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In Vitro Activity of Telavancin against Resistant Gram-Positive Bacteria▽

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The in vitro activity of telavancin was tested against 743 predominantly antimicrobial-resistant, gram-positive isolates. Telavancin was highly active against methicillin-resistant staphylococci (MIC_{90}, 0.5 to 1 μg/ml), streptococci (all MICs, ≤0.12 μg/ml), and VanB-type enterococci (all MICs, ≤2 μg/ml). Time-kill studies demonstrated the potent bactericidal activity of telavancin.

The pervasiveness of multidrug-resistant, gram-positive bacteria in the hospital setting and their increasing occurrence in the community present a significant challenge for the management of serious infections (1, 10, 11). The worldwide prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCoNS) poses a particular threat (2, 6, 10, 11).

Telavancin, an investigational, multivalent lipoglycopeptide active against gram-positive pathogens, has been evaluated in phase 3 clinical trials for the treatment of complicated skin and skin structure infections (cSSSI) and hospital-acquired pneumonia (G. R. Corey, M. E. Stryjewski, W. D. O'Riordan, V. G. Fowler, Jr., A. Hopkins, M. M. Kitt, and S. L. Barriere, presented at the 14th Annual Meeting of the Infectious Diseases Society of America, Torono, Canada, 12 to 15 October 2006; E. Rubinstein, G. R. Corey, M. E. Stryjewski, H. W. Boucher, R. N. Daly, F. C. Genter, S. L. Barriere, M. M. Kitt, and H. D. Friedland, presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 19 to 22 April 2008).

Preliminary surveillance studies have documented the in vitro activity of telavancin against gram-positive pathogens, including MRSA and CoNS, with reduced susceptibility to glycopeptides and other resistant gram-positive species (5, 7–9, 13). In this report, we describe the results of broth microdilution susceptibility testing of telavancin and comparator agents against a diverse collection of multiresistant gram-positive bacteria including MRSA, MRCoNS, streptococci, including multidrug-resistant *Streptococcus pneumoniae* (MDRSP), and vancomycin-resistant enterococci (VRE). Time-kill kinetic studies were also performed with representative drug-resistant isolates to further profile the bactericidal activity of telavancin.

A total of 743 gram-positive clinical isolates collected globally between 1998 and 2006 were assembled for this study. Clinical isolates of MRSA (n = 98) were obtained from patients with cSSSI, bacteremia, endocarditis, osteomyelitis, or foreign body infections. Other clinical isolates included 91 MRCoNS, 131 *S. pneumoniae* isolates, 203 β-hemolytic streptococci, 8 viridans group streptococci, and 212 VRE. Five reference strains (including three quality control strains and two type strains used for time-kill studies) were also tested.

Telavancin was prepared by Theravance, Inc. (South San Francisco, CA). All other antibiotics for MIC testing were supplied independently by TREK Diagnostic Systems (Cleveland, OH). Comparator agents for time-kill studies included vancomycin (Sigma Chemical Co., St. Louis, MO) and linezolid (Zyvox; Pfizer). Susceptibility tests were performed by reference broth microdilution methodology as defined by the CLSI using frozen form panels prepared by TREK Diagnostic Systems (Cleveland, OH) (3). MICs for all streptococci were determined in panels supplemented with 2 to 5% lysed horse blood. Vancomycin and teicoplanin MIC results were used to define the resistance determinants of VRE. *S. pneumoniae* strains exhibiting concurrent resistance to at least three of the following agents were defined as MDRSP: cefuroxime, penicillin, tetracycline, erythromycin, or trimethoprim-sulfamethoxazole.

Time-kill experiments were performed according to CLSI (formerly NCCLS) defined methodology (12) for seven isolates: MRSA MED 2028 (osteomyelitis isolate), MRSA MED 1805 (bloodstream isolate), methicillin-resistant *S. epidermidis* (MRSE) ATCC 35984 (American Type Culture Collection, Manassas, VA), MDRSP MED 1090 (Massachusetts General Hospital, Boston, MA), *Streptococcus agalactiae* MED 2038 and *Streptococcus pyogenes* MED 2040 (both cSSSI isolates) (G. R. Corey et al., presented at the 14th Annual Meeting of the Infectious Diseases Society of America, Torono, Canada, 12 to 15 October 2006), and VanB-type vancomycin-resistant *Enterococcus faecalis* ATCC 51575 (American Type Culture Collection).

The MIC profiles of telavancin and comparator agents against all tested isolates are summarized in Table 1. Based upon MIC_{90} comparisons, telavancin was among the most-active agents tested against clinical strains of MRSA (MIC_{90} = 0.5 μg/ml); all isolates were inhibited by ≤1 μg/ml telavancin. Concurrent resistance to comparators had no effect on telavancin activity. Telavancin MICs for two daptomycin-nonsusceptible isolates (daptomycin MICs of 4 and 8 μg/ml) were 0.5 and 0.25 μg/ml. Based upon MIC_{90} comparisons, daptomycin and quinupristin-dalfopristin were as potent as telavancin, followed by teicoplanin, vancomycin, gentamicin, and linezolid.

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TABLE 1. In vitro activity of telavancin against resistant staphylococci, streptococci, and enterococci

Organism (no. tested) and antibiotic	MIC (μg/ml)[g]			% Susceptible[a]
	Range	50%	90%	
S. aureus, methicillin resistant (98)				
Telavancin	0.06–1	0.25	0.5	—
Vancomycin	0.25–2	0.5	1	100
Teicoplanin	0.25–4	0.5	1	100
Ciprofloxacin	≤0.06–>8	8	16	32
Daptomycin	0.12–>1	0.25	0.5	98
Linezolid	1–8	2	4	98
Quinupristin-dalfopristin	≤0.12–0.5	0.25	0.5	99
Gentamicin	≤0.06–>16	0.5	2	97
Erythromycin	0.5–>16	>16	>16	2
Telithromycin	0.06–>8	0.25	16	83
Trimethoprim-sulfamethoxazole[b]	≤0.5–4	≤0.5	≤0.5	99
S. epidermidis, methicillin resistant (74)				
Telavancin	0.25–1	0.5	1	—
Vancomycin	0.5–4	2	2	100
Teicoplanin	0.25–16	8	16	81
Ciprofloxacin	≤0.12–>8	4	>8	28
Daptomycin	0.25–1	0.5	1	100
Linezolid	≤0.5–4	1	1	100
Quinupristin-dalfopristin	≤0.12–4	0.25	2	93
Gentamicin	≤0.06–>16	16	>16	35
Erythromycin	≤0.12–>16	>16	>16	15
Telithromycin	0.06–>8	0.5	>8	43
Trimethoprim-sulfamethoxazole[b]	≤0.5–>4	>4	>4	37
CoNS, methicillin resistant (17)[c]				
Telavancin	0.06–1	0.5	1	—
Vancomycin	0.25–4	2	2	100
Teicoplanin	≤0.12–32	4	32	88
Ciprofloxacin	≤0.06–>8	>8	>8	35
Daptomycin	0.12–1	0.25	1	100
Linezolid	0.5–2	1	2	100
Quinupristin-dalfopristin	≤0.12–1	0.25	0.5	100
Gentamicin	≤0.06–>16	16	>16	29
Erythromycin	≤0.12–>16	>16	>16	18
Telithromycin	0.12–>8	>8	>8	29
Trimethoprim-sulfamethoxazole[b]	≤0.5–>4	>4	>4	29
S. pneumoniae, penicillin intermediate (12)				
Telavancin	0.004–0.12	0.015	0.06	—
Vancomycin	≤0.06–0.5	0.25	0.5	100
Daptomycin	0.06–1	0.12	0.5	—
Linezolid	0.5–2	1	1	100
Penicillin	0.12–1	1	1	0
Clindamycin	0.06–>0.25	0.06	0.5	83
Erythromycin	0.03–>1	>1	>1	42
Telithromycin	0.008–0.12	0.03	0.12	100
Trimethoprim-sulfamethoxazole[b]	≤0.06–>4	2	4	8
Cefuroxime	0.5–>4	2	4	17
Ceftriaxone	0.25–2	0.5	1	92
Levofloxacin	0.25–8	0.5	1	92
Tetracycline	≤0.06–>8	0.12	>8	67
S. pneumoniae, penicillin resistant (59)				
Telavancin	0.008–0.12	0.015	0.03	—
Vancomycin	0.12–1	0.25	0.25	100
Daptomycin	0.06–0.5	0.12	0.12	—
Linezolid	0.5–2	1	1	100
Penicillin	2–>2	2	>2	0
Clindamycin	≤0.03–>0.25	0.06	>0.25	76
Erythromycin	0.03–>1	>1	>1	20
Telithromycin	0.004–0.5	0.06	0.5	100
Trimethoprim-sulfamethoxazole[b]	≤0.06–>4	4	>4	3
Cefuroxime	1–>4	>4	>4	2
Ceftriaxone	0.5–>4	1	2	73
Levofloxacin	≤0.12–>8	0.5	1	97
Tetracycline	≤0.06–>8	>8	>8	41
MDRSP (60)[d]				
Telavancin	0.008–0.12	0.015	0.03	—
Vancomycin	0.12–1	0.25	0.25	100
Daptomycin	0.06–0.5	0.12	0.12	—
Linezolid	0.5–2	1	1	100
Penicillin	1–>2	2	>2	0
Clindamycin	≤0.03–>0.25	0.06	>0.25	73
Erythromycin	0.03–>1	>1	>1	13
Telithromycin	0.004–0.5	0.06	0.5	100

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TABLE 1—*Continued*

Organism (no. tested) and antibiotic	MIC (μg/ml)[g]			% Susceptible[a]
	Range	50%	90%	
Trimethoprim-sulfamethoxazole[b]	≤0.06–>4	4	>4	3
Cefuroxime	1–>4	>4	>4	2
Ceftriaxone	0.5–>4	1	2	77
Levofloxacin	≤0.12–>8	0.5	1	95
Tetracycline	≤0.06–>8	>8	>8	37
S. pyogenes, group A (122)				
Telavancin	≤0.001–0.12	0.03	0.06	—
Vancomycin	≤0.06–>1	0.25	0.5	98
Daptomycin	≤0.03–1	≤0.03	0.25	100
Linezolid	≤0.012–>2	1	1	98
Penicillin	≤0.06–>2	≤0.06	≤0.06	93
Clindamycin	≤0.03–>0.25	≤0.03	0.06	98
Erythromycin	≤0.015–>1	0.03	>1	89
Telithromycin	0.004–1	0.015	0.015	—
Trimethoprim-sulfamethoxazole[b]	≤0.06–4	≤0.06	0.12	—
Cefuroxime	≤0.12–>4	≤0.12	0.25	—
Ceftriaxone	≤0.015–>4	≤0.015	0.12	92
Levofloxacin	≤0.12–>8	0.5	1	98
Tetracycline	≤0.06–>8	0.12	4	89
S. agalactiae, group B (81)				
Telavancin	0.03–0.12	0.06	0.06	—
Vancomycin	0.25–1	0.25	0.5	100
Daptomycin	0.06–0.5	0.25	0.25	100
Linezolid	0.25–2	1	1	100
Penicillin	≤0.06–>2	≤0.06	≤0.06	96
Clindamycin	≤0.03–>0.25	0.06	>0.25	86
Erythromycin	≤0.015–>1	0.06	>1	62
Telithromycin	0.004–0.5	0.015	0.25	—
Trimethoprim-sulfamethoxazole[b]	≤0.06–2	0.12	0.12	—
Cefuroxime	≤0.12–>4	≤0.12	≤0.12	—
Ceftriaxone	0.03–>4	0.06	0.06	96
Levofloxacin	≤0.12–>8	0.5	1	99
Tetracycline	≤0.06–>8	>8	>8	16
Viridans group streptococci (8)[f]				
Telavancin	0.015–0.06	N/A[e]	N/A	—
Vancomycin	0.25–1	N/A	N/A	100
Daptomycin	0.25–1	N/A	N/A	100
Linezolid	0.5–2	N/A	N/A	100
Penicillin	≤0.06–>2	N/A	N/A	62
Clindamycin	≤0.03–>0.25	N/A	N/A	88
Erythromycin	≤0.015–>1	N/A	N/A	63
Telithromycin	0.004–0.25	N/A	N/A	—
Trimethoprim-sulfamethoxazole[b]	≤0.06–4	N/A	N/A	—
Cefuroxime	≤0.12–>4	N/A	N/A	—
Ceftriaxone	0.03–>4	N/A	N/A	75
Levofloxacin	≤0.12–1	N/A	N/A	100
Tetracycline	0.12–>8	N/A	N/A	75
E. faecalis, vancomycin resistant, VanA (21)				
Telavancin	4–32	8	16	—
Vancomycin	128–>512	512	>512	0
Teicoplanin	32–>128	64	>128	0
Ampicillin	≤0.25–128	1	64	81
Ciprofloxacin	0.25–>32	>32	>32	14
Daptomycin	0.5–4	1	2	100
Linezolid	1–2	1	2	100
E. faecalis, vancomycin resistant, VanB (5)				
Telavancin	0.25–1	N/A	N/A	—
Vancomycin	32–256	N/A	N/A	0
Teicoplanin	0.5–1	N/A	N/A	100
Ampicillin	≤0.25–64	N/A	N/A	60
Ciprofloxacin	32–>32	N/A	N/A	0
Daptomycin	0.5–4	N/A	N/A	100
Linezolid	0.5–2	N/A	N/A	100
E. faecium, vancomycin resistant, VanA (159)				
Telavancin	2–16	8	16	—
Vancomycin	64–>512	512	>512	0
Teicoplanin	16–>128	64	>128	0
Ampicillin	16–>128	64	128	0
Ciprofloxacin	2–>32	>32	>32	0
Daptomycin	0.5–8	2	4	98
Linezolid	0.25–32	2	2	99
Quinupristin-dalfopristin	0.25–16	0.5	1	98

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TABLE 1—*Continued*

Organism (no. tested) and antibiotic	MIC (μg/ml)[g]			% Susceptible[a]
	Range	50%	90%	
E. faecium, vancomycin resistant, VanB (27)				
Telavancin	0.06–2	0.5	2	—
Vancomycin	32–>512	512	>512	0
Teicoplanin	0.25–4	0.5	1	100
Ampicillin	0.5–128	64	64	22
Ciprofloxacin	8–>32	>32	>32	0
Daptomycin	0.25–8	2	4	93
Linezolid	0.5–4	2	2	96
Quinupristin-dalfopristin	0.5–>32	1	8	67

[a] MIC interpretive criteria from CLSI document M100–S17 used for determination of % Susceptible (—, breakpoint not available) (4).
[b] MICs reported based on concentration of trimethoprim.
[c] Includes two isolates of *S. auricularis*, one *S. capitis*, five *S. haemolyticus*, eight *S. hominis* subsp. *novobiosepticus*, and one *S. saprophyticus*.
[d] Multidrug-resistant *S. pneumoniae*.
[e] For MIC_{50} and MIC_{90}, N/A indicates that the sample size was insufficient to calculate.
[f] Includes three isolates of *S. mitis*, two *S. intermedius*, and one each of *S. oralis, S. constellatus*, and *S. viridans*.
[g] Telavancin quality controls for all MIC experiments were within CLSI-defined ranges: *S. aureus* ATCC 29213, 0.12 to 1 μg/ml; *S. pneumoniae* ATCC 49619, 0.004 to 0.03 μg/ml; and *E. faecalis* ATCC 29212, 0.12 to 0.5 μg/ml (4).

Trimethoprim-sulfamethoxazole was the most-active agent tested against these strains.

The telavancin MIC_{90} against 74 MRSE and 17 other CoNS that were also resistant to methicillin was 1 μg/ml. Based on MIC_{90} comparisons, telavancin was more potent against this group of organisms than were vancomycin (MIC_{90} = 2 μg/ml) and teicoplanin (MIC_{90} = 16 μg/ml). Telavancin MICs against 16 teicoplanin nonsusceptible MRCoNS ranged from 0.25 to 0.5 μg/ml.

All streptococci were highly susceptible to telavancin, including penicillin-intermediate and -resistant *S. pneumoniae* and MDRSP (MIC_{90} = 0.03 μg/ml for all), group A and group B streptococci (MIC_{90} = 0.06 μg/ml), and viridans group streptococci (MIC range, 0.015 to 0.06 μg/ml). All streptococci were inhibited by ≤0.12 μg/ml of telavancin. The activities of telavancin (MIC_{90} = 0.03 μg/ml), vancomycin (MIC_{90} = 0.5 μg/ml), linezolid (MIC_{90} = 1 μg/ml), and telithromycin (MIC_{90} = 0.5 μg/ml) against all tested streptococci were unaffected by resistance to other agents, including the activities against MDRSP isolates with concurrent resistance to penicillin, erythromycin, trimethoprim-sulfamethoxazole, cefuroxime, and tetracycline. Some strains of MDRSP tested in this study were also nonsusceptible to other agents, including levofloxacin (5% nonsusceptible; MIC_{90} = 1 μg/ml), clindamycin (27% nonsusceptible; MIC_{90} = >0.25 μg/ml), and ceftriaxone (23% nonsusceptible; MIC_{90} = 2 μg/ml).

Telavancin activity against all 212 tested VRE covered a broad MIC range (0.06 to 32 μg/ml). Based upon MIC_{90} comparisons, telavancin was at least 32- and 8-fold more active than vancomycin and teicoplanin, respectively, against all tested enterococci. A bimodal distribution of telavancin MICs was observed (Fig. 1). All 32 VanB-type isolates were inhibited by ≤2 μg/ml telavancin and displayed susceptibility (MIC_{90} = 2 μg/ml) comparable to that reported for vancomycin-sensitive

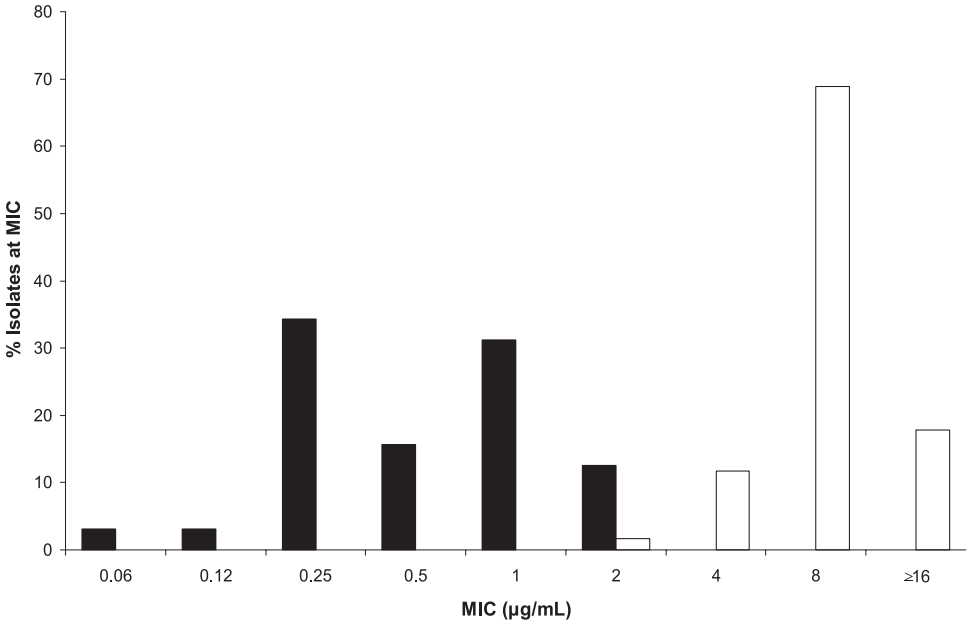

FIG. 1. Distribution of telavancin MICs against VRE. Filled bars, VanB-type isolates; open bars, VanA-type isolates.

TABLE 2. Kill kinetics of telavancin and comparators against resistant gram-positive isolates

Organism[b]	Antibiotic	MIC (μg/ml)	Concentration tested (μg/ml)	Change in $\log_{10}$ CFU/ml at indicated time (h)[a]			
				2	4	8	24
S. aureus	Telavancin	0.5	1	−0.7	−1.3	**−3.4**[c]	−2.1
			2	−0.6	−1.6	**−3.1**	**−3.4**
			4	−0.7	−1.7	**−3.4**	**−3.4**
	Vancomycin	1	8	−0.4	−2.2	**−3.4**	**−3.4**
	Linezolid	2	16	−0.3	−0.8	−2.3	**−3.4**
S. aureus	Telavancin	0.5	1	−0.9	−1.8	−3.2	−2.7
			2	−1.0	−2.8	−2.7	−2.8
			4	−1.2	−1.8	−3.0	**−3.3**
	Vancomycin	0.5	4	−0.7	−1.6	−2.9	**−3.3**
	Linezolid	2	16	−0.2	0.03	−0.7	−3.1
S. epidermidis	Telavancin	1	2	−1.0	−1.8	−3.2	**−3.3**
			4	−0.5	−2.7	**−3.3**	**−3.3**
			8	−0.5	−3.2	**−3.3**	**−3.3**
	Vancomycin	2	16	−0.2	−1.4	−3.3	−2.4
	Linezolid	2	16	−1.2	−1.1	−1.4	−2.3
S. pneumoniae	Telavancin	0.015	0.03	−1.1	−2.7	**−3.4**	**−3.4**
			0.06	−1.0	−2.1	**−3.4**	**−3.4**
			0.12	−1.1	−1.9	−3.3	**−3.4**
	Vancomycin	0.25	2	−1.8	−3.0	**−3.4**	**−3.4**
	Linezolid	1	8	−1.2	−1.7	−2.6	**−3.4**
S. agalactiae	Telavancin	0.06	0.12	−1.0	−0.8	−2.3	−0.6
			0.25	−1.0	−0.9	−1.6	**−3.6**
			0.5	−0.87	−1.0	−1.6	**−3.6**
	Vancomycin	0.25	2	−0.8	−0.8	−1.0	−2.7
	Linezolid	1	8	−1.1	−0.9	−1.8	**−3.7**
S. pyogenes	Telavancin	0.06	0.12	−0.4	−0.4	−0.5	2.2
			0.25	−0.7	−1.8	−2.5	−2.2
			0.5	−0.9	−1.6	−2.3	**−3.1**
	Vancomycin	0.25	2	−1.8	−2.7	**−3.1**	**−3.1**
	Linezolid	1	8	−0.6	−1.2	−2.7	−2.7
E. faecalis	Telavancin	1	2	−0.5	−0.5	−0.6	−0.8
			4	−0.5	−0.5	−0.7	−1.2
			8	−0.5	−0.5	−0.7	−1.1
	Linezolid	1	8	−0.2	−0.2	−0.5	−1.0

[a] Data represent mean values obtained from three independent experiments.
[b] *S. aureus*, MED 2028 (top) and MED 1805 (bottom); *S. epidermidis*, ATCC 35984; *S. pneumoniae*, MED 1090; *S. agalactiae*, MED 2038; *S. pyogenes*, MED 2040; *E. faecalis*, ATCC 51575.
[c] Bold type indicates plate counts that reached the lower limit of quantitation.

enterococci (7, 8). Telavancin MICs were elevated against VanA-type VRE ($MIC_{50/90}$ = 8 and 16 μg/ml). Daptomycin and linezolid were the most-active agents tested against the 212 VRE with respective MIC_{90}s of 4 and 2 μg/ml. Quinupristin-dalfopristin was one of the most-active agents against vancomycin-resistant *Enterococcus faecium*, with an MIC_{90} of 1 μg/ml.

Time-kill curve study results for seven strains are presented in Table 2. Telavancin was bactericidal (≥3-$\log_{10}$ inoculum reduction) against all three methicillin-resistant staphylococci by 8 h at ≥2× MIC. Vancomycin was also bactericidal against these strains, with regrowth seen against the MRSE isolate by 24 h at 8× MIC, while linezolid produced a bactericidal effect at 8× MIC against two of the three strains tested by 24 h. Telavancin was bactericidal against all tested streptococci at concentrations ranging from 2× MIC (0.03 μg/ml) for the MDRSP isolate to 8× MIC (0.5 μg/ml) for the *S. pyogenes* isolate. Vancomycin and linezolid were both bactericidal against two of the three tested streptococci at 8× MIC. Telavancin and linezolid were both bacteriostatic against the VanB *E. faecalis* isolate, reducing the initial inoculum by 1.1 and 1.0 $\log_{10}$ CFU/ml, respectively, at 8× MIC.

Our results confirm the potent in vitro inhibitory and bactericidal activities of telavancin against important and emerging antimicrobial-resistant, gram-positive pathogens. Based upon MIC_{90} comparisons, telavancin was consistently more active than vancomycin and teicoplanin against all organisms tested and showed potency equal to or greater than daptomycin and linezolid against all strain types except VanA-type VRE. These results, in concert with previously published reports, highlight the potential role of telavancin in the treatment of serious gram-positive infections and support the continued clinical evaluation of this new agent.

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