# Telavancin In Vitro Activity Tested against a USA Collection of Methicillin-Resistant *Staphylococcus aureus*, Including a Multidrug-Resistant Subset (2011–2013)

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## ABSTRACT

**Background.** The broth microdilution (BMD) method for telavancin was recently revised by the U.S. Food and Drug Administration (FDA) and Clinical Laboratory Standards Institute (CLSI). This study assessed telavancin activity using a revised BMD (rBMD) method, following the CLSI guidelines for water-insoluble agents. Polysorbate-80 was added in the test medium. This rBMD method was deemed necessary for greater accuracy and reproducibility of telavancin minimum inhibitory concentrations (MIC) results.

**Methods.** 9610 *Staphylococcus aureus* isolates collected from 28 sites in the United States were included. Susceptibility testing was performed based on CLSI guidelines (M07-A9 and M100-S24). MIC interpretation was guided by FDA (telavancin) and CLSI (2014) criteria. Methicillin-resistant *S. aureus* (MRSA) resistant to ≥3 drug classes was defined as multidrug-resistant (MDR).

**Results.** Telavancin had $MIC_{50}$, $MIC_{90}$, and $MIC_{100}$ of 0.03, 0.06, and 0.12 µg/mL, respectively, against methicillin-susceptible *S. aureus*, MRSA, non-MDR, and MDR subsets. MRSA with vancomycin MIC = 2–4 µg/mL had telavancin $MIC_{50}$ (0.06 µg/mL) 2-fold higher than those MRSA with vancomycin MIC at ≤1 µg/mL ($MIC_{50}$, 0.03 µg/mL). These telavancin $MIC_{50}$ results were equivalent to those noted for MRSA categorized by the daptomycin MIC values. However, telavancin had $MIC_{90}$ and $MIC_{100}$ results of 0.06 and 0.12 µg/mL, respectively, regardless of MRSA subset. Vancomycin ($MIC_{50/90}$, 1/1 µg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), and linezolid ($MIC_{50/90}$, 1/1 µg/mL) were active against MDR (≥99.7% susceptible); however, telavancin had MICs 8- to 32-fold lower than these comparators.

**Conclusion.** Telavancin had potent activity against *S. aureus*, including less susceptible and MDR subsets, inhibiting all *S. aureus* at the FDA breakpoint for susceptibility (≤0.12 µg/mL). These results provide a new reference for the drug's potency.

## INTRODUCTION

- Vancomycin has been considered the primary treatment option for invasive infections caused by *Staphylococcus aureus*, including methicillin-resistant strains (MRSA). However, recent reports have described increasing treatment failures due to infections caused by strains displaying elevated vancomycin minimum inhibitory concentrations (MIC) values (ie, ≥1.5 µg/mL).
  - Treatment failures have been associated with bacteremias caused by both methicillin-susceptible (MSSA) and MRSA, regardless of treatment with vancomycin or β-lactam agents.
  - These reports suggest that increasing vancomycin MIC values may reflect an unidentified host marker or organism factor(s) that significantly affect treatment outcomes.
- Skin and skin structure infections (SSSIs) are often caused by aerobic Gram-positive cocci, including *S. aureus* and β-hemolytic streptococci.
- In the past decade, new strains of MRSA (especially USA300, sequence type 8) have emerged as an important cause of community-associated SSSIs in the United States.
- MRSA isolates were shown to be responsible for as many as 60% (98% of MRSA isolates are USA300-like) of the acute purulent SSSI in USA emergency departments.
- These serious invasive infections and/or community-associated SSSIs caused by MRSA isolates have challenged the current treatment guidelines.

- Telavancin was approved in the United States and Canada for the treatment of adult patients with complicated SSSI (cSSSI) caused by susceptible Gram-positive pathogens, including MSSA and MRSA.
- Telavancin was also approved in the United States for the treatment of adult patients with hospital-acquired bacterial pneumonia (HABP), including ventilator-associated bacterial pneumonia (VABP) due to susceptible isolates of *S. aureus*, including MSSA and MRSA, when alternative treatments are not suitable.
- In addition, telavancin was granted approval in the European Union for the treatment of adult patients with HABP/VABP caused by susceptible isolates of MRSA when alternative treatments are not suitable.
- Early in 2014, a revised broth microdilution (rBMD) susceptibility testing method for telavancin was approved by the U.S. Food and Drug Administration (FDA) and published in a labeling supplement for VIBATIV® (telavancin).
  - This rBMD method follows the Clinical and Laboratory Standards Institute (CLSI) guidelines for water-insoluble agents. It consists of the use of dimethyl sulfoxide (DMSO) as solvent for stock solution preparation and as a diluent for stock solution when preparing 96-well plates for MIC testing.
  - This revised method resembles those applied for other members of the lipoglycopeptide class (ie, oritavancin and dalbavancin) due to the addition of polysorbate-80 (P-80; 0.002%) to the test medium.
- This study was conducted to assess and update the activity of telavancin against a contemporary (2011–2013) collection of *S. aureus* clinical isolates and resistant subsets collected from medical centers in the United States using the recently approved rBMD method.

## MATERIALS AND METHODS

### Bacterial strain collection

- A total of 9610 *S. aureus* isolates collected from 28 sites in the United States were included in this analysis. These isolates were recovered from blood (1937; 20.2%); SSSI (4851; 50.5%); and from patients with HABP (2283; 23.8%), urinary tract infections (163; 1.7%), and other less prevalent or undetermined infection sources (376; 3.9%).
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), as part of the SENTRY Antimicrobial Surveillance Program for the United States. Isolates were initially identified by the participating laboratory and identification confirmed by the reference monitoring laboratory using standard algorithms and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

### Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by BMD following the CLSI guidelines (M07-A9). Telavancin susceptibility was determined using the revised testing method following the CLSI (M100-S24) and product package insert information. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event.
- MIC values were quality assured by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* American Type Culture Collection [ATCC] 29213 and *Enterococcus faecalis*).
  - Acceptable telavancin MIC ranges when tested against ATCC strains were those for the revised method recently approved/published by the FDA and CLSI, while MIC QC ranges from CLSI were applied for comparator agents. All QC results were within acceptable FDA/CLSI ranges.

### MIC interpretation and data analysis

- Telavancin MIC interpretation for *S. aureus* applied the recently approved breakpoint criterion (≤0.12 µg/mL for susceptible) appropriate for the rBMD testing method, according to the updated product package insert or the European Committee on Antimicrobial Susceptibility Testing (EUCAST; for MRSA only). Current (2014) CLSI M100-S24 and EUCAST breakpoint criteria were applied for comparator agents.
- MRSA isolates were categorized according to the vancomycin (≤1 and 2–4 µg/mL) and daptomycin (≤0.5 and 1–2 µg/mL) MIC results. In addition, MRSA strains showing a resistant phenotype to 3 or more classes of antimicrobial agents were defined as multidrug-resistant (MDR).

## RESULTS

- Telavancin in vitro activity against *S. aureus* and resistant subsets (**Table 1**).
  - Overall, telavancin demonstrated $MIC_{50}$ and $MIC_{90}$ values of 0.03 and 0.06 µg/mL against *S. aureus* (100.0% susceptible), respectively. These $MIC_{50}$ and $MIC_{90}$ values were also observed against the MSSA, MRSA, non-MDR, and MDR subsets.
  - When tested against MRSA isolates displaying vancomycin MIC results of 2 or 4 µg/mL, the telavancin $MIC_{50}$ value (0.06 µg/mL) was 2-fold higher than that of MRSA with vancomycin MIC results at ≤1 µg/mL ($MIC_{50}$, 0.03 µg/mL).
  - The telavancin $MIC_{50}$ result (0.06 µg/mL) obtained against MRSA isolates displaying vancomycin MIC values of 2 or 4 µg/mL was equivalent to that noted for MRSA strains with elevated daptomycin MIC values (1–2 µg/mL).
  - However, telavancin demonstrated consistent $MIC_{90}$ results (0.06 µg/mL) against all MRSA subsets analyzed.

**Table 1. Antimicrobial activity and MIC distribution for telavancin against a contemporary (2011–2013) USA collection of *S. aureus* clinical isolates using a recently approved and revised susceptibility testing method**

| *S. aureus*[a] (no. tested) | MIC (µg/mL) | | Number (cumulative %) inhibited at MIC (µg/mL)[b] | | | |
|---|---|---|---|---|---|---|
| | 50% | 90% | ≤0.015 | 0.03 | 0.06 | 0.12 |
| All (9610) | 0.03 | 0.06 | 364 (3.8) | **6210 (68.4)** | 3012 (99.8) | 24 (100.0) |
| MSSA (4959) | 0.03 | 0.06 | 242 (4.9) | **3272 (70.9)** | 1437 (99.8) | 8 (100.0) |
| MRSA (4651) | 0.03 | 0.06 | 122 (2.6) | **2938 (65.8)** | 1575 (99.7) | 16 (100.0) |
| Vancomycin MIC, ≤1 µg/mL (4561) | 0.03 | 0.06 | 119 (2.6) | **2930 (66.8)** | 1502 (99.8) | 10 (100.0) |
| Vancomycin MIC, 2–4 µg/mL (90) | 0.06 | 0.06 | 3 (3.3) | 8 (12.2) | **73 (93.3)** | 6 (100.0) |
| Daptomycin MIC, ≤0.5 µg/mL (4607) | 0.03 | 0.06 | 122 (2.6) | **2928 (66.2)** | 1545 (99.7) | 12 (100.0) |
| Daptomycin MIC, 1–2 µg/mL (43) | 0.06 | 0.06 | 0 (0.0) | 9 (20.9) | **30 (90.7)** | 4 (100.0) |
| MDR (1371) | 0.03 | 0.06 | 37 (2.7) | **749 (57.3)** | 574 (99.2) | 11 (100.0) |
| Non-MDR (3280) | 0.03 | 0.06 | 85 (2.6) | **2189 (69.3)** | 1001 (99.8) | 5 (100.0) |

[a] MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant.
[b] Modal MIC values are shown in bold.

**Table 2. Antimicrobial activity of telavancin and comparator agents when tested against a contemporary (2011–2013) USA collection of clinical isolates using a recently approved and revised susceptibility testing method**

| Organism[a] (no. tested) Antimicrobial agent | MIC (µg/ml) | | % Susceptible / % Intermediate / % Resistant[b] | | |
|---|---|---|---|---|---|
| | 50% | 90% | FDA | CLSI | EUCAST |
| MSSA (4959) | | | | | |
| Telavancin | 0.03 | 0.06 | 100.0 / -[c] / - | - / - / - | - / - / - |
| Vancomycin | 1 | 1 | | 100.0 / 0.0 / 0.0 | 100.0 / 0.0 / 0.0 |
| Daptomycin | 0.25 | 0.5 | | >99.9 / - / - | >99.9 / 0.0 / <0.1 |
| Linezolid | 1 | 1 | | >99.9 / 0.0 / <0.1 | >99.9 / 0.0 / <0.1 |
| Levofloxacin | 0.25 | 4 | | 88.8 / 0.9 / 10.3 | 88.8 / 0.3 / 10.3 |
| Erythromycin | 0.25 | >16 | | 65.6 / 3.7 / 30.7 | 66.0 / 1.3 / 32.7 |
| Clindamycin | ≤0.25 | ≤0.25 | | 95.2 / 0.1 / 4.7 | 94.8 / 0.4 / 4.8 |
| Gentamicin | ≤1 | ≤1 | | 99.2 / 0.2 / 0.6 | 99.0 / 0.0 / 1.0 |
| Tetracycline | ≤0.25 | ≤0.25 | | 96.2 / 0.7 / 3.1 | 95.3 / 0.2 / 4.5 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 99.5 / 0.0 / 0.5 | 99.5 / 0.1 / 0.4 |
| MRSA (4651) | | | | | |
| Telavancin | 0.03 | 0.06 | 100.0 / - / - | - / - / - | 100.0 / - / - |
| Vancomycin | 1 | 1 | | >99.9 / <0.1 / 0.0 | >99.9 / 0.0 / <0.1 |
| Daptomycin | 0.25 | 0.5 | | >99.9 / - / - | >99.9 / 0.0 / <0.1 |
| Linezolid | 1 | 1 | | 99.9 / 0.0 / 0.1 | 99.9 / 0.0 / 0.1 |
| Levofloxacin | 4 | >4 | | 31.3 / 2.2 / 66.5 | 31.3 / 2.2 / 66.5 |
| Erythromycin | >16 | >16 | | 10.4 / 1.9 / 87.7 | 10.6 / 0.5 / 88.9 |
| Clindamycin | ≤0.25 | >2 | | 70.5 / 0.1 / 29.4 | 70.2 / 0.3 / 29.5 |
| Gentamicin | ≤1 | ≤1 | | 96.8 / 0.1 / 3.1 | 96.5 / 0.0 / 3.5 |
| Tetracycline | ≤0.25 | 1 | | 94.9 / 0.4 / 4.7 | 92.6 / 2.0 / 5.4 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 97.8 / 0.0 / 2.2 | 97.8 / 0.2 / 2.0 |
| MRSA with vancomycin MIC, 2–4 µg/mL (90) | | | | | |
| Telavancin | 0.06 | 0.06 | 100.0 / - / - | - / - / - | 100.0 / - / - |
| Vancomycin | 2 | 2 | | 98.9 / 1.1 / 0.0 | 98.9 / 0.0 / 1.1 |
| Daptomycin | 0.5 | 1 | | 97.8 / - / - | 97.8 / 0.0 / 2.2 |
| Linezolid | 1 | 2 | | 98.9 / 0.0 / 1.1 | 98.9 / 0.0 / 1.1 |
| Levofloxacin | >4 | >4 | | 14.4 / 0.0 / 85.6 | 14.4 / 0.0 / 85.6 |
| Erythromycin | >16 | >16 | | 5.6 / 1.1 / 93.3 | 5.6 / 1.1 / 93.3 |
| Clindamycin | >2 | >2 | | 36.7 / 0.0 / 63.3 | 36.7 / 0.0 / 63.3 |
| Gentamicin | ≤1 | 2 | | 91.1 / 0.0 / 8.9 | 88.9 / 0.0 / 11.1 |
| Tetracycline | ≤0.25 | 2 | | 95.6 / 1.1 / 3.3 | 88.9 / 6.7 / 4.4 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 97.8 / 0.0 / 2.2 | 97.8 / 1.1 / 1.1 |
| MRSA with daptomycin MIC, 1–2 µg/mL (43) | | | | | |
| Telavancin | 0.06 | 0.06 | 100.0 / - / - | - / - / - | 100.0 / - / - |
| Vancomycin | 1 | 2 | | 97.7 / 2.3 / 0.0 | 97.7 / 0.0 / 2.3 |
| Daptomycin | 1 | 1 | | 95.3 / - / - | 95.3 / 0.0 / 4.7 |
| Linezolid | 1 | 1 | | 100.0 / 0.0 / 0.0 | 100.0 / 0.0 / 0.0 |
| Levofloxacin | >4 | >4 | | 18.6 / 2.3 / 79.1 | 18.6 / 2.3 / 79.1 |
| Erythromycin | >16 | >16 | | 14.3 / 2.4 / 83.3 | 14.3 / 2.4 / 83.3 |
| Clindamycin | >2 | >2 | | 46.5 / 2.3 / 51.2 | 46.5 / 0.0 / 53.5 |
| Gentamicin | ≤1 | >8 | | 88.4 / 0.0 / 11.6 | 88.4 / 0.0 / 11.6 |
| Tetracycline | ≤0.25 | 1 | | 93.0 / 0.0 / 7.0 | 90.7 / 2.3 / 7.0 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 97.7 / 0.0 / 2.3 | 97.7 / 0.0 / 2.3 |
| MRSA MDR (1371) | | | | | |
| Telavancin | 0.03 | 0.06 | 100.0 / - / - | - / - / - | 100.0 / - / - |
| Vancomycin | 1 | 1 | | 99.9 / 0.1 / 0.0 | 99.9 / 0.0 / 0.1 |
| Daptomycin | 0.25 | 0.5 | | 99.9 / - / - | 99.9 / 0.0 / 0.1 |
| Linezolid | 1 | 1 | | 99.7 / 0.0 / 0.3 | 99.7 / 0.0 / 0.3 |
| Levofloxacin | >4 | >4 | | 0.9 / 0.3 / 98.8 | 0.9 / 0.3 / 98.8 |
| Erythromycin | >16 | >16 | | 0.5 / 0.4 / 99.1 | 0.5 / 0.1 / 99.4 |
| Clindamycin | >2 | >2 | | 6.3 / 0.0 / 93.7 | 6.3 / 0.0 / 93.7 |
| Gentamicin | ≤1 | 4 | | 90.2 / 0.2 / 9.6 | 90.0 / 0.0 / 10.0 |
| Tetracycline | ≤0.25 | >8 | | 88.6 / 0.2 / 11.2 | 82.4 / 6.1 / 11.5 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 93.9 / 0.0 / 6.1 | 93.9 / 0.7 / 5.4 |

[a] MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MDR = multidrug-resistant.
[b] Telavancin breakpoint criteria for *S. aureus* according to the labeling supplement for the product (VIBATIV®) and EUCAST (MRSA only) at ≤0.12 µg/mL for susceptible.
[c] Breakpoint not available.

- Comparative in vitro activity analysis of telavancin and other anti-Gram-positive agents against *S. aureus* and resistant subsets (**Table 2**).
  - Telavancin ($MIC_{50/90}$, 0.03/0.06 µg/mL) showed $MIC_{50}$ and $MIC_{90}$ values 8-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL) and 16- to 32-fold lower than vancomycin ($MIC_{50/90}$, 1/1 µg/mL) or linezolid ($MIC_{50/90}$, 1/1 µg/mL) against MSSA, the overall MRSA, and the MRSA-MDR subset.
  - Gentamicin, tetracycline, and trimethoprim-sulfamethoxazole demonstrated antimicrobial coverage (>90.0% susceptible) when tested against the overall MRSA subset, while these agents and clindamycin were active against MSSA.
  - Daptomycin MIC results ($MIC_{50/90}$, 0.5/1 µg/mL) obtained against MRSA isolates with vancomycin MIC values of 2–4 µg/mL were 2-fold higher than those obtained against MRSA with vancomycin MIC data points at ≤1 µg/mL ($MIC_{50/90}$, 0.25/0.5 µg/mL; data not shown).
  - Telavancin had MIC results 8- to 32-fold lower than vancomycin, daptomycin, and linezolid when tested against MRSA isolates with elevated MIC values for the comparator agents vancomycin or daptomycin (**Table 2**).
  - The in vitro activity of other comparator agents, such as gentamicin, tetracycline, and trimethoprim-sulfamethoxazole against MRSA subsets was variable (82.4–97.8% susceptible; **Table 2**).

## CONCLUSIONS

- Telavancin had potent activity against *S. aureus*, including MRSA isolates and those subsets exhibiting decreased susceptibility to comparator agents.
- Telavancin inhibited all *S. aureus* at the FDA breakpoint for susceptibility (≤0.12 µg/mL), regardless of phenotype.
- Telavancin potency against this current collection of *S. aureus* isolates was consistently greater than those of comparators.
- These results establish a new benchmark for telavancin activity and provide a new reference for the drug's potency.

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