SYSTEMATIC REVIEW

# Re-thinking antimicrobial resistance transmission dynamics: a meta-analysis of cross-sectional studies at referral hospitals in Uganda [version 1; peer review: 1 approved with reservations]

Gerald Mboowa [1-3], Ivan Sserwadda [1], Dickson Aruhomukama [1,3]

[1]Department of Immunology and Molecular Biology, School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Central, 7072, Uganda
[2]African Center of Excellence in Bioinformatics and Data Intensive Sciences, the Infectious Disease Institute, Makerere University, Kampala, Central, 22418, Uganda
[3]Department of Medical Microbiology, School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Central, 7072, Uganda

**v1** **First published:** 03 Aug 2020, **9**:878
https://doi.org/10.12688/f1000research.24638.1
**Latest published:** 03 Aug 2020, **9**:878
https://doi.org/10.12688/f1000research.24638.1

## Abstract

**Background:** Antimicrobial resistance threatens the achievements of modern medicine as well as the sustainability of effective global public health responses to the threat posed by infectious diseases. Extended-spectrum β-lactamase production in bacteria provides the main mechanism of resistance in gram-negative bacteria, particularly those belonging to the Enterobacteriaceae family as well as gram-positive bacteria. This study hence aimed at providing insights into the potential role of in-patients, their immediate hospital environments, out-patients, and their communities in the transmission of antimicrobial resistance via identifying gram-negative and gram-positive bacteria commonly isolated in samples collected from each of these patients/sites as well as their antimicrobial susceptibility profiles using extended-spectrum β-lactamase production in the same as the basis.

**Methods:** Our study reviewed four cross-sectional studies conducted at national and regional referral hospitals in Uganda. Data on bacterial aetiology and antimicrobial susceptibility testing retrieved from the studies was imported into Microsoft Excel, cleaned, sand then exported to IBM SPSS statistics (version 16) for statistical analysis. The databases used were PubMed and Embase.

**Results:** We report that; *Escherichia coli* and *Klebsiella pneumoniae* are the most prevalent Enterobacteriaceae species in the samples that were collected in the studies reviewed; these species account for the highest proportions of extended-spectrum β-lactamase producers; *Staphylococcus aureus* is the most prevalent of the gram-positive

**Open Peer Review**

**Reviewer Status** ?

| | Invited Reviewers |
|---|---|
| | **1** |
| **version 1** 03 Aug 2020 | ? report |

1. **Fredrick Haraka**, Ifakara Health Institute, Bagamoyo, Tanzania

Any reports and responses or comments on the article can be found at the end of the article.

bacteria isolated from the same samples, and accounts for the highest proportions of extended-spectrum β-lactamase producers in the gram-positive bacteria isolated, and similar Enterobacteriaceae species and gram-positive bacteria, are predominant in samples from in-patients, their immediate hospital environments, and out-patients.
**Conclusion:** The insights provided indicate antimicrobial resistance transmission dynamics be re-thought and more comprehensive studies aimed at investigating the same be done to ascertain the source and transmission routes of antimicrobial-resistant bacteria in clinical settings.

**Keywords**
Antimicrobial resistance, Transmission dynamics, Extended-spectrum β-lactamases, Uganda

This article is included in the Antimicrobial Resistance collection.

**Corresponding author:** Dickson Aruhomukama (dickson.aruhomukama@chs.mak.ac.ug)

**Author roles: Mboowa G**: Conceptualization, Formal Analysis, Funding Acquisition, Methodology, Supervision, Validation, Visualization, Writing – Review & Editing; **Sserwadda I**: Formal Analysis, Methodology, Validation, Visualization, Writing – Review & Editing; **Aruhomukama D**: Conceptualization, Formal Analysis, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

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

**Grant information:** This work was supported through the Grand Challenges Africa programme [GCA/AMR/rnd2/058]. Grand Challenges Africa is a programme of the African Academy of Sciences (AAS) implemented through the Alliance for Accelerating Excellence in Science in Africa (AESA) platform, an initiative of the AAS and the African Union Development Agency (AUDA-NEPAD). GC Africa is supported by the Bill & Melinda Gates Foundation (BMGF) and The African Academy of Sciences and partners. The views expressed herein are those of the author(s) and not necessarily those of the AAS and it's partners.
*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*



**How to cite this article:** Mboowa G, Sserwadda I and Aruhomukama D. **Re-thinking antimicrobial resistance transmission dynamics: a meta-analysis of cross-sectional studies at referral hospitals in Uganda [version 1; peer review: 1 approved with reservations]** F1000Research 2020, **9**:878 https://doi.org/10.12688/f1000research.24638.1

**First published:** 03 Aug 2020, **9**:878 https://doi.org/10.12688/f1000research.24638.1

## Introduction

Antimicrobial resistance not only threatens the achievements of modern medicine but also the sustainability of effective global public health responses to the threat posed by infectious diseases[1,2]. Extended-spectrum β-lactamase production in bacteria confers antimicrobial resistance and provides the main mechanism of resistance in gram-negative bacteria, particularly those belonging to the Enterobacteriaceae family as well as gram-positive bacteria[3,4]. Extended-spectrum β-lactamase producing bacteria exhibit resistance to all penicillin-like antibiotics except cephamycins and carbapenems; resistance in these bacteria frequently spans to other classes of antibiotics, including the quinolones and aminoglycosides[5–7]. Resistance to β-lactam antibiotics is mostly plasmid-borne and can be disseminated among bacterial species via horizontal gene transfer; this has consequently led to clonal distribution within and between clinical settings, communities as well as across local and international boarders via patient mobility[7,8]. Combating antimicrobial resistance requires continuous and timely monitoring, surveillance, and assessment systems as well as mechanisms to detect extended-spectrum β-lactamase producing bacteria. In Uganda, the acquisition and transmission dynamics of extended-spectrum β-lactamase producing bacteria at referral hospitals and community settings have not been elucidated. The aim of this study was therefore to provide insights into the potential role of in-patients, their immediate hospital environments, out-patients, and their communities in the transmission of extended-spectrum β-lactamase producing bacteria via identifying gram-negative and gram-positive bacteria commonly isolated in samples collected from each of these patients/sites as well as their antimicrobial susceptibility profiles using extended-spectrum β-lactamase production in the same as the basis.

## Methods

We conducted a systematic review of cross-studies on bacterial aetiology and antimicrobial susceptibility profiles conducted at national and regional referral hospitals in Uganda.

### Eligibility criteria

The application of the inclusion and exclusion criteria was undertaken independently by the reviewers (GM, IS, and DA) and any difference in opinion was resolved by discussion among the reviewers. Also, the inclusion and exclusion criteria were the same for both the systematic review as well as the meta-analysis.

Included studies were as follows:

- Studies whose designs were cross-sectional.
- Studies that were conducted in Ugandan national and regional referral hospitals.
- Studies that reported bacterial aetiology and antimicrobial susceptibility profiles.
- Studies with the requirements above that had been published within the last ten years.

Excluded studies were as follows:

- Studies that had been published as reviews
- Studies in which data had been reported only as abstracts.
- Studies whose designs were not cross-sectional (i.e. retrospective and prospective)

***Search strategy.*** The Pubmed and Embase electronic databases were searched for eligible studies. We used the search string [“Antimicrobial resistance”] AND [“Referral Hospitals”] AND [“Uganda”]. We also sought additional studies through screening the references of the selected studies.

### Data extraction

Data extraction was done by GM, IS and DA. Data were entered in prespecified spreadsheet in Microsoft Excel (2019 version). The extracted data elements consisted of (1) bacterial aetiology and (2) antimicrobial susceptibility profiles.

***Risk of bias.*** For the bias risk analysis, an appraisal tool for cross-sectional studies, AXIS was used[9]. In addition, quality assessment of the included studies referred to a modified method composed of the design of the studies, participant, sites and settings selection methodology and laboratory tests that included; determination of bacterial aetiology, antimicrobial susceptibility testing and screening for the production of Extended-spectrum β-lactamases (extended data[10]).

***Statistical analysis.*** The main outcomes of interest in the data analysis were: 1) the proportion of gram-positive and negative bacteria isolated from the samples collected in the studies; and 2) the proportion of the gram-positive and negative bacteria isolated that were producers of Extended-spectrum β-lactamases.

For all the selected studies, data on bacterial aetiology and antimicrobial susceptibility testing was extracted using Microsoft Excel (2019 version). Following data extraction, several tables containing dichotomous data were generated for the relative and cumulative calculation of the frequencies of the outcomes of interest. For all of the meta-analysis procedures, IBM SPSS Statistics (version 16) was used. In SPSS, forest and funnel plots and charts were generated. The proportions of either the gram- positive and negative bacteria was determined by the number of the same divided by the total number bacteria isolated in the studies. A similar approach was used to determine the proportions of gram-positive and negative bacteria isolated that were producers of Extended-spectrum β-lactamases. The $I^2$ test was used to access the existence of heterogenicity of between the studies ($I^2$ = 75–100%, $p<0.05$)[11,12]. Due to the nature of the studies, heterogenicity was expected; we therefore chose to use the random effects model for the meta-analysis as proposed by DerSimonian-Laird[13]. We also performed a sensitivity analysis to test for the effect of the individual influence of each study on the overall estimate, and a subgroup analysis was also performed to reduce the existence of heterogenicity. In addition, we evaluated the existence of publication bias by visual inspection of Begg’s funnel plots as well as by Egger’s test calculation[14,15].

## Results

Primarily, during the search for studies in the digital databases as well as additional records from other sources, 52 reference

studies were found. After the application of the inclusion and exclusion criteria, we refined the results, and 4 eligible studies constituted the present meta-analysis[16–19]. The flowchart of this selection is shown in the PRISMA diagram is shown in Figure 1.

Of the 4 studies included in the meta-analysis, 2/4 (i.e. Study 1 (Seni *et al.*, 2013) and Study 2 (Masifa *et al.*, 2018)) collected samples from in-patients; the samples collected in the two studies included wound and pus swabs, these samples had only been obtained from patients with wound sepsis based on evidence of post-operative wound infection during the respective study periods (i.e. September 2011 to April 2012 and June to October 2015 respectively) from the General Surgery, Obstetrics and Gynecology, Orthopedic and General Surgery, Obstetrics and Gynecology wards respectively[16,17]; 1/4 (i.e. Study 3 – Kateregga *et al.*, 2015) collected samples from both in-patients and out-patients, the samples collected included urine, swabs (i.e. oral, high vaginal, and wound), blood, and cerebrospinal fluid; the samples had been collected by purposive sampling from patients attending different hospital wards; these wards included Surgical wards (i.e. General Surgical and Surgical Out-patient Department), Medical wards (i.e. General, Medical Out-patient Department, Medical assessment Center, Uganda Cancer Institute-Liquid Tumor Cancer, and Uganda Heart Institute), Pediatric wards, General wards (i.e. Out-patient Department, Medical Out-patient Department, and the Sexually Transmitted Diseases Department); the samples were collected from January to April 2014[18]; 1/4 (Study 4 – Sserwadda *et al.*, 2018) collected samples from the hospital environment, specifically, from medical equipment (i.e. scissors, infusion stands), patients' beds and work surfaces

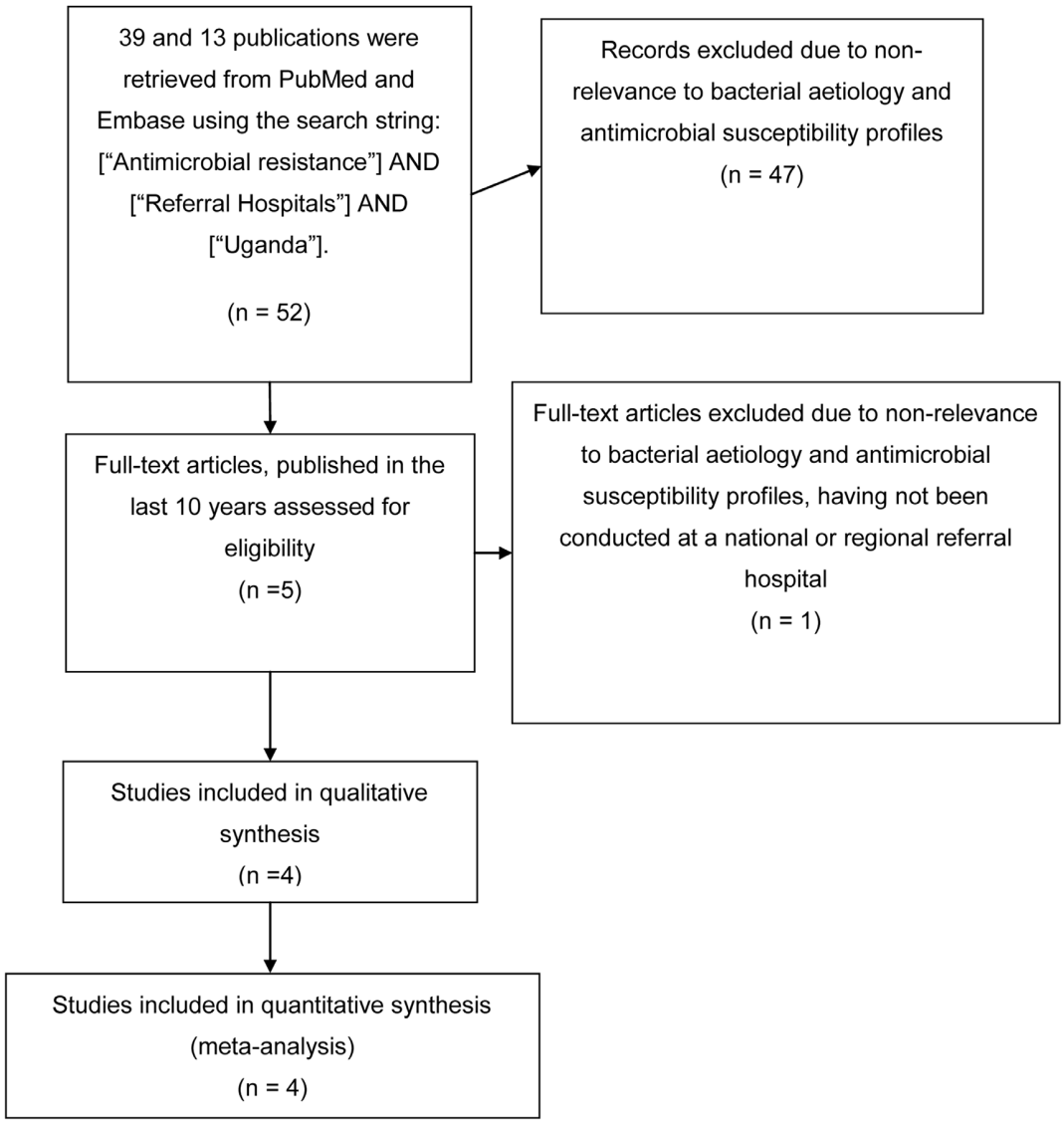


**Figure 1. PRISMA Chart was constructed to illustrate the workflow of the selection process.**

(i.e. tables, sink taps and light switches); the samples had been collected by purposive sampling from the different sites, consideration was given to sites with constant hand contact, and the samples were collected from June to December 2015[19].

### Bacterial aetiology and antimicrobial susceptibility profiles of gram-negative isolates

Studies 1, 2, 3, and 4 reported Enterobacteriaceae making up 47.7%, 49%, 46.9%, and 25.6% out of the total isolates obtained from these respective studies (Table 1). *Escherichia coli* was found to be the most predominant of the Enterobacteriaceae isolates obtained from studies 1, 2, and 3 accounting for 49.7%, 43.1%, and 53.9% respectively; second to *Escherichia coli* was *Klebsiella pneumoniae*, this accounted for 12.8%, 29.4%, and 28.7% of the Enterobacteriaceae isolates in studies 1, 2, and 3 respectively. In a similar regard, *Klebsiella pneumoniae* was found to be the most predominant of the Enterobacteriaceae isolates in study 4 representing 46.7%; second to *Klebsiella pneumoniae was Proteus vulgaris,* this represented 33.3% of the Enterobacteriaceae isolates (Table 1).

Extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae were reported in all the four studies, these represented 81.4%, 76.5%, 62% and 20% for studies 1, 2, 3 and 4 respectively. In studies 1 and 2, *Escherichia coli* was found to be the main extended-spectrum β-lactamase producer accounting for 48.3% and 41% respectively while *Klebsiella pneumonia* was the main extended-spectrum β-lactamase producer for studies 3 and 4 accounting for 72.7% and 100% respectively (Table 1).

### Bacterial aetiology and antimicrobial susceptibility profiles of gram-positive isolates

*Staphylococcus aureus* was the most predominant gram-positive isolate obtained from studies 1, 2 and 4 accounting for 67.4%, 93.2% and 75.4% respectively (Table 2). Study 3 did not isolate any gram-positive bacteria as it only considered gram-negative bacteria (Table 2). Proportions of extended-spectrum β-lactamase producing *Staphylococcus aureus* were 67.4%, 75% and 70.5% for studies 1, 2 and 4 respectively. Study 3 did not isolate any gram-positive bacteria and therefore no extended-spectrum β-lactamase production was reported (Table 2).

**Table 1. Bacterial aetiology and antimicrobial susceptibility profiles of gram-negative isolates.**

| Samples source | In-patients and Out-patients | | | Hospital Environment |
|---|---|---|---|---|
| | Study 1 | Study 2 | Study 3 | Study 4 |
| **Total Enterobacteriaceae** | 145/304 (47.7%) | 51/104 (49.0%) | 115/245 (46.9%) | 15/61 (25.6%) |
| **Most predominant Enterobacteriaceae** | *E. coli* 72/145, (49.7%) | *E. coli* 22/51, (43.1%) | *E. coli* 62/115, (53.9%) | *K. pneumoniae* 7/15, (46.7%) |
| **Second most predominant Enterobacteriaceae** | *K. pneumoniae* 39/145,12.8% | *K. pneumoniae* 15/51,29.4% | *K. pneumoniae* 33/115,28.7% | *P. vulgaris* 5/15,33.3% |
| **% of ESBL producers of (*n*)** | 118/145,81.4% | 39/51,76.5% | 71/115,62% | 3/15,20% |
| **Isolate type with highest ESBL production** | *E. coli* 57/118,48.3% | *E. coli* 18/39,41.1% | *K. pneumoniae* 52/71,72.7% | *K. pneumoniae* 3/3,100% |

Key: Study 1 – Seni *et al.*, 2013; Study 2 – Masifa *et al.*, 2018; Study 3 – Kateregga *et al.*, 2015; Study 4 – Sserwadda *et al.*, 2018; ESBL - Extended-spectrum β-lactamase

**Table 2. Bacterial aetiology and antimicrobial susceptibility profiles of gram-positive isolates.**

| Sample source | In-patients and Out-patients | | | Hospital Environment |
|---|---|---|---|---|
| | Study 1 | Study 2 | Study 3 | Study 4 |
| **Total gram-positive bacteria (*n*)** | 95/304, 31.2% | 44/104, 42.3% | 0/0, 0% | 46/61, 75.4% |
| **Most predominant gram-positive bacteria** | *S. aureus* (64/95, 67.4%) | *S. aureus* (41/44,93.2%) | NA | *S. aureus* (46/61,75.4%) |
| **% of ESBL producers of *(n)*** | 64/95 isolates, 67.4% | 33/44 isolates, 75% | No ESBL producers | 43/61 isolates, 70.5% |

**Key:** Study 1 – Seni *et al.*, 2013; Study 2 – Masifa *et al.*, 2018; Study 3 – Kateregga *et al.*, 2015; Study 4 – Sserwadda *et al.*, 2018; NA- No gram-positive bacteria isolated; ESBL - Extended-spectrum β-lactamase.

## Discussion

This study reviewed four cross-sectional studies on bacterial aetiology and antimicrobial susceptibility profiles conducted at referral hospitals in Uganda with the aim of providing insights into the potential role of in-patients, their immediate hospital environments, out-patients, and their communities in the transmission of antimicrobial resistance via identifying gram-negative and gram-positive bacteria commonly isolated in samples collected from each of these patients/sites as well as their antimicrobial susceptibility profiles using extended-spectrum βlactamase production in the same as the basis.

This study achieved the objectives for which it was conducted; the major findings were that; (i) *Escherichia coli* and *Klebsiella pneumoniae* are the most prevalent Enterobacteriaceae species in the samples that had been collected in the studies reviewed; (ii) these species (i.e. *Escherichia coli* and *Klebsiella pneumoniae*) account for the highest proportions of extended-spectrum β-lactamase producers; (iii) *Staphylococcus aureus* is the most prevalent of the gram-positive bacteria isolated from the same samples, and accounts for the highest proportions of extended-spectrum β-lactamase producers in the gram-positive bacteria isolated, and (iv) similar Enterobacteriaceae species and gram-positive bacteria are predominant in samples from in-patients, their immediate hospital environments, and out-patients.

The findings of this study with regards to *Escherichia coli* and *Klebsiella pneumoniae* being the most prevalent Enterobacteriaceae species in the samples are consistent with those of similar studies; these studies have not only highlighted these bacterial species to be the most prevalent in samples from in-patients[20–24], but have also indicated them to be the most prevalent in samples from out-patients as well in those from the hospital environment[7,25–27]. The findings of this study with regards to the isolation of similar Enterobacteriaceae species from in-patient samples, those from their immediate hospital environments, and out-patients could be suggestive of the possibility of complex transmission dynamics of the same.

In a similar light, despite the fact that these remain the most prevalent Enterobacteriaceae species, this study as well the studies reviewed did not ascertain the source of these; however, speculate that these could be from both nosocomial and community sources.

In addition, the findings of this study with regards to these Enterobacteriaceae species being the main extended-spectrum β-lactamase producers of the gram-negative isolates are consistent with those of similar studies[20,22].

The prevalence of these species in samples collected from both the community and hospital settings continues to increase. The source of ESBL-PE in samples from the community could be as a consequence of the introduction by individuals that had visited health-care settings or had interacted with health-care workers in the same settings, this has also been suggested in other studies[28,29]. Some studies have however suggested that population exposures to antibiotics could offer an explanation to the observation[25,30], while some have demonstrated carriage of the same bacteria in individuals with no history of having taken antibiotics[31] and have highlighted food products from animals as potential sources of the bacteria[32].

According to the 2017 World Health Organization list of priority pathogens, these Enterobacteriaceae species have been identified to belong to the priority one or critical category, and particularly when these are producers of extended-spectrum β-lactamases. Extended-spectrum β-lactamases confer resistance to all penicillin derivative antibiotics as well as cephalosporins, except cephamycins and carbapenems[7,33]; despite the fact that this study and the studies reviewed did not ascertain which extended-spectrum β-lactamase encoding genes were mediating the observed β-lactam resistance and how these are potentially disseminated in the isolates, our study speculates that the extended-spectrum β-lactamase encoding genes could have been either or a combination of the $bla_{\text{CTX-M}}$, $bla_{\text{SHV}}$ and $bla_{\text{TEM}}$, and that horizontal gene transfer could be a plausible mechanism by which the dissemination of these genes could be occurring. This is because, not only have most extended-spectrum β-lactamase encoding genes described so far been derivatives of the *bla*CTX-M, *bla*SHV and *bla*TEM, but these have also been reported to be the most prevalent in isolates just like those in the studies reviewed; these genes have also been documented to be mostly encoded by conjugative plasmids; these are mobile genetic elements (MGEs)[7,8,33,34].

Besides extended-spectrum β-lactamase encoding genes, these MGEs have also been documented to carry genes that confer resistance to other antibiotic classes that include fluoroquinolones, aminoglycosides, and trimethoprim/sulfamethoxazole; these have also been documented to contribute to the selection and persistence of multidrug-resistant extended-spectrum β-lactamase producing strains in samples from in-patients, their immediate hospital environments, and out-patients; this could explain the resistance to other antibiotics observed in the studies reviewed[5,7,8,35,36].

The findings of our study with regards to *Staphylococcus aureus* being the most prevalent of the gram-positive bacteria isolated from the samples collected in the studies, and accounting for the highest proportions of extended-spectrum β-lactamase producers in the gram-positive bacteria species from in-patient samples, those from their immediate hospital environments, and out-patients are consistent with those of similar studies; these studies have not only highlighted these bacterial species to be the most prevalent in samples from in-patients, but have also indicated them to be the most prevalent in samples from out-patients, as well in those from the hospital environments[37–39]. In a similar light, despite the fact that these remain the most prevalent gram-positive bacteria species, our study as well as the studies reviewed did not ascertain the source of these, however, similar to the case of the Enterobacteriaceae species, this study speculates that these could be from both nosocomial and community sources.

According to the 2017 World Health Organization list of priority pathogens, *Staphylococcus aureus*, has been identified to belong to the priority two or high category, and particularly when these are producers of extended-spectrum β-lactamases or which exhibit methicillin-resistance (MRSA). Despite the fact that MRSA has long been a pathogen of nosocomial origin, in recent times, it has emerged as a problematic pathogen in community settings[40,41]. These same studies have also indicated the possibility of community-associated MRSA being replaced by nosocomial-associated MRSA.

## Conclusion

The results of our study indicate that similar extended–spectrum β-lactamase producing Enterobacteriaceae species and gram-positive bacteria are predominant in samples from in-patients, their immediate hospital environments, and out-patients. This study offers insights into the potential role of in-patients, their immediate hospital environments, out-patients, and their communities in the transmission of antimicrobial resistance. In addition, the results of our study, underscores the need for continuous monitoring and surveillance of antimicrobial resistance in clinical and community settings, together with efforts to promote the rational and judicious use of antibiotics. Lastly, with the insights provided here, antimicrobial resistance transmission dynamics should be re-thought and more comprehensive studies aimed at investigating the same should be done to ascertain the source and transmission routes of antimicrobial resistant bacteria in community and clinical settings.

## 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

Figshare: S1 File.docx. https://doi.org/10.6084/m9.figshare.12563153.v1[10]

This project contains the following extended data:

- S1 File.docx (Summary of included study characteristics)

### Reporting guidelines

Figshare: PRISMA checklist for 'Re-thinking antimicrobial resistance transmission dynamics: a meta-analysis of cross-sectional studies at referral hospitals in Uganda' https://doi.org/10.6084/m9.figshare.12563318.v1[42]



## References


1. Utt E, Wells C: **The global response to the threat of antimicrobial resistance and the important role of vaccines.** *Pharm Policy Law.* 2016; **18**(1–4): 179–97.
Publisher Full Text
2. Prestinaci F, Pezzotti P, Pantosti A: **Antimicrobial resistance: a global multifaceted phenomenon.** *Pathog Glob Health.* 2015; **109**(7): 309–18.
PubMed Abstract | Publisher Full Text | Free Full Text
3. Cag Y, Caskurlu H, Fan Y, *et al.*: **Resistance mechanisms.** *Ann Transl Med.* 2016; **4**(17): 326.
PubMed Abstract | Publisher Full Text | Free Full Text
4. Tang SS, Apisarnthanarak A, Hsu LY: **Mechanisms of β-lactam antimicrobial resistance and epidemiology of major community-and healthcare-associated multidrug-resistant bacteria.** *Adv Drug Deliv Rev.* 2014; **78**: 3–13.
PubMed Abstract | Publisher Full Text
5. Carattoli A: **Plasmids and the spread of resistance.** *Int J Med Microbiol.* 2013; **303**(6–7): 298–304.
PubMed Abstract | Publisher Full Text
6. Umadevi S, Kandhakumari G, Joseph NM, *et al.*: **Prevalence and antimicrobial susceptibility pattern of ESBL producing gram negative bacilli.** *J Clin Diagn Res.* 2011; **5**(2): 236–9.
Reference Source
7. Barguigua A, El Otmani F, Talmi M, *et al.*: **Characterization of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae isolates from the community in Morocco.** *J Med Microbiol.* 2011; **60**(Pt 9): 1344–52.
PubMed Abstract | Publisher Full Text
8. Haque SF, Ali SZ, Mohammed TP, *et al.*: **Prevalence of plasmid mediated blaTEM-1 and blaCTX-M-15 type extended spectrum beta-lactamases in patients with sepsis.** *Asian Pac J Trop Med.* 2012; **5**(2): 98–102.
PubMed Abstract | Publisher Full Text
9. Downes MJ, Brennan ML, Williams HC, *et al.*: **Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS).** *BMJ Open.* 2016; **6**(12): e011458.
PubMed Abstract | Publisher Full Text | Free Full Text
10. Aruhomukama D: **S1 File.docx.** *figshare.* Online resource. 2020.
http://www.doi.org/10.6084/m9.figshare.12563153.v1
11. Higgins JPT, Thompson SG: **Quantifying heterogeneity in a meta-analysis.** *Stat Med.* 2002; **21**(11): 1539–58.
PubMed Abstract | Publisher Full Text
12. von Hippel PT: **The heterogeneity statistic I(2) can be biased in small meta-analyses.** *BMC Med Res Methodol.* 2015; **15**: 35.
PubMed Abstract | Publisher Full Text | Free Full Text
13. DerSimonian R, Laird N: **Meta-analysis in clinical trials.** *Control Clin Trials.* 1986; **7**(3): 177–88.
PubMed Abstract | Publisher Full Text
14. Egger M, Smith GD, Schneider M, *et al.*: **Bias in meta-analysis detected by a simple, graphical test.** *BMJ.* 1997; **315**(7109): 629–34.
PubMed Abstract | Publisher Full Text | Free Full Text
15. Begg CB, Mazumdar M: **Operating characteristics of a rank correlation test for publication bias.** *Biometrics.* 1994; **50**(4): 1088–101.
PubMed Abstract
16. Seni J, Najjuka CF, Kateete DP, *et al.*: **Antimicrobial resistance in hospitalized surgical patients: a silently emerging public health concern in Uganda.** *BMC Res Notes.* 2013; **6**(1): 298.
PubMed Abstract | Publisher Full Text | Free Full Text
17. George M, Iramiot JS, Muhindo R, *et al.*: **Bacterial Aetiology and Antibiotic Susceptibility Profile of Post-Operative Sepsis among Surgical Patients in a Tertiary Hospital in Rural Eastern Uganda.** *Microbiol Res J Int.* 2018; **24**(2): MRJL.41690.
PubMed Abstract | Publisher Full Text | Free Full Text
18. Kateregga JN, Kantume R, Atuhaire C, *et al.*: **Phenotypic expression and prevalence of ESBL-producing Enterobacteriaceae in samples collected from patients in various wards of Mulago Hospital, Uganda.** *BMC Pharmacol Toxicol.* 2015; **16**(1): 14.
PubMed Abstract | Publisher Full Text | Free Full Text
19. Sserwadda I, Lukenge M, Mwambi B, *et al.*: **Microbial contaminants isolated from items and work surfaces in the post-operative ward at Kawolo general hospital, Uganda.** *BMC Infect Dis.* 2018; **18**(1): 68.
PubMed Abstract | Publisher Full Text | Free Full Text
20. Moyo SJ, Aboud S, Kasubi M, *et al.*: **Antimicrobial resistance among producers**

**and non-producers of extended spectrum beta-lactamases in urinary isolates at a tertiary Hospital in Tanzania.** *BMC Res Notes.* 2010; **3**(1): 348.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Maina D, Revathi G, Kariuki S, *et al.*: **Genotypes and cephalosporin susceptibility in extended-spectrum beta-lactamase producing enterobacteriaceae in the community.** *J Infect Dev Ctries.* 2012; **6**(06): 470–7.
PubMed Abstract | Publisher Full Text

22. Mpogoro FJ, Mshana SE, Mirambo MM, *et al.*: **Incidence and predictors of surgical site infections following caesarean sections at Bugando Medical Centre, Mwanza, Tanzania.** *Antimicrob Resist Infect Control.* 2014; **3**(1): 25.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Chahoud J, Kanafani Z, Kanj SS: **Surgical site infections following spine surgery: eliminating the controversies in the diagnosis.** *Front Med (Lausanne).* 2014; **1**: 7.
PubMed Abstract | Publisher Full Text | Free Full Text

24. de Lissovoy G, Fraeman K, Hutchins V, *et al.*: **Surgical site infection: incidence and impact on hospital utilization and treatment costs.** *Am J Infect Control.* 2009; **37**(5): 387–97.
PubMed Abstract | Publisher Full Text

25. Najjuka CF, Kateete DP, Kajumbula HM, *et al.*: **Antimicrobial susceptibility profiles of *Escherichia coli* and *Klebsiella pneumoniae* isolated from outpatients in urban and rural districts of Uganda.** *BMC Res Notes.* 2016; **9**(1): 235.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Muhammad UK, Isa MA, Aliyu ZM: **Distribution of potential nosocomial pathogens isolated from environments of four selected hospital in Sokoto, North Western Nigeria.** *J Microbiol Biotechnol Res.* 2013; **3**(1): 139–43.
Reference Source

27. Ekrami A, Kayedani A, Jahangir M, *et al.*: **Isolation of common aerobic bacterial pathogens from the environment of seven hospitals, Ahvaz, Iran.** 2011.
Reference Source

28. Naseer U, Haldorsen B, Simonsen GS, *et al.*: **Sporadic occurrence of CMY-2-producing multidrug-resistant *Escherichia coli* of ST-complexes 38 and 448, and ST131 in Norway.** *Clin Microbiol Infect.* 2010; **16**(2): 171–8.
PubMed Abstract | Publisher Full Text

29. Young BE, Lye DC, Krishnan P, *et al.*: **A prospective observational study of the prevalence and risk factors for colonization by antibiotic resistant bacteria in patients at admission to hospital in Singapore.** *BMC Infect Dis.* 2014; **14**(1): 298.
PubMed Abstract | Publisher Full Text | Free Full Text

30. Woerther PL, Angebault C, Jacquier H, *et al.*: **Characterization of fecal extended-spectrum-β-lactamase-producing *Escherichia coli* in a remote community during a long time period.** *Antimicrob Agents Chemother.* 2013; **57**(10): 5060–6.
PubMed Abstract | Publisher Full Text | Free Full Text

31. Bailey JK, Pinyon JL, Anantham S, *et al.*: **Commensal *Escherichia coli* of healthy humans: a reservoir for antibiotic-resistance determinants.** *J Med Microbiol.* 2010; **59**(Pt 11): 1331–9.
PubMed Abstract | Publisher Full Text

32. Overdevest I, Willemsen I, Rijnsburger M, *et al.*: **Extended-spectrum β-lactamase genes of *Escherichia coli* in chicken meat and humans, The Netherlands.** *Emerg Infect Dis.* 2011; **17**(7): 1216–22.
PubMed Abstract | Publisher Full Text | Free Full Text

33. Aruhomukama D: **Phenotypic Assays for Detection of Extended Spectrum Β-Lactamases and Carbapenemases: A Laboratory Guide for Microbiologists.** 2018. [cited 2018 Sep 24].
Reference Source

34. Doi Y, Adams-Haduch JM, Peleg AY, *et al.*: **The role of horizontal gene transfer in the dissemination of extended-spectrum beta-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae* isolates in an endemic setting.** *Diagn Microbiol Infect Dis.* 2012; **74**(1): 34–8.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Moura A, Henriques I, Ribeiro R, *et al.*: **Prevalence and characterization of integrons from bacteria isolated from a slaughterhouse wastewater treatment plant.** *J Antimicrob Chemother.* 2007; **60**(6): 1243–50.
PubMed Abstract | Publisher Full Text

36. Bush K: **Alarming β-lactamase-mediated resistance in multidrug-resistant Enterobacteriaceae.** *Curr Opin Microbiol.* 2010; **13**(5): 558–64.
PubMed Abstract | Publisher Full Text

37. Salgado CD, Farr BM, Calfee DP: **Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors.** *Clin Infect Dis.* 2003; **36**(2): 131–9.
PubMed Abstract | Publisher Full Text

38. David MZ, Daum RS: **Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic.** *Clin Microbiol Rev.* 2010; **23**(3): 616–87.
PubMed Abstract | Publisher Full Text | Free Full Text

39. Hiramatsu K, Cui L, Kuroda M, *et al.*: **The emergence and evolution of methicillin-resistant *Staphylococcus aureus*.** *Trends Microbiol.* 2001; **9**(10): 486–93.
PubMed Abstract | Publisher Full Text

40. Popovich KJ, Weinstein RA, Hota B: **Are community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) strains replacing traditional nosocomial MRSA strains?** *Clin Infect Dis.* 2008; **46**(6): 787–94.
PubMed Abstract | Publisher Full Text

41. Huang H, Flynn NM, King JH, *et al.*: **Comparisons of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and hospital-associated MSRA infections in Sacramento, California.** *J Clin Microbiol.* 2006; **44**(7): 2423–7.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Aruhomukama D: **DA_PRISMA 2009 checklist_2.doc.** *figshare.* Online resource. 2020.
http://www.doi.org/10.6084/m9.figshare.12563318.v1

# Open Peer Review

## Current Peer Review Status: ?

**Version 1**

Reviewer Report 20 October 2020

https://doi.org/10.5256/f1000research.27177.r71664



?

**Fredrick Haraka**
Ifakara Health Institute, Bagamoyo, Tanzania

**This manuscript has been reviewed in consideration of the PRISMA guideline and checklist**

Mboowa G *et al.*, aimed at investigating anti-microbial resistance transmission dynamics in a hospital setting by pulling existing evidence through systematic review and meta-analysis. Mboowa G *et al.*, searched two databases and restricted their search to Uganda. They found that *Escherichia coli* and *Klebsiella pneumoniae* were the most prevalent Enterobacteriaceae species and these species account for the highest proportions of extended-spectrum β-lactamase producers among gram-negative bacteria.
*Staphylococcus aureus* was the most prevalent. The authors' topic is relevant for both patient and policy decisions, however, the authors will need to revise the manuscript before it can be accepted. Specifically;

**Major comments:**

- The authors will need to redo and expand their search of relevant articles, indicate the time bound of the search and all relevant databases. The description of the search strategy must be detailed to include all components of the PICO question they intend to address.

- The authors will need to adhere to the PRISMA guideline and rewrite the manuscript accordingly.

- I'm afraid the results do not reflect the analysis planned. I did not see any meta-analysis. The two tables presented do not show any results of pulled data.

- Reviews are meant to provide a summary effect of an intervention/approach/test/drug etc. While it is important to define the PICO question clearly, restricting to a particular geographical region e.g. Uganda may unlikely provide the expected 'global effect" of a review and meta-analysis. The authors might want to expand on this.

**Minor comments**

- In their title, the authors have indicated that they conducted a meta-analysis, however, it is disturbing to see that the authors did not report any summary measures in the abstract.

- Although the authors have included key summary structure, the information is definitely not exhaustive. The authors might want to look into the PRISMA checklist for guidance.
- The authors might want to rewrite their introduction in a manner that allows the reader to explicitly understand why this review was necessary. The authors have spent a substantial amount of time discussing mechanisms of anti-microbial resistance and little on current evidence and critically highlight the gap this review is expected to fill. Specifically, a reader does not clearly get the PICO question being addressed.

- The authors might want to mention whether or not there were any language restrictions.

- No mention of if there was an existing protocol that was published before the actual review is conducted. It is important for the reader to know if any part of the initial planned objectives or analysis changed and why.

**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?**
Partly

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

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

***Reviewer Expertise:*** Infectious disease, evidence synthesis

**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, however I have significant reservations, as outlined above.**