Antimicrobial Resistance and Infection Control

REVIEW

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Global trends of ceftazidime–avibactam resistance in gram-negative bacteria: systematic review and meta-analysis

Yang Wang[1], Mohammad Sholeh[2], LunDi Yang[1*], Matin Zafar Shakourzadeh[3], Masoumeh Beig[2] and Khalil Azizian[4,5*]

Abstract

Background The emergence of antimicrobial resistance in Gram-negative bacteria (GNB) is a major global concern. Ceftazidime–avibactam (CAZ–AVI) has been identified as a potential treatment option for complicated infections.

Objectives This meta-analysis aimed to evaluate the global resistance proportions of GNB to CAZ–AVI comprehensively.

Methods Studies were searched in Scopus, PubMed, and EMBASE (until September 2024), and statistical analyses were conducted using STATA software (version 20.0).

Results CAZ–AVI resistance proportions were determined in 136 studies, with 25.8% (95% CI 22.2–29.7) for non-fermentative gram-negative bacilli and 6.1% (95% CI 4.9–7.4) for *Enterobacterales*. The CAZ–AVI resistance proportion significantly increased from 5.6% (95% CI 4.1–7.6) of 221,278 GNB isolates in 2015–2020 to 13.2% (95% CI 11.4–15.2) of 285,978 GNB isolates in 2021–2024. Regionally, CAZ–AVI resistance was highest in Asia 19.3% (95% CI 15.7–24.23.4), followed by Africa 13.6% (95% CI 5.6–29.2), Europe 11% (95% CI 7.8–15.2), South America 6.1% (95% CI 3.2–11.5) and North America 5.3% (95% CI 4.2–6.7). Among GNB resistance profiles, colistin-resistant isolates and XDR isolates exhibited the highest resistance proportions (37.1%, 95% CI 14–68 and 32.1%, 95% CI 18.5–49.6), respectively), followed by carbapenem-resistant isolates and MDR isolates [(25.8%, 95% CI 22.6–29.3) and (13%, 95% CI 9.6, 17.3)].

Conclusion A high proportion of GNB isolates from urinary tract infections remained susceptible to CAZ–AVI, indicating its potential as a suitable treatment option. However, the increasing resistance trends among GNB are concerning and warrant continuous monitoring to maintain CAZ–AVI's effectiveness against GNB infections.

Keywords Ceftazidime–avibactam, Resistance, Gram-negative bacteria, Non-fermentative gram-negative bacilli, Enterobacterales, Systematic review and meta-analysis

*Correspondence:
LunDi Yang
yld_nccdc@163.com
Khalil Azizian
k.azizian86@gmail.com
Full list of author information is available at the end of the article

Introduction

Antimicrobial resistance in Gram-negative bacteria (GNB) is a significant and urgent global public health concern requiring immediate attention [1, 2]. Traditionally, β-lactams and carbapenems have been reliable treatment choices for infections caused by GNB, providing consistent and effective therapeutic options against these pathogens [3]. Unfortunately, the extensive usage of β-lactams and carbapenems has resulted in a concerning surge in antimicrobial resistance, compromising their efficacy against GNB and necessitating alternative therapeutic approaches [4]. The primary factor contributing to the development of resistance in GNB is often the production of β-lactamases, enzymes produced by bacteria that render β-lactam antibiotics ineffective [5, 6]. Carbapenemase-producing GNB contributes significantly to increased mortality worldwide by rendering carbapenem antibiotics ineffective, thereby limiting treatment options and worsening health outcomes [7]. β-lactam/β-lactamase inhibitor combination therapy effectively treats GNB infections, including those resistant to other antibiotics, by countering bacterial resistance mechanisms. Examples include ceftazidime–avibactam (CAZ–AVI) and meropenem-vaborbactam [4, 8]. CAZ–AVI gained approval from the US Food and Drug Administration (FDA) in 2015 and the European Medicines Agency (EMA) in 2016. This combination therapy effectively treats complicated infections caused by GNB, including those resistant to other antibiotics. The FDA initially approved CAZ–AVI for treating complicated urinary tract infections and complicated intra-abdominal infections in adults. At the same time, subsequent approvals have expanded its use to hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia [3, 7]. CAZ–AVI demonstrates efficacy against various GNBs such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Klebsiella oxytoca, Enterobacter cloacae, Citrobacter freundii* complex, *Serratia marcescens*, and *Haemophilus influenzae*. Its broad-spectrum activity makes it a valuable treatment option for multidrug-resistant infections involving these pathogens [9]. CAZ–AVI effectively treats infections caused by drug-resistant GNB, including ESBL, AmpC, KPC, OXA-48-producing Enterobacterales, and MDR, XDR, ceftazidime-non-susceptible, and carbapenem-resistant *P. aeruginosa* strains. Its broad-spectrum activity results from the synergistic effect of ceftazidime and avibactam, which targets critical bacterial resistance mechanisms [7, 10, 11]. CAZ–AVI is the preferred treatment for complicated intra-abdominal, urinary tract, and hospital-acquired pneumonia due to its efficacy against drug-resistant GNB.

Clinical trials support this recommendation, and local susceptibility patterns should be considered during use [2, 3]. β-lactamase-mutants may compromise current inhibitors' efficacy, necessitating robust surveillance, responsible antibiotic use, and investment in novel treatments [7]. CAZ–AVI has a favorable pharmacological profile and shows potential as an empirical therapy option for severe GNB infections, as supported by systematic reviews and real-world experiences. Its efficacy against carbapenem-resistant Enterobacterales and *P. aeruginosa* further highlights its importance in managing multi-drug resistant infections [9, 12]. CAZ–AVI is effective against carbapenem-resistant *Enterobacterales* and *P. aeruginosa*, as supported by systematic reviews, meta-analyses, and clinical trials. Its efficacy in managing multi-drug resistant infections makes it a valuable option for treating severe GNBs [13] and *Enterobacterales* in the bloodstream [14]. To address the lack of statistical evaluations on CAZ–AVI resistance in non-fermentative Gram-negative bacilli (NFGNB) and *Enterobacterales* across all infection types, our study aimed to document the current resistance landscape by analyzing relevant published literature. Our findings contribute to the ongoing efforts to preserve the efficacy of CAZ–AVI combination therapy and inform treatment decisions.

Methods

Eligibility criteria

For inclusion in the meta-analysis, articles had to meet the following eligibility criteria: Firstly, we included articles that investigated CAZ–AVI resistance in Gram-negative isolates. Secondly, we considered articles that provided information on sample size. Lastly, articles must report resistance proportions in full-text English-published articles for inclusion. The following were excluded: Firstly, articles written in languages other than English were not considered. Secondly, we should have included case reports, cohort, and pharmacokinetic studies. Thirdly, articles with duplicate or overlapping data were excluded. Lastly, articles that did not state resistance proportions were excluded from our analysis.

Search strategy

We systematically searched Scopus, PubMed, and EMBASE databases up to September 16, 2024. The search syntax was adapted for each database using relevant keywords and Boolean operators (AND, OR): "ceftazidime–avibactam", "Zavicefta", "Avycaz", "resistant", "susceptible", "*Enterobacterales*", "enterobacteriaceae", "*Escherichia*", "*Klebsiella*", "*Enterobacter*", "*Citrobacter*", "*Proteus*", "*Serratia*", "*Salmonella*", "*Shigella*", "Non-fermenting Gram-negative bacilli", "*Pseudomonas*",

"*Acinetobacter*", "*Stenotrophomonas*" in the Title/Abstract/Keywords fields.

Selection process

After removing duplicates, the systematic search results from online databases were imported into EndNote (version 20). To minimize bias, two authors (KHA and MZ) independently searched for and analyzed relevant publications. Any discrepancies were resolved by a third author (LY). Reference lists of included articles were reviewed to gather additional data.

Selection criteria and data extraction

Two reviewers (KHA and MZ) designed a data extraction form to maintain consistency and accuracy and collected relevant data from eligible studies. The extracted data were organized by the first author's name, publication year, study areas, infection source, sample size of GNB, CAZ–AVI-resistant GNB isolates, and AST methodology. Table 1 summarizes the CAZ–AVI susceptibility breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) [15] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [16] for *Enterobacterales* and *P. aeruginosa*. Prevalence was calculated as the proportion of CAZ–AVI-resistant Gram-negative isolates ([resistant isolates / total Gram-negative isolates] × 100). Additional reviewers (LY) confirmed the data extraction process. Our review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary File) [1].

Study risk of bias assessment

Two blinded reviewers independently assessed study quality using the Newcastle–Ottawa Scale adapted for cross-sectional studies (Supplementary File). The scale evaluates three domains: selection, comparability, and outcome/exposure, with a maximum score of 8 indicating high quality [2]. Studies that received a score of ≥ 6 stars were considered good quality, those with a score of 4–5 stars were considered fair, and those with a ≤ 3 stars were regarded as poor quality. Any disagreements in the assessment were discussed and resolved by a third reviewer.

Study outcomes

The primary outcome was CAZ–AVI resistance proportion in GNB. Subgroup analyses were performed based on publication year (2015–2020, 2021–2024), geographic location (continent/country), infection source, GNB groups (NFGNB and *Enterobacterales*), resistance profiling of GNB groups, GNB species, and AST methodology. We aimed to identify potential trends and factors associated with CAZ–AVI resistance, which can inform targeted interventions and public health strategies to mitigate the spread of antimicrobial resistance.

Statistics

The relevant data regarding the resistance of GNB to CAZ–AVI was included in the metadata. The Meta-prop method in the R statistical software R 3.6.0 was utilized for all subgroups [17, 18]. The estimate of $\tau^{\wedge 2}$, the Q-test to assess heterogeneity of effect-size estimates from the individual studies [19, 20]. Meta-regression models were employed to investigate the variation in CAZ–AVI resistance over time. Egger's and Begg's tests were conducted to evaluate potential publication bias. The resistance proportions were reported with 95% confidence intervals.

Results

Descriptive statistics

Our systematic search generated 2449 records, managed using EndNote version 20. After removing duplicates and screening titles and abstracts, 250 full-text articles were assessed, leading to the exclusion of 114 articles. This multistep process ensured that only relevant, high-quality studies were included in the final analysis, thus enhancing the robustness and reliability of our findings on CAZ–AVI resistance. Ultimately, this systematic review and meta-analysis included 136 eligible studies [21–156]. The screening and selection process is illustrated in the PRISMA flowchart (Fig. 1). The included studies originated from 31 countries (China, Turkey, Taiwan, United Kingdom, Portugal, United States, Colombia, Czechia, Qatar, Kuwait, India, Italy, Brazil, Greece, France, Thailand, Germany, Hungary, Belgium, Spain, Nigeria, Egypt, Saudi Arabia, Canada, Poland, Singapore, Serbia, Uruguay, Chile, Japan, Bahrain) across four continents and covered the years 2015 to 2024. The funnel plot (Fig. 2) visually represents CAZ–AVI resistance in GNB.

Table 1 The breakpoints for ceftazidime–avibactam resistance for *Enterobacterales* and *P. aeruginosa* [15, 16]

Bacteria	CLSI MIC-methods (μg/mL)	CLSI Disk diffusion (mm)	EUCAST MIC-methods (μg/mL)	EUCAST Disk diffusion (mm)
Enterobacterales	≤ 8/4	≥ 21	≤ 8	≥ 17
Pseudomonas aeruginosa	16/4	≤ 20	≤ 8	≥ 17

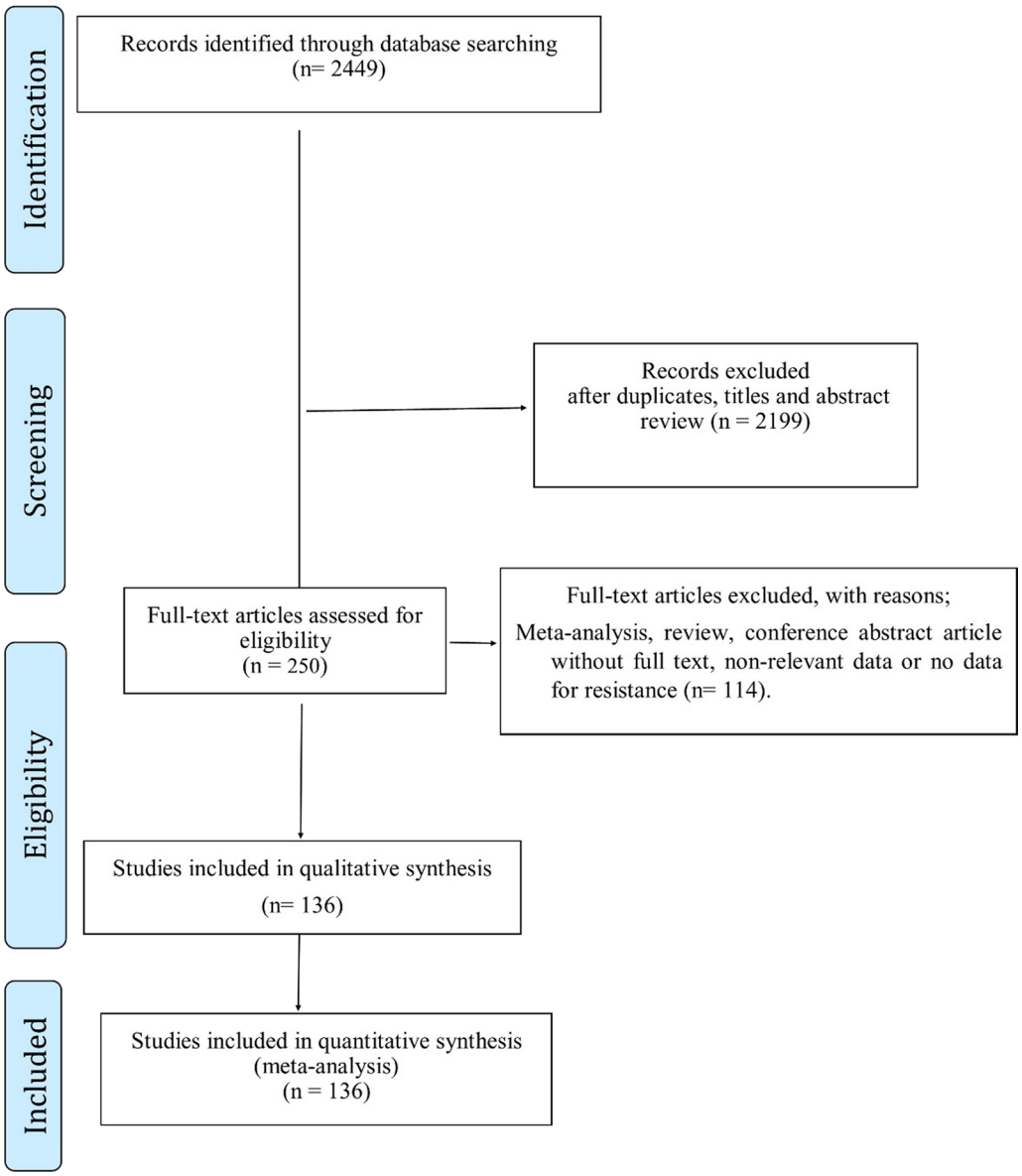


Fig. 1 Flow Diagram Showing the Study Selection Process

Table 2 details the proportion of CAZ–AVI resistance in GNB and results from subgroup analyses. A summary of resistance proportions is provided below: Overall CAZ–AVI resistance proportion in GNB. Resistance trends by publication year, geographic location, infection source, and bacterial species. Subgroup analyses based on GNB groups, resistance profiling, and AST methodology. Our study contributes to a more comprehensive understanding of its global epidemiology by examining these different aspects of CAZ–AVI resistance. It can inform targeted strategies for antibiotic stewardship and develop novel antimicrobial therapies.

CAZ–AVI resistance in GNB

A total of 507,254 GNB isolates were included in the CAZ–AVI resistance analysis. The overall proportion of CAZ–AVI resistance was 10.4% (95% CI 9.1–11.8). Substantial heterogeneity was observed between the studies ($I^2 = 99.06\%$, $P < 0.001$), and significant publication bias was detected (Egger rank correlation test, $P < 0.001$). The analysis included 135 studies examining NFGNB (137,052 isolates) and *Enterobacterales* (370,186 isolates), with CAZ–AVI resistance proportions of 25.8% (95% CI 22.2–29.7) and 6.1% (95% CI 4.9–7.4), respectively. Substantial heterogeneity

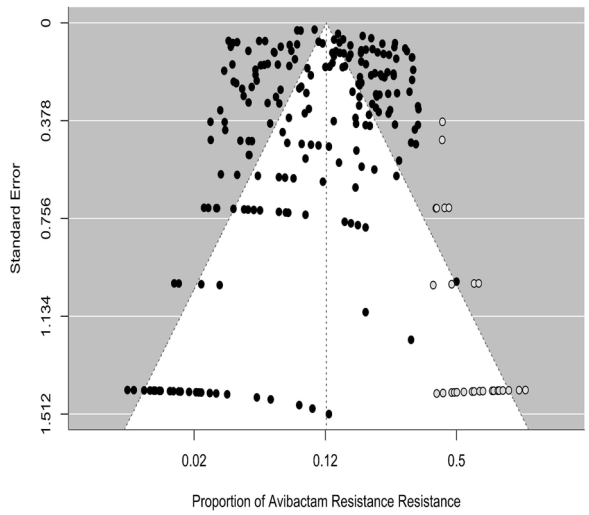


Fig. 2 The funnel plot of the resistance of Gram-negative bacteria to CAZ–AVI

was found between the studies ($I^2 > 98\%$, $P < 0.001$). According to the GNB resistance profiles, the highest CAZ–AVI resistance proportion was reported in colistin-resistant isolates (37.1%, 95% CI 14–68) and XDR isolates (32.1%, 95% CI 18.5–49.6). This was followed by carbapenem-resistant isolates and MDR isolates [(25.8%, 95% CI 22.6–29.3) and (13%, 95% CI 9.6, 17.3)] (Table 2). A statistically significant disparity was found in CAZ–AVI resistance proportions among various GNB species ($P < 0.001$). The lowest resistance proportions were reported in *Citrobacter* spp. (0.8%, 95% CI 0.3–2.7), *Serratia marcescens* (1.1%, 95% CI 0.4–2.7), *Enterobacter spp.* (2.1%, 95% CI 0.5–8.3), and *Klebsiella oxytoca* (2.8%, 95% CI 0.6–12). Conversely, the highest resistance proportions were observed in *A. baumannii* (88.6%, 95% CI 66.1–95.7), *Pseudomonas* spp. (65.7%, 95% CI 61.4–69.8), *P. aeruginosa* (22.8%, 95% CI 19.5–26.4), and *Klebsiella* spp. (22.5%, 95% CI 7.2–52.2).

CAZ–AVI resistance in GNB over time

A subgroup analysis showed a statistically significant difference in CAZ–AVI resistance proportions over time. To analyze trends in resistance changes, we conducted a subgroup analysis for 2015–2020 and 2021–2024 (Table 2, Fig. 3). As shown in Table 2, the CAZ–AVI resistance proportion significantly increased from 5.6% (95% CI 4.1–7.6) of 221278isolates in 2015–2020 to 13.2% (95% CI 11.4–15.2) of 285,978 GNB isolates in 2021–2024, indicating a > twofold increase in frequency ($P < 0.001$). Meta-regression confirmed that the CAZ–AVI resistance proportion increased over time ($r = 0.212$, $P < 0.001$; Fig. 3).

CAZ–AVI resistance in GNB at different locations

The subgroup analysis revealed significant variations in CAZ–AVI resistance proportions across different geographic regions (Table 2, Fig. 4). The prevalence of CAZ–AVI resistance was as follows: Asia: 19.3% (95% CI 15.7–24.23.4) among 132,027 GNB isolates, Africa: 13.6% (95% CI 5.6–29.2) among 3814 GNB isolates, Europe: 11% (95% CI 7.8–15.2) among 153,368 GNB isolates, South America: 6.1% (95% CI 3.2–11.5) among 25,082 GNB isolates, North America: 5.3% (95% CI 4.2–6.7) among 187,799 GNB isolates. The highest CAZ–AVI resistance proportions were reported in Japan (88.9%, 95% CI 60.4–97.7), Greece (80.7%, 95% CI 1.8–99.9), Thailand (58.5%, 95% CI 24.5–86), Uruguay (58%, 95% CI 41.7–72.7), and Saudi Arabia (50.4%, 95% CI 27.8–72.9). Conversely, the lowest rates were observed in Qatar (0.9%, 95% CI 0.1–6.2), Portugal (1.7%, 95% CI 24.5–86), and Chile (2.4%, 95% CI 0.3–17.9). Out of the 31 reporting countries, twelve (Turkey, India, Greece, Thailand, Egypt, Germany, Singapore, Serbia, Uruguay, Japan, Nigeria, and Saudi Arabia) had resistance proportions exceeding 25% of isolates. The differences in CAZ–AVI proportions between countries/continents were statistically significant (Table 2; Fig. 4).

CAZ–AVI resistance in GNB based on infection source

The subgroup analysis demonstrated a statistically significant difference in CAZ–AVI resistance proportions among various infection sources (respiratory tracts, bloodstream, urinary, and mixed) (Table 2). Urinary infections exhibited the lowest reported CAZ–AVI resistance proportion at 1% (95% CI 0.2–4). Conversely, bloodstream infections showed the highest resistance proportion, reaching 12.6% (95% CI 10.4–14.6).

CAZ–AVI resistance in GNB based on AST methods

The subgroup analysis showed a statistically significant difference in CAZ–AVI resistance proportions among various AST methods. Broth microdilution was the most commonly used AST method in the included studies. The CAZ–AVI resistance proportions were: Disk diffusion agar method: 35.9% (95% CI 22.1–52.5), E-test 31.4% (95% CI 23.3–40.8), and Broth microdilution 9.3% (95% CI 8.1–10.7).

Discussion

The present systematic review and meta-analysis incorporated 135 eligible studies examining 507,254 GNB, comprising 137,052 NFGNB and 370,186 *Enterobacterales* isolates. The analysis results provide substantial evidence supporting the hypothesis that CAZ–AVI demonstrates superior efficacy against *Enterobacterales*

Table 2 Proportion of Ceftazidime–Avibactam resistant in Gram-negative bacteria based on year of study, continents, countries, pathogens, infection source, resistance profiling, and AST

Category	Subgroup	K (n, N)	Proportion (%) 95%CI (LCI, HCI)	I^2 (%)	*P*. value
Overall		(37,817, 507,254)	10.4 (9.1, 11.8)	96.06	
Year group	2021–2024	(28,876, 285,976)	13.2 (11.4, 15.2)	99.01	$p < 0.001$
	2015–2020	(8941, 221,278)	5.6 (4.1, 7.6)	99.15	
Countries	Bahrain	(34, 152)	22.4 (16.4, 29.7)	0.00	$p < 0.001$
	Belgium	(411, 2833)	23.2 (5.3, 61.8)	98.85	
	Brazil	(3, 76)	5.0 (1.1, 20.0)	28.90	
	Canada	(992, 8613)	12.3 (5.9, 23.9)	99.01	
	Chile	(211, 1615)	2.4 (0.3, 17.9)	95.37	
	China	(7027, 88,099)	16.5 (12.3, 21.7)	98.90	
	Colombia	(83, 1317)	3.2 (0.3, 24.8)	97.70	
	Czechia	(68, 2340)	2.6 (0.3, 21.1)	98.26	
	Egypt	(39, 111)	34.9 (24.8, 46.6)	26.85	
	France	(42, 351)	11.6 (4.4, 27.0)	83.91	
	Germany	(287, 938)	29.6 (12.9, 54.3)	95.95	
	Greece	(51, 87)	80.7 (1.8, 99.9)	93.12	
	Hungary	(1146, 22,674)	6.4 (3.2, 12.4)	99.17	
	India	(1571, 6681)	33.7 (20.4, 50.2)	98.89	
	Italy	(865, 10,723)	19.6 (9.2, 37.0)	98.11	
	Japan	(350, 379)	88.9 (60.4, 97.7)	92.91	
	Kuwait	(77, 935)	16.7 (4.9, 43.7)	94.94	
	Nigeria	(47, 175)	30.6 (0.0, 99.9)	97.59	
	Poland	(0, 19)	2.5 (0.2, 29.8)	0.00	
	Portugal	(974, 106,860)	1.7 (0.9, 3.3)	98.47	
	Qatar	(1, 109)	0.9 (0.1, 6.2)	0.00	
	Saudi Arabia	(50, 105)	50.4 (27.8, 72.9)	82.21	
	Serbia	(37, 143)	25.9 (19.4, 33.7)	0.00	
	Singapore	(246, 858)	30.7 (23.7, 38.6)	77.41	
	Spain	(485, 3023)	23.6 (10.9, 43.9)	98.04	
	Taiwan	(6405, 33,370)	9.9 (5.2, 18.1)	99.10	
	Thailand	(2663, 5590)	58.5 (24.5, 86.0)	99.50	
	Turkey	(146, 432)	38.7 (23.6, 56.3)	84.53	
	United Kingdom	(395, 3263)	7.1 (1.7, 25.3)	98.01	
	United States	(11,905, 179,781)	4.9 (3.9, 6.2)	98.96	
	Uruguay	(23, 39)	58.0 (41.7, 72.7)	0.00	
Continent	Asia	(17,727, 132,027)	19.3 (15.7, 23.4)	99.06	$p < 0.001$
	Europe	(4829, 153,368)	11.0 (7.8, 15.2)	98.99	
	North America	(12,897, 187,799)	5.3 (4.2, 6.7)	98.97	
	South America	(1252, 25,082)	6.1 (3.2, 11.5)	98.60	
	Africa	(337, 3814)	13.6 (5.6, 29.2)	97.62	
	multi-continents	(775, 5164)	7.8 (2.2, 24.2)	99.42	
Infection source	MIX	(8597, 124,517)	8.1 (6.0, 10.8)	99.14	$p < 0.001$
	Urinary	(31, 1806)	1.0 (0.2, 4.0)	61.82	
	Respiratory	(421, 12,540)	1.4 (0.4, 4.6)	97.48	
	Bloodstream	(26,521, 312,965)	12.6 (10.8, 14.6)	99.05	
Bacterial groups	NFGNB	(26,058, 137,052)	25.8 (22.2, 29.7)	99.26	$p < 0.001$
	Enterobacterales	(11,746, 370,186)	6.1 (4.9, 7.4)	98.59	
Microbial Profiling	*Acinetobacter baumannii*	(1086, 1247)	86.8 (66.1, 95.7)	95.61	$p < 0.001$
	Citrobacter freundii	(81, 4593)	4.9 (2, 11.7)	90.46	

Table 2 (continued)

Category	Subgroup	K (n, N)	Proportion (%) 95%CI (LCI, HCI)	I^2 (%)	*P*. value
	Citrobacter spp.	(45, 5480)	0.8 (0.3, 2.7)	80.18	
	Enterobacter cloacae	(355, 6389)	14.8 (6.4, 30.5)	97.78	
	Enterobacter spp.	(148, 12,267)	2.1 (0.5, 8.3)	97.37	
	Escherichia coli	(879, 97,625)	4.9 (2.6, 8.8)	98.14	
	Klebsiella oxytoca	(61, 7196)	2.8 (0.6, 12)	95.25	
	Klebsiella pneumoniae	(3904, 92,538)	10.2 (7.5, 13.5)	98.13	
	Klebsiella spp	(187, 403)	22.5 (7.2, 52.2)	83.49	
	Morganella morganii	(2, 103)	3 (0.9, 9.8)	0.00	
	Proteus mirabilis	(21, 4101)	4.5 (0.4, 34.7)	95.35	
	Pseudomonas aeruginosa	(24,705, 135,402)	22.8 (19.5, 26.4)	99.25	
	Pseudomonas spp.	(320, 487)	65.7 (61.4, 69.8)	0.00	
	Serratia marcescens	(21, 3530)	1.1 (0.4, 2.7)	71.31	
	Providencia stuartii	(2, 28)	7.1 (1.8, 24.5)	0.00	
Resistance profiling	Colistin-resistant	(13, 42)	37.1 (14, 68)	61.54	$p < 0.001$
	MDR	(4033, 25,042)	13 (9.6, 17.3)	98.40	
	Carbapenem-resistant	(13,808, 45,098)	25.8 (22.6, 29.3)	96.71	
	ESBL	(3557, 39,991)	12.1 (5.9, 23.1)	98.70	
	XDR	(1146, 2426)	32.1 (18.5, 49.6)	97.36	
AST	Broth microdilution	(36,778, 503,796)	9.3 (8.1, 10.7)	99.14	$p < 0.001$
	E-test	(785, 2171)	31.4 (23.3, 40.8)	87.32	
	Disk diffusion	(209, 516)	35.9 (22.1, 52.5)	88.91	
	Agar dilution	(0, 695)	0.1 (0, 1.1)	0.00	

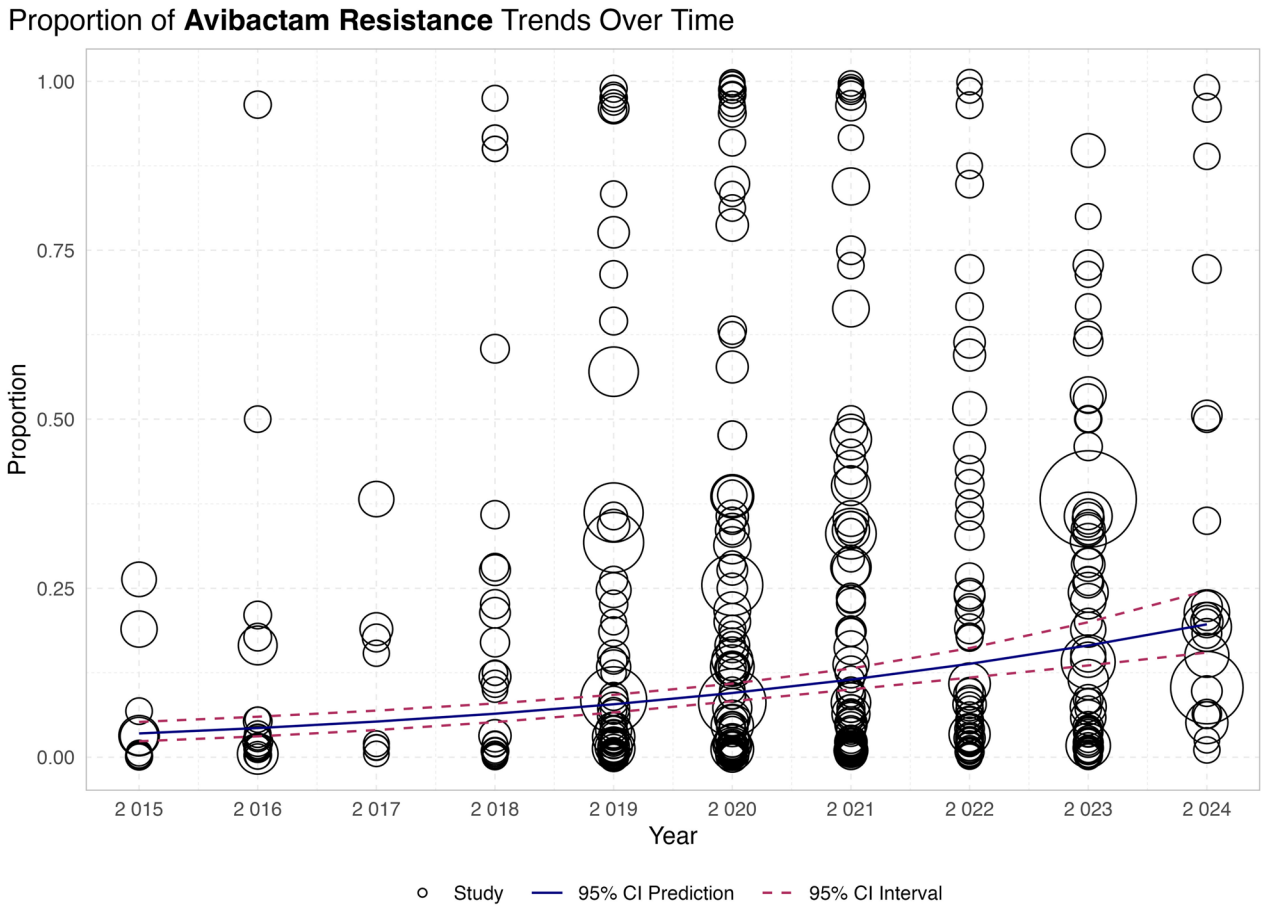
Caption; K number of studies, *n* Number of resistant isolates, *N* Number of total isolates, *LCI* 95% Lower Limit Confidence Interval, *HCI* 95% Higher Limit Confidence Interval, *P*-value of difference between groups. I^2: Heterogeneity, *AST* Antimicrobial susceptibility testing, *MDR* Multidrug resistance, *ESBL* Extended spectrum beta-lactamase, *XDR* Extensively drug-resistant

compared to NFGNB. This finding highlights the importance of considering bacterial species when assessing the potential effectiveness of CAZ–AVI in clinical settings.

MDR and XDR GNB are well-known contributors to complex infectious diseases, notably complicated urinary tract infections (cUTI). Carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant or MDR/XDR *P. aeruginosa* have emerged as significant concerns, substantially impacting global morbidity and mortality rates. Reported fatality rates associated with these resistant pathogens range from 46 to 60%, emphasizing the urgent need for effective treatment options and improved antimicrobial stewardship to combat the spread of resistance [3, 157]. According to the Centers for Disease Control and Prevention (CDC), CRE alone is responsible for over 13,000 nosocomial infections and approximately 1000 deaths annually in the United States. This highlights CRE's significant public health threat, emphasizing the importance of effective infection control measures and antimicrobial stewardship in healthcare settings [158]. The β-lactam antibiotics, including penicillins, cephalosporins, monobactams, and carbapenems, constitute the most widely utilized and effective agents against bacterial infections [159]. Among these, carbapenems such as imipenem, meropenem, ertapenem, and doripenem exhibit the broadest spectrum of activity and historically have been highly effective against GNBs [160]. However, the alarming increase in resistance to carbapenems observed recently is likely attributed to their misuse [160]. Notably, India has witnessed a significant surge in resistance proportions, ranging from 22.16 to 65% against carbapenem antibiotics targeting GNBs [161, 162].

One of the most effective strategies to counter β-lactamase-producing GNB involves combining a β-lactam antimicrobial agent with a β-lactamase inhibitor [4, 8]. Historically, classical β-lactamase inhibitors like clavulanic acid, tazobactam, and sulbactam have been utilized; however, their limited activity against most classes of β-lactamases has restricted their usage [11]. Presently, the novel generations of β-lactamase inhibitors, such as vaborbactam, relebactam, and avibactam (AVI), are commonly deployed against various classes of β-lactamases [2].

AVI is a synthetic, non-β-lactam β-lactamase inhibitor with no antibiotic activity. It helps protect β-lactam agents against β-lactamase-producing bacteria. Key



The correlation is statistically significant (r = 0.212, *p*-value = <0.001, 95% CI [0.141, 0.282]).

Fig. 3 Meta-regression analysis for changes in the proportion of CAZ–AVI resistance to gram-negative bacilli isolates over time

advantages include a prolonged half-life, effective β-lactamase interaction, and low molecular weight. AVI demonstrates significant efficacy against Ambler classes A (e.g., ESBLs, KPCs), C (AmpC cephalosporinases), and D (OXA-48) β-lactamases but does not affect class B or Metallo-β-lactamases [10].

Previous studies have investigated the effectiveness of combinations such as imipenem/relebactam, meropenem/vaborbactam, and CAZ–AVI, all of which have demonstrated favorable results [163, 164]. Among these, CAZ–AVI is the first approved combination currently in clinical use. Ceftazidime, a bactericidal agent with broad-spectrum third-generation cephalosporin properties, acts by binding to penicillin-binding proteins (PBPs) and inhibiting cell wall synthesis [10, 157]. Consequently, this combination proves effective against β-lactamases-producing isolates. Thus, the current meta-analysis focuses on the resistance proportion of CAZ–AVI in GNB. In this review, 89.6% of GNB isolates were susceptible to CAZ–AVI, while less than 10.4% showed resistance (NFGNB: 25.8% and *Enterobacterales*: 6.1%).

The strong correlation between colistin-resistant, XDR, carbapenem-resistant, and MDR isolates with CAZ–AVI resistance underscores the necessity for prudent selection of treatment options for multidrug-resistant infections. This observation emphasizes the significance of antimicrobial stewardship programs and continuous surveillance to track resistance trends and guide treatment guidelines. The underlying mechanisms responsible for this correlation may involve multiple factors, including [2, 165, 166] horizontal gene transfer: the exchange of genetic material between bacteria may result in the simultaneous acquisition of resistance genes to various antibiotics, including CAZ–AVI, leading to the emergence of MDR and XDR strains. Co-selection: Exposure to one antibiotic may facilitate the development of resistance to other unrelated antibiotics, potentially due to cross-resistance mechanisms or shared genetic elements. Clonal spread: successful MDR and XDR strains can rapidly disseminate within healthcare settings and communities, increasing the prevalence of MDR isolates, including

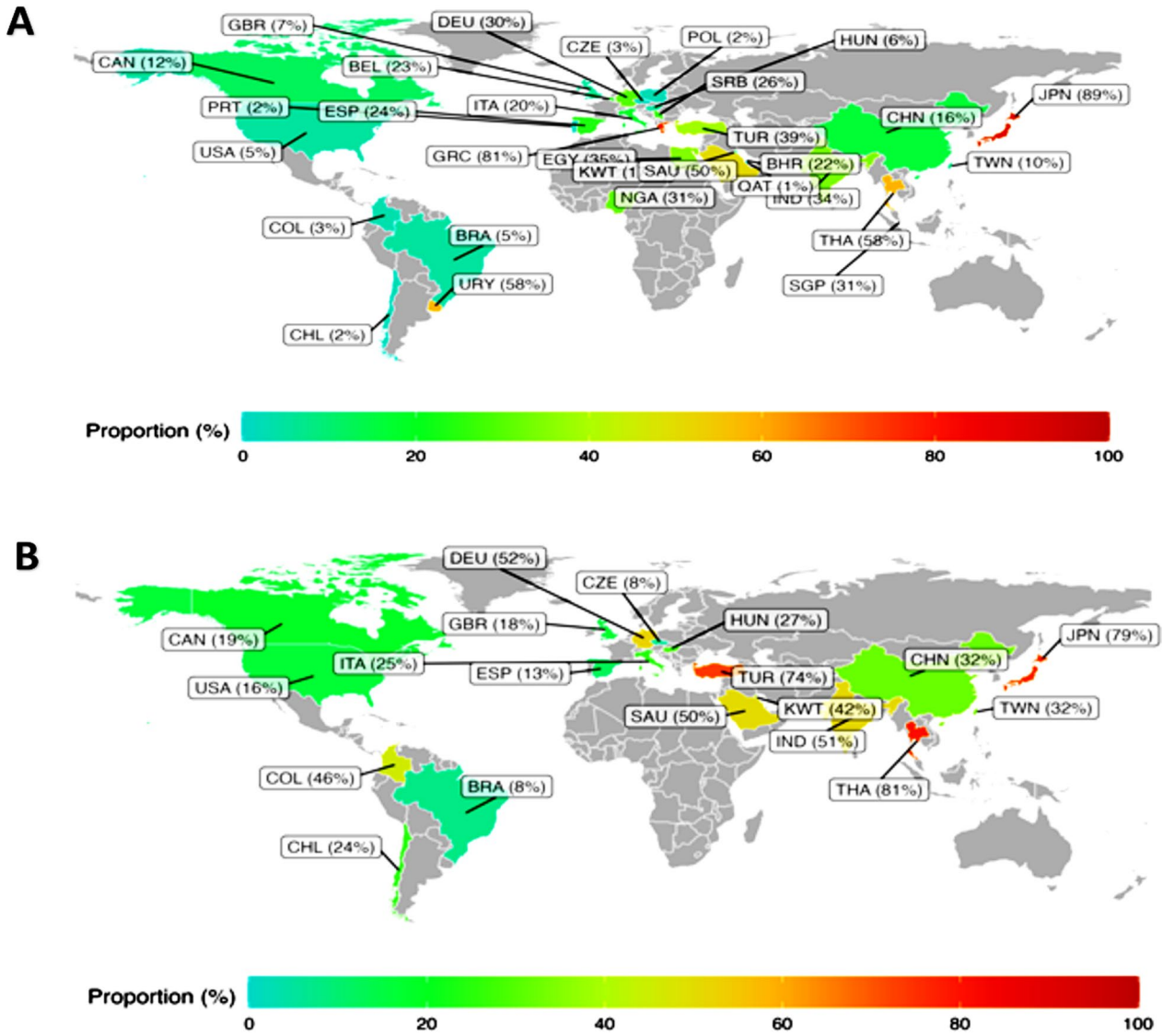


Fig. 4 The proportions of CAZ–AVI resistance of GNB isolates (**A** *Enterobacterales*, **B** Non-fermentative gram-negative bacilli) based on countries

CAZ–AVI-resistant strains. Understanding these mechanisms and their contribution to the observed correlation is crucial for developing targeted strategies to counteract resistance and optimize the efficacy of existing and future antibiotics.

However, 12.1% of ESBL-producing GNB isolates demonstrated CAZ–AVI resistance. ESBL-producing isolates degrade ceftazidime (CAZ) before acting on its target, as AVI is ineffective against class B β-lactamases or MBLs [167]. AVI cannot protect CAZ from Metallo-β-lactamases, leading to resistance in MBL-producing isolates. High resistance proportions are also observed in isolates producing ESBLs and carbapenemases among non-fermentative bacteria. CAZ–AVI resistance in these bacteria primarily stems from mutations within β-lactamase enzymes, with prior studies identifying mutations and modifications in the *KPC* gene (a known β-lactamase) as key contributors [168]. Reduced drug influx from decreased porin expression or mutations and efflux pump overexpression for antibiotic efflux contribute to CAZ–AVI resistance in GNB [169, 170]. These multifaceted insights underscore the diverse challenges encountered in combatting CAZ–AVI resistance among different strains of GNBs.

On the other hand, having resistance to colistin among GNBs can increase the chances of severe infection and mortality. Thus, other options are required. CAZ–AVI is one potential candidate for infections from

colistin-resistant isolates, but this study shows that approximately one-third of these isolates were resistant to CAZ–AVI.

This meta-analysis review indicates that non-fermenter bacteria such as *Acinetobacter* and *Pseudomonas* exhibit the highest resistance proportions. This suggests that these species may have intrinsic or acquired mechanisms contributing to CAZ–AVI resistance, which warrants further investigation. Over the past two decades, *A. baumannii* has become a significant global concern. The World Health Organization (WHO) recognizes carbapenem-resistant *A. baumannii* as a first-priority pathogen, emphasizing the urgent need for research and development of novel antibiotics to combat this MDR bacterium [171]. *A. baumannii* is notorious for its rapid growth of drug resistance, primarily due to its ability to modify outer membrane proteins and upregulate the expression of efflux pumps. These adaptive traits enable the bacterium to withstand a wide range of antibiotics, rendering it resistant to multiple drugs and particularly challenging to treat [169]. The unique characteristics of *A. baumannii*, such as its adaptability and rapid development of drug resistance, highlight the urgency of addressing this significant public health threat. Overcoming *A. baumannii's* resistance mechanisms necessitates exploring and implementing innovative treatment strategies, underscoring the critical need for continued research and investment in developing effective antimicrobial therapies. Rising CAZ–AVI resistance proportions necessitate continuous monitoring, effective antimicrobial stewardship, and further research into resistance mechanisms. Antibiotic misuse, CAZ–AVI exposure, and bacterial population selective pressure contribute to the global antimicrobial resistance surge.

Regional resistance variations highlight the need for tailored strategies to combat resistance in high-burden areas [172]. Regional disparities in CAZ–AVI resistance proportions stem from differences in consumption, government regulations, and ESBL prevalence. Tailored interventions and region-specific antibiotic stewardship programs are vital to combat resistance effectively. Continuous surveillance and monitoring of resistance trends inform public health policies and promote responsible antibiotic use, particularly in high-resistance regions [172, 173]. On another note, the Middle East, North Africa, and Turkey report the highest prevalence of OXA-48-producing bacteria [174], indicating that mutations in this β-lactamase gene contribute to resistance to CAZ–AVI [175–177]. The multifactorial nature of regional resistance patterns emphasizes the necessity of targeted interventions and surveillance strategies to address the global challenge of antimicrobial resistance effectively. By accounting for local factors such as consumption, government regulations, and the prevalence of specific resistance mechanisms, tailored approaches can help curb resistance proportions and ensure the continued efficacy of CAZ–AVI and other antibiotics. CAZ–AVI is a suitable prescription for cUTIs due to its high susceptibility rates. meropenem-vaborbactam (MER-VAB) effectively targets class A and C β-lactamases, with resistance observed in class D or B enzyme-producing isolates. Regional resistance disparities require targeted interventions, antibiotic stewardship, and continuous surveillance for effective resistance management [178]. The investigation of the aztreonam–ceftazidime–avibactam (ATM-CZA) exhibits intense activity against NDM-producing CRE and GES-producing CR-PA resistant to CAZ–AVI. It holds promise as a potential treatment option for MDR infections but requires further research and clinical trials to confirm safety and efficacy in patients [179]. However, resistance was noted in strains of *P. aeruginosa* producing NDM or VIM when exposed to ATM-CZA. An intriguing alternative explored in this context involves the use of Metallo-β-lactamase (MBL) inhibitors, such as 4-chloromercuribenzoic acid (CMB), in combination with β-lactam antimicrobials, offering the potential for treating infections caused by CRE and CR-PA isolates [160].

Several limitations need to be discussed in this study. First, the significant heterogeneity across studies raises concerns about the appropriateness of pooling data for meta-analysis. Future research should explore alternative methods or stricter inclusion criteria to address this issue. Second, the absence of moderator analyses prevents the determination of the impact of different variables on the mean effect size and direction of differences between subgroups. Including such analyses would strengthen the validity of the subgroup analyses—the variability in AST methods employed across the included studies. Although the analysis incorporated all commonly used AST methods (disc diffusion, MIC-based methods), this variability should be considered when interpreting the findings.

Additionally, the study focuses primarily on specific regions, limiting the generalizability of the findings. Incorporating data from a broader range of geographical locations would provide a more comprehensive understanding of global resistance patterns. Furthermore, the variability in sample sizes across studies may affect the reliability and precision of estimated resistance proportion, so future studies should strive for more consistent sample sizes. Lastly, the potential impact of publication bias on the findings should be assessed and discussed, as it can influence the credibility of the conclusions drawn from the meta-analysis. By addressing these limitations, the authors can provide a more thorough and accurate representation of the study's constraints and guide future research in addressing these issues.

Conclusions

In conclusion, the global prevalence of CAZ–AVI resistance in GNB is a significant public health concern, with varying resistance proportions observed among different bacterial species. Genetic factors and bacterial adaptive mechanisms primarily drive the development of resistance to this crucial antibiotic combination. As we continue to witness an increase in CAZ–AVI resistance, it is essential to implement targeted interventions, such as routine surveillance and antimicrobial stewardship programs, to preserve the efficacy of this therapeutic option. Furthermore, an in-depth understanding of the molecular mechanisms underlying resistance can help guide the development of novel antimicrobial agents and therapeutic strategies. Continuous monitoring of CAZ–AVI resistance trends will be instrumental in informing public health policies and clinical practices to combat the spread of multidrug-resistant GNB.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13756-025-01518-5.

Additional file 1.

Additional file 2.

Acknowledgements
None.

Author contributions
YW, MZSH, LY, MSH substantially contributed to the conception, design, drafting, interpretation of the relevant literature, and analysis of the review article of the work. MZSH, MB substantially contributed to the analysis of the work. KHA, LY have been involved in writing and acquisition of data or revising the review article for intellectual content. All authors agreed and confirmed the manuscript for publication.

Funding
This work was supported by Medical Research Project of Chongqing Municipal Health Commission (No.2025WSJK095); Chonqing Public Health Key Discipline Project, Chongqing Municipal Health Commission, China; the second batch of Science and Technology Projects, Nanchuan District Science Planning Bureau, Chongqing, China (No.Cx202308).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Nanchuan District Center for Disease Control and Prevention, Chongqing 408400, China. [2]Department of Bacteriology, Pasteur Institute of Iran, Tehran, Iran. [3]Department of Laboratory Sciences, Faculty of Paramedicine, Golestan University of Medical Sciences, Gorgān, Iran. [4]Department of Microbiology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran. [5]Zoonosis Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran.

Received: 18 April 2024 Accepted: 13 January 2025
Published online: 11 February 2025

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