Diagnostic Microbiology and Infectious Disease 103 (2022) 115673

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Antimicrobial Susceptibility Studies

Selection of the appropriate avibactam concentration for use with ceftibuten in broth microdilution susceptibility testing

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ARTICLE INFO

Article history:
Received 24 January 2022
Revised in revised form 27 February 2022
Accepted 3 March 2022
Available online 10 March 2022

Keywords:
β-lactamase inhibitor combination
Oral cephalosporins
Enterobacterales
ESBL
KPC

ABSTRACT

Ceftibuten is an oral cephalosporin approved by the US Food and Drug Administration in 1995 that is in early clinical development to be combined with an oral prodrug of avibactam. We evaluated the activity of ceftibuten-avibactam against molecularly characterized Enterobacterales that produced clinically relevant β-lactamases and assessed the best avibactam concentration to be combined with ceftibuten for susceptibility testing. Resistance mechanisms were evaluated by whole genome sequencing. MIC values were determined by broth microdilution of ceftibuten, avibactam, and ceftibuten combined with fixed concentrations (2, 4, and 8 mg/L) and ratios (1:1 and 2:1) of avibactam. The organism collection (n = 71) included Enterobacterales producing ESBLs, KPC, metallo-β-lactamases, AmpC, K-1, OXA-48, and SME, as well as isolates with porin alterations. The ceftibuten-avibactam combination that best separated isolates with β-lactamases inhibited by avibactam from isolates with resistance mechanisms that are not affected by avibactam was the combination with avibactam at a fixed concentration of 4 mg/L.

1. Introduction

Ceftibuten is an oral third-generation cephalosporin originally approved in 1995 for the treatment of upper and lower respiratory tract infections [1–3]. Although not approved for these indications, ceftibuten has also been used to treat complicated and uncomplicated urinary tract infections (UTIs) in adults and children [4,5]. Ceftibuten is highly potent against Enterobacterales and stable against many class A and B β-lactamases produced by these organisms, including some extended-spectrum β-lactamases (ESBLs) [3,6]. Moreover, ceftibuten has favourable pharmacokinetic properties, including high bioavailability following oral administration (75%–90%), long elimination half-life (2–3 hours), once daily dosing, good tolerability profile in adults and children, and high fractional excretion in urine [3].

Avibactam is a synthetic diazabicyclooctane (DBO) non–β-lactam inhibitor. Avibactam is available for clinical use in combination with ceftazidime as an IV formulation. A formulation for oral use is currently being developed. Compared with clavulanic acid, sulbactam, and tazobactam, avibactam provides excellent inhibition of the clinically relevant class A and C β-lactamases such as ESBLs, KPCs, and AmpC β-lactamases from *Enterobacter* spp. and *Pseudomonas aeruginosa.* In addition, avibactam follows a different mechanism of inhibition than the previous β-lactamase inhibitors (BLIs). Avibactam binds in a covalent, but reversible manner to most β-lactamases tested, followed by the regeneration of active enzyme and intact inhibitor via deacylation and recyclization of the 5-membered urea ring of avibactam [7]. Avibactam was the first of a new series of β-lactamase inhibitor to receive US FDA approval as the combination ceftazidime-avibactam [8].

Using *in vitro* hollow fiber and *in vivo* mouse models of infection, the pharmacokinetic/pharmacodynamic (PK/PD) index for avibactam in combination with ceftazidime was shown to be best described by the *%fT* that avibactam exceeded a required critical concentration threshold (C_T) (i.e., *%fT*>C_T), and a minimum C_T of 0.5 mg/L avibactam was shown to be appropriate for the avibactam Enterobacterales PK/PD target [9,10]. Ceftazidime-avibactam was initially approved by the US FDA in February 2015 and by the European Medicines Agency (EMA) in June 2016 for the treatment of complicated urinary tract infection (cUTI) and for the treatment of complicated intra-abdominal infection (cIAI) when used in combination with metronidazole. Later, it received approval for treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) [11,12].

We evaluated the *in vitro* activity of ceftibuten-avibactam against molecularly characterized Enterobacterales that produced the most common β-lactamases and assessed the most appropriate avibactam concentration to be combined with ceftibuten for susceptibility testing.

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https://doi.org/10.1016/j.diagmicrobio.2022.115673

2. Methods

A total of 71 Enterobacterales isolates were analyzed, including 66 molecularly characterized clinical isolates and 5 quality control (QC) strains. The organism collection is shown in Table 1 and included isolates producing ESBLs (26; CTX-M, SHV, and TEM), KPCs (8), MBLs (7; NDM, VIM, and IMP), chromosomal AmpC (3), plasmid AmpC (3), OXA-48-like (2), K-1 (2), and SME (2) as well as isolates with porin alterations (5) and wild-type organisms (13).

The broth microdilution (BMD) tests were performed following CLSI standards using cation-adjusted Mueller-Hinton broth as well as CLSI QC recommendations [13]. Susceptibility test panels were produced at JMI Laboratories from freshly prepared antimicrobial stocks of ceftibuten, avibactam, and ceftazidime. The panel lots were stored at -70 °C or below until use. Ceftibuten was tested with avibactam at fixed concentrations of 2 mg/L, 4 mg/L, or 8 mg/L and fixed ceftazidime:avibactam ratios of 1:1 and 2:1. Ceftibuten was tested at dilution ranges of 0.015 to 32 mg/L when tested with avibactam and 0.06 to 128 mg/L when tested alone.

Resistance mechanisms were evaluated by whole genome sequencing (WGS), as previously described [14]. Organisms were predefined for the susceptibility to ceftibuten-avibactam based on produced β-lactamases and the known spectrum of avibactam β-lactamase inhibition. Ceftibuten-avibactam MIC distributions for the various combinations were grouped as follows:

- Inhibited (n = 46): Organisms that expressed β-lactamases that were completely inhibited by avibactam. This group included isolates producing derepressed chromosomal AmpC (3), plasmidic AmpC (3), ESBLs (26), K-1 (2), or serine carbapenemases (12).
- Not inhibited (n = 12): Organisms that contained at least 1 β-lactamase that was not inhibited by avibactam and/or expressed other resistance mechanisms to ceftibuten that were not affected by avibactam. This group either had metallo-β-lactamse (MBL) producers (7 isolates) or porin alterations but not ESBLs, K-1, serine carbapenemases, or AmpC enzymes (5).
- Wild-type organisms (n = 13): Organisms where WGS analysis did not reveal ESBLs, K-1, serine carbapenemases, AmpC enzymes, MBLs, porin alterations, or any known resistance mechanism that affects broad spectrum cephalosporins.

3. Results

The MIC distribution for the 3 groups of isolates (inhibited, not inhibited, and wild type) when testing ceftibuten combined with avibactam at various ratios or concentrations and avibactam alone are displayed in Fig. 1 and supplemental Figs. 1 to 3. The fixed avibactam concentration of 4 mg/L best separated ceftibuten-avibactam-susceptible from ceftibuten-avibactam-resistant isolates (Fig. 1B). Of note, 20 (28.2%) and 21 (29.6%) isolates showed avibactam MICs of 8 mg/L and 16 mg/L, respectively (supplemental Fig. 3).

When tested against isolates with β-lactamases inhibited by avibactam, MIC values were ≤4 mg/L for the 1:1 ratio and fixed 4 mg/L combinations. Three isolates had an MIC of 4 mg/L for the 1:1 ratio (supplemental Fig. 1). Only 1 isolate had a MIC of 4 mg/L for the fixed 4 mg/L combination (Fig. 1B). MIC values were as high as 8 mg/L for the 2:1 ratio and the fixed 2 mg/L concentration (Fig. 1C and supplemental Fig. 2). MIC values for the fixed 8 mg/L combination ranged from ≤0.015 to 1 mg/L, with 76.1% of isolates (35/46) showing an MIC of ≤0.015 mg/L. These results indicate that most isolates were inhibited by the avibactam component of the combination (Fig. 1C).

When testing isolates with porin alterations or β-lactamases not inhibited by avibactam, MIC values ranged from 4 mg/L to >32 mg/L for the 1:1 ratio and fixed 4 mg/L concentration combinations (Fig. 1B and supplemental Fig. 1) and from 8 mg/L to >32 mg/L for the 2:1 ratio and fixed 2 mg/L concentration (Fig. 1A and supplemental Fig. 2). MIC values for the fixed 8 mg/L combination ranged from ≤0.015 to >32 mg/L (Fig. 1C). Two isolates showed very low MICs for the fixed 8 mg/L combination. One isolate had an MIC of ≤0.015 mg/L for ceftibuten-avibactam at a fixed 8 mg/L concentration and an MIC of 8 mg/L for avibactam tested alone, while another isolate had an MIC of 0.12 mg/L for ceftibuten-avibactam at a fixed 8 mg/L and 16 mg/L concentration for avibactam tested alone (data not shown).

The MIC_{50}, MIC_{90}, and overall MIC range of ceftibuten against wild-type isolates was 0.25 mg/L, 0.5 m/L, and 0.06-1 mg/L, respectively (Table 1). MIC values decreased 4- to 8-fold when ceftibuten was combined with avibactam at 1:1 or 2:1 ratios ($MIC_{50/90}$, 0.03–0.06/0.12 mg/L) and 4- to ≥16-fold when ceftibuten was combined with avibactam at fixed 2, 4, or 8 mg/L concentrations ($MIC_{50/90}$, ≤0.015/0.12–0.25 mg/L; Table 1). Notably, 23.1% of wild-type isolates (3/13) exhibited an avibactam MIC of 8 mg/L and could be inhibited by the avibactam component of the combination if avibactam was combined at a fixed concentration of 8 mg/L.

The activities of ceftibuten-avibactam at fixed 4 mg/L and ceftibuten tested alone are summarized in Table 1 and Fig. 2. Ceftibuten-avibactam (fixed 4 mg/L) was very active against Enterobacterales producing ESBLs ($MIC_{50/90}$, 0.03/0.12 mg/L), including CTX-M-15 ($MIC_{50/90}$, 0.03/0.12 mg/L), KPC (MIC_{50}, 0.06 mg/L), derepressed AmpC (MIC range, 1–2 mg/L), plasmidic AmpC (MIC range, 0.12–0.5 mg/L), SME (MIC range, 0.06–0.12 mg/L), and OXA-48-like (MIC range, 0.5–4 mg/L). As expected, ceftibuten-avibactam exhibited limited activity against MBL producers (MIC_{50}, >32 mg/L) and isolates with porin alterations (MIC_{50}, 32 mg/L; Table 1 and Fig. 2).

Ceftibuten was highly active against SME producers (MIC, 0.12–0.25 mg/L) and showed some activity against KPC producers (MIC_{50}, 4 mg/L; MIC range, 2–16 mg/L) and ESBL producers ($MIC_{50/90}$, 4/64 mg/L), but it exhibited very limited activity against MBL, AmpC derepressed, plasmidic AmpC, and OXA-48-like producers (MIC_{50} values of 128 to >128 mg/L; Fig. 2).

4. Discussion

The objective of susceptibility testing is to discriminate between isolates that are likely to respond (susceptible) from those that are unlikely to respond (nonsusceptible) to therapy with the tested antimicrobial agent. When testing a β-lactam-β-lactamase inhibitor combination, the inhibitor concentration chosen should be able to suppress β-lactamase activity to restore the underlying activity of the parent β-lactam antibacterial. It has been shown that performing broth microdilution tests with ceftazidime in the presence of a fixed concentration of 4 mg/L of avibactam restored the MIC frequency distribution of ceftazidime against β-lactamase-producing isolates of Enterobacterales to reflect that of ceftazidime alone against wild-type isolates [15,16].

The results of this study demonstrated that the best method for determining ceftibuten-avibactam MIC values was to use doubling dilutions of ceftibuten in the presence of a fixed concentration of 4 mg/L of avibactam. MIC values for ceftibuten-avibactam were ≤4 mg/L against isolates with β-lactamases known to be inhibited by avibactam and ≥4 mg/L against isolates with β-lactamases that were not inhibited by avibactam or had porin alterations. Although similar results were obtained with the 1:1 ratio, the number of isolates with an MIC of 4 mg/L was higher in the inhibited group (3 isolates) when testing ceftibuten-avibactam at 1:1 ratio than with fixed 4 mg/L (1 isolate). When testing ceftibuten-avibactam at a 2:1 ratio and fixed 2 mg/L concentration, the MIC values for isolates with β-lactamases inhibited by avibactam were as high as 8 mg/L, which may result in false-resistant results. In contrast, isolates with β-lactamases that were not inhibited by avibactam (MBLs) or that had porin alterations

Table 1
Antimicrobial activity of ceftibuten-avibactam (fixed 4 mg/L) and ceftibuten against well-characterized organisms stratified by resistance mechanism.

β-Lactamase / Resistance mechanism (no. of isolates)	No. and cumulative % of isolates inhibited at ceftibuten-avibactam (fixed 4 mg/L) and ceftibuten MIC (mg/L) of:												
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
ESBL (26)													
Ceftibuten-avibactam (fix4)[a]	6 (23.1)	8 (53.8)	6 (76.9)	6 (100.0)									
Ceftibuten			1 (3.8)	0 (3.8)	0 (3.8)	4 (19.2)	7 (46.2)	0 (46.2)	4 (61.5)	1 (65.4)	4 (80.8)	2 (88.5)	3 (100.0)
CTX-M-15 (12)													
Ceftibuten-avibactam (fix4)[a]	3 (25.0)	4 (58.3)	3 (83.3)	2 (100.0)									
Ceftibuten						1 (8.3)	1 (16.7)	0 (16.7)	3 (41.7)	1 (50.0)	4 (83.3)	1 (91.7)	1 (100.0)
KPC (8)													
Ceftibuten-avibactam (fix4)[a]		1 (12.5)	3 (50.0)	2 (75.0)	2 (100.0)								
Ceftibuten								3 (37.5)	3 (75.0)	0 (75.0)	2 (100.0)		
MBL (7)													
Ceftibuten-avibactam (fix4)[a]										1 (14.3)	0 (14.3)	0 (14.3)	6 (100.0)
Ceftibuten										1 (14.3)	0 (14.3)	0 (14.3)	6 (100.0)
AmpC derepressed (3)													
Ceftibuten-avibactam (fix4)[a]							1 (33.3)	2 (100.0)					
Ceftibuten													3 (100.0)
Plasmid AmpC (3)													
Ceftibuten-avibactam (fix4)[a]				2 (66.7)	0 (66.7)	1 (100.0)							
Ceftibuten												1 (33.3)	2 (100.0)
SME (2)													
Ceftibuten-avibactam (fix4)[a]			1 (50.0)	1 (100.0)									
Ceftibuten				1 (50.0)	1 (100.0)								
OXA-48-like (2)													
Ceftibuten-avibactam (fix4)[a]						1 (50.0)	0 (50.0)	0 (50.0)	1 (100.0)				
Ceftibuten													2 (100.0)
K-1 (2)													
Ceftibuten-avibactam (fix4)[a]				2 (100.0)									
Ceftibuten							1 (50.0)		1 (100.0)				
Porin alterations (5)													
Ceftibuten-avibactam (fix4)[a]									1 (20.0)	0 (20.0)	1 (40.0)	1 (60.0)	2 (100.0)
Ceftibuten												1 (20.0)	4 (100.0)
Wild type (13)													
Ceftibuten-avibactam (fix4)[a]	8 (61.5)	0 (61.5)	3 (84.6)	0 (84.6)	1 (92.3)	1 (100.0)							
Ceftibuten			5 (38.5)	1 (46.2)	4 (76.9)	2 (92.3)	1 (100.0)						

[a] Avibactam at fixed concentration of 4 mg/L.

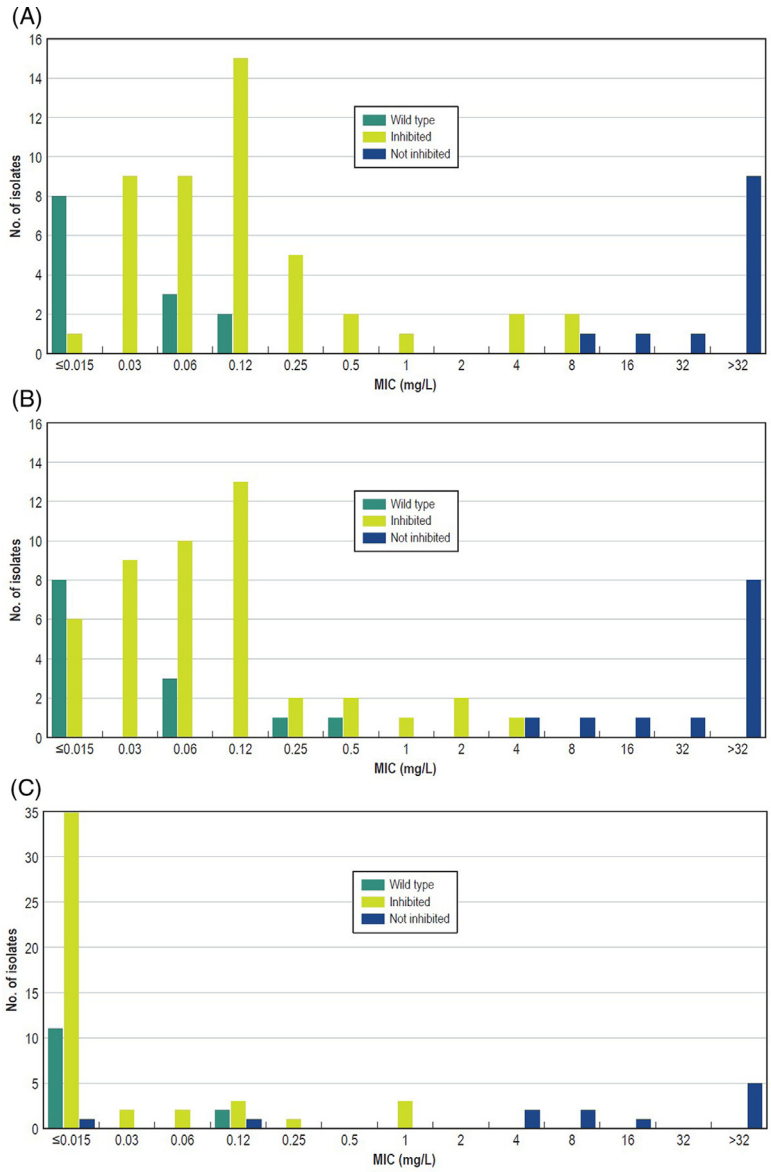

Fig. 1. MIC distributions of ceftibuten combined with avibactam at fixed concentration of 2 mg/L (A), 4 mg/L (B) and 8 mg/L (C) tested against isolates susceptible to ceftibuten (wild type), isolates harboring β-lactamases inhibited by avibactam (inhibited), and isolates harboring β-lactamases that were not inhibited by avibactam or had porin alterations (not inhibited).

showed low MIC values for ceftibuten-avibactam at a fixed 8 mg/L concentration or false-susceptible results.

Our results are in line with those previously reported for ceftazidime-avibactam. Bradford et al. evaluated ceftazidime in combination with avibactam at various constant concentrations (1, 2, 4, or 8 mg/L) or in ratios (1:1, 2:1, 4:1, 8:1, or 16:1) against 60 Enterobacterales and 27 *P. aeruginosa* isolates with characterized β-lactamases. The investigators concluded that the best method for determining ceftazidime-avibactam MIC values was to use doubling dilutions of ceftazidime in the presence of a constant concentration of 4 mg/L of avibactam [15].

In summary, ceftibuten-avibactam showed potent *in vitro* activity against *Enterobacterales* producing most clinically relevant β-lactamases, including ESBLs, KPCs, OXA-48-like, and AmpC, for which limited oral treatment options are available. The results of this investigation also showed that the ceftibuten-avibactam combination that best separated isolates with β-lactamases inhibited by avibactam from isolates with resistance mechanisms that are not affected by avibactam was the combination with avibactam at a fixed concentration of 4 mg/L. Our results, coupled with the results pharmacodynamic/pharmacokinetic and *in vivo* studies published by other investigators [17–19], support the clinical development of ceftibuten-avibactam for the treatment of complicated UTI.

Ethical approval

Not required.

Credit statement

Helio Sader: Conceptualization, Software, Validation, Formal Analysis, Data Curation, Writing – Original Draft, Visualization, Funding Acquisition. *Jill Lindley:* Methodology, Formal Analysis, Investigation, Data Curation, Writing – Review & Edit, Project Administration. *Lalitagauri M. Deshpande:* Methodology, Software, Validation, Investigation, Data Curation, Supervision. *Timothy Doyle: Methodology*, Formal Analysis, Resources, Writing – Review

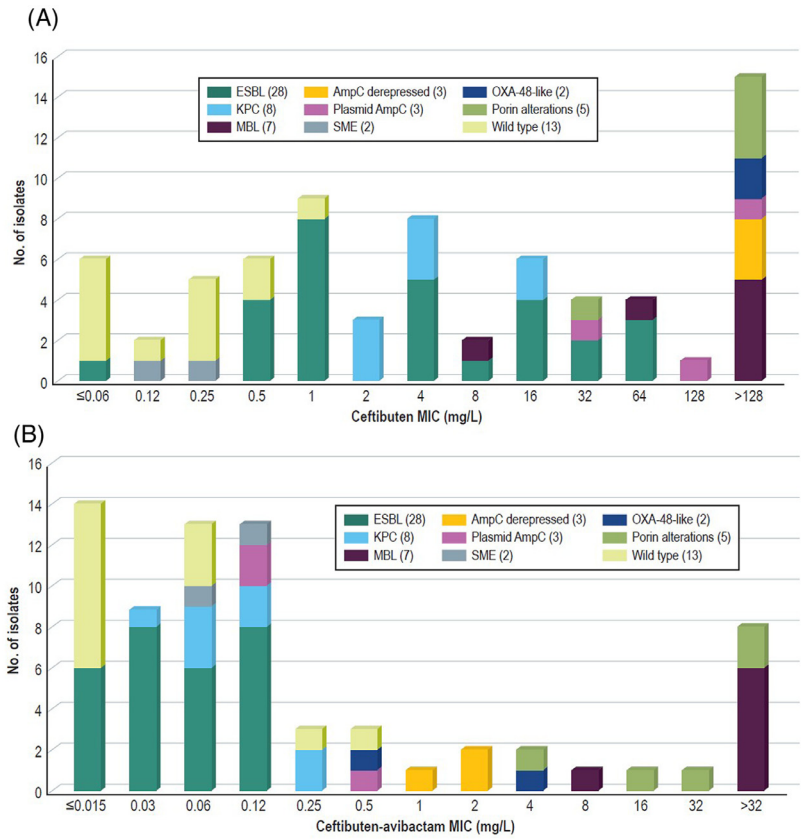

Fig. 2. Antimicrobial activity of ceftibuten (A) and ceftibuten-avibactam at fixed 4 mg/L (B) against well-characterized organisms stratified by resistance mechanism.

& Edit, Project Administration. *Mariana Castanheira:* Conceptualization, Validation, Resources, Writing – Review & Edit, Visualization, Supervision, Funding Acquisition.

Acknowledgments

The authors thank all participants of the SENTRY Antimicrobial Surveillance Program for their work in providing isolates. Editorial support was provided by Amy Chen, Sean DeVries, and Judy Oberholser at JMI Laboratories and was funded by Pfizer.

Funding

This study was supported by Pfizer Inc Helio S. Sader, Jill Lindley, Gauri M. Deshpande, Timothy Doyle, and Mariana Castanheira are employees of JMI Laboratories, which was paid consultant to Pfizer in connection with the development of this manuscript.

Conflicts of interest

None of the authors has a conflict of interest.

Author disclosure statement

JMI Laboratories contracted to perform services in 2018 to 2021 for Achaogen, Inc, Affinity Biosensors, Albany College of Pharmacy and Health Sciences, Allecra Therapeutics, Allergan, Amicrobe Advanced Biomaterials, Inc, American Proficiency Institute, AmpliPhi Biosciences Corp., Amplyx Pharma, Antabio, Arietis Corp., Arixa Pharmaceuticals, Inc, Artugen Therapeutics USA, Inc, Astellas Pharma Inc, Athelas, Becton, Basilea Pharmaceutica Ltd, Bayer AG, Becton, Beth Israel Deaconess Medical Center, BIDMC, bioMerieux, Inc, bioMerieux SA, BioVersys Ag, Boston Pharmaceuticals, Bugworks Research Inc, CEM-102 Pharmaceuticals, Cepheid, Cidara Therapeutics, Inc, Cipla, Contrafect, Cormedix Inc, Crestone, Inc, Curza, CXC7, DePuy Synthes, Destiny Pharma, Dickinson and Company, Discuva Ltd, Dr Falk Pharma GmbH, Emery Pharma, Entasis Therapeutics, Eurofarma Laboratorios SA, Fedora Pharmaceutical, F. Hoffmann-La Roche Ltd, Fimbrion Therapeutics, US Food and Drug Administration, Fox Chase Chemical Diversity Center, Inc, Gateway Pharmaceutical LLC, GenePOC Inc, Geom Therapeutics, Inc, GlaxoSmithKline plc, Guardian Therapeutics, Hardy Diagnostics, Harvard University, Helperby, HiMedia Laboratories, ICON plc, Idorsia Pharmaceuticals Ltd, IHMA, Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences, KBP Biosciences, Laboratory Specialists, Inc, Luminex, Matrivax, Mayo Clinic, Medpace, Meiji Seika Pharma Co, Ltd, Melinta Therapeutics, Inc, Menarini, Merck & Co, Inc, Meridian Bioscience Inc, Micromyx, Microchem Laboratory, MicuRx Pharmaceutics, Inc, Mutabilis Co, N8 Medical, Nabriva Therapeutics plc, National Institutes of Health, NAEJA-RGM, National University of Singapore, North Bristol NHS Trust, Novartis AG, Novome Biotechnologies, Oxoid Ltd, Paratek Pharmaceuticals, Inc, Pfizer, Inc, Pharmaceutical Product Development, LLC, Polyphor Ltd, Prokaryotics Inc, QPEX Biopharma, Inc, Ra Pharmaceuticals, Inc, Rhode Island Hospital, RIHML, Roche, Roivant Sciences, Ltd, Safeguard Biosystems, Salvat, Scynexis, Inc, SeLux Diagnostics, Inc, Shionogi and Co, Ltd, SinSa Labs, Specific Diagnostics, Spero Therapeutics, Summit Pharmaceuticals International Corp., SuperTrans Medical LT, Synlogic, T2 Biosystems, Taisho Pharmaceutical Co, Ltd, TenNor Therapeutics Ltd, Tetraphase Pharmaceuticals, The Medicines Company, The University of Queensland, Theravance Biopharma, Thermo Fisher Scientific, Tufts Medical Center, Universite de Sherbrooke, University of Colorado, University of Southern California-San Diego, University of Iowa, University of Iowa Hospitals

and Clinics, University of North Texas Health Science Center, University of Wisconsin, UNT System College of Pharmacy, URMC, UT Southwestern, VenatoRx, Viosera Therapeutics, Vyome Therapeutics Inc, Wayne State University, Wockhardt, Yukon Pharmaceuticals, Inc, Zai Lab, and Zavante Therapeutics, Inc There are no speakers' bureaus or stock options to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.diagmicrobio.2022.115673.

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