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Original Article

Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam activities against multidrug-resistant Enterobacterales from United States Medical Centers (2018–2022)

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ABSTRACT

A total of 35,360 Enterobacterales isolates were consecutively collected from 75 US medical centers in 2018–2022. Among these isolates, 2612 (7.4%) were categorized as multidrug-resistant (MDR). Isolates were susceptibility tested by reference broth microdilution methods. Carbapenem-resistant Enterobacterales (CRE) were screened for carbapenemase (CPE) genes by whole genome sequencing. The highest MDR rates was observed among *Klebsiella pneumoniae* (12.2%), followed by *Raoultella* spp. (10.9%) and *Providencia stuartii* (9.8%). Ceftazidime-avibactam and meropenem-vaborbactam were very active and showed identical susceptibility rates against MDR isolates (97.9%). Imipenem-relebactam (93.5% susceptible [S]) exhibited slightly lower susceptibility rates due to its limited activity against Morganellaceae family. The most active β-lactamase inhibitor combination (BLI) against CRE isolates (n = 310) was ceftazidime-avibactam (84.2%S), followed by meropenem-vaborbactam (81.9%S) and imipenem-relebactam (74.8%S). All 3 BLIs were very active against KPC producers and none were active against MBL producers. Ceftazidime-avibactam exhibited greater activity against OXA-48–type producers than meropenem-vaborbactam and imipenem-vaborbactam.

1. Introduction

Treatment options for infections caused by multidrug-resistant (MDR) Enterobacterales are limited and these infections are associated with high clinical failure and mortality rates, especially in vulnerable patients [1,2]. Moreover, the choice of antimicrobial therapy is not the only factor associated with patient outcomes. Time to appropriate therapy is one of the strongest predictors of mortality in patients with MDR infections; therefore, these infections require promptly introducing effective antimicrobial therapy [3–5].

The approval of new β-lactamase inhibitor combinations (BLI) in the last few years, such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, represented remarkable progress for the treatment of infections caused by MDR Enterobacterales [6–8]. Although these compounds have demonstrated potent activity and broad spectrum against MDR Enterobacterales causing infection in US medical centers, large studies comparing the activities of these 3 BLIs are scarce. We evaluated the activity of ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam as well as their comparator agents against a large collection of contemporary (2018–2022) MDR Enterobacterales organisms causing infections in patients from US medical centers.

2. Materials and methods

2.1. Bacterial isolates

A total of 35,360 Enterobacterales isolates were collected from 75 medical centers in 36 states from all 9 US Census Divisions in 2018–2022 as part of the International Network for Optimal Resistance Monitoring (INFORM) and the SENTRY Antimicrobial Surveillance Programs [9,10]. These isolates were collected from patients with bloodstream infections (n = 7,064; 20.0%), intra-abdominal infections (n = 1870; 5.3%), pneumonia (n = 5480; 15.5%), urinary tract infections (n = 15,068; 42.6%), skin and skin structure infections (n = 4558; 12.9%), and other infection types (n = 1320; 3.7%) according to defined protocols [11]. Only isolates determined to be significant by local criteria as the reported probable cause of infection was included in the program. Species identification was confirmed by standard biochemical tests and using the MALDI Biotyper (Bruker Daltonics, Billerica, MA) according to the manufacturer instructions.

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2.2. Resistant subsets

Isolates were categorized as MDR or extensively drug-resistant (XDR) according to criteria defined in 2012 by the joint European and US Centers for Disease Control [12]. These criteria define MDR as non-susceptible to ≥1 agent in ≥3 antimicrobial classes and XDR as susceptible to ≤2 classes. The following antimicrobial class representative agents and CLSI interpretive criteria were applied for Enterobacterales: ceftriaxone (≥2 mg/L), meropenem (≥2 mg/L), piperacillin/tazobactam (≥16/4 mg/L), levofloxacin (≥1 mg/L), gentamicin (≥8 mg/L), tigecycline (≥4 mg/L), and colistin (≥4 mg/L). Carbapenem-resistant Enterobacterales (CRE) was defined as displaying imipenem or meropenem MIC values at ≥4 mg/L. Imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to their intrinsically elevated MIC values. Categorical interpretations for all antimicrobials were those found in CLSI M100 document [13].

2.3. Susceptibility testing

All isolates were susceptibility tested using the reference broth microdilution method as described by the CLSI [14]. MIC values were interpreted according to CLSI breakpoint criteria, except for colistin [13]. CLSI does not currently publish a colistin susceptible breakpoint and categorizes isolates with an MIC ≤2 mg/L as intermediate and ≥4 mg/L as resistant; thus, the EUCAST susceptible breakpoint of ≤2 mg/L was applied to calculate the percentage of isolates that were susceptible to colistin. Ceftazidime-avibactam, imipenem-relebactam, ceftolozane-tazobactam, and piperacillin-tazobactam were tested with a β-lactamase inhibitor at a fixed concentration of 4 mg/L; meropenem-vaborbactam was tested with vaborbactam at a fixed concentration of 8 mg/L [13,14]. Relebactam powder was not available until 2020; thus, only isolates collected in 2020–2022 were tested against imipenem-relebactam. CLSI [13] and the US FDA (https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria) susceptibility interpretive criteria were used to determine susceptibility/resistance rates.

2.4. Screening for β-lactamases

All CRE isolates from the MDR subset that were collected in 2018–2021 (n = 310) were tested for β-lactamase–encoding genes by applying genome sequencing and *in silico* screening, as previously described [15]. Total genomic DNA was used as input material for library construction and sequencing using either the Nextera XT library construction protocol and index kit on a MiSeq Sequencer (Illumina, San Diego, CA) with a MiSeq Reagent Kit v3 (600 cycles) or the Illumina DNA library construction protocol and index kit on a NextSeq 1000 Sequencer (Illumina) using NextSeq1000/2000 P2 Reagents (300 cycles). FASTQ format files for each sample set were assembled independently using the *de novo* assembler SPAdes 3.15.3 with K-values of 21, 33, 55, 77, and 99 plus careful mode on to reduce the number of mismatches. This process produced a FASTA-format file of contiguous sequences with the best N50 value. An in-house proprietary bioinformatics pipeline and a JMI-curated resistance gene database based on the NCBI Bacterial Antimicrobial Resistance Reference Gene Database (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047) was used for the *in silico* screening of β-lactamase genes. These genes were used as queries to align β-lactamase resistance determinants against the target assembled sequences. Hits with identities greater than 94% and 40% minimum coverage length were selected for further analysis and the final assignment of β-lactamase alleles [16,17].

3. Results

A total of 2,612 isolates (7.4%) were categorized as MDR (Tables 1 and 2). The highest MDR rates were observed among *K. pneumoniae* (12.2%), followed by *Raoultella* spp. (10.9%), *Providencia stuartii* (9.8%), and *Citrobacter freundii* complex (7.8%; Table 1). Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam exhibited similar activity against species with the highest MDR rates, except against *P. stuartii* and *Morganella morganii*, where imipenem-relebactam was less active than the other 2 compounds (Table 1).

When results were stratified by US Census Division, the highest MDR and CRE rates at 13.5% and 2.4%, respectively, were observed in the Middle Atlantic region (5,670 isolates tested) (Supplementary Table S1). Nine medical centers were surveyed in this Census Division: 4 in New York (3138 isolates), 3 in New Jersey (1796 isolates), and 2 in Pennsylvania (736). The highest MDR and CRE rates of 18.2% and 3.2%, respectively, were detected in New York (data not shown). The second highest MDR (11.1%) and CRE (1.4%) rates were observed in the West South Central Division (Supplementary Table S1), where 3756 isolates from 3 states (Arkansas, Louisiana, and Texas) were evaluated. The lowest MDR and CRE rates were observed in the West North Central Division, at 3.1% and 0.1%, respectively (Supplementary Table S1). A total of 3,359 isolates from 9 medical centers in 6 states (Iowa, Kansas, Minnesota, Missouri, North Dakota, and Nebraska) were evaluated in this region.

Ceftazidime-avibactam ($MIC_{50/90}$, 0.25/1 mg/L; 97.9% susceptible) and meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.12 mg/L; 97.9% susceptible) were very active and showed identical susceptibility rates against MDR isolates (Table 2). Imipenem-relebactam ($MIC_{50/90}$, 0.12/1 mg/L; 93.5% susceptible) exhibited slightly lower susceptibility rates due to its limited activity against Morganellaceae family, which includes *Proteus mirabilis* and indole-positive Proteeae species. Imipenem-relebactam was active against 46.6% of MDR Morganellaceae, and when these organisms were excluded from the analysis, susceptibility rates were 97.9%, 97.8%, and 96.4% for ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, respectively (data not shown). The most active comparator agents were tigecycline ($MIC_{50/90}$, 0.5/2 mg/L; 93.0% susceptible per US FDA criteria) and meropenem ($MIC_{50/90}$, 0.03/4 mg/L; 87.4% susceptible per CLSI and US FDA criteria; Table 2). Notably, susceptibility rates for amikacin ($MIC_{50/90}$, 4/16 mg/L) were 94.2% according to 2022 CLSI criteria (data not shown) and dropped to 69.0% when the revised 2023 CLSI criteria was applied (Table 2).

Ceftazidime-avibactam ($MIC_{50/90}$, 1/>32 mg/L; 81.5% susceptible), meropenem-vaborbactam ($MIC_{50/90}$, 0.12/32 mg/L; 78.7% susceptible), and imipenem-relebactam ($MIC_{50/90}$, 0.25/>8 mg/L; 70.6% susceptible) retained good activity against XDR isolates (Table 2). Tigecycline ($MIC_{50/90}$, 0.5/2 mg/L) was active against 94.0% of XDR isolates per US FDA criteria. Amikacin was active against only 40.7% of isolates per 2023 CLSI criteria compared to 72.2% when 2022 CLSI criteria was applied (data not shown).

The most active β-lactamase inhibitor combination against CRE isolates (n = 310) was ceftazidime-avibactam ($MIC_{50/90}$, 1/>32 mg/L; 84.2% susceptible), followed by meropenem-vaborbactam ($MIC_{50/90}$, 0.06/16 mg/L; 81.9% susceptible) and imipenem-relebactam ($MIC_{50/90}$, 0.25/>8 mg/L; 74.8% susceptible; Table 2). All CRE isolates collected in 2018–2021 (n = 274) were sequenced. KPC was the most common carbapenemase (n = 179; 65.3% of CREs), followed by NDM (n = 33; 12.0%) and OXA-48 type (n = 13; 4.7%; Table 3). A carbapenemase was not identified in 50 CRE isolates (18.2%). Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam were highly active against KPC-producing CRE isolates, with susceptibility rates ranging from 97.8% to 98.8% (Table 4). All 3 compounds exhibited limited activity against MBL producers, and ceftazidime-avibactam showed greater activity against OXA-48–type producers than meropenem-vaborbactam and imipenem-relebactam (Table 4). Four of 13 OXA-48–type producers were ceftazidime-avibactam resistant and all 4 harbored an NDM (2 NDM-1 and 2 NDM-5) in addition to the OXA-48 type (3 OXA-181 and 1 OXA-232; data not shown); an OXA-48–type enzyme was the only carbapenemase identified on the remaining 9 OXA-48–type producing isolates.

Table 1
Activity of ceftazidime-avibactam (CAZ-AVI), meropenem-vaborbactam (MEM-VAB), and imipenem-relebactam (IMI-REL) against multidrug-resistant (MDR) organisms stratified by species and ranked by MDR rate.

Organism	No. tested	No. of MDR	% of MDR	% Susceptible per CLSI		
				CAZ-AVI	MEM-VAB	IMI-REL
Klebsiella pneumoniae	7153	871	12.2	97.8	97.1	95.0
Raoultella spp.	175	19	10.9	100.0	100.0	100.0
Providencia stuartii	285	28	9.8	92.9	100.0	50.0
Citrobacter freundii complex	1176	92	7.8	98.9	97.8	100.0
Escherichia coli	12,705	973	7.7	99.5	99.6	99.4
Enterobacter cloacae complex	3021	210	7.0	91.4	91.9	92.6
Morganella morganii	839	53	6.3	100.0	100.0	65.2
Serratia marcescens	1692	90	5.3	97.8	98.9	89.7
Klebsiella aerogenes	1267	67	5.3	98.5	97.0	92.1
Klebsiella oxytoca	2083	99	4.8	96.0	98.0	92.7

4. Discussion

The approval of BLI compounds provided significant options for treating MDR Gram-negative infections to the market. The addition of these new β-lactamase inhibitors, such as avibactam, vaborbactam, and relebactam, restores the β-lactam activity against Gram-negative bacilli that acquired β-lactam resistance through expression of the Ambler class A ESBLs, chromosomal or mobile class C β-lactamases, and most serine carbapenemases [18,19].

In this investigation, we evaluated the *in vitro* activity of the 3 most recently approved BLIs against a large collection of clinical MDR Enterobacterales isolates from US hospitals. The overall MDR rate was 7.4%, but rates varied widely among Enterobacterales species as well as between Census Divisions. The highest MDR rate was observed with *K. pneumoniae* (12.2%), which was the second most commonly isolated species, representing 20.2% of Enterobacterales isolates. Notably, less commonly isolated organisms, such as *Raoultella* spp. and *P. stuartii*, exhibited elevated MDR rates at 10.9% and 9.8%, respectively. It is important to recognize that these species are more likely to be MDR when introducing empiric antimicrobial therapy. It is also important to note that some of the species with elevated MDR rates, such as *P. stuartii* (9.8%) and *M. morganii* (6.3%), are generally less susceptible to imipenem-relebactam compared to ceftazidime-avibactam and meropenem-vaborbactam (Table 1) [20].

In general, all 3 new BLIs demonstrated potent activity against MDR, but some differences were noted on the spectrum of activity of these compounds. As shown by other investigators, imipenem-relebactam showed limited activity against organisms of the Morganellaceae family, which included *Proteus* spp., *Providencia* spp., and *Morganella* spp., among others [7,20]. These organisms represented 13.5% of the Enterobacterales collection and 6.7% of MDR isolates. The susceptibility rates of the MDR Morganellaceae isolates (n = 174) were 96.6%, 98.3%, and 46.6% for ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, respectively (data not shown). Imipenem-relebactam was also less active against MDR *Serratia marcescens* (n = 90; $MIC_{50/90}$, 0.5/2 mg/L; 89.7% susceptible) compared to ceftazidime-avibactam ($MIC_{50/90}$, 0.5/1 mg/L; 97.8% susceptible) and meropenem-vaborbactam ($MIC_{50/90}$, 0.06/0.12 mg/L; 98.9% susceptible; data not shown).

Overall, 11.9% (310/2,612) of MDR isolates were CRE. Some differences were noted on the spectrum of the new BLIs against this important subset of MDR isolates. Mainly, ceftazidime-avibactam was more active (69.2% susceptible) against OXA-48–type producers when compared to meropenem-vaborbactam and imipenem-relebactam (Table 4). Notably, all ceftazidime-avibactam–resistant OXA-48–type producers harbored an MBL (NDM-1 or NDM-5) in addition to the OXA-48 type.

The limited activity of imipenem-relebactam and meropenem-vaborbactam against OXA-48 producers has been reported by various investigators and is related to the poor inhibition of OXA-48–like enzymes by relebactam and vaborbactam [18]. Haider et al. [21] evaluated 100 molecularly characterized CRE isolates and showed that ceftazidime-avibactam was active against OXA-48 producers whereas imipenem-relebactam was not active against those organisms. Canver et al. [22] also reported greater activity of ceftazidime-avibactam compared to imipenem-relebactam when testing 20 OXA-48–like CRE isolates. Lee et al. [23] evaluated 395 *K. pneumoniae* that produced OXA-48–like and reported susceptibility rates of 98.7% for ceftazidime-avibactam and only 4.6% for meropenem-vaborbactam. It is becoming more critical to recognize the activity differences of these new BLIs against OXA-48–like producers since the prevalence of these enzymes appear to be increasing in US medical centers in recent years [24].

It is also important to note that ceftazidime-avibactam was the most active BLI against non–carbapenemase-producing CRE isolates (96.0% susceptibility), followed by meropenem-vaborbactam (86.0% susceptible) and imipenem-relebactam (73.9% susceptible). Moreover, all 3 BLIs were very active against KPC producers and none of the 3 were active against MBL producers.

The main limitation of the study was the fact that isolates collected in 2018 and 2019 were not tested against imipenem-relebactam. These isolates were not tested against imipenem-relebactam because we were not able to obtain relebactam powder until 2020 and isolates are tested in the calendar year that they are collected. In order to evaluate the impact of this limitation on the results and conclusions of the study, we re-analyzed the results for the subset of isolates tested against all 3 BLIs. The results of this sensitive analysis are displayed in Supplementary Table S2 and indicate that susceptibility rates for ceftazidime-avibactam and meropenem-vaborbactam against MDR, XDR, CRE, and CPE producers were very similar to those obtained with the entire collection (Tables 2 and 4). Thus, it is very unlikely that this limitation introduced significant bias to the results and conclusions of the study.

In conclusion, the results of this investigation showed that the 3 most recently approved BLIs, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, are very active against MDR Enterobacterales from US medical centers and represent valuable options for the treatment of infections caused by these organisms. Moreover, our results detected some differences in the spectrum of these 3 compounds, which should be considered especially when the antimicrobial agents are used empirically.

Declaration of competing interest

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

Table 2
Activity of ceftazidime-avibactam and comparator antimicrobial agents when tested against Enterobacterales resistant subsets.

Organism / antimicrobial (no. tested)	MIC_{50}	MIC_{90}	CLSI 2023 [a]		
			%S	%I	%R
MDR (2612)					
Ceftazidime-avibactam	0.25	1	97.9		2.1
Meropenem-vaborbactam	0.03	0.12	97.9	0.5	1.7
Imipenem-relebactam[b]	0.12	1	93.5 [b]	3.2	3.2
Ceftolozane-tazobactam	1	>16	68.4	5.9	25.7
Piperacillin-tazobactam	16	>128	36.1	18.8	45.1
Meropenem	0.03	4	87.4	2.3	10.3
Imipenem	≤0.12	4	81.6	6.3	12.1
Ceftriaxone	>8	>8	4.5	2.0	93.6
Cefepime	>32	>32	18.0	12.2	69.8
Levofloxacin	8	32	17.7	10.4	71.8
Gentamicin	>16	>16	34.5	3.4	62.1
Amikacin	4	16	69.0	16.8	14.2
Tigecycline[c]	0.5	2	93.0	6.1	0.9
Colistin	0.25	>8		87.3	12.7
XDR (216)					
Ceftazidime-avibactam	1	>32	81.5		18.5
Meropenem-vaborbactam	0.12	32	78.7	3.7	17.6
Imipenem-relebactam[b]	0.25	>8	70.6	5.9	23.5
Ceftolozane-tazobactam	>16	>16	2.8	1.4	95.8
Piperacillin-tazobactam	>128	>128	0.0	0.5	99.5
Meropenem	16	>32	5.1	9.7	85.2
Imipenem	8	>8	6.9	6.9	86.1
Ceftriaxone	>8	>8	0.0	0.0	100.0
Cefepime	>32	>32	1.4	9.7	88.9
Levofloxacin	16	>32	6.0	9.3	84.7
Gentamicin	8	>16	27.8	3.7	68.5
Amikacin	8	>32	40.7	14.9	44.4
Tigecycline[c]	0.5	2	94.0	4.6	1.4
Colistin	0.25	>8		84.7	15.3
CRE (310)[d]					
Ceftazidime-avibactam	1	>32	84.2		15.8
Meropenem-vaborbactam	0.06	16	81.9	3.9	14.2
Imipenem- relebactam[b]	0.25	8	74.8	3.7	21.5
Ceftolozane-tazobactam	>16	>16	3.2	3.9	92.9
Piperacillin-tazobactam	>128	>128	0.0	1.0	99.0
Levofloxacin	8	>32	24.5	9.4	66.1
Gentamicin	2	>16	48.4	5.1	46.5
Amikacin	4	32	61.0	9.6	29.4
Tigecycline[c]	0.5	2	94.2	4.8	1.0
Colistin	0.25	>8		86.0	14.0

MDR = multidrug-resistant; XDR = extensively drug-resistant; CRE = carbapenem-resistant Enterobacterales.
[a] Criteria as published by CLSI [13].
[b] Isolates collected in 2018 and 2019 were not tested against imipenem-relebactam.
[c] Breakpoints are from the US FDA package insert.
[d] Organisms include *Citrobacter freundii* species complex (9), *C. koseri* (1), *Enterobacter cloacae* species complex (48), *Escherichia coli* (18), *Hafnia alvei* (1), *Klebsiella aerogenes* (19), *K. oxytoca* (19), *K. pneumoniae* (171), *Proteus mirabilis* (1), *Providencia rettgeri* (3), *Raoultella ornithinolytica* (1), *Serratia marcescens* (15), and unspeciated *Raoultella* (4).

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Table 3
Frequency of carbapenemase genes among carbapenem-resistant Enterobacterales (CRE) isolates from 2018–2021.[b]

β-Lactamase	No. of isolates	% of CREs
KPC type	179	65.3
KPC-2	72	26.3
KPC-3	101	36.9
Others[a]	6	2.2
MBL	38	13.9
NDM type	33	12.0
IMP type	3	1.1
VIM type	2	0.7
OXA-48 type	13	4.7
≥2 carbapenemases	6	2.2
No carbapenemase	50	18.2
Total CPEs	224	81.8
CRE isolates tested[c]	274	100.0

[a] Includes KPC-4 (2 isolates), KPC-6 (2), KPC-58 (1), and KPC-59 (1).
[b] Includes NDM-1 (24 isolates) and NDM-5 (10).
[c] Includes only CRE categorized as MDR from 2018–2021. Isolates from 2022 were not sequenced.

Table 4
Activity of ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam against CRE isolates stratified by carbapenemase type (2018–2021).

β-Lactamase	% Susceptible per CLSI		
(no. of isolates)	Ceftazidime-avibactam	Meropenem-vaborbactam	Imipenem-relebactam
KPC producers (179)	97.8	98.3	98.8
MBL producers (38)[a]	2.6	15.8	0.0
OXA-48 type producers (13)	69.2[b]	15.4	0.0
2 carbapenemases (6)	0.0	16.7	0.0
No carbapenemase producer (50)	96.0	86.0	73.9
All CPE producers (224)[b]	82.6	81.7	76.9

[a] Includes NDM (33 isolates), IMP (3), and VIM (2) producers (see Table 3).
[b] All ceftazidime-avibactam resistant isolates (4 of 13) harbored an NDM in addition to the OXA-48–like.

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Authors' contributions

Helio Sader: Conceptualization, Formal Analysis, Data Curation, Writing – Original Draft, Visualization, Funding Acquisition; Rodrigo Mendes: Conceptualization, Validation, Resources, Writing – Review & Edit, Supervision, Funding Acquisition; Leonard Duncan: Methodology, Formal Analysis, Investigation, Data Curation, Software, Validation, Supervision; John Kimbrough: Methodology, Formal Analysis, Investigation, Data Curation, Review & Edit, Software, Validation, Supervision; Mariana Castanheira: Conceptualization, Validation, Resources, Writing – Review & Edit, Supervision, Funding Acquisition.

Patient Consent Statement

Our study does not include factors necessitating patient consent.

Ethical approval

Not required.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diagmicrobio.2023.115945.

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