12 deaths per 1000 livebirths or fewer by 2030 within the region is slow; however, west and central Africa have the highest proportion of countries requiring major shifts in their mortality 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 the risk of mortality from neonatal infections is higher than the risk of motality from other neonatal conditions,[5] yet there is a substantial gap in aetiology-specific data from the region, with no published trends regarding which organisms provide the most risk. Across the region, geographical differences in the prevalence of causal pathogens might also exist, particularly given the diverse prevalence of maternal risk factors (HIV, urinary tract infections, and other antenatal infections), neonatal risk factors (preterm birth, low birthweight), and varying health system contexts, including differential rates of facility birth.[6] WHO guidelines for the management of suspected neonatal infections recommend empirical treatment with ampicillin (or benzylpenicillin; cloxacillin if staphylococcal infection is suspected) plus gentamicin sulphate as first-line therapy, with a third-generation cephalosporin as second-line therapy for non-responders or patients in whom drug-susceptibility testing of bacterial isolates indicates resistance to first-line therapy.[7] These guidelines

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Research in context

Evidence before this study

Neonatal deaths account for 47% of deaths in children aged younger than 5 years globally and infections are one of the leading causes of mortality. Linked to the 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 suboptimal hygiene, placing mothers and newborns at risk of hospital-acquired infections with associated morbidity, mortality, and cost. WHO recommends ampicillin (or benzylpenicillin; cloxacillin if staphylococcal infection is suspected) plus gentamicin sulphate as treatment for serious infections in neonates and infants younger than 2 months. Antimicrobial resistance is an increasing global threat leading to poor treatment outcomes and the potential to erode the gains in neonatal survival of the past few decades. Cause-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

To our knowledge, this is the first systematic review of causes of neonatal infection in sub-Saharan Africa, with extensive inputs from more than 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 are few population-based studies investigating causes of neonatal infection, yet clearly a huge burden of infection among neonates in hospitals, including hospital-acquired infections. *Staphylococcus aureus*, *Klebsiella* spp, and *Escherichia coli* were the leading reported causes of bacteraemia or sepsis, supporting the view that inappropriate 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 and present specific opportunities for prevention through maternal immunisation. The scarce 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 is also a need for strengthening capacity for microbiological diagnosis in local hospitals or facilities, 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 are urgently needed.

do not take into account timing of the infection (early *vs* late) or infants born in hospital and discharged only to return to the hospital at a later date with signs of an infection. The rise and spread of antimicrobial resistance (AMR) threatens treatment of neonatal infection, with the potential to erode 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 yet been explored.

Neonatal infection aetiology and AMR data are essential to inform policies and appropriate management strategies, yet remain an unknown in sub-Saharan Africa.[13] African biomedical research is often 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) checklist[20] 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 STROBE[21] checklist with 28 additional elements specifically relating to neonatal infection. The effect 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 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 Jan 1, 1980, to

June 6, 2018 (date of last search), which reported aetiology of invasive bacterial infections (bacteraemia, sepsis, septicaemia, or meningitis), and 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" (appendix pp 3–5). There were no language restrictions on the search.

Studies were excluded if they presented data aggregated with regions beyond sub-Saharan Africa; reported on a single pathogen (because this might lead to a biased estimate of the significance of that pathogen), solely high-risk subpopulations (such as very low birthweight, extremely premature, or having encephalopathy), or only newborns with potentially confounding comorbidities (malaria, tetanus, syphilis, tuberculosis, or HIV); contained erroneous, incomplete, or internally inconsistent data; or assessed the diagnostic accuracy of any test using only positive samples and not in the clinical context of suspected neonatal infection. Preterm and low birthweight 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 group B streptococcus 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) and duplicates were removed, and then reviewed individually by two investigators (UO and ENKA) to identify potentially eligible articles. All 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 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. Studies published between 1980 and 2007 were not included in the meta-analysis.

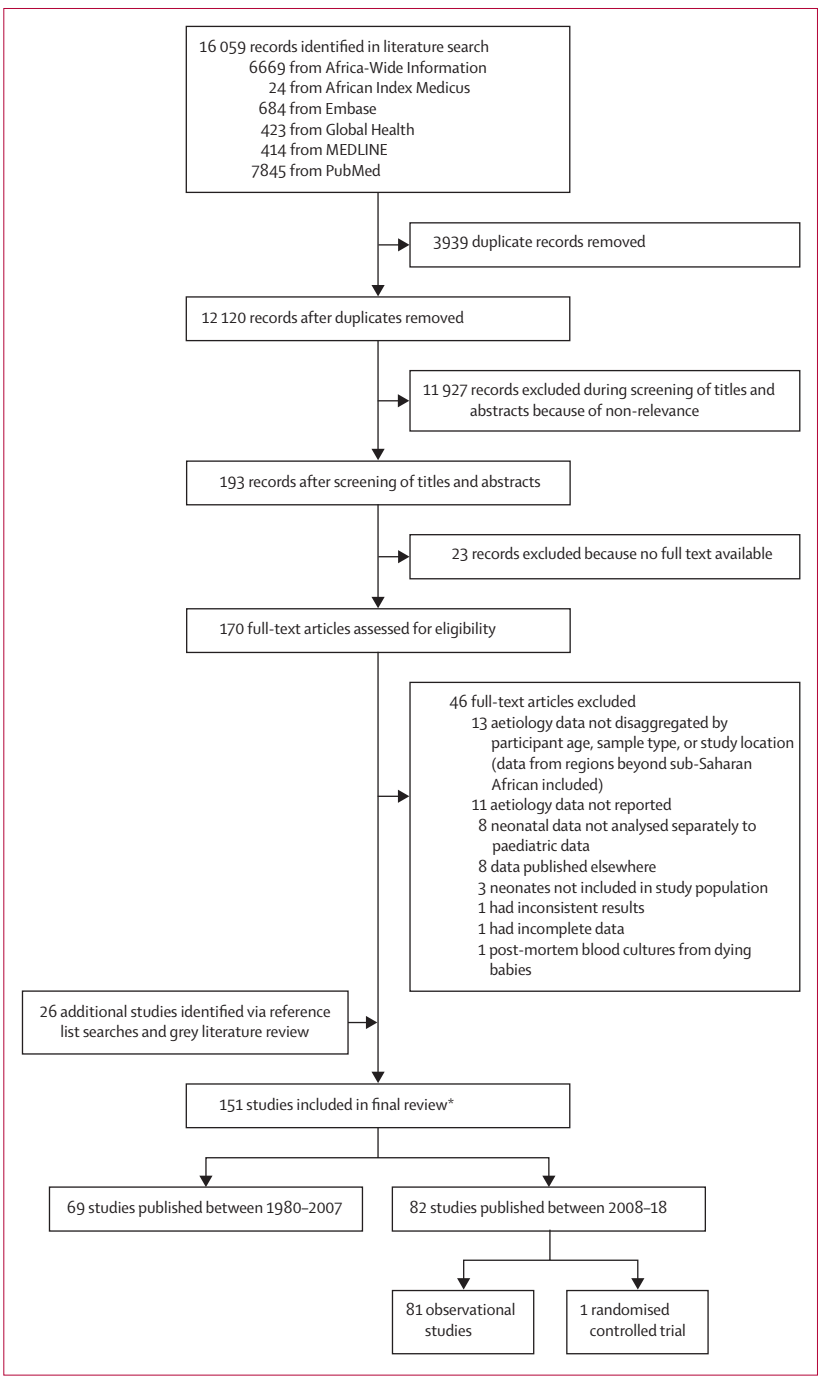

Figure 1: **Study selection**

Data analysis

Information was independently extracted from selected articles by two investigators (UO 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, when available, results of antimicrobial susceptibility testing. Previous reviews excluded coagulase-negative staphylococci (CoNS), which

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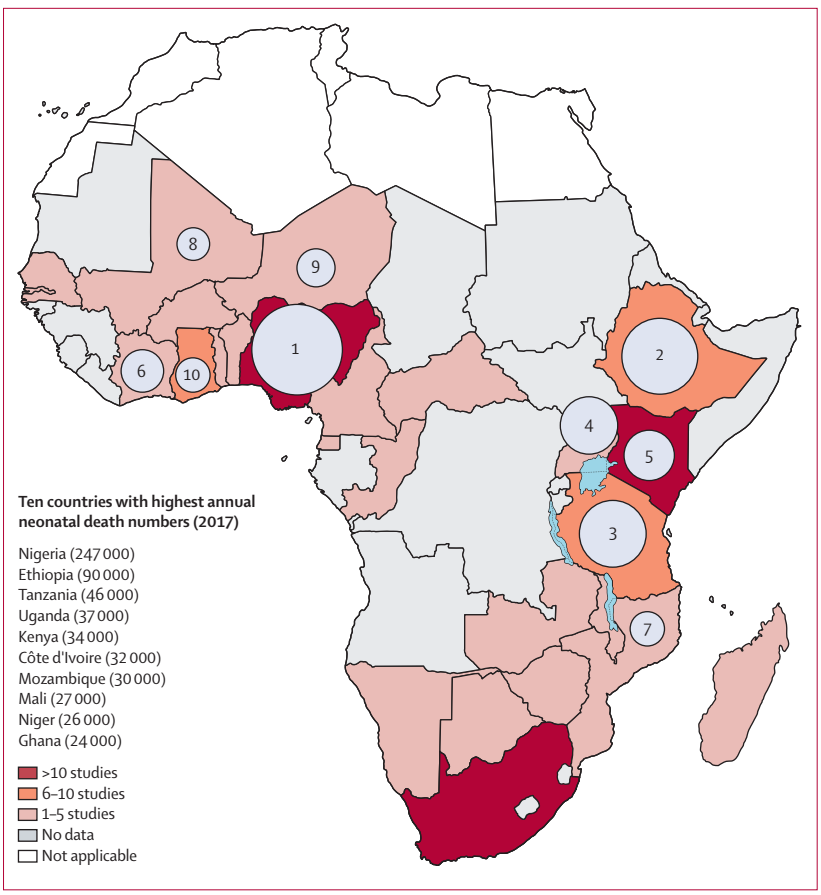

Figure 2: **Geographical representation of included studies and neonatal mortality**
Study locations and variation between in the number of studies per country reporting microbiological data on neonatal invasive bacterial infections (bacteraemia or sepsis, or meningitis) in sub-Saharan Africa between 1980 and 2018.

are potentially pathogenic in very preterm neonates who are in intensive care with ventilator support and in-dwelling devices that are 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 extraction were resolved by further review of the original papers.

Data reporting completeness was assessed by applying the STROBE-NI checklist (appendix pp 6–8) for studies published after 2007. Each study was assessed independently by two investigators (UO and ENKA), and item reporting classified as "not reported or unclear", "some information mentioned but insufficient", or "clear and detailed information provided".

To analyse the aetiological data, studies were arranged into two groups according to the year of publication: 1980–2007 and 2008–18. Data on invasive bacterial infections (bacteraemia or sepsis and meningitis) were collated for each period. However, to assess current aetiology and antimicrobial resistance, 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 stabilise variances.[25,26] We used random effects models to allow for interstudy heterogeneity.[27] We also did post-hoc subgroup analyses by country in each region, and other study characteristics (by data collection, data source, study area, study design, type of health-care facility, blood culture method, and geographical area) in countries with more than ten 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 16 059 records (figure 1), from which we identified 150 eligible studies (including nine theses and dissertations[28–36]) meeting our inclusion criteria. For 23 potentially eligible studies, we were unable to obtain the full text (appendix p 9). 75 (50%) of 150 included studies were identified only in African databases. One study[37] reported data from two west African countries and was counted as two separate studies, resulting in a total of 151 included studies, for which study characteristics can be found in the appendix (pp 10–28). 11 studies[29,32,37–45] were in French and the rest were in English; no studies in Portuguese or any African language were identified. The total study population included 84 534 neonates from 26 sub-Saharan African nations (figure 2), a third of which were from Nigeria (49 [33%] of 151).

132 studies investigated only neonatal patient populations, and from the other 19 studies[40,45–62] 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 whereas others reported data from predominantly rural populations: five studies from Kenya,[54,61,64,65,68] three from Mozambique,[59,72,73] two from Nigeria,[79,80] and one from Cameroon.[77] 88 studies involved prospective data collection, 61 were retrospective reviews (26 laboratory-based surveillance of aetiological data), and two studies had both retrospective and prospective components. There was one randomised trial,[28] one before-and-after study,[81] three case-control studies,[42,78,82] six observational cohort studies,[38,48,63,83–85] and the remaining 139 studies were cross-sectional designs.

69 studies were published between 1980 and 2007, with the remaining 82 studies published between

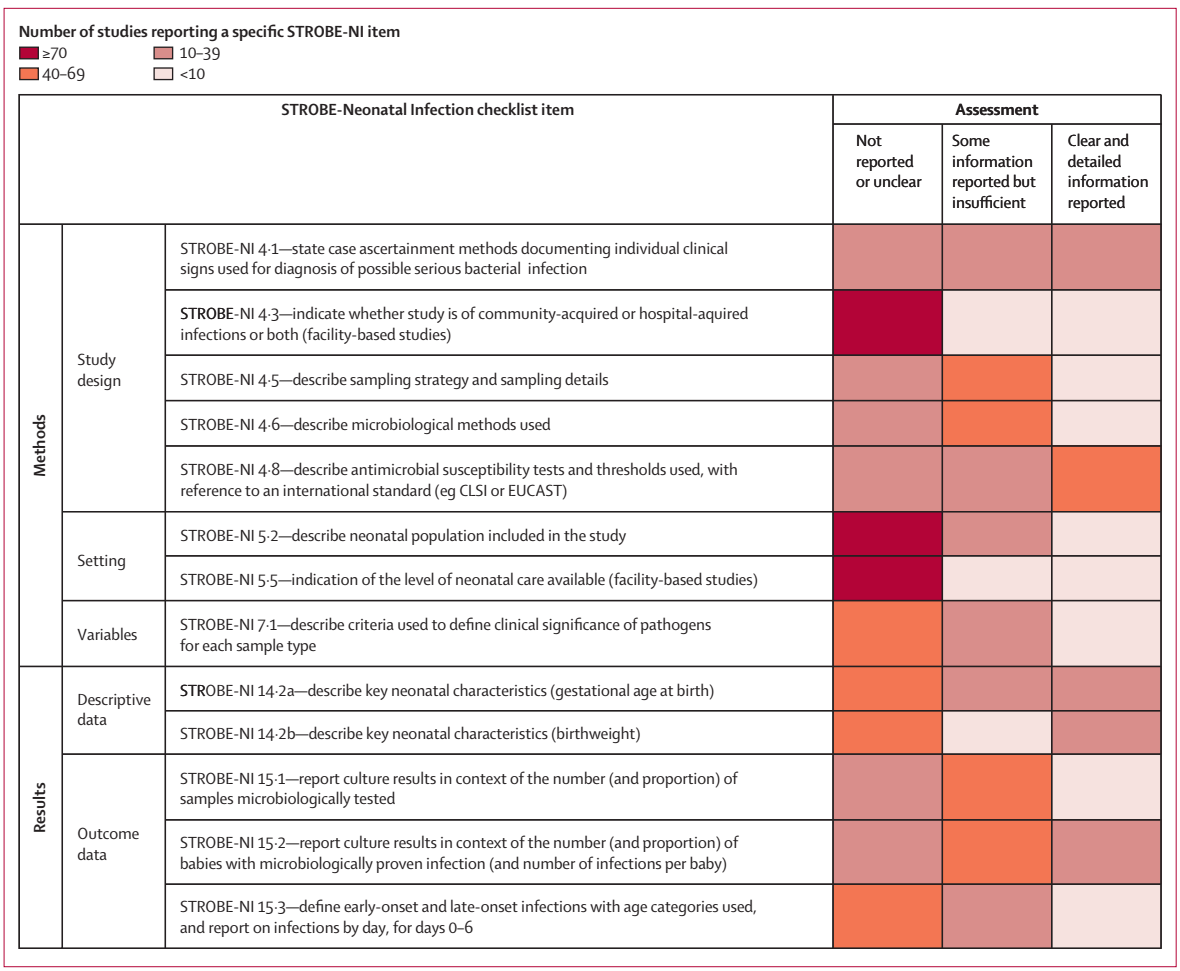

Figure 3: **Assessment of reporting completeness and quality of included studies**
A heat map showing grading of reporting completeness and quality for selected items according to Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI) criteria from 81 observational studies on neonatal infections in sub-Saharan Africa.

2008 and 2018. Figure 3 summarises the completeness of reporting from 81 observational studies (excluding 1 randomised trial) published after 2007, as outlined in the STROBE-NI checklist. Case ascertainment by physician diagnosis was reported in 44 (54%) of 81 observational studies, 26 of which documented the individual clinical signs used for the diagnosis of neonatal sepsis or meningitis. Only seven studies[36,63,74,86–89] reported using the WHO/IMCI clinical algorithm, two studies[90,91] used the French National Agency for Accreditation and Health clinical diagnostic criteria,[92] and one Ugandan study[93] reported using criteria adopted from International Paediatric Sepsis Consensus[94] and Indian Academy of Paediatrics.[95] 30 (37%) of these observational studies reported microbiological or laboratory criteria for diagnosis of neonatal infection syndromes (sepsis or meningitis), and 56 studies (69%) described microbiological sample type and sampling strategy (clinical indication *vs* routine sampling) as well as number of neonates sampled. 60 studies reported only blood culture data, 11 studies reported only cerebrospinal fluid data, and ten studies reported both blood and cerebrospinal fluid data of which only eight 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 studies[88,89,93,96–101] reported submission of two blood cultures from each neonate, whereas all other studies 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 (appendix p 29). Few studies (15 of 70; 21%) reported the timing of sampling in relation to antimicrobial administration. Blood volume for culture was reported by 36 (51%) studies, ranging from 0·4–5 mL. 62 (80%) of 70 studies included data on the number (and proportion) of blood samples cultured, number (and proportion) that were positive, and the number of pathogens isolated. Although 53 (76%) of these studies reporting blood

	1980–2007		2008–18	
	Number of isolates	Proportion (95% CI)	Number of isolates	Proportion (95% CI)
Bacteraemia or sepsis				
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 or 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 (0–0·05)	71	0·03 (0·01–0·05)
Other *Streptococcus* species	63	0·03 (0·01–0·05)	209	0·05 (0·03–0·07)
Other or unspecified Gram-positives	86	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 (0–0·02)	10	0·01 (0–0·03)
Neisseria meningitidis	0	..	17	0·03 (0–0·08)
Acinetobacter species	94	0·05 (0·02–0·07)	299	0·05 (0·03–0·07)
Other or 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	0·02 (0·01–0·04)
Meningitis				
Gram-positive				
S aureus	77	0·18 (0·07–0·32)	92	0·12 (0·03–0·25)
S pyogenes	10	0·01 (0–0·03)	8	0·07 (0·03–0·12)
Group B streptococcus	297	0·26 (0·18–0·35)	416	0·24 (0·16–0·33)
Group D streptococcus or enterococcus	8	0·03 (0–0·07)	68	0·03 (0·01–0·06)
S pneumoniae	210	0·15 (0·11–0·21)	157	0·17 (0·09–0·26)
Viridians streptococci	0	..	13	0·01 (0–0·03)
Other *Streptococcus* species	36	0·06 (0·02–0·11)	37	0·03 (0·02–0·04)
Other or unspecified Gram-positives	23	0·04 (0·02–0·07)	12	0 (0–0·01)

(Table 1 continues on the next page)

culture data also described the methods used, the 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; appendix p 29), and one study reported using both. Between eight and 44% of cultures were positive among studies using automated techniques, and 14–87% among studies using manual methods.

Of 19 studies that reported disaggregated cerebrospinal fluid culture data, only 11[31,48,63,68,73,89,90,102–105] reported on both the number of lumbar punctures carried out and the number of these that were positive. Across these studies, 1738 lumbar punctures were reported, of which 135 (8%) were positive, with positivity ranging from 0 to 100% (appendix p 30).

41 (51%) studies clearly described the antimicrobial susceptibility tests used, the most widely reported of which was the Kirby-Bauer disc diffusion method. Only few studies reported use of Etest[72,73,106,107] or microdilution[59] on all or some isolates. Several established guidelines for resistance interpretation were referenced: Clinical and Laboratory Standards Institute (CLSI; 36 studies),[24,31,36,56,59,63,70,72,73,84,86–88,93,96,99,103,106,108–125] EUCAST,[107] British Society for Antimicrobial Therapy,[60,61,71,97] and French Society of Microbiology.[91]

Only 12 (15%) of 81 observational 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", referring to being born in a particular facility rather than at home or a different health facility, and only one study[34] mentioned all neonatal presentations to the neonatal unit. Important neonatal characteristics such as gestational age and birthweight were each reported by fewer than 38 (47%) of the studies, most of which presented data in discrete categories with summary statistics (medians and ranges). Data on comorbidities (eg, encephalopathy) and feeding were rarely reported, and only six of the included studies reported neonatal HIV exposure or testing.

71 (88%) of 81 studies did not report the level or type of neonatal care (appendix p 32), with the context poorly described across all studies, regarding basic neonatal care (resuscitation and breastfeeding), intensive neonatal care (oxygen supplementation, invasive and non-invasive respiratory support, and indwelling devices), nurse-to-patient ratio, and non-microbiological investigations. Only 25 (31%) of 81 studies reported the antimicrobial guidelines used for empirical management of neonatal sepsis (appendix p 31).

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 study[126] and two Nigerian studies[88,89] stated criteria used to identify the clinical significance of detected organisms. Only 13 (16%) of 81 studies listed pathogens excluded as contaminants. Although often reported as contaminants, several studies reported CoNS,[24,34,38,55,71,74,86–89,96,98,103,106,109,111–113,115–118,120,126–132] viridians streptococci,[61,85] *Staphylococcus epidermidis*,[84,99,125,133,134] *Bacillus* spp,[106,130] and *Micrococcus* spp[122] as neonatal pathogens. However, among the studies that reported CoNS as a pathogen, few provided a rationale for identifying the clinical significance of the infection.[24,36,122,131,132,135] Four studies[36,60,107,121] cited laboratory quality control measures, and only one study[107] sent samples to an external laboratory for confirmation.

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

Only one paper[136] delineated hospital-acquired and community-acquired pathogens, with a similar prevalence of *Klebsiella* spp among neonates with hospital-acquired infection (31% [10/32] *vs* 17% [8/48]; p=0·126) and a similar prevalence of *S aureus* among those with community-acquired infection (17% [8/48] *vs* 13% [4/32]; p=0·609). Three studies[61,63,72] specifically examined community-acquired infections, and two studies[24,81] 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 because of the poor reporting of these data across the studies.

	1980–2007		2008–18	
	Number of isolates	Proportion (95% CI)	Number of isolates	Proportion (95% CI)
(Continued from previous page)				
Gram-negative				
Klebsiella species	150	0·15 (0·09–0·21)	39	0·10 (0·04–0·18)
E 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 (0–0·08)
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 (0–0·06)
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 (0–0·11)
H influenzae	36	0·04 (0·02–0·07)	10	0·01 (0–0·04)
N meningitidis	25	0·02 (0–0·08)	20	0·04 (0–0·10)
Acinetobacter species	9	0·04 (0·01–0·08)	9	0·10 (0·04–0·17)
Other or 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 (0–0·02)

Bacteraemia or sepsis pathogens represent data pooled across 43 studies in 1980–2007, and 71 studies in 2008–18. Meningitis pathogens represent data pooled across 38 studies in 1980–2007, and 19 studies in 2008–18.

Table 1: **Pooled pathogen prevalence estimates of neonatal infections in sub-Saharan Africa, by period of publication**

Table 2 shows the regional distribution of reported causes of neonatal bacteraemia or sepsis. In central and southern Africa, *Klebsiella* spp was the predominant isolate representing 34% (95% CI 15–56) of bacteraemic infections in central Africa and 25% (10–41) in southern Africa; whereas *S aureus* was the most common isolate accounting for 20% (14–28) of cases in east Africa and 32% (25–39) in west Africa (table 2). We observed both intraregional 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 appendix pp 33–53). We completed further sensitivity analyses stratifying for important study characteristics, which showed significant differences in the prevalence of *S aureus* bacteraemia between countries in each region (appendix pp 76–79). 1020 (80%) of 1282 *S aureus* isolates in west Africa were reported from Nigerian studies. Of these, the prevalence of *S aureus* bacteraemia was higher among retrospective studies compared with prospective studies (47% *vs* 30%, p=0·043), and among studies reported from tertiary health-care facilities compared with those from secondary facilities and (36% *vs* 23%; p=0·020; appendix pp 80–86).

Table 1 also shows pooled pathogen prevalence associated with neonatal meningitis by time period. Group B streptococcus (26%, 95% CI 18–35) was the most commonly reported cause of meningitis between 1980 and 2007, followed by *S aureus* (18%, 7–32), *S pneumoniae* (15%, 11–21), *Klebsiella* spp (15%, 9–21), and *E coli* (15%, 10–20). Between 2008 and 2018, group B streptococcus, *S pneumoniae*, and *S aureus* remained the major reported causes of neonatal meningitis (table 1). Group B streptococcus was predominant in east Africa (19%, 11–28) and southern Africa (31%, 21–41), although most of the data were from South Africa (table 2). We observed variable heterogeneity (0–87%) in the cause of neonatal meningitis between regions (figure 4 and appendix pp 54–75).

63 (78%) of 81 included studies reported in-vitro antibiotic susceptibility data but only 29 studies specified individual pathogens and reported isolates numbers. No study reported minimum inhibitory concentrations to the antibiotics reported, making it difficult to assess intermediate or decreased susceptibility. Table 3 presents findings for the most prevalent isolates.

22 studies[36,63,74,79,84,86,88,91,93,97,98,106,112,113,118,123–127,132,135] reported resistance among *Klebsiella* spp (predominantly *K pneumoniae,* with few cases of *Klebsiella oxytoca*), documenting a non-susceptibility to gentamicin of 66% (95% CI 47–83), ceftriaxone of 49% (28–71), and cefotaxime of 78% (55–95). Reported resistance to amikacin, an alternative to gentamicin, was low (14%, 7–23).[63,113,124–126,132,135] High frequencies of extended spectrum β-lactamase (ESBL)-producing *K pneumoniae* were reported from South Africa,[24,126,131,132] Tanzania (49%; 24/50),[86] and Botswana (60%; 16/27).[135] In one South African study,[126] resistance to piperacillin-tazobactam, was higher among ESBL-producing *K pneumoniae* isolates (90%; 9/10) than in the non-ESBL producing isolates (43%; 3/7). Non-susceptibility to carbapenems was reported in at least one country in each

	Central Africa		Eastern Africa		Southern Africa		West Africa		All regions	
	n	Proportion (95% CI)	n	Proportion (95% CI)	n	Proportion (95% CI)	n	Proportion (95% CI)	n	Proportion (95% CI)
Bacteraemia or sepsis										
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 (0–0·11)	46	0·06 (0·05–0·08)	50	0·04 (003–0·05)	19	0·03 (0–0·09)	117	0·04 (0·02–0·07)
Group B streptococci	2	0·08 (0·02–0·24)	35	0·02 (0–0·06)	290	0·10 (0·05–0·17)	15	0·05 (0–0·27)	342	0·06 (0·03–0·10)
Group D streptococci or 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 (0–0·03)	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 (0–0·01)	71	0·03 (0·01–0·05)
Other *Streptococcus* species or unspecified	4	0·07 (0·01–0·16)	22	0·03 (0·01–0·06)	72	0·04 (0–0·11)	111	0·06 (0·03–0·10)	209	0·05 (0·03–0·07)
Other or unspecified Gram positives	..	..	30	0·14 (0–0·43)	87	0·03 (0–0·07)	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 (0–0·13)	17	0·02 (0–0·06)	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 (0–0·04)	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 (0–0·01)	2	0 (0–0·01)	4	0·04 (0·01–0·09)	10	0·01 (0–0·03)
Neisseria meningitidis	0	..	12	0·01 (0–0·02)	3	0·01 (0–0·02)	2	0·04 (0·01–0·13)	17	0·03 (0–0·08)
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 or 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	0·02 (0·01–0 ·04)	0	..	0	..	9	0·02 (0·01–0 ·04)
Meningitis										
All Gram positives	1	..	67	..	697	..	40	..	805	..
S 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)
S 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 or enterococcus	0	..	3	0·03 (0–0·08)	60	0·05 (0·03–0·06)	5	0·08 (0–0·25)	68	0·03 (0·01–0·06)
S pneumoniae	0	..	31	0·18 (0·08–0·30)	113	0·12 (0·04–0·24)	13	0·27 (0–0·70)	157	0·17 (0·09–0·26)
Viridians streptococci	0	..	2	0·02 (0–0·07)	11	0·01 (0·01–0·02)	0	..	13	0·01 (0–0·03)
Other *Streptococcus* species or 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 or unspecified Gram positives	0	..	1	0·05 (0·01–0·24)	13	0·01 (0·01–0·02)	0	..	14	0 (0–0·01)
All Gram negatives	3	..	83	..	431	..	48	..	565	..
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)
E 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 (0–0·20)	1	0·02 (0–0·09)	3	0·03 (0–0·10)	6	0·03 (0–0·08)
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 (0–0·06)	0	..	0	..	2	0·01 (0–0·06)
Salmonella species	0	..	10	0·08 (0·03–0·13)	7	0·12 (0·06–0·22)	2	0·06 (0–0·19)	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 (0–0·11)

(Table 2 continues on next page)

	Central Africa		Eastern Africa		Southern Africa		West Africa		All regions	
	n	Proportion (95% CI)	n	Proportion (95% CI)	n	Proportion (95% CI)	n	Proportion (95% CI)	n	Proportion (95% CI)
(Continued from previous page)										
H influenzae	0	..	2	0·02 (0–0·07)	6	0 (0–0·01)	2	0·04 (0·01–0·13)	10	0·01 (0–0·04)
N meningitidis	0	..	7	0·04 (0–0·13)	9	0·02 (0–0·14)	4	0·04 (0–0·11)	20	0·04 (0–0·10)
Acinetobacter species	0	..	9	0·10 (0·04–0·17)	0	..	0	..	9	0·10 (0·04–0·17)
Other or unspecified Gram negatives	0	..	15	0·06 (0–0·20)	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	0·01 (0–0·02)	0	..	11	0·01 (0–0·02)

The extracted culture data were baseline data except for an intervention study from Senegal,[81] where blood culture data were extracted before and after the intervention. Neonatal bacteraemia or sepsis pathogens represent data pooled across four studies from central Africa, 17 studies from eastern Africa, 13 studies from southern Africa, and 37 studies from west Africa. Neonatal meningitis pathogens represent data pooled across two studies from central Africa, six studies from eastern Africa, five studies from southern Africa, and six studies from west Africa.

Table 2: **Regional distribution of pathogens causing serious bacterial neonatal infections, 2008–18**

region,[63,86,88,91,106,125,126,132] with low resistance rates (4%, 95% CI 1–10).

Pooled prevalence of non-susceptibility of *E coli* isolates to ampicillin[63,74,79,84,86,88,98,106,112,113,118,124,125,127,132,135] was 89% (95% CI 77–97) and was 47% (25–69) to gentamicin.[63,74,79,84,86,88,91,97,98,106,126,127,113,118,132,135,123–125] A third of *E coli* isolates were resistant to ceftriaxone.[74,79,84,86,88,97,98,106,112,113,118,122,133] The reported prevalence of ESBL-producing *E coli* isolates ranged from 12% (7/58) in South Africa[24] to 46% (10/22) in Tanzania.[86] Resistance to piperacillin-tazobactam was also low (7%, 0–27).[63,125,132,135] Only two studies reported carbapenem resistant isolates: one each from Tanzania[86] and South Africa.[126]

For *S aureus* infection, WHO recommends first-line treatment with cloxacillin, which has a pooled resistance of 40% (95% CI 8–79),[79,84,93,97,98,123,124,127] and gentamicin, for which the pooled resistance was 27% (14–41).[63,79,84,88,93,97,98,106,111,113,118,123,124,127,135] Meticillin resistance was reported by eight studies,[24,86,112,118,121,126,131,137] with 50% (30–70) of isolates non-susceptible. Resistance to cefoxitin, the recommended antibiotic to identify meticillin-resistant *S aureus* strains (MRSA) when using the disk diffusion method,[138] 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 group B streptococcus infections documented non-susceptibility to any antibiotic.[124,135]

Discussion

To our knowledge, this study is the largest systematic review of neonatal infection aetiology and AMR from sub-Saharan Africa, and a strength of the study 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 more relevant studies than would have been identified only through the use of usual major databases, although central Africa is still poorly represented. Our review represents a notable increase in studies from Africa compared with previous reviews in which the number of included sub-Saharan African studies ranged from seven to 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.

In many sub-Saharan African hospitals, sick newborn children do not routinely undergo microbiological investigations.[133,139] Considering that the annual need-to-treat population for possible serious bacterial infection in sub-Saharan Africa is 2·6 million, with around ten cases of possible severe bacterial infection diagnosed for each associated neonatal death,[140] the 31 874 blood cultures and 1742 lumbar punctures reported in the studies identified in this review (of which 25% and 8% respectively were culture-positive) revealed 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 six had a result), and even fewer had a lumbar puncture result.[139] A lumbar puncture is part of the diagnostic work-up for all sick newborn children with possible serious bacterial infection to identify meningitis and give the most appropriate antibiotic for the correct time period. Routine investigations for neonates such as blood cultures and lumbar punctures 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 colleagues[15] reported group B streptococcus, *S pneumoniae*, *Salmonella* spp, and *S aureus*, as dominant pathogens associated with invasive bacterial infection in African neonates. However, this study did not distinguish between causes of bacteraemia or sepsis and meningitis, or assess sub-

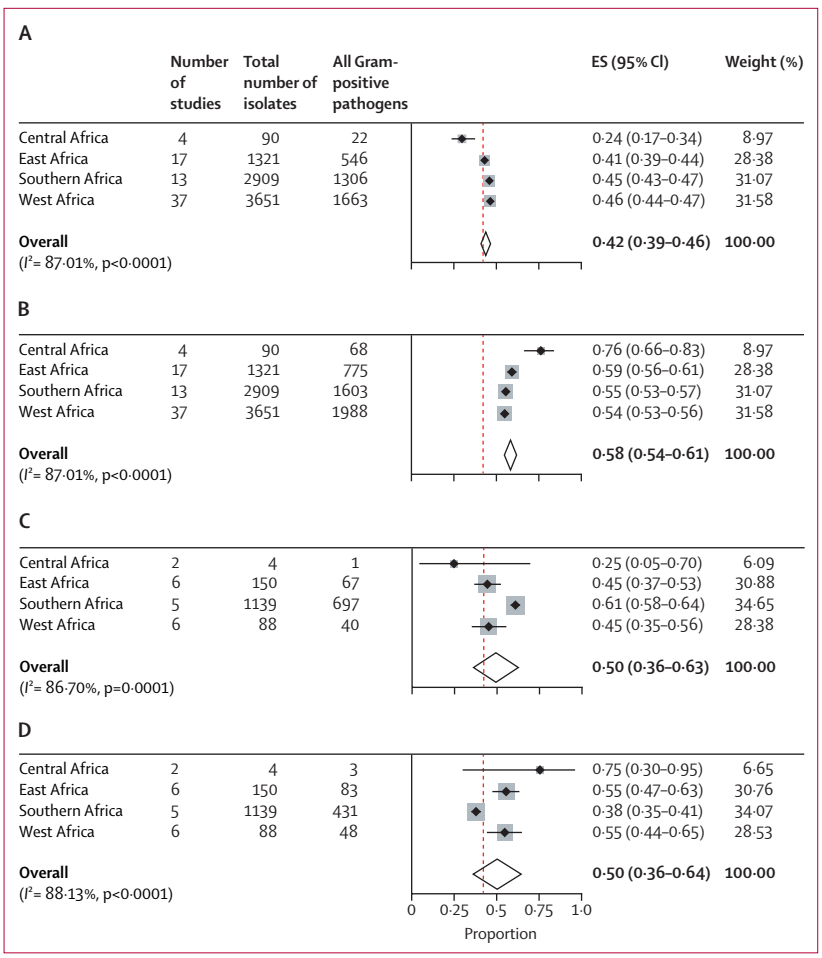

Figure 4: **Forest plot of neonatal bacteraemia and meningitis, 2008–18**
A summary estimate and 95% CI of the prevalence of pathogens causing invasive neonatal infection across regions in sub-Saharan Africa from studies published between 2008 and 2018: (A) Gram-positive and (B) Gram-negative causes of neonatal bacteraemia or sepsis; (C) Gram-positive and (D) Gram-negative causes of neonatal meningitis. Weights are from random effects analysis. ES=estimate (proportion). I^2 and p values are measures for heterogeneity between the studies.

regional differences in pathogen distribution. In our review, *S aureus* was a more important cause of bacteraemia or sepsis over the same period (1980–2007), whereas group B streptococcus and *S pneumoniae* accounted for over a 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 and sepsis, especially in hospital settings, whereas group B streptococcus and *S pneumoniae* are important causes of neonatal meningitis with differences in pathogen distribution between and within regions. Group B streptococcus and *S pneumoniae* present specific opportunities for interventions, for example by maternal immunisation.[141–143]

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 group B streptococcus infections compared with 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,[9,144] a specific focus on group B streptococcus research in South Africa could have led to geographical publication bias. In spite of this potential bias, true geographical differences in disease epidemiology or regional differences in virulence and host susceptibility cannot be ruled out.[141,145] Variability in group B streptococcus disease might also reflect differences in case ascertainment (especially among home births), before antibiotic treatment, blood culture or lumbar puncture practices, variability in laboratory capacity, and the quality of microbiological investigations.[145] A South African study[146] reported significant variation in neonatal invasive group B streptococcus disease incidence by province with differential access to health care, poor laboratory capacity, and varying diagnostic procedures.[146] Because early-onset group B streptococcus infection usually occurs within the first 24 h of life, with most presenting within hours of being born,[147] those born at home or with limited access to health care are missed because they die at home.[148]

Another notable finding was the difference in the prevalence of *S aureus* bacteraemia or 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 or sepsis differed substantially according to how data was collected and the level of health-care facility. Potential explanations for the higher prevalence of infection in retrospective studies than in prospective studies include variability in what is defined as clinically significant and missing data, be that from ineffective study design or reporting. The higher prevalence of *S aureus* bacteraemia or 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,[149,150] and nosocomial outbreaks can go unrecognised.

Klebsiella spp and *E coli* normally colonise the maternal genital tract and can cause early-onset neonatal infections.[151] However, multidrug-resistant ESBL-producing organisms observed in several studies are usually acquired from contaminated hospital environments,[152] with increased risk of mortality, especially among preterm babies.[153] 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 the spread of strains from one hospital to another due to patient transfers.[154] This finding underlines the crucial need for

	Central Africa		East Africa		Southern Africa		West Africa		All sub-regions	
	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										
Cloxacillin[36,79,84,93,97,98,123,124,127]	ND	..	39	52% (36–68)	ND	..	227	41% (8–79)	266	40% (8–79)
Oxacillin[63,86,88,106,113,135]	ND	..	82	..	11	..	23	..	116	..
Gentamicin[36,63,79,84,88,93,97,98,106,111,113,118,123,124,127,135]	ND	..	119	21% (2–47)	8	63% (24–95)	279	26% (11–44)	406	27% (14–41)
Meticillin[24,86,126,112,118,121,127,137]	ND	..	120	35% (13–62)	140	73% (57–86)	13	31% (13–58)	273	50% (30–70)
Cefoxitin[36,88,113]	ND	..	49	27% (16–40)	ND	..	35	14% (3–28)	84	16% (3–37)
Ciprofloxacin[36,79,86,88,97,106,112,113,123]	ND	..	98	26% (9–47)	3	0 (0–56)	172	13% (3–27)	273	16% (6–27)
Vancomycin[63,86,88,112,126]	ND	..	50	0 (0–12)	5	0 (0–43)	23	35% (19–55)	78	5% (0–24)
***Klebsiella* spp**										
Gentamicin[63,74,79,84,86,88,91,97,98,106,113,118,123–127,132,135]	28	86% (70–97)	150	71% (33–97)	188	83% (57–99)	211	47% (26–69)	577	66% (47–83)
Cefotaxime[36,63,86,88,91,98,106,125,132,135]	28	98% (87–100)	56	52% (38–66)	176	89% (57–100)	49	54% (11–93)	309	78% (55–95)
Ceftazidime[36,74,86,88,91,97,98,106,113,127,132]	12	92% (65–99)	69	36% (25–48)	130	96% (92–99)	139	44% (11–80)	350	58% (28–86)
Ceftriaxone[36,74,79,84,86,88,97,98,106,112,113,118,124,127]	ND	..	160	53% (34–71)	51	94% (84–98)	186	38% (13–66)	397	49% (28–71)
Ciprofloxacin[36,63,79,86,91,97,106,112,113,118,123,135]	12	92% (65–99)	144	14% (3–30)	98	58% (48–68)	135	26% (1–66)	389	30% (12–53)
Amikacin[63,126,113,124,125,132,135]	16	19% (7–43)	47	5% (0–15)	110	21% (8–38)	ND	..	173	14% (7–23)
Carbapenem†[63,86,88,91,106,125,126,132]	28	11% (1–26)	56	0 (0–6)	154	3% (0–11)	24	17% (1–10)	238	4% (1–10)
Piperacillin tazobactam[63,125,126,132,135]	16	44% (23–67)	5	0 (0–43)	103	44% (22–67)	ND	..	124	37% (19–57)
Escherichia coli										
Ampicillin[36,63,74,79,84,86,88,98,106,112,118,124,125,127,132,135]	4	100% (51–100)	66	93% (75–100)	28	84% (67–97)	51	78% (55–96)	149	89% (77–97)
Amoxycillin[36,63,79,84,86,88,91,97,98,113,118,123,125]	6	72% (24–100)	46	52% (13–90)	9	19% (0–57)	94	39% (11–71)	155	45% (24–66)
Cefotaxime[36,63,86,91,98,106,125,132,135]	6	55% (10–96)	24	44% (21–68)	29	34% (12–69)	15	39% (12–69)	74	37% (12–66)
Ceftazidime[36,74,86,88,91,97,98,106,113,123,127,132]	2	100% (34–100)	34	33% (18–51)	19	68% (43–88)	63	41% (10–76)	118	48% (26–72)
Ceftriaxone[74,79,84,86,88,97,98,106,112,113,124,127]	ND	..	64	40% (18–63)	5	100% (57–100)	64	24% (4–50)	133	38% (19–58)
Ciprofloxacin[36,63,79,86,88,97,106,112,123,135]	ND	..	40	4% (0–16)	8	64% (24–96)	52	13% (0–34)	100	14% (3–30)
Gentamicin[36,63,74,79,84,86,88,91,97,98,106,113,118,123–127,132,135]	6	26% (0–74)	60	43% (13–75)	29	48% (9–88)	98	52% (13–90)	193	47% (25–69)
Amikacin[63,124–126,132,135]	4	0 (0–49)	16	0 (0–7)	23	8% (0–34)	ND	..	43	1% (0–11)
Carbapenem†[63,86,88,91,106,125,126,132]	6	0 (0–30)	24	0 (0–13)	21	1% (0–28)	8	0 (0–32)	59	0 (0–5)
Piperacillin tazobactam[63,125,132,135]	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.

Table 3: **Antimicrobial resistance in organisms causing serious bacterial neonatal infections across 29 studies from sub-Saharan Africa, 2008–18**

improved infection prevention measures particularly in congested neonatal units with high antimicrobial exposure and poor infection control.[14,81,150,155]

In our study, we identified a high prevalence of resistance to recommended empirical therapies, in keeping with reports from older paediatric and adult populations in Africa.[9,156,157] Similar high resistance rates have been reported among South Asian neonates, including in India where an excess of 80 000 neonates die each year from resistance-attributable neonatal sepsis.[8,158] Alternative therapeutic options such as fluoroquinolones, carbapenems, and piperacillin with tazobactam are scarce, expensive, and inappropriate for use in community settings, and are therefore considered antibiotics of last resort.[11,159] We have found low to moderate rates of resistance to these antimicrobials in studies included in this review. Our high reported rates of MRSA are in keeping with a previous review MRSA in Africa,[160] 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.[161] 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.[162] 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 aetiological 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 similar neonatal mortality, particularly in conflict and post-conflict countries. Second, there was high heterogeneity between studies, although this was expected because of the differences in case ascertainment, microbiological methods, and data collection methods between the included studies. Third, because most of the studies reported collection of only one sample, it was difficult to identify instances that a specific organism should be considered a contaminant or not, particularly in the case of CoNS which we excluded from our review. 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, stillbirths, and disability.[163] With poor quality care, dangers of infection transmission and AMR threaten the gains of neonatal survival. Reducing the burden of neonatal infection mortality and morbidity requires a multipronged approach. Infection prevention and surveillance of hospital-acquired infections is crucial together with expanded and improved clinical microbiology services for pathogen detection and optimum treatment. Tailored local antimicrobial guidelines, implementation of antimicrobial stewardship policies, and effective antimicrobial surveillance are necessary strategies to tackle AMR.[9] Innovative point-of-care diagnostics would be transformative. Although there is potential for maternal vaccines against group B streptococcus 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, and many neonates never receive treatment when sick.[6] The scarcity of aetiology and AMR data from community-based studies poses a crucial 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.[148] No such study has yet been completed in Africa where rates of infection and pathogens seen are likely to be different from those seen in Asia.

Our findings also underscore the current research waste 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 waste of data in high-burden regions.[20] However, although 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 health-care systems, while 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.

Declaration of interests

BK reports grants from the National Institutes for Health, National Institute for Health Research Biomedical Research Centres, Wellcome Trust, and the Thrasher Foundation for research into infection and immunity in neonates. All other authors declare no competing interests.

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