Lack of association between patients characteristics and carriage of extended-spectrum β-lactamase producing Enterobacteriaceae in community settings in Blantyre, Malawi

Onduru Gervas Onduru (ogyonduru@yahoo.com)
University of Malawi College of Medicine https://orcid.org/0000-0001-8954-2794

Susan Fred Rumisha
Directorate of Information Technology and Communication, National institute for medical Research, P.0.Box 9653, Dar es Salaam, Tanzania

Rajhab Sawasawa Mkakosya
University of Malawi College of Medicine

Gabriel Kambale Bunduki
University of Malawi College of Medicine

Said Aboud
Muhimbili University College of Health Sciences: Muhimbili University of Health and Allied Sciences

Research note

**Keywords:** ESBL carriage, Enterobacteriaceae, Community, associated factors, Malawi

**DOI:** https://doi.org/10.21203/rs.3.rs-322264/v2

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** Infections caused by extended-spectrum β-lactamase (ESBL) producing bacteria are global health threat contributing to increased morbidity and mortality in resource-constrained countries. This cross sectional study examined factors associated with the carriage of ESBL-producing Enterobacteriaceae (ESBL-E) in community patients in Blantyre, Malawi.

**Methods:** We collected rectal swabs and urine samples from randomly recruited participants and screened for ESBL-E on CHROMagar™ ESBL medium (CHROMagar, Paris, France). The ESBL-E isolates were identified using commercially acquired biochemical strips (Microbact™ GNB, Oxoid, UK) and production of ESBL was confirmed by the combination disk test using cefotaxime and ceftazidime disks with and without clavulanic acid. Antibiotic susceptibility test was done by the disc diffusion method and interpreted according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) 2019. Univariate logistic regression was used to evaluate association between ESBL-E carriage and the associated factors. To quantify relationships, dichotomous variables were compared using Pearson’s chi-square test or Fisher exact test as appropriate and continuous variables were compared using the Student’s t-test. Results were expressed as odds ratio (OR) with a 95% confidence interval.

**Results**

A total of 50 community patients with ESBL-E phenotypes were identified from 300 adults recruited in the study, which gave a ESBL-E prevalence of 16.67% (50/300, 95% CI=12.43-20.91%). The mean age ±SD of participants was 32.41±12.07 years; range, 18-75 years and 54.33% (163/300) were women. On unadjusted logistic regression, no association between carriage of ESBL-E and community patient characteristics was observed.

**Conclusions**

The carriage of ESBL-E is prevalent in the community in Blantyre-Malawi. Nevertheless, factors associated with this carriage remain unidentified. Further investigations including large case-control and molecular studies using one health approach are required to confirm community-based transmission of ESBLs and to determine the factors, reservoirs and vehicles associated with the dissemination of ESBL within the community in Blantyre, Malawi.

**Introduction**

Extended-spectrum β-lactamase produced by many Gram-negative bacteria mediate resistance against penicillins, extended-spectrum cephalosporins and monobactams. Infections caused by ESBL-producing pathogens has become a public health problem in different countries causing longer hospitalization, increased healthcare costs and higher morbidity and mortality as a result of the decreased therapeutic value of most common antibiotics used to manage patients.
While the acquisition of ESBL-E was initially considered nosocomial, the current trends in antimicrobial resistance continue to show increased evidence of higher rates of ESBL-E carriage in the community settings.

Studies conducted to define the risk factors for acquiring infection caused by ESBL-E in the community settings are very limited. Of the factors for the introduction of ESBL-E into the community that have been identified included travel to areas with a higher prevalence of ESBL-E, previous hospitalization, antibiotic treatments, old age, comorbidities like diabetes and previous infection by members of Enterobacteriaceae.

Transmission and spread of ESBL-E strains in the community have also been suggested to occur through the food chain and companion animals. A study conducted in Dutch patients, retail chicken meat and poultry revealed that human and poultry shared the same ESBL stains genes and plasmids, this alone indicated that carriage of ESBL-E in food-producing animals, contamination of retail meat and environment can contribute to higher incidences of infections with ESBL-producing bacteria in humans. Even though carriage of ESBL-E differs between persons, indefinite carriage overtime may increase the risk of community acquisition and transmission of ESBL pathogens. Furthermore, poor hygiene and weak implementation of antimicrobial policy perpetuate the spread of antibiotic resistance in the community.

Previous studies in Malawi have estimated the prevalence of invasive and carriage ESBL-E isolated from blood cultures of hospitalized patients to range from 0.7% to 90.5% in 2005 and 2017 respectively. Despite the increase of prevalence which was exclusively reported in hospital settings, no study has been conducted in Malawi and Blantyre in particular reporting predictive factors of ESBL-E in either hospital or community settings. Investigating predictors of contracting strains of ESBL-E in community settings is potentially important to understand causal mechanisms that can guide formulation and implementation of successful infection and antimicrobial use control strategies and empirical ESBL targeted antimicrobial therapy to both community and hospital patients. Therefore, this study examined factors associated with carriage of ESBL-E in community patients in Blantyre, Malawi.

**Materials And Methods**

**Study design and setting**

This was a cross-sectional study carried out between March and September 2020 to assess for the factors associated with ESBL-E carriage in randomly selected community patients attending outpatient health centres in Blantyre, Malawi. The three health centres that were selected randomly included Limbe, Zingwangwa and Ndirande health centres.

**Study population and Sample collection**
The study participants comprised of 300 adult (≥18 years old) outpatients. Participants present on the day of data collection were recruited randomly into the study regardless of their reason to seek health care. Social demographic characteristics and clinical data including age, sex, education, occupation, history of prior hospitalization, history of surgery and prior history of antibiotic use were collected using a standard questionnaire. From each participant, either rectal swab or urine sample was purposely collected for ESBL-E screening. Urine samples were collected exclusively from patients that had complained of UTI symptoms. Samples were taken using standard microbiological procedures and were immediately sent to the microbiology laboratory at Kamuzu university of Health Sciences (KUHeS) for laboratory procedures.

**ESBL-E screening**

Initial screening for potential ESBL-E was performed by culture on a chromogenic selective medium (CHROMagar™ ESBL) supplemented with ESBL supplement containing a selective mixture of antibiotics enabling selective growth of ESBL-E and inhibiting the growth of non-ESBL-E (CHROMagar™, Paris, France). The putative culture of ESBL producers was phenotypically confirmed using combination disk test method (CDT) by comparing the inhibition zone diameter around cefotaxime (CTX-30μg) and ceftazidime (CAZ-30μg) disks with and without clavulanic acid as previously described 24.

**Biochemical identification of Enterobacteriaceae**

Presumably, identification of common ESBL-E isolates was done based on bacterial colonial morphology and chromogenic characteristics on CHROMagar™ medium plates according to the manufacturers’ instructions. Subsequently, the identity of Enterobacteriaceae was confirmed using the commercially acquired biochemical substrate strips (Microbact™, Oxoid, GNB 12A) according to the manufacturer’s instructions.

For quality control purposes, ESBL-producing *Klebsiella pneumonia* (ATCC 700603) and Non-ESBL producing *E. coli* (ATCC 25922) were used as positive and negative control respectively.

**Statistical analysis**

The summary and descriptive statistics were generated as percentages, proportions, mean and standard deviation. Dichotomous variables were compared using Pearson’s chi-square test or Fisher exact test as appropriate and continuous variables were compared using the Student’s *t*-test. To identify the association between patients characteristics and carriage of ESBL-E, the univariate logistic regression was used. A p-value ≤ 0.05 was considered statistically significant. Effect sizes of associations of patients characteristics and ESBL-E carriage were reported using Odd ratios (OR) and 95% confidence intervals (CI). During logistic regression analysis, participants who had separated, divorced, widow and single marital status were combined to obtain single variable (unmarried) and was compared with married or cohabiting participants. History of admission prior to data collection was omitted from the model because all individuals with confirmed ESBL-E phenotypes (dependent variable) had no history of
admission in the past three months. All statistical analyses were performed with STATA version 12 (Stata Corp., College Station, Texas, USA).

Ethics approval and consent to participate

This study was approved by the College of Medicine Research Ethics Committee (COMREC) of the University of Malawi (Approval No. P:07/19/2720 of November 22, 2019). Blantyre district health authority granted permission to conduct research in health centres. Written informed consent was obtained from participants before enrolment into the study.

Results

Characteristics of study participants

A total of 50 community patients with ESBL-E carriage were identified from 300 adults recruited into the study, which gave a prevalence of 16.67% (95% CI=12.43-20.91%). The average age ± standard deviation of participants was 32.41±12.07 years; the age range was between 18 and 75 years old. Majority of participants were women 54.33% (163/300). The prevalence of ESBL-E was higher in male (9.33%) similar to married or cohabiting participants, 8% for unemployed and 7.6% for those with primary education (table 1).

Table 1: Characteristics of the study participants
| Factors                                    | Frequency n(%) | ESBL phenotype |        |        |
|-------------------------------------------|----------------|----------------|-------|-------|
|                                           |                | Positive n(%)  | Negative n(%) |
| **Age**                                   |                |                |       |       |
| 18-27                                     | 125(41.67%)    | 20(6.67%)      | 105(35.00%) |
| 28-37                                     | 95(31.67%)     | 13(4.34%)      | 82(27.33%)  |
| 38-47                                     | 43(14.33%)     | 10(3.33%)      | 33(11.00%)  |
| 48-57                                     | 20(6.67%)      | 3(1.00%)       | 17(5.67%)   |
| ≥58                                       | 17(5.67%)      | 4(1.33%)       | 13(4.34%)   |
| **Sex**                                   |                |                |       |       |
| Male                                      | 137(45.67%)    | 28(9.33%)      | 109(36.33%) |
| Female                                    | 163(54.33%)    | 22(7.34%)      | 141(47.00%) |
| **Marital status**                        |                |                |       |       |
| Single                                    | 116 (38.67%)   | 22 (7.34%)     | 94 (31.33%) |
| Married or cohabiting                     | 184 (61.33%)   | 28 (9.33%)     | 156 (52.00%) |
| **Education**                             |                |                |       |       |
| Primary                                   | 133 (44.33%)   | 23 (7.67%)     | 110 (36.67%) |
| Secondary                                 | 115 (38.33%)   | 16 (5.33%)     | 99 (33.00%) |
| College/University                        | 6 (2.00%)      | 2 (0.67%)      | 4 (1.33%)   |
| Didn't attend any school                  | 46 (15.33%)    | 9 (3.00%)      | 37 (12.33%) |
| **Occupation**                            |                |                |       |       |
| Unemployed                                 | 138(46%)       | 24(8.00%)      | 114(38.005) |
| Self-employment or business               | 57(19%)        | 12(4.00%)      | 45(15.00%)  |
| Employed                                  | 78(26%)        | 8(2.67%)       | 70(23.33%)  |
| Student                                   | 27(9%)         | 6(2.00%)       | 21(7.00%)   |
| **History of prior antibiotic use in last 3 months** |        |                |       |       |
| Yes                                       | 66 (22.00%)    | 10 (3.33%)     | 56 (18.67%) |
| No                                        | 234 (78.00%)   | 40 (13.33%)    | 194 (64.67%) |
| **History of surgery in previous 3 months** |        |                |       |       |
|                  | Yes       | No         |      |
|------------------|-----------|------------|------|
|                  | 29 (9.67%)| 6 (2.00%)  | 23 (7.67%) |
| History of admission in previous 3 months |           |            |      |
| Yes              | 7 (2.33%) | 0 (0.00%)  | 7 (2.33%)  |
| No               | 293 (97.67%) | 50 (16.67%) | 243 (81.00%) |
| Outpatient health centre |           |            |      |
| Limbe            | 99 (33.00%) | 13 (4.33%) | 86 (28.67%) |
| Ndirande         | 100 (33.33%) | 22 (7.33%) | 78 (26.00%) |
| Zingwangwa      | 101 (33.67%) | 15 (5.00%) | 86 (28.67%) |

**Association of participant’s characteristics and risk factors for ESBL-E carriage**

The analysis of the risk factors for ESBL-E carriage and community patient characteristics showed statistically insignificant association. Neither prior antibiotic use (OR= 0.87, 95%, CI: 0.41-1.84) nor the history of surgery three months before the study (OR=1.35, 95%, CI: 0.52-3.49) was associated with carriage of ESBL-E in community patients.

**Table 2:** Independent non-predictors of ESBL-producing *Enterobacteriaceae* in community patients in Blantyre, Malawi.
| Factor                          | OR (95%, CI)      | p-value † |
|--------------------------------|-------------------|-----------|
| Age (mean±SD)                  | 1.01(0.99-1.04)   | 0.25      |
| Sex (Male) n(%)                | 1.65(0.89-3.04)   | 0.11      |
| Marital status n(%)            |                   |           |
| Married or cohabiting          | 0.77(0.41-1.42)   | 0.39      |
| Education level n(%)           |                   |           |
| Primary                        | 0.42(0.07-2.42)   | 0.33      |
| Secondary                      | 0.32(0.05-1.91)   | 0.21      |
| Did no attend to any school    | 0.49(0.08-3.08)   | 0.45      |
| Occupation n(%)                |                   |           |
| Employed                       | 0.4(0.12-1.28)    | 0.12      |
| Self-employment or business    | 0.92(0.31-2.82)   | 0.90      |
| Unemployed                     | 0.74(0.23-2.02)   | 0.55      |
| Antibiotic use in the past 3 months n(%) |       |           |
| Yes                            | 0.87(0.41-1.84)   | 0.71      |
| Surgery in previous 3 months n(%) |                   |           |
| Yes                            | 1.35(0.52-3.49)   | 0.54      |

†Chi square test for dichotomous variables and Student’s t test for continuous variables

**Discussion**

Our data showed 16% prevalence of ESBL-E in community patients in Blantyre and there were no significant factors associated with ESBL-E carriage. Previous studies have suggested that the prevalence of ESBL-E in communities vary widely by geographic region and settings. Although hospitalized patients carrying hospital-acquired ESBL-producing bacteria over an extended period have been linked with the spread of ESBL-E to the community, in the current study, community emergence of ESBL-E could arise from irrational antibiotic use by community patients.

We found low prevalence of ESBL-E in community patients with no prior history of hospital admissions. This is an indication that patients from the community in Blantyre were likely to have been exposed to several courses of antibiotics due to irrational use as a result of weak restrictions and over the counter availability. Consequently, community patients could have acquired ESBL-E through selection from the existing gastrointestinal flora after antibiotics exposure. Similar low prevalence of ESBL-E was reported...
in other studies\textsuperscript{11,14,28,31–33}. The probable explanation for the low prevalence of ESBL-E in community patients detected in this study could be lack of patients’ prior history of hospitalization which have been reported as the main factor driving the spread of ESBL pathogens in the community.

While the current study highlights the lack of association between ESBL-E carriage in community patients and their clinical or social-demographic characteristics, several risk factors for community-acquired ESBL-E infections have been identified. These included the history of recurrent UTIs, urinary catheter placement, previous hospital admission, outpatient exposure to \(\beta\)-lactams (e.g. penicillins, cephalosporins) and quinolones, comorbidities, old age, male gender, and travel to areas with high rates of ESBL infections\textsuperscript{11,25,26,34–39}. Similar to our findings, a study by Sanneh \textit{et al}.,\textsuperscript{40} did not find an association between demographic characteristics and ESBL-E Carriage in the community settings. Neither admission in the hospital, nor close contact with hospitalized individuals was significantly associated with the carriage of ESBL-E in studies by Kurz \textit{et al} and Briongos-Figuero \textit{et al} respectively\textsuperscript{41,42}. We anticipate that these factors may have a causal relationship with ESBL-E carriage but may only lack statistical significance association because most of them have validity and biologic plausibility for a causal relationship with ESBL-E carriage as previously described\textsuperscript{4,26,39,43}.

In previous studies, the male gender was reported as a risk factor for ESBL-E carriage\textsuperscript{8,44}. However, in this study, males had a higher proportion of ESBL-E carriage than women but male gender was not a statistically significant predictor of ESBL-E.

**Conclusion**

The current study provides evidence that ESBL-producing \textit{Enterobacteriaceae} carriage is prevalent in the community in Blantyre. Nevertheless, factors associated with this carriage remain unidentified. Even though further investigations including large case-control and molecular studies using one health approach are required to confirm community-based transmission of ESBLs and to determine associated factors, reservoirs and vehicles for the dissemination of ESBL within the community in Blantyre Malawi; the findings of the current study can answer the question on the importance of routine screening for ESBL producing pathogens to aid ESBL-E targeted antimicrobial therapy.

**Declarations**

**Acknowledgements**

This research was supported by the Africa Centre of Excellence in Public Health and Herbal Medicine as part of the first author’s Ph.D fellowship. The funders had no role in the design of the study, data collection, analysis and interpretation or writing the manuscript. A preliminary version of this manuscript has been presented as preprint in Research square and can be accessed through the following link, https://www.researchsquare.com/article/rs-322264/v1
Authors’ contributions

OGO conceptualized, designed, collected and analyzed the data and drafted the manuscript. SFR, RSM, GKB and SA reviewed and contributed to content. All authors approved the final manuscript.

Competing interests

The authors declare no competing interests

References

1. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev*. 2001;14(4):933-951. doi:10.1128/CMR.14.4.933-951.2001

2. Peralta G, Sánchez MB, Garrido JC, et al. Impact of antibiotic resistance and of adequate empirical antibiotic treatment in the prognosis of patients with Escherichia coli bacteraemia. *J Antimicrob Chemother*. 2007;60(4):855-863. doi:10.1093/jac/dkm279

3. Kim BN, Woo JH, Kim MN, Ryu J, Kim YS. Clinical implications of extended-spectrum β-lactamase-producing Klebsiella pneumoniae bacteraemia. *J Hosp Infect*. 2002;52(2):99-106. doi:10.1053/jhin.2002.1288

4. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae: Risk factors for infection and impact of resistance on outcomes. *Clin Infect Dis*. 2001;32(8):1162-1171. doi:10.1086/319757

5. Falagas ME, Karageorgopoulos DE. Extended-spectrum beta-lactamase-producing organisms. *J Hosp Infect*. 2009;73(4):345-354. doi:10.1016/j.jhin.2009.02.021

6. Tandé 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;15(3):472-474. doi:10.3201/eid1503.071637

7. Rodríguez-Baño J, Navarro MD, Romero L, et al. Epidemiology and Clinical Features of Infections Caused by Extended-Spectrum Beta-Lactamase-Producing Escherichia coli in Nonhospitalized Patients. *J Clin Microbiol*. 2004;42(3):1089-1094. doi:10.1128/JCM.42.3.1089-1094.2004

8. Colodner R, Rock W, Chazan B, Keller N, Guy N, Sakran W. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. *Eur J Clin Microbiol Infect Dis*. 2004;23(3):163-167. doi:10.1007/s10096-003-1084-2

9. Valverde A, Coque TM, Sánchez-Moreno MP, Rollán A, Baquero F, Cantón R. Dramatic Increase in prevalence of fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae during
nonoutbreak situations in Spain. *J Clin Microbiol*. 2004;42(10):4769-4775. doi:10.1128/JCM.42.10.4769-4775.2004

10. Cantón R, Novais A, Valverde A, et al. Prevalence and spread of extended-spectrum \( \beta \)-lactamase-producing Enterobacteriaceae in Europe. *Clin Microbiol Infect*. 2008;14:144-153. doi:10.1111/J.1469-0691.2007.01850.X

11. Kader AA, Kamath KA. Faecal carriage of extended-spectrum \( \beta \)-lactamase-producing bacteria in the community. *East Mediterr Heal J*. 2009;15(6):1365-1370.

12. 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;100(1):47-53. doi:10.1016/j.jhin.2018.05.017

13. Marando R, Seni J, Mirambo MM, et al. Predictors of the extended-spectrum-beta lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. *Int J Med Microbiol*. 2018;308(7):803-811. doi:10.1016/j.ijmm.2018.06.012

14. Woerther P-L, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum \( \beta \)-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev*. 2013;26(4):744-758. doi:10.1128/CMR.00023-13

15. Paltansing S, Vlot JA, Kraakman MEM, et al. Extended-spectrum \( \beta \)-lactamase-producing enterobacteriaceae among travelers from the Netherlands. *Emerg Infect Dis*. 2013;19(8):1206-1213. doi:10.3201/eid.1908.130257

16. Kantele A, Laaveri T, Mero S, et al. Antimicrobials Increase Travelers’ Risk of Colonization by Extended-Spectrum Betalactamase-Producing Enterobacteriaceae. *Clin Infect Dis*. 2015;60(6):837-846. doi:10.1093/cid/ciu957

17. Peirano G, Laupland KB, Gregson DB, Pitout JDD. Colonization of returning travelers with CTX-M-producing Escherichia coli. *J Travel Med*. 2011;18(5):299-303. doi:10.1111/j.1708-8305.2011.00548.x

18. Saputra S, Jordan D, Mitchell T, et al. Antimicrobial resistance in clinical Escherichia coli isolated from companion animals in Australia. *Vet Microbiol*. 2017;211:43-50. doi:10.1016/j.vetmic.2017.09.014

19. Kluytmans JA JW, Overdevest ITMA, Willemsen I, et al. Extended-Spectrum \( \beta \)-Lactamase-Producing Escherichia coli From Retail Chicken Meat and Humans: Comparison of Strains, Plasmids, Resistance Genes, and Virulence Factors. *Clin Infect Dis*. 2013;56(4):478-487. doi:10.1093/cid/cis929

20. Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. *Clin Microbiol Infect*. 2011;17(6):873-880. doi:10.1111/j.1469-0691.2011.03497.x
21. Hong JS, Song W, Park HM, et al. Clonal spread of extended-spectrum cephalosporin-resistant enterobacteriaceae between companion animals and humans in South Korea. *Front Microbiol.* 2019;10(2019):1371. doi:10.3389/fmicb.2019.01371

22. Musicha P, Cornick JE, Bar-zeev N, 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(10):1042-1052. doi:10.1016/S1473-3099(17)30394-8

23. Musicha P, Msefula CL, Mather AE, et al. Genomic analysis of Klebsiella pneumoniae isolates from Malawi reveals acquisition of multiple ESBL determinants across diverse lineages. *J Antimicrob Chemother.* 2019;74(5):1223-1232. doi:10.1093/jac/dkz032

24. M’Zali FH, Chanawong A, Kerr KG, Birkenhead D, Hawkey PM. Detection of extended-spectrum -lactamases in members of the family Enterobacteriaceae: comparison of the MAST DD test, the double disc and the Etest ESBL. *J Antimicrob Chemother.* 2000;45(6):881-885. doi:10.1093/jac/45.6.881

25. Kang CI, Song JH, Chung DR, et al. Risk factors and treatment outcomes of community-onset bacteraemia caused by extended-spectrum β-lactamase-producing Escherichia coli. *Int J Antimicrob Agents.* 2010;36(3):284-287. doi:10.1016/j.ijantimicag.2010.05.009

26. Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Clinical and molecular epidemiology of community-onset, extended-spectrum β-lactamase-producing Escherichia coli infections in Thailand: A case-case-control study. *Am J Infect Control.* 2007;35(9):606-612. doi:10.1016/j.ajic.2007.05.008

27. Pulss S, Stolle I, Stamm I, et al. Multispecies and clonal dissemination of OXA-48 carbapenemase in Enterobacteriaceae from companion animals in Germany, 2009-2016. *Front Microbiol.* 2018;9(2018):1265. doi:10.3389/fmicb.2018.01265

28. Nakane K, Kawamura K, Goto K, Arakawa Y. Long-term colonization by blaCTX-M-harboring Escherichia coli in healthy Japanese people engaged in food handling. *Appl Environ Microbiol.* 2016;82(6):1818-1827. doi:10.1128/AEM.02929-15

29. Randall LP, Clouting C, Horton RA, et al. Prevalence of Escherichia coli carrying extended-spectrum β-lactamases (CTX-M and TEM-52) from broiler chickens and turkeys in Great Britain between 2006 and 2009. *J Antimicrob Chemother.* 2011;66(1):86-95. doi:10.1093/jac/dkq396

30. Heseltine P. Has resistance spread to the community? *Clin Microbiol Infect.* 2014;6(2):11-16. doi:10.1046/j.1469-0691.2000.00004.x

31. Kiiru J, Kariuki S, Goddeeris BM, Butaye P. Analysis of -lactamase phenotypes and carriage of selected -lactamase genes among Escherichia coli strains obtained from Kenyan patients during an 18-year period. *BMC Microbiol.* 2012;12(155):1471-2180. doi:10.1186/1471-2180-12-155
32. Janatova M, Albrechtova K, Petrzelkova KJ, et al. Antimicrobial-resistant Enterobacteriaceae from humans and wildlife in Dzanga-Sangha Protected Area, Central African Republic. *Vet Microbiol*. 2014;171(3-4):422-431. doi:10.1016/j.vetmic.2014.02.014

33. Lonchel CM, Meex C, Gangoué-Piéboji J, et al. Proportion of extended-spectrum β-lactamase-producing Enterobacteriaceae in community setting in Ngaoundere, Cameroon. *BMC Infect Dis*. 2012;12. doi:10.1186/1471-2334-12-53

34. Goyal D, Dean N, Neill S, Jones P, Dascomb K. Risk factors for community-acquired extended-spectrum beta-lactamase-producing Enterobacteriaceae infections-a retrospective study of symptomatic urinary tract infections. *Open Forum Infect Dis*. 2019;6(2):1-6. doi:10.1093/ofid/ofy357

35. Rodríguez-Baño J, Picón E, Gijón P, et al. Community-onset bacteremia due to extended-spectrum β-lactamase-producing Escherichia coli: Risk factors and prognosis. *Clin Infect Dis*. 2010;50(1):40-48. doi:10.1086/649537

36. Harris AD, McGregor JC, Johnson JA, et al. Risk factors for colonization with extended-spectrum β-lactamase-producing bacteria and intensive care unit admission. *Emerg Infect Dis*. 2007;13(8):1144-1149. doi:10.3201/eid1308.070071

37. Tumbarello M, Trecarichi EM, Bassetti M, et al. Identifying patients harboring extended-spectrum-β-lactamase-producing Enterobacteriaceae on hospital admission: Derivation and validation of a scoring system. *Antimicrob Agents Chemother*. 2011;55(7):3485-3490. doi:10.1128/AAC.00009-11

38. Park SY, Kang C-I, Wi YM, et al. Risk factors and molecular epidemiology of community-onset, multidrug resistance extended-spectrum β-lactamase-producing Escherichia coli infections. *Korean J Intern Med*. 2017;32(1):146-157. doi:10.3904/kjim.2015.113

39. Hsieh CJ, Shen YH, Hwang KP. Clinical Implications, Risk Factors and Mortality Following Community-onset Bacteremia Caused by Extended-spectrum β-lactamase (ESBL) and non-ESBL Producing Escherichia coli. *J Microbiol Immunol Infect*. 2010;43(3):240-248. doi:10.1016/S1684-1182(10)60038-2

40. Sanneh B, Kebbeh A, Jallow HS, et al. Prevalence and risk factors for faecal carriage of Extended Spectrum β-lactamase producing Enterobacteriaceae among food handlers in lower basic schools in West Coast Region of The Gambia. Singer AC, ed. *PLoS One*. 2018;13(8):e0200894. doi:10.1371/journal.pone.0200894

41. Kurz MSE, Bayingana C, Ndoli JM, 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*. 2017;22(2):210-220. doi:10.1111/tmi.12824
42. Briongos-Figuero LS, Gómez-Traveso T, Bachiller-Luque P, et al. Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. *Int J Clin Pract*. 2012;66(9):891-896. doi:10.1111/j.1742-1241.2012.02991.x

43. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant Staphylococcus aureus, enterococcus, gram-negative bacilli, Clostridium difficile, and Candida. *Ann Intern Med*. 2002;136(11):834-844. doi:10.7326/0003-4819-136-11-200206040-00013

44. Søgaard M, Heide-Jørgensen U, Vandenbroucke JP, Schønheyder HC, Vandenbroucke-Grauls CMJE. Risk factors for extended-spectrum β-lactamase-producing Escherichia coli urinary tract infection in the community in Denmark: a case–control study. *Clin Microbiol Infect*. 2017;23(12):952-960. doi:10.1016/j.cmi.2017.03.026