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Research article

# High prevalence of carbapenem-resistant *Enterobacterales* (CRE) in human samples from Nigeria: A systematic review and meta-analysis

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ABSTRACT

*Objectives:* The rise in Carbapenem-resistant *Enterobacterales* (CRE) is perturbing. To curb the menace of CRE, a comprehensive understanding of its prevalence and epidemiology is crucial. As varying reports abound, the true prevalence of CRE in Nigeria remains unknown. Here, we conducted a systematic review and meta-analysis following standard guidelines to assess the situation of CRE in Nigeria.

*Methods:* We searched electronic databases including Pubmed, ScienceDirect, Scopus, Web of Science, and Google Scholar for articles providing information on CRE in Nigeria. The data gathered were analyzed using OpenMeta Analyst and Comprehensive Meta-Analysis software. The random-effect model was employed to calculate pooled resistance to carbapenem antibiotics.

*Results:* From 321 retrieved records, 57 were finally included. The studies were predominantly from the South-West region (n = 19). *Escherichia coli* and *Klebsiella pneumoniae* were the most frequently tested *Enterobacterales* among the included studies. The pooled prevalence estimate for imipenem resistance among CRE was 11.2 % (95 % CI: 7.9–15.7). Meropenem resistance had an estimate of 13.5 % (95 % CI: 9.1–19.6), whereas ertapenem and doripenem were estimated at

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17.0 % (95 % CI: 9.9–27.7) and 37.9 % (95 % CI: 15.0–67.8), respectively. High heterogeneity ($I^2$>85 %, $p < 0.001$) was observed for the estimates. The highest resistance rate to imipenem (28.4 %), meropenem (37.2 %) and ertapenem (46.5 %) were observed for the South-South region. Based on specific CRE genera, *Morganella* sp. was the most resistant (37.0 %) while *Escherichia* sp. was the least (9.4 %). Our analyses also revealed a progressive increase in resistance to carbapenem antibiotics over the years.

*Conclusion:* This study highlights carbapenem resistance as a concern in Africa's most populous nation, underscoring the need for proactive measures to address and mitigate the threat of CRE.

## 1. Introduction

The global healthcare systems face substantial challenges due to antibiotic resistance. Based on predictive statistical models [1], bacterial antimicrobial resistance was linked to approximately 4.95 million deaths in 2019, with 1.27 million directly attributed to bacterial antimicrobial resistance. The rates of resistance are more elevated in low-income nations compared to their high-income counterparts. In numerous low-income settings, substantial data gaps exist, potentially indicating a more severe resistance situation in these countries than suggested by the available data [2].

In 2017, the World Health Organization identified carbapenem-resistant *Enterobacterales* (CRE) as one of the three primary categories of drug-resistant bacteria worldwide requiring immediate attention for the development of new antibiotics [3]. CRE, as defined by the Centers for Disease Control and Prevention (CDC) of the United States, are *Enterobacterales* exhibiting *in vitro* resistance to at least one carbapenem [4]. CRE resistance mechanisms encompass antibiotic degradation, hindrance of antibiotic penetration into bacterial cells, alteration of antibiotic binding targets, mutation or deletion of pore proteins, heightened activation of efflux pumps, and alteration of penicillin-binding proteins and biofilm composition [5]. Antibiotic degradation can result from the organism's production of carbapenemases, enzymes that degrade carbapenem antibiotics and render them ineffective. Notable examples include *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-beta-lactamase (NDM), and oxacillinase-48 (OXA-48), produced by various *Enterobacterales* [5]. Porin proteins, which are channels in the bacterial cell wall that permits the entry of antibiotics may be mutated. These mutations can reduce carbapenem uptake, diminishing their effectiveness [5]. Additionally, bacteria can overexpress efflux pumps, increasing the expulsion of antibiotics from the cell before they can reach their targets [6]. This mechanism is significant in β-lactam resistance for pathogens like *Pseudomonas aeruginosa*, *Escherichia coli*, and *Neisseria gonorrhoeae* [6]. Furthermore, bacteria often combine these mechanisms, resulting in high-level resistance to carbapenems.

Carbapenems represent a highly effective category of broad-spectrum antibiotics [7]. They are regarded as one of the last-line antibiotics in many hospitals. However, the emergence of resistance to carbapenems poses a considerable restriction on the available antibiotic options for treating challenging infections. The prevalence of CRE has markedly increased over the years, and these resistant bacteria have been reported in virtually all parts of the world, including North America, Europe, the Mediterranean, South Asia, and Africa [8–13]. This is particularly worrisome as CRE infections are linked to higher morbidity and mortality rates compared to other pathogens, especially among patients with severe underlying health conditions or those admitted to the intensive care unit [14,15].

The rise of CRE poses an escalating global threat to human health. In dealing with CRE infections, extended therapy durations become necessary, resulting in higher treatment costs and the need for approaches with elevated toxicities compared to strains susceptible to carbapenems. Given the rising challenges of carbapenem resistance and the limited therapeutic alternatives available, it is essential to completely understand the epidemiology of CRE infections. This information holds significance in enhancing infection prevention and control, implementing effective antimicrobial stewardship, and other strategic initiatives aimed at mitigating carbapenem resistance. Because varying prevalence rates have been reported in different parts of Nigeria, the true prevalence of CRE in Nigeria, and the different regions of the country is unknown. This knowledge is especially important because Nigeria, being the most populous country in Africa, sees a significant flow of people both into and out of the country for various reasons. Thus, in this study, we aimed to provide a comprehensive overview of the situation in the country. To our knowledge, this study represents the first meta-analysis to be conducted on this subject in Nigeria.

## 2. Methods

This systematic review and meta-analysis followed the guidelines established in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [16]. A study protocol was also developed and registered with PROSPERO (registration number: CRD42023418296) to avoid any redundancy with already existing or ongoing studies.

### 2.1. Literature search/sources of data

We employed a set of keywords, including "Carbapenem," "Ertapenem," "Imipenem," "Meropenem," "CRE," "Enterobacterales," "Enterobacteriaceae," "*Escherichia coli*," "*E. coli*," "Enterobacter," "Klebsiella," "Shigella," "Citrobacter," and "Nigeria," to conduct a thorough search across four electronic databases (Scopus, Google Scholar, Pubmed, Web of Science, and Science Direct) for studies that reported the prevalence of CRE in Nigeria. The detailed search strategy utilized for accessing all databases is available in the

supplementary document (File S1). To ensure a comprehensive search, no filters based on study design, language, or publication year were applied. The initial search took place on February 25, 2023, and a final updated search, yielding a total of 321 records, was performed on April 14, 2023. The retrieved records from the databases were exported to EndNote X8 software for duplicate removal and initial screening.

### 2.2. Criteria for study eligibility

This study encompassed research focusing on CRE in the human population of Nigeria. We excluded (1) case reports, reviews, editorials, letters, book chapters, and opinions; (2) studies reporting CRE data from countries outside Nigeria; (3) studies evaluating CRE from sources other than humans; (4) articles with unavailable full texts; (5) investigations involving known cases of CRE that do not reflect prevalence among a sampled population.

All authors established the criteria for screening, selecting, and evaluating articles. Working independently, at least two authors conducted initial screening based on the title and abstract, followed by a thorough assessment of the full texts of the screened articles. In cases of disagreements during the screening and assessment process, the involvement of other authors was sought to reach a consensus.

### 2.3. Extraction of data and quality evaluation

Data extraction involved the utilization of a pre-established Excel spreadsheet. Independently, three authors extracted the following details from the incorporated studies: study ID, duration of the study, study location, study design, *Enterobacterales* members examined, method employed for resistance determination, sample type, count of resistant organisms, and the overall number of *Enterobacterales* evaluated.

The methodological quality of the incorporated studies was evaluated using the Joanna Briggs Institute (JBI) critical appraisal checklist designed for prevalence data [17] (File S2). Two authors conducted independent assessments, assigning a total quality score ranging from 0 to 9. Adequate quality was defined as a score of 7 or higher [18].

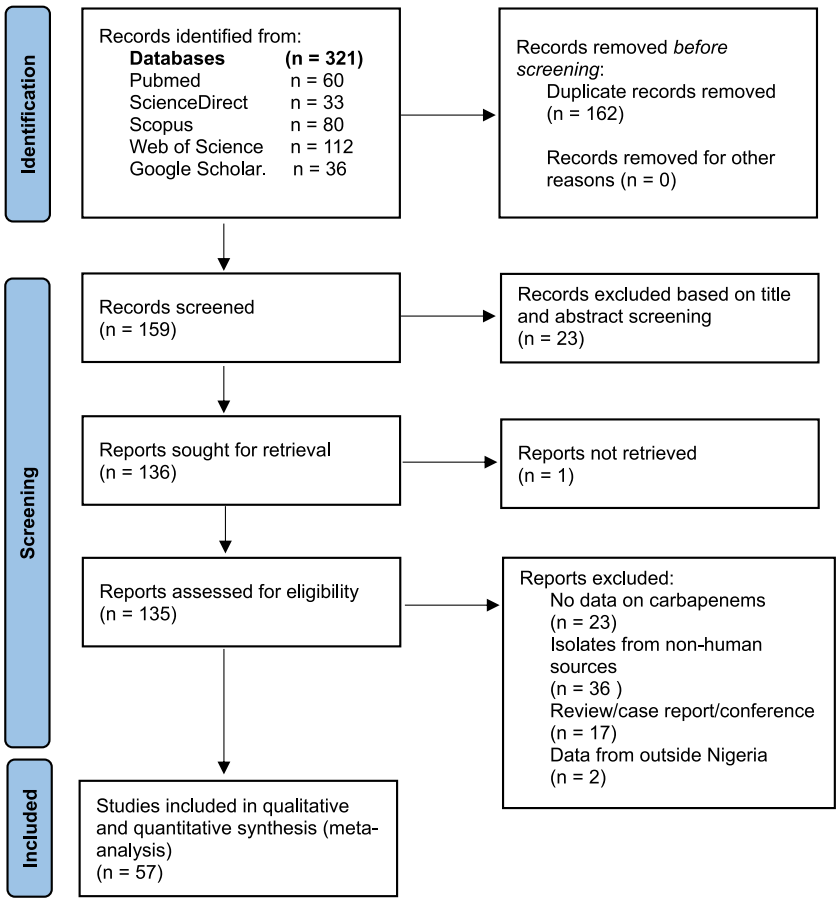


**Fig. 1.** Overview of the process for searching and selecting articles.

### 2.4. Quantitative analysis and synthesis of data

The collected data underwent scrutiny to identify and address potential duplications before being analyzed. OpenMeta Analyst and Comprehensive Meta-Analysis 3.0 (CMA 3.0) software were employed for analyses. Summary estimates regarding resistance to each of the carbapenems (imipenem, meropenem, ertapenem, and doripenem) were generated using the DerSimonian-Laird method of meta-analysis and the random-effect model. To assess potential publication bias, a funnel plot was generated. Egger's regression test was conducted to evaluate the plot's asymmetry, and a Trim and Fill sensitivity test was performed to assess changes in prevalence estimates. Cochran's Q test was utilized to examine heterogeneity in study-level estimates, with $I^2$ statistics used for quantification; $I^2$ values of 25 %, 50 %, and 75 % indicated low, moderate, and high heterogeneity, respectively [19,20]. Subgroup meta-analysis was performed to explore sources of heterogeneity and to determine the prevalence of CRE in various subgroups. In all tests, statistical significance was defined by a $p$-value of $<0.05$.

## 3. Results

### 3.1. Selection of studies

The process of article identification and selection in this study is outlined in Fig. 1. Our search across five electronic databases yielded 321 records. Following the removal of duplicates and exclusion of studies not meeting the predetermined inclusion criteria, we assessed the full text of 135 studies for eligibility. Fifty-seven studies met the eligibility criteria and were consequently included in both the qualitative and quantitative synthesis.

### 3.2. Characteristics of the included studies

This study encompassed research conducted at various locations across Nigeria, with all regions of the country represented. While the majority of the reports originated after 2010, diverse sample types, such as urine, blood, sputum, stool, cerebrospinal fluid, wound swab, nasal swab, and rectal swab, among others, were utilized for assessing *Enterobacterales*. Carbapenem resistance evaluation encompassed a range of *Enterobacterales*, with *E. coli* and *K. pneumoniae* being the most frequently tested. Various testing methods, including disk diffusion techniques, broth microdilution method, Epsilometer test, and assessment using automated systems were employed. A comprehensive overview of the features of the included studies is provided in Table 1.

### 3.3. Pooled prevalence

Out of the 57 studies included in this meta-analysis, data on resistance of CRE to imipenem were available in 37 studies, meropenem in 33 studies, ertapenem in 14 studies, and doripenem in 4 studies. The total number of tested *Enterobacterales* was 4209 for imipenem, 3511 for meropenem, 1731 for ertapenem, and 513 for doripenem. Using the random-effect model to calculate summary estimates, the aggregated prevalence estimate for imipenem resistance among CRE was 11.2 % (95 % CI: 7.9–15.7). Meropenem resistance had an estimate of 13.5 % (95 % CI: 9.1–19.6), while ertapenem and doripenem were estimated at 17.0 % (95 % CI: 9.9–27.7) and 37.9 % (95 % CI: 15.0–67.8), respectively (Figs. 2–5). Notably, high heterogeneity ($I^2$>85 %, $p < 0.001$) was observed for all the estimates.

### 3.4. Prevalence of CRE in various subgroups

The resistance rates of the examined *Enterobacterales* against imipenem, meropenem, ertapenem, and doripenem antibiotics underwent additional scrutiny, considering variables such as the study period, geographical region, and study design. Further, analyses based on specific genera of CRE were performed. These comprehensive analyses aimed to offer a thorough perspective on resistance rates and investigate the observed heterogeneity. Forest plots for all subgroup analyses are available in the supplementary document (File S3).

#### 3.4.1. Prevalence of imipenem resistance in CRE in various subgroups

Table 2 provides a summary of the imipenem resistance prevalence in CRE based on various analyzed variables. The subgroup analysis included studies from the six geopolitical zones of Nigeria, with the South-West region being the most represented (n = 13). South-South region exhibited the highest resistance rate at 28.4 % (95 % CI: 14.0–49.2), while the North-East region had the lowest at 0.1 % (95 % CI: 0.0–2.2). The majority of studies (n = 16) were conducted between 2016 and 2020, accounting for a resistance of 13.1 % (95 % CI: 8.2–20.3). Nonetheless, the highest CRE resistance rate (25.0 %, 95 % CI: 11.7–45.6) was observed in the 2021–2023 period. However, the estimate was contributed by only one study. Regarding study design, the analyzed studies were predominantly cross-sectional studies (n = 16). The highest resistance rate was observed in a prospective study (17.4 %, 95 % CI: 6.7–38.2), followed by cross-sectional studies (12.1 %, 95 % CI: 6.9–20.4). While various parameters indicated high heterogeneity, studies conducted in the 2011–2015 period demonstrated moderate heterogeneity ($I^2 = 52.26$ %).

#### 3.4.2. Prevalence of meropenem resistance in CRE in various subgroups

The subgroup analysis on meropenem resistance included studies from all the six geopolitical zones of the country, with the South-

**Table 1**
Major characteristics of the included studies.

| Study ID | Study period | Location | Study design | Organism tested | Method | Sample type | Total *Enterobacterales* | Reference |
|---|---|---|---|---|---|---|---|---|
| Adegoke 2022 | NR | Akwa Ibom | Cross-sectional | *E. coli* | DDM | Urine | 39 | [21] |
| Adekanmbi 2022 | 2019–2020 | Oyo | NR | *K. pneumoniae, K. oxytoca, P. mirabilis, E. cloacae* | DDM | Urine | 20 | [22] |
| Adekanmbi 2021 | 2019–2020 | Oyo | NR | *E. coli* | DDM | Urine | 49 | [23] |
| Adenipekun 2016 | 2012–2013 | Lagos | NR | *E. coli* | BMM | Urine, stool | 247 | [24] |
| Adeosun 2019 | 2018–2019 | Osun | NR | *K. pnuemoniae* | DDM | Urine, wound swab, ear swab, eye swab, other collection sites | 62 | [25] |
| Adesanya 2020 | 2018 | Oyo | Retrospective | *K. pneumoniae*, *E. coli*, *K. oxytoca*, *P. mirabilis*, *E. cloacae*, *P. vulgaris*, *Providencia* sp. | DDM | Urine, wound swab, tracheal aspirate, sputum, catheter tip swab, pleural fluid, eye swab, pus, ear swab, tissue biopsy, rectal swab, CSF | 114 | [26] |
| Adesina 2019 | NR | Lagos | NR | *E. fergusonii* | DDM | Wound swab | 3 | [27] |
| Agbo 2015 | 2012–2013 | Enugu | NR | *E. coli*, *Klebsiella* sp. | DDM | Urine, stool, sputum wound swab, high vaginal swab | 113 | [28] |
| Akani 2022 | 2022 | Port Harcourt | NR | *Salmonella* sp., *Shigella* sp. | DDM | Stool | 10 | [29] |
| Akinlabi 2020 | 2017–2018 | Kano, katsina, Abuja | Cross-sectional | *E. coli* | DDM | Blood, Ear swab, wound swab, eye swab, urine, stool, high vaginal swab, cerebrospinal fluid | 104 | [30] |
| Akinpelu 2020 | NR | Lagos | NR | *Klebsiella* sp. | DDM | Urine, blood, sputum | 18 | [31] |
| Akinyemi 2021 | 2015 | Lagos | NR | *K. pnuemoniae* | DDM | Blood, urine, stool, wound swab, nasal swab | 43 | [32] |
| Akujobi 2013 | NR | Anambra | NR | *E. coli* | DDM | Urine, semen, wound swab, high vaginal swab, ear swab, sputum | 46 | [33] |
| Aminu 2021 | 2018 | Kano | Cross-sectional | *E. coli*, *K. pneumoniae*, *E. aerogenes*, *P. mirabilis*, *P. vulgaris*, *E. agglomerans*, *E. ozaenae*, *K. oxytoca*, *E. cloacae*, *C. freundii*, *S. odorifera*, *Salmonella* sp. | DDM | Blood, urine, sputum, tracheal aspirate, swabs of other parts | 76 | [34] |
| Anibijuwon 2018 | 2016–2017 | Ekiti, Osun, Oyo | Cross-sectional | *E. coli*, *E. aerogenes*, *Klebsiella* sp., *Proteus* sp. | DDM | Blood, urine | 59 | [35] |
| Aworh 2019 | 2018–2019 | Abuja | Cross-sectional | *E. coli* | DDM | Stool | 48 | [36] |
| Bashir 2019 | 2016 | Kano | Cross-sectional | *E. coli, Klebsiella* sp., *Proteus* sp. | DDM | Urine, wound/pus, urine catheter, nasal feed tube | 80 | [37] |
| Brinkac 2019 | 2016 | Abuja | NR | *Klebsiella* sp. | E-test | Blood | 7 | [38] |
| Brown 2017 | 2013–2014 | Ibadan | Cross-sectional | *K. pnuemoniae, S. pullorum, Salmonella* subsp *II* | DDM | Blood | 6 | [39] |
| Duru 2020 | 2008–2016 | FCT, Kano | NR | *Citrobacter* sp., *Serratia* sp., *Pantoea* sp., *Enterobacter* sp., *K. pneumoniae, E. coli* | DDM | Blood | 160 | [40] |
| Enyinnaya 2022 | NR | Abuja | Cross-sectional | *E. coli* | DDM, E-test | Blood, urine, wound biopsy/swab, CSF, sputum, aspirates, ear, eye swabs | 400 | [41] |

(*continued on next page*)

**Table 1** (*continued*)

| Study ID | Study period | Location | Study design | Organism tested | Method | Sample type | Total *Enterobacterales* | Reference |
|---|---|---|---|---|---|---|---|---|
| Fadeyi 2016 | 2013–2015 | Ilorin | Cross-sectional | *K. oxytoca, K. pneumoniae* | DDM | Blood, sputum, wound, urine, ear, eye & throat swabs | 50 | [42] |
| Fakorede 2023 | 2021 | Lagos | Cross-sectional | *Salmonella* sp. | DDM | Blood | 24 | [43] |
| Ibadin 2017 | 2016 | Benin City | NR | *Citrobacter* sp., *E. coli, Klebsiella* sp., *P. mirabilis, P. vulgaris, Providencia* sp., *S. marcescens* | DDM | Ear swab, eye swab, throat swab, vaginal swabs, wound swab, catheter tip, sputum, stool, urine & aspirates | 258 | [44] |
| Iduh 2020 | NR | Sokoto | NR | *E. coli, K. pneumoniae, Salmonella* sp. | DDM | Stool | 177 | [45] |
| Iliyasu 2016 | 2011–2014 | Kano | Retrospective | *E. coli, K. pneumoniae, P. mirabilis, Enterococcus* sp. | – | NR | 17 | [46] |
| Iregbu 2015 | 2010–2012 | Abuja | Retrospective | *E. coli, K. pneumoniae* | – | CSF | 10 | [47] |
| Isaiah 2011 | NR | Yola | NR | *E. coli* | DDM | Urine, sputum, blood, stool, high vaginal swabs, wound swabs & Abscess | 350 | [48] |
| Jamal 2022 | 2019 | Abuja | NR | *E. coli, K. pneumoniae, S. marcescens, P. mirabilis, M. morganii, C. freundii, E. cloacae* | E-test | NR | 200 | [49] |
| John 2023 | NR | Cross River | NR | *P. mirabilis, Klebsiella* sp., *E. coli, Providencia* sp., *Enterobacter* sp., *Citrobacter* sp. | DDM | Wound swab, throat swab | 37 | [50] |
| Kankara 2022 | 2018 | Katsina | Prospective | *E. coli, K. pneumoniae, E. aerogenes, P. mirabilis,* | DDM | Urine, wound swabs, hand swabs, sputum, stool, catheter swab | 15 | [51] |
| Kingsley 2013 | 2011–2012 | Uyo | Cross-sectional | *E. coli, K. pneumoniae, Enterobacter* sp, *P. mirabilis, S. typhi* | DDM | Blood | 57 | [52] |
| Makanjuola 2018 | 2014 | Ibadan | NR | *Klebsiella* sp., *E. coli, Proteus* sp., *Enterobacter* sp. | DDM | Blood, urine, wound swabs, biopsies, tracheal aspirates | 39 | [53] |
| Medugu 2022 | 2019–2020 | Abuja | Cross-sectional | *E. coli* | VITEK 2 AST-280/ VITEK 2 AST-281 cards | Stool, CSF, aspirate, endocervical swab, wound swab, blood, urine | 107 | [54] |
| Mofolorunsho 2021 | 2018 | Anyibga | Cross-sectional | *E. coli, K. pneumoniae* | DDM | Urine | 78 | [55] |
| Mohammed 2015 | 2014 | Borno | Cross-sectional | *K. pneumoniae, E. coli, P. mirabilis, K. oxytoca, M. morganii, C. freundii, S. marcescens, E. aerogenes, K. ozaenae, H. alvei, C. sedlakii* | DDM | Blood, urine, cerebrospinal fluid, stool, and swabs of patients with invasive diseases | 225 | [56] |
| Motayo 2013 | NR | Abeokuta | NR | *E. coli, K. pneumoniae* | DDM | Blood, urine, CSF, genitals, etc. | 21 | [57] |
| Nkup 2022 | 2020 | Jos | Prospective | *K. pneumoniae* | DDM | Urine, sputum, wound swab | 8 | [58] |
| Nwafia 2019 | 2016–2017 | Enugu | Cross-sectional | *E. coli* | DDM | Urine, pleural & peritoneal aspirate, blood, wound swabs, CSF | 70 | [59] |
| Oduyebo 2015 | 2013 | Lagos | NR | *K. pneumoniae, K. oxytoca, K. ozaenae, E. coli, E. agglomerans, E. aerogenes, E. cloacae, P. mirabilis, P. vulgaris,* | DDM | Urine, blood, sputum, wound, pus | 177 | [60] |

(*continued on next page*)

**Table 1** (*continued*)

| Study ID | Study period | Location | Study design | Organism tested | Method | Sample type | Total *Enterobacterales* | Reference |
|---|---|---|---|---|---|---|---|---|
| | | | | *S. rubidaea, M. morganii, C. freundi, P. rettgeri* | | | | |
| Ojuawo 2020 | 2017 | Ilorin | Prospective | *K. oxytoca, K. pneumoniae* | DDM | Blood, sputum | 23 | [61] |
| Okpalanwa 2019 | 2018 | Ankpa | Cross-sectional | *Salmonella* sp. | DDM | Stool | 9 | [62] |
| Oladipo 2021 | NR | Ibadan | NR | *K. pneumoniae* | DDM | Wound swab | 100 | [63] |
| Oli 2017 | 2016 | Awka | Cross-sectional | *E. coli, Salmonella* sp. | DDM | Urine | 110 | [64] |
| Oli 2019a | 2017 | Anambra | NR | *E. coli, K. pneumoniae, K. oxytoca* | DDM | Urine, anal swab, wound swab, sputum | 78 | [65] |
| Oli 2019b | NR | Enugu | NR | *E. coli, K. pneumoniae, Enterobacter* sp, *Citrobacter* sp., *Proteus* sp., *Serratia* sp. | DDM | Urine, stool | 32 | [66] |
| Omoyibo 2018 | 2014 | South-West | Cross-sectional | *E. coli, M. morganii, P. mirabilis, S. odorifera, E. cloacae, E. gergoviae* | DDM | Wound swab | 19 | [67] |
| Onanuga 2020 | 2019 | Bayelsa | Cross-sectional | *E. coli, K. pneumoniae* | DDM | Urine | 42 | [68] |
| Onanuga 2019 | 2015 | Port Harcourt | Cross-sectional | *E. coli, K. pneumoniae* | DDM | Urine | 81 | [69] |
| Onyedibe 2018 | 2014 | Jos | Cross-sectional | *E. coli* | DDM | Urine, blood, swabs, aspirates | 220 | [70] |
| Oyekale 2022 | 2020–2021 | Ekiti | Cross-sectional | *E.coli, K. aerogenes, P. vulgaris, P. mirabilis* | DDM | Blood | 20 | [71] |
| Raji 2013 | 2011 | Lagos | Cross-sectional | *E. coli, K. pneumoniae, P. mirabilis, E. cloacae* | E-test | Urine, blood, skin swab, soft tissue, surgical site, nasal swab, ear swab, body fluids | 96 | [72] |
| Romanus 2009 | 2009 | Enugu | NR | *K. pneumoniae* | DDM | Urine, blood, sputum | 186 | [73] |
| Shitta 2021 | 2016–2017 | Osun | Cross-sectional | *E. coli, Klebsiella* sp., *P. vulgaris, S. rubidae, Citrobacter* sp., *Enterobacter* sp., *S. typhi* | DDM | Urine, wound, high vaginal swab, stool, eye swab, ear swab, endocervical swab | 356 | [74] |
| Ugah 2022 | 2019–2021 | Abia, Enugu, Ebonyi, Imo, Anambra | Cross-sectional | *E. coli, K. pneumoniae, K. oxytoca, M. morganii, C. freundii, S. marcescens, P. mirabilis, E. cloacae, S. dysenteriae, S. enterica, P. vulgaris, enterocolytica* | DDM | Urine, sputum, CSF, stool, blood, etc. | 400 | [75] |
| Uzoamaka 2017 | 2014–2016 | Enugu | NR | *E. coli, K. pneumoniae, Proteus* sp. | DDM | Sputum | 259 | [76] |
| Yusuf 2014 | NR | Kano | NR | *E. coli, K. pneumoniae, Enterobacter* spp, *Salmonella* sp, *P. mirabilis, P. vulgaris* | DDM | Urine, catheter tip swab, stool, semen, urogenital swab, abscesses | 547 | [77] |

NR, Not reported; DDM, disk diffusion method; BMD, broth microdilution method; E-test, Epsilometer test.

West being the most represented (n = 11) (Table 3). The South-South region exhibited the highest pooled resistance rate at 37.2 % (95 % CI: 26.0–50.0), while the lowest was from the North-East (9.8 %, 95 % CI: 6.5–14.4). Studies conducted from 2016 to 2020 were the most abundant (n = 14), constituting the period with the highest pooled resistance rate to meropenem antibiotics at 24.7 % (95 % CI: 17.1–34.1). Cross-sectional studies were the most common in terms of study design (n = 14). A substantial meropenem resistance rate of 43.5 % (95 % CI: 25.2–63.8) was estimated for the prospective study design. A moderate heterogeneity was observed for studies conducted in the South-South region (51.38 %), and no heterogeneity was found for studies in the prospective study design.

### *3.4.3. Prevalence of ertapenem resistance in CRE in various subgroups*

The South-West region contributed more studies (n = 5) to the ertapenem subgroup analysis, with the highest pooled resistance rate observed for the South-South at 46.5 % (95 % CI: 35.5–57.8) (Table 4). Further, there were more studies conducted in the 2016–2020

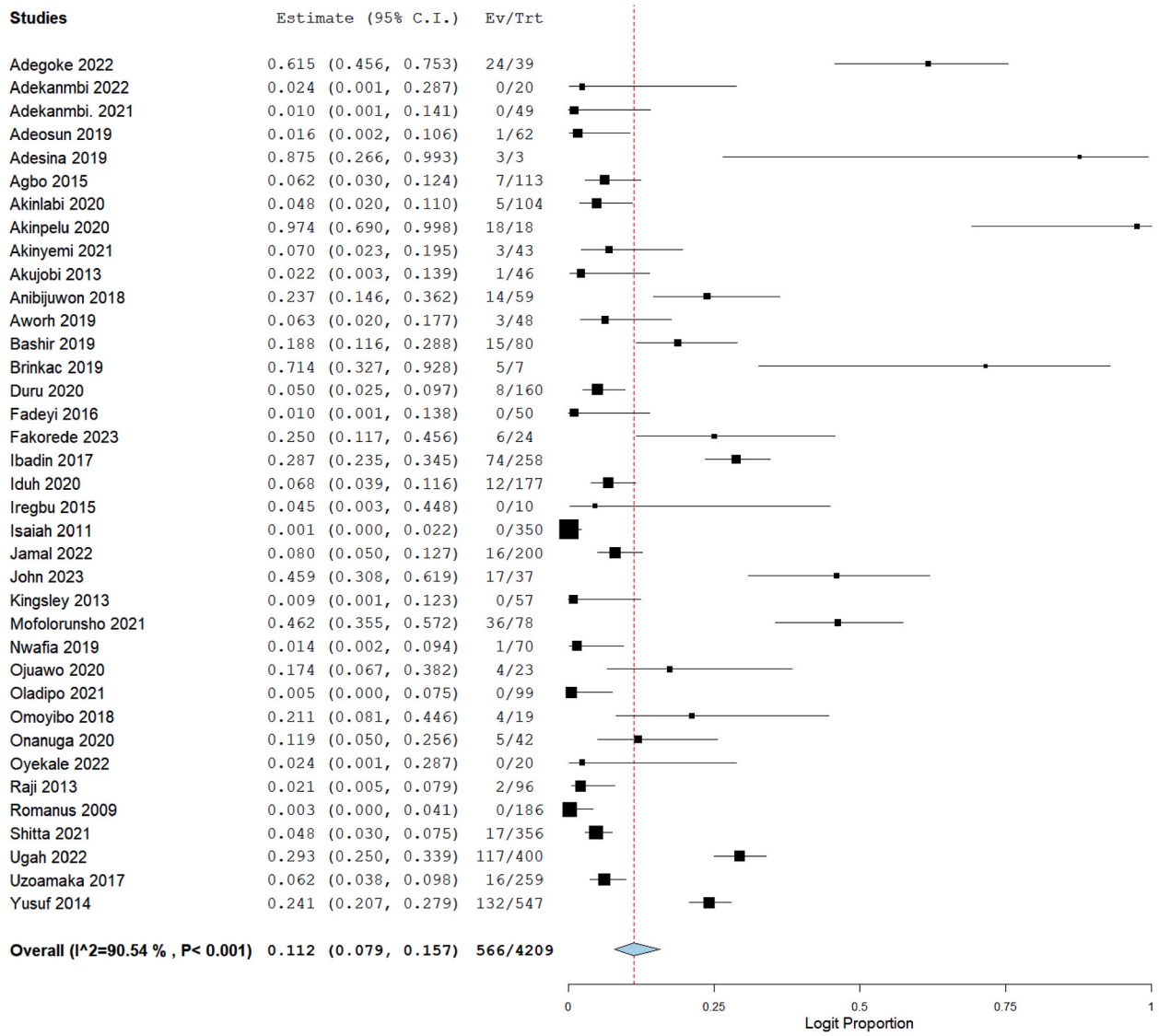


**Fig. 2.** Forest plot illustrating the pooled prevalence of imipenem resistance in CRE.

study period (n = 7). However, the highest resistance rate of 98 % (95 % CI: 74.9–99.9) was in the 2021–2023 study period. It is worthy of note, however, that this high resistance rate was contributed by a single study. Except for studies conducted in the South-South region, high heterogeneity (>90 %) was observed in the variables assessed for ertapenem resistance.

### *3.4.4. Prevalence of carbapenem resistant organisms*

The prevalence of specific genera of CRE to at least one carbapenem antibiotic was also evaluated. The estimates revealed *Morganella* sp. as the most resistant CRE (37.0 % [95 % CI: 22.9–53.7]) followed by *Salmonella* sp. (36.9 % [95 % CI: 16.8–62.9]). In contrast, *Escherichia* sp. was the least resistant (9.4 % [95 % CI: 6.3–13.8]) among the CRE analyzed (Fig. 6).

## *3.5. Evaluation of study quality and assessment of publication bias*

The evaluation of methodological quality using the JBI tool indicated that the included studies demonstrated good quality (File S4). Funnel plots were generated to scrutinize potential publication bias, and their asymmetry, as depicted in Fig. 7, suggested the likelihood of publication bias. Further investigation into funnel plot asymmetry was conducted using Egger's regression test. Some tests yielded significant *p*-values for studies contributing to the estimates of imipenem ($p = 0.0039$) (Fig. 7A), meropenem ($p = 0.0166$) (Fig. 7B), and ertapenem ($p = 0.2559$) (Fig. 7C) resistance. To address potential biases, a Trim and Fill analysis was performed, with adjusted values revealing changes in resistance estimates: imipenem from 11.2 % to 15.6 % (95 % CI: 11.2–21.3), meropenem from

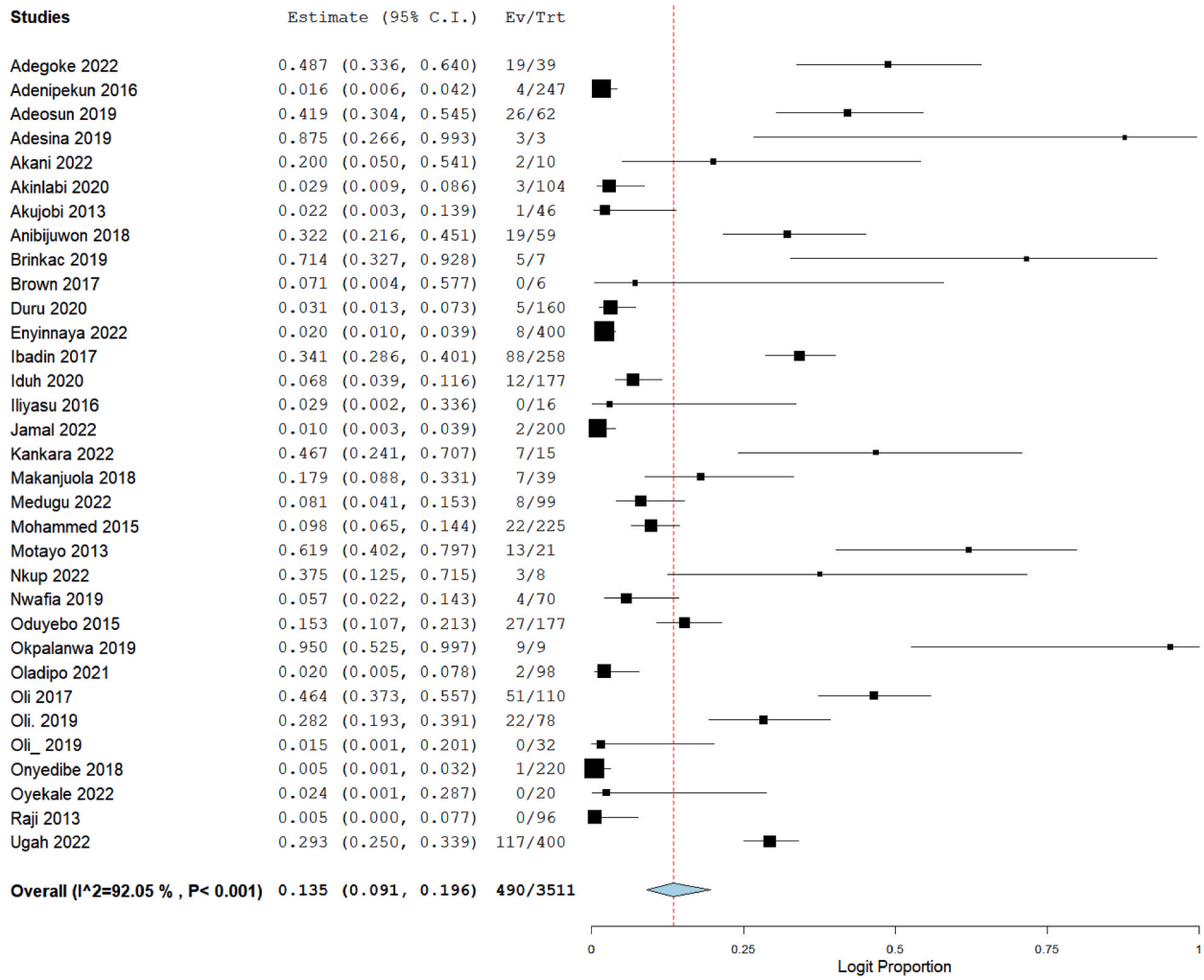


**Fig. 3.** Forest plot illustrating the pooled prevalence of meropenem resistance in CRE.

13.5 % to 17.0 % (95 % CI: 11.7–24.1), and ertapenem from 17.0 % to 14.6 % (95 % CI: 8.3–24.5) (File S5).

## 4. Discussion

CRE pose a significant and evolving threat to global public health. These multidrug-resistant bacteria have developed resistance to carbapenem antibiotics, which are considered last-line treatments for many severe bacterial infections. The emergence and spread of CRE raise critical concerns due to their potential to cause difficult-to-treat infections, increased morbidity and mortality rates, and the limited availability of effective antibiotics. Surveillance data indicate a rising prevalence of CRE, with reports from healthcare facilities highlighting its emergence in both community and hospital settings. Understanding the geographical distribution and prevalence rates is crucial for implementing targeted interventions. In this study, we provide an overview of CRE in Nigeria, the most populous African nation.

The studies included in this work were conducted in various locations within Nigeria, representing all regions of the country. However, the studies were predominantly from the South-West region (n = 19) followed by the North central. This observed distribution may be attributed to heightened surveillance and reporting activities in these areas. However, the limited representation of CRE data from other regions of the country does not necessarily indicate a lower prevalence of CRE; rather, it could be indicative of a constrained capacity for molecular epidemiology and surveillance studies or a reduced interest in CRE research. Additionally, it is likely that other infectious diseases such as malaria and HIV/AIDS are prioritized over antimicrobial resistance in those regions. Further, the majority of the studies were conducted after 2015, indicating increased interest in CRE research in recent years, which may have been warranted by the global trends in carbapenem resistance [78–80].

Further, *E. coli* and *K. pneumoniae* were the most frequently tested *Enterobacterales* among the included studies. These bacteria are commonly associated with various infections, especially in the urinary tract, respiratory system, and bloodstream [81,82]. The choice

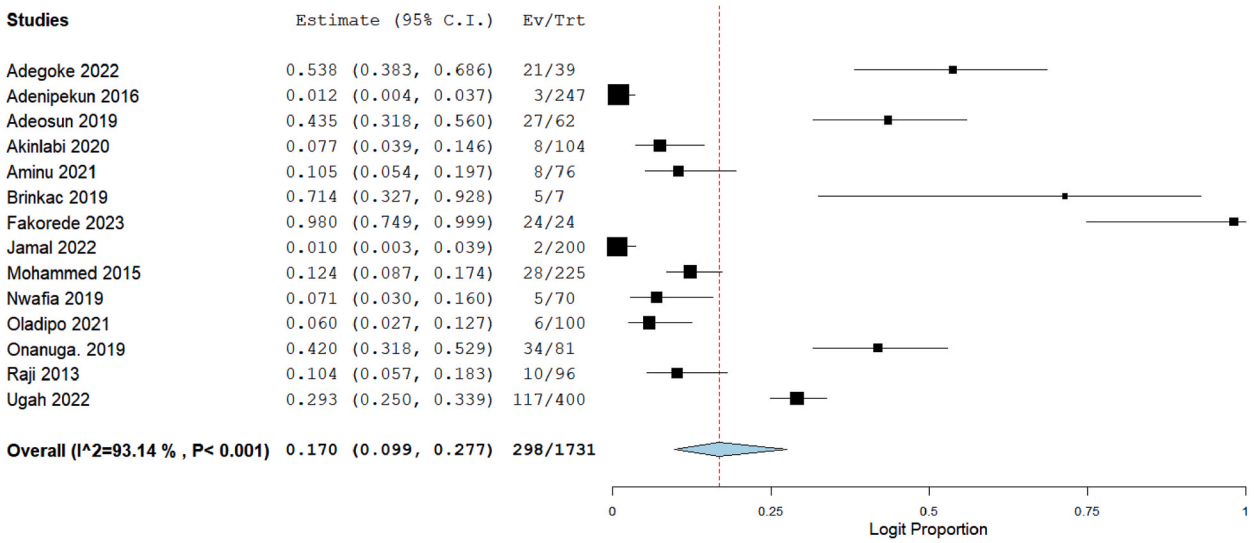


**Fig. 4.** Forest plot illustrating the pooled prevalence of ertapenem resistance in CRE.

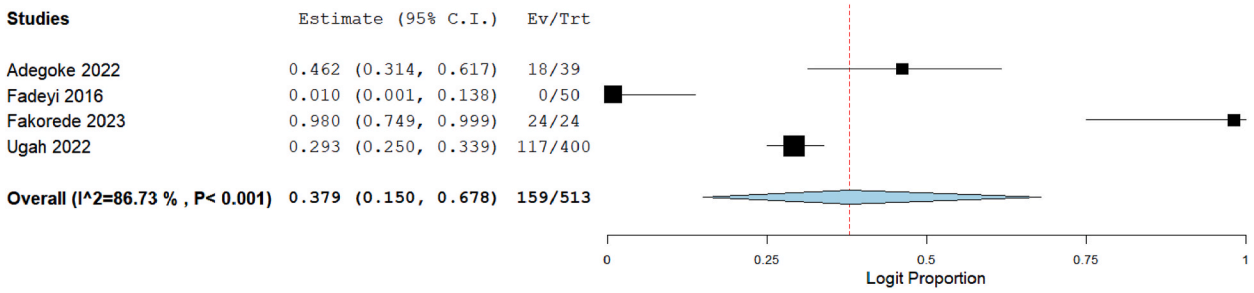


**Fig. 5.** Forest plot illustrating the pooled prevalence of doripenem resistance in CRE.

**Table 2**
Prevalence of imipenem resistance in CRE in different subgroups.

| Subgroup | Number of studies | Prevalence (%) | 95 % CI | Heterogeneity test | | |
|---|---|---|---|---|---|---|
| | | | | Q | $I^2$ (%) | p-value |
| **Region** | | | | | | |
| South-South | 5 | 28.4 | 14.0–49.2 | 33.08 | 87.91 | <0.001 |
| South-West | 13 | 9.6 | 4.2–20.6 | 72.60 | 83.47 | <0.001 |
| South-East | 6 | 4.6 | 1.3–14.6 | 83.01 | 93.98 | <0.001 |
| North-Central | 7 | 15.1 | 5.0–37.4 | 64.33 | 90.67 | <0.001 |
| North-West | 3 | 15.3 | 7.2–29.6 | 22.24 | 91.01 | <0.001 |
| North-East | 1 | 0.1 | 0.0–2.2 | NA | NA | NA |
| Overall | 35 | 12.0 | 8.4–16.8 | 347.63 | 90.22 | <0.001 |
| **Study period** | | | | | | |
| 2006–2010 | 1 | 0.3 | 0.0–4.1 | NA | NA | NA |
| 2011–2015 | 7 | 5.3 | 2.4–11.2 | 12.57 | 52.26 | 0.05 |
| 2016–2020 | 16 | 13.1 | 8.2–20.3 | 166.37 | 90.98 | <0.001 |
| 2021–2023 | 1 | 25.0 | 11.7–45.6 | NA | NA | NA |
| Overall | 25 | 10.0 | 6.5–15.1 | 220.50 | 89.12 | <0.001 |
| **Study design** | | | | | | |
| Cross-sectional | 16 | 12.1 | 6.9–20.4 | 170.56 | 91.21 | <0.001 |
| Retrospective | 1 | 4.5 | 0.3–44.8 | NA | NA | NA |
| Prospective | 1 | 17.4 | 6.7–38.2 | NA | NA | NA |
| Overall | 18 | 12.2 | 7.2–19.8 | 172.61 | 90.15 | <0.001 |

**Table 3**
Prevalence of meropenem resistance in CRE in different subgroups.

| Subgroup | Number of studies | Prevalence (%) | 95 % CI | Heterogeneity test | | |
|---|---|---|---|---|---|---|
| | | | | Q | $I^2$ (%) | p-value |
| **Region** | | | | | | |
| South-South | 3 | 37.2 | 26.0–50.0 | 4.11 | 51.38 | 0.128 |
| South-West | 11 | 14.3 | 6.5–28.6 | 98.24 | 89.82 | <0.001 |
| South-East | 6 | 18.9 | 10.3–32.1 | 42.07 | 88.12 | <0.001 |
| North-Central | 7 | 11.5 | 2.6–38.5 | 68.62 | 91.26 | <0.001 |
| North-West | 3 | 13.1 | 2.0–53.1 | 18.38 | 89.12 | <0.001 |
| North-East | 1 | 9.8 | 6.5–14.4 | NA | NA | NA |
| Overall | 31 | 15.0 | 10.2–21.6 | 361.94 | 91.71 | <0.001 |
| **Study period** | | | | | | |
| 2011–2015 | 8 | 5.3 | 2.4–11.2 | 37.98 | 81.57 | <0.001 |
| 2016–2020 | 14 | 24.7 | 17.1–34.1 | 114.55 | 88.65 | <0.001 |
| 2021–2023 | 1 | 20.0 | 5.0–54.1 | NA | NA | NA |
| Overall | 23 | 16.0 | 10.9–23.0 | 234.94 | 90.64 | <0.001 |
| **Study design** | | | | | | |
| Cross-sectional | 14 | 11.3 | 5.8–21.0 | 206.01 | 93.69 | <0.001 |
| Retrospective | 1 | 2.9 | 0.2–33.6 | NA | NA | NA |
| Prospective | 2 | 43.5 | 25.2–63.8 | 0.18 | 0 | 0.673 |
| Overall | 17 | 13.2 | 7.3–22.8 | 213.49 | 92.51 | <0.001 |

**Table 4**
Prevalence of ertapenem resistance in CRE in different subgroups.

| Subgroup | Number of studies | Prevalence (%) | 95 % CI | Heterogeneity test | | |
|---|---|---|---|---|---|---|
| | | | | Q | $I^2$ (%) | p-value |
| **Region** | | | | | | |
| South-South | 2 | 46.5 | 35.5–57.8 | 1.49 | 32.64 | 0.223 |
| South-West | 5 | 18.4 | 4.1–54.2 | 75.24 | 94.68 | <0.001 |
| South-East | 2 | 15.9 | 3.5–49.5 | 12.43 | 91.96 | <0.001 |
| North-Central | 2 | 13.5 | 0.1–97.2 | 25.21 | 96.03 | <0.001 |
| North-West | 1 | 10.5 | 5.4–19.7 | NA | NA | NA |
| North-East | 1 | 12.4 | 8.7–17.4 | NA | NA | NA |
| Overall | 13 | 18.1 | 10.4–29.7 | 176.73 | 93.21 | <0.001 |
| **Study period** | | | | | | |
| 2011–2015 | 4 | 10.7 | 3.2–30.1 | 60.89 | 95.07 | <0.001 |
| 2016–2020 | 7 | 15.4 | 7.1–30.2 | 76.48 | 92.15 | <0.001 |
| 2021–2023 | 1 | 98.0 | 74.9–99.9 | NA | NA | NA |
| Overall | 12 | 16.2 | 9.0–27.3 | 158.26 | 93.05 | <0.001 |

to frequently test *E. coli* and *K. pneumoniae* for carbapenem resistance may have been driven by their potential to cause serious infections and their propensity to acquire resistance, which can limit treatment options [81,82]. Moreover, prophages, which are significant vectors of horizontal gene transfer, have been detected in these organisms [83,84]. By integrating into bacterial genomes, prophages can spread resistance genes among bacterial populations, enabling the host bacteria to swiftly acquire new resistance traits under antibiotic pressure or other adverse environmental conditions [84]. This mechanism facilitates the rapid adaptation and survival of bacteria in challenging environments [84]. Thus, monitoring the prevalence of carbapenem resistance in these pathogens is crucial for understanding the scope of the issue and implementing effective infection control measures. It is worth noting that the focus on these specific pathogens does not diminish the importance of monitoring other members of the *Enterobacterales* for carbapenem resistance, as resistance can emerge in various species within this bacterial group. Moreover, other members, including species of *Salmonella*, *Enterobacter,* and *Citrobacter*, among others, were tested, and the pooled prevalence of carbapenem-resistant *Morganella* sp. was determined to be the highest among the CRE in this study. Comprehensive surveillance and testing strategies are essential to addressing the broader challenge of antimicrobial resistance and ensuring appropriate patient care.

We were interested in elucidating the overall pooled resistance rates of the *Enterobacterales* to the major carbapenem antibiotics: imipenem, meropenem, ertapenem and doripenem. Our findings revealed doripenem as the antibiotics with the highest resistance rate (37.9 %) among CRE, followed by ertapenem (17.0 %). Although the lowest resistance rate (11.2 %) was against the imipenem antibiotics, the observed rate is also worthy of concern. The high rates of carbapenem resistance may be attributed to frequent, inappropriate, and inaccurate administration of antimicrobial drugs in empirical treatment, coupled with insufficient infection control practices. The carbapenem resistance rates in this study are higher than reports from other countries, including the reported 3 % in Lebanon [85], 3.4 % in Afghanistan [86], 3.5 % in Belgium [87], and 5.74 % in Malaysia [88]. In contrast to our findings, higher carbapenem resistance rates have been reported in Jordan (41.2 %) [89] and Egypt (54.1 %) [90]. The observed variation may be attributed to differences in the methods employed for antibiotic susceptibility testing, the characteristics of the target population, sample types, the variety and quantity of bacterial isolates, disparities in antibiotic use policies, and variations in geographical

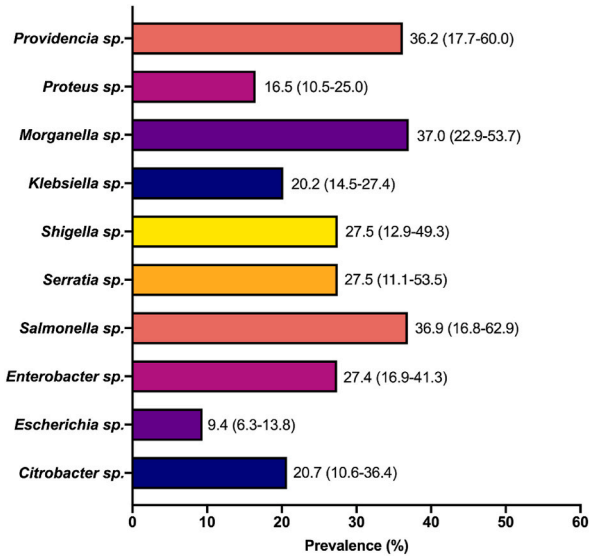


**Fig. 6.** Prevalence of specific CRE genera. Values in parenthesis are 95 % confidence intervals.

locations.

In this study, we found the carbapenem resistance rates to vary among the regions of the country. Notably, the highest resistance rate to imipenem (28.4 %), meropenem (37.2 %) and ertapenem (46.5 %) were observed for the South-South region of Nigeria. The reason for the observed high carbapenem resistance in this region is unclear, but it could be linked to the misuse of antibiotics [91]. In contrast, much lower carbapenem resistance rates were observed for the North-East region of the country. This observation may be attributed to the limited number of reports from the region, as only one study contributed to the estimate from the region. Additionally, our analyses indicate a progressive increase in resistance to carbapenem antibiotics over the years in Nigeria. CRE have become a growing concern in Nigeria, mirroring global trends in antimicrobial resistance. The emergence and spread of CRE in the country may have been influenced by various factors, including antibiotic misuse, inadequate infection control practices, and challenges in healthcare infrastructure. The epidemiology of CRE in Nigeria is characterized by an increasing prevalence, affecting both community and hospital settings. Studies suggest that CRE strains have been isolated from clinical specimens, including blood, urine, and wound cultures, indicating the diverse range of infections associated with these resistant bacteria [60,73,74].

Based on the specific members of the *Enterobacterales* assessed in this study, species of *Providencia*, *Morganella* and *Salmonella* were the most prevalent CRE, with prevalence hovering around 37 %. Previous report in Japan recorded low proportion of *Providencia stuartii* (1.3 %) and *Providencia rettgeri* (0.5 %) among the isolated *Enterobacterales* strains [92]. Moreover, there has been a growing focus on less common carbapenem-resistant CRE species, such as *P. rettgeri* and *K. oxytoca*, which are emerging as significant clinical concerns [93,94]. Similarly, in a different report, 9 *Morganella morganii* were found among 312 carbapenem-resistant Gram-negative bacteria from India [95]. Hence, addressing the notably high prevalence rate observed in this study is essential. In contrast, although *E. coli* was one of the most frequently tested *Enterobacterales* in this study, *Escherichia* sp. was the least prevalent CRE (9.4 %). Nonetheless, the observed rate is lower than the documented rates of carbapenem-resistant *E. coli* in many other parts of the world, including the 11 % in the United States, 31 % in Singapore, 22 % in Thailand, 18.7 % in Korea and 29 % in Canada [95].

CRE are of significant epidemiological concern due to their association with unfavorable outcomes and their ability to rapidly disseminate within healthcare systems [96]. Previous investigations have consistently demonstrated that CRE infections are linked to a higher mortality rate compared to non-CRE infections. For instance, a study conducted in China revealed a 30-day mortality rate of 65.4 % for CRE bloodstream infections, in contrast to a significantly lower rate of 17.2 % for non-CRE bloodstream infections. They attributed this heightened mortality to host conditions such as endogenous infections and invasive surgical procedures [97]. Furthermore, 30-day mortality rates for CRE infections are also reported to be higher when compared to infections caused by other pathogens exhibiting a broad spectrum of resistance mechanisms [98].

## 5. Strengths and limitations

This study has its strengths and limitations. To our knowledge, this is the first meta-analysis evaluating the prevalence of CRE from human samples in Nigeria. Because we did not apply any filter for the year in which the studies were performed or published, we believe our report is robust, accommodating all relevant published data. We were, however, unable to perform elaborate analysis on resistance rates to the doripenem antibiotics due to the limited number of available studies.

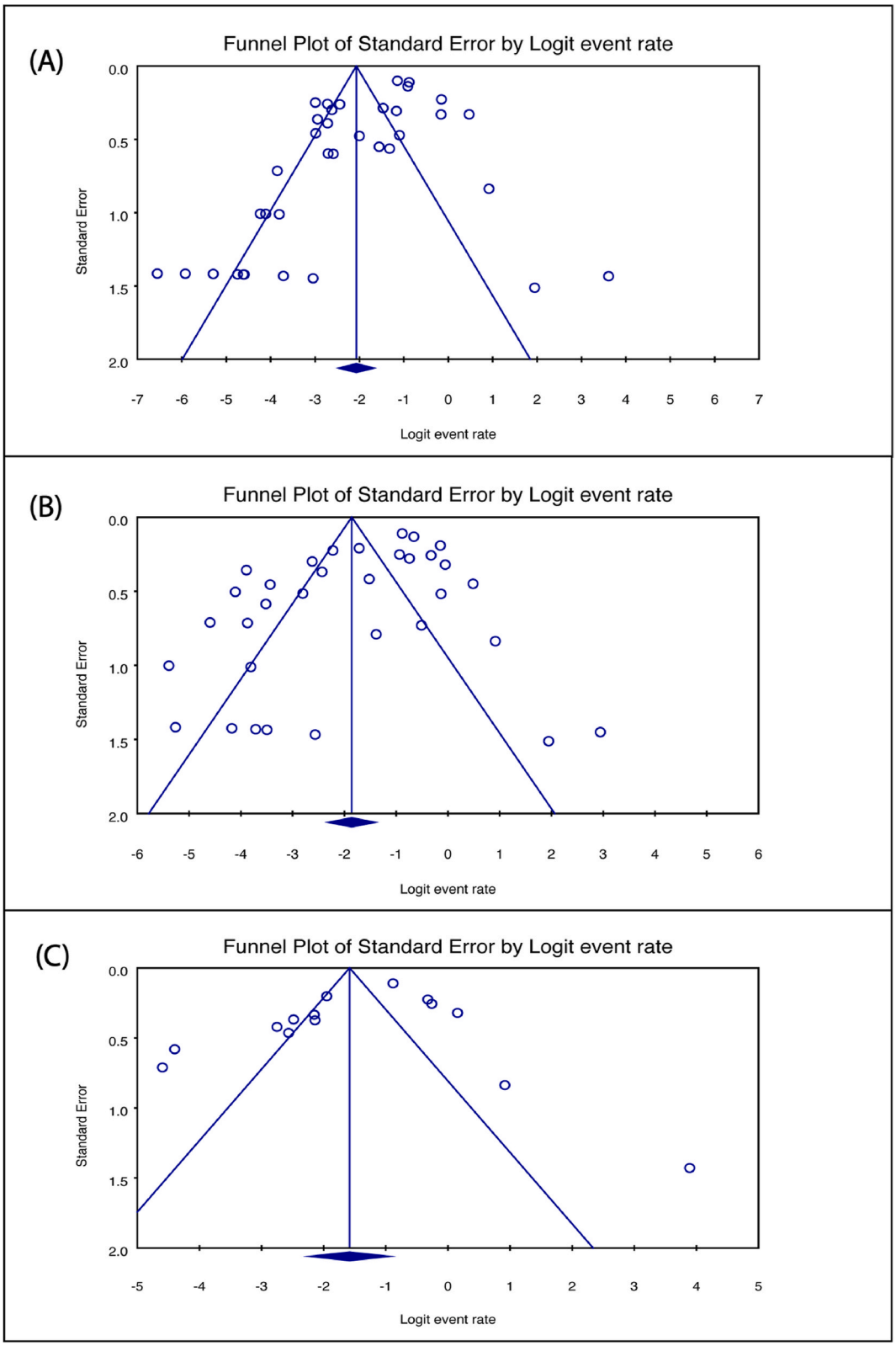


**Fig. 7.** Funnel plot of publication bias assessment for (A) imipenem [Egger's test, $p = 0.0039$] (B) meropenem [Egger's test, $p = 0.0166$] and (C) ertapenem [Egger's test, $p = 0.2559$] resistance estimates.

## 6. Conclusion

A comprehensive overview of the status of CRE derived from human samples in Nigeria was provided in this study. Resistance to the major carbapenems (imipenem, meropenem, ertapenem, doripenem) were identified, and ranged from 11.2 % for imipenem to 37.9 % for doripenem antibiotics. Our analyses indicated a progressive increase in resistance to carbapenem antibiotics over the years, with the South-South region of the country accounting for higher carbapenem resistance rates. Proactive measures should, therefore, be put in place to check these rising rates of carbapenem resistance in the country to prevent the likely proliferation to other nations. A comprehensive management approach, including antimicrobial stewardship programs, infection prevention and control measures, and surveillance systems should be employed to limit the spread of CRE. Additionally, promoting rational antibiotic use and educating healthcare professionals are essential components of a sustainable strategy.

Future research on CRE should prioritize the development of novel antimicrobial agents and treatment strategies to combat this emerging public health threat. The mechanisms of resistance, transmission dynamics, and genetic evolution of CRE strains should be investigated across different healthcare settings to enhance our understanding of their epidemiology and to ensure the adoption of effective infection control measures. Additionally, exploring the role of environmental reservoirs and potential vectors in CRE spread can provide insights into preventive strategies.

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## Ethical approval

Not required.

## Ethics statement

Not applicable.

## Data availability

All data accessed and analyzed in this study are available in the article and its supplementary materials.

## CRediT authorship contribution statement

**Ahmad Adebayo Irekeola:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Rafidah Hanim Shueb:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Engku Nur Syafirah Engku Abd Rahman:** Writing – review & editing, Methodology, Investigation. **Hafeez Abiola Afolabi:** Writing – original draft, Validation, Methodology, Investigation. **Yusuf Wada:** Writing – review & editing, Validation, Methodology, Investigation. **Abdirahman Hussein Elmi:** Writing – review & editing, Methodology, Investigation. **Muath Abdu Hakami:** Writing – review & editing, Methodology, Investigation. **Sfeeah Mofareah Alghzwani:** Writing – review & editing, Methodology, Investigation. **Osman AE. Elnoubi:** Writing – review & editing, Methodology, Investigation. **Ahmad A. Alshehri:** Writing – review & editing, Supervision, Project administration, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We are thankful to the authors who provided additional information when contacted regarding their articles.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34926.

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