**Prevalence of and risk factors for gut mucosal colonisation with extended-spectrum beta lactamase producing *Enterobacteriaceae* in sub-Saharan Africa: a systematic review and meta-analysis**

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Running tittle: Prevalence and risk factors for ESBL-E carriage in sSA

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**Synopsis**

**Background**

Extended-spectrum beta lactamase producing Enterobacteriaceae (ESBL-E) are a threat to human health, and unaffordability of carbapenemsmay render ESBL-E infections untreatable in sub-Saharan Africa (sSA). Gut mucosal colonisation is thought to precede infection, making prevention of colonisation an attractive target for intervention, but the epidemiology of ESBL-E in sSA is poorly described.

**Objectives**

We performed a systematic review and meta-analysis to 1) describe ESBL-E colonisation prevalence in sSA and 2) identify risk factors associated with ESBL-E carriage.

**Methods**

Systematic searches of PubMed and Scopus with random-effect meta-analysis of proportions.

**Results**

We screened 2975 abstracts and 32 studies of 8619 participants were included. Overall prevalence was heterogeneous between studies. Pooled community ESBL-E carriage was 18% (95% CI 11-29), rising to 55% (95% CI 49-60%) in inpatients. Hospitalisation and antimicrobial use were frequently associated with increased risk of ESBL-E carriage, and protected water sources or water treatment by boiling may reduce risk. Only six studies were longitudinal, and no longitudinal studies followed patients beyond hospital discharge.

**Conclusions.**

ESBL-E carriage is endemic in sSA, but determinants and routes of transmission are poorly understood. Longitudinal long-term and community sampling studies are necessary to fully describe transmission in sSA and to design interventions to interrupt transmission in this setting.

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**Introduction**

Extended spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E) are a significant threat to human health, and have been identified by the World Health Organisation as pathogens of critical importance1. In sub-Saharan Africa (sSA), it is increasingly clear that a significant proportion of invasive *Enterobacteriaceae* infections are ESBL-E and the absence of second line antimicrobials can render infections with these pathogens locally untreatable2. Strategies to interrupt ESBL-E transmission that can be practically deployed at scale in low resource settings are urgently needed.

Gut mucosal colonisation with *Enterobacteriaceae* is thought to precede invasive infection 3,4, and so preventing ESBL-E colonisation is an attractive strategy for prevention of invasive disease. However, data describing the basic epidemiology of ESBL-E colonisation in sSA, necessary to inform putative interventions targeted at reducing colonisation, are poorly described. A 2016 meta-analysis of community ESBL-E carriage prevalence among healthy individuals, found only four studies from sSA with a pooled prevalence of 15% (95% CI 4-31%), and significant between-study heterogeneity5. No studies described risk factors from Africa. We were aware of a number of studies that had been published since 2016 including a number that described ESBL-E carriage in any population, so undertook a systematic review and meta-analysis with two aims: firstly, to describe the prevalence of ESBL-E gut mucosal colonisation in sSA; and secondly, to describe any risk factors associated with colonisation.

**Materials and methods**

PubMed and Scopus were searched in all fields using the search terms (((ESBL) OR Extended-spectrum beta-lactamase)) AND (((Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Republic of the Congo OR Congo Brazzaville OR Democratic republic of the Congo OR Cote d'Ivoire OR Djibouti OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Reunion OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Eswatini OR Tanzania OR Togo OR Uganda OR Western Sahara OR Zambia OR Zimbabwe) OR Africa)). Abstracts were extracted into Endnote X7.8 (Thomson Reuters, United States) and independently reviewed against inclusion criteria by two authors (JL and RL), with disagreements settles by consensus. Inclusion criteria were any cross-sectional or study that had screened for gut mucosal carriage of ESBL-E in any population in sub-Saharan Africa for which it was possible to extract a numerator and denominator to calculate an ESBL-E carriage prevalence. Studies were excluded if it the sampled population was not clearly defined in a reproducible way (i.e. laboratory-based studies), or if the laboratory techniques aimed to isolate only a particular organism or type of organism (e.g. Enteropathogenic *E. coli).*

Full-text review of included studies was then undertaken, with studies assessed against the same inclusion criteria, again with disagreements settled by consensus. Data were then extracted into a Microsoft Excel spreadsheet (Microsoft, United States): study title and authors, year of publication, dates of sample collection, inclusion criteria, median age or participants, details of microbiologic testing procedures, number of participants and number of participants from whom ESBL-E were isolated, and any risk factors for ESBL-E that were assessed and/or found to be associated with ESBL-E carriage. Data were extracted by two authors independently (RL and JL) and any inconsistencies corrected by re-review of the original paper. For cohort studies only the baseline prevalence was included. Prevalence was presented as forest plots with exact binomial confidence intervals. Age group (neonate, child, adult, as per study definition) and location of sampling (community, outpatient, on hospital admission, defined as a hospital inpatient for < 24hr, hospitalised, defined as a hospital inpatient for > 24hr) were selected as *a priori* subgroups that we hypothesised may explain heterogeneity in ESBL-E prevalence, and analyses were stratified by these subgroups. Effect size of risk factors for ESBL-E carriage were presented as odds ratios; if odds ratios were not provided by the original studies then they were calculated, with 0.5 added to zero cells. Pooled random effect summary estimates of prevalence, where calculated, were generated using the *metaprop* package in R using the inverse variance method with a logit transformation. All analysis was undertaken using R v3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Risk of bias of included studies was assessed with a modified Critical Appraisal Skills Programme (CASP) checklist, designed to fit our research question (Supplementary Figure S1). The risk of bias assessment was performed by JL and RL, and any disagreements were resolved by consensus.

The protocol of this review was published on PROSPERO (PROSPERO ID CRD42019123559) and the review was undertaken as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA) guidelines.

**Results**

Of 2975 identified unique studies, 32 were included in this review6–37 (Figure 1), from 19 countries in sSA (Table 1). Studies from three countries – Tanzania (n=7), Madagascar (n=4) and Cameroon (n=4) together made up 15/32 (47%) of the available studies. In total, 8619 participants were included and for 7232/8619 (84%) it was possible to disaggregate the participants into age groups: 4313/7232 (60%) were adults, 2470/7232 (34%) children and 449/7232 (6%) neonates. 2302/8619 (27%) of included participants were community members, 1729/8619 (20%) were outpatients, 2836/8619 (33%) were sampled on admission to hospital, and 1534/8619 (18%) were inpatients. 6/32 studies were cohort studies; all of these studies followed patients up whilst hospitalised. Details of the microbiological testing procedures are shown in Supplementary Table S1 in the supplementary appendix.

The results of the risk of bias assessment are shown in Figure 2. The most notable potential for biased ESBL-E prevalence estimates resulted from selection of study populations. Several studies recruited a selected group such as pregnant women, street children, children and staff of an orphanage, or food handlers in schools and as such are likely to produce a biased estimate of community prevalence. Though microbiological culture methods were frequently described in a reproducible manner, few studies reported quality control procedures, resulting in an assessment of moderate risk of bias for the majority of studies across this domain.

Overall ESBL-E carriage prevalence was extremely heterogeneous across studies ranging from 5-84% with no trend by year of publication (Supplementary Figure S2). Some heterogeneity was explained by location of sampling (Figure 3): inpatients tended to have the highest carriage prevalence with community members the least. There was no clear difference in prevalence between neonates, children or adults (Supplementary Figure S3). Pooled summary estimates were therefore calculated for community members (18% [95% CI 11-28%]), outpatients (27% [95% CI 14-44%]), inpatients on hospital admission (30% [95% CI 23-39%]) and inpatients (55% [95% CI 49-60%]), though in each stratum significant heterogeneity remained (I2 76-97%) so these summary estimates should be treated with caution (Figure 3).

Two-thirds (21/32) of studies performed an analysis to identify factors associated with ESBL-E carriage (Table 2). Prior hospitalisation was assessed as a risk factor in 13 studies, and a statistically significant association found in 4/13, with odds ratios of 2.1-8.5. Antimicrobial exposure was assessed in 13 studies, and a statistically significant association found in 5/13 with odds ratios of 1.6-27.0. Using water from a borehole28, boiling water before drinking14 and having private inside access to drinking water10 were found to be associated with a lower prevalence of ESBL-E colonisation in three different studies. One study found that a higher socio-economic status was associated with a lower ESBL-E prevalence29, and one the opposite13. Only two studies addressed the association between HIV status and ESBL-E colonisation status; one, in adults found no association9, whereas the other, in children, found a strong association17. Only one study assessed the association between animals in the home as ESBL-E carriage10, finding no association.

Of the 6 cohort studies, all sampled participants on admission to hospital and on discharge, a median 5.6-8 days later, and all found an increase in ESBL-E carriage prevalence between the two sampling points (Table 3). No study longitudinally sampled ESBL carriage in the community, either in community dwellers or in those discharged from hospital.

**Discussion**

ESBL-E carriage is likely endemic across sub-Saharan Africa, though with significant unexplained heterogeneity between study locations and populations. Community ESBL-E carriage ranges from 5% in adults in Gambia in 2015 to 59% in children in the Central African Republic in 2013, the latter comparable to the highest described carriage prevalence in the world5. Our pooled estimate suggests 18% (95% CI 11-29%) of people in sSA are colonised with ESBL-E, a higher prevalence than in high income settings. In Europe, community prevalence of ESBL-E carriage is reported to range from 3.7% in Spain in 2004 to 7.3% in the UK in 201438–41, similar to the United States where a community prevalence of 3.4% was reported in healthy children42. In many of the estimates of studies included in this review, the reported prevalence of ESBL-E is more comparable to that reported in Asia (46% [95% CI 29-63%] 5).

The profound differences in community ESBL-E carriage prevalence between sSA and high-resource settings warrants further investigation, beyond the assessment of risk factors we have identified in this review. Hospitalisation and antimicrobial use are likely drivers of carriage in the studies, with higher prevalence seen in hospitalised individuals and prior hospitalisation and antimicrobial exposure frequently identified as risk factors for carriage. Obversely and consistent with a putative faecal-oral transmission route, use of borehole water, a private indoor water source and boiling water before drinking were associated with reduced ESBL-E carriage risk, and it may be that poor water, sanitation and hygiene (WASH) infrastructure and practices in sSA are driving high ESBL-E carriage prevalence. This speaks to a role for poverty in driving ESBL-E carriage, however this is likely complex, and context-dependant, as evidenced by conflicting findings of the effect of socio-economic status on carriage from two studies in different settings.

More broadly, this review highlights areas where data that could inform interventions to interrupt ESBL-E transmission, are lacking. In the community, long-term longitudinal ESBL-E carriage studies are necessary to understand the dynamics of community ESBL-E transmission, particularly the role of within household transmission, and the role of household animals. In health facilities, the determinants of apparent ESBL-E acquisition need to be clearly identified to design pragmatic intervention studies in the context of limited resources. Surprisingly, the role of HIV in driving the high ESBL-E carriage prevalence in sSA is unknown. HIV is known to profoundly affect gut function, but we identified only two studies which have assessed HIV status as a risk factor for ESBL-E carriage.

There are limitations of our review. Our search strategy may have missed studies that would otherwise be included. However, using broader inclusion criteria than a recent review of worldwide ESBL-E community carriage prevalence, we have identified many more studies from sSA. Risk of bias assessment in observational studies is difficult, with no gold standard, and the tool we have used may misclassify studies with regard to bias. Significant heterogeneity remaining despite stratification warrants caution in interpreting summary estimates.

In conclusion, ESBL-E carriage in sSA is common, and in places comparable to the highest prevalence in the world, though with significant unexplained heterogeneity between countries and populations. Hospitalisation, antimicrobial use, and poor WASH infrastructure and practices may be contributing to high prevalence; the roles of HIV and animal-human transmission remain unknown. Given the threat to human health of ESBL-E, data to fully characterise routes and drivers of transmission in sSA are necessary to design interventions to interrupt transmission in this setting.

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**Transparency declarations**

We have no conflicts of interest to declare.

**Figure Captions**

**Figure 1:** Flow chart of included studies.

**Figure 2:** Results of risk of bias assessment. Domain 1: are the characteristics of the participants included in the study adequately described? Domain 2:Are the eligibility criteria to enter the study explicit and appropriate? Domain 3: Were stool culture results precise and reported? Domain 4: Were the methods of ESBL confirmatory testing precise?

**Figure 3:** ESBL carriage by study with pooled random effect summary estimates stratified by location of sampling. ESBL prop. = proportion of ESBL-E

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