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SYSTEMATIC REVIEW

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Prevalence of colistin-resistant *Enterobacteriaceae* isolated from clinical samples in Africa: a systematic review and meta-analysis

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Abstract

Background Antimicrobial resistance among *Enterobacteriaceae* poses a significant global threat, particularly in developing countries. Colistin, a critical last-resort treatment for infections caused by carbapenem-resistant and multidrug-resistant strains, is increasingly facing resistance due to inappropriate use of colistin and the spread of plasmid-mediated resistance genes. Despite the significance of this issue, comprehensive and updated data on colistin resistance in Africa is lacking. Thus, the current study was aimed to determine the pooled prevalence of colistin-resistant *Enterobacteriaceae* in Africa.

Methods A systematic search was conducted across PubMed, Scopus, ScienceDirect, and Google Scholar to identify relevant studies. Forty-one studies reporting on the prevalence of colistin resistance in *Enterobacteriaceae* isolates from clinical specimens in Africa were included in the analysis. Stata 17 software was used to calculate the pooled prevalence of colistin resistance, employing a random-effects model to determine the event rate of resistance. Heterogeneity across studies was assessed using the I^2 statistic, and publication bias was evaluated using Egger's test. Subgroup analyses were performed to address any identified heterogeneity.

Results This systematic review analyzed the colistin resistance profile of 9,636 *Enterobacteriaceae* isolates. The overall pooled prevalence of colistin resistance was 26.74% (95% CI: 16.68–36.80). Subgroup analysis by country revealed significant variability in resistance rates, ranging from 0.5% in Djibouti to 50.95% in South Africa. Species-specific prevalence of colistin resistance was as follows: *K. pneumoniae* 28.8% (95% CI: 16.64%-41.05%), *E. coli* 24.5% (95% CI: 11.68%-37.3%), *Proteus spp.* 50.0% (95% CI: 6.0%-106.03%), and *Enterobacter spp.* 1.22% (95% CI: -0.5%-3.03%).

Analysis based on AST methods revealed significant differences in colistin resistance rates ($p = 0.001$). The resistance rates varied between 12.60% for the disk diffusion method and 28.0% for the broth microdilution method. Additionally, a subgroup analysis of clinical specimens showed significant variation ($p < 0.001$) in colistin resistance. Stool

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specimen isolates had the highest resistance rate at 42.0%, while blood specimen isolates had a much lower resistance rate of 3.58%.

Conclusions Colistin resistance in *Enterobacteriaceae* is notably high in Africa, with significant variation across countries. This underscores the urgent need for effective antimicrobial stewardship, improved surveillance, and the development of new antibiotics.

Keywords Colistin resistance, *Enterobacteriaceae*, Clinical sample, Prevalence, Meta-analysis, Africa

Introduction

Antimicrobial resistance (AMR) is a growing global public health threat, particularly among Gram-negative bacteria (GNB), which contribute significantly to disease burden and mortality. In 2019, AMR directly caused an estimated 1.27 million deaths, and an additional 5 million deaths were associated to it [1]. A major concern is the rise of drug-resistant infections, especially those caused by antibiotic-resistant bacteria acquired in hospitals, which are becoming more common in developing countries [2–4].

The *Enterobacteriaceae* family includes important pathogens such as *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Proteus spp.*, and *Enterobacter spp*. These bacteria are responsible for nearly 60% of hospital-acquired infections and also cause severe community-acquired infections [5]. The *Enterobacteriaceae* causes a range of infections, including urinary tract infections, bloodstream infections, and gastrointestinal illnesses [6]. A big issue with *Enterobacteriaceae* is the rising of antimicrobial resistance [7]. Many of these bacterial strains are resistant to several antibiotics, including the latest ones like β-lactams and carbapenems. This makes treatment more challenging, especially in resource limiting countries [8, 9].

To fight multidrug-resistant (MDR) strains, healthcare systems have increasingly turned to last-line antibiotics like colistin, which is used to treat severe infections caused by MDR Gram-negative bacteria (GNB) [10]. Colistin is a polycationic antibiotic with broad-spectrum bactericidal activity. It targets the lipopolysaccharides in the cell walls of GNB, disrupting their outer membrane and causing the bacteria to break apart and die [11]. Colistin was initially restricted to veterinary medicine due to its nephrotoxicity and neurotoxicity [12]. However, the rise of MDR and carbapenem-resistant *Enterobacteriaceae* has led to its renewed use in humans [13]. Unfortunately, the increasing resistance to this critical antibiotic is becoming a global challenge, as it is becoming less effective in treating resistant infections, making patient care even more difficult [14].

The increasing prevalence of colistin-resistant infections is primarily driven by alterations in the bacterial cell wall [15] and the dissemination of plasmid-mediated colistin resistance genes (mcr genes), including mcr-1 through mcr-10 [16]. A single global review report indicated that colistin resistance among *E. coli* isolates in Africa was 2.3% [17]. Knowing and monitoring colistin-resistant *Enterobacteriaceae* isolates is essential for developing effective treatment and intervention strategies to prevent their spread in various environments, including hospitals and community settings. However, there is a significant lack of comprehensive data on colistin resistance in clinical isolates of *Enterobacteriaceae* in Africa. This gap in knowledge makes it difficult to fully understand the extent of colistin resistance across the continent. As a result, efforts to combat the spread of resistant bacteria are hindered, potentially worsening the challenges that healthcare systems already face. To address this issue, there is an urgent need for detailed surveillance and research initiatives to guide evidence-based strategies for controlling colistin-resistance in Africa. Hence, we conducted this systematic review and meta-analysis study to highlight the pooled prevalence of colistin resistance among clinical isolates of *Enterobacteriaceae* in Africa.

Methods

Protocol

This systematic review and meta-analysis adhere strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] (Fig. 1).

Literature search

A systematic literature search was conducted from November 15, 2023, to January 15, 2024, to identify articles reporting colistin resistance from 2010 until December 2023. The search utilized four well-known biomedical repositories: PubMed, Scopus, Science Direct, and the Google Scholar search engine. Medical Subject Headings (MeSH) and other relevant keywords were combined using Boolean operators "AND" and "OR," such as ["prevalence" OR "epidemiology," "colistin" OR "polymyxin," OR "colistin-resistant" OR "Enterobacteriaceae" OR "Gram-negative" AND Africa]. Each African country was also paired with search keywords to retrieve relevant articles. The complete search strategy and search strings used in

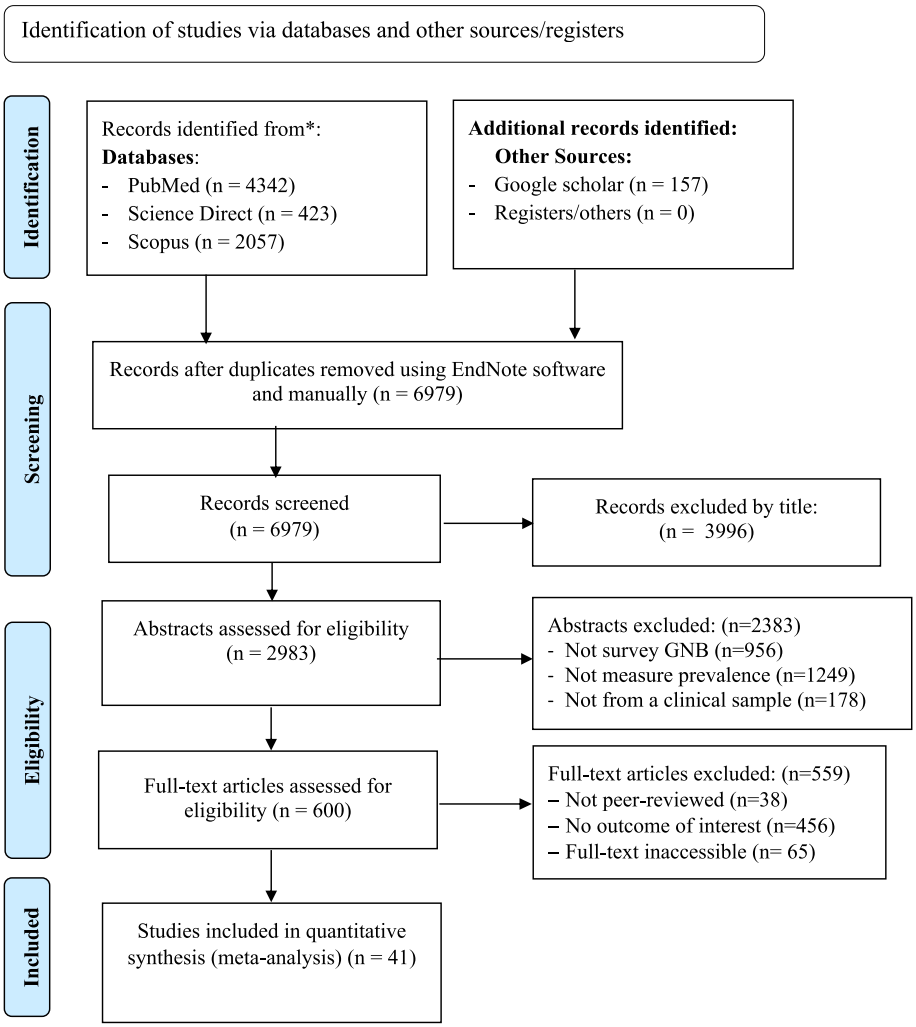

Fig. 1 PRISMA flow diagram showed the results of the search and reasons for exclusion

the databases are detailed in the supplementary file (Supplementary file, Table S1).

Eligible criteria

To identify eligible articles, we applied predetermined inclusion and exclusion criteria. Inclusion criteria were: (a) articles published in English; (b) original research in peer-reviewed journals; (c) studies reporting the prevalence of colistin resistance in Enterobacteriaceae isolates; (d) research conducted on clinical samples; (e) studies conducted in Africa and (f) studies published between January 1, 2010, and December 31, 2023,(g) Researches done by broth microdilution, VITEK2, disk diffusion methods were included. Exclusion criteria included: (a) studies not reporting or lacking clear prevalence data on colistin resistance in clinical Enterobacteriaceae isolates; (b) unrelated studies; (c) studies in languages other than English; (d) publications outside the specified time frame; (e) studies with non-human or unclear specimen origins; and (f) letters, editorials, conference papers, and systematic reviews or meta-analyses. Currently, available tests for colistin resistance are molecular or phenotypic. As recommended jointly by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Test (EUCAST), broth microdilution (BMD) method is now the only gold standard for determining colistin minimum inhibition concentration (MIC) values [19].

Study selection

Two reviewers (Y.G. and M.A.R.) independently conducted the literature search, and the retrieved articles were imported into EndNote version 20 (Thomson Reuters, New York) for reference management, where

duplicates were removed. A total of 6,979 non-duplicate, potentially relevant studies were identified from the databases and Google Scholar. Four reviewers (Y.G., M.A.R., Z.A., and A.S.) independently screened the titles, abstracts, and full-text assessment.

Quality assessments

The included studies were assessed for quality using the Joanna Briggs Institute's (JBI) critical appraisal tool for prevalence data [20]. Two independent reviewers (Y.G. and M.A.R.) critically appraised each study. All the included studies in the analysis had a score of 50% or higher on the checklist, indicating high quality (Supplementary file, Table S2).

Data extraction

Three reviewers (Y.G., Z.A., and A.S.) independently extracted relevant data from the included articles using a standardized data extraction form in Microsoft Excel 2013. Extracted data included: country, first author's surname, year of publication, Type of Antimicrobial susceptibility test (AST) methods (BMD, Disk diffusion and VITEK2), and sample size, types of clinical samples (e.g., urine, blood, sputum, endotracheal aspirate, and swabs), bacterial species isolated, MDR isolates, and colistin susceptibility profiles. Any disagreements during data extraction were resolved through discussion and consensus. If consensus could not be reached, other investigators (M.A.R. and S.T.) were consulted.

Data analysis

The data extracted using Microsoft Excel 2013 were exported to STATA 17.0 software (StataCorp, Texas, USA) for analysis of the pooled prevalence of colistin resistance among clinical isolates. Random effect model was used to compute the pooled prevalence and the inverse variance (I^2) test was performed to assess heterogeneity across studies, with I^2 values interpreted as follows: 0% (no heterogeneity), 0–25% (low heterogeneity), 25–50% (medium heterogeneity), and > 75% (high heterogeneity) [21]. To calculate the pooled prevalence of colistin resistance, a continuity correction was made for zero and one hundred percent colistin resistance values reported from certain studies, to circumvent the zero standard error during the pooled meta-analysis [22]. Subgroup analysis was performed for specific categories such as year, country, AST methods used, species and specimen type to explore sources of heterogeneity among the studies. Egger's test was used to detect potential publication bias, with a significance value, $p < 0.05$ at 95% CI. Additionally, a trim-and-fill analysis was conducted to adjust for any potential bias.

Results

Searching results

A total of 6,979 non-duplicate, potentially relevant studies were identified and retrieved from the databases. After screening the titles and abstracts, 6,379 articles were considered irrelevant and excluded, and the remaining 600 full-text articles were assessed for eligibility; only 41 articles met the inclusion criteria and were included in the final meta-analysis (Fig. 1).

A descriptive summary of studies included

This systematic review included 41 studies [3, 23–62] from 19 countries reporting the colistin resistance profile of *Enterobacteriaceae.* Specifically, 30 studies focused on *K. pneumoniae*, 26 on *E. coli*, 10 on Enterobacter species, and 4 on Proteus species. The majority of studies were from Egypt ($n = 12$), Nigeria ($n = 5$), Tunisia ($n = 4$), South Africa ($n = 4$), and Algeria ($n = 2$). The remaining studies came from Morocco, Rwanda, Democratic Republic of the Congo, Djibouti, Ethiopia, Sudan, Kenya, Mali, Senegal, Somalia, Libya, Ghana, Burkina Faso, and Mozambique (each $n = 1$) (Table 1). All studies included in this final quantitative review employed a cross-sectional study design and most of the articles used BMD AST method.

The review included 41 studies, covering a total of 9,636 *Enterobacteriaceae* isolates. Among these, 1,624 were MDR and 581 were resistant to colistin, collected from various clinical specimens. There were approximately 7,420 non-MDR isolates, with 282 being colistin-resistant. Additionally, 1,192 MDR isolates were identified, of which 229 were colistin-resistant. In the current study, a total of 5,021 K. *pneumoniae* isolates were identified, of which 915 were MDR and 350 were resistant to colistin. Additionally, 4,442 *E. coli* isolates were reported, with 685 being MDR and 215 resistant to colistin. Among the MDR isolates, *K. pneumoniae* was the most prevalent (915 isolates), with 160 of these showing both MDR and colistin resistance. *E. coli* was also the second most common MDR isolate (685 isolates), with 78 of them showing both MDR and colistin resistance **(**Table 1**).**

Meta-analysis

Prevalence of colistin-resistant Enterobacteriaceae

The initial pooled prevalence of colistin-resistant Enterobacteriaceae (*K. pneumoniae*, *E. coli*, *Enterobacter*, and *Proteus spp*.) was estimated at 26.74% (95% CI: 16.68–36.80) based on the included studies. However, significant heterogeneity was observed ($I^2 = 99.95\%$, $P < 0.001$) (Fig. 2). Additionally, the funnel plot (Supplementary file, Figure S1) and Egger's test ($P = 0.0228$) indicated the presence of publication bias. To address this,

Table 1 Summary of studies included on colistin-resistant *Enterobacteriaceae* species in Africa

First author	Publication year	Country	Type of bacteria Isolated	No of Isolates	No.of CST-S isolates	MDR Isolates	No CST-R isolates	Guideline (s) used	Quality Score
Abozahra et al. [40]	2023	Egypt	*K. pneumoniae*	82	50	0	32	CLSI	8
Adeosun [41]	2019	Nigeria	*K. pneumoniae*	62	44	52	18	CLSI	8
Adil F. et al. [42]	2022	Morocco	*K. pneumoniae*	16	16	10	0	CA- SFM&	9
			Enterobacter	7	7	4	0	EUCAST	
Azzab et al. [43]	2017	Egypt	*K. pneumoniae*	37	37	0	0		
			E. coli	4	4	0	0	CLSI	9
Carrol et al. [26]	2016	Rwanda	*K. pneumoniae*	975	973	0	2		
			E. coli	2473	2438	0	35	CLSI	8
El-kholy et al. [28]	2020	Egypt	*K. pneumoniae*	266	249	266	17	EUCAST	
			E. coli	219	219	219	0		9
Elbaradei et al. [27]	2022	Egypt	*K. pneumoniae*	301	299	246	2		
			E. coli	109	107	60	2	CLSI	9
			Enterobacter	14	14	7	0		
Hasanin et al. [30]	2014	Egypt	*K. pneumoniae*	145	145	0	0	CA-SFM &	8
			E. coli	80	80	0	0	EUCAST	
			Proteus species	30	30	0	0		
Irenge et al. [31]	2023	DR.Congo	*K. pneumoniae*	37	37	37	0	EUCAST	9
Jalal et al. [32]	2021	Egypt	*K. pneumoniae*	28	24	25	13	EUCAST	8
Mbelle et al. [33]	2020	S.Africa	*K. pneumoniae*	42	32	42	10	EUCAST	7
Romandan et al. [36]	2022	Egypt	*K. pneumoniae*	73	65	65	8	CLSI	9
Zafer et al. [39]	2019	Egypt	*K. pneumoniae*	234	212	0	22	CLSI	9
			E. coli	200	188	0	18		
			Enterobacter	16	16	0	0		
Gizachew et al. [29]	2019	Ethiopia	*K. pneumoniae*	24	6	18	18	CLSI	8
			E. coli	55	5	52	50		
			Proteus species	5	0	5	5		
Yousfi et al. [38]	2018	Algeria	*K. pneumoniae*	3	0	0	3	EUCAST	7
Abdelmagid et al. [24]	2023	Sudan	*K. pneumoniae*	61	47	0	14	CLSI	7
Aminata et al. [25]	2023	Mali	*K. pneumoniae*	16	13	9	3		7
			E. coli	16	13	10	3	CA-SFM	
			Enterobacter	7	7	3	0		

Table 1 (continued)

First author	Publication year	Country	Type of bacteria Isolated	No of Isolates	No.of CST-S isolates	MDR Isolates	No CST-R isolates	Guideline (s) used	Quality Score
Sarr et al. [37]	2023	Senegal	*K. pneumoniae*	52	52	0	0		9
			E. coli	146	146	0	0	CLSI	
			Enterobacter	33	32	0	1		
Mohammed HS et al. [35]	2022	Djibouti	*K. pneumoniae*	14	14	0	0		8
			E. coli	117	117	59	0	EUCAST	
			Enterobacter	4	4	0	0		
			Proteus species	2	2	0	0		
El-Mahallawy et al. [62]	2022	Egypt	*K. pneumoniae*	100	61	100	39		9
			E. coli	89	50	89		CLSI	
			Enterobacter	7					
Abdel salam et al. [23]	2020	Egypt	*K. pneumoniae*	24	2	32	29		8
			E. coli	8	1			CLSI	
Mohammed et al. [34]	2022	Somalia	*K. pneumoniae*	13	13	6	0		9
			E. coli	26	26	5	0	CLSI	
Synman et al. [58]	2021	S.Africa	*K. pneumoniae*	7	2	0	5		7
			E. coli	22	10	0	12	EUCAST	
Kieffer et al. [50]	2018	Libya	*K. pneumoniae*	33	27	0	6		7
			E. coli	16	15	0	1	CLSI	
Mezghani et al. [54]	2012	Tunisia	*K. pneumoniae*	73	64	0	9		8
			E. coli	16	15	0	0	EUCAST	
			Enterobacter	33	28	0	5		
Battikh et al. [46]	2017	Tunisia	*K. pneumoniae*	21	0	0	21	EUCAST	9
Ayandele et al. [3]	2020	Nigeria	*K. pneumoniae*	48	4	7	44	CLSI	7
Budel et al. [47]	2019	Tunisia	*K. pneumoniae*	54	32	0	22	EUCAST	8
			E. coli	72	52	0	20		
Newton-Foot et al. [56]	2017	S.Africa	*K. pneumoniae*	20	16	0	4	EUCAST	9
Messaoudi et al. [53]	2019	Tunisia	*K. pneumoniae*	2160	2151	0	9	EUCAST	7
Aworh et al. [45]	2021	Nigeria	*E. coli*	47	40	39	7	EUCAST	7
Deku et al. [48]	2022	Ghana	*E. coli*	135	132	0	3	EUCAST	8
El-Mokhtar et al. [49]	2021	Egypt	*E. coli*	140	119	0	21	CLSI	9
Maina et al. [52]	2023	Kenya	*E. coli*	30	25	27	5		7
			Enterobacter	3	3	0	0	CLSI	
			Proteus species	4	0	0	4		

Table 1 (continued)

First author	Publication year	Country	Type of bacteria Isolated	No of Isolates	No.of CST-S isolates	MDR Isolates	No CST-R isolates	Guideline (s) used	Quality Score
Zakkaria et al. [60]	2021	Egypt	*E. coli*	67	61	60	6	CLSI	9
Afolayan et al. [44]	2022	Nigeria	*E. coli*	67	67	59	0	CLSI	7
Poirel et al. [61]	2016	S.Africa	*E. coli*	7	0	0	7	_	7
Nabti et al. [55]	2019	Algeria	*E. coli*	237	237	1	0	EUCAST	8
Konate et al. [51]	2017	Burkina Faso	*E. coli*	31	12	5	19	EUCAST	7
Sumbana et al. [59]	2022	Mozambique	*Enterobacter*	8	7	5	1	EUCAST	8
Otokunefor et al.[57]	2019	Nigeria	*E. coli*	13	7	0	6	EUCAST	7
Total isolates				9636	9,055	1624	581		
Species	**Total i**solates per spp.	**MDR** isolates	**CST-R** Isolates	**CST-S** Isolates	MDR isolates	CST-R among MDR isolates			
K.pneumoniae	5021	915	350	4,671	915	160			
E. coli	4442	685	215	4,227	685	78			
Enterobacter spp.	132	19	7	125					
Proteus spp.	41	5	9	32					
Total	9636	1624	581	9,055					
	Non-MDR isolates	Only MDR isolates	CST-R From Non-MDR isolates	CST-R From Only MDR Isolates					
	7420	1192	282	229					

Keys: *CA-SFM* Antibiogram Committee of the French Microbiology Society, *CLSI* Clinical and Laboratory Standards Institute, *CST-R* colistin resistance, *CST-S* colistin susceptible, *EUCAST* European Committee on Antimicrobial Susceptibility Testing, *MDR* multi-drug resistance

a trim-and-fill analysis was performed, resulting in the imputation of six studies. After adjusting for publication bias, the final pooled prevalence of colistin resistance was recalculated at 32.31% (95% CI: 22.93–41.69%) (Supplementary file, Table S3).

Subgroup-analysis

Subgroup analyses were conducted based on year, country, AST methods, species, and specimen type to identify potential sources of variation. The analysis revealed significant differences in colistin resistance across these factors. Country-based analysis showed notable variations in resistance levels. South Africa had the highest colistin resistance at 50.95% (95% CI: 14.10–87.80), followed by Nigeria at 36.18% (95% CI: 4.49–67.87). In contrast, Egypt had a lower prevalence of colistin resistance at 19.93% (95% CI: 5.10–34.77). The high heterogeneity observed across these countries ($I^2 = 97\%$ −99.87%) highlighted the substantial variation in resistance.

The type of AST method used revealed notable differences in prevalence of colistin resistance. Studies using the BMD method found a resistance rate of 27.96% (95% CI: 16.40–39.52) and the VITEK2 method showed a prevalence of 18.83% (95% CI: −0.96–38.62). In contrast, the disk diffusion method reported a lower resistance rate of 12.59% (95% CI: 0.74–24.43). Additionally, there was considerable heterogeneity across all methods, with I^2 values ranging from 87.31% to 99.97%.

Species wise analysis showed that, colistin resistance was highest in *Proteus spp*. (50.02%, 95% CI: 17.25–33.14), followed by *K. pneumoniae* (28.84%, 95% CI: 16.64–41.50) and *E. coli* (24.50%, 95% CI: 11.68–37.31). *Enterobacter spp*. showed very low resistance (1.22%, 95% CI: −0.59–3.03) with no significant heterogeneity ($I^2 = 0\%$) (Table 2). Subgroup analysis of clinical specimens also showed significant variation ($p < 0.001$). According to the analysis, stool specimen isolates had the highest colistin resistance at 42.0% (95% CI: 0.41%−83.36%), while blood specimen isolates had a lower resistance rate of 3.58%

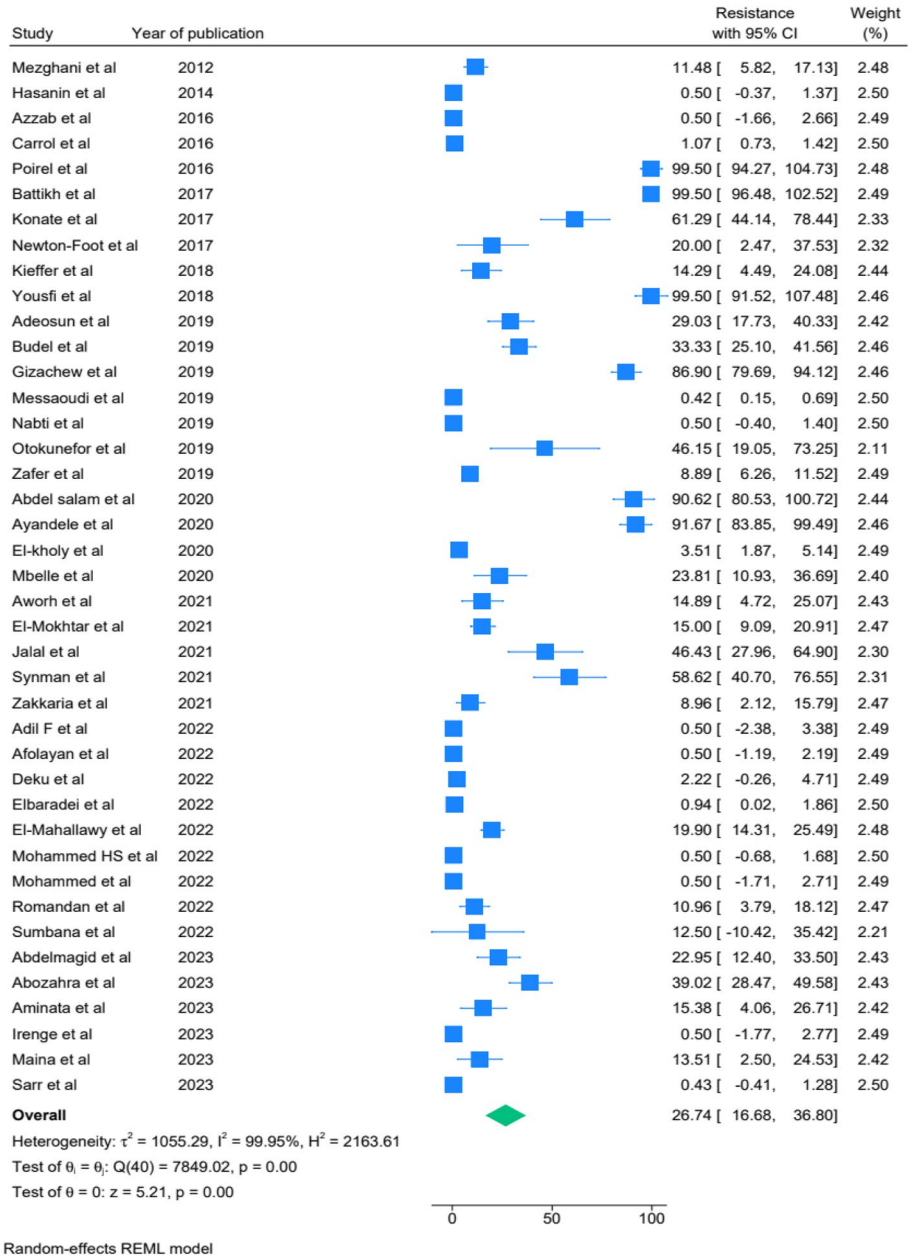

Fig. 2 Forest plot showing the pooled prevalence of colistin-resistant *Enterobacteriaceae* in Africa

(95% CI: −2.03%−9.2%). The prevalence of colistin resistance in mixed clinical isolates was steady at 25.23% (95% CI: 12.90%−37.62%). (Table 2).

Pooled prevalence of colistin resistance among each *Enterobacteriaceae* species

In this meta-analysis, the pooled prevalence of colistin-resistant *K. pneumoniae* was 28.8% (95% CI: 16.64–41.05%) (Fig. 3). However, the Egger's test indicated the presence of publication bias, prompting a trim-and-fill analysis that adjusted the prevalence to 32.1% (95% CI: 20.48–43.73%) (Supplementary file, Table S4). Similarly, the pooled prevalence of colistin-resistant *E. coli* was found to be 24.5% (95% CI: 11.68–37.3%) (Fig. 4), but publication bias was also detected (Supplementary file, Figure S3), leading to a revised prevalence of 26.5% (95% CI: 14.34–38.74%) after trim-and-fill analysis (Supplementary file, Table S5). For *Enterobacter* species, the pooled prevalence of colistin resistance was considerably lower at 1.22% (95% CI: −3.03%) (Fig. 5), with no detected

Table 2 Subgroup analysis for colistin-resistant *Enterobacteriaceae*

Category	Characteristics	No. of studies	Pooled prevalence at 95% CI	I^2	*p*-value
Year	2010–2018	9	40.74 (13.19—68.28)	99.96	< 0.001
	2019–2023	32	22.08 (12.43- 31.73)	99.9	< 0.001
Country	Egypt	12	19.93 (5.10 –34.77	99.82	0.01
	Nigeria	5	36.18(4.49–67.87)	98.76	0.03
	South Africa	4	50.95 (14.10–87.80)	97.28	0.01
	Tanzania	4	36.19 (7.39–79.78)	99.87	0.1
	Algeria	2	49.92(–47.10–146.94)	99.83	0.31
AST method	Broth MIC	34	27.96(16.40–39.52)	99.97	0.001
	Disk diffusion	3	12.59 (0.74–24.43)	92.25	0.001
	VITEK2	4	18.83 (–0.96–38.62)	87.31	0.001
Species	*K. pneumoniae*	30	28.84 (16.64 –41.50)	99.91	0.001
	E. coli	25	24.50(11.68–37.31)	99.96	0.001
	Enterobacter spp.	10	1.22 (–0.59–3.03)	0.00	0.40
	Proteus spp.	4	50.02 (17.25–33.14)	99.95	0.001
Specimens	Stool	4	42.0% (0.41%–83.36%)	99.17	0.04
	Urine	7	17.90% (–5.31–41.1%)	99.95	0.13
	Blood	4	3.58% (–2.03%–9.2%)	85.40	0.21
	Mixed	22	25.23% (12.90%–37.62)	99.92	0.001

Keys: Mixed: urine, blood, sputum, pus, wound, swab, endotracheal aspirate, stool

heterogeneity or publication bias (Supplementary file, Figure S4). In contrast, *Proteus* species exhibited the highest pooled prevalence of colistin resistance at 50.0% (95% CI: 6.0–106.03%) (Fig. 6). However, this analysis revealed high levels of heterogeneity and publication bias, after imputing one additional study to account for potential publication bias, the prevalence increased to 66.58% (Supplementary file, Figure S5 & Table S6).

Discussion

The widespread emergence of MDR *Enterobacteriaceae* bacteria has raised significant concerns, driving the increased use of colistin as a last-resort antibiotic. However, the growing prevalence of MDR bacterial infections has led to the rising threat of colistin-resistant *Enterobacteriaceae* [63]. This resistance, primarily linked to the mobile colistin resistance (mcr) gene, including mcr-1 through mcr-10, is spreading rapidly worldwide, intensifying the challenges in managing infections caused by these pathogens. The development of colistin-resistant strains is particularly problematic, as it significantly limits its treatment options [64].

The present study documented a total of 9,636 *Enterobacteriaceae* isolates, with *K. pneumoniae* being the most predominant (5,021 isolates) followed by *E. coli* (4,442 isolates).The study identified 5,021 K. *pneumoniae* isolates, of which 915 were MDR and 350 resistant to colistin. Additionally, 4,442 *E. coli* isolates were reported, with 685 MDR and 215 colistin-resistant. Among the MDR isolates, *K. pneumoniae* was most common (915 isolates), with 160 showing both MDR and colistin resistance, while *E. coli* followed with 685 MDR isolates, 78 of which were also resistant to colistin. In our study, we highlights the significant presence of both MDR and colistin resistance in *K. pneumoniae* and *E. coli*, with *K. pneumoniae* being more commonly associated with both types of resistance. The impact of concomitant resistance in *K. pneumoniae* and *E. coli* significantly affects treatment options, patient outcomes, infection control, and public health [65].

The pooled prevalence of colistin resistance among *Enterobacteriaceae* in the current review was 26.74%, which was higher than the global prevalence of 9.1% [66], Iran (0.8%) [67], Spain (0.7%) [68] and lower than the study conducted in Gaza, it was 41% among tested clinical isolates [69]. This might be due to different drug susceptibility testing methods used, different geographical locations, social-economic differences, and also the differences in healthcare systems, including antimicrobial resistance control policies.

Klebsiella pneumoniae is one of the major hospital-acquired bacteria, which is associated with causing life-threatening infections like pneumonia and bacteremia [70]. Currently, *K. pneumoniae* resistance to several antibiotics has increased drastically, and the dissemination of carbapenems-resistant *K. pneumoniae* isolates has been reported globally [71]. In the current review, the pooled rate of colistin resistance for *K. pneumoniae* was 28.8%.

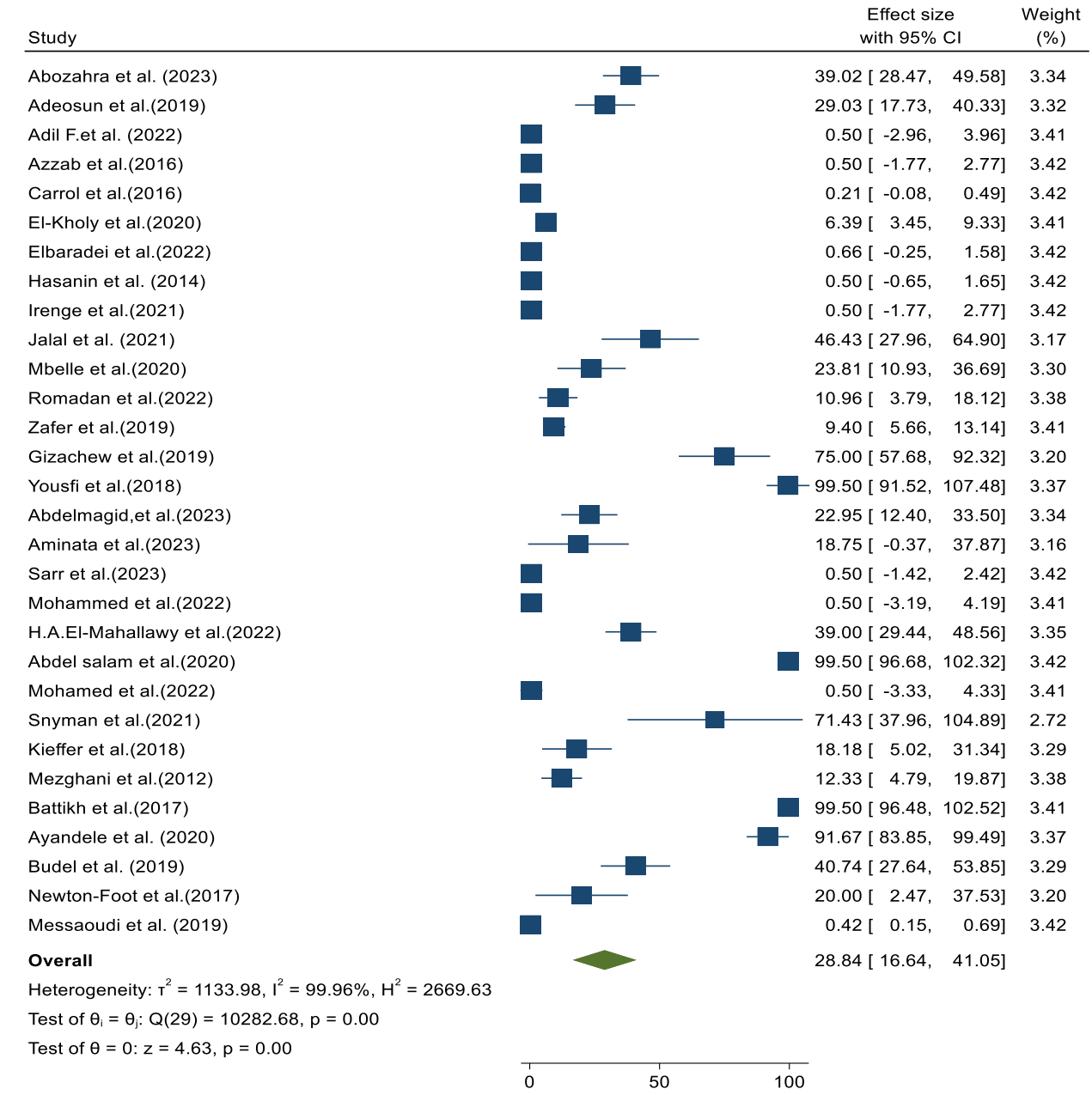

Fig. 3 Forest plot illustrating the pooled prevalence of colistin resistance among Klebsiella pneumoniae isolates

Our finding indicates, it was higher than the global pooled prevalence of colistin resistance at 3.1% [72], while it was consistent with study reports in Iran at 16.9% [73], Turkey (27.5%), and United Arab Emirates (31.4%) [73]. However, the finding was lower than the study reported in Greece (61%) [74], Saudi Arabia (75.4%) [75], and Hungary (88.9%) [76].

The pooled rate of colistin resistance for *E. coli* was 24.50%. *E. coli* is the most common Gram-negative bacteria in the human gastrointestinal tract and lacks virulence in this setting. However, when found outside of the intestinal tract, *E. coli* can cause urinary tract infections (UTI), pneumonia, bacteremia, and peritonitis [77]. The present study result reveals it is higher than the global pooled prevalence of colistin resistance 3.44% [66] and Asia at 3.64% [17], America (0.48%), Europe (0.62%), Russia (0.01%) [17] as well as previously studied data in Africa (2.27%) [17] but it was lower than reported from

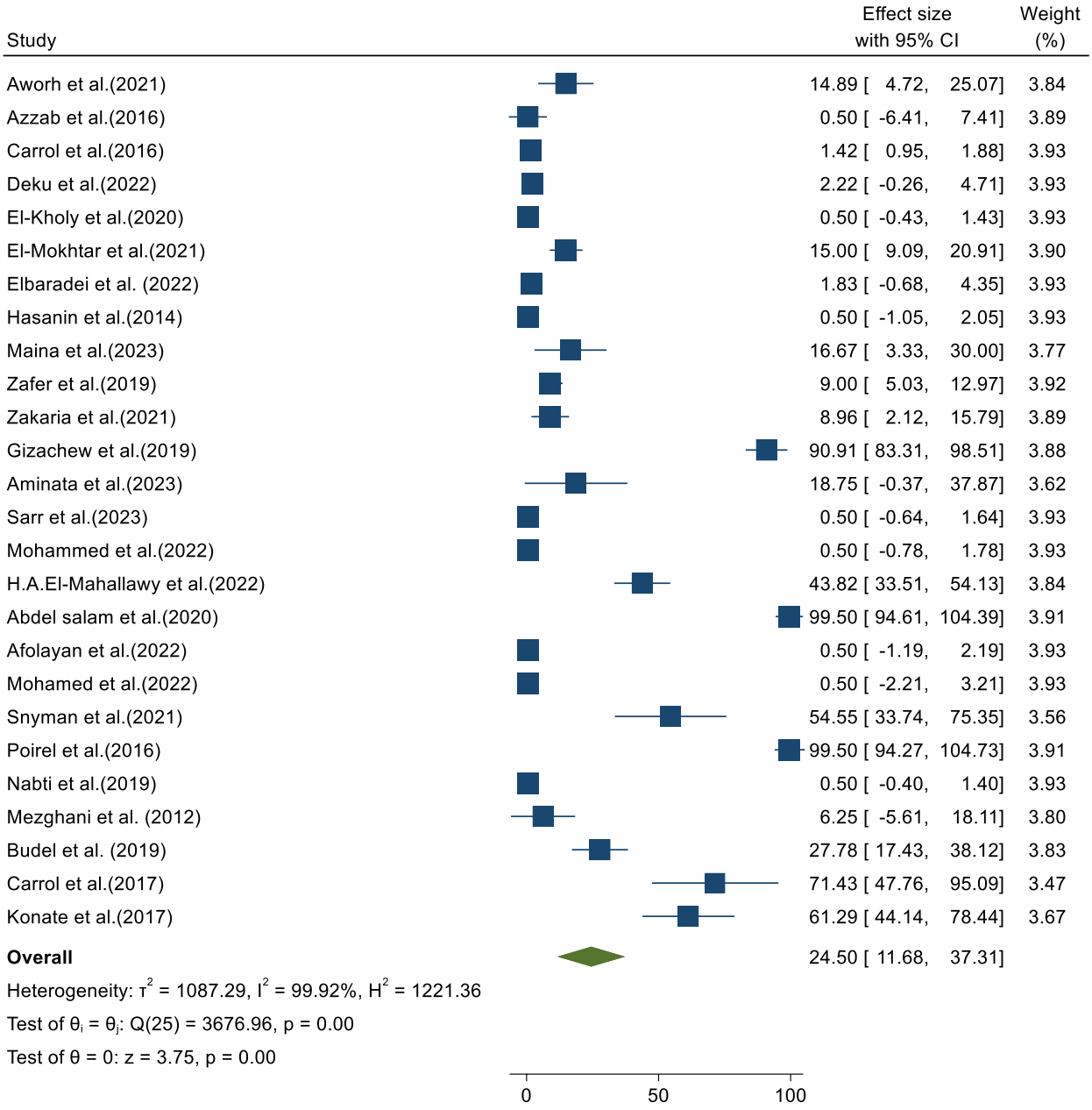

Fig. 4 Forest plot for pooled prevalence of colistin resistance among *E. coli isolates* in Africa from 2010 to 2023

Burkina Faso (61.3%) [51], Ireland, Finland, Portugal, and Austria (100%), and the Netherlands (85.71%) [17]. Concomitant MDR *K. pneumoniae* and *E. coli* infections present a particularly complex and challenging clinical scenario, as both pathogens are commonly associated with serious infections and are increasingly resistant to multiple classes of antibiotics [78].

Colistin resistance prevalence in *proteus* was 50.02%, which was the highest in our result compared to other bacteria. This finding is comparable to the study reported in Gaza (63.2%) [69]. Proteus *spp.* are known to exhibit intrinsic resistance to certain antibiotics. This resistance is part of their natural characteristics and is due to several mechanisms: such as Beta-lactamase production, Efflux pumps, Altered porin channels, and intrinsic low permeability. Hence, these mechanisms contribute to its resistance to being high. Concomitant MDR *Proteus spp*. also makes the treatment of infections caused by this

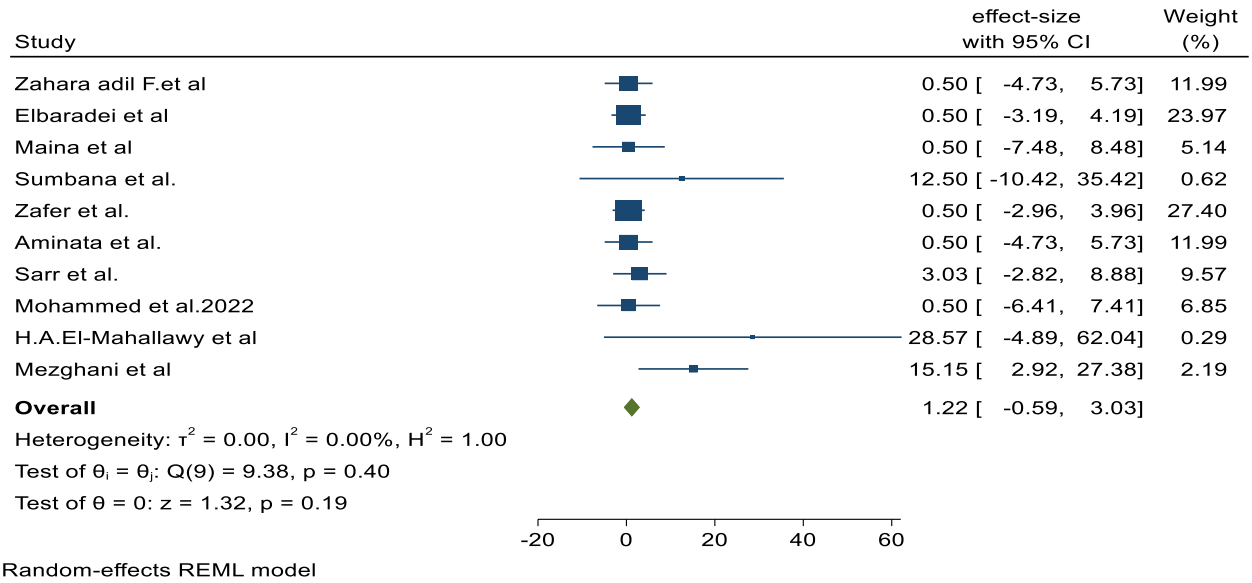

Fig. 5 Forest plot for pooled prevalence of colistin resistance among *Enterobacter species* isolates in Africa from 2010 to 2023

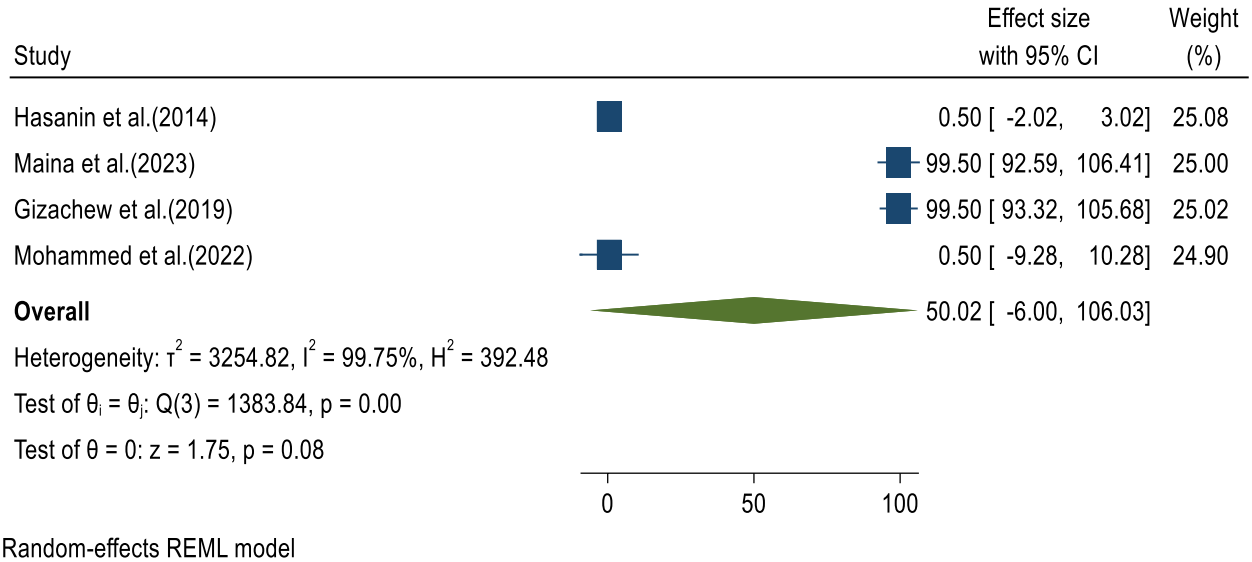

Fig. 6 Forest plot for pooled prevalence of colistin resistance among *Proteus spp.* isolates in Africa from 2010 to 2023 G.C

strain much more challenging, as fewer antibiotics would be effective [14].

The country-based analysis revealed notable differences in resistance levels. South Africa exhibited the highest colistin resistance at 50.95% (95% CI: 14.10–87.80), followed by Nigeria at 36.18% (95% CI: 4.49–67.87). In contrast, Egypt had a significantly lower of prevalence of colistin resistance at 19.93% (95% CI: 5.10–34.77). The substantial variation in resistance across these countries was highlighted by the high heterogeneity observed ($I^2 > 97\%$). The differences in colistin resistance among such countries could be attributed to several factors, including differences in antimicrobial usage, healthcare infrastructure, surveillance systems, methodological difference, and regional microbial characteristics [79].

The analysis based on types of AST method revealed notable differences in resistance prevalence. Studies using the BMD method found a resistance rate of 27.96% (95% CI: 16.40–39.52) and the VITEK2 method showed a prevalence of 18.83% (95% CI: −0.96–38.62). In contrast, the disk diffusion method reported a lower resistance rate of 12.59% (95% CI: 0.74–24.43). The minimum inhibitory

concentration (MIC) method for determining colistin resistance in *Enterobacteriaceae* is primarily conducted using BMD, which is recommended by both EUCAST and CLSI as the reference method. This method is crucial for accurately assessing colistin susceptibility due to the challenges associated with other testing methods. It may provide a more sensitive and precise result, capturing lower levels of resistance that other methods might miss. This could explain the higher resistance prevalence of 27.96% observed in studies using BMD method [80]. The VITEK2 system is an automated method that uses a combination of biochemical tests and a special reagent to determine antimicrobial susceptibility. While the VITEK2 method is generally reliable and widely used, it may have inherent limitations in sensitivity or the ability to detect certain resistance mechanisms compared to the MIC method [81].

The disk diffusion method for colistin susceptibility testing has been found to be unreliable due to the poor diffusion characteristics of colistin, which is a large molecule that adheres to plastic surfaces. This results in high error rates and low reproducibility, making it less suitable for accurately determining colistin resistance in *Enterobacteriaceae*. While this is a simple and widely used method, it tends to be less sensitive compared to MIC testing, especially for detecting low-level resistance. The observed resistance rate of 12.59% in the disk diffusion method is lower, which may indicate that this method fails to detect some resistance that other methods like MIC can identify [82].

The subgroup analysis of clinical specimens revealed significant differences in colistin resistance, with stool specimens showing the highest resistance at 42.0% (CI: 0.41%−83.36%), while blood specimens had a lower resistance rate of 3.58% (−2.03%−9.2%, $p < 0.001$). The higher colistin resistance observed in stool specimens can be attributed to factors such as the high bacterial diversity and the presence of selective pressures within the gut [83] while the lower colistin resistance in blood specimens is linked to the sterile nature of blood, immune system activity, and reduced bacterial colonization [84]. However, the prevalence of colistin resistance in mixed clinical isolates was steady at 25.23% (95% CI: 12.90%−37.62%).This stability may be due to the fact that the isolates came from various clinical specimens, with the rate of colistin resistance remaining relatively unchanged across different studies and samples.

Strength and limitations

This review investigates the prevalence of colistin resistance in clinical *Enterobacteriaceae* isolates over 14 years in Africa, revealing significant rise in resistance. The study provides crucial insights to help researchers and organizations assess the scope of the issue. However, the review had several limitations: There was significant data variability and publication bias. The exclusion of studies not published in English or lacking full texts. Additionally, correction factors used for cases with 100% prevalence or zero standard errors may have led to inflated estimates. The absence of data from certain regions could also affect the overall prevalence estimates for the continent.

Conclusion and Recommendation

Colistin resistance in *Enterobacteriaceae* is notably high in Africa, with significant variation between countries. This underscores the need for effective antimicrobial stewardship, improved surveillance, and the development of new antibiotics. Additionally, it highlights the importance of establishing diagnostic laboratories and ensuring access to antimicrobial susceptibility testing in resource-limited African countries.

Future perspectives

Resistance to the last-resort drugs is a global issue requiring an international alliance. The research highlights a significant rise in colistin-resistant strains and stresses the importance of molecular epidemiological studies to monitor the spread of mcr genes. It advocates for a One Health approach, integrating both clinical and non-clinical specimens, using reliable methods endorsed by CLSI and EUCAST. The study also notes gaps in data from some countries, underscoring the need for improved laboratory diagnostics and greater accessibility.

Abbreviations

AMR Antimicrobial resistance
MDR Multidrug-resistance

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Y.G. led the systematic review and meta-analysis, overseeing the study's conceptualization, article selection, data extraction, statistical analysis, and manuscript preparation. Y.G., M.A.R, Z.A., E.G., S.T., and A.S. were involved in searching for relevant articles, conducting data extraction, performing statistical analysis, contributing to manuscript drafting, and writing editing. M.A.R., B.B.A., and A. A.K. were involved in statistical analysis consultation of the overall process of this systematic review and meta-analysis. M.T., B.G., G.B., T.M., W.A., A.A., Z.D., G.K., S.G. M.G., A.J., and W.K., involved in article searching, data extraction, statistical analysis, manuscript writing, editing, and ensuring accuracy and completeness. Additionally, all authors actively engaged in critically reviewing

the study's progress, data analysis, and manuscript preparation, involved in the approval of the final manuscript for submission, thereby affirming their endorsement of its content and findings.

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Data availability
Data used to support the findings of this study are included in this manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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