Gut mucosal colonisation with extended-spectrum beta-lactamase producing Enterobacteriaceae in sub-Saharan Africa: a systematic review and meta-analysis [version 1; peer review: 2 approved]

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Abstract

Background: Extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E) threaten human health; and, in areas of sub-Saharan Africa (sSA) where carbapenems are not available, may render ESBL-E infections untreatable. Gut mucosal colonisation probably occurs before infection, making prevention of colonisation an attractive target for intervention, but the epidemiology of ESBL-E in sSA is poorly described.

Objectives: Describe ESBL-E colonisation prevalence in sSA and risk factors associated with colonisation.

Methods: Studies included were prospective cross-sectional or cohort studies reporting gut mucosal ESBL-E colonisation in any population in sSA. We searched PubMed and Scopus on 18 December 2018. We summarise the range of prevalence across sites and tabulated risk factors for colonisation. The protocol was registered (Prospero ID CRD42019123559).

Results: From 2975 abstracts we identified 32 studies including a total of 8619 participants from a range of countries and settings. Six studies were longitudinal; no longitudinal studies followed patients beyond hospital discharge. Prevalence varied between 5 and 84% with a median of 31%, with a relationship to setting: pooled ESBL-E colonisation in community studies was 18% (95% CI 12 to 28, 12 studies); in studies recruiting people at admission to hospital colonisation was 32% (95% CI 24 to 41% 8 studies); and for inpatients, colonisation was 55% (95% CI 49 to 60%, 7 studies). Antimicrobial use was associated with increased risk of ESBL-E colonisation, and protected water sources or water treatment by boiling may reduce risk.

Conclusions: ESBL-E colonisation is common in sSA, but how people become carriers and why is not well understood. To inform the design of interventions to interrupt transmission in this setting requires longitudinal, community studies.
Keywords
ESBL, Extended-spectrum beta-lactamase, Africa south of the Sahara, Antimicrobial resistance

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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 importance. 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 untreatable. 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, and so preventing ESBL-E colonisation is an attractive strategy for prevention of invasive disease. Data describing the basic epidemiology of ESBL-E colonisation in sSA, will help inform the design of interventions targeted at reducing colonisation. A 2016 meta-analysis of community ESBL-E colonisation 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. 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 colonisation 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. In terms of the PRISMA (preferred reporting items for systematic reviews and meta analyses) PICOS (participants, interventions, comparisons, outcomes and study design) approach, our questions can be framed as: what is the prevalence of ESBL-E gut mucosal colonisation (the outcome) and risk factors for colonisation (comparisons) in any population in sSA (the population) as measured in prospective cross-sectional or cohort studies (study design).

Methods
Inclusion criteria were any prospective cross-sectional or cohort study that had screened for gut mucosal colonisation of ESBL-E in any population in sSA for which it was possible to extract a numerator and denominator to calculate an estimate of prevalence of ESBL-E in any population in sSA for which it was possible to extract a numerator and denominator to calculate an estimate of ESBL-E colonisation prevalence. Exclusion criteria were studies that had screened for gut mucosal colonisation in individuals found only four studies from sSA with a pooled prevalence of 15% (95% CI 4–31%), and significant between-study heterogeneity. 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 colonisation 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. In terms of the PRISMA (preferred reporting items for systematic reviews and meta analyses) PICOS (participants, interventions, comparisons, outcomes and study design) approach, our questions can be framed as: what is the prevalence of ESBL-E gut mucosal colonisation (the outcome) and risk factors for colonisation (comparisons) in any population in sSA (the population) as measured in prospective cross-sectional or cohort studies (study design).

Risk of bias of included studies was assessed with a modified Critical Appraisal Skills Programme (CASP) checklist, designed to fit our research question (full tool available as extended data). The risk of bias assessment was performed by JL and RL, and any disagreements resolved by consensus.

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 for Mac v16.27 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 colonisation. Two authors extracted data 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 [including health centre attendees], 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. Studies were additionally classified as being carried out in a special population (if they were carried out in a subgroup of a subgroup (for example, pregnant women in the community). Effect size of risk factors for ESBL-E colonisation 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).

Table 1. Systematic review 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)) |
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 (PRISMA) guidelines (PRISMA checklist available Reporting guidelines).

**Results**

Of 2975 identified unique studies, 32 were included in this review\(^6\)-\(^37\) (Figure 1), from 19 countries in sSA (Table 2). 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 only. Many studies were carried out in special populations, including the majority of community studies: 9/12 community studies were in special populations, as well as 3/7 outpatient studies, 3/8 studies of participants on hospital admission and 2/7 inpatient studies. It was not possible to classify patients from two studies into our predefined categories: one sampled staff and children of an orphanage, and the other hospital workers and their families. These studies were excluded from the pooled analyses. Details of the microbiological testing procedures are shown in Table 3.

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, which we defined as a special population: pregnant women, street children, children and staff of an orphanage, or food handlers in schools. These 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 colonisation prevalence was extremely heterogeneous across studies ranging from 5–84% (median 31%) with no trend by year of publication (Figure 3). Some heterogeneity was explained by location of sampling (Figure 4): inpatients tended to have the highest colonisation prevalence with community members the least. There was no clear difference in prevalence between neonates, children or adults (Figure 5). Pooled random-effect summary estimates were therefore calculated for differing location of sampling: community members (18% [95% CI 11–28%]), outpatients (23% [95% CI 13–39%]), inpatients on hospital admission (32% [95% CI 24–41%]) and inpatients (55% [95% CI 49-60%]), though in each stratum significant heterogeneity remained (I\(^2\) 76–97%) so these summary estimates should be treated with caution (Figure 4).

Two-thirds (21/32) of studies performed an analysis to identify factors associated with ESBL-E colonisation (Table 4). 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\(^{28}\), boiling water before drinking\(^{14}\) and having private inside access to drinking water\(^{10}\) 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

![Figure 1. Flow chart of included studies.](image)
Table 2. 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 media.

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

**Table 3. Details of microbiologic testing procedures.** NR = not reported; API = analytical profile index; MALDI-TOF = Matrix-Assisted Laser Desorption/Ionization-Time of Flight.
| Study                | Sample type          | Screening method                                                                 | Speciation method | ESBL confirmation method |
|---------------------|----------------------|----------------------------------------------------------------------------------|-------------------|--------------------------|
| 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                | CLED with cephalosporin                                                          | 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             | vilek                    |
| 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               |

**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 extended-spectrum beta-lactamase (ESBL) confirmatory testing precise?
associated with a lower ESBL-E prevalence\(^29\), and one the opposite\(^11\). Only two studies addressed the association between HIV status and ESBL-E colonisation status; one, in adults found no association\(^9\), whereas the other, in children, found a strong association\(^17\). Only one study assessed the association between animals in the home as ESBL-E colonisation\(^10\), 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 colonisation prevalence between the two sampling points (Table 5). No study longitudinally sampled ESBL colonisation in the community, either in community dwellers or in those discharged from hospital.

**Discussion**

ESBL-E colonisation is common across sSA, though with significant unexplained heterogeneity between study locations and populations. Community ESBL-E colonisation 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 colonisation prevalence in the world\(^5\). 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 colonisation is reported to range from 3.7% in Spain in 2004 to 7.3% in the UK in 2014\(^38–41\), similar to the United States where a community prevalence of 3.4% was reported in healthy children\(^42\). 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%])

The profound differences in community ESBL-E colonisation 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 colonisation in the studies, with higher prevalence seen in hospitalised individuals and prior hospitalisation and antimicrobial exposure frequently identified as risk factors for colonisation. Conversely and consistent with a putative faecal-oral transmission route, use of borehole water, a private indoor water source and boiling water before drinking

![Figure 3. Overall extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E) colonization prevalence by study.](image-url)
### Study Details

| Study            | n   | ESBL prop | 95% CI       |
|------------------|-----|-----------|--------------|
| **Inpatient**    |     |           |              |
| Marando 2018     | 304 | 0.55      | [0.49; 0.60] |
| Nikema Pessinaba 2018 | 81 | 0.60      | [0.49; 0.71] |
| Desta 2016       | 267 | 0.52      | [0.46; 0.58] |
| Tellevnik, 2016  | 353 | 0.50      | [0.45; 0.56] |
| Lonchel 2013     | 121 | 0.55      | [0.46; 0.64] |
| Magoue 2013      | 208 | 0.67      | [0.60; 0.74] |
| Schaumburg 2013  | 200 | 0.45      | [0.38; 0.52] |
| **Random effects model** | 1534 | 0.55 | [0.49; 0.60] |
| Heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.0598$, $p < 0.01$ |     |           |              |

| **On hospital admission** |     |           |              |
| Fournou 2018         | 43  | 0.37      | [0.23; 0.53] |
| Moremi 2018          | 930 | 0.24      | [0.21; 0.27] |
| Magwenzi 2017        | 154 | 0.32      | [0.28; 0.37] |
| Kurz 2016            | 753 | 0.33      | [0.29; 0.37] |
| Nelson 2014          | 239 | 0.22      | [0.17; 0.28] |
| Isendahl 2012        | 408 | 0.31      | [0.19; 0.45] |
| Woerther 2011        | 55  | 0.32      | [0.24; 0.41] |
| Andriahina 2010      | 244 | 0.22      | [0.17; 0.28] |
| **Random effects model** | 2836 | 0.32 | [0.24; 0.41] |
| Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.2715$, $p < 0.01$ |     |           |              |

| **Outpatient**       |     |           |              |
| Herindrainy 2018     | 275 | 0.20      | [0.15; 0.25] |
| Stanley 2018         | 300 | 0.09      | [0.06; 0.13] |
| Wilmore 2017         | 175 | 0.14      | [0.09; 0.20] |
| Djukoue 2016         | 86  | 0.66      | [0.55; 0.76] |
| Magoue 2013          | 232 | 0.45      | [0.38; 0.51] |
| Lonchel 2012         | 208 | 0.23      | [0.18; 0.29] |
| Herindrainy 2011     | 453 | 0.11      | [0.08; 0.14] |
| **Random effects model** | 1729 | 0.23 | [0.13; 0.39] |
| Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.9382$, $p < 0.01$ |     |           |              |

| **Community**        |     |           |              |
| Cherindeza 2018      | 275 | 0.20      | [0.15; 0.25] |
| Katakweba 2018       | 70  | 0.31      | [0.21; 0.44] |
| Sanneh 2018          | 565 | 0.05      | [0.03; 0.07] |
| Moremi 2017          | 107 | 0.32      | [0.23; 0.41] |
| Farra 2016           | 134 | 0.59      | [0.50; 0.67] |
| Mshana 2016          | 334 | 0.16      | [0.13; 0.21] |
| Ribeiro 2016         | 18  | 0.22      | [0.06; 0.48] |
| Tellevnik, 2016      | 250 | 0.12      | [0.08; 0.16] |
| Chereau 2015         | 356 | 0.19      | [0.15; 0.23] |
| Albrechtova 2012     | 23  | 0.17      | [0.05; 0.39] |
| Lonchel 2012         | 150 | 0.07      | [0.03; 0.12] |
| Ruppe 2009           | 20  | 0.10      | [0.01; 0.32] |
| **Random effects model** | 2302 | 0.18 | [0.12; 0.28] |
| Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.7959$, $p < 0.01$ |     |           |              |

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**Figure 4.** Extended-spectrum beta-lactamase (ESBL) colonisation by study with pooled random effect summary estimates stratified by location of sampling. ESBL prop. = proportion of ESBL producing Enterobacteriaceae.
| Study                        | n   | ESBL prop. | 95% CI       |
|------------------------------|-----|------------|--------------|
| **Children**                 |     |            |              |
| Nikema Pessinaba 2018        | 81  | 0.60       | [0.49; 0.71] |
| Magwenzi 2017                | 164 | 0.52       | [0.45; 0.60] |
| Moremi 2017                  | 107 | 0.32       | [0.23; 0.41] |
| Wilmore 2017                 | 175 | 0.14       | [0.09; 0.20] |
| Desta 2016                   | 94  | 0.59       | [0.48; 0.69] |
| Farr 2016                    | 134 | 0.59       | [0.50; 0.67] |
| Tellevik, 2016               | 603 | 0.34       | [0.31; 0.38] |
| Schaumburg 2013              | 200 | 0.45       | [0.38; 0.52] |
| Isendahl 2012                | 408 | 0.33       | [0.28; 0.37] |
| Harindrainy 2011             | 147 | 0.11       | [0.06; 0.17] |
| Woerther 2011                | 55  | 0.31       | [0.19; 0.45] |
| Andratahina 2010             | 244 | 0.22       | [0.17; 0.28] |
| Ruppe 2009                   | 20  | 0.10       | [0.01; 0.32] |
| **Heterogeneity:** $I^2 = 94\%$, $\chi^2 = 4.0446, p < 0.01$ |

| Study                        | n   | ESBL prop. | 95% CI       |
|------------------------------|-----|------------|--------------|
| **Adults**                   |     |            |              |
| Chiridze 2018                | 275 | 0.20       | [0.15; 0.25] |
| Founou 2018                  | 43  | 0.37       | [0.23; 0.53] |
| Harindrainy 2018             | 275 | 0.20       | [0.15; 0.25] |
| Katakweba 2018               | 70  | 0.31       | [0.21; 0.44] |
| Moremi 2018                  | 930 | 0.24       | [0.21; 0.27] |
| Sanneh 2018                  | 585 | 0.05       | [0.03; 0.07] |
| Desta 2016                   | 154 | 0.45       | [0.37; 0.54] |
| Djuikoue 2016                | 86  | 0.66       | [0.55; 0.76] |
| Ribeiro 2016                 | 18  | 0.22       | [0.06; 0.48] |
| Chereau 2015                 | 356 | 0.19       | [0.15; 0.23] |
| Nelson 2014                  | 113 | 0.15       | [0.09; 0.23] |
| Lonchel 2013                 | 121 | 0.55       | [0.46; 0.64] |
| Magoue 2013                  | 440 | 0.55       | [0.51; 0.60] |
| Albrechtova 2012             | 23  | 0.17       | [0.05; 0.39] |
| Lonchel 2012                 | 358 | 0.16       | [0.13; 0.20] |
| Harindrainy 2011             | 306 | 0.11       | [0.08; 0.15] |
| **Heterogeneity:** $I^2 = 97\%$, $\chi^2 = 0.8210, p < 0.01$ |

| Study                        | n   | ESBL prop. | 95% CI       |
|------------------------------|-----|------------|--------------|
| **Neonates**                 |     |            |              |
| Marando 2018                 | 304 | 0.55       | [0.49; 0.60] |
| Desta 2016                   | 19  | 0.74       | [0.49; 0.91] |
| Nelson 2014                  | 126 | 0.25       | [0.18; 0.34] |
| **Heterogeneity:** $I^2 = 94\%$, $\chi^2 = 0.7505, p < 0.01$ |

Figure 5. Extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E) carriage prevalence stratified by age group.
Table 4. Assessed and significant risk factors in the included studies. mv = multivariate, uv = univariate, HH = household, abx = antibiotics, SES = socio-economic status, HC = health centre, ART = antiretroviral 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     | 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, diagnosis, abx within 3m, hospitalisation within 1yr           | 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)      |
| Schaumburg 2013 | Age, hospitalisation, residence, sex, diagnosis, abx use                           | mv       | Antibiotic use                                        | 10.8 (0.6 - 186)*  |
|            | For neonates: Gestation, birthweight, gender, delivery method, ward, abx use          | uv       | Nothing                                               |                    |
|            | For mothers: Delivery mode, admission within 30d, abx within 3m, abx within 30d, current abx, catheter, HIV status |          |                                                      |                    |
| Nelson 2014 | 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)      |
| Chereau 2015 | 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)   |
| Desta 2016  | Age, pregnancy, abx last 3m, hospital last 3m                                        | uv       | None                                                  |                    |
| Djuikoue 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) |
| Farra 2016  | Age, gender, comorbidity, SES, nutritional status, animals at home, toilets, urban/rural, hh members, meals | mv       | ESBL colonised caregiver                               | 2.88 (1.80-4.61)   |
|            | ESBL colonised caregiver                                                             |          | 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)                                     |
| Kurz 2016  | Age, gender, residence, ward, referral, other healthcare 3m, abx 3m, education, SES, water source, food, time to HC, caregiver ESBL status | mv       | Older age (per yr),                                   | 1.07 (1.04–1.10)   |
|            | ESBL colonised caregiver                                                             |          | Hospital admission last yr                           | 7.4 (1.43-38.5)    |
|            | ESBL colonised caregiver                                                             |          | Abx last 3m                                          | 27 (6.63–116)      |
| Mshana 2016 | Age, region, no of children in house, abx use within 1m, admission within 1yr         | mv       | HIV vs no HIV,                                        | 9.99 (2.52–39.57), |
|            | ESBL colonised caregiver                                                             |          | Kinondoni district,                                   | 2.62 (1.49–4.60)   |
|            | ESBL colonised caregiver                                                             |          | Abx last 14d                                         | 1.61 (1.07–2.41)   |
| Tellevik, 2016 | Age, gender, residence, parental education, child group, nutritional status, use of abx within 14 days | mv       | Local herb use,                                       | 3.3 (1.31–8.31),   |
|            | ESBL colonised caregiver                                                             |          | Sleep on streets vs not                               | 2.8 (1.04–7.65)    |
were associated with reduced ESBL-E colonisation risk, and it may be that poor water, sanitation and hygiene (WASH) infrastructure and practices in sSA are driving high ESBL-E colonisation prevalence. This speaks to a role for poverty in driving ESBL-E colonisation; however, this is likely complex, and context-dependant, as evidenced by conflicting findings of the effect of socio-economic status on colonisation 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 colonisation 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 colonisation 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 colonisation.

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 colonisation 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 colonisation 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.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Zenodo: Risk of bias tool and PRISMA checklist used for the publication: Gut mucosal colonisation with extended-spectrum beta-lactamase producing Enterobacteriaceae in sub-Saharan Africa: a systematic review and meta-analysis, http://doi.org/10.5281/zenodo.3478278

This project contains the following extended data:

- Risk of bias tool used in the study

Reporting guidelines

Zenodo: PRISMA checklist for: Gut mucosal colonisation with extended-spectrum beta-lactamase producing Enterobacteriaceae in sub-Saharan Africa: a systematic review and meta-analysis, http://doi.org/10.5281/zenodo.3478278

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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Among the targets of the AntiMicrobial Resistance, ESBL-producing Enterobacteriaceae are a real worldwide issue not well-studied in Africa. The previous review of Storberg (2014) showed ESBL-producing Enterobacteriaceae are a large problem in African healthcare institutions and communities. However, this author highlighted the scarcity of African data about this topic. This new review shows the same trend with only 32 considered studies from 19 countries and among them 15 studies from 3 countries (Tanzania, Madagascar, and Cameroon).

"Inclusion criteria were any prospective cross-sectional or cohort study that had screened for gut mucosal colonization of ESBL-E in any population in sSA for which it was possible to extract a numerator and denominator to calculate an ESBL-E colonization prevalence." Is that enough to explain that only 32 studies to 2975 were included? These results ask about other countries' lab capacities and about the quality of some works: 2975 identified and 32 included. Does that mean 2943 studies were laboratory-based studies?

However, the methodology seems to be strong. The risk of bias was included and figure 2 a good way to assess the studies. Could we imagine from this review some proposals for better-implementing studies about this topic, leading to facilitating comparison between countries?

About prevalence and risk factors the authors seem to be surprised by differences between countries but it is a picture of the high diversity of the Africa region. Once, higher socio-economic status will be a protector because of sanitation and in another country this status will be a risk factor because the load of antimicrobial exposure will be more serious.

Because of the design of the studies included in this review, the livestock transmission is not evocated as one of the such risk factors. In discussion, the authors should have to point to the lack of studies concerning assessment of risk from livestock.

Undoubtedly, the most relevant intervention to reduce the carriage of ESBL-E will be the systematic implementation of WASH infrastructures. However, this kind of intervention will need to be assessed for convincing decision-makers to involve themselves in this strategy.
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Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

**Author Response 23 Jan 2020**

**Joseph Lewis**, Liverpool School of Tropical Medicine, Liverpool, UK

We thank the reviewer for their review, and agree that systematic WaSH interventions are likely crucial for tackling antimicrobial resistance in sSA.

2943 studies were excluded at the abstract review stage, largely because they were not relevant to the subject of the review (i.e. were not concerned with ESBL-E carriage at all); others did not take place in sSA, or were review articles, case reports, or studies looking at invasive ESBL-E infection. Unfortunately we did not capture the reasons for rejection for each abstract.

We agree that risk factors for ESBL-E carriage are likely to be context dependent across the diverse settings of sSA. We also agree that there are a number of risk factors (including livestock) that are not explored as potential drivers of ESBL-E carriage in the available studies, and hence their role is not clear. We have amended the limitations section to highlight this.

**Competing Interests:** None

**Reviewer Report 06 November 2019**

https://doi.org/10.21956/wellcomeopenres.16981.r36859
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Extended spectrum beta-lactamase (ESBL) producing enteric pathogens are a major cause of hospitalization and mortality in sub-Saharan Africa (SSA), more so because alternative options for effective treatment of infections are either too expensive to afford or are completely unavailable in these settings. I believe this review is timely as it provides information on the extent to which data from the region could provide insight into the extent of gut mucosal colonization (a precursor for invasive disease when immune-suppression may happen) and ensure that we institute policies that effectively reduce colonization and control of infections in these settings.

The authors observed a rather disturbing trend in data spread across the continent as only a meager 32 studies could qualify to have had data on gut colonization and ESBL testing done. Indeed only 6 of these studies followed up patients beyond the hospital discharge. The authors observed that antimicrobial use was associated with increased risk of ESBL-E colonization, and protected water sources or water treatment by boiling may reduce risk in affected patients.

The authors did their best to review all available data to answer their key review questions. The methodology was robust and systematic, and the analysis is complex but easy to follow. The major weakness in this review (which is really non-methodological) is the small number of studies available for the large population of SSA and for which major conclusions to be drawn from such a small sample size would be greatly flawed. There is no doubt that gut mucosal colonization with ESBL-producing gut pathogens plays a major role as a risk factor for invasive disease in hospitalized patients, this has been shown in studies in other parts of the world and such evidence is therefore crucial to compare with SSA. The poor implementation of WaSH in communities and Infection Prevention and control (IPC) strategies in healthcare settings certainly add to the challenges associated with prevention of gut-associated mucosal colonization with ESBL-producing bacteria. It is crucial that the authors clearly indicate the major flaw with the conclusion especially as it is based on a rather small and thinly spread number of studies in SSA. Although HIV and the role of livestock transmission of these zoonotic pathogens in studies in SSA was inconclusive, the fact that the studies reviewed may not necessarily have had these as study objectives cannot be ruled out. Interpretation of such review data should be therefore done with caution especially pertaining to possible key risk factors in disease transmission and gut colonization.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Epidemiology and genomics of enteric pathogens and antimicrobial resistance

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Jan 2020

**Joseph Lewis**, Liverpool School of Tropical Medicine, Liverpool, UK

We thank the reviewer for their review, and agree that the available data are scanty and it is not at all clear that the findings are generalisable across the diverse countries of sub-Saharan Africa, especially as some countries are over-represented in the dataset. We have amended the limitations section of our manuscript to highlight the lack of data and, in particular, that the role of animal to human transmission and HIV infection play in driving ESBL-E colonisation in sSA is unclear.

**Competing Interests:** None