Antimicrobial Activity and Spectrum of Daptomycin Tested Against Gram-positive Strains Collected in European Hospitals: Results from 7 Years of Surveillance (2003-2009)

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HS SADER, DJ FARRELL, GJ MOET, RN JONES
JMI Laboratories, North Liberty, Iowa, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
helio-sader@jmilabs.com

AMENDED ABSTRACT

Objective: To evaluate the in vitro activity and spectrum of daptomycin (DAP) and comparators tested against clinical isolates from European (EU) hospitals. DAP is a cyclic lipopeptide approved by EU Medicines Agency (EMEA) for the treatment of complicated skin and soft tissue infections (cSSTI) and *S. aureus* (SA) bacteremia and endocarditis.

Methods: 36,769 consecutive strains were collected in 34 medical centres located in 13 EU countries, Turkey and Israel, including SA (18,362; 27.2% MRSA); coagulase-negative staphylococci (CoNS; 6,874; 76.6% oxacillin [OXA]-resistant [R]), *Enterococcus* spp. (ENT; 7,241; 9.4% vancomycin [VAN]-R), beta-haemolytic (BHS; 3,009), viridans group streptococci (VGS; 1,176), and *S. bovis/gallolyticus* (SB; 107). The organisms were isolated mainly from patients with bacteremia (56%) or cSSTI (23%). The strains were tested for susceptibility (S) against DAP and comparators by CLSI broth microdilution methods in cation-adjusted Mueller-Hinton broth with 50 mg/L of calcium for DAP tests.

Results: DAP was very active against SA and CoNS ($MIC_{50/90}$, 0.25/0.5 mg/L for both organisms) and its activity was not adversely influenced by OXA-R. MRSA varied from 1.3% in Sweden to as high as 61.3% in Portugal and 55.9% in Greece. MRSA exhibited high R rates to levofloxacin (88.7) and clindamycin (40.2%), and high S rates to DAP ($MIC_{50/90}$, 0.25/0.5 mg/L; 100.0% S), linezolid (LZD; $MIC_{50/90}$, 1/2 mg/L; 99.9% S), tigecycline (TIG; $MIC_{50/90}$, 0.12/0.25 mg/L; >99.9% S) and VAN ($MIC_{50/90}$, 1/1 mg/L; 100.0% S). All *E. faecalis* were S to DAP. VAN-R *E. faecium* (VREFM) was observed in 13 of 15 countries evaluated and was highest in Ireland (62.4%) and UK (44.2%). DAP ($MIC_{50/90}$, 2/2 mg/L; 100.0% S), LZD ($MIC_{50/90}$, 1/2 mg/L; 99.7% S) and TIG ($MIC_{50/90}$, 0.06/0.12 mg/L; 99.5% S) were the most active agents tested against VREFM. VAN-S and -R ENT were equally S to DAP. DAP was also active against BHS ($MIC_{50/90}$, 0.06/0.25 mg/L; 100.0% S), VGS ($MIC_{50/90}$, 0.25/0.5 mg/L; 99.8% S) and SB ($MIC_{50/90}$, 0.06/0.12 mg/L; 100.0% S).

	DAP MIC_{50} / MIC_{90} in mg/L (%S)				
Year	*S. aureus*	*E. faecalis*	*E. faecium*	MRSA[a]	VREFM[b]
2003	0.25/0.5 (>99.9)[c]	0.5/1 (100.0)	2/4 (99.4)	27.6	9.0
2004	0.25/0.5 (100.0)	1/1 (100.0)	4/4 (100.0)	24.5	13.2
2005	0.25/0.5 (100.0)	0.5/1 (100.0)	2/4 (100.0)	28.9	17.9
2006	0.25/0.5 (100.0)	0.5/1 (100.0)	1/2 (100.0)	27.4	26.6
2007	0.25/0.5 (100.0)	1/1 (100.0)	2/2 (100.0)	28.4	26.3
2008	0.25/0.5 (100.0)	1/2 (100.0)	2/4 (100.0)	27.0	28.2
2009	0.25/0.5 (100.0)	1/2 (100.0)	2/4 (100.0)	25.8	27.0
Overall	0.25/0.5 (>99.9)[c]	1/1 (100.0)	2/4 (>99.9)	27.2	24.7

a. OXA-R (MRSA) rates.
b. VAN-R rates among *E. faecium*.
c. Only 1 non-S strain.

Conclusions: DAP was highly active against a large collection (36,769) of Gram-positive (GP) organisms isolated in European hospitals and its activity remained stable across the 7-year period evaluated (2003-2009) using reference methods. Decrease in DAP potency has not been observed since EMEA approval and widespread clinical use, and emerging R to other compounds did not adversely influence the DAP potency against GP species.

INTRODUCTION

Daptomycin is a natural 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 European Medicines Agency (EMEA) in 2005 for the treatment of complicated skin and skin soft tissue infections (cSSTI) caused by susceptible Gram-positive bacteria using a dose of 4 mg/kg every 24 hours. In 2007, daptomycin received approval for the treatment of right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* and *S. aureus* (including oxacillin-resistant strains [MRSA]) bacteremia associated with cSSTI or RIE at a dose of 6 mg/kg every 24 hours.

Daptomycin has been widely used in Europe, United States (USA) and various other geographic regions for several years with high rates of clinical success. Therefore, it is important to monitor its in vitro potency and emergence of resistance among indicated species. In the present study, we evaluated the in vitro activity and spectrum of daptomycin and comparators tested against clinical isolates from European hospitals over a 7-year period (2003-2009).

MATERIALS AND METHODS

Bacterial Isolates: Consecutive unique patient strains of clinical significance (n = 36,769) were collected between January 2003 and December 2009 from 34 medical centers located in 13 European countries, Turkey and Israel. Only Gram-positive organisms were included in the study and *Streptococcus pneumoniae* strains were excluded from the analysis. The isolates were collected primarily from bloodstream infections (56%) and cSSTI (23%) in hospitalized patients according to a common surveillance design. The collection of organisms tested included: 18,362 *S. aureus* (27.2% oxacillin-resistant [MRSA]), 6,874 coagulase-negative staphylococci (CoNS; 76.6% oxacillin-resistant); 4,635 *E. faecalis* (1.6% vancomycin-non-susceptible [VRE; vancomycin MIC, ≥8 mg/L]), and 2,355 *E. faecium* (24.7% VRE), 253 *Enterococcus* spp. (non-*faecalis*/non-*faecium* species), 1,176 viridans group streptococci, 107 *Streptococcus bovis/gallolyticus* and 3,009 β-haemolytic streptococci.

The bacterial isolates originated from (no. of medical centers; no. of isolates): Belgium (2; 986), France (6; 7,285), Germany (4; 6,181), Greece (2; 900), Ireland (2; 2,348), Israel (1; 1,300), Italy (3; 3,303), Poland (1; 1,233), Portugal (1; 310), Russia (1; 116), Spain (3; 2,461), Sweden (2; 2,967), Switzerland (1; 1,873), Turkey (2; 2,691), and the United Kingdom ([UK] 3; 2,815). The majority of medical centers were characterized as large tertiary hospitals.

Susceptibility Testing: Daptomycin and various comparator agents were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods in validated, microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). The test medium was Mueller-Hinton broth adjusted to contain physiological levels of calcium (50 mg/L) when testing daptomycin. 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 mg/L was applied for *S. aureus*, while ≤4 mg/L 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 mg/L, 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; and all QC results were within published limits.

RESULTS

- The overall MRSA rate was 27.2%, and it was slightly higher among *S. aureus* from BSI (27.4%) compared to cSSTI (23.0%). The highest MRSA rates were observed in Portugal (61.3%), Greece (50.1%) and Ireland (46.1%), while the lowest rates were found in Sweden (1.3%), Switzerland (14.2%) and Germany (15.4%; Table 1).
- The overall MRSA rate (all countries combined) varied slightly during the study period, but with no significant tendency toward an increase or decrease (data not shown).
- VRE (vancomycin MIC, ≥8 mg/L) rates were 1.6 and 24.7% among *E. faecalis* and *E. faecium*, respectively; and a great variation was detected among the countries monitored (Table 1). The overall VRE rate (all countries combined) increased consistently amongst *E. faecium* isolates from 9.0% in 2003 to 26.6% in 2006, and remained somewhat stable from 2006 through 2009 (data not shown).
- VRE rates among *E. faecalis* varied from nil in Belgium, Portugal, Spain, Sweden, Switzerland and Turkey to as high as 14.3% in Russia (only 14 strains tested) and 9.3% in the UK. Amongst *E. faecium*, the highest VRE rates were observed in Ireland (62.4%), UK (44.6%), Greece (36.8%) and Poland (33.7%) and the lowest VRE rates (0.0-2.9%) were noted in Russia, Spain, Sweden and Switzerland (Table 1).
- The most active compounds tested against *S. aureus* were daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; >99.9% susceptible), linezolid (MIC_{50} and MIC_{90}, 2 mg/L; >99.9% susceptible), teicoplanin (MIC_{50} and MIC_{90}, ≤2 mg/L; 98.9% susceptible by EUCAST criteria) and vancomycin (MIC_{50} and MIC_{90}, 1 mg/L; >99.9% susceptible). Only one *S. aureus* strain (0.005%) was considered non-susceptible to daptomycin (France, 2003).
- MRSA isolates demonstrated high rates of co-resistance with various antimicrobials, including levofloxacin (88.7%), erythromycin (70.2%), clindamycin (40.2%; not including inducible resistance) and tetracycline (18.2%; Table 2).
- Daptomycin (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; 99.9% susceptible) was also very active against CoNS (Table 2). Only eight isolates (0.1%) showed decreased susceptibility to daptomycin (MIC, ≥2 mg/L).
- All *E. faecalis* strains were susceptible to daptomycin (MIC_{50} and MIC_{90}, 1 mg/L). Ampicillin (MIC_{50}, ≤1 mg/L and MIC_{90}, 2 mg/L; 99.3% susceptible by EUCAST breakpoint criteria) and linezolid (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L; 99.9% susceptible) were also active against *E. faecalis*, including vancomycin-non-susceptible strains (Table 2).
- Daptomycin (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L; >99.9% susceptible) and linezolid (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L, 99.8% susceptible by EUCAST breakpoint criteria) were the most active agents tested against *E. faecium* (Table 2). Teicoplanin, vancomycin and quinupristin/dalfopristin were active against only 80.2, 75.3 and 80.2% of strains at the EUCAST susceptible breakpoints, respectively.
- All VRE strains were susceptible to daptomycin. Furthermore, vancomycin-susceptible and -resistant strains exhibited very similar daptomycin MIC distributions. Daptomycin was also active against non-faecalis/non-faecium strains of *Enterococcus* spp. (MIC_{50}, 1 mg/L and MIC_{90}, 4 mg/L; 100.0% susceptible; Table 2).
- Daptomycin was also very active against β-haemolytic streptococci (MIC_{50}, ≤0.12 mg/L and MIC_{90}, 0.25 mg/L), *S. bovis/gallolyticus* (MIC_{50}, ≤0.06 mg/L and MIC_{90}, 0.12 mg/L) and viridans group streptococci (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L; Table 2).

Table 1. Occurrence of oxacillin-resistant *S. aureus* (MRSA) and vancomycin-non-susceptible (MIC, ≥8 mg/L) *E. faecalis* (VREF) and *E. faecium* (VREFM) by country.

	% resistant (no. tested)				% resistant (no. tested)		
Country	MRSA	VREF	VREFM	Country	MRSA	VREF	VREFM
Belgium	32.3	0.0	6.4	Portugal	61.3	0.0	4.4
France	27.7	0.3	3.6	Russia	28.3	14.3[a]	0.0
Germany	15.4	1.1	27.0	Spain	22.8	0.0	2.9
Greece	50.1	4.9	36.8	Sweden	1.3	0.0	2.5
Ireland	46.1	1.9	62.4	Switzerland	14.2	0.0	0.0
Israel	42.4	3.0	21.8	Turkey	27.0	0.0	22.4
Italy	30.8	2.9	19.2	UK	37.8	9.3	44.2
Poland	29.0	5.8	33.7	Overall	27.2	1.6	24.7

a. Only 14 strains tested.

Table 2. Activity of daptomycin and comparator antimicrobial agents when tested against Gram-positive organisms from European medical centers (2003-2009).

Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (18,362)					
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -	>99.9 / <0.1
Oxacillin	0.5	>2	≤0.25 – >2	72.8 / 27.2	72.8 / 27.2
Clindamycin	≤0.25	>2	≤0.25 – >2	87.1 / 12.7	86.7 / 12.9
Erythromycin	≤0.25	>2	≤0.25 – >2	69.9 / 29.2	70.4 / 29.3
Levofloxacin	≤0.5	>4	≤0.5 – >4	71.3 / 28.0	71.3 / 28.0
Linezolid	2	2	0.12 – >8	>99.9 / <0.1	>99.9 / <0.1
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	98.9 / 1.1
Tetracycline	≤2	≤2	≤2 – >8	90.6 / 8.7	90.3 / 9.7
Trim/sulfa[b]	≤0.5	≤0.5	≤0.5 – >2	98.5 / 1.5	98.5 / 1.5
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Oxacillin-susceptible *S. aureus* (13,370)					
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -	>99.9 / <0.1
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.4 / 2.5	97.0 / 2.6
Erythromycin	≤0.25	>2	≤0.25 – >2	85.2 / 14.0	85.7 / 14.1
Levofloxacin	≤0.5	≤0.5	≤0.5 – >4	94.3 / 5.4	94.3 / 5.4
Linezolid	2	2	0.12 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	99.7 / 0.3
Tetracycline	≤2	≤2	≤2 – >8	94.2 / 5.5	93.8 / 6.1
Trim/sulfa[b]	≤0.5	≤0.5	≤0.5 – >2	99.5 / 0.5	99.5 / 0.5
Vancomycin	1	1	≤0.12 – 4	>99.9 / 0.0	>99.9 / <0.1
Oxacillin-resistant *S. aureus* (4,992)					
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	59.8 / 40.0	59.2 / 40.2
Erythromycin	>2	>2	≤0.25 – >2	28.8 / 70.0	29.5 / 70.2
Levofloxacin	>4	>4	≤0.5 – >4	9.6 / 88.7	9.6 / 88.7
Linezolid	1	2	0.12 – >8	99.9 / 0.1	99.9 / 0.1
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	96.6 / 3.4
Tetracycline	≤2	>8	≤2 – >8	81.2 / 17.4	80.8 / 19.2
Trim/sulfa[b]	≤0.5	≤0.5	≤0.5 – >2	96.0 / 4.0	96.0 / 4.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Coagulase-negative staphylococci (6,874)					
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1
Oxacillin	>2	>2	≤0.25 – >2	23.4 / 76.6	23.4 / 76.6
Clindamycin	≤0.25	>2	≤0.25 – >2	71.4 / 27.8	69.5 / 28.6
Erythromycin	>2	>2	≤0.25 – >2	36.9 / 62.8	37.0 / 62.8
Levofloxacin	4	>4	≤0.5 – >4	43.2 / 51.3	43.2 / 51.3
Linezolid	1	1	≤0.06 – >8	99.9 / 0.1	99.9 / 0.1
Teicoplanin	≤2	4	≤2 – >16	97.8 / 0.3	90.8 / 9.2
Tetracycline	≤2	>8	≤2 – >8	83.5 / 15.3	78.6 / 19.6
Trim/sulfa[b]	≤0.5	>2	≤0.5 – >2	60.9 / 39.1	60.9 / 39.1
Vancomycin	1	2	≤0.12 – 4	100.0 / 0.0	99.4 / 0.6
Enterococcus faecalis (4,635)					
Daptomycin	1	1	≤0.06 – 4	100.0 / -	- / -
Ampicillin	≤1	2	≤1 – >16	99.5 / 0.5	99.3 / 0.5
Levofloxacin	1	>4	≤0.5 – >4	66.4 / 33.0	- / -
Linezolid	1	2	0.12 – >8	99.9 / <0.1	>99.9 / <0.1
Teicoplanin	≤2	≤2	≤2 – >16	98.8 / 1.1	98.7 / 1.3
Tetracycline	>8	>8	≤2 – >8	26.7 / 73.0	- / -
Vancomycin	1	2	0.25 – >16	98.4 / 1.5	98.4 / 1.6
Vancomycin-susceptible *E. faecalis* (4,559)					
Daptomycin	1	1	≤0.06 – 4	100.0 / -	- / -
Ampicillin	≤1	2	≤1 – >16	99.5 / 0.5	99.3 / 0.5
Levofloxacin	1	>4	≤0.5 – >4	67.3 / 32.1	- / -
Linezolid	1	2	0.12 – >8	99.9 / <0.1	>99.9 / <0.1
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	99.9 / 0.1
Tetracycline	>8	>8	≤2 – >8	26.9 / 72.9	- / -
Vancomycin	1	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Vancomycin-non-susceptible *E. faecalis* (76)					
Daptomycin	0.5	1	0.25 – 2	100.0 / -	- / -
Ampicillin	2	4	≤1 – 8	100.0 / 0.0	98.7 / 0.0
Levofloxacin	>4	>4	0.5 – >4	13.2 / 86.8	- / -
Linezolid	1	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Teicoplanin	>16	>16	≤2 – >16	26.3 / 69.7	23.7 / 76.3
Tetracycline	>8	>8	≤2 – >8	19.7 / 78.9	- / -
Vancomycin	>16	>16	8 – >16	0.0 / 92.1	0.0 / 100.0
E. faecium (2,355)					
Daptomycin	2	4	0.12 – 8	>99.9 / -	- / -
Ampicillin	>16	>16	≤1 – >16	8.5 / 91.5	7.5 / 91.5
Levofloxacin	>4	>4	≤0.5 – >4	15.1 / 79.7	- / -
Linezolid	1	2	0.25 – >8	99.7 / 0.2	99.8 / 0.2
Q/D[b]	1	>2	≤0.25 – >2	72.5 / 16.3	72.5 / 16.3
Teicoplanin	≤2	>16	≤2 – >16	81.4 / 16.7	80.2 / 19.8
Tetracycline	≤2	>8	≤2 – >8	70.3 / 29.3	- / -
Vancomycin	1	>16	≤0.12 – >16	75.3 / 23.0	75.3 / 24.7
Vancomycin-susceptible *E. faecium* (1,773)					
Daptomycin	2	4	0.12 – 8	99.9 / -	- / -
Ampicillin	>16	>16	≤1 – >16	11.1 / 88.9	9.8 / 88.9
Levofloxacin	>4	>4	≤0.5 – >4	17.1 / 76.3	- / -
Linezolid	1	2	0.25 – >8	99.8 / 0.1	99.9 / 0.1
Q/D[b]	1	>2	≤0.25 – >2	69.4 / 18.6	69.4 / 18.6
Teicoplanin	≤2	≤2	≤2 – 8	100.0 / 0.0	99.8 / 0.2
Tetracycline	≤2	>8	≤2 – >8	68.4 / 31.1	- / -
Vancomycin	1	1	≤0.12 – 4	100.0 / 0.0	100.0 / 0.0
Vancomycin-non-susceptible *E. faecium* (582)					
Daptomycin	2	2	0.12 – 4	100.0 / -	- / -
Ampicillin	>16	>16	≤1 – >16	0.3 / 99.7	0.3 / 99.7
Levofloxacin	>4	>4	1 – >4	8.8 / 90.0	- / -
Linezolid	1	2	0.5 – >8	99.3 / 0.3	99.7 / 0.3
Q/D[b]	1	2	≤0.25 – >2	82.0 / 9.3	82.0 / 9.3
Teicoplanin	>16	>16	≤2 – >16	24.6 / 67.4	20.4 / 79.6
Tetracycline	≤2	>8	≤2 – >8	76.1 / 23.7	- / -
Vancomycin	>16	>16	8 – >16	0.0 / 93.0	0.0 / 100.0
Enterococcus spp.[b] (251)					
Daptomycin	1	4	≤0.06 – 4	100.0 / -	- / -
Ampicillin	≤1	>16	≤1 – >16	77.3 / 22.7	75.7 / 22.7
Levofloxacin	2	>4	≤0.5 – >4	76.1 / 16.7	- / -
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Q/D[b]	2	>2	≤0.25 – >2	24.3 / 35.9	24.3 / 35.9
Teicoplanin	≤2	≤2	≤2 – >16	96.0 / 2.8	96.0 / 4.0
Tetracycline	≤2	>8	≤2 – >8	56.2 / 43.4	- / -
Vancomycin	1	8	0.25 – >16	89.6 / 4.0	89.6 / 10.4
β-haemolytic streptococci (3,009)					
Daptomycin	≤0.06	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Penicillin	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 4	99.9 / -	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.5 / 7.0	93.0 / 7.0
Erythromycin	≤0.25	>2	≤0.25 – >2	82.6 / 16.8	82.6 / 16.8
Levofloxacin	≤0.5	1	≤0.5 – >4	99.6 / 0.4	95.6 / 0.4
Linezolid	1	1	≤0.06 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤2	>8	≤2 – >8	53.0 / 44.7	53.0 / 47.0
Trim/sulfa[b]	≤0.5	≤0.5	≤0.5 – >2	- / -	98.9 / 0.6
Vancomycin	0.25	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Group A β-haemolytic streptococci (1,288)					
Daptomycin	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Penicillin	≤0.03	≤0.03	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.4 / 4.4	95.6 / 4.4
Erythromycin	≤0.25	>2	≤0.25 – >2	84.8 / 14.9	84.8 / 14.9
Levofloxacin	≤0.5	1	≤0.5 – 2	100.0 / 0.0	93.1 / 0.0
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤2	>8	≤2 – >8	83.8 / 15.6	83.8 / 16.2
Trim/sulfa[b]	≤0.5	≤0.5	≤0.5 – >2	- / -	98.3 / 1.2
Vancomycin	0.25	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Group B β-haemolytic streptococci (1,142)					
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Penicillin	0.06	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 4	99.8 / -	100.0 / 0.0
Clindamycin	≤0.25	1	≤0.25 – >2	89.0 / 10.2	89.8 / 10.2
Erythromycin	≤0.25	>2	≤0.25 – >2	80.0 / 19.1	80.0 / 19.1
Levofloxacin	≤0.5	1	≤0.5 – >4	99.6 / 0.4	98.1 / 0.4
Linezolid	1	1	≤0.06 – 2	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤2 – >8	18.3 / 80.7	18.3 / 81.7
Trim/sulfa[b]	≤0.5	≤0.5	≤0.5 – >2	- / -	99.4 / 0.1
Vancomycin	0.5	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Other β-haemolytic streptococci[e] (579)					
Daptomycin	≤0.06	0.12	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Penicillin	≤0.03	≤0.03	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.7 / 6.6	93.4 / 6.6
Erythromycin	≤0.25	>2	≤0.25 – >2	82.7 / 16.6	82.7 / 16.6
Levofloxacin	≤0.5	1	≤0.5 – >4	98.4 / 1.6	96.2 / 1.6
Linezolid	1	1	0.25 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤2	>8	≤2 – >8	52.8 / 38.4	52.8 / 47.2
Trim/sulfa[b]	≤0.5	≤0.5	≤0.5 – >2	- / -	99.5 / 0.5
Vancomycin	0.25	0.5	≤0.12 – 1	100.0 / -	100.0 / 0.0
Streptococcus bovis/gallolyticus (107)					
Daptomycin	≤0.06	0.12	≤0.06 – 0.5	100.0 / -	- / -
Penicillin	0.06	0.06	≤0.03 – 8	98.1 / 0.9	98.1 / 0.9
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 2	98.1 / 0.0	97.2 / 2.8
Clindamycin	≤0.25	>2	≤0.25 – >2	73.8 / 25.2	74.8 / 25.2
Erythromycin	≤0.25	>2	≤0.25 – >2	63.6 / 36.4	- / -
Levofloxacin	1	2	≤0.5 – >4	96.3 / 3.7	- / -
Linezolid	1	1	0.25 – 2	100.0 / -	- / -
Tetracycline	>8	>8	≤2 – >8	28.8 / 70.2	- / -
Vancomycin	0.25	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Viridans group streptococci[d] (1,176)					
Daptomycin	0.25	0.5	≤0.06 – 2	99.8 / -	- / -
Penicillin	0.06	2	≤0.03 – >32	74.2 / 7.6	81.3 / 7.6
Ceftriaxone	≤0.25	1	≤0.25 – >32	90.2 / 6.0	86.0 / 14.0
Clindamycin	≤0.25	>2	≤0.25 – >2	88.6 / 10.8	89.2 / 10.8
Erythromycin	≤0.25	>2	≤0.25 – >2	61.6 / 35.8	- / -
Levofloxacin	1	2	≤0.5 – >4	97.6 / 1.6	- / -
Linezolid	1	1	≤0.06 – 2	100.0 / -	- / -
Tetracycline	≤2	>8	≤2 – >8	66.4 / 30.8	- / -
Vancomycin	0.5	1	≤0.12 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI and EUCAST, β-lactam susceptibility should be directed by the oxacillin test results.
b. Trim/sulfa=Trimethoprim/sulfamethoxazole; Q/D=Quinupristin/dalfopristin.
c. Includes: *Enterococcus avium* (67 strains), *E. casseliflavus* (39 strains), *E. durans* (38 strains), *E. gallinarum* (66 strains), *E. hirae* (15 strains), *E. raffinosus* (four strains) and unspeciated *Enterococcus* (22 strains).
d. Includes: *Streptococcus acidominimus* (five strains), *S. anginosus* (143 strains), *S. constellatus* (74 strains), *S. gordonii* (eight strains), *S. intermedius* (37 strains), *S. milleri* (60 strains), *S. mitis* (238 strains), *S. mutans* (14 strains), *S. oralis* (143 strains), *S. parasanguinis* (36 strains), *S. salivarius* (82 strains), *S. sanguinis* (81 strains), *S. sobrinus* (one strain), *S. uberis* (three strains), *S. vestibularis* (16 strains), unspeciated *Streptococcus* (32 strains), unspeciated alpha-haemolytic streptococci (55 strains) and unspeciated viridans group streptococci (180 strains).
e. Includes: *Streptococcus dysgalactiae* (120 strains), *S. equi* (5 strains), *S. equisimilis* (16 strains), Group C β-haemolytic streptococci (85 strains), Group F β-haemolytic streptococci (11 strains), Group G β-haemolytic streptococci (330 strains) and unspeciated β-haemolytic streptococci (12 strains).

CONCLUSIONS

- Daptomycin was highly active against a large collection (36,769 strains) of Gram-positive organisms isolated in European hospitals and its activity remained stable across the 7-year period evaluated (2003-2009) using reference methods.
- Decrease in daptomycin potency has not been observed since EMEA approval and widespread clinical use in Europe.
- Emerging resistance to other compounds, including vancomycin resistance among enterococci, did not adversely influence the daptomycin potency against Gram-positive species.

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