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Antimicrobial resistance and ESBL production in uropathogenic *Escherichia coli*: a systematic review and meta-analysis in Ethiopia

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Background: Antimicrobial resistance (AMR) is a serious threat to global health systems. *Escherichia coli* is a major cause of urinary tract infections (UTIs). Understanding the AMR patterns of uropathogenic *E. coli* (UPEC) is crucial for effective public health interventions worldwide.

Objectives: This systematic review and meta-analysis aimed to consolidate existing research and provide a comprehensive information on AMR UPEC in Ethiopia.

Methods: We systematically searched databases such as PubMed, Web of Science, and Science Direct, along with including articles from Google Scholar. Data were extracted into Microsoft Excel and analysed using STATA 17.0. Cohen's kappa was computed to assess reviewer agreement, while the I^2 statistic evaluated heterogeneity. Egger's tests were conducted to detect publication bias, and random-effects models were utilized to estimate the pooled resistance, with AMR rates for each antibiotic pooled separately.

Results: UPEC showed resistance rates, ranging from 3.64% (95% CI: −4.38% to 11.67%) for amikacin to 85.32% (95% CI: 78.6%–92.04%) for ampicillin. Highest resistance was to ampicillin (85.32%), followed by amoxicillin at 82.52% (95% CI: 74.3%–90.74%), tetracycline at 60.67% (95% CI: 51.53%–69.81%) and trimethoprim/sulfamethoxazole at 57.17% (95% CI: 49.93%–64.42%). Conversely, resistance rates were lower for amikacin at 3.64% and meropenem at 5.26% (95% CI: 2.64%–7.88%). UPEC demonstrated a pooled MDR rate of 79.17% (95% CI: 70.32%–88.01%) and a pooled ESBL production rate of 29.16% (95% CI: 22.36%–38.55%).

Conclusions: High levels of AMR were observed in UPEC strains, highlighting a critical public health issue requiring urgent action through robust antimicrobial stewardship and surveillance to preserve effective UTI treatment options.

Introduction

Since the discovery of penicillin, the first antibiotic in the 1920s, antibiotics remain among the most potent remedies for combating life-threatening infections. However, individuals worldwide face mortality from untreatable infections due to the rise and dissemination of antimicrobial resistance (AMR).[1]

AMR arises when microorganisms such as bacteria, viruses, fungi and parasites develop the capability to adapt and thrive in the presence of medications, evading the mechanisms by which drugs act to eradicate them.[2,3] Bacteria can exhibit resistance to antibiotics either intrinsically, stemming from inherent bacterial properties, or acquire resistance through mechanisms such as gene transfer or mutation of antibiotic targets.[3,4] MDR in bacteria is characterized by their lack of susceptibility to at least one agent in three or more antimicrobial agent categories.[5]

AMR poses a significant global threat to health systems, with an estimated 4.95 million deaths associated with bacterial AMR in 2019, including 1.27 million deaths directly attributable to bacterial AMR.[6] In addition to mortality and morbidity, additional costs to healthcare systems are attributable to AMR. In the USA, AMR infections have an additional cost of as high as 55 billion USD each year due to additional visits to healthcare providers and loss of productivity.[7]

Urinary tract infections (UTIs) are one of the most common infections worldwide.[8] MDR *Escherichia coli* is the leading cause of UTI. *E. coli* resists the effect of antimicrobial agents through the production of ESBL and carbapenemase enzymes that are able to hydrolyse third-generation cephalosporins and carbapenems.[8]

Antimicrobial-resistant *E. coli* are the leading bacteria responsible for the majority of disease associated with bacterial AMR.[6] Uropathogens are microorganisms, typically bacteria, which can cause UTIs.[9] In Ethiopia, the Food, Medicine and Health Care Administration and Control Authority of the country recommends trimethoprim/sulfamethoxazole, nitrofurantoin and ciprofloxacin as empirical treatment for UTI.[10]

Knowledge on AMR is crucial for comprehensively understanding AMR patterns, informing public health interventions and policy development, and contributing to the global effort to combat AMR. While some previously published papers have shown AMR of *E. coli* ranging from 0% to 100% to different antibiotics,[11–13] the findings are not conclusive due to inconsistencies. Moreover, there is a lack of systematic review and meta-analysis that provide a nationwide profile of AMR of uropathogenic *E. coli* (UPEC) in Ethiopia. Systematic review and meta-analysis, particularly in light of inconsistent findings on AMR patterns, are essential to provide a comprehensive synthesis of available data, clarify discrepancies, identify prevailing resistance trends, and offer valuable insights for guiding evidence-based interventions and policymaking efforts aimed at combating AMR effectively in the Ethiopian context. Therefore, this systematic review and meta-analysis aimed to consolidate existing research on AMR in UPEC strains in Ethiopia.

Methods

Search strategy

Systematic searches were conducted across PubMed, Web of Science, and Science Direct databases, alongside Google Scholar and online repository sites of various institutions, to retrieve published articles. Utilizing appropriate Medical Subject Headings (MeSH) terms and keywords, articles published in English between 1 January 2014 and 30 August, 2023, were sought from the specified databases: ((((((Antimicrobial resistance) OR (Antibiotic resistance)) OR (Microbial drug resistance)) AND (*Escherichia coli*)) OR (Uropathogenic *Escherichia coli*)) AND (Urinary tract infection)) AND Ethiopia. Our systematic review and meta-analysis have been registered with PROSPERO (International Prospective Register of Systematic Reviews) under registration number CRD42023462711. This registration ensures transparency and adherence to established protocols in conducting and reporting our study.

Eligibility criteria

Studies retrieved from the mentioned databases, Google scholar and repositories of different institutions were exported into Endnote X7 reference managing software (Thomson Reuters, Toronto, Ontario, Canada), duplicates were removed, and two authors (Z.A. and M. E.) screened the title and abstract of each article followed by detailed screening of the full text. To identify eligible articles, predetermined inclusion and exclusion criteria were applied. The inclusion criteria encompassed articles published in Ethiopia from 2014 up to August 2024 in English that reported AMR profiles of UPEC isolated from urine specimens of both symptomatic UTI and asymptomatic bacteriuria using appropriate phenotypical methods of susceptibility testing. For the meta-analysis of MDR UPEC, studies that reported MDR based on the definition that UPEC isolates showed non-susceptibility to at least one agent in three or more antimicrobial categories were included. Studies that didn't satisfy the above inclusion criteria were excluded from the study. Furthermore, articles that had difficulty to access the full text (after e-mailing the respective authors two times to obtain full texts) and studies that did not report the primary outcomes of interest were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was used to select articles in the review process (Figure 1).[14]

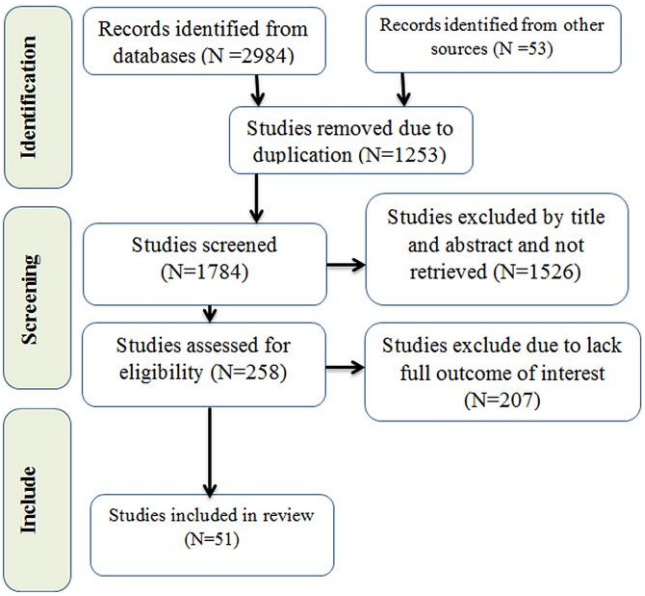

Figure 1. PRISMA flow chart for selection of studies on AMR of UPEC.

Quality assessments

The Joanna Briggs Institute tool designed for prevalence studies was used to assess the quality of each study.[15] Two impartial reviewers (Z.A. and M.E.) critically appraised each study. Discussions among the two reviewers were used to resolve disagreements on inclusion and exclusions of studies. If the two independent reviewers couldn't reach an agreement on inclusion and exclusion of studies, a third reviewer (W.A.) was involved to resolve the disagreement. Studies with a final quality score of 50% or higher were included in this systematic review and meta-analysis (Table S1, available as Supplementary data at *JAC-AMR* Online).

Data extraction

Data were extracted by two authors (Z.A. and W.A.) using a standardized format in Microsoft Excel 2016. The extraction process covered the various pieces of information, including author(s), study year, study region, study design, sample size, total number of UPEC isolated, AMR of UPEC to different antibiotics, the prevalence of MDR isolates, and the prevalence of ESBL-producing isolates detected using phenotypical or molecular methods. Cohen's kappa was computed to assess the inter-rater reliability during data extraction. The agreement between the two reviewers was 94%.

Statistical analysis

Following the data entry process into Microsoft Excel 2016, the dataset was exported to STATA 17.0 software (StataCorp, TX, USA) for comprehensive analysis. Heterogeneity across studies was evaluated using the inverse variance (I^2) test, where I^2 values of 0%, 25%–50%, 50%–75% and >75% were interpreted as representing no, low, medium and high heterogeneity, respectively. Subgroup analyses were conducted based on geographical regions and study years. Pooled prevalence estimates of resistance profiles of UPEC to various antibiotics, MDR profiles and ESBL production were derived using a random-effects model. Furthermore, Egger's tests were utilized to identify potential publication bias, employing a significance threshold of $P<0.05$. In instances where publication bias was detected, trim-and-fill analysis was executed.

Results

Search results

This systematic review and meta-analysis included 51 studies[11–13,16–63] that reported AMR to at least 1 of the 18 commonly assessed antibiotics. In total, 15 791 study participants were assessed for UTI, and from these cases, 1561 UPEC were isolated and analysed for AMR, MDR and ESBL production (Table 1). After data extraction, meta-analysis was conducted for antibiotics to which AMR was reported by more than five studies. The number of studies included in the meta-analysis varied for different antibiotics, ranging from 6 studies for tobramycin to 46 studies for ciprofloxacin and trimethoprim/sulfamethoxazole, covering a spectrum of antibiotic resistance patterns. All the studies incorporated into this systematic review and meta-analysis had a quality assessment score exceeding 77.8% (Table S1).

AMR profiles of UPEC

This comprehensive systematic review and meta-analysis investigated the AMR pattern of UPEC to 18 different antibiotics. From this review the pooled prevalence of UPEC-associated UTI was 9.2%. The pooled prevalence of AMR in UPEC for the assessed 18 antibiotics varied from 3.64% (95% CI: −4.38% to 11.67%) for amikacin to 82.52% (95% CI: 78.6%–92.04%) for ampicillin (Table 2); forest plots of pooled AMR of UPEC to each antibiotic are depicted in Figures S1–S18.

UPEC exhibited elevated pooled resistance rates to penicillin antibiotics, varying from 52.45% (95% CI: 43.17%–61.19%) to 82.52% (95% CI: 74.3%–90.74%), nalidixic acid at 41.64% (95% CI: 30.73%–52.55%) and trimethoprim/sulfamethoxazole at 57.17% (95% CI: 49.93%–64.42%). Conversely, resistance levels were notably lower for amikacin (3.64%), meropenem at 5.26% (95% CI: 2.64%–7.88%) and nitrofurantoin at 25.1% (95% CI: 20.18%–30.01%). UPEC isolates showed a pooled resistance of 27.93% (95% CI: 15.46%–40.39%) for the second-generation cephalosporin cefoxitin, and a closely related resistance for three different antibiotics under the category of third-generation cephalosporins (ceftazidime, cefotaxime and ceftriaxone) ranging from 33.18% to 35.6% (Table 2).

The Egger's test revealed evidence of publication bias in the studies utilized to compute the combined resistance rates of several antibiotics, including amikacin, gentamicin, meropenem, cefoxitin, nitrofurantoin, trimethoprim/sulfamethoxazole and ampicillin. Subsequently, a trim-and-fill analysis was conducted to address this bias. The outcomes of the trim-and-fill analysis prompted adjustments in the pooled resistance rates, with the exception of gentamicin and cefoxitin, which remained unaffected. Following the trim-and-fill analysis, adjustments were made to the pooled resistance rates of UPEC to amikacin, meropenem, nitrofurantoin, trimethoprim/sulfamethoxazole and ampicillin (Table 2), after imputation of different numbers of studies for each antibiotics. (Tables S2–S8); funnel plots before and after trim-and-fill analysis are depicted in Figures S19–S28.

The studies used to estimate the pooled resistance for each antibiotic exhibited high heterogeneity, surpassing 68.8%. Consequently, subgroup analyses were performed based on the year of the study and the regions where the studies were conducted to pinpoint the source of this heterogeneity. Subgroup analysis based on regions revealed a noteworthy contrast across various regions of the country. Specifically, cefoxitin, cefotaxime, nalidixic acid and chloramphenicol displayed significantly heightened resistance in Southern Nations, Nationalities and Peoples' Region (SNNPR), whereas amikacin exhibited elevated resistance in the Amhara region. Additionally, subgroup analysis based on the year demonstrated significant differences in resistance to amoxicillin and tobramycin over time, with resistance to amoxicillin displaying an escalating trend across the years (Table S10).

MDR profile of UPEC

This systematic review and analysis encompassed 34 studies reporting MDR profiles of 1022 UPEC isolates. The pooled MDR profile of UPEC was calculated to be 66.28% (95% CI: 58.57%–73.99%) (Figure 2). Egger's test revealed significant publication bias (P value <0.001), prompting the implementation of trim-and-fill analysis. This analysis yielded a pooled resistance rate of 79.17% (95% CI: 70.32%–88.01%) after the imputation of 12 studies to correct the bias (Table S9); funnel plots before and after trim-and-fill analysis are depicted in Figures S29 and S30.

The inverse of variance (I^2) statistics indicated a high level of heterogeneity at 96.13% (P value <0.001) among the included studies. Subsequently, subgroup analysis was conducted based on the study year and the regions where the studies were conducted. Subgroup analysis by region revealed a notable variation, with relatively higher MDR rates exceeding 70% observed in Addis Ababa, Tigray and the SNNPR (Figure 3). However, subgroup analysis by year did not show significant variation.

ESBL production profile of UPEC

We included 11 studies that examined ESBL production among 342 cases of UPEC. The overall pooled ESBL production rate among UPEC was found to be 29.16% (95% CI: 22.36%–38.55%) (Figure 4). Heterogeneity assessment revealed significant heterogeneity across the studies with an I^2 value of 66.32% and a significant P value of <0.001. Notably, Egger's test revealed no evidence of publication bias among the included studies. To address the observed heterogeneity, we conducted subgroup analyses based on the year of study and the region where the studies were conducted.

Upon subgroup analysis, we observed notable variations, particularly in ESBL production rates over time and across different regions. Specifically, we found that the ESBL production rate of UPEC tended to increase over the years, indicating a concerning trend of rising ESBL prevalence. Furthermore, our analysis revealed that ESBL production rates were higher in the Tigray and southern regions of Ethiopia compared with other areas (Figures S31 and S32).

Discussion

While antibiotics are crucial for combating infectious diseases, the global threat of microorganisms' ability to undermine their effectiveness is significant. This systematic review and meta-analysis revealed pooled antibiotic resistance rates among

Table 1. Studies included in the systematic review and meta-analysis of AMR of UPEC in Ethiopia

ID	Author	Year	Region	Study participants	Sample size	Number of UPEC isolates	Reports	References
1	Abate *et al.*	2020	Harari	All age women	651	42	AMR	16
2	Abu *et al.*	2021	Benshangul	Pregnant women	283	21	AMR	17
3	Adugna *et al.*	2021	Amhara	All age and sex	422	44	AMR	18
4	Agegnehu *et al.*	2020	SNNPR	Paediatrics	284	32	AMR, MDR, ESBL	19
5	Alemu *et al.*	2020	Amhara	Diabetic patients	336	12	AMR, MDR	20
6	Ayelign *et al.*	2018	Amhara	Paediatrics	310	45	AMR	21
7	Belete Y *et al.*	2019	Amhara	Paediatrics	259	14	AMR, MDR	22
8	Belete MA *et al.*	2020	Amhara	Pregnant women	223	17	AMR, ESBL	23
9	Biset *et al.*	2020	Amhara	Pregnant women	384	30	AMR, MDR, ESBL	24
10	Bitew *et al.* (2017)	2017	Addis Ababa	All age and sex	712	135	AMR	25
11	Bitew *et al.* (2022)	2022	Addis Ababa	Paediatrics	227	21	AMR	12
12	Bizuayehu *et al.*	2022	Addis Ababa	Adults in ICU	220	8	AMR, MDR	11
13	Bizuwork *et al.*	2021	Addis Ababa	Pregnant women	281	17	AMR, MDR	26
14	Dadi *et al.*	2018	Addis Ababa	All age and sex	780	200	AMR, MDR	27
15	Derbie *et al.*	2017	Amhara	All age and sex	446	72	AMR	28
16	Diriba *et al.*	2019	SNNPR	Diabetic and hypertensive patients	158	9	AMR, MDR	29
17	Derese *et al.*	2023	Dire Dawa	Pregnant	186	7	AMR, MDR	30
18	Duffa *et al.*	2018	Addis Ababa	Paediatrics	384	25	AMR, MDR	31
19	Ejerssa *et al.*	2021	Harari	Pregnant women	200	14	AMR, MDR	32
20	Eshetie et al	2015	Amhara	All age and sex	442	104	AMR, MDR	33
21	Fenta *et al.*	2020	Amhara	Paediatrics	299	28	AMR, MDR, ESBL	34
22	Gebremariam *et al.*	2019	Tigray	All age and sex	341	36	AMR, MDR, ESBL	35
23	Gebremedhin *et al.*	2023	Tigray	All age and sex	64	46	AMR, MDR, ESBL	36
24	Gessese *et al.*	2017	Oromia	Pregnant women	300	26	AMR	38
25	Gutema *et al.*	2018	Oromia	Diabetic patients	233	10	AMR	37
26	Hantalo *et al.*	2020	SNNPR	HIV patients	217	13	AMR, MDR	39
27	Kasew *et al.*	2021	Amhara	Patients with kidney stones	300	14	AMR, MDR, ESBL	40
28	Kiros *et al.*	2023	Amhara	Paediatrics	220	19	AMR, MDR	41
29	Mama *et al.*	2019	SNNPR	Diabetic patients	239	43	AMR	42
30	Mamuye *et al.*	2016	Addis Ababa	All age and sex	424	53	AMR, MDR	43
31	Marami *et al.* (2019)	2019	Harari	HIV patients	350	24	AMR	44
32	Marami *et al.* (2022)	2022	Harari	Women with fistulae	146	8	AMR	45
33	Mechal *et al.*	2021	Sidama	Adults	387	46	AMR, MDR	46
34	Mekonnen *et al.*	2023	Harari	Paediatrics	332	23	AMR, MDR	47
35	Mitku *et al.*	2022	SNNPR	All age and sex	422	42	AMR, MDR	48
36	Nigussie *et al.*	2017	SNNPR	Diabetic patients	240	11	AMR, MDR	49
37	Oumer Y *et al.*	2022	SNNPR	Diabetic patients	282	19	AMR, MDR	50
38	Oumer O *et al.*	2021	Amhara	All age and sex	231	17	AMR, MDR	51
39	Seid *et al.*	2023	SNNPR	Sexually active women	296	22	AMR, MDR, ESBL	52
40	Sime *et al.*	2020	Addis Ababa	Cancer patients	292	8	AMR, MDR	53
41	Simeneh *et al.*	2022	SNNPR	HIV patients	251	16	AMR, MDR, ESBL	54

Continued

Table 1. *Continued*

ID	Author	Year	Region	Study participants	Sample size	Number of UPEC isolates	Reports	References
42	Tadesse E *et al.*	2014	SNNPR	Pregnant women	244	16	AMR	55
43	Tadesse S *et al.*	2018	Tigray	Pregnant women	259	19	AMR	56
44	Teferi *et al.*	2023	Oromia	All age women	386	38	AMR, MDR, ESBL	57
45	Tigabu *et al.*	2020	Amhara	Cancer patients	240	9	AMR, MDR	58
46	Tula *et al.*	2020	SNNPR	Pregnant women	296	11	AMR	59
47	Wabe *et al.*	2020	Addis Ababa	Pregnant women	290	22	AMR, MDR	60
48	Woldemariam *et al.*	2019	Addis Ababa	Diabetic patients	248	13	AMR	61
49	Worku YG *et al.*	2021	Addis Ababa	Diabetic patients	225	14	AMR, MDR	62
50	Worku S *et al.*	2022	Amhara	Diabetic patients	250	5	AMR	13
51	Zerefaw *et al.*	2022	Amhara	Paediatrics	299	21	AMR, MDR	63

SNNPR, Southern Nation Nationality and People Region; AMR, Antimicrobial resistance; MDR, Multi-drug Resistance; ESBL, Extended-spectrum Beta-lactamase; HIV, Human Immunodeficiency Virus.

Table 2. Antibiotic resistance profile of UPEC in Ethiopia from 2014 to 2023

Antibiotic category	Antibiotics	No. of studies pooled	Pooled resistance (%)	95% CI	Pooled prevalence after trim-and-fill analysis (95% CI), no. of studies imputed during trim-and-fill analysis	Heterogeneity I^2 (%), *P* value	Eggers test *P* value
Aminoglycosides	Amikacin	11	10.10	4.50–15.69	3.64 (−4.38 to 11.67), 6	68.82, <0.01	<0.01
	Gentamicin	44	32.60	25.94–39.27	No effect after trim-and-fill	91.24, <0.01	<0.01
	Tobramycin	6	28.57	14.78–42.36		100, <0.01	0.75
Carbapenems	Meropenem	12	6.80	4.11–9.48	5.26 (2.64–7.88), 4	0.00, <0.01	0.03
Cephalosporins	Cefotaxime	15	35.31	25.99–44.63		83.54, <0.01	0.96
	Cefoxitin	13	27.93	15.46–40.39	No effect after Trim-and-fill	92.51, <0.01	0.01
	Ceftazidime	28	33.18	24.18–42.19		91.95, <0.01	0.25
	Ceftriaxone	31	35.60	26.85–44.35		91.95, <0.01	0.63
Nitrofurans	Nitrofurantoin	31	20.45	15.66–25.25	25.10 (20.18–30.01), 7	79.02, <0.01	<0.01
Penicillins	Amoxicillin	9	82.52	74.30–90.74		75.02, <0.01	0.14
	AMC	35	52.45	43.71–61.19		92.70, <0.01	0.62
	Ampicillin	30	77.67	72.2–83.14	85.32 (78.60–92.04), 10	87.88, <0.01	<0.01
Phenicols	Chloramphenicol	14	30.08	18.74–41.42		91.21, <0.01	0.60
Quinolones	Ciprofloxacin	46	32.64	25.96–39.33		93.16, <0.01	0.16
	NA	15	41.64	30.73–52.55		89.24, <0.01	0.32
	Norfloxacin	24	28.14	19.93–36.34		88.27, <0.01	0.22
Sulphonamides	SXT	46	58.83	51.65–66.01	57.17 (49.93–64.42), 2	100, <0.01	0.04
Tetracyclines	Tetracycline	29	60.67	51.53–69.81		92.97, <0.01	0.25

AMC, amoxicillin/clavulanic acid; NA, nalidixic acid; SXT, trimethoprim/sulfamethoxazole.

UPEC to 18 different antibiotics, ranging from 3.64% for amikacin to 85.32% for ampicillin. This comprehensive meta-analysis revealed the presence of carbapenem-resistant UPEC and an increased resistance of UPEC to the recommended empirical antimicrobial agents for UTI in Ethiopia.[10]

In this systematic review and meta-analysis, UPEC exhibited varying resistance levels to β-lactam antibiotics. Specifically, resistance rates were 5.26% for meropenem, 27.93%–35.6% for cephalosporins, and 52.45%–85.32% for penicillins. Notably, our findings regarding resistance to cefotaxime, ceftazidime and ceftriaxone (35.31%, 33.18%, and 35.6%, respectively) were consistent with similar studies in Malawi and Iran. In Malawi, resistance rates were reported as 35.9%, 42.1% and 29.3% for these antibiotics, while in Iran, they were found to be 40%, 42% and 35%

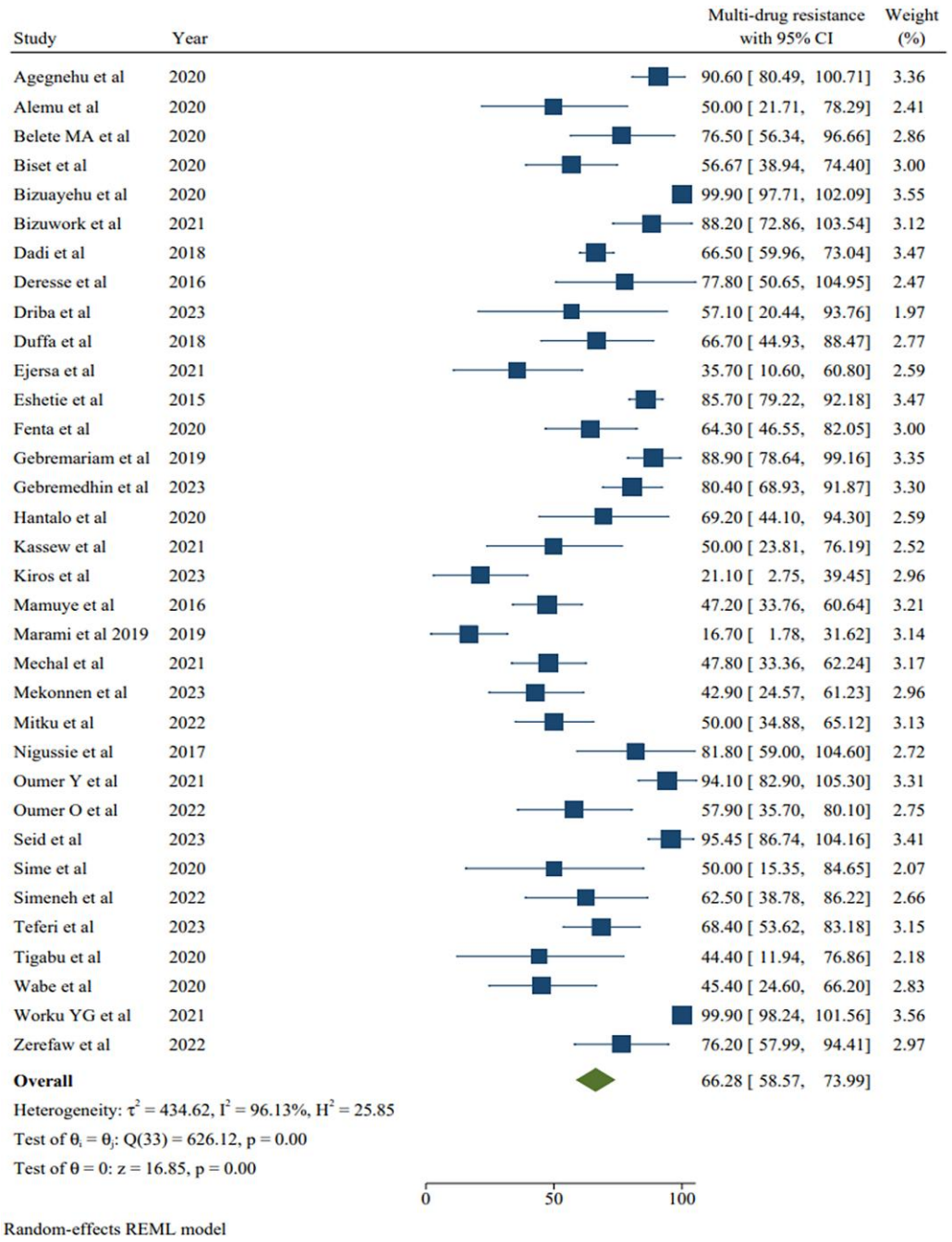

Figure 2. Forest plot for the pooled MDR profile of UPEC in Ethiopia from 2014 to 2023.

respectively.[64,65] In this study, the resistance of UPEC to ampicillin was found to be 85.32%, consistent with previous reports. Specifically, studies from Malawi reported a resistance of 75%, while those from Iran and West Africa reported resistance rates of 86%, 74.6% and 75% respectively.[64–67] Furthermore, in this study, resistance to amoxicillin and amoxicillin/clavulanic acid was observed at rates of 82.52% and 52.45%, respectively. These findings align with reported resistance rates from Malawi, which were 72.7% for amoxicillin and 40.8% for amoxicillin/clavulanic acid.[65]

In this systematic review, UPEC resistance to the last-resort antibiotic meropenem was 5.26%, which is higher than resistance reported from Malawi (0.3%).[65] The presence of meropenem-resistant UPEC in this systematic review and meta-analysis emphasizes the urgent necessity for enhanced antimicrobial stewardship, robust infection control measures, and improved access to alternative treatments. This trend underscores the potential for a future burden of infectious diseases that may become untreatable, highlighting the critical importance of proactive intervention strategies.

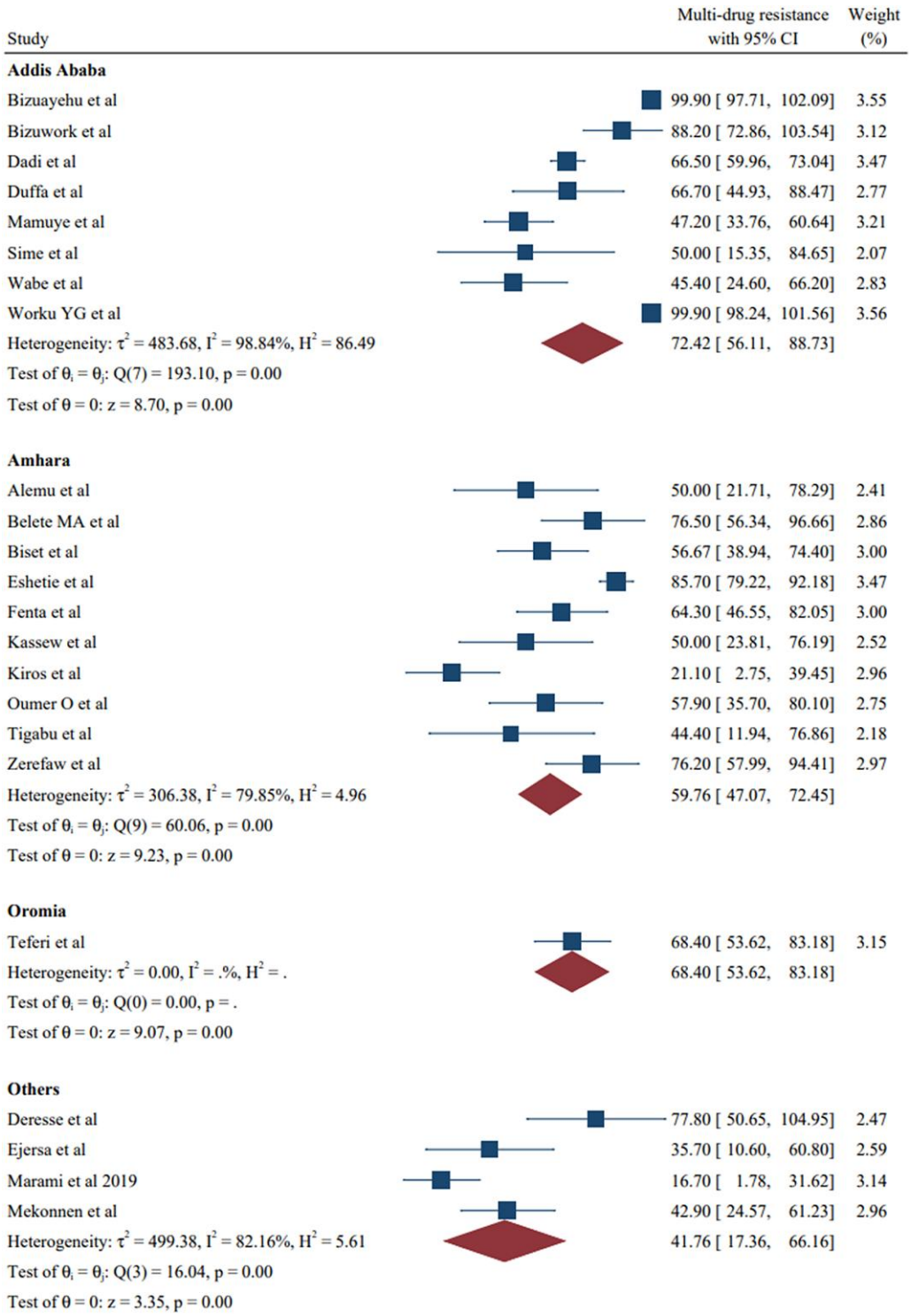

Figure 3. Subgroup analysis of MDR in UPEC by region.

The pooled resistance of UPEC to different cephalosporin group antibiotics indicated that cefoxitin resistance was 27.93%, which is higher compared with reports from Malawi, which indicated resistance rate of 14.7%.[65] Furthermore, the resistance to ceftriaxone observed in this study was higher compared with the resistance reported from the Philippines (1.1%) and Korea (3%).[68,69] However, the resistance to ceftazidime in this review was lower than the reported resistance from Iran (51.4% and 83.6%). Similarly, the resistance to cefotaxime was lower than the reported resistance from Iran

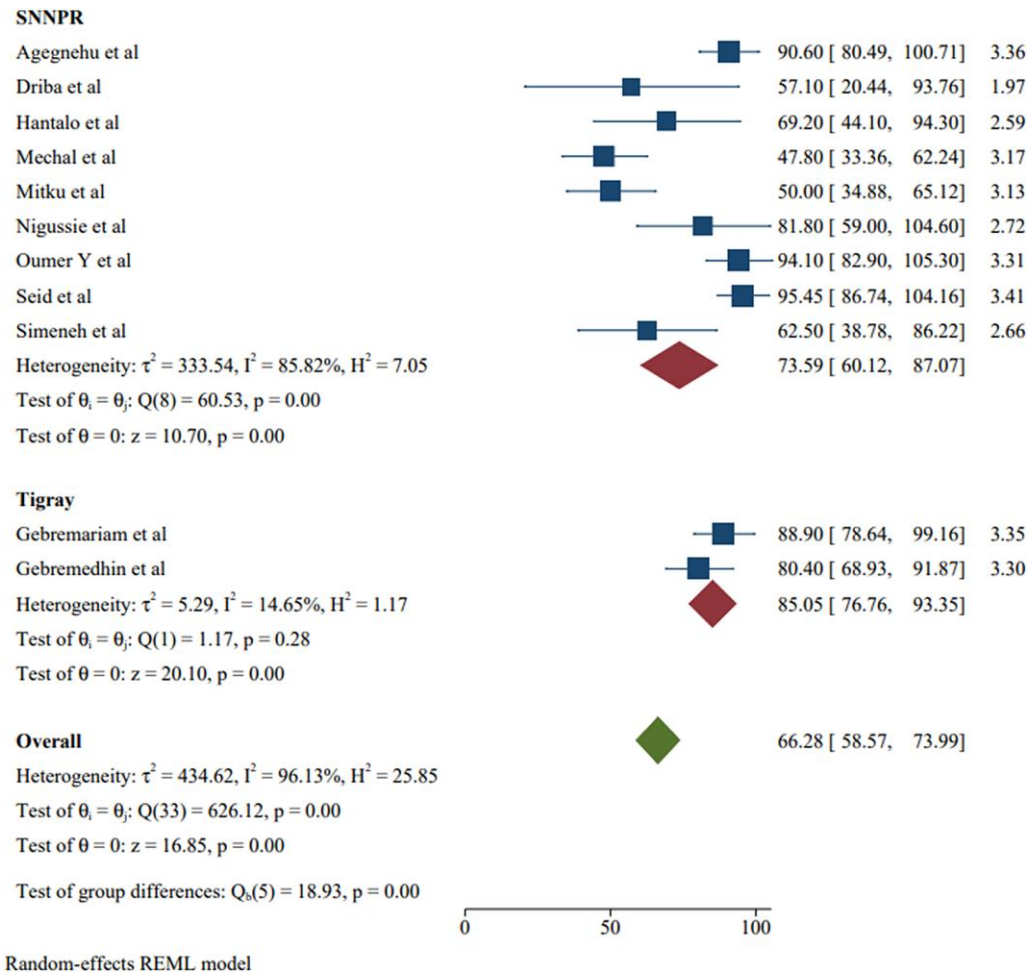

Figure 3. Continued

(62.9%).[66,70] The proportion of ESBL production among UPEC in this study was 29.16%, consistent with rates reported in studies from Romania (32.8%),[71] Palestine (33.3%)[72] and Iran (34.6%).[73] The proportion of ESBL production is higher than in a study in Uganda (16.7%),[74] but lower than in studies in Jordan (62%),[75] Nepal (50.9%)[76] and Mexico (49%).[77] Variations in ESBL production rates among UPEC may stem from differences in ESBL detection methods, study populations, settings, healthcare practices and antibiotic usage.[78,79] Subgroup analysis by year and region underscores the dynamic nature of ESBL prevalence, stressing the need for region-specific surveillance and interventions to effectively tackle this public health concern.

The pooled resistance of UPEC to aminoglycosides in this review varied, showing low resistance to amikacin (3.64%), and moderate resistance to tobramycin (28.57%) and gentamicin (32.6%). Notably, the resistance of UPEC to amikacin observed in this study was lower than that reported in Malawi (19.9%) and Iran (17%–38.4%).[64–66,70] Resistance to gentamicin and tobramycin observed in this study aligned closely with reports from Malawi, showing resistance rates of 33.7% for gentamicin and 28.0% for tobramycin.[65] However, the observed gentamicin resistance was higher than that reported in the USA[80] and the Philippines (6.7%).[68] Similarly, resistance to tobramycin was higher compared with reports from Iran (10.8%).[66]

The Food, Medicine and Health Care Administration and Control Authority of Ethiopia recommends trimethoprim/sulfamethoxazole, nitrofurantoin and ciprofloxacin as empirical treatment for UTI,[10] even though the findings from this systematic review and meta-analysis revealed increased AMR in UPEC to these antibiotics. The pooled resistance of UPEC nitrofurantoin (25.1%) and trimethoprim/sulfamethoxazole (57.17%) observed in this study corresponds closely with findings from a systematic review in Malawi, indicating resistance of 20% for nitrofurantoin and 59.3% for trimethoprim/sulfamethoxazole.[65] The resistance of UPEC in this study to chloramphenicol (28.41%), ciprofloxacin (31.09%), nalidixic acid (39.54%), norfloxacin (27.51%) and tetracycline (60.67%) is comparatively lower than that reported in a systematic review and meta-analysis conducted in Cameroon.[81] The variation in UPEC resistance profiles to various antibiotics across countries could stem from differences in study settings and bacterial exposure to antibiotics. Additionally, variations may be attributed to differences in infection prevention and control practices, and hospital overcrowding, as well as disparities in lifestyles, income levels, educational attainment and health knowledge among study participants.

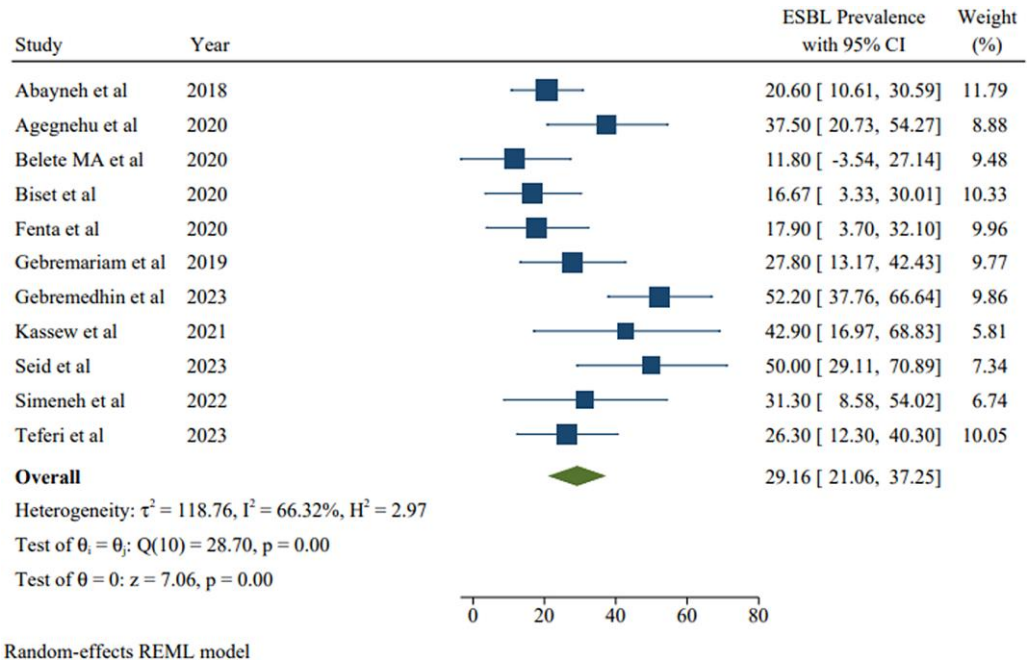

Figure 4. Pooled prevalence of ESBL-producing UPEC in Ethiopia from 2014 to 2023.

The pooled proportion of MDR among UPEC in this study was 79.17%, consistent with findings from a review conducted in Iran (81.1%).[82] However, this rate was higher compared with another report from Iran (49.4%)[83] and Nepal (34.2%). The proportion of ESBL production among UPEC in this study was 29.16%, consistent with rates reported in studies from Romania (32.8%),[71] Palestine (33.3%)[72] and Iran (34.6%).[73] The proportion of ESBL production is higher than a study in Uganda (16.7%),[74] whereas lower than studies in Jordan (62%),[75] Nepal (50.9%)[76] and Mexico (49%).[77] Variations in MDR rates among UPEC may stem from differences in study populations, settings, healthcare practices and antibiotic usage.[78,79]

Several interconnected factors might be responsible for the increased AMR in developing countries included in our systematic review and meta-analysis. These factors include the overuse and misuse of antibiotics due to inadequate regulation and oversight, limited access to healthcare facilities and diagnostics, poor infection control practices in healthcare settings, lack of robust surveillance systems to monitor resistance patterns, environmental contamination from antibiotic disposal, socioeconomic factors such as poverty and poor sanitation, and the prevalence of substandard or counterfeit antibiotics.[84,85]

For the future, research could focus on developing novel antimicrobial agents, exploring the molecular epidemiology of AMR genes in UPEC, assessing the predisposing factors, and evaluating interventions to reduce AMR. In Ethiopia, there is a pressing need for the establishment of a comprehensive surveillance system on AMR to identify the most effective antimicrobial agents for use as empirical therapy against various infections in the future.

Strength and limitations

This systematic review and meta-analysis has strengths such as employing a predefined protocol for the overall process of the systematic review and meta-analysis, and using internationally recognized tools for critical appraisal of the quality of each study However, limitations were observed due to inability to synthesize data regarding the molecular epidemiology of the bacterial strains and resistance genes due to the lack of existing literature.

Conclusions

This systematic review and meta-analysis reveal a significant increase in AMR, MDR and ESBL production among UPEC strains in Ethiopia. These findings underscore a pressing public health challenge, necessitating urgent action to implement comprehensive strategies for antimicrobial stewardship, infection control and the exploration of alternative treatment options for UTI caused by UPEC in Ethiopia.

Based on the data from this systematic review and meta-analysis, the following recommendations are proposed: strengthen antimicrobial stewardship, enhance infection prevention and control measures; surveillance of AMR, and public awareness and education are required to decrease AMR.

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Transparency declarations

The authors declare that they have no conflict of interests.

Author contributions

Z.A. led the systematic review and meta-analysis, overseeing the study's conceptualization, article selection, data extraction, statistical analysis and manuscript preparation. Z.A. and W.A. played a pivotal role in

searching for relevant articles, conducting data extraction, performing statistical analysis, and contributing to manuscript drafting. M.E. and E.T. provided valuable support in data extraction and statistical analysis to ensure accuracy and completeness. Additionally, all authors actively engaged in critically reviewing the study's progress, data analysis and manuscript preparation, culminating in the collective approval of the final manuscript for submission, thereby affirming their endorsement of its content and findings.

Supplementary data

Figures S1 to S32 and Tables S1 to S10 are available as Supplementary data at *JAC-AMR* Online.

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