Smithson Valley, Texas, [3]Department of Medicine, Division of Cardiology, Stanford University, Stanford, California, [4]Department of Radiology, Department of Medicine, Stanford University, Stanford, California, [5]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford, California, [6]Centro de Pesquisas René Rachou, FIOCRUZ, Belo Horizonte, Brazil, [7]Division of Infectious Diseases and Geographic Medicine, Stanford University, Stanford, California

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Background. Trypanosoma cruzi is the etiologic agent of Chagas disease, which can result in severe cardiomyopathy. Trypanosoma cruzi is endemic to the Americas, and of particular importance in Latin America. In the United States and other nonendemic countries, rising case numbers have been observed. The only drugs available so far are benznidazole and nifurtimox, which have limited efficacy during chronic infection. We repurposed itraconazole, originally an antifungal, in combination with amiodarone, an antiarrhythmic, with the goal to interfere with Tc infection. Both drugs inhibit sterol synthesis, while amiodarone also inhibits calcium metabolism of *Trypanosoma cruzi*.

Methods. Human pluripotent stem cells (HiPSC) were differentiated to cardiomyocytes (HiPSC-CM). Vero cells or HiPSC-CM were infected with the *T. cruzi* trypomastigotes Y strain in the presence of itraconazole and/or amiodarone. After 48 hours, infection and multiplication were evaluated by Giemsa stain. Benznidazole was used as a reference compound. Cell viability was verified by XTT assay.

Results. Itraconazole and amiodarone showed dose-dependent interference with *T. cruzi* infection of Vero cells or HiPSC-CM. The combination of itraconazole and amiodarone was more potent than the single substances, or benznidazole at therapeutic concentrations, without affecting host cell metabolism. In addition to effects on infection, itraconazole, or amiodarone affected *T. cruzi* multiplication. Here, itraconazole/amiodarone combinations were more potent than either alone, both, in Vero cells, and HiPSC-CM.

Conclusion. Our *in vitro* data suggest that a combination of itraconazole and amiodarone might serve as an effective new treatment option for Chagas disease, particularly cardiac involvement, in human and animal patients.

Disclosures. **All authors:** No reported disclosures.

1358. *In vitro* Activity of Ceftazidime–Avibactam and Comparator Agents Against *Pseudomonas aeruginosa* Causing Intra-Abdominal, Lower Respiratory, and Urinary Tract Infections Collected in Latin America as Part of the INFORM Global Surveillance Program, 2012–2016

Mark Wise, PhD[1]; Krystyna Kazmierczak, PhD[1]; Gregory G. Stone, PhD[2] and Dan Sahm, PhD[3]; [1]IHMA, Inc., Schaumburg, Illinois, [2]Pfizer, Inc., New York, New York, [3]International Health Management Associates, Inc., Schaumburg, Illinois

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Background. The non-β-lactam β-lactamase inhibitor avibactam (AVI) is active against class A, C, and some class D β-lactamases, in combination with ceftazidime (CAZ) has been approved by the FDA and EMA for treatment of intra-abdominal infections (IAI), lower respiratory tract infections (LRTI), and urinary tract infections (UTI). This study reports on the *in vitro* activity of (CAZ-AVI) and comparators vs. *P. aeruginosa* collected from IAIs, LRTIs, and UTIs in Latin America as part of the INFORM surveillance study from 2012 to 2016.

Methods. For INFORM surveillance over 2012–2016 in Latin America, 1,595 nonduplicate *P. aeruginosa* isolates linked to IAIs, LRTIs, and UTIs were collected from 26 clinical sites in six countries. Susceptibility testing was done using broth microdilution according to CLSI guidelines and using CLSI 2018 breakpoints. CAZ was tested with AVI at a fixed concentration of 4 mg/mL. Meropenem (MEM) nonsusceptible organisms were screened for β-lactamase genes by PCR.

Results. Among the full collection of *P. aeruginosa*, CAZ-AVI showed consistently higher % susceptibilities than all comparators except for colistin (CST) for all infection sources. The addition of AVI to CAZ resulted in an increase in susceptibility ranging from 14.2% (IAI) to 19.5% (UTI). Against the non-metallo-β-lactamase (MBL) harboring subset, CAZ-AVI showed extremely potent activity (MIC_{90}, 8 mg/mL) for all infection sources. In this subset, the activity of CAZ-AVI approached that of colistin for IAIs (susceptibility of 93.3% vs. 96.4%, respectively).

Organism/Phenotype/Infection Source (*n*)	Drug (MIC90 [µg/mL]/% Susceptible)							
	CAZ-AVI		CAZ		MEM		CST	
P. aeruginosa, All sources (1595)[a]	16	86.0	64	68.7	>8	61.9	2	96.2
IAI (295)	32	85.1	64	70.9	>8	62.4	2	96.7
LRTI (942)	16	86.8	128	69.3	>8	60.7	2	96.3
UTI (358)	32	84.6	64	65.1	>8	64.8	2	95.8
P aeruginosa MBL-negative, All sources (1488)[b]	8	91.9	64	73.5	>8	66.1	2	96.1
IAI (269)	8	93.3	64	77.7	>8	68.0	2	96.4
LRTI (889)	8	91.8	64	73.3	>8	64.0	2	96.0
UTI (330)	8	91.2	64	70.3	>8	70.3	2	96.2

% susceptible defined using CLSI 2018 breakpoints.

[a]CST not tested in 2012 or 2013; totals for IAI, *n* = 215; LRTI, *n* = 721; UTI, *n* = 286.

[b]CST not tested in 2012 or 2013; totals for IAI, *n* = 196; LRTI, *n* = 677; UTI, *n* = 260.

Conclusion. CAZ-AVI demonstrated very good *in vitro* activity against *P. aeruginosa* isolates, especially those without MBLs. More isolates were susceptible to CAZ-AVI than to MEM for all infection types.

Disclosures. **M. Wise**, Pfizer Inc.: Consultant, Consulting fee. IHMA, Inc.: Employee, Salary. **K. Kazmierczak**, Pfizer Inc.: Consultant, Consulting fee. IHMA, Inc.: Employee, Salary. **G. G. Stone**, Pfizer Inc.: Employee, Salary. AstraZeneca: Former Employee and Shareholder, Salary. **D. Sahm**, Pfizer Inc.: Consultant, Consulting fee. IHMA, Inc.: Employee, Salary.

1359. Activity of Meropenem/Nacubactam Combination Against Gram-Negative Clinical Isolates: ROSCO Global Surveillance 2017

Rusudan Okujava, PhD[1]; Fernando Garcia-Alcalde, PhD[1]; Andreas Haldimann, PhD[1]; Claudia Zampaloni, PhD[1]; Ian Morrissey, PhD[2]; Sophie Magnet, PhD[2]; Nimmi Kothari, MSc[2]; Ian Harding, PhD[3] and Kenneth Bradley, PhD[1]; [1]Roche Pharma Research and Early Development, Immunology, Inflammation and Infectious Diseases, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland, [2]IHMA Europe Sàrl, Monthey, Switzerland, [3]Micron Research Ltd., Ely, Cambs, UK

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Background. Nacubactam (NAC, OP0595, RG6080) is a novel member of the diazabicyclooctane inhibitor family with a dual mode of action, acting as a β-lactamase inhibitor and an antibacterial agent by means of PBP2 inactivation. NAC restores and extends the activity of β-lactam antibiotics, such as meropenem (MEM), when used in combination against a variety of carbapenem-resistant *Enterobacteriaceae* (CRE). The first year results of the ROSCO surveillance study for MEM/NAC against contemporary clinical isolates are presented here.

Methods. Isolates (*n* = 4,695) collected in 2017 from 50 sites in the United States and European hospitals included 30 different species of *Enterobacteriaceae* (EB, *n* = 3,306), *Pseudomonas* spp. (*n* = 960) and *Acinetobacter* spp. (*n* = 429). The predominant species of EB are shown in figure below. MICs were determined by broth microdilution following CLSI methodology for MEM/NAC at a fixed 1:1 ratio (w:w) and by titrating MEM with a constant concentration of NAC at 4 mg/L. Results were compared with MIC values of MEM and NAC alone and standard of care antibiotics, including ceftazidime/avibactam (CAZ/AVI).

Results. $MIC_{50/90}$ for MEM, NAC, and MEM/NAC against all EB isolates and by species are shown in the figure below. NAC alone displayed a bimodal MIC distribution for EB, with a prominent separation at ≤4 mg/L. MEM/NAC 1:1 inhibited 99.5, 99.7, and 99.9% of the 3,306 EB isolates tested, at ≤2, ≤4, and ≤8 mg/L, respectively; while MEM inhibited 96.5, 96.8, and 97.3% of the isolates at the same concentrations. Of 117 (3.5% of total EB) MEM nonsusceptible (by EUCAST) and multidrug resistant (MDR, by Magiorakos AP, et al., 2012) EB, 87.2, 92.3, and 96.6% were inhibited by MEM/NAC 1:1 at ≤2, ≤4, and ≤8 mg/L, respectively. Additionally, MEM/NAC1:1 displayed MIC ≤8 mg/L for 33 out of 37 CAZ/AVI-resistant MDR EB isolates. MEM/NAC had a similar activity to MEM alone against *Pseudomonas* spp. and *Acinetobacter* spp.

Species	$MIC_{50/90}$ (mg/L)				
	MEM	MEM/NAC 1:1	MEM/NAC (4 mg/L)	CAZ/AVI (4 mg/L)	NAC
Enterobacteriaceae, n=3306	0.03/0.06	0.03/0.06	≤0.004/0.03	0.12/0.5	2/>32
E. coli, n=956	0.03/0.03	0.015/0.03	≤0.004/≤0.004	0.06/0.25	1/2
K. pneumoniae, n=892	0.03/4	0.03/0.5	≤0.004/0.015	0.12/0.5	4/>32
S. marcescens, n=414	0.06/0.12	0.06/0.12	0.03/0.06	0.25/0.5	>32/>32
E. cloacae, n=268	0.03/0.12	0.03/0.12	≤0.004/≤0.004	0.25/1	2/4
C. freundii, n=108	0.03/0.06	0.03/0.06	≤0.004/0.008	0.12/0.5	2/32
Pseudomonas spp., n=960	0.5/8	0.5/8	0.25/8	2/8	>32/>32
Acinetobacter spp., n=429	1/>32	1/>32	1/>32	16/>32	>32/>32

MIC for MEM/NAC combination is recorded as MEM concentration
MEM= meropenem, NAC= nacubactam, CAZ/AVI= ceftazidime/avibactam (avibactam fixed at 4 mg/L)

Conclusion. MEM/NAC combination shows excellent *in vitro* activity against current clinical EB isolates and the potential to extend MEM activity to MDR, MEM nonsusceptible and CAZ/AVI-resistant isolates, which supports the continued clinical development of MEM/NAC for infections caused by CREs. This project has been funded in part under HHS BARDA Contract HHSO100201600038C.

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1360. Antimicrobial Activity of Cefepime in Combination with VNRX-5133 Against a Global Collection of *Enterobacteriaceae* Including Resistant Phenotypes

Meredith Hackel, Ph.D[1] and Dan Sahm, PhD[2]; [1]IHMA, Inc., Schaumburg, Illinois, [2]International Health Management Associates, Inc., Schaumburg, Illinois

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Background. VNRX-5133 is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and