**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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**Abstract**

Words 227 (max 250)

**Background**

Extended-spectrum beta lactamase producing Enterobacteriaceae (ESBL-E) are a threat to human health, and lack of second line antimicrobials may render them 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 included. Overall prevalence was heterogeneous between studies. Overall pooled prevalence was ? 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. The role of HIV as a driver of ESBL-E carriage was assessed in only two studies, with conflicting results. Only six studies were longitudinal, and no 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.

**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**

**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 a pathogen of critical importance[1]. In sub-Saharan Africa (sSA), it is increasingly clear that a significant proportion of invasive Enterobacteriaceae infections are/carry ESBL and the absence of second line antimicrobials can render infections with these pathogens locally untreatable[2]. 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 infection/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 heterogeneity[5]/and no studies describing risk factors from Africa. We were aware of a number of studies that had been published since 2016/or….Including studies describing ESBL-E carriage in any population, we undertook a 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 settles 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, hospital) 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 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 X). 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 review[6–37] (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 Table S1 in the supplementary appendix.



Figure 1: Flow chart of included studies.

The results of the risk of bias assessment is shown in Supplementary Table X. The most notable potential for biased ESBL-E prevalence estimates, resulted from selection of study populations recruiting from community settings. Several studies recruited a selected group such as pregnant women, street children, or food handlers in schools and as such are likely to produce a biased estimate of community prevalence.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Year Pub. | Study Period | Country | Study Type | Inclusion | Age group | Median age | n |
| Ruppe 2009 | 2009 | NR | Senegal | Cross sec. | Children in village selected for remoteness | Children | 6.9yr\* | 20 |
| Tande 2009 | 2009 | 2003 | Mali | Cross sec. | Orphanage children | Children | NR | 38 |
|  |  |  |  |  | Orphanage staff | Adults | NR | 30 |
| Andriatahina 2010 | 2010 | 2008 | Madagascar | Cohort | Inpatients | Children | 38.3m | 244 |
| Herindrainy 2011 | 2011 | 2009 | Madagascar | Cross sec. | Health centre attendees | Adults | NR | 306 |
|  |  |  |  |  | Health centre attendees | Children | NR | 147 |
| Woerther 2011 | 2011 | 2007-08 | Niger | Cohort | Children with SAM, inpatients | Children | 16.3m\* | 55 |
| Albrechtova 2012 | 2012 | 2009 | Kenya | Cross sec. | Community members | Adults | NR | 23 |
| Isendahl 2012 | 2012 | 2010 | Guinea-Bissau | Cross sec. | Children att. hospital w/ fever or tachycardia | Children | NR | 408 |
| Lonchel 2012 | 2012 | 2009 | Cameroon | Cross sec. | Students in the community | Adults | 24.7yr\* | 150 |
|  |  |  |  |  | Outpatients | Adults | 36.9yr\* | 208 |
| Lonchel 2013 | 2013 | 2009 | Cameroon | Cross sec. | Inpatients | Adults | 46.8yr\* | 121 |
| Magoue 2013 | 2013 | 2010 | Cameroon | Cross sec. | Hospital workers and their families | Adults | NR | 87 |
|  |  |  |  |  | Inpatients | Adults | NR | 208 |
|  |  |  |  |  | Relatives and carers of inpatients | Adults | NR | 63 |
|  |  |  |  |  | Outpatients | Adults | NR | 232 |
| Schaumburg 2013 | 2013 | 2010-11 | Gabon | Cross sec. | Hospital inpatients | Children | NR | 200 |
| Nelson 2014 | 2014 | 2013 | Tanzania | Cohort | Pregnant women and neonates, inpatient | Neonate | 0d | 126 |
|  |  |  |  |  |  | Adults | 26.5yr\* | 113 |
| Chereau 2015 | 2015 | 2013-14 | Madagascar | Cross sec. | Pregnant women in the community | Adults | 26yr\* | 356 |
| Desta 2016 | 2016 | 2012 | Ethiopia | Cross sec. | Inpatients | Adults | 35yr | 154 |
|  |  |  |  |  | Inpatients | Children | 7yr | 94 |
|  |  |  |  |  | Inpatients | Neonate | 9d | 19 |
| Djuikoue 2016 | 2016 | 2011-12 | Cameroon | Cross sec. | Outpatient women with susp. UTI | Adults | NR | 86 |
| Farra 2016 | 2016 | 2013 | CAR | Cross sec. | Healthy community controls from diarrhoea study | Children | 10.5m | 134 |
| Kurz 2016 | 2016 | 2014 | Rwanda | Cohort | Inpatients and one main caregiver | both | 29yr | 753 |
| Mshana 2016 | 2016 | 2014 | Tanzania | Cross sec. | Community members | both | 10yr | 334 |
| Ribeiro 2016 | 2016 | 2013 | Angola | Cross sec. | Community members no antibiotics/hospital exposure last 3 m | Adults | NR | 18 |
| Tellevik 2016 | 2016 | 2010-11 | Tanzania | Cross sec. | <2yr attending health centre for vaccine | Children | NR | 250 |
|  |  |  |  |  | Inpatients | Children | NR | 353 |
| Magwenzi 2017 | 2017 | 2015 | Zimbabwe | Cohort | Inpatient within 24hr of admission | Children | 1.0yr | 164 |
| Moremi 2017 | 2017 | 2015 | Tanzania | Cross sec. | Street children | Children | 14.2yr\* | 107 |
| Wilmore 2017 | 2017 | 2014-15 | Zimbabwe | Cross sec. | Outpatient, HIV infected, stable on ART | Children | 11yr | 175 |
| Chirindze 2018 | 2018 | 2016 | Mozambique | Cross sec. | Students in the community | Adults | NR | 275 |
| Founou 2018 | 2018 | 2017 | South Africa | Cohort | On hospital admission | Adults | NR | 43 |
| Herindrainy 2018 | 2018 | 2015-16 | Madagascar | Cross sec. | Pregnant women at delivery (home/facility) | Adults | 26yr\* | 275 |
| Katakweba 2018 | 2018 | 2011-13 | Tanzania | Cross sec. | Community members | Adults | NR | 70 |
| Marando 2018 | 2018 | 2016 | Tanzania | Cross sec. | Neonates with sepsis | Neonate | 6d | 304 |
| Moremi 2018 | 2018 | 2014-15 | Tanzania | Cohort | On hospital admission | Adults | NR | 930 |
| Nikema Pessinaba 2018 | 2018 | 2015-16 | Togo | Cross sec. | <5yr with febrile gastroenteritis | Children | NR | 81 |
| Sanneh 2018 | 2018 | 2015 | The Gambia | Cross sec. | Food handlers in schools | Adults | 37yr\* | 565 |
| Stanley 2018 | 2018 | 2017 | Uganda | Cross sec. | Participants who reared animals, attending health facility with a fever and/or diarrhoea but without malaria | both | 21.7yr\* | 300 |

Table 1: Details of included studies. CAR = Central African Republic; ART = antiretroviral therapy; UTI = urinary tract infection; NR = not reported. yr = year; m = months, d = days, hr = hours. \* = mean rather than median

Overall ESBL-E carriage prevalence was extremely heterogeneous across studies ranging from 5-84% with no trend by year of publication (Supplementary Figure S1). Some heterogeneity was explained by location of sampling (Figures 2 and 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 (Figures 2). 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 borehole and boiling water before drinking were found to be associated with a lower prevalence of ESBL-E colonisation in two different studies. One study found that a higher socio-economic status was associated with a lower ESBL-E prevalence, and one the opposite. Only two studies addressed the association between HIV status and ESBL-E colonisation status; one, in adults found no association, whereas the other, in children, found a strong association. Only one study assessed the association between animals in the home as ESBL-E carriage, 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 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.



Figure 2: ESBL carriage by study stratified by location of sampling and age group. Adults are shown in blue, children in red, and neonates in green.



Figure 3: ESBL carriage by study with pooled random effect summary estimates stratified by location of sampling.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Risk factors assessed** | **Analysis** | **Significant risk factors** | **Odds ratio (95% CI)** |
| Tande 2009 | Adults with direct contact with the children in orphanage | uv | Contact with orphanage children | 19.7 (3.2 - 201.3) |
| Andriatahina 2010 | Age, gender, patient origin (home vs health facility), abx or hospitalisation last 30days, admitting dx, infection on admission | mv | Hospitalisation last 30d | 7.4 (2.9-18.3) |
| Herindrainy 2011 | SES, no. of rooms occupied, ratio occupants:room | mv | Occupation HH head unemployed vs manager | 9.1 (1.6-53.9) |
| Isendahl 2012 | Age, gender, weight, MUAC, breastfeeding, bedsharing, children in HH, abx, hospitalisation | uv | Bedsharing | 1.9 (1.0 - 3.4) |
| Lonchel 2013 | Age, gender, hospital, diagnois, abx within 3m, hospitalisation within 1yr | mv | Hospitalisation during the previous year | 4.13 (1.37–12.78) |
| Admission with infection | 0.30 (0.10–0.82) |
| Intermediate vs tertiary hospital | 4.10 (1.77–9.59) |
| Schaumburg 2013 | Age, hospitalisation, residence, sex, diagnosis, abx use | mv | Age <=5 | 2.2 (1.1–4.8) |
| Hospitalization 5–7 days vs < 5 | 5.1 (1.6–18.4) |
| Hospitalization for ≥7 days vs < 5 | 30.6 (5.8–566.0) |
| Hospital stay during the past 12 months | 2.1 (1.1–4.0) |
| Nelson 2014 | For neonates: Gestation, birthweight, gender, delivery method, ward, abx use | uv | Antibiotic use | 10.8 (0.6 - 186)\* |
| For mothers: Delivery mode, admission within 30d, abx within 3m, abx within 30d, current abx, catheter, HIV status | Nothing |  |
| Chereau 2015 | Study area, age, education, marital status, type house, electricity, type of birth attendant, toilets, water, animals at home, hospitalisation, abx use | mv | Private inside access to drinking water | 0.3 (0.1–0.8) |
| Desta 2016 | Higher maximum bed capacity per room, increasing number of patients admitted in single room | uv | Sharing room vs not | 4.0 (2.3 to 5.3) |
| Djuikoue 2016 | Age, pregnancy, abx last 3m, hospital last 3m | uv | None |  |
| Farra 2016 | Age, gender, comorbidity, SES, nutritional status, animals at home, toilets, urban/rural, hh members, meals | mv | Highest SES class vs lowest | 31.06 (2.49–387.13) |
| Kurz 2016 | Age, gender , residence, ward, referral, other healthcare 3m, abx 3m, education, SES, water source, food, time to HC, caregiver ESBL status | mv | ESBL colonised caregiver, | 2.88 (1.80-4.61) |
| Antibiotics within 3 months, | 2.70 (1.59-4.58) |
| Frequently consume eggs | 6.52 (1.75-24.31) |
| Boil water prior to drinking | 0.59 (0.37-0.92) |
| Mshana 2016 | Age, region, no of children in house, abx use within 1m, admission within 1yr | mv | Older age (per yr), | 1.07 (1.04–1.10) |
| Hospital admission last yr | 7.4 (1.43–38.5) |
| Abx last 3m | 27 (6.63–116), |
| Tellevik, 2016 | Age, gender, residence, parental education, child group, nutritional status, use of abx within 14 days | mv | HIV vs no HIV, | 9.99 (2.52–39.57), |
| Kinondoni district, | 2.62 (1.49–4.60) |
| Abx last 14d | 1.61 (1.07–2.41) |
| Moremi 2017 | Age, education, herb use, source of income, source of food, street child type | mv | Local herb use, | 3.3 (1.31–8.31), |
| Sleep on streets vs not | 2.8 (1.04–7.65) |
| Wilmore 2017 | Age, gender, CD4, VL, ART duration, admitted to hospital with pneumonia in last 12m, adm to hispital in at 12 m | mv | ART <1yr | 8.47 (2.22–2.27) |
| Admission withi pneumonia in last 12m | 8.47 (1.12–64.07) |
|  |  |
| Marando 2018 | Age, gender, weight, admission where, clinical factors, abx use, PROM | mv | Current abx use | 1.73 (1.00-2.97), |
| ESBL colonised mother | 2.19 (1.26-3.79) |
| Moremi 2018 | Age, gender, history of antibiotic use, history of admission, history of surgery | mv | Older age (per year) | 1.01 (1.00–1.02) |
| Nikema Pessinaba 2018 | Age, gender, site, drinking water source, time to sample analysis | mv | Drink non borehole water vs borehole | 3.47 (1.22-9.82) |
| Sanneh 2018 | WASH behaviours, hospitalised within 3m, invasive procedures, abx within 3m, abx from street, completing abx, diarrhoea/UTI 3m, food handling training | uv | Lack of food handling training and knowledge of the principle of food safety | NR |
| Abx within 3m | NR |
|  |  |
| Stanley 2018 | Age, gender, health facility, presentation | uv | none |  |

Table 2: Assessed and significant risk factors in the included studies. mv = multivariate, uv = univariate, HH = household, abx = antibiotics, SES = socio-economic status, HC = ealth centre, ART = antretroviral therapy, VL = viral load, PROM = premature rupture of membranes, WASH = water, sanitation and hygiene. UTI = urinary tract infection, NR = not reported. \* confidence interval crosses 1; original publication used fisher’s exact test and found p < 0.05.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Study population** | **ESBL prevalence** | | **Median follow up** |
| **Admission** | **Discharge** |
| Andriatahina 2010 | Children | 51/244 (21%) | 88/154 (57%) | 5.7d |
| Woerther 2011 | Children | 17/55 (31%) | 15/16 (94%) | 8d |
| Nelson 2014 | Neonates | 32/126 (25%) | 77/126 (61%) | 7d |
| Kurz 2016 | Adults and children | 195/392 (50%) | 173/208 (83%) | 6d |
| Magwenzi 2017 | Children | 86/164 (52%) | 115/164 (70%) | 5.6d |
| Moremi 2018 | Adults | 220/930 (24%) | 143/272 (53%) | NR\* |

Table 3: longitudinal ESBL prevalence in included cohort studies. NR = not reported. \* = median not given but admission length was 2-10 days.

**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 world (ref CID?). Significant heterogeneity warrants caution in interpreting summary estimates, but 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 described in published reports, ranges from 3.7% in Spain (ref), to 7.3% in the UK(ref) and in the US…. (was estimated be 7.3% in the UK in 2014 in a large community study[38], 4.5% in the Netherlands in 2012[39], 4.7% in Sweden in 2012/13[40] and 3.7% in Spain in 2003[41]), similar to the United States where a community prevalence of 3.4% was reported in healthy children[42]. In many sSA countries, the reported prevalence of ESBL-E is more comparable to that reported in Asia (46% [95% CI 29-63%] [5]), and amongst the highest in the world.

The reasons for these profound differences between sSA and high-resource settings in terms of community ESBL-E carriage prevalence warrant further investigation, and cannot be explained by the assessment of risk factors we have identified in this review because of …heterogeneity in methods….(or something). Hospitalisation and antimicrobial use are likely drivers of carriage in the studies we have identified, with higher prevalence seen in hospitalised individuals and prior hospitalisation and antimicrobial exposure frequently identified as risk factors for carriage. 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 poverty and poor water, sanitation and hygiene (WASH) infrastructure and practices in sSA are driving high ESBL-E carriage prevalence. The role of poverty in driving ESBL-E carriage 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. Suprisingly, 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. We have calculated summary estimates despite significant unexplained heterogeneity. 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..

In conclusion, ESBL-E carriage in sSA is common, and 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.

**References**

1. World Health Organisation. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva; 2017.

2. Musicha P, Cornick JE, Bar-Zeev N, French N, Masesa C, Denis B, et al. Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study. Lancet Infect Dis. 2017;17:1042–52.

3. Denis B, Lafaurie M, Donay J-L, Fontaine J-P, Oksenhendler E, Raffoux E, 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. Elsevier; 2015;39:1–6.

4. Gorrie CL, Mirceta M, Wick RR, Judd LM, Wyres KL, Thomson NR, et al. Antimicrobial-Resistant Klebsiella pneumoniae Carriage and Infection in Specialized Geriatric Care Wards Linked to Acquisition in the Referring Hospital. Clin Infect Dis. Oxford University Press; 2018;67:161–70.

5. 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. Narnia; 2016;63:310–8.

6. Ruppe E, Woerther PL, Diop A, Sene AM, Da Costa A, Arlet G, et al. Carriage of CTX-M-15-producing Escherichia coli isolates among children living in a remote village in Senegal. Antimicrob Agents Chemother. 2009/04/15. 2009;53:3135–7.

7. Tande D, Jallot N, Bougoudogo F, Montagnon T, Gouriou S, Sizun J. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in a Malian orphanage. Emerg Infect Dis. 2009/02/26. 2009;15:472–4.

8. Schaumburg F, Alabi A, Kokou C, Grobusch MP, Kock R, Kaba H, et al. High burden of extended-spectrum beta-lactamase-producing Enterobacteriaceae in Gabon. J Antimicrob Chemother. 2013/05/07. 2013;68:2140–3.

9. Nelson E, Kayega J, Seni J, Mushi MF, Kidenya BR, Hokororo A, 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. 2014/06/03. 2014;7:279.

10. Chereau F, Herindrainy P, Garin B, Huynh BT, Randrianirina F, Padget M, et al. Colonization of extended-spectrum-beta-lactamase- and NDM-1-producing Enterobacteriaceae among pregnant women in the community in a low-income country: a potential reservoir for transmission of multiresistant Enterobacteriaceae to neonates. Antimicrob Agents Chemother. 2015/04/08. 2015;59:3652–5.

11. Desta K, Woldeamanuel Y, Azazh A, Mohammod H, Desalegn D, Shimelis D, et al. High Gastrointestinal Colonization Rate with Extended-Spectrum beta-Lactamase-Producing Enterobacteriaceae in Hospitalized Patients: Emergence of Carbapenemase-Producing K. pneumoniae in Ethiopia. PLoS One. 2016/08/31. 2016;11:e0161685.

12. Djuikoue IC, Woerther PL, Toukam M, Burdet C, Ruppe E, Gonsu KH, et al. Intestinal carriage of Extended Spectrum Beta-Lactamase producing E. coli in women with urinary tract infections, Cameroon. J Infect Dev Ctries. 2016/11/02. 2016;10:1135–9.

13. Farra A, Frank T, Tondeur L, Bata P, Gody JC, Onambele M, et al. High rate of faecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in healthy children in Bangui, Central African Republic. Clin Microbiol Infect. 2016/07/13. 2016;22:891.e1-891.e4.

14. Kurz MS, Bayingana C, Ndoli JM, Sendegeya A, Durst A, Pfuller R, 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 Heal. 2016/12/10. 2017;22:210–20.

15. Mshana SE, Falgenhauer L, Mirambo MM, Mushi MF, Moremi N, Julius R, et al. Predictors of blaCTX-M-15 in varieties of Escherichia coli genotypes from humans in community settings in Mwanza, Tanzania. BMC Infect Dis. 2016/05/01. 2016;16:187.

16. Ribeiro TG, Novais Â, Peixe L, Machado E. Atypical epidemiology of CTX-M-15 among Enterobacteriaceae from a high diversity of non-clinical niches in Angola. J Antimicrob Chemother. 2016;71:1169–73.

17. Tellevik MG, Blomberg B, Kommedal O, Maselle SY, Langeland N, Moyo SJ. High Prevalence of Faecal Carriage of ESBL-Producing Enterobacteriaceae among Children in Dar es Salaam, Tanzania. PLoS One. 2016/12/10. 2016;11:e0168024.

18. Andriatahina T, Randrianirina F, Hariniana ER, Talarmin A, Raobijaona H, Buisson Y, et al. High prevalence of fecal carriage of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in a pediatric unit in Madagascar. BMC Infect Dis. 2010/07/14. 2010;10:204.

19. 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. 2017/01/18. 2017;6:10.

20. 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. 2017/09/13. 2017;12:e0184592.

21. Wilmore SMS, Kranzer K, Williams A, Makamure B, Nhidza AF, Mayini J, et al. Carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae in HIV-infected children in Zimbabwe. J Med Microbiol. 2017/05/18. 2017;66:609–15.

22. Chirindze LM, Zimba TF, Sekyere JO, Govinden U, Chenia HY, Sundsfjord A, et al. Faecal colonization of E. coli and Klebsiella spp. producing extended-spectrum beta-lactamases and plasmid-mediated AmpC in Mozambican university students. BMC Infect Dis. 2018/05/31. 2018;18:244.

23. Founou RC, Founou LL, Essack SY. Extended spectrum beta-lactamase mediated resistance in carriage and clinical gram-negative ESKAPE bacteria: a comparative study between a district and tertiary hospital in South Africa. Antimicrob Resist Infect Control. 2018/11/27. 2018;7:134.

24. Herindrainy P, Rabenandrasana MAN, Andrianirina ZZ, Rakotoarimanana FMJ, Padget M, de Lauzanne A, et al. Acquisition of extended spectrum beta-lactamase-producing enterobacteriaceae in neonates: A community based cohort in Madagascar. PLoS One. 2018/03/02. 2018;13:e0193325.

25. Katakweba AAS, Muhairwa AP, Lupindu AM, Damborg P, Rosenkrantz JT, Minga UM, et al. First Report on a Randomized Investigation of Antimicrobial Resistance in Fecal Indicator Bacteria from Livestock, Poultry, and Humans in Tanzania. Microb Drug Resist. 2018;24:260–8.

26. Marando R, Seni J, Mirambo MM, Falgenhauer L, Moremi N, Mushi MF, et al. Predictors of the extended-spectrum-beta lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. Int J Med Microbiol. 2018/07/08. 2018;308:803–11.

27. Moremi N, Claus H, Rutta L, Frosch M, Vogel U, Mshana SE. High carriage rate of extended-spectrum beta-lactamase-producing Enterobacteriaceae among patients admitted for surgery in Tanzanian hospitals with a low rate of endogenous surgical site infections. J Hosp Infect. 2018/06/01. 2018;100:47–53.

28. Nikiema Pessinaba C, Landoh DE, Dossim S, Bidjada B, Kere-Banla A, Tamekloe TA, et al. Screening for extended-spectrum beta-lactamase-producing Enterobacteriaceae intestinal carriage among children aged under five in Lome, Togo. Med Mal Infect. 2018/09/08. 2018;48:551–4.

29. Herindrainy P, Randrianirina F, Ratovoson R, Ratsima Hariniana E, Buisson Y, Genel N, et al. Rectal carriage of extended-spectrum beta-lactamase-producing gram-negative bacilli in community settings in Madagascar. PLoS One. 2011/08/11. 2011;6:e22738.

30. Sanneh B, Kebbeh A, Jallow HS, Camara Y, Mwamakamba LW, Ceesay IF, et al. Prevalence and risk factors for faecal carriage of Extended Spectrum beta-lactamase producing Enterobacteriaceae among food handlers in lower basic schools in West Coast Region of The Gambia. PLoS One. 2018/08/14. 2018;13:e0200894.

31. Stanley IJ, Kajumbula H, Bazira J, Kansiime C, Rwego IB, Asiimwe BB. Multidrug resistance among Escherichia coli and Klebsiella pneumoniae carried in the gut of out-patients from pastoralist communities of Kasese district, Uganda. PLoS One. 2018;13.

32. Woerther PL, Angebault C, Jacquier H, Hugede HC, Janssens AC, Sayadi S, et al. Massive increase, spread, and exchange of extended spectrum beta-lactamase-encoding genes among intestinal Enterobacteriaceae in hospitalized children with severe acute malnutrition in Niger. Clin Infect Dis. 2011/09/06. 2011;53:677–85.

33. Albrechtova K, Dolejska M, Cizek A, Tausova D, Klimes J, Bebora L, et al. Dogs of nomadic pastoralists in northern Kenya are reservoirs of plasmid-mediated cephalosporin- and quinolone-resistant Escherichia coli, including pandemic clone B2-O25-ST131. Antimicrob Agents Chemother. 2012/04/18. 2012;56:4013–7.

34. Isendahl J, Turlej-Rogacka A, Manjuba C, Rodrigues A, Giske CG, Naucler P. Fecal carriage of ESBL-producing E. coli and K. pneumoniae in children in Guinea-Bissau: a hospital-based cross-sectional study. PLoS One. 2013/01/04. 2012;7:e51981.

35. Lonchel CM, Meex C, Gangoué-Piéboji J, Boreux R, Assoumou MCO, Melin P, et al. Proportion of extended-spectrum ß-lactamase-producing Enterobacteriaceae in community setting in Ngaoundere, Cameroon. BMC Infect Dis. 2012;12.

36. Lonchel CM, Melin P, Gangoue-Pieboji J, Assoumou MC, Boreux R, De Mol P. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in Cameroonian hospitals. Eur J Clin Microbiol Infect Dis. 2012/08/14. 2013;32:79–87.

37. Magoue CL, Melin P, Gangoue-Pieboji J, Okomo Assoumou MC, Boreux R, De Mol P. Prevalence and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae in Ngaoundere, Cameroon. Clin Microbiol Infect. 2013/05/08. 2013;19:E416-20.

38. McNulty CAM, Lecky DM, Xu-McCrae L, Nakiboneka-Ssenabulya D, Chung K-T, Nichols T, et al. CTX-M ESBL-producing Enterobacteriaceae: estimated prevalence in adults in England in 2014. J Antimicrob Chemother. Oxford University Press; 2018;73:1368–88.

39. Wielders CCH, van Hoek AHAM, Hengeveld PD, Veenman C, Dierikx CM, Zomer TP, et al. Extended-spectrum β-lactamase- and pAmpC-producing Enterobacteriaceae among the general population in a livestock-dense area. Clin Microbiol Infect. Elsevier; 2017;23:120.e1-120.e8.

40. Ny S, Löfmark S, Börjesson S, Englund S, Ringman M, Bergström J, et al. Community carriage of ESBL-producing *Escherichia coli* is associated with strains of low pathogenicity: a Swedish nationwide study. J Antimicrob Chemother. 2017;72:582–8.

41. Valverde A, Coque TM, Sanchez-Moreno MP, Rollan A, Baquero F, Canton R. Dramatic Increase in Prevalence of Fecal Carriage of Extended-Spectrum  -Lactamase-Producing Enterobacteriaceae during Nonoutbreak Situations in Spain. J Clin Microbiol. 2004;42:4769–75.

42. Islam S, Selvarangan R, Kanwar N, Mchenry R, Chappell JD, Halasa N, et al. Intestinal Carriage of Third-Generation Cephalosporin-Resistant and Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae in Healthy US Children.

**Supplementary appendix**

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| --- | --- | --- | --- | --- |
| **Study** | **Sample type** | **Screening method** | **Speciation method** | **ESBL confirmation method** |
| Ruppe 2009 | Stool | Drigalski and chromagar | NR | Double disc |
| Tande 2009 | Stool | Drigalski with cephalosporin | API | Double disc |
| Andriatahina 2010 | Rectal Swab | Drigalski with cephalosporin | API | Double disc |
| Herindrainy 2011 | Stool | Drigalski with cephalosporin | API | Double disc |
| Woerther 2011 | Stool | Chromagar | API | PCR |
| Albrechtova 2012 | Rectal Swab | Mackonkey with cephalosporin | API | Double disc |
| Isendahl 2012 | Rectal Swab | Chromagar | Vitek | Vitek |
| Lonchel 2012 | Stool | Mackonkey or Drigalski and cephalosporin | MALDI-TOF | Double disc |
| Lonchel 2013 | Stool | Mackonkey or Drigalski and cephalosporin | MALDI-TOF | Double disc |
| Magoue 2013 | Stool | Mackonkey or Drigalski and cephalosporin | NR | Double disc |
| Schaumburg 2013 | Rectal Swab | Chromagar | Vitek | Double disc |
| Nelson 2014 | Rectal Swab | Mackonkey with cephalosporin | Biochemical | Double disc |
| Chereau 2015 | Stool | Drigalski with cephalosporin | API | Double disc |
| Desta 2016 | Stool | Chromagar | Vitek | Vitek |
| Djuikoue 2016 | Stool | Drigalski with cephalosporin | MALDI-TOF | Double disc |
| Farra 2016 | Stool | Chromagar | NR | Double disc |
| Kurz 2016 | Rectal Swab | Chromagar | API | Combination disc |
| Mshana 2016 | Stool | Mackonkey with cephalosporin | API | Chromagar and vitek |
| Ribeiro 2016 | Stool | Chromagar | MALDI-TOF | PCR |
| Tellevik, 2016 | Stool | Chromagar | MALDI-TOF | Combination disc |
| Magwenzi 2017 | Stool or Rectal Swab | Chromagar and Mackonkey with cephalosporin and nutrient broth with cephalosporin | API | Double disc |
| Moremi 2017 | Stool | Mackonkey with cephalosporin | Biochemical | Double disc |
| Wilmore 2017 | Stool | CLEDwith cephalosproin | API and MALDI | Combination disc |
| Chirindze 2018 | Stool | Mackonkey with cephalosporin | API | Double disc |
| Founou 2018 | Rectal Swab | Mackonkey with cephalosporin | API | Combination disc |
| Herindrainy 2018 | Stool or Rectal Swab | Chromagar | MALDI-TOF | Double disc |
| Katakweba 2018 | Stool | Mackonkey with cephalosporin | MALDI-TOF | Double disc |
| Marando 2018 | Rectal swab | Mackonkey with cephalosporin | Biochemical | Double disc |
| Moremi 2018 | Rectal swab | Mackonkey with cephalosporin | vitek | vitek |
| Nikema Pessinaba 2018 | Stool | Drigalski with cephalosporin | NR | NR |
| Sanneh 2018 | Stool | Drigalski And Cephalosporin | NR | Double disc |
| Stanley 2018 | Stool | AST | BD phoenix | BD phoenix |

Supplementary table S1: details of microbiologic testing procedures.



Supplementary figure S1: Overall ESBL-E colonization prevalence by study.