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Short Communication

Glycopeptide resistance in *Enterococcus* spp. and coagulase-negative staphylococci from hospitalised patients in Germany: occurrence, characteristics and dalbavancin susceptibility

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ABSTRACT

Objectives: The aim of this study was to evaluate the occurrence of glycopeptide resistance in enterococci and coagulase-negative staphylococci (CoNS) and to determine the susceptibilities of the identified glycopeptide-resistant isolates to dalbavancin.
Methods: Twenty-two medical laboratories participated in the study conducted in 2016/17 by the Paul-Ehrlich-Society for Chemotherapy. Each laboratory was asked to collect 30 *Enterococcus* spp. (limited to *Enterococcus faecalis* and *Enterococcus faecium*) and 30 CoNS isolates consecutively from hospitalised patients with a proven or suspected infection.
Results: A total of 1285 isolates were collected, comprising 364 *E. faecalis*, 291 *E. faecium* and 630 CoNS. No *E. faecalis* isolates (0%) but 76 *E. faecium* isolates (26.1%) were vancomycin-resistant, of which 21 showed the VanA type and 55 the VanB type. The proportion of vancomycin-resistant strains among *E. faecium* isolates from patients in intensive care units (21.6%) was significantly lower than that from patients on regular wards (30.5%). Among the CoNS, 67 isolates (10.6%) were teicoplanin-resistant but none were vancomycin-resistant, with resistance only detected in *Staphylococcus epidermidis* (12.2%), *Staphylococcus haemolyticus* (17.9%) and *Staphylococcus hominis* (13.2%). Dalbavancin at ≤0.25 mg/L inhibited all VanB-type enterococci and 95.5% of teicoplanin-resistant CoNS.
Conclusion: The level of glycopeptide resistance in *E. faecalis* remains very low in Germany but achieved 26% in *E. faecium* and was >10% in CoNS. Dalbavancin appears to be a feasible option for treating infections caused by VanB-type vancomycin-resistant *E. faecium* and teicoplanin-resistant CoNS.

1. Introduction

Enterococci and coagulase-negative staphylococci (CoNS) are common causes of healthcare-associated infections [1]. Glycopeptides play an important role in the management of healthcare-associated infections caused by β-lactam-resistant Gram-positive cocci. Vancomycin is the only glycopeptide approved for marketing in the USA, while teicoplanin became a second glycopeptide available in Europe [2,3]. Resistance to teicoplanin in CoNS has been reported, and resistance to vancomycin and teicoplanin has

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emerged in *Enterococcus* spp., especially *Enterococcus faecium* [2,4]. Glycopeptide resistance in clinical enterococci is attributable to the acquisition of the gene clusters *vanA* and *vanB*, although the intact *vanB* operon is not induced by teicoplanin [4]. CoNS isolates are more commonly resistant to teicoplanin than vancomycin, and resistance occurs mostly in *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* [2].

An increased frequency of resistance to glycopeptides among Gram-positive cocci has led to the development of the lipoglycopeptides [3,5]. Dalbavancin, a semisynthetic derivative of the teicoplanin-like antibiotic A40926, has been demonstrated to be more potent than vancomycin or teicoplanin against Gram-positive cocci [3,6]. Dalbavancin has received regulatory approval for the treatment of acute bacterial skin and skin-structure infections in adults, but the drug has also been used off-label for the treatment of other infections such as prosthetic joint infection, osteomyelitis and infective endocarditis [7,8]. Dalbavancin, however, is not active against teicoplanin-resistant enterococci (VanA type) [6], but circumvents VanB-type glycopeptide resistance mechanisms [9].

The present surveillance study was conducted by the Paul-Ehrlich-Society for Chemotherapy (Paul-Ehrlich-Gesellschaft für Chemotherapie, PEG). We performed a cross-sectional analysis (i) to evaluate the occurrence of glycopeptide-resistant strains among clinical isolates of *Enterococcus faecalis* and *E. faecium* as well as CoNS and (ii) to determine the susceptibility of identified VanB-type vancomycin-resistant enterococci and teicoplanin-resistant CoNS (TRCoNS) to dalbavancin.

2. Materials and methods

2.1. Sample collection

Non-duplicate, consecutive isolates were prospectively collected between October 2016 and March 2017 at 22 medical laboratories (mostly affiliated with tertiary care medical centres). Each laboratory was asked to provide 30 *Enterococcus* spp. (limited to *E. faecalis* and *E. faecium*) and 30 CoNS from hospitalised patients who had a proven or suspected infection. Clinical isolates from all anatomical sites as well as medical devices were accepted. No restrictions were applied regarding patient age, sex, medical history or previous use of antimicrobials.

2.2. Species identification and antimicrobial susceptibility testing

Verification of species identification and antimicrobial susceptibility testing were performed at a central laboratory. Species identification was verified by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) (MALDI Biotyper®, microflex®; Bruker Daltonik GmbH, Bremen, Germany). Minimum inhibitory concentrations (MICs) were determined by broth microdilution (BMD) according to standard ISO 20776-1 [10]. The antimicrobial agents tested were vancomycin, teicoplanin, dalbavancin, linezolid, ciprofloxacin, gentamicin and ampicillin (*Enterococcus* spp. only) as well as oxacillin, erythromycin, clindamycin, doxycycline, trimethoprim/sulfamethoxazole (SXT) and rifampicin (all CoNS only). Inducible clindamycin resistance in CoNS was detected by using 4 mg/L erythromycin plus 0.5 mg/L clindamycin. BMD panels of dalbavancin were prepared in-house, while industrially manufactured trays containing the other antimicrobial agents were purchased from Merlin Diagnostika GmbH (Bornheim, Germany). *Staphylococcus aureus* ATCC 29213 and *E. faecalis* ATCC 29212 were used as quality control strains.

2.3. Minimum inhibitory concentration (MIC) interpretive criteria

Species-related breakpoints (version 11.0) issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were applied for interpretation of MICs [11], but criteria published by the Clinical and Laboratory Standards Institute (CLSI) were additionally applied to interpret MICs of dalbavancin [12]. Of note, EUCAST has established a dalbavancin breakpoint for *Staphylococcus* spp. (susceptible, ≤0.125 mg/L; resistant, >0.125 mg/L) but not for *Enterococcus* spp. In comparison, the CLSI has set a dalbavancin susceptibility breakpoints for *S. aureus* and vancomycin-susceptible *E. faecalis* (susceptible, ≤0.25 mg/L each). These criteria, which have also been recognised by the US Food and Drug Administration (FDA), were used as 'CLSI breakpoints' to assess the susceptibility of CoNS and *E. faecium* to dalbavancin, respectively.

2.4. Molecular detection of antimicrobial resistance genes

Molecular analysis of bacterial isolates was performed at the Robert Koch Institute. Genomic DNA was isolated using a commercial DNA extraction kit (DNeasy® Tissue Kit; QIAGEN, Hilden, Germany). The presence of *vanA* and *vanB* genes was determined by multiplex PCR [13]. Molecular mechanisms of linezolid resistance [23S rDNA gene mutations and/or gene-based (*cfr, optrA, poxtA*)] were determined according to published methods [14].

2.5. Statistical evaluation

The statistical significance of differences in resistance rates was determined by comparing Wilson 95% confidence intervals (CIs). If resistance rate A did not fall into the CI of resistance rate B and vice versa, a significance of $P < 0.05$ was assumed.

3. Results

3.1. Source of isolates

Overall, 1285 isolates were collected. The collection comprised 364 *E. faecalis*, 291 *E. faecium* and 630 CoNS (Supplementary Table S1). The most frequently isolated CoNS were *S. epidermidis* and *S. haemolyticus* (Supplementary Table S2). Moreover, 826 (64.2%), 403 (31.4%) and 56 (4.4%) isolates were obtained from patients on regular wards, in intensive care units (ICUs) and at outpatient clinics, respectively. Regarding the source, 333 isolates (25.9%) were recovered from blood and 952 isolates (74.1%) were from other specimens (Supplementary Tables S2 and S3).

3.2. Enterococcus spp

All 364 *E. faecalis* isolates were susceptible to ampicillin, vancomycin, teicoplanin and linezolid. Resistance to ciprofloxacin and high-level resistance (HLR) to gentamicin was each found in 89 isolates (24.5%).

Of the 291 *E. faecium* isolates, 76 (26.1%) were glycopeptide-resistant, of which 21 isolates (7.2%) were resistant to both vancomycin and teicoplanin (VanA type) and 55 (18.9%) were resistant to vancomycin only (VanB type). Moreover, 270 isolates (92.8%) were each resistant to ampicillin and ciprofloxacin, while HLR to gentamicin was detected in 50 isolates (17.2%). Three isolates were linezolid-resistant, all of which were susceptible to vancomycin and teicoplanin and had the G→T conversion at position 2576 of the 23S rRNA gene.

Vancomycin-resistant *E. faecium* (VR*Efm*) were detected at 19 of the 22 participating laboratories. Of the 76 VR*Efm* isolates, 46 (60.5%) and 29 (38.2%) were obtained from patients on regular

Table 1
Distribution of vancomycin and teicoplanin MICs for E. faecium and CoNS as well as percent (%) susceptible and resistant isolates

Species / type / (gene)	No. of isolates	Glycopeptide	MIC (mg/l)									MIC_{50} (mg/l)	MIC_{90} (mg/l)	% S	% R
			≤ 0.25	0.5	1	2	4	8	16	32	> 32				
E. faecium	291	Vancomycin	1	81	128	4	1			2	74	1	> 32	73.9	26.1
		Teicoplanin	149	108	12	1		1	9	5	6	≤ 0.25	1	92.8	7.2
VR*Efm*	76	Vancomycin								2	74	> 32	> 32	0	100
		Teicoplanin	25	25	4	1		1	9	5	6	0.5	32	72.4	27.4
VanA-type / *vanA*	20	Vancomycin									20	> 32	> 32	0	100
		Teicoplanin						1	9	4	6	16	> 32	> 32	100
VanB-type / *vanB*	55	Vancomycin								2	53	> 32	> 32	0	100
		Teicoplanin	25	25	4	1						0.5	0.5	100	0
VanA-type / *vanA* + *vanB*	1	Vancomycin									1	-	-	(0)	(100)
		Teicoplanin								1		-	-	(0)	(100)
CoNS	630	Vancomycin		64	209	350	7					2	2	100	0
		Teicoplanin	144	61	56	113	189	58	8	1		2	8	89.4	10.6
TRCoNS	67	Vancomycin			4	57	6					2	2	100	0
TSCoNS	563	Vancomycin		64	205	293	1					2	2	100	0

The vertical solid lines indicate the EUCAST breakpoints: *E. faecium* - vancomycin (susceptible ≤ 4 mg/l, resistant > 4 mg/l), teicoplanin (susceptible ≤ 2 mg/l, resistant > 2 mg/l); CoNS – vancomycin (susceptible ≤ 4 mg/l, resistant > 4 mg/l), teicoplanin (susceptible ≤ 4 mg/l, resistant, > 4 mg/l)

CoNS, coagulase-negative staphylococci; VR*Efm*, vancomycin-resistant *E. faecium*; TRCoNS, teicoplanin-resistant CoNS; TSCoNS, teicoplanin-susceptible CoNS

wards and in ICUs, respectively. The remaining isolate was recovered from a patient in an outpatient urological clinic. Moreover, of the 76 VR*Efm* isolates, 20 (26.3%) harboured only the *vanA* gene, 55 (72.4%) only the *vanB* gene and 1 isolate (1.3%; VanA type) carried both genes (Supplementary Table S4). The distributions of MICs of vancomycin and teicoplanin for the VR*Efm* isolates are presented in Table 1.

Of note, the proportion of vancomycin-resistant strains among *E. faecium* isolates from patients in ICUs [29/134; 21.6% (95% CI 15.5–29.4%)] was significantly lower than that from patients on regular wards [46/151; 30.5% (95% CI 23.7–38.2%)]. VanA-type VR*Efm* isolates, however, were significantly more frequently isolated from patients in ICUs [15/29; 51.7% (95% CI 34.4–68.6%)] than from patients on regular wards [6/46; 13.0% (95% CI 6.1–25.7%)]. VanA-type VR*Efm* strains also tended to occur more frequently among blood culture isolates [6/14; 42.9% (95% CI 21.4–67.4%)] than non-blood culture isolates [15/62; 24.2% (95% CI 15.3–36.2%)].

All VR*Efm* were additionally resistant to ampicillin and ciprofloxacin. Combined HLR to gentamicin was detected in 16 (21.1%) of 76 VR*Efm*, namely in 6 (28.6%) of the 21 isolates with VanA type and in 10 (18.2%) of the 55 isolates with the VanB type.

3.3. Coagulase-negative staphylococci (CoNS)

Glycopeptide-resistant CoNS were detected at 20 laboratories. Among the 630 CoNS isolates collected, 67 (10.6%) were resistant to teicoplanin but none to vancomycin (Table 1). Teicoplanin resistance was only detected in isolates of *S. epidermidis* (12.2%), *S. haemolyticus* (17.9%) and *Staphylococcus hominis* (13.2%). A total of 57 TRCoNS displayed a teicoplanin MIC of 8 mg/L and 9 isolates a teicoplanin MIC of 16 mg/L. The remaining isolate, an *S. haemolyticus* blood isolate recovered from a patient on a haematology/oncology ward, displayed a teicoplanin MIC of 32 mg/L and a vancomycin MIC of 4 mg/L (Table 1).

The resistance rates for CoNS to oxacillin, erythromycin, clindamycin (inducible resistance/constitutive resistance), doxycycline, SXT, gentamicin, rifampicin and ciprofloxacin were at 62.4%, 63.0%, 46.2% (10.0%/36.2%), 8.6%, 24.6%, 41.3%, 8.9% and 53.3%, respectively. Resistance to oxacillin, erythromycin, clindamycin and rifampicin was significantly more frequently distributed among TRCoNS than teicoplanin-susceptible CoNS (TSCoNS) (Table 2). Four *S. epidermidis* and one *S. haemolyticus* (5/630; 0.8%) were linezolid-resistant. All were additionally resistant to oxacillin, erythromycin, clindamycin (constitutive), doxycycline, SXT, gentamicin, rifampicin and ciprofloxacin, and two of them were also resistant to teicoplanin. The plasmid-encoded *cfr* gene was detected in two of the four *S. epidermidis* isolates as well as in the *S. haemolyticus* isolate.

Of note, blood isolates [13.8% (95% CI 9.9–19.0%)] were significantly more frequently teicoplanin-resistant than isolates from other specimen sources [8.9% (95% CI 6.5–12.0%)], while there were no significant differences in the teicoplanin resistance rates between isolates from patients in ICUs [13.3% (95% CI 9.2–18.7%)], on regular wards [9.7% (95% CI 7.2–13.0%)] and at outpatient clinics [4.3% (95% CI 0.8–21.0%)] (Supplementary Table S5).

Table 2
Resistance rates (%) of teicoplanin-resistant coagulase-negative staphylococci (TRCoNS) and teicoplanin-susceptible coagulase-negative staphylococci (TSCoNS) to various antibiotics

Antimicrobial agent	Phenotype TRCoNS (n = 67)	TSCoNS (n = 563)	Difference[a] (95% CI)
Oxacillin	77.6	60.6	17.0 (5.1–26.3)
Erythromycin	82.1	60.7	21.3 (9.8–29.8)
Clindamycin	61.2	44.4	16.8 (4.1–28.3)
IR	11.9	9.8	2.2 (–4.2 to 12.3)
CR	49.3	34.6	14.6 (2.3–26.9)
Doxycycline	13.4	8.0	5.4 (–1.3 to 15.8)
SXT	23.9	24.7	–0.8 (–10.2 to 11.1)
Gentamicin	47.8	40.5	7.3 (–5.0 to 19.7)
Rifampicin	16.4	8.0	8.4 (1.0–19.2)
Ciprofloxacin	64.2	52.0	12.1 (–0.5 to 23.3)

CI, confidence interval; IR, inducible resistance; CR, constitutive resistance; STX, trimethoprim/sulfamethoxazole.
[a] Resistance rate TRCoNS minus resistance rate TSCoNS.

Table 3
Distribution of dalbavancin minimum inhibitory concentrations (MICs) for vancomycin-resistant *Enterococcus faecium* (VR*Efm*) and teicoplanin-resistant coagulase-negative staphylococci (TRCoNS) isolates as well as percent (%) susceptible isolates

Species / type (gene)	No. of isolates	MIC (mg/l)											MIC_{50} (mg/l)	MIC_{90} (mg/l)	% susceptible	
		≤ 0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	> 8			EUCAST	CLSI[1]
VR*Efm*	76		12	32	9	2				7	10	4	0.06	8		72.4
VanA-type / (*vanA*)	20									7	10	3	8	>8	No breakpoint available	0
VanB-type / (*vanB*)	55		12	32	9	2							0.06	0.125		100
VanA-type / (*vanA* + *vanB*)	1											1	(> 8)	(> 8)		0
TRCoNS	67		1	26	20	17	2			1			0.125	0.25	70.1	95.5
S. epidermidis	48		1	25	15	6	1						0.06	0.25	85.4	97.9
S. haemolyticus	14				4	9				1			0.25	0.25	28.6	92.9
S. hominis	5			1	1	2	1						0.25	0.5	40.0	80.0

The solid vertical line indicates the EUCAST breakpoint for *Staphylococcus* spp. and the dashed vertical line indicates the "CLSI breakpoints". Note, that EUCAST has not established a dalbavancin breakpoint for *Enterococcus* spp.

[1]The CLSI susceptibility breakpoints for *S. aureus* and vancomycin-susceptible *E. faecalis* were applied.

VR*Efm*, vancomycin-resistant *E. faecium*; TRCoNS, teicoplanin-resistant coagulase-negative staphylococci

3.4. Susceptibility of glycopeptide-resistant Enterococcus faecium and teicoplanin-resistant coagulase-negative staphylococci (TRCoNS) to dalbavancin

Dalbavancin concentrations required to inhibit 50% and 90% of the strains ($MIC_{50/90}$) were 8/>8 mg/L (range, 4 to >8 mg/L) for VanA-type isolates and 0.06/0.125 mg/L (range, 0.03–0.25 mg/L) for VanB-type isolates (Table 3). If the dalbavancin breakpoint set by the CLSI for vancomycin-susceptible *E. faecalis* (susceptible, ≤0.25 mg/L), recently proposed as a tentative epidemiological cut-off value (ECOFF) for *E. faecium* [9], was applied to interpret the MICs, all VanA-type isolates would be considered dalbavancin-resistant, as expected, and all VanB-type isolates would be considered dalbavancin-susceptible.

Dalbavancin MICs for TRCoNS ranged from 0.03 mg/L to 4 mg/L, with a tendency to lower MICs for *S. epidermidis* than *S. haemolyticus* and *S. hominis* (Table 3). Overall, $MIC_{50/90}$ values of dalbavancin were 0.125/0.25 mg/L. The median MIC of dalbavancin was 0.125 mg/L for the 58 teicoplanin-resistant CoNS isolates with a teicoplanin MIC of 8 mg/L and 0.094 mg/L for the 8 isolates with a teicoplanin MIC of 16 mg/L, while the MIC was 4 mg/L for the isolate with a teicoplanin MIC of 32 mg/L.

Applying the EUCAST breakpoint for *Staphylococcus* spp. (susceptible, ≤0.125 mg/L), 47 TRCoNS (70.1%) were dalbavancin-susceptible and 20 (29.9%) were dalbavancin-resistant. Of the 20 dalbavancin-resistant TRCoNS, 17 had an MIC of 0.25 mg/L, which would be classified dalbavancin-susceptible if the CLSI breakpoint for *S. aureus* (susceptible, ≤0.25 mg/L) was applied. Dalbavancin at ≤0.25 mg/L inhibited 56 (96.6%) of 58 TRCoNS with a teicoplanin MIC of 8 mg/L and 8 (100%) of 8 TRCoNS with an MIC of 16 mg/L.

4. Discussion

This study evaluated the susceptibility of *Enterococcus* spp. (limited to *E. faecalis* and *E. faecium* as no other enterococcal species were requested during the surveillance study) and CoNS to vancomycin and teicoplanin and assessed the susceptibility of the identified glycopeptide-resistant isolates to dalbavancin.

Glycopeptide resistance in *E. faecalis* does not represent a major therapeutic challenge, while VR*Efm* belong to the group of multidrug-resistant bacteria that poses a public-health threat, especially in healthcare settings. The World Health Organization (WHO) has assessed VR*Efm* to have a high priority for finding new treatment options [15]. The present study found that in 2016/17 resistance rates to vancomycin and teicoplanin were 26.1% and 7.2%, respectively, for *E. faecium* isolates from Germany. The frequency of VR*Efm* has risen sharply compared with the results of previous studies performed by the PEG. In 2010 and 2013, vancomycin resistance rates were 12.6% and 16.6%, respectively. In contrast, the frequency of resistance to teicoplanin has changed comparatively little, with rates of 5% in 2010 and 7.5% in 2013. These results, indicating an increase of VanB-type isolates, coincide with other surveillance data and outbreak descriptions from Germany [16], including the German Antibiotic Resistance Surveillance (ARS) System focusing on *E. faecium* blood culture isolates (https://ars.rki.de).

The European Antimicrobial Resistance Surveillance Network (EARS-Net), investigating invasive isolates, also reported a strong increase of VR*Efm* isolates. The EU/EEA population-weighted mean resistance rate rose from 10.5% in 2015 to 18.3% in 2019 [17]. Large intercountry variations, however, were noted, ranging from ≤1% to 50%. The proportion of VR*Efm* isolates from Germany significantly increased during the period 2015–2019, namely from 10.5% to 26.3%.

High VR*Efm* rates were also reported from Australia (49.3% [18]) and the USA (41% [19]).

CoNS, although less virulent than *S. aureus*, may cause severe infections, particularly in patients in neonatal ICUs, and are a major cause of device-related and prosthetic joint infections. Resistance to antibiotics is widespread among CoNS, limiting therapeutic options. The glycopeptides are among the first-line drugs used for the treatment of infections caused by CoNS, but decreased susceptibility and resistance to glycopeptides in CoNS have been reported

from many parts of the world [6,20]. The present study found that 12.2% of the *S. epidermidis* isolates collected in 2016/17 were teicoplanin-resistant, but none were vancomycin-resistant. According to ARS data, the prevalence of teicoplanin-resistant *S. epidermidis* was <1% before 2010, then rose to 12.6% in 2012, and varied between 16.4% and 19.2% until 2019, while the rate of vancomycin resistance during the study period was no more than 0.1% [https://ars.rki.de].

Applying the EUCAST criteria for interpretation of dalbavancin MICs, 70% of the TRCoNS in the present study were classified susceptible, but the susceptibility rate would be 96% if the CLSI breakpoint for *S. aureus* was applied. However, a new analysis of work on population pharmacokinetics and non-clinical target attainment analysis projected that >99% of subjects would achieve the new pharmacokinetic/pharmacodynamic (PK/PD) 24-h free area under concentration–time curve/MIC ratio (*f*AUC/MIC) bacterial stasis target of 27.1 for *S. aureus* at MIC ≤ 2 mg/L [21,22].

This raises the question of the clinical efficacy of dalbavancin in the treatment of TRCoNS infections. Unfortunately, data are scarce here. However, there is some evidence that dalbavancin is superior to vancomycin in patients with catheter-related bloodstream infections. In a study by Raad et al., infected patients who received weekly dalbavancin (n = 33) had an overall success rate of 87.0% (95% CI 73.2–100%) that was significantly higher than that of those who received vancomycin (n = 34) (50.0%; 95% CI 31.5–68.5%) [23].

In summary, resistance to glycopeptides in *E. faecalis* remains very rare in Germany but achieved a level of 26% in *E. faecium*. Furthermore, >10% of CoNS were teicoplanin-resistant. Considering that vancomycin-susceptible *Enterococcus* spp. and TSCoNS are always inhibited at the EUCAST PK/PD breakpoint of dalbavancin (susceptible, ≤0.25 mg/L), 96.8% of the 655 *Enterococcus* spp. and 99.5% of the 630 CoNS can be deemed to be dalbavancin-susceptible. Clinical conclusions, however, cannot be made from the study results as data on the clinical efficacy of dalbavancin for therapy of infections caused by VanB-type VR*Efm* and TRCoNS are little or lacking.

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Competing interests

MK is a partner and CEO of Antiinfectives Intelligence GmbH, a research organisation providing services to pharmaceutical companies; EW is Head of Laboratory of Antiinfectives Intelligence GmbH. All other authors declare no competing interests.

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2021.12.016.

Appendix. : Further members of the Study Group 'Antimicrobial Resistance' of the Paul-Ehrlich-Society for Chemotherapy

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