Carriage of third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales among children in sub-Saharan Africa: a systematic review and meta-analysis

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

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

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Summary

Background The increasing resistance of Enterobacterales to third-generation cephalosporins and carbapenems in sub-Saharan Africa (SSA) is a major public health concern. We did a systematic review and meta-analysis of studies to estimate the carriage prevalence of Enterobacterales not susceptible to third-generation cephalosporins or carbapenems among paediatric populations in SSA.

Methods We performed a systematic literature review and meta-analysis of cross-sectional and cohort studies to estimate the prevalence of childhood (0–18 years old) carriage of extended-spectrum cephalosporin-resistant Enterobacterales (ESCR-E) or carbapenem-resistant Enterobacterales (CRE) in SSA. Medline, EMBASE and the Cochrane Library were searched for studies published from 1 January 2005 to 1 June 2022. Studies with <10 occurrences per bacteria, case reports, and meta-analyses were excluded. Quality and risk of bias were assessed using the Newcastle–Ottawa scale. Meta-analyses of prevalences and odds ratios were calculated using generalised linear mixed-effects models. Heterogeneity was assessed using I^2 statistics. The protocol is available on PROSPERO (CRD42021260157).

Findings Of 1111 studies examined, 40 met our inclusion criteria, reporting on the carriage prevalence of Enterobacterales in 9408 children. The pooled carriage prevalence of ESCR-E was 32.2% (95% CI: 25.2%–40.2%). Between-study heterogeneity was high (I^2 = 96%). The main sources of bias pertained to participant selection and the heterogeneity of the microbiological specimens. Carriage proportions were higher among sick children than healthy ones (35.7% *vs* 16.9%). The pooled proportion of nosocomial acquisition was 53.8% (95% CI: 32.1%–74.1%) among the 922 children without ESCR-E carriage at hospital admission. The pooled odds ratio of ESCR-E carriage after antibiotic treatment within the previous 3 months was 3.20 (95% CI: 2.10–4.88). The proportion of pooled carbapenem-resistant for Enterobacterales was 3.6% (95% CI: 0.7%–16.4%).

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*Corresponding author. Division of Paediatric Emergency Medicine, Children's Hospital, Geneva University Hospitals and Faculty of Medicine, Rue Willy Donzé 6, Geneva 1205, Switzerland.
E-mail address: Annick.galetto@hcuge.ch (A. Galetto-Lacour).
[n]Joint senior authors.

Interpretation This study suggests that ESCR-E carriage among children in SSA is frequent. Microbiology capacity and infection control must be scaled-up to reduce the spread of those multidrug-resistant microorganisms.

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Keywords: Third-generation cephalosporin-resistant Enterobacterales; Carbapenem-resistant Enterobacterales; Sub-Saharan Africa; Child; Carriage; Systematic review and meta-analysis

Research in context

Evidence before this study

The increase in Enterobacterales resistant to third-generation cephalosporins and carbapenems in sub-Saharan Africa (SSA) is a major public health concern. Synthesised data about childhood carriage of MDR bacteria in SSA are lacking and a literature review to estimate the current prevalence of antibiotic resistance was needed to inform interventions to reduce their spread.

A scoping literature review using Medline and EMBASE limited to publications from 2005 to 2022 identified multiple studies reporting on the carriage prevalence of MDR Enterobacterales. These provided the rationale for a systematic review and meta-analysis.

Added value of this study

To our knowledge, this is the first systematic review and meta-analysis to report on carriage prevalence among a large cohort of almost 10,000 children in SSA. The pooled prevalence of carriage of extended-spectrum cephalosporin-resistant Enterobacterales (ESCR-E) was close to one-third of children. The influence of hospitalisation was highlighted by the fact that hospitalised children had a significantly higher prevalence than outpatients and that nosocomial acquisition was 50% among children without ESCR-E carriage at admission. The risk of ESCR-E carriage was >3 times higher among those treated with antibiotics in the previous 3 months, reinforcing the potentially negative consequences of prior antibiotic treatment. The role of MDR resistant *Klebsiella* spp. in neonatal infections was underlined by its predominance among newborns. The prevalence of carbapenem resistant Enterobacterales varied widely between studies but remained below 4% on average.

Implications of all the available evidence

This review suggests that there may be worrying rates of MDR Enterobacterales carriage among children in SSA. The relatively high prevalence among healthy children suggests an important spread within the community. The high rates of nosocomial acquisition and the impact of prior antibiotic use on the development of MDR Enterobacterales confirm the need to scale up the implementation of antimicrobial stewardship interventions.

Introduction

Antimicrobial resistance (AMR) is a major global health concern, especially in low- and middle-income countries such as in sub-Saharan Africa (SSA).[1] Antibiotic resistance results in considerable morbidity and mortality.[2–4] Vulnerable populations in these countries, such as children and neonates, are disproportionately affected by antibiotic-resistant infections. Based on recent data, approximately 30% of newborns with sepsis die due to bacterial infections resistant to first-line antibiotics.[5]

The overuse of broad-spectrum antibiotics, such as the Watch antibiotics included in the WHO's AWaRe (Access, Watch, Reserve) framework[6] is probably a significant cause of such high levels of antibiotic resistance. The overuse of antibiotics is often the consequence of the inability to adequately identify bacterial species and perform antimicrobial susceptibility testing.[7] Other factors contributing to the overuse of antibiotics include healthcare workers' lack of training and awareness about antimicrobial resistance, short consultation times, the low cost of antibiotics, the lack of regulations prohibiting the purchase of antibiotics without a prescription, and the fear of missing severe bacterial infections. This results in 83%–100% of children hospitalised in Africa being treated with antibiotics.[8,9] This, combined with the lack of development of new antibiotics, is worrisome, particularly for pan-drug-resistant Gram-negative bacteria such as metal beta-lactamase-producing Enterobacterales.[10]

An overview of the prevalence of antibiotic resistance in infants and neonates in SSA countries is needed to develop specific clinical guidelines.[7] The Global Antimicrobial Resistance Surveillance System (GLASS) is an effective system to foster the surveillance of antimicrobial resistance, but only a minority of African countries report data on GLASS, and these reports do not focus on childhood populations.[11]

Determining the carriage of MDR Enterobacterales is important since carriage precedes and predicts subsequent infections.[12] Moreover, unlike data obtained from infectious clinical cases, carriage data are less

dependent on patients' health care-seeking behavior and health care workers' willingness to identify resistant pathogens. Thus, carriage data may help provide more comprehensive data on the spread of AMR.[13] Carriage studies also enable us to evaluate the nosocomial acquisition of antibiotic-resistant germs and the influence of previous antibiotic consumption.

There is a lack of synthesised data about childhood carriage of MDR bacteria in Africa. A literature review to estimate the current prevalence of antibiotic resistance among children in SSA was needed to inform interventions to reduce their spread. The present study aimed to estimate the carriage prevalence of extended-spectrum cephalosporin-resistant Enterobacterales (ESCR-E) and carbapenem-resistant Enterobacterales (CRE) among children in SSA.

Methods

We performed a systematic review and meta-analysis of the literature. The protocol is available on the PROSPERO registry (CRD42021260157) and was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.

The main outcome was the carriage prevalence of Enterobacterales not susceptible to third-generation cephalosporins or carbapenems among paediatric populations in SSA.

The secondary outcomes were:

- Factors that might be associated with the carriage prevalence of ESCR-E and CRE. Those factors were a priori selected by AGL and NW.
- The susceptibility of ESCR-E and CRE to other antibiotics than those mentioned above.
- The prevalence of different genes of antimicrobial resistance to third-generation cephalosporins and carbapenems.
- The impact of previous or current antibiotic treatments on the development of MDR bacteria. We compared the prevalence of ESCR-E carriage between children who had and had not received antibiotics in the previous 3 months, and we compared the prevalence between children currently receiving, or not, antibiotics.
- In order to evaluate hospitalisation consequences on carriage, we compared the carriage prevalence of ESCR-E at hospital admission against carriage at least >2 days of hospitalisation, and investigated nosocomial acquisition rates among children who had not tested positive for ESCR-E at hospital admission.

ESCR-E were defined as Enterobacterales non-susceptible to ceftriaxone, ceftazidime or cefotaxime.[14] CRE were defined as Enterobacterales non-susceptible to imipenem, meropenem, or ertapenem. The term 'non-susceptible' is used for Enterobacterales considered resistant or intermediate to a given antibiotic, according to the final interpretative results presented by each study. Carriage prevalence was defined as the number of children with faecal, rectal, or surface swabs positive for at least one ESCR-E or CRE divided by the number of children screened. Studies of the same population performed at different times were included only once, with the exception of the sub-analyses for nosocomial detection or acquisition, where two samples were recorded per child: one on admission and one at least >2 days of hospitalisation.

Inclusion criteria, search strategy and study selection

Cross-sectional or cohort studies were eligible if they reported on the carriage of ESCR-E or CRE in the paediatric populations (0–18 years) of SSA, but excluding South Africa. We excluded South Africa because we wanted to focus on countries with limited available data and healthcare resources. Predefined exclusion criteria included case reports, meta-analyses, and studies involving fewer than ten occurrences per bacteria.

We searched Medline, EMBASE and the Cochrane Central Register of Controlled Trials for studies published from 1 January 2005 to 1 June 2022. The search strategy is described in detail in the Supplementary Material (Appendix pp 2). We used Covidence® software (Melbourne, Australia) to manage the screening and selection of studies. Three reviewers (AGL, MR, BO) independently and in duplicate screened study titles and abstracts and subsequently assessed the potential eligibility of relevant full texts. Reviewers resolved any discrepancies in their selections through discussion.

Data extraction and risk of bias

Working independently and in duplicate, four reviewers (MR, BO, NW, AGL) extracted appropriate data from each eligible study, resolving disagreements through discussion. We collected data on study dates (patient inclusion), country, geographical area, participants' ages, numbers and health status (healthy or ill; healthy children were enrolled in community settings, healthy neonates, or during health visits for vaccination), subpopulations, nosocomial detection (at admission *vs* after 2 days of hospitalisation) and acquisition (for children negative at admission), previous history of antibiotic or ongoing antibiotic treatment, study design, types of samples, antibiotic susceptibility testing methods, numbers of children positive for the carriage of ESCR or CRE for *Escherichia coli*, *Klebsiella* spp., or at least one Enterobacterales bacteria, susceptibility to various antibiotics for ESCR-E or CRE, and the determination of genotypes of resistance to third-generation cephalosporin and carbapenem. We contacted study authors to try to obtain any missing data whenever suitable.

Each study's quality and risk of bias were assessed using the Newcastle–Ottawa assessment scale for cohort studies. The Newcastle–Ottawa Scale (NOS) is a risk of bias assessment tool for observational studies that is recommended by the Cochrane Collaboration.[15] Quality assessment items were tailored to our research question: participant selection, adequate description of participant characteristics, missing data, exposure assessment and outcome assessment. Study quality was assessed in duplicate by four independent, blinded reviewers, and disagreements were resolved by consensus.

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

Statistical analysis

Due to the expected between-study heterogeneity, the proportions of antibiotic resistance were combined across studies, systematically using models with random effects. To do this, we used one mixed-effects logistic regression model per bacteria and per antibiotic with a random intercept.[16] The level of heterogeneity between studies was assessed using the I^2 statistic.[17] Sources of heterogeneity were investigated by comparing sub-groups according to types of patients (healthy *vs* sick patients, newborn *vs* paediatric populations, hospitalised children *vs* outpatients), regions of SSA, dates covered by the study, and the use of selective *vs* non-selective culture media. No sensitivity analyses were planned.

The associations between antibiotic consumption and ESCR-E carriage were investigated among children currently receiving or not receiving antibiotics and among children with or without a history of antibiotic use in the previous three months: pooled odds ratios were assessed using generalised linear mixed-effects models.

All the statistical analyses used a 5% two-sided alpha risk and were performed using *R* software v4.0.2 (the R foundation for statistical computing, Vienna, Austria) and the *meta* package.[18]

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

The initial literature search yielded 1111 potential studies; 586 of these were excluded based on their titles or abstracts, and 485 were excluded after reading of the entire text (see Fig. 1 for reasons for exclusion). This left 40 studies,[19–58] involving a total of 9408 children, that reported on the carriage prevalence of Enterobacterales resistant to third-generation cephalosporins or carbapenems.

The studies' characteristics, including the methods used for antibiotic susceptibility testing and geographical areas, are shown in the Appendix (pp 3–5) and Fig. 2. The selection of study participants (e.g. specific populations of malnourished or HIV-positive patients) or the origins of the samples (e.g. nasopharyngeal or skin samples, mixed with stool cultures) were the main sources of potential bias highlighted by the Newcastle–Ottawa assessment scale (Appendix pp 6–7). Of the 40 studies, 28 were cross-sectional, and 12 were

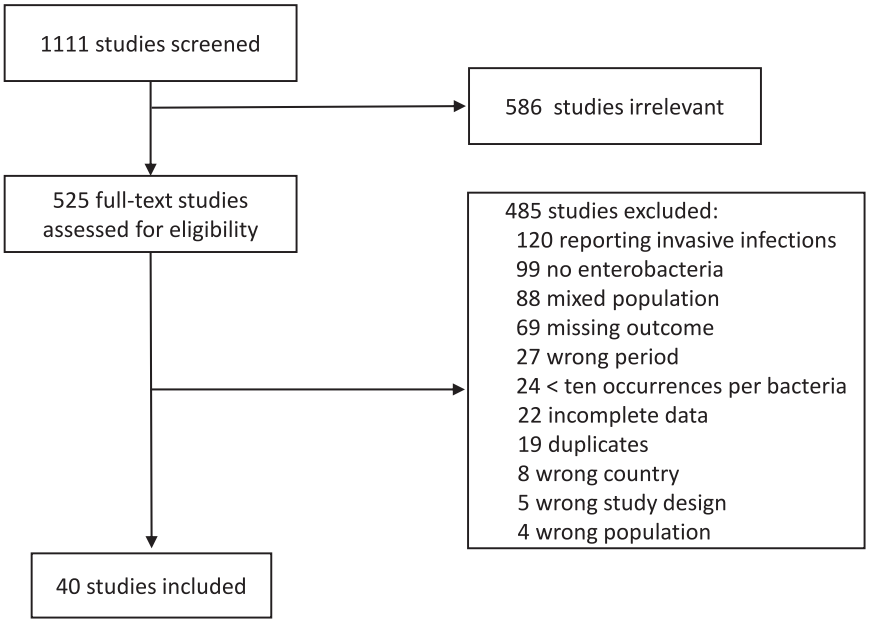

Fig. 1: **Study selection.**

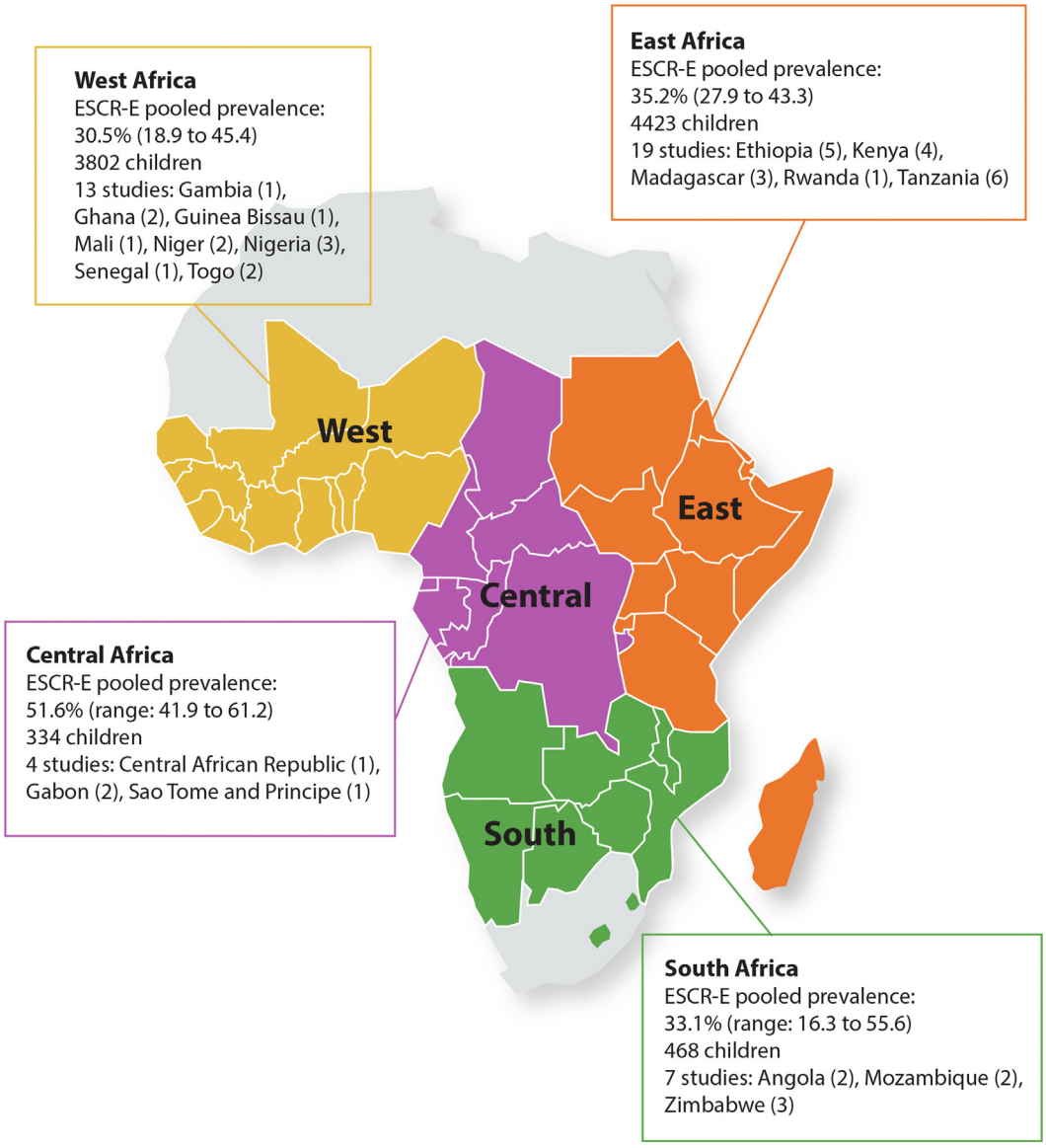

Fig. 2: **Pooled prevalence of ESCR-E by region, number of studies, and number of children screened by region, and number of studies by country.** ESCR-E = extended-spectrum cephalosporin-resistant Enterobacterales pooled prevalence (%) (95% CI). One study reported the ESCR-E prevalence in multiple countries: Gambia, Kenya, Mozambique, and Mali.

cohort studies. Most studies used selective culture media to select MDR bacteria from stool samples (n = 30). Nine studies included neonates, 11 included healthy children, and 28 included hospitalised children (0–18 years).

The reported prevalence of ESCR-E carriage was highly heterogeneous (from 0 to 61% for 9146 children), with a pooled prevalence of 32.2% (95% CI: 25.2%–40.2%) for the carriage of at least one Enterobacterales bacteria (Fig. 3), 17.3% (95% CI: 12.7%–23.2%) for *E. coli* (Appendix pp 8), and 11.8% (95% CI: 7.6%–17.9%) for *Klebsiella* spp. (Appendix pp 9).

The between-study heterogeneity in the prevalence of ESCR-E was high (I^2 = 94%). The pooled prevalence of ESCR-E was higher among hospitalised children than among outpatients (Table 1, Appendix pp 10–11). The pooled prevalence of ESCR *Klebsiella* spp. carriage was four times higher among hospitalised children (26.3% of 1578 children) than among outpatients (6.5% of 2411 children). Healthy children had an ESCR-E carriage rate of 16.9% (95% CI: 8.5%–30.8%) among 2979 children. The prevalence of ESCR-E carriage was twice as high among sick children than among healthy children. Fewer newborns carried ESCR-*E. coli* (9.3% of 1672

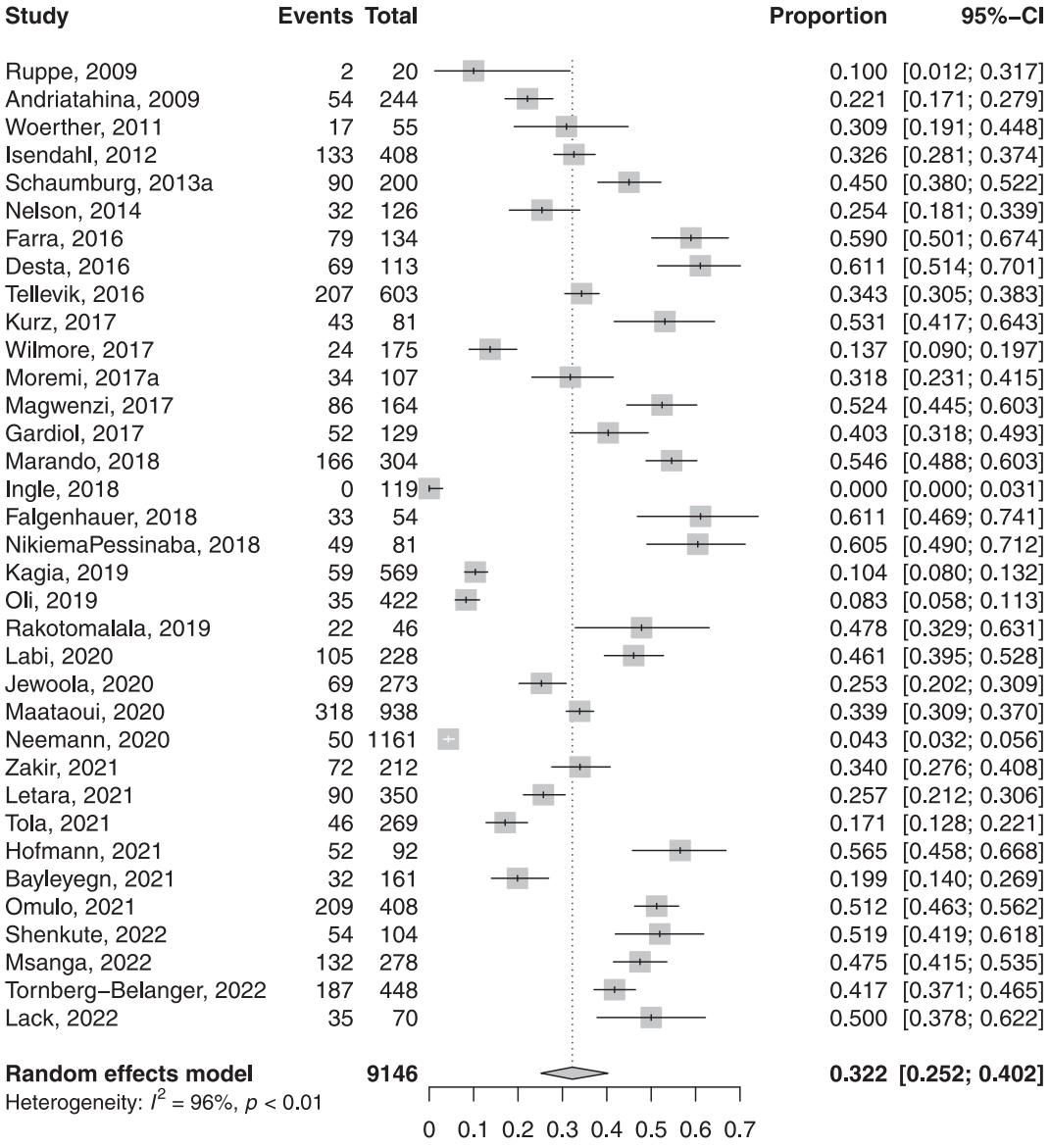

Fig. 3: **Forest plot for the carriage prevalence of extended-spectrum cephalosporin-resistant Enterobacterales among children in sub-Saharan Africa.** I^2 = level of heterogeneity. CI = confidence interval.

neonates *vs* 20.0% of 4238 children), but they more frequently carried ESCR-*Klebsiella* spp. (22.1% of 1672 neonates *vs* 10.3% of 3270 children), although this difference was not statistically significant. No associations were found with the other study characteristics, such as studies' dates or the use of ESCR-selective media. The exception was for geographical area, but this association was driven by just two studies with higher ESCR-E carriage in Central Africa (*p* value: 0.030) (Table 1, Appendix pp 10–11).

Six studies assessed the impact of hospitalisation, involving a total of 1386 children.[26,33,36,39,40,52] Their pooled prevalence of ESCR-E carriage was 29.5% (95% CI: 18.1%–44.2%) at admission, which increased to 75.6% (95% CI: 52.0%–89.9%) after 2 days of hospitalisation (Table 2, Appendix pp 12). Pooled prevalence of nosocomial acquisition was 53.8% (95% CI: 32.1%–74.1%) among 922 children without ESCR-E carriage at admission. Some 137 (9.8%) children were lost to follow-up between admission and discharge, either leaving hospital without being tested or dying.

Nine studies involving 1842 children evaluated associations between ongoing antibiotic treatments and ESCR-E carriage by comparing children with and without current antibiotic treatment.[21,30,35,40,44,45,47,53,56] The pooled OR was 3.78 (95% CI: 1.85–7.71). The risk of

	Enterobacterales[a]			*E. coli*			*Klebsiella* spp.		
	N	Pooled prevalence (95% CI)	I^2 (%)	N	Pooled prevalence (95% CI)	I^2 (%)	N	Pooled prevalence (95% CI)	I^2 (%)
West	12	30.5 (18.9–45.4)	97.6	8	23.0 (13.5–36.4)	93.3	5	17.8 (10.2–29.3)	93.8
Central	2	51.6 (41.9–61.2)	83.9	2	24.7 (12.1–44.0)	95.4	2	25.4 (15.9–37.9)	89.5
East	17	35.2 (27.9–43.3)	95.9	14	16.3 (11.3–22.8)	95.7	13	10.6 (6.2–17.4)	95.8
South	3	33.1 (16.3–55.6)	96.2	3	17.7 (7.5–36.2)	95.3	1	0.6 (0.1–3.9)	NA
p-value		0.0305			0.5947			0.0003	
Healthy	11	16.9 (8.5–30.8)	97.5	7	11.1 (5.0–23.0)	92.3	4	6.4 (3.1–12.9)	89.7
Sick	28	35.7 (28.3–43.9)	94.9	21	18.3 (12.7–25.5)	94.8	16	13.1 (7.8–21.0)	95.2
p-value		0.0213			0.2417			0.1065	
Outpatients	18	23.2 (14.9–34.2)	95.8	13	11.4 (6.9–18.3)	92.2	11	6.5 (3.7–11.2)	89
Hospitalised	17	39.0 (29.0–50.1)	97	12	26.1 (18.2–36.0)	94.3	8	26.3 (20.3–33.3)	87.6
p-value		0.0366			0.006			<0.0001	
Neonates	7	27.7 (13.7–48.1)	98.7	6	9.3 (6.0–14.0)	90.1	6	22.1 (9.2–44.4)	97.7
Other children	29	34.2 (26.7–42.6)	94	23	20.0 (14.3–27.3)	92.9	16	10.3 (6.3–16.5)	92
p-value		0.5305			0.0046			0.1301	
Selective CM	23	35.8 (27.4–45.3)	97.1	17	21.2 (15.1–28.9)	93.4	14	10.7 (5.9–18.6)	95.4
Non-selective CM	9	22.2 (10.2–41.6)	95.5	7	10.2 (4.2–22.8)	96.6	5	15.0 (6.5–30.8)	96
p-value		0.1857			0.1163			0.5089	
2008–2015	17	30.7 (20.7–42.8)	94.8	14	17.1 (10.1–27.6)	93.7	12	12.8 (7.5–21.1)	93.1
2016–2022	17	35.2 (25.5–46.3)	97.6	12	19.0 (12.8–27.2)	95.5	9	10.7 (5.2–20.8)	96.6
p-value		0.5685			0.7427			0.6888	

N = number of studies. I^2(%) = level of heterogeneity. CI = confidence interval. ESCR-E = extended-spectrum cephalosporin-resistant Enterobacterales. CM = culture media.
[a]Carriage of at least one Enterobacterales.

Table 1: **Comparison of pooled carriage prevalence of extended-spectrum cephalosporin-resistant Enterobacterales and level of heterogeneity by region, healthy *vs* sick children, outpatients *vs* hospitalised, neonates *vs* other children, selective culture media for ESCR-E *vs* non-selective culture media, and period.**

ESCR-E carriage also increased significantly among patients who had received antibiotics in the previous three months, with an OR of 3.20 (95% CI: 2.10–4.88) in the eight studies (2580 children) that examined this issue (Table 3, Appendix pp 13).[25,37,42,43,46,48,50,51]

ESCR-E susceptibility to other antibiotics was also assessed (Table 4). Non-susceptibility to gentamicin was high (44.5% for *E. coli*; 90.2% for *Klebsiella* spp.), with non-susceptibility to amikacin much lower (5.1% for *E. coli*; 2% for *Klebsiella* spp.), although only about two hundred samples of ESCR-E were tested for amikacin. ESCR-*E. coli* and ESCR-*Klebsiella* spp. non-susceptibility to ciprofloxacin was around 50% (54% of 465 for *E. coli* and 46.3% of 446 for *Klebsiella* spp.).

Twelve studies analysed the extended-spectrum beta-lactamase resistance genes of 925 samples, either by using specific PCR tests (9 studies) or through whole genome sequencing (3 studies). A *bla*CTX-M-1 group genotype, particularly the *bla*CTX-M-15 allele, was detected in most of the ESCR-E samples (Table 5).

The prevalence of CRE carriage ranged substantially across studies, from 0 to 78% among 2817 children (Fig. 4), with a pooled prevalence of 3.6% (95% CI: 0.7%–16.4%). The pooled prevalence of CRE was higher when using CRE-selective media *vs* not using selective media, among hospitalised children than among outpatients, and higher among sick children than among healthy ones, even if only the former association was statistically significant (Table 6, Appendix pp 16–17).

Again, we observed a high level of non-susceptibility to gentamicin (49.6% for *E. coli*; 75.2% for *Klebsiella* spp.), whereas amikacin remained relatively efficient for

	Studies (No.)	Patients (No.)	ESCR-E positive patients (No.)	Pooled ESCR-E positivity rate (95% CI)	I^2 (%)
At admission	6	1386	327	29.5 (18.1–44.2)	96.6%
After >2 days of hospitalisation	6	1249	715	75.6 (52.0–89.9)	94.5%
After >2 days of hospitalisation for patients negative at admission	6	922	388	53.8 (32.1–74.1)	91.7%

I^2(%) = level of heterogeneity. CI = confidence interval. ESCR-E = extended-spectrum cephalosporin-resistant Enterobacterales.

Table 2: **Meta-analysis of studies examining associations with hospitalisation and carriage of extended-spectrum cephalosporin-resistant Enterobacterales.**

	Studies (No.)	Patients (No.) (treated/not treated)	ESCR-E positive patients (No.) (treated/not treated)	OR (95%CI)	I^2 (%)
Currently on antibiotics	9	1071/771	578/325	3.78 (1.85–7.71)	85.8
Antibiotics received in past three months	8	654/1926	304/477	3.20 (2.10–4.88)	75.4

I^2(%) = level of heterogeneity. CI = confidence interval. ESCR-E = extended-spectrum cephalosporin-resistant Enterobacterales.

Table 3: **Meta-analysis of studies examining associations between previous antibiotic exposure and carriage of extended-spectrum cephalosporin-resistant Enterobacterales.**

E. coli (17.3%) but not for *Klebsiella* spp. (73.5%) (Table 4). The two CRE genotypes detected in four of the studies were OXA-181 and NDM (Table 7).

Discussion

This meta-analysis found a high prevalence of ESCR-E carriage among children in SSA. The prevalence was higher among hospitalised children than among outpatients, and higher among sick children than among healthy ones. Our review also confirmed significant nosocomial acquisitions and substantial increases in detectable ESCR-E carriage within three months of having received antibiotics.

We found an overall ESCR-E carriage prevalence of 32% among the children sampled in SSA. This is much higher than the 5% prevalence found in the meta-analysis by Kanarika et al. However, their review included healthy children from different continents, with only one study carried out in SSA.[59] Synthesised carriage data from children from SSA are almost non-existent. Most studies have reported ESCR-E prevalence in populations including children and adults, with an overall prevalence of 21% among healthy individuals[60] and of 30% among a mixed population of healthy and sick individuals in SSA.[61]

We revealed an ESCR-E carriage prevalence that was twice as high among sick children than among healthy ones. Lewis et al. also revealed a higher prevalence among sick patients.[61] The relatively high prevalence among healthy children—when many of these studies included individuals with little to no exposure to formal healthcare or antibiotic use—suggests an important spread within the community.

Synthesised data on neonate carriage of ESCR-E were also scarce, with just one meta-analysis describing three studies with carriage rates ranging from 25% to 75%.[61] We observed a 27.7% pooled prevalence of ESCR-E colonisation among neonates, with different prevalence proportions of antibiotic resistance depending on the bacteria tested: ESCR-*E. coli* was less prevalent among neonates than among other children, but ESCR-*Klebsiella* spp. tended to be more common among neonates. This may be because of difficulty to implement specific infection control measures in resource-limited settings, especially for *Klebsiella* spp. which are well-known nosocomial pathogens.[62]

Surprisingly, we could not demonstrate any increase in the prevalence of ESCR-E over time, despite Bezabih et al.[63] having shown a 1.3%–1.5% yearly increase in the prevalence of extended-spectrum beta-lactamase when analysing the years 2000–2021. We also found no differences in prevalence when studies used a culture medium selective for the growth of ESCR-E, despite these media usually being more sensitive for detecting resistant bacteria.

We also found that ongoing or recent antibiotic treatments (past three months) were associated with the

	ESCR *E. coli* (N = 502)	N	I^2	ESCR *Klebsiella* spp. (N = 446)	N	I^2	CRE *E. coli* (N = 82)	N	I^2	CRE *Klebsiella* spp. (N = 49)	N	I^2
Chloramphenicol	36.8% (27.9–46.8)	270	52	52.8% (34–70.8)	223	84.7	••	••	••	••	••	••
Gentamicin	44.5% (30.5–59.4)	495	87.7	90.2% (81.5–95.1)	416	75.2	49.6% (9.2–90.5)	52	94.4	75.2% (48.6–90.7)	49	79.9
Amikacin	5.1% (2.6–9.9)	156	0	2% (0.2–17.6)	83	0	17.3% (9.3–30)	52	0	73.5% (9.9–98.6)	49	93.1
Cotrimoxazole	91.1% (82.4–95.7)	502	75.1	98% (88.4–99.7)	396	64.9	••	••	••	••	••	••
Ciprofloxacin	54% (42.6–65)	465	79.7	46.3% (34.7–58.4)	446	84.5	100% (88.1–100)	29	NA	100% (86.3–100)	25	NA
Nitrofurantoin	20.5% (9.3–36.5)	39	NA	••	0		••	••	••	••	••	••
Piperacillin-tazobactam	52.3% (19.8–82.9)	371	81.8	85.6% (77.9–90.9)	299	68.8	••	••	••	••	••	••
Meropenem	0.2% (0–6.4)	421	0	0.3% (0–8.7)	395	0	••	••	••	••	••	••
Ertapenem	1.2% (0–31.3)	108	0	1.5% (0–33.4)	88	0	••	••	••	••	••	••
Imipenem	0 (0 to NA)	193	0	0.5% (0–47.1)	115	0	••	••	••	••	••	••

ESCR-E = extended-spectrum cephalosporin-resistant Enterobacterales. CRE = carbapenem-resistant Enterobacterales. N = number of ESCR-E or CRE tested. I^2 = level of heterogeneity (%). CI = confidence interval. NA = not applicable.

Table 4: **Pooled prevalence of antibiotic non-susceptibility (95% CI) of carriage of extended-spectrum cephalosporin-resistant and carbapenem-resistant Enterobacterales and CRE.**

	N	*bla*CTX-M-1 group[a]	*bla*CTX-M-1	*bla*CTX-M-15	*bla*CTX-M-9	*bla*CTX-M-14	*bla*CTX-M-27	*bla*CTX-M[b]	*bla*SHV[c]	*bla*TEM[d]	*bla*-CMY (AmpC)	*bla*-DHA-1 (AmpC)
ESCR-*E. coli*	430	93	34	286	14	12	••	2	6	60	6	2
ESCR-*Klebsiella spp*	380	86	2	235	2	••	••	33	53	57	••	••
ESCR-*Enterobacter cloacae*	31	••	0	27	••	••	••	••	2	9	••	••
ESCR-non specified Enterobacterales	84	1	0	81	••	••	1	••	0	0	••	••
Total number of ESCR-E	925	180	36	629	16	12	1	35	61	126	6	2

N: number of ESBL tested. [a]In these studies the exact allele within the group was not tested. [b]Exact allele not determined. [c]Exact allele not determined, the alleles possibly encompass non ESBL blaSHV. [d]Exact allele not determined, the alleles possibly encompass non ESBL blaTEM.

Table 5: **Extended spectrum beta-lactamase (ESBL) Enterobacterales genotypes.**

intestinal carriage of ESCR-E. This had been identified previously in reports on adult populations[59,64] and for a population of children, but with antibiotics other than cephalosporins.[65] This reinforces the growing evidence about the harmful consequences of antibiotic selective pressure, since the carriage of resistant strains can persist over time (for over 12 months[66]) and carriage increases the risk of invasive infections.[30,62]

The pooled prevalence of nosocomial acquisition of ESCR-E among children who were not colonised on admission was 50%. In addition, the prevalence of children with ESCR-E after two days of hospitalisation was double than the prevalence at admission. Lewis et al. found a similar trend: 32% of patients carrying ESCR-E at admission *vs* 55% of hospitalised patients.[61] The almost systematic use of antibiotics during hospitalisation plays a major role in antibiotic selective pressure, through either the selection of bacteria that were already present or new acquisition.[8] As mentioned earlier, the lack of infection prevention and control measures may also contribute to this phenomenon.[67]

The genotyping techniques used in the different studies were heterogenous and did not systematically target all the existing ESBL genes, however a CTX-M genotype, particularly *bla*CTX-M-15, was detected in most of the ESCR-E samples. This was also found in a meta-analysis examining the genotypes of ESCR-E carriage and in clinical samples in Africa.[68]

This meta-analysis found a higher prevalence of ESCR-E resistance to cotrimoxazole and gentamicin than to amikacin and ciprofloxacin. Gentamicin is widely used throughout Africa, particularly combined with amoxicillin for the empirical treatment of neonatal infections, as recommended by the AWaRe antibiotic guidebook.[69] Given the high rates of carriage of ESCR-E resistant to gentamicin, using amikacin may be more appropriate, and the treatment guidance for neonatal sepsis may need to be adapted. The rate of carbapenem resistance remained less than 1.5%.

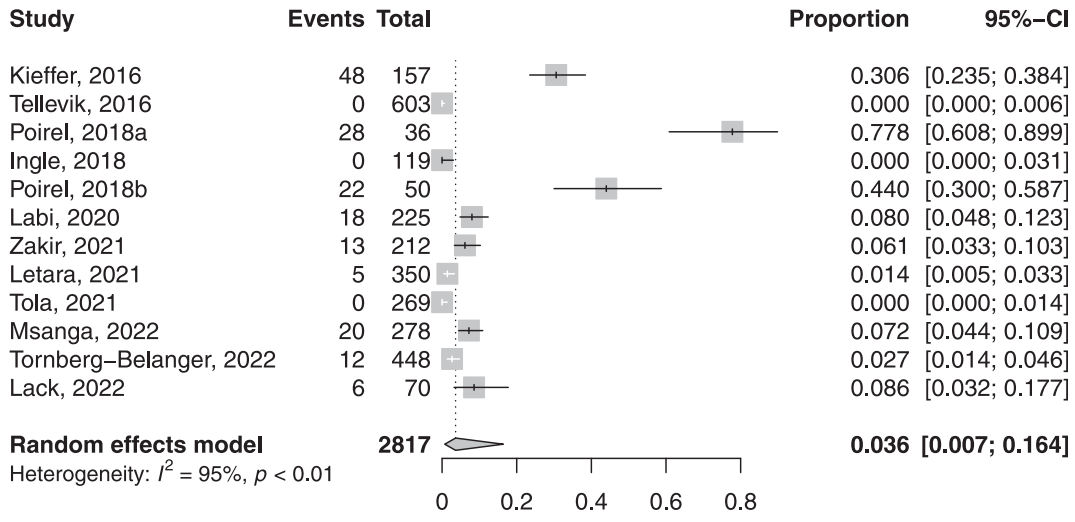

Fig. 4: **Forest plot for the carriage prevalence of carbapenem-resistant Enterobacterales among children in sub-Saharan Africa.** I^2 = level of heterogeneity. CI = confidence interval.

	Enterobacterales[a]		
	N	Pooled prevalence (95% CI)	I^2 (%)
West	2	8.1 (5.5–11.9)	0
Central	1	44.0 (31.0–57.9)	NA[b]
East	6	1.0 (0.2–6.0)	68.9
South	2	54.3 (21.5–83.7)	95.6
p-value		<0.0001	
Healthy	3	0.2 (0.0–18.8)	0
Sick	9	8.7 (2.7–24.9)	95.3
p-value		0.1246	
Outpatients	3	0.1 (0.0–35.1)	0
Hospitalised	6	15.2 (4.5–40.7)	96.5
p-value		0.1173	
Neonates	2	3.0 (1.1–8.3)	87.4
Other children	10	5.7 (1.1–25.8)	94.8
p-value		0.5236	
Selective CM	3	50.3 (27.5–73.0)	91.4
Non-selective CM	9	1.4 (0.3–5.8)	63.1
p-value		<0.0001	
2008–2015	3	0.0 (0.0–98.2)	0
2016–2022	9	6.9 (1.8–22.9)	95.3
p-value		0.3194	

CRE = carbapenem-resistant Enterobacterales. N = number of studies. I^2 (%) = level of heterogeneity. CI = confidence interval. [a]Carriage of at least one. [b]Not assessed because of a single study.

Table 6: **Comparison of pooled prevalence of carbapenem-resistant Enterobacterales and level of heterogeneity by region, healthy *vs* sick children, outpatients *vs* hospitalised, neonates *vs* other children, selective culture media for CRE *vs* non-selective culture media for CRE, and period.**

We found an extremely heterogeneous prevalence of CRE, ranging from 0 to 78%. Very high prevalence, exceeding 60%, was surprising, especially among children living in isolated areas, such as on the island of Sao Tomé,[38] or without access to this class of antibiotics, such as in Angola.[31] However, CRE carriage does not only depend on carbapenem use. Three of the 12 studies describing carbapenem resistance found no CRE carriage.[25,32,49] The variable prevalence of CRE could partly be the consequence of overdispersion because the studies included were often smaller. Another meta-analysis also found a highly variable prevalence of CRE carriage in the community, from 0 to 29%, but it included no studies from Africa.[70] Mitgang et al. reported prevalences from 0 to more than 5% in clinical specimens from mixed populations of children and adults in several African countries, but the authors stressed the paucity of available data.[71] The three studies showing high resistance rates had used a selective enrichment broth before plating on chromogenic-selective media, thereby maximising the sensitivity for detecting CRE compared to simply inoculating MacConkey agars.[72] This high rate of CRE carriage is undoubtedly a threat to children's health because carriage precedes invasive infections. Four studies reported CRE genotyping sub-types, with OXA-181 and NDM preponderating. Another study found similar results but based on samples that were mainly from North Africa.[73] It should be noted that these four studies included in this review only covered Angola, Sao Tomé and Ghana.

	N	OXA-181	NDM-1
CRE *E. coli*	82	64	19
CRE *Klebsiella* spp.	71	56	15
Total number of CRE E	162	125	38

CRE = Carbapenem resistant Enterobacterales. N = number CRE tested.

Table 7: **Carbapenem-resistant Enterobacterales (CRE) genotypes.**

To the best of our knowledge, this study was the first meta-analysis of studies including only children from SSA countries to have examined the carriage prevalence of ESCR-E among healthy children in the community, its nosocomial acquisition and the influence of past antibiotic exposure.

Our study has some limitations. The high heterogeneity in ESCR-E carriage levels in the studies examined is partially explained by the different subgroups: sick *vs* healthy, hospitalised *vs* outpatients, or neonates *vs* other children. However, even after stratification, the significant remaining heterogeneity warrants caution in interpreting summary estimates. Heterogeneity was due to the different types of populations studied, from different sub-Saharan regions, including rural *vs* urban settings, but undoubtedly also to the diversity of treatment management protocols and the variability in the availability of antibiotics without a medical prescription. Moreover, differences in participating laboratories' procedures could also have had an impact on prevalence. For instance, the use of a selective culture medium for MDR bacteria showed a difference in carriage prevalence for CRE but not for ESCR-E. Finally, the different methods used to isolate, culture, transport and detect the carriage of MDR bacteria undoubtedly also explain some of the considerable heterogeneity.

Local data are essential to developing and then implementing appropriate and effective clinical guidelines. Data collected through meta-analyses cannot infer true local prevalence or be a substitute for epidemiological surveillance. However, they can enhance situational awareness.

Moreover, assessing the risk of bias in observational studies is difficult—there is no gold standard for this procedure. We used a quality assessment tool based on the Newcastle–Ottawa assessment scale for cohort studies, but there may be some residual risks of bias that we were unable to identify.

Four recent studies were published after our search literature and were not included in our review. They assessed healthy children in the community,[74,75] sick children,[76] and hospitalised newborns.[77] These studies

have disclosed comparable ESCR-E carriage prevalence in children within the confidence interval of the cumulative prevalence reported in our manuscript. It is unlikely that these studies modify sensitively our findings on prevalence of ESCR-E.

The present meta-analysis revealed high rates of carriage of MDR Enterobacterales among children. Given the morbidity and mortality caused by invasive infections of MDR bacteria, particularly in SSA, limiting their carriage and spread should be a major public health goal.[78,79]

Antimicrobial stewardship measures, including clinical guidelines promoting the targeted use of antibiotics, as well as infection prevention and control measures are essential to reduce the spread of antibiotic resistance. The development of recommendations should be informed by the AwaRe classification developed by WHO, and specific guidelines will be updated in the WHO Essential Medicines List Antibiotic Book in 2023.[69]

Optimising therapies for individual patients is challenging in the absence of data on microbiology and biomarker values. In two recent surveys from Nigeria and Tanzania, only one third of healthcare facilities had access to a bacteriology laboratory, and only 20% could test for antibiotic susceptibility.[80,81] Algorithms combining rapid, pathogen-specific testing, clinical signs, and biomarker measurements have been shown to be effective in safely reducing the use of antibiotics in low-income countries.[82,83] The introduction and use of mini-labs is a promising means of improving access to microbiological testing in the more remote areas of SSA.[84]

Finally, coordinating all these approaches at the regional, national, and continental levels is crucial. Initiatives like the WHO Global Action Plan Against Antimicrobial Resistance and the African Centres for Disease Control and Prevention's Framework for Antimicrobial Resistance Control need the committed backing of every public health and political leader in SSA.

MDR Enterobacterales carriage in children in SSA is common. High rates of nosocomial acquisition and the impact of prior antibiotic use on the development of MDR Enterobacterales confirm the need to scale up the implementation of antimicrobial stewardship interventions. This includes urgently increasing the microbiological analysis capacity of health services in SSA to improve the surveillance of MDR bacteria and to inform the development of locally appropriate and effective clinical guidelines.

Contributors

All the authors contributed significantly to the study. MR, SE, AM, GC, MK, CC, NW and AG participated in the conceptualization; MR, BO, GC, MK, NW and AG worked on data curation; SE, AM, DA and CC carried out the formal analysis; MR, SE, AG, BO, CG, DA, MK, NW and AG worked on the investigation; MR, SE, AM, JD, CG, DA, MK, SH, CC, NW and AG worked on the methodology; NW and AG administered the project; AM provided the analytical tools; SE, JD, SH, NW and AG supervised the study; MR, SE, AM, JD, BO, GC, DA, MK SH, CC, NW and AG validated the data; MR, SE, BO, DA, CC, NW and AG worked on data presentation and visualisation; MR, SE, JD, CC and AG write the original draft; and MR, SE, AM, JD, BO, DA, SH, CC, NW and AG wrote, reviewed and edited the final draft. All authors had full access to all the data used in the study and share the 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. Following publication, all the data collected will be shared upon reasonable request, with no end date, to anyone who wishes to access the data for any purpose. Requests should be directed to annick.galetto@hcuge.ch.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102508.

References

1 *Antimicrobial resistance*; 2021. published online April 28 https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed April 28, 2021.
2 Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol*. 2005;43:745–749.
3 Denis B, Lafaurie M, Donay J-L, et al. Prevalence, risk factors, and impact on clinical outcome of extended-spectrum beta-lactamase-producing Escherichia coli bacteraemia: a five-year study. *Int J Infect Dis*. 2015;39:1–6.
4 Stewardson AJ, Marimuthu K, Sengupta S, et al. Effect of carbapenem resistance on outcomes of bloodstream infection caused by Enterobacteriaceae in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study. *Lancet Infect Dis*. 2019;19:601–610.
5 Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet Lond Engl*. 2016;387:168–175.
6 Sharland M, Pulcini C, Harbarth S, et al. Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe. *Lancet Infect Dis*. 2018;18:18–20.
7 World Health Organization. Worldwide country situation analysis: response to antimicrobial resistance. http://apps.who.int/iris/bitstream/10665/163468/1/9789241564946_eng.pdf?ua=1&ua=1; 2015. Accessed April 28, 2021.
8 Umeokonkwo CD, Madubueze UC, Onah CK, et al. Point prevalence survey of antimicrobial prescription in a tertiary hospital in South East Nigeria: a call for improved antibiotic stewardship. *J Glob Antimicrob Resist*. 2019;17:291–295.
9 Kakolwa MA, Woodd SL, Aiken AM, et al. Overuse of antibiotics in maternity and neonatal wards, a descriptive report from public hospitals in Dar es Salaam, Tanzania. *Antimicrob Resist Infect Control*. 2021;10:142.
10 World Health Organization. *2020 Antibacterial agents in clinical and preclinical development: an overview and analysis*. 2021. CC BY-NC-SA 3.0 IGO.
11 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.
12 Tompkins K, Juliano JJ, van Duin D. Antimicrobial resistance in Enterobacterales and its contribution to sepsis in sub-Saharan Africa. *Front Med*. 2021;8:615649.
13 Styczynski A, Herzig C, Luvsansharav U-O, McDonald LC, Smith RM. Using colonization to understand the burden of antimicrobial resistance across low- and middle-income countries. *Clin Infect Dis*. 2023;77:S70–S74.
14 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.
15 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. http://www.cochrane-handbook.org.
16 Lin L, Chu H. Meta-analysis of proportions using generalized linear mixed models. *Epidemiology*. 2020;31:713–717.
17 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
18 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22:153–160.
19 Ruppé E, Woerther P-L, Diop A, et al. Carriage of CTX-M-15-producing *Escherichia coli* isolates among children living in a remote village in Senegal. *Antimicrob Agents Chemother*. 2009;53:3135–3137.
20 Schaumburg F, Alabi A, Kokou C, et al. High burden of extended-spectrum β-lactamase-producing Enterobacteriaceae in Gabon. *J Antimicrob Chemother*. 2013;68:2140–2143.
21 Nelson E, Kayega J, Seni J, et al. Evaluation of existence and transmission of extended spectrum beta lactamase producing bacteria from post-delivery women to neonates at Bugando Medical Center, Mwanza-Tanzania. *BMC Res Notes*. 2014;7:279.
22 Farra A, Frank T, Tondeur L, et al. High rate of faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae in healthy children in Bangui, Central African Republic. *Clin Microbiol Infect*. 2016;22:891.e1–891.e4.
23 Kieffer N, Nordmann P, Aires-de-Sousa M, Poirel L. High prevalence of carbapenemase-producing enterobacteriaceae among hospitalized children in luanda, Angola. *Antimicrob Agents Chemother*. 2016;60:6189–6192.
24 Desta K, Woldeamanuel Y, Azazh A, et al. High gastrointestinal colonization rate with extended-spectrum β-lactamase-producing enterobacteriaceae in hospitalized patients: emergence of carbapenemase-producing K. pneumoniae in Ethiopia. *PLoS One*. 2016;11:e0161685.
25 Tellevik MG, Blomberg B, Kommedal Ø, Maselle SY, Langeland N, Moyo SJ. High prevalence of faecal carriage of ESBL-producing enterobacteriaceae among children in dar es salaam, Tanzania. *PLoS One*. 2016;11:e0168024.
26 Kurz MSE, Bayingana C, Ndoli JM, et al. Intense pre-admission carriage and further acquisition of ESBL-producing Enterobacteriaceae among patients and their caregivers in a tertiary hospital in Rwanda. *Trop Med Int Health*. 2017;22:210–220.
27 Wilmore SMS, Kranzer K, Williams A, et al. Carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in HIV-infected children in Zimbabwe. *J Med Microbiol*. 2017;66:609–615.
28 Moremi N, Claus H, Vogel U, Mshana SE. Faecal carriage of CTX-M extended-spectrum beta-lactamase-producing Enterobacteriaceae among street children dwelling in Mwanza city, Tanzania. *PLoS One*. 2017;12:e0184592.
29 Herindrainy P, Rabenandrasana MAN, Andrianirina ZZ, et al. Acquisition of extended spectrum beta-lactamase-producing enterobacteriaceae in neonates: a community based cohort in Madagascar. *PLoS One*. 2018;13:e0193325.
30 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.
31 Poirel L, Goutines J, Aires-de-Sousa M, Nordmann P. High rate of association of 16S rRNA methylases and carbapenemases in enterobacteriaceae recovered from hospitalized children in Angola. *Antimicrob Agents Chemother*. 2018;62:e000211-18.
32 Ingle DJ, Levine MM, Kotloff KL, Holt KE, Robins-Browne RM. Dynamics of antimicrobial resistance in intestinal Escherichia coli from children in community settings in South Asia and sub-Saharan Africa. *Nat Microbiol*. 2018;3:1063–1073.
33 Magwenzi MT, Gudza-Mugabe M, Mujuru HA, Dangarembizi-Bwakura M, Robertson V, Aiken AM. Carriage of antibiotic-resistant Enterobacteriaceae in hospitalised children in tertiary hospitals in Harare, Zimbabwe. *Antimicrob Resist Infect Control*. 2017;6:10.
34 Falgenhauer L, Imirzalioglu C, Oppong K, et al. Detection and characterization of ESBL-producing Escherichia coli from humans and poultry in Ghana. *Front Microbiol*. 2019;9:3358.
35 Nikiema Pessinaba C, Landoh DE, Dossim S, et al. Screening for extended-spectrum beta-lactamase-producing Enterobacteriaceae intestinal carriage among children aged under five in Lomé, Togo. *Med Maladies Infect*. 2018;48:551–554.
36 Woerther P-L, Angebault C, Jacquier H, et al. Massive increase, spread, and exchange of extended spectrum -Lactamase-Encoding genes among intestinal enterobacteriaceae in hospitalized children with severe acute malnutrition in Niger. *Clin Infect Dis*. 2011;53:677–685.
37 Isendahl J, Turlej-Rogacka A, Manjuba C, Rodrigues A, Giske CG, Nauclér P. Fecal carriage of ESBL-producing E. coli and K. pneumoniae in children in Guinea-bissau: a hospital-based cross-sectional study. *PLoS One*. 2012;7:e51981.
38 Poirel L, Aires-de-Sousa M, Kudyba P, Kieffer N, Nordmann P. Screening and characterization of multidrug-resistant gram-negative bacteria from a remote african area, São Tomé and Príncipe. *Antimicrob Agents Chemother*. 2018;62:e010211-18.
39 Kagia N, Kosgei P, Ooko M, et al. Carriage and acquisition of extended-spectrum β-Lactamase–producing Enterobacterales among neonates admitted to hospital in kilifi, Kenya. *Clin Infect Dis*. 2019;69:751–759.
40 Andriatahina T, Randrianirina F, Hariniana ER, et al. High prevalence of fecal carriage of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a pediatric unit in Madagascar. *BMC Infect Dis*. 2010;10:204.
41 Pons MJ, Mandomando I, Vubil D, et al. Antimicrobial resistance and other challenges in the treatment of bacterial infections in the developing world Antimicrobial resistance levels among diarrheogenic and commensal Escherichia coli from Southern Mozambique, 16SUPPL 178 Blackwell Publ Ltd 2011 Ref ID 70589092 *Trop Med Int Health*. 2011;16(SUPPL. 1):78.
42 Gardiol C, Aiken A, Magwenzi M. Risk factors associated with faecal carriage of extended-spectrum b-lactamase (ESBL) producing enterobacteriaceae in hospitalised children in Harare, Zimbabwe-Meeting abstracts from International Conference on Prevention & Infection Control (ICPIC 2017): Geneva, Switzerland. 20-23 June 2017. *Antimicrob Resist Infect Control*. 2017;6:52, 137566-17-0201–4.
43 Shenkute D, Legese MH, Yitayew B, et al. High magnitude of fecal carriage of extended-spectrum beta-lactamase-producing enterobacteriaceae at debre berhan comprehensive specialized hospital, Ethiopia. *Infect Drug Resist*. 2022;15:2445–2458.
44 Zakir A, Regasa Dadi B, Aklilu A, Oumer Y. Investigation of extended-spectrum β-lactamase and carbapenemase producing gram-negative bacilli in rectal swabs collected from neonates and their associated factors in neonatal intensive care units of southern Ethiopia. *Infect Drug Resist*. 2021;14:3907–3917.
45 Labi A-K, Bjerrum S, Enweronu-Laryea CC, et al. High carriage rates of multidrug-resistant gram-negative bacteria in neonatal intensive care units from Ghana. *Open Forum Infect Dis*. 2020;7:ofaa109.
46 Msanga DR, Silago V, Massoza T, et al. High fecal carriage of multidrug resistant bacteria in the community among children in northwestern Tanzania. *Pathogens*. 2022;11:379.
47 Tornberg-Belanger SN, Rwigi D, Mugo M, et al. Antimicrobial resistance including Extended Spectrum Beta Lactamases (ESBL) among E. coli isolated from kenyan children at hospital discharge. *PLoS Negl Trop Dis*. 2022;16:e0010283.
48 Letara N, Ngocho JS, Karami N, et al. Prevalence and patient related factors associated with Extended-Spectrum Beta-Lactamase producing Escherichia coli and Klebsiella pneumoniae carriage and infection among pediatric patients in Tanzania. *Sci Rep*. 2021;11:22759.
49 Tola MA, Abera NA, Gebeyehu YM, Dinku SF, Tullu KD. High prevalence of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae fecal carriage among children under five years in Addis Ababa, Ethiopia. *PLoS One*. 2021;16:e0258117.
50 Hofmann P, Alabi A, Manouana GP, et al. High ESBL-E colonization rate among children in Gabon: a follow-up study. *J Med Microbiol*. 2021;70:1405. https://doi.org/10.1099/jmm.0.001405.

51 Bayleyegn B, Fisaha R, Kasew D. Fecal carriage of extended spectrum beta-lactamase producing Enterobacteriaceae among HIV infected children at the University of Gondar Comprehensive Specialized Hospital Gondar, Ethiopia. *AIDS Res Ther*. 2021;18:19.
52 Jewoola O, Bode-Sojobi I, Ogunsola F, Okonji P. High carriage rates of extended-spectrum beta-lactamase-producing enterobacteriaceae in children at admission into paediatric wards of a university teaching hospital in Lagos, Nigeria. *Niger Postgrad Med J*. 2020;27:136.
53 Maataoui N, Langendorf C, Berthe F, et al. Increased risk of acquisition and transmission of ESBL-producing Enterobacteriaceae in malnourished children exposed to amoxicillin. *J Antimicrob Chemother*. 2020;75:709–717.
54 Neemann K, Olateju EK, Izevbigie N, et al. Neonatal outcomes associated with maternal recto-vaginal colonization with extended-spectrum β-lactamase producing Enterobacteriaceae in Nigeria: a prospective, cross-sectional study. *Clin Microbiol Infect*. 2020;26:463–469.
55 Oli AN, Ogbuagu VI, Ejikeugwu CP, et al. Multi-antibiotic resistance and factors affecting carriage of extended spectrum β-lactamase-producing enterobacteriaceae in pediatric population of enugu metropolis, Nigeria. *Med Sci*. 2019;7:104.
56 Lack F, Tsogbalé A, Doumegno JK, Dossim S, Dagnra A, Salou M. Faecal carriage of multi-drug resistant enterobacteriaceae in hospitalized children at university teaching hospital sylvanus olympio of lomé, Togo. *Afr J Clin Exp Microbiol*. 2022;23:49–56.
57 Omulo S, Luvsansharav U-O, Ita T, et al. Colonization rates for antimicrobial-resistant bacteria in Kenya: an antibiotic resistance in communities and hospitals (ARCH) study. *Open Forum Infect Dis*. 2021;8:S727.
58 Rivo R, Annie R, Francine R, et al. Intestinal carriage of ESBL-E in pediatric unit of an university hospital center in Madagascar. Proceedings of the world congress of gastroenterology. *Turk J Gastroenterol*. 2020;30:S136–S912.
59 Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase-producing enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2016;63:310–318.
60 Bezabih YM, Sabiiti W, Alamneh E, et al. The global prevalence and trend of human intestinal carriage of ESBL-producing *Escherichia coli* in the community. *J Antimicrob Chemother*. 2021;76:22–29.
61 Lewis JM, Lester R, Garner P, Feasey NA. Gut mucosal colonisation with extended-spectrum beta-lactamase producing Enterobacteriaceae in sub-Saharan Africa: a systematic review and meta-analysis. *Wellcome Open Res*. 2019;4:160.
62 Stapleton PJ, Murphy M, McCallion N, Brennan M, Cunney R, Drew RJ. Outbreaks of extended spectrum beta-lactamase-producing Enterobacteriaceae in neonatal intensive care units: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2016;101:72–78.
63 Bezabih YM, Bezabih A, Dion M, et al. Comparison of the global prevalence and trend of human intestinal carriage of ESBL-producing *Escherichia coli* between healthcare and community settings: a systematic review and meta-analysis. *JAC-Antimicrob Resist*. 2022;4:dlac048.
64 Hu Y, Matsui Y, Riley L W. Risk factors for fecal carriage of drug-resistant Escherichia coli: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2020;9:31.
65 Bryce A, Costelloe C, Hawcroft C, Wootton M, Hay AD. Faecal carriage of antibiotic resistant Escherichia coli in asymptomatic children and associations with primary care antibiotic prescribing: a systematic review and meta-analysis. *BMC Infect Dis*. 2016;16:359.
66 Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. *J Antimicrob Chemother*. 2016;71:2729–2739.
67 Tartari E, Tomczyk S, Pires D, et al. Implementation of the infection prevention and control core components at the national level: a global situational analysis. *J Hosp Infect*. 2021;108:94–103.
68 Onduru OG, Mkakosya RS, Aboud S, Rumisha SF. Genetic determinants of resistance among ESBL-producing enterobacteriaceae in community and hospital settings in east, central, and southern Africa: a systematic review and meta-analysis of prevalence. *Can J Infect Dis Med Microbiol*. 2021;2021:1–9.
69 The WHO essential Medicines list antibiotic Book: improving antibiotic AWaReness - draft for public comment. https://www.who.int/publications/m/item/the-who-essential-medicines-list-antibiotic-book-improving-antibiotic-awareness.
70 Kelly AM, Mathema B, Larson EL. Carbapenem-resistant Enterobacteriaceae in the community: a scoping review. *Int J Antimicrob Agents*. 2017;50:127–134.
71 Mitgang EA, Hartley DM, Malchione MD, Koch M, Goodman JL. Review and mapping of carbapenem-resistant Enterobacteriaceae in Africa: using diverse data to inform surveillance gaps. *Int J Antimicrob Agents*. 2018;52:372–384.
72 Sadek M, Poirel L, Nordmann P. Optimal detection of extended-spectrum β-lactamase producers, carbapenemase producers, polymyxin-resistant Enterobacterales, and vancomycin-resistant enterococci from stools. *Diagn Microbiol Infect Dis*. 2020;96:114919.
73 Brink AJ. Epidemiology of carbapenem-resistant Gram-negative infections globally. *Curr Opin Infect Dis*. 2019;32:609–616.
74 Mannathoko N, Mosepele M, Gross R, et al. Colonization with extended-spectrum cephalosporin-resistant Enterobacterales (ESCrE) and carbapenem-resistant Enterobacterales (CRE) in healthcare and community settings in Botswana: an antibiotic resistance in communities and hospitals (ARCH) study. *Int J Infect Dis*. 2022;122:313–320.
75 Osei M-M, Dayie NTKD, Azaglo GSK, et al. Alarming levels of multidrug resistance in aerobic gram-negative bacilli isolated from the nasopharynx of healthy under-five children in accra, Ghana. *Int J Environ Res Public Health*. 2022;19:10927.
76 Akenten CW, Khan NA, Mbwana J, et al. Carriage of ESBL-producing Klebsiella pneumoniae and Escherichia coli among children in rural Ghana: a cross-sectional study. *Antimicrob Resist Infect Control*. 2023;12:60.
77 Obadare TO, Adeyemo AT, Odetoyin BW, et al. Rectal carriage of extended-spectrum β-lactamase-producing Enterobacteriales among neonates admitted into a special care baby unit, southwest Nigeria. *Trans R Soc Trop Med Hyg*. 2023;117:528–535.
78 Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399:629–655.
79 Iroh Tam P-Y, Bekker A, Bosede Bolaji O, et al. Neonatal sepsis and antimicrobial resistance in Africa. *Lancet Child Adolesc Health*. 2023;7:677–679.
80 Sangeda RZ, Kibona J, Munishi C, et al. Assessment of implementation of antimicrobial resistance surveillance and antimicrobial stewardship programs in Tanzanian health facilities a year after launch of the national action plan. *Front Public Health*. 2020;8:454.
81 Egwuenu A, Ejikeme A, Tomczyk S, et al. Baseline study for improving diagnostic stewardship at secondary health care facilities in Nigeria. *Antimicrob Resist Infect Control*. 2022;11:65.
82 Ciccone EJ, Kabugho L, Baguma E, et al. Rapid diagnostic tests to guide case management of and improve antibiotic stewardship for pediatric acute respiratory illnesses in resource-constrained settings: a prospective cohort study in Southwestern Uganda. *Microbiol Spectr*. 2021;9:e016944-21.
83 Bessat C, Zonon NA, D'Acremont V. Large-scale implementation of electronic Integrated Management of Childhood Illness (eIMCI) at the primary care level in Burkina Faso: a qualitative study on health worker perception of its medical content, usability and impact on antibiotic prescription and resistance. *BMC Publ Health*. 2019;19:449.
84 ANTIBIOGO DIAGNOSTIC TOOL A free diagnostic aid application to counter antibiotic resistance. https://fondation.msf.fr/en/projects/antibiogo.