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Extended-spectrum β-lactamase production and antimicrobial resistance among Enterobacteriaceae causing clinical infections in Africa: a systematic review and meta-analysis (2012–2020)

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Abstract

Background Worldwide, antimicrobial resistance (AMR) has grown to represent a serious threat to the diagnosis, management, and prevention of bacterial diseases. Due to their multidrug resistance attributes, the WHO has classified extended-spectrum-β-lactamase-producing Enterobacteriaceae (ESBL-PE)-associated infections as infections of critical significance, posing a serious risk to human health. Thus, the goal of this systematic review and meta-analysis was to assess the pooled prevalence of ESBL-PE and AMR among strains causing clinical infections in Africa.

Methods In this systematic review and meta-analysis, two investigators independently made an electronic search in Google Scholar and PubMed databases using related keywords and corresponding "MeSH." terms for the PubMed. The accessed studies were screened, assessed for eligibility, and critically evaluated as per the PRISMA guidelines. The prevalence and 95% confidence intervals (CI) for ESBL-PE in Africa were evaluated using a random-effects model of a meta-analysis. As a visual and statistical way assessment, the funnel plot and Egger's test were utilized to assess the risk of bias or publication bias, with a statistically significant level of bias being determined at $p < 0.05$.

Results Twenty-six studies were included in the meta-analysis. Among the included studies done in Africa, the overall pooled proportion of ESBL-PE was reported to be 28% (95% CI 25–31%). ESBL-PE prevalence differed by region, the pooled estimates for East and North Africa were 29% (95% CI 20–38%) and 19% (95% CI 6–33%), respectively. The greatest sub-group analysis of pooled estimates among bacterial isolates was found in *Klebsiella. pneumoniae*, at 73% (95% CI 62–85%), while *Proteus mirabilis* had the lowest, at 40% (95% CI 1–81%).

Conclusions In Africa, ESBL-PE is noticeably prevalent. The included studies demonstrated a significant variation in ESBL-PE resistance among the countries. This illustrates the necessity of actively monitoring antimicrobial resistance in Africa to develop interventions aimed at halting the spread of ESBL-PE.

Keywords Antimicrobial resistance, Extended-spectrum ß-lactamase, Enterobacteriaceae, Africa

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Background

Antimicrobial resistance (AMR) has become a major global health threat impeding the diagnosis, treatment, and prevention of bacterial illnesses. In both developed and developing nations, AMR increases health care costs, and length of hospital stay [1]. AMR leads in high rates of morbidity and mortality in low- and middle-income countries [2]. However, low- and middle-income countries, particularly Asian countries and the WHO Africa region has one of the largest gaps in data on the prevalence of AMR. This is mostly due to limited laboratory capacity, budgetary constraints, lack of skilled manpower and weak surveillance networks [3, 4].

AMR arises through a range of mechanisms, such as target site modification or bypass of target sites, enzymatic degradation of antimicrobial, reduced uptake through quorum sensing, efflux and reduced permeability of bacterial outer membrane [5–7]. Several resistance genes, either innately occurring or evolving due to pressure from antimicrobial selection brought about by improper use of antimicrobial medications mediate this resistance [8–10].

Extended-Spectrum-Beta-Lactamase producing Enterobacteriaceae (ESBL-PE) are those bacterial species that belong to the family Enterobacteriaceae and possess the ability to hydrolyze β-lactam antibiotics. In historical perspective, the development of resistance to β-lactam antibiotics started prior to the discovery of penicillin, which is the first β-lactam. Before penicillin was approved for use in medicine, *Escherichia coli* was found to contain β-lactamase [11, 12].

The major resistance mechanism for β-lactam antibiotics is β-lactamase enzyme-mediated hydrolytic antibiotic degradation employed by many Gram-negative bacteria, particularly members of the family the Enterobacteriaceae. These include *Escherichia*, *Klebsiella*, *Morganella*, *Citrobacter*, *Proteus*, *Enterobacter* and *Serratia*. In addition, non Enterobacteriaceae including *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are known β-lactamase producing species of bacteria [13].

ESBL-PE are derived from genes related to the narrow-spectrum beta-lactamases by mutations that alter the amino acid configuration around the enzyme active site [14]. Usually, plasmids that are easily interchanged between bacterial species encode Beta-lactamase determining genes. Most often, members of the Enterobacteriaceae family particularly those belonging to the *E. coli* and *Klebsiella* species produce these enzymes. ESBL-PE have been recognized as pathogens of critical importance (priority 1), because they pose a serious risk to human health [15–17]. Collectively, the *bla*SHV, *bla*TEM, *bla*CTX-M genes are the mainly responsible with ESBL production. The CTX-M gene is the predominant one, and it has regional differences in prevalence. For instance, in Africa, the blaCTM-X 15 is the most prevalent genotype [18–20]. On top of the above mentioned genotypes, the minor ESBL genotypes (PER, GES and VEB) and the Carbapenemases including the KPV, IMP, VIM, OXA-48-1ike and OXA-1-like are among the ESBL genotypes [19].

From a clinical stand point, ESBL-PE are important, because they are widely distributed and confer resistance to several significant antimicrobials; ESBL-PE-associated infections are significantly associated with excess risk of mortally (nearly two fold higher odds of mortality) compared to non ESBL-PE-associated infections [21, 22]. AMR, which is currently estimated to be responsible for more than 700,000 deaths annually worldwide, is causing increasing concern on a global scale [23]. A recent report projected that by 2050, 10 million deaths will be linked to AMR, and if appropriate measures are not taken to contain the threat, 100 trillion USD of the world's economic output will be lost [24, 25].

Studies indicate that, the rate of ESBL-PE colonization (34–37%) is high worldwide, particularly in hospitalized individuals [26]. Globally, there is increasing burden of ESBL-PE, and the COVID-19 pandemic has exacerbated the incidence of ESBL-PE attributable infections [27]. According to CDC, there was a 50% increase in ESBL-PE caused infections 2013 through 2019 in the US [28]. Low/middle income countries took the highest share of ESBL-PE prevalence, and approximately 20% of health individuals in Africa harbor these strains [29]. ESBL-PE-associated infections are significantly fatal with various determinants of death, including sever sepsis, respiratory tract infections, underlying comorbidities, nosocomial infection and neutropenia. Moreover, the odds of ESBL-PI-associated mortality is almost threefold higher among those who were previously exposure to antibiotics, which could be an indication of misuse and empiric therapy [30].

The spread of ESBL-PE in Africa needs comprehensive interventions due their cyclic patterns on environment, livestock, community [31], intra-family transmission, healthcare acquired infections [32], and traveler-associated infections [33]. According to the evidences from West and Central Humans take the highest share of ESBL-PE (up to 72%) followed by Animals and wastewater [34]. Evidences in Egypt indicated that ESBL-PE are responsible for 52–75% of community-acquired infections and 55–68% of health-care-associated infections [35]. In sub-Saharan Africa, the empiric use of antibiotics has aggravated the rate of ESBL-PE carriage (71%), and high rate of mortalities due to drug resistance (33–100%) [36, 37]. The irrational antibiotic use, high rate of gastrointestinal carriage, and fecal shedding posed a risk of community spread of ESBL-PE and invasive infections

[38, 39]. Due to their multi-drug resistance nature [40], this fecal carriage of multidrug resistant ESBL-PE strains is a great health risk to the public at large, and vulnerable populations including children [39, 41], pregnant women and people living with HIV [38, 42, 43].

With these considerations, the presence of concrete scientific evidences that inform on policy makers is one of the main pillars of intervention. Therefore, the objective of this systematic review and meta-analysis was to enlist peer-reviewed articles and gather data on the presence of ESBL-PE and their antimicrobial resistance profile in Africa, and to determine the pooled prevalence of ESBL-PE in human studies.

Methodology

Search strategy, information sources and eligibility criteria

Overall, the search strategy was made as per the recommendations on the reporting of meta-analysis of observational studies in epidemiology as published in JAMA [44] and depending on the preferred reporting items for systematic review and meta-analysis (PRISMA) statement published by Moher et al., in Annals of Internal Medicine [45]. The study was conducted with the notion to produce primary and secondary outcomes. The primary outcomes were the pooled prevalence of ESBL-PE, and pooled estimates of AMR prevalence for each ESBL-PE. In addition, the study assessed the secondary outcomes including the study designs, study subjects, clinical samples, research methods and guidelines used to characterize ESBL-PE in the African continent. Two investigators made the electronic search in Google Scholar and PubMed databases, and the electronic search covered studies published from January 1, 2012, through June 28, 2020. ESBL-PE, OR extended-spectrum-beta-lactamase-producing, OR extended spectrum β-lactamase-producing, and "(Enterobacteriaceae OR resistant OR resistance OR 'non-susceptible' OR "not susceptible") were among the keywords included in the search strategy. The key words were aligned to "MeSH" words in the PubMed. The search results were further filtered by year, type of article, text availability, and language. We tried to include non-open access articles, and the articles that report only abstracts through direct email communication with the primary author and corresponding author. However, no effort was made to include papers published in languages other than English.

The search included results of research on Enterobacteriaceae etiologic isolates that produce ESBLs and exhibit antibiotic resistance from African countries. Studies with any design, any age group, any clinical samples, studies using any type of laboratory technique, original research articles, studies published between January 1, 2012, and June 30, 2020, and published in English-language were all deemed eligible for inclusion in this review. Whereas, studies carried out on environmental and animal samples, published before the year 2012, and studies conducted in non-African nations were excluded from the study.

Study selection

Included for screening were research publications with information on ESBL-PE, antibiotic susceptibility patterns, and the specific etiology. The accessed studies were categorized as either eligible or excluded based on these criteria including the relevance of the research title in terms of the aims of the review, objective consistency, clarity and use of recommended methods used to report ESBl-PE and type of study design employed, population type, sample and data quality assurance procedures in place, use of appropriate statistical tools to analyze results, and the clarity of result presentation [44]. After reading the title and the abstract, research titles and objectives not in line with the aim of the current review were excluded; studies that did not differentiate ESBL-PE and non-ESBL-PE were excluded. In addition, after the full article assessment, studies on environmental samples, studies conducted on animals, studies reporting no pathogens of interest, studies without AMR profiling, studies out of Africa, and studies conducted before specified period were excluded. Furthermore, critical appraisal of the accessed articles was made by the Joanna Briggs Institute (JBI) tool for systematic reviews [46]. The selection process was double-checked by two independent reviewers to ensure fair selection and data representation as per the PRISMA statement [45].

Data collection and data items

During the data extraction, two investigators recorded each data set using a pre-designed excel sheet. During the data extraction the recorded data information incudes name of the first author, a year of publication, country, study design, study setting (community or hospital), study population, total number of the study participants, the source of clinical samples, and laboratory diagnostic methods., In addition, the species of Enterobacteriaceae screened for ESBL production, the total number of ESBL-PE isolates,, a proportion of ESBL-PE, and the AMR pattern of each bacterial isolate were extracted from the enrolled studies.

Statistical analysis, summary measures and assumptions

STATA version 14.2 was used to analyze the extracted data to get the pooled estimates. The pooled estimate of ESBL-PE and rates of AMR was determined using the random effect model based on the assumptions that there were differences in the population

characteristics, study design and setting [47]. The individual estimates, the corresponding 95% confidence interval and the weight of each study were presented in a forest plot. The heterogeneity (I^2) statistics were used to determine the between-study variability (degree of heterogeneity) among the included studies, with significance considered at $p < 0.05$ [48]. To minimize the degree of heterogeneity, we conducted subgroup analysis based on the regions of Africa, and based on the type of bacterial isolate. In addition, the sensitivity analysis was done by excluding outliers from the meta-analysis. As a visual and statistical way of assessment, the funnel plot and Egger's test were utilized to assess the risk of bias or publication bias, with a statistically significant level of bias being determined at $p < 0.05$ [49, 50].

Results

Search results

During the literature search, 108,050 studies were identified using the electronic database search (10 of the articles accessed through indirect ways from the authors). The predefined inclusion and exclusion criteria ensured that 26 research study publications based on human studies met the desired outcome. The number of screened studies, eligible after assessment and included in the study are presented diagrammatically below (Fig. 1).

Data and study characteristics

The data extraction and descriptive summaries revealed that a total of 108,040 patient samples were analyzed from the ultimately selected 26 studies for analysis. Across the regions of African (UN statistics division), East Africa had the majority of studies (12/26; 46%), followed by Western Africa (7/26; 26.9%) and Northern

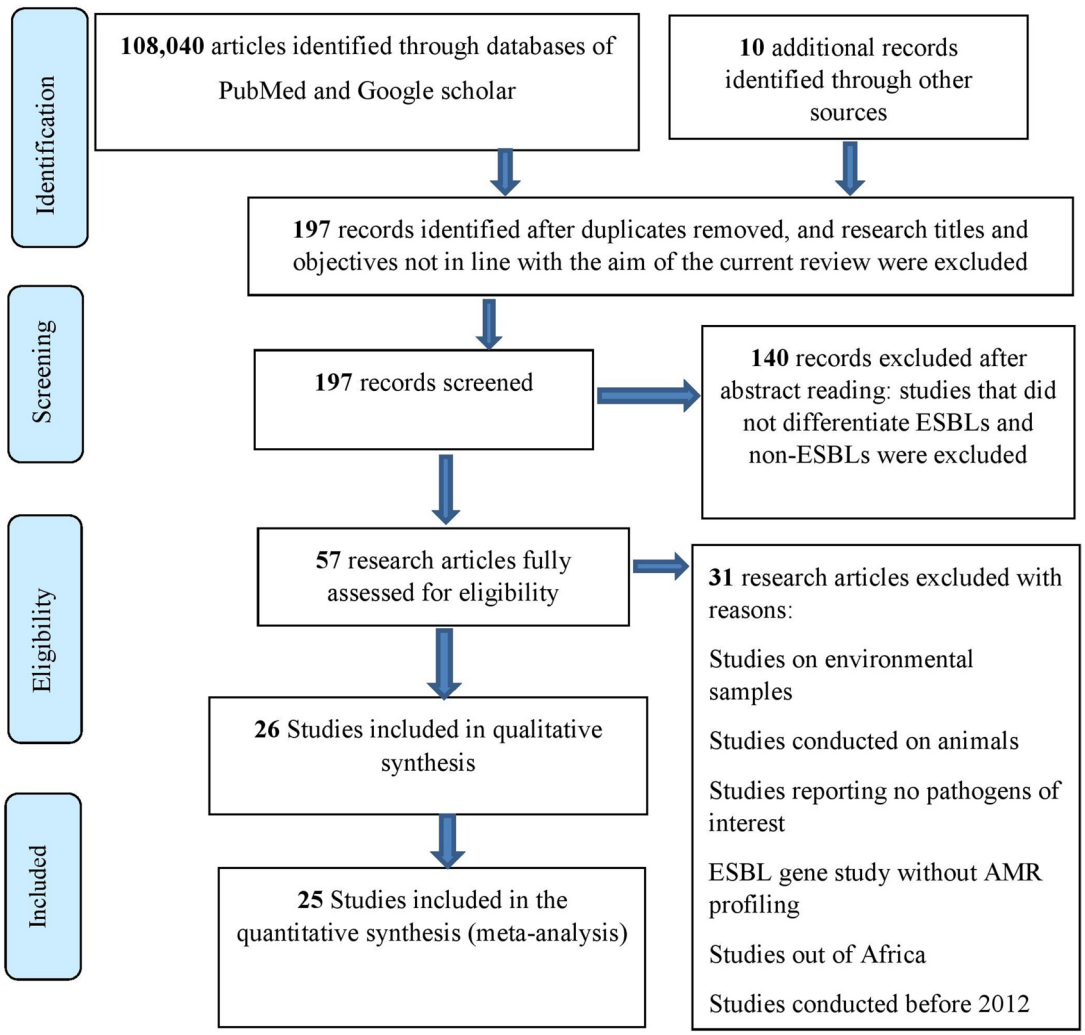

Fig. 1 PRISMA diagram for selection procedure of published articles between January 2012 and June 2020

Africa (5/26; 19.2%). The regions with the least number of researches were found in Central and Southern Africa (1/26 each; 3.85%) (Fig. 2).

The final research articles that were included were published within the years 2012 through 2020, with the majority of the published data in 2017 (6/26; 23%). All, 26 (100%) of the studies were cross-sectional studies. The published studies assessed for AMR and ESBL-PE were on isolates from multiple sample cultures (16/26; 61.5%), stool culture (4/26; 15.5%), urine culture (3/26; 11.5), both blood and wound swabs (1/26, 3.9%), and both blood and urine culture (1/26, 3.9%). In the various studies, four distinct methodologies were applied for susceptibility testing and five distinct interpretation guidelines were utilized. With regard to the ESBL-PE, *K. pneumoniae*, *E. coli*, *E. cloacae* and *P. mirabilis* were the ESBL-PE species frequently reported in the included studies (Table 1).

Pooled prevalence of ESBL-PE in Africa

The pooled proportionate estimates of ESBL-PE in African nations were 28% (95% CI 25–31%) based on the available data. Of the countries included, central Côte d'Ivoire [76] had the largest pooled proportion of ESBL production (84% [76–90%]), followed by Nigeria [66] with 74% [0.68–0.80] and Ethiopia [51] with 58% [0.53–0.62].The overall heterogeneity was significant ($I^2 = 99.35\%$, $p = 0.001$) (Fig. 3).

The variation across the studies attributable to heterogeneity was 99.35%. Subgroup analysis by inter-region was varied, the pooled rates for each region were as follows, 30% (95% CI 0.26–0.34) for West Africa, 29% (95% CI 21–38%) for East Africa, and 19% (95% CI 6–33%) for North Africa (Fig. 4). The Egger's plot was utilized to test the publication bias in various regions. The results indicated a significant bias across all regions in Africa (t-statistic = 9.11; $p = 0.001$).

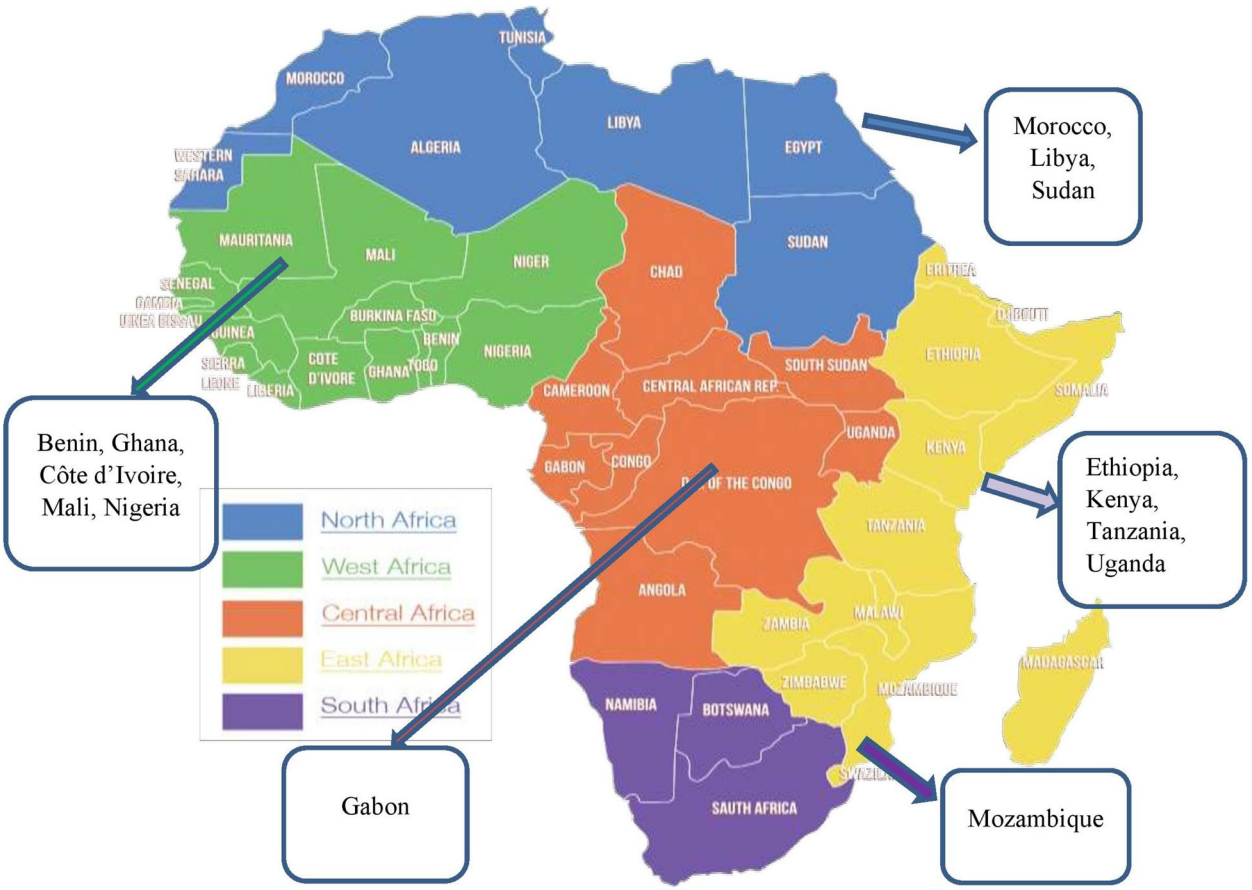

Fig. 2 Geographical distribution of selected studies between January 2012 and June 2020 in different African countries. Regional Map—Africa by Region into Northern Africa, Western Africa, East Africa Central Africa and Southern Africa, grouped countries based on the Shop

Table 1 Description of eligible published research articles from January 2012 to June 2020 included in the systematic review in Africa

Authors, year	Country	Setting	Study design	Specimen site	Study population	Guidelines used	Lab. Methods	Sample size	Reported ESBL-PE in the included studies
[51] Teklu et al. 2019	Ethiopia	HF	CS	Multiple	1 day–91 years	CLSI date not specified	CDT	426	*E. coli* 228, *K. pneumoniae* 103
[52] Beyene et al. 2019	Ethiopia	HF	CS	Multiple	Not specified	Not specified	VITEK ESBL test panel	440	E. coli 339, *K. pneumonia* 56, *P. mirabilis* 14, *E. cloacae* 11
[53] Bitew and Tsige 2020	Ethiopia	HF	CS	Multiple	Not specified	Not specified	CDT	947	*E. coli* 144, *K. pneumoniae* 72, E. cloacae 16
[54] Moges et al. 2019	Ethiopia	HF	CS	Multiple	< 6–> 60 years	CLSI date not specified	DDST	532	E. coli 14, *K. pneumoniae* 79, *E. cloacae* 6
[55] Zeynudin et al. 2018	Ethiopia	HF	CS	Multiple	< 28 days– ≥ 21 years	Not specified	DDST	274	E. coli 71, K. pneumoniae 34, *P. mirabilis* 6, *E. cloacae* 7
[56] Abera et al. 2016	Ethiopia	HF	CS	Multiple	Not specified	EUCAST date not specified	VITEK® 2 heck-MDR array	224	*E. coli* 13, *K. pneumoniae* 30, *E. cloacae* 12
[57] Legese et al. 2017	Ethiopia	HF	CS	Blood and urine	< 15 years	CLSI date not specified	CDT, DDST	322	*E. coli* 5, *K. pneumoniae* 19,
[58] Maina et al. 2013	Kenya	HF	CS	Urine	2 days–90 years	CLSI 2009	CDT	159	*E. coli* 109, *K. pneumoniae* 50
[59] Kajeguka et al. 2015	Tanzania	HF	CS	Multiple	1–80 years	CLSI, 2011	CDT	330	*E. coli* 54, *K. pneumoniae* 54, *P. mirabilis* 44
[60] Meromi et al. 2017	Tanzania	CB	CS	Stool	7–17 years	Not specified	CHROMagar™ ESBL	107	*E. coli* 30, *K. pneumoniae* 6
[61] Manyahi et al. 2017	Tanzania	HF	CS	Urine	Not specified	Not specified	*E*-test ESBL strips	172	*E. coli* 15, *K. pneumoniae* 9, *E. cloacae* 6, *P. mirabilis* 5
[62] Dirar et al. 2020	Sudan	HF	CS	Multiple	Not specified	CLSI date not specified	DDST	165	*E. coli* 81, *K. pneumoniae* 52, *P. mirabilis* 10, *E. cloacae* 8
[63] Hamid et al. 2019	Sudan	HF	CS	Urine	20–65 years	CLSI 2011	DDST	350	*E. coli* 13, *K. pneumoniae* 8
[64] Chukwunwejim et al. 2018	Nigeria	CB	CS	Stool	18–26 years	CLSI date not specified	DDST	273	*E. coli* 20, *K. pneumoniae* 2,
[65] Oli et al. 2017	Nigeria	HF	CS	Multiple	Not specified	CLSI date not specified	DDST	63	*E. coli* 10, *K. pneumoniae* 5
[66] Iliasu et al. 2018	Nigeria	HF	CS	Multiple	1–70 years	CLSI, 2012	DDST	219	*E. coli* 163
[67] Zorgani and Bashein 2017	Libya	HF	CS	Urine	3 days–93 years	CLSI date not specified	VITEK 2	1790	*E. coli* 14, *K. pneumoniae* 14

Table 1 (continued)

Authors, year	Country	Setting	Study design	Specimen site	Study population	Guidelines used	Lab. Methods	Sample size	Reported ESBL-PE in the included studies
[68] Abujnah et al. 2015	Libya	HF	CS	Multiple	1–14 years	CLSI date not specified	ESBL chromogen media, *E*-test strips	915	*E. coli* 77
[69] Feglo and Opoku 2014	Ghana	HF	CS	Multiple	Not specified	CLSI 2010	DDST	5859	*P. mirabilis* 38
[70] Kateregga et al. 2015	Uganda	HF	CS	Multiple	Not specified	CLSI 2010	DDST	245	*E. coli* 36, *K. pneumoniae* 24, *E. cloacae* 1, *P. mirabilis* 10
[71] Chrindze et al. 2018	Mozambique	CB	CS	Stool	19–32 years	CLSI date not specified	PCR	275	*E. coli* 35,
[72] Sangare et al. 2017	Mali	HF	CS	Blood	Not specified	EUCAST date not specified	PCR	611	*E. coli* 20, *K. pneumoniae* 20, *E. cloacae* 8
[73] Anago et al. 2015	Benin	HF	CS	Multiple	Not specified	NCCLS date not specified	DDST	84	*E. coli* 29
[74] Schaumburg et al. 2013	Gabon	HF	CS	Rectal swab (Stool)	Not specified	EUCAST 2011	DDST	200	*E. coli* 18, *K. pneumoniae* 53, *E. cloacae* 3
[75] Fatima et al. 2012	Morocco	HF	CS	Multiple	Not specified	CLSI, 2008	DDST	148	*E. coli* 16, *K. pneumoniae* 9
[76] Müller-Schulte et al. 2020	Côte d'Ivoire	HF	CS	Blood and wound swab	Not specified	EUCAST version 7.1	DDST	107	*K. pneumoniae* 90

CB Community-based, *CDT* Combination disk test, *CLSI* Clinical Laboratory Standards Institute, *CS* Cross-sectional, *DDST* Double disk synergy test, *ESBL* Extended spectrum β-lactamase, *EUCAST* European Committee for Antimicrobial Susceptibility Testing, *HF* health facility, *NCCLS* National Committee for Clinical Laboratory Standards, *PCR* polymerase chain reaction

The pooled prevalence of antimicrobial resistance of ESBL-PE isolates by antimicrobial agent

In this review, four members of the Enterobacteriaceae family namely, *E. coli*, *K. pneumoniae, P. mirablilis,* and *E. cloacae,* were the leading ESBL-PE (Table 2). The resistance profiles of each of these species were assessed for a total of 19 antimicrobial agents from different classes. According the meta-analysis, Tetracycline 80% (75–85%), trimethoprim/sulfamethoxazole 71% (63–80%), cefepime 65% (0.38–0.91) and amoxicillin–clavulanic acid 63% (52–75%) were the highly resisted antimicrobial agents. Conversely, amikacin 18% (10–25%), meropenem 21% (12–29%), cefoxitin 29% (23–36%) and nitrofurantoin 32% (24–39%) were the least resisted ones. The forest plots, Egger's test and Funnel plots for each antimicrobial agent by species are presented in the figures of supplementary file 1. Furthermore, the resistance profiles of each ESBL-PE species by each antimicrobial agent and the pooled estimates are summarized below (Table 2).

Publication bias

Assessment of publications bias was performed in occasions of significant heterogeneity; there was no statistically significant publication bias in most of the antimicrobials agents whereas statistically significant heterogeneity and publication bias were noticed in cefoxitin, meropenem, trimethoprim/sulfamethoxazole, Gentamicin, Ceftriaxone and Nitrofurantoin (for further details refer supplementary file 1). Heterogeneity continued despite the subgroup analysis, and exclusion of outliers for sensitivity analysis.

Discussion

This systematic review meta-analysis, which exhaustively summarized data from various studies published in Africa, found that the overall pooled prevalence of ESBL-PE was 28% (95% CI 25–31%). There was significant overall heterogeneity across the studies (I^2 99.35, $p < 0.001$) which may be due to the differences in the

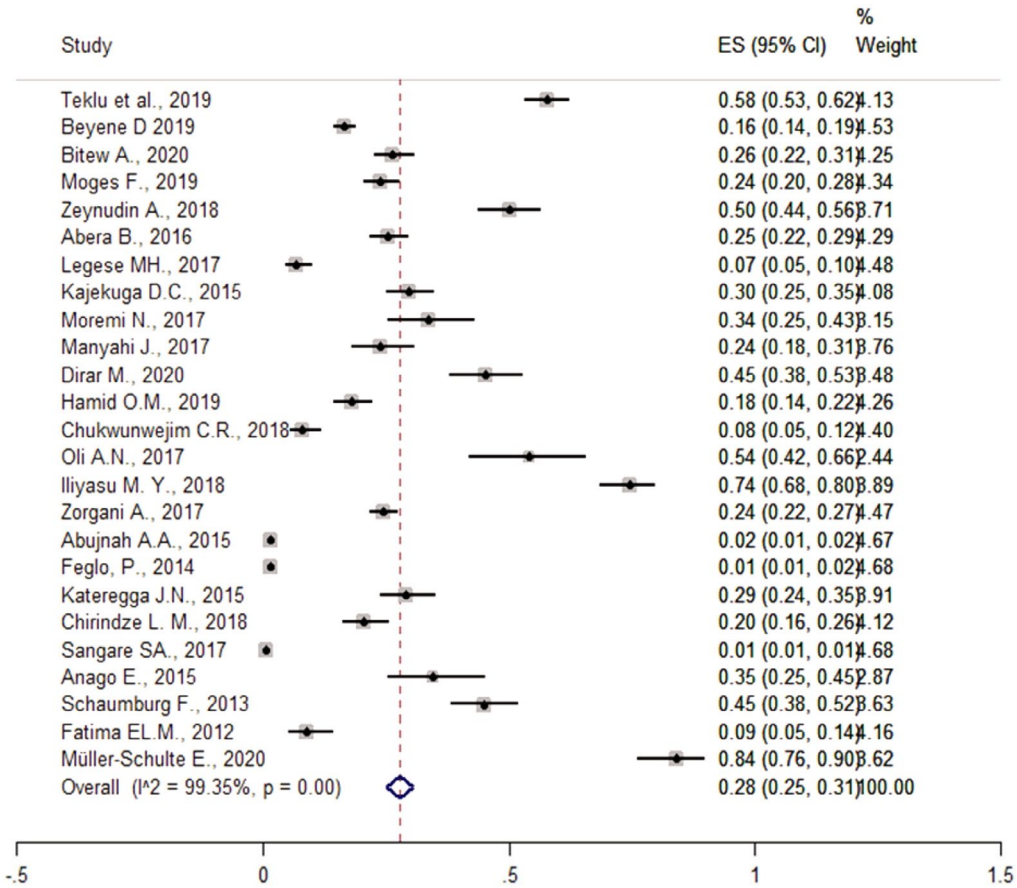

Fig. 3 Pooled estimates of ESBL-producing Enterobacteriaceae in Africa

setting, methodology, study group and clinical sample or disease. Comparing the countries in our review the highest 84% (76–90%) pooled proportion of ESBL-PE was observed in central Côte d'Ivoire [76] followed by 74% (68–80%) Nigeria [66] and 58% (0.53–0.62) from Ethiopia [51]. Though the differences in the number of published studies on ESBL-PE might have affected the comparison between the five African regions, entirely, the pooled prevalence of ESPL-PE in Africa is high with policy implications. According to this meta-analysis, ESBL-PE-associated infections in Africa affect 25 to 35 peoples out of 100 people. This is an indication of the necessities to implement strong AMR surveillance strategies, capacitating diagnostic facilities, and coherent regulation of antibiotic misuse. In addition, improving the socioeconomic and knowledge of the society towards investigation based medication and rational antibiotic use may largely contribute to the reduction of ESPL-PE-related causalities.

The Africa's overall pooled estimate of ESBL-PE according to a survey of hospitals in East Africa were 42% (95% CI 34–50%) [11], and the pooled prevalence of EBL-PE isolates form from community-acquired and hospital acquired infections were 60% (95% CI 54–65%) [35] in which both are higher than the current finding. However, the current finding (28%) is higher than the previous pooled estimate of the ESBL-PE [17% (95% CI 10–23%)], which was a work on maternal colonization in Africa [77], isolates from gut mucosal colonization, sub-Saharan Africa [18% (95% CI 12–28%)] [16], and an international investigation on isolates from urinary tract infection [25% (95% CI 18%, 32%)] [78]. In addition, the pooled ESBL-PE in the current estimates are higher than the pooled estimates of ESBL-PE isolated from bloodstream infections in previous findings from Africa (15%), Asia and Europe (4%) and South America (12%) [41]. The geographic differences, study population, and type of syndrome or presentation might explain the noticed differences. Furthermore, due to the cyclic spread of ESBL-PE in humans, livestock and environment, various factors including a lack of integrated tackling strategies (one health), low water, hygiene and sanitation coverage (WASH), poor facility-based infection prevention practices, poor AMR surveillance system, lack of robust diagnostic facilities, lack of trained workforce, inequalities on

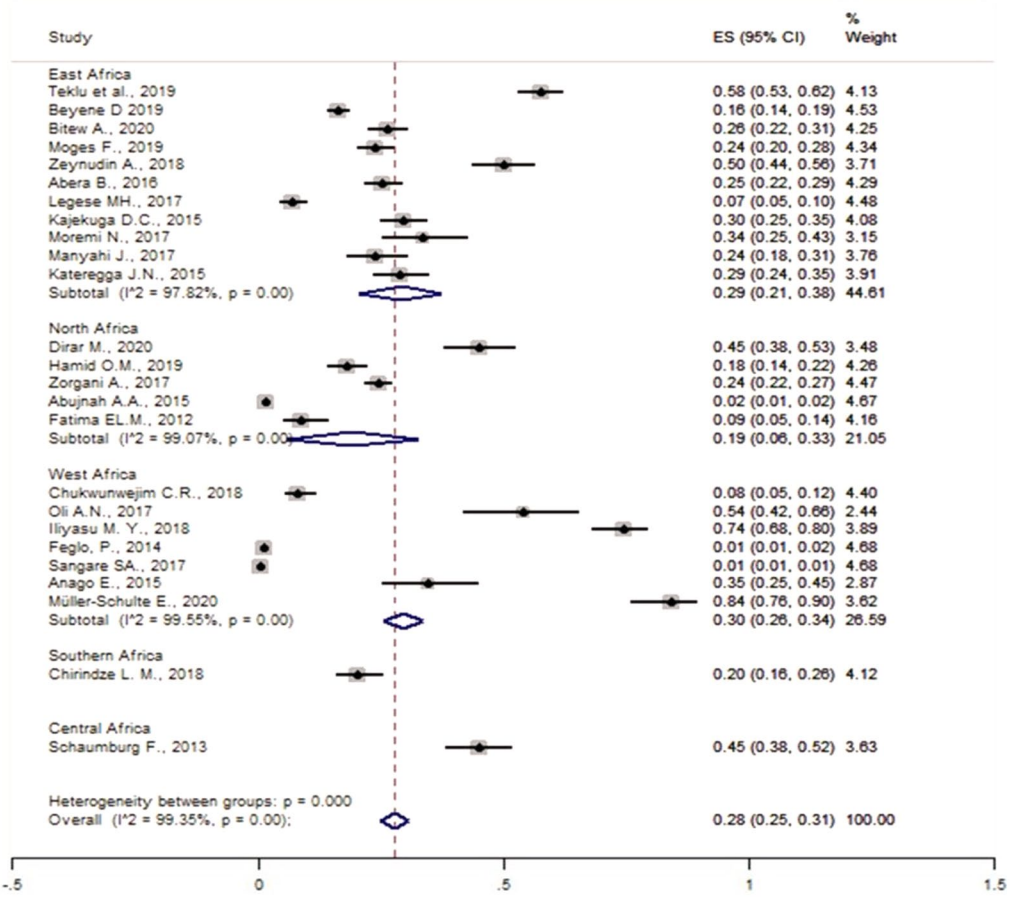

Fig. 4 Sub-group analysis and pooled estimates of ESBL-producing Enterobacteriaceae by regions of Africa

access to health-care, antibiotic misuse and weak regulatory mechanisms may determine the high prevalence of ESBL-PE in Africa [79–82].

Regarding the pooled estimates of AMR among ESBL-PE isolates, the highest pooled estimates for amoxicillin–clavulanic acid were seen in *K. pneumoniae* 73% (95% CI 62–85%), *E. clocae* 71% (95% CI 58–84%), followed by *E. coli* 60% (95% CI 42–77%), and *P. mirabilis* 40% (95% CI −1–81%). A comparable rates of amoxicillin–clavulanic acid resistance were reported in *E. coli*, *K. pneumoniae* and *P. mirabilis* 8% (95% CI 5–11%) isolates in a systematic review and meta-analysis of literatures on wound infection in Ethiopia [83]. However, the study did not report on the ESBL production of these isolates. In addition to the high rate of amoxicillin–clavulanic acid (73%) resistance, *K. pneumoniae* isolates had higher rates of antimicrobial resistance to trimethoprim/sulfamethoxazole (79%) and ceftazidime (70%) while low resistance to amikacin (12%), norfloxacin (21%), and meropenem (24%). Similarly, *E. coli* highest rate of resistance to tetracycline (86%), while least resisted to amikacin (22%), and meropenem (16%). The pooled estimates of resistance for ciprofloxacin (53%) (95% CI 44–63%) and gentamycin (46%) (95% CI 37–54%) in this review was higher than the previous pooled prevalence findings in Ethiopia which were 24% (95% CI 16–33%) and 27% (95% CI 16–37%) for ciprofloxacin and Gentamycin, respectively [83]. The rates of antibiotic resistance to ciprofloxacin among *E. coli* isolates reported from West Africa were 3.4% (95% CI 0–15.7%) [12], which was much lower than the rates reported in the current review [59% (95% CI 46–72%)]. The rate of Nitrofurantoin resistance in *E. coli* was reported as 22% (13–31%); however, 13.55% resistance rates were found in a previous research in Ethiopia [84].

Overall, the patterns of resistance may vary depending on the local prescription trends, antibiotic misuse and resistance strategy of each bacterium. In the WHO Africa region, it was reported that the limited supply chains posed repeated oral use of antimicrobials including Trimethoprim/sulfamethoxazole and amoxicillin–clavulanic acid, which might have triggered

Table 2 Meta-analysis; pooled estimates on antimicrobial resistance by bacterial isolates in Africa; 2012–2020

Antimicrobial agents	Overall pooled prevalence (95% CI)	Publication bias ($P<0.05$)	Overall Heterogeneity (I^2)	Species sub-group pooled ES (95% CI)				I^2 Between group ($P<0.05$)
				E. coli	*K. pneumoniae*	*P. mirabilis*	*E. cloacae*	
AMC	63% (52–75%)	$P=0.888$	$I^2=97.82\%$	60% (42–77%)	73% (62–85%)	40% (10–81%)	0.71 (0.58–0.84)	$P=0.309$
CAF	58% (46–70%)	$P=0.123$	$I^2=87.17\%$	56% (35–76%)	60% (52–69%)	51% (35–67%)	NA	$P=0.590$
TET	80% (75–85%)	NA	$I^2=63.11\%$	86% (81–91%)	77% (67–87%)	76% (60–91%)	0.58 (0.41–0.75)	$P=0.013$
AMK	18% (10–25%)	NA	$I^2=97.53$	22% (09–34%)	12% (5–19%)	NA	NA	$P=0.198$
CTX	59% (46–73%)	P = 0.052	$I^{2=}$ 98.48%	60% (41–80%)	62% (25–99%)	57% (44–69%)	59% (46–73%)	$P=0.980$
CTZ	59% (48–70%)	$P=0.686$	NA	NA	70% (53–88%)	NA	42% (20–65%)	NA
FOX	29% (23–36%)	$P=0.001$	$I^2=93.74\%$	20% (13–27%)	20% (10–30%)	71% (55%–86%)	72% (57–87%)	$P=0.001$
MER	21% (12–29%)	$P=0.026$	$I^2=97.48\%$	16% (6–27%)	24% (5–43%)	NA	NA	0.482
CIP	53% (44–63%)	$P=0.826$	$I^2=97.55\%$	59% (46–72%)	45% (36–54%)	NA	NA	$P=0.085$
SXT	71% (63–80%)	$P=0.022$	NA	NA	79% (68–89%)	NA	59% (63–80%)	$P=0.061$
NOR	37% (26–49%)	$P=0.873$	91.43%	51% (46–56%)	21% (13–29%)	NA	25% (26–49%)	$P=0.001$
GEN	46% (37–54%)	$P=0.003$	NA	NA	NA	NA	NA	NA
CRO	52% (39–66%)	$P=0.049$	$I^2=98.61\%$	44% (24–64%)	65% (46–84%)	51% (34–68%)	NA	$P=0.294$
CFP	65% (38–91%)	$P=0.992$	$I^2=99.67\%$	55% (6–104%)	75% (59–92%)	NA	57% (41–73%)	$P=0.265$
CPD	62% (52–73%)	$P=0.314$	$I^2=82.33\%$	65% (47–83%)	66% (57–75%)	55% (39–71%)	NA	$P=0.511$
LEV	33% (13–53%)	$P=0.926$	$I^2=98.75\%$	45% (12–77%)	32% (7–57%)	8% (3–18%)	NA	0.034
NIT	32% (24–39%)	$P=0.001$	$I^2=96.68\%$	22% (13–31%)	42% (0.12–0.77)	39% (–3 to 80%)	39% (23–55%)	$P=0.026$
TOB	58% (27–89%)	$P=0.001$	$I^2=98.09\%$	36% (32–41%)	83% (77–88%)	NA	57% (42–72%)	$P=0.001$

Amoxicillin (AMP), Amoxicillin-clavulanic acid (AMC), Chloramphenicol (CAF), Tetracycline (TET), Amikacin (AMK), Cefotaxime (CTX), Ceftazidime (CTZ), Cefoxitin (FOX), Meropenem (MER), Ciprofloxacin (CIP), Trimethoprim/sulfamethoxazole (SXT), Norfloxacin (NOR), Gentamycin (GEN), Ceftriaxone (CRO), Cefepime (CFP), Cefpodoxime (CPD), Levofloxacin (LEV), Nitrofurantoin (NIT), Cefuroxime (CXM), Tobramycin (TOB); CI: Confidence Interval

co-selection and spread of resistant bacterial strains; the co-selection might be further augmented through environmental agents, genetic linkage within plasmids and simultaneous regulation [85]. This may explain that *K. pneumoniae* and *E.coli* that are resistant to β-lactamase and or β-lactamase inhibitors were two of the four leading causes of AMR-related mortalities in Africa according to the cross-country analysis reports [82]. In addition to the above factors, transposition-related mutations, and the spread of β-lactamase genes through horizontal gene transfer might have contributed to the high rate ESBL-PE [86]. Even inside a colonized human host, ongoing transmission of ESBL genes is possible among ESBL-PE strains of *E.coli* and *K. pneumoniae* [87]. Due the lack of strong infection control measures, the environmental, inter-host and intra-host gene transfer among ESBL-PE strains may incur risks of nosocomial infections, and increased healthcare costs in the Africa setting.

With regard to the aminoglycosides, fluoroquinolones and the carbapenems, the resistances rates observed are relatively low but alarming. Carbapenems are considered as the drugs of choice for severe/complicated ESBL-PE-associated infections. However, the signs of resistance to this group of drugs is an indication for sparing treatment options, which may include ceftolozane/tazobactam and ceftazidime/avibactam [88–90]. Due to the expression of carbapenemase genes, *E.coli* (*bla*VIM and *bla*NDM genes) and *K. pneumoniae* (*bla*IMP, *bla*KPC, *bla*OXA-48-like, *bla*NDM, and *bla*VIM genes) emerged to be carbapenem resistant [91]. In developing countries where there is economic limitations to access alternative antimicrobials, the emergence of resistance to aminoglycosides, fluoroquinolone and carbapenem group of drugs will pose challenges in controlling ESBL-PE-associated infections.

Evidences show that travel across continents aggravate frequent use of antimicrobials and ESBL-PE colonization, which is an indication of travelers infections and inappropriate antibiotic use during travel times [33, 92]. This phenomenon also may aggravate the spread of ESBL-PE across continents with great community level and individual threats. Hence, the current finding on ESBL-PE and AMR rates have paramount importance from the continental and global perspective, because the spread of ESBL-PE affects public health and clinical practice, globally. This is majorly due to ESBL-PE-associated nosocomial infections, therapeutic challenges, huge demands in infection control measures [93, 94], and high rate of fecal shedding and risk of community onset of ESBL attributable infections [95].

The prevention and control of ESBL-PE attributable mortalities and morbidities need multidimensional approaches. The rational use of antibiotics, which is the major driver of ESBL-PE, can be improved through health educations targeting health care workers and the community [96]. On top of this, fitting sites for emerging infections and surveillance program can help determining new incidences and adapt targeted interventions as has been practiced in US [97]. The surveillance systems involving active screening, contact tracing and isolation can have better outcome in preventing hospital acquired infections [98]. Effective hand washing practices, health care oriented infection prevention and control measures, water and food safety, travel-associated food and water precautions can help ameliorate ESBL-attributable infections [99]. Particularly, in the hospital setting, strains are expected to be MDR, and comprehensive cleaning measures targeting patients, medical equipment, sinks and surfaces, hand hygiene of physicians is critically important in controlling their spread [98]. Finally, a one health oriented efforts such as the "One Health Plan of Action" on humans, animals, food and environment can boost the control measures on ESBL-PE, and enable track the actual source or antimicrobial resistant strains [100, 101]. As per the WHO protocol, this integrated surveillance of AMR in ESBL-PE is applicable globally including in resource-limited countries [102].

The study has limitations in that databases other than Google Scholar and PubMed were not included during the literature search. In addition, most of the studies used phenotypic methods, and the limited number of highly sensitive molecular (PCR based) studies in Africa might have reduced the pooled estimates of ESBL-PE in Africa.

Conclusion

ESBL-PE are widespread throughout Africa. The studies included showed a wide difference in resistance due to ESBL-PE among the countries and the regions as well. Relative to the existing evidences in sub-Saharan Africa, the pooled estimate of ESBL-PE rates in the current meta-analysis was higher. The scarcity of data on the ESBL-PE in some regions of Africa reflects the need for surveillance of antimicrobial resistance to design interventions focused on preventing the spread of ESBL-PE. Furthermore, this review may aid in the creation of regional and national guidelines for appropriate ESBL screening as well as standardized methods for managing patients' burden of antibiotic resistance brought on by ESBL-PE. The majority of the research studies incorporated in this systematic review and meta-analysis were conducted in medical institutions. Therefore, prevention of ESBL-PE acquisition in the health care setting should be the primary focus of actions aimed at lowering ESBL-PE rates in Africa, and reducing the intercontinental spread of ESBL-PE.

Supplementary Information

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Supplementary material 1: Forest plot, egger's test, and funnel plot results for the assessment of ESBL-producing species by each antimicrobial agent.

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References

1. Tsaku PA, Ngwai YB, Pennap GR, Ishaleku D, Ibrahim T, Nkene IH, Abimiku RH. Extended-spectrum beta-lactamase–production in Escherichia coli isolated from door handles in Nasarawa State University, Keffi, Nigeria. Heliyon. 2019;5(8):e02177.
2. Pokharel S, Raut S, Adhikari B. Tackling antimicrobial resistance in low-income and middle-income countries. BMJ Glob Health. 2019;4(6):e002104.
3. Aldrazi FA, Rabaan AA, Alsuliman SA, Aldrazi HA, Alabdalslam MJ, Alsadiq SA, Alhani HM, Bueid AS. ESBL expression and antibiotic

resistance patterns in a hospital in Saudi Arabia: do healthcare staff have the whole picture? J Infect Public Health. 2020;13(5):759–66.
4. Gandra S, Alvarez-Uria G, Turner P, Joshi J, Limmathurotsakul D, van Doorn HR. Antimicrobial resistance surveillance in low-and middle-income countries: progress and challenges in eight South Asian and Southeast Asian countries. Clin Microbiol Rev. 2020;33(3):10–128.
5. Parmanik A, Das S, Kar B, Bose A, Dwivedi GR, Pandey MM. Current treatment strategies against multidrug-resistant bacteria: a review. Curr Microbiol. 2022;79(12):388.
6. Mohanty H, Pachpute S, Yadav RP. Mechanism of drug resistance in bacteria: efflux pump modulation for designing of new antibiotic enhancers. Folia Microbiol. 2021;66(5):727–39.
7. Raju DV, Nagarajan A, Pandit S, Nag M, Lahiri D, Upadhye V. Effect of bacterial quorum sensing and mechanism of antimicrobial resistance. Biocatal Agric Biotechnol. 2022;43:102409.
8. Ali J, Rafiq QA, Ratcliffe E. Antimicrobial resistance mechanisms and potential synthetic treatments. Future Sci OA. 2018;4(4):FSO290.
9. Cantón R, Horcajada JP, Oliver A, Garbajosa PR, Vila J. Inappropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resistance. Enferm Infecc Microbiol Clin. 2013;31:3–11.
10. Andersson DI, Hughes D. Evolution of antibiotic resistance at non-lethal drug concentrations. Drug Resist Updates. 2012;15(3):162–72.
11. Sonda T, Kumburu H, van Zwetselaar M, Alifrangis M, Lund O, Kibiki G, Aarestrup FM. Meta-analysis of proportion estimates of extended-spectrum-beta-lactamase-producing Enterobacteriaceae in East Africa hospitals. Antimicrob Resist Infect Control. 2016;5:1–9.
12. Bernabe KJ, Langendorf C, Ford N, Ronat JB, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and meta-analysis. Int J Antimicrob Agents. 2017;50(5):629–39.
13. Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. PLoS ONE. 2017;12(12):e0189621.
14. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. Clin Microbiol Rev. 2005;18(4):657–86.
15. Bradford PA. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev. 2001;14(4):933–51.
16. Lewis JM, Lester R, Garner P, Feasey NA. Gut mucosal colonisation with extended-spectrum beta-lactamase producing Enterobacteriaceae in sub-Saharan Africa: a systematic review and meta-analysis. Wellcome Open Res. 2019;4:160.
17. World Health Organization (WHO). WHO publishes list of bacteria for which new antibiotics are urgently needed. Last updated 27 Feburary. 2017. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed. Accessed 18 Dec 2023.
18. Tekiner İH, Özpınar H. Occurrence and characteristics of extended spectrum beta-lactamases-producing Enterobacteriaceae from foods of animal origin. Braz J Microbiol. 2016;47:444–51.
19. Fadare FT, Okoh AI. The abundance of genes encoding ESBL, pAmpC and non-β-lactam resistance in multidrug-resistant Enterobacteriaceae recovered from wastewater effluents. Front Environ Sci. 2021;9:711950.
20. Brolund A. Overview of ESBL-producing Enterobacteriaceae from a Nordic perspective. Infect Ecol Epidemiol. 2014;4(1):24555.
21. Ling W, Furuya-Kanamori L, Ezure Y, Harris PN, Paterson DL. Adverse clinical outcomes associated with infections by Enterobacterales producing ESBL (ESBL-E): a systematic review and meta-analysis. JAC-antimicrob Resist. 2021;3(2):dlab068.
22. Ray S, Anand D, Purwar S, Samanta A, Upadhye KV, Gupta P, Dhar D. Association of high mortality with extended–spectrum β-lactamase (ESBL) positive cultures in community acquired infections. J Crit Care. 2018;44:255–60.
23. Uddin TM, Chakraborty AJ, Khusro A, Zidan BR, Mitra S, Emran TB, Dhama K, Ripon MK, Gajdács M, Sahibzada MU, Hossain MJ. Antibiotic resistance in microbes: history, mechanisms, therapeutic strategies and future prospects. J Infect Public Health. 2021;14(12):1750–66.
24. Moxon CA, Paulus S. Beta-lactamases in Enterobacteriaceae infections in children. J Infect. 2016;72:S41–9.
25. Tadesse BT, Ashley EA, Ongarello S, Havumaki J, Wijegoonewardena M, González IJ, Dittrich S. Antimicrobial resistance in Africa: a systematic review. BMC Infect Dis. 2017;17:1–7.
26. Abera D, Alemu A, Mihret A, Negash AA, Abegaz WE, Cadwell K. Colonization with extended spectrum beta-lactamase and carbapenemases producing Enterobacteriaceae among hospitalized patients at the global level: a systematic review and meta-analysis. PLoS ONE. 2023;18(11):e0293528.
27. Mai HT, Espinoza JL. The impact of COVID-19 pandemic on ESBL-producing Enterobacterales infections: a scoping review. Antibiotics. 2023;12(6):1064.
28. CDC. Antibiotic resistance threats in the United States, 2019. Atlanta: Centers for Disease Control and Prevention; 2019.
29. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase–producing Enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. Rev Infect Dis. 2016;63(3):310–8.
30. Namikawa H, Imoto W, Yamada K, Tochino Y, Kaneko Y, Kakeya H, Shuto T. Predictors of mortality from extended-spectrum beta-lactamase-producing Enterobacteriaceae bacteremia. Emerg Microb Infect. 2023;12(1):2217951.
31. Geuther N, Mbarushimana D, Habarugira F, Buregeya JD, Kollatzsch M, Pfüller R, Mugabowindekwe M, Ndoli J, Mockenhaupt FP. ESBL-producing Enterobacteriaceae in a rural Rwandan community: carriage among community members, livestock, farm products and environment. Trop Med Int Health. 2023;28(11):855–63.
32. Lautenbach E, Mosepele M, Smith RM, Styczynski A, Gross R, Cressman L, Jaskowiak-Barr A, Alby K, Glaser L, Richard-Greenblatt M, Cowden L. Risk factors for community colonization with extended-spectrum cephalosporin-resistant enterobacterales (ESCrE) in Botswana: an antibiotic resistance in communities and hospitals (ARCH) study. Clin Infect Dis. 2023;77:S89-96.
33. Wuerz TC, Kassim SS, Atkins KE. Acquisition of extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE) carriage after exposure to systemic antimicrobials during travel: systematic review and meta-analysis. Travel Med Infect Dis. 2020;37:101823.
34. Mahamat OO, Kempf M, Lounnas M, Tidjani A, Hide M, Benavides JA, Carrière C, Bañuls AL, Jean-Pierre H, Ouedraogo AS, Dumont Y. Epidemiology and prevalence of extended-spectrum β-lactamase-and carbapenemase-producing Enterobacteriaceae in humans, animals and the environment in West and Central Africa. Int J Antimicrob Agents. 2021;57(1):106203.
35. Azzam A, Khaled H, Samer D, Nageeb WM. Prevalence and molecular characterization of ESBL-producing Enterobacteriaceae in Egypt: a systematic review and meta-analysis of hospital and community-acquired infections. Antimicrob Resist Infect Control. 2024;13(1):1–4.
36. Tufa TB, Fuchs A, Tufa TB, Stötter L, Kaasch AJ, Feldt T, Häussinger D, Mackenzie CR. High rate of extended-spectrum beta-lactamase-producing gram-negative infections and associated mortality in Ethiopia: a systematic review and meta-analysis. Antimicrob Resist Infect Control. 2020;9:1.
37. Heinemann M, Kleinjohann L, Rolling T, Winter D, Hackbarth N, Ramharter M, Addo M, Eibach D, Phillips RO, Owusu-Ofori A, Vinnemeier CD. Impact of antibiotic intake on the incidence of extended-spectrum β-lactamase–producing Enterobacterales in sub-Saharan Africa: results from a community-based longitudinal study. Clin Microbiol Infect. 2023;29(3):340–5.
38. Manyahi J, Moyo SJ, Tellevik MG, Langeland N, Blomberg B. High prevalence of fecal carriage of extended spectrum β-lactamase-producing Enterobacteriaceae among newly HIV-diagnosed adults in a community setting in Tanzania. Microb Drug Resist. 2020;26(12):1540–5.
39. Kibwana UO, Manyahi J, Sandnes HH, Blomberg B, Mshana SE, Langeland N, Moyo SJ. Gastrointestinal colonization of extended-spectrum beta-lactamase-producing bacteria among children below five years of age hospitalized with fever in Dar es Salaam, Tanzania. J Glob Antimicrob Resist. 2022;30:107–14.
40. Abera D, Negash AA, Fentaw S, Mekonnen Y, Cataldo RJ, Wami AA, Mihret A, Abegaz WE. High prevalence of colonization with extended-spectrum β-lactamase-producing and multidrug-resistant Enterobacterales in the community in Addis Ababa Ethiopia: risk

factors, carbapenem resistance, and molecular characterization. BMC Microbiol. 2024;24(1):402.
41. Flokas ME, Karanika S, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing Enterobacteriaceae in pediatric bloodstream infections: a systematic review and meta-analysis. PLoS ONE. 2017;12(1):e0171216.
42. Dimani BD, Founou RC, Zemtsa JR, Mbossi A, Koudoum PL, Founou LL, Kouanfack C, Sone LH. Faecal carriage of multidrug-resistant and extended-spectrum β-lactamase-producing Enterobacterales in people living with HIV in Yaoundé, Cameroon. J Glob Antimicrob Resist. 2023;35:26–34.
43. Sintondji K, Fabiyi K, Hougbenou J, Koudokpon H, Lègba B, Amoussou H, Haukka K, Dougnon V. Prevalence and characterization of ESBL-producing Escherichia coli in healthy pregnant women and hospital environments in Benin: an approach based on Tricycle. Front Public Health. 2023;11:1227000.
44. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283(15):2008–12.
45. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.
46. Porritt K, Gomersall J, Lockwood C. JBI's systematic reviews: study selection and critical appraisal. AJN Am J Nurs. 2014;114(6):47–52.
47. Spineli LM, Pandis N. Meta-analysis: random-effects model. Am J Orthod Dentofac Orthop. 2020;157(2):280–2.
48. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc. 2009;172(1):137–59.
49. Mathur MB, VanderWeele TJ. Sensitivity analysis for publication bias in meta-analyses. J R Stat Soc Ser C Appl Stat. 2020;69(5):1091–119.
50. Jin ZC, Zhou XH, He J. Statistical methods for dealing with publication bias in meta-analysis. Stat Med. 2015;34(2):343–60.
51. Teklu DS, Negeri AA, Legese MH, Bedada TL, Woldemariam HK, Tullu KD. Extended-spectrum beta-lactamase production and multi-drug resistance among Enterobacteriaceae isolated in Addis Ababa, Ethiopia. Antimicrob Resist Infect Control. 2019;8:1–2.
52. Beyene D, Bitew A, Fantew S, Mihret A, Evans M. Multidrug-resistant profile and prevalence of extended spectrum β-lactamase and carbapenemase production in fermentative Gram-negative bacilli recovered from patients and specimens referred to National Reference Laboratory, Addis Ababa, Ethiopia. PLoS ONE. 2019;14(9):e0222911.
53. Bitew A, Tsige E. High prevalence of multidrug-resistant and extended-Spectrum β-lactamase-producing Enterobacteriaceae: a cross-sectional study at Arsho advanced medical laboratory, Addis Ababa, Ethiopia. J Trop Med. 2020. https://doi.org/10.1155/2020/6167234.
54. Moges F, Eshetie S, Abebe W, Mekonnen F, Dagnew M, Endale A, Amare A, Feleke T, Gizachew M, Tiruneh M. High prevalence of extended-spectrum beta-lactamase-producing Gram-negative pathogens from patients attending Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar, Amhara region. PLoS ONE. 2019;14(4):e0215177.
55. Zeynudin A, Pritsch M, Schubert S, Messerer M, Liegl G, Hoelscher M, Belachew T, Wieser A. Prevalence and antibiotic susceptibility pattern of CTX-M type extended-spectrum β-lactamases among clinical isolates of gram-negative bacilli in Jimma, Ethiopia. BMC Infect Dis. 2018;18(1):1.
56. Abera B, Kibret M, Mulu W. Extended-Spectrum beta (β)-lactamases and Antibiogram in Enterobacteriaceae from clinical and drinking water Sources from Bahir Dar City, Ethiopia. PLoS ONE. 2016;11(11):e0166519.
57. Legese MH, Weldearegay GM, Asrat D. Extended-spectrum beta-lactamase-and carbapenemase-producing Enterobacteriaceae among Ethiopian children. Infect Drug Resist. 2017;10:27–34.
58. Maina D, Makau P, Nyerere A, Revathi G. Antimicrobial resistance patterns in extended-spectrum β-lactamase producing Escherichia coli and Klebsiella pneumoniae isolates in a private tertiary hospital, Kenya. Microbiol Discov. 2013;1(5):1.
59. Kajeguka DC, Nambunga PP, Kabissi F, Kamugisha B, Kassam N, Nyombi B, Mataro C, Maro V, Chilongola JO. Antimicrobial resistance patterns of phenotype extended spectrum beta-lactamase producing bacterial isolates in a referral hospital in northern Tanzania. Tanzania J Health Res. 2015. https://doi.org/10.4314/thrb.v17i3.2.
60. Moremi N, Claus H, Vogel U, Mshana SE. Faecal carriage of CTX-M extended-spectrum beta-lactamase-producing Enterobacteriaceae among street children dwelling in Mwanza city, Tanzania. PLoS ONE. 2017;12(9):e0184592.
61. Manyahi J, Moyo SJ, Tellevik MG, Ndugulile F, Urassa W, Blomberg B, Langeland N. Detection of CTX-M-15 beta-lactamases in Enterobacteriaceae causing hospital-and community-acquired urinary tract infections as early as 2004, in Dar es Salaam, Tanzania. BMC Infect Dis. 2017;17:1–7.
62. Dirar M, Bilal N, Ibrahim ME, Hamid M, Hamid ME. Resistance patterns and phenotypic detection of β-lactamase enzymes among enterobacteriaceae isolates from referral hospitals in Khartoum State, Sudan. Cureus. 2020. https://doi.org/10.7759/cureus.7260.
63. Hamid OM, Gumaa SA, Ibrahim AA. Extended spectrum beta-lactamase producing Enterobacteriaceae: hospital-acquired urinary tract infections, Khartoum-Sudan. Ann Microbiol Res. 2019;3(1):76–82.
64. Chukwunwejim CR, Eze PM, Ujam NT, Abonyi IC, Ejikeugwu CP, Abony DO, Esimone CO. Incidence of community acquired ESBL-producing bacteria among asymptomatic University students in Anambra State, Nigeria. Eur J Biol Res. 2018;8(3):138–47.
65. Oli AN, Eze DE, Gugu TH, Ezeobi I, Maduagwu UN, Ihekwereme CP. Multi-antibiotic resistant extended-spectrum beta-lactamase producing bacteria pose a challenge to the effective treatment of wound and skin infections. Pan Afr Med J. 2017. https://doi.org/10.11604/pamj.2017.27.66.10226.
66. Iliyasu MY, Uba A, Agbo EB. Phenotypic detection of multidrug resistant extended-spectrum beta-lactamase (ESBL) producing Escherichia coli from clinical samples. Afr J Cell Pathol. 2018;10(2):25–32.
67. Zorgani A, Bashein A. Extended-spectrum beta-Lactamase-and carbapenemase-producing Enterobacteriaceae among Libyan Children. 2017. https://uot.edu.ly/publication_item.php?pubid=748&lang=en
68. Abujnah AA, Zorgani A, Sabri MA, El-Mohammady H, Khalek RA, Ghenghesh KS. Multidrug resistance and extended-spectrum β-lactamases genes among0 Escherichia coli from patients with urinary tract infections in Northwestern Libya. Libyan J Med. 2015;10(1):26412.
69. Feglo P, Opoku S. AmpC beta-lactamase production among Pseudomonas aeruginosa and Proteus mirabilis isolates at the Komfo Anokye Teaching Hospital, Kumasi, Ghana. J Microbiol Antimicrob. 2014;6(1):13–20.
70. Kateregga JN, Kantume R, Atuhaire C, Lubowa MN, Ndukui JG. Phenotypic expression and prevalence of ESBL-producing Enterobacteriaceae in samples collected from patients in various wards of Mulago Hospital, Uganda. BMC Pharmacol Toxicol. 2015;16:1–6.
71. Chirindze LM, Zimba TF, Sekyere JO, Govinden U, Chenia HY, Sundsfjord A, Essack SY, Simonsen GS. Faecal colonization of E. coli and Klebsiella spp. producing extended-spectrum beta-lactamases and plasmid-mediated AmpC in Mozambican university students. BMC Infect Dis. 2018;18:1–8.
72. Sangare SA, Rondinaud E, Maataoui N, Maiga AI, Guindo I, Maiga A, Camara N, Dicko OA, Dao S, Diallo S, Bougoudogo F. Very high prevalence of extended-spectrum beta-lactamase-producing Enterobacteriaceae in bacteriemic patients hospitalized in teaching hospitals in Bamako, Mali. PLoS ONE. 2017;12(2):e0172652.
73. Anago E, Ayi-Fanou L, Akpovi CD, Hounkpe WB, Agassounon-Djikpo Tchibozo M, Bankole HS, Sanni A. Antibiotic resistance and genotype of beta-lactamase producing Escherichia coli in nosocomial infections in Cotonou, Benin. Ann Clin Microbiol Antimicrob. 2015;14:1–6.
74. Schaumburg F, Alabi A, Kokou C, Grobusch MP, Köck R, Kaba H, Becker K, Adegnika AA, Kremsner PG, Peters G, Mellmann A. High burden of extended-spectrum β-lactamase-producing Enterobacteriaceae in Gabon. J Antimicrob Chemother. 2013;68(9):2140–3.
75. Fatima EL, Meriem EL, Said B. Plasmid mediated quinolones resistance ESBL-Enterobacteriaceae in Moroccan. Pham Anal Acta. 2012;15:006.
76. Müller-Schulte E, Tuo MN, Akoua-Koffi C, Schaumburg F, Becker SL. High prevalence of ESBL-producing Klebsiella pneumoniae in clinical samples from central Côte d'Ivoire. Int J Infect Dis. 2020;91:207–9.
77. Bulabula AN, Dramowski A, Mehtar S. Maternal colonization or infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae in Africa: a systematic review and meta-analysis. Int J Infect Dis. 2017;64:58–66.
78. Mansouri F, Sheibani H, Javedani Masroor M, Afsharian M. Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and

urinary tract infections in pregnant/postpartum women: a systematic review and meta-analysis. Int J Clin Pract. 2019;73(12):e13422.
79. Muleme J, Musoke D, Balugaba BE, Kisaka S, Makumbi FE, Buregyeya E, Isunju JB, Wambi R, Mugambe RK, Kankya C, Munyeme M. Epidemiology of extended-spectrum beta-lactamase-producing Escherichia coli at the human-animal-environment interface in a farming community of central Uganda. PLOS Glob Public Health. 2023;3(6):e0001344.
80. Moyo P, Moyo E, Mangoya D, Mhango M, Mashe T, Imran M, Dzinamarira T. Prevention of antimicrobial resistance in sub-Saharan Africa: what has worked? What still needs to be done? J Infect Public Health. 2023;16(4):632–9.
81. Gulumbe BH, Haruna UA, Almazan J, Ibrahim IH, Faggo AA, Bazata AY. Combating the menace of antimicrobial resistance in Africa: a review on stewardship, surveillance and diagnostic strategies. Biol Proced online. 2022;24(1):19.
82. Sartorius B, Gray AP, Weaver ND, Aguilar GR, Swetschinski LR, Ikuta KS, Mestrovic T, Chung E, Wool EE, Han C, Hayoon AG. The burden of bacterial antimicrobial resistance in the WHO African region in 2019: a cross-country systematic analysis. Lancet Glob Health. 2024;12(2):e201-16. https://doi.org/10.1016/S2214-109X(23)00539-9.
83. Sisay M, Worku T, Edessa D. Microbial epidemiology and antimicrobial resistance patterns of wound infection in Ethiopia: a meta-analysis of laboratory-based cross-sectional studies. BMC Pharmacol Toxicol. 2019;20(1):1–9.
84. Tuem KB, Gebre AK, Atey TM, Bitew H, Yimer EM, Berhe DF. Drug resistance patterns of Escherichia coli in Ethiopia: a meta-analysis. BioMed Res Int. 2018. https://doi.org/10.1155/2018/4536905.
85. Murray LM, Hayes A, Snape J, Kasprzyk-Hordern B, Gaze WH, Murray AK. Co-selection for antibiotic resistance by environmental contaminants. Npj Antimicrob Resist. 2024;2(1):9.
86. Shaikh S, Fatima J, Shakil S, Rizvi SM, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases: types, epidemiology and treatment. Saudi J Biol Sci. 2015;22(1):90–101.
87. Aguilar-Bultet L, García-Martín AB, Vock I, Maurer Pekerman L, Stadler R, Schindler R, Battegay M, Stadler T, Gómez-Sanz E, Tschudin-Sutter S. Within-host genetic diversity of extended-spectrum beta-lactamase-producing Enterobacterales in long-term colonized patients. Nat Commun. 2023;14(1):8495.
88. Karaiskos I, Giamarellou H. Carbapenem-sparing strategies for ESBL producers: when and how. Antibiotics. 2020;9(2):61.
89. Son SK, Lee NR, Ko JH, Choi JK, Moon SY, Joo EJ, Peck KR, Park DA. Clinical effectiveness of carbapenems versus alternative antibiotics for treating ESBL-producing Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. J Antimicrob Chemother. 2018;73(10):2631–42.
90. Amer WH, Elshweikh SA, Hablas NM. Comparative study between β-lactam/β-lactamase inhibitors as alternatives for carbapenems in the treatment of extended-spectrum β-lactamase–producing Enterobacteriaceae. Infect Dis Clin Pract. 2019;27(3):138–42.
91. Alizadeh N, Ahangarzadeh Rezaee M, Samadi Kafil H, Hasani A, Soroush Barhaghi MH, Milani M, Yeganeh Sefidan F, Memar MY, Lalehzadeh A, Ghotaslou R. Evaluation of resistance mechanisms in carbapenem-resistant Enterobacteriaceae. Infect Drug Resist. 2020;13:1377–85.
92. Woerther PL, Andremont A, Kantele A. Travel-acquired ESBL-producing Enterobacteriaceae: impact of colonization at individual and community level. J Travel Med. 2017;24:S29-34.
93. Pana ZD, Zaoutis T. Treatment of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLs) infections: what have we learned until now. F1000Res. 2018;7:1347. https://doi.org/10.12688/f1000research.14822.1.
94. Zahar JR, Lesprit P, Ruckly S, Eden A, Hikombo H, Bernard L, Harbarth S, Timsit JF, Brun-Buisson C, Aissa N, Losniewski A. Predominance of healthcare-associated cases among episodes of community-onset bacteraemia due to extended-spectrum β-lactamase-producing Enterobacteriaceae. Int J Antimicrob Agents. 2017;49(1):67–73.
95. Godonou AM, Lack F, Gbeasor-Komlanvi FA, Konlani L, Dossim S, Ameyapoh YA, Ekouevi K, Dagnra AY, Salou M. High faecal carriage of extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL-PE) among hospitalized patients at Sylvanus Olympio Teaching Hospital, Lomé, Togo in 2019. Afr J Clin Exp Microbiol. 2022;23(1):40–8.
96. Ouedraogo AS, Sanou M, Kissou A, Sanou S, Solaré H, Kaboré F, Poda A, Aberkane S, Bouzinbi N, Sano I, Nacro B. High prevalence of extended-spectrum ß-lactamase producing enterobacteriaceae among clinical isolates in Burkina Faso. BMC Infect Dis. 2016;16:1–9.
97. Duffy N, Karlsson M, Reses HE, Campbell D, Daniels J, Stanton RA, Janelle SJ, Schutz K, Bamberg W, Rebolledo PA, Bower C. Epidemiology of extended-spectrum β-lactamase–producing Enterobacterales in five US sites participating in the Emerging Infections Program, 2017. Infect Control Hosp Epidemiol. 2022;43(11):1586–94.
98. Zeng M, Xia J, Zong Z, Shi Y, Ni Y, Hu F, Chen Y, Zhuo C, Hu B, Lv X, Li J. Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli. J Microbiol Immunol Infect. 2023;56(4):653–71.
99. CDC. ESBL-producing Enterobacterales. U.S. Centers for Disease Prevention and Control. Aprill 11, 2024. https://www.cdc.gov/esbl-producing-enterobacterales/about/index.html. Accessed December 2024.
100. Europe W. Action against antimicrobial resistance requires a One Health approach, World Health Organization, 2024. Regional Office for Europe. Switzerland. https://coilink.org/20.500.12592/0p2nnqb on 17 Dec 2024. COI: 20.500.12592/0p2nnqb.
101. Husna A, Rahman MM, Badruzzaman AT, Sikder MH, Islam MR, Rahman MT, Alam J, Ashour HM. Extended-spectrum β-lactamases (ESBL): challenges and opportunities. Biomedicines. 2023;11(11):2937.
102. World Health Organization. WHO integrated global surveillance on ESBL-producing E. coli using a "One Health" approach: implementation and opportunities. World Health Organization. 2021. https://www.who.int/publications/i/item/9789240021402#:~:text=WHO%20and%20the%20Advisory%20Group,92-4-002140-2. Accessed December 2024.

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