The magnitude of extended-spectrum beta-lactamase-producing Enterobacteriaceae from clinical samples in Ethiopia: a systematic review and meta-analysis

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Abstract

Background. The rapid spread of resistance among extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae is a serious problem around the world. It results in serious clinical complications in humans and has become a global threat. Therefore, this systematic review and meta-analysis was aimed to estimate the pooled prevalence of ESBL-producing Enterobacteriaceae in different clinical samples in Ethiopia.

Methods. A systematic search was conducted on PubMed, Web of Science, Embase, Google Scholar and the Cochrane Library. All identified observational studies reporting the prevalence of ESBL-producing Enterobacteriaceae from clinical samples in Ethiopia were included. Four authors independently extracted data and analysed using R software version 3.6.1 and STATA statistical software version 13. A random-effects model was computed to estimate the pooled prevalence of ESBL-producing Enterobacteriaceae in Ethiopia.

Results. Of 142 articles reviewed, 14 studies that fulfilled the inclusion criteria were included in the meta-analysis. The pooled prevalence of ESBL-producing Enterobacteriaceae in the different clinical specimens in Ethiopia was 49% (95% CI: 39, 60). Klebsiella pneumoniae was the leading ESBL-producing Enterobacteriaceae followed by Escherichia coli and Acinetobacter baumannii with a prevalence of 74, 67 and 60%, respectively. ESBL-producing isolates showed a high rate of resistance to cefotaxime, ceftriaxone, ceftazidime, Amoxicillin clavulanic acid (AMC), ampicillin and aztreonam. The better options for the treatment of ESBL-producing Enterobacteriaceae are amikacin and Imipenem.

Conclusion. The magnitude of ESBL-producing Enterobacteriaceae in different clinical samples in Ethiopia is alarmingly high and represents a threat to human health. Hence, a coordinated effort needs to be implemented for the prevention and control of these Enterobacteriaceae.

BACKGROUND

Enterobacteriaceae are a huge, heterogeneous group of gram-negative rods whose natural habitat is the intestinal tract of humans and animals [1]. These microorganisms have emerged as one of the most important reasons for nosocomial and community-obtained infections [2–5]. Enterobacteriaceae are typically associated with a range of infections [6], among which urinary tract infections, bloodstream infections, heath facility-associated pneumonia and some intra-abdominal infections are the most crucial [7, 8].

Studies conducted in different underdeveloped countries indicate a high case fatality rate associated with bloodstream infection, due to Enterobacteriaceae [9, 10]. Antibiotics play a vital role in decreasing the load of communicable diseases worldwide [11]. Microbial resistance to antimicrobial agents is rising remarkably worldwide [12–14]. This rapid spread of resistance among pathogenic microorganisms is a serious problem globally [2, 4], because it limits drug treatment against infections...
Antimicrobial resistance has been recognized as one of the most important problems facing human health by the World Health Organization (WHO) [15, 16]. Frequent isolation of multidrug resistant (MDR) pathogens in both hospital and community-acquired infections has further intensified the problem of antimicrobial resistance [5]. Currently, extended-spectrum $\beta$-lactamase (ESBL)-producing *Enterobacteriaceae* represent a serious public health issue globally [1]. They become resistant to beta-lactam antibiotics via the production of beta-lactamase enzymes that inactivate beta-lactam antibiotics, and this continues to be the prominent cause of $\beta$-lactam antibiotic resistance among *Enterobacteriaceae* [17, 18]. They can rapidly develop resistance against a range of important broad-spectrum antimicrobials [19, 20]. Inappropriate and irrational use of antimicrobial drugs, and poor sanitary and infection control practices in the area may play a critical role in the increased prevalence of resistant bacteria in a community, providing favourable conditions for resistant microorganisms to emerge and spread [21, 22]. This can lead to a proliferation of organisms with broad-spectrum $\beta$-lactamase activity that threatens the future of the $\beta$-lactam class in clinical care [21]. The increasing rate of human infections caused by antimicrobial resistance strains of *Enterobacteriaceae* makes clinical management more difficult by prolonging the illness and compromising treatment [5]. This can have a potentially serious impact on human health. The situation is more common in developing countries where there is widespread and uncontrolled use of antibiotics [16]. Data on ESBL-producing *Enterobacteriaceae* in Ethiopia are limited and are not currently available in aggregate form. Therefore, this systematic review and meta-analysis aimed to determine the pooled prevalence of ESBL-producing *Enterobacteriaceae* using available studies in Ethiopia.

*Fig. 1.* Flow chart of the study selection for systematic review and meta-analysis of the prevalence of ESBL-producing *Enterobacteriaceae* from clinical samples.
METHODS

Study design

A systematic review and meta-analysis was conducted to estimate the prevalence of ESBL-producing *Enterobacteriaceae* from clinical samples from patients attending health institutions in Ethiopia following the methodological framework suggested by Arksey and O’Malley [23].

| Authors          | Year | Study method | Characterization   | Study area     | *Enterobacteriaceae* cases | Prevalence (95% CI) |
|------------------|------|--------------|--------------------|----------------|---------------------------|---------------------|
| Engda et al. [54]| 2018 | Cross-sectional | Phenotypic method | Gondar town    | 57                         | 9                   | 16 (7–28)          |
| Legese et al. [55]| 2017 | Cross-sectional | Phenotypic method | Addis Ababa    | 43                         | 34                  | 79 (64–90)         |
| Bitew et al. [56]| 2019 | Cross-sectional | Phenotypic method | Addis Ababa    | 135                        | 66                  | 49 (40–58)         |
| Abayneh et al. [57]| 2019 | Cross-sectional | Phenotypic method | Jimma town     | 168                        | 35                  | 21 (15–28)         |
| Beyene et al. [58]| 2019 | Cross-sectional | Phenotypic method | Addis Ababa    | 238                        | 158                 | 66 (60–72)         |
| Desta et al. [59]| 2016 | Cross-sectional | Phenotypic method | Addis Ababa    | 295                        | 151                 | 51 (48–82)         |
| Abayneh et al. [60]| 2018 | Cross-sectional | Phenotypic method | Jimma town     | 74                         | 17                  | 23 (18–35)         |
| Gashaw et al. [61]| 2018 | Cross-sectional | Phenotypic method | Jimma town     | 100                        | 51                  | 51 (41–61)         |
| Zeynudin et al. [62]| 2018 | Cross-sectional | Genotypic analysis | Jimma town     | 112                        | 71                  | 63 (54–72)         |
| Teklu et al. [86]| 2019 | Cross-sectional | Phenotypic method | Addis Ababa    | 426                        | 246                 | 58 (53–62)         |
| Moges et al. [84]| 2019 | Cross-sectional | Phenotypic method | Bahar dar      | 185                        | 127                 | 69 (61–75)         |
| Solomon et al. [87]| 2017 | Cross-sectional | Phenotypic method | Wolaita Sodo   | 67                         | 39                  | 58 (46, 70)        |
| Abera et al. [73]| 2016 | Cross-sectional | Phenotypic method | Harar          | 57                         | 19                  | 33 (21, 47)        |
| Abayneh et al. [57]| 2018 | Cross-sectional | Phenotypic method | Jimma town     | 100                        | 51                  | 51 (41–61)         |
| Gashaw et al. [61]| 2018 | Cross-sectional | Phenotypic method | Jimma town     | 112                        | 71                  | 63 (54–72)         |
| Zeynudin et al. [62]| 2018 | Cross-sectional | Genotypic analysis | Jimma town     | 112                        | 71                  | 63 (54–72)         |
| Teklu et al. [86]| 2019 | Cross-sectional | Phenotypic method | Addis Ababa    | 426                        | 246                 | 58 (53–62)         |
| Moges et al. [84]| 2019 | Cross-sectional | Phenotypic method | Bahar dar      | 185                        | 127                 | 69 (61–75)         |
| Solomon et al. [87]| 2017 | Cross-sectional | Phenotypic method | Wolaita Sodo   | 67                         | 39                  | 58 (46, 70)        |
| Abera et al. [73]| 2016 | Cross-sectional | Phenotypic method | Harar          | 57                         | 19                  | 33 (21, 47)        |

Search strategies

All relevant articles were searched without date limits using the following databases: PubMed, Web of Science, Embase, Google Scholar, Cochrane Library and Science Direct according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [24]. All searches were limited to articles written in English given that such language...
restriction does not alter the outcome of the systematic reviews and meta-analysis [25]. Grey literature of observational studies was searched through the review of reference lists and input of content experts. The search of the literature was conducted from May 2005 to September 2019. All papers published until the end of 2019 that fulfilled the inclusion criteria were considered. The search used the following keywords: ‘Extended-spectrum β-lactamase; β-lactams resistance; antibiotic resistance; Enterobacteriaceae; K. pneumoniae; E. coli; Ethiopia’. We searched all terms with the help of Boolean operators such as ‘AND’ or ‘OR’.

Eligibility criteria

Studies conducted in Ethiopia and articles reported in English were considered. Only studies involving humans and published articles were included. All observational study designs reporting data regarding the proportion of ESBL-producing Enterobacteriaceae isolated from humans were eligible for this review. Studies with the following characteristics were excluded from the analysis: review articles, letters, articles that had no original data, articles that did not identify the species and the origin of isolates, articles that were not fully accessible, performed outside Ethiopia, duplicate publications of the same study and studies involving animals.

Statistical analysis

Following data extraction, systematic review and meta-analysis were carried out using R software version 3.6.1 and STATA statistical software (version 13) with user-contributed commands for meta-analyses: metaprop, metan, metainf, metabias and metareg [27]. The effect sizes and SEs of the studies were pooled using a random-effects model to calculate the pooled prevalence of ESBL-producing Enterobacteriaceae in different clinical samples in Ethiopia. A meta-analysis was also planned to assess the antibiotic resistance profile of ESBL-producing Enterobacteriaceae.

Risk of bias and sensitivity analysis

The standard error for each original study was calculated using the binomial distribution formula. Evidence for statistical heterogeneity among reported prevalence was
using the Cochrane Q-test and $I^2$ statistics [28]. The pooled proportion was estimated by using the back-transform of the weighted mean of the transformed proportions for both the fixed-effects model and the random-effects model [29]. A significance level of $P<0.10$ and $I^2>50\%$ was interpreted as evidence of heterogeneity [30]. A potential source of heterogeneity was investigated by subgroup analysis and meta-regression analysis [31]. Where statistical pooling was not possible, the findings were presented in a narrative form including tables and figures to aid in data presentation where appropriate.

Sensitivity analyses were conducted to determine the relative influence of each individual study on the pooled effect size using a user-written function, metainf. The presence of publication bias was assessed informally by visual inspection of funnel plots [32]. Point prevalence, as well as 95% confidence intervals, was presented in the forest plot format.

**RESULTS**

**Study selection**

The database searches identified a total of 142 articles reporting the prevalence of ESBL-producing *Enterobacteriaceae* in different clinical samples using the range of databases previously described. From these initial articles, 63 were excluded due to duplication. From the remaining 79 articles, 39 were excluded after review of their titles and abstracts confirmed non-relevance to this review, 40 articles were assessed with respect to their eligibility for inclusion, which resulted in the further exclusion of 26 articles primarily due to the study being done in other countries [33–53], and 14 studies were included in the final systematic review and meta-analysis (Fig. 1).

**Description of included studies**

In this review, 14 articles published between 2005 and 2019 and that reported the prevalence of ESBL-producing *Enterobacteriaceae* in different clinical specimens were included. In this systematic review and meta-analysis, 2167 *Enterobacteriaceae* isolates were used to determine the pooled prevalence of ESBL-producing *Enterobacteriaceae* in different clinical specimen. The number of *Enterobacteriaceae* isolated in different studies ranged from 57 to 426. The lowest prevalence (16%) of ESBL-producing *Enterobacteriaceae* was reported in studies conducted in Gondar town [54] and the highest prevalence (79%) was reported in Addis Ababa [55]. Most of the studies were from Addis Ababa [55–59] and from the Oromia region [57, 60–62] (Table 1).

**Risk of bias**

A risk of bias tool [63] was used to assess the risk of bias for the included studies and >90% of the studies had a low risk of bias. In almost all studies, different clinical samples were collected from patients who attended different health institutions. All *Enterobacteriaceae* were screened for ESBL production using cefotaxime and ceftazidime, and double-disc synergy methods were used for detection of ESBL-producing strains in almost all of the studies.

**Prevalence of ESBL-producing *Enterobacteriaceae* in Ethiopia**

The pooled prevalence of ESBL-producing *Enterobacteriaceae* in different clinical specimen in Ethiopia was 49% (95% CI: 39, 60). Due to the presence of high heterogeneity ($I^2=62$, $P<0.01$), a random effect meta-analysis model was explored to assess the pooled prevalence of *Campylobacter* species in children less than 5 years old in Ethiopia (Fig. 2).
To identify sources of heterogeneity, we assessed the year when the study was published, study area and sample size using univariate meta-regression models, but all were statistically non-significant for the included study (Table 2). A funnel plot showed an irregular distribution of the articles.

Subgroup analysis

In the current study, subgroup analysis was done based on the area where the study was performed. Based on subgroup analysis, the distribution of ESBL-producing Enterobacteriaceae throughout the country varied from region to region. A high prevalence of ESBL-producing Enterobacteriaceae was reported in Addis Ababa followed by SNNPR, with a prevalence of 63.5 and 58% respectively (Table 3).

The magnitude of ESBL-producing Enterobacteriaceae in different clinical samples in different study areas in Ethiopia

In this study, we tried to assess the prevalence of ESBL-producing Enterobacteriaceae in different clinical specimen collected from patients. About 1962 Enterobacteriaceae among 11 species were collected from 14 studies conducted in Ethiopia. Klebsiella pneumoniae was the leading ESBL-producing Enterobacteriaceae followed by Escherichia coli and Acinetobacter baumannii with prevalences of 74, 67 and 60%, respectively. Proteus species were the least frequent ESBL-producing Enterobacteriaceae with a prevalence of 17% (Fig. 3).

Distribution of ESBL-producing Enterobacteriaceae in different specimens

In the present study, ESBL-producing Enterobacteriaceae were found predominantly in blood specimens (62.3%), followed by urine specimens (41.2%) and wounds (35%). Based on the data collected from the included studies, none of the ESBL-producing Enterobacteriaceae was isolated from body fluid, nasal swab or sputum sample (0%) (Table 4).

Antibiotic resistance profile of ESBL-producing Enterobacteriaceae

In the present systematic review and meta-analysis, ESBL-producing isolates were highly resistant to both third-generation cephalosporins and non-beta lactam antimicrobial agents. Higher resistance rates were recorded among cefotaxime, ceftriaxone, amoxicillin clavulanic acid, ampicillin and aztreonam with values of >90% (Table 5).

The resistance rates of ESBL-producing isolates to ceftazidime, tetracycline, SXT and chloramphenicol were 77–89%. However, amikacin and impenem showed greater efficacy against ESBL-producing Enterobacteriaceae with efficacy rates of 84–97% (Table 5).

DISCUSSION

Data on the magnitude of ESBL-producing Enterobacteriaceae in different clinical samples collected from different studies conducted in Ethiopia are limited and are not currently available in aggregated form. The emergence and rapid spread of multidrug resistance strains of ESBL-producing Enterobacteriaceae is a serious public health issue worldwide. Rapid expansion of ESBLs is greatly affecting the activity of broad-spectrum antibiotics, creating major therapeutic difficulties with a significant impact on patient outcomes [64].

The phenotypic information obtained in the current meta-analysis indicates a significant prevalence of ESBL producers. The overall magnitude of ESBL-producing Enterobacteriaceae in different clinical samples obtained from this study was 49%, indicating a remarkable health problems in developing and developed countries [65]. Our finding is consistent with studies conducted in Tanzania [66], Nigeria [43], Burkina Faso [67] and Ghana [68] with prevalence ranging from 44 to 58%. However, it is higher than for studies conducted in Italy [69], Egypt [70] and Turkey [71] with prevalence ranging from 0.5 to 24% respectively. This variation might be explained by methodological differences, differences in study area and quality of media used. The use of low-quality antibiotics, inappropriate use of antibiotics, and weak infection prevention measures may additionally contribute to the high prevalence of ESBLs.

Based on this meta-analysis, K. pneumonia was the leading ESBL-producing Enterobacteriaceae with a prevalence of 74%, followed by E. coli (67%) and A. baumannii (60%). This was in agreement with studies conducted in Uganda [72] with

| Sample no. | Specimen      | Number of Enterobacteriaceae isolated | ESBL-producing Enterobacteriaceae | Prevalence of ESBL-producing Enterobacteriaceae |
|------------|---------------|--------------------------------------|----------------------------------|-----------------------------------------------|
| 1          | Urine         | 587                                  | 242                              | 41.2%                                         |
| 2          | Blood         | 377                                  | 235                              | 62.3%                                         |
| 3          | Wound         | 120                                  | 42                               | 35%                                           |
| 4          | Ear           | 38                                   | 1                                | 2.6%                                          |
| 5          | Body fluid    | 25                                   | 0                                | 0%                                            |
| 6          | Nasal         | 9                                    | 0                                | 0%                                            |
| 7          | Sputum        | 7                                    | 0                                | 0%                                            |
prevalence of *K. pneumoniae* (72.7 %) and *E. coli* (58.1 %) and elsewhere [73] with prevalence of *K. pneumoniae* (69.8 %) and *E. coli* (58.2 %). However, *E. coli* was a predominant ESBL producer compared to *K. pneumoniae* according to studies in Burkina Faso [67] (*E. coli* 67.5 %, *K. pneumoniae* 26 %), India [69] (*E. coli* 61.4 %, *K. pneumoniae* 46.2 %) and Central India [74] (*E. coli* 50.14 %, *K. pneumoniae* 48.27 %). Rapid adaptation to selective changes in environmental pressures, upregulation of the intrinsic resistance mechanisms, and acquisition and transfer of drug resistance genes through mobile genetic elements such as plasmids and transposons could be a possible explanation for an elevated overall drug resistance prevalence rate against different categories of drugs.

In the present study, a high prevalence of ESBL-producing *Enterobacteriaceae* was found in blood specimens (62.3 %), followed by urine specimens (41.2 %) and wounds (35 %). This is in line with studies conducted in Iran [75] (87.8 % in blood, 48.5 % in urine), India [76] (66.67 % in blood, 54.67 % in urine), Burkina Faso [67] (75 % in blood) and north-west India [77] (79.2.0 % in blood). However, studies conducted in Uganda [72] (64.9 % in urine, 47.4 % in pus), Bangladesh [78] (70.4 % in urine, 16.5 % in blood) and central India [79] (52.28 % in urine) reported urine specimens as the major source of ESBL-producing *Enterobacteriaceae*. This indicates that ESBL-producing *Enterobacteriaceae* are becoming a serious problem in the treatment of invasive bacterial infections.

In this meta-analysis, ESBL-producing *Enterobacteriaceae* were highly resistant to ampicillin, followed by cefotaxime, aztreonam, AMC and ceftazidime, with resistance rates ranging from 88 to 100 %, while the lowest resistance was found against amikacin and imipenem, 3–16 %. Our finding agrees with studies conducted in Burkina Faso [67], Ghana [68], Saudi Arabia [80], Israel [81], Poland [82] and Sierra Leone [83]. This indicates that ESBL-producing *Enterobacteriaceae* were rapidly emerging in developing countries. In this meta-analysis, ESBL-producing *Enterobacteriaceae* were resistant not only to third-generation cephalosporins but also to other non-β lactam group antibiotics. The findings of this meta-analysis showed that amikacin and imipenem had better performance against ESBL-producing *Enterobacteriaceae* than other antibiotics, including cephalosporins. Mogens and colleagues [84] also reported that amikacin and imipenem performed better in the treatment of ESBL-producing *Enterobacteriaceae*.

The multidrug resistance nature of ESBL-producing *Enterobacteriaceae* may be explained by the fact that they are plasmid-mediated enzymes that carry multiresistance genes by plasmids, transposons and integrons, and also that they are readily transferred to other bacteria through conjugation, transduction or transformation. Those bacteria may not necessarily be of the same species. Bacteria with multiple resistance to antibiotics are now widely distributed in hospitals, are increasingly being isolated from community settings and have become a serious problem throughout the world

### Table 5. Pooled prevalence of antibiotic resistance profiles of ESBL-producing *Enterobacteriaceae* to different antibiotics, 2020

| Antibiotic | R | S | R | S | R | S | R | S | R | S |
|------------|---|---|---|---|---|---|---|---|---|---|
| Cefotaxime | 6 | 1 | 147 | 4 | 17 | 0 | 11 | 4 | – | – |
| Ceftriaxone | 6 | 1 | 140 | 11 | 14 | 3 | – | – | – | – |
| AMC        | 1 | 6 | 95  | 56 | 11 | 6 | – | – | – | – |
| Amikacin   | 0 | 7 | 2   | 149| 4  | 13| – | – | – | – |
| Ciprofloxacin | 1 | 6 | 117 | 34 | 13 | 4 | – | – | 69 | 51 |
| Tetracycline | 6 | 1 | – | – | 14 | 3 | – | – | – | – |
| SXT        | 6 | 1 | 140 | 11| 14 | 3 | – | – | 98 | 22 |
| Aztreonam  | – | – | 147 | 4 | – | – | 10 | 5 | – | – |
| Imipenem   | – | – | – | – | 0  | 17 | 5 | 10 | – | – |
| C          | – | – | – | – | 12 | 5 | – | – | 94 | 26 |

| | [Abayneh et al. [57]](ESBL=7) | [Desta et al. [59]](ESBL=151) | [Abayneh et al. [60]](ESBL=17) | [Solomon et al. [87]](ESBL=15) | [Abera et al. [73]](ESBL=120) |
| | R | S | R | S | R | S | R | S | R | S |
| | 181 | 95.3 | 9 | 4.7 | 169 | 88.9 | 21 | 11.1 | 36 | 92.3 |
| | 160 | 91.4 | 15 | 8.6 | 24 | 100 | 0 | 0.0 | 107 | 61.1 |
| | 6 | 3.4 | 169 | 96.6 | 258 | 87.5 | 37 | 12.5 | 20 | 83.3 |
| | 89 | 61.1 | 95 | 38.9 | 157 | 94.6 | 9 | 5.4 | 156 | 83.2 |
| | 200 | 67.8 | 95 | 32.2 | 154 | 82.8 | 27 | 7.2 | 106 | 77.4 |

AMC, amoxicillin-clavulanic acid; C, chloramphenicol; SXT, trimethoprim-sulphamethoxazole.
Limitations of the study

The articles for this study were limited to the English language. With the study method (most of them were cross-sectional), this can affect the outcome variable by other confounding variables. Additionally, the small sample size could affect the estimated pooled prevalence of ESBL-producing Enterobacteriaceae. This meta-analysis represented studies reported from a limited study area, which may reflect under-representation due to the limited number of studies included. The authors of the primary studies did not mention or characterize whether the isolates studied were hospital-acquired or community-based. This may be the source for the outcome of the study. Furthermore, differences in the methods used to characterize the bacterial isolates may also affect the estimated outcome.

CONCLUSION

In this meta-analysis, there was a high prevalence of ESBL-producing Enterobacteriaceae, which might contribute to the occurrence of multidrug resistance. Most ESBL-producing isolates were found primarily in blood and urine specimens. The most frequent ESBL-producing Enterobacteriaceae were K. pneumoniae, E. coli and A. baumannii. ESBL-producing isolates showed a high rate of resistance to cefotaxime, ceftriaxone, ceftazidime, AMC, ampicillin and aztreonam. The best options for the treatment of ESBL-producing Enterobacteriaceae are amikacin and imipenem. The rise of ESBL-producing Enterobacteriaceae requires strict infection prevention and control strategies and strengthening of diagnostic capacity of laboratory professionals for the detection and surveillance of antibiotic resistance.

Data availability statement

All data relevant to the study are included in the article or have been uploaded as online supplementary information.

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