Potent *In vitro* Activity of Telavancin When Tested against European Streptococcal Isolates Displaying an Array of Antibiogram Profiles

Rodrigo E. Mendes, Robert K. Flamm, Helio S. Sader, Ronald N. Jones, David J. Farrell

JMI Laboratories, North Liberty, Iowa USA

Contact Information:
Rodrigo E. Mendes, PhD
JMI Laboratories
345 Beaver Kreek Ctr, Ste A
North Liberty, IA 52317
USA
Phone: 319-665-3370
Fax: 319-665-3371
rodrigo-mendes@jmilabs.com

ABSTRACT

Objectives. To evaluate the telavancin *in vitro* activity against *S. pneumoniae*, viridans group streptococci (VGS) and β-haemolytic streptococci (BHS) recovered from hospitalized patients in European hospitals and adjacent geographic regions.

Methods. A total of 1527 *S. pneumoniae*, 400 VGS and 767 BHS isolates from 34 medical sites located in 15 European countries, and Russia, Turkey and Israel were included. Isolates were submitted to a monitoring laboratory as part of the SENTRY Antimicrobial Surveillance Program for 2012-2013. Identification was confirmed by MALDI-TOF and susceptibility testing was performed by CLSI methods. MIC interpretation used the FDA (telavancin), CLSI and/or EUCAST criteria. Telavancin and comparator activities were evaluated according to antibiogram resistance patterns (CLSI criteria). Isolates displaying resistance phenotype to at least three classes of drugs were considered as multidrug-resistant (MDR).

Results. 19 antibiogram patterns were observed among *S. pneumoniae* with 62.1 and 20.9% displaying wildtype (susceptible to all tested drugs) and MDR phenotypes, respectively. The majority of MDR phenotype among *S. pneumoniae* was comprised of the erythromycin, clindamycin and tetracycline resistance pattern, followed by the penicillin (MIC, ≥2 mg/L), erythromycin, clindamycin and tetracycline resistance pattern. Telavancin demonstrated similar activity (MIC_{50}/MIC_{90}, ≤0.015/≤0.015 mg/L) against wildtype and each of the resistance antibiogram patterns evaluated. Vancomycin (100.0% susceptible), linezolid (100.0% susceptible) and levofloxacin (98.6% susceptible) were also active against the overall population of *S. pneumoniae* and resistance subsets. Nine resistance patterns were noted among VGS, and only nine (2.3%) isolates exhibited a MDR phenotype. Telavancin (100.0% susceptible) had a MIC_{50} value at least 16-fold lower than vancomycin (MIC_{50}/MIC_{90}, 0.5/1 mg/L; 100.0% susceptible), daptomycin (MIC_{50}/MIC_{90}, 0.25-0.5/1 mg/L; 100.0% susceptible), linezolid (MIC_{50}/MIC_{90}, 0.5/1 mg/L; 100.0% susceptible) and levofloxacin (MIC_{50}/MIC_{90}, 0.5/1 mg/L; 97.4–100.0% susceptible) against VGS and resistance subsets. Among BHS, 59 (7.7%) isolates had a MDR phenotype. Telavancin (100.0% susceptible), vancomycin (100.0% susceptible), daptomycin (100.0% susceptible) and linezolid (100.0% susceptible) were active against BHS, while susceptibility rates for levofloxacin varied according to resistance patterns and breakpoint criteria (CLSI vs EUCAST).

Conclusions. Telavancin demonstrated potent *in vitro* activity against this contemporary (2012–2013) collection of streptococcal isolates from European hospitals and adjacent geographic regions, regardless of resistance phenotype. Other comparator agents also exhibited activity, albeit showing higher MIC values when compared with telavancin.

INTRODUCTION

- Telavancin is a parenteral semi-synthetic lipoglycopeptide with a convenient administration schedule (once daily).
- Telavancin was approved in 2009 in the USA and Canada for the treatment of adults with complicated skin and soft tissue infections caused by susceptible organisms.[1,2] In addition, it was granted approval in the USA and Europe for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *Staphylococcus aureus* (methicillin-resistant *S. aureus* only in Europe) when alternative treatments are not suitable.[1,3]
- The telavancin activity originates from a dual mechanism of action consisting of inhibition of peptidoglycan biosynthesis, similar to the glycopeptides, as well as interaction with the bacterial membrane to effect changes in membrane permeability and depolarization.
- These characteristics grant telavancin a bactericidal activity against common Gram-positive pathogens, such as *S. aureus*, coagulase-negative staphylococci, streptococci and enterococci, except for *vanA*-carrying strains.
- The objective of this investigation was to reassess the activity of telavancin when tested against a contemporary collection of streptococci recovered from hospitalized patients in European and adjacent countries.

MATERIALS AND METHODS

Bacterial strain collection

- A total of 1527 *S. pneumoniae*, 400 viridans group streptococci (VGS) and 767 β-haemolytic streptococci non-duplicate isolates were included.
- These isolates originated from 34 medical sites located in 15 European countries (Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Slovenia, Spain, Sweden, UK and Ukraine) and Russia, Turkey and Israel.
- These isolates were recovered mostly from lower (39.5%) and upper (31.9%) respiratory tract, skin and soft tissue (20.2%) and blood (14.4%) specimens, and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the SENTRY Antimicrobial Surveillance Program during 2012–2013.
- Isolates were initially identified by the participating laboratory and identification confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document.[4]
- Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event. Affirmation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619).
- Expected telavancin MIC ranges when tested against ATCC strains were those available in the current M100-S25 document, as follows:[5]
  - *S. aureus* ATCC 29213 (0.03–0.12 mg/L); *E. faecalis* ATCC 29212 (0.03–0.12 mg/L); and *S. pneumoniae* ATCC 49619 (0.004–0.015 mg/L). All QC results were within published acceptable ranges.
- MIC interpretations for telavancin applied the breakpoint criteria available in the product package insert (3/2014), as follows:
  - *Streptococcus pyogenes* and *Streptococcus agalactiae* at ≤0.12 mg/L for susceptible (utilized for BHS; and *Streptococcus anginosus* group at ≤0.06 mg/L for susceptible (used for VGS).
- The CLSI M100-S24 (2014) or European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2014)[6] breakpoint criteria were applied for comparator agents, as available. Isolates were categorized based on the antibiogram profile, and those exhibiting a resistance phenotype to at least three drug classes were considered as multidrug-resistant (MDR).

RESULTS

- A total of 19 antibiogram patterns were observed among *S. pneumoniae* with 62.1% (948/1527) and 20.9% (319/1527) of the isolates displaying wildtype (susceptible to all tested drugs) and MDR phenotypes (resistant to ≥3 drug classes), respectively (**Table 1**).
- The majority of MDR phenotypes among *S. pneumoniae* comprised the erythromycin, clindamycin and tetracycline resistance pattern, followed by the penicillin (MIC, ≥2 mg/L), erythromycin, clindamycin and tetracycline resistance pattern (**Table 1**).
- Telavancin demonstrated similar activity ($MIC_{50/90}$, ≤0.015/≤0.015 mg/L) against wildtype, MDR and each of the antibiogram patterns observed among *S. pneumoniae* (**Table 1**). Vancomycin ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 0.5–1/1 mg/L; 100.0% susceptible) showed activity against the overall population of *S. pneumoniae* and resistance subsets (**Table 2**).
- Overall, levofloxacin ($MIC_{50/90}$, 1/1 mg/L; 98.3–100.0% susceptible) also remained active against *S. pneumoniae* and resistance subsets, with a slight change in the MIC_{90} value ($MIC_{50/90}$, 1/2 mg/L; 95.3% susceptible) when tested against MDR isolates of *S. pneumoniae* (data not shown).
- Nine resistance patterns were noted among VGS, and only nine (2.3%) isolates exhibited an MDR phenotype (**Table 1**). Telavancin ($MIC_{50/90}$, 0.03/0.03 mg/L; 100.0% susceptible) had an MIC_{50} value at least eight-fold lower than vancomycin ($MIC_{50/90}$, 0.5/0.5–1 mg/L; 100.0% susceptible), daptomycin ($MIC_{50/90}$, 0.25–0.5/0.5-1 mg/L; 98.9–100.0% susceptible), linezolid ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% susceptible) and levofloxacin ($MIC_{50/90}$, 1/2 mg/L; 97.4–100.0% susceptible) against VGS and resistance subsets (**Table 2**).
- The MIC_{50} value for levofloxacin (MIC_{50}, 2 mg/L; 55.6% susceptible) obtained against MDR isolates of VGS was two-fold higher than that observed for wildtype isolates ($MIC_{50/90}$, 1/2 mg/L; 100.0% susceptible; data not shown).
- Among BHS, 59 (7.7%) isolates had an MDR phenotype. The most common MDR pattern consisted of erythromycin, clindamycin and tetracycline, against which telavancin ($MIC_{50/90}$, 0.03/0.03 mg/L) had an MIC_{50} value two-fold higher than that observed against the wildtype subset ($MIC_{50/90}$, ≤0.015/0.03 mg/L; **Table 1**).
- Telavancin (100.0% susceptible), vancomycin (100.0% susceptible), daptomycin (100.0% susceptible) and linezolid (100.0% susceptible) were active against BHS, whereas susceptibility rates for levofloxacin varied according to resistance patterns and breakpoint criteria (88.9–100.0% susceptible).

Table 1. Antimicrobial activity and MIC distribution for telavancin when tested against wildtype, MDR and most common resistant patterns among streptococcal clinical isolates from European and adjacent geographic regions, as part of the SENTRY Antimicrobial Surveillance Program

Organism[a] (no. tested)	MIC (mg/L)		No. (cumulative %) inhibited at telavancin MIC (mg/L)[b]			
	50%	90%	≤0.015	0.03	0.06	0.12
S. pneumoniae (1527)	≤0.015	≤0.015	**1503 (98.4)**	23 (99.9)	1 (100.0)	–
Wildtype (948)	≤0.015	≤0.015	**938 (98.9)**	10 (100.0)	–	–
ERY+CLI+TET (150)	≤0.015	≤0.015	**145 (96.7)**	4 (99.3)	1 (100.0)	–
PEN+ERY+CLI+TET (116)	≤0.015	≤0.015	**111 (95.7)**	5 (100.0)	–	–
ERY (78)	≤0.015	≤0.015	**77 (98.7)**	1 (100.0)	–	–
PEN (57)	≤0.015	≤0.015	**57 (100.0)**	–	–	–
TET (40)	≤0.015	≤0.015	**40 (100.0)**	–	–	–
ERY+CLI (32)	≤0.015	≤0.015	**32 (100.0)**	–	–	–
ERY+TET (28)	≤0.015	≤0.015	**28 (100.0)**	–	–	–
PEN+ERY+TET (26)	≤0.015	≤0.015	**26 (100.0)**	–	–	–
PEN+ERY (14)	≤0.015	≤0.015	**14 (100.0)**	–	–	–
PEN+ERY+CLI (14)	≤0.015	≤0.015	**14 (100.0)**	–	–	–
MDR (319)	≤0.015	≤0.015	**307 (96.2)**	11 (99.7)	1 (100.0)	–
VGS[c] (400)	≤0.015	0.03	**244 (61.0)**	145 (97.3)	11 (100.0)	–
Wildtype (239)	≤0.015	0.03	**138 (57.7)**	92 (96.2)	9 (100.0)	–
ERY (95)	≤0.015	0.03	**70 (73.7)**	24 (98.9)	1 (100.0)	–
ERY+CLI (39)	≤0.015	0.03	**22 (56.4)**	17 (100.0)	–	–
PEN+ERY (10)	≤0.015	0.03	**5 (50.0)**	4 (90.0)	1 (100.0)	–
MDR (9)	0.03	0.03	**3 (33.3)**	6 (100.0)	–	–
BHS[d] (767)	≤0.015	0.03	**518 (67.5)**	226 (97.0)	21 (99.7)	2 (100.0)
Wildtype (389)	≤0.015	0.03	**323 (83.0)**	58 (97.9)	7 (99.7)	1 (100.0)
TET (229)	≤0.015	0.03	**113 (49.3)**	106 (95.6)	10 (100.0)	–
ERY+CLI+TET (56)	0.03	0.03	22 (39.3)	**33 (98.2)**	0 (98.2)	1 (100.0)
ERY+TET (43)	≤0.015	0.03	**24 (55.8)**	16 (93.0)	3 (100.0)	–
ERY (23)	≤0.015	0.03	**19 (82.6)**	3 (95.7)	1 (100.0)	–
ERY+CLI (18)	≤0.015	0.03	**14 (77.8)**	4 (100.0)	–	–
MDR (59)	0.03	0.03	22 (37.3)	**36 (98.3)**	0 (98.3)	1 (100.0)

MDR = multidrug-resistant isolates (resistance to at least three drug classes); ERY = erythromycin; CLI = clindamycin; TET = tetracycline; PEN = penicillin; VGS = viradans group streptococci; BHS = ß-haemolytic streptococci.
[a] Wildtype: isolates susceptible to all drugs tested.
[b] Modal MIC values are shown in bold.
[c] Includes *S. anginosus* group (140 strains), *S. bovis/gallolyticus* group (23 strains), *S. mitis/oralis* (209 strains), *Streptococcus mutans* (one strain), *Streptococcus salivarius* (22 strains), and unspeciated VGS (five strains).
[d] *S. agalactiae* (274 strains), *S. dysgalactiae* (103 strains), *S. equi* (one strain), *S. pyogenes* (314 strains), Group C *Streptococcus* (24 strains), Group F *Streptococcus* (two strains), Group G *Streptococcus* (48 strains) and unspeciated BHS (one strain).

Table 2. Antimicrobial activity and spectrum of telavancin and comparator agents tested against wildtype, MDR and most common resistant patterns among streptococcal clinical isolates from European and adjacent geographic regions, as part of the 2012-2013 SENTRY Antimicrobial Surveillance Program

Species/Group[a] (no. tested)	$MIC_{50/90}$ (mg/L) and % susceptible[b] for each agent														
Phenotype	Telavancin			Penicillin			Vancomycin			Daptomycin			Linezolid		
Antibiogram	50%	90%	%S	50%	90%	%S	50%	90%	%S	50%	90%	%S	50%	90%	%S
S. pneumoniae (1527)															
Wildtype (948)	≤0.015	≤0.015	–[c]	≤0.06	0.12	100	0.25	0.5	100	0.12	0.25	–	1	1	100
MDR (319)	≤0.015	≤0.015	–	2	4	21.6	0.25	0.5	100	0.12	0.25	–	1	1	100
ERY+CLI+TET (150)	≤0.015	≤0.015	–	0.12	1	43.3	0.25	0.5	100	0.12	0.25	–	1	1	100
PEN+ERY+CLI+TET (116)	≤0.015	≤0.015	–	2	4	0.0	0.25	0.5	100	0.12	0.25	–	0.5	1	100
PEN+ERY+TET (26)	≤0.015	≤0.015	–	2	4	0.0	0.25	0.5	100	0.12	0.25	–	1	1	100
VGS[d] (400)															
Wildtype (239)	≤0.015	0.03	100	≤0.06	0.5	89.1	0.5	1	100	0.25	1	99.6	1	1	100
MDR (9)	0.03	–	100	4	–	33.3	0.5	–	100	0.5	–	100	0.5	–	100
ERY (95)	≤0.015	0.03	100	0.12	1	77.9	0.5	0.5	100	0.25	1	98.9	0.5	1	100
ERY+CLI (39)	≤0.015	0.03	100	≤0.06	1	87.2	0.5	1	100	0.5	0.5	100	0.5	1	100
BHS[e] (767)															
Wildtype (389)	≤0.015	0.03	100	≤0.06	≤0.06	100	0.25	0.5	100	≤0.06	0.25	100	1	1	100
MDR (59)	0.03	0.03	100	≤0.06	≤0.06	100	0.5	0.5	100	0.25	0.25	100	0.5	1	100
TET (229)	0.03	0.03	100	≤0.06	≤0.06	100	0.5	0.5	100	0.12	0.25	100	1	1	100
ERY+CLI+TET (56)	0.03	0.03	100	≤0.06	≤0.06	100	0.5	0.5	100	0.25	0.25	100	0.5	1	100
ERY+TET (43)	≤0.015	0.03	100	≤0.06	≤0.06	100	0.25	0.5	100	0.12	0.25	100	1	1	100
ERY (23)	≤0.015	0.03	100	≤0.06	≤0.06	100	0.25	0.25	100	≤0.06	0.12	100	1	1	100
ERY+CLI (18)	≤0.015	0.03	100	≤0.06	≤0.06	100	0.25	0.5	100	≤0.06	0.25	100	0.5	1	100

MDR = multidrug resistant isolates (resistance phenotype to at least three dru classes); S = susceptible; ERY = erythromycin; CLI = clindamycin; TET = tetracyline; PEN = penicillin; VGS = viridans group streptococci; BHS = ß-haemolytic streptococci.
[a] Wildtype; isolates susceptible to all drugs tested.
[b] Breakpoint criteria for telavancin according to the labeling supplement for the product VIBATIV®, as available. The FDA-approved breakpoint for telavancin against VGS was that from *S. anginosus* group (≤0.06 mg/L for susceptible); while the interpretive criterion for *S. pyogenes* and *S. agalactiae* (≤0.12 mg/L for susceptible) was applied for other BHS. Breakpoint criteria for comparator agents were those from EUCAST, except for daptomycin and linezolid against viridans group streptococci that utilized CLSI criteria.
[c] Breakpoint not available.
[d] Includes *S. anginosus* group (140 strains), *S. bovis/gallolyticus* group (23 strains), *S. mitis/oralis* (209 strains), *Streptococcus mutans* (one strain), *Streptococcus salivarius* (22 strains), and unspeciated VGS (five strains).
[e] Includes *S. agalactiae* (274 strains), *S. dysgalactiae* (103 strains), *S. equi* (one strain), *S. pyogenes* (314 strains), Group C *Streptococcus* (24 strains), Group F *Streptococcus* (two strains), Group G *Streptococcus* (48 strains) and unspeciated BHS (one strain).

CONCLUSIONS

- Several antibiogram profiles were observed among this collection of streptococcal isolates, with resistance to erythromycin, clindamycin and tetracycline being the most common. In addition, a total of 14.4% (387/2694) of tested isolates exhibited an MDR phenotype.
- Telavancin demonstrated potent *in vitro* activity against this contemporary (2012–2013) collection of streptococcal isolates from European countries and adjacent geographic regions regardless of resistance phenotype. These potency results were consistently higher than comparators agents.

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