Prevalence of carbapenem-resistant gram-negative bacteria among neonates suspected for sepsis in Africa: a systematic review and meta-analysis

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Abstract

Background The emergence and rapid spread of gram-negative bacteria resistant to carbapenems among newborns is concerning on a global scale. Nonetheless, the pooled estimate of gram-negative bacteria resistant to carbapenem that cause neonatal sepsis in developing nations remains unknown. Thus, this study aimed to determine the combined prevalence of gram-negative bacteria resistant to carbapenem in African newborns who were suspected of having sepsis.

Methods All studies published from January 1, 2010, up to December 30, 2023, from PubMed, Science Direct, Scopus electronic databases, and the Google Scholar search engine were researched. Isolates tested for carbapenem from neonates with sepsis, English language papers conducted in Africa, and cross-sectional and cohort studies papers were included. Using PRISMA guidelines, we systematically reviewed and meta-analyzed studies that assessed the prevalence of carbapenem-resistant gram-negative bacteria. The "Joanna Briggs Institute" was used critically to evaluate the quality of the included studies. The data analysis was carried out using STATA™ version 17. Heterogeneity across the studies was evaluated using Q and I ^{2} tests. The subgroup analysis was done and, funnel plot and Egger's regression test were used to detect publication bias. A sensitivity analysis was conducted.

Results All 36 studies were included in the meta-analysis and systematic review. The pooled prevalence of carbapenem resistance in Africa was 30.34% (95% CI 22.03–38.64%). The pooled estimate of gram-negative bacteria resistant to imipenem, and meropenem was 35.57% (95% CI 0.67–70.54%) and 34.35% (95% CI 20.04% – 48.67%), respectively. *A. baumannii* and *Pseudomonas spp.* had pooled prevalence of 45.9% (95% CI 33.1–58.7%) and 43.0% (95% CI 23.0–62.4%), respectively. Similarly, *Pseudomonas spp.* and *A. baumannii* also exhibited strong meropenem

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resistance, with a pooled prevalence of 29.2% (95% CI 4.8–53.5%) and 36.7% (95% CI 20.1–53.3%), respectively. *E. coli* and *K. pneumoniae* were the two most common isolates.

Conclusion There should be urgent antimicrobial stewardship practices, strengthened surveillance systems and effective treatment for neonates with sepsis. There was remarkable variation in resistance across the continent.

Keywords Carbapenem-resistant, Gram-negative bacteria, Neonates, Sepsis, Africa, Systematic review and meta-analysis

Introduction

Sepsis is a serious inflammatory condition marked by fever and shock, which occurs when bacteria enter the bloodstream [1]. Neonatal septicemia continues to be a significant concern for newborn patients in neonatal intensive care units globally [2]. As a result of shifting antibiotic usage patterns and lifestyle modifications, the range of microorganisms responsible for newborn sepsis varies geographically and changes over time [3]. Approximately ten cases of probable severe bacterial infection are reported for every neonatal mortality, and there is a yearly population of two million that requires treatment for suspected infections [4]. There could be various reasons for neonatal mortality but septicemia continues to be a major cause and its incidence varies from country to country [5].

Epidemiological studies on neonatal sepsis reported an estimated 3.9 million annual cases [6] which is a primary cause of neonatal mortality within low and middle-income countries, bearing 99% of global neonatal mortality [7]. Every year, an estimated 2.5 million neonates die in their first month of life, accounting for nearly one-half of deaths in children under 5 years of age [8]. Adhering to established standards for managing neonatal sepsis and promptly initiating more potent drugs would greatly decrease the morbidity and death rate of babies caused by sepsis [9].

Antibiotic resistance is prioritized by the World Health Organization (WHO) as a pressing public health issue that requires immediate attention [10]. Due to the high rate of disease progression and the difficulty in accessing laboratory evaluations in the African nations [11], WHO recommended empirical treatment which are ampicillin and gentamicin or amikacin, and third-generation cephalosporins [12, 13]. In general, empirical antibiotic regimens should be guided by the local antimicrobial resistance patterns of bacterial isolates commonly detected in neonatal intensive care unit (NICU) or in the community setting [14].

Carbapenems are listed in the 'watch group' of WHO Access, Watch, Reserve classification as critically important antimicrobials for human medicine with a higher resistance potential [15]. Carbapenem-resistant gram-negative bacilli (CRGNB) have recently evolved and are spreading rapidly, raising global concerns [16]. Bacteria can break down β-lactam antibiotics, including penicillin, cephalosporin, and monobactams, using carbapenemase, an enzyme that hydrolyzes carbapenems [17]. Infections caused by CRGNB are known to be associated with significant morbidity and mortality, and these pathogens are now reported to be on the increase in children and neonates [18]. Carbapenem-resistant infections result in longer hospital admissions, higher healthcare costs, and increased mortality than carbapenem-susceptible bacterial infections [19]. Since the first CRGNB epidemic, many nations have seen a sharp rise in the prevalence of CRGNB infections [20]. Due to the extremely high rates of extended-spectrum beta-lactamase synthesis among gram-negative bacteria, carbapenem antibiotics are used extensively, which has led to the evolution of plasmid-mediated resistance to carbapenems [21].

It is estimated that at least 5,880 deaths can be attributed to these illnesses [22]. The emergence of bacteria resistant to carbapenem puts treatment strategy in jeopardy. Few drug options, like polymyxins, tigecycline, and fosfomycin, may be effective to treat infections by CRGNB. However, these antibiotics are rarely used as a monotherapy to treat these infections, either because of its complex pharmacokinetics or toxicity or unknown optimal therapeutic doses [23]. The fact that carbapenemase-producing bacteria are so prevalent around the globe makes them clinically important [24]. Several nations do not have prevalence estimates of carbapenem resistance in neonates, even though this age group is extremely susceptible. The pooled estimates of common gram-newgative bacteria (GNB) that cause neonatal sepsis in developing countries that are resistant to carbapenem medications are presently unknown [25]. Therefore this systematic review and meta-analysis aimed to provide an update on the rising of these CRGNB.

Methods

The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [26]. The protocol for this study was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) and was assigned the identification number (CRD42024547715).

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Data source and searching strategy

Electronic databases and search engines were used to gather important data about carbapenem-resistant Enterobacteriaceae causing neonatal sepsis. The search was done from data available from January 1, 2010, up to December 30, 2023 and the search was conducted from January 15, 2024- March 1, 2024. A systematic search was carried out using PubMed/Medline, Scopus, and Science Direct electronic databases. Additionally, articles available on Google Scholar and online repositories/registers of different institutions were also retrieved as part of the search process. We strictly followed the PRISMA flow diagram to report this study [26]. Appropriate MeSH (Medical Subject Headings) terms and key searching words were employed to retrieve relevant articles published in the English language. Our search string was developed using the following keywords: "prevalence", "Carbapenem", "carbapenem-resistant", "carbapenemase-producers" *"Enterobacteriaceae"*, "gram-negative", *"Klebsiella"*, *"pseudomonas"*, *"E.coli"*, "neonates", "newborn", "Sepsis", and "bloodstream infection", "Africa. These search words/phrases were further paired with each other or combined using "AND" and "OR" Boolean operators. Additionally, the remaining papers were screened at the reference lists to identify additional relevant data. The complete search strategy and searching strings for the PubMed/MEDLINE database are depicted in the supplementary file (Table S1). Furthermore, we reviewed the reference lists of primary studies and review papers to identify grey literature.

Study selection and quality assessment

All retrieved studies were exported into the EndNote reference manager software (Tomson Reuters, London), and duplicated studies were removed. Reviewers (AS, GK, ZA, YG, EG, and MAR) independently screened the titles, abstracts, and full texts to determine the eligibility of each study. Where there was disagreement, a decision was reached after discussion and consensus among all reviewers. Five reviewers (AS, ZA, GK, YG, EG, and MAR) independently assessed the quality of the full-text articles. The discrepancy was resolved through discussion to reach on consensus and to include articles in the final analysis. The critical quality assessment checklist recommended by the "Joanna Briggs Institute (JBI)" was used to evaluate the quality of the included studies studies [27]. The domain paper quality assessment criteria for prevalence studies were clearly stated (Table S2). Disagreements between the reviewers were resolved by taking the mean score of the two reviewers' evaluations. Studies with a final quality score of 50% or higher were considered for inclusion in this systematic review and meta-analysis.

Eligibility criteria

After retrieving potential papers from the databases, they were subjected to eligibility screening. Thus, papers were included if they report; (a) GNB isolates tested for carbapenem, (b) CRGNB isolates from neonates, (c) neonates suspected of sepsis, (d) English language papers, (e) papers conducted in Africa, (f) and cross-sectional, and cohort studies. Papers were excluded if they reported antibiotic sensitivity other than carbapenem drugs. Review studies, letters, case reports, case control, and conference papers were excluded. Also, we excluded studies that have methodological problems and flaws (lack of clear measurement, incomplete diagnostic criteria, selection bias, and unclear presentation of the study population).

Data extraction

All articles included in the final analysis were reviewed and relevant data were recorded by two reviewers independently using standardized data extraction tools prepared in the Microsoft Excel sheet. The following data were extracted from each original article: author's name, year of publication, study country, study design, sample size, number of bacteria isolates tested for carbapenem-resistant, and the prevalence of carbapenem resistance.

Outcome measurement

Molecular and culture confirmed sepsis with carbapenem resistant gram negative bacteria was considered. Carbapenem-resistance was defned as resistance to any one of meropenem, imipenem, or ertapenem according to the US Central Laboratory Standards Institute.

Data processing and analysis

The extracted relevant data were exported to STATA 17 for final analysis. The overall pooled prevalence of GNB which was tested for carbapenem resistance among neonates suspected of sepsis in Africa was calculated using the random effect model, due to the existence of heterogeneity across studies. The presence of heterogeneity across studies was examined using the Q and the I^2 statistics. In this study, the I^2 statistic value of zero indicates true homogeneity, whereas the values 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively [28]. A *p*-value of less than 0.05 was used to declare the presence of heterogeneity. Subgroup analysis was done by the study country, year of publication, and methods of isolation to assess the difference in the pooled estimates. Publication bias was checked by the funnel plot and more objectively through Egger's regression test [29]. Sensitivity analysis was employed to examine the effect of a single study on the overall estimation of the pooled prevalence. To calculate the pooled prevalence of carbapenem resistance, the continuity correction was made

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for zero and one hundred% carbapenem resistance values which resulted in zero standard error [30].

Results

Searching results

As illustrated in Fig. 1, we identified a total of 7,365 potentially relevant studies from searched electronic databases and search engines, and 1,623 articles were excluded due to duplication. After reviewing the titles and abstracts, 5,361 articles were excluded because they did not meet the objectives and the inclusion criteria of the review. Accordingly, 381 full-text articles were reviewed in-depth based on the preset inclusion criteria, of which 345 articles were excluded due to full-text inaccessibility, lack of carbapenem susceptibility testing, studies outside Africa, and failure to include the study subject's age of interest. Finally, 36 studies were included and used for the final quantitative analysis (meta-analysis) (Fig. 1).

Results of quality assessment

The critical quality assessment checklist recommended by the "Joanna Briggs Institute (JBI)" Studies with a final quality score of 50% or higher were considered in this systematic review and meta-analysis.

Characteristics of included studies

As illustrated in Table 1, for all the included studies (*n*=36), the final quantitative analysis was done. From these, 24 studies were cross-sectional [18, 31–53], and 12 were retrospective [54–65] by study design. The included studies were conducted in eleven countries in Africa. These were eleven studies from Egypt, one study from Equatorial Guinea, five studies from Ethiopia, two studies from Ghana, one study from Morocco, two studies from Nigeria, two studies from Sudan, six studies from South Africa, four studies from Tanzania, one study from Uganda, and one study from Zambia (Table 1).

Meta-analysis

The pooled prevalence of carbapenem resistant isolates

The resistance test used in this meta-analysis included 7,116 isolates for carbapenem (2,946, 2,618, and 1,552 isolates for meropenem, imipenem, and, ertapenem respectively). The pooled prevalence of carbapenem resistance in GNB was 30.34% (95%CI 22.03–38.64) (Fig. 2). Whereas the meta-analysis produced the pooled estimates of isolates with resistance to meropenem, imipenem, and ertapenem of 26.11% (95% CI: 15.82–36.40), 34.35% (95% CI: 20.04–48.67%) and 35.57 (95% CI 0.60-70.54) (Figs. 3, 4 and 5) respectively. In this review, the most frequently tested isolate for carbapenem drugs was *K. pneumoniae* which accounts for 2,719 (38.2%) of all isolates. In this study, a total of 1,231 *A. baumannii*

isolates were tested for carbapenem resistance. The results indicated a significant prevalence of carbapenem resistance, with 45.9% (95%CI 33.1–58.7) of the isolates demonstrating strong resistance. Similarly, this bacterium exhibited the highest pooled prevalence of meropenem resistance, with 36.7% (95% CI: 20.1–53.3) of the 565 tested isolates showing resistance, In contrast, *E. coli* exhibited the lowest pooled prevalence of meropenem resistance, with only 6.9% (95% CI: 2.0–11.8) of the 318 tested isolates showing resistance (Table 2).

Level of heterogeneity

The included studies' level of heterogeneity was evaluated. Thus, 99.7% of the studies showed considerable heterogeneity for carbapenem (Fig. 2). The I^2 test results for each drug were 99.37% for meropenem (Figs. 3), 99.73% for imipenem (Fig. 4), and 99.9% for ertapenem (Fig. 5). Furthermore, notable variations were observed between the investigations for every isolated species. The I^2 revealed 99.8% for *pseudomonas spp.*, 98.8% for *A. baumannii*, 96.3% for *Citrobacter spp.*, 98.7% for *E. coli*, 99.0% for *Enterobacter spp.*, 99.5% for *K. pneumoniae*, 99.8% for *Klebsiella spp.*, and 99.8% for *Serratia spp.* for carbapenem resistance (Table 2).

Sub-group analysis for carbapenem

Having significant heterogeneity for carbapenem resistance across the included studies, a sub-group analysis was carried out by year of publication, study country and methods of isolation. The pooled prevalence of carbapenem-resistant bacterial isolates among newborns suspected of sepsis was reported to be 20.8% (95% CI 12.2 - 29.4%), 29.1% (95% CI 13.9 −44.3%), and 32.7% (95% CI 21.0 −44.5%), with I^2 of 77.7%, 99.8% and 99.6 for the years 2010–2015, 2016–2020, and 2021–2023, respectively. There is also a variation of a pooled estimate of carbapenem resistance across countries ranging from 0.5% (95% CI -1.2-2.2) in Sudan to 57.9% (95% CI -3.7-28.7) in Egypt (Table 3).

Sub-group analysis for meropenem

The pooled prevalence of meropenem-resistant bacteria among newborns suspected of sepsis was reported to be 14.3% (95% CI 7.6–21.0), 31.3% (95% CI 11.3–51.3), and 24.8% (95% CI 11.3–38.2) for the years 2010–2015, 2016–2020, and 2021–2023, respectively, based on the year of publication. Our meta-analysis found that there was a variation in the pooled prevalence of carbapenem-resistant GNB isolates among neonates suspected of sepsis across countries, from 2.25% (95% CI -1.2- 5.7) in Ghana to 57.1% (95% CI 33.4, 80.7) in Egypt (Table 3).

Identification of studies via databases and other sources/registers

Identification

Records identified from*:6,010
Databases:
- PubMed (n =4,804)
- Science Direct (n =1,000)
- Scopus (n =206)

Additional records identified:
  Other Sources:
- Google scholar (n =1,340)
- Registers/others (n = 15)

Screening

Duplicates removed using EndNote software and manually (n = 1,623)

Records screened
(n =5,742)

Records excluded by title:
(n = 4,959)

Eligibility

Abstracts assessed for eligibility
(n =783)

Abstracts excluded (402)
- Review paper (n =131)
- Outside Africa: (n = 271)

Full-text articles assessed for eligibility (n = 381)

Full-text articles excluded :(345)
- No age of interest (n = 128)
- Studies outside Africa: (n = 101)
- No carbapenem drug test (n = 105)
- Full-text inaccessible (n=11)

Included

Studies included in quantitative synthesis (meta-analysis)
(n = 36)

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

Sub-group analysis for imipenem

The pooled prevalence of imipenem-resistant GNB from neonates with suspected bloodstream infections were found 54.5% (95% CI 35.6% -73.3%) in Egypt, 49.0% (95% CI -45.4% −43.5%) in Ethiopia, 11.5% (95% CI -3.7 -26.7%) in South Africa, and 0.5% (95% CI -1.7 -2.7%) in

Sudan according to the study country. Our meta-analysis revealed a variation in the pooled prevalence of CRGNB isolates among neonates suspected of sepsis. This variation was attributed to differences in isolation methods. The prevalence was 30.0% (95% CI: 10.0–42.9) using

Table 1 Characteristics of included studies in this systematic review and meta-analysis for the prevalence of meropenem, imipenem, and ertapenem) resistance GNB

Name of authors	Year of Study	Country	study design	Meropenem				Imipenem				Methods of isolation
				NI	NT	NR	p	NI	NT	NR	P	
Ballot et al. [57]	2019	South Africa	RS	465	325	13	4	465	463	23	4.9	A.C
Almohammady et al. [55]	2020	Egypt	RS	49	42	39	92.9	49	49	46	93.9	C.C
Awad et al. [56]	2016	Egypt	RS	175	175	36	20.6	175	175	45	25.7	A.C
Braima et al. [31]	2021	Sudan	CS	22	22	0	0.5	22	22	0	0.5	C.C
Gashaw et al. [48]	2019	Ethiopia	CS	65	65	11	16.9	---	---	---	---	A.C
Hassan et al. [49]	2022	Egypt	CS	101	101	30	29.7	---	---	---	---	A.C
Kabwe et al. [32]	2016	Zambia	CS	---	---	---	---	81	78	1	1.3	A.C
Kayange et al. [33]	2010	Tanzania	CS	72	72	11	15.3	---	---	---	---	C.C
Majigo et al. [34]	2023	Tanzania	CS	72	67	23	34.3	---	---	---	---	A.C
Onyedibe et al. [35]	2015	Nigeria	CS	32	32	4	12.5	---	---	---	---	C.C
Pillay [58]	2021	South Africa	RS	155	155	51	32.9	155	155	55	35.5	C.C
Gaballah [36]	2022	Egypt	CS	328	328	242	73.8	328	323	246	76.2	A.C
Silago et al. [37]	2020	Tanzania	CS	56	56	9	16.1	---	---	---	---	C.C
Solomon et al. [50]	2021	Ethiopia	CS	118	118	1	0.9	118	118	1	0.8	A.C
Thomas et al. [59]	2018	South Africa	RS	399	379	11	2.9	399	379	6	1.6	A.C
Weldu et al. [38]	2020	Ethiopia	CS	96	95	55	57.9	---	---	---	---	C.C
Worku et al. [39]	2022	Ethiopia	CS	108	108	13	12.0	108	108	105	97.2	C.C
Tumuhamye et al. [40]	2020	Uganda	CS	---	---	---	---	12	12	4	33.3	A.C
Tetteh et al. [60]	2022	Ghana	RS	13	13	0	0.5	---	---	---	---	C.C
Perez-Palacios et al. [61]	2023	Morocco	RS	74	60	16	26.7	74	60	13	21.7	A.C
DM Ghaiz et al. [41]	2020	Egypt	CS	23	23	13	56.5	23	23	19	82.6	A.C
Raafat et al. [51]	2023	Egypt	CS	252	252	242	96.0	252	252	242	96.0	A.C
van Staaden et al. [62]	2021	South Africa	RS	59	59	2	3.4	76	59	3	5.1	A.C
Shatalov et al. [43]	2015	Equatorial Guinea	CS	---	---	---	---	24	16	2	12.5	A.C
Panwar et al. [42]	2023	Egypt	CS	---	---	---	---	31	31	14	45.2	C.C
Shehab et al. [52]	2015	Egypt	CS	---	---	---	---	54	47	13	27.7	C.C
Fahmey [64]	2013	Egypt	RS	---	---	---	---	119	119	20	16.8	C.C
Lebea and Davies [65]	2017	South Africa	RS	115	98	17	17.3	---	---	---	---	C.C
Uwe et al. [44]	2022	Nigeria	CS	44	34	14	41.2	---	---	---	---	A.C
Fenta et al. [45]	2022	Ethiopia	CS	36	36	5	13.9	---	---	---	---	C.C
Acheampong et al. [63]	2022	Ghana	RS	109	100	4	4	---	---	---	---	A.C
Msanga et al. [46]	2021	Tanzania	CS	41	41	3	7.3	---	---	---	---	C.C
Amer et al. [53]	2021	Egypt	CS	72	72	21	29	72	72	23	32	C.C
Manal et al. [54]	2015	Egypt	CS					31	31	14	45.2	C.C
Babiker et al. [47]	2018	Sudan	CS					19	19	0	0.5	C.C
Ertapenem												
Name of authors	year	Country	study design	NI	NT	NR	p					
Ballot et al. [57]	2019	South Africa	RS	465	434	12	2.8	---	---	---	---	A.C

Table 1 (continued)

Name of authors	Year of Study	Country	study design	Meropenem				Imipenem				Methods of isolation
				NI	NT	NR	p	NI	NT	NR	p	
Solomon et al. [50]	2021	Ethiopia	CS	118	118	8	6.8	---	---	---	---	A. C
Reddy et al. [66]	2021	South Africa	RS	888	688	688	119	---	---	---	---	A. C
Raafat et al. [51]	2023	Egypt	CS	252	252	243	96.5	---	---	---	---	A. C
Perez-Palacios et al. [61]	2023	Morocco	RS	74	60	33	55	---	---	---	---	A. C

Note: NI: number of isolates NR: number of resistant isolates NT: number of isolates tested for each drugs P: prevalence; RS: retrospective; CS: cross-sectional; A.C: automated culture; C. C: conveintional culture

automated methods and 39.6% (95% CI: 18.5–60.7) using conventional culture methods (Table 3).

Publication bias
To assess the prevalence of publication bias in the included studies, a variety of methods were utilized. The funnel plot showed an uneven distribution of studies for carbapenem and for specific carbapenem drug groups (meropenem, imipenem, and ertapenem) (Figure S 1, 2, 3, and 4). However, Egger's regression test for publication bias revealed marginally insignificant for carbapenem ($p=0.22$) and also for each carbapenem group of drugs (meropenem ($p=0.24$), imipenem ($p=0.52$) and ertapenem ($p=0.72$) (Figure S 5, 6, 7,8).

Sensitivity analysis
A leave-one-out sensitivity analysis was employed to identify the potential source of heterogeneity in the analysis of the pooled prevalence of resistance of bacteria that cause neonatal sepsis in Africa. The sensitivity analysis showed the effect of individual studies on the pooled estimate was insignificant, suggesting the robustness of the aggregated estimate. Therefore, the pooled prevalence of resistance of bacterial isolates for carbapenem, meropenem and imipenem was steady when examined by neglecting one study at a time (Figure: S 9. 10, 11).

Discussion
Estimating national and global prevalence data for neonatal sepsis, particularly cases caused by CRGNB, is crucial for prioritizing and implementing effective control measures [11]. In settings without microbiology capacity, treating newborns with clinical symptoms of sepsis with "big gun" antibiotics is harmful by increasing antibiotic resistance or adverse side effects [66]. This study aimed to present the updated pooled resistance estimate of GNB to carbapenem drugs among neonates with sepsis in African nations. Knowledge gaps on the population-based epidemiology of neonatal sepsis remain in most of low and middle income countries due the lack of a robust research infrastructure, formal healthcare systems or prioritisation of other important healthcare issues [67]. This study aimed to present the updated pooled resistance estimate of GNB to carbapenem drugs among neonates with sepsis in African nations.

In this systematic review and meta-analysis, the overall pooled prevalence of carbapenem-resistant isolates was 30.34%. This finding aligns with results from a study conducted across twelve African and Asian countries [68]. However, this result was higher compared to several other studies, including those from Asia and Africa on the burden of antibiotic resistance in neonates from developing societies (BARNARDS) [69], studies conducted across thirty nations [22], a systematic review
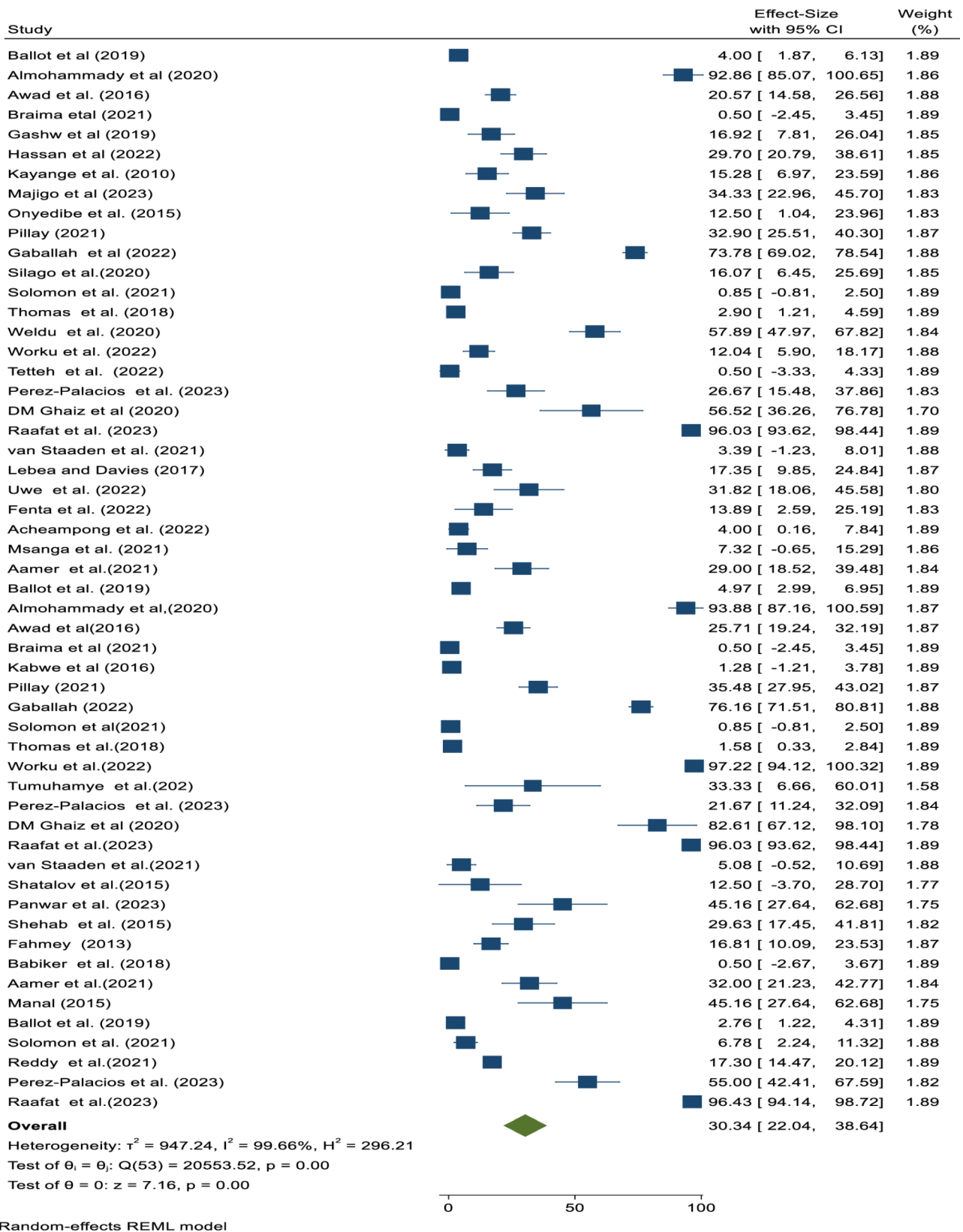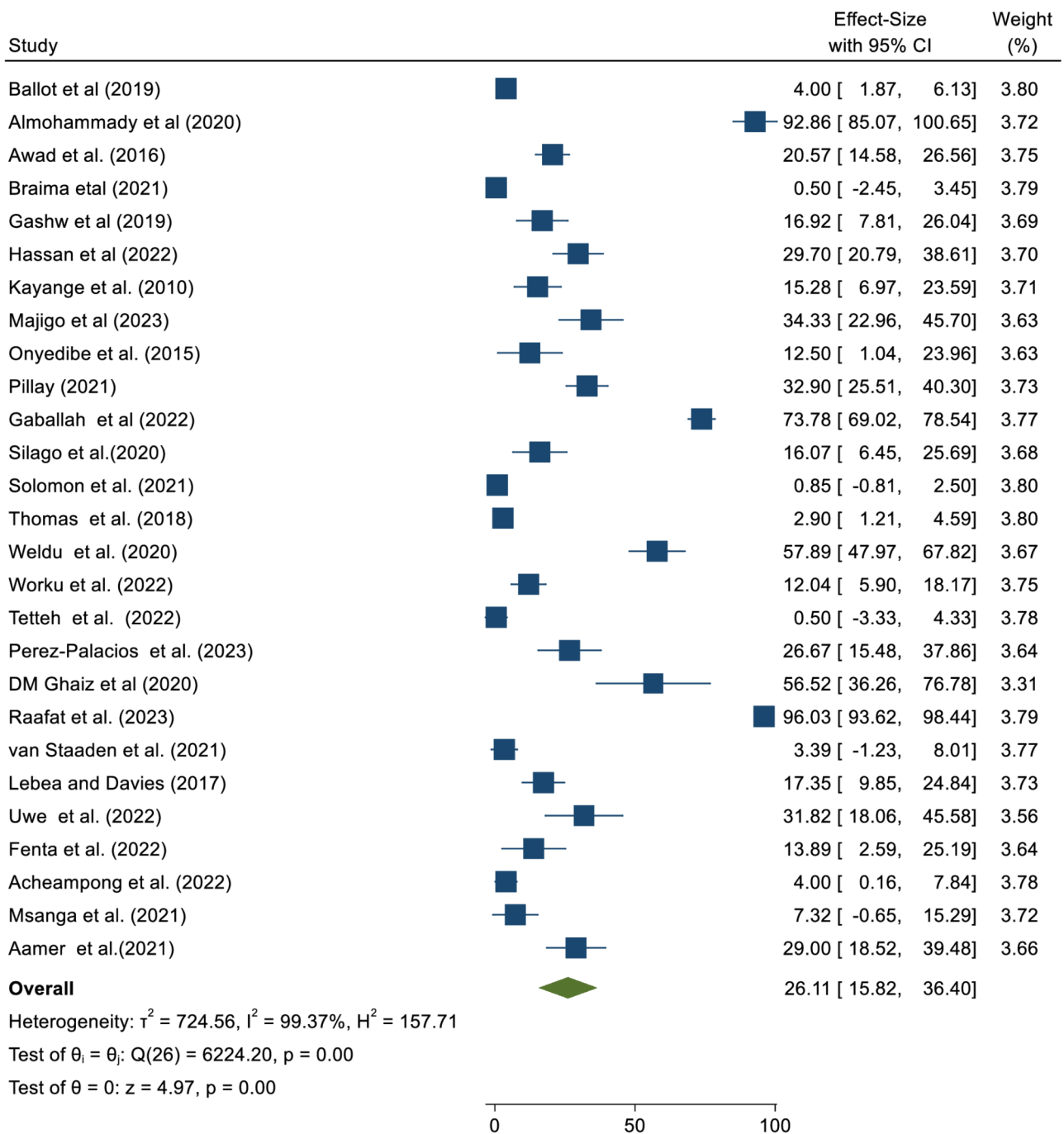
	Effect-Size with 95% CI	Weight (%)
Study		
Ballot et al (2019)	4.00 [1.87, 6.13]	1.89
Almohammady et al (2020)	92.86 [85.07, 100.65]	1.86
Awad et al. (2016)	20.57 [14.58, 26.56]	1.88
Braima etal (2021)	0.50 [-2.45, 3.45]	1.89
Gashw et al (2019)	16.92 [7.81, 26.04]	1.85
Hassan et al (2022)	29.70 [20.79, 38.61]	1.85
Kayange et al. (2010)	15.28 [6.97, 23.59]	1.86
Majigo et al (2023)	34.33 [22.96, 45.70]	1.83
Onyedibe et al. (2015)	12.50 [1.04, 23.96]	1.83
Pillay (2021)	32.90 [25.51, 40.30]	1.87
Gaballah et al (2022)	73.78 [69.02, 78.54]	1.88
Silago et al.(2020)	16.07 [6.45, 25.69]	1.85
Solomon et al. (2021)	0.85 [-0.81, 2.50]	1.89
Thomas et al. (2018)	2.90 [1.21, 4.59]	1.89
Weldu et al. (2020)	57.89 [47.97, 67.82]	1.84
Worku et al. (2022)	12.04 [5.90, 18.17]	1.88
Tetteh et al. (2022)	0.50 [-3.33, 4.33]	1.89
Perez-Palacios et al. (2023)	26.67 [15.48, 37.86]	1.83
DM Ghaiz et al (2020)	56.52 [36.26, 76.78]	1.70
Raafat et al. (2023)	96.03 [93.62, 98.44]	1.89
van Staaden et al. (2021)	3.39 [-1.23, 8.01]	1.88
Lebea and Davies (2017)	17.35 [9.85, 24.84]	1.87
Uwe et al. (2022)	31.82 [18.06, 45.58]	1.80
Fenta et al. (2022)	13.89 [2.59, 25.19]	1.83
Acheampong et al. (2022)	4.00 [0.16, 7.84]	1.89
Msanga et al. (2021)	7.32 [-0.65, 15.29]	1.86
Aamer et al.(2021)	29.00 [18.52, 39.48]	1.84
Ballot et al. (2019)	4.97 [2.99, 6.95]	1.89
Almohammady et al,(2020)	93.88 [87.16, 100.59]	1.87
Awad et al(2016)	25.71 [19.24, 32.19]	1.87
Braima et al (2021)	0.50 [-2.45, 3.45]	1.89
Kabwe et al (2016)	1.28 [-1.21, 3.78]	1.89
Pillay (2021)	35.48 [27.95, 43.02]	1.87
Gaballah (2022)	76.16 [71.51, 80.81]	1.88
Solomon et al(2021)	0.85 [-0.81, 2.50]	1.89
Thomas et al.(2018)	1.58 [0.33, 2.84]	1.89
Worku et al.(2022)	97.22 [94.12, 100.32]	1.89
Tumuhamye et al.(202)	33.33 [6.66, 60.01]	1.58
Perez-Palacios et al. (2023)	21.67 [11.24, 32.09]	1.84
DM Ghaiz et al (2020)	82.61 [67.12, 98.10]	1.78
Raafat et al.(2023)	96.03 [93.62, 98.44]	1.89
van Staaden et al.(2021)	5.08 [-0.52, 10.69]	1.88
Shatalov et al.(2015)	12.50 [-3.70, 28.70]	1.77
Panwar et al. (2023)	45.16 [27.64, 62.68]	1.75
Shehab et al. (2015)	29.63 [17.45, 41.81]	1.82
Fahmey (2013)	16.81 [10.09, 23.53]	1.87
Babiker et al. (2018)	0.50 [-2.67, 3.67]	1.89
Aamer et al.(2021)	32.00 [21.23, 42.77]	1.84
Manal (2015)	45.16 [27.64, 62.68]	1.75
Ballot et al. (2019)	2.76 [1.22, 4.31]	1.89
Solomon et al. (2021)	6.78 [2.24, 11.32]	1.88
Reddy et al.(2021)	17.30 [14.47, 20.12]	1.89
Perez-Palacios et al. (2023)	55.00 [42.41, 67.59]	1.82
Raafat et al.(2023)	96.43 [94.14, 98.72]	1.89
Overall	30.34 [22.04, 38.64]	

Heterogeneity: $\tau^2 = 947.24$, $I^2 = 99.66\%$, $H^2 = 296.21$
Test of $\theta_i = \theta_j$: $Q(53) = 20553.52$, $p = 0.00$
Test of $\theta = 0$: $z = 7.16$, $p = 0.00$

0   50   100

Random-effects REML model

Fig. 2 Forest plot showing the pooled prevalence of carbapenem resistance profile of GNB isolates among neonates with suspected bloodstream infections in Africa
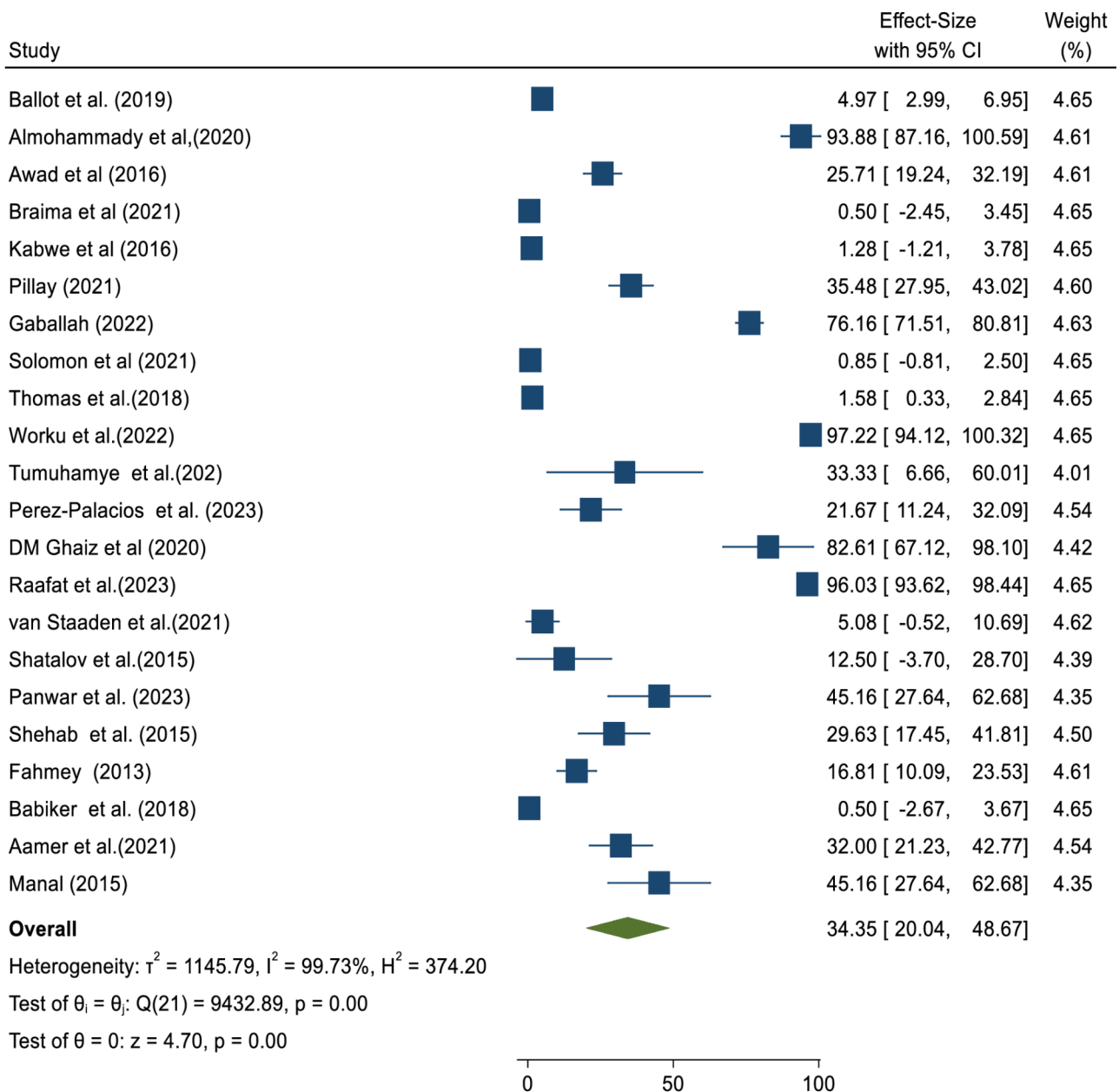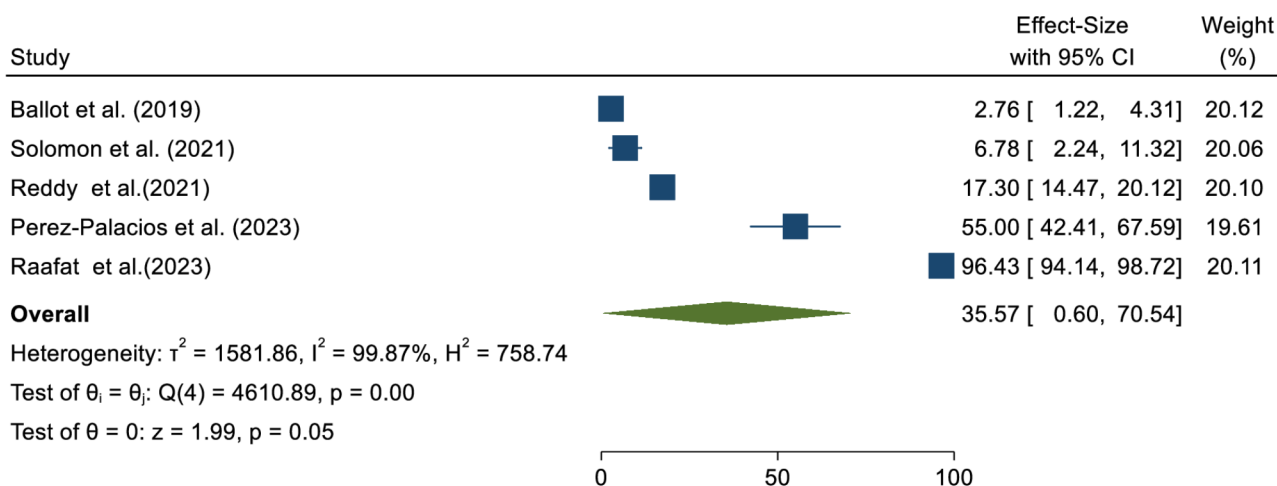
Fig. 3 Forest plot showing the pooled prevalence of meropenem resistance profiles GNB isolates from neonates with suspected bloodstream infections in Africa

from Iran [70], and research from China [71], a study focusing on low- and lower-middle-income countries [72], and a study conducted from seven Asian and African countries [73]. The elevated rate of pooled resistance could be attributed to the population's growing resistance to antibiotics that are currently effective against GNB [74]. Additionally, globalization may contribute to the spread of antibiotic-resistant strains to regions where certain antibiotics have not yet been introduced which underscores considering regional variations in antibiotic sensitivity when developing treatment guidelines for neonatal sepsis and selecting new empirical antibiotics [75]. Furthermore, inadequate dosing or incomplete courses

Study	Effect-Size with 95% CI	Weight (%)
Ballot et al. (2019)	4.97 [2.99, 6.95]	4.65
Almohammady et al,(2020)	93.88 [87.16, 100.59]	4.61
Awad et al (2016)	25.71 [19.24, 32.19]	4.61
Braima et al (2021)	0.50 [-2.45, 3.45]	4.65
Kabwe et al (2016)	1.28 [-1.21, 3.78]	4.65
Pillay (2021)	35.48 [27.95, 43.02]	4.60
Gaballah (2022)	76.16 [71.51, 80.81]	4.63
Solomon et al (2021)	0.85 [-0.81, 2.50]	4.65
Thomas et al.(2018)	1.58 [0.33, 2.84]	4.65
Worku et al.(2022)	97.22 [94.12, 100.32]	4.65
Tumuhamye et al.(202)	33.33 [6.66, 60.01]	4.01
Perez-Palacios et al. (2023)	21.67 [11.24, 32.09]	4.54
DM Ghaiz et al (2020)	82.61 [67.12, 98.10]	4.42
Raafat et al.(2023)	96.03 [93.62, 98.44]	4.65
van Staaden et al.(2021)	5.08 [-0.52, 10.69]	4.62
Shatalov et al.(2015)	12.50 [-3.70, 28.70]	4.39
Panwar et al. (2023)	45.16 [27.64, 62.68]	4.35
Shehab et al. (2015)	29.63 [17.45, 41.81]	4.50
Fahmey (2013)	16.81 [10.09, 23.53]	4.61
Babiker et al. (2018)	0.50 [-2.67, 3.67]	4.65
Aamer et al.(2021)	32.00 [21.23, 42.77]	4.54
Manal (2015)	45.16 [27.64, 62.68]	4.35
Overall	34.35 [20.04, 48.67]	

Heterogeneity: $\tau^2 = 1145.79$, $I^2 = 99.73\%$, $H^2 = 374.20$

Test of $\theta_i = \theta_j$: Q(21) = 9432.89, p = 0.00

Test of $\theta = 0$: z = 4.70, p = 0.00

Random-effects REML model

Fig. 4 Forest plot showing the pooled prevalence of imipenem resistance profile GNB isolated from neonates with suspected b loodstream infections in Africa

of treatment may also play a significant role in the emergence of antimicrobial resistance [76].

The overall pooled prevalence of meropenem resistance among isolates was 26.11%. This rate is higher compared to findings from a study across seven countries in Asia and Africa on antibiotic resistance in neonates from developing societies [69], as well as another study conducted in Asian and African countries [73]. Elevated rates of this condition are commonly observed and can vary significantly worldwide for various reasons.

In Africa, the higher prevalence is often attributed to factors such as inadequate healthcare infrastructure, socioeconomic challenges, limited maternal health services, suboptimal infection control practices, insufficient diagnostic stewardship, and cultural practices that influence essential newborn care [77].

In this systematic review and meta-analysis, the overall pooled prevalence of imipenem resistance was 34.35%. This rate was comparable to findings from a systematic review and meta-analysis conducted in Iran [78].

Fig. 5 Forest plot showing the pooled prevalence of ertapenem resistance profile GNB isolated from neonates with suspected bloodstream infections in Africa

Table 2 The pooled prevalence of carbapenem and specific groups of carbapenem drugs (meropenem and imipenem) resistance profiles of GNB isolates from neonates suspected of sepsis in African countries

Type of isolate	Carbapenem				Meropenem				Imipenem			
	No of study	Pooled prevalence	I^2	*p*-value	No of study	Pooled prevalence	I^2	*p*-value	No of study	Pooled prevalence at 95% CI	I^2	*p*-value
A. baumannii	27	45.9 (33.1–58.7)	98.8	< 0.001	14	36.7 (20.1–53.3)	95.68	< 0.001	11	53.1 (32.2–74.1)	98.1	< 0.001
Citrobacter spp	16	28.1 (9.2–46.9)	96.3	< 0.001	8	17.8 (-1.4- 37.0)	90.56	0.069	6	29.7 (-3.0 - 62.4)	94.4	0.075
E. Coli	37	12.3 (5.4–19.2)	98.7	< 0.001	18	6.9 (2.0- 11.8)	89.5	< 0.001	15	17.9 (3.2–32.6)	98.7	0.017
Enterobacter spp	20	31.7 (15.9–47.3)	99.0	< 0.001	9	27.1 (3.5–50.7)	98.0	0.022	8	41.2 (13.2–69.1)	98.9	0.004
K. pneumoniae	36	23.8 (14.4–33.3)	99.5	< 0.001	19	21.9 (9.1–34.8)	99.5	< 0.001	14	24.4 (8.3– 40.5)	99.6	0.003
Klebsiella spp	20	36.7 (17.9–55.5)	99.8	< 0.001	9	25.4 (-0.7- 51.5)	99.6	0.056	7	52.3 (18.9 - 85.7)	99.7	0.002
Pseudomonas spp	19	43.0 (23.0-62.4)	99.8	< 0.001	9	29.2 (4.8–53.5)	96.01	0.019	9	49.7 (20.0–79.7)	99.2	0.002
Serrtia spp	9	22.2 (-6.0-56.5)	99.8	0.12	4	24.9 (-23.2- 73.0)	99.68	0.31	4	25.1 (-23.2–73.4)	99.8	0.3

However, it was higher than results from studies involving seven countries in Asia and Africa on antibiotic resistance in neonates from developing societies (BARNARDS) [69], nother systematic review from Iran [70],, and studies from various Asian and African countries [73]. This higher prevalence may be attributed to factors such as increased self-medication, overuse of antibiotics, and the use of insufficient doses or incomplete treatment courses [76]. Additionally, a global point prevalence survey of antimicrobial prescribing in neonatal and pediatric sepsis found that less than a quarter of neonates received WHO-recommended first- or second-line empirical antibiotics [79].

To address this global health threat, it is essential to implement robust infection prevention measures, antimicrobial stewardship, and strict surveillance of infections and antimicrobial resistance (AMR). This is particularly crucial as third-line medications and carbapenems are increasingly losing their effectiveness [80]. This finding highlights a persistently high pooled prevalence of carbapenem-resistant bacterial isolates, with *A. baumannii* exhibiting the highest resistance rate at 45.9%, followed by *Pseudomonas* spp. at 43.0%, and *Klebsiella* spp. at 36.7%. These results are consistent with studies conducted in low- and middle-income countries [72], across thirty nations [22], and Iran [81]. In contrast, other studies have reported different patterns of carbapenem

Table 3 Subgroup analysis for carbapenem and specific groups of carbapenem drugs (meropenem and imipenem) resistance by year of publication, country, study design and methods of isolation

Category	Characteristics	Carbapenem				Meropenem				Imipenem			
		Pooled prevalence at 95% CI	NT	I²	p-value	Pooled prevalence at 95% CI	NT	I²	p-value	Pooled prevalence at 95% CI	NT	I²	p-value
By year of publication	2010–2015	20.8 (12.2–29.4)	324	77.7	0.01	14.3 (7.6, 21.0)	108	0.00	0.7	25.1 (12.0–38.3)	220	77.8	0.01
	2016–2020	29.1 (13.9–44.3)	2949	99.8	<0.001	31.3 (11.3, -51.3)	1258	99.4	<0.001	30.1 (3.7–56.5)	1198	99.8	<0.001
	2021–2023	32.7 (21.0–44.5)	3843	99.6	<0.001	24.8 (11.3–38.2)	1584	99.3	<0.001	41.1 (17.8–64.3)	1200	99.7	<0.001
By study country	Egypt	57.9 (43.7–72.7)	2382	99.3	<0.001	57.1 (33.4–80.7)	1001	99.1	<0.001	54.5 (35.6–73.3)	1129	98.7	<0.001
	Ethiopia	25.8 (2.0–49.6)	766	99.8	<0.001	20.1 (1.0–39.2)	422	98.7	0.022	49.0 (-45.4–43.5)	226	99.9	<0.001
	Ghana	2.3 (-1.2–5.7)	113	37.4	0.2	2.25 (-1.2–5.7)	113	37.4	0.2	-	-		-
	Nigeria	21.8 (2.9–40.7)	76	77.6	0.03	21.8 (2.9–40.7)	76	77.6	0.03				
	South Africa	11.2 (4.1–18.4)	3194	98.9	<0.001	11.7 (0.5–23.0)	1016	98.3	0.04	11.5 (-3.7–26.7)	1056	99.2	0.14
	Tanzania	17.7 (7.02–8.5)	236	81.6	<0.001	17.7 (6.9–28.5)	136	81.8	<0.001	-		-	-
	Sudan	0.5 (-1.2–2.2)	63	0.00	0.57	-		-	-	0.5 (-1.7–2.7)	41	0.65	<0.001
By isolation method	Authomated culture	29.2 (18.4–39.9)	5718	99.8	<0.001	26.6 (13.0–40.2)	2208	99.5	<0.001	30.0 (10.0–42.9)	1958	99.8	<0.001
	Convetional culture	32.1 (18.9–45.4)	1398	99.1	<0.001	25.4 (9.0–41.8)	738	98.7	<0.001	39.6 (18.5–60.7)	660	99.4	<0.001

Note, NT: number of isolates tested for each drugs

resistance. For instance, research conducted in Sub-Saharan African countries identified *K. pneumoniae* as the most resistant, followed by *E. coli* [82]. In Iran, *Enterobacter* spp. was most resistant, followed by *Pseudomonas* spp. [70], while another study in Sub Sharan Africa found *Klebsiella* spp. to be the most resistant, followed by *E. coli* [83]. Additionally, a study from China reported *E. coli* as the most resistant, with *K. pneumoniae* following [84]. The variation might be attributed to differences in the implementation of policies related to the control of drug-resistant bacteria. These policies can influence factors such as infection prevention measures, antimicrobial stewardship practices, and surveillance systems, which in turn affect the prevalence and types of resistant strains observed in different regions.

In this study, *K. pneumoniae* was identified as the most common isolate causing neonatal sepsis. This predominance of *K. pneumoniae* as the primary causative agent of neonatal sepsis is more pronounced in studies from Iran [70, 78], seven countries of Asia and Africa on the burden of antibiotic resistance in neonates from developing societies [69], Sub-Saharan African countries [82], studies conducted from Asian and African countries [73]. In contrast to this studies from China [84] *E. coli* followed

by *Klebsiella spp* and Iran [85] *Enterobacter spp* followed by *K. pneumoniae* were the main causative pathogens of neonatal sepsis. National disparities in microbiology may result from changes in community flora, varying incidence of maternal and neonatal risk factors, and differences in neonatal healthcare practices [82]. Additionally, the observed dissimilarities could be due to epidemiological variations in bacterial strains and shifts in the incidence and etiology of bloodstream infections over time [86].

The examined studies displayed significant heterogeneity regarding publication year, isolation methods, and study country. The percentage of carbapenem-resistant isolates varied widely between countries, from 0.5% in Sudan to 57.9% in Egypt. This variability is supported by studies from diverse settings across 12 countries [68], in sub-Saharan Africa [82], and other studies conducted across thirty nations [22]. These variations can be attributed to several factors, including the fact that some pooled estimates were derived from studies with small sample sizes and highly variable blood culture positivity rates. Additionally, differences in detection capacities, population density, malnutrition prevalence, health-seeking behaviors, and the effectiveness of infection

prevention and control measures in healthcare facilities can also contribute to the observed variability in carbapenem resistance rates [87]. These limitations are crucial when interpreting our findings. Additionally, factors such as the preventive measures implemented in each country, the clinical criteria used to diagnose sepsis, the sensitivity and specificity of culture methods in various laboratories, the hygienic conditions in delivery areas, and the social and economic conditions of the nations may all contribute to explaining these regional differences [88].

Limitations of the study

There were various restrictions on our review. Initially, the analysis in this study was limited to papers written in the English language. Second, there may 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 were based on studies with few isolates and highly fluctuating carbapenem resistance rates.

Conclusions

Overall, this meta-analysis showed a broad range of gram-negative bacilli. Furthermore, there was a significant difference in the carbapenem resistance patterns of the isolates across these countries. Stronger microbiology laboratory capacity to diagnose drug resistance is required in countries with a high burden of neonatal sepsis. This inturn will enable more accurate detection, timely diagnosis, and effective monitoring of these resistant strains which lead to more targeted and effective treatments and informed treatment decisions.

Feature perspective

The feature perspective involves identifying and analyzing the specific traits and mechanisms that contribute to this resistance. This approach helps in understanding how resistance develops, how it can be detected, and what strategies might be effective in combating it. Key features include: Mechanisms of resistance, genetic elements, phenotypic characteristics and environmental and contextual factors.

The added value of this study

This is the first comprehensive review of carbapenem-resistant gram-negative bacterial infections in neonates in Africa, as far as we are aware. Our analysis evaluates geographical variations in pathogen dominance and carbapenem resistance patterns in addition to filling in the information gap about carbapenem-resistant bacteria that cause invasive bacterial infections.

Recommendation

Platforms that provide data in a timely and useful manner should be created since the types of GNB infections and the corresponding carbapenem resistances are altered over time. The observed increase in GNB resistance to carbapenem drugs 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 and ensure effective treatment of GNB infections in Africa. Additionally, collaborative efforts at local, national, and international levels are warranted to address the multifaceted factors contributing to AMR and mitigate its impact on public health.

Abbreviations

AMR	Antimicrobial Resistance
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
CRGNB	Carbapenem-Resistant Gram-Negative Bacilli
EOS	Early Onset Sepsis
GNB	Gram-Negative Bacteria
JBI	Joanna Briggs Institute
LOS	Late-Onset Sepsis
MeSH	Medical Subject Headings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO	World Health Organization

Supplementary Information

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> Supplementary Material 1

Author contributions

AS: led the systematic review and meta-analysis, overseeing the study's conceptualization, article selection, data extraction, statistical analysis, and manuscript writing. AS, ZA, MAR, EG, ST, and YG: involved in searching for relevant articles, conducting data extraction, performing statistical analysis, and involved in manuscript drafting. BBA, MAR, and AAK were involved in statistical analysis, consultation of the overall process of this systematic review, and meta-analysis. WA, TM, AA, MG, CM, AAL, GK, MN, SA, AJ, SG, ZD and WK, 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.

Data availability

All generated data and research materials used during this systematic review and meta analysis are available from paper and supplementary material.

Declarations

Ethics approval and consent to participate

In this study, ethics approval and consent to participate were not required as it exclusively utilized publicly available aggregated data.

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Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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