AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Surveillance of Omadacycline Activity against Clinical Isolates from a Global Collection (North America, Europe, Latin America, Asia-Western Pacific), 2010-2011

Michael A. Pfaller,[a,b] Michael D. Huband,[a] Paul R. Rhomberg,[a] Robert K. Flamm[a]

JMI Laboratories, North Liberty, Iowa, USA[a]; University of Iowa, Iowa City, Iowa, USA[b]

ABSTRACT Omadacycline is a broad-spectrum aminomethylcycline in late-stage clinical development for the treatment of acute bacterial skin and skin structure infections and community-acquired pneumonia as an oral and an intravenous once-daily formulation. In this study, omadacycline and comparators were tested against 69,246 nonduplicate bacterial isolates collected prospectively during 2010 and 2011 from medical centers in Asia-Pacific (11,397 isolates), Europe (23,490 isolates), Latin America (8,038 isolates), and North America (26,321 isolates). Omadacycline was tested by broth microdilution following Clinical and Laboratory Standards Institute M07-A10 (2015) methods. A total of 99.9% of *Staphylococcus aureus* isolates were inhibited by ≤2 μg/ml of omadacycline ($MIC_{50/90}$, 0.12/0.25 μg/ml), including 100.0% of methicillin-susceptible *S. aureus* isolates and 99.8% of methicillin-resistant *S. aureus* isolates. Omadacycline potencies were comparable for *Streptococcus pneumoniae* ($MIC_{50/90}$, 0.06/0.06 μg/ml), viridans group streptococci ($MIC_{50/90}$, 0.06/0.12 μg/ml), and beta-hemolytic streptococci ($MIC_{50/90}$, 0.06/0.12 μg/ml) regardless of species and susceptibility to penicillin. Omadacycline was active against *Enterobacteriaceae* and was most active against *Escherichia coli* ($MIC_{50/90}$, 0.5/2 μg/ml), *Enterobacter aerogenes* ($MIC_{50/90}$, 2/4 μg/ml), *Klebsiella oxytoca* ($MIC_{50/90}$, 1/4 μg/ml), and *Citrobacter* spp. ($MIC_{50/90}$, 1/4 μg/ml). Omadacycline was active against *Haemophilus influenzae* ($MIC_{50/90}$, 1/1 μg/ml) regardless of β-lactamase status and against *Moraxella catarrhalis* ($MIC_{50/90}$, 0.12/0.25 μg/ml). The potent activity of omadacycline against Gram-positive and Gram-negative bacteria indicates that omadacycline merits further study in serious infections in which multidrug resistance and mixed Gram-positive and Gram-negative infections may be a concern.

KEYWORDS aminomethylcycline, omadacycline, resistance, surveillance

Received 4 January 2017 **Returned for modification** 24 January 2017 **Accepted** 13 February 2017

Accepted manuscript posted online 21 February 2017

Citation Pfaller MA, Huband MD, Rhomberg PR, Flamm RK. 2017. Surveillance of omadacycline activity against clinical isolates from a global collection (North America, Europe, Latin America, Asia-Western Pacific), 2010-2011. Antimicrob Agents Chemother 61:e00018-17. https://doi.org/10.1128/AAC.00018-17.

Address correspondence to Robert K. Flamm, robert-flamm@jmilabs.com.

Antimicrobial resistance (AMR) is a global problem that requires a coordinated response to prevent further erosion of the ability to address established and emerging threats to human health (1). In the United States, AMR infections cost an estimated additional $20 billion annually and associated production losses of $35 billion per year (2). In the United Kingdom, it is estimated that drug-resistant infections might account for 10 million deaths per year by 2050, with total costs of $100 trillion in lost output (1). Collection of AMR surveillance and antibiotic consumption data is an essential approach to both defining the scope of the resistance problem and developing interventions that improve appropriate use of antibiotics and decrease resistance selection pressure (1, 3). Another important effort is to understand the mechanisms of resistance whereby bacteria avoid the effects of antibiotics and to use this information to develop new agents, or modify older agents, such that potent activity is retained against the key target pathogens (4–6).

Tetracyclines are broad-spectrum agents with activity against Gram-positive cocci (GPC) and Gram-negative bacilli (GNB), as well as intracellular *Chlamydia*, *Mycoplasma*, and *Rickettsia* and both protozoan and helminthic parasites (7). Tetracyclines have been used extensively in clinical and veterinary medicine and in agriculture and for a variety of noninfectious conditions (e.g., acne) for many years (7, 8). Broad use of tetracyclines has resulted in emergence of tetracycline-resistant bacteria and limited the use of the older members of this class (tetracycline, doxycycline, and minocycline) in treating bacterial disease (7, 8). A great deal is known about resistance mechanisms that bacterial strains have developed to the tetracyclines. Genes encoding for efflux pumps and ribosomal protection proteins have been described in both GPC and GNB and confer resistance to tetracycline, doxycycline, and minocycline (7–10). Chemical modification of minocycline has led to the development of tigecycline, a glycylcycline (11), and omadacycline, an aminomethylcycline (9), both of which specifically overcome tetracycline resistance mechanisms and are not affected by resistance to other classes of antibiotics (8, 9, 11).

Omadacycline is a semisynthetic derivative of minocycline and the first member of the novel aminomethylcycline class (9, 12, 13). Similar to the older tetracyclines (doxycycline, minocycline, and tetracycline), omadacycline binds to the 30S ribosomal subunit of target GPC and GNB with resultant inhibition of protein synthesis (7, 9, 12). Notably, omadacycline remains active against ribosomal protection and efflux tetracycline resistance genes (8, 9, 13). Omadacycline also maintains its activity against difficult-to-treat pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Enterobacteriaceae* strains that produce a wide array of extended-spectrum β-lactamases (ESBLs) and carbapenemases, in addition to multidrug-resistant (resistant to $\geq$3 classes of agents) strains of *Acinetobacter* spp. and *Stenotrophomonas maltophilia* (8). Omadacycline does not have useful activity against *Pseudomonas aeruginosa* (8). Omadacycline was shown to be noninferior to linezolid in a phase 2 study of the treatment of acute bacterial skin and skin structure infections (ABSSSI) (14), and phase 3 studies for treatment of ABSSSI and community-acquired bacterial pneumonia (CABP) are ongoing and nearing completion (8). A phase 1B study of omadacycline for treatment of uncomplicated urinary tract infections (UTIs) reported positive top-line pharmacokinetic proof-of-principle data in November 2016 (Paratek Pharmaceuticals, unpublished data).

In the present study, we evaluated the antimicrobial activity of omadacycline to establish its baseline activity against isolates of GPC and GNB collected in 2010 and 2011 from individual medical centers in the Asia-Pacific (APAC) region (including China, Australia, and New Zealand), Europe (EU), Latin America (LA), and North America (NA) as part of the SENTRY Antimicrobial Surveillance Program. Evaluations of resistant subsets for most of the pathogen groups were included in the analysis.

A total of 69,246 nonduplicate bacterial isolates were collected prospectively from medical centers located in the APAC region (42 sites, 11,397 isolates), EU (45 sites, 23,490 isolates), LA (14 sites, 8,038 isolates), and NA (46 sites, 26,321 isolates) for the years 2010 and 2011. All organisms were isolated from hospitalized patients with bloodstream infection (22,791 isolates), community-acquired respiratory tract infection (RTI) (8,693 isolates), hospital-associated RTI (9,282 isolates), ABSSSI (10,755 isolates), or another type of infection (17,725 isolates). Isolates were identified to the species level at each participating medical center, and all identifications were confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) using the Vitek 2 system (bioMérieux, Hazelwood, MO, USA) or matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker, Billerica, MA, USA), when necessary.

MIC values were determined by the monitoring laboratory (JMI Laboratories) using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (15). The susceptibility testing for omadacycline for 2010 and 2011 surveillance was done with dry-form panels manufactured by TREK (Oakwood Village, OH, USA). Upon receipt of the panels at the monitoring laboratory (JMI Laboratories), each batch

of panels was tested against the appropriate CLSI quality control (QC) organisms in triplicate, and all MIC values were within the established testing range (16). The quality of results was further ensured by concurrent testing of CLSI quality control organisms (strains *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *E. coli* ATCC 25922, and *H. influenzae* ATCC 49247) on each day of testing. For the 2010 and 2011 surveillance years, respectively, 99.4% (489/492) and 98.7% (528/535) of omadacycline results were in range, and repeat testing provided in-range results. QC and interpretation of results were performed in accordance with CLSI M100-S26 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2016 guidelines (16, 17). *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* isolates were grouped as an "ESBL screening-positive (SP) phenotype" based on the CLSI screening criteria for potential ESBL production (i.e., a ceftazidime and/or ceftriaxone and/or aztreonam MIC of >1 μg/ml) (16) for the purpose of analyzing susceptibility testing results. Although other β-lactamases, such as AmpC and *Klebsiella pneumoniae* carbapenemase (KPC), may also produce an ESBL SP phenotype, these strains were grouped together because they demonstrate resistance to various broad-spectrum β-lactam compounds. Isolates of the *Enterobacter cloacae* species complex (SC) were classified as ceftazidime susceptible (MIC, ≤4 μg/ml) and ceftazidime nonsusceptible (NS) (MIC, ≥8 μg/ml).

The 69,246 isolates tested included 18,577 *S. aureus* isolates, 2,992 coagulase-negative staphylococcus (CoNS) isolates, 5,519 *Enterococcus* species isolates, 1,955 *Enterococcus faecium* isolates, 6,253 *S. pneumoniae* isolates, 1,538 viridans group streptococcus isolates, 3,196 beta-hemolytic streptococcus isolates (including 1,576 *Streptococcus* pyogenes isolates, 1,570 *Streptococcus* agalactiae isolates, and 50 other beta-hemolytic isolates), 20,305 *Enterobacteriaceae* isolates (including 8,519 *E. coli* isolates, 4,181 *K. pneumoniae* isolates, 1,978 *Enterobacter cloacae* SC isolates, 816 *Citrobacter* species isolates, 846 indole-positive *Proteus* species isolates, 1,292 *Serratia* species isolates, and 204 *Salmonella* species isolates), 2,101 *Acinetobacter baumannii-Acinetobacter calcoaceticus* species complex isolates, 604 *Stenotrophomonas maltophilia* isolates, 3,383 *Haemophilus influenzae* isolates, and 1,226 *Moraxella catarrhalis* isolates (Table 1). The frequency of key resistant phenotypes included 7,741 (41.7%) MRSA isolates, 2,155 (72.0%) methicillin-resistant (MR) CoNS isolates, 936 (47.9%) vancomycin-nonsusceptible *E. faecium* isolates, 1,466 (23.4%) penicillin-resistant *S. pneumoniae* isolates, 1,947 (22.9%) ESBL SP phenotype *E. coli* isolates, 1,475 (35.3%) ESBL SP phenotype *K. pneumoniae* isolates, and 622 (31.4%) ceftazidime-NS *E. cloacae* SC isolates (Table 1).

The MIC distributions for each organism or organism group from the 147 participating medical centers are shown in Table 1. Although the isolates were tested in 2010 and 2011, the omadacycline MIC values for the key target pathogens establish a baseline level of activity for omadacycline. Omadacycline was very potent when tested against *S. aureus* isolates (18,577 isolates tested; $MIC_{50/90}$, 0.12/0.25 μg/ml) (Table 1). Of these, 18,560 (99.9%) isolates were inhibited by ≤2 μg/ml of omadacycline (MIC range, ≤0.015 to 4 μg/ml), including 100.0% of methicillin-susceptible *S. aureus* (MSSA) and 99.8% of MRSA isolates (Table 1). All CoNS isolates were susceptible to omadacycline at ≤2 μg/ml ($MIC_{50/90}$, 0.25/1 μg/ml).

Omadacycline was slightly more active against *E. faecium* ($MIC_{50/90}$, 0.06/0.12 μg/ml) than against other *Enterococcus* spp. ($MIC_{50/90}$, 0.06/0.25 μg/ml), and its activity was not adversely affected by vancomycin resistance when tested against organisms with resistance to this agent (Table 1). The potencies of omadacycline against *S. pneumoniae* isolates ($MIC_{50/90}$, 0.06/0.06 μg/ml), viridans group streptococci ($MIC_{50/90}$, 0.06/0.12 μg/ml), and beta-hemolytic streptococci ($MIC_{50/90}$, 0.06/0.12 μg/ml) were comparable regardless of species or susceptibility to penicillin (Table 1). All streptococcal isolates were inhibited by an MIC of ≤0.5 μg/ml of omadacycline.

Omadacycline also has useful activity against most *Enterobacteriaceae* isolates except those of *Proteus mirabilis* ($MIC_{50/90}$, 16/32 μg/ml) and indole-positive *Proteus* spp. ($MIC_{50/90}$, 8/32 μg/ml) (Table 1). Omadacycline was active against 20,305 *Enterobacteriaceae* isolates ($MIC_{50/90}$, 2/8 μg/ml; 86.3% inhibited at ≤4 μg/ml; Table 1). It was most

TABLE 1 Antimicrobial activity of omadacycline against the main organisms and organism groups of isolates studied

Organism/organism group (no. of isolates)	No. (cumulative %) of isolates at MIC (μg/ml) of:													MIC_{50}	MIC_{90}
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Staphylococcus aureus (18,577)	4 (<0.1)	100 (0.6)	1754 (10.0)	11833 (73.7)	3821 (94.3)	707 (98.1)	235 (99.3)	106 (99.9)	17 (100.0)					0.12	0.25
MSSA (10,836)	3 (<0.1)	71 (0.7)	1106 (10.9)	7099 (76.4)	2170 (96.4)	356 (99.7)	24 (99.9)	7 (100.0)						0.12	0.25
MRSA (7,741)	1 (<0.1)	29 (0.4)	648 (8.8)	4734 (69.9)	1651 (91.2)	351 (95.8)	211 (98.5)	99 (99.8)	17 (100.0)					0.12	0.25
CoNS (2,992)	17 (0.6)	121 (4.6)	751 (29.7)	589 (49.4)	385 (62.3)	771 (88.0)	339 (99.4)	19 (100.0)						0.25	1
MS-CoNS (837)	9 (1.1)	65 (8.8)	291 (43.6)	206 (68.2)	89 (78.9)	121 (93.3)	54 (99.8)	2 (100.0)						0.12	0.5
MR-CoNS (2,155)	8 (0.4)	56 (3.0)	460 (24.3)	383 (42.1)	296 (55.8)	650 (86.0)	285 (99.2)	17 (100.0)						0.25	1
Enterococcus spp. (5,519)	32 (0.6)	564 (10.8)	2189 (50.5)	1594 (79.3)	856 (94.9)	251 (99.4)	30 (99.9)	2 (>99.9)	1 (100.0)					0.06	0.25
Vancomycin susceptible (4,456)	24 (0.5)	437 (10.3)	1668 (47.8)	1331 (77.6)	755 (94.6)	221 (99.6)	17 (99.9)	2 (>99.9)	1 (100.0)					0.12	0.25
Vancomycin nonsusceptible (1,063)	8 (0.8)	127 (12.7)	521 (61.7)	263 (86.5)	101 (96.0)	30 (98.8)	13 (100.0)							0.06	0.25
Enterococcus faecalis (3,346)	21 (0.6)	266 (8.6)	1032 (39.4)	1097 (72.2)	697 (93.0)	212 (99.4)	18 (99.9)	2 (>99.9)	1 (100.0)					0.12	0.25
Vancomycin susceptible (3,254)	17 (0.5)	260 (8.5)	1010 (39.6)	1061 (72.2)	680 (93.1)	207 (99.4)	16 (99.9)	2 (>99.9)	1 (100.0)					0.12	0.25
Vancomycin nonsusceptible (92)	4 (4.3)	6 (10.9)	22 (34.8)	36 (73.9)	17 (92.4)	5 (97.8)	2 (100.0)							0.12	0.25
Enterococcus faecium (1,955)	8 (0.4)	269 (14.2)	1053 (68.0)	434 (90.2)	143 (97.5)	36 (99.4)	12 (100.0)							0.06	0.12
Vancomycin susceptible (1,019)	5 (0.5)	149 (15.1)	571 (71.1)	217 (92.4)	64 (98.7)	12 (99.9)	1 (100.0)							0.06	0.12
Vancomycin nonsusceptible (936)	3 (0.3)	120 (13.1)	482 (64.6)	217 (87.8)	79 (96.3)	24 (98.8)	11 (100.0)							0.06	0.25
Other *Enterococcus* spp. (218)	3 (1.4)	29 (14.7)	104 (62.4)	63 (91.3)	16 (98.6)	3 (100.0)								0.06	0.12
Streptococcus pneumoniae (6,253)	209 (3.3)	2402 (41.8)	3105 (91.4)	426 (98.2)	88 (99.6)	23 (100.0)								0.06	0.06
Penicillin susceptible (≤0.06) (3,747)	157 (4.2)	1573 (46.2)	1724 (92.2)	237 (98.5)	46 (99.7)	10 (100.0)								0.06	0.06
Penicillin intermediate (≥0.12 and ≤1) (1,040)	30 (2.9)	392 (40.6)	541 (92.6)	64 (98.8)	11 (99.8)	2 (100.0)								0.06	0.06
Penicillin resistant (≥2) (1,466)	22 (1.5)	437 (31.3)	840 (88.6)	125 (97.1)	31 (99.2)	11 (100.0)								0.06	0.12
Viridans group streptococci (1,538)	85 (5.5)	528 (39.9)	629 (80.8)	235 (96.0)	55 (99.6)	6 (100.0)								0.06	0.12
Beta-hemolytic streptococci (3,196)	8 (0.3)	740 (23.4)	1695 (76.4)	694 (98.2)	52 (99.8)	7 (100.0)								0.06	0.12
Streptococcus pyogenes (1,576)	3 (0.2)	547 (34.9)	898 (91.9)	114 (99.1)	11 (99.8)	3 (100.0)								0.06	0.06
Streptococcus agalactiae (1,570)	5 (0.3)	186 (12.2)	776 (61.6)	567 (97.7)	34 (99.9)	2 (100.0)								0.06	0.12
Other beta-hemolytic streptococci (50)	0 (0.0)	7 (14.0)	21 (56.0)	13 (82.0)	7 (96.0)	2 (100.0)								0.06	0.25
Enterobacteriaceae (20,305)		0 (0.0)	1 (<0.1)	17 (0.1)	582 (3.0)	4052 (22.9)	4840 (46.7)	5403 (73.4)	2638 (86.3)	1191 (92.2)	846 (96.4)	511 (98.9)	224 (100.0)	2	8
Escherichia coli (8,519)			0 (0.0)	15 (0.2)	561 (6.8)	3708 (50.3)	2612 (80.9)	1167 (94.6)	376 (99.1)	69 (99.9)	9 (>99.9)	2 (100.0)		0.5	2
ESBL-negative *Escherichia coli* (6,572)			0 (0.0)	10 (0.2)	495 (7.7)	3171 (55.9)	1938 (85.4)	713 (96.3)	205 (99.4)	35 (99.9)	4 (>99.9)	1 (100.0)		0.5	2
ESBL SP phenotype *Escherichia coli* (1,947)			0 (0.0)	5 (0.3)	66 (3.6)	537 (31.2)	674 (65.8)	454 (89.2)	171 (97.9)	34 (99.7)	5 (99.9)	1 (100.0)		1	4
Klebsiella pneumoniae (4,181)			0 (0.0)	1 (<0.1)	11 (0.3)	80 (2.2)	967 (25.3)	1908 (71.0)	648 (86.5)	310 (93.9)	159 (97.7)	66 (99.3)	31 (100.0)	2	8
ESBL-negative *Klebsiella pneumoniae* (2,706)			0 (0.0)	1 (<0.1)	5 (0.2)	59 (2.4)	743 (29.9)	1385 (81.0)	297 (92.0)	106 (95.9)	76 (98.7)	26 (99.7)	8 (100.0)	2	4
ESBL SP phenotype *Klebsiella pneumoniae* (1,475)				0 (0.0)	6 (0.4)	21 (1.8)	224 (17.0)	523 (52.5)	351 (76.3)	204 (90.1)	83 (95.7)	40 (98.4)	23 (100.0)	2	8
Klebsiella oxytoca (762)				0 (0.0)	3 (0.4)	21 (3.1)	440 (60.9)	212 (88.7)	44 (94.5)	30 (98.4)	11 (99.9)	1 (100.0)		1	4
Other *Klebsiella* spp. (94)					0 (0.0)	6 (6.4)	21 (28.7)	44 (75.5)	15 (91.5)	6 (97.9)	1 (98.9)	0 (98.9)	1 (100.0)	2	4

(Continued on following page)

TABLE 1 (Continued)

Organism/organism group (no. of isolates)	No. (cumulative %) of isolates at MIC (μg/ml) of:													MIC_{50}	MIC_{90}
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Enterobacter cloacae sp. complex (1,978)					0 (0.0)	16 (0.8)	272 (14.6)	1057 (68.0)	417 (89.1)	98 (94.0)	63 (97.2)	42 (99.3)	13 (100.0)	2	8
Ceftazidime-susceptible *Enterobacter cloacae* sp. complex (1,356)					0 (0.0)	13 (1.0)	218 (17.0)	774 (74.1)	264 (93.6)	45 (96.9)	25 (98.7)	12 (99.6)	5 (100.0)	2	4
Ceftazidime-nonsusceptible *Enterobacter cloacae* sp. complex (622)					0 (0.0)	3 (0.5)	54 (9.2)	283 (54.7)	153 (79.3)	53 (87.8)	38 (93.9)	30 (98.7)	8 (100.0)	2	16
Other *Enterobacter* spp. (658)		0 (0.0)	1 (0.2)	0 (0.2)	0 (0.2)	19 (3.0)	167 (28.4)	335 (79.3)	79 (91.3)	21 (94.5)	22 (97.9)	12 (99.7)	2 (100.0)	2	4
Citrobacter spp. (816)				0 (0.0)	4 (0.5)	139 (17.5)	282 (52.1)	249 (82.6)	93 (94.0)	29 (97.5)	12 (99.0)	6 (99.8)	2 (100.0)	1	4
Proteus mirabilis (PM) (949)						0 (0.0)	4 (0.4)	10 (1.5)	44 (6.1)	169 (23.9)	372 (63.1)	259 (90.4)	91 (100.0)	16	32
Indole-positive *Proteus* spp. (846)						0 (0.0)	8 (0.9)	42 (5.9)	189 (28.3)	281 (61.5)	164 (80.9)	93 (91.8)	69 (100.0)	8	32
Serratia marcescens (1,221)						0 (0.0)	15 (1.2)	274 (23.7)	687 (79.9)	170 (93.9)	30 (96.3)	30 (98.8)	15 (100.0)	4	8
Other *Serratia* spp. (71)				0 (0.0)	1 (1.4)	4 (7.0)	15 (28.2)	18 (53.5)	27 (91.5)	5 (98.6)	1 (100.0)			2	4
Salmonella spp. (204)			0 (0.0)	1 (0.5)	2 (1.5)	56 (28.9)	36 (46.6)	87 (89.2)	18 (98.0)	2 (99.0)	2 (100.0)			2	4
Acinetobacter baumannii-Acinetobacter calcoaceticus sp. complex (2,101)		0 (0.0)	23 (1.1)	150 (8.2)	137 (14.8)	186 (23.6)	275 (36.7)	642 (67.3)	509 (91.5)	149 (98.6)	23 (99.7)	6 (>99.9)	1 (100.0)	2	4
Other *Acinetobacter* spp. (292)	1 (0.3)	1 (0.7)	13 (5.1)	69 (28.8)	67 (51.7)	27 (61.0)	28 (70.5)	32 (81.5)	41 (95.5)	13 (100.0)				0.25	4
Pseudomonas aeruginosa (2,630)				0 (0.0)	1 (<0.1)	2 (0.1)	18 (0.8)	18 (1.5)	33 (2.7)	118 (7.2)	687 (33.3)	843 (65.4)	910 (100.0)	32	>32
Stenotrophomonas maltophilia (604)				0 (0.0)	2 (0.3)	22 (4.0)	87 (18.4)	236 (57.5)	146 (81.6)	77 (94.4)	26 (98.7)	7 (99.8)	1 (100.0)	2	8
Haemophilus influenzae (3,383)			1 (<0.1)	7 (0.2)	106 (3.4)	1512 (48.1)	1509 (92.7)	224 (99.3)	18 (99.8)	6 (100.0)				1	1
β-Lactamase-positive *Haemophilus influenzae* (736)				0 (0.0)	18 (2.4)	292 (42.1)	371 (92.5)	52 (99.6)	3 (100.0)					1	1
β-lactamase-negative *Haemophilus influenzae* (2,647)			1 (<0.1)	7 (0.3)	88 (3.6)	1220 (49.7)	1138 (92.7)	172 (99.2)	15 (99.8)	6 (100.0)				1	1
Moraxella catarrhalis (1,226)			174 (14.2)	782 (78.0)	225 (96.3)	40 (99.6)	5 (100.0)							0.12	0.25

active against *E. coli* ($MIC_{50/90}$, 0.5/2 μg/ml), *E. aerogenes* ($MIC_{50/90}$, 2/4 μg/ml; data not shown), *K. oxytoca* ($MIC_{50/90}$, 1/4 μg/ml), and *Citrobacter* spp. ($MIC_{50/90}$, 1/4 μg/ml) (Table 1). Omadacycline activity was somewhat greater against the non-ESBL SP phenotype than against the ESBL SP phenotype strains of *E. coli* ($MIC_{50/90}$, 0.5/2 versus 1/4 μg/ml, respectively) and *K. pneumoniae* ($MIC_{50/90}$, 2/4 versus 2/8 μg/ml, respectively). Against ceftazidime-NS *E. cloacae* isolates (MIC, ≥8 μg/ml; AmpC-derepressed phenotype isolates), omadacycline was less active ($MIC_{50/90}$, 2/16 μg/ml; 79.3% inhibited at ≤4 μg/ml) (Table 1) than it was against ceftazidime-susceptible isolates ($MIC_{50/90}$, 2/4 μg/ml; 93.6% inhibited at ≤4 μg/ml) (Table 1).

Omadacycline ($MIC_{50/90}$, 2/4 μg/ml) inhibited 91.5% of 2,101 *A. baumannii* isolates at ≤4 μg/ml (Table 1). Against a collection of other *Acinetobacter* species isolates (n = 292), omadacycline ($MIC_{50/90}$, 0.25/4 μg/ml) inhibited 95.5% of the isolates at ≤4 μg/ml (Table 1). Omadacycline demonstrated good *in vitro* activity against *S. maltophilia* ($MIC_{50/90}$, 2/8 μg/ml; 81.6% inhibited at ≤4 μg/ml) (Table 1). Omadacycline was not active against *P. aeruginosa* ($MIC_{50/90}$, 32/>32 μg/ml).

Omadacycline was equally active against β-lactamase-negative ($MIC_{50/90}$, 1/1 μg/ml) and β-lactamase-positive ($MIC_{50/90}$, 1/1 μg/ml) isolates of *H. influenzae* (Table 1). Omadacycline was also very active against the *M. catarrhalis* isolates tested ($MIC_{50/90}$, 0.12/0.25 μg/ml) (Table 1).

Antibiotic resistance is a growing problem worldwide (18). Active surveillance and antimicrobial stewardship efforts are essential for combating this threat to patient safety across all health care settings (3, 19). In the present survey, we have established the baseline *in vitro* susceptibility profiles of omadacycline for 69,246 isolates of GPC and GNB from medical centers in the APAC region, EU, LA, and NA for the years 2010 and 2011.

An additional approach to combating antimicrobial resistance is to develop antibacterials with novel mechanisms of action and greater potency against resistant strains of bacteria (4–6). Chemical modifications to minocycline produces omadacycline, which has several advantages over the older tetracyclines, such as doxycycline and minocycline, including a low propensity for selection of resistance, enhanced binding to the 30S ribosomal subunit, an ability to overcome tetracycline resistance mechanisms, lack of effect of other resistance mechanisms, availability as an intravenous or oral formulation, a prolonged half-life, and once-daily administration (8).

The data from the present survey document the *in vitro* activity of omadacycline against bacterial isolates from a global survey. Omadacycline was active against MRSA, MR-CoNS, VRE, viridans group streptococci, beta-hemolytic streptococci, and penicillin-resistant *S. pneumoniae* (Table 1). Omadacycline was also active against the ESBL SP phenotype strains of *E. coli* but less active against the ESBL SP phenotype strains of *K. pneumoniae* and ceftazidime-NS *E. cloacae*. Omadacycline demonstrated useful activity against *Acinetobacter* spp. and *S. maltophilia*.

These data build on information reported by previous investigators (8, 9, 12, 13) and indicate that omadacycline merits further study in the treatment of ABSSSI, CABP, and UTIs, where mixed GPC and GNB infections are common.

ACKNOWLEDGMENTS

This study was performed by JMI Laboratories and supported by Paratek Pharmaceuticals (King of Prussia, PA), which included funding for services related to preparing this article.

JMI Laboratories, Inc., has also received research and educational grants in 2014 to 2015 from Achaogen, Actavis, Actelion, Allergan, American Proficiency Institute (API), AmpliPhi, Anacor, Astellas, AstraZeneca, Basilea, BD, Cardeas, Cellceutix, CEM-102 Pharmaceuticals, Cempra, Cerexa, Cidara, CorMedix, Cubist, Debiopharm, Dipexium, Dong Wha, Durata, Enteris, Exela, Forest Research Institute, Furiex, Genentech, GSK, Helperby, ICPD, Janssen, Lannett, Longitude, Medpace, Meiji Seika Kasha, Melinta, Merck, Motif, Nabriva, Novartis, Pfizer, Pocared, PTC Therapeutics, Rempex, Roche, Salvat, Scynexis, Seachaid, Shionogi, Tetraphase, The Medicines Co., Theravance, Thermo Fisher, Vena-

toRx, Vertex, Wockhardt, Zavante, and some other corporations. In regard to speakers bureaus and stock options, we declare no conflicts.

REFERENCES

1. Queenan K, Hasler B, Rushton J. 2016. A One Health approach to antimicrobial resistance surveillance: is there a business case for it? Int J Antimicrob Agents 48:422–427. https://doi.org/10.1016/j.ijantimicag.2016.06.014.
2. Centers for Disease Control and Prevention. 2014. Transatlantic Taskforce on Antimicrobial Resistance: progress report. Centers for Disease Control and Prevention, Atlanta, GA. https://www.cdc.gov/drugresistance/pdf/tatfar-progress_report_2014.pdf.
3. Perez F, Villegas MV. 2015. The role of surveillance systems in confronting the global crisis of antibiotic-resistant bacteria. Curr Opin Infect Dis 28:375–383. https://doi.org/10.1097/QCO.0000000000000182.
4. Brogan DM, Mossialos E. 2013. Incentives for new antibiotics: the Options Market for Antibiotics (OMA) model. Glob Health 9:58. https://doi.org/10.1186/1744-8603-9-58.
5. Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP, Mueller A, Schaberle TF, Hughes DE, Epstein S, Jones M, Lazarides L, Steadman VA, Cohen DR, Felix CR, Fetterman KA, Millett WP, Nitti AG, Zullo AM, Chen C, Lewis K. 2015. A new antibiotic kills pathogens without detectable resistance. Nature 517:455–459. https://doi.org/10.1038/nature14098.
6. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, Bartlett JG, Edwards J, Jr. 2008. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 46:155–164. https://doi.org/10.1086/524891.
7. Roberts MC. 2003. Tetracycline therapy: update. Clin Infect Dis 36:462–467. https://doi.org/10.1086/367622.
8. Villano S, Steenbergen J, Loh E. 2016. Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections. Future Microbiol 11:1421–1434. https://doi.org/10.2217/fmb-2016-0100.
9. Honeyman L, Ismail M, Nelson ML, Bhatia B, Bowser TE, Chen J, Mechiche R, Ohemeng K, Verma AK, Cannon EP, Macone A, Tanaka SK, Levy S. 2015. Structure-activity relationship of the aminomethylcyclines and the discovery of omadacycline. Antimicrob Agents Chemother 59:7044–7053. https://doi.org/10.1128/AAC.01536-15.
10. Nelson ML, Levy SB. 2011. The history of the tetracyclines. Ann N Y Acad Sci 1241:17–32. https://doi.org/10.1111/j.1749-6632.2011.06354.x.
11. Pankey GA. 2005. Tigecycline. J Antimicrob Chemother 56:470–480. https://doi.org/10.1093/jac/dki248.
12. Draper MP, Weir S, Macone A, Donatelli J, Trieber CA, Tanaka SK, Levy SB. 2014. Mechanism of action of the novel aminomethylcycline antibiotic omadacycline. Antimicrob Agents Chemother 58:1279–1283. https://doi.org/10.1128/AAC.01066-13.
13. Macone AB, Caruso BK, Leahy RG, Donatelli J, Weir S, Draper MP, Tanaka SK, Levy SB. 2014. In vitro and in vivo antibacterial activities of omadacycline, a novel aminomethylcycline. Antimicrob Agents Chemother 58:1127–1135. https://doi.org/10.1128/AAC.01242-13.
14. Noel GJ, Draper MP, Hait H, Tanaka SK, Arbeit RD. 2012. A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother 56:5650–5654. https://doi.org/10.1128/AAC.00948-12.
15. CLSI. 2015. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—10th ed. CLSI document M07-A10. CLSI, Wayne, PA.
16. CLSI. 2016. Performance standards for antimicrobial susceptibility testing: 26th informational supplement. CLSI document M100-S26. CLSI, Wayne, PA.
17. EUCAST. 2016. Breakpoint tables for interpretation of MICs and zone diameters, version 6.0, January 2016. http://www.eucast.org/ast_of_bacteria/previous_versions_of_documents/.
18. Friedman ND, Temkin E, Carmeli Y. 2016. The negative impact of antibiotic resistance. Clin Microbiol Infect 22:416–422. https://doi.org/10.1016/j.cmi.2015.12.002.
19. Schuts EC, Hulscher ME, Mouton JW, Verduin CM, Stuart JW, Overdiek HW, van der Linden PD, Natsch S, Hertogh CM, Wolfs TF, Schouten JA, Kullberg BJ, Prins JM. 2016. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 16:847–856. https://doi.org/10.1016/S1473-3099(16)00065-7.