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In Vitro Activity of Telavancin Against Clinically Important Gram-Positive Pathogens from 69 U.S. Medical Centers (2015): Potency Analysis by U.S. Census Divisions

Michael A. Pfaller,[1] Helio S. Sader,[1] Robert K. Flamm,[1] Mariana Castanheira,[1] Jennifer I. Smart,[2,*] and Rodrigo E. Mendes[1]

A total of 8,072 gram-positive isolates collected from 69 medical centers among all 9 U.S. Census Divisions during the 2015 SENTRY Antimicrobial Surveillance Program were included. Telavancin had minimal inhibitory concentration $(MIC)_{50}$ and MIC_{90} values of 0.03/0.06 μg/mL, respectively, against methicillin-susceptible (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA). Similar activity was also observed among coagulase-negative staphylococci ($MIC_{50/90}$, 0.03/0.06 μg/ml; 100.0% inhibited by ≤0.12 μg/ml). Telavancin was active against vancomycin-susceptible *Enterococcus faecalis* ($MIC_{50/90}$, 0.12/0.12 μg/ml) and *Enterococcus faecium* ($MIC_{50/90}$, 0.03/0.06 μg/ml), but was less active against vancomycin-resistant *E. faecium* (MIC_{90}, >2 μg/ml) and *E. faecalis* (MIC_{90}, >2 μg/ml). Streptococci showed modal MIC results of 0.008 μg/ml (*Streptococcus pneumoniae*) to 0.015 μg/ml (β-hemolytic streptococci and viridans group streptococci). Potency variations for telavancin within Census Divisions were not observed. Telavancin remains potent *in vitro* against indicated pathogens recovered from U.S. medical centers (2015).

Keywords: telavancin, lipoglycopeptide, U.S. census, *in vitro* testing

Introduction

Telavancin is a parenteral, bactericidal, semisynthetic lipoglycopeptide agent that has been shown to be noninferior to vancomycin in phase 3 clinical trials of adult patients with complicated skin and skin structure infections (cSSSI) and in hospital-acquired bacterial pneumonia (HAP), including ventilator-associated pneumonia (VAP), due to susceptible gram-positive pathogens and *Staphylococcus aureus*, respectively.[1–4] Telavancin has been approved for clinical use by the U.S. Food and Drug Administration (FDA) in the treatment (once daily) of cSSSI and HAP/VAP and demonstrated efficacy in treating patients with either cSSSI or HAP/VAP who had concurrent *S. aureus* bacteremia.[4]

Previous studies have demonstrated potent activity of telavancin against *S. aureus*, including methicillin-resistant (MRSA) strains, as well as heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and VISA isolates and vancomycin-susceptible *Enterococcus faecalis*.[5,6] Not only does telavancin inhibit peptidoglycan synthesis but it also interacts with the bacterial cell membrane, causing depolarization and increased membrane permeability.[7] This dual mechanism of action contributes to the bactericidal activity of telavancin and might also prevent the emergence of resistance when it is used clinically. In fact, only one report has been published of *in vivo* development of a nonsusceptible phenotype while on telavancin therapy (Swartz *et al.*, 2013).

Recently, the broth microdilution (BMD) method recommended by the Clinical and Laboratory Standards Institute (CLSI) for testing telavancin was modified to conform to CLSI guidelines for water-insoluble agents.[6,8,9] The revised method includes the use of dimethyl sulfoxide (DMSO) as both the solvent and diluent of stock solutions as well as the addition of polysorbate 80 (P-80; 0.002%) to the test medium.[4,9] The net effects of these modifications are improved solubility and decreased binding on plastic trays of the active agent with resultant improved accuracy and

[1]JMI Laboratories, North Liberty, Iowa.
[2]Theravance Biopharma US, Inc., South San Francisco, California.
Present affiliation: Basilea Pharmaceutica International AG, Basel, Switzerland.

reproducibility of *in vitro* test results.[9] As might be expected, these modifications result in lower minimal inhibitory concentration values for the target pathogens requiring. The FDA, CLSI, and European Committee on Antimicrobial Susceptibility Testing (EUCAST) to reestablish quality control (QC) MIC ranges and interpretive breakpoints.[4,6,8,9] Mendes *et al.*[6] subsequently used the revised BMD method to assess the baseline activity of telavancin against gram-positive target species obtained from a limited number ($N=28$ sites) of U.S. hospitals in 2011–2012. The objective of the present study was to expand on the study of Mendes *et al.*[6] by including isolates from a total of 69 institutions (35 states) across all 9 U.S. Census Divisions for the year 2015. Testing was performed using the revised CLSI method with the new QC MIC ranges and interpretive criteria.[8]

Materials and Methods

Organism collection

During 2015, a total of 8,072 gram-positive bacterial pathogens were collected from 69 medical centers in 35 states across all 9 U.S. Census Bureau Divisions. Each participating laboratory followed a protocol to submit consecutive isolates (1 per patient episode) determined to be pathogens to the monitoring laboratory (JMI Laboratories, North Liberty, IA). These isolates were deemed responsible for SSSI (42.8%), pneumonia in hospitalized patients (22.5%), bloodstream infections (18.5%), urinary tract infections (5.3%), community-acquired pneumonia (4.8%), intra-abdominal infections (2.8%), and other unknown or less prevalent infections (3.1%). There were 3 to 12 medical centers in each U.S. Census Bureau Division, and a total of 631 to 1,526 strains were contributed per division. Among the 8,072 isolates tested, there were 5,123 of *S. aureus* (2,822 methicillin-susceptible and 2,301 MRSAs), 328 of coagulase-negative staphylococci (CoNS), 815 of *Enterococcus* spp., 447 of *Streptococcus pneumoniae*, 1,083 of β-hemolytic streptococci (BHS), and 276 of viridans group streptococci (VGS). See footnote of Table 1 for complete list of isolates included in the study. The isolates were identified locally and forwarded to the central monitoring laboratory for confirmation of species identification, using matrix-assisted laser desorption–ionization time-of-flight mass spectrometry [MALDI-TOF-MS] and/or manual methods), and reference antimicrobial susceptibility testing.

Susceptibility testing

Isolates were tested for susceptibility to telavancin and comparator agents by BMD following the CLSI-approved standard.[10] Testing was performed using panels manufactured by JMI Laboratories (North Liberty, IA). These panels provide telavancin MIC results equivalent to the revised FDA-approved BMD method.[4,6,8,9] Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event. Validation of MIC values was performed by concurrent testing of CLSI-recommended QC reference strains: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619.[4,8] All QC results were within published acceptable ranges. The MIC interpretations for telavancin and comparator agents, when tested against clinical isolates, were based on the most updated breakpoint criteria from CLSI (2016). The EUCAST breakpoint for teicoplanin (≤2/>2 μg/ml for susceptible and resistant, respectively) was applied against BHS and VGS.[11]

Results

Activity of telavancin and comparators against S. aureus

Overall, 2,822 (55.1%) of *S. aureus* isolates were MSSAs and 2,301 (44.9%) were MRSAs. At least 50% of *S. aureus* isolates from U.S. Census Divisions 2 (Mid-Atlantic, 50.0%), 6 (East South Central, 56.6%), and 7 (West South Central, 52.4%) were MRSAs, whereas <40% of isolates from divisions 1 (New England, 35.3%) and 4 (West North Central, 33.6%) exhibited that phenotype (Table 2).

Telavancin $MIC_{50/90}$ values (0.03/0.06 μg/ml) were identical for both MSSA and MRSA and 100.0% of isolates of *S. aureus* were inhibited at the approved breakpoint for susceptibility (*i.e.*, ≤0.12 μg/ml) (Tables 1 and 3). The activity of telavancin (MIC_{50} values) against *S. aureus* was similar across all nine U.S. Census Divisions with MIC_{90} values of 0.03–0.06 μg/ml (Table 2). Using CLSI breakpoints, 100.0% of isolates tested were also susceptible to daptomycin, teicoplanin, and vancomycin (Table 3). Susceptibility rates (CLSI interpretations) to erythromycin and levofloxacin were 40.8% and 62.0%, respectively. Susceptibility percentages were much higher to ceftaroline (98.4%), gentamicin (97.2%), linezolid (>99.9%), tetracycline (95.2%), and trimethoprim–sulfamethoxazole (98.4%). These agents showed comparable activity against both MSSA and MRSA (Table 3).

Activity of telavancin against CoNS

All CoNS were inhibited by ≤0.12 μg/ml of telavancin (Table 1). The rate of methicillin-resistant CoNS (MR-CoNS) was 55.8% overall, ranging from 24.0% in the Mountain Division to 71.4% in the West South Central Division (Table 2). The activity of telavancin did not vary across the nine U.S. Census Divisions (MIC_{90}, 0.06–0.12 μg/ml) (Table 2). All CoNS were susceptible to daptomycin and vancomycin (Table 3). Susceptibility percentages to linezolid and teicoplanin were also high against methicillin-susceptible CoNS (MS-CoNS) (both 100.0%) and MR-CoNS (both 98.4%). Relative to telavancin MIC_{90} values, ceftaroline and daptomycin were 4- to 8-fold less potent, linezolid was 16-fold less potent, and vancomycin was 16- to 32-fold less potent against both MS- and MR-CoNS (Table 3). Other agents tested against CoNS did not show useful (susceptibility >90%) *in vitro* activity, with susceptibility of ≤85.4% (range 41.5–85.4%) and MIC_{90} values of >2 μg/ml (Table 3).

Susceptibility to clindamycin, erythromycin, gentamicin, levofloxacin, tetracycline, and trimethoprim–sulfamethoxazole was lower for MR-CoNS than for MS-CoNS (Table 3). For example, susceptibility to erythromycin was 24.6% for MR-CoNS and 62.8% for MS-CoNS (Table 3). Susceptibility to levofloxacin was 35.5% for MR-CoNS and 86.2% for MS-CoNS (Table 3).

Activity of telavancin against E. faecalis

A total of 815 enterococci were tested, of which 53.7% were *E. faecalis* (Table 1). These isolates were very susceptible to

TABLE 1. ANTIMICROBIAL ACTIVITY AND MINIMAL INHIBITORY CONCENTRATION DISTRIBUTION OF TELAVANCIN WHEN TESTED AGAINST CONTEMPORARY (2015) CLINICAL ISOLATES OF GRAM-POSITIVE COCCI FROM U.S. MEDICAL CENTERS USING CLINICAL AND LABORATORY STANDARDS INSTITUTE BROTH MICRODILUTION METHODS

Organism (no. tested)	*No. of isolates (cumulative%) inhibited at MIC (μg/ml)*												*MIC (μg/ml)*	
	≤0.002	*0.004*	*0.008*	*0.015*	*0.03*	*0.06*	*0.12*	*0.25*	*0.5*	*1*	*2*	*>2*	*50%*[a]	*90%*[a]
Staphylococcus aureus (5,123)		1 (<0.1)	10 (0.2)	289 (5.9)	4,264 (89.1)	553 (99.9)	6 (100.0)						0.03	0.06
MSSA (2,822)			6 (0.2)	195 (7.1)	2,312 (89.1)	307 (99.9)	2 (100.0)						0.03	0.06
MRSA (2,301)		1 (<0.1)	4 (0.2)	94 (4.3)	1,959 (89.1)	246 (99.8)	4 (100.0)						0.03	0.06
CoNS (328)[b]			2 (0.6)	17 (5.8)	149 (51.2)	151 (97.3)	9 (100.0)						0.03	0.06
MS-CoNS (145)			2 (1.4)	12 (9.7)	85 (68.3)	39 (95.2)	7 (100.0)						0.03	0.06
MR-CoNS (183)				5 (2.7)	64 (37.7)	112 (98.9)	2 (100.0)						0.06	0.06
Enterococcus spp.[c] (815)				31 (3.8)	76 (13.1)	88 (23.9)	291 (59.6)	57 (66.6)	8 (67.6)	42 (72.8)	106 (85.8)	116 (100.0)	0.12	>2
Enterococcus faecalis (438)				1 (0.2)	5 (1.4)	76 (18.7)	287 (84.2)	39 (93.2)	1 (93.4)	0 (93.4)	1 (93.6)	28 (100.0)	0.12	0.25
Van-S (405)				1 (0.2)	5 (1.5)	76 (20.2)	283 (90.1)	39 (99.8)	1 (100.0)				0.12	0.12
VanA (29)										0 (0.0)	1 (3.4)	28 (100.0)	>2	>2
VanB (4)						0 (0.0)	4 (100.0)						0.12	-
Enterococcus faecium (346)				25 (7.2)	65 (26.0)	11 (29.2)	1 (29.5)	3 (30.3)	7 (32.4)	41 (44.2)	105 (74.6)	88 (100.0)	2	>2
Van-S (99)				25 (25.3)	63 (88.9)	11 (100.0)							0.03	0.06
VanA (237)							1 (0.4)	1 (0.8)	6 (3.4)	37 (19.0)	105 (63.3)	87 (100.0)	2	>2
VanB (10)					2 (20.0)	0 (20.0)	0 (20.0)	2 (40.0)	1 (50.0)	4 (90.0)	0 (90.0)	1 (100.0)	0.5	1
Streptococcus pneumoniae (447)		13 (2.9)	344 (79.9)	88 (99.6)	2 (100.0)								0.008	0.015
BHS[d] (1,083)	1 (0.1)	0 (0.1)	8 (0.8)	392 (37.0)	645 (96.6)	33 (99.6)	4 (100.0)						0.03	0.03
VGS[e] (276)	2 (0.7)	2 (1.4)	32 (13.0)	165 (72.8)	67 (97.1)	8 (100.0)							0.015	0.03

[a]50%/90%, MIC encompassing 50% and 90% of isolates tested, respectively.

[b]Includes *Staphylococcus auricularis* [1], *S. capitis* [15], *S. caprae* [5], *S. cohnii* [1], *S. condimenti* [1], *S. epidermidis* [191], *S. felis* [1], *S. haemolyticus* [22], *S. hominis* [30], *S. lugdunensis* [46], *S. pettenkoferi* [2], *S. pseudintermedius* [1], *S. pseudintermedius/intermedius/delphini* [1], *S. saprophyticus* [5], and *S. warneri* [1].

[c]Includes *Enterococcus avium* [5], *E. casseliflavus* [7], *E. durans* [3], *E. faecalis* [438], *E. faecium* [346], *E. gallinarum* [12], *E. raffinosus* [3], and *E. thailandicus* [1].

[d]Includes *Streptococcus pyogenes* [454], *S. agalactiae* [494], and *S. dysgalactiae* [135].

[e]Includes *Streptococcus anginosus* [66], *S. anginosus* group [11], *S. australis* [2], *S. constellatus* [9], *S. cristatus* [3], *S. equinus* [1], *S. gallolyticus* [12], *S. gordonii* [2], *S. infantarius* [1], *S. infantis* [3], *S. intermedius* [11], *S. lutetiensis* [4], *S. mitis* [8], *S. mitis* group [8], *S. mitis/oralis* [55], *S. mutans* [3], *S. oralis* [35], *S. parasanguinis* [18], *S. salivarius* [7], *S. salivarius* group [5], *S. sanguinis* [9], and *S. vestibularis* [3].

BHS, β-hemolytic streptococci; CoNS, coagulase-negative staphylococci; MIC, minimal inhibitory concentration; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; MS-CoNS, methicillin-susceptible coagulase-negative staphylococci; MSSA, methicillin-susceptible *S. aureus*; VanA phenotype, vancomycin and teicoplanin MIC values of >4 and >8 μg/ml, respectively; VanB phenotype, vancomycin and teicoplanin MIC values of >4 and ≤8 μg/ml, respectively; Van-S, vancomycin-susceptible; VGS, viridans group streptococci.

TABLE 2. ANTIMICROBIAL ACTIVITY OF TELAVANCIN TESTED AGAINST GRAM-POSITIVE CLINICAL ISOLATES FROM EACH OF THE NINE U.S. CENSUS BUREAU DIVISIONS

Division (no. of sites)	*Organism*	*No. tested*	*MIC (μg/ml)*			*% Susceptible*[a]
			Range	*50%*	*90%*	
1. New England (3)	*S. aureus*	430	0.008 to 0.006	0.03	0.06	100.0
	MSSA	278	0.008 to 0.06	0.03	0.06	100.0
	MRSA	152	0.015 to 0.06	0.03	0.06	100.0
	CoNS	18	0.015 to 0.06	0.03	0.06	
	MS-CoNS	11	0.015 to 0.06	0.03	0.06	
	MR-CoNS	7	0.03 to 0.06	0.06	—	
	E. faecalis	36	0.06 to >2	0.12	0.25	
	Van-S	35	0.06 to 0.25	0.12	0.25	100.0
	E. faecium	18	0.015 to >2	2	>2	
	Van-S	7	0.015 to 0.06	0.03	—	
	S. pneumoniae	36	0.008 to 0.03	0.008	0.015	
	BHS	63	0.008 to 0.03	0.03	0.03	100.0
	VGS	19	0.008 to 0.03	0.015	0.03	100.0
2. Mid-Atlantic (7)	*S. aureus*	508	0.008 to 0.06	0.03	0.06	100.0
	MSSA	254	0.015 to 0.06	0.03	0.06	100.0
	MRSA	254	0.008 to 0.06	0.03	0.06	100.0
	CoNS	29	0.03 to 0.12	0.06	0.12	
	MS-CoNS	13	0.03 to 0.12	0.06	0.12	
	MR-CoNS	16	0.03 to 0.12	0.06	0.06	
	E. faecalis	50	0.06 to >2	0.12	0.25	
	Van-S	44	0.06 to 0.25	0.12	0.25	100.0
	E. faecium	48	0.015 to >2	2	>2	
	Van-S	8	0.015 to 0.06	0.03	0.06	
	S. pneumoniae	42	0.004 to 0.015	0.008	0.015	
	BHS	113	0.008 to 0.12	0.03	0.03	100.0
	VGS	30	0.008 to 0.03	0.015	0.03	100.0
3. East North Central (12)	*S. aureus*	922	0.008 to 0.06	0.03	0.03	100.0
	MSSA	516	0.008 to 0.06	0.03	0.06	100.0
	MRSA	406	0.008 to 0.06	0.03	0.03	100.0
	CoNS	64	0.008 to 0.06	0.03	0.06	
	MS-CoNS	30	0.008 to 0.06	0.03	0.06	
	MR-CoNS	34	0.03 to 0.06	0.06	0.06	
	E. faecalis	81	0.015 to >2	0.12	0.25	
	Van-S	77	0.015 to 0.25	0.12	0.12	100.0
	E. faecium	63	0.015 to >2	2	>2	
	Van-S	21	0.015 to 0.06	0.03	0.06	
	S. pneumoniae	100	0.004 to 0.015	0.008	0.015	
	BHS	234	0.002 to 0.12	0.03	0.03	100.0
	VGS	56	0.008 to 0.06	0.015	0.03	100.0
4. West North Central (7)	*S. aureus*	541	0.008 to 0.12	0.03	0.06	100.0
	MSSA	359	0.008 to 0.06	0.03	0.06	100.0
	MRSA	182	0.008 to 0.12	0.03	0.03	100.0
	CoNS	29	0.015 to 0.06	0.03	0.06	
	MS-CoNS	11	0.015 to 0.06	0.03	0.06	
	MR-CoNS	18	0.015 to 0.06	0.06	0.06	
	E. faecalis	44	0.06 to >2	0.12	0.25	
	Van-S	40	0.06 to 0.25	0.12	0.25	100.0
	E. faecium	22	0.015 to >2	0.03	>2	
	Van-S	11	0.015 to 0.03	0.03	0.03	
	S. pneumoniae	50	0.004 to 0.015	0.008	0.015	
	BHS	147	0.015 to 0.06	0.03	0.03	100.0
	VGS	38	0.002 to 0.06	0.015	0.03	100.0
5. South Atlantic (9)	*S. aureus*	842	0.004 to 0.12	0.03	0.06	100.0
	MSSA	428	0.008 to 0.12	0.03	0.06	100.0
	MRSA	414	0.004 to 0.12	0.03	0.06	100.0
	CoNS	56	0.015 to 0.06	0.03	0.06	
	MS-CoNS	21	0.015 to 0.06	0.03	0.06	
	MR-CoNS	35	0.03 to 0.06	0.06	0.06	
	E. faecalis	53	0.06 to >2	0.12	0.25	

(*continued*)

TABLE 2. (CONTINUED)

Division (no. of sites)	Organism	No. tested	MIC (μg/ml)			% Susceptible[a]
			Range	50%	90%	
	Van-S	46	0.06 to 0.25	0.12	0.12	100.0
	E. faecium	43	0.015 to >2	2	>2	
	Van-S	9	0.015 to 0.03	0.03	—	
	S. pneumoniae	47	0.004 to 0.015	0.008	0.015	
	BHS	126	0.015 to 0.12	0.03	0.03	100.0
	VGS	34	0.008 to 0.06	0.015	0.03	100.0
6. East South Central (6)	*S. aureus*	426	0.05 to 0.06	0.03	0.06	100.0
	MSSA	185	0.015 to 0.06	0.03	0.06	100.0
	MRSA	241	0.0115 to 0.06	0.03	0.06	100.0
	CoNS	23	0.015 to 0.06	0.03	0.06	
	MS-CoNS	8	0.015 to 0.06	0.03	—	
	MR-CoNS	15	0.015 to 0.06	0.03	0.06	
	E. faecalis	50	0.06 to >2	0.12	0.25	
	Van-S	48	0.06 to 0.25	0.12	0.25	100.0
	E. faecium	29	0.015 to >2	2	>2	
	Van-S	3	0.015 to 0.03	0.03	—	
	S. pneumoniae	31	0.004 to 0.015	0.008	0.015	
	BHS	70	0.015 to 0.06	0.03	0.03	100.0
	VGS	20	0.004 to 0.03	0.015	0.015	100.0
7. West South Central (7)	*S. aureus*	361	0.015 to 0.12	0.03	0.03	100.0
	MSSA	172	0.015 to 0.12	0.03	0.03	100.0
	MRSA	189	0.015 to 0.06	0.03	0.03	100.0
	CoNS	35	0.015 to 0.12	0.06	0.06	
	MS-CoNS	10	0.03 to 0.12	0.06	0.12	
	MR-CoNS	25	0.015 to 0.12	0.06	0.06	
	E. faecalis	38	0.03 to >2	0.12	0.5	
	Van-S	35	0.03 to 0.5	0.12	0.12	97.1
	E. faecium	57	0.015 to >2	2	>2	
	Van-S	18	0.015 to 0.06	0.03	0.06	
	S. pneumoniae	43	0.004 to 0.015	0.008	0.015	
	BHS	78	0.008 to 0.06	0.03	0.03	100.0
	VGS	14	0.008 to 0.06	0.015	0.03	100.0
8. Mountain (6)	*S. aureus*	446	0.015 to 0.06	0.03	0.03	100.0
	MSSA	256	0.015 to 0.06	0.03	0.03	100.0
	MRSA	190	0.015 to 0.06	0.03	0.06	100.0
	CoNS	25	0.008 to 0.12	0.03	0.06	
	MS-CoNS	19	0.008 to 0.12	0.03	0.06	
	MR-CoNS	6	0.03 to 0.06	0.06	—	
	E. faecalis	25	0.06 to >2	0.12	0.12	
	Van-S	24	0.06 to 0.12	0.12	0.12	100.0
	E. faecium	34	0.015 to 2	2	>2	
	Van-S	22	1 to >2	2	>2	
	S. pneumoniae	20	0.004 to 0.03	0.008	0.015	
	BHS	11	0.008 to 0.06	0.03	0.03	100.0
	VGS	28	0.008 to 0.03	0.015	0.03	100.0
9. Pacific (11)	*S. aureus*	647	0.008 to 0.12	0.03	0.06	100.0
	MSSA	374	0.008 to 0.06	0.03	0.06	100.0
	MRSA	273	0.015 to 0.12	0.03	0.06	100.0
	CoNS	49	0.015 to 0.12	0.06	0.06	
	MS-CoNS	22	0.015 to 0.12	0.03	0.06	
	MR-CoNS	27	0.015 to 0.06	0.06	0.06	
	E. faecalis	61	0.03 to >2	0.12	0.25	
	Van-S	56	0.03 to 0.25	0.12	0.12	100.0
	E. faecium	32	0.015 to >2	1	>2	
	Van-S	12	0.015 to 0.06	0.03	0.06	
	S. pneumoniae	68	0.004 to 0.015	0.008	0.015	
	BHS	141	0.008 to 0.06	0.03	0.03	100.0
	VGS	37	0.008 to 0.06	0.015	0.03	100.0

[a]Criteria as published by CLSI (2016) against indicated pathogens. Breakpoint for *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus dysgalactiae*, and *Streptococcus anginosus* group *S. anginosus* group applied for BHS and VGS.

CLSI, Clinical and Laboratory Standards Institute.

TABLE 3. ANTIMICROBIAL ACTIVITY OF TELAVANCIN AND COMPARATOR AGENTS TESTED AGAINST GRAM-POSITIVE CLINICAL ISOLATES FROM THE UNITED STATES USING THE CLINICAL AND LABORATORY STANDARDS INSTITUTE BROTH MICRODILUTION TESTING METHOD

		MIC (μg/ml)			*% By category*[a]		
Organism (no. tested)	*Agent*	*Range*	*50%*	*90%*	*S*	*I*	*R*
S. aureus (5,123)	Telavancin	≤0.004 to 0.12	0.03	0.06	100.0		
	Ceftaroline	≤0.06 to 2	0.25	1	98.4	1.6	0.0
	Clindamycin	≤0.25 to >2	≤0.25	>2	84.4	0.3	15.3
	Daptomycin	≤0.12 to 1	0.25	0.5	100.0		
	Erythromycin	≤0.06 to >8	>8	>8	40.8	5.9	53.3
	Gentamicin	≤1to >8	≤1	≤1	97.2	0.2	2.7
	Levofloxacin	≤0.03 to >4	0.25	>4	62.0	1.0	36.9
	Linezolid	≤0.12 to 8	1	1	>99.9		<0.1
	Oxacillin	≤0.25 to >2	1	>2	55.1		44.9
	Teicoplanin	≤0.5 to 8	≤0.5	≤0.5	100.0	0.0	0.0
	Tetracycline	≤0.5 to >8	≤0.5	≤0.5	95.2	0.9	3.8
	TMX-SMX	≤0.5 to >4	≤0.5	≤0.5	98.4		1.6
	Vancomycin	≤0.12 to 2	0.5	1	100.0	0.0	0.0
MSSA (2,822)	Telavancin	0.008 to 0.12	0.03	0.06	100.0		
	Ceftaroline	≤0.06 to 0.5	0.25	0.25	100.0	0.0	0.0
	Clindamycin	≤0.25 to >2	≤0.25	≤0.25	94.8	0.2	5.0
	Daptomycin	≤0.12 to 1	0.25	0.5	100.0		
	Erythromycin	≤0.06 to >8	0.25	>8	64.6	7.4	27.9
	Gentamicin	≤1 to >8	≤1	≤1	98.5	0.2	1.3
	Levofloxacin	≤0.03 to >4	0.12	4	88.3	0.4	11.3
	Linezolid	≤0.12 to 2	1	1	100.0		0.0
	Oxacillin	≤0.25 to 2	0.5	1	100.0		0.0
	Teicoplanin	≤0.5 to 8	≤0.5	≤0.5	100.0	0.0	0.0
	Tetracycline	≤0.5 to >4	≤0.5	≤0.5	96.5	0.8	2.8
	TMX-SMX	≤0.5 to >4	≤0.5	≤0.5	99.6		0.4
	Vancomycin	≤0.12 to 2	0.5	1	100.0	0.0	0.0
MRSA (2,301)	Telavancin	≤0.004 to 0.12	0.03	0.06	100.0		
	Ceftaroline	0.25 to 2	0.5	1	96.4	3.6	0.0
	Clindamycin	≤0.25 to >2	≤0.25	>2	71.7	0.4	27.9
	Daptomycin	≤0.12 to 1	0.25	0.5	100.0		
	Erythromycin	≤0.06 to >8	>8	>8	11.6	4.0	84.4
	Gentamicin	≤1 to >8	≤1	≤1	95.5	0.1	4.4
	Levofloxacin	0.12 to >4	4	>4	29.9	1.8	68.3
	Linezolid	≤0.12 to 8	1	1	>99.9		<0.1
	Oxacillin	>2 to >2	>2	>2	0.0		100.0
	Teicoplanin	≤0.5 to >8	≤0.5	≤0.5	100.0	0.0	0.0
	Tetracycline	≤0.5 to >8	≤0.5	1	93.7	1.1	5.2
	TMX-SMX	≤0.5 to >4	≤0.5	≤0.5	96.9		3.1
	Vancomycin	≤0.12 to 2	0.5	1	100.0	0.0	0.0
CoNS (328)	Telavancin	0.008 to 0.12	0.03	0.06			
	Ceftaroline	≤0.06 to 4	0.25	0.5			
	Clindamycin	≤0.25 to >2	≤0.25	>2	72.6	3.0	24.4
	Daptomycin	≤0.12 to 1	0.5	0.5	100.0		
	Erythromycin	≤0.06 to >8	>8	>8	41.5	1.8	56.7
	Gentamicin	≤1 to >8	≤1	>8	79.0	2.4	18.6
	Levofloxacin	≤0.03 to >4	0.25	>4	57.9	1.5	40.5
	Linezolid	≤0.12 to >8	0.5	1	99.1		0.9
	Oxacillin	≤0.25 to >2	2	>2	44.2		55.8
	Teicoplanin	≤0.5 to 16	2	4	99.1	0.9	0.0
	Tetracycline	≤0.5 to >8	≤0.5	>8	85.4	1.5	13.1
	Vancomycin	≤0.12 to 2	1	2	100.0	0.0	0.0
MS-CoNS (145)	Telavancin	0.008 to 0.12	0.03	0.06			
	Ceftaroline	≤0.06 to 0.25	≤0.06	0.25			
	Clindamycin	≤0.25 to >2	≤0.25	0.5	90.3	1.4	8.3
	Daptomycin	≤0.12 to 1	0.25	0.5	100.0		
	Erythromycin	≤0.06 to >8	0.12	>8	62.8	2.1	35.2
	Gentamicin	≤1 to >8	≤1	≤1	97.9	0.0	2.1
	Levofloxacin	≤0.03 to >4	0.25	>4	86.2	0.0	13.8
	Linezolid	≤0.12 to 2	0.5	1	100.0		0.0
	Oxacillin	≤0.25 to 1	≤0.25	0.5	100.0		0.0
	Teicoplanin	≤0.5 to 8	≤0.5	4	100.0	0.0	0.0
	Tetracycline	≤0.5 to >8	≤0.5	2	90.3	2.8	6.9
	TMX-SMX	≤0.5 to >4	≤0.5	1	92.4		7.6
	Vancomycin	≤0.12 to 2	0.5	2	100.0	0.0	0.0

(*continued*)

TABLE 3. (CONTINUED)

Organism (no. tested)	Agent	MIC (μg/ml)			% By category[a]		
		Range	50%	90%	S	I	R
MR-CoNS (183)	Telavancin	0.015 to 0.12	0.06	0.06			
	Ceftaroline	≤0.06 to 4	0.25	0.5			
	Clindamycin	≤0.25 to >2	≤0.25	>2	58.5	4.4	37.2
	Daptomycin	≤0.12 to 1	0.5	0.5	100.0		
	Erythromycin	≤0.06 to >8	>8	>8	24.6	1.6	73.8
	Gentamicin	≤1 to >8	≤1	>8	63.9	4.4	31.7
	Levofloxacin	0.06 to >4	>4	>4	35.5	2.7	61.7
	Linezolid	0.25 to >8	0.5	1	98.4		1.6
	Oxacillin	0.5 to >2	>2	>2	0.0		100.0
	Teicoplanin	≤0.5 to 16	2	4	98.4	1.6	0.0
	Tetracycline	≤0.5 to >8	≤0.5	>8	81.4	0.5	18.0
	TMX-SMX	≤0.5 to >4	1	>4	62.8		37.2
	Vancomycin	≤0.12 to 2	1	2	100.0	0.0	0.0
E. faecalis (438)	Telavancin	≤0.015 to 0.5	0.12	0.12	90.1/99.8[b]		
	Ampicillin	≤0.5 to 2	≤0.5	1	100.0		0.0
	Daptomycin	≤0.25 to 4	0.5	1	100.0		
	Levofloxacin	≤0.5 to >4	1	>4	73.3	0.0	26.7
	Linezolid	≤0.25 to 4	1	1	99.8	0.2	0.0
	Tetracycline	≤1 to >8	>8	>8	24.4	1.6	74.0
	Teicoplanin	≤2 to >16	≤2	≤2	93.4	0.0	6.6
	Vancomycin	≤0.5 to >16	1	2	92.5	0.0	7.5
E. faecium (346)	Telavancin	≤0.015 to >2	2	>2			
	Ampicillin	≤0.5 to >8	>8	>8	16.5		83.5
	Daptomycin	≤0.25 to >8	1	2	99.4		
	Levofloxacin	≤0.5 to >4	>4	>4	11.3	5.5	83.2
	Linezolid	≤0.25 to 8	1	2	99.4	0.0	0.6
	Tetracycline	≤1 to >8	>8	>8	24.9	4.6	70.5
	Teicoplanin	≤2 to >16	>16	>16	31.5	9.2	59.2
	Vancomycin	≤0.5 to >16	>16	>16	28.6	0.3	71.1
S. pneumoniae (447)	Telavancin	0.004 to 0.03	0.008	0.015			
	Ceftaroline	≤0.008 to 0.5	≤0.008	0.12	100.0		
	Clindamycin	≤0.12 to >1	≤0.12	>1	85..5	0.9	13.6
	Erythromycin	≤0.015 to >2	0.06	>2	54.4	0.2	45.4
	Levofloxacin	0.5 to >4	1	1	99.3	0.0	0.7
	Linezolid	0.12 to 2	1	1	100.0		
	Penicillin[c]	≤0.06 to 4	≤0.06	1	96.2	3.8	0.0
	Tetracycline	≤0.012 to >4	0.25	>4	79.8	0.2	20.0
	Vancomycin	0.06 to 0.5	0.25	0.25	100.0		
BHS (1, 083)	Telavancin	≤0.002 to 0.12	0.03	0.03	100.0		
	Ceftaroline	≤0.008 to 0.03	≤0.008	0.015	100.0		
	Clindamycin	≤0.015 to >2	0.06	>2	79.2	0.5	20.3
	Daptomycin	≤0.06 to 1	0.12	0.5	100.0		
	Erythromycin	≤0.03 to >4	0.06	>4	62.1	0.8	37.0
	Levofloxacin	0.06 to >4	0.5	1	99.5	0.3	0.2
	Linezolid	0.5 to 1	1	1	100.0		
	Penicillin	≤0.03 to 0.12	≤0.03	0.06	100.0		
	Tetracycline	≤0.25 to >8	0.5	>8	51.2	2.0	46.7
	Teicoplanin	≤0.06 to 0.5	0.12	0.25	100.0[d]		0.0
	Vancomycin	≤0.06 to 1	0.25	0.5	100.0		
VGS (278)	Telavancin	≤0.002 to 0.06	0.015	0.03	100.0		
	Ceftaroline	≤0.008 to 0.5	0.015	0.06			
	Clindamycin	≤0.015 to >2	0.03	>2	83.7	0.7	15.6
	Daptomycin	≤0.06 to 1	0.5	0.5	100.0		
	Erythromycin	≤0.03 to >4	0.5	>4	47.1	4.3	48.6
	Levofloxacin	≤0.03 to >4	1	2	92.4	0.7	6.9
	Linezolid	≤0.06 to 1	0.5	1	100.0		
	Penicillin	≤0.03 to >4	≤0.03	0.5	79.0	18.8	2.2
	Tetracycline	≤0.25 to >8	0.5	>8	56.2	3.6	40.2
	Teicoplanin[d]	≤0.06 to 2	0.12	0.25	100.0		0.0
	Vancomycin	≤0.06 to 1	0.5	0.5	100.0		

[a]Criteria as published by CLSI (2016).
[b]Or 99.8% against vancomycin-susceptible *E. faecalis* only ($N = 405$).
[c]Using parenteral nonmeningitis breakpoints.
[d]Using EUCAST (2016) breakpoints.
I, intermediate; R, resistant; S, susceptible; TMX-SMX, trimethoprim–sulfamethoxazole.

telavancin ($MIC_{50/90}$, 0.12/0.12 μg/ml; 93.2% susceptible of all isolates or 99.8% of vancomycin-susceptible *E. faecalis*), ampicillin (100.0%), daptomycin (100.0%), linezolid (99.8%), teicoplanin (93.4%), and vancomycin (92.5%).

Activity of telavancin against Enterococcus faecium

Daptomycin and linezolid showed elevated susceptibility percentages (99.4%) against *Enterococcus faecium* isolates and a total of 71.1% were vancomycin resistant with 96.0% displaying a VanA phenotype (Tables 1 and 3). Vancomycin resistance rates among *E. faecium* isolates varied by U.S. Census Bureau Division, ranging from 50.0% (West North Central) to 89.7% (East South Central) (Table 2).

Telavancin was most active against vancomycin-susceptible *E. faecium* ($MIC_{50/90}$, 0.03/0.06 μg/ml). Whereas telavancin was active against VanB isolates of *E. faecium* ($MIC_{50/90}$, 0.5/1 μg/ml), it was inactive against strains of both species with a VanA phenotype (MIC_{90}, >2 μg/ml) (Table 1).

Activity of telavancin tested against S. pneumoniae

Telavancin was active against *S. pneumoniae* ($MIC_{50/90}$, 0.008/0.015 μg/ml) and all strains were inhibited at ≤0.03 μg/ml (Table 1). Ceftaroline ($MIC_{50/90}$, ≤0.008/0.12 μg/ml; 100.0% susceptible), levofloxacin ($MIC_{50/90}$, 1/1 μg/ml; 99.3% susceptible), linezolid ($MIC_{50/90}$, 1/1 μg/ml; 100.0% susceptible), and vancomycin ($MIC_{50/90}$, 0.25/0.25 μg/ml; 100.0% susceptible) were highly active against U.S. strains of pneumococci (Table 3). Penicillin nonsusceptibility (MIC, ≥4 μg/ml) occurred at a rate of 3.8% and erythromycin resistance (MIC, ≥1 μg/ml) occurred at 45.6% (Table 3). Penicillin nonsusceptibility varied by U.S. Census Division, ranging from 17.6% (Pacific Division) to 53.5% (West South Central) (data not shown).

Activity of telavancin tested against BHS and VGS

A total of 1,083 BHS were tested, 45.6% of which were *Streptococcus agalactiae*, 41.9% of which were *Streptococcus pyogenes*, and 12.5% of which were *Streptococcus dysgalactiae* (Table 1). Telavancin, ceftaroline, daptomycin, linezolid, penicillin, teicoplanin, and vancomycin inhibited all BHS tested at their respective breakpoints (Tables 1 and 3). Susceptibility to levofloxacin was 99.5% (Table 3). High rates of resistance occurred for clindamycin (constitutive resistance at 20.3%), erythromycin (37.0%), and tetracycline (46.7%) (Table 3). Macrolide resistance varied by division from a low of 22.0% (Pacific) to a high of 45.7% (East South Central) (data not shown).

The VGS were highly susceptible (100.0%) to telavancin, daptomycin, linezolid, and vancomycin (Table 3). All strains of VGS were inhibited by ≤0.5 μg/ml of ceftaroline ($MIC_{50/90}$, 0.015/0.06 μg/ml) (Table 3). The susceptibility of the VGS was reduced to erythromycin (47.1%), penicillin (79.0%), and tetracycline (56.2%) (Table 3). Susceptibility to clindamycin was 83.7% and levofloxacin resistance was 6.9% (Table 3). Telavancin MIC values among the VGS were predominantly from 0.008 to 0.03 μg/ml (modal MIC 0.015 μg/ml) and no isolate exhibited a telavancin MIC value at the susceptible breakpoint of ≤0.12 μg/ml (Table 1).

Discussion

Telavancin susceptibility testing of >8,000 gram-positive pathogens demonstrated excellent activity and a sustained susceptibility percentage of >99.9% overall against indicated species/groups (99.9% during the period 2011–2012). Telavancin MIC population distributions were determined using the revised BMD method and have remained stable without evidence of MIC creep among all monitored species.[6,9] Whereas the revised method demonstrates almost 100% coverage (susceptibility) of staphylococci, streptococci, and vancomycin-susceptible *E. faecalis*, telavancin is not active against the VanA phenotype of vancomycin-resistant enterococci (VRE) (MIC_{90}, >2 μg/ml). These data confirm and extend the observations noted previously by Mendes *et al.*[6] for U.S. isolates of gram-positive cocci when applying the appropriate BMD method and interpretive criteria.

Although resistance to other highly active anti-gram-positive agents has emerged throughout the United States, it generally is low in most divisions of the country.[6,12] In the present study, nonsusceptibility among target species (staphylococci, streptococci, and vancomycin-susceptible enterococci) to daptomycin, ceftaroline, and linezolid was virtually nil (range 0.0–0.9%). Teicoplanin-intermediate and -resistant *S. aureus* and CoNS were not detected in 2015. Likewise, there were no vancomycin-intermediate or -resistant strains of *S. aureus* or CoNS detected in this sampling of U.S. sites. However, VRE and MRSA rates remain high and vary considerably across the United States. Overall rates of VRE and MRSA in 2015 (68.5% and 44.9%, respectively) were lower than those reported by Mendes *et al.*[6] from 2011 to 2012 (73% and 48%, respectively), trends reported elsewhere.[13,14]

In conclusion, we have expanded on the previous results of Mendes *et al.*[6] demonstrating sustained potency and spectrum of telavancin against contemporary gram-positive clinical isolates from across the United States. We have employed the modified BMD method along with revised clinical breakpoints to confirm an 8- to 32-fold greater potency of telavancin over daptomycin, linezolid, and vancomycin when tested against staphylococci and streptococci, irrespective of their resistance to other gram-positive agents. These results coupled with those of Mendes *et al.*[6] should serve as the new benchmark for monitoring the *in vitro* activity of this lipoglycopeptide agent.

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Address correspondence to:
Rodrigo E. Mendes, PhD
JMI Laboratories
345 Beave Kreek Centre, Suite A
North Liberty, IA 52317

E-mail: rodrigo-mendes@jmilabs.com