Antimicrobial resistance in Enterobacterales infections among children in sub-Saharan Africa : a systematic review and meta-analysis

Kowalski, Morgane; Minka Epse Obama, Basilice Mireille; Catho, Gaud; Dewez, Juan Emmanuel; Merglen, Arnaud; Ruef, Micaela Claude; Andrey, Diego Olivier; Hassoun-Kheir, Nasreen; De Kraker, Marlieke; Combescure, Christophe; Emonet, Stéphane Paul; Galetto-Lacour, Annick; Wagner, Noémie

How to cite

KOWALSKI, Morgane et al. Antimicrobial resistance in Enterobacterales infections among children in sub-Saharan Africa : a systematic review and meta-analysis. In: EClinicalMedicine, 2024, vol. 70, p. 102512. doi: 10.1016/j.eclinm.2024.102512

This publication URL: https://archive-ouverte.unige.ch//unige:178037
Publication DOI: 10.1016/j.eclinm.2024.102512

Antimicrobial resistance in Enterobacterales infections among children in sub-Saharan Africa: a systematic review and meta-analysis

Morgane Kowalski,[a] Basilice Minka Obama,[b,c] Gaud Catho,[d,e] Juan Emmanuel Dewez,[f] Arnaud Merglen,[g] Micaela Ruef,[a] Diego O. Andrey,[h,i] Nasreen Hassoun-Kheir,[j] Marlieke E. A. de Kraker,[j] Christophe Combescure,[k] Stephane Emonet,[d,h] Annick Galetto-Lacour,[l,m] and Noémie Wagner[b,f,m,*]

[a]Children's Hospital, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[b]Paediatric Infectious Diseases Unit, Children's Hospital, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[c]Regional Hospital Centre for Ebolowa, Ebolowa, Cameroon
[d]Division of Infectious Diseases, Central Institute, Hospital of Valais, Switzerland
[e]Infection Control Division, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[f]Medical Department, Médecins Sans Frontières, Operational Centre Geneva, Geneva, Switzerland
[g]Division of General Paediatrics, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[h]Division of Infectious Diseases, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[i]Division of Laboratory Medicine, Department of Diagnostics, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[j]Infection Control Programme, Geneva University Hospitals and Faculty of Medicine, WHO Collaborating Centre, Geneva, Switzerland
[k]Centre for Clinical Research, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[l]Division of Paediatric Emergency Medicine, Children's Hospital, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

eClinicalMedicine 2024;70: 102512
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102512

Summary

Background The burden of antimicrobial resistance (AMR) has been estimated to be the highest in sub-Saharan Africa (SSA). The current study estimated the proportion of drug-resistant Enterobacterales causing infections in SSA children.

Methods We searched MEDLINE/PubMed, Embase and the Cochrane Library to identify retrospective and prospective studies published from 01/01/2005 to 01/06/2022 reporting AMR of Enterobacterales causing infections in sub-Saharan children (0–18 years old). Studies were excluded if they had unclear documentation of antimicrobial susceptibility testing methods or fewer than ten observations per bacteria. Data extraction and quality appraisal were conducted by two authors independently. The primary outcome was the proportion of Enterobacterales resistant to antibiotics commonly used in paediatrics. Proportions were combined across studies using mixed-effects logistic regression models per bacteria and per antibiotic. Between-study heterogeneity was assessed using the I^2 statistic. The protocol was registered with PROSPERO (CRD42021260157).

Findings After screening 1111 records, 122 relevant studies were included, providing data on more than 30,000 blood, urine and stool isolates. *Escherichia coli* and *Klebsiella* spp. were the predominant species, both presenting high proportions of resistance to third-generation cephalosporins, especially in blood cultures: 40.6% (95% CI: 27.7%–55%; I^2: 85.7%, number of isolates (n): 1032) and 84.9% (72.8%–92.2%; I^2: 94.1%, n: 2067), respectively. High proportions of resistance to other commonly used antibiotics were also observed. *E. coli* had high proportions of resistance, especially for ampicillin (92.5%; 95% CI: 76.4%–97.9%; I^2: 89.8%, n: 888) and gentamicin (42.7%; 95% CI: 30%–56.5%; I^2: 71.9%, n: 968). Gentamicin-resistant *Klebsiella* spp. were also frequently reported (77.6%; 95% CI: 65.5%–86.3%; I^2: 91.6%, n: 1886).

Interpretation High proportions of resistance to antibiotics commonly used for empirical treatment of infectious syndromes were found for Enterobacterales in sub-Saharan children. There is a critical need to better identify local patterns of AMR to inform and update clinical guidelines for better treatment outcomes.

Funding No funding was received.

DOI of original article: https://doi.org/10.1016/j.eclinm.2024.102508
*Corresponding author. Children Hospital, Rue Willy-Donzé 6, Geneva 1205, Switzerland.
E-mail address: noemie.wagner@hug.ch (N. Wagner).
[m]Joint senior authors.

Keywords: Antimicrobial resistance; Children; Neonates; Africa; Enterobacterales; *E coli*; *Klebsiella*

Research in context

Evidence before this study

It has been estimated that sub-Saharan Africa (SSA) has the world's highest incidence of deaths due to antimicrobial resistance (AMR). However, in most areas in SSA, access to diagnostic and microbiological testing is limited and empirical data on the burden of AMR are scarce, particularly for children. The eleven previous meta-analyses on drug-resistant infections in SSA presented alarming rates of AMR but included relatively few studies, some of which were outdated. Most did not focus on children. A previous literature review, published in The Lancet Infectious Diseases in 2018, identified 18 studies on AMR conducted among sub-Saharan children. Several articles have been published since then, therefore an updated systematic review expands the current knowledge base. We searched MEDLINE/PubMed, Embase and the Cochrane Library on the 01/06/2022 to identify retrospective and prospective studies published from 01/01/2005 to 01/06/2022 reporting AMR of Enterobacterales causing infections in sub-Saharan children (0–18 years old).

Added value of this study

We included 122 studies providing data on more than 30,000 bacterial isolates from blood, stool or urine samples obtained from children with a clinical infection in SSA. To the best of our knowledge, this is the most comprehensive review on this subject to date, which provides important new insights in the threat of AMR in SSA.

Compared to previous reviews, our meta-analysis found a higher proportion of Enterobacterales resistant to third-generation cephalosporins in children in this region. In the reported blood cultures, 40.6% of *Escherichia coli* and 84.9% of *Klebsiella* spp. were resistant to these antibiotics. At the same time, these isolates were reported to have high proportions of resistance to other commonly used antibiotics like amoxicillin, gentamicin, ciprofloxacin or cotrimoxazole. There is, therefore, a significant risk of administering inappropriate empirical treatments to children with infections in SSA.

Implications of all the available evidence

This review supports the growing view that there is an urgent need to strengthen local-level capacities in microbiological analysis in SSA to support antimicrobial stewardship measures. Coupling this with other measures, such as strengthening infection prevention and control in healthcare services, could dramatically improve patients' outcomes in the region.

Introduction

Despite recent improvements, sub-Saharan Africa (SSA) has the highest child mortality rates globally, with 74 deaths per 1000 live births.[1] Infectious diseases, including pneumonia, malaria, diarrhoeal diseases and sepsis, remain the major cause of death among children under five.[2] Bloodstream infections are responsible for 6% of newborn deaths and 14% of childhood deaths worldwide.[3,4] Enterobacterales are among the most common bacteria isolated from blood cultures in low- and middle-income countries. In SSA, *Klebsiella* spp. predominate in the blood isolates of newborns and *Salmonella* spp. predominate among older children.[3,5]

Concurrently, antimicrobial resistance (AMR) has become a major global health problem. It has been estimated that SSA has the world's highest risk of death due to AMR. In western SSA, the death rate attributed to AMR exceeds 100 per 100,000 individuals.[6] Enterobacterales are species with a high potential for resistance acquisition.[6] Thus, they may be a major contributor to AMR in children in SSA.

In this context, treating childhood infections in SSA effectively has become increasingly challenging. Access to microbiological testing is limited, and treatment decisions are mainly based on empirical recommendations that may not be adapted to current AMR patterns.

Data are essential to measure the extent of this problem. Unfortunately, they remain scarce in SSA, mainly due to limited access to microbiology laboratories and the lack of AMR surveillance network.[7] Few meta-analyses on the prevalence of AMR in SSA have been conducted, and most are outdated, did not focus on children and could only include a small numbers of studies. However, they all showed that Enterobacterales displayed very high rates of resistance to ampicillin, gentamicin and third-generation cephalosporins (3GCs), which represent the first- and second-line treatments for sepsis in children.[3,8,9]

The present study summarised the current publicly available evidence on the prevalence of Enterobacterales' AMR among children with infections in SSA.

Methods

The study protocol is available online (PROSPERO registry CRD42021260157) and was informed by the PRISMA guidelines for systematic reviews,[10] Our primary outcome was the proportion of Enterobacterales

resistant to 3GCs in clinical samples of children with an infection in SSA, secondary outcomes included resistance to alternative antibiotics (penicillin, other cephalosporins, carbapenem, quinolones, aminoglycosides and cotrimoxazole).

As it is a meta-analysis, an ethics approval was not required.

Search strategy and selection criteria

We used a combination of MeSH and free terms (Appendix pp 3–5) to search MEDLINE/PubMed, Embase and the Cochrane Library. No language restrictions were applied. To be included, studies had to be published between 1 January 2005 and 1 June 2022 and present AMR data on Enterobacterales in clinical samples from paediatric patients (0–18 years old) in SSA. We chose these dates to gather as much information as possible and to capture the spread of ESBL in more recent years. We included studies conducted in both inpatient and outpatient settings. Studies from South Africa were excluded because the availability of AMR data from this country is greater than for other SSA countries, and we did not want South Africa data to have an excessive weight in our results as we are primarily interested in less studied and less well equipped SSA countries.[8]

We excluded case reports, systematic reviews and meta-analyses, studies not reporting on Enterobacterales or on the prevalence of AMR in paediatric patients, studies that did not clearly document the antimicrobial susceptibility testing methods used. We also excluded studies reporting fewer than ten observations per bacteria as small studies may disrupt models with random effects in meta-analyses of trials.[11] As this review focused on Enterobacterales causing infections, we excluded studies reporting solely on screening isolates.

Titles and abstracts were screened, followed by full-text analysis of selected manuscripts. Five investigators (MK, NW, BO, GC or AG) selected eligible studies, independently and in duplicate. Disagreements were resolved via consensus by a third investigator (NW or AG). The investigators discussed the inclusion criteria in detail and in depth before the screening process and held weekly meetings to discuss any doubts about their application to standardise their approach as much as possible. We contacted the authors of papers if relevant data was missing. We used Covidence systematic review software to manage article selection (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org).

Data extraction

Two investigators independently entered the following data into Excel® spreadsheets: year of publication and data collection, country, sample size, participants' ages, population characteristics (e.g. HIV+, sickle cell disease, neonates, malnutrition, etc.), study design, types of clinical samples, and bacterial susceptibilities to reported antibiotics. We recorded data on the prevalence of antibiotic non-susceptibility for the following Enterobacterales: *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp., *Shigella* spp., *Salmonella* typhi and Enterobacterales species that were not classified into subspecies. The *Proteus, Citrobacter, Providencia, Morganella* and *Serratia* genera were grouped into a category named 'other Enterobacterales'. This review focused on specimens from blood, urine and stool (only *Salmonella* and *Shigella* spp. were considered in stools), but data from other sample types were also extracted.

Definitions

Children have been defined as individuals aged 0–18 years old, with neonates as a subgroup aged 0–1 month old.

For clarity and ease of reading throughout this paper, Enterobacterales considered resistant or intermediately resistant to a given antibiotic were group into one group that we called « resistant ».

Extended-spectrum cephalosporin-resistant (ESCR) Enterobacterales have been defined as phenotypically non-susceptible to either ceftriaxone, ceftazidime or cefotaxime.[12] Carbapenem-resistant Enterobacterales (CRE) have been defined as phenotypically non-susceptible to either imipenem, meropenem or ertapenem. Susceptibility profiles were accepted if they were based on phenotypic (disk diffusion, E-test MIC determination and double-disk synergy test for ESBL) or genotypic methods.

Sample types other than blood, urine, stool and cerebrospinal fluid, were grouped as 'other samples' (mainly throat, middle ear and wound swabs). 'All samples' refers to all of the reported categories.

Risk of bias

Each study's quality and risk of bias were assessed using the Newcastle–Ottawa assessment scale (NOS) for cohort studies. The NOS is a risk of bias assessment tool for observational studies that is recommended by the Cochrane Collaboration.[13] We adapted the Newcastle–Ottawa Quality Assessment Form for Cohort Studies to assess the risk of bias in the included studies.[13] Five reviewers (MK, NW, BO, GC or AG) independently and in duplicate assessed risks of bias, and any disagreements were resolved by consensus (Appendix pp 6–7).

Statistical analysis

Due to the expected between-study heterogeneity, proportions of resistance were combined across studies by systematically using models with random effects. For this purpose, we used mixed-effects logistic regression models per bacteria and per antibiotic, with a random intercept.[14] The approach's advantage is that it does not require a continuity correction when some studies report zero events. Between-study heterogeneity was assessed

using the I^2 statistic.[15] Planned univariable subgroup analyses (neonates versus children, geographical regions, year of publication and sample types) investigated potential sources of heterogeneity by introducing them as variables in the models. Leave-one-out sensitivity analyses were conducted to identify influential studies. The level of significance was set at 5%, and statistical tests were two-sided. Statistical analyses were carried out using R software, v4.0.2 (R Core Team, 2020).[16]

Role of the funding source

There was no funding source for this study.

All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results

Overview of the studies included

The initial search yielded 1111 non-duplicated records. After reviewing titles and abstracts, 525 titles were selected for full-text screening, of which 122 fulfilled the inclusion criteria. The most common reasons for exclusion were studies not reporting on Enterobacterales (N: 95) or not reporting a separate proportion of AMR for paediatric patients (N: 88) (Fig. 1).[17–35,36–72,73–102,103–138] Five authors were contacted because relevant data were missing, and they provided the missing information from two studies, allowing their inclusion.[61,107]

Characteristics of the included studies

The 122 included studies reported AMR data from 24 African countries, of which most came from eastern African countries (56/122, 45.9%) (Fig. 2). There were 54 (54/122, 44.3%) prospective studies and 35 (35/122, 28.7%) cross-sectional studies. The remaining studies used observational and retrospective case–control and cohort designs. Of these 122 studies, 47 (38.5%) reported data from blood cultures, 40 (32.8%) reported results from stools, and 16 (13%) reported results from urine. Seventeen studies (13.9%) focused on neonates, the remainder focused either on older children either on a mixed population including neonates and children. A number of studies selected specific risk groups, including six (4.9%) on malnourished children, two on children with HIV and one on children with sickle cell disease (Appendix pp 8–15). No information was reported to distinguish community-acquired from healthcare-acquired, or healthcare-associated infections. Over 160,000 samples were collected across all the studies, yielding more than 30,000 Enterobacterales isolates.

Proportion of resistant Enterobacterales in blood, urine and stool samples

Blood samples

Of 1032 *E. coli* isolates from positive blood samples, we found a pooled ESCR proportion of 40.6% (95% CI: 27.7%–55%; I^2: 85.7%, number of studies (N): 19). Of 2067 *Klebsiella* spp. isolates, pooled ESCR proportion was 84.9% (95% CI: 72.8%–92.2%; I^2: 94.1%, N: 26). By contrast, a pooled proportion of only 3.3% (95% CI: 1.1%–9.9%; I^2: 82.7%, N: 13) of *Salmonella* spp. were ESCR on 2196 positive blood cultures. Of the 750 *Salmonella typhi* isolated in blood culture, none was ESCR (Table 1 and Appendix pp 16–17).

Carbapenem resistance was uncommon, with a pooled proportion of CRE in blood of 1.9% (95% CI: 0.5%–7.2%, N: 5) on 106 *E. coli* isolates and 2% (95% CI: 0.5%–7.5%, N: 11) on 897 *Klebsiella* spp isolates (Table 1 and Appendix p 18-19 for forest plots).

E. coli isolates were generally resistant to ampicillin (pooled resistance proportion 92.5%; 95% CI: 76.4%–97.9%, N: 13) and frequently also to ciprofloxacin (25.3%; 95% CI: 16.3%–37.1%, N: 17), cotrimoxazole (80.1%; 95% CI: 67.8%–88.5%, N: 14) and to gentamicin (42.7%; 95% CI: 30%–56.5%, N: 17). The pooled proportion of *E. coli* resistance to amikacin was lower, at 10.4% (95% CI: 16.3%–37.1%, N: 5).

We observed even higher pooled resistance proportions for *Klebsiella* spp. in blood samples, with isolates showing resistance pooled proportions of 77.6% to gentamicin on 1886 isolates (95% CI: 65.5%–86.3; N: 22), 89.9% to cotrimoxazole on 1653 isolates (95% CI: 79.7%–95.3%, N: 14), 35.4% to ciprofloxacin on 1862 isolates (95% CI: 22.7%–50.6%, N: 20) and 23.8% to amikacin on 782 isolates (95% CI: 10.3%–45.8%, N: 11) (Table 1 and Appendix pp 20–22 for forest plots).

Salmonella spp. and *S. typhi* found in blood cultures were generally resistant to cotrimoxazole but remained highly sensitive to ciprofloxacin (Table 1).

Urine samples

Pooled estimates ESCR proportions were 41.2% (95% CI: 30.1%–53.3%, N: 13) on 221 urine samples positive for *E. coli* and 55.5% (95% CI: 28.1%–79.9%, N: 4) on 78 urine samples positive for *Klebsiella* spp. (Table 1).

Stool samples

In stool samples, the susceptibility of *Shigella* spp. and *Salmonella* spp. to 3GCs was usually conserved, with a low pooled proportions of ESCR of 9% on 384 isolates (95% CI: 2.9%–25%, N: 12) and 11.8% on 425 isolates (95% CI: 9.0%–15.2%, N: 4), respectively. As in blood cultures, *Salmonella* spp. were generally resistant to cotrimoxazole, but remained highly sensitive to ciprofloxacin (Table 2).

The proportion of Enterobacterales resistant to the various antibiotics calculated for all the samples together can be found in the Appendix on page 23.

Neonates

Sixteen studies presented data specific for neonates from 2118 positive blood cultures. Resistance to 3GCs in blood cultures was slightly but not significantly

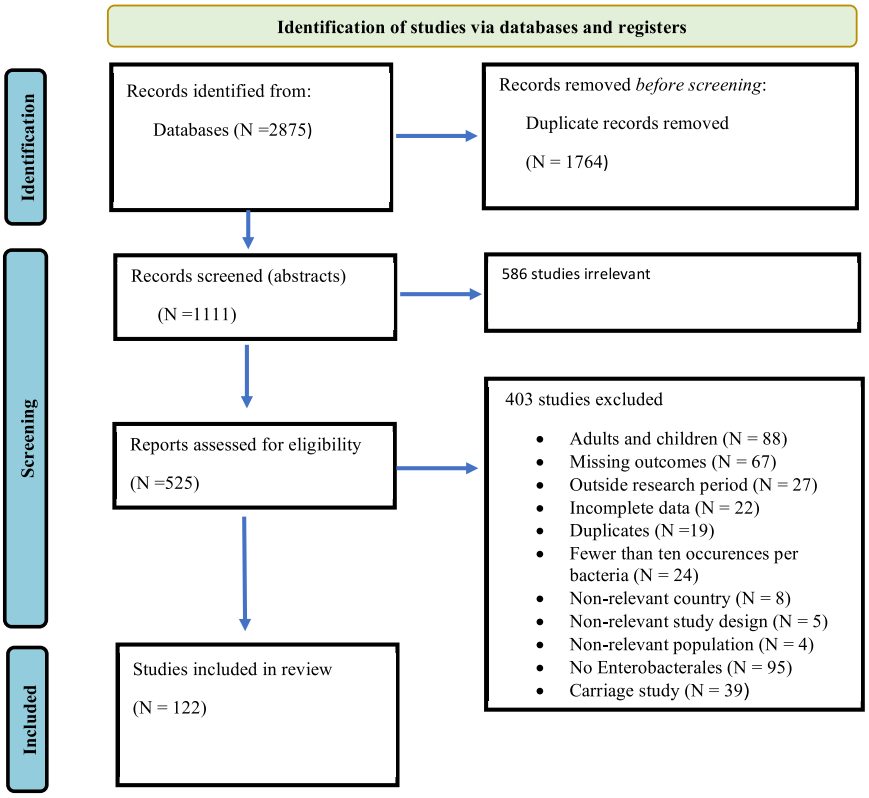

Fig. 1: Study selection process based on the PRISMA flowchart. Abbreviations: N = number of studies.

higher among neonates than among other children for *E. coli* and *Klebsiella* spp., with pooled resistance proportions of 48.6% (63/129; 95% CI: 36.3%–61.0%; I^2: 46.9%) and 85.8% (579/728; 95% CI: 67.6%–94.6%; I^2: 91.9%), respectively. However, we observed a significant higher proportion of *E. coli* resistant to gentamicin (56.0%; 95% CI: 32.0%–77.5%, N: 3) and *Klebsiella* spp resistant to amikacin in neonates (42.6%; 95% CI: 17.7%–71.9%, N: 6) compared to children (Table 3).

Heterogeneity

Across all the samples and specifically in blood cultures, the heterogeneity in proportion of ESCR Enterobacterales and Enterobacterales resistant to aminoglycosides were very high (Table 4 and Appendix pp 16–17 and 20–22). The following potential sources of heterogeneity were investigated.

Age groups (neonates versus children)

In blood cultures, no significant difference was found between neonates and children in the prevalence of ESCR *E. coli* (*p*-value 0.34) and ESCR *Klebsiella* spp. (*p*-value 0.83). However, proportion of *E coli* resistant to gentamicin was significantly higher among neonates (*p*-value 0.03). The factors affecting the heterogeneity of *E. coli* resistant to amikacin could not be investigated due to the small number of studies (N: 5) reporting this outcome.

Significant higher proportion of *Klebsiella* spp. resistant to amikacin was found among neonates (*p*-value 0.01) but no significant difference was found for *Klebsiella* spp. resistant to gentamicin (*p*-value 0.97) (Table 4 and Appendix pp 24–30).

Regions

Reported resistance proportions among blood cultures revealed no significant differences between regions for ESCR *Klebsiella* spp, for *Klebsiella* spp. resistant to gentamicin and amikacin, or for *E. coli* resistant to gentamicin. The only significant inter-regional difference was a lower prevalence of ESCR *E. coli* in southern SSA compared to eastern and western regions. However, as only one study for the southern region was included, this result should be treated cautiously (Table 4, Appendix pp 24–30).

Period

We noticed a non-significant trend towards an overall increase in ESCR *E. coli* and ESCR *Klebsiella* spp. in blood cultures from 2004 to 2022 (Table 4 and Appendix pp 24–27). Although no significant differences in *E. coli* resistant to gentamicin were found over time, we found

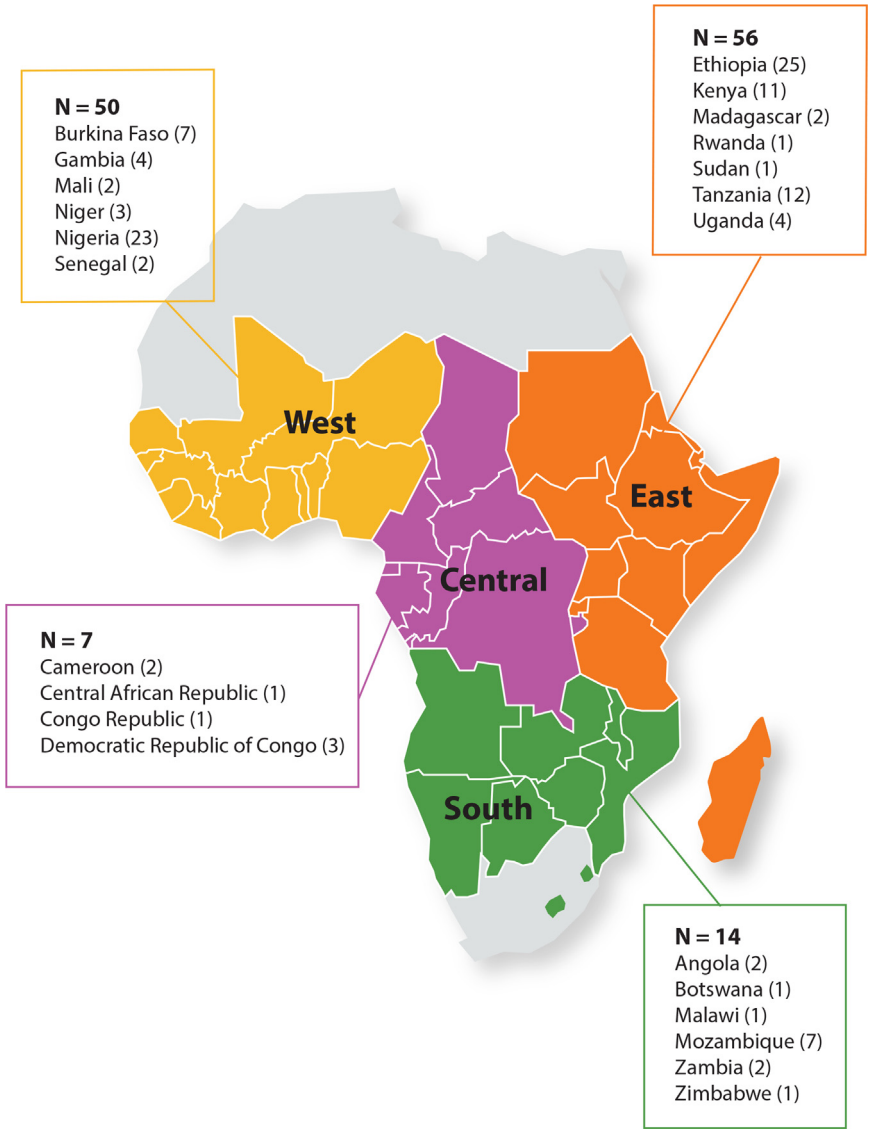

Fig. 2: Study location. Abbreviations: N = number of studies by region; Country (number of studies by country). The total number of countries does not correspond to the total number of studies included because two studies examined multiple countries in different regions.

significant increases in *Klebsiella* spp. resistant to gentamicin and amikacin when comparing 2004–2010, 2011–2015 and 2016–2022 (p-value < 0.01) (Appendix pp 28–30).

Quality of studies and risk of bias assessment

Because their respective studies included subgroups of children, such as neonates, 33.6% (57/122) of the populations examined were not representative of SSA's general paediatric population. In about 7.3% (9/122) of studies, descriptions of participants were considered insufficient because children's precise ages were not given. In 31.1% of studies (38/122), the samples were not sterile (stool, urine, smear) with the risk of interpreting colonising bacteria as pathogenic (exposure bias) (Appendix pp 6–7).

Discussion

We identified 122 studies from SSA providing data on AMR from more than 30,000 Enterobacterales isolates obtained from children and neonates with bacterial infections. In blood samples, we found high proportions of ESCR *E. coli and Klebsiella* spp., of 40.6% and 84.9% of isolates, respectively. Most *E. coli* isolates were resistant to ampicillin. Around half of *E. coli* and most *Klebsiella* spp. isolates were resistant to gentamicin. In addition, 25.3% of *E. coli* and 35.4% of *Klebsiella* spp.

Blood cultures	*Escherichia coli*				*Klebsiella* spp.				*Salmonella typhi*				*Salmonella* spp.			
	% (CI)	I^2	n	N	% (CI)	I^2	n	N	% (CI)	I^2	n	N	% (CI)	I^2	n	N
ESCR	40.6 (27.7–55)	85.7	1032	19	84.9 (72.8–92.2)	94.1	2067	26	0 (0–100)	0	750	7	3.3 (1.1–9.9)	82.7	2196	13
CRE	1.9 (0.5–7.2)	0	106	5	2 (0.5–7.5)	66.7	897	11	0 (0–23.2)	..	14	1	0 (0–N/A)	0	881	2
Ampicillin	92.5 (76.4–97.9)	89.8	888	13	..	..	..	..	63.8 (27.2–89.3)	92.5	700	6	77.9 (58.1–89.9)	94.8	2372	13
Amoxicillin and clavulanic acid	51.8 (30.4–72.6)	87.7	517	11	82.2 (62.2–92.8)	93.5	1217	18	..	..	..	0	61.6 (42.7–77.5)	84.5	341	6
Piperacillin and tazobactam	35.9 (22.5–51.9)	0	39	2	16.8 (2.8–58.7)	96.1	481	3	..	..	..	0	..	..	..	0
Cefuroxime	43.8 (29.7–59)	49.8	80	5	68.1 (22.7–93.9)	85.8	592	7	..	..	..	0	42.5 (25.6–61.4)	79.9	187	3
Ceftriaxone	45.4 (27.9–64.1)	89.7	893	13	85 (66.4–94.2)	93.2	1397	15	0 (0–100)	00	738	6	2 (0.5–7.9)	84.2	2097	10
Cefepime	43.5 (23.2–65.5)	..	23	1	88.3 (83.2–92.1)	0	206	2	..	..	..	0	..	..	..	0
Gentamicin	42.7 (30–56.5)	71.9	968	17	77.6 (65.5–86.3)	91.6	1886	22	52.9 (27.8–77)	Na	17	1	22.5 (15.4–31.6)	0	262	5
Amikacin	10.4 (0.1–90.6)	0	91	5	24.7 (9.8–49.7)	92.1	782	11	..	..	..	0	..	..	..	0
Co-trimoxazole	80.1 (67.8–88.5)	90.7	839	14	89.9 (79.7–95.3)	92.9	1653	14	84.1 (71.9–91.7)	90.1	818	8	80.8 (71.7–87.5)	89.7	2342	13
Ciprofloxacin	25.3 (16.3–37.1)	79.1	951	17	35.4 (22.7–50.6)	92.8	1862	20	0.5 (0–24.7)	84.7	796	7	0.7 (0–9.7)	75.7	1492	12
Imipenem	0 (0–14.8)	..	23	1	1.1 (0.1–9)	0	454	6	0	..	0	0	0 (0–6.3)	..	57	1
Meropenem	0.9 (0.1–6.4)	0	106	5	2.7 (0.7–9.6)	73	751	8	0 (0–23.2)	..	14	1	0 (0-NaN)	0	881	2
Urine samples																
ESCR	41.2 (30.1–53.3)	80.7	512	13	55.5 (28.1–79.9)	76.9	78	4	..	..	..	..	..	..	..	..
CRE	2.6 (0.8–7.7)	0.0	116	5	4.9 (0.7–27.5)	0.0	37	2	..	..	..	..	..	..	..	..
Ampicillin	95.9 (82.5–99.2)	37.8	253	8	..	..	..	..	..	..	..	..	..	..	..	..
Amoxicillin and clavulanate	71.6 (56.7–82.9)	80.9	285	10	75.5 (65.9–83.2)	15.3	94	5	..	..	..	..	..	..	..	..
Ceftriaxone	27.4 (18.8–38.1)	62.1	251	7	35.3 (11.3–70.2)	74.6	61	3	..	..	..	..	..	..	..	..
Gentamicin	40.7 (26.7–56.4)	71.2	250	9	64.3 (43.7–80.7)	70.3	74	4	..	..	..	..	..	..	..	..
Amikacin	3.1 (0.4–19.1)	0.0	32	2	11.8 (1.5–36.4)	..	17	1	..	..	..	..	..	..	..	..
Co-trimoxazole	68.1 (53.8–79.6)	77.2	298	10	85.5 (75.1–92.0)	0.0	78	4	..	..	..	..	..	..	..	..
Ciprofloxacin	19.2 (12.6–28.3)	54.4	336	11	23.2 (14.5–34.9)	31.7	37	5	..	..	..	..	..	..	..	..

'n' represents the number of isolates and **'N'** represents the number of studies assessing for resistance to specific antibiotics. CI = confidence interval. ESCR = extended-spectrum cephalosporin-resistant. CRE = carbapenem non-susceptible Enterobacterales. N/A = not applicable.

Table 1: **Non-susceptibility of Enterobacterales in blood and urine samples (all populations included).**

pathogens were resistant to ciprofloxacin, and 80.1% of *E. coli* and most *Klebsiella* spp., *Salmonella* spp. and *S. typhi* isolates were resistant to cotrimoxazole. *E. coli* isolates were usually susceptible to amikacin, but 24.7% of *Klebsiella* spp. were resistant to that antibiotic. In contrast to ESCR, resistance to carbapenem was low. We did not find any significant differences in patterns of C3G resistance between neonates and children. However, we observed a significant higher proportion of *E. coli* resistant to gentamicin and *Klebsiella* spp resistant to amikacin in neonates compared to children. In urine samples, around half of *E. coli* and *Klebsiella* spp. isolates were resistant to cephalosporins. Finally, *Salmonella* spp. in stool samples were generally resistant to

	Shigella spp.				*Salmonella* spp.			
	% (CI)	I^2 (%)	n	N	% (CI)	I^2	n	N
ESCR	9.0 (2.9–25.0)	25.7	384	12	11.8 (9.0–15.2)	11.8	425	4
CRE	0.0 (0.0–2.8)	..	128	1	0.0 (0.0–1.0)	..	360	1
Ampicillin	85.4 (69.1–93.9)	39.4	320	15	68.7 (34.2–90.3)	89.9	154	5
Amoxicillin and clavulanic acid	36.2 (13.0–68.3)	87.8	293	6	14.2 (7.1–26.4)	73.0	415	2
Ceftriaxone	12.0 (4.4–28.7)	44.4	225	10	3.4 (0.3–26.8)	0.0	48	2
Gentamicin	11.5 (4.2–28.1)	65.7	402	13	6.3 (2.8–13.4)	14.6	489	5
Amikacin	7.8 (0.2–81.3)	0	180	3	6.7 (0.5–52.9)	96.6	377	2
Co-trimoxazole	74.7 (62.1–84.1)	62.1	506	16	47.8 (17.3–80.1)	91.6	552	6
Ciprofloxacin	6.7 (1.5–24.5)	56.5	420	14	3.3 (0.4–20.3)	0.0	448	5

'n' represents the number of isolates and **'N'** represents the number of studies assessing for resistance to specific antibiotics. CI = confidence interval. ESCR = extended-spectrum cephalosporin-resistant. CRE = carbapenem non-susceptible Enterobacterales.

Table 2: **Non-susceptibility of Enterobacterales in stool samples (all populations included).**

	Pooled prevalence (95% CI)	I^2 (%)	n	N
Escherichia coli				
ESCR	**48.6 (36.3–61.0)**	**46.9**	**129**	**8**
CRE	**2.6 (0.4–16.5)**	**0.0**	**38**	**2**
Ampicillin	93.8 (65.0–99.2)	0.2	136	7
Amoxicillin	97.2 (85.5–99.9)	..[a]	36	1
Ceftriaxone	50.0 (30.4–69.6)	73.6	115	6
Gentamicin	56.0 (32.0–77.5)	29.5	178	9
Amikacin	2.4 (0.0–66.6)	0.0	46	3
Ciprofloxacin	17.7 (7.2–37.3)	37.1	142	8
Meropenem	2.6 (0.4–16.5)	0.0	38	2
***Klebsiella* spp.**				
ESCR	**85.8 (67.6–94.6)**	**91.9**	**728**	**14**
CRE	**2.3 (0.5–9.7)**	**77.7**	**463**	**6**
Ceftriaxone	78.7 (41.9–95.0)	93.5	433	8
Gentamicin	77.1 (53.8–90.7)	92.9	688	12
Amikacin	42.6 (17.7–71.9)	93.2	370	6
Ciprofloxacin	27.6 (12.1–51.5)	92.1	655	11
Meropenem	4.5 (1.1–16.4)	83.3	336	4

'n' represents the number of isolates and **'N'** represents the number of studies assessing for resistance to specific antibiotics. CI = confidence interval. ESCR = extended-spectrum cephalosporin-resistant. CRE = carbapenem non-susceptible Enterobacterales. [a]Heterogeneity was not assessed because a single study reported this prevalence.

Table 3: **Non-susceptibility of Enterobacterales in blood cultures from neonates.**

ampicillin and cotrimoxazole. These findings indicate that Enterobacterales had high proportions of resistance to several of the antibiotics that are usually recommended in clinical guidelines used in SSA and in WHO guidelines.[9]

We found higher overall proportions of ESCR *E. coli* and *Klebsiella* spp. isolates than previous studies (Table 5).[3,8,139–146] The most recent meta-analysis by the World Health Organization (WHO), which included children and adults in Africa, reported a prevalence of cephalosporin resistance of 10.2% in *E. coli* isolates and 3.3% in *Klebsiella* spp. isolates, but this was based on very small numbers of samples (123 and 57, respectively). On the other hand, a recent systematic review by Wen et al., focusing on neonates and including studies from 2010 to 2021 found ESCR rates of 88% among *Klebsiella* spp. These results are in line with our findings.[143]

The high proportion of ESCR *Klebsiella* spp. were found also in neonates. This is an alarming finding given that a recent review identified *Klebsiella* spp. as the leading cause of neonatal sepsis in Africa.[147] Indeed, many sub-Saharan countries have reported nosocomial outbreaks of resistant *Klebsiella* spp. infections in neonatal units.[148–150]

We observed a high level of heterogeneity in the proportion of patients with Klebsiella spp. resistant to amikacin. It should be noted that this result was strongly influenced by data from two studies focusing on neonates and involving only one hospital.[79,110] These high proportions could have been the result of ongoing outbreaks of *Klebsiella* spp. resistant to amikacin or of a diagnostic bias as blood cultures might be 'reserved' for use in the most severe cases or for multi-treated children.

The overuse of antibiotics is a key cause of AMR.[151] Saleem et al. reviewed current patterns of antibiotic consumption in Africa's hospitals. Rates of antimicrobial prescription were high across most of the countries

	Escherichia coli			***Klebsiella* spp.**		
	N	Pooled prev. (95% CI)	I^2 (%)	N	Pooled prev. (95% CI)	I^2 (%)
Geographic region[a]						
West	8	43.2 (22.4–66.8)	86.5	9	78.5 (42.8–94.7)	94.9
Central	0	..	..	1	89.5 (66.3–97.4)	..
East	11	42.2 (27.1–59.0)	77.0	12	85.6 (71.3–93.4)	92.9
South	1	22.3 (18.0–27.2)	..	5	91.5 (69.8–98.1)	94.0
p-value		0.0101			0.7785	
Age range						
Neonates	8	48.6 (36.3–61.0)	46.9	14	85.8 (67.6–94.6)	91.9
Children over 1 month[b]	11	36.5 (19.1–58.3)	86.6	12	83.8 (65.3–93.4)	95.8
p-value		0.3394			0.8352	
Periods						
2004–2010	5	37.4 (7.6–81.2)	89.1	6	73.5 (32.7–94.0)	82.8
2011–2015	5	38.9 (23.1–57.4)	78.5	7	79.6 (48.8–94.1)	93.2
2016–2022	9	45.4 (30.5–61.2)	79.0	13	90.5 (79.7–95.8)	91.7
p-value		0.8491			0.3427	

Prev. = prevalence. CI = confidence interval. N = number of included studies. [a]Recording the WHO African region. South Africa was excluded. [b]Including those listed as of paediatric age or children.

Table 4: **Sources of heterogeneity for ESCR proportion in blood cultures.**

Authors, year	Population	Inclusion period	Number of studies included	Countries	Sample types	% *E. coli* resistance	% *Klebsiella* spp. resistance
Williams et al., 2016	Children	2005–2016	18	Sub-Saharan Africa	Blood mainly	16% (95% CI: 12%–34%) N = 387	Range 33%–50% (NA) N = 110
Le Doare et al., 2015	Children	2002–2013	10	Africa	Blood	0 (IQR: 0%–10.9%) N = 338	30% (IQR: 0%–64.0%) N = 921
Le Doare et al., 2015	Neonates	2002–2013	3	Africa	Blood	0 (IQR: 0%–50%) N = 7	50% (IQR: 0%–86.5%) N = 109
Droz et al., 2019	Children	1990–2019	11	Africa	Blood	21.2% (95% CI: NA)	NA
Bernabe et al., 2017	Children and adults	1990–2012	120 (112 for BC)	West Africa	Blood[a]	11.9% (95% CI: 4.3%–22%) N = 720	24.2% (95% CI: 8.1%–44.8%) N = 476
Tadesse et al., 2017	Children and adults	2013–2016	144	Africa	Blood, urine, pus	31.5% (IQR: 6.9%–47.7%) N = 2800	47.3% (IQR: 25%–62.8%) N = 1547
Okomo et al., 2019	Neonates	2008–2018	151	Sub-Saharan Africa	Blood, CSF	Around 33% ("one third") (95% CI: NA) N = NA	49% (95% CI: 47%–83%) N = NA
Wen et al., 2021	Neonates	2010–2021	88	Africa[b]	Blood	47% (95% CI: 28%–68%) N = 474	88% (95% CI: 72%–96%) N = 1209
WHO Regional Office for Africa	Children and adults	2016–2020	167	WHO African region	Blood, urine	10.2% (95% CI: NA) N = NA	3.3% (95% CI: NA) N = NA
Haindongo et al., 2022	Children and adults	2008–2019	27	Africa	Blood	32% (95% CI: 9%–69%) N = 416	NA
Lester et al., 2020	Children and adults	1990–2019	40	Sub-Saharan Africa	Blood	18.4% (95% CI:10.5%–35.2%); N = NA	54.4% (95% CI: 24.3%–81.2%) N = NA

BC = blood culture, CSF = cerebrospinal fluid, IQR = interquartile range, N = number of isolates, NA = Not available, WHO = World Health Organization, CI = confidence interval. [a]We only report blood culture results, but Bernabe et al. also reported results for urine, cerebrospinal fluid, stools, blood, sputum, bronchoalveolar liquid and pleural fluid. [b]Wen et al. also collected data from Asia and the Middle East, but we only report their data from Africa.

Table 5: **Meta-analyses reporting on the 3GC resistance of *E. coli* and *Klebsiella* spp. in Africa.**

included in our study. Hospitals in Nigeria saw the highest antimicrobial utilization rates at 59.6–97.6% of in-patients surveyed.[152] Moreover, the frequent use of over-the-counter antibiotics in SSA is a major barrier to antibiotic stewardship.[153] The worldwide dissemination of successful ESBL-producing Enterobacterales clones over the last decade could also partly explain the high rates of resistance that we found.[154–157]

There was a lot of heterogeneity in the results among the reviewed studies. Multiple factors may be at play, such as different access and exposure to antibiotics across different settings, use of antibiotics in local food industries, administration of first-line antibiotics prior to blood cultures, difference in microbiological methods used by the hospital laboratories, and bias due to patient selection for culturing and variable culturing rates in different settings.

Four recent studies focusing on blood cultures were published after our literature search and could not be included in this review. They assessed neonates with sepsis in Ethiopia[158,159] and Zambia[160] and children under 15 years old (including neonates) suffering of suspected bacterial infections in Rwanda.[161] The three studies on neonates found a majority of *Klebsiella* spp in positive blood cultures, which showed ESCR proportions between 95 and 100%.[158–160] In the Rwandan paediatric study, most of the positive blood cultures concerned neonates and also showed a majority of *Klebsiella* spp, with an ESCR proportion of 100%.[161] These recent studies illustrate once again the very high proportion of *Klebsiella* spp ESCR in children in Sub-Saharan Africa. They showed an even higher proportion of resistance than those found in our meta-analysis suggesting a possible worsening over time.

There are some limitations that should be considered when interpreting our results. The ability to perform a culture depends on available resources, including trained personnel who can gather sterile samples and process them, access to a microbiology laboratory and the affordability of the test (often charged to the patient). Moreover, the indications for performing cultures differ in each healthcare centre, leading to multiple biases in patient selection in the studies included in this systematic review. In addition, bacteriology laboratories are not widely available in SSA, usually only in large hospitals. The sickest children, or those who have not responded to first-line treatments, will be referred to these tertiary centres, inducing a supplementary selection bias. In some studies, the decision to perform blood cultures may have been driven by suspicions of an infectious outbreak, particularly in neonatal units. All of these reasons may have led to an over-representation of multi-resistant Enterobacterales. Results from stool and urine samples must also be interpreted with

caution, as these might indicate colonization rather than infection, as definitions of 'symptomatic patients' varied across studies and were often unclear. In addition, most of the included studies were from the western and eastern regions of SSA and we excluded South Africa limiting the representativeness of these findings.

Since we could not distinguish community-acquired from hospital-acquired infections, as this information was not provided, it is difficult to indicate whether the presented results are representative of AMR in the community or hospital settings.

Despite these limitations, and to the best of our knowledge, this review is the most comprehensive synthesis of AMR Enterobacterales in children from SSA, including data from a large number of isolates collected in 24 African countries, applying robust statistical methods to generate pooled estimates.

Our findings suggest that antibiotics such as ampicillin, gentamicin and ceftriaxone, which are the currently recommended treatment for sepsis in children,[9] may frequently be ineffective. Amikacin (the current WHO-recommended second-line treatment for neonatal sepsis in combination with cloxacillin) may represent a better alternative for bloodstream infections and could help to save carbapenems.

These data, and the limitations inherent in our meta-analysis, showed the crucial importance of conducting prospective studies on drug resistance among children in SSA in the community and in primary and secondary healthcare structures.

Local microbiological data should inform antibiotic usage recommendations, but these are scarce in SSA.[162] At the individual patient level, this information is essential to informing therapeutic decisions and avoiding any unnecessary escalation to second-line regimens. At the hospital level, this information is crucial to identifying potential sources of nosocomial infections and informing infection prevention and control measures. At the regional and national levels, microbiological data is key to monitoring the spread of AMR and informing the development of effective regional or national clinical guidelines.

Although microbiology laboratories are costly and require highly trained personnel, recent initiatives could help to scale up microbiology capacities in SSA. For example, Doctors Without Borders and their partners are currently testing the feasibility of using a transportable, stand-alone clinical bacteriology laboratory that can be operated by relatively inexperienced technicians in remote settings.[163]

In conclusion, even if more research is needed to address some of this review's limitations and to have a better picture of AMR at the community and hospital levels, the present review suggests that the situation concerning AMR in SSA is alarming. Adapting antibiotic recommendations at local level, based on local patterns of AMR, are urgently needed to provide effective treatments to patients. This will require a dramatic scaling up of SSA's microbiology capacity. The present review also suggests that some antibiotics remain highly effective and their efficacy must be protected. Antimicrobial stewardship measures, which have been extensively described in the literature, must be expanded and strengthened at the community level, in the food industry, and in all healthcare services. Relevant policymakers and key stakeholders should take ownership of the importance of addressing AMR. They should prioritise the development of policies addressing its determinants and secure funding to implement the measures mentioned above.

Contributors

Every author contributed to the study. MK, GC, AM, CC, AGL, and NW participated in the conceptualization; MK, BO, GC, MR, AGL, and NW in the data curation; AM and CC in the formal analysis; MK, BO, GC, AM, MR; AGL, and NW in the investigation; MK GC, AM, CC, AGL, and NW in the methodology; AGL and NW in the project administration; AM in providing analysis tools; JD, KN, MdK, AGL and NW in supervision; MK, BO, GC, AM, DA, MR, JD, KN, MdK, CC, AGL and NW in validation of the data; MK, BO; AGL, and NW in visualization and data presentation; MK, BO, JD, CC, and NM in writing the original draft; and MK, BO, GC, AM, DA, JD, KN, MdK, CC, AGL, and NW in writing, review and editing the final draft. All authors have full access to all the data in the study and had final responsibility for the decision to submit for publication. AGL and MR directly accessed and verified the underlying data reported in the manuscript.

Data sharing statement

The protocol study is registered and available in Prospero, ID: CRD42021260157. All the data collected will be shared following publication upon request without end date, to anyone who wishes to access the data for any purpose. Requests should be directed to noemie.wagner@hcuge.ch.

Declaration of interests

We declare no competing interests.

Acknowledgements

We gratefully thank Benedikt Huttner for his valuable advice on designing the study and writing the manuscript.

We acknowledge the contributions of Bieke Tack and Kathryn Thomson for providing the relevant data and results from their study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102512.

References

1 World Health Organization. Child Mortality [fact sheet 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/levels-and-trends-in-child-under-5-mortality-in-2020.
2 Perin J, Mulick A, Yeung D, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the sustainable development goals. *Lancet Child Adolesc Health*. 2022;6:106–115.
3 Le Doare K, Bielicki J, Heath PT, Sharland M. Systematic review of antibiotic resistance rates among gram-negative bacteria in children with sepsis in resource-limited countries. *J Pediatric Infect Dis Soc*. 2015;4:11–20.
4 Kissoon N, Carapetis J. Pediatric sepsis in the developing world. *J Infect*. 2015;71(Suppl 1):S21–S26.
5 Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10:417–432.

6 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399:629–655.
7 Okolie OJ, Igwe U, Ismail SU, Ighodalo UL, Adukwu EC. Systematic review of surveillance systems for AMR in Africa. *J Antimicrob Chemother*. 2022;78:31–51.
8 Tadesse BT, Ashley EA, Ongarello S, et al. Antimicrobial resistance in Africa: a systematic review. *BMC Infect Dis*. 2017;17:616.
9 World Health Organization. *The WHO AWaRe (access, watch, reserve) antibiotic book*. 2022.
10 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
11 IntHout J, Ioannidis JPA, Borm GF, Goeman JJ. Small studies are more heterogeneous than large ones: a meta-meta-analysis. *J Clin Epidemiol*. 2015;68:860–869.
12 Renggli L, Gasser M, Plüss-Suard C, Harbarth S, Kronenberg A. Temporal and structural patterns of extended-spectrum cephalosporin-resistant Klebsiella pneumoniae incidence in Swiss hospitals. *J Hosp Infect*. 2022;120:36–42.
13 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.
14 Lin L, Chu H. Meta-analysis of proportions using generalized linear mixed models. *Epidemiology*. 2020;31:713–717.
15 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
16 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Mental Health*. 2019;22:153–160.
17 Ekwochi U, Ifediora CO, Osuorah C. A 4-Year prospective study of clinico-bacterial profile and antibiogram of neonatal bacterial sepsis at a tertiary health facility in a resource-limited setting. *J Clin Neonatol*. 2018;7:80.
18 Lamorde M, Mpimbaza A, Walwema R, et al. A cross-cutting approach to surveillance and laboratory capacity as a platform to improve health security in Uganda. *Health Secur*. 2018;16:S76–S86.
19 Nwadioha I, Nwokedi E, Kashibu E, Odimayo M, Okwori E. A review of bacterial isolates in blood cultures of children with suspected septicemia in a Nigerian tertiary Hospital. *Afr J Microbiol Res*. 2010;4:222–225.
20 Boadi-Kusi S, Kyei S, Holdbrook S, Abu E, Ntow J, Ateko A. A study of ophthalmia neonatorum in the central reion of Ghana: causative agents and antibiotic susceptibility patterns. *Global Pediatric Health*. 2021;8:2333794X2110197.
21 Abera B, Jember T, Beza L, Mulu W, Shita E, Kibret M. Aetiology of acute diarrhoea and antimicrobial usage among children aged under five years at health centres in Bahir Dar, Ethiopia. *Trop Doct*. 2020;50:004947552091255.
22 Pelkonen T, Urtti S, dos Anjos E, et al. Aetiology of bacterial meningitis in infants aged <90 days: prospective surveillance in Luanda, Angola. *Int J Infect Dis*. 2020;97:251–257.
23 Ikumapayi U, Kanteh A, Manneh J, Lamin M, Mackenzie G. An outbreak of Serratia liquefaciens at a rural health center in the Gambia. *J Infect Dev Countr*. 2016;10:791–798. https://doi.org/10.3855/jidc.7184.
24 Vubil D, Balleste-Delpierre C, Mabunda R, et al. Antibiotic resistance and molecular characterization of Shigella isolates recovered from children less than 5 years in Manhiça, Southern Mozambique. *Int J Antimicrob Agents*. 2018;51:881–887. https://doi.org/10.1016/j.ijantimicag.2018.02.005.
25 Were T, Davenport G, Hittner J, et al. Antibiotic resistance of invasive non typhoidal Salmonella (NTS) isolates in children from western Kenya. *Am J Trop Med Hyg*. 2011;85:329.
26 Bonko MA, Tahita M, Kiemde F, et al. Antibiotic susceptibility profile of bacterial isolates from febrile children under 5 years of age in Nanoro, Burkina Faso. *Trop Med Int Health*. 2021;26(10):1220–1230. https://doi.org/10.1111/tmi.13644.
27 Chaw PS, Meyer-Schlinkmann K, Raupach-Rosin H, et al. Antibiotic use on paediatric inpatients in a teaching hospital in the Gambia, a retrospective study. *Antimicrob Resist Infect Control*. 2018;7:82. https://doi.org/10.1186/s13756-018-0380-7.
28 Williams PC, Qazi SA, Agarwal R, et al. Antibiotics needed to treat multidrug-resistant infections in neonates. *Bull World Health Organ*. 2022;100:797–807.
29 Moyo S, Aboud S, Kasubi M, Lyamuya E, Maselle S. Antimicrobial resistance among producers and non-producers of extended spectrum beta-lactamases in urinary isolates at a tertiary Hospital in Tanzania. *BMC Res Notes*. 2010;3:348.
30 Pons MJ. *Antimicrobial resistance levels among diarrheogenic and commensal Escherichia coli from Southern Mozambique*. 2011 [published online Oct].
31 Randrianirina F, Hariniana E, Lova R, et al. Antimicrobial resistance of bacterial enteropathogens isolated from stools in Madagascar. *BMC Infect Dis*. 2014;14:104.
32 Mava Y, Bello MA, Ambe JP, Zailani SB. Antimicrobial sensitivity pattern of organisms causing urinary tract infection in children with sickle cell anemia in Maiduguri, Nigeria. *Niger J Clin Pract*. 2012;15(4):420–423.
33 Kpoda DS, Guessennd NK, Somda NS, et al. Antimicrobial susceptibility of extended-spectrum beta-lactamase producing Enterobacteriaceae causing urinary tract infections in Ouagadougou, Burkina Faso. *Afr J Clin Exp Microbiol*. 2017;18:139–144.
34 Bachou H, Tylleskär T, Kaddu-Mulindwa D, Tumwine J. Bacteraemia among severely malnourished children infected and uninfected with the human immunodeficiency virus-1 in Kampala, Uganda. *BMC Infect Dis*. 2006;6:160.
35 Moyo SJ, Manyahi J, Blomberg B, et al. Bacteraemia, malaria, and case fatality among children hospitalized with fever in dar es salaam, Tanzania. *Front Microbiol*. 2020;11:2118. https://doi.org/10.3389/fmicb.2020.02118.
36 Ilechukwu G, Ilechukwu C, Ubesie A, Okoroafor I, Chukwuemeka B, Ojinnaka N. Bacterial agents of the discharging middle ear among children seen at the University of Nigeria Teaching Hospital, Enugu. *Pan Afr Med J*. 2017;26:87. https://doi.org/10.11604/pamj.2017.26.87.9243.
37 Abdeta A, Bitew A, Zena N. Bacterial and fungal profile, antibiotic susceptibility patterns of bacterial pathogens and associated risk factors of urinary tract infection among symptomatic pediatrics patients attending St. Paul's hospital millennium medical college: a cross-sectional study. *Infect Drug Resist*. 2022;15:1613–1624. https://doi.org/10.2147/IDR.S358153.
38 Bonkoungou I, Haukka K, Österblad M, et al. Bacterial and viral etiology of childhood diarrhea in Ouagadougou, Burkina Faso. *BMC Pediatr*. 2013;13:36.
39 G/eyesus T, Moges F, Eshetie S, Yeshitila B, Abate E. Bacterial etiologic agents causing neonatal sepsis and associated risk factors in Gondar, Northwest Ethiopia. *BMC Pediatr*. 2017;17:137. https://doi.org/10.1186/s12887-017-0892-y.
40 Okomo U, Garba D, Fombah A, et al. Bacterial isolates and antibiotic sensitivity among Gambian children with severe acute malnutrition. *Int J Pediatr*. 2011;2011:825123.
41 Eshetu B, Gashaw M, Solomon S, et al. Bacterial isolates and resistance patterns in preterm infants with sepsis in selected hospitals in Ethiopia: a longitudinal observational study. *Glob Pediatr Health*. 2020;7:2333794X2095331.
42 Ayelign B, Abebe B, Shibeshi A, et al. Bacterial isolates and their antimicrobial susceptibility patterns among pediatric patients with urinary tract infections. *Türk Üroloji Dergisi/Turk J Urol*. 2017;44:62–69. https://doi.org/10.5152/tud.2017.33678.
43 Akingbade OA, Akinjinmi AA, Oluwatayo IO, Okerentugba P, Babatunde O, Okonko I. Bacterial organisms isolated from children with diarrhoea in Abeokuta, Nigeria. *Stem Cell*. 2013;4:5–9.
44 Tadesse B, Shimelis T, Worku M. Bacterial profile and antibacterial susceptibility of otitis media among pediatric patients in Hawassa, Southern Ethiopia: cross-sectional study. *BMC Pediatr*. 2019;19:398.
45 Belete Y, Asrat D, Woldeamanuel Y, Yihenew G, Gize A. Bacterial profile and antibiotic susceptibility pattern of urinary tract infection among children attending felege hiwot referral hospital, bahir dar, northwest Ethiopia. *Infect Drug Resist*. 2019;12:3575–3583.
46 Fenta A, Dagnew M, Eshetie S, Belachew T. Bacterial profile, antibiotic susceptibility pattern and associated risk factors of urinary tract infection among clinically suspected children attending at Felege-Hiwot comprehensive and specialized hospital, Northwest Ethiopia. A prospective study. *BMC Infect Dis*. 2020;20:673.
47 Zerefaw G, Tadesse S, Derbie A. Bacterial uropathogens, antimicrobial susceptibility profile and associated factors among pediatric patients in bahir dar, Northwest Ethiopia. *Ethiop J Health Sci*. 2022;32:81–92.
48 Peterside O, Pondei K, Akinbami F. Bacteriological profile and antibiotic susceptibility pattern of neonatal sepsis at a teaching hospital in Bayelsa state, Nigeria. *Trop Med Health*. 2015;43:183–190. https://doi.org/10.2149/tmh.2015-03.

49 Zamarano H, Musinguzi B, Kabajulizi I, et al. Bacteriological profile, antibiotic susceptibility and factors associated with neonatal Septicaemia at Kilembe mines hospital, Kasese District Western Uganda. *BMC Microbiol*. 2021;21:303.
50 Dzon HB, Ngouoni GC, Diembi S, et al. Bacteriological profiles of acute suppurative otitis media in children in Brazzaville, Congo. *Afr J Clin Exp Microbiol*. 2019;20:342.
51 Sorsa A, Früh J, Stötter L, Adula S. Blood culture result profile and antimicrobial resistance pattern: a report from neonatal intensive care unit (NICU), Asella teaching and referral hospital, Asella, south East Ethiopia. *Antimicrob Resist Infect Control*. 2019;8:42. https://doi.org/10.1186/s13756-019-0486-6.
52 Mahende C, Ngasala B, Lusingu J, Premji Z. Bloodstream bacterial infection among outpatient children with acute febrile illness in North-Eastern Tanzania. *Trop Med Int Health*. 2015;20:116.
53 Labi A-K, Enweronu-Laryea CC, Nartey ET, et al. Bloodstream infections at two neonatal intensive care units in Ghana: multidrug resistant Enterobacterales undermine the usefulness of standard antibiotic regimes. *Pediatr Infect Dis J*. 2021;40(12):1115–1121. https://journals.lww.com/pidj/Fulltext/2021/12000/Bloodstream_Infections_at_Two_Neonatal_Intensive.19.aspx.
54 Nitiema L, Nordgren J, Ouermi D, et al. Burden of rotavirus and other enteropathogens among children with diarrhea in Burkina Faso. *Int J Infect Dis*. 2011;15:e646–e652.
55 Ogunlesi T, Ogunfowora O, Osinupebi O, Olanrewaju D. Changing trends in newborn sepsis in Sagamu, Nigeria: bacterial aetiology, risk factors and antibiotic susceptibility. *J Paediatr Child Health*. 2010;47:5–11.
56 Kariuki S, Revathi G, Kariuki N, Kiiru J, Mwituria J, Hart CA. Characterisation of community acquired non-typhoidal Salmonella from bacteraemia and diarrhoeal infections in children admitted to hospital in Nairobi, Kenya. *BMC Microbiol*. 2006;6:101.
57 Ifeanyi C, Ikeneche N, Enya Bassey B, Al-Gallas N, Casmir A, Nnennaya I. Characterization of toxins and colonization factors of enterotoxigenic Escherichia coli isolates from children with acute diarrhea in Abuja, Nigeria. *Jundishapur J Microbiol*. 2017;11(1):e64269. https://doi.org/10.5812/jjm.64269. In Press.
58 Odetoyin B, Labar A, Lamikanra A, Aboderin A, Okeke I. Classes 1 and 2 integrons in faecal Escherichia coli strains isolated from mother-child pairs in Nigeria. *PLoS One*. 2017;12:e0183383.
59 Kenga DB, Gebretsadik T, Simbine S, et al. Community-acquired bacteremia among HIV-infected and HIV-exposed uninfected children hospitalized with fever in Mozambique. *Int J Infect Dis*. 2021;109:99–107.
60 Seni J, Mwakyoma A, Mashuda F, et al. Deciphering risk factors for blood stream infections, bacteria species and antimicrobial resistance profiles among children under five years of age in North-Western Tanzania: a multicentre study in a cascade of referral health care system. *BMC Pediatr*. 2019;19:32. https://doi.org/10.1186/s12887-019-1411-0.
61 Thomson KM, Dyer C, Liu F, et al. Effects of antibiotic resistance, drug target attainment, bacterial pathogenicity and virulence, and antibiotic access and affordability on outcomes in neonatal sepsis: an international microbiology and drug evaluation prospective substudy (BARNARDS). *Lancet Infect Dis*. 2021;21:1677–1688.
62 Omoregie R, Egbe C, Ogefere H, Igbarumah I, Omijie R. Effects of gender and seasonal variation on the prevalence of bacterial septicemia among young children in Benin city, Nigeria. *Libyan J Med*. 2009;4:107–109.
63 Oneko M, Kariuki S, Muturi-Kioi V, et al. Emergence of community-acquired, multidrug-resistant invasive nontyphoidal Salmonella disease in rural western Kenya, 2009–2013. *Clin Infect Dis*. 2015;61:S310–S316.
64 Prah I, Ayibieke A, Mahazu S, et al. Emergence of oxacillinase-181 carbapenemase-producing diarrheagenic Escherichia coli in Ghana: OXA-181 carbapenemase-producing E. coli in Ghana. *Emerg Microb Infect*. 2021;10:1–43.
65 Tam P-Y, Musicha P, Kawaza K, et al. Emerging resistance to empiric antimicrobial regimens for pediatric bloodstream infections in Malawi (1998-2017). *Clin Infect Dis*. 2018;69:61–68. https://doi.org/10.1093/cid/ciy834.
66 Langendorf C, Hello S, Moumouni A, et al. Enteric bacterial pathogens in children with diarrhea in Niger: diversity and antimicrobial resistance. *PLoS One*. 2015;10:e0120275. https://doi.org/10.1371/journal.pone.0120275.
67 Zenebe T, Shenkute D, Tilahun A, Craddock H, Gishen N. Enteropathogens in under-five children with diarrhea in health facilities of debre berhan town, North Shoa, Ethiopia. *Ethiop J Health Sci*. 2019;29:203–214.
68 Phoba M-F, De Boeck H, Ifeka BB, et al. Epidemic increase in Salmonella bloodstream infection in children, Bwamanda, the Democratic Republic of Congo. *Eur J Clin Microbiol Infect Dis*. 2014;33:79–87.
69 Webale M, Christine W, Guyah B, et al. Epidemiological patterns and antimicrobial resistance of bacterial diarrhea among children in Nairobi city, Kenya. *Gastroenterol Hepatol Bed Bench*. 2020;13(3):238–246. https://doi.org/10.22037/ghfbb.v13i3.1910.
70 Konaté A, Dembélé R, Guessennd N, et al. Epidemiology and antibiotic resistance phenotypes of diarrheagenic Escherichia coli responsible for infantile gastroenteritis in ouagadougou, Burkina Faso. *Eur J Microbiol Immunol*. 2017;7:1–8.
71 Msemo O, Mbwana J, Mahende C, et al. Epidemiology and antimicrobial susceptibility of Salmonella enterica bloodstream isolates among febrile children in a rural district in northeastern Tanzania: a cross-sectional study. *Clin Infect Dis*. 2019;68:S177–S182.
72 Ndir A, Diop A, Faye P, Cissé M, Ndoye B, Astagneau P. Epidemiology and burden of bloodstream infections caused by extended-spectrum beta-lactamase producing enterobacteriaceae in a pediatric hospital in Senegal. *PLoS One*. 2016;11:e0143729.
73 Ranosiarisoa ZN, El Harrif S, Andrianirina AZ, et al. Epidemiology of early-onset bacterial neonatal infections in Madagascar. *Pediatr Infect Dis J*. 2019;38(1):76–81. https://journals.lww.com/pidj/Fulltext/2019/01000/Epidemiology_of_Early_onset_Bacterial_Neonatal.16.aspx.
74 Nyanga P, Onyuka J, Webale M, Were T, Budambula V. Escherichia coli pathotypes and Shigella sero-groups in diarrheic children in Nairobi city, Kenya. *Gastroenterol Hepatol Bed Bench*. 2017;10:220–228.
75 Mekonnen GK, Mengistie B, Sahilu G, Kloos H, Mulat W. Etiologies of diarrhea and drug susceptibility patterns of bacterial isolates among under-five year children in refugee camps in Gambella Region, Ethiopia: a case control study. *BMC Infect Dis*. 2019;19:1008.
76 Karppinen M, Bernardino L, Anjos E, et al. Etiology of childhood otorrhea in luanda, Angola, and a review of otitis media in african children. *Pediatr Infect Dis J*. 2018;38:1.
77 Mulinganya GM, Claeys M, Balolebwami SZ, et al. Etiology of early-onset neonatal sepsis and antibiotic resistance in bukavu, democratic republic of the Congo. *Clin Infect Dis*. 2021;73:e976–e980.
78 Kabwe M, Tembo J, Chilukutu L, et al. Etiology, antibiotic resistance and risk factors for neonatal sepsis in a large referral center in Zambia. *Pediatr Infect Dis J*. 2016;35:e191–e198. https://doi.org/10.1097/INF.0000000000001154.
79 Chimhini G, Olaru ID, Fitzgerald F, et al. Evaluation of a novel culture system for rapid pathogen identification and detection of cephalosporin resistance in neonatal gram-negative sepsis at a tertiary referral unit in harare, Zimbabwe. *Pediatr Infect Dis J*. 2021;40(9):785–791. https://journals.lww.com/pidj/Fulltext/2021/09000/Evaluation_of_a_Novel_Culture_System_for_Rapid.2.aspx.
80 Eibach D, Campos C, Krumkamp R, et al. Extended spectrum beta-lactamase producing Enterobacteriaceae causing bloodstream infections in rural Ghana, 2007-2012. *Int J Med Microbiol*. 2016;306(4):249–254. https://doi.org/10.1016/j.ijmm.2016.05.006.
81 Abera B, Kibret M, Mulu W. Extended-spectrum beta (β)-Lactamases and antibiogram in enterobacteriaceae from clinical and drinking water sources from bahir dar city, Ethiopia. *PLoS One*. 2016;11:e0166519.
82 Meeren B, Chhaganlal K, Pfeiffer A, et al. Extremely high prevalence of multi-resistance among uropathogens from hospitalised children in Beira, Mozambique. *South Afr Med J = Suid-Afrikaanse Tydskrif vir Geneeskunde*. 2013;103:382–386.
83 Maltha J, Guiraud I, Kaboré B, et al. Frequency of severe malaria and invasive bacterial infections among children admitted to a rural hospital in Burkina Faso. *PLoS One*. 2014;9:e89103.
84 Kabanangi F, Joachim A, Nkuwi EJ, Manyahi J, Moyo S, Majigo M. High level of multidrug-resistant gram-negative pathogens causing burn wound infections in hospitalized children in dar es salaam, Tanzania. *Int J Microbiol*. 2021;2021:6644185.
85 Nkrumah NO, Twum-Danso K, Krogfelt K, Newman M. High levels of extended-spectrum beta-lactamases in a major teaching hospital in Ghana: the need for regular monitoring and evaluation of antibiotic resistance. *Am J Trop Med Hyg*. 2013;89:960–964. https://doi.org/10.4269/ajtmh.12-0642.

86 Djie-Maletz A, Reither K, Danour S, et al. High rate of resistance to locally used antibiotics among enteric bacteria from children in Northern Ghana. *J Antimicrob Chemother*. 2008;61:1315–1318.
87 Breurec S, Bouchiat C, Sire J-M, et al. High third-generation cephalosporin resistant Enterobacteriaceae prevalence rate among neonatal infections in Dakar, Senegal. *BMC Infect Dis*. 2016;16(1):587. https://doi.org/10.1186/s12879-016-1935-y.
88 Patil R, Kabera B, Muia C, Ale B. Hospital acquired infections in a private paediatric hospital in Kenya: a retrospective cross-sectional study. *Pan Afr Med J*. 2022;41:28. https://doi.org/10.11604/pamj.2022.41.28.25820.
89 Chiyangi H, Muma J, Malama S, et al. Identification and antimicrobial resistance patterns of bacterial enteropathogens from children aged 0-59 months at the University Teaching Hospital, Lusaka, Zambia: a prospective cross sectional study. *BMC Infect Dis*. 2017;17:117.
90 Page A-L, de Rekeneire N, Sayadi S, et al. Infections in children admitted with complicated severe acute malnutrition in Niger. *PLoS One*. 2013;8:e68699.
91 Gebreegziabher G, Asrat D, W/Amanuel Y, Hagos T. Isolation and antimicrobial susceptibility profile of Shigella and Salmonella species from children with acute diarrhoea in mekelle hospital and semen health center, Ethiopia. *Ethiop J Health Sci*. 2018;28:197–206.
92 Massinga AJ, Garrine M, Messa A, et al. Klebsiella spp. cause severe and fatal disease in Mozambican children: antimicrobial resistance profile and molecular characterization. *BMC Infect Dis*. 2021;21:526.
93 Gezmu AM, Bulabula A, Dramowski A, et al. Laboratory-confirmed bloodstream infections at two large neonatal units in Sub-Saharan Africa. *Int J Infect Dis*. 2020;103:201–207. https://doi.org/10.1016/j.ijid.2020.11.169. published online Nov 20.
94 Hayamo M, Tsegaye A, Tadesse B, Mitiku E, Bedawi Z. Magnitude, risk factors and antimicrobial susceptibility pattern of Shigella and Salmonella , among children with diarrhea in Southern Ethiopia: a Cross-sectional Study. *SAGE Open Medicine*. 2021;9:205031212110097.
95 Huenger F, Agyekum A, Nkrumah B, et al. *Massive emergence of multidrug- resistant Enterobacteriaceae in blood culture isolates of children in Ghana*. 2010. published online 13th.
96 Saeed A, Abd H, Sandström G. Microbial aetiology of acute diarrhoea in children under five years of age in khartoum, Sudan. *J Med Microbiol*. 2015;64(Pt 4):432–437. https://doi.org/10.1099/jmm.0.000043.
97 Omoregie R, Egbe C, Dirisu J, Ogefere H. Microbiology of neonatal septicemia in a tertiary hospital in Benin City, Nigeria. *Biomark Genom Med*. 2013;5:142–146.
98 Ifeanyi C, Ikeneche N, Enya Bassey B, Morabito S, Graziani C, Caprioli A. Molecular and phenotypic typing of enteropathogenic Escherichia coli isolated in childhood acute diarrhea in Abuja, Nigeria. *J Infect Dev Countr*. 2017;11:527.
99 Manhique-Coutinho L, Chiani P, Michelacci V, et al. Molecular characterization of diarrheagenic Escherichia coli isolates from children with diarrhea: a cross-sectional study in four provinces of Mozambique: diarrheagenic Escherichia coli in Mozambique. *Int J Infect Dis*. 2022;121:190–194.
100 Duru C, Olanipekun G, Odili V, et al. Molecular characterization of invasive Enterobacteriaceae from pediatric patients in Central and Northwestern Nigeria. *PLoS One*. 2020;15:e0230037.
101 Saka H, Id S, García Soto S, et al. Molecular detection of extended spectrum β-lactamase genes in Escherichia coli clinical isolates from diarrhoeic children in Kano, Nigeria. *PLoS One*. 2020;15:1–8.
102 Okafor A, David E. Multi-Drug resistance and biofilm production among diarrheagenic Escherichia coli pathotypes isolated from stools of children with acute diarrhoeal disease. *Russian Journal of Infection and Immunity*. 2021;11:958.
103 Ahmed M, Moremi N, Mirambo M, et al. Multi-resistant gram negative enteric bacteria causing urinary tract infection among malnourished underfives admitted at a tertiary hospital, northwestern, Tanzania. *Ital. J Pediatr*. 2015;41:44.
104 Chigor V, Umoh V, Smith S, Igbinosa E, Okoh A. Multidrug resistance and plasmid patterns of Escherichia coli O157 and other E. coli isolated from diarrhoeal stools and surface waters from some selected sources in zaria, Nigeria. *Int J Environ Res Publ Health*. 2010;7:3831–3841.
105 Zachariah OH, Lizzy MA, Rose K, Angela MM. Multiple drug resistance of Campylobacter jejuni and Shigella isolated from diarrhoeic children at Kapsabet County referral hospital, Kenya. *BMC Infect Dis*. 2021;21:109.
106 Weldu Y, Naizgi M, Hadgu A, et al. Neonatal septicemia at intensive care unit, Ayder Comprehensive Specialized Hospital, Tigray, North Ethiopia: bacteriological profile, drug susceptibility pattern, and associated factors. *PLoS One*. 2020;15:e0235391.
107 Tack B, Phoba M-F, Barbé B, et al. Non-typhoidal Salmonella bloodstream infections in Kisantu, DR Congo: emergence of O5-negative Salmonella Typhimurium and extensive drug resistance. *PLoS Neglected Trop Dis*. 2020;14:e0008121.
108 Mshana S, Gerwing L, Minde M, et al. Outbreak of a novel Enterobacter sp carrying bla(CTX-M-15) in a neonatal unit of a tertiary care hospital in Tanzania. *Int J Antimicrob Agents*. 2011;38:265–269.
109 Kayange N, Kamugisha E, Mwizamholya D, Seni J, Mshana S. Predictors of positive blood culture and deaths among neonates with suspected Neonatal sepsis in a tertiary hospital, Mwanza-Tanzania. *BMC Pediatr*. 2010;10:39.
110 Marando R, Seni J, Mirambo MM, et al. Predictors of the extended-spectrum-beta lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. *Int J Med Microbiol*. 2018;308:803–811.
111 Pantalius N, Assob J, Akoachere J-F. Predictors of urinary tract infections in children and antibiotic susceptibility pattern in the buea health district, south WestRegion, Cameroon. *BioMed Res Int*. 2020;2020:11.
112 Akingbade A, Olasunkanmi OI, Akintunde A, Okerentugba P, Babatunde O, Okonko I. Prevalence and antibiotic profile of Enterobacter species isolated from children with diarrhea in abeokuta, Ogun state, Nigeria. *Stem Cell*. 2013;4:1–4.
113 Sang W, Oundo V, Schnabel D. Prevalence and antibiotic resistance of bacterial pathogens isolated from childhood diarrhoea in four provinces of Kenya. *J Infect Dev Countr*. 2012;6:572–578.
114 Iroha I, Onyia U, Moses I, Ejikeugwu C, Nwakaeze E, Nnabuike U. Prevalence and antibiotic resistance profiles of extended spectrum β-lactamase-producing Escherichia coli among paediatric patients with urinary tract infection in St. Patricks' Hospital, Mile Four, Abakaliki, Ebonyi State, Nigeria. *Afr J Clin Exp Microbiol*. 2019;20:332.
115 Abebe W, Earsido A, Taye S, Assefa M, Eyasu A, Godebo G. Prevalence and antibiotic susceptibility patterns of Shigella and Salmonella among children aged below five years with Diarrhoea attending Nigist Eleni Mohammed memorial hospital, South Ethiopia. *BMC Pediatr*. 2018;18:241. https://doi.org/10.1186/s12887-018-1221-9.
116 Moremi N, Othman A, Msaki B, Mshana S. Prevalence and antimicrobial sensitivity of Shiga-toxin-producing Escherichia coli among underfives presenting with diarrhoea at hospitals in Mwanza City, Tanzania. *Tanzan J Health Res*. 2017;19:7. https://doi.org/10.4314/thrb.v19i1.7.
117 Duffa Y, Kitila K, Gebretsadik D, Bitew A. Prevalence and antimicrobial susceptibility of bacterial uropathogens isolated from pediatric patients at yekatit 12 hospital medical college, addis ababa, Ethiopia. *Int J Microbiol*. 2018;2018:1–8.
118 Assefa A, Girma M. Prevalence and antimicrobial susceptibility patterns of Salmonella and Shigella isolates among children aged below five years with diarrhea attending Robe General Hospital and Goba Referral Hospital, South East Ethiopia. *Trop Dis Travel Med Vaccines*. 2019;5:19. https://doi.org/10.1186/s40794-019-0096-6.
119 Agyekum A. *Prevalence of bacteria causing bacteraemia in children under five years in agogo, Asante-Akyem and their antimicrobial susceptibility patterns*. 2010.
120 Yimer R, Geda B, Teklemariam Z, Weldegebreal F, Balakrishnan S. Prevalence of childhood diarrhoea and associated risk factors in Dire Dawa, Eastern Ethiopia. *J Public Health*. 2018;26:29–37. https://doi.org/10.1007/s10389-017-0843-y.
121 Djim-Adjim-Ngana K, Oumar L, Mbiakop B, et al. Prevalence of extended-spectrum beta-lactamase-producing enterobacterial urinary infections and associated risk factors in small children of Garoua, Northern Cameroon. *Pan Afr Med J*. 2020;36:157.
122 Mulatu G, Beyene G, Zeynudin A. Prevalence of Shigella, Salmonella and cmpylobacter species and their susceptibility patters among under five children with diarrhea in hawassa town, south Ethiopia. *Ethiop J Health Sci*. 2014;24:101–108.
123 Alemu A, Geta M, Taye S, Eshetie S, Engda T. Prevalence, associated risk factors and antimicrobial susceptibility patterns of Shigella infections among diarrheic pediatric population attending at

Gondar town healthcare institutions, Northwest Ethiopia. *Trop Dis Travel Med Vaccines*. 2019;5:7.
124 Shah M, Kathiiko C, Wada A, et al. Prevalence, seasonal variation, and antibiotic resistance pattern of enteric bacterial pathogens among hospitalized diarrheic children in suburban regions of central Kenya. *Trop Med Health*. 2016;44:39. https://doi.org/10.1186/s41182-016-0038-1.
125 GebreSilasie YM, Tullu KD, Yeshanew AG. Resistance pattern and maternal knowledge, attitude and practices of suspected Diarrheagenic Escherichia coli among children under 5 years of age in Addis Ababa, Ethiopia: cross sectional study. *Antimicrob Resist Infect Control*. 2018;7:110.
126 Adamu I, Ishaleku D. Resistance to ciprofloxacin in hospital-acquired urinary tract infections due to Escherichia coli in children population: risk factors Determinants. *Int J Infect Dis*. 2020;101:46.
127 Andersen C, Langendorf C, Garba S, et al. Risk of community- and hospital-acquired bacteremia and profile of antibiotic resistance in children hospitalized with severe acute malnutrition in Niger. *Int J Infect Dis*. 2022;119:163–171. https://doi.org/10.1016/j.ijid.2022.03.047.
128 Appiah GD, Mpimbaza A, Lamorde M, et al. Salmonella bloodstream infections in hospitalized children with acute febrile illness-Uganda, 2016-2019. *Am J Trop Med Hyg*. 2021;105(1):37–46.
129 Kasumba IN, Sen S, Sayed N, et al. *Salmonella enterica serovars isolated from stool children enrolled in the global enteric multicenter study*. 2017:545.
130 Ejikeugwu C, Iroha I, Adikwu M, Charles E. Susceptibility and detection of extended spectrum β-Lactamase enzymes from Otitis media pathogens. *Am J Infect Dis*. 2013;9:24–29.
131 Schwarz NG, Sarpong N, Hünger F, et al. Systemic bacteraemia in children presenting with clinical pneumonia and the impact of non-typhoid salmonella (NTS). *BMC Infect Dis*. 2010;10:319.
132 David E, Yameen A, Igwenyi I, et al. The frequency of virulent genes and antimicrobial resistance patterns of diarrheagenic Escherichia coli isolated from stools of children presenting with diarrhea in a tertiary hospital in Abakaliki, Nigeria. *Int J One Health*. 2020;6(2):147–152. https://doi.org/10.14202/IJOH.2020.147-152.
133 Seni J, Peirano G, Mshana S, Pitout J, DeVinney R. The importance of Escherichia coli clonal complex 10 and ST131 among Tanzanian patients on antimicrobial resistance surveillance programs. *Eur J Clin Microbiol Infect Dis*. 2021. https://doi.org/10.1007/s10096-021-04271-w. published online May 19.
134 Ughasoro MD, Akpeh JO, Echendu N, et al. The profile of microorganisms that associate with acute tonsillitis in children and their antibiotics sensitivity pattern in Nigeria. *Sci Rep*. 2021;11:20084.
135 Jemal M, Tinshku F, Nigussie Y, et al. Trend analysis of multidrug-resistant bacterial pathogens causing neonatal sepsis at university of gondar comprehensive specialized hospital, northwest Ethiopia: a retrospective study. *Int J Microbiol*. 2021;2021:9992994.
136 Savadogo H, Dao L, Tondé I, et al. [Urinary tract infections in a pediatric setting: bacterial ecology and antibiotic susceptibility at the Pediatric Teaching Hospital Charles-de-Gaulle in Ouagadougou (Burkina Faso)]. *Nephrol Ther*. 2021;17:532–537.
137 Sangare S, Rondinaud E, Maataoui N, et al. Very high prevalence of extended-spectrum beta-lactamase-producing Enterobacteriaceae in bacteriemic patients hospitalized in teaching hospitals in Bamako, Mali. *PLoS One*. 2017;12:e0172652.
138 Nebbioso A, Ogundipe O, Repetto E, et al. When first line treatment of neonatal infection is not enough: blood culture and resistance patterns in neonates requiring second line antibiotic therapy in Bangui, Central African Republic Open Access. *BMC Pediatr*. 2021;21:570.
139 Williams PCM, Isaacs D, Berkley JA. Antimicrobial resistance among children in sub-Saharan Africa. *Lancet Infect Dis*. 2018;18:e33–e44.
140 Droz N, Hsia Y, Ellis S, Dramowski A, Sharland M, Basmaci R. Bacterial pathogens and resistance causing community acquired paediatric bloodstream infections in low- and middle-income countries: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2019;8:207.
141 Bernabé KJ, Langendorf C, Ford N, Ronat J-B, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2017;50:629–639.
142 Okomo U, Akpalu ENK, Le Doare K, et al. 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. *Lancet Infect Dis*. 2019;19:1219–1234.
143 Wen SCH, Ezure Y, Rolley L, et al. Gram-negative neonatal sepsis in low- and lower-middle-income countries and WHO empirical antibiotic recommendations: a systematic review and meta-analysis. *PLoS Med*. 2021;18:e1003787.
144 World Health Organization. *Regional office for Africa. Antimicrobial resistance in the WHO african region: a systematic literature review*. 2021.
145 Haindongo EH, Ndakolo D, Hedimbi M, Vainio O, Hakanen A, Vuopio J. Antimicrobial resistance prevalence of Escherichia coli and Staphylococcus aureus amongst bacteremic patients in Africa: a systematic review. *J Glob Antimicrob Resist*. 2022;32:35–43.
146 Lester R, Musicha P, van Ginneken N, et al. Prevalence and outcome of bloodstream infections due to third-generation cephalosporin-resistant Enterobacteriaceae in sub-Saharan Africa: a systematic review. *J Antimicrob Chemother*. 2020;75:492–507.
147 Zelellw DA, Dessie G, Worku Mengesha E, Balew Shiferaw M, Mela Merhaba M, Emishaw S. A systemic review and meta-analysis of the leading pathogens causing neonatal sepsis in developing countries. *BioMed Res Int*. 2021;2021:6626983.
148 Essel V, Tshabalala K, Ntshoe G, et al. A multisectoral investigation of a neonatal unit outbreak of Klebsiella pneumoniae bacteraemia at a regional hospital in Gauteng Province, South Africa. *S Afr Med J*. 2020;110:783–790.
149 Bor M, Ilhan O. Carbapenem-resistant Klebsiella pneumoniae outbreak in a neonatal intensive care unit: risk factors for mortality. *J Trop Pediatr*. 2021;67:fmaa057.
150 Cornick J, Musicha P, Peno C, et al. Genomic investigation of a suspected Klebsiella pneumoniae outbreak in a neonatal care unit in sub-Saharan Africa. *Microb Genom*. 2021;7:000703.
151 Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA*. 2018;115:E3463–E3470.
152 Saleem Z, Godman B, Cook A, et al. Ongoing efforts to improve antimicrobial utilization in hospitals among African countries and implications for the future. *Antibiotics (Basel)*. 2022;11:1824.
153 Belachew SA, Hall L, Selvey LA. Non-prescription dispensing of antibiotic agents among community drug retail outlets in Sub-Saharan African countries: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2021;10:13.
154 McDanel J, Schweizer M, Crabb V, et al. Incidence of extended-spectrum β-lactamase (ESBL)-Producing Escherichia coli and Klebsiella infections in the United States: a systematic literature review. *Infect Control Hosp Epidemiol*. 2017;38:1209–1215.
155 Lukac PJ, Bonomo RA, Logan LK. Extended-spectrum β-lactamase-producing Enterobacteriaceae in children: old foe, emerging threat. *Clin Infect Dis*. 2015;60:1389–1397.
156 Adler A, Katz DE, Marchaim D. The continuing plague of extended-spectrum β-lactamase-producing enterobacteriaceae infections. *Infect Dis Clin North Am*. 2016;30:347–375.
157 Ouchar Mahamat O, Kempf M, Lounnas M, et al. Epidemiology and prevalence of extended-spectrum β-lactamase- and carbapenemase-producing Enterobacteriaceae in humans, animals and the environment in West and Central Africa. *Int J Antimicrob Agents*. 2021;57:106203.
158 Sherif M, Abera D, Desta K. Prevalence and antibiotic resistance pattern of bacteria from sepsis suspected neonates at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. *BMC Pediatr*. 2023;23:575.
159 Worku E, Fenta DA, Ali MM. Bacterial etiology and risk factors among newborns suspected of sepsis at Hawassa, Ethiopia. *Sci Rep*. 2022;12:20187.
160 Egbe FN, Cowden C, Mwananyanda L, et al. Etiology of bacterial sepsis and isolate resistance patterns in hospitalized neonates in Zambia. *Pediatr Infect Dis J*. 2023;42:921–926.
161 Munyemana JB, Gatare B, Kabanyana P, et al. Antimicrobial resistance profile of bacteria causing pediatric infections at the university teaching hospital in Rwanda. *Am J Trop Med Hyg*. 2022;107:1308–1314.
162 Gulumbe BH, Haruna UA, Almazan J, Ibrahim IH, Faggo AA, Bazata AY. Combating the menace of antimicrobial resistance in Africa: a review on stewardship, surveillance and diagnostic strategies. *Biol Proced Online*. 2022;24:19.
163 Natale A, Ronat J-B, Mazoyer A, et al. The Mini-Lab: accessible clinical bacteriology for low-resource settings. *Lancet Microbe*. 2020;1:e56–e58.