Baseline Activity of Telavancin against Gram-Positive Clinical Isolates Responsible for Documented Infections in U.S. Hospitals (2011-2012) as Determined by the Revised Susceptibility Testing Method

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Telavancin had MIC₅₀ and MIC₉₀ values of 0.03 and 0.06 µg/ml (100.0% susceptible), respectively, against methicillin-resistant and -susceptible *Staphylococcus aureus*. Telavancin was active against vancomycin-susceptible *Enterococcus faecalis* (MIC_{50/90}, 0.12/0.12 µg/ml; 100% susceptible) and *Enterococcus faecium* (MIC_{50/90}, 0.03/0.06 µg/ml), while higher MIC values were obtained against vancomycin-resistant *E. faecium* (MIC_{50/90}, 1/2 µg/ml) and *E. faecalis* (MIC_{50/90}, >2/>2 µg/ml). Streptococci showed telavancin modal MIC results of ≤0.015 µg/ml, except against *Streptococcus agalactiae* (i.e., 0.03 µg/ml). This study reestablishes the telavancin spectrum of activity against isolates recovered from the United States (2011-2012) using the revised broth microdilution method.

Telavancin is a once-daily parenteral semisynthetic lipoglycopeptide agent approved in the United States and Canada for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive pathogens. Telavancin was also approved in the United States and Europe for the treatment of adult patients with hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia (HABP/VABP) due to susceptible isolates of *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA] strains only in Europe), when alternative medicines are unsuitable (1, 2). These indications were based on phase 3 clinical trials demonstrating noninferiority of telavancin over vancomycin (3, 4).

Telavancin possesses bactericidal activity against clinically relevant pathogens, such as *S. aureus*, including MRSA, heterogeneous vancomycin-intermediate *S. aureus* (hVISA) and VISA isolates, and vancomycin-susceptible enterococci (5–11). This bactericidal activity derives from a dual mechanism of action consisting of inhibition of peptidoglycan biosynthesis, similar to the glycopeptides, and interaction with the bacterial membrane to effect changes in membrane permeability and depolarization (12).

Early in 2014, the Food and Drug Administration (FDA) approved a labeling supplement for Vibativ (telavancin) containing a revised broth microdilution method (1) that is similar to that utilized for other members of the lipoglycopeptide class (i.e., oritavancin and dalbavancin) (13, 14). This revised method includes the use of dimethyl sulfoxide (DMSO) as the solvent for stock solution preparations and as the diluent for the dilution of stock solutions when manufacturing 96-well MIC plates. This procedure follows the current Clinical and Laboratory Standards Institute (CLSI) guidelines for water-insoluble agents (1, 15, 16). Moreover, this revised method includes the addition of polysorbate 80 (P-80; 0.002%) to the test medium (1, 15, 16).

This revised broth microdilution method for telavancin provides more accurate and reproducible results by minimizing drug loss during panel preparation (increased solubility) and testing (decreasing binding on plastic trays) (16). However, this revised broth microdilution method also provides lower MIC results than those obtained by the previously established method. Consequently, quality control (QC) MIC ranges and interpretive break-

points were reestablished (1, 15, 17). The objective of this investigation was to reassess the activity of telavancin when tested against a contemporary collection of isolates recovered from hospitalized patients in the United States (2011-2012) using the revised MIC testing method.

A total of 10,920 consecutive, nonduplicate isolates were collected from 28 U.S. sites located in 21 states in the nine U.S. Census regions. These isolates were recovered mostly from patients with SSSI (36%), bacteremia (26%), and respiratory tract infections (24%) and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA) as part of the 2011-2012 SENTRY Antimicrobial Surveillance Program. The isolates were primarily identified by the participating laboratory. Identification was confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and Vitek 2 (bioMérieux, Hazelwood, MO) and/or by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany) when initial identification performed by the participating laboratory was believed to be erroneous upon receipt of the isolate.

Isolates were tested for susceptibility by broth microdilution by following the CLSI approved standard (18). Testing was performed using panels manufactured by Thermo Fisher Scientific (Cleveland, OH). These panels provide telavancin MIC results

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TABLE 1 Antimicrobial activity and MIC distribution for telavancin when tested against contemporary (2011–2012) clinical isolates from U.S. medical centers using the revised broth microdilution testing method

Organism ^a	No. tested	MIC (μg/ml) data		Number (cumulative %) inhibited at telavancin MIC (μg/ml) of:							
		MIC ₅₀	MIC ₉₀	≤0.015	0.03	0.06	0.12	0.25	0.5	1	>1
<i>S. aureus</i>	6,264										
MSSA	3,245	0.03	0.06	144 (4.4)	1,979 (65.4)^b	1,113 (99.7)	9 (100.0) ^c				
MRSA	3,019	0.03	0.06	73 (2.4)	1,664 (57.5)^b	1,267 (99.5)	15 (100.0) ^c				
Vancomycin MIC, ≥1 μg/ml	6,149	0.03	0.06	214 (3.5)	3,629 (62.5)^b	2,290 (99.7)	16 (100.0) ^c				
Vancomycin MIC, 2–4 μg/ml ^d	115	0.06	0.06	3 (2.6)	14 (14.8)	90 (93.0)	8 (100.0) ^c				
CoNS	461	0.06	0.06	76 (16.5)	126 (43.8)	248 (97.6)^b	11 (100.0)				
<i>E. faecalis</i>	649	0.12	0.12	2 (0.3)	13 (2.3)	181 (30.2)	421 (95.1)^b	11 (96.8) ^{c,e}	0 (96.8)	4 ^f (97.4)	17 ^f (100.0)
<i>E. faecium</i>	328										
Vancomycin susceptible	81	0.03	0.06	19 (23.5)	43 (76.5)^b	17 (97.5)	2 (100.0)				
VanA phenotype	241	1	>1 ^g	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.7)	25 (12.0)	101 (53.9)	111 (90.5)^b
<i>S. pneumoniae</i>	1,801	≤0.015	≤0.015	1,778 (98.7)^b	22 (1.2)	1 (100.0)					
VGS	446	≤0.015	0.03	246 (55.2)^b	176 (94.6)	24 (100.0) ^c					
<i>S. anginosus</i> group	120	≤0.015	0.03	75 (62.5)^b	38 (94.2)	7 (100.0) ^c					
BHS	971	0.03	0.06	434 (44.7)^b	307 (76.3)	207 (97.6)	23 (100.0) ^c				
<i>S. pyogenes</i>	449	≤0.015	0.03	326 (72.6)^b	95 (93.8)	28 (100.0)	0 (100.0) ^c				
<i>S. agalactiae</i>	393	0.03	0.06	28 (7.1)	171 (50.6)^b	171 (94.1)^b	23 (100.0) ^c				

^a MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; VanA phenotype, vancomycin and teicoplanin MICs of >4 and >8 μg/ml, respectively; VGS, viridans group streptococci; BHS, beta-hemolytic streptococci.

^b Modal MICs values are shown in bold.

^c Percentage of susceptible isolates at updated FDA-approved breakpoints as follows: *S. aureus* at ≤0.12 μg/ml for susceptible, EUCAST breakpoint for telavancin against MRSA at ≤0.12 μg/ml for susceptible, *E. faecalis* (vancomycin susceptible) at ≤0.25 μg/ml for susceptible; breakpoint for VGS was that from *Streptococcus anginosus* group (≤0.06 μg/ml for susceptible), while the interpretive criterion for *Streptococcus pyogenes* and *Streptococcus agalactiae* (≤0.12 μg/ml for susceptible) was applied for BHS.

^d All *S. aureus* isolates exhibited vancomycin MIC results of 2 μg/ml, except for a single isolate (MIC, 4 μg/ml).

^e All vancomycin-susceptible (*n* = 625) and vancomycin-resistant (VanB; *n* = 3) *E. faecalis* isolates were susceptible to telavancin (i.e., all inhibited at ≤0.25 μg/ml).

^f All VanA phenotype isolates (*n* = 21).

^g MIC₉₀, 2 μg/ml.

(dilution range applied, 0.015 to 2 μg/ml) equivalent to the revised FDA-approved broth microdilution method (1, 15, 16). Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event. Validation of the MIC values was performed by concurrent testing of CLSI-recommended QC reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619) (1, 15). All QC results were within published acceptable ranges. The MIC interpretations for telavancin when tested against the clinical isolates were based on updated breakpoint criteria for the revised method recently approved by the FDA (1). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) updated breakpoint (≤0.12 μg/ml for susceptible) for telavancin was applied against MRSA isolates. The CLSI (2014) and EUCAST (2014) breakpoint criteria were applied for comparator agents, as available (15, 19).

Telavancin (MIC_{50/90}, 0.03/0.06 μg/ml) was equally potent when tested against methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates and inhibited 100.0% of *S. aureus* isolates at the FDA breakpoint for susceptibility (i.e., ≤0.12 μg/ml) (Table 1). The telavancin MIC₅₀ and MIC₉₀ results were 8-fold lower than those of daptomycin (MIC_{50/90}, 0.25/0.5 μg/ml), and 16- to 32-fold lower than those of linezolid (MIC_{50/90}, 1/1 μg/ml) and van-

comycin (MIC_{50/90}, 1/1 μg/ml) against MRSA (Table 2). Other comparators, such as gentamicin, tetracycline, and trimethoprim-sulfamethoxazole, were also active against MRSA (≥92.1% susceptible). When telavancin activity was analyzed against a subset of *S. aureus* isolates exhibiting elevated MIC results for vancomycin (i.e., 2 to 4 μg/ml), slightly higher (2-fold) modal MIC and MIC₅₀ values (0.06 μg/ml for both, 100.0% susceptible) were obtained compared with those of the control group (i.e., vancomycin MIC, ≤1 μg/ml; modal MIC and MIC₅₀ values of 0.03 μg/ml; 100.0% susceptible) (Table 1). Overall, a total of 66.6% of coagulase-negative staphylococci (CoNS) were methicillin resistant, and telavancin (MIC_{50/90}, 0.06/0.06 μg/ml) showed MIC results 16- to 32-fold lower than those of vancomycin (MIC_{50/90}, 1/2 μg/ml) and 4- to 16-fold lower than those of daptomycin (MIC_{50/90}, 0.25/0.5 μg/ml) and linezolid (MIC_{50/90}, 0.5/1 μg/ml) (Tables 1 and 2). Other agents tested against CoNS did not show *in vitro* activity, with susceptibility rates of ≤86.1% and MIC₉₀ values of >2 μg/ml (Table 2).

All *E. faecalis* isolates were inhibited by telavancin at the FDA-approved breakpoint for susceptibility (i.e., ≤0.25 μg/ml), including vancomycin-resistant isolates (VanB phenotype), except for 21 (3.2% of total) vancomycin-resistant isolates displaying a VanA phenotype (Table 1). Telavancin (MIC_{50/90}, 0.12/0.12 μg/

TABLE 2 Antimicrobial activity of telavancin and comparator agents tested against Gram-positive clinical isolates from the United States using a revised broth microdilution testing method

Organism ^a (no. tested) and antimicrobial agent	Range	MIC (μg/ml) data		% susceptible/intermediate/resistant using breakpoint from ^b :		
		MIC ₅₀	MIC ₉₀	CLSI	FDA	EUCAST
MRSA (3,019)						
Telavancin	≤0.015 to 0.25	0.03	0.06	NA ^c	100.0/NA/NA	100.0/NA/NA
Vancomycin	0.25 to 4	1	1	>99.9/<0.1/0.0		>99.9/0.0/<0.1
Daptomycin	0.12 to 2	0.25	0.5	99.9/NA/NA		99.9/0.0/0.1
Linezolid	0.25 to 8	1	1	99.9/0.0/0.1		99.9/0.0/0.1
Levofloxacin	≤0.12 to >4	4	>4	30.9/2.6/66.5		30.9/2.6/66.5
Erythromycin	≤0.12 to >16	>16	>16	10.1/1.9/88.0		10.3/0.3/89.4
Clindamycin	≤0.25 to >2	≤0.25	>2	70.1/0.2/29.7		69.9/0.2/29.9
Gentamicin	≤1 to >8	≤1	≤1	96.9/0.1/3.0		96.4/0.0/3.6
Tetracycline	≤0.25 to >8	≤0.25	1	94.8/0.5/4.7		92.1/2.5/5.4
Trimethoprim-sulfamethoxazole	≤0.5 to >4	≤0.5	≤0.5	97.9/0.0/2.1		97.9/0.3/1.8
CoNS (461)						
Telavancin	≤0.015 to 0.12	0.06	0.06	NA	NA	NA
Oxacillin	≤0.25 to >2	1	>2	33.4/0.0/66.6		33.4/0.0/66.6
Vancomycin	0.5 to 4	1	2	100.0/0.0/0.0		100.0/0.0/0.0
Daptomycin	≤0.06 to 1	0.25	0.5	100.0/NA/NA		100.0/0.0/0.0
Linezolid	0.25 to >8	0.5	1	99.3/0.0/0.7		99.3/0.0/0.7
Levofloxacin	≤0.12 to >4	0.5	>4	55.1/1.9/43.0		55.1/1.9/43.0
Erythromycin	≤0.12 to >16	>16	>16	38.4/1.9/59.7		39.0/0.5/60.5
Clindamycin	≤0.25 to >2	≤0.25	>2	72.5/2.6/24.9		71.2/1.3/27.5
Gentamicin	≤1 to >8	≤1	>8	80.9/4.3/14.8		77.4/0.0/22.6
Tetracycline	≤0.25 to >8	≤0.25	>8	86.1/0.9/13.0		76.8/9.1/14.1
Trimethoprim-sulfamethoxazole	≤0.5 to >4	≤0.5	>4	69.2/0.0/30.8		69.2/12.1/18.7
Vancomycin-susceptible <i>E. faecalis</i> (625)						
Telavancin	≤0.015 to 0.25	0.12	0.12	NA	100.0/NA/NA	NA
Ampicillin	≤0.25 to >8	1	2	99.8/0.0/0.2		99.7/0.1/0.2
Vancomycin	0.5 to 4	1	2	100.0/0.0/0.0		100.0/0.0/0.0
Daptomycin	≤0.06 to 4	1	2	100.0/NA/NA		NA
Linezolid	0.25 to 2	1	2	100.0/0.0/0.0		100.0/0.0/0.0
Levofloxacin	0.25 to >4	1	>4	73.8/0.8/25.4		NA
Tetracycline	≤0.25 to >8	>8	>8	24.6/1.0/74.4		NA
Vancomycin-susceptible <i>E. faecium</i> (81)						
Telavancin	≤0.015 to 0.12	0.03	0.06	NA	NA	NA
Ampicillin	≤0.25 to >8	>8	>8	38.3/0.0/61.7		37.0/1.3/61.7
Vancomycin	0.25 to 4	1	1	100.0/0.0/0.0		100.0/0.0/0.0
Daptomycin	0.5 to 8	2	4	98.8/NA/NA		NA
Linezolid	0.25 to 2	1	2	100.0/0.0/0.0		100.0/0.0/0.0
Levofloxacin	0.5 to >4	>4	>4	33.3/7.4/59.3		NA
Tetracycline	≤0.25 to >8	>8	>8	27.2/2.4/70.4		NA
Vancomycin-resistant <i>E. faecium</i> (241)						
Telavancin	0.12 to >2	1	2	NA	NA	NA
Ampicillin	4 to >8	>8	>8	0.8/0.0/99.2		0.4/0.4/99.2
Vancomycin	>16	>16	>16	0.0/0.0/100.0		0.0/0.0/100.0
Daptomycin	0.5 to >4	2	2	99.6/NA/NA		NA
Linezolid	0.5 to 4	1	1	99.6/0.4/0.0		100.0/0.0/0.0
Levofloxacin	>4	>4	>4	0.0/0.0/100.0		NA
Tetracycline	≤0.25 to >8	>8	>8	19.1/1.2/79.7		NA
<i>S. pneumoniae</i> (1,801)						
Telavancin	≤0.015 to 0.06	≤0.015	≤0.015	NA	NA	NA
Penicillin	≤0.06 to 8	≤0.06	4	89.0/9.7/1.3 ^d		NA
Penicillin	≤0.06 to 8	≤0.06	4	57.3/23.1/19.6 ^e		57.3/31.7/11.0
Vancomycin	≤0.12 to 0.5	0.25	0.5	100.0/NA/NA		100.0/0.0/0.0
Linezolid	≤0.12 to 2	1	1	100.0/NA/NA		100.0/0.0/0.0
Levofloxacin	≤0.12 to >4	1	1	98.9/0.2/0.9		98.9/0.0/1.1

(Continued on following page)

TABLE 2 (Continued)

Organism ^a (no. tested) and antimicrobial agent	Range	MIC (μg/ml) data		% susceptible/intermediate/resistant using breakpoint from ^b :		
		MIC ₅₀	MIC ₉₀	CLSI	FDA	EUCAST
Erythromycin	≤0.12 to >16	≤0.12	>16	57.1/0.5/42.4		57.1/0.5/42.4
Clindamycin	≤0.25 to >2	≤0.25	>2	81.0/0.6/18.4		81.6/0.0/18.4
Tetracycline	≤0.25 to >8	≤0.25	>8	76.3/0.3/23.4		76.3/0.3/23.4
VGS (446)						
Telavancin	≤0.015 to 0.06	≤0.015	0.03	NA	100.0/NA/NA	NA
Penicillin	≤0.06 to >8	≤0.06	1	74.0/22.9/3.1		82.1/14.8/3.1
Vancomycin	≤0.12 to 1	0.5	1	100.0/NA/NA		100.0/0.0/0.0
Daptomycin	≤0.06 to 1	0.25	1	100.0/NA/NA		NA
Linezolid	≤0.12 to 2	1	1	100.0/NA/NA		NA
Levofloxacin	≤0.12 to >4	1	2	92.4/1.3/6.3		NA
Erythromycin	≤0.12 to >16	1	>16	47.3/2.3/50.4		NA
Clindamycin	≤0.25 to >2	≤0.25	>2	85.4/0.9/13.7		86.3/0.0/13.7
Tetracycline	≤0.25 to >8	0.5	>8	61.2/5.8/33.0		NA
BHS (971)						
Telavancin	≤0.015 to 0.12	0.03	0.06	NA	100.0/NA/NA	NA
Penicillin	≤0.06 to 0.12	≤0.06	≤0.06	100.0/NA/NA		100.0/0.0/0.0
Vancomycin	0.25 to 1	0.5	0.5	100.0/NA/NA		100.0/0.0/0.0
Daptomycin	≤0.06 to 0.5	≤0.06	0.25	100.0/NA/NA		100.0/0.0/0.0
Linezolid	0.25 to 2	1	1	100.0/NA/NA		100.0/0.0/0.0
Levofloxacin	≤0.12 to >4	0.5	1	98.9/0.3/0.8		94.1/4.8/1.1
Erythromycin	≤0.12 to >16	≤0.12	>16	68.7/0.4/30.9		68.7/0.4/30.9
Clindamycin	≤0.25 to >2	≤0.25	>2	83.1/0.4/16.5		83.5/0.0/16.5
Tetracycline	≤0.25 to >8	1	>8	51.4/1.6/47.0		50.4/1.0/48.6

^a MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; VGS, viridans group streptococci; BHS, beta-hemolytic streptococci.

^b Breakpoint criteria for telavancin according to the labeling supplement for Vibativ, as available: *S. aureus* at ≤0.12 μg/ml for susceptible, EUCAST breakpoint for telavancin against MRSA at ≤0.12 μg/ml for susceptible, *E. faecalis* (vancomycin susceptible) at ≤0.25 μg/ml for susceptible; breakpoint for VGS was that from *S. anginosus* group (≤0.06 μg/ml for susceptible), while the interpretive criterion for *S. pyogenes* and *S. agalactiae* (≤0.12 μg/ml for susceptible) was applied for BHS. Breakpoint criteria for comparator agents were those from CLSI (M100-S24; 2014) and EUCAST (2014), as available.

^c NA, breakpoint not available.

^d Susceptibility breakpoints for parenteral penicillin (nonmeningitis).

^e Susceptibility breakpoints for oral penicillin.

ml) was at least 8-fold more active than the comparator agents tested against vancomycin-susceptible *E. faecalis*, including ampicillin (MIC_{50/90}, 1/2 μg/ml), vancomycin (MIC_{50/90}, 1/2 μg/ml), and daptomycin (MIC_{50/90}, 1/2 μg/ml) (Table 2). While telavancin was active against vancomycin-susceptible *E. faecium* (MIC_{50/90}, 0.03/0.06 μg/ml), higher MIC values were obtained against VanA phenotype strains (MIC_{50/90}, 1/2 μg/ml) (Tables 1 and 2). Telavancin (MIC_{50/90}, 1/2 μg/ml), daptomycin (MIC_{50/90}, 2/2 μg/ml; 99.6% susceptible), and linezolid (MIC_{50/90}, 1/1 μg/ml; 99.6 to 100.0% susceptible) had in-range MIC₅₀ and MIC₉₀ results against the latter group (Table 2). The tested streptococcal isolates showed low MIC results for telavancin, with MIC₅₀ results of ≤0.015 μg/ml, except for *Streptococcus agalactiae*, which exhibited MIC₅₀ and MIC₉₀ results of 0.03 and 0.06 μg/ml, respectively (Table 1). In addition, telavancin showed MIC₅₀ and MIC₉₀ values lower than those of comparator agents when tested against *S. pneumoniae* and viridans group streptococci, with telavancin and penicillin demonstrating the lowest and similar MIC results against beta-hemolytic streptococci (Table 2).

The results presented here were obtained using the recent FDA-approved revised broth microdilution method (16), which ensures a proper assessment of the telavancin MIC determination, especially when tested against staphylococci and enterococci. The MIC values described herein are lower than those obtained by the

previously established broth microdilution method (20, 21). However, the telavancin antimicrobial susceptibility rates remain high (100.0% susceptible) and very similar to those observed in earlier investigations (20, 21). Although the revised method results in potent and lower MIC values for staphylococci, streptococci, and vancomycin-susceptible enterococci than the previous method, telavancin was less active against VanA phenotype vancomycin-resistant enterococcus, regardless of the method used (22, 23). Moreover, these *in vitro* MIC results are now comparable to those reported for other lipoglycopeptide agents (i.e., oritavancin and dalbavancin) that utilize similar susceptibility testing methodologies to telavancin (24, 25) and are mostly lower than those for other comparators. Finally, this study reestablishes the *in vitro* potencies and susceptibility profiles of telavancin (using updated interpretive criteria) against isolates recovered from the United States (2011-2012).

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