

Antimicrobial activity of ceftazidime/avibactam, ceftolozane/tazobactam and comparator agents against *Pseudomonas aeruginosa* from cystic fibrosis patients

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Objectives: To evaluate the antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* isolates collected from the lower respiratory tract of cystic fibrosis (CF) patients.

Methods: We susceptibility tested 273 contemporary *P. aeruginosa* isolates from 39 hospitals worldwide (17 countries) by the reference broth microdilution method.

Results: Ceftazidime/avibactam [MIC_{50/90}, 2/8 mg/L; 96.0% susceptible (S)] was the most active agent, followed by ceftolozane/tazobactam (MIC_{50/90}, 1/4 mg/L; 90.5% S), ceftazidime (MIC_{50/90}, 2/>32 mg/L; 80.6% S), piperacillin/tazobactam (MIC_{50/90}, 4/128 mg/L; 80.2% S) and tobramycin (MIC_{50/90}, 2/>16 mg/L; 76.6% S). Ceftazidime/avibactam retained activity against *P. aeruginosa* isolates non-susceptible to meropenem (86.5% S to ceftazidime/avibactam), piperacillin/tazobactam (85.2% S to ceftazidime/avibactam) or ceftazidime (79.2% S to ceftazidime/avibactam). MDR phenotype was observed among 36.3% of isolates, and 88.9% and 73.7% of MDR isolates were susceptible to ceftazidime/avibactam and ceftolozane/tazobactam, respectively. Against isolates non-susceptible to meropenem, piperacillin/tazobactam and ceftazidime, susceptibility rates were 78.9% for ceftazidime/avibactam and 47.4% for ceftolozane/tazobactam. Ceftazidime/avibactam was active against 65.4% of ceftolozane/tazobactam-non-susceptible isolates and ceftolozane/tazobactam was active against 18.2% of ceftazidime/avibactam-non-susceptible isolates.

Conclusions: Ceftazidime/avibactam and ceftolozane/tazobactam exhibited potent and broad-spectrum activity against *P. aeruginosa* isolated from CF patients worldwide, but higher susceptibility rates for ceftazidime/avibactam compared with ceftolozane/tazobactam were observed among the resistant subsets. Ceftazidime/avibactam and ceftolozane/tazobactam represent valuable options to treat CF pulmonary exacerbations caused by *P. aeruginosa*.

Introduction

Pseudomonas aeruginosa is the most common cultured respiratory pathogen in individuals with cystic fibrosis (CF) and is associated with a more rapid decline in lung function. More than 50% of CF individuals aged 18 years and older in the USA are infected with *P. aeruginosa*, of whom approximately one-third are infected with an MDR strain. Over time, most individuals with CF become chronically infected with *P. aeruginosa*, and a mucoid phenotype of *P. aeruginosa* frequently becomes the predominant form found in culture. Moreover, chronic *P. aeruginosa* infection is associated with greater rates of morbidity and mortality irrespective of pulmonary function.¹⁻³

Ceftazidime/avibactam and ceftolozane/tazobactam are β -lactamase inhibitor combinations approved by the US FDA and

by the EMA to treat hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia (HABP/VABP), complicated intra-abdominal infections (cIAIs) in combination with metronidazole, and complicated urinary tract infections (cUTIs), including pyelonephritis.⁴⁻⁶ Both compounds have demonstrated potent activity against clinical *P. aeruginosa* isolates, including MDR isolates, but studies evaluating these two compounds against *P. aeruginosa* from CF patients are very limited.⁷ The objective of this study was to evaluate the *in vitro* activity and spectrum of these two combinations and comparator agents currently used to treat Gram-negative infections against contemporary *P. aeruginosa* isolated from CF patients.

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Materials and methods

Isolates were collected as part of SENTRY Antimicrobial Surveillance Program.⁸ Medical centres were asked to collect consecutive bacterial isolates from lower respiratory tract sites of CF patients from January 2018 to December 2019. Each participant centre could contribute up to 40 *P. aeruginosa* isolates. Only isolates from invasive sampling, including transtracheal aspiration, bronchoalveolar lavage, protected brush samples or qualified sputum samples were accepted.

The isolate collection included 273 *P. aeruginosa* isolates from 39 medical centres in 17 countries. The majority of isolates were from the USA ($n = 130$; 47.6%) and 11 European countries ($n = 117$; 42.9%). The European country that contributed the largest number of isolates was Spain ($n = 43$; two medical centres), followed by Poland ($n = 20$; one medical centre), Sweden ($n = 16$; one medical centre), and France ($n = 15$; two medical centres; [Table S1](#), available as [Supplementary data](#) at [JAC-AMR Online](#)). Species identification was performed at the participating medical centres and confirmed at JMI Laboratories by standard biochemical tests and using the MALDI Biotyper (Bruker Daltonics, Billerica, MA, USA) according to the manufacturer instructions, where necessary. Isolates were categorized as MDR or XDR according to criteria defined in 2012 by the joint European and US Centres for Disease Control. These criteria define MDR as non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial classes and XDR as susceptible to ≤ 2 classes.⁹ The antimicrobial classes and drug representatives in this analysis included cephalosporins (ceftazidime and cefepime), carbapenems (imipenem and meropenem), broad-spectrum penicillins combined with a β -lactamase-inhibitor (piperacillin/tazobactam), fluoroquinolones (ciprofloxacin and levofloxacin), aminoglycosides (gentamicin, tobramycin and amikacin) and the polymyxins (colistin).

Broth microdilution test methods were conducted according to CLSI criteria to determine the antimicrobial susceptibility of ceftazidime/avibactam, ceftolozane/tazobactam (inhibitor at fixed concentration of 4 mg/L for both combinations) and comparator agents.¹⁰ Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures. All QC results were within published ranges. CLSI and EUCAST susceptibility interpretive criteria were used to determine susceptibility/resistance rates for ceftazidime/avibactam, ceftolozane/tazobactam and comparator agents.^{11,12}

Isolates resistant to either ceftazidime/avibactam or ceftolozane/tazobactam were submitted to WGS. Total genomic DNA was extracted and used as input material for library construction. DNA libraries were prepared using the Nextera XT library construction protocol and index kit (Illumina, San Diego, CA, USA) and sequenced on a MiSeq sequencer (Illumina) using a minimum of 20% coverage, as previously described.¹³

Results

Ceftazidime/avibactam (MIC_{50/90}, 2/8 mg/L; 96.0% susceptible per CLSI and EUCAST) was the most active agent, followed by ceftolozane/tazobactam (MIC_{50/90}, 1/4 mg/L; 90.5% susceptible per CLSI and EUCAST), ceftazidime (MIC_{50/90}, 2/>32 mg/L; 80.6% susceptible per CLSI), piperacillin/tazobactam (MIC_{50/90}, 4/128 mg/L; 80.2% susceptible per CLSI) and tobramycin (MIC_{50/90}, 2/>16 mg/L; 76.6%/63.7% susceptible per CLSI/EUCAST). Colistin (MIC_{50/90}, 0.5/1 mg/L) was active against 98.2% of isolates when EUCAST breakpoint criteria were applied ([Table 1](#) and [Figure 1](#)).

The ceftazidime/avibactam susceptibility rate was slightly higher in the USA compared with Europe (98.5% versus 94.0%); whereas susceptibility rates for cefepime (66.9% in the USA and 75.2% in Europe), meropenem (70.0% versus 77.8%), imipenem (61.5% versus 72.6%), levofloxacin (36.2% versus 45.3%), tobramycin (71.5% versus 86.3%), amikacin (59.2% versus 71.8%) and gentamicin (40.0% versus 55.6%) were lower in the USA compared with Europe. Moreover, susceptibility rates for ceftolozane/tazobactam, ceftazidime, piperacillin/tazobactam and colistin were similar in both geographic regions (0.4% to 2.1% difference; [Table S2](#)).

Interestingly, higher susceptibility rates for ceftazidime/avibactam compared with ceftolozane/tazobactam were more noticeable within the resistant subsets. When tested against meropenem-non-susceptible isolates ($n = 74$), susceptibility rates were 86.5% for ceftazidime/avibactam (MIC_{50/90}, 4/16 mg/L) and 66.2% for ceftolozane/tazobactam (MIC_{50/90}, 2/>16 mg/L; [Table 2](#) and [Figure 1](#)).

Table 1. Activity of ceftazidime/avibactam, ceftolozane/tazobactam and comparator antimicrobial agents against 273 *P. aeruginosa* isolates collected from CF patients (2018–19)

Antimicrobial agent	mg/L		CLSI ^a			EUCAST ^a		
	MIC ₅₀	MIC ₉₀	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Ceftazidime/avibactam	2	8	96.0		4.0	96.0		4.0
Ceftolozane/tazobactam	1	4	90.5	2.9	6.6	90.5		9.5
Ceftazidime	2	>32	80.6	3.7	15.8	^c	80.6 ^c	19.4
Cefepime	8	32	71.4	13.9	14.7	^c	71.4 ^c	28.6
Piperacillin/tazobactam	4	128	80.2	8.4	11.4	^c	80.2 ^c	19.8
Meropenem	0.5	16	72.9	5.1	22.0	72.9		13.6
Imipenem	1	>8	66.3	6.2	27.5	^c	72.5 ^c	27.5
Levofloxacin	2	16	40.3	18.7	41.0	^c	40.3 ^c	59.7
Tobramycin	2	>16	76.6	8.1	15.4	63.7 ^b		36.3
Amikacin	16	>32	65.9	14.7	19.4	65.9 ^b		34.1
Gentamicin	8	>16	46.9	18.7	34.4			
Colistin	0.5	1		98.2	1.8	98.2		1.8

^aCriteria as published by CLSI¹¹ and EUCAST.¹²

^bInfections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with another active therapy.

^cAn arbitrary susceptible breakpoint of ≤ 0.001 mg/L and/or > 50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure.¹²

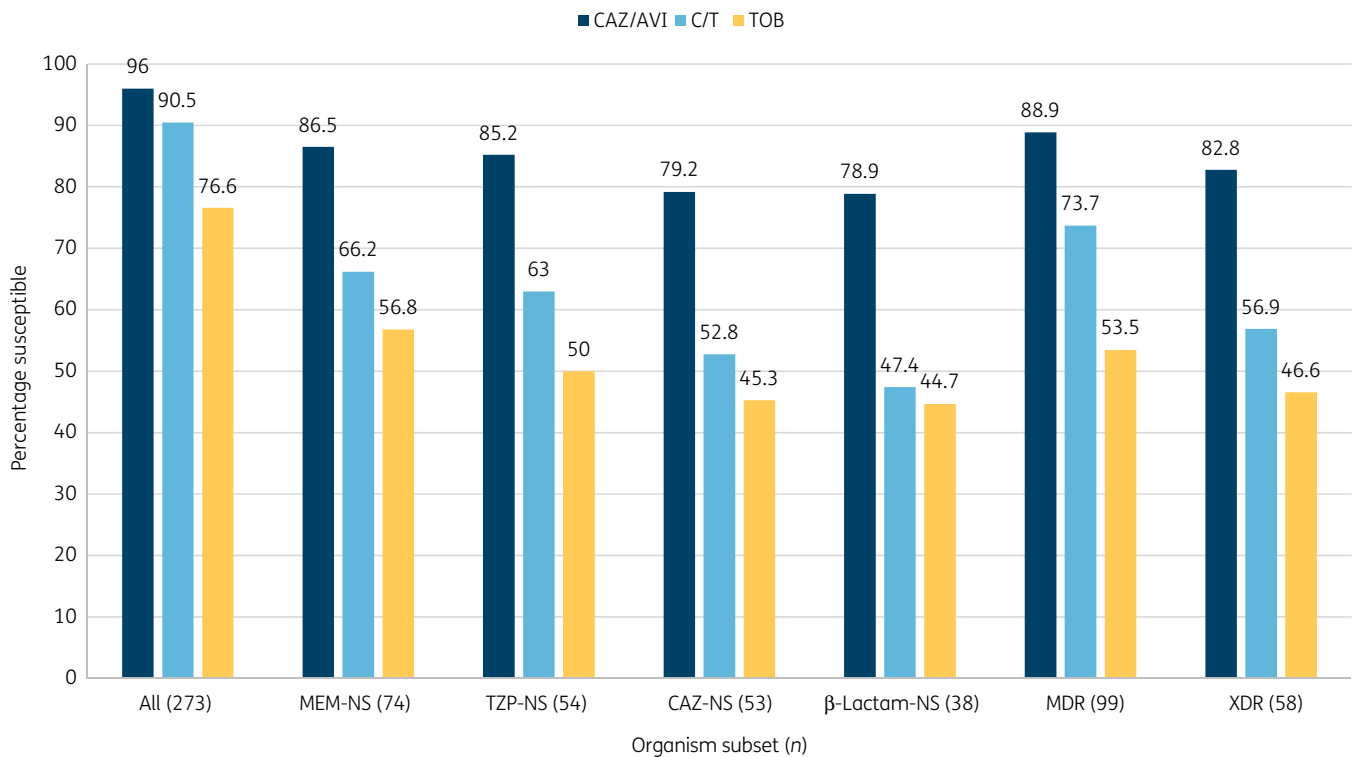


Figure 1. Antimicrobial activity of ceftazidime/avibactam (CAZ/AVI), ceftolozane/tazobactam (C/T) and tobramycin (TOB) tested against *P. aeruginosa* resistant subsets collected from CF patients (2018–19). MEM, meropenem; NS, non-susceptible; TZP, piperacillin/tazobactam; CAZ, ceftazidime; β-lactam-NS, isolates not susceptible to meropenem, piperacillin/tazobactam and ceftazidime.

Similarly, against piperacillin/tazobactam-non-susceptible isolates ($n = 54$), susceptibility rates were 85.2% for ceftazidime/avibactam ($MIC_{50/90}$, 4/32 mg/L) and 63.0% for ceftolozane/tazobactam ($MIC_{50/90}$, 4/>16 mg/L). Against ceftazidime-non-susceptible isolates ($n = 53$), susceptibility rates were 79.2% for ceftazidime/avibactam ($MIC_{50/90}$, 4/32 mg/L) and 52.8% for ceftolozane/tazobactam ($MIC_{50/90}$, 4/>16 mg/L; Table 2 and Figure 1).

When tested against isolates non-susceptible to meropenem, piperacillin/tazobactam, and ceftazidime ($n = 38$), susceptibility rates were 78.9% for ceftazidime/avibactam ($MIC_{50/90}$, 8/32 mg/L) and only 47.4% for ceftolozane/tazobactam ($MIC_{50/90}$, 8/>16 mg/L; Figure 1). Moreover, 65.4% of ceftolozane/tazobactam-non-susceptible isolates remained susceptible to ceftazidime/avibactam and only 18.2% of ceftazidime/avibactam-non-susceptible isolates remained susceptible to ceftolozane/tazobactam (Table 2).

MDR and XDR phenotypes were observed in 36.3% ($n = 99$) and 21.2% ($n = 58$) of isolates, respectively. Susceptibility rates against the MDR and XDR subsets were 88.9% and 82.8% for ceftazidime/avibactam and 73.7% and 56.9% for ceftolozane/tazobactam, respectively (Figure 1).

Possible mechanisms of resistance to ceftazidime/avibactam or ceftolozane/tazobactam and MLST were evaluated by analysing WGS data and these results are summarized in Table 3. Among the 29 isolates resistant to either one of these agents, 9 isolates were resistant to both agents, 2 isolates were resistant to ceftazidime/avibactam and susceptible to ceftolozane/tazobactam, and 17 isolates were resistant to ceftolozane/tazobactam and susceptible to ceftazidime/avibactam; 28 of these 29

isolates were available to be submitted to WGS. An ESBL or carbapenemase was observed in only 3 isolates: 1 isolate that was resistant to ceftolozane/tazobactam and susceptible to ceftazidime/avibactam had a GES-1 and 2 isolates that were resistant to both compounds had a VIM-type β-lactamase (VIM-2 and VIM-20). Fifteen isolates, including 3 isolates resistant to both compounds and 12 isolates resistant to ceftolozane/tazobactam and susceptible to ceftazidime/avibactam, had early terminations/deletions in the OprD incompatible to a functional protein. Moreover, a great genetic diversity was observed among these isolates, with 26 MLSTs observed among the 28 isolates submitted to WGS.

Discussion

Many studies have shown that ceftazidime/avibactam and ceftolozane/tazobactam are both very active and exhibit similar coverage against *P. aeruginosa* isolates causing infections in US hospitals.^{14–17} It has also been shown that these compounds remain active against most isolates resistant to other β-lactams, but susceptibility rates of ceftazidime/avibactam and ceftolozane/tazobactam may vary more widely when testing resistant subsets of *P. aeruginosa*. Grupper *et al.*¹⁸ evaluated 290 carbapenem-resistant *P. aeruginosa* isolates from 34 US medical centres against these two compounds and found susceptibility rates of 81% for ceftazidime/avibactam and 91% for ceftolozane/tazobactam. Humphries *et al.*¹⁹ studied 309 β-lactam-resistant *P. aeruginosa* isolates from three institutions located in the Los Angeles area and

Table 2. Cross-resistance among β -lactams and β -lactamase inhibitor combinations when tested against *P. aeruginosa* isolates collected from CF patients (2018–19)

Antimicrobial	Percentage susceptible by resistant subset (no. of isolates) ^a				
	MEM-NS (74)	TZP-NS (54)	CAZ-NS (53)	C/T-NS (26)	CAZ/AVI-NS (11)
MEM	0.0	20.4	17.0	3.8	9.1
TZP	41.9	0.0	15.1	3.8	27.2
CAZ	40.5	16.7	0.0	3.8	0.0
C/T	66.2	63.0	52.8	0.0	18.2
CAZ/AVI	86.5	85.2	79.2	65.4	0.0

CAZ, ceftazidime; MEM, meropenem; TZP, piperacillin/tazobactam; C/T, ceftolozane/tazobactam; AVI, avibactam; NS, non-susceptible.

^aIsolates were categorized as non-susceptible based on CLSI criteria.

Table 3. Summary of WGS results of isolates resistant to either ceftazidime/avibactam or ceftolozane/tazobactam

Collection number	Susceptibility		Carbapenemase/ESBL	PDC	Major OprD changes	MLST
	CAZ/AVI	C/T				
1077179	R	R	none	PDC-16	deletions starting in aa 185	298
1084588	R	R	none	PDC-35	early termination (Q166X)	235
1111576	R	R	none	PDC-179	none	633-like
1111644	R	R	none	PDC-97	frameshift starting in aa 415	3694
1118232	R	R	VIM-2	PDC-3	frameshift starting in aa 29	111
1127896	R	R	none	PDC-97	early termination (W138X)	1497-like
1131386	R	R	none	PDC-20	none	508-like
1131387	R	R	VIM-20	PDC-1	frameshift starting in aa 28	175
1131419	R	R	NT	NT	NT	NT
1131383	R	S	none	PDC-1	none	500
1067332	R	S	none	PDC-3	none	903-like
1044749	S	R	none	PDC-3	none	260
1044750	S	R	none	PDC-129	none	260
1047619	S	R	none	PDC-168	early termination (W277X)	132
1055361	S	R	none	PDC-147	deletion (M1→K34)	809
1067334	S	R	none	PDC-8	deletion (S267→X442)	17
1067975	S	R	none	PDC-31	deletions starting in aa 208	1233
1072979	S	R	none	PDC-97	deletions starting in aa 208	3473-like ^a
1084581	S	R	GES-1	PDC-35	early termination (T103X)	235
1102272	S	R	none	PDC-116	deletion (S267→X442)	274-like
1118222	S	R	none	PDC-8	early termination (W415X)	258
1120958	S	R	none	PDC-1	frameshift starting at aa 391	2587
1126957	S	R	none	PDC-5	deletion (I411→X442)	262-like
1130447	S	R	none	PDC-116	early termination (Q158X)	274-like
1130449	S	R	none	PDC-31	frameshift starting at aa 23	2708
1130451	S	R	none	PDC-71	none	390-like
1131423	S	R	none	PDC-24	deletion (M1→A10)	198
1132066	S	R	none	PDC-169	deletions starting in aa 208	282

aa, amino acid; CAZ/AVI, ceftazidime/avibactam; C/T, ceftolozane/tazobactam; PDC, *Pseudomonas*-derived cephalosporinases; R, resistant; S, susceptible; NT, not tested/sequenced.

^aDouble loci variant. All other 'likes' were single loci variants.

found that 61.8% and 72.5% of these isolates were susceptible to ceftazidime/avibactam and ceftolozane/tazobactam, respectively. Moreover, 36.4% of the ceftazidime/avibactam-resistant isolates were susceptible to ceftolozane/tazobactam and only 9.1% of ceftolozane/tazobactam-resistant isolates were susceptible to

ceftazidime/avibactam.¹⁹ These two studies showed slightly greater susceptibility for ceftolozane/tazobactam compared with ceftazidime/avibactam.^{18,19} In contrast, this investigation found a greater spectrum of activity for ceftazidime/avibactam compared with ceftolozane/tazobactam.

We evaluated 273 *P. aeruginosa* isolates from CF patients in 17 countries. Ceftazidime/avibactam (96.0% susceptible) was slightly more active than ceftolozane/tazobactam (90.5% susceptible) against the entire collection of organisms. Interestingly, a greater coverage of ceftazidime/avibactam over ceftolozane/tazobactam was more evident when testing resistant subsets of organisms. For example, among isolates non-susceptible to meropenem, piperacillin/tazobactam and ceftazidime, which were collected from 21 medical centres in 9 countries, susceptibility rates were 78.9% for ceftazidime/avibactam and only 47.4% for ceftolozane/tazobactam. WGS results of isolates resistant to either ceftazidime/avibactam or ceftolozane/tazobactam showed that β -lactamase production was responsible for resistance to these agents in only 10.7% (3/28) of isolates. The most common WGS finding was the presence of OprD alterations, and we could not identify any specific mechanism that could be responsible for resistance to one or both compounds.²⁰

Differences in the activities of these two β -lactamase inhibitor combinations against drug-resistant *P. aeruginosa* reflect the variety of resistance mechanisms expressed by these organisms and illustrate how these mechanisms may have different impacts on each of these compounds. Mechanisms of resistance to ceftazidime/avibactam and ceftolozane/tazobactam are complex and caused by the presence and interaction of multiple mutation-driven resistance mechanisms.²¹ Therefore, the activity of these two compounds, and especially the rates of cross-resistance between them, may vary widely depending on selective pressure due to previous antibiotic usage and other factors.

In summary, ceftazidime/avibactam exhibited potent activity and broad spectrum against *P. aeruginosa* from CF patients and retained activity against isolates resistant to other antipseudomonal β -lactams as well as against MDR and XDR isolates. Our results indicated that ceftazidime/avibactam and ceftolozane/tazobactam represents a valuable option to treat CF patients with respiratory tract infections caused by *P. aeruginosa*.

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Transparency declarations

JMI Laboratories contracted to perform services in 2019–20 for Albany College of Pharmacy and Health Sciences, Allegra Therapeutics, Allergan, AmpliPhi Biosciences Corp., Amicrobe Advanced Biomaterials, Amplyx, Antabio, American Proficiency Institute, Arietis Corp., Arixa Pharmaceuticals Inc., Astellas Pharma Inc., Athelas, Basilea Pharmaceutica Ltd, Bayer AG, Becton, Boston Pharmaceuticals, Bugworks

Research Inc., CEM-102 Pharmaceuticals, Cidara Therapeutics Inc., Cipla Pharmaceuticals; CorMedix Inc., DePuy Synthes, Destiny Pharma, Discuva Ltd, Dr. Falk Pharma GmbH, Emery Pharma, Entasis Therapeutics, US Food and Drug Administration, Fox Chase Chemical Diversity Center Inc., Gateway Pharmaceutical LLC, GenePOC Inc., Geom Therapeutics Inc., GlaxoSmithKline plc, Harvard University, Helperby, HiMedia Laboratories, F. Hoffmann-La Roche Ltd, ICON plc, Idorsia Pharmaceuticals Ltd, Iterum Therapeutics plc, Laboratory Specialists Inc., Melinta Therapeutics Inc., Merck & Co. Inc., Microchem Laboratory, Micromyx, MicuRx Pharmaceuticals Inc., Mutabilis Co., Nabriva Therapeutics plc, NAEJA-RGM, Novartis AG, Paratek Pharmaceuticals Inc., Pfizer Inc., Polyphor Ltd, Pharmaceutical Product Development, LLC, Prokaryotics Inc., Qpex Biopharma Inc., Roivant Sciences Ltd, Safeguard Biosystems, Scynexis Inc., SeLux Diagnostics Inc., Shionogi and Co. Ltd, SinSa Labs, Spero Therapeutics, Summit Pharmaceuticals International Corp., Synlogic, T2 Biosystems Inc., Taisho Pharmaceutical Co. Ltd, TenNor Therapeutics Ltd, Tetrphase Pharmaceuticals, Theravance Biopharma, University of Colorado, University of Southern California-San Diego, University of North Texas Health Science Center, VenatoRx Pharmaceuticals Inc., Viosera Therapeutics, Vyome Therapeutics Inc., Wockhardt, Yukon Pharmaceuticals Inc., Zai Lab and Zavante Therapeutics Inc. There are no speakers' bureaus or stock options to declare.

Supplementary data

Tables S1 and S2 are available as [Supplementary data](#) at JAC-AMR Online.

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