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

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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 MIC90 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 (MIC50/90, 0.12/0.12 μg/ml) and Enterococcus faecium (MIC50/90, 0.03/0.06 μg/ml), but was less active against vancomycin-resistant E. faecium (MIC90, >2 μg/ml) and E. faecalis (MIC90, >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.3

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 non-susceptible 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...
reproducibility of in vitro test results. 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. Mendes et al. 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. 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.

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 MRSA), 328 of coagulase-negative staphylococci (CoNS), 471 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. 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. 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. 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.

Results

Activity of telavancin and comparators against S. aureus

Overall, 2,822 (55.1%) of S. aureus isolates were MSSA and 2,301 (44.9%) were MRSA. 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 MRSA, whereas ≤40% of isolates from divisions 1 (New England, 35.3%) and 4 (West North Central, 33.6%) exhibited that phenotype (Table 2). Telavancin MIC₉₀₀ 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 (MIC₉₀ values) against S. aureus was similar across all nine U.S. Census Divisions with MIC₉₀ 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 (MIC₉₀, 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 MIC₉₀ 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 MIC₉₀ 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

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**IN VITRO ACTIVITY OF TELAVANCIN BY U.S. CENSUS DIVISION**
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%<sup>a</sup> 90%<sup>a</sup> |             |
| 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)<sup>b</sup> | 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.<sup>c</sup> (815) | 31 (3.8) 76 (13.1) 88 (23.9) 291 (59.6) 57 (97.3) 9 (100.0) 0.03 0.06 |
| 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 (93.4) 28 (99.4) 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 (100.0) 0.12 0.12 |
| VanA (29) | 0 (0.0) 0 (0.0) 4 (100.0) 0.12 - |
| VanB (4) | 0 (0.0) 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<sup>d</sup> (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<sup>e</sup> (276) | 2 (0.7) 2 (1.4) 32 (13.0) 165 (72.8) 67 (97.1) 8 (100.0) 0.015 0.03 |

<sup>a</sup>50%/90%, MIC encompassing 50% and 90% of isolates tested, respectively.

<sup>b</sup>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. pseudo-intermedius [1], S. pseudo-intermedius/intermedius/delphini [1], S. saprophyticus [5], and S. warneri [1].

<sup>c</sup>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].

<sup>d</sup>Includes Streptococcus pyogenes [454], S. agalactiae [494], and S. dysgalactiae [135].

<sup>e</sup>Includes Streptococcus anginosus [66], S. anginosus group [11], S. australis [2], S. constellatus [9], S. cristatus [3], S. equinus [1], S. galalyliticus [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) | RNA | 50%  | 90%  | % Susceptible^a |
|------------------------|-------------------|------------|-------------|-----|------|------|-----------------|
| 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 | 100.0        |
|                        | MS-CoNS           | 11         | 0.015 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | MR-CoNS           | 7          | 0.03          | 0.06 | —    | —             |
|                        | E. faecalis       | 36         | 0.06 to >2    | 0.12 | 0.25 | 100.0        |
|                        | Van-S             | 35         | 0.06 to 0.25  | 0.12 | 0.25 | 100.0        |
|                        | E. faecium        | 18         | 0.015 to >2   | 2    | >2   | 100.0        |
|                        | Van-S             | 7          | 0.015 to 0.06  | 0.03 | —    | —             |
|                        | S. pneumoniae     | 36         | 0.008 to 0.03  | 0.008 | 0.015 | 100.0        |
|                        | 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 | 100.0        |
|                        | MS-CoNS           | 13         | 0.03 to 0.12   | 0.06 | 0.12 | 100.0        |
|                        | CoNS              | 16         | 0.03 to 0.12   | 0.06 | 0.12 | 100.0        |
|                        | E. faecalis       | 50         | 0.06 to >2    | 0.12 | 0.25 | 100.0        |
|                        | Van-S             | 44         | 0.06 to 0.25   | 0.12 | 0.25 | 100.0        |
|                        | E. faecium        | 48         | 0.015 to >2   | 2    | >2   | 100.0        |
|                        | Van-S             | 8          | 0.015 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | S. pneumoniae     | 42         | 0.004 to 0.015 | 0.008 | 0.015 | 100.0        |
|                        | 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 | 0.06 | 100.0        |
|                        | MSSA              | 516        | 0.008 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | MRSA              | 406        | 0.008 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | CoNS              | 64         | 0.008 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | MS-CoNS           | 30         | 0.008 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | MR-CoNS           | 34         | 0.03 to 0.06   | 0.06 | 0.06 | 100.0        |
|                        | E. faecalis       | 81         | 0.015 to >2   | 0.12 | 0.25 | 100.0        |
|                        | Van-S             | 77         | 0.015 to 0.25  | 0.12 | 0.12 | 100.0        |
|                        | E. faecium        | 63         | 0.015 to >2   | 2    | >2   | 100.0        |
|                        | Van-S             | 21         | 0.015 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | S. pneumoniae     | 100        | 0.004 to 0.015 | 0.008 | 0.015 | 100.0        |
|                        | 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 | 0.06 | 100.0        |
|                        | CoNS              | 29         | 0.015 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | MS-CoNS           | 11         | 0.015 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | MR-CoNS           | 18         | 0.015 to 0.06  | 0.06 | 0.06 | 100.0        |
|                        | E. faecalis       | 44         | 0.06 to >2    | 0.12 | 0.25 | 100.0        |
|                        | Van-S             | 40         | 0.06 to 0.25   | 0.12 | 0.25 | 100.0        |
|                        | E. faecium        | 22         | 0.015 to >2   | 0.03 | >2   | 100.0        |
|                        | Van-S             | 11         | 0.015 to 0.03  | 0.03 | 0.03 | 100.0        |
|                        | S. pneumoniae     | 50         | 0.004 to 0.015 | 0.008 | 0.015 | 100.0        |
|                        | 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 | 100.0        |
|                        | MS-CoNS           | 21         | 0.015 to 0.06  | 0.03 | 0.06 | 100.0        |
|                        | MR-CoNS           | 35         | 0.03 to 0.06   | 0.06 | 0.06 | 100.0        |
|                        | E. faecalis       | 53         | 0.06 to >2    | 0.12 | 0.25 | 100.0        |

(continued)
| Division (no. of sites) | Organism     | No. tested | MIC (µg/ml) | Range   | 50%     | 90%     | % Susceptiblea |
|------------------------|--------------|------------|-------------|---------|---------|---------|----------------|
|                        |              |            |             |         |         |         |                |
|                        | 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   |                |

aCriteria 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

| Organism (no. tested) | Agent | MIC (µg/ml) | % By category<sup>a</sup> |
|-----------------------|-------|-------------|---------------------------|
|                       |       | 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 0.2 | 0.25 | 1    | 96.4 | 1.6 | 0.0 |
| Clindamycin            |       | ≤0.25 to >2 | ≤0.25 ≥2 | 82.4 | 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             |       | ≤1 to >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 | 0.0 |
| 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 ≥2 | 94.8 | 0.2 | 5.0 |
| Daptomycin             |       | ≤0.12 to 0.25 | 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 | 0.0 |
| Oxacillin              |       | ≤0.25 to 0.5 | 0.12 | 0.5 | 100.0 | 0.0 | 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 | 2.6 |
| TMX-SMX                |       | ≤0.5 to >4 | ≤0.5 ≤0.5 | 99.6 | 0.4 | 0.0 |
| 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 0.5 | 0.25 | 0.5 | 100.0 |
| Clindamycin            |       | ≤0.25 to >2 | ≤0.25 ≥2 | 71.7 | 0.4 | 27.9 |
| Daptomycin             |       | ≤0.12 to 0.25 | 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           |       | ≤0.25 to >4 | 0.12 | >4 | 29.9 | 1.8 | 68.3 |
| Linezolid              |       | ≤0.12 to 0.25 | 0.25 | >2 | >99.9 | <0.1 |
| Oxacillin              |       | ≤0.25 to 0.5 | 0.12 | 0.5 | 100.0 | 0.0 | 0.0 |
| Teicoplanin            |       | ≤0.5 to 8 | ≤0.5 ≤0.5 | 100.0 | 0.0 | 0.0 |
| Tetracycline           |       | ≤0.5 to >8 | ≤0.5 ≤0.5 | 93.7 | 1.1 | 5.2 |
| TMX-SMX                |       | ≤0.5 to >4 | ≤0.5 ≤0.5 | 96.9 | 3.1 | 0.0 |
| Vancomycin             |       | ≤0.12 to 0.5 | 1 | 1 | 100.0 | 0.0 | 0.0 |
| **CoNS (328)**         |       |             |      |      |     |     |     |
| Telavancin             |       | ≤0.008 to 0.12 | 0.03 | 0.06 | 100.0 |
| Ceftaroline            |       | ≤0.06 to 4 | 0.25 | 0.5 | 100.0 |
| Clindamycin            |       | ≤0.25 to >2 | ≤0.25 ≥2 | 72.6 | 3.0 | 24.4 |
| Daptomycin             |       | ≤0.12 to 0.5 | 0.25 | 0.5 | 100.0 |
| Erythromycin           |       | ≤0.06 to >8 | >8 ≥8 | 41.5 | 1.8 | 56.7 |
| Gentamicin             |       | ≤1 to >8 | ≤1 | ≤1 | 79.0 | 2.4 | 18.6 |
| Levofloxacin           |       | ≤0.03 to >4 | 0.25 ≥4 | 57.9 | 1.5 | 40.5 |
| Linezolid              |       | ≤0.12 to 0.5 | 0.5 | 1 | 99.1 | 0.9 | 0.0 |
| Oxacillin              |       | ≤0.25 to >2 | 2 ≥2 | 44.2 | 55.8 |
| Teicoplanin            |       | ≤0.5 to >16 | ≤0.5 ≥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 | 100.0 |
| Ceftaroline            |       | ≤0.06 to 0.25 | ≤0.06 | 0.25 | 100.0 |
| Clindamycin            |       | ≤0.25 to >2 | ≤0.25 ≥2 | 90.3 | 1.4 | 8.3 |
| Daptomycin             |       | ≤0.12 to 0.5 | 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 0.5 | 0.5 | 1 | 100.0 | 0.0 | 0.0 |
| Oxacillin              |       | ≤0.25 to 0.5 | 0.25 | 0.5 | 100.0 | 0.0 | 0.0 |
| Teicoplanin            |       | ≤0.5 to 8 | ≤0.5 ≤0.5 | 100.0 | 0.0 | 0.0 |
| Tetracycline           |       | ≤0.5 to >8 | ≤0.5 ≤0.5 | 90.3 | 2.8 | 6.9 |
| TMX-SMX                |       | ≤0.5 to >4 | ≤0.5 ≤0.5 | 92.4 | 7.6 | 0.0 |
| Vancomycin             |       | ≤0.12 to 0.5 | 0.5 | 2 | 100.0 | 0.0 | 0.0 |

(continued)
| Organism (no. tested) | Agent   | MIC (µg/ml) | % By category<sup>a</sup> |
|-----------------------|---------|-------------|-------------------------|
|                       |         | Range       | 50% | 90% | S   | I   | R   |
| MR-CoNS (183)         | Telavancin | ≤0.015 to 0.12 | 0.12 | 0.12 | 90.1/99.8<sup>b</sup> |
|                       | Amoxicillin | ≤0.5 to 2 | ≤0.5 | 1 | 100.0 |
|                       | Daptomycin | ≤0.25 to 4 | 1 | ≥4 | 73.3 |
|                       | Linezolid | ≤0.25 to 4 | 1 | 1 | 99.8 |
|                       | Tetracycline | ≤0.5 to >8 | ≤0.5 | ≥8 | 81.4 |
|                       | Vancomycin | ≤0.5 to >16 | 1 | 2 | 92.5 |
| E. faecalis (438)     | Telavancin | ≤0.015 to 0.5 | 0.12 | 0.12 | 90.1/99.8<sup>b</sup> |
|                       | Ampicillin | ≤0.5 to >8 | ≤0.5 | ≥8 | 73.3 |
|                       | Daptomycin | ≤0.25 to >8 | 1 | ≥4 | 99.4 |
|                       | Linezolid | ≤0.25 to 4 | 1 | 1 | 99.8 |
|                       | Tetracycline | ≤0.5 to >8 | ≤0.5 | ≥8 | 81.4 |
|                       | Vancomycin | ≤0.5 to >16 | 1 | 2 | 92.5 |
| S. pneumoniae (447)   | Telavancin | 0.004 to 0.03 | 0.008 | 0.015 | 100.0 |
|                       | Ampicillin | ≤0.008 to 0.5 | ≤0.008 | 0.12 | 100.0 |
|                       | Daptomycin | ≤0.12 to >1 | ≥0.12 | >1 | 85.3 |
|                       | Linezolid | ≤0.25 to 4 | 1 | 2 | 99.9 |
|                       | Penicillin<sup>c</sup> | ≤0.06 to 4 | ≤0.06 | 1 | 96.2 |
|                       | Tetracycline | ≤0.012 to >4 | ≤0.25 | ≥4 | 79.8 |
|                       | 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 |
|                       | Ampicillin | ≤0.008 to 0.03 | ≤0.008 | 0.015 | 100.0 |
|                       | Daptomycin | ≤0.015 to >2 | 0.06 | ≥2 | 79.2 |
|                       | Linezolid | 0.5 to 1 | 0.5 | 1 | 100.0 |
|                       | Penicillin<sup>c</sup> | ≤0.03 to 0.12 | ≤0.03 | 0.06 | 100.0 |
|                       | Tetracycline | ≤0.25 to >8 | ≤0.5 | ≥8 | 51.2 |
|                       | Vancomycin | ≤0.06 to 0.5 | 0.12 | 0.25 | 100.0<sup>d</sup> |
| VGS (278)             | Telavancin | ≤0.002 to 0.06 | 0.015 | 0.03 | 100.0 |
|                       | Ampicillin | ≤0.008 to 0.5 | 0.015 | 0.06 | 100.0 |
|                       | Daptomycin | ≤0.015 to >2 | ≥0.03 | >2 | 83.7 |
|                       | Linezolid | 0.5 to 1 | 0.5 | 1 | 100.0 |
|                       | Penicillin<sup>c</sup> | ≤0.03 to 0.12 | ≤0.03 | 0.06 | 100.0 |
|                       | Tetracycline | ≤0.25 to >8 | ≤0.5 | ≥8 | 51.2 |
|                       | Vancomycin | ≤0.06 to 0.5 | 0.25 | 0.5 | 100.0 |

<sup>a</sup>Criteria as published by CLSI (2016).

<sup>b</sup>Or 99.8% against vancomycin-susceptible E. faecalis only (N=405).

<sup>c</sup>Using parenteral nonmeningitis breakpoints.

<sup>d</sup>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), levofoxacin (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 levofoxacin 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 levofoxacin 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.\(^1,3,14\)

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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