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Prevalence of genes encoding carbapenem-resistance in *Klebsiella pneumoniae* recovered from clinical samples in Africa: systematic review and meta-analysis

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Abstract

Background The potential of *Klebsiella pneumoniae* (*K. pneumoniae*) to acquire and spread carbapenem-resistant genes is the most concerning characteristic of the bacteria. In hospitals and other healthcare settings, multidrug-resistant *K. pneumoniae* can be prevalent and cause severe infections, posing significant challenges to patient management. Studying genetic variants and drug-resistant mutations in pathogenic bacteria of public health importance is essential. Therefore, this study aimed to assess the overall prevalence of carbapenemase-encoding genes in *K. pneumoniae* across Africa.

Methods All studies published between January 2010, and December 2023, were retrieved from the electronic databases PubMed, Science Direct, and Scopus, as well as through the Google Scholar search engine. This systematic review and meta-analysis adhered strictly to the PRISMA guidelines. Data analysis was performed using STATA version 17. The quality of the included studies was critically evaluated using the "Joanna Briggs Institute" criteria. To evaluate heterogeneity among the studies, inverse variance (I2) tests were utilized. Subgroup analysis was conducted when heterogeneity exists among studies. To assess publication bias, we used a funnel plot and Egger's regression test. A random effects model was used to calculate the weighted pooled prevalence of genetic variants associated with carbapenem resistance in *K. pneumoniae*.

Results A total of 49 potential studies were included in this systematic review and meta-analysis, encompassing 8,021 *K. pneumoniae* isolates. Among these isolates, 2,254 (28.1%) carbapenems-resistance-conferring genes were identified. The overall pooled prevalence of carbapenemase-encoding genes in *K. pneumoniae* isolated from clinical specimens across Africa was found to be 34.0% (95% CI: 26.01–41.98%). Furthermore, the pooled prevalence of the carbapenemase genes $bla_{\text{OXA-48}}$ and $bla_{\text{NDM-1}}$ was 16.96% (95% CI: 12.17–21.76%) and 15.08% (95% CI: 9.79–20.37%), respectively. The pooled prevalence of carbapenemase genes in *K. pneumoniae* isolates from clinical samples across Africa increased over time, reported as 20.4%(-0.7–41.4%) for 2010–2015, 34.5% (20.2–48.8%) for 2016–2020, and 35.2% (24.8–45.5%) for 2021–2023, with heterogeneity (I2) values of 36.5%, 96.7%, and 99.3%, respectively.

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Conclusions The emergence and spread of carbapenemase-encoding genes in *K. pneumoniae* pose a major threat to public health. Knowledge on the genetic mechanisms of carbapenem resistance is crucial for developing effective strategies to combat these multidrug-resistant infections and reduce their impact on healthcare systems. The carbapenemase genes bla_{OXA-48} and bla_{NDM-1} were the most prevalent and showed an increasing trend over time.

Keywords Carbapenemase-encoding genes, Bla_{OXA-48}, Bla_{NDM-1}, *K. pneumoniae*, Clinical samples, Meta-analysis

Introduction

Klebsiella pneumoniae (K. pneumoniae) is an opportunistic pathogen that causes range of infections, including pneumonia, bloodstream infections, and urinary tract infections, which can be acquired in both healthcare settings and the community [1]. Carbapenem-resistant *K. pneumoniae* is included in the World Health Organization's (WHO's) 2024 list of priority bacterial pathogens, underscoring its status as a significant public health concern [1, 2]. Strains of *K. pneumoniae* capable of causing severe and invasive infections have emerged, fueled by their ability to adapt through gene transfer, pathogenicity, and the convergence of resistance mechanisms [3]. For infections caused by *K. pneumoniae*-producing extended-spectrum β-lactamases (ESBL), carbapenems are the recommended drug of choice [4]. Carbapenems, as last-resort antibiotics for treating multidrug-resistant (MDR) Gram-negative bacteria (GNB), have a unique structure that provides broad-spectrum antibacterial activity [5].

However, nearly three decades after their introduction for treating antibiotics-resistant GNB, carbapenems resistance still poses an increasing public health threat, with carbapenemase-encoding genes now widespread in many regions globally [6]. Carbapenem resistance mainly arises from the overproduction of β-lactamases with low affinity for carbapenems, increased expression of carbapenemase genes, modifications in penicillin-binding proteins, decreased drug permeability, or the presence of efflux pumps that lower drug susceptibility [7]. Genes encoding carbapenemases produce enzymes that can hydrolyze the β-lactam ring of carbapenem antibiotics [7, 8]. Notable examples include *K. pneumoniae* carbapenemase (bla_{KPC}), oxacillinase (bla_{OXA}), Verona integron-encoded metallo-β-lactamase (bla_{VIM}), imipenemase (bla_{IMP}), and New Delhi metallo-β-lactamase (bla_{NDM}) [8]. The increase in carbapenemase production has primarily been associated with the extensive use of carbapenems to treat severe infections caused by organisms that produce ESBLs [9].

Carbapenem resistance is a significant public health concern, as carbapenems are often the last-line drug of choice for the treatment of MDR bacteria that are resistant to most other antibiotics [10]. Bacteria that produce carbapenemases are particularly challenging to treat, as they can degrade all β-lactam antibiotics, including carbapenems, rendering them ineffective [11]. The increasing prevalence of carbapenem-resistant *K. pneumoniae* is particularly concerning, as it jeopardizes the effectiveness of carbapenems, which are often relied upon as"last-resort"antibiotics in hospitals and long-term care facilities [12]. Moreover, there has been a steady increase in carbapenem-resistant *Enterobacteriaceae* (CRE), though this issue has not been thoroughly documented [13]. CRE, including *K. pneumoniae*, has been identified by the WHO and the Centers for Disease Control (CDC) as a significant group of pathogens responsible for infections resistant to multiple antibiotics. They emphasized that some of the most critical resistance challenges globally are attributed to CRE, including species such as *K. pneumoniae* [14, 15].

Because they have limited treatment options and are associated with higher rates of morbidity, mortality, and healthcare costs, strains of carbapenem-resistant bacteria are often referred to as"superbugs"or"nightmare bacteria" [16, 17]. The high frequency of *K. pneumoniae* that produces carbapenemase leads to increased hospital stays, death, and healthcare service usage [18]. If antibiotic resistance continues on its current trajectory, it is projected that by 2030, 24 million people will be pushed into extreme poverty, and by 2050, it could lead to as many as 10 million deaths each year [19]. Carbapenem-resistant *K. pneumoniae* (CRKP) has emerged as a global crisis, posing a significant and challenging threat with increased mortality risk for hospitalized patients compared to those infected with drug-susceptible strains [20, 21]. Certain antimicrobials are reserved for treating life-threatening or difficult-to-treat infections to stay ahead of microbial resistance. Nevertheless, many GNBs, including *K. pneumoniae*, have developed resistance to these prescribed medications, such as carbapenems and polymyxins [22]. However, Africa faces a range of socioeconomic, infrastructural, health, sanitation, and well-furnished laboratory, and labor-related challenges that complicate efforts to combat antimicrobial resistance [23]. There is limited data on the pooled prevalence of carbapenem-resistance conferring gene mutations in clinical isolates of *K. pneumoniae* across Africa, hindering a better understanding of this issue. Therefore, the main aim of this comprehensive systematic review and meta-analysis was to evaluate

the pooled prevalence of carbapenemase-encoding gene variants in *K. pneumoniae* isolates from clinical samples in Africa.

Methods

Protocol and registration

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. The study protocol was developed and submitted to the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024585390).

Data source and search strategy

Electronic databases and search engines were employed to retrieve potential papers reporting on genes encoding carbapenemase in *K. pneumoniae.* A systematic search was performed using PubMed/Medline, Scopus, and Science Direct. Additional articles were retrieved from the Google Scholar search engine and online repositories or registers from various institutions. The findings of this study were reported in strict adherence to the PRISMA flow diagram [24]. Relevant articles published in English from January 2010 to December 2023 were retrieved from databases and search engines using appropriate MeSH (Medical Subject Headings) terms and key search words. The search string was developed using the following search keywords: "prevalence", "epidemiology", "carbapenemases", "carbapenemase gene", "bla_{OXA}", "bla_{NDM}", "bla_{VIM}", "bla_{KPC}", "bla_{IMP}", "*Klebsiella Pneumoniae*", "Enterobacteriaceae", and "Africa". These search words/phrases were further paired with each other or combined using "AND" and "OR" Boolean operators. To access and retrieve relevant papers, we performed searches for each African country using the connectors"AND"and"OR"along with the aforementioned search keywords. The complete search strategy and searching strings for the PubMed/MEDLINE database are depicted in the supplementary file (S1 Table in S1 File).

Eligibility criteria

After retrieving potential papers from the databases, all articles were screened for eligibility. Papers were included if they met the following criteria: (a) studies that reported *K. pneumoniae* isolates tested for carbapenemase gene production, (b) utilized appropriate techniques for carbapenemase gene detection, (c) involved *K. pneumoniae* isolates from clinical samples, (d) were published in English, (e) were published between January 2010, and December 2023 (f) were conducted in Africa, and (g) were retrospective or prospective in design. However, we excluded articles that were review papers, letters, case reports, case–control studies, or conference papers. Additionally, studies with methodological issues such as unclear measurements, incomplete diagnostic criteria, selection bias, or poorly defined study populations and specimens were also excluded.

Study selection and quality assessment

The EndNote reference management software (Thomson Reuters, London) was used to export all retrieved studies, and duplicates were subsequently removed**.** The titles and abstracts of the papers were independently assessed by the reviewers (AS, GK, MN, and MAR) to determine the eligibility of each study. In cases of disagreement between the reviewers'evaluation reports, a third reviewer (MAR) is consulted to resolve the differences through discussion and mutual agreement, ensuring consensus. The full texts of the articles were independently reviewed by the reviewers (AS, MAR, GK, and MN). Disagreements were resolved through discussion to reach a consensus on which articles to include in the final analysis. Following the evaluation of articles based on the inclusion and exclusion criteria, all selected articles underwent quality assessment using the critical appraisal checklist recommended by the Joanna Briggs Institute (JBI) [25]. The quality assessment criteria for the domain paper were clearly outlined using checklists specifically designed for prevalence studies. The appraisal tool consists of nine questions, each answered as Yes (Y), No (N), or Not Identified (NI). Studies were included in the systematic review and meta-analysis if they obtained a final quality score of 50% or higher (S2 Table in S1 file).

Data extraction from included studies

All articles included in the final analysis were independently reviewed by two reviewers (AS and MAR), and relevant data were recorded using a standardized data extraction sheet prepared in Microsoft Excel. The following relevant information was extracted from each original article: author's name, year of publication, country of study, study design, sample size, type of clinical sample/s, number of bacterial isolates tested for gene production, methods used for carbapenemase detection, type of carbapenemase-encoding gene in *K. pneumoniae*, number of carbapenemase-encoding genes in *K. pneumoniae*, and the *K. pneumoniae* genotype (Sequence Type (ST)) (Table 1).

Study outcome/s

The outcome of this systematic review and meta-analysis was the pooled prevalence of carbapenemase-encoding genes in *K. pneumoniae* recovered from various clinical specimens. Only molecularly confirmed *K. pneumoniae*

Table 1 Characteristics of included studies for the prevalence carbapenemase encoding genes from clinical isolates in Africa

Name of authors	Publication year	Country	study design	Type of clinical sample/s	Sample size (N)	*K. pneumoniae* (N)	Type of genes (N)	isolation Method	Sequence Types (N)
Kieffer et al. [26]	2016	Angola	PR	Rectal swab	157	69	$bla_{\text{OXA-181}}$ (24), $bla_{\text{NDM-1}}$ (1)	PCR	NR
Bourafa et al. [27]	2018	Algeria	PR	Urine, blood, wound, body fluid	NR	20	$bla_{\text{OXA-48}}$ (4)	PCR	ST101, ST 147, ST 163, ST2017
Khaldi et al. [28]	2022	Algeria	PR	NR	76	9	$bla_{\text{NDM-1}}$ (2), bla_{VIM} (2), bla ($_{\text{NDM}}+_{\text{VIM}}$) (2)	PCR	NR
Awoke et al. [29]	2022	Ethiopia	PR	Urine, body fluid, Sputum, blood, wound	NR	132	$bla_{\text{NDM-1}}$ (26), bla_{KPC} (1)	PCR	NR
Tekele et al. [30]	2021	Ethiopia	PR	Urine, Pus, body fluid, ear and eye discharge, stool	312	43	$bla_{\text{OXA-48}}$ (2), $bla_{\text{NDM-1}}$ (1), bla ($_{\text{OXA-48}}+_{\text{KPC}}$) (1)	MCIM	NR
Abdeta et al. [31]	2021	Ethiopia	PR	Ear swabs, sputum, urine, pus, CSF, blood, aspirates	1337	109	$bla_{\text{OXA-48}}$ (4), bla_{IMP} (5), bla_{KPC} (1)	PCR	NR
Legese et al. [32]	2022	Ethiopia	PR	Blood	1416	103	bla ($_{\text{NDM-5}}+_{\text{OXA-181}}$) (4), $bla_{\text{NDM-1}}$ (13), $bla_{\text{OXA-181}}$ (4), $bla_{\text{NDM-5}}$ (4)	PCR	ST14, ST437, ST101, ST883
Sherif et al. [33]	2021	Egypt	PR	blood, respiratory, and urine cultures	NR	39	$bla_{\text{OXA-48}}$ (12), $bla_{\text{NDM-1}}$ (13), $bla_{\text{NDM-5}}$ (1), bla_{KPC} (1), $bla_{\text{OXA-181}}$ (2)	PCR	ST101, ST147, ST383, ST489, ST16, ST11, ST 464
Khalifa et al. [34]	2017	Egypt	PR	Blood, urine, sputum, wound	158	89	$bla_{\text{OXA-48}}$ (20), $bla_{\text{NDM-1}}$ (19), bla_{VIM} (3), $bla_{\text{OXA-48}}+_{\text{NDM-1}}$ (2),	PCR	NR
Gandor et al. [35]	2022	Egypt	RS	Blood, urine, sputum, wound, CSF, central catheter, peritoneal fluid	815	180	bla_{KPC} (18), $bla_{\text{NDM-1}}$ (40), bla_{OXA} (25), bla ($_{\text{KPC}}+_{\text{NDM}}$) (2), $bla_{\text{KPC}}+_{\text{OXA}}$ (3), $bla_{\text{NDM}}+_{\text{OXA}}$ (6),	PCR	NR
Taha et al. [36]	2023	Egypt	PR	blood, CSF, urine, wound, and sputum	500	160	bla_{KPC} (7), $bla_{\text{IMP-1}}$(12), bla_{VIM} (24) bla_{NDM} (6), $bla_{\text{OXA-48}}$ (25)	PCR	
Tawfik et al. [37]	2020	Egypt	PR	blood, CVC, wound, pus, sputum, ear swab	135	79	$bla_{\text{NDM-1}}$ (40), $bla_{\text{OXA-48}}$ (24), bla_{KPC} (1), $bla_{\text{OXA-23}}$ (12)	PCR	NR

Table 1 (continued)

Name of authors	Publication year	Country	study design	Type of clinical sample/s	Sample size (N)	*K. pneumoniae* (N)	Type of genes (N)	isolation Method	Sequence Types (N)
Ghaith et al. [38]	2019	Egypt	PR	rectal swab	413	70	bla_{OXA-48} (15), bla_{NDM-1} (20), bla_{VIM} (8), $bla_{(NDM-1+OXA-48)}$ (2), $bla_{(OXA-48+VIM)}$ (2), $bla_{(NDM-1+OXA-48+VIM)}$ (1)	PCR	NR
Hamed et al. [39]	2022	Egypt	PR	Urine, sputum	100	31	bla_{KPC} (7), bla_{OXA-48} (6)	PCR	NR
Abdelaziz [40]	2022	Egypt	PR	Sputum, urine, blood, wound, stool	NR	76	bla_{NDM} (31), bla_{VIM} (14), bla_{KPC} (10), bla_{OXA-48} (11), bla_{IMP} (5)	PCR	NR
Mohamed [41]	2023	Egypt	PR	Urine, blood, sputum, wound, CVC	NR	190	bla_{NDM-1} (38), bla_{OXA-48} (35), bla_{KPC} (7), $bla_{(NDM-1+OXA-48+KPC)}$ (2), $bla_{(NDM-1+OXA-48)}$ (13)	PCR	NR
Badawy [42]	2020	Egypt	PR	Sputum, urine, CVC, wound, urinary catheter	NR	96	bla_{NDM-1}(3), bla_{OXA-48} (14), $bla_{OXA-181}$ (4), bla_{OXA-51}(2), bla_{OXA-23} (1), bla_{NDM-25} (2)	PCR	NR
Domany et al. [43]	2021	Egypt	PR	Urine, blood, sputum, wound	1005	230	bla_{NDM-1} (31), bla_{OXA-48} (21)	PCR	NR
Aboulela et al. [44]	2023	Egypt	PR	Urine, Sputum, wound, blood	150	81	bla_{NDM-1}(8), $bla_{(OXA-48+NDM-1)}$ (14), bla_{OXA-48} (15)	PCR	NR
Osama et al. [45]	2021	Egypt	PR	Blood, CVC, urine, wound, sputum	149	68	bla_{OXA-48} (30), bla_{NDM-1} (12), bla_{IMP} (2), bla_{VIM} (1)	PCR	NR
Dwomoh et al. [46]	2022	Ghana	PR	wound, urine, sputum, blood, vaginal swab, ear swab	144	44	bla_{OXA-48} (3), bla_{NDM-1} (1)	PCR	NR
Owusu et al. [47]	2023	Ghana	PR	Urine, wound swab, blood, throat swab, stool, ear swab	161	30	bla_{OXA-48} (2), $bla_{(NDM-1+OXA-48+VIM)}$ (1), bla_{NDM-1}(1)	PCR	NR

Table 1 (continued)

Name of authors	Publication year	Country	study design	Type of clinical sample/s	Sample size (N)	*K. pneumoniae* (N)	Type of genes (N)	isolation Method	Sequence Types (N)
Muraya et al. [48]	2022	Kenya	PR	Urine, wound swabs, pus	NR	83	bla_{OXA-48} (1), bla_{NDM-1} (1)	PCR	ST15 (4), ST17 (3), ST607 (3),ST14, ST37, ST39, ST 48, ST147, ST307 (2), ST(20, 45, 101, 198, 336, 391, 751, 1927, 2010, 3717)
Daniel [49]	2017	Kenya	PR	Sputum, urine, blood, wound	NR	38	bla_{NDM-1} (1), bla_{OXA-48} (1)	PCR	NR
Kalambry et al. [50]	2023	Mali	PR	pleural effusion	110	13	bla_{NDM-1} (1), bla_{VIM} (1)	PCR	NR
Kumwenda et al. [51]	2019	Malawi	PR	Blood, urine	200	69	bla_{KPC} (7)	PCR	ST340
Ojo et al. [52]	2021	Nigeria	PR	Stool, urinary catheter, urine	170	58	bla_{KPC} (4)	PCR	NR
Odewale et al. [53]	2023	Nigeria	PR	stool, Tracheal aspirate, Urine, wound swab	420	128	bla_{OXA-48} (26), bla_{VIM} (45), bla_{IMP} (19), bla_{NDM-1}(11), bla_{KPC} (10)	PCR	ST307 (5), ST 258, ST11, ST147, ST15, ST321 (1)
Afolayan et al. [54]	2021	Nigeria	PR	Blood, urine, rectal swab, ear and throat swab		134	bla_{NDM-1} (8), bla_{OXA-48} (1), bla_{NDM-5} (2)	PCR	ST17, ST25, ST307, ST5241
Suwaiba [55]	2020	Nigeria	PR	Urine	NR	46	bla_{VIM} (3)	PCR	NR
Barguigua et al. [56]	2015	Morocco	PR	urine, pus, blood, sputum,	NR	166	bla_{OXA-48} (9), bla_{NDM-1} (2)	PCR	NR
Perez-Palacios et al. [57]	2023	Morocco	PR	Blood	199	40	bla_{OXA-48} (11), bla_{NDM-7} (4), bla_{NDM-1} (13)	PCR	ST [1805 (10), 307 (8), 147 (4), 478 (4) 25 (4)
Zalegh et al. [58]	2023	Morocco	PR	urine, pus and wound swabs, pleural fluid endotracheal tubes, and blood	851	12	bla_{OXA-48} (6), bla_{NDM} (1)	PCR	NR
Arhoune et al. [59]	2021	Morocco	PR	Rectal swab	NR	319	bla_{OXA-48} (35)	PCR	NR
Kopotsa [60]	2020	South Africa	PR	Blood. urinary catheter, wound, urine, aspirate	NR	56	bla_{OXA-48} (31), $bla_{(NDM-1+OXA-48)}$ (5), bla_{NDM-1} (13)	PCR	ST307, ST607, ST17, ST39 and ST3559
Vasaikar [61]	2017	South Africa	PR	swabs from abscesses, eye, ear, and vagina, sputum and throat swabs, urine, blood	202	169	bla_{KPC} (1), bla_{NDM-1} (1)	PCR	NR

Table 1 (continued)

Name of authors	Publication year	Country	study design	Type of clinical sample/s	Sample size (N)	*K. pneumoniae* (N)	Type of genes (N)	isolation Method	Sequence Types (N)
Lowe et al. [62]	2019	South Africa	PR	urine, skin, blood, CVC, sputum, rectal specimens	350	1247	bla_{OXA-48} (451), bla_{NDM-1} (48) bla_{VIM} (31), bla_{KPC} (10)	PCR	ST307 (350)
Adam [63]	2018	Sudan	PR	urine, wound, sputum, blood, ear swab, CSF	200	50	bla_{IMP} (8), $bla_{(VIM+NDM)}$ (3), $bla_{(IMP+NDM)}$ (1)	PCR	NR
Elbadawi et al. [64]	2021	Sudan	PR	Blood, wound, urine, body fluids, catheter tips, sputum	206	82	bla_{NDM} (58), bla_{OXA-48} (1), bla_{IMP} (3), bla_{VIM} (1)	PCR	NR
Albasha et al. [65]	2020	Sudan	CS	Blood, urine, wound, sputum	NR	60	bla_{OXA-48} (40), bla_{NDM} (8), bla_{KPC} (5), bla_{IMP} (2), $bla_{(OXA-48+NDM-5)}$ (3)	PCR	NR
Osman et al. [66]	2023	Sudan	PR	Blood, urine, wound, sputum	NR	60	bla_{OXA-48} (4), bla_{NDm-1} (18), bla_{NDM-5} (6), $bla_{OXA-232}$ (1)	PCR	ST147 (9), ST20 (7), ST437 (7), ST101 (6), ST15 (6), ST307 (6), ST383 (5), ST17 (4)
Martha et al. [67]	2014	Tanzania	PR	Urine, blood, sputum, wound	234	68	$bla_{OXA-181}$ (4), bla_{VIM} (11), bla_{IMP} (9), bla_{KPC} (3), bla_{NDM-1} (2)	PCR	NR
Ktari [68]	2011	Tunisia	PR	NR	157	153	bla_{OXA-48} (21)	PCR	NR
Mansour et al. [69]	2017	Tunisia	PR	NR	940	220	bla_{OXA-48} (19), bla_{NDM-1} (6)	PCR	ST101 (16), ST147 (11), ST392 (1)
tanfous et al. [70]	2016	Tunisia	RS	NR	NR	315	bla_{OXA-48} (19)	PCR	NR
Messaoudi et al. [71]	2019	Tunisia	RS	Urine, blood, sputum, wound	NR	2160	bla_{NDM-1} (17), bla_{OXA-48} (203)	PCR	NR
Ssekatawa et al. [72]	2021	Uganda	RS	Urine, wound, blood, rectal swab, vaginal swab, tracheal aspirate, sputum	NR	227	bla_{NDM} (8), bla_{VIM} (12), bla_{KPC} (12), bla_{OXA} (25), bla_{IMP} (18), $bla_{(NDM+OXA-48)}$ (2), $bla_{(KPC+OXA-48)}$ (2), $bla_{(IMP+OXA-48)}$ (2), $bla_{(VIM+OXA-48)}$ (2),	PCR	NR
Turugurwa et al. [73]	2019	Uganda	PR	Urine, sputum, pus, ear swab	192	22	bla_{OXA-48} (3), bla_{KPC} (2), $bla_{(KPC+OXA-48)}$ (1), $bla_{(KPC+VIM)}$ (1)	PCR	NR

Table 1 (continued)

Name of authors	Publication year	Country	study design	Type of clinical sample/s	Sample size (N)	*K. pneumoniae* (N)	Type of genes (N)	isolation Method	Sequence Types (N)
Okoche et al. [74]	2016	Uganda	PR	Blood, wound swab, Sputum, urine, tracheal aspirate, vaginal swab	196	78	bla_{NDM} (4), bla_{VIM} (16), bla_{IMP} (3), bla_{KPC} (5), bla_{OXA} (7)	PCR	NR

Abbreviations: CVC Central venous catheter, *CSF Cerebrospinal fluid*, *NR* Not reported, *PCR* polymerase chain reaction, *PR* Prospective, *RS* Retrospective, *ST* Sequence type

isolates that produce carbapenemase genes were considered.

Data processing and analysis

The relevant extracted data were imported into STATA 17 for final statistical analysis. The overall pooled prevalence of carbapenemase-producing genes in *K. pneumoniae* obtained from various clinical samples in Africa was calculated using a random-effects model, which accounted for heterogeneity across studies. Heterogeneity across studies was evaluated using the inverse variance (I2) statistic. In this meta-analysis, an I2 value of zero indicates no heterogeneity, while values of 25%, 50%, and 75% indicate low, moderate, and high levels of heterogeneity, respectively [75]. A *p*-value of less than 0.05 was considered indicative of the presence of heterogeneity. Subgroup analyses were conducted based on the study country, year of publication, and sample size to assess differences in the pooled estimates. Publication bias was evaluated using a funnel plot and further assessed objectively through Egger's regression test [76]. Sensitivity analysis was performed to evaluate the impact of each study on the overall estimation of the pooled prevalence. A random-effects model for meta-analysis was also employed to estimate the pooled prevalence of genes coding for carbapenemase production. Continuity correction was applied to studies reporting zero percent values for genes coding for carbapenemase production in *K. pneumoniae*, as this led to a zero standard error [77].

Results

Searching results

This systematic review and meta-analysis identified a total of 11,376 potentially relevant studies from searched electronic databases, search engines, and institutional repositories or registries, with 2,033 articles excluded due to duplication. After reviewing the titles and abstracts, 8,580 articles were excluded for not meeting the objectives and inclusion criteria of the review. Accordingly, 763 full-text articles were reviewed in depth according to the preset inclusion criteria, of which 714 were excluded due to full-text inaccessibility, lack of gene identification, studies conducted outside Africa, and failure to include the age of the study subjects of interest. Finally, 49 potential studies were included in the final quantitative analysis (meta-analysis) (Fig. 1).

Characteristics of included studies

The final quantitative analysis (meta-analysis) was conducted for all included studies ($n=49$). The included studies were conducted across fifteen African countries: Angola [$n=1$] [26], Algeria [$n=2$] [27, 28], Ethiopia [$n=4$] [29–32], Egypt [$n=13$] [31–45], Ghana [$n=2$] [46, 47], Kenya [$n=2$] [48, 49], Mali [$n=1$] [50], Malawi [$n=1$] [51], Nigeria [$n=4$], [52–55], Morocco [$n=4$], [56–59], South Africa [$n=3$] [60–62], Sudan [$n=4$] [63–66], Tanzania [$n=1$] [67], Tunisia [$n=4$] [68–71], and Uganda [$n=3$] [72–74]. From these, forty-four studies were prospective [26–34, 36–69, 73, 74], and the remaining were retrospectively studied [35, 70–72]. This systematic review and meta-analysis reported various genotypes (sequence types, ST) of *K. pneumoniae* isolates. A total of 2,237 carbapenemase-producing genes were identified, representing 27.89% of the 8,021 isolates. Among these, $bla_{\text{OXA-48}}$ was the most frequently detected gene, accounting for 1,223 cases (54.7%) of all identified genes followed by NDM- 1, VIM, and KPC genes which account for 627 (28.0%), 184 (8.2%), 114, (5.1%) respectively (Table 1).

Meta-analysis

The pooled prevalence of carbapenemase genes in K. pneumoniae

In this meta-analysis, the overall pooled prevalence of carbapenemase-encoding genes in *K. pneumoniae* was estimated at 34.0% (95% CI: 26.01–41.98%). The heterogeneity among the included studies was thoroughly assessed (I2 =99.3%), revealing significant variation in the investigations for each gene (Fig. 2). Due to these substantial differences, a subgroup analysis was conducted, categorizing the studies by publication year, country of research, and sample size. The pooled prevalence of the carbapenemase gene was analyzed across two time periods: 2010–2016, and 2017–2023, with prevalence rates of 22.73% (95% CI: 9.52–35.94%), and 35.52% (95% CI: 26.66–44.37%) respectively (Table 2). The corresponding I^2 values, which indicate the degree of heterogeneity, were 97.12%, and 99.36%, reflecting high level of variability (Table 2). Furthermore, the pooled prevalence of carbapenemase genes displayed significant variation across different countries. In Kenya, which recorded the lowest prevalence at 2.9% (95%CI: − 0.1 – 5.9%), Egypt showed a prevalence of 50.2% (95%CI: 36.4–63.9%), while Sudan had the highest prevalence at 65.0% (95%CI: 38.0–92.0%) (Table 2). To evaluate the prevalence of publication bias in the included studies, various methods were employed. The funnel plot revealed an uneven distribution for all genes in the included studies (Fig. 3) and Egger's regression test for publication bias revealed marginally insignificant for all genes with a *p*-value of 0.57 (S1 figure in S1 File). Sensitivity analysis was conducted to identify potential sources of heterogeneity in the pooled prevalence of genes produced by *K. pneumoniae isolates* from clinical samples in Africa. The analysis indicated that the impact of individual studies on the pooled estimate was insignificant, suggesting the robustness of the aggregated

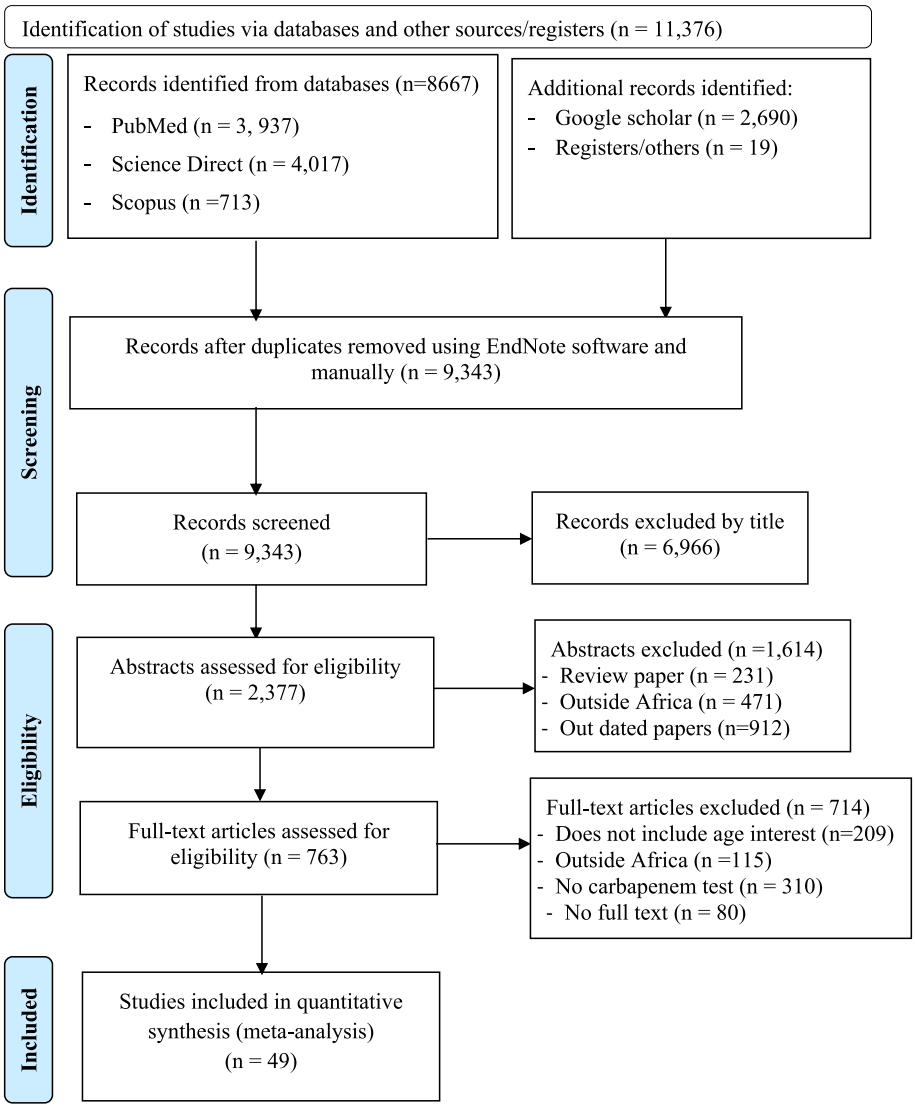

Fig. 1 PRISMA flow diagram showed the results of the search and reasons for exclusion of studies [24]

estimate. Thus, the pooled prevalence of genes isolated from *K. pneumoniae* remained stable when each study was excluded one at a time (S3 Table in S1 File).

The pooled prevalence of bla$_{OXA-48}$genes

The overall estimated prevalence of the *bla*$_{OXA-48}$ gene was 16.96% (95% CI: 12.17–21.76%). The level of heterogeneity among the included studies was assessed, revealing an I^2 value of 98.1% for the *bla*$_{OXA-48}$ gene (Fig. 4). Given the significant heterogeneity among the included studies, a subgroup analysis was conducted based on publication year, study country, and sample size. The pooled prevalence of *bla*$_{OXA-48}$ genes was reported as 7.8% (95% CI: 4.6–11.1%) for the years 2010–2016, and 18.5% (95% CI: 13.1–23.9%) for the year 2017–2023, based on the year of publication (Table 2). Our meta-analysis revealed variation in the pooled prevalence of *bla*$_{OXA-48}$ genes encoding carbapenemase enzymes among *K. pneumoniae* isolates from clinical samples in Africa, ranging from 1.5% (95%CI: – 0.7 – 3.6%) in Kenya to 50.3% (95%CI: 24.3–76.2%) in South Africa (Table 2).

The presence of publication bias in the included studies was assessed, with the funnel plot showing an uneven distribution for *bla*$_{OXA-48}$ genes across the included studies (S2 figure in S1 File). Moreover, Egger's regression test for publication bias showed marginal significance for *bla*$_{OXA-48}$, with a p-value of < 0.001(S3 figure in S1 file). To account for publication bias, a trim-and-fill analysis was performed, and after incorporating seven additional studies, the prevalence of the *bla*$_{OXA-48}$ gene

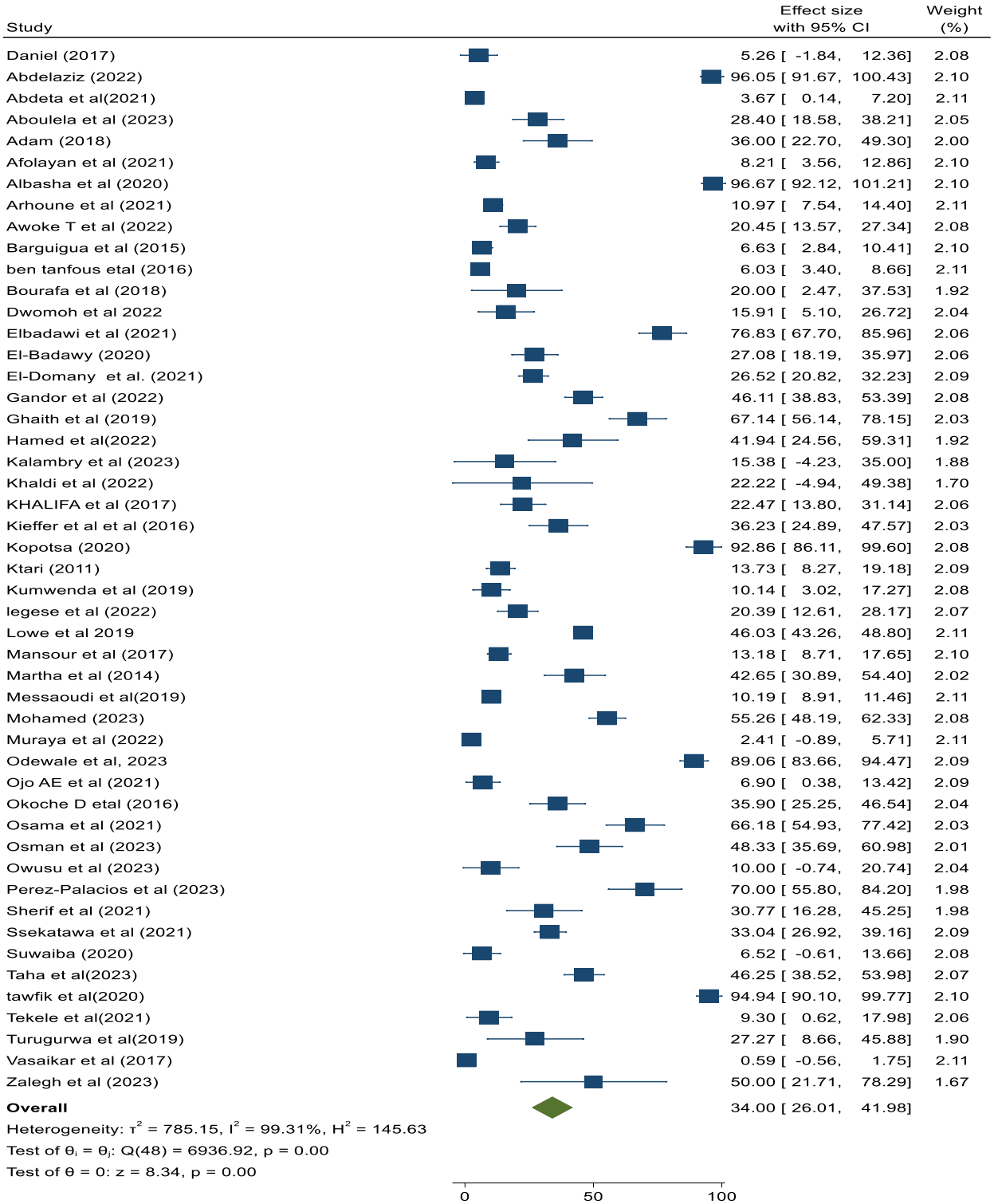

Fig. 2 Forest plot showing the pooled prevalence of carbapenemase gene variants in *K. pneumoniae* from a clinical sample in Africa

Table 2 Subgroup analysis for all genes and specific groups of genes (bla_{OXA-48} and bla_{NDM-1}) by year, country, and sample size

			Overall genes				bla_{OXA-48}				bla_{NDM-1}		
Category	**Characteristics**	**NS**	**Pooled prevalence, (95%CI)**	I^2	***p*-value**	**NS**	**Pooled prevalence (95%CI)**	I^2	***p*-value**	**NS**	**Pooled prevalence (95%CI)**	I^2	***p*-value**
By year	2010–2016	6	22.7(9.5–35.9)	97.1	< 0.001	5	7.8 (4.6–11.1)	55.3	0.11	4	1.7 (0.4–3.0)	0.00	0.45
	2016–2020	43	35.5(26.7–4.4)	99.4	< 0.001	44	18.5 (13.1–23.9)	98.2	< 0.001	45	15.1(9.8–20.3)	99.3	< 0.001
By study country	Egypt	13	50.1 (36.4–63.9)	97.7	< 0.001	13	20.6(16.1–25.2)	78.7	< 0.001	13	24.5 (13.7–5.3)	97.4	< 0.001
	Algeria	2	20.7(5.9–35.4)	0.00	0.9	–	–	–	–		–	–	–
	Kenya	2	2.9 (– 0.1 –5.9)	0.00	0.5	2	1.5 (– 0.7 – 3.6)	0.00	0.6	2	1.5 (– 0.7 – 3.6)	0.00	0.6
	Ethiopia	4	13.1 (4.6–21.7)	86.1	< 0.001	2	3.9 (0.8–6.983)	0.00	0.8	3	11.0 (1.4–0.7)	87.8	< 0.001
	Ghana	2	12.6 (5.3–20.6)	0.00	0.4	2	6.8 (1.0–12.5)	0.00	0.9	2	2.6 (– 1.0 – 6.2)	0.00	0.8
	Nigeria	4	27.7(– 12.5 – 67.8)	99.5	< 0.001	2	10.6 (– 9.3 –30.5)	96.7	< 0.001	2	7.3 (4.0–10.6)	6.6	0.3
	South Africa	3	46.4 (– 5.8 – 98.6)	99.9	< 0.001	2	50.3 (24.3–76.2)	93.9	< 0.001	3	10.2 (– 6.0 – 6.5)	99.7	< 0.001
	Uganda	3	33.2 (28.2–38.4)	0.00	0.7	3	10.6 (7.3–13.9)	0.00	0.8	2	14.9 (9.5–20.3)	0.00	0.6
	Sudan	4	65.0 (38.0–92.0)	97.2	< 0.001	3	25.1(– 16.8 – 7.0)	99.3	< 0.001	4	30.7 (2.9–58.6)	97.3	< 0.001
	Morocco	4	33.2 (2.5–63.9)	99.0	< 0.001	4	19.6 (3.2–35.9)	96.5	< 0.001	3	13.1 (– 5.5 – 31.8)	88.6	< 0.001
	Tunisia	4	42.6 (30.9–54.4)	80.5	0.006	4	9.2 (6.6–11.8)	68.6	0.4	2	1.7 (– 0.6 – 4.0)	74.9	0.05
Sample size	< 100	31	39.3 (28.6–49.9)	98.1	< 0.001	24	20.4 (12.9–7.8)	96.5	< 0.001	25	18.7(10.6–26.6)	97.9	< 0.001
	> 100	18	25.2 (14.5–35.9)	99.5	< 0.001	15	12.5 (7.9–17.1)	97.1	< 0.001	15	8.6 (4.4–12.9)	98.9	< 0.001

Abbreviation: *NS* Number of studies, *PP* Pooled prevalence

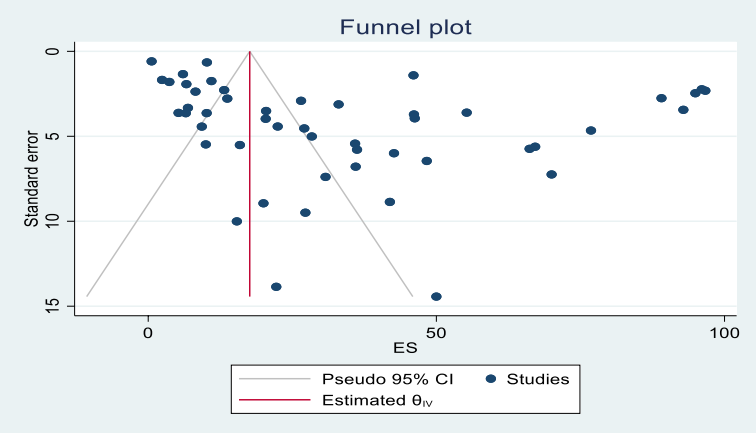

Fig. 3 Funnel plot showing publication biases of all carbapenemase gene variants in *K. pneumoniae* from clinical sample in Africa

was adjusted to 20.4% (95%CI: 15.7–25.1%) (S4 figure in S1 file). A sensitivity analysis was conducted to identify potential sources of heterogeneity for the $bla_{\text{OXA-48}}$ gene. The analysis revealed that the impact of individual studies on the pooled estimate was insignificant, indicating the robustness of the overall estimate. Thus, the pooled prevalence of carbapenem-resistant genes isolated from *K. pneumoniae* remained consistent when each study was excluded one at a time, both for all genes and specifically for $bla_{\text{OXA-48}}$ (S4 Table in S1 file).

The pooled prevalence of $bla_{\text{NDM-1}}$ genes

The pooled prevalence estimate for the $bla_{\text{NDM-1}}$ gene was 15.08% (95% CI: 9.79–20.37%), with an I^2 value of 99.5%, indicating a high level of heterogeneity for this gene (Fig. 5). Thus, a subgroup analysis was performed, revealing the following pooled prevalence rates for $bla_{\text{NDM-1}}$ carbapenemase-encoding genes among *K. pneumoniae* isolates from clinical samples in Africa: for the years 2010–2016, the prevalence was 1.7% (95% CI: 0.4–3.0%), and for the years 2017–2023, it increased to 15.1% (95% CI: 9.8–20.3%) (Table 2). Country-wise variations were also noted, with Kenya reporting the lowest pooled prevalence at 1.5% (95% CI: − 0.7 – 3.6%), while Sudan showed the highest prevalence at 30.7% (95% CI: 2.9–58.6%). In terms of sample size, the pooled prevalence of $bla_{\text{NDM-1}}$ genes was 18.7% (95% CI: 10.6–26.6%) for studies with a sample size of less than 100, while it was 8.6% (95% CI: 4.4–12.9%) for studies with a sample size greater than 100 (Table 2).

Additionally, the funnel plot displayed an uneven distribution of studies (S5 Figure in S1 file), and Egger's regression test for publication bias indicated marginal significance, with a p-value of <0.001 (S6 figure in S1 file). After conducting the trim-and-fill analysis, the prevalence of the $bla_{\text{NDM-1}}$ gene was found to be 19.3% (95% CI: 14.3–24.2%) (S7 figure in S1 file). A sensitivity analysis was conducted to identify potential sources of heterogeneity. The results indicated that the impact of individual studies on the pooled estimate was insignificant, suggesting the robustness of the aggregated estimate (S5 Table in S1 file).

The pooled prevalence of bla_{VIM}, bla_{IMP}, and bla_{KPC} genes

In this meta-analysis, we have also conducted a weighted pooled prevalence estimate for the less frequently occurred/recorded carbapenem-resistant genes in clinical isolates of *K. pneumoniae*. Thus, the pooled prevalence estimates for the bla_{VIM}, bla_{IMP}, and bla_{KPC} genes were 10.64% (95%CI: 6.02–15.25%), 6.59% (95%CI: 4.40–8.78%), and 4.87% (95%CI: 3.01–6.73%), respectively. Additionally, significant variability was observed among the studies for these genes, with I^2 values of 56.1% for bla_{IMP}, 95.0% for bla_{VIM}, and 90.5% for bla_{KPC} (Fig. 6). Furthermore, the funnel plot indicated an uneven distribution of studies for the specific genes bla_{IMP}, bla_{KPC}, and bla_{VIM} (S8, 9 & 10 Figure in S1 file). However, Egger's regression test for publication bias indicated marginal significance for bla_{IMP}, bla_{KPC}, and bla_{VIM}, with p-values of 0.003, <0.001, and 0.013, respectively (S11, 12 & 13 Figure in S1 file). Due to the presence of publication bias, a trim-and-fill analysis was conducted for the bla_{KPC} gene, which showed a prevalence of 2.4% (95%CI: 0.2–4.5%) after the imputed study (S14 figure in S1 file).

The pooled prevalence for co-existed genes

Carbapenem-resistant isolates co-producing multiple carbapenemase genes tend to be highly resistant and their incidence is high. We have also estimated the weighted pooled prevalence of co-existing carbapenem-resistant genes in clinical isolates of *K. pneumoniae*.

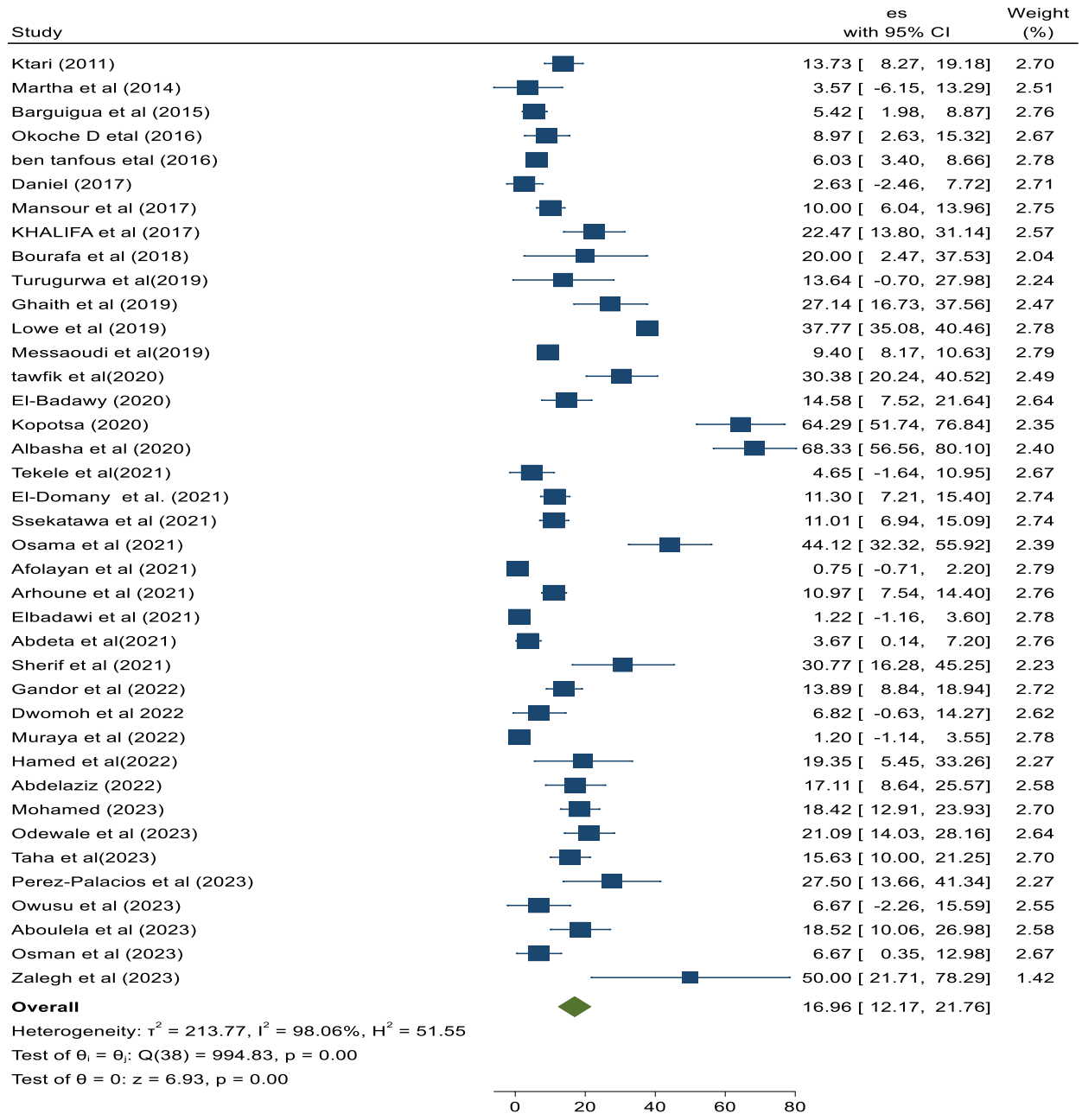

Fig. 4 Forest plot showing the pooled prevalence of $bla_{\text{OXA-48}}$ genes in *K. pneumoniae* isolates from clinical samples in Africa

This systematic review and meta-analysis also revealed the co-existence of carbapenem-resistance-conferring gene mutations within a single *K. pneumoniae* isolate. Therefore, the pooled prevalence estimates for the $bla_{\text{VIM+OXA-48}}$, $bla_{\text{IMP+OXA-48}}$, and $bla_{\text{NDM+OXA-48}}$ genes were 2.5% (95% CI: 1.1–3.9%), 1.5% (95% CI: 0.4–2.6%), and 4.5% (95% CI: 2.4–6.7%), respectively (Fig. 7).

Country wise distribution of genes encoding carbapenem resistance

The country-wise distribution of genes encoding carbapenem resistance in *K. pneumoniae* isolates shows marked regional variation. Egypt and South Africa report notably higher prevalence rates, accounting for 31.9% and 26.4%, respectively, highlighting significant regional hotspots for resistance (S15 figure in S1 File).

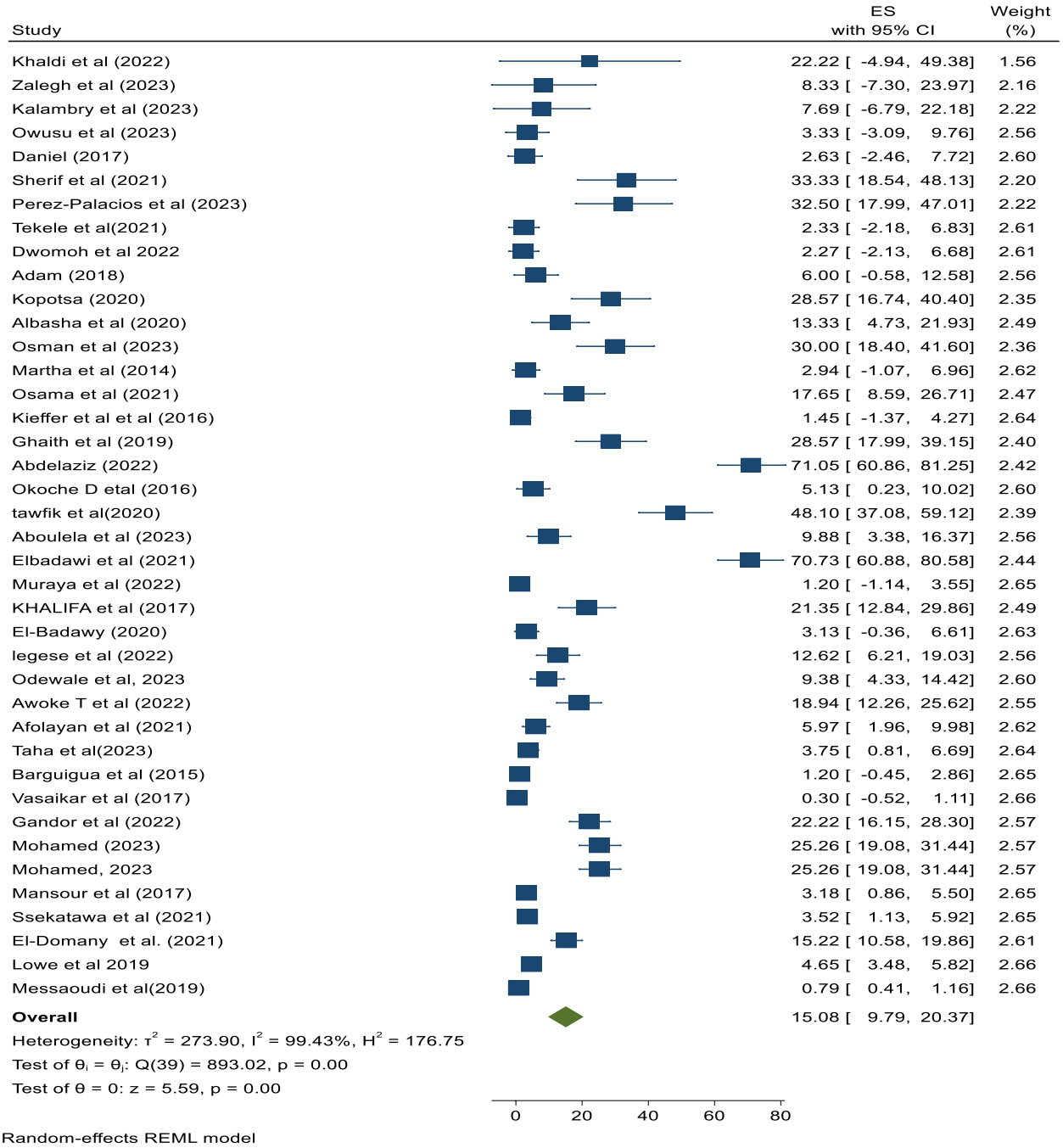

Fig. 5 Forest plot showing the pooled prevalence of $bla_{\text{NDM-1}}$ genes in *K. pneumoniae* isolates from clinical samples in Africa

Discussion

K. pneumoniae is one of the top priority pathogens globally [2], responsible for 54.9% of deaths along with five major pathogenic bacteria worldwide [78]. Since the first report of carbapenem-resistant *K. pneumoniae* (CRKP) in 1996, the incidence of this multidrug-resistant pathogen has risen significantly [79]. Resistance primarily arises from the production of acquired carbapenemases, including bla_{KPC}, bla_{OXA}, bla_{NDM}, bla_{IMP}, and bla_{VIM}, as well as the combinatorial mechanisms involving ESBL activity [79]. Multidrug-resistant *K. pneumoniae* isolates have developed resistance to various antibiotics, including third-generation cephalosporins, aminoglycosides, fluoroquinolones, and carbapenems [80]. This

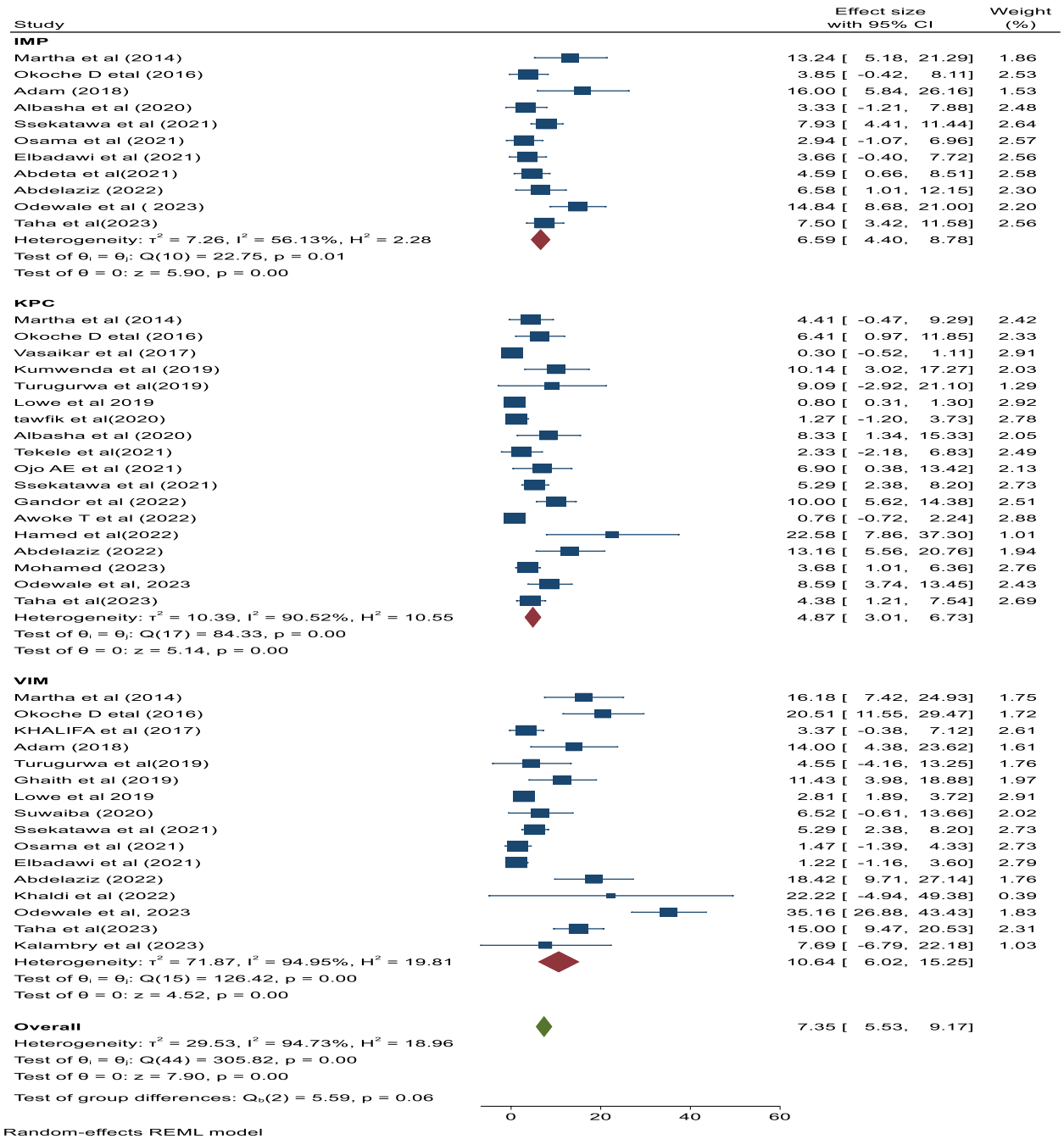

Fig. 6 Forest plot showing pooled prevalence of bla_{IMP}, bla_{VIM}, and bla_{KPC} genes in *K. pneumoniae* isolates from clinical samples in Africa

has become worrisome, particularly at a time when no new promising antimicrobial agents are on the horizon. Therefore, it is essential to understand their emergence and distribution across various geographical regions [81]. Moreover, understanding their prevalence is essential to curb the spread of carbapenemases and determine the most effective containment and prevention strategies. Given the issues with improper antibiotic usage across Africa, this study aimed to conduct a systematic review and meta-analysis to consolidate the diverse data from the continent.

In this systematic review and meta-analysis, the overall pooled prevalence of carbapenemase-encoding genes in *K. pneumoniae* isolates in Africa was 34.0%. The result was inline systematic review conducted from Asian countries 32.5% [82]. However the result was lower

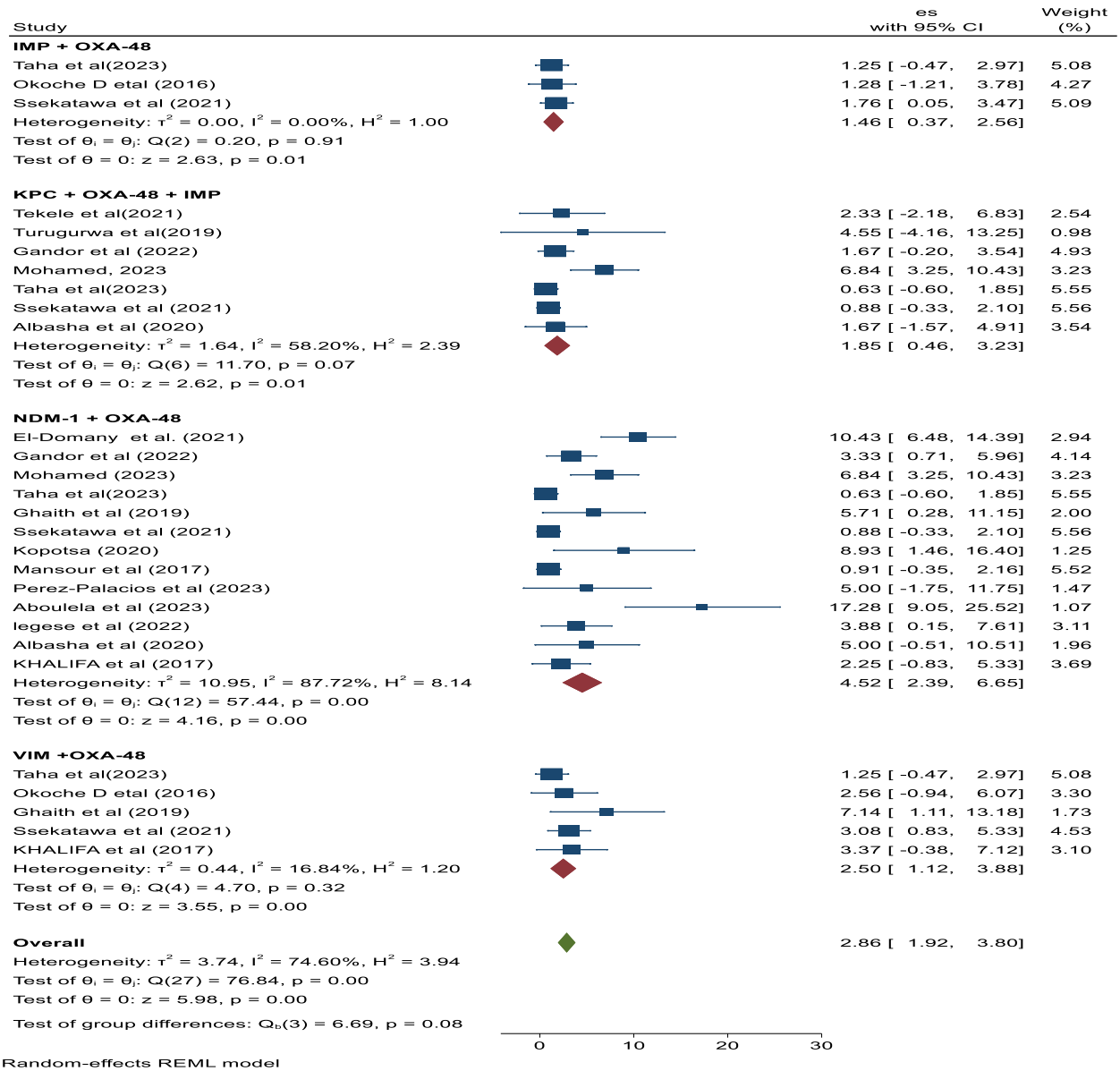

Fig. 7 Forest plot showing the pooled prevalence of co-existence of genes ($bla_{\text{NDM-1+OXA-48}}$, $bla_{\text{KPC+OXA-48}}$, and $blal_{\text{MP+OXA-48}}$) genes in *K. pneumoniae* isolates from clinical samples in Africa

as compared to multicentric retrospective study from India which was 55.4% [83] and Iran 42.1%, [84] and higher than study from Iran which was 23.0% [85]. Possible contributing factors include the length of hospital stays, prior antibiotic exposure, the invasive spread of carbapenem-resistant strains from high-resistance areas, repeated misuse of antibiotics, and insufficient infection control measures [86].

Currently, $bla_{\text{OXA-48}}$ like producing *K. pneumoniae* clones is a cause of nosocomial infections [87]. The prevalence of $bla_{\text{OXA-48}}$-like genes has significantly increased, partly due to challenges in laboratory detection and subsequent delays in implementing infection control measures [88]. In this systematic review and meta-analysis, the overall pooled prevalence of $bla_{\text{OXA-48}}$ genes in *K. pneumoniae* clinical isolates from Africa was found to be 16.96%. This was consistent with a study from China which was 14.98% [89] and reports from a systematic review conducted in low-and middle-income countries [90]. This result was lower than studies from Iran which was 44.3% [91] and 38.01%% [84]. Furthermore, this study was higher as compared

to studies from, and studies from Iran which acounts 5.96% [92] and 1.1% [85].

bla_{NDM}-producing CRKP is known to be associated with high morbidity and mortality worldwide and it has been rising in China [93], and India [3]. Currently, *K. pneumoniae* is developing multi-resistance determining genes like bla_{NDM} and becoming a worldwide threat [94]. In this study, the overall pooled prevalence of bla_{NDM-1} genes from *K. pneumoniae* isolates in Africa was found to be 15.08%. This was lower than the study from the multicentric study from India which was 24.4% [83], a study from Arabian Gulf countries which was 26.9% [95], systematic review conducted from Asian countries 32.5% [82] and study from Iran 29.8% [84]. However, this was higher than the study from, China 6.6% [93], Turkey 1.3% [96]. This highlights the importance of surveillance for these genes in hospital settings to ensure effective infection prevention and control.

In this study, the pooled prevalence of co-existed genes was highest for $bla_{OXA-48} + bla_{NDM-1}$ with a prevalence of 4.52%. To address this global health threat, it is essential to implement continuous infection prevention measures, antimicrobial stewardship, and strict surveillance of infections. This is particularly crucial as carbapenems are increasingly losing their effectiveness [97]. Our findings highlight a persistently high pooled prevalence of CRKP isolates with a pooled prevalence of 26.2%. This was in line with research conducted in Nigeria which was 26.3% [98], studies conducted from a network of long-term acute care hospitals in the United States 24.6% [99], and global studies conducted on of hospital-acquired carbapenem-resistant *K. pneumoniae* 28.69% [100]. This was lower than the two studies from Iran 42.1% [84] and 45.8% [91], and China 41.25% [101], However this result was higher as compared to a systematic review and meta-analysis from low and middle-income countries which was 0.3% [90], systematic review and meta-analysis conducted on *K. pneumoniae* colonization 5.43% [102], and systematic review conducted in East Africa 15.0% [103]. The variation may also result from differences in the implementation of policies aimed at controlling drug-resistant bacteria, which, in turn, influence the prevalence of resistant strains observed across various regions.

A subgroup analysis was conducted based on the year of publication, study country, and sample size. The pooled prevalence of genes encoding carbapenem resistance increased from 22.7% for the year category of 2010–2016 to 35.5% for the year category of 2017–2023. This might be due to improved detection techniques, Increased Usage of Carbapenems, increased reporting of data, increased global travel and trade have facilitated the dissemination of resistant bacterial strains across countries. Additionally, factors such as differences in methods of detection and detection capacities, the hygienic conditions in delivery areas may all contribute to explaining these differences [104].

Limitations of the study

The analysis in this study was limited to papers written in the English language. The examined studies displayed significant heterogeneity regarding study country. There may also be variances in interpretations and conclusions due to changes in antimicrobial susceptibility standards and interpretive criteria over time, and the pooled estimates of carbapenem resistance might be based on studies with few isolates and highly fluctuating carbapenem resistance rates.

Conclusions

Overall, this meta-analysis showed a broad range of genes encoding carbapenemase of *K. pneumoniae* with a high pooled prevalence. Furthermore, there was a significant difference across different African countries. Genes (bla_{OXA-48} and bla_{NDM}) were the most prevalent genes responsible for carbapenemase production in *K. pneumoniae.*

Recommendation

In African countries, surveillance is often inconsistent because of insufficient integration and non-representativeness of local data, inconsistent laboratory quality, and scarce microbiological diagnostic facilities. Platforms that provide data in a timely and useful manner should be created since the types of infections and the corresponding carbapenem resistances are altered over time. The observed increase in genes encoding carbapenemase in *K. pneumoniae* indicates that there should be an urgent need for enhanced infection control measures, careful antimicrobial stewardship practices, and strengthened surveillance systems to curb the spread of resistant strains.

Implication of the study

CRKP is a severe threat to this vulnerable population worldwide, in particular to those in LMICs. Worryingly, we show here that *K. pneumoniae* isolated in Africa are endowed with rich in carbapenemase genes that make them almost pan-drug resistant. Individualized approaches that are informed by local data may be needed for designing countermeasures. The dominance of carbapenemase genes imposes challenges to the effective treatment of neonatal infection. Our findings support the need for ongoing research into effective therapeutics.

Abbreviations

CI	Confidence Interval
CRE	Carbapenem Resistant *Enterobacteriaceae*

CLSI	Clinical & Laboratory Standards Institute
CRKP	Carbapenem-Resistant *Klebsiella pneumoniae*
ESBL	Extended Spectrum β-Lactamases
GNB	Gram-Negative Bacteria
IMP	Imipenemase
JBI	Joanna Briggs Institute
KPC	*Klebsiella pneumoniae* Carbapenemase
K. Pneumoniae	*Klebsiella pneumoniae*
LMICs	Low-and-middle-income countries
MeSH	Medical Subject Headings
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
NDM	New Delhi Metallo-β-Lactamase
OXA	Oxacillinase
VIM	Verona Integron-Encoded Metallo-**B**-Lactamase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10959-7.

Supplementary Material 1.

Authors' contributions

AS: led the systematic review and meta-analysis, overseeing the study's conceptualization, article selection, data extraction, statistical analysis, and manuscript writing. AS, MAR, HMG and GK: involved in searching for relevant articles, conducting data extraction, performing statistical analysis, and involved in manuscript drafting. MAR and GK were involved in statistical analysis, consultation of the overall process of this systematic review, and meta-analysis. AS, MAR, GK, YG and MN, were involved in data extraction, statistical analysis, manuscript writing, editing, and ensuring the accuracy and completeness of the data. Additionally, all authors actively engaged in critically reviewing the study's progress, data analysis, and manuscript writing, involved in the approval of the final manuscript for submission, thereby affirming their endorsement of its content and findings.

Funding

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Data availability

All generated data and research materials are available from paper and supplementary materials.

Declarations

Ethics approval and consent to participate

Not required as it exclusively utilized publicly available aggregated data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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