Dalbavancin Activity When Tested against *Streptococcus pneumoniae* Isolated in Medical Centers on Six Continents (2011 to 2014)

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Dalbavancin, a novel lipoglycopeptide, was approved for use in 2014 by regulatory agencies in the United States and Europe for the treatment of skin and skin structure infections. The activity of dalbavancin was also widely assessed by determination of its activity against *Streptococcus pneumoniae* clinical isolates collected from patients on six continents monitored during two time intervals (2011 to 2013 and 2014). A total of 18,186 pneumococcal isolates were obtained from 49 nations and submitted to a monitoring laboratory as part of the SENTRY Antimicrobial Surveillance Program for reference susceptibility testing. The potency of dalbavancin against *S. pneumoniae* was consistent across the years that it was monitored, with the MIC₅₀ and MIC₉₀ being 0.015 and 0.03 µg/ml, respectively, and all isolates were inhibited by ≤0.12 µg/ml. The activity of dalbavancin was not adversely influenced by nonsusceptibility to β-lactams (ceftriaxone or penicillin), macrolides, clindamycin, fluoroquinolones, or tetracyclines or multidrug resistance (MDR). Regional variations in dalbavancin activity were not detected, but *S. pneumoniae* strains isolated in the Asia-Pacific region were more likely to be nonsusceptible to penicillin and ceftriaxone as well as to be MDR than strains isolated in North or South America and Europe. Direct comparisons of potency illustrated that dalbavancin (MIC₅₀ and MIC₉₀, 0.015 and 0.03 µg/ml, respectively) was 16-fold or more active than vancomycin (MIC₅₀, 0.25 µg/ml), linezolid (MIC₅₀, 1 µg/ml), levofloxacin (MIC₅₀, 1 µg/ml), ceftriaxone (MIC₉₀, 1 µg/ml), and penicillin (MIC₉₀, 2 µg/ml). In conclusion, dalbavancin had potent and consistent activity against this contemporary (2011 to 2014) collection of *S. pneumoniae* isolates.

Dalbavancin (formerly BI397, MDL 63,399, A-A1, and VER001), a novel lipoglycopeptide with an extended serum elimination half-life (1–3), was developed for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in the United States and Europe (4–6). The greater potency of dalbavancin than that of vancomycin or linezolid (8- to 16-fold greater) has positioned this new agent for possible application against multidrug-resistant (MDR) Gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA), streptococci, and some *Enterococcus* species (7, 8). The spectrum and activity of dalbavancin have been documented in *in vitro* development studies and resistance surveillance investigations over the last decade (9–14), and its potential application against uncommonly isolated Gram-positive cocci (15) and pathogens not associated with cutaneous infections (16, 17) has been described. Expanded clinical trials supplementing registrational studies (4, 18, 19) have focused on the recently approved single-dose regimens (20) and its use in pediatric patient populations and for a proposed trial of community-acquired bacterial pneumonia (CABP) (<https://clinicaltrials.gov/ct2/results?term=dalbavancin&Search=Search>).

CABP continues to be a significant concern of primary care providers and emergency room physicians, although the prevalence of pathogens causing CABP that was previously dominated by *Streptococcus pneumoniae* and *Haemophilus influenzae* has been markedly altered by vaccine introductions (21). Concurrently, cases of pneumonia caused by MRSA have become more common, as has the emergence of MDR pneumococcal strains of non-vaccine serotypes, in the United States and Canada (4, 21–23). Recommendations for empirical therapy, especially for those severe pneumonia cases that require intensive care and that are associated with influenza, should consider the use of vancomycin or linezolid to cover MRSA, in addition to ceftriaxone (21). Agents that have recently been approved for use by the U.S. Food and Drug Administration (FDA) and that are active against both

ceftriaxone-resistant *S. pneumoniae* and MRSA (ceftaroline and lipoglycopeptides) could also be excellent treatment options (16, 17, 21, 24).

In this presentation, we report on the *in vitro* activity of dalbavancin against two very large worldwide collections of *S. pneumoniae* isolates tested by reference MIC methods: (i) 14,097 isolates from cultures of samples collected from patients in 2011 to 2013 and (ii) 4,099 *S. pneumoniae* isolates recovered from patients worldwide (North America, South America, Europe, Asia, and Australia) during 2014.

(The results for isolates collected from 2011 to 2013 were presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases [ECCMID], 25 to 28 April 2015, Copenhagen, Denmark.)

MATERIALS AND METHODS

Bacterial isolates. The initial studies utilized a total of 14,097 *S. pneumoniae* isolates collected in 2011 to 2013 from numerous hospitals in North America (2 countries, 172 centers), Latin America (11 countries, 21 sites), Europe and adjacent areas (22 countries, 57 sites), the Asia-Pacific (APAC) region (13 countries, 39 sites), and South Africa (1 site) (see Tables 1 and 2 and Fig. 1). Subsequently, in 2014, samples were collected from 214 medical centers from 40 nations on five continents (North and

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TABLE 1 Activity of dalbavancin against a worldwide collection of 14,097 *S. pneumoniae* clinical isolates (2011 to 2013)

Phenotype ^a (MIC, no. of isolates tested)	MIC (μg/ml)		No. (cumulative %) of isolates inhibited at dalbavancin MIC (μg/ml) of:		
	50%	90%	≤0.03	0.06	0.12
All (14,097)	≤0.03	≤0.03	13,649 (96.8)	442 (>99.9)	6 (100.0)
PEN ^S (≤2 μg/ml, 12,574)	≤0.03	≤0.03	12,146 (96.6)	422 (>99.9)	6 (100.0)
PEN ^{NS} (≥4 μg/ml, 1,523)	≤0.03	≤0.03	1,503 (98.7)	20 (100.0)	
CRO ^S (≤1 μg/ml, 12,645)	≤0.03	≤0.03	12,220 (96.6)	419 (>99.9)	6 (100.0)
CRO ^{NS} (≥2 μg/ml, 1,452)	≤0.03	≤0.03	1,429 (98.4)	23 (100.0)	
MDR (3,351)	≤0.03	≤0.03	3,274 (97.7)	75 (>99.9)	2 (100.0)

^a Data analysis was performed with data for all isolates and also stratified by the penicillin and ceftriaxone MIC values (CLSI breakpoint criteria). PEN^S, penicillin susceptible; PEN^{NS}, penicillin nonsusceptible; CRO^S, ceftriaxone susceptible; CRO^{NS}, ceftriaxone nonsusceptible. *S. pneumoniae* isolates displaying a phenotype of nonsusceptibility to at least three drug classes were considered multidrug resistant (MDR). The drugs and breakpoints for NS included in the analysis of MDR were as follows: penicillin, ≥4 μg/ml; ceftriaxone, ≥2 μg/ml; levofloxacin, ≥4 μg/ml; erythromycin, ≥0.5 μg/ml; clindamycin, ≥0.5 μg/ml; and tetracycline, ≥2 μg/ml (29).

South America, Europe, Asia, and Australia) (see Table 3 and Fig. 2). All pneumococci came from the lower respiratory tract or bloodstream.

Isolates were determined to be clinically significant on the basis of local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) as a part of the SENTRY Antimicrobial Surveillance Program (2011 to 2014). Isolates were originally identified to be *S. pneumoniae* by the participating laboratory, and bacterial identifications were confirmed by the reference, monitoring laboratory by the use of a standard identification algorithm, supported by matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing. The *S. pneumoniae* isolates were tested for susceptibility by the broth microdilution method following the guidelines in Clinical and Laboratory Standards Institute (CLSI) documents (25, 26). Testing was performed using validated panels manufactured by Thermo Fisher Scientific (Cleveland, OH, USA) (27). The dalbavancin MIC dilution range for the 2011 to 2013 data set (0.03 to 4 μg/ml) was extended to a lower concentration of 0.002 μg/ml in 2014 to better define the limits of the MICs for the susceptible wild-type population that included the MIC₅₀ (0.015 μg/ml) and MIC₉₀ (0.03 μg/ml) values. Quality assurance was performed by concurrent testing of CLSI-recommended quality control (QC) reference strain *S. pneumoniae* ATCC 46919 (26), as well as *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212. All results for dalbavancin and the comparator agents for the QC strain were within published acceptable limits (26, 27).

Breakpoint criteria for comparator agents were those from CLSI (26), the European Committee on Antimicrobial Susceptibility Testing (EUCAST; v5.0, 2015) (6, 28), and the FDA product package insert for dalbavancin (5), i.e., ≤0.25 μg/ml. Analysis of the data for both organism subsets was performed with data for all isolates in aggregate and also according to the MIC values for penicillin and ceftriaxone susceptibility or nonsusceptibility (NS). *S. pneumoniae* isolates displaying a phenotype of NS to penicillin (MIC, ≥4 μg/ml), ceftriaxone (MIC, ≥2 μg/ml), or at least three drug classes were considered MDR and assessed separately. The tested drug classes (marker agent) were penicillins (penicillin), cephalosporins (ceftriaxone), fluoroquinolones (levofloxacin), macrolides (erythromycin), lincosamides (clindamycin), and tetracyclines (tetracycline HCl) (29).

RESULTS AND DISCUSSION

The *S. pneumoniae* isolates were collected and tested for drug susceptibility by reference MIC methods. The two groups of isolates evaluated in this study (those collected from 2011 to 2013 and those collected in 2014) were analyzed separately. For the isolates in each group, susceptibility to dalbavancin was compared to that to eight antimicrobials (see Tables 2 and 3). For isolates collected from 2011 to 2013, dalbavancin was processed using a log₂ dilu-

tion schedule beginning at 0.03 μg/ml (Table 1), and the MIC₅₀ and MIC₉₀ for all strains and resistant strain subsets were ≤0.03 and ≤0.03 μg/ml, respectively; the dalbavancin MIC values for all 14,097 pneumococci were ≤0.12 μg/ml, the breakpoint concentration for susceptibility for other streptococci published by EUCAST (28). In fact, >99.9% of all *S. pneumoniae* isolates were inhibited by ≤0.06 μg/ml of dalbavancin (Table 1), and the FDA breakpoint was elevated to ≤0.25 μg/ml in early 2016 (5).

Among the comparator agents, the highest rates of susceptibility, determined using CLSI breakpoints (26)/EUCAST breakpoints (28), were documented to be linezolid (100.0/100.0%), vancomycin (100.0/100.0%), levofloxacin (98.7/98.7%), ceftriaxone (89.7/77.5%), and high-dose penicillin (89.2/59.3%) (Table 2). A poor coverage of year 2011 to 2013 *S. pneumoniae* isolates was exhibited for erythromycin (57.3%), clindamycin (76.3 to 76.8%), and tetracyclines (69.6%). The penicillin-NS, ceftriaxone-NS, and MDR pneumococcal isolate subsets remained very susceptible to linezolid and vancomycin (100.0% for both at the CLSI and EUCAST breakpoints), as well as levofloxacin (96.5 to 98.9%). The rates of resistance to erythromycin, clindamycin, and tetracycline among the 3,351 MDR strains (Table 2) were extremely high at 99.8, 92.5, and 96.7%, respectively. Resistance to the older orally available agents dominated the MDR organism analyses (Tables 1 and 2; Fig. 1).

Regional variations in the patterns of resistance to penicillin, ceftriaxone, and multiple drugs (Fig. 1) were documented for the larger sample of isolates collected from 2011 to 2013. In general, the order of the occurrence of resistance was as follows: APAC region > Latin America = North America (United States and Canada) > Europe. A greater proportion of *S. pneumoniae* isolates (54.4%) from the APAC region than the other regions had the MDR phenotype, and this was primarily driven by resistance to macrolides, clindamycin, and tetracyclines, although strains NS to penicillin and ceftriaxone were also twice as common in the APAC region than in the other regions (Europe, Latin America, and North America; Fig. 1). MDR isolates made up 23.8% of the overall population of *S. pneumoniae* isolates collected from 2011 to 2013 tested, with the rates being 19.4 to 21.7% in regions other than the APAC region.

In 2014, the dilution schedule for the testing of dalbavancin was extended to a lower concentration of 0.002 μg/ml; in contrast, it had been 0.03 μg/ml in the prior years (Tables 1 and 2). Table 3 compares the dalbavancin MIC₅₀ and MIC₉₀ results for 4,099 *S.*

TABLE 2 Antimicrobial activity of dalbavancin and comparator agents against a worldwide collection of 14,097 *S. pneumoniae* clinical isolates (2011 to 2013)

Phenotype ^a (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% of isolates susceptible/intermediate/ resistant according to the following breakpoint criteria ^b :	
	Range	50%	90%	CLSI	EUCAST
All isolates (14,097)					
Dalbavancin	≤0.03–0.12	≤0.03	≤0.03	—/—/—	—/—/—
Penicillin ^c	≤0.06–>8	≤0.06	4	89.2/9.5/1.3	59.3/29.9/10.8
Penicillin ^d	≤0.06–>8	≤0.06	4	59.3/—/40.7	59.3/—/40.7
Ceftriaxone ^c	≤0.06–>8	≤0.06	2	89.7/8.4/1.9	77.5/20.6/1.9
Erythromycin ^e	≤0.12–>16	≤0.12	>16	57.3/0.5/42.2	57.3/0.5/42.2
Clindamycin	≤0.25–>2	≤0.25	>2	76.3/0.5/23.2	76.8/—/23.2
Levofloxacin	≤0.12–>4	1	1	98.7/0.2/1.1	98.7/—/1.3
Linezolid	≤0.12–2	1	1	100.0/—/—	100.0/0.0/0.0
Tetracycline ^f	≤0.25–>8	≤0.25	>8	69.6/0.4/30.1	69.6/0.4/30.1
Vancomycin	≤0.12–1	0.25	0.5	100.0/—/—	100.0/—/0.0
PEN^s (12,574)					
Dalbavancin	≤0.03–0.12	≤0.03	≤0.03	—/—/—	—/—/—
Ceftriaxone ^c	≤0.06–8	≤0.06	1	97.7/2.1/0.2	86.7/13.1/0.2
Erythromycin ^e	≤0.12–>16	≤0.12	>16	63.8/0.6/35.6	63.8/0.6/35.6
Clindamycin	≤0.25–>2	≤0.25	>2	83.8/0.5/15.7	84.3/—/15.7
Levofloxacin	≤0.12–>4	1	1	98.9/0.2/1.0	98.9/—/1.1
Linezolid	≤0.12–2	1	1	100.0/—/—	100.0/0.0/0.0
Tetracycline ^f	≤0.25–>8	≤0.25	>8	76.9/0.4/22.7	76.9/0.4/22.7
Vancomycin	≤0.12–1	0.25	0.5	100.0/—/—	100.0/—/0.0
PEN^{NS} (1,523)					
Dalbavancin	≤0.03–0.06	≤0.03	≤0.03	—/—/—	—/—/—
Ceftriaxone ^c	≤0.06–>8	2	8	23.2/60.1/16.7	0.9/82.5/16.7
Erythromycin ^e	≤0.12–>16	>16	>16	3.3/0.1/96.6	3.3/0.1/96.6
Clindamycin	≤0.25–>2	>2	>2	14.3/0.2/85.5	14.5/—/85.5
Levofloxacin	0.5–>4	1	1	97.7/0.3/2.0	97.7/—/2.3
Linezolid	0.25–2	0.5	1	100.0/—/—	100.0/0.0/0.0
Tetracycline ^f	≤0.25–>8	>8	>8	8.9/0.2/90.9	8.9/0.2/90.9
Vancomycin	≤0.12–1	0.25	0.5	100.0/—/—	100.0/—/0.0
CRO^s (12,645)					
Dalbavancin	≤0.03–0.12	≤0.03	≤0.03	—/—/—	—/—/—
Penicillin ^c	≤0.06–8	≤0.06	2	97.2/2.8/0.1	66.1/31.1/2.8
Penicillin ^d	≤0.06–8	≤0.06	2	66.1/—/33.9	66.1/—/33.9
Erythromycin ^e	≤0.12–>16	≤0.12	>16	63.2/0.6/36.2	63.2/0.6/36.2
Clindamycin	≤0.25–>2	≤0.25	>2	82.8/0.5/16.7	83.3/—/16.7
Levofloxacin	0.12–>4	1	1	98.9/0.2/0.9	98.9/—/1.1
Linezolid	≤0.12–2	1	1	100.0/—/—	100.0/0.0/0.0
Tetracycline ^f	≤0.25–>8	≤0.25	>8	76.2/0.4/23.4	76.2/0.4/23.4
Vancomycin	≤0.12–1	0.25	0.5	100.0/—/—	100.0/—/0.0
CRO^{NS} (1,452)					
Dalbavancin	≤0.03–0.06	≤0.03	≤0.03	—/—/—	—/—/—
Penicillin ^c	≤0.06–>8	4	8	19.5/68.4/12.1	0.6/18.9/80.5
Penicillin ^d	≤0.06–>8	4	8	0.6/—/99.4	0.6/—/99.4
Erythromycin ^e	≤0.12–>16	>16	>16	5.9/0.1/94.0	5.9/0.1/94.0
Clindamycin	≤0.25–>2	>2	>2	19.5/0.3/80.2	19.8/—/80.2
Levofloxacin	0.5–>4	1	1	97.5/0.2/2.3	97.5/—/2.5
Linezolid	≤0.12–2	0.5	1	100.0/—/—	100.0/0.0/0.0
Tetracycline ^f	≤0.25–>8	>8	>8	11.9/0.3/87.8	11.9/0.3/87.8
Vancomycin	≤0.12–1	0.25	0.5	100.0/—/—	100.0/—/0.0

(Continued on following page)

TABLE 2 (Continued)

Phenotype ^a (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% of isolates susceptible/intermediate/ resistant according to the following breakpoint criteria ^b :	
	Range	50%	90%	CLSI	EUCAST
MDR (3,351)					
Dalbavancin	≤0.03–0.12	≤0.03	≤0.03	—/—/—	—/—/—
Penicillin ^c	≤0.06–>8	2	4	56.5/38.3/5.3	16.8/39.6/43.5
Penicillin ^d	≤0.06–>8	2	4	16.8/—/83.2	16.8/—/83.2
Ceftriaxone ^e	≤0.06–>8	1	2	89.9/32.1/8.0	38.6/53.4/8.0
Erythromycin ^e	≤0.12–>16	>16	>16	0.1/0.1/99.8	0.1/0.1/99.8
Clindamycin	≤0.25–>2	>2	>2	6.6/0.8/92.5	7.5/—/92.5
Levofloxacin	≤0.12–>4	1	1	96.5/0.4/3.1	96.5/—/13.5
Linezolid	≤0.12–2	0.5	1	100.0/—/—	100.0/0.0/0.0
Tetracycline ^f	≤0.25–>8	>8	>8	2.8/0.5/96.7	2.8/0.5/96.7
Vancomycin	≤0.12–1	0.25	0.5	100.0/—/—	100.0/—/0.0

^a Data analysis was performed with data for all isolates in aggregate and also according to the penicillin and ceftriaxone MIC values (CLSI breakpoint criteria). PEN^s, penicillin susceptible (MIC, ≤2 μg/ml); PEN^{NS}, penicillin nonsusceptible (MIC, ≥4 μg/ml); CRO^s, ceftriaxone susceptible (MIC, ≤1 μg/ml); CRO^{NS}, ceftriaxone nonsusceptible (MIC, ≥2 μg/ml). *S. pneumoniae* isolates displaying a phenotype of nonsusceptibility to at least three other drug classes were considered multidrug resistant (MDR). The drugs and breakpoints included in the MDR analysis were as follows: penicillin, ≥4 μg/ml; ceftriaxone, ≥2 μg/ml; levofloxacin, ≥4 μg/ml; erythromycin, ≥0.5 μg/ml; clindamycin, ≥0.5 μg/ml; and tetracycline, ≥2 μg/ml (29).

^b Breakpoint criteria for comparator agents were those from CLSI (26) and EUCAST (28). —, breakpoint not available.

^c Susceptibility breakpoints for parenteral (nonmeningitis) therapies.

^d Susceptibility breakpoints for meningitis isolates.

^e Predicts rates of susceptibility to azithromycin and clarithromycin.

^f Predicts rates of susceptibility to doxycycline and minocycline.

pneumoniae isolates collected and tested by reference methods to those for the same eight comparator agents (25, 26). Consistent values of the dalbavancin MIC₅₀ and MIC₉₀ (0.015 and 0.03 μg/ml, respectively) were observed for all *S. pneumoniae* isolates and resistant isolate subsets analyzed (Table 1). All isolates were inhibited by dalbavancin at ≤0.06 μg/ml, and 97.5% of the *S. pneumoniae* isolates had MICs of ≤0.03 μg/ml (the proportion was 96.8% for strains collected from 2011 to 2013; Tables 1 and 3). The most potent and broadly active comparison drugs were vancomy-

cin (MIC₅₀ and MIC₉₀, 0.25 and 0.5 μg/ml, respectively; 100.0% were susceptible by the use of CLSI breakpoint criteria), linezolid (MIC₅₀ and MIC₉₀, 1 and 1 μg/ml, respectively; 100.0% were susceptible by the use of CLSI breakpoint criteria), levofloxacin (MIC₅₀ and MIC₉₀, 1 and 1 μg/ml, respectively; 98.3% were susceptible by the use of CLSI breakpoint criteria), penicillin (MIC₅₀ and MIC₉₀, ≤0.06 and 2 μg/ml, respectively; 93.5% were susceptible by the use of CLSI breakpoint criteria but only 62.0% were susceptible by the use of the EUCAST breakpoint criteria), and

FIG 1 Proportion of penicillin-nonsusceptible (PEN-NS), ceftriaxone-nonsusceptible (CRO-NS), and MDR isolates among a worldwide collection of 14,087 *S. pneumoniae* clinical isolates (2011 to 2013).

TABLE 3 Comparative activity of dalbavancin and eight other agents against 4,599 *S. pneumoniae* collected worldwide in the SENTRY Antimicrobial Surveillance Program (2014)

Antimicrobial agent and phenotype ^a (no. of isolates tested)	MIC ($\mu\text{g/ml}$)	% isolates susceptible according to the following breakpoint criteria:			
	Range	50%	90%	CLSI	EUCAST
Dalbavancin (4,099)	≤ 0.002 – 0.06	0.015	0.03	(100.0) ^b	(100.0)
PEN ^{NS} (268)	0.008– 0.06	0.015	0.03	(100.0)	(100.0)
CRO ^{NS} (276)	0.008– 0.06	0.015	0.03	(100.0)	(100.0)
MDR (747)	0.004– 0.06	0.015	0.03	(100.0)	(100.0)
Penicillin ^c	≤ 0.06 – >8	≤ 0.06	2	93.5	62.0
Ceftriaxone ^c	≤ 0.06 – >8	≤ 0.06	1	93.3	81.6
Erythromycin ^d	≤ 0.12 – >16	≤ 0.12	>16	58.9	58.9
Clindamycin	≤ 0.25 – >2	≤ 0.25	>2	81.7	82.2
Levofloxacin	≤ 0.12 – >4	1	1	98.3	98.3
Linezolid	≤ 0.12 –2	1	1	100.0	100.0
Tetracycline ^e	≤ 0.5 – >8	≤ 0.5	>8	75.2	75.2
Vancomycin	≤ 0.12 –1	0.25	0.5	100.0	100.0

^a Data analysis was performed with data for all isolates in aggregate and also according to the penicillin and ceftriaxone MIC values (CLSI breakpoint criteria) (26). PEN^{NS}, penicillin nonsusceptible (MIC, ≥ 4 $\mu\text{g/ml}$); CRO^{NS}, ceftriaxone nonsusceptible (MIC, ≥ 2 $\mu\text{g/ml}$). *S. pneumoniae* isolates displaying a phenotype of nonsusceptibility to at least three other drug classes were considered multidrug resistant (MDR). The drugs and nonsusceptible breakpoints included in the MDR analysis were as follows: penicillin, ≥ 4 $\mu\text{g/ml}$; ceftriaxone, ≥ 2 $\mu\text{g/ml}$; levofloxacin, ≥ 4 $\mu\text{g/ml}$; erythromycin, ≥ 0.5 $\mu\text{g/ml}$; clindamycin, ≥ 0.5 $\mu\text{g/ml}$; and tetracycline, ≥ 2 $\mu\text{g/ml}$ (29).

^b Dalbavancin susceptibility breakpoint criteria (≤ 0.12 $\mu\text{g/ml}$) for other streptococci (β -hemolytic streptococci or *Streptococcus anginosus*) published by EUCAST (6) and FDA (5) are found in parentheses.

^c Breakpoint for parenteral (nonmeningitis) therapies.

^d Predicts susceptibility to azithromycin and clarithromycin.

^e Predicts susceptibility to doxycycline and minocycline.

ceftriaxone (MIC₅₀ and MIC₉₀, ≤ 0.06 and 1 $\mu\text{g/ml}$, respectively; 93.3% were susceptible by the use of CLSI breakpoint criteria and 81.6% were susceptible by the use of EUCAST breakpoint criteria) (26, 28).

The dalbavancin MICs for isolates collected in 2014 clearly defined the treatable wild-type *S. pneumoniae* population of isolates (MIC range, ≤ 0.002 to 0.06 $\mu\text{g/ml}$), for which the modal MIC was 0.015 $\mu\text{g/ml}$ (MIC₉₀, 0.03 $\mu\text{g/ml}$). A graph of the cumulative percentage of isolates that were inhibited (Finland-o-Gram; Fig. 2) was plotted for year 2014 *S. pneumoniae* isolates to illustrate the stark differences in antimicrobial activity among the six most active agents. Dalbavancin was 16-fold more potent than vancomycin and ≥ 32 -fold more active than either levofloxacin or linezolid. Note that the glycopeptides (dalbavancin, vancomycin), an oxazolidinone (linezolid), and a fluoroquinolone (levofloxacin) had very narrow MIC ranges compared to those of the β -lactams tested (ceftriaxone, penicillin). The recently modified FDA breakpoint for dalbavancin (≤ 0.25 $\mu\text{g/ml}$) when testing indicated the presence of streptococci (5) was 16-fold above the dalbavancin MIC₅₀ (0.015 $\mu\text{g/ml}$) (Table 3).

The reference broth microdilution method required for testing the new lipoglycopeptides (dalbavancin, oritavancin, telavancin) utilizes a polysorbate-80 (P-80; 0.002%) supplement to minimize drug binding to the plastic trays used in the reference test method (25, 26, 30). This binding can have a profound negative effect on antimicrobial potency, a phenomenon not observed with some other glycopeptides, such as vancomycin. Dalbavancin was identified early in clinical development as needing the P-80 supplement, demonstrating a very potent activity (MICs, ≤ 0.12 $\mu\text{g/ml}$) against common Gram-positive bacterial pathogens (30). This required validation of several alternative commercial products (the Sensititre test, Etest) to routinely test dalbavancin in clinical microbiology laboratories; however, the poor diffusion of lipoglyco-

peptides through Mueller-Hinton agar has compromised application of the disk diffusion method (30–32). To facilitate early applications of dalbavancin in the absence of commercial susceptibility testing products, a vancomycin MIC susceptibility surrogate result can be used with confidence to predict dalbavancin susceptibility (33, 34).

Prior to FDA approval of dalbavancin for the treatment of ABSSSIs in 2014, a large volume of clinical and *in vitro* surveillance information on its activity against key pathogens, such as *S. aureus*, beta-hemolytic streptococci, viridans group streptococci, and vancomycin-susceptible *Enterococcus* spp., was accumulated (9–14, 16). More recent surveillance samples were expanded to *S. pneumoniae*, as clinical trials of the activity of dalbavancin in patients with CABP were initially considered (<https://clinicaltrials.gov/ct2/results?term=dalbavancin&Search=Search>). This report illustrates the contemporary (2011 to 2014) potency of dalbavancin when tested against *S. pneumoniae* isolates collected worldwide (Tables 1 to 3; Fig. 1 and 2). These data provide a baseline level of dalbavancin activity as the lipoglycopeptide class is introduced more widely into clinical practice. Previously reported *S. pneumoniae* dalbavancin MIC values were often obtained by test methods without P-80 (17).

The breadth of dalbavancin coverage against tabulated pneumococcal resistance phenotypes was most like that of vancomycin or oxazolidinones, therefore offering their potential use in patients with serious CABPs, where these agents may be indicated by published practice guidelines (21, 35) for the treatment of MDR pathogens or MRSA. Dalbavancin was routinely ≥ 16 -fold more potent than glycopeptides (vancomycin) and linezolid against Gram-positive bacterial pathogens (Tables 2 and 3 and Fig. 2), and no adverse effects of lung surfactants have been detected (36). The concentrations of dalbavancin in epithelial lining fluid should also be determined. The dalbavancin MIC₉₀ for *S. au-*

FIG 2 Cumulative (Cum.) percent inhibition plots (Finland-o-grams) for dalbavancin and five comparator agents tested against a worldwide collection of 4,099 *S. pneumoniae* isolates (2014).

reus isolates from the 2014 surveillance population was only 0.06 µg/ml (data not shown), like that reported for isolates from the 2011 and 2012 surveillance samples (13, 14). We eagerly await the results from the expanded clinical trials of the use of dalbavancin for the treatment of hematogenous osteomyelitis (37), for indications in hospitalized children and adolescents, and, possibly, for CABP (<https://clinicaltrials.gov/ct2/results?term=dalbavancin&Search=Search>).

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REFERENCES

- Malabarba A, Goldstein BP. 2005. Origin, structure, and activity in vitro and in vivo of dalbavancin. *J Antimicrob Chemother* 55(Suppl 2):ii15–ii20.
- Zhanel GG, Calic D, Schweizer F, Zelenitsky S, Adam H, Lagace-Wiens PR, Rubinstein E, Gin AS, Hoban DJ, Karlowicz JA. 2010. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 70:859–886. <http://dx.doi.org/10.2165/11534440-000000000-00000>.
- Andes D, Craig WA. 2007. In vivo pharmacodynamic activity of the glycopeptide dalbavancin. *Antimicrob Agents Chemother* 51:1633–1642. <http://dx.doi.org/10.1128/AAC.01264-06>.
- Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. 2014. Once-weekly dalbavancin versus daily conventional therapy for skin infection. *N Engl J Med* 370:2169–2179. <http://dx.doi.org/10.1056/NEJMoa1310480>.
- Allergan. 2016. Dalvance™ package insert. Allergan, Parsippany, NJ. Accessed February 2016.
- EUCAST. 2015. Clinical breakpoints and QC recommendations for the new agents dalbavancin, oritavancin and tedizolid. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Addenda/New_EUCAST_breakpoints_final.pdf. Accessed August 2015.
- Moellering RC, Jr. 2012. MRSA: the first half century. *J Antimicrob Chemother* 67:4–11. <http://dx.doi.org/10.1093/jac/dkr437>.
- Jones RN, Sader HS, Moet GJ, Farrell DJ. 2010. Declining antimicrobial susceptibility of *Streptococcus pneumoniae* in the United States: report from the SENTRY Antimicrobial Surveillance Program (1998–2009). *Diagn Microbiol Infect Dis* 68:334–336. <http://dx.doi.org/10.1016/j.diagmicrobio.2010.08.024>.
- Streit JM, Fritsche TR, Sader HS, Jones RN. 2004. Worldwide assessment of dalbavancin activity and spectrum against over 6,000 clinical isolates. *Diagn Microbiol Infect Dis* 48:137–143. <http://dx.doi.org/10.1016/j.diagmicrobio.2003.09.004>.
- Jones RN, Fritsche TR, Sader HS, Goldstein BP. 2005. Antimicrobial spectrum and potency of dalbavancin tested against clinical isolates from Europe and North America (2003): initial results from an international

- surveillance protocol. *J Chemother* 17:593–600. <http://dx.doi.org/10.1179/joc.2005.17.6.593>.
11. Biedenbach DJ, Ross JE, Fritsche TR, Sader HS, Jones RN. 2007. Activity of dalbavancin tested against *Staphylococcus* spp. and beta-hemolytic *Streptococcus* spp. isolated from 52 geographically diverse medical centers in the United States. *J Clin Microbiol* 45:998–1004. <http://dx.doi.org/10.1128/JCM.02368-06>.
  12. Biedenbach DJ, Bell JM, Sader HS, Turnidge JD, Jones RN. 2009. Activities of dalbavancin against a worldwide collection of 81,673 gram-positive bacterial isolates. *Antimicrob Agents Chemother* 53:1260–1263. <http://dx.doi.org/10.1128/AAC.01453-08>.
  13. Jones RN, Sader HS, Flamm RK. 2013. Update of dalbavancin spectrum and potency in the USA; report from the SENTRY Antimicrobial Surveillance Program (2011). *Diagn Microbiol Infect Dis* 75:304–307. <http://dx.doi.org/10.1016/j.diagmicrobio.2012.11.024>.
  14. Jones RN, Flamm RK, Sader HS. 2013. Surveillance of dalbavancin potency and spectrum in the United States (2012). *Diagn Microbiol Infect Dis* 76:122–123. <http://dx.doi.org/10.1016/j.diagmicrobio.2013.01.003>.
  15. Jones RN, Stilwell MG. 2013. Comprehensive update of dalbavancin activity when tested against uncommonly isolated streptococci, *Corynebacterium* spp., *Listeria monocytogenes* and *Micrococcus* spp. (1,357 strains). *Diagn Microbiol Infect Dis* 76:239–240. <http://dx.doi.org/10.1016/j.diagmicrobio.2013.01.002>.
  16. Karlowsky JA, Adam HJ, Poutanen SM, Hoban DJ, Zhanel GG. 2011. In vitro activity of dalbavancin and telavancin against staphylococci and streptococci isolated from patients in Canadian hospitals: results of the CANWARD 2007–2009 study. *Diagn Microbiol Infect Dis* 69:342–347. <http://dx.doi.org/10.1016/j.diagmicrobio.2010.10.031>.
  17. Lin G, Smith K, Ednie LM, Appelbaum PC. 2005. Antipneumococcal activity of dalbavancin compared to other agents. *Antimicrob Agents Chemother* 49:5182–5184. <http://dx.doi.org/10.1128/AAC.49.12.5182-5184.2005>.
  18. Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, Krause D, Satilovs I, Endzinas Z, Breau J, O'Riordan W. 2005. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 41:1407–1415. <http://dx.doi.org/10.1086/497271>.
  19. Seltzer E, Dorr MB, Goldstein BP, Perry M, Dowell JA, Henkel T. 2003. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin Infect Dis* 37:1298–1303. <http://dx.doi.org/10.1086/379015>.
  20. Dunne MW, Puttagunta S, Giordano P, Krievins D, Zelasky M, Baldassarre J. 2016. A randomized clinical trial of single-dose versus weekly dalbavancin for treatment of acute bacterial skin and skin structure infection. *Clin Infect Dis* 62:545–551. <http://dx.doi.org/10.1093/cid/civ982>.
  21. Musher DM, Thorner AR. 2014. Community-acquired pneumonia. *N Engl J Med* 371:1619–1628. <http://dx.doi.org/10.1056/NEJMra1312885>.
  22. Golden AR, Rosenthal M, Fultz B, Nichol KA, Adam HJ, Gilmour MW, Baxter MR, Hoban DJ, Karlowsky JA, Zhanel GG. 2015. Characterization of MDR and XDR *Streptococcus pneumoniae* in Canada, 2007–13. *J Antimicrob Chemother* 70:2199–2202. <http://dx.doi.org/10.1093/jac/dkv107>.
  23. Mendes RE, Costello AJ, Jacobs MR, Biek D, Critchley IA, Jones RN. 2014. Serotype distribution and antimicrobial susceptibility of USA *Streptococcus pneumoniae* isolates collected prior to and post introduction of 13-valent pneumococcal conjugate vaccine. *Diagn Microbiol Infect Dis* 80:19–25. <http://dx.doi.org/10.1016/j.diagmicrobio.2014.05.020>.
  24. Flamm RK, Sader HS, Farrell DJ, Jones RN. 2014. Antimicrobial activity of ceftaroline tested against drug resistant subsets of *Streptococcus pneumoniae* from United States medical centers. *Antimicrob Agents Chemother* 58:2468–2471. <http://dx.doi.org/10.1128/AAC.02557-13>.
  25. Clinical and Laboratory Standards Institute. 2015. M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard, 10th ed. Clinical and Laboratory Standards Institute, Wayne, PA.
  26. Clinical and Laboratory Standards Institute. 2015. M100-S25. Performance standards for antimicrobial susceptibility testing; 25th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.
  27. Anderegg TR, Biedenbach DJ, Jones RN. 2003. Initial quality control evaluations for susceptibility testing of dalbavancin (BI397), an investigational glycopeptide with potent gram-positive activity. *J Clin Microbiol* 41:2795–2796. <http://dx.doi.org/10.1128/JCM.41.6.2795-2796.2003>.
  28. EUCAST. 2015. Breakpoint tables for interpretation of MICs and zone diameters, version 5.0, January. http://www.eucast.org/clinical_breakpoints/. Accessed January 2015.
  29. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 18: 268–281. <http://dx.doi.org/10.1111/j.1469-0691.2011.03570.x>.
  30. Rennie RP, Koeth L, Jones RN, Fritsche TR, Knapp CC, Killian SB, Goldstein BP. 2007. Factors influencing broth microdilution antimicrobial susceptibility test results for dalbavancin, a new glycopeptide agent. *J Clin Microbiol* 45:3151–3154. <http://dx.doi.org/10.1128/JCM.02411-06>.
  31. Fritsche TR, Rennie RP, Goldstein BP, Jones RN. 2006. Comparison of dalbavancin MIC values determined by Etest (AB Biodisk) and reference dilution methods using gram-positive organisms. *J Clin Microbiol* 44: 2988–2990. <http://dx.doi.org/10.1128/JCM.00640-06>.
  32. Jones RN, Streit JM, Fritsche TR. 2004. Validation of commercial dry-form broth microdilution panels and test reproducibility for susceptibility testing of dalbavancin, a new very long-acting glycopeptide. *Int J Antimicrob Agents* 23:197–199. <http://dx.doi.org/10.1016/j.ijantimicag.2003.07.008>.
  33. Jones RN, Farrell DJ, Flamm RK, Sader HS, Dunne MW, Mendes RE. 2015. Surrogate analysis of vancomycin to predict susceptible categorization of dalbavancin. *Diagn Microbiol Infect Dis* 82:73–77. <http://dx.doi.org/10.1016/j.diagmicrobio.2015.01.017>.
  34. Jones RN, Sader HS, Fritsche TR, Hogan PA, Sheehan DJ. 2006. Selection of a surrogate agent (vancomycin or teicoplanin) for initial susceptibility testing of dalbavancin: results from an international antimicrobial surveillance program. *J Clin Microbiol* 44:2622–2625. <http://dx.doi.org/10.1128/JCM.00576-06>.
  35. Musher DM, Thorner AR. 2015. Community-acquired pneumonia. *N Engl J Med* 372:294. <http://dx.doi.org/10.1056/NEJMc1414306>.
  36. Dunne M, Koeth LM, Windau AR. 2012. The effect of lung surfactant on the in vitro activity of dalbavancin against *Staphylococcus aureus* and *Streptococcus pneumoniae*, abstr 1622. IDWeek, San Diego, CA.
  37. Barnea Y, Lerner A, Aizic A, Navon-Venezia S, Rachi E, Dunne MW, Puttagunta S, Carmeli Y. 2016. Efficacy of dalbavancin in the treatment of MRSA rat sternal osteomyelitis with mediastinitis. *J Antimicrob Chemother* 71:460–463. <http://dx.doi.org/10.1093/jac/dkv357>.