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In vitro activity of cefiderocol against multidrug-resistant Gram-negative bacteria and molecular characterization of carbapenem-resistant isolates in Niger

Issoufou Noma Massir

drmantcha425@gmail.com

Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

Yacouba Abdourahamane

Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

Tapha Ounoussa

Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

Kiemou Ismael

Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

Hamidou Oumou

Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

Ousmane Abdoulaye

Département des sciences biologiques appliquées, Faculté des sciences de la santé, Université Dan Dicko Dankoulodo

Moussa Harouna

Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

Mahaman Moustapha Lamine

Laboratoire de Recherche Clinique et des Systèmes de Santé, Université André Salifou

Brah Souleymane

Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

Mahamadou Doutchi

Département de médecine et des spécialités médicales, Faculté des sciences de la santé, Université André Salifou

Ibrahim Mamane Laminou
Centre de Recherche Médicale et Sanitaire

Mamadou Saidou
Laboratoire National de Référence sur la Surveillance de Résistance aux Antimicrobiens, Hôpital National Amirou Boubacar Diallo

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Abstract

Background

The emergence and spread of multidrug-resistant (MDR) Gram-negative bacteria represent a major public health threat worldwide, particularly in low- and middle-income countries where therapeutic options are limited. Cefiderocol is a novel siderophore cephalosporin with a unique mechanism of iron-dependent cellular uptake that enables it to overcome many common resistance mechanisms, including carbapenemases. However, data on its in vitro activity against MDR isolates from West Africa remain scarce. This study aimed to evaluate the in vitro activity of cefiderocol against a collection of MDR Gram-negative bacilli isolated in Niger and to characterize the underlying carbapenemase genes.

Methods

A total of 464 non-duplicate MDR Gram-negative clinical isolates were retrospectively collected between November 2024 and July 2025 from the National Reference Laboratory for Antimicrobial Resistance Surveillance in Niger. The collection comprised extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E, n = 329), carbapenem-resistant Enterobacterales (CRE, n = 95), carbapenem-resistant *Acinetobacter baumannii* (CRAB, n = 18), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA, n = 22). Minimum inhibitory concentrations of cefiderocol were determined by E-test (0.016–256 mg/L) on Mueller-Hinton agar, and susceptibility was interpreted according to EUCAST 2024 breakpoints (susceptible ≤ 2 mg/L). The presence of carbapenemase genes (bla_{KPC}, bla_{NDM-1}, bla_{VIM}, $bla_{OXA-48\text{-}like}$) was investigated by real-time PCR.

Results

Overall, 452 of 464 isolates (97.4%; 95% CI 95.5–98.7%) were susceptible. Susceptibility rates were 100% (329/329) among ESBL-E, 95.5% (21/22) among CRPA, 94.4% (17/18) among CRAB, and 89.5% (85/95) among CRE. Among the 135 carbapenem-resistant isolates, 33 (24.4%) carried at least one carbapenemase gene: bla_{NDM-1} (40.7%), bla_{VIM} (39.0%), $bla_{OXA-48\text{-}like}$ (18.6%), and bla_{KPC} (1.7%). Twelve isolates (2.6%) were resistant to cefiderocol (MIC > 2 mg/L). High-level resistance (MIC ≥ 64 mg/L) was observed in five isolates, four of which carried bla_{NDM-1} (alone or in combination). One *Escherichia coli* isolate with high-level resistance (MIC = 256 mg/L) carried no detectable carbapenemase gene, suggesting alternative mechanisms.

Conclusions

Cefiderocol shows potent in vitro activity against MDR Gram-negative bacilli from clinical specimens in Niger (97.4% susceptible). Resistance remains rare (2.6%) but is associated with NDM-1 producers and

one isolate without detected carbapenemase genes. These findings support cefiderocol as a potential last-line option, while emphasising the urgent need for routine susceptibility testing, active surveillance, and antimicrobial stewardship in West Africa.

Background

The emergence and global spread of antimicrobial resistance (AMR) constitute one of the most critical public health threats of the 21st century, affecting both human and veterinary medicine [1, 2]. Since the early 2000s, a dramatic increase in the incidence of infections caused by multidrug-resistant (MDR) bacteria has been reported worldwide. Of particular concern are Gram-negative bacilli, including extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). The dissemination of these resistant pathogens severely limits therapeutic options and is associated with increased morbidity, mortality, and healthcare costs, potentially leading to therapeutic dead ends [2]. In response to this urgent situation, the World Health Organization (WHO) has published a priority list of antibiotic-resistant bacteria for which the development of novel antibiotics is critically needed, placing carbapenem-resistant Enterobacterales, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in the critical priority category [3].

The successful propagation of MDR Gram-negative bacteria is largely driven by the emergence and dissemination of high-risk international clones. These clones possess an enhanced ability to cause nosocomial outbreaks and to acquire and maintain resistance determinants, including those encoding carbapenemases. Horizontal gene transfer, particularly through the spread of conjugative plasmids carrying carbapenemase genes such as bla_{NDM}, bla_{VIM}, bla_{KPC}, and $bla_{\text{OXA-48-like}}$, represents a major mechanism contributing to the success of these epidemic lineages [4]. The increasing prevalence of such clones in both hospital and community settings underscores the urgent need for novel antibiotics capable of circumventing existing resistance mechanisms.

Recognizing the gravity of the AMR crisis, the WHO has called for coordinated global action, emphasizing the necessity of developing new antibiotics to combat MDR pathogens [5, 6]. In recent years, several novel antimicrobial agents have received marketing authorizations from the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [7]. Among these novel antimicrobial agents, cefiderocol stands out due to its unique structure and mechanism of action. Cefiderocol is a siderophore cephalosporin characterized by the presence of a catechol moiety that chelates ferric iron, enabling active transport across the outer membrane of Gram-negative bacteria via the bacterial iron-uptake system. This innovative "Trojan horse" strategy allows cefiderocol to achieve high periplasmic concentrations independently of classical porin pathways, thereby overcoming many common resistance mechanisms such as porin loss or altered membrane permeability [8, 9].

In addition to its siderophore function, cefiderocol incorporates structural elements found in ceftazidime and cefepime that confer enhanced stability against a broad spectrum of β-lactamases, including both

serine-β-lactamases (ESBLs, KPC, and OXA-48-like enzymes) and metallo-β-lactamases (NDM and VIM). This dual mechanism of enhanced penetration through porins and resistance to enzymatic degradation makes cefiderocol particularly potent against a wide range of MDR Gram-negative bacilli, including non-fermentative species such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [10, 11]. Preclinical and clinical studies have demonstrated its efficacy against isolates resistant to nearly all available antibiotics, positioning it as a valuable last-line therapeutic option.

Despite the growing body of evidence supporting the use of cefiderocol in high-income countries, data on its in vitro activity against MDR Gram-negative isolates from sub-Saharan Africa, particularly West Africa, remain scarce. In Niger, recent studies have highlighted a worrying prevalence of multidrug-resistant bacteria. A nationwide surveillance study reported that ESBL-producing Enterobacterales accounted for 75.5% of clinical isolates, indicating a high burden of resistance to expanded-spectrum cephalosporins [12]. Furthermore, a series of carbapenem-resistant Enterobacterales isolates from infants under one year of age revealed that **bla**$_{\text{NDM}^{-1}}$ was the most frequently detected carbapenemase (50.0%), followed by *bla*$_{\text{VIM}}$ (28.6%), *bla*$_{\text{KPC}}$ (14.3%), and *bla*$_{\text{OXA-48-Like-48}}$ (7.1%), confirming the circulation of carbapenemase-producing Enterobacterales (CRE) in Niger [13]. Collectively, these data indicate that both ESBL producers and CRE are widely present in clinical settings, severely limiting therapeutic options for severe infections caused by these resistant pathogens. However, despite this alarming resistance landscape, no previous study has evaluated the in vitro activity of cefiderocol against MDR Gram-negative bacilli isolated in Niger, leaving a critical evidence gap for clinical decision-making and antimicrobial stewardship. Niger, like many low- and middle-income countries, faces a dual burden of high antimicrobial resistance rates and limited access to newer antibiotics. The National Reference Laboratory for Antimicrobial Resistance Surveillance (NRL-AMR) in Niger serves as a central repository for MDR isolates collected through national surveillance efforts, providing a unique opportunity to assess the activity of novel antibiotics against locally circulating strains.

In this context, the present study was undertaken to evaluate the in vitro activity of cefiderocol against a large collection of MDR Gram-negative bacilli, including ESBL-E, CRE, CRAB, and CRPA, isolated from clinical specimens in Niger between November 2024 and July 2025. Additionally, we sought to characterize the molecular epidemiology of carbapenem resistance among these isolates by detecting the most prevalent carbapenemase genes (*bla*$_{\text{KPC}}$, *bla*$_{\text{NDM}}$, *bla*$_{\text{VIM}}$, and *bla*$_{\text{OXA-48-like}}$). The findings of this study will provide essential baseline data to guide empirical and targeted antibiotic therapy, inform antimicrobial stewardship programmes, and contribute to the regional mapping of antimicrobial resistance in West Africa.

Methods

Study design and setting

This was a descriptive cross-sectional study conducted retrospectively using isolates stored at the National Reference Laboratory for Antimicrobial Resistance Surveillance (NRL-AMR) in Niger. The

isolates were originally collected between November 2024 and July 2025. The laboratory serves as the central repository for multidrug-resistant (MDR) bacterial isolates collected from various healthcare facilities across the country as part of the national antimicrobial resistance surveillance programme.

Study population and sampling

The study population comprised all non-duplicate MDR bacterial isolates obtained from clinical specimens (urine, pus, vaginal swabs, and other pathological products) that were stored at – 80°C in the NRL-AMR biobank. Sampling was exhaustive and non-probabilistic; all isolates meeting the inclusion criteria during the study period were included.

Inclusion and exclusion criteria

Isolates were eligible for inclusion if they belonged to one of the following resistance phenotypes: extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), or carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Duplicate isolates from the same patient and isolates with incomplete or unusable data were excluded.

Study variables

The primary outcome variable was the result of the cefiderocol susceptibility test (sensitive or resistant) determined by minimum inhibitory concentration (MIC). Independent variables included sociodemographic characteristics of the patients (sex, age, origin), clinical data (type of specimen, hospital department), and bacteriological characteristics of the isolates (bacterial species, resistance phenotype, and presence of carbapenemase genes).

Bacterial isolation and identification

Frozen isolates were subcultured on appropriate agar plates and incubated at 37°C for 24 h. Identification was performed using a standard microbiological workflow: colonial morphology examination, Gram staining, oxidase test, and biochemical profiling with the Analytical Profile Index (API) 20E and API 20NE systems (bioMérieux, Marcy-l'Étoile, France).

Antimicrobial susceptibility testing

Antimicrobial susceptibility profiles were determined by the disk diffusion method (Kirby-Bauer) on Mueller-Hinton agar following the 2024 guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The double-disk synergy test was used to confirm ESBL production; a synergy image between ceftazidime (10 µg) and amoxicillin-clavulanate (20/10 µg) disks placed 30 mm

apart was interpreted as positive. Carbapenem resistance was screened using meropenem (10 µg) and imipenem (10 µg) disks. Isolates were classified as MDR if they exhibited non-susceptibility to at least one antibiotic in three or more antimicrobial categories, in accordance with published consensus definitions [14].

Cefiderocol susceptibility testing

Cefiderocol MICs were determined using E-test gradient strips (Liofilchem® MTS™) on iron-depleted Mueller-Hinton agar, according to the manufacturer's instructions and EUCAST recommendations for gradient diffusion [15]. Strips with a concentration range of 0.016–256 mg/L were applied to plates inoculated with a 0.5 McFarland standard suspension. Plates were incubated at 37°C for 24 h (re-examined at 48 h if necessary). The MIC was read as the lowest concentration at which the edge of the inhibition ellipse intersected the strip. Susceptibility was interpreted using EUCAST 2024 clinical breakpoints (susceptible ≤ 2 mg/L, resistant > 2 mg/L) [14]. Although broth microdilution on iron-depleted medium is the reference method for cefiderocol, Etest was used due to logistical constraints in our resource-limited setting. We followed EUCAST recommendations for iron-depleted agar and included quality control strains.

Molecular detection of carbapenemase genes

Genomic DNA was extracted from bacterial isolates using the QIAamp DNA Mini Kit (Qiagen GmbH, Germany), according to the manufacturer's instructions. DNA concentration and purity were assessed using the Qubit™ 4 Fluorometer with the Qubit™ 1X dsDNA HS Assay Kit (Thermo Fisher Scientific, USA). The detection of carbapenemase-encoding genes (bla_{KPC}, bla_{NDM}, bla_{VIM}, and $bla_{OXA-48\text{-}like}$) was performed by quantitative real-time PCR (qPCR). Primer sequences, expected amplicon sizes, and annealing temperatures are provided in Additional file 1. Amplification reactions were performed in a final volume of 25 µL containing 12.5 µL of 2X SYBR Green qPCR Master Mix (Ampliqon, Denmark), 30 ng of template DNA, 0.5 µM of each forward and reverse primer (final concentration), and nuclease-free water to complete the reaction volume. Real-time PCR was carried out on a QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems, USA). Thermal cycling conditions consisted of an initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 15 seconds, annealing at 47–58°C (depending on the target gene) for 30 seconds, and extension at 72°C for 30 seconds. Fluorescence signals were acquired at the end of each extension step. A melting curve analysis was performed at the end of amplification to verify the specificity of the PCR products. Positive controls for each target gene and a no-template control (NTC) were included in each run. A cycle threshold (Ct) value ≤ 35 was considered positive. This threshold was validated using known positive controls (mean Ct values ranging from 18 to 28 depending on the target gene) and non-template controls (no amplification up to 40 cycles). No internal housekeeping gene (e.g., 16S rRNA) was used because DNA quality was verified by spectrophotometry (A260/280 ratio 1.8–2.0) and all samples amplified the positive control.

Quality control

Quality control for cefiderocol Etest was performed using *Escherichia coli* ATCC 25922 with MICs within the accepted ranges by EUCAST 2024 [14].

Statistical analysis

Descriptive statistics were calculated for all variables. Proportions are presented with 95% confidence intervals computed using the exact Clopper-Pearson method. MIC50 and MIC90 were determined empirically; 95% confidence intervals for MIC50/MIC90 were estimated by non-parametric bootstrap (2,000 replications, percentile method). MIC distributions were compared using the Wilcoxon rank-sum test; the test statistic (W) and exact p-value are reported. Proportions were compared using Fisher's exact test. For multiple pairwise comparisons, the Benjamini-Hochberg false discovery rate procedure was applied. No formal correlation analysis was performed because the number of isolates carrying specific gene combinations was small; only descriptive associations are reported. All analyses were performed in RStudio (version 2026.01.1 Build 403) using packages *boot*, *binom*, and *base stats*.

Results

Characteristics of isolates and sociodemographic features of the patients included

A total of 464 non-duplicate MDR Gram-negative bacilli were collected from various clinical samples of outpatients and inpatients across different medical departments. Among them, ESBL-producing Enterobacterales were the most prevalent (n = 329, 70.9%; 95% CI 66.6–75.0%), followed by carbapenem-resistant Enterobacterales (n = 95, 20.5%; 95% CI 16.9–24.4%). The majority of isolates originated from urine (n = 395, 85.1%; 95% CI 81.5–88.3%). The medical department was the most represented (n = 260, 74.1%; 95% CI 69.2–78.6%). Regarding patient demographics, 349 patients (75.2%; 95% CI 71.0–79.1%) were male, and 115 (24.8%; 95% CI 20.9–29.0%) were female. The median age was 42 years (IQR 28–58). Patients aged ≥ 40 years accounted for 261 cases (56.2%; 95% CI 51.6–60.8%), while 203 patients (43.8%; 95% CI 39.2–48.4%) were under 40 years of age (Table 1). The complete dataset including demographic, clinical, and microbiological characteristics, antimicrobial susceptibility profiles, and detected carbapenemase genes for each isolate is provided in **Additional file 2**.

Table 1
Characteristics of the MDR Gram-negative isolates and sociodemographic features of the patients included in the study

Characteristics	Frequency (n)	%	
Age (years)			
< 40	203	43.8	
≥ 40	261	56.2	
Sex			
Male	349	75.2	
Female	115	24.8	
Specimen type			
Urine		395	85.1
Pus		61	13.1
Others*		8	1.7
Provenance			
Outpatient		113	24.4
Inpatient		351	75.6
Hospital department			
Medical		260	74.1
Surgical		31	8.8
Emergencies and ICU**		60	17.1
CRAB (n = 18)			
Acinetobacter baumannii	18	3.9	
CRE (n = 95)			
Aeromonas hydrophila	1	0.2	
Citrobacter spp.	3	0.6	
Enterobacter spp.	2	0.4	
Escherichia coli	59	12.7	
Hafnia alvei	1	0.2	
Klebsiella oxytoca	5	1.1	

Characteristics	Frequency (n)	%
Age (years)		
Klebsiella pneumoniae	17	3.7
Morganella morganii	1	0.2
Proteus mirabilis	1	0.2
Salmonella spp.	1	0.2
Serratia odorifera	3	0.6
Yersinia pseudotuberculosis	1	0.2
ESBL-E (n = 329)		
Citrobacter spp.	6	1.3
Enterobacter spp.	5	1.1
Escherichia coli	206	44.4
Klebsiella oxytoca	17	3.7
Klebsiella pneumoniae	58	12.5
Morganella morganii	1	0.2
Pantoea spp.	12	2.6
Proteus mirabilis	8	1.7
Salmonella spp.	2	0.4
Serratia liquefasciens	1	0.2
Serratia marcescens	5	1.1
Serratia odorifera	8	1.7
CRPA (n = 22)		
Pseudomonas aeruginosa	22	4.7

ESBL-E: Extended-spectrum beta-lactamases producing Enterobacterales; **CRAB**: Carbapenem-resistant *A. baumannii*; **CRE**: Carbapenem-resistant Enterobacterales; **CRPA**: Carbapenem-resistant *Pseudomonas aeruginosa*; ***Other specimens**: venous catheter (n = 4), stool (n = 3), vaginal swab (n = 2), cerebrospinal fluid (n = 1), abdominal fluid (n = 2). ICU: intensive care unit. ****ICU**: intensive care unit.

Antibiotic resistance patterns of MDR isolates

The resistance rates to conventional antibiotics varied among the four phenotypic groups. CRAB and CRPA isolates were uniformly resistant to sulfamethoxazole-trimethoprim (100% each), while ESBL-E and CRE showed resistance rates of 94.0% (95% CI 91.0–96.3%) and 99.0% (95% CI 94.3–100%), respectively. Nitrofurantoin remained inactive against CRAB and CRPA but retained activity against a portion of Enterobacterales (Fig. 1).

In vitro activity of cefiderocol

Cefiderocol showed overall activity, with 97.4% (452/464; 95% CI 95.5–98.7%) of isolates susceptible according to EUCAST 2024 breakpoints (MIC ≤ 2 mg/L). Resistance was observed in 2.6% (12/464; 95% CI 1.3–4.5%) of isolates (Fig. 2a). Phenotype-based analysis showed susceptibility rates of 100% for ESBL E (329/329; 95% CI 98.9–100%), 95.5% for CRPA (21/22; 95% CI 77.2–99.9%), 94.4% for CRAB (17/18; 95% CI 72.7–99.9%), and 89.5% for CRE (85/95; 95% CI 81.5–94.8%) (Fig. 2b). The differences in susceptibility rates among the four phenotypic groups were statistically significant (Fisher's exact test, $p < 0.001$). Pairwise comparisons using Fisher's exact test with Benjamini–Hochberg correction showed that ESBL-E had significantly higher susceptibility than CRE (adjusted $p = 0.004$); all other pairwise differences were not significant after correction (adjusted $p > 0.05$).

The distribution of cefiderocol MICs differed significantly between susceptible and resistant isolates **(**Wilcoxon rank-sum test, $W = 1245$, $p < 0.001$**).** The median MIC for susceptible isolates was 0.032 mg/L, whereas that for resistant isolates was 5 mg/L, reflecting a clear separation of MIC values. The box plots (Fig. 3) show that all resistant isolates had MICs ≥ 1 mg/L, while the majority of susceptible isolates exhibited MICs ≤ 0.5 mg/L, with the highest concentration of values at or below 0.064 mg/L. The overall MIC50 and MIC90 (determined empirically with 95% bootstrap confidence intervals based on 2,000 replications) were 0.032 mg/L (95% CI 0.016–0.064) and 0.38 mg/L (95% CI 0.25–0.75), respectively. Individual cefiderocol MICs and their interpretation according to EUCAST 2025 breakpoints are listed in **Additional file 3**.

Distribution of carbapenemase genes according to bacterial species

Among the 135 carbapenem-resistant isolates, 33 (24.4%; 95% CI 17.5–32.3%) harboured at least one carbapenemase gene. A total of 59 genes were detected (some isolates carried multiple genes). The most common genes were $bla_{\text{NDM-1}}$ (n = 24, 40.7% of detected genes; 95% CI 28.0–54.2%) and bla_{VIM} (n = 23, 39.0%; 95% CI 26.5–52.4%), followed by $bla_{\text{OXA-48-like}}$ (n = 11, 18.6%; 95% CI 9.7–30.9%) and bla_{KPC} (n = 1, 1.7%; 95% CI 0.04–9.1%). Gene combinations were present in 18 isolates (54.5% of positive isolates; 95% CI 36.4–71.9%). The most frequent association was $bla_{\text{NDM-1}}$ + bla_{VIM} (8 isolates, 44.4% of combinations; 95% CI 21.5–69.2%), followed by the triple combination $bla_{\text{NDM-1}}$ + bla_{VIM} + $bla_{\text{OXA-48-like}}$ (6 isolates, 33.3%; 95% CI 13.3–59.0%). A single isolate of *Acinetobacter baumannii* carried all four genes (5.6%; 95% CI 0.1–27.3%). The distribution of carbapenemase genes varied considerably across species

(Fig. 4). *Escherichia coli* was the most frequently affected species, accounting for 17 of the 33 positive isolates (51.5%; 95% CI 33.5–69.2%). In *Escherichia coli*, the most common gene was $bla_{\text{NDM-1}}$ alone (n = 6, 35.3% of positive *Escherichia coli* isolates; 95% CI 14.2–61.7%), followed by $bla_{\text{OXA-48-like}}$ alone (n = 4, 23.5%; 95% CI 6.8–49.9%) and bla_{VIM} alone (n = 3, 17.6%; 95% CI 3.8–43.4%). Combinations were also observed: $bla_{\text{NDM-1}}$ +bla_{VIM} (n = 3, 17.6%; 95% CI 3.8–43.4%) and $bla_{\text{NDM-1}}$+bla_{VIM}+$bla_{\text{OXA-48-like}}$ (n = 1, 5.9%; 95% CI 0.1–28.7%). Among *Klebsiella pneumoniae* (n = 6 positive isolates), the triple combination predominated (n = 4, 66.7%; 95% CI 22.3–95.7%). *Acinetobacter baumannii* (n = 8 positive isolates) exhibited a more balanced distribution: bla_{VIM} alone (n = 3, 37.5%; 95% CI 8.5–75.5%), $bla_{\text{NDM-1}}$ alone (n = 2, 25%; 95% CI 3.2–65.1%), $bla_{\text{OXA-48-like}}$ alone (n = 2, 25%; 95% CI 3.2–65.1%), and the quadruple combination (n = 1, 12.5%; 95% CI 0.3–52.7%). Other species (*Citrobacter* spp., *Aeromonas hydrophila*, *Serratia odorifera*, *Pseudomonas aeruginosa*) each contributed a few positive isolates, with various gene profiles.

Correlation between carbapenemase gene and cefiderocol susceptibility among CR-GNB

Among the 33 isolates carrying carbapenemase genes, 28 (84.8%; 95% CI 68.1–94.9%) were susceptible to cefiderocol. The highest resistance rates were observed in isolates carrying $bla_{\text{NDM-1}}$ alone (2/9, 22.2%; 95% CI 2.8–60.0%) and those with the triple combination $bla_{\text{NDM-1}}$+bla_{VIM}+$bla_{\text{OXA-48-like}}$ (2/6, 33.3%; 95% CI 4.3–77.7%). All isolates harbouring bla_{VIM} alone (n = 5, 100% susceptible; 95% CI 47.8–100%), $bla_{\text{OXA-48-like}}$ alone (n = 1, 100%; 95% CI 2.5–100%), $bla_{\text{NDM-1}}$+bla_{VIM} (n = 8, 100%; 95% CI 63.1–100%), or the quadruple combination (n = 1, 100%; 95% CI 2.5–100%) were susceptible. The MIC50 and MIC90 values (with 95% bootstrap CIs) reflected the reduced activity against NDM-positive isolates: for $bla_{\text{NDM-1}}$ alone, MIC50 was 0.75 mg/L (95% CI 0.38–1.5) and MIC90 was 256 mg/L (95% CI 128–256) (Table 4). A Fisher's exact test comparing resistance proportions between $bla_{\text{NDM-1}}$ alone and the triple combination was not significant (p = 0.99), due to the small sample size.

Table 4
Correlation between carbapenemase genes and cefiderocol susceptibility among carbapenem-resistant Gram-negative bacilli (n = 135)

Gene detected	Tested n	Resistant n (%)	Susceptible n (%)	MIC50 (mg/l)	MIC90 (mg/l)	Range (mg/l)
bla$_{VIM}$	5	0	5 (100.0)	0.75	1.5	0.125–1.5
bla$_{NDM-1}$	9	2 (22.2)	7 (77.8)	0.75	256	0.016–256
bla$_{OXA-48-like}$	1	0	1 (100.0)	0.38	0.38	0.38
bla$_{NDM-1}$ + *bla*$_{VIM}$	8	0	8 (100.0)	0.38	1.5	0.19–1.5
bla$_{VIM}$ + *bla*$_{OXA-48-like}$	3	1 (33.3)	2 (66.7)	0.5	4	0.38–4
bla$_{NDM-1}$ + *bla*$_{VIM}$ + *bla*$_{OXA-48-like}$	6	2 (33.3)	4 (66.7)	1	256	0.125–256
bla$_{NDM-1}$ + *bla*$_{VIM}$ + *bla*$_{KPC}$ + *bla*$_{OXA-48-like}$	1	0	1 (100.0)	0.38	0.38	0.38
Total	**33**	**5 (15.2)**	**28 (84.8)**			

Percentages are calculated within each genotype. **bla$_{OXA-48-like}$**: Oxacillinase β-lactamase type 48; **bla$_{NDM-1}$**: New Delhi metallo-β-lactamase; **bla$_{VIM}$**: Verona Integron-encoded Metallo-β-lactamase; **bla$_{KPC}$**: *Klebsiella pneumoniae* carbapenemase

Characteristics of cefiderocol-resistant isolates

A total of 12 isolates (8.9% of the 135 carbapenem-resistant isolates; 95% CI, 4.7–15.0%) exhibited cefiderocol resistance (MIC > 2 mg/L). Their detailed features are presented in Table 5. Among these, five isolates carried carbapenemase genes: one *Escherichia coli* with *bla*$_{NDM-1}$ alone (MIC 256 mg/L), one *Klebsiella pneumoniae* with *bla*$_{NDM-1}$ alone (MIC 64 mg/L), one *Serratia odorifera* with *bla*$_{VIM}$+*bla*$_{OXA-48-like}$ (MIC 4 mg/L), and two *Escherichia coli* with *bla*$_{NDM-1}$+*bla*$_{VIM}$+*bla*$_{OXA-48-like}$ (MIC 256 mg/L each). The remaining seven resistant isolates had no detectable carbapenemase genes, including four *Escherichia coli* (MICs 3, 4, 4, 256 mg/L), one *Klebsiella pneumoniae* (MIC 4 mg/L), one *Acinetobacter baumannii* (MIC 6 mg/L), and one *Pseudomonas aeruginosa* (MIC 4 mg/L). High-level resistance (MIC ≥ 64 mg/L) was observed in five isolates; four of these carried *bla*$_{NDM-1}$ (alone or in combination), and one *E. coli* with no detected genes also showed MIC 256 mg/L.

Table 5
Detailed characteristics of the 12 cefiderocol-resistant CR-GN isolates.

Specimen	Species	Phenotype	Carbapenemase genes	Cefiderocol MIC (mg/L)
Urine	*Escherichia coli*	CRE	NDM-1 + VIM + OXA-48-like	256
Urine	*Escherichia coli*	CRE	Not detected	256
Urine	*Serratia odorifera*	CRE	VIM + OXA-48-like	4
Urine	*Acinetobacter baumannii*	CRAB	Not detected	6
Pus	*Klebsiella pneumoniae*	CRE	Not detected	4
Urine	*Klebsiella pneumoniae*	CRE	NDM-1	64
Urine	*Pseudomonas aeruginosa*	CRPA	Not detected	4
Urine	*Escherichia coli*	CRE	Not detected	3
Urine	*Escherichia coli*	CRE	NDM-1	256
Urine	*Escherichia coli*	CRE	NDM-1 + VIM + OXA-48-like	256
Urine	*Escherichia coli*	CRE	Not detected	4
Urine	*Escherichia coli*	CRE	Not detected	4

CRE: carbapenem-resistant *Enterobacterales*; **CRAB**: carbapenem-resistant *Acinetobacter baumannii*; **CRPA**: carbapenem-resistant *Pseudomonas aeruginosa*. **$bla_{OXA-48-like}$**: Oxacillinase β-lactamase type 48; **bla_{NDM-1}**: New Delhi metallo-β-lactamase; **bla_{VIM}**: Verona Integron-encoded Metallo-β-lactamase; **bla_{KPC}**: *Klebsiella pneumoniae* carbapenemase. *Not detected* indicates negative PCR for bla_{KPC}, bla_{NDM-1}, bla_{VIM}, and $bla_{OXA-48-like}$. Other carbapenemase genes (e.g., bla_{IMP}, bla_{GES}) were not screened.

Discussion

This study provides the first evaluation of the in vitro activity of cefiderocol against a large collection of multidrug-resistant Gram-negative bacilli isolated in Niger. Our overall susceptibility rate of 97.4% (95% CI 95.5–98.7%) is consistent with data from major international surveillance programmes. For instance, the SENTRY programme reported that cefiderocol inhibited 99.8% of Enterobacterales and 98.2% of carbapenem-resistant Enterobacterales [16, 17], and remained active against 98.1% of difficult-to-treat *Pseudomonas aeruginosa* [18]. The near-universal activity against ESBL-E (100%) suggests that cefiderocol could serve as a reliable carbapenem-sparing option, which is particularly valuable in resource-limited settings. Susceptibility remained high across CRPA (95.5%), CRAB (94.4%), and CRE

(89.5%). The slightly lower activity against CRE aligns with a French study on carbapenemase-producing Enterobacterales from patients returning from sub-Saharan Africa, which reported a susceptibility rate of approximately 73%, with the lowest activity observed against NDM and OXA-48-like co-producers [19].

Our molecular characterisation of carbapenem-resistant isolates revealed a predominance of metallo-β-lactamases, particularly *bla*$_{\text{NDM-1}}$ (40.7%) and *bla*$_{\text{VIM}}$ (39.0%), followed by *bla*$_{\text{OXA-48-like}}$ (18.6%). These findings are in line with regional data from West and Central Africa, where NDM and OXA-48-like enzymes are the most common carbapenemases [20]. Studies from Senegal and Mali have similarly reported a high prevalence of *bla*$_{\text{NDM}}$ and *bla*$_{\text{OXA-48-like}}$ [21]. The frequent occurrence of gene combinations (18 of 33 positive isolates, 54.5%) is an important finding. The most common association was *bla*$_{\text{NDM-1}}$+*bla*$_{\text{VIM}}$ (44.4% of combinations), followed by the triple combination *bla*$_{\text{NDM-1}}$+*bla*$_{\text{VIM}}$+*bla*$_{\text{OXA-48-like}}$ (33.3%). Co-production of multiple carbapenemases, especially involving both serine- and metallo-β-lactamases, severely limits treatment options and has been associated with therapeutic failures even with novel antibiotics [17]. The detection of an *Acinetobacter baumannii* isolate carrying all four genes (*bla*$_{\text{KPC}}$+*bla*$_{\text{NDM-1}}$+*bla*$_{\text{VIM}}$+*bla*$_{\text{OXA-48-like}}$) is particularly alarming, as such pan-drug-resistant organisms leave virtually no therapeutic options.

The correlation between carbapenemase genotype and cefiderocol susceptibility provides valuable insights. Among the 135 carbapenem-resistant isolates, those without any detected carbapenemase gene (n = 102) showed a susceptibility rate of 93.1%, with an MIC90 of 2 mg/L, indicating that mechanisms other than acquired carbapenemases (e.g., porin loss, AmpC overproduction) do not markedly compromise cefiderocol activity. Isolates carrying *bla*$_{\text{NDM-1}}$ alone exhibited a lower susceptibility rate (77.8%) and an MIC90 of 256 mg/L, reflecting the reduced activity of cefiderocol against some metallo-β-lactamase producers, as noted in other studies [22]. However, not all NDM producers were resistant; the majority (7/9) remained susceptible, underscoring the heterogeneity of MICs within this genotype. The highest resistance rates were observed among isolates harbouring *bla*$_{\text{VIM}}$+*bla*$_{\text{OXA-48-like}}$ (33.3%, 1 out of 3) and the triple combination *bla*$_{\text{NDM-1}}$+*bla*$_{\text{VIM}}$+*bla*$_{\text{OXA-48-like}}$ (33.3%, 2 out of 6), albeit based on very small numbers (n = 3 and n = 6, respectively), which limits the precision of these estimates. These findings are consistent with a recent report from Senegal, where insertions in the gene encoding PBP3 were identified in *Escherichia coli* isolates co-producing NDM and OXA-48, leading to reduced cefiderocol susceptibility even before this antibiotic became available in the region [21].

The 12 cefiderocol-resistant isolates identified in our collection (2.6% of all MDR isolates, 8.9% of carbapenem-resistant isolates) merit detailed discussion. High-level resistance (MIC ≥ 64 mg/L) was observed in five isolates. Four of these carried *bla*$_{\text{NDM-1}}$ (alone or in combination), while one *E. coli* with no detected carbapenemase gene also showed MIC 256 mg/L, indicating that alternative mechanisms can occasionally produce high-level resistance The remaining resistant isolates displayed MICs between 3 and 6 mg/L, just above the EUCAST breakpoint; the clinical significance of such low-level resistance remains uncertain and may depend on the infection site and achievable drug concentrations. The

emergence of cefiderocol resistance, although still rare, is a cause for concern and highlights the need for continuous surveillance, particularly in settings where metallo-β-lactamases are endemic.

The clinical implications of our findings are substantial. In Niger, as in many low- and middle-income countries, the therapeutic arsenal against MDR Gram-negative infections is severely constrained. Carbapenems are often the last reliable option, but their effectiveness is increasingly compromised by the spread of carbapenemase producers. Cefiderocol, with its unique siderophore-mediated uptake mechanism, could fill this critical gap. The high susceptibility of ESBL-E (100%) supports its use as a carbapenem-sparing antibiotic, while the activity against CRE (89.5%), CRAB (94.4%), and CRPA (95.5%) makes it a valuable last-line option. Nevertheless, the high cost and limited availability of cefiderocol in low-income countries like Niger currently restrict its routine use. Our findings should encourage local advocacy and international support for access to novel antibiotics. However, the presence of resistant isolates, particularly those with high MICs, underscores the need for susceptibility testing whenever possible before therapy. The high resistance rates to conventional antibiotics observed in our study, such as nearly universal resistance to sulfamethoxazole-trimethoprim among CRAB and CRPA (100%) and very high resistance among CRE (99%), further emphasise the urgent need for new options. From a public health perspective, our study provides baseline data for Niger and contributes to the regional mapping of carbapenemase epidemiology in West Africa. The predominance of $bla_{\text{NDM-1}}$ and bla_{VIM}, often combined with $bla_{\text{OXA-48-like}}$, suggests that infection control measures should be reinforced to prevent the spread of these highly resistant clones within hospitals and communities.

This study has several limitations. Firstly, because most isolates (85.1%) originated from urine, we could not reliably distinguish between true urinary tract infection and asymptomatic bacteriuria. Therefore, our results refer to carriage or isolation from clinical specimens, not necessarily clinical infection. Secondly, the collection originated from a single reference laboratory and may not fully represent the diversity of MDR organisms circulating in all regions of Niger or in community settings. Thirdly, molecular characterisation was limited to the most common carbapenemase genes (bla_{KPC}, $bla_{\text{NDM-1}}$, bla_{VIM}, $bla_{\text{OXA-48-like}}$); the absence of screening for other carbapenemase genes (e.g., bla_{IMP}, bla_{GES}, or $bla_{\text{OXA-23}}$ in *Acinetobacter baumannii*) means that some resistance mechanisms may have been missed, particularly among the 102 isolates with no detected genes. We also did not perform whole-genome sequencing to identify non-enzymatic mechanisms (e.g., PBP3 mutations, iron-uptake alterations) that could explain high-level resistance in the isolate without detected carbapenemase genes. Fourthly, while cefiderocol MICs were determined using the recommended iron-depleted medium, the lack of clinical outcome data prevents direct correlation of in vitro findings with therapeutic efficacy. Fifthly, the cross-sectional design precludes analysis of temporal trends. Sixthly, the relatively small number of isolates in some subgroups (CRAB, CRPA, and specific carbapenemase combinations) limits statistical power. Moreover, the heterogeneity among resistance mechanisms (different carbapenemase types, combinations, and non-enzymatic resistance) may affect the generalisability of susceptibility rates to other settings. Despite these limitations, our study provides the first comprehensive dataset on cefiderocol activity and

carbapenemase epidemiology in Niger, offering a crucial foundation for clinical guidance, antimicrobial stewardship, and future surveillance efforts in the region.

Conclusion

This first comprehensive evaluation of cefiderocol against multidrug-resistant Gram-negative bacilli in Niger demonstrates potent in vitro activity, with an overall susceptibility rate of 97.4%. Susceptibility remained high across ESBL-producing Enterobacterales (100%) and carbapenem-resistant phenotypes (*Pseudomonas aeruginosa* 95.5%, *Acinetobacter baumannii* 94.4%, Enterobacterales 89.5%). Metallo-β-lactamases, mainly $bla_{\text{NDM-1}}$ and bla_{VIM}, often combined with $bla_{\text{OXA-48-like}}$, predominated among resistant isolates. Resistance was largely associated with $bla_{\text{NDM-1}}$, though one isolate without detectable carbapenemase genes suggests emerging alternative mechanisms. Cefiderocol represents a potential therapeutic option in Niger, but the emergence of resistance, particularly among NDM-producing isolates, mandates ongoing surveillance and responsible antibiotic use. Routine whole-genome sequencing of isolates with high cefiderocol MICs or discordant profiles (very high MICs without detected genes) should be prioritised, together with expansion of the molecular panel to include less common carbapenemases. These data support the inclusion of cefiderocol in local treatment guidelines and underscore its potential to address critical therapeutic gaps in low- and middle-income countries. Future studies incorporating clinical outcome data, molecular typing of resistant clones, and investigation of emerging resistance mechanisms will be essential to fully define the role of cefiderocol in combating antimicrobial resistance in West Africa.

Abbreviations

AMR: Antimicrobial resistance; API: Analytical Profile Index; ATCC: American Type Culture Collection; CI: Confidence interval; CRAB: Carbapenem-resistant *Acinetobacter baumannii*; CRE: Carbapenem-resistant Enterobacterales; CRPA: Carbapenem-resistant *Pseudomonas aeruginosa*; Ct: Cycle threshold; DNA: Deoxyribonucleic acid; EMA: European Medicines Agency; ESBL-E: Extended-spectrum β-lactamase-producing Enterobacterales; EUCAST: European Committee on Antimicrobial Susceptibility Testing; FDA: Food and Drug Administration; IQR: Interquartile range; MDR: Multidrug-resistant; MIC: Minimum inhibitory concentration; NRL-AMR: National Reference Laboratory for Antimicrobial Resistance Surveillance; PCR: Polymerase chain reaction; qPCR: Quantitative real-time PCR; WHO: World Health Organization.

Declarations

Ethics approval and consent to participate

The study was approved by the National Health Research Ethics Committee of Niger (Ref. No. 16/2025/CNERS) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective and anonymized design of this study, which relied exclusively on routine laboratory data

with no direct patient contact or identifiable clinical information, the National Health Research Ethics Committee of Niger granted a waiver of informed consent (Ref. No. 16/2025/CNERS).

Consent for publication

Not applicable.

Availability of data and materials

The original contributions presented in the study are included in the article/Additional file. Further inquiries can be directed to the corresponding author. The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

DM and YA contributed to the study's design. INM, HO, and MH contributed to data collection. INM and HO contributed to laboratory analyses. AY, OT, KI, and INM contributed to data analysis and interpretation. INM, YA, MML, and OT contributed tomanuscript drafting. BS, OA, MS, and MLI to manuscript review and editing. All authors read and approved the final version of the manuscript.

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Clinical trial number

Not applicable.

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Figures

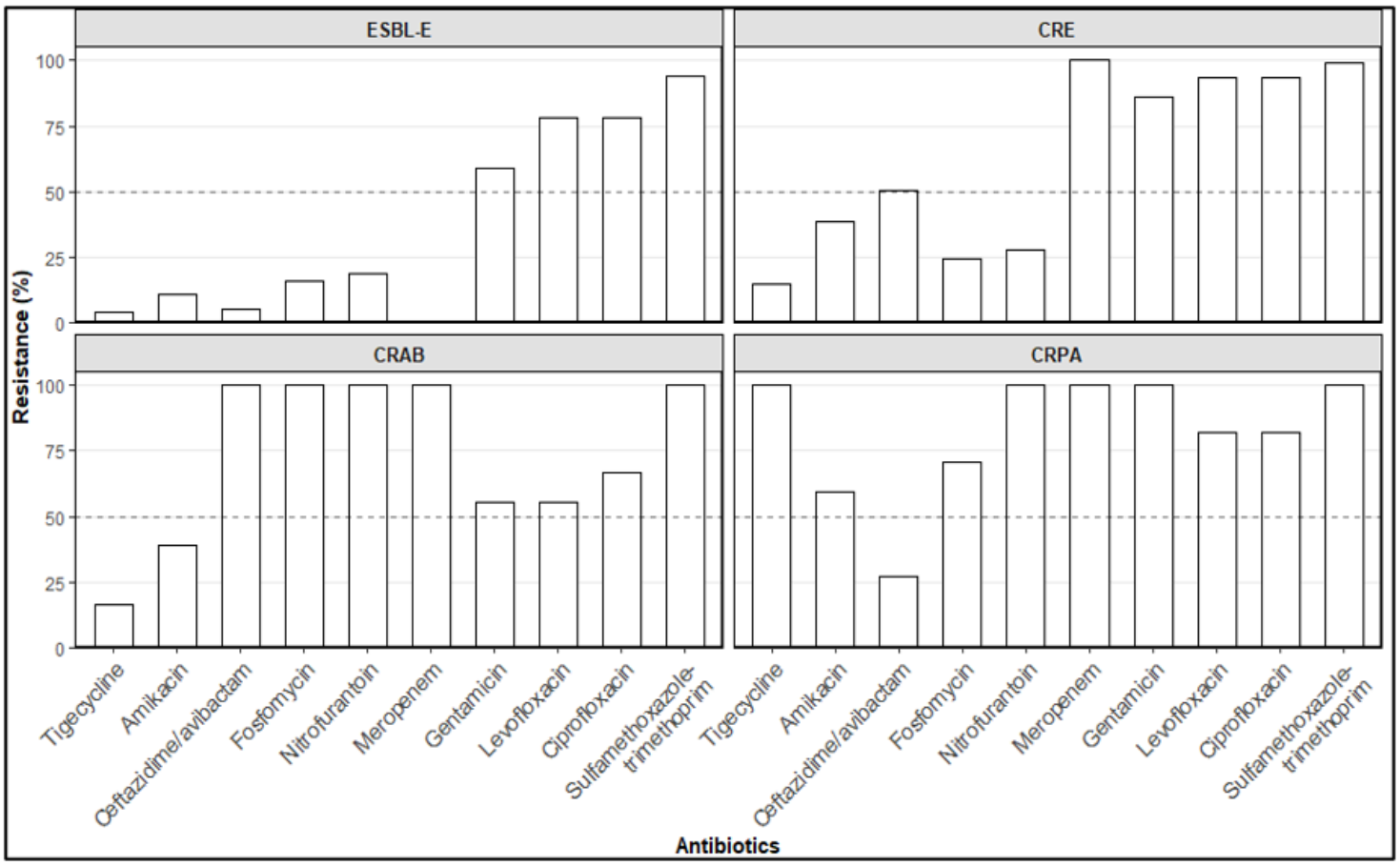


Figure 1

Resistance rates of MDR Gram-negative isolates to a panel of antibiotics. **ESBL-E**: Extended-spectrum beta-lactamases producing Enterobacterales; **CRAB:** Carbapenem-resistant Acinetobacter baumannii; **CRE**: Carbapenem-resistant Enterobacterales; **CRPA**: Carbapenem-resistant Pseudomonas aeruginosa.

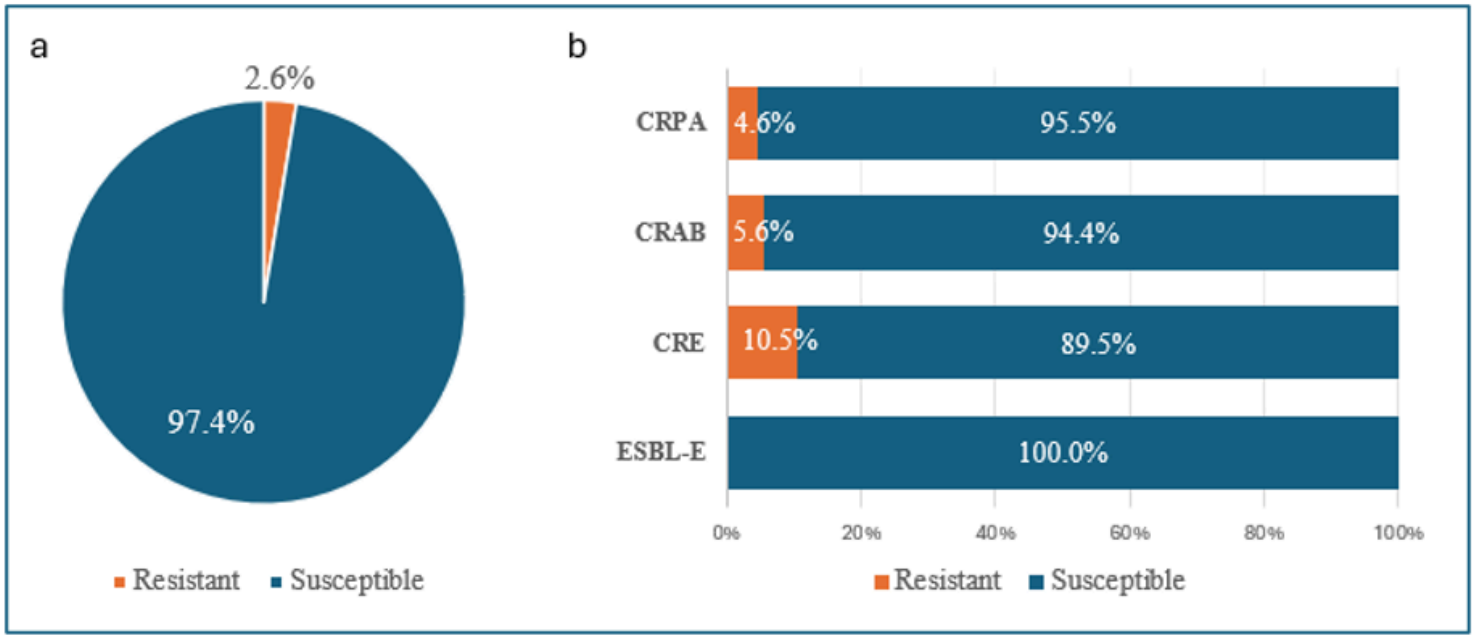


Figure 2

In vitro activity of cefiderocol: (**a**): Frequency of activity of cefiderocol; (**b**): cefiderocol in vitro activity according to the phenotype of the isolates. **ESBL-E**: Extended-spectrum beta-lactamases producing Enterobacterales; **CRE**: Carbapenem-resistant Enterobacterales; **CRAB**: Carbapenem-resistant Acinetobacter baumannii; **CRPA**: Carbapenem-resistant Pseudomonas aeruginosa.

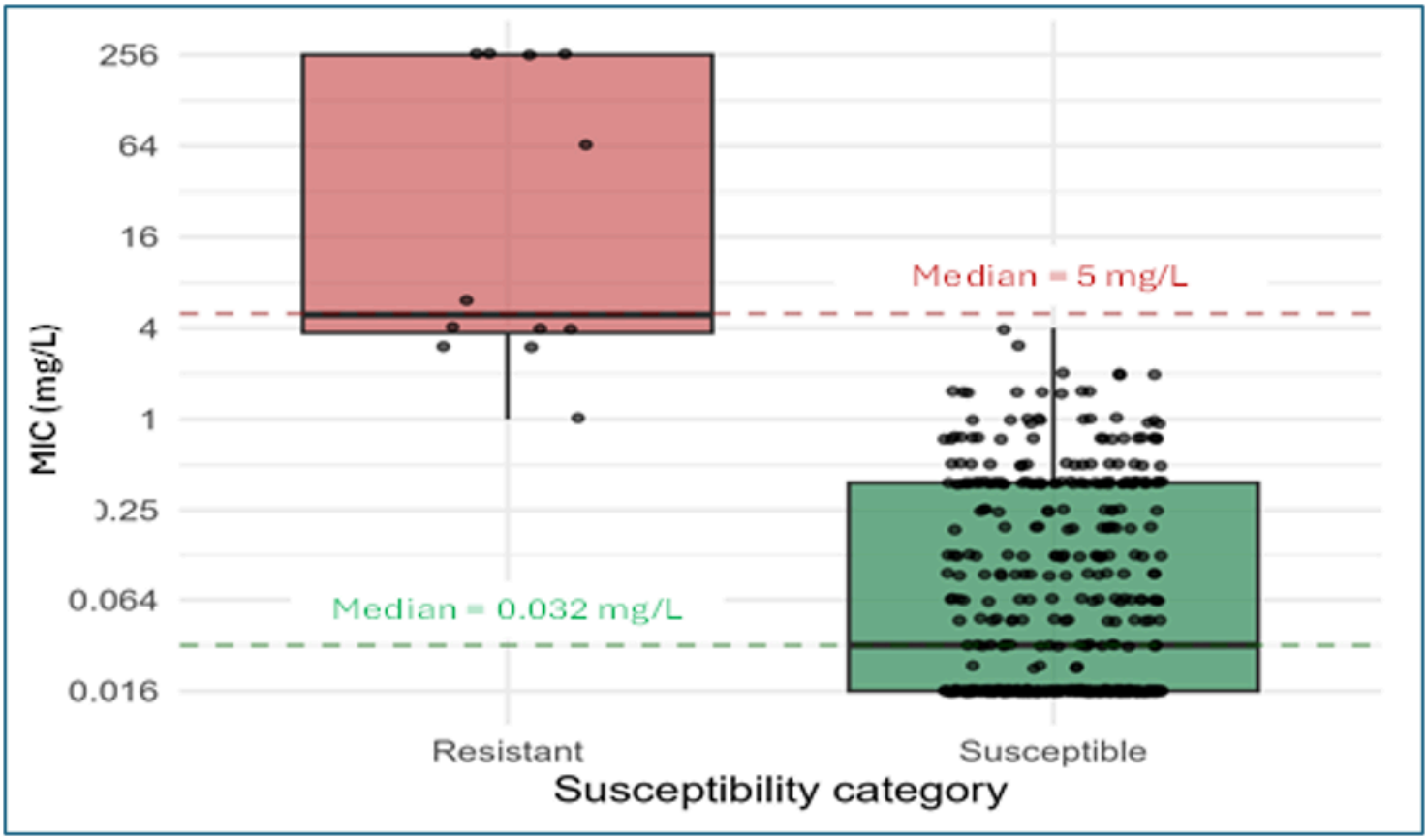


Figure 3

Box plots comparing cefiderocol MICs (mg/L) for susceptible (n = 452) and resistant (n = 12) isolates. The y-axis is log10-transformed. The horizontal line inside each box indicates the median (0.032 mg/L for susceptible; 5 mg/L for resistant). Whiskers extend to the lowest and highest values within 1.5×IQR. Points beyond whiskers are outliers. $p < 0.001$ (Wilcoxon rank-sum test).

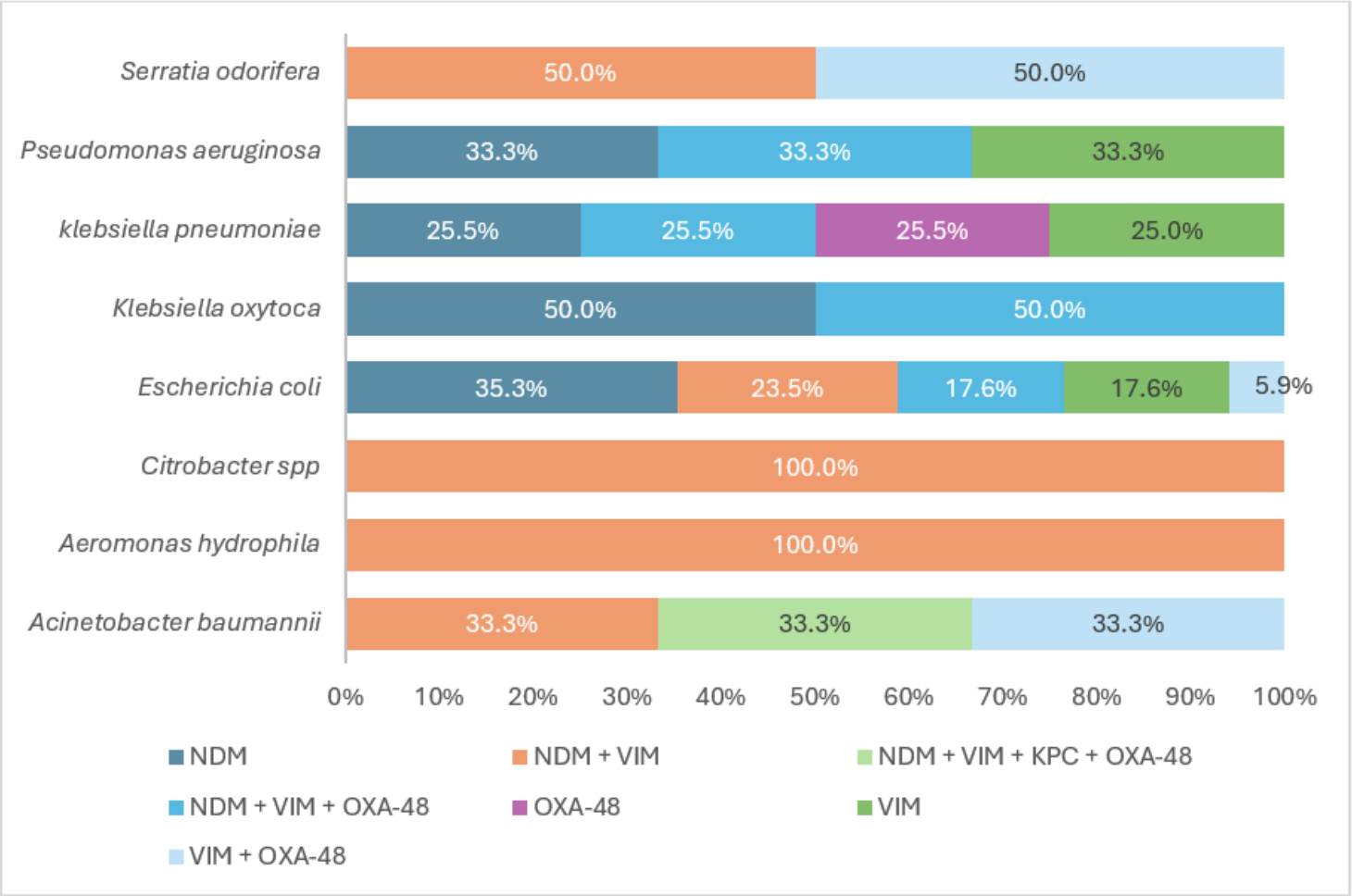


Figure 4

Distribution of carbapenemase genes by bacterial species among carbapenem-resistant isolates (n = 33 positive isolates). ***bla*$_{\text{OXA-48-like}}$**: oxacillinase; ***bla*$_{\text{NDM-1}}$**: New Delhi metallo-β-lactamase; ***bla*$_{\text{VIM}}$**: Verona integron-encoded metallo-β-lactamase; ***bla*$_{\text{KPC}}$**: *Klebsiella pneumoniae* carbapenemase.

Supplementary Files

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