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In Vitro Activity of Omadacycline and Comparator Compounds against Gram-Positive Isolates Collected in the US During 2016 as Part of a Global Surveillance Program

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INTRODUCTION

- Omadacycline is a potent broad-spectrum aminomethylcycline protein synthesis inhibitor in late-stage clinical development (oral and intravenous formulations) for treating acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP)
- The spectrum of activity of omadacycline includes a broad range of gram-positive (staphylococci, streptococci, and enterococci) and gram-negative (*Haemophilus influenzae* and *Moraxella catarrhalis*) bacterial pathogens commonly associated with ABSSSI and CABP
- Omadacycline is highly active against gram-positive bacterial clinical isolates expressing common tetracycline-, penicillin/oxacillin-, fluoroquinolone-, and macrolide-resistance mechanisms that include *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), enterococci, and streptococci (*Streptococcus pneumoniae*, viridans group, and β-haemolytic streptococci)
- *In vitro* susceptibility results for omadacycline and comparator agents against a large collection of gram-positive bacterial clinical isolates collected from medical centers in the United States (US) participating in a global surveillance program during 2016 are presented

MATERIALS AND METHODS

- A total of 4,122 (non-duplicate) gram-positive bacterial isolates were collected from patients with multiple infection types in 30 medical centers in the US during 2016 and included 2,366 staphylococci, 1,252 streptococci, and 504 enterococci; 1 isolate per patient/infection episode was included
- Bacterial isolates were initially identified by the submitting laboratories and confirmed by JMI Laboratories using matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany)
- Susceptibility testing was performed according to CLSI (M07-A10, 2015) reference broth microdilution methodology, results were interpreted using CLSI (M100-S27; 2017) breakpoint interpretive criteria, and American Type Culture Collection quality control (QC) reference strains were tested concurrently including *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, and *Pseudomonas aeruginosa* ATCC 27853

RESULTS

- Cumulative percent inhibition data for omadacycline against staphylococci, streptococci, and enterococci including the percentage of 2016 US gram-positive surveillance isolates by organism/organism group are presented in Table 1 and Figure 1, respectively
- Omadacycline demonstrated potent *in vitro* activity against *S. aureus* isolates ($MIC_{50/90}$ 0.12/0.25 µg/mL) and retained a high level of activity against isolates displaying tetracycline (doxycycline and tetracycline), fluoroquinolone (levofloxacin), macrolide (erythromycin), lincosamide (clindamycin), and/or oxacillin resistance phenotypes with corresponding doxycycline, tetracycline, levofloxacin, erythromycin, clindamycin, and oxacillin *S. aureus* resistance rates of 0.2%, 3.4%, 36.5%, 51.4%, 15.2%, and 44.9%, respectively (Table 2)
- Against methicillin-resistant *S. aureus*, omadacycline (MIC_{90}, 0.25 µg/mL) was 2-fold more active than doxycycline (MIC_{90}, 0.5 µg/mL) and 4-fold more active than tetracycline (MIC_{90}, 1 µg/mL; Table 2)
- The highest rates of MRSA in the US occurred in the East South Central (54.6%), Middle Atlantic (52.1%), and South Atlantic (50.8%) census divisions, whereas the lowest rates of MRSA occurred in the Mountain (25.0%) and New England (29.5%) census divisions (Figure 2)
- Omadacycline was also very active against coagulase-negative staphylococci (CoNS) and methicillin-resistant CoNS (MR-CoNS) isolates with MIC_{90} values of 0.5 µg/mL (Table 2). Doxycycline (MIC_{90}, 4 µg/mL) and tetracycline (MIC_{90}, >8 µg/mL) were 8- and ≥16-fold less active than omadacycline against MR-CoNS (Table 2)
- Doxycycline, tetracycline, levofloxacin, erythromycin, and clindamycin resistance rates in CoNS from the US were 0.3%, 12.0%, 38.3%, 53.5%, and 29.7%, respectively, and increased to 0.5%, 18.4%, 60.5%, 67.0%, and 43.8%, respectively, in MR-CoNS (Table 2)
- *S. pneumoniae* isolates, including penicillin-resistant strains (PRSP), were highly susceptible to omadacycline ($MIC_{50/90}$, 0.06/0.06-0.12 µg/mL), whereas 19.7% of *S. pneumoniae* and 56.8% of PRSP isolates were resistant to tetracycline (MIC_{90}, >8 µg/mL; Table 2)
- Viridans group streptococci were inhibited by low concentrations of omadacycline ($MIC_{50/90}$, 0.06/0.12 µg/mL); however, tetracycline ($MIC_{50/90}$, 2/>8 µg/mL; 42.5% resistant), erythromycin ($MIC_{50/90}$, 0.03/>32 µg/mL; 45.3% resistant), and clindamycin ($MIC_{50/90}$, ≤0.25/>2 µg/mL; 15.1% resistant) were considerably less active (Table 2)

RESULTS (CONT.)

- Omadacycline ($MIC_{50/90}$, 0.06/0.12 µg/mL) was highly active against β-haemolytic streptococci, including *Streptococcus agalactiae*, *S. dysgalactiae*, and *S. pyogenes* that had high levels of resistance to tetracycline (46.9% resistant), clindamycin (17.2% resistant), and erythromycin (33.7% resistant; Table 2)
- Omadacycline was 2-fold more active against *Enterococcus faecium* ($MIC_{50/90}$ 0.06/0.12 µg/mL) compared to *E. faecalis* ($MIC_{50/90}$ 0.12/0.25 µg/mL), and its activity was unchanged against *E. faecalis* and *E. faecium* isolates displaying resistance to tetracycline (72.5% and 69.5% resistant, respectively) and vancomycin (4.3% and 66.5% resistant, respectively; Tables 1 and 2)

Figure 1 Incidence of gram-positive pathogens from the omadacycline 2016 US surveillance program

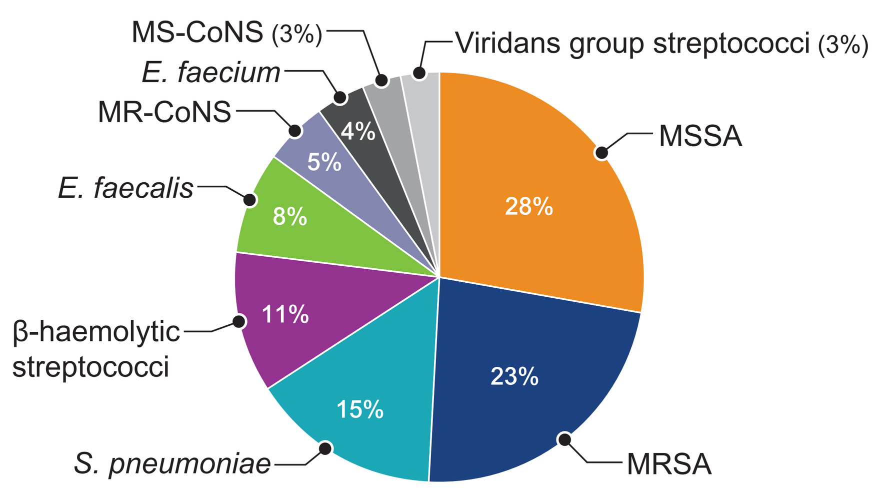
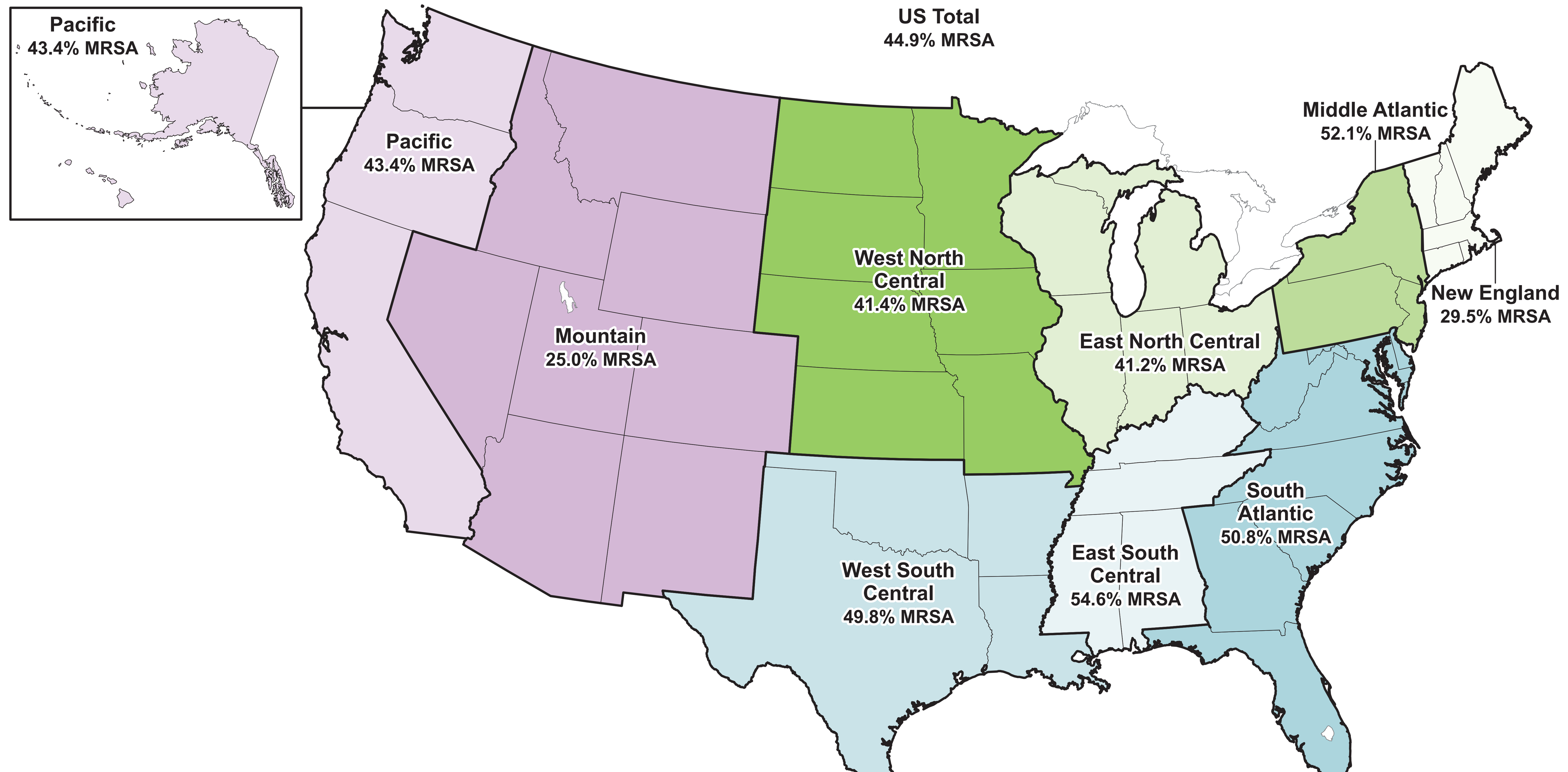


Figure 2 MRSA rates in the US by census division (2016)



CONCLUSIONS

- Omadacycline was highly active against *S. aureus* ($MIC_{50/90}$ 0.12/0.25 µg/mL) and CoNS ($MIC_{50/90}$ 0.12/0.5 µg/mL) isolates from the United States that included MRSA, MR-CoNS, and strains displaying resistance to doxycycline, tetracycline, levofloxacin, erythromycin, and/or clindamycin
- Streptococci, including penicillin-susceptible and -resistant *S. pneumoniae*, viridans group streptococci, and β-haemolytic streptococci, were inhibited by low levels of omadacycline ($MIC_{50/90}$ values of 0.06–0.12 µg/mL)
- Omadacycline remained highly active against tetracycline-resistant streptococci including penicillin-resistant *S. pneumoniae* (56.8% tetracycline-resistant), viridans group streptococci (42.5% tetracycline-resistant), and β-haemolytic streptococci (46.9% tetracycline-resistant)
- Omadacycline exhibited potent *in vitro* activity against vancomycin-susceptible and -resistant isolates of *E. faecalis* ($MIC_{50/90}$ 0.12/0.25 µg/mL) and *E. faecium* ($MIC_{50/90}$ 0.06/0.12 µg/mL), and tetracycline demonstrated little utility against *E. faecalis* (72.5% resistant) and *E. faecium* (69.5% resistant) isolates
- Results of this 2016 surveillance study support the continued development of omadacycline in infections where resistant isolates of staphylococci, streptococci, and enterococci are likely to occur, including ABSSSI and CABP

ACKNOWLEDGMENTS

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Clinical and Laboratory Standards Institute (2017). *M100-S27. Performance standards for antimicrobial susceptibility testing: 27th informational supplement.* Wayne, PA: CLSI.

Table 1 *In vitro* activity of omadacycline tested against 2016 gram-positive surveillance isolates from the United States

Organism / organism group (no. of isolates)	No. of isolates at MIC (µg/mL; cumulative %)[a] ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>	MIC_{50}	MIC_{90}
Staphylococcus aureus (2,050)	1 <0.1	47 2.3	818 42.2	839 83.2	**241** **94.9**	54 97.6	31 99.1	15 99.8	3 >99.9	1 100.0		0.12	0.25
MSSA (1,130)	1 0.1	24 2.2	444 41.5	491 85.0	**151** **98.3**	15 99.6	4 100.0					0.12	0.25
MRSA (920)	0 0.0	23 2.5	374 43.2	348 81.0	**90** **90.8**	39 95.0	27 97.9	15 99.6	3 99.9	1 100.0		0.12	0.25
Coagulase-negative staphylococci (316)[b]	4 1.3	47 16.1	79 41.1	64 61.4	63 81.3	**48** **96.5**	10 99.7	1 100.0				0.12	0.5
MS-CoNS (131)	2 1.5	34 27.5	50 65.6	23 83.2	**9** **90.1**	12 99.2	1 100.0					0.06	0.25
MR-CoNS (185)	2 1.1	13 8.1	29 23.8	41 45.9	54 75.1	**36** **94.6**	9 99.5	1 100.0				0.25	0.5
Enterococcus faecalis (328)	4 1.2	18 6.7	106 39.0	147 83.8	**47** **98.2**	6 100.0						0.12	0.25
Vancomycin-susceptible *Enterococcus faecalis* (314)	3 1.0	18 6.7	104 39.8	139 84.1	**44** **98.1**	6 100.0						0.12	0.25
Vancomycin-nonsusceptible *Enterococcus faecalis* (14)	1 7.1	0 7.1	2 21.4	8 78.6	**3** **100.0**							0.12	0.25
Enterococcus faecium (167)	3 1.8	17 12.0	77 58.1	**58** **92.8**	4 95.2	6 98.8	2 100.0					0.06	0.12
Vancomycin-susceptible *Enterococcus faecium* (55)	1 1.8	5 10.9	35 74.5	**13** **98.2**	0 98.2	1 100.0						0.06	0.12
Vancomycin-nonsusceptible *Enterococcus faecium* (112)	2 1.8	12 12.5	42 50.0	**45** **90.2**	4 93.8	5 98.2	2 100.0					0.06	0.12
Streptococcus pneumoniae (605)	12 2.0	120 21.8	**415** **90.4**	56 99.7	2 100.0							0.06	0.06
Penicillin-susceptible *Streptococcus pneumoniae* (≤0.06) (389)	11 2.8	93 26.7	**264** **94.6**	21 100.0								0.06	0.06
Penicillin-intermediate *Streptococcus pneumoniae* (≥0.12 and ≤1) (142)	0 0.0	23 16.2	97 84.5	**20** **98.6**	2 100.0							0.06	0.12
Penicillin-resistant *Streptococcus pneumoniae* (≥2) (74)	1 1.4	4 6.8	54 79.7	**15** **100.0**								0.06	0.12
Viridans group streptococci (106)[c]	11 10.4	21 30.2	36 64.2	**28** **90.6**	10 100.0							0.06	0.12
β-haemolytic streptococci (541)[d]	0 0.0	20 3.7	273 54.2	**206** **92.2**	34 98.5	8 100.0						0.06	0.12
Streptococcus pyogenes (247)	0 0.0	13 5.3	207 89.1	**23** **98.4**	4 100.0							0.06	0.12
Streptococcus agalactiae (232)	0 0.0	5 2.2	47 22.4	**160** **91.4**	19 99.6	1 100.0						0.12	0.12

[a] MIC_{50} values are underlined; MIC_{90} values are bold
[b] Organisms include: *Staphylococcus capitis* (24), *S. caprae* (2), *S. cohnii* (3), *S. epidermidis* (179), *S. haemolyticus* (11), *S. hominis* (35), *S. lugdunensis* (32), *S. pettenkoferi* (9), *S. saprophyticus* (6), *S. schleiferi* (5), *S. simulans* (5), *S. warneri* (4), unspeciated coagulase-negative staphylococci (1)
[c] Organisms include: *Streptococcus anginosus* (23), *S. anginosus* group (10), *S. australis* (1), *S. bovis* group (1), *S. constellatus* (4), *S. cristatus* (1), *S. gallolyticus* (6), *S. gordonii* (5), *S. intermedius* (5), *S. lutetiensis* (3), *S. massiliensis* (1), *S. mitis* group (29), *S. parasanguinis* (10), *S. salivarius* (3), *S. salivarius/vestibularis* (2), *S. sanguinis* (2)
[d] Organisms include: *Streptococcus agalactiae* (232), *S. canis* (2), *S. dysgalactiae* (60), *S. pyogenes* (247)

Table 2 *In vitro* activity of omadacycline and comparator antimicrobials against staphylococci, streptococci, and enterococci from patients in United States medical centers during 2016

Organism (no. tested) antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	%I	%R
***S. aureus* (2,050)**						
Omadacycline	0.12	0.25	≤0.015–8	—	—	—
Doxycycline	≤0.06	0.25	≤0.06–>8	98.4	1.4	0.2
Tetracycline	≤0.5	≤0.5	≤0.5–>8	96.0	0.6	3.4
Tigecycline	0.06	0.12	≤0.015–1	>99.9		b
Oxacillin	1	>2	≤0.25–>2	55.1		44.9
Levofloxacin	0.25	>4	≤0.03–>4	62.3	1.2	36.5
Erythromycin	8	>8	≤0.06–>8	41.5	7.1	51.4
Clindamycin	≤0.25	>2	≤0.25–>2	84.5	0.3	15.2
Linezolid	1	1	≤0.12–4	100.0		0.0
Daptomycin	0.5	0.5	≤0.12–1	100.0		
Vancomycin	0.5	1	0.25–2	100.0	0.0	0.0
MRSA (920)						
Omadacycline	0.12	0.25	0.03–8	—	—	—
Doxycycline	≤0.06	0.5	≤0.06–>8	97.6	2.2	0.2
Tetracycline	≤0.5	1	≤0.5–>8	95.2	0.5	4.2
Tigecycline	0.06	0.12	≤0.015–1	99.9		b
Levofloxacin	4	>4	0.12–>4	28.2	1.7	70.1
Erythromycin	>8	>8	≤0.06–>8	10.9	4.6	84.6
Clindamycin	≤0.25	>2	≤0.25–>2	69.9	0.5	29.6
Linezolid	1	1	0.25–4	100.0		0.0
Daptomycin	0.5	0.5	≤0.12–1	100.0		
Vancomycin	0.5	1	0.25–2	100.0	0.0	0.0
CoNS (316)[c]						
Omadacycline	0.12	0.5	≤0.015–2	—	—	—
Doxycycline	0.12	2	≤0.06–>8	96.8	2.8	0.3
Tetracycline	≤0.5	>8	≤0.5–>8	88.0	0.0	12.0
Tigecycline	0.06	0.12	≤0.015–0.5	—	—	—
Oxacillin	2	>2	≤0.25–>2	41.5		58.5
Levofloxacin	0.25	>4	≤0.03–>4	60.1	1.6	38.3
Erythromycin	>8	>8	≤0.06–>8	42.7	3.8	53.5
Clindamycin	≤0.25	>2	≤0.25–>2	69.6	0.6	29.7
Linezolid	0.5	1	≤0.12–>8	96.8		3.2
Daptomycin	0.25	0.5	≤0.12–1	100.0		
Vancomycin	1	2	≤0.12–2	100.0	0.0	0.0
MR-CoNS (185)						
Omadacycline	0.25	0.5	≤0.015–2	—	—	—
Doxycycline	0.25	4	≤0.06–>8	94.6	4.9	0.5
Tetracycline	≤0.5	>8	≤0.5–>8	81.6	0.0	18.4
Tigecycline	0.12	0.25	0.03–0.5	—	—	—
Levofloxacin	>4	>4	0.06–>4	36.8	2.7	60.5
Erythromycin	>8	>8	≤0.06–>8	27.0	5.9	67.0
Clindamycin	≤0.25	>2	≤0.25–>2	55.1	1.1	43.8
Linezolid	0.5	1	≤0.12–>8	94.6		5.4
Daptomycin	0.5	0.5	≤0.12–1	100.0		
Vancomycin	1	2	≤0.12–2	100.0	0.0	0.0
***S. pneumoniae* (605)**						
Omadacycline	0.06	0.06	≤0.015–0.25	—	—	—
Tetracycline	≤0.25	>8	≤0.25–>8	79.8	0.5	19.7
Tigecycline	0.03	0.06	0.015–0.12	99.3		b
Penicillin	0.015	2	≤0.004–4	64.3	23.5	12.2[d]
Ceftriaxone	0.03	1	≤0.015–>2	97.8	1.8	0.3[e]
Levofloxacin	1	1	0.25–>4	99.3	0.2	0.5
Azithromycin	0.12	>32	0.015–>32	54.2	1.7	44.1
Erythromycin	0.06	>32	≤0.015–>32	53.7	0.8	45.5
Clindamycin	≤0.25	>2	≤0.25–>2	85.6	0.3	14.0
Linezolid	1	2	0.25–2	100.0		
***S. pneumoniae* PRSP (74)**						
Omadacycline	0.06	0.12	≤0.015–0.12	—	—	—
Tetracycline	>8	>8	≤0.25–>8	43.2	0.0	56.8
Tigecycline	0.06	0.06	0.015–0.06	100.0		b
Penicillin	2	4	2–4	0.0	0.0	100.0[d]
Ceftriaxone	1	2	0.5–>2	82.4	14.9	2.7[e]
Levofloxacin	1	1	0.5–>4	98.6	0.0	1.4
Azithromycin	32	>32	0.03–>32	6.8	4.1	89.2
Erythromycin	32	>32	0.03–>32	6.8	0.0	93.2
Clindamycin	≤0.25	>2	≤0.25–>2	51.4	0.0	48.6
Linezolid	1	2	0.5–2	100.0		
Viridans group streptococci (106)[f]						
Omadacycline	0.06	0.12	≤0.015–0.25	—	—	—
Tetracycline	2	>8	≤0.25–>8	51.9	5.7	42.5
Tigecycline	0.03	0.12	≤0.008–0.25	100.0		b
Penicillin	0.06	1	≤0.004–8	69.8	24.5	5.7
Ceftriaxone	0.12	1	≤0.015–>2	91.5	2.8	5.7
Levofloxacin	1	2	0.25–>4	92.5	0.0	7.5
Erythromycin	0.03	>32	≤0.015–>32	53.8	0.9	45.3
Clindamycin	≤0.25	>2	≤0.25–>2	84.0	0.9	15.1
Linezolid	1	1	0.25–2	100.0		
Daptomycin	0.25	1	≤0.06–1	100.0		
Vancomycin	0.5	1	≤0.06–1	100.0		
β-haemolytic streptococci (541)[g]						
Omadacycline	0.06	0.12	0.03–0.5	—	—	—
Tetracycline	1	>8	≤0.25–>8	51.7	1.5	46.9
Tigecycline	0.06	0.06	0.015–0.25	100.0		b
Penicillin	0.015	0.06	≤0.004–0.12	100.0		
Levofloxacin	0.5	1	0.12–>4	99.6	0.0	0.4
Erythromycin	0.06	>32	≤0.015–>32	65.7	0.6	33.7
Clindamycin	≤0.25	>2	≤0.25–>2	82.3	0.6	17.2
Linezolid	1	1	0.25–2	100.0		
Daptomycin	≤0.06	0.25	≤0.06–0.5	100.0		
Vancomycin	0.25	0.5	0.12–1	100.0		
***E. faecalis* (328)**						
Omadacycline	0.12	0.25	≤0.015–0.5	—	—	—
Tetracycline	>16	>16	≤0.12–>16	25.7	1.8	72.5
Tigecycline	0.06	0.12	≤0.015–0.12	100.0		b
Levofloxacin	1	>4	≤0.03–>4	76.8	0.3	22.9
Linezolid	1	1	0.25–2	100.0	0.0	0.0
Ampicillin	1	2	≤0.5–4	100.0		0.0
Vancomycin	1	2	0.25–>16	95.7	0.0	4.3
***E. faecium* (167)**						
Omadacycline	0.06	0.12	≤0.015–1	—	—	—
Tetracycline	>16	>16	≤0.12–>16	26.3	4.2	69.5
Tigecycline	0.03	0.06	≤0.015–0.5	—	—	—
Levofloxacin	>4	>4	0.5–>4	14.4	6.0	79.6
Linezolid	1	2	0.25–8	99.4	0.0	0.6
Ampicillin	>16	>16	≤0.5–>16	22.8		77.2
Vancomycin	>16	>16	0.25–>16	32.9	0.6	66.5

[a] Criteria as published by CLSI [2017]
[b] Breakpoints from FDA Package Insert revised 12/2014
[c] Organisms include: *Staphylococcus capitis* (24), *S. caprae* (2), *S. cohnii* (3), *S. epidermidis* (179), *S. haemolyticus* (11), *S. hominis* (35), *S. lugdunensis* (32), *S. pettenkoferi* (9), *S. saprophyticus* (6), *S. schleiferi* (5), *S. simulans* (5), *S. warneri* (4), unspeciated coagulase-negative staphylococci (1)
[d] Using oral breakpoints
[e] Using non-meningitis breakpoints
[f] Organisms include: *Streptococcus anginosus* (23), *S. anginosus* group (10), *S. australis* (1), *S. bovis* group (1), *S. constellatus* (4), *S. cristatus* (1), *S. gallolyticus* (6), *S. gordonii* (5), *S. intermedius* (5), *S. lutetiensis* (3), *S. massiliensis* (1), *S. mitis* group (29), *S. parasanguinis* (10), *S. salivarius* (3), *S. salivarius/vestibularis* (2), *S. sanguinis* (2)
[g] Organisms include: *Streptococcus agalactiae* (232), *S. canis* (2), *S. dysgalactiae* (60), *S. pyogenes* (247)