Review Article

Decadal Analysis of ESBL-*Escherichia coli* Antibiotic Resistance Patterns in Urine Samples from Nepal: A Systematic Review and Meta-Analysis

Bibek Rana Chhetri,[1,2] Rajat Thapa,[2,3] Megha Raj Banjara[4]

[1] Faculty of Medicine and Life Sciences, Chester Medical School, University of Chester, UK, [2]Department of Microbiology, St. Xavier's College, Maitighar, Kathmandu, Nepal, [3]Angel Fertility Clinic, Kathmandu, Nepal, [4]Central Department of Microbiology, Tribhuvan University, Kirtipur, Kathmandu, Nepal.

ABSTRACT

Background: This systematic review aimed to determine the antimicrobial resistance pattern of the extended-spectrum β-lactamases producing *Escherichia coli* (ESBL-EC) in urine samples in Nepal.

Methods: Systematic literature review was conducted to locate all articles reporting ESBL-EC in urine samples published between January 2012 to December 2022. The Egger's weighted regression analysis was done to assess the publication bias. A random-effects model was used to calculate the pooled prevalence and corresponding 95% confidence interval due to significant between-study heterogeneity. The strength of correlation between multidrug resistance and ESBL production in *E.coli* strains was determined using Pearson's correlation coefficient. The data were analyzed using R-language 4.2.2. software.

Results: The combined prevalence of *E.coli* in urine samples was found to be 14 % (95% CI, 11-18), while the overall pooled prevalence of ESBL *E.coli* and MDR *E.coli* were 30% (95% CI, 20-42) and 70% (95% CI, 38-90) respectively. A strong positive correlation of 0.99 (95% CI, 0.89-1.0) was found between ESBL production and MDR among *E.coli* isolates. Imipenem was the drug of choice against ESBL-*E.coli* in urine specimens.

Conclusions: Our analyses showed the overall ESBL-EC and MDR-EC burden in Nepal is considerably high. Likewise, the study also infers an increasing trend of antibiotic resistance pattern of ESBL-EC in urine samples.

Keywords: ESBL-*E.coli;* multi-drug resistance; Nepal; urine.

INTRODUCTION

In the 21st century, the "antimicrobial resistance" phenomenon has posed a major threat to public health globally. In 2019 alone, antimicrobial resistance (AMR) was directly responsible for an estimated 1.27 million deaths worldwide.[1] The seriousness of this lies on the staggering fact that these numbers nearly equaled the number of deaths caused by HIV (680,000) and malaria (627,000) combined in that same year, [2] and the region of Southeast Asia is subjected to have one of the highest burdens of AMR in the world considering its high population density, burden of disease and availability of antibiotics. [3]

It was in the 1980s when extended spectrum beta lactamases (ESBLs) were first introduced and to combat them, more stable beta-lactam antibiotics were developed. However, it was not too late enough, that the bacilli developed resistance against them.[4] This mechanism of resistance is attributed to bacilli's mobile genetic components, namely plasmids, that carry genes that encode for enzymes such as TEM-1, SHV-1, CTX-M, OXA, and AmpC lactamases which enzymatically neutralize broad classes of antibiotics used. Since these genes are being incorporated in a mobile plasmid, the rate of transfer of resistance remains high, thus resulting in the development of multidrug-resistant

Correspondence: Assoc. Prof. Megha Raj Banjara Central Department of Microbiology, Tribhuvan University, Kritipur, Kathmandu, Nepal. Email: megha.banjara@cdmi.tu.edu.np.

(MDR) strains. [5-9]

With emerging resistance and spread of ESBL *E.coli* in the community and hospital, UTIs being one of the most common infections, do pose a serious threat to public health.[10] The seriousness of this is very major in developing countries like Nepal, as recent literatures indicate that the prevalence of MDR and ESBL producing pathogen is as high as 90%, which is likely to be brought about by self-medications, over-prescriptions, prior-culture prescriptions and over-the-counter sale. [11,12] Additionally, with inadequate clinical expertise and unavailability of proper diagnostic tools, Nepal is at high risk of becoming the spot with high prevalence of MDR and ESBLs. Hence, considering the urgency of the situation, as per our best knowledge, this is the first systematic review and meta-analysis on the burden of ESBL-*E.coli* in urine samples in Nepal. This study aimed to estimate the pooled prevalence of ESBL-*E. coli* in urine samples and their antibiotic resistance profile, and relationship between ESBL production and multidrug resistance by analyzing available studies. This study could aid in designing and implementing control strategies to minimize the occurrence and spread of ESBL-*E.coli* in urine.

METHODS

Protocol documentation

The systematic review is registered in PROSPERO (CRD42023460823). It is documented as per the guidelines of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE), available as Supplementary file 1. [13]

Study selection

In order to determine the prevalence of ESBL-*E. coli* in human urine specimens in Nepal, an extensive literature search was conducted of all articles published from January 2012 to December 2022. The search was conducted using electronic databases such as PubMed, EMBASE, Scopus, Google Scholar, and NepJOL, with the search terms "*Escherichia coli*", "extended-spectrum ß-lactamases", "urine", "ESBL *E.coli*" and "Nepal". The search was restricted to articles published in the English language. The selected studies were thoroughly scrutinized for any additional relevant articles mentioned in their discussions or references. The final search strategy for the included database is provided in Supplementary file 2. Initially, the titles and abstracts of potential articles were scrutinized by a single reviewer (BRC) to determine their eligibility for inclusion in the review. Subsequently, the next stage involved a more in-depth analysis of the full-text articles, with eligible studies then reviewed and evaluated by authors (BRC, RT). The final review of the selected studies was then done by the author (MRB).

Eligibility criteria

To be included in this meta-analysis, studies had to meet following criteria : (i) reporting the prevalence of ESBL-EC in Nepal between January 2012 and December 2022 (ii) isolating ESBL-EC from human urine specimens; (iii) reporting the antibiotic susceptibility patterns of ESBL-EC; (iv) specifying the laboratory methods used to detect ESBL-EC. Studies were excluded for the following reasons: (i) articles reporting ESBL-EC on non-human subjects, duplicate studies, undifferentiated spp., review articles, case reports, posters, retrospective studies; (ii) articles without AST of ESBL-EC and those reporting ESBL-EC only among MDR isolates; (iii) articles with the combined results of AST of ESBL-EC and other pathogens; (iv) articles with combined result of AST of ESBL-EC isolated from other clinical samples along with urine; (v) Studies from countries other than Nepal.

These objective-driven eligibility criteria allowed us to exclude the studies that do not correspond with our outcome. The included studies were assessed for quality by using Newcastle-Ottawa Scale for cross-sectional studies.

Data extraction

The reviewers (BRC and RT) extracted data independently from eligible studies and entered it into an MS Excel spreadsheet. The data extracted were then cross-checked between them to exclude any duplicated studies. Then the final extracted data included details such as the first author's surname, year of publication, study area, study setting, sample size, total number of MDR-EC, ESBL diagnostic method, prevalence of ESBL-EC, antibiogram of ESBL-EC, and the gene variants encoding ESBL. The extracted data was reviewed twice by both reviewers (BRB, RT) to minimize the risk of errors, and then cross-checked by author MRB to ensure accuracy and completeness.

Statistical analysis With the extracted data, the prevalence of ESBL-*E.coli* in urine samples and their resistance proportions were analyzed through meta-analysis using the R programming language version 4.2.2., employing the random effect model. [14] The

heterogeneity of the included studies was tested by I^2 statistics and to ascertain the variability of the true effect size, a prediction interval was provided. [15] The overall prevalence of ESBL-*E.coli* was consolidated through a forest plot with a 95% confidence interval (CI) and the publication bias was evaluated using a contour-enhanced funnel plot and Egger's weighted regression method. [16] The bias was considered to be statistically significant when the p-value was less than 0.05.

Outcome measurements

The primary objective of this study was to evaluate the antibiogram of ESBL-*Escherichia coli* in urine samples. The study also aimed to determine the prevalence of MDR- *Escherichia coli* and its correlation with ESBL production. The secondary objective was to provide valuable information on ESBL-*Escherichia coli* in urine specimens thereby incentivizing clinicians and policymakers to help guide appropriate treatment strategies.

Quality assessment of studies

The quality of individual studies included in the meta-analysis was evaluated independently by two reviewers (BRC and MRB) using a checklist provided by the Newcastle-Ottawa Scale adapted for cross-sectional studies.[17] Any differences were resolved and checked through discussion with the second author (RT). The checklist consists of 10 questions that each reviewer answered separately for each study. Scores varied from 0 to 10, and studies with $\geqslant$ 5 points were included in the systematic review and meta-analysis. (Supplementary Table S1)

RESULTS

Search results

In conducting a meta-analysis, a systematic review was conducted to identify studies meeting the inclusion criteria. Out of 1297 articles identified, 1209 were excluded based on their titles and abstracts. Duplicate studies and retrospective studies were also excluded, leaving 52 articles for full-text assessment. After further applying inclusion and exclusion criteria, only 10 studies met the requirements and were included in the final meta-analysis. The flowchart of article selection along with exclusion reasons are presented in the PRISMA flowchart (figure 1), and the main characteristics of the included studies are provided in table 1.

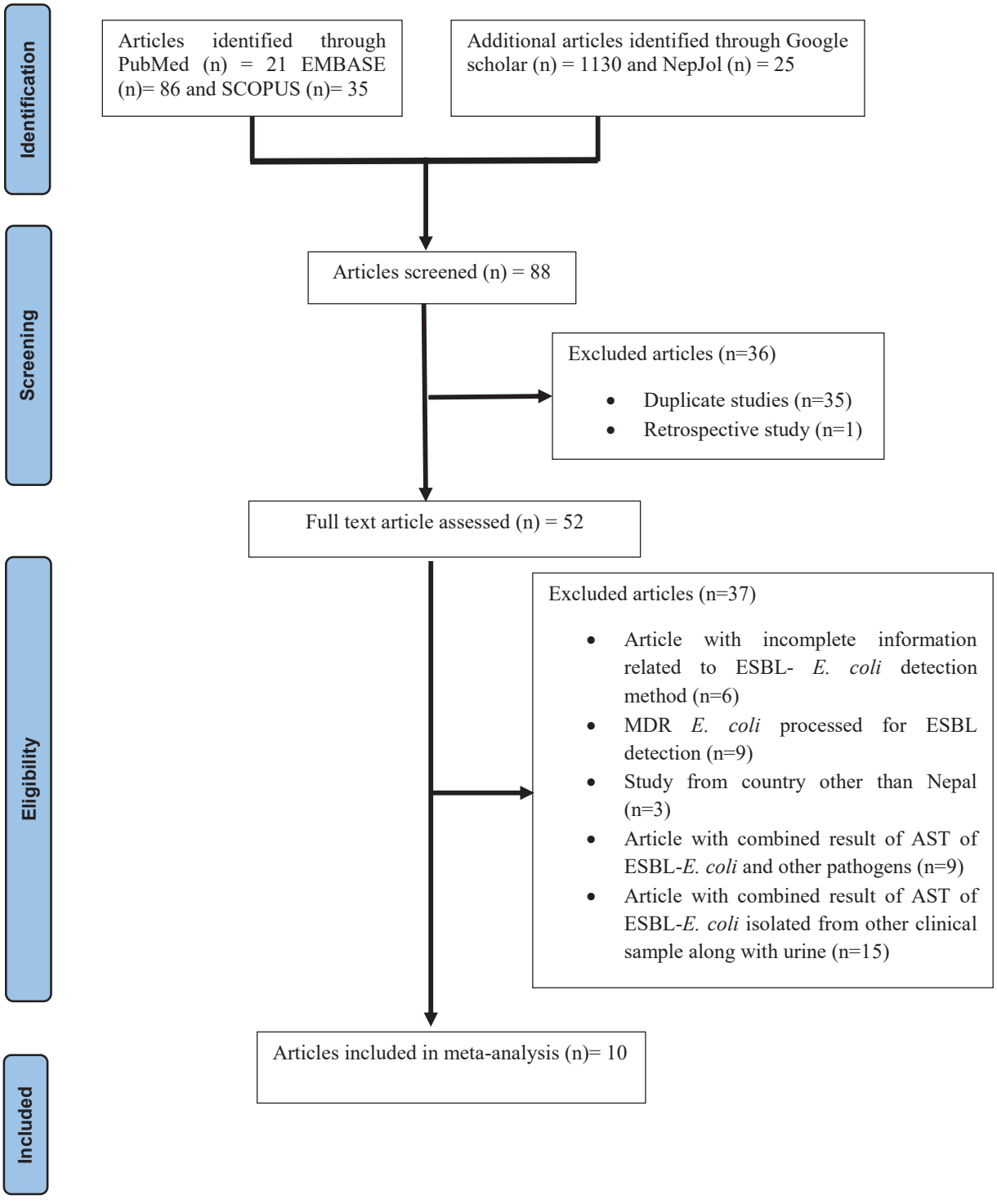


Figure 1. PRISMA flow diagram summarizing the process of literature search and selection.

Table 1. Characteristics of studies included in the meta-analysis

Study ID	Study hospital	District, Province	Total Sample size (Urine)	*E. coli*	No. of MDR (%)	No. of ESBL (%)	Diagnostic Test	ESBL genes detected
Chakrawarti et al [18]	Bijayapur Hospital	Sunsari, Koshi	752	69	60 (86.95)	12 (17.3)	CDT	-
Singh et al [19]	KIST Medical College Teaching Hospital	Lalitpur, Bagmati	1258	198	_	76(38.38)	CDT	-
Yadav et al [20]	National Kidney Center	Kathmandu, Bagmati	450	67	64 (95.52)	18 (26.86)	CDT	-
Parajuli et al [21]	Manmohan Memorial Medical College and Teaching Hospital	Kathmandu, Bagmati	5484	739	480 (64.95)	288(38.97)	CDT	-
Rimal et al [22]	International Friendship Children Hospital	Kathmandu, Bagmati	1018	200	68(34)	51(25.5)	CDT	-
Mahato et al [23]	Koshi Zonal Hospital	Morang, Koshi	3666	281	111 (39.5)	64 (22.77)	CDT	-
Mahaseth et al [24]	College of Medical Sciences and Teaching Hospital	Chitwan, Bagmati	5564	1219	-	102 (8.36)	CDT	-
Yadav et al [25]	Nobel Medical College Teaching Hospital	Morang, Koshi	2567	288	-	203(70.48)	CDT	-
Subedi et al [26]	International Children Friendship Hospital	Kathmandu, Bagmati	388	82	-	34(41.46)	CDT	-
Sah et al [27]	Shahid Gangalal National Heart Centre	Kathmandu, Bagmati	304	44	-	12(27.27)	CDT and PCR	blaCTX-M and blaTEM

Prevalence of *E.coli* in urine specimens in Nepal

A systematic review and meta-analysis of eligible studies were conducted to determine the prevalence of *E.coli* in urine specimens in the Nepalese population. The analysis revealed the prevalence to be 14 % (95% CI, 11- 18) with significant heterogeneity (I^2 = 98%; p < 0.01)

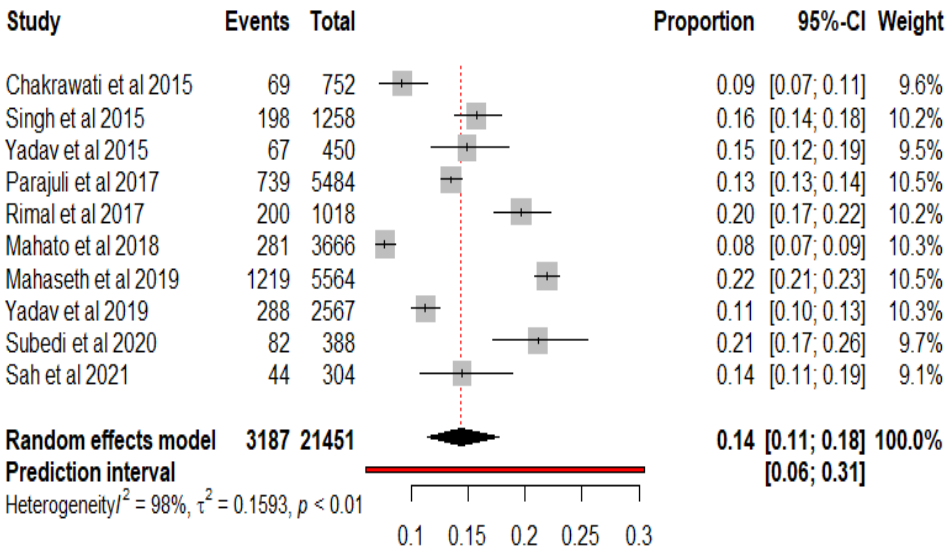
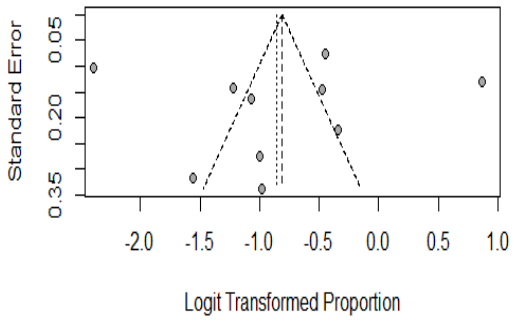


Figure 2. Forest plot depicting the pooled prevalence of *E. coli* isolated from urine in Nepal

Prevalence of ESBL-*E.coli* in urine specimens in Nepal

The overall pooled prevalence of ESBL-*E.coli* in urine specimens was found to be 30 %. We found substantial heterogeneity among the studies (I^2 = 98% and p < 0.01), potentially resulting from difference in study population, study design and limitation of specimen type. Furthermore, there was no apparent publication bias based on the symmetry of the funnel plot and Egger's weighted regression analysis (p = 0.9140).

a.



Heterogeneity test

I^2 = 98% (p<0.01)

Egger's Test

t = -0.11

(p=0.9140)

b.

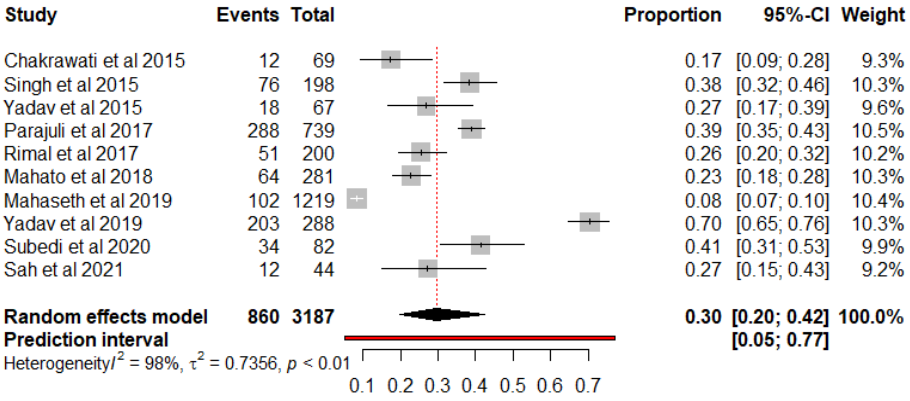


Figure 3. ESBL-EC prevalence in urine samples in Nepal, 2012-2022, (a) A funnel plot to test the publication bias among studies (b) The pooled prevalence of ESBL-EC in 10 studies.

Among 10 eligible studies 5 studies reported MDR *E.coli*. Based on the available evidence, it appears that MDR *E.coli* is a significant public health concern, as the overall pooled prevalence of these isolates was 70 % (95% CI, 38 – 90) among the included 5 studies. However, the studies showed a high level of heterogeneity (I^2 = 97%, p < 0.01) which means that there was a significant variation in the results of the studies. Figure 4 is the graphical representation of the meta-analysis result.

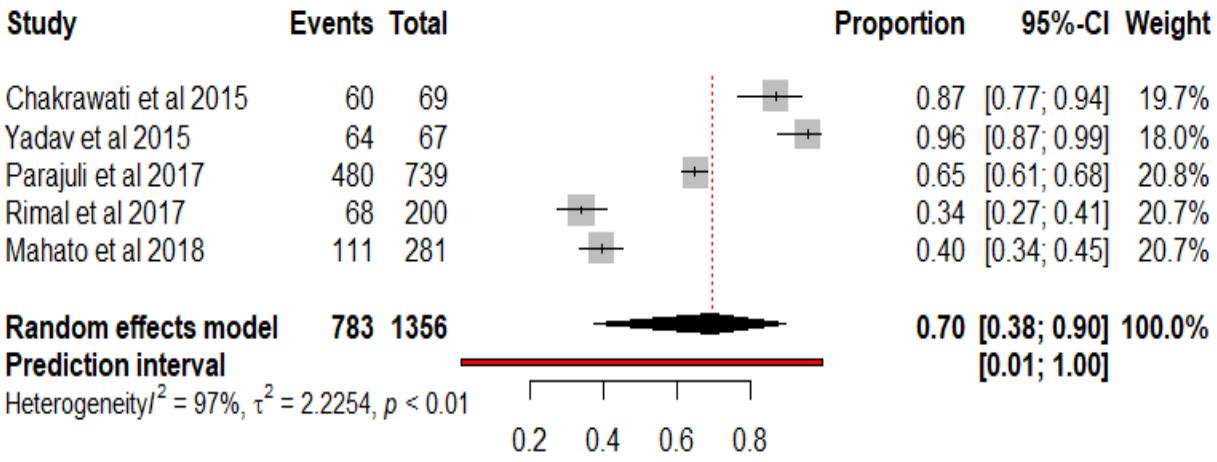


Figure 4. Forest plot of pooled prevalence of multidrug resistance among *E.coli* in urine samples in Nepal

Antimicrobial resistance patterns in ESBL-*E coli*

The antibiotic resistivity pattern of ESBL-EC is shown in table 3. Imipenem was found to be the most effective antibiotic (89.29% sensitive) against ESBL producing strains of *E.coli*, followed by amikacin (86.09% sensitive). The resistance towards ampicillin was very high (99.90%). Higher resistance was also observed against cefotaxime (96.46%), ceftazidime (85.66%), and gentamicin (50.90%).

Table 2. Antibiotic resistance profile of ESBL-*E coli* isolated from urine specimen

Antibiotics	Resistance (Pooled estimation)	95% CI	Test of heterogeneity		Number of studies reviewed
			I^2 (%)	p-value	
Amikacin	19.87	[2.82;32.91]	99.99	0.0199	6
Gentamicin	45.27	[36.71;53.83]	99.94	<.0001	5
Nalidixic Acid	88.22	[75.74;100.69]	99.97	<.0001	3
Ofloxacin	80.90	[72.04;89.77]	99.95	<.0001	4
Levofloxacin	63.92	[51.91;75.93]	99.96	<.0001	4
Norfloxacin	79.45	[65.79;93.11]	99.98	<.0001	4
Ciprofloxacin	84.43	[76.90;91.96]	99.97	<.0001	5
Ceftriaxone	85.64	[60.35;110.93]	100	<.0001	7
Cefotaxime	96.46	[89.55;103.37]	99.99	<.0001	5
Cefepime	79.48	[59.86;99.10]	99.99	<.0001	4
Ceftazidime	85.66	[65.53;105.79]	100	<.0001	8
Ampicillin	99.99	[99.98;99.99]	0	<.0001	3
Nitrofurantoin	30.98	[12.67;49.29]	99.99	0.0009	6
Cotrimoxazole	70.60	[61.72;79.48]	99.98	<.0001	8
Imipenem	10.71	[4.43;17.00]	99.90	0.0008	3
Meropenem	13.91	[-3.5937;31.4308]	99.99	0.1193	3

Correlation between MDR and ESBL production among *E.coli* isolates

A robust positive correlation was found between ESBL production and multidrug resistance in *E.coli* strains, with a Pearson's correlation coefficient of 0.99 and a 95% confidence interval ranging from 0.89 to 1.0.

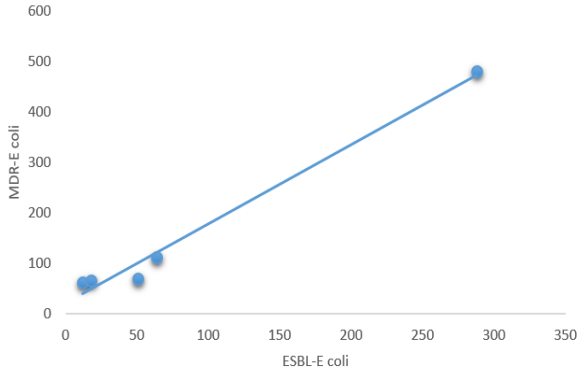


Figure 5. Relationship between multidrug resistance and ESBL production in *E. coli* isolates

DISCUSSION

Urinary tract infections (UTIs) are one of the most common bacterial infections in humans, and have been reported to be highly prevalent worldwide. The vast majority of UTIs globally is caused by gram-negative organism of the family Enterobacteriaceae, most commonly by uro-pathogenic *Escherichia coli*. [28-30] This bacillus in urine can be notorious to treat considering the rate at which it is becoming resistant to available antibiotics. [31] Despite, beta lactam antibiotics still being the choice of drug against it, the emergence of ß-lactamase producers have been a matter of concern. [4] As per our knowledge, there has not been a prior attempt to systematically integrate, analyze and combine individual studies addressing ESBL-*E.coli* prevalence in urine samples in Nepal.

This meta-analysis showed the pooled prevalence of *E.coli* in urine samples to be 14% in Nepal, which seemed a bit low compared to the studies conducted in Africa (33.4%) [32] and Ethiopia (41%). [33] This variation in results could be due to the design of our study where we included people of all ages and gender. The occurrence of multi-drug resistant *E.coli* has caused trouble in treating infectious diseases thus increasing mortality and creating a greater health cost burden. [34] In our study, the pooled prevalence of MDR isolates in *E.coli* from urine samples was estimated to be 70%, which is in moderate agreement with the studies conducted in Pakistan (66.2%) [35] and India (76.51%) [36]. However, it was significantly higher than reported in studies from Libya (33.2%) [37] and Portugal (23.3%). [38] This subsequent high resistance may be attributed to antibiotic abuse, self-medication, poor personal hygiene, improper management of food animals, inaccurate diagnosis, and disinfectant overuse. [39-40] This study found a strong positive correlation between ESBL production and multidrug resistance, which might be due to the fact that ESBL genes are incorporated in the mobile plasmid of the bacilli which also harbors other resistance-conferring genes. [41-43]

Since the bacilli's first beta-lactamase activity reported in 1940 [44] there have been persistent exposure of *E.coli* to diverse classes of beta-lactams, which have further induced production and mutations of beta-lactamases in the bacilli helping it to expand its resistance against the newly developed beta-lactam antibiotics. [45,46] In this, the pooled prevalence of ESBL-EC was 30%. Our result is in accordance with studies conducted in Pakistan (33.3%), [47] Saudi Arabia (33.49%), [48] and Iran (35.7%).[49] However, it seemed comparatively low when compared to studies conducted in Mexico (49%) [50] and Ethiopia (76.5%). [51] The number of ESBL producers *E.coli* have risen and disseminated worldwide, which have become a vital cause for community and nosocomial infections with possible severity. [20]

Nevertheless, what's alarming is the trend of rising antibiotic resistance in Nepal. The study on antibiotic resistance of ESBL-EC revealed an overall increase in the resistance pattern of ESBL-EC against all antibiotics as compared to studies conducted in Sudan, [52] Ethiopia, [53] Thailand, [54] and Poland. [55] The increase in resistance towards these antibiotics is composite. The United Nations (UN) reported that the escalation of antimicrobial use in food animals can partially be the cause of rising AMR. [55] The same can be said for Nepal where the irrational use of high doses of antibiotics for growth promotion in animals has grown over the years and along with it, the burden of AMR. [57] Additionally, the widespread use of antibiotics without a proper prescription due to the significant gaps observed in the knowledge, and attitude practices related to antibiotics among the general population in Nepal have contributed to this rising resistance. [12]

We also found that the susceptibility pattern of carbapenems: imipenem and meropenem (89.29% and 86.09%) has been significantly lower when compared to studies conducted in India (94.1% and 95.5%) [58]

and Iran (94.2 and 99.2%). [59] This significant rise of resistance can be multifactorial, besides ESBL production, the capability to form biofilm and other hydrolyzing enzymes to combat antibiotics contributes to this emerging resistance. [60] It's applaudable of the Government of Nepal to have taken some initiatives to tackle the ongoing threat through a National Action Plan for the Containment of Antimicrobials Resistance and One Health approach. However, they are still in their infancy and face various challenges in their proper implementation. [61] Nonetheless, this rise is an unavoidable evolutionary result, and we have to catch up with this evolution by developing and investing on novel approaches to combat it. [40]

This is the first study to calculate the pooled prevalence of ESBL-EC in urine samples in Nepal. Our analysis revealed the overall pooled prevalence of ESBL-EC in urine samples and their correlation with ESBL production. We explored the antibiotic resistance pattern of ESBL-EC against commonly used antibiotics in the country and found an increasing resistance towards the last reserve of drugs, which can be helpful for clinicians and health policymakers. However, our study did have some limitations. Specifically, we did not include unpublished reports or under-review publications and publications before 2011 and after 2022, which may have resulted in the omission of important findings. Moreover, we did not consider the uniformity of methodology used across the studies that we analyzed, which may have contributed to increased heterogeneity in our study. Furthermore, due to the limited data available, we did not classify data according to age and sex, which may have imparted a risk of bias and variation across the studies. However, upon regression Egger's test for publication bias, it showed there was no statistically significant bias. Additionally, the investigation was mostly based on ESBL phenotypes as studies on ESBL genotypes are limited in Nepal. We also couldn't stress on the other dynamics that could have added to the increase in ESBL-EC resistance such as previous clinical histories, socio-economic conditions, and prior antibiotic use solely due to limited data available. The tendency to condense and analyze large amounts of varying findings using a single number can be a subject of disagreement. [62]

CONCLUSIONS

High ESBL production was seen in ESBL-*Escherichia coli* which contributed to high multi-drug resistance. An increasing trend of resistance was shown by ESBL-EC toward commonly prescribed antibiotics. This study infers that the better option for the treatment of ESBL-EC could be imipenem, meropenem, and amikacin. However, a rational use of these antibiotics is suggested, considering their lowering susceptibilities.

ACKNOWLEDGEMENTS

The authors would like to express their heartfelt gratitude to all the researchers whose studies were included in this meta-analysis. Moreover, authors are also grateful to Sir Chandra Bhusan Yadav of Nepal Health Research Council's Library for providing us with access to the databases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2019;10325;399:629-655. [PMC free article] [PubMed] [The Lancet]

2. Laxminarayan R. The overlooked pandemic of antimicrobial resistance. The Lancet. 2022;10325(399): 606-607. [PMC free article] [PubMed]

3. San T, Moe I, Ashley EA, and San N. High burden of infections caused by ESBL-producing MDR *Escherichia coli* in paediatric patients, Yangon, Myanmar. JAC-Antimicrobial Resistance, 2021;3(1):dlab011. [PubMed] [PMC free article]

4. Aruna K, Mobashshera T. Prevalence of extended spectrum beta-lactamase production among uropathogens in south Mumbai and its antibiogram pattern. EXCLI Journal. 2012; 11:363-372. [PMC free article] [ResearchGate]

5. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev. 2001;14:933-951. [PMC free article] [PubMed] [Google Scholar]

6. Philippon A, Arlet G, Jacoby GA. Plasmid-determined AmpC-type beta-lactamases', Antimicrobial Agents and Chemotherapy. 2002;46(1):1-11. [PMC free article]

7. Pitout JD, et al. Emergence of Enterobacteriaceae producing extended-spectrum ß-lactamases (ESBLs) in the community. Journal of Antimicrobial Chemotherapy. 2005;56(1): 52-59. [PMC free article]

8. Jacoby GA. AmpC beta-lactamases. Clin Microbiol Rev. 2009;22(1):161-182. [PMC free article] [PubMed]

9. Bajaj P, Singh NS, Virdi JS. *Escherichia coli* ß-Lactamases: What Really Matters. Front Microbiol. 2016;7: 417. [PMC free article] [Google Scholar]

10. Khoshnood S, et al. Drug-resistant gram-negative uropathogens: A review. Biomedicine & Pharmacotherapy. 2017;94:982-994. [PubMed] [ScienceDirect]

11. Shilpakar A, et al. Prevalence of multidrug-resistant and extended-spectrum beta-lactamase producing Gram-negative isolates from clinical samples in a tertiary care hospital of Nepal. Trop Med Health. 2021;49(23). [PMC free article] [PubMed]

12. Rijal KR, et al. Use of antimicrobials and antimicrobial resistance in Nepal: a nationwide survey. Sci Rep. 2021;11:11554. [PMC free article]

13. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA Surg. 2021;156(8):787-788. [PubMed]

14. Dettori JR, Norvell DC, Chapman, JR. Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. Global Spine Journal. 2022;12(7):1624-1626. [PMC free article] [Google Scholar]

15. Borenstein M. In a meta-analysis the I-squared statistic does not tell us how much the effect size varies. Journal of Clinical Epidemiology. 2022;152:281-284. [PMC free article] [ScienceDirect]

16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109): 629-634. [PMC free article] [PubMed] [Google Scholar]

17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25: 603-605. [PubMed] [Google Scholar]

18. Chakrawarti A, et al. Extended Spectrum Beta Lactamases Detection and Multiple Antibiotic Resistance Indexing of *Escherichia coli* from Urine Samples of patients from a referral hospital of Eastern Nepal. International Journal of Applied Science and Biotechnology. 2015; 3(3): 423-426. [Google Scholar]

19. Singh VK, Tuladhar R, Chaudhary MK. Beta Lactamase Producing *Escherichia coli*, *Klebsiella pneumoniae* and Methicillin Resistant *Staphylococcus aureus* among Uropathogens. Nepal Journal of Science and Technology. 2015;16(1):105-112. [NepJol]

20. Yadav KK, et al. Multidrug resistant Enterobacteriaceae and extended spectrum ß-lactamase producing *Escherichia coli*: a cross-sectional study in National Kidney Center, Nepal. Antimicrob Resist Infect Control . 2015;4(42). [BMC]

21. Parajuli NP, et al. High rates of multidrug resistance among uropathogenic *Escherichia coli* in children and analyses of ESBL producers from Nepal. Antimicrobial Resistance and Infection Control. 2017;6(9). [PMC free article] [PubMed]

22. Rimal, U, Thapa S. Maharjan R. Prevalence of Extended Spectrum Beta-Lactamase Producing *Escherichia coli* and *Klebsiella* species from Urinary Specimens of Children attending Friendship International Children's Hospital. Nepal Journal of Biotechnology. 2017;5(1):32-38. [NepJol]

23. Mahato S, Mahato A, Yadav J. Prevalence and Identification of Uropathogens in Eastern Nepal and Understanding their Antibiogram due to Multidrug Resistance and ESBL. Asian Pacific Journal of Microbiology Research. 2018;2(1):9-17. [Google Scholar]

24. Mahaseth S. et al. Prevalence of Extended Spectrum Beta-Lactamase Producing *Escherichia coli* and *Klebsiella pneumoniae* Isolated from Urinary Tract Infected Patients Attending Tertiary Care Hospital of Central Nepal. Journal of College of Medical Sciences-Nepal. 2019;15(3):211-217. [Google Scholar]

25. Yadav KR, et al. Study of Extended Spectrum

Beta-Lactamases Producing *Escherichia Coli* and *Klebsiella* Species in a Tertiary Care Hospital, Biratnagar, Nepal. Journal of Nobel Medical College. 2019;8(2):31–36. [NepJol]

26. Subedi K, et al. Phenotypic detection of Extended Spectrum Beta lactamase production from *E. coli* and *K. pneumoniae* in urinary samples among children. Tribhuvan University Journal of Microbiology. 2020;7:75-82. [Google Scholar]

27. Sah RSP, et al. Detection of *TEM* and *CTX-M* Genes in *Escherichia coli* Isolated from Clinical Specimens at Tertiary Care Heart Hospital, Kathmandu, Nepal. Diseases. 2021;9(1):15. [PMC free article]

28. Kaper JB, Nataro JP, Mobley HL. Pathogenic *Escherichia coli*. Nat Rev Microbiol. 2004;2(2):123-140. [PMC free article] [PubMed] [Nature]

29. Arana DM, et al. ESBL-producing-multidrug resistant *E. coli* population from urinary tract infections is less diverse than non-ESBL-multidrug resistant population. Enferm Infecc Microbiol Clin (Engl Ed.) 2019;37;10:652–655. [PubMed] [ScienceDirect]

30. Bitsori M, Galanakis E. Treatment of Urinary Tract Infections Caused by ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae*. Pediatr Infect Dis J. 2019;38;12: e332–e335. [PMC free article] [PubMed]

31. Lee DS, Lee SJ, Choe HS. Community-Acquired Urinary Tract Infection by *Escherichia coli* in the Era of Antibiotic Resistance. BioMed Research International. 2018;7656752. [PMC free article] [PubMed]

32. Awoke N, Tekalign T, Teshome M, Lolaso T, Dendir G, Obsa MS. Bacterial Profile and asymptomatic bacteriuria among pregnant women in Africa: A systematic review and meta-analysis. EClinicalMedicine. 2021;37:100952. [PMC free article]

33. Chelkeba L, Fanta K, Mulugeta T, Melaku T. Bacterial profile and antimicrobial resistance patterns of common bacteria among pregnant women with bacteriuria in Ethiopia: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics. 2022;306(3):663–686. [PMC free article]

34. Ibrahim ME, Bilal NE, Hamid ME. Increased multi-drug resistant *Escherichia coli* from hospitals in Khartoum state, Sudan. African Health Sciences. 2012;12(3):368–375. [PMC free article]

35. Nazir H, Aziz M, Mirani ZA, Sheikh AS, Qamar Saeed M, Ahmed Khan A, Ruby T, Rauf N. Correlation between antibiotic resistance and phylogenetic types among multidrug-resistant *Escherichia coli* isolated from urinary tract infections. Iranian Journal of Basic Medical Sciences. 2021; 24(3):400-407. [PubMed] [PMC free article]

36. Niranjan V, Malin A. Antimicrobial resistance pattern in *Escherichia coli* causing urinary tract infection among inpatients. The Indian Journal of Medical Research. 2014;139(6):945–948. [PubMed] [PMC free article]

37. Abujnah AA, Zorgani A, Sabri MA, El-Mohammady H, Khalek RA, Ghenghesh KS. Multidrug resistance and extended-spectrum ß-lactamases genes among *Escherichia coli* from patients with urinary tract infections in Northwestern Libya. Libyan Journal of Medicine.2015;10(1):26412. [PubMed] [PMC free article]

38. Silva A, Costa E, Freitas A, Almeida A. Revisiting the Frequency and Antimicrobial Resistance Patterns of Bacteria Implicated in Community Urinary Tract Infections. Antibiotics. 2022;11(6):768. [PubMed] [PMC free article]

39. Mc Carlie S, Boucher CE, Bragg RR. Molecular basis of bacterial disinfectant resistance. Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy. 2020;48:100672. [PubMed] [ScienceDirect]

40. Uddin TM, Chakraborty AJ, Khusro A, Zidan BRM, Mitra S, Emran TB, Dhama K, Ripon MKH, Gajdács M, Sahibzada MUK, Hossain MJ, Koirala N. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. Journal of infection and public health. 2021;14(12):1750¤1766. [PubMed] [ScienceDirect]

41. Rawat D, Nair D. Extended-spectrum ß-lactamases in Gram Negative Bacteria. Journal of global infectious diseases. 2010;2(3):263–274. [PMC free article]

42. Aabed K, Moubayed N, Alzahrani S. Antimicrobial

resistance patterns among different *Escherichia coli* isolates in the Kingdom of Saudi Arabia. Saudi Journal of Biological Sciences. 2021:28(7):3776-3782. [PMC free article]

43. Abdelaziz SM, Aboshanab KM, Yahia IS, Yassien MA, Hassouna NA. Correlation between the Antibiotic Resistance Genes and Susceptibility to Antibiotics among the Carbapenem-Resistant Gram-Negative Pathogens. Antibiotics. 2021;10(3):255. [PubMed] [PMC free article]

44. Bush K. Past and present perspectives on ß-lactamases. Antimicrob Agents and Chemother. 2018;62;10:e01076-18. [PMC free article] [PubMed]

45. Shaikh S, et al. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi Journal of Biological Sciences. 2015;22(1):90–101. [PMC free article]

46. Teklu DS, Negeri AA, Legese MH, et al. Extended-spectrum beta-lactamase production and multi-drug resistance among Enterobacteriaceae isolated in Addis Ababa, Ethiopia. Antimicrob Resist Infect Control. 2019;08(39). [PMC free article]

47. Jamil J, Haroon M, Sultan A, Khan MA, Gul N, Kalsoom. Prevalence, antibiotic sensitivity and phenotypic screening of ESBL/MBL producer *E. coli* strains isolated from urine; District Swabi, KP, Pakistan. JPMA. The Journal of the Pakistan Medical Association, 2018;68(11): 1704–1707. [PubMed]

48. Abalkhail A, AlYami AS, Alrashedi SF, Almushayqih KM, Alslamah T, Alsalamah YA, Elbehiry A. The Prevalence of Multidrug-Resistant *Escherichia coli* Producing ESBL among Male and Female Patients with Urinary Tract Infections in Riyadh Region, Saudi Arabia. Healthcare. 2022;10(9):1778. [PubMed] [PMC free article]

49. Gharavi MJ, Zarei J, Roshani-Asl P, Yazdanyar Z, Sharif M, Rashidi N. Comprehensive study of antimicrobial susceptibility pattern and extended spectrum beta-lactamase (ESBL) prevalence in bacteria isolated from urine samples. Scientific Reports, 2021;11(1):578. [PubMed] [PMC free article]

50. Sierra-Díaz E, Hernández-Ríos CJ, Bravo-Cuellar A. Antibiotic resistance: Microbiological profile of urinary tract infections in Mexico. Cirugia y cirujanos, 2019;87(2):176–182. [PubMed]

51. Abayneh M, Tesfaw G, Abdissa A. Isolation of Extended-Spectrum ß-lactamase- (ESBL-) Producing *Escherichia coli* and *Klebsiella pneumoniae* from Patients with Community-Onset Urinary Tract Infections in Jimma University Specialized Hospital, Southwest Ethiopia. Canadian Journal of Infectious Diseases and Medical Microbiology. 2018;2018:4846159. [PMC free article]

52. Moglad EH. Antibiotics Profile, Prevalence of Extended-Spectrum Beta-Lactamase (ESBL), and Multidrug-Resistant Enterobacteriaceae from Different Clinical Samples in Khartoum State, Sudan. International Journal of Microbiology. 2020;2020:8898430. [PMC free article]

53. Tuem, K. B., Gebre, A. K., Atey, T. M., Bitew, H., Yimer, E. M., & Berhe, D. F.. Drug Resistance Patterns of *Escherichia coli* in Ethiopia: A Meta-Analysis. BioMed Research International. 2018;2018:4536905. [PubMed] [PMC free article]

54. Siriphap A, Kitti T, Khuekankaew A, Boonlao C, Thephinlap C, Thepmalee C, Suwannasom N, Khoothiam K. High prevalence of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates: A 5-year retrospective study at a Tertiary Hospital in Northern Thailand. Frontiers in Cellular and Infection Microbiology. 2022;12:955774. [PMC free article]

55. Michno M, Sydor A, Wałaszek M, Sułowicz W. Microbiology and Drug Resistance of Pathogens in Patients Hospitalized at the Nephrology Department in the South of Poland. Polish Journal of Microbiology. 2018;67(4):517–524. [PubMed] [PMC free article]

56. Zhou N, Cheng Z, Zhang X, et al. Global antimicrobial resistance: a system-wide comprehensive investigation using the Global One Health Index. Infectious Diseases of Poverty. 2022;11(92). [BMC]

57. Acharya KP, Wilson RT. Antimicrobial Resistance in Nepal. *Frontiers Medicine*. 2019; 6:105. [PMC free article] [PubMed] [Google Scholar]

58. Prasada S, Bhat A, Bhat S, Shenoy Mulki S, Tulasidas S. Changing antibiotic susceptibility pattern in uropathogenic Escherichia coli over a period of 5

years in a tertiary care center. Infection and Drug Resistance. 2019;12:1439–1443. [PubMed] [PMC free article]

59. Sadeghi M, Sedigh Ebrahim-Saraie H, Mojtahedi A. Prevalence of ESBL and AmpC genes in *E. coli* isolates from urinary tract infections in the north of Iran. New Microbes and New Infections. 2021;45:100947. [PubMed] [PMC free article]

60. Shyaula M, Khadka C, Dawadi P, Banjara MR. Systematic Review and Meta-analysis on Extended-Spectrum ß-lactamases Producing *Klebsiella pneumoniae* in Nepal. Microbiology Insights. 2023;16:11786361221145179. [PubMed] [PMC free article]

61. Acharya KP, Karki S, Shrestha K, Kaphle, K. One health approach in Nepal: Scope, opportunities and challenges' *One Health*. 2019;8:100101. [PMC free article] [PubMed] [ScienceDirect]

62. Lee YH. Strengths and limitations of meta-analysis. Korean Journal of Medicine. 2019;94: 391-395. [Google Scholar]