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Five-year analysis of the *in vitro* activity of tedizolid against a worldwide collection of indicated species causing clinical infections: results from the Surveillance of Tedizolid Activity and Resistance (STAR) programme

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Objectives: The Surveillance of Tedizolid Activity and Resistance (STAR) programme monitored the tedizolid activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group. We evaluated the antimicrobial susceptibility of 47 400 unique Gram-positive clinical isolates from the STAR programme collected from USA (21 243), Europe (17 674), Asia-Pacific (4954) and Latin America (3529) medical centres (2015–19).

Methods: All isolates were tested for susceptibility by reference broth microdilution method. WGS and *in silico* analysis were performed on linezolid-non-susceptible (NS) isolates.

Results: Tedizolid was active against ≥99.9% of *S. aureus* (100.0% of MSSA and >99.9% of MRSA), *E. faecalis*, *S. pyogenes*, *S. agalactiae* and *S. anginosus* group isolates, with MIC_{50} values ranging from 0.12 to 0.25 mg/L and MIC_{90} values of 0.25 mg/L. Linezolid, vancomycin and daptomycin were also active agents against these organisms. Tedizolid inhibited all VRE and 73.1% of linezolid-NS *E. faecalis* isolates. Ampicillin and daptomycin retained 100.0% activity against VRE and linezolid-NS *E. faecalis* isolates. Linezolid-NS *E. faecalis* isolates carried mostly the *optrA* gene. G2576T alterations in the 23S rRNA were observed in one linezolid-NS *S. aureus* isolate and one linezolid-NS *E. faecalis* isolate.

Conclusions: No resistance trends were observed for tedizolid during the study period.

Introduction

Gram-positive pathogens frequently cause community and healthcare-associated infections (HAIs). *Staphylococcus aureus* (11.8%; ranked second), *Enterococcus faecalis* (7.9%; fifth), coagulase-negative staphylococci (6.8%; sixth) and *Enterococcus faecium* (3.8%; eighth) were among the top 10 pathogens reported to the CDC's National Healthcare Safety Network (NHSN) as causes of >350 000 HAIs in 2015–17 in the USA.[1] In Europe, the overall number of invasive isolates reported to the WHO Regional Office for Europe and ECDC increased in 2020 compared with 2019 for most Gram-positive bacterial species evaluated, including *S. aureus*, *E. faecalis* and *E. faecium*, with the exception of *Streptococcus pneumoniae*.[2] Moreover, *S.aureus*, *S. pneumoniae*, β-haemolytic streptococci and viridans group streptococci are common causes of community-acquired respiratory and skin and skin structure infections worldwide.[3,4] Resistance to multiple antimicrobials is frequently observed among *S. aureus* and *Enterococcus* spp. isolates, including MRSA and VRE.

Tedizolid is an oxazolidinone antimicrobial approved by the US FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult and paediatric patients (12–18 years old).[5] The *in vitro* activity of tedizolid against *S. aureus*, *E. faecalis* and streptococci was monitored worldwide by the Surveillance of Tedizolid Activity and Resistance (STAR) programme. In this study, the tedizolid activity and potential antimicrobial resistance trends over a 5 year period were evaluated against Gram-positive clinical isolates recovered worldwide as part of the STAR programme. In addition, the mechanisms of oxazolidinone resistance were characterized in linezolid-non-susceptible (NS) isolates.

Materials and methods

During the study period (2015–19), a total of 47 400 Gram-positive organisms were collected from the indicated species: *S. aureus* (*n* = 35 978; 75.9%), *E. faecalis* (*n* = 4992; 10.5%), *Streptococcus pyogenes* (*n* = 3240; 6.8%), *Streptococcus agalactiae* (*n* = 2509; 5.3%) and *Streptococcus anginosus* group (*n* = 681; 1.4%). The isolates were collected from 107 medical

Table 1. Activity of tedizolid and comparators agents against Gram-positive isolates and resistance phenotypes split by region (2015–19)

Organism (no. tested)/ Antimicrobial agent	MIC (mg/L)		CLSI[a]		EUCAST[a]		USA (no. tested) %S[b]	EU (no. tested) %S[b]	LATAM (no. tested) %S[b]	APAC (no. tested) %S[b]
	MIC_{50}	MIC_{90}	%S	%R	%S	%R				
MSSA (24 210)							(9285)	(10 428)	(1919)	(2578)
Tedizolid	0.12	0.25	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Linezolid	1	2	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Ceftaroline	0.25	0.25	100.0	0.0	100.0[c]	0.0	100.0[c]	100.0[c]	NT	NT
Clindamycin	≤0.25	≤0.25	97	2.9	96.7	3.0	95.6	98.4	NT	NT
Daptomycin	0.25	0.5	>99.9	—	>99.9	<0.1	>99.9	>99.9	100.0	100.0
Erythromycin	0.25	>8	75.9	19.6	76.4	21.7	65.9	82.9	70.1	87.7
SXT	≤0.5	≤0.5	99.5	0.5	99.5	0.4	99.5	99.7	99.5	99.1
Vancomycin	1	1	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
MRSA (11 768)							(6944)	(2827)	(827)	(1170)
Tedizolid	0.12	0.25	>99.9	<0.1	>99.9	<0.1	>99.9	100.0	100.0	100.0
Linezolid	1	2	>99.9	<0.1	>99.9	<0.1	>99.9	100.0	100.0	100.0
Ceftaroline	1	1	92.9	0.0	92.9[c]	<0.1	95.0[c]	87.0[c]	NT	NT
Clindamycin	≤0.25	>2	73.5	26.2	73.3	26.5	72.3	76.8	NT	NT
Daptomycin	0.25	0.5	>99.9	—	>99.9	<0.1	>99.9	100.0	100.0	99.9
Erythromycin	>8	>8	23.9	72.1	24.3	74.4	12.9	39.9	40.5	38.7
SXT	≤0.5	≤0.5	96.4	3.6	96.4	3.1	96.1	98.9	97.1	92.1
Vancomycin	1	1	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
E. faecalis (4992)							(2138)	(2112)	(422)	(320)
Tedizolid	0.25	0.25	99.9	—	—	—	>99.9	99.9	99.8	99.1
Linezolid	1	2	99.5	0.1	99.9	0.1	99.8	99.6	99.3	96.9
Ampicillin	1	1	100.0	0.0	>99.9	0.0	100.0	100.0	100.0	100.0
Daptomycin	0.5	1	99.6	0.0	—	—	99.6	99.5	100.0	100.0
Vancomycin	1	2	98.1	1.9	98.1	1.9	97	99.1	97.9	99.1
LZD-NS[b] *E. faecalis* (26)							(4)	(9)	(3)	(10)
Tedizolid	0.5	1	73.1	—	—	—	75	77.8	66.7	70
Linezolid	4	8	0.0	15.4	84.6	15.4	0.0	0.0	0.0	0.0
Ampicillin	1	1	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Daptomycin	1	1	100.0	0.0	—	—	100.0	100.0	100.0	100.0
Vancomycin	1	1	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
VRE *E. faecalis*[b] (95)							(65)	(18)	(9)	(3)
Tedizolid	0.12	0.25	100.0	—	—	—	100.0	100.0	100.0	100.0
Linezolid	1	2	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Ampicillin	1	2	100.0	0.0	98.9	0.0	100.0	100.0	100.0	100.0
Daptomycin	0.5	1	100.0	—	—	—	100.0	100.0	100.0	100.0
Vancomycin	>16	>16	0.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0
S. pyogenes (3240)							(1486)	(1159)	(161)	(434)
Tedizolid	0.12	0.25	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Linezolid	1	2	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Clindamycin	≤0.25	≤0.25	95.9	3.7	96.3	3.7	96.2	95.5	NT	NT
Daptomycin	≤0.06	0.12	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Erythromycin	≤0.03	1	88.2	10.9	88.2	10.9	83.3	91.6	93.8	94.0
Levofloxacin	0.5	1	99.8	0.1	99.8[d]	0.2	99.9	99.7	99.0	100.0
Penicillin	≤0.03	≤0.03	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Vancomycin	0.25	0.5	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
S. agalactiae (2509)							(1150)	(832)	(181)	(346)
Tedizolid	0.25	0.25	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Linezolid	1	2	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Clindamycin	0.25	>2	68.1	30.1	69.9	30.1	61.4	78.4	NT	NT
Daptomycin	0.25	0.25	100.0	0.0	100.0	0	100.0	100.0	100.0	100.0

Continued

Table 1. *Continued*

Organism (no. tested)/ Antimicrobial agent	MIC (mg/L)		CLSI[a]		EUCAST[a]		USA (no. tested)	EU (no. tested)	LATAM (no. tested)	APAC (no. tested)
	MIC_{50}	MIC_{90}	%S	%R	%S	%R	%S[b]	%S[b]	%S[b]	%S[b]
Erythromycin	0.06	>4	56.4	42	56.4	42.0	40.6	68.3	77.3	69.9
Levofloxacin	1	1	96.6	3.2	96.6[d]	3.4	98.8	97.1	86.8	88.3
Penicillin	0.06	0.06	99.8	—	99.9	0.1	100.0	100.0	100.0	98.8
Vancomycin	0.5	0.5	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
S. anginosus group (681)							(240)	(316)	(19)	(106)
Tedizolid	0.12	0.25	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0
Linezolid	1	1	100.0	0.0	—	—	100.0	100.0	100.0	100.0
Clindamycin	≤0.25	>2	85.9	13.6	86.4	13.6	84.6	86.9	NT	NT
Daptomycin	0.25	0.5	99.8		—	—	100.0	99.7	100.0	100.0
Erythromycin	≤0.03	4	78.0	19.4	—	—	71.2	79.7	84.2	86.8
Levofloxacin	0.5	1	99.0	1.0	—	—	98.8	99.3	100.0	97.7
Penicillin	≤0.03	0.06	99	0.3	99.1	0.3	98.8	99.1	100.0	99.1
Vancomycin	0.5	1	100.0	0.0	100.0	0.0	100.0	100.0	100.0	100.0

S, susceptible; R, resistant; —, breakpoint not available; SXT, trimethoprim/sulfamethoxazole; NT, not tested; LZD-NS, linezolid-non-susceptible.
[a]Criteria as published by CLSI[7] and EUCAST.[8]
[b]Using CLSI[7] criteria.
[c]Using other than pneumonia breakpoints.
[d]Susceptible, increased exposure.

centres in the USA (21 243 isolates), Europe (EU; 17 674 isolates), the Asia-Pacific region (APAC; 4954 isolates) and Latin America (LATAM; 3529 isolates). Only one isolate per patient was included in this surveillance study. Isolates recovered from skin and skin structure infections (SSSI; 44.2%), bloodstream infections (BSI; 25.4%), pneumonia in hospitalized patients (PIHP; 17.5%), intra-abdominal infections (IAI; 3.7%), urinary tract infections (UTI; 3.5%) and other sites of infection (5.8%) were deemed clinically significant by algorithms in place at participant medical centres. Species identification was performed at the participant medical centre and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) by MALDI-TOF (Bruker Daltonics, Billerica, MA, USA) and standard phenotypic tests, as necessary.

All isolates were susceptibility tested using the reference broth microdilution method as described by CLSI.[6] Frozen-form panels were manufactured by JMI Laboratories and contained CAMHB; 2.5%–5% lysed horse blood was added for streptococci and calcium (Ca^{2+}) supplementation (50 mg/L) was used to test daptomycin. Categorical interpretations for all antimicrobials were those found in CLSI M100[7] and EUCAST.[8] Linezolid-NS (MIC >2 and >4 mg/L for enterococci and staphylococci, respectively) isolates were screened for oxazolidinone resistance genes (*cfr*, *cfr*(B), *cfr*(C), *cfr*(D), *cfr*(E), *optrA* and *poxtA*) by WGS and *in silico* analysis, as previously described.[9] Additionally, DNA sequences associated with the 23S rRNA and ribosomal proteins (L3, L4 and L22) were analysed for the presence of mutations.[9]

Results

Tedizolid was active against *S. aureus* ($MIC_{50/90}$, 0.12/0.25 mg/L; >99.9% susceptible) regardless of the methicillin-resistance profile, either MSSA ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible) or MRSA ($MIC_{50/90}$, 0.12/0.25 mg/L; >99.9% susceptible; Table 1). All *S. aureus* from the USA were susceptible to tedizolid, except for one isolate with a tedizolid MIC >1 mg/L and a linezolid MIC >8 mg/L recovered from a patient with SSSI in Louisiana. This isolate was also resistant to methicillin and erythromycin. The G2576T nucleotide alterations (all five alleles) were detected in the 23S rRNA domain V (Table 2). Overall, linezolid, daptomycin, trimethoprim/sulfamethoxazole and vancomycin displayed >95% susceptibility against both *S. aureus* subsets, MRSA and MSSA, regardless of the region. Notably, ceftaroline showed a lower susceptibility rate for MRSA isolates from EU (87.0%) when compared with MRSA isolates from the USA (95.0%). Moreover, clindamycin (susceptibility range, 72.3%–76.8%; USA and EU; data from APAC and LATAM were not available) and erythromycin (susceptibility range, 12.9%–40.5%; all regions) showed limited activity against MRSA isolates.

All *S. pyogenes*, *S. agalactiae* and *S. anginosus* group isolates were inhibited by tedizolid at MIC values of ≤0.5 mg/L, ≤0.5 mg/L and ≤0.25 mg/L, respectively, which are the CLSI susceptible breakpoints for these species. Penicillin, levofloxacin, daptomycin, vancomycin and linezolid also displayed high susceptibility rates (>98.0%) against *S. pyogenes*, *S. agalactiae* and *S. anginosus* group isolates. Clindamycin was active against *S. pyogenes* isolates from the USA (96.2% susceptible) and EU (95.5% susceptible), but limited activity was noted against *S. agalactiae* (61.4% and 78.4% susceptible) and *S. anginosus* group (84.6% and 86.9% susceptible) from these regions. Erythromycin remained active only against *S. pyogenes* isolates (susceptibility rate range, 91.6%–94.0%) from all regions but the USA (83.3% susceptible). Limited activity was observed for erythromycin against *S. agalactiae* (susceptibility rate range, 40.6%–77.3%) and *S. anginosus* group (71.2%–86.8%), regardless of region.

Tedizolid ($MIC_{50/90}$, 0.25/0.25 mg/L; 99.9% susceptible) displayed activity similar to or greater than linezolid ($MIC_{50/90}$, 1/2 mg/L; 99.5% susceptible), ampicillin ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible),

Table 2. Characterization of oxazolidinone resistance mechanisms in linezolid-NS *E. faecalis* and *S. aureus* isolates (2015–19)

			MIC (mg/L)		Resistance mechanism			
Organism	Year	Country	linezolid	tedizolid	mutations[a]	*cfr*[b]	*poxtA*	*optrA*
S. aureus	2018	USA	>8	>1	G2576T	–	–	–
E. faecalis	2015	Ireland	8	>1	–	–	–	+
E. faecalis	2015	USA	4	0.5	–	–	–	+
E. faecalis	2016	Taiwan	4	0.5	–	–	–	+
E. faecalis	2016	France	4	0.25	–	–	–	+
E. faecalis	2016	Mexico	4	0.5	–	–	–	+
E. faecalis	2016	Mexico	4	1	–	–	–	+
E. faecalis	2017	Germany	4	0.5	–	–	–	+
E. faecalis	2017	Mexico	4	0.5	–	–	–	+
E. faecalis	2018	Australia	8	1	–	–	–	+
E. faecalis	2018	Malaysia	4	0.5	–	–	–	+
E. faecalis	2018	Malaysia	4	0.5	–	–	–	+
E. faecalis	2018	Philippines	4	0.5	–	–	–	+
E. faecalis	2018	Taiwan	4	0.5	–	–	–	+
E. faecalis	2018	Taiwan	4	0.5	–	–	–	+
E. faecalis	2018	Vietnam	4	1	–	–	–	+
E. faecalis	2018	Vietnam	4	1	–	–	–	+
E. faecalis	2018	Italy	>8	>1	G2576T	–	–	–
E. faecalis	2018	USA	4	0.5	–	–	–	+
E. faecalis	2019	Australia	4	0.5	–	–	–	+
E. faecalis	2019	Hungary	4	0.5	–	–	–	+
E. faecalis	2019	Poland	4	0.5	–	–	–	+
E. faecalis	2019	Poland	4	0.5	–	–	–	+
E. faecalis	2019	Sweden	4	0.5	–	–	–	+
E. faecalis	2019	Turkey	4	0.5	–	–	–	+
E. faecalis	2019	USA	8	1	–	–	–	+
E. faecalis	2019	USA	4	0.5	–	–	–	+

[a]All isolates were screened for nucleotide alterations in the 23S rRNA gene and amino acid alterations in the ribosomal proteins (L3, L4 and L22).
[b]All isolates were screened for *cfr*, *cfr*(B), *cfr*(C), *cfr*(D) and *cfr*(E) genes.

daptomycin ($MIC_{50/90}$, 0.5/1 mg/L; 99.6% susceptible) and vancomycin ($MIC_{50/90}$, 1/2 mg/L; 98.1% susceptible) against *E. faecalis* isolates. Tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible) was 8- and 4-fold more potent than linezolid ($MIC_{50/90}$, 1/2 mg/L; 100.0% susceptible) and daptomycin ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% susceptible), respectively, for the VRE subset. VRE was detected mostly in the USA (65/2138 isolates; 3.0%), followed by LATAM (9/422; 2.1%), EU (18/2112; 0.9%) and APAC (3/320; 0.9%). Linezolid-NS isolates (0.5% of all *E. faecalis*) were more frequently detected in APAC (10/320; 3.1%) than in LATAM (3/422; 0.7%), EU (9/2112; 0.4%) and the USA (4/2138; 0.2%). Tedizolid inhibited 73.1% of 26 linezolid-NS *E. faecalis* isolates at ≤0.5 mg/L, and 7 isolates were also non-susceptible to tedizolid (3 from APAC, 2 from EU, 1 from the USA and 1 from LATAM; Table 2). All linezolid-NS isolates were inhibited by ampicillin, daptomycin and vancomycin at their respective susceptible breakpoints (Table 1). All but one linezolid-NS *E. faecalis* isolate carried the mobile oxazolidinone resistance gene *optrA* (Table 2). A single isolate from Italy displaying linezolid MIC of >8 mg/L and tedizolid MIC of >1 mg/L harboured the G2576T mutations in two of four 23S rRNA alleles. No other mobile resistant genes or amino acid alterations in the ribosomal proteins (L3, L4 and L22) were observed.

Discussion

MRSA and VRE rates appear to be decreasing in the past decade possibly owing to improvements in the healthcare practices, stewardship programmes and hospital infection prevention policies.[10] However, Gram-positive pathogens, especially staphylococci and enterococci, still pose a concern due to the high number of difficult-to-treat infections they cause. Furthermore, the emergence of linezolid resistance in *Enterococcus* spp. and *S. aureus* isolates generated global concern. This study showed that occurrence of tedizolid resistance (≤0.2%) remains rare among *S. aureus*, streptococci and *E. faecalis* clinical isolates from different regions, as previously described.[11–13] Due to the unique mechanism of action of oxazolidinones, resistance to these drugs should not readily develop in clinical practice. Tedizolid inhibits bacterial protein biosynthesis at a very early stage, preventing the formation of the 70S ribosomal initiation complex. In addition, the tedizolid molecule modification in the C- and D-ring system is responsible for its enhanced potency (4- to 8-fold) relative to linezolid due to additional binding interactions with the peptidyl transferase centre (PTC) of the 50S ribosomal unit.[14,15]

The first clinical linezolid-resistant *S. aureus* isolate reported carried the G2576T mutation in the 23S rRNA.[16] Although numerous mutations in the 23S rRNA have been described, G2576T remains the most commonly detected in resistant strains.[17,18] In this study, the G2576T alteration was only detected in a single *S. aureus* displaying linezolid and tedizolid resistance among almost 36 000 isolates. Besides mutations in the 23S rRNA, linezolid resistance may also be due to modifications in the genes coding for the ribosomal proteins L3 (*rplC*) and L4 (*rplD*) or the acquisition of mobile oxazolidinone resistance genes, such as *cfr*(B), *cfr*(C), *cfr*(D), *cfr*(E), *optrA* and *poxtA*.[15] The *cfr* gene encodes an RNA methyltransferase responsible for the additional methylation in the 23S rRNA that prevents the binding of phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A antibiotics.[19] Although not observed in any *S. aureus* isolate from this collection, the *cfr* gene is reported widely in different species of staphylococci. In contrast, this gene has rarely been detected among members of the *Enterococcus* spp.[15] The *optrA* gene, a mobile oxazolidinone resistance gene that encodes an ABC-F protein able to confer resistance by ribosome protection, was first detected in 2015 and is mainly reported in *E. faecalis* isolates.[20,21] Over the past decades, an epidemiological shift was noted on the mechanism associated with linezolid resistance in *E. faecalis*. Previous reports showed that 23S rRNA alterations (G2576T) were the main linezolid resistance factor detected in *E. faecalis*, while the frequency of isolates carrying the *optrA* gene has risen considerably in the past 5 years to become the main mechanism of linezolid resistance worldwide, as noted in the present study.[11,22] Notably, tedizolid remains active (MIC, ≤0.5 mg/L) against >75% of *E. faecalis* isolates carrying the *optrA* gene. This finding might be caused by OptrA variants that were previously suggested to be associated with different oxazolidinone susceptibility/resistance profiles.[15]

In summary, these tedizolid MIC_{50} and MIC_{90} results agree with those previously published by the STAR programme that provided contemporary and longitudinal information on the *in vitro* activity of tedizolid and comparator agents.[23–26] Combined, these results suggest the sustained potency of tedizolid over time, with no indication of decreased susceptibility in *S. aureus*, *E. faecalis* and streptococci isolates. Linezolid resistance was rarely detected (<0.1% in *S. aureus* and *E. faecalis*). While the single *S. aureus* isolate that was non-susceptible to both oxazolidinones displayed the well-known G2576T alteration on the 23S rRNA, an epidemiological shift was confirmed in *E. faecalis* marking the *optrA* gene the main mechanism of linezolid resistance in this species. Tedizolid remained active against >75% of linezolid NS *E. faecalis* isolates carrying the *optrA* gene. These results support the continued long-term and stable *in vitro* activity of tedizolid against clinical Gram-positive pathogens causing infections worldwide.

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Transparency declarations

JMI Laboratories contracted to perform services in 2021 for AbbVie Inc., Affinity Biosensors, AimMax Therapeutics Inc., Alterity Therapeutics, Amicrobe Inc., Arietis Pharma, Armata Pharmaceuticals Inc., Astrellas Pharma Inc., Basilea Pharmaceutica AG, Becton, Dickinson and Company (BD), bioMérieux Inc., Boost Biomes, Brass Dome Ventures Ltd, Bravos Biosciences, Bugworks Research Inc., Centers for Disease Control and Prevention, Cerba Research, Cidara Therapeutics, Cipla Ltd, ContraFect Corp., CXC7, DiamondV, Enveda Biosciences, Fedora Pharmaceuticals Inc., Fimbrion Therapeutics, First Light Diagnostics, Forge Therapeutics Inc., Fox Chase Cancer Center, GlaxoSmithKline plc (GSK), Harvard University, Institute for Clinical Pharmacodynamics (ICPD), International Health Management Associates (IHMA) Inc., Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences Inc., Laboratory Specialists Inc. (LSI), Meiji Seika Pharma Co. Ltd, Melinta Therapeutics, Menarini Group, Merck & Co. Inc., MicuRx Pharmaceuticals Inc., Mutabilis, Nabriva Therapeutics, National Institutes of Health, Novome Biotechnologies, Omnix Medical Ltd, Paratek Pharma, Pattern Bioscience, Pfizer Inc., Prokaryotics Inc., Pulmocide Ltd, QPEX Biopharma Inc., Roche Holding AG, Roivant Sciences, SeLux Diagnostics Inc., Shionogi Inc., Sinovent Pharmaceuticals Inc., SNIPR Biome ApS, Spero Therapeutics, Summit Therapeutics Inc., T2 Biosystems, TenNor Therapeutics, Thermo Fisher Scientific, University of Southern California, University of Wisconsin, USCAST, U.S. Food and Drug Administration, Venatorx Pharmaceutics Inc., Weill Cornell Medicine and Wockhardt Ltd.

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References

1 Weiner-Lastinger LM, Abner S, Edwards JR *et al*. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015-2017. *Infect Control Hosp Epidemiol* 2020; **41**: 1–18. https://doi.org/10.1017/ice.2019.296

2 WHO Regional Office for Europe/ECDC. Antimicrobial Resistance Surveillance in Europe 2022–2020 Data. https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2022-2020-data.

3 Metlay JP, Waterer GW, Long AC *et al*. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; **200**: e45–67. https://doi.org/10.1164/rccm.201908-1581ST

4 Hindy JR, Haddad SF, Kanj SS. New drugs for methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections. *Curr Opin Infect Dis* 2022; **35**: 112–9. https://doi.org/10.1097/QCO.0000000000000800

5 FDA. SINVEXTRO®. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205435s008,205436s004lbl.pdf.

6 CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Eleventh Edition: M07*. 2018.

7 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing—Thirty-First Edition: M100*. 2021.

8 EUCAST. Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 11.0, January 2021. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf.

9 Deshpande LM, Castanheira M, Flamm RK *et al*. Evolving oxazolidinone resistance mechanisms in a worldwide collection of enterococcal clinical isolates: results from the SENTRY Antimicrobial Surveillance Program. *J Antimicrob Chemother* 2018; **73**: 2314–22. https://doi.org/10.1093/jac/dky188

10 CDC. Antibiotic Resistance Threats in the United States, 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.

11 Mendes RE, Hogan PA, Jones RN *et al*. Surveillance for linezolid resistance via the Zyvox® Annual Appraisal of Potency and Spectrum (ZAAPS) programme (2014): evolving resistance mechanisms with stable susceptibility rates. *J Antimicrob Chemother* 2016; **71**: 1860–5. https://doi.org/10.1093/jac/dkw052

12 Pfaller MA, Mendes RE, Streit JM *et al*. ZAAPS Program results for 2015: an activity and spectrum analysis of linezolid using clinical isolates from medical centres in 32 countries. *J Antimicrob Chemother* 2017; **72**: 3093–9. https://doi.org/10.1093/jac/dkx251

13 Mendes RE, Deshpande L, Streit JM *et al*. ZAAPS programme results for 2016: an activity and spectrum analysis of linezolid using clinical isolates from medical centres in 42 countries. *J Antimicrob Chemother* 2018; **73**: 1880–7. https://doi.org/10.1093/jac/dky099

14 Zhanel GG, Love R, Adam H *et al*. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens. *Drugs* 2015; **75**: 253–70. https://doi.org/10.1007/s40265-015-0352-7

15 Schwarz S, Zhang W, Du XD *et al*. Mobile oxazolidinone resistance genes in Gram-positive and Gram-negative bacteria. *Clin Microbiol Rev* 2021; **34**: e0018820. https://doi.org/10.1128/CMR.00188-20

16 Tsiodras S, Gold HS, Sakoulas G *et al*. Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet* 2001; **358**: 207–8. https://doi.org/10.1016/S0140-6736(01)05410-1

17 Stefani S, Bongiorno D, Mongelli G *et al*. Linezolid resistance in staphylococci. *Pharmaceuticals (Basel)* 2010; **3**: 1988–2006. https://doi.org/10.3390/ph3071988

18 Long KS, Vester B. Resistance to linezolid caused by modifications at its binding site on the ribosome. *Antimicrob Agents Chemother* 2012; **56**: 603–12. https://doi.org/10.1128/AAC.05702-11

19 Long KS, Poehlsgaard J, Kehrenberg C *et al*. The Cfr rRNA methyltransferase confers resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A antibiotics. *Antimicrob Agents Chemother* 2006; **50**: 2500–5. https://doi.org/10.1128/AAC.00131-06

20 Wang Y, Lv Y, Cai J *et al*. A novel gene, optrA, that confers transferable resistance to oxazolidinones and phenicols and its presence in *Enterococcus faecalis* and *Enterococcus faecium* of human and animal origin. *J Antimicrob Chemother* 2015; **70**: 2182–90. https://doi.org/10.1093/jac/dkv116

21 Sharkey LK, Edwards TA, O'Neill AJ. ABC-F proteins mediate antibiotic resistance through ribosomal protection. *mBio* 2016; **7**: e01975. https://doi.org/10.1128/mBio.01975-15

22 Ross JE, Farrell DJ, Mendes RE *et al*. Eight-year (2002-2009) summary of the linezolid (Zyvox(R) Annual Appraisal of Potency and Spectrum; ZAAPS) Program in European countries. *J Chemother* 2011; **23**: 71–6. https://doi.org/10.1179/joc.2011.23.2.71

23 Pfaller MA, Flamm RK, Jones RN *et al*. Activities of tedizolid and linezolid determined by the reference broth microdilution method against 3,032 Gram-positive bacterial isolates collected in Asia-Pacific, Eastern Europe, and Latin American countries in 2014. *Antimicrob Agents Chemother* 2016; **60**: 5393–9. https://doi.org/10.1128/AAC.00881-16

24 Carvalhaes CG, Sader HS, Flamm RK *et al*. Tedizolid *in vitro* activity against Gram-positive clinical isolates causing bone and joint infections in hospitals in the USA and Europe (2014-17). *J Antimicrob Chemother* 2019; **74**: 1928–33. https://doi.org/10.1093/jac/dkz120

25 Carvalhaes CG, Sader HS, Flamm RK *et al*. Assessment of tedizolid *in vitro* activity and resistance mechanisms against a collection of *Enterococcus* spp. causing invasive infections, including isolates requiring an optimized dosing strategy for daptomycin from U.S. and European medical centers, 2016 to 2018. *Antimicrob Agents Chemother* 2020; **64**: e00175-20. https://doi.org/10.1128/AAC.00175-20

26 Carvalhaes CG, Sader HS, Rhomberg PR *et al*. Tedizolid activity against a multicentre worldwide collection of *Staphylococcus aureus* and *Streptococcus pneumoniae* recovered from patients with pneumonia (2017-2019). *Int J Infect Dis* 2021; **107**: 92–100. https://doi.org/10.1016/j.ijid.2021.04.014