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

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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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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

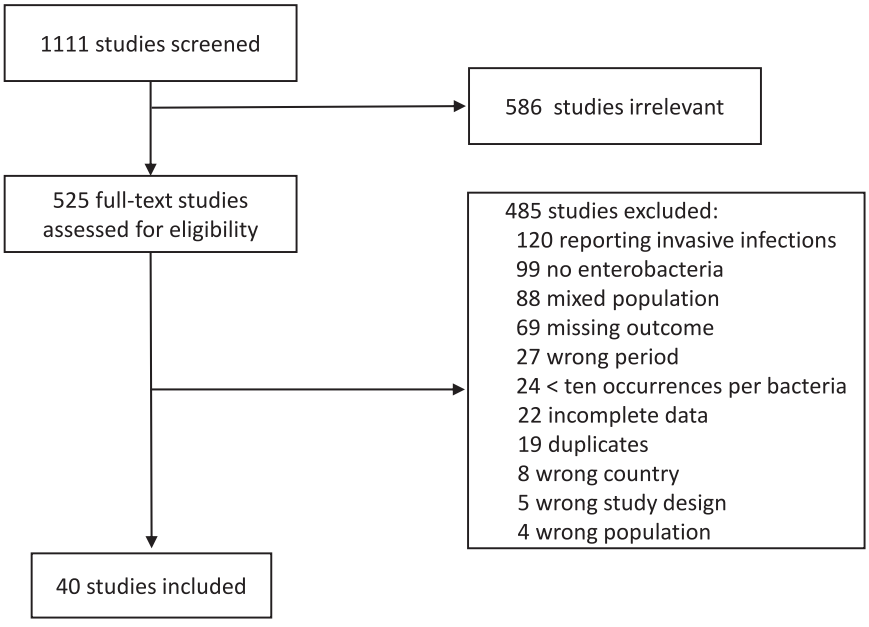

Fig. 1: **Study selection.**

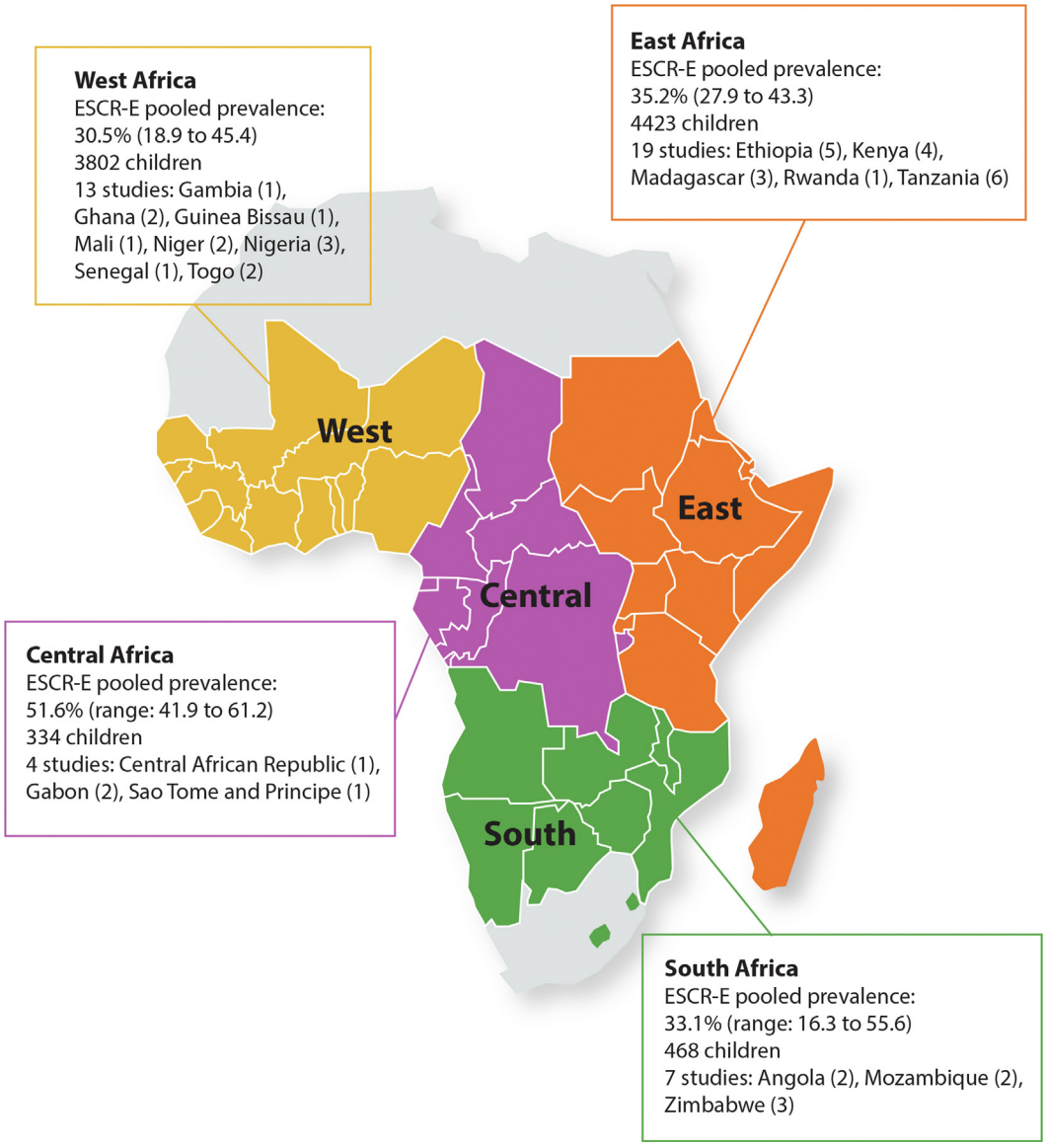

Fig. 2: **Pooled prevalence of ESCR-E by region, number of studies, and number of children screened by region, and number of studies by country.** ESCR-E = extended-spectrum cephalosporin-resistant Enterobacterales pooled prevalence (%) (95% CI). One study reported the ESCR-E prevalence in multiple countries: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

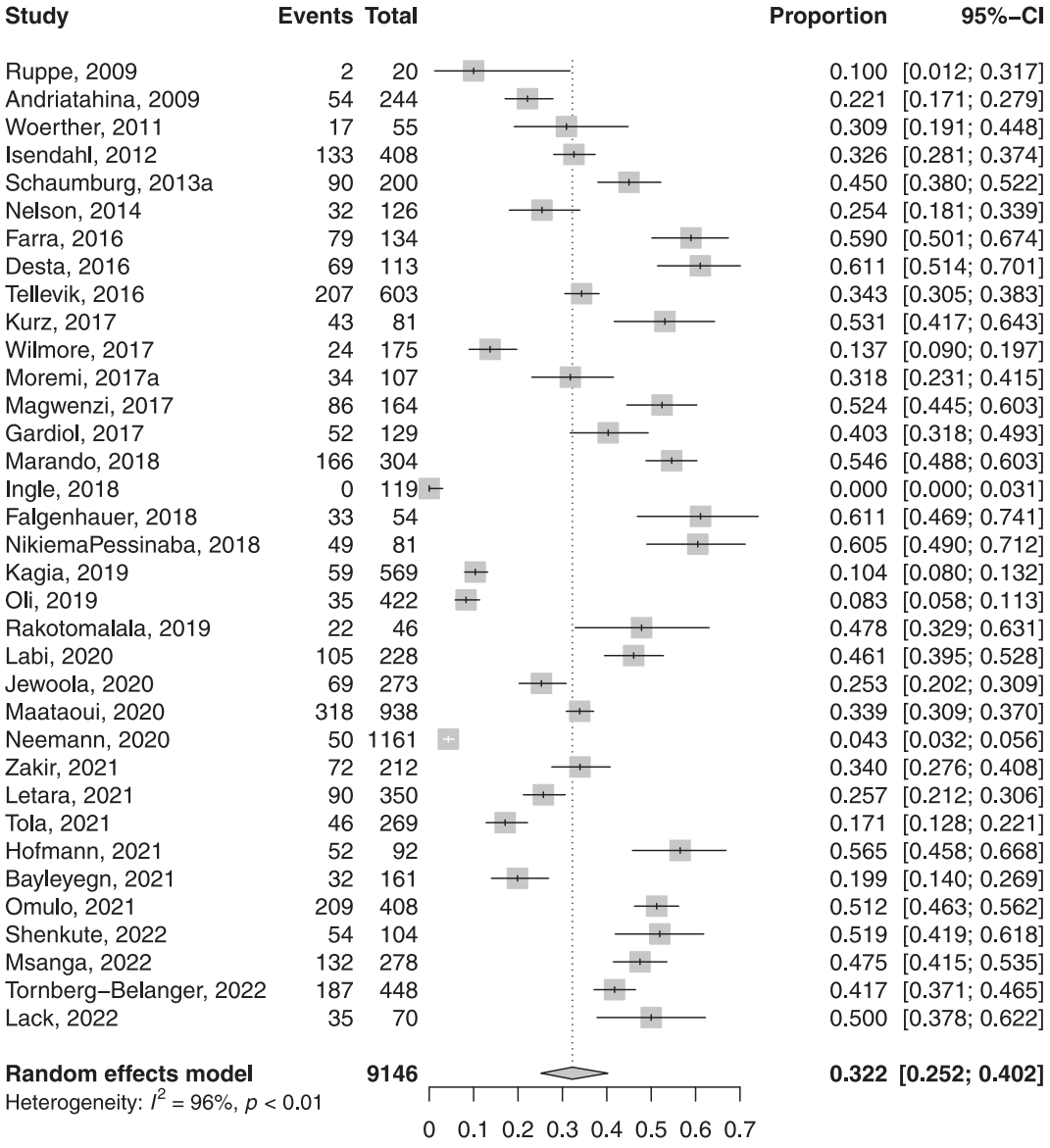

Fig. 3: **Forest plot for the carriage prevalence of extended-spectrum cephalosporin-resistant Enterobacterales among children in sub-Saharan Africa.** I^2 = level of heterogeneity. CI = confidence interval.

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%.

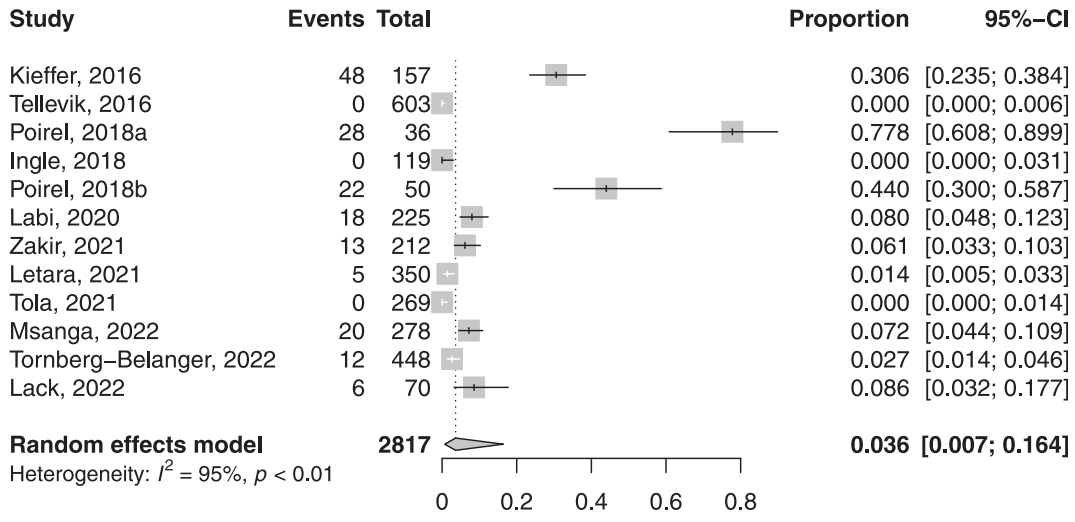

Fig. 4: **Forest plot for the carriage prevalence of carbapenem-resistant Enterobacterales among children in sub-Saharan Africa.** I^2 = level of heterogeneity. CI = confidence interval.

	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.

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