# Evaluation of Daptomycin Activity Tested against 164,457 Bacterial Strains from Hospitalized Patients: Summary of 8 Years of Surveillance Program Worldwide (2005-2012)

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## AMENDED ABSTRACT

**Background**: Daptomycin (DAP) is increasingly being used for treatment of skin and skin structure infection (SSSI) therapy and S. aureus bacteremia in the United States (USA) and worldwide (WW). We report the results for 8 years of the Daptomycin Surveillance Program WW.

Methods: Consecutive, non-duplicate bacterial isolates (prevalence design) were collected in 2005 - 2012 from patients with documented infections in 410 medical centers WW. The isolates were collected by site of infection according to study protocols and susceptibility (S) tested against >30 antimicrobials by broth microdilution methods following CLSI guidelines. Ca<sup>++</sup> content of the broth was adjusted (50 mg/L) for testing DAP.

**Results**: 164,457 Gram-positive (GP) isolates were evaluated, including: 97,542 S. aureus (SA), 21,413 coagulase-negative staphylococci (CoNS), 29,619 enterococci and 15,883 β-haemolytic streptococci (BHS). Isolates were mainly from bacteremia and SSSI. Overall MRSA rates were highest in North America (NA; 51.9%) > Latin America (LA; 41.7%) = Asia-Pacific region (41.7%) > Europe (27.6%). Vancomycin (VAN) resistance (R) among E. faecalis (EF)/E. faecium (EFM) were also highest in NA (4.3/74.5%) and LA (3.5/43.0%). Against SA, DAP MIC<sub>50/90</sub> was 0.25/0.5 μg/ml in all geographic regions (99.95% S overall). Only 53 DAP-non-S SA strains (0.05%) were observed, and the vast majority (49; 92.5%) had a DAP MIC only one log<sub>2</sub> dilution above the published S breakpoint (highest MIC, 4 µg/ml). Yearly activity of DAP against SA is summarized in the Table 3 and is similar across WW regions. DAP was also highly active against CoNS  $(MIC_{50/90}, 0.25/0.5 \mu g/ml; 99.8\% S), EF (MIC_{50/90}, 1/1 \mu g/ml; 99.98% S);$ EFM (MIC<sub>50/90</sub>, 2/4 μg/ml; 99. 8% S), including VAN-non-S strains (3,096 strains; MIC<sub>50/90</sub>, 2/2  $\mu$ g/ml; 99.8% S) and BHS (MIC<sub>50/90</sub>, 0.12/0.25  $\mu$ g/ml; 100.0% S). DAP remained very active and no significant year-to-year or regional variation in DAP activity was observed (2005-2012).

**Conclusions**: DAP was highly active against an extensive longitudinal collection of clinically important GP pathogens. Decreased S to DAP remains very rare after >8 years of clinical use, and non-S isolates (0.07%) usually have only slightly elevated DAP MIC results. R to oxacillin or VAN did not adversely affect DAP activity.

### INTRODUCTION

- Daptomycin is a lipopeptide with rapid *in vitro* bactericidal activity against a wide spectrum of Gram-positive organisms, including multidrug-resistant strains of staphylococci and enterococci.
- Daptomycin was initially approved by the United States (USA) Food and Drug Administration (FDA) in 2003 and by the European Medicines Agency (EMA) in 2005 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive bacteria using a dose of 4 mg/kg every 24 hours. In 2006 (USA) and 2007 (Europe), daptomycin received approval for the treatment of right-sided infective endocartidis (RIE) due to Staphylococcus aureus and for S. aureus bacteremia when associated with RIE or ABSSSI at a dose of 6 mg/kg every 24 hours.
- A large number of reports have shown that daptomycin is highly active against staphylococci, enterococci and streptococci; nevertheless, daptomycin non-susceptible isolates have been rarely detected worldwide with the mechanism being attributed to various gene mutations (*mprF*, YycFG, RNA polymerase subunits), changes in membrane fluidity and cell wall thickness, and alterations in membrane charge.
- In order to understand the progression of daptomycin non-susceptibility in staphylococci (MIC, ≥2 µg/ml), enterococci (MIC, ≥8 µg/ml) and streptococci (MIC, ≥2 µg/ml) since the initial approval of daptomycin for clinical use by the USA-FDA, we analyzed the results of eight years (2005 – 2012) of the Daptomycin Surveillance Program Worldwide.

## **METHODS**

- <u>Bacterial isolates</u>: A total of 164,457 consecutive unique patient strains of clinical significance were collected between January 2005 and December 2012. Only Grampositive organisms were included in this study and Streptococcus pneumoniae strains were excluded from the analysis. Isolates were collected from North America (NA; 77,552 strains), Europe/Mediterranean region (EMR; 46,081), Latin America (LA; 17,070) and Asia-Pacific region (APAC; 23,754). A total of 410 medical centers participated in the program, 204 from NA, 75 from EMR, 26 from LA and 105 from APAC. The collection includes 97,542 S. aureus (43.3% MRSA), 21,413 coagulase-negative staphylococci (CoNS), 29,619 enterococci (18,740 Enterococcus faecalis; 9,678 E. faecium and 1,201 non-faecalis-non-faecium) and 15,883 β-haemolytic streptococci.
- Susceptibility testing: Daptomycin and various comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI; 2012) broth microdilution methods in validated, microdilution panels manufactured by ThermoFisher, Inc. (Cleveland, Ohio, USA). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. Additionally, 2.5-5% lysed horse blood supplement was used for testing fastidious streptococci. CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria were used to categorize the isolates as susceptible, intermediate and resistant. A daptomycin susceptibility breakpoint of ≤1 µg/ml was applied for S. aureus and streptococci, while ≤4 µg/ml was used for the enterococcal results, as recommended by the CLSI and the USA-FDA EUCAST has established daptomycin susceptible and resistant breakpoints for *S. aureus* (≤1 and ≥2 μg/ml, respectively), but has not published daptomycin breakpoints for enterococcal strains. The following quality control (QC) organisms were concurrently tested: S. aureus ATCC 29213, E. faecalis ATCC 29212 and S. pneumoniae ATCC 49619; all QC results were within published limits.

## RESULTS

- Against S. aureus (97,542 strains tested), daptomycin MIC<sub>50/90</sub> was 0.25/0.5 μg/ml in all geographic regions (99.95% susceptibility overall). Only 53 daptomycin-non-susceptible S. aureus strains (0.05%) were observed, and the vast majority (49; 92.5%) had a daptomycin MIC only one log<sub>2</sub> dilution above the published susceptible breakpoint
- Overall MRSA rates were highest in North America (51.9%) > Latin America (41.7%) = Asia-Pacific region (41.7%) > Europe (27.6%; data not shown); and daptomycin activity against MRSA (MIC<sub>50/90</sub> was 0.25/0.5 µg/ml) were almost identical to that against MSSA (MIC<sub>50/90</sub> was 0.25/0.5  $\mu$ g/ml; **Tables 1**, **2** and **3**). Furthermore, daptomycin remained very active and no significant year-to-year or regional variation in daptomycin activity against S. aureus was observed (Table 2).
- Daptomycin was also highly active against CoNS (21,413 strains; MIC<sub>50/90</sub>, 0.25/0.5 μg/ml; 99.81% susceptible), *E. faecalis* (18,740; MIC<sub>50/90</sub>, 1/1 μg/ml; 99.98% susceptible); E. faecium (9,678; MIC<sub>50/90</sub>, 2/4 µg/ml; 99.82% susceptible), including vancomycin-non-susceptible strains (4,521; MIC<sub>50/90</sub>, 2/2 μg/ml; 99.76% susceptible) and β-haemolytic streptococci (15,883; MIC<sub>50/90</sub>, ≤0.06/0.25 µg/ml; 100.0% susceptible; Table 1).
- Daptomycin activities against vancomycin-non-susceptible *E. faecalis* (MIC<sub>50/90</sub>, 1/1-2 μg/ml) and E. faecium (MIC<sub>50/90</sub>, 2/2-4 μg/ml) were very similar to those against vancomycin-susceptible strains in all geographic regions (Table 3). Vancomycin nonsusceptibility (MIC, ≥8 µg/ml) among *E. faecalis/E. faecium* was highest in NA (4.3/74.5%), followed by LA (3.5/43.0%), EU (1.3/26.7%) and APAC (0.7/16.9%; data not
- The prevalence of daptomycin-non-susceptible strains was extremely low for all species in all geographic regions. Overall, the highest prevalence of non-susceptible strains was observed among CoNS (0.19%), followed by E. faecium (0.18%), S. aureus (0.05%), E. faecalis (0.02%) and β-haemolytic streptococci (0.00%; **Table 4**).
- No tendency toward increasing daptomycin resistance (non-susceptibility) was observed for any species in any geographic region during the study period (2005-2012; **Table 4**).
- Daptomycin was also highly active against 22,508 S. aureus strains isolated from bloodstream infections worldwide (MIC<sub>50/90</sub>, 0.25/0.5 µg/ml; 99.94% susceptibility). Only 14 strains had daptomycin MIC values of ≥2 μg/ml, 12 strains at 2 μg/ml and two strains at 4 µg/ml. Among these 14 daptomycin-non-susceptible strains, vancomycin MIC values were 2 μg/ml for nine strains and 4 μg/ml (vancomycin-intermediate *S. aureus* [VISA]) for two strains (data not shown).

#### **Table 1**. Summary of daptomycin activity when tested against 164,457 bacterial strains from hospitalized patients worldwide (2005-2012).

	No. of isolates (cumulative %) inhibited at MIC (μg/ml):										
Organism (no. tested)	≤0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC <sub>50</sub>	MIC <sub>90</sub>
S. aureus (97,542)	112 (0.1)	2,819 (3.0)	66,819 (71.5)	26,696 (98.9)	1,043 (99.9)	49 (>99.9)	4 (100.0)			0.25	0.5
MSSA (55,281)	87 (0.2)	2,042 (3.9)	40,875 (77.8)	11,922 (99.4)	345 (>99.90)	9 (>99.9)	1 (100.0)			0.25	0.5
MRSA (42,261)	25 (0.1)	777 (1.9)	25,944 (63.3)	14,774 (98.2)	698 (99.9)	40 (>99.9)	3 (100.0)			0.25	0.5
CoNS (21,413)	277 (1.3)	1,801 (9.7)	10,451 (58.5)	7,989 (95.8)	854 (99.8)	39 (>99.9)	2 (100.0)			0.25	0.5
Enterococcus spp. (29,619)	85 (0.3)	152 (0.8)	665 (3.0)	7,254 (27.5)	12,777 (70.7)	7,452 (95.8)	1211 (99.9)	18 (>99.9)	5 (100.0)	1	2
E. faecalis (18,740)	51 (0.3)	100 (0.8)	494 (3.4)	6,438 (37.8)	9,748 (89.8)	1,794 (99.4)	112 (>99.9)	3 (100.0)		1	2
vancomycin-susc. (18,221)	48 (0.3)	100 (0.8)	475 (3.4)	6,215 (37.5)	9,511 (89.7)	1,760 (99.4)	109 (>99.9)	3 (100.0)		1	2
vancomycin-non-susc. (519)	3 (0.6)	0 (0.6)	19 (4.2)	223 (47.2)	237 (92.9)	34 (99.4)	3 (100.0)			1	1
E. faecium (9,678)	9 (0.1)	32 (0.4)	94 (1.4)	462 (6.2)	2,672 (33.8)	5,380 (89.4)	1,012 (99.8)	12 (99.9)	5 (100.0)	2	4
vancomycin-susc. (5,157)	5 (0.1)	18 (0.4)	57 (1.6)	246 (6.3)	1,166 (28.9)	2,973 (86.6)	686 (99.9)	5 (>99.9)	1 (100.0)	2	4
vancomycin-non-susc. (4,521)	4 (0.1)	14 (0.4)	37 (1.2)	216 (6.0)	1,506 (39.3)	2,407 (92.5)	326 (99.8)	7 (99.9)	4 (100.0)	2	2
β-haemolytic strep. (15,883)	8,197 (51.6)	3,369 (72.8)	4,006 (98.0)	311 (100.0)						≤0.06	0.25

	N	North America			Europe			Latin America			APAC		
Organism	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	No.	MIC <sub>50</sub>	MIC <sub>90</sub>	
S. aureus	49,106	0.25	0.5	24,202	0.25	0.5	9,489	0.25	0.5	14,745	0.25	0.5	
MSSA	23,632	0.25	0.5	17,525	0.25	0.5	5,531	0.25	0.5	8,593	0.25	0.5	
MRSA	25,474	0.25	0.5	6,677	0.25	0.5	3,958	0.5	0.5	6,152	0.5	0.5	
CoNS	8,534	0.25	0.5	7,586	0.25	0.5	2,879	0.25	0.5	2,414	0.5	0.5	
Enterococcus spp.	12,638	1	2	9,274	1	2	3,326	1	2	4,381	1	2	
E. faecalis	7,959	1	1	5,728	1	1	2,470	1	1	2,583	1	2	
vancomycin-susceptible	7,619	1	1	5,653	1	1	2,384	1	1	2,565	1	2	
vancomycin-non-susc.	340	1	1	75	1	1	86	1	1	18	1	2	
E. faecium	4,155	2	2	3,247	2	2	660	2	2	1,616	2	4	
vancomycin-susceptible	1,059	2	4	2,379	2	4	376	2	4	1,343	2	4	
vancomycin-non-susc.	3,096	2	2	868	2	2	284	2	2	273	2	4	
β-haemolytic streptococci	7,274	0.12	0.25	5,019	≤0.06	0.25	1,376	≤0.06	0.25	2,214	≤0.06	0.25	

Region /			No	. of daptomycin r	on-susceptible	isolates (%) by y	/ear		
Organism (no.)	2005	2006	2007	2008	2009	2010	2011	2012	All
North America									
S. aureus (49,106)	2 (0.05)	6 (0.10)	7 (0.11)	10 (0.18)	1 (0.02)	6 (0.10)	2 (0.03)	3 (0.03)	37 (0.08)
CoNS (8,534)	1 (0.16)	0 (0.00)	6 (0.45)	6 (0.48)	0 (0.00)	0 (0.00)	1 (0.11)	3 (0.30)	17 (0.20)
E. faecalis (7,959)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.10)	2 (0.17)	0 (0.00)	0 (0.00)	3 (0.04)
E. faecium (4,155)	0 (0.00)	1 (0.16)	0 (0.00)	4 (0.77)	2 (0.38)	6 (0.85)	1 (0.25)	2 (0.06)	16 (0.38)
β-haemolytic strep. (7,274)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Europe									
S. aureus (24,202)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.03)	4 (0.13)	2 (0.07)	7 (0.03)
CoNS (7,586)	1 (0.10)	5 (0.41)	1 (0.09)	1 (0.11)	0 (0.00)	2 (0.19)	1 (0.16)	0 (0.00)	11 (0.15)
E. faecalis (5,728)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
E. faecium (3,247)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
β-haemolytic strep. (5,019)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Latin America									
S. aureus (9,489)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.08)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.01)
CoNS (2,879)	0 (0.00)	2 (0.63)	0 (0.00)	2 (0.56)	3 (0.67)	1 (0.23)	0 (0.00)	0 (0.00)	8 (0.28)
E. faecalis (2,470)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
E. faecium (660)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
β-haemolytic strep. (1,376)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Asia-Pacific									
S. aureus (14,745)	0 (0.00)	1 (0.06)	2 (0.06)	1 (0.05)	0 (0.00)	2 (0.11)	1 (0.06)	1 (0.11)	8 (0.05)
CoNS (2,414)	0 (0.00)	1 (0.04)	2 (0.38)	1 (0.32)	0 (0.00)	1 (0.35)	0 (0.00)	0 (0.00)	5 (0.21)
E. faecalis (2,583)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
E. faecium (1,616)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.34)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.06)
β-haemolytic strep. (2,214)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
All regions combined									
S. aureus (97,542)	2 (0.02)	7 (0.06)	9 (0.06)	12 (0.10)	1 (0.01)	9 (0.07)	7 (0.06)	6 (0.04)	53 (0.05)
CoNS (21,413)	2 (0.10)	8 (0.25)	9 (0.26)	10 (0.35)	3 (0.10)	4 (0.14)	2 (0.09)	3 (0.16)	41 (0.19)
E. faecalis (18,740)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)	2 (0.07)	0 (0.00)	0 (0.00)	3 (0.02)
E. faecium (9,678)	0 (0.00)	1 (0.07)	0 (0.00)	5 (0.35)	2 (0.15)	6 (0.41)	1 (0.10)	2 (0.25)	17 (0.18)
β-haemolytic strep. (15,883)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

#### **Table 2**. Daptomycin MIC distributions for 97.542 *S. aureus* from medical centers worldwide (2005-2012).

	No. of		No. of	isolates (cumula	ative %) inhibite	ed at MIC (µg/m	I):			
Year	Isolates	≤0.06	0.12	0.25	0.5	1	2	4	MIC <sub>50</sub>	MIC <sub>90</sub>
All S. aureus										
2005	8,036	8 (0.1)	249 (3.2)	5,244 (68.5)	2,470 (99.2)	63 (>99.9)	2 (100.0)		0.25	0.5
2006	12,194	26 (0.2)	471 (4.1)	8,906 (77.1)	2,633 (98.7)	151 (99.9)	6 (>99.9)	1 (100.0)	0.25	0.5
2007	14,181	25 (0.2)	595 (4.4)	10,423 (77.9)	2,969 (98.8)	160 (99.9)	9 (100.0)		0.25	0.5
2008	12,213	9 (0.1)	277 (2.3)	7,581 (64.4)	4,146 (98.4)	188 (99.9)	9 (>99.9)	3 (100.0)	0.25	0.5
2009	11,627	9 (0.1)	166 (1.5)	5,807 (51.4)	5,446 (98.3)	198 (>99.9)	1 (100.0)		0.25	0.5
2010	13,272	14 (0.1)	518 (4.0)	9,948 (79.0)	2,696 (99.3)	87 (99.9)	9 (100.0)		0.25	0.5
2011	11,982	6 (0.1)	193 (1.7)	8,449 (72.2)	3,257 (99.4)	70 (99.9)	7 (100.0)		0.25	0.5
2012	14,037	15 (0.1)	350 (2.6)	10,461 (77.1)	3,079 (99.1)	126 (>99.9)	6 (100.0)		0.25	0.5
MSSA										
2005	4,843	5 (0.1)	196 (4.2)	3,490 (76.2)	1,130 (99.5)	21 (>99.9)	1 (100.0)		0.25	0.5
2006	6,644	18 (0.3)	339 (5.4)	5,195 (83.6)	1,034 (99.1)	57 (>99.9)		1 (100.0)	0.25	0.5
2007	7,672	18 (0.2)	414 (5.6)	6,074 (84.8)	1,122 (99.4)	42 (>99.9)	2 (100.0)		0.25	0.5
2008	6,792	9 (0.1)	195 (3.0)	4,694 (72.1)	1,845 (99.3)	48 (>99.9)	1 (100.0)		0.25	0.5
2009	6,778	7 (0.1)	122 (1.9)	3,892 (59.3)	2,702 (99.2)	55 (100.0)			0.25	0.5
2010	7,780	13 (0.2)	395 (5.2)	6,117 (83.9)	1,226 (99.6)	29 (100.0)			0.25	0.5
2011	6,945	5 (0.1)	138 (2.1)	5,256 (77.7)	1,514 (99.5)	28 (99.9)	4 (100.0)		0.25	0.5
2012	7,827	12 (0.2)	243 (3.3)	6,157 (81.9)	1,349 (99.2)	65 (>99.9)	1 (100.0)		0.25	0.5
MRSA										
2005	3,193	3 (0.1)	53 (1.8)	1,754 (56.7)	1,340 (98.7)	42 (>99.9)	1 (100.0)		0.25	0.5
2006	5,550	8 (0.1)	132 (2.5)	3,711 (69.4)	1,599 (98.2)	94 (99.9)	6 (100.0)		0.25	0.5
2007	6,509	7 (0.1)	181 (2.9)	4,349 (69.7)	1,847 (98.1)	118 (99.9)	7 (100.0)		0.25	0.5
2008	5,421	0 (0.0)	82 (1.5)	2,887 (54.8)	2,301 (97.2)	140 (99.8)	8 (99.9)	3 (100.0)	0.25	0.5
2009	4,849	2 (0.0)	44 (0.9)	1,915 (40.4)	2,744 (97.0)	143 (>99.9)	1 (100.0)		0.5	0.5
2010	5,492	1 (0.0)	123 (2.3)	3,831 (72.0)	1,470 (98.8)	58 (99.8)	9 (100.0)		0.25	0.5
2011	5,037	1 (0.0)	55 (1.1)	3,193 (64.5)	1,743 (99.1)	42 (99.9)	3 (100.0)		0.25	0.5
2012	6,210	3 (0.0)	107 (1.8)	4,304 (71.1)	1,730 (98.9)	61 (99.9)	5 (100.0)		0.25	0.5

#### Table 5. Activity of daptomycin and comparator antimicrobial agents tested against 22,508 S. aureus isolated from bloodstream infections worldwide (2005-2012).

Organism (no. tested)/		MIC (µg/m	ıl)	%S / %R			
antimicrobial agent	50%	90%	Range	CLSIa	EUCASTª		
S. aureus (22,508)							
Daptomycin	0.25	0.5	≤0.06 – 4	>99.9 / -	>99.9 / 0.1		
Oxacillin	0.5	>2	≤0.25 ->2	61.0 / 39.0	61.0 / 39.0		
Erythromycin	0.5	>2	≤0.25 ->2	53.8 / 45.1	54.1 / 45.5		
Clindamycin	≤0.25	>2	≤0.25 - >2	79.5 / 20.3	79.1 / 20.5		
Levofloxacin	≤0.5	>4	≤0.5 ->4	63.7 / 35.5	63.7 / 35.5		
Linezolid	1	2	≤0.12 ->8	>99.9 / <0.1	>99.9 / <0.		
Tetracycline	≤2	≤2	≤2 ->8	91.3 / 8.1	90.5 / 9.2		
TMP/SMX <sup>b</sup>	≤0.5	≤0.5	≤0.5 ->2	96.8 / 3.2	96.8 / 3.1		
Tigecyclinec	0.12	0.25	≤0.03 – 1	>99.9 / -	>99.9 / <0.		
Teicoplanin	≤2	≤2	≤2 ->8	>99.9 / <0.1	99.3 / 0.7		
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.		
MSSA (13,737)							
Daptomycin	0.25	0.5	≤0.06 – 4	>99.9 / -	>99.9 / <0.		
Erythromycin	≤0.25	>2	≤0.25 ->2	79.0 / 19.9	79.2 / 20.3		
Clindamycin	≤0.25	≤0.25	≤0.25 ->2	96.2 / 3.6	95.8 / 3.8		
Levofloxacin	≤0.5	≤0.5	≤0.5 ->4	92.7 / 6.8	92.7 / 6.8		
Linezolid	1	2	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0		
Tetracycline	≤2	≤2	≤2 ->8	94.3 / 5.1	93.8 / 6.1		
TMP/SMX <sup>b</sup>	≤0.5	≤0.5	≤0.5 ->2	99.0 / 1.0	99.0 / 1.0		
Tigecyclinec	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0		
Teicoplanin	≤2	≤2	≤2 ->8	>99.9 / <0.1	99.9 / 0.1		
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.		
MRSA (8,771)							
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1		
Erythromycin	>2	>2	≤0.25 ->2	14.5 / 84.6	14.8 / 84.9		
Clindamycin	≤0.25	>2	≤0.25 ->2	53.3 / 46.4	52.9 / 46.7		
Levofloxacin	>4	>4	≤0.5 ->4	18.3 / 80.4	18.3 / 80.4		
Linezolid	1	2	0.25 ->8	>99.9 / <0.1	>99.9 / <0		
Tetracycline	≤2	>8	≤2 ->8	86.6 / 12.8	85.3 / 14.0		
TMP/SMX <sup>b</sup>	≤0.5	≤0.5	≤0.5 ->2	93.4 / 6.6	93.4 / 6.5		
Tigecyclinec	0.12	0.25	≤0.03 – 1	>99.9 / -	>99.9 / <0		
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	98.4 / 1.6		
Vancomycin	1	1	0.25 - 4	99.9 / 0.0	99.9 / 0.1		

- TMP/SMX = trimethoprim/sulfamethoxazole.
- In the absence of CLSI breakpoint, USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].

## CONCLUSIONS

- Daptomycin was highly active against an extensive longitudinal collection (164,457 strains) of clinically important Gram-positive pathogens.
- Decreased susceptibility to daptomycin remains very rare after >8 years of clinical use, and non-susceptible isolates (0.07%) usually have only slightly elevated daptomycin MIC values.
- Resistance to oxacillin or vancomycin did not adversely affect daptomycin activity.
- Daptomycin-non-susceptibility rates were extremely low and did not show tendency toward increase for any species in any geographic region during the study period.

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