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Antibiotic susceptibility patterns of viridans group streptococci isolates in the United States from 2010 to 2020

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Background: Viridans group streptococci (VGS) are typically part of the commensal flora but can also cause severe invasive diseases such as infective endocarditis. There are limited data available showing antibiotic susceptibility over time for VGS.

Objectives: To evaluate antibiotic susceptibility trends in VGS over time.

Methods: *In vitro* susceptibility patterns for 33 antibiotics were examined for *Streptococcus mitis*, *Streptococcus oralis*, and non-speciated VGS isolates from patients in Veterans Affairs (VA) Medical Centers in the United States between 2010 and 2020. Susceptibility determinations were made by the individual clinical microbiology laboratories and data were retrospectively collected from the VA Corporate Data Warehouse. Susceptibility trends were analysed using Poisson regression.

Results: A total of 14 981 VGS isolates were included of which 19.5%, 0.7% and 79.8% were *S. mitis*, *S. oralis* and non-speciated VGS isolates, respectively. Cumulative susceptibility rates across all years were similar between species for ceftriaxone (range: 96.0% to 100%), clindamycin (81.3% to 84.5%), and vancomycin (99.7% to 100%). For penicillin, susceptibility rates were 71.0%, 80.9% and 86.3% for *S. mitis*, *S. oralis* and non-speciated isolates, respectively. From 2010 to 2020, susceptibility of non-speciated VGS isolates decreased for erythromycin ($P=0.0674$), penicillin ($P=0.0835$), and tetracycline ($P=0.0994$); though the decrease was only significant for clindamycin ($P=0.0033$). For *S. mitis*, a significant susceptibility rate decrease was observed for erythromycin ($P=0.0112$).

Conclusions: Susceptibility rates for some clinically relevant antibiotics declined between 2010 and 2020. This worrisome trend highlights the need to improve antimicrobial stewardship efforts to limit unnecessary antibiotic use and preserve empirical treatment options.

Introduction

Viridans group streptococci (VGS) are common inhabitants of the oral cavity and they may cause severe infections, such as bacteraemia and/or infective endocarditis, which are associated with in-hospital mortality rates of ∼10%.[1] VGS can also cause infections in the oral cavity that range from dental caries to severe, deep space odontogenic infections.[2,3] Though VGS are often commensal, exposure of normally sterile sites (e.g. bloodstream, dental pulp) to these bacteria can lead to infection. Features of VGS that enable them to cause infection include their propensity to adhere to endothelial tissue, fibrin and platelets as well as their ability to evade the immune system.[4,5] Antibiotics used for treatment of VGS infections are frequently chosen empirically and without susceptibility data, especially for odontogenic infections. Thus, monitoring susceptibility patterns over time is critical to detect potential increases in antibiotic resistance and support initial selection of appropriate antibiotics.

Table 1. β-Lactam susceptibility rates for non-speciated VGS isolates from all culture sites obtained from VA Hospitals in the United States, 2010–20

	2010		2011		2012		2013		2014		2015		2016		2017		2018		2019		2020		Total (2010–20)	
	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*
AMX[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	100.0	2	87.5	24	82.1	39	95.0	20	87.1	85
AMC[a]	100.0	11	100.0	12	100.0	12	100.0	2	100.0	18	100.0	7	100.0	3	100.0	1	100.0	3	—	—	—	—	100.0	69
AMP	94.5	181	95.2	165	95.0	221	93.2	279	91.9	495	89.9	477	89.3	477	89.4	547	90.2	610	87.9	644	86.2	441	90.2	4537
SAM[a]	100.0	6	100.0	4	100.0	8	100.0	7	100.0	4	85.7	7	100.0	6	100.0	3	100.0	2	100.0	2	100.0	2	98.0	51
CFZ[a]	100.0	38	100.0	23	100.0	28	100.0	7	92.3	26	81.8	11	80.0	5	100.0	1	100.0	2	—	—	—	—	96.5	141
FEP	100.0	61	91.7	72	95.9	98	96.7	152	98.0	202	99.0	209	98.5	200	97.6	210	99.0	198	98.5	204	99.3	140	98.0	1746
CTX	99.1	106	96.6	88	99.2	118	98.0	250	96.9	452	97.0	508	97.6	506	97.0	534	95.4	564	94.3	575	93.9	360	96.4	4061
CRO	95.6	500	95.5	538	97.1	728	97.5	806	97.3	862	95.9	786	97.5	766	96.9	842	97.3	842	97.6	956	96.5	622	96.9	8248
CEF[a]	100.0	8	100.0	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	100.0	10
IPM[a]	100.0	1	100.0	1	100.0	2	100.0	2	100.0	3	100.0	2	—	—	—	—	—	—	—	—	—	—	100.0	11
MEM	100.0	12	100.0	17	100.0	32	100.0	51	100.0	77	100.0	95	100.0	87	99.0	105	100.0	73	100.0	71	100.0	49	99.9	669
OXA[a]	84.2	19	88.0	25	81.3	16	87.5	8	66.7	3	40.0	5	60.0	5	100.0	2	0.0	1	0.0	1	100.0	1	79.1	86
PEN	87.8	539	90.8	590	89.9	713	87.7	1021	86.5	1140	85.5	1061	85.3	1017	85.3	1064	84.8	1078	84.8	1148	84.6	746	86.3	10117

n S, susceptible; *n*, number of unique isolates; AMX, amoxicillin; AMC, amoxicillin/clavulanate; AMP, ampicillin; SAM, ampicillin/sulbactam; CFZ, cefazolin; FEP, cefepime; CTX, cefotaxime; CRO, ceftriaxone; CEF, cefalotin; IPM, imipenem; MEM, meropenem; OXA, oxacillin; PEN, penicillin.

[a]β-Lactams with fewer than 10 isolates (*n*) in at least 1 year.

Penicillin G and ceftriaxone are primary treatment options for bacteraemia or infective endocarditis caused by VGS isolates that are susceptible to penicillin.[6] The aminopenicillins (e.g. ampicillin or amoxicillin) are also active against penicillin-susceptible VGS isolates and are often used to treat odontogenic infections. Vancomycin is also an option for patients with an immediate-type hypersensitivity reaction to penicillins or when the isolate is penicillin resistant. However, susceptibility to some antibiotics, such as penicillin, has recently been reported to be below 90% in VGS, which may have important clinical consequences.

Some previous studies have reported the susceptibility for clinical VGS isolates collected across a short period of time.[7–10] Very little data exists that evaluates the susceptibility trends in VGS over longer time periods. Here, we report antibiotic susceptibility patterns of clinically relevant antibiotics in VGS obtained from patients in Veterans Affairs (VA) Medical Centers between 2010 and 2020.

Methods

Antibiotic susceptibility data for VGS isolates from patients, and their demographic, medical and facility level covariates were obtained retrospectively from VA Medical Centers, as previously described.[11] *Streptococcus mitis*, *Streptococcus oralis* and non-speciated VGS isolates with susceptibility data collected between 2010 and 2020 at 122 VA Medical Centers across the United States were included. Susceptibility data originated from testing performed by each VA Medical Center and were pulled from the electronic medical records via the Corporate Data Warehouse. Isolates obtained from any culture site were utilized. The subset of isolates that were from blood cultures represented a likely group of the VGS isolates to be causing infection and were also analysed as a subgroup.

S. mitis and VGS that did not have their species identified (non-speciated) were evaluated for the primary analysis. Too few *S. oralis* isolates were identified so these data were excluded from the primary analysis and are instead reported in Table S1 (available as Supplementary data at *JAC-AMR* Online). Susceptibility patterns were obtained for 13 β-lactam antibiotics (amoxicillin, amoxicillin/clavulanate, ampicillin, ampicillin/sulbactam, cefazolin, cefepime, cefotaxime, ceftriaxone, cefalotin, imipenem, meropenem, oxacillin and penicillin) and 20 non-β-lactam antibiotics (azithromycin, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, daptomycin, erythromycin, gatifloxacin, gentamicin, levofloxacin, linezolid, minocycline, moxifloxacin, nitrofurantoin, quinupristin/dalfopristin, rifampicin, tetracycline, tigecycline, trimethoprim/sulfamethoxazole and vancomycin). Determination of susceptible, intermediate and resistant interpretations of the MIC data was based on the reporting from each institution and using CLSI breakpoints when available.[12]

Poisson regression was applied as a trend test to assess changes over time. Two-sided *P* values <0.05 were considered statistically significant. SAS version 9.4 (SAS Inc.; Cary, NC, USA) was used for data and statistical analysis. Analyses were performed for antibiotics with $n \geq 10$ isolates tested for each year from 2010 to 2020.

Results

There was a total of 14 981 unique VGS isolates included in this analysis. Non-speciated VGS were most common (79.8%) followed by *S. mitis* (19.5%) and *S. oralis* (0.7%). The number of isolates tested for each species against each antibiotic ranged from $n=0$ to 10 590 isolates/antibiotic since susceptibility testing was not performed for every antibiotic against each isolate (Table S1).

Table 2. Susceptibility rates for non-β-lactam antibiotics for non-speciated VGS isolates from all culture sites obtained from VA Hospitals in the United States, 2010–20

	2010		2011		2012		2013		2014		2015		2016		2017		2018		2019		2020		Total (2010–20)	
	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*
AZM	61.8	34	40.0	35	55.4	65	69.2	65	70.5	78	65.9	88	64.9	74	69.8	106	68.5	92	65.7	70	76.2	42	65.7	749
CHL	96.5	173	97.3	183	98.6	219	97.9	239	99.5	197	99.5	190	98.2	165	99.0	193	97.8	183	98.6	148	98.9	94	98.3	1984
CIP[a]	79.2	24	57.7	26	97.0	33	94.2	52	89.7	39	76.2	21	33.3	3	0.0	1	100.0	2	—	—	100.0	1	84.2	202
CLR[a]	—	—	—	—	—	—	—	—	25.0	4	60.0	25	33.3	3	—	—	—	—	—	—	—	—	53.1	32
CLI	90.5	462	87.0	486	83.1	604	84.4	646	80.5	722	76.8	630	81.1	647	81.9	669	76.1	674	77.8	725	78.6	487	81.3	6752
DAP[a]	100.0	5	93.3	15	100.0	8	100.0	9	100.0	18	100.0	57	100.0	56	100.0	41	100.0	49	100.0	39	100.0	23	99.7	320
ERY	65.9	583	63.4	558	66.5	722	63.2	834	59.6	832	59.1	738	60.7	715	61.9	751	59.2	736	60.1	725	61.7	470	61.8	7664
GAT[a]	92.3	13	100.0	9	100.0	19	93.3	15	100.0	19	88.2	17	81.0	21	85.7	28	90.0	20	85.7	14	75.0	4	90.5	179
GEN[a]	82.4	17	82.1	28	72.2	36	83.8	37	94.1	17	61.5	13	100.0	4	100.0	4	50.0	2	100.0	2	100.0	2	80.9	162
LVX	93.2	162	89.9	217	94.3	265	94.9	389	94.4	552	90.3	595	92.9	564	94.0	585	91.0	625	91.8	583	92.1	394	92.6	4931
LZD	100.0	99	100.0	132	98.7	151	99.4	165	100.0	194	98.9	279	99.7	292	100.0	295	100.0	346	99.7	313	100.0	191	99.7	2457
MIN[a]	—	—	100.0	5	100.0	3	—	—	—	—	100.0	1	—	—	—	—	—	—	—	—	—	—	100.0	9
MXF	91.7	12	91.7	36	93.8	48	96.2	52	93.8	16	96.5	57	91.3	69	98.9	88	92.8	181	94.5	253	97.8	136	94.8	948
NIT[a]	93.8	16	100.0	11	100.0	10	100.0	14	100.0	13	100.0	12	83.3	6	100.0	4	100.0	4	100.0	2	100.0	1	97.8	93
Q/D[a]	85.2	27	87.3	55	94.8	58	88.1	42	93.1	29	100.0	5	100.0	1	100.0	1	—	—	—	—	100.0	1	90.4	219
RIF[a]	96.9	32	96.8	31	97.4	38	100.0	35	100.0	30	100.0	10	100.0	2	100.0	7	100.0	3	100.0	2	100.0	2	98.4	192
TET	56.3	199	62.0	250	62.0	263	64.2	391	61.2	629	54.1	553	54.6	538	57.9	584	58.4	620	53.1	616	58.2	402	57.9	5045
TGC[a]	100.0	1	100.0	2	100.0	4	100.0	1	—	—	100.0	7	100.0	1	100.0	35	100.0	114	100.0	126	100.0	79	100.0	370
SXT[a]	55.8	43	46.7	30	40.0	35	68.0	25	90.9	22	83.3	30	82.8	29	78.9	19	93.3	15	57.1	7	100.0	4	67.6	259
VAN	99.7	735	99.8	804	99.5	990	99.7	1092	99.8	1105	99.2	1013	99.8	968	100.0	1005	99.9	1034	99.7	1109	100.0	735	99.7	10590

S, susceptible; *n*, number of unique isolates; AZM, azithromycin; CHL, chloramphenicol; CIP, ciprofloxacin; CLR, clarithromycin; CLI, clindamycin; DAP, daptomycin; ERY, erythromycin; GAT, gatifloxacin; GEN, gentamicin; LVX, levofloxacin; LZD, linezolid; MIN, minocycline; MXF, moxifloxacin; NIT, nitrofurantoin; Q/D, quinupristin/dalfopristin; RIF, rifampicin; TET, tetracycline; TGC, tigecycline; SXT, trimethoprim/sulfamethoxazole; VAN, vancomycin.

[a]Antibiotics with fewer than 10 isolates (*n*) in at least 1 year.

Table 3. β-Lactam susceptibility rates for *S. mitis* isolates from all culture sites obtained from VA Hospitals in the United States, 2010–20

	2010		2011		2012		2013		2014		2015		2016		2017		2018		2019		2020		Total (2010–20)	
	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*
AMX[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	100.0	4	87.5	8	81.6	38	84.6	13	83.3	60
AMC[a]	100.0	4	100.0	1	100.0	4	100.0	3	100.0	7	100.0	5	100.0	1	—	—	—	—	—	—	—	—	100.0	25
AMP	83.0	47	82.4	17	92.6	27	84.4	45	79.8	99	74.7	99	78.1	128	79.2	173	82.8	174	79.4	214	86.3	160	81.0	1183
SAM[a]	—	—	100.0	1	—	—	100.0	1	100.0	1	—	—	100.0	2	—	—	100.0	1	—	—	—	—	100.0	6
CFZ[a]	100.0	8	100.0	1	100.0	4	100.0	2	100.0	3	100.0	1	100.0	1	—	—	—	—	—	—	—	—	100.0	20
FEP	91.3	23	79.2	24	87.5	24	92.7	41	89.6	48	89.7	39	93.4	61	97.2	71	98.3	60	97.5	81	97.1	35	93.7	507
CTX	96.8	31	100.0	14	100.0	26	89.2	65	96.2	133	94.8	154	96.4	166	97.1	205	96.9	196	93.1	233	93.3	150	95.3	1373
CRO	96.7	61	93.2	74	95.1	82	94.2	156	96.1	180	94.3	176	96.5	198	96.9	259	96.9	259	97.1	314	95.8	215	96.0	1974
CEF[a]	—	—	100.0	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	100.0	2
IPM[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
MEM[a]	100.0	5	100.0	1	100.0	3	100.0	11	100.0	10	100.0	17	100.0	22	100.0	30	100.0	17	97.4	39	100.0	20	99.4	175
OXA[a]	75.0	4	50.0	2	100.0	3	—	—	—	—	—	—	—	—	66.7	3	—	—	—	—	—	—	75.0	12
PEN	77.4	93	77.8	81	84.5	110	77.4	195	71.1	242	69.0	242	66.5	266	68.3	315	69.0	316	68.9	344	71.3	230	71.0	2434

S, susceptible; *n*, number of unique isolates; AMX, amoxicillin; AMC, amoxicillin/clavulanate; AMP, ampicillin; SAM, ampicillin/sulbactam; CFZ, cefazolin; FEP, cefepime; CTX, cefotaxime; CRO, ceftriaxone; CEF, cefalotin; IPM, imipenem; MEM, meropenem; OXA, oxacillin; PEN, penicillin.
[a]β-Lactams with fewer than 10 isolates (*n*) in at least 1 year.

Of the VGS isolates included in this study, 32.4% were from blood, 27.6% were from urine, 0.7% were from lungs and the other 39.3% isolates originated from other sources.

The most common clinically tested antibiotics against VGS isolates were ceftriaxone, penicillin and vancomycin. Cumulative susceptibility rates for each species from all culture sites were >93% for every tested cephalosporin, carbapenem and β-lactam/β-lactamase inhibitor combination (Tables 1, 3 and S1). Among non-β-lactams, cumulative susceptibility rates were >94% for chloramphenicol, daptomycin, linezolid, moxifloxacin, nitrofurantoin, rifampicin, tigecycline and vancomycin (Tables 2, 4 and S1). Susceptibility rates varied between species more so for the other fluoroquinolones: ciprofloxacin (range: 84.2%–93.8%), gatifloxacin (81.0%–90.5%) and levofloxacin (91.2%–100.0%). Clindamycin had activity against 81.3%–84.5% of isolates. Susceptibility patterns were generally similar between isolates defined as *S. oralis* and *S. mitis* and those without a species identification (Table S1). However, penicillin susceptibility was lower for *S. mitis* (71.0%) than for *S. oralis* or non-speciated VGS (80.9%–86.3%) Azithromycin and erythromycin susceptibility rates were also lower in *S. mitis* isolates (>20% lower). There were too few *S. oralis* isolates to make comparisons for most antibiotics.

Susceptibility rates were generally similar between cultures obtained from all sites and the subset of cultures obtained from blood (Tables S2–S5), with a few notable exceptions. First, non-speciated VGS isolates from the blood had lower susceptibility to penicillin (80.1% versus 86.3%) and higher susceptibility to tetracycline (66.8% versus 57.9%) compared with isolates from all culture sources. Second, *S. mitis* isolates from blood had higher susceptibility rates to clindamycin (88.3% versus 83.8%).

There was a tendency toward decreased susceptibility for some β-lactams in non-speciated VGS isolates between 2010 and 2020 (Figure 1). Specifically, ampicillin, cefotaxime and penicillin susceptibility rates decreased by ∼3%–8%. Trend analysis revealed that the decrease was not statistically significant for ampicillin ($P=0.10$), cefotaxime ($P=0.41$) or penicillin ($P=0.084$) (Table 5). For the subset of non-speciated VGS isolates from the blood, a similar trend was noted for ampicillin ($P=0.13$) but not for cefotaxime or penicillin, which had relatively unchanged susceptibilities over time. Susceptibility rates among non-speciated VGS isolates also changed over time for some of the non-β-lactam antibiotics (Figure 1). For example, the percentage of VGS isolates susceptible to clindamycin decreased by 11.9% between 2010 and 2020, which was a significant decrease ($P=0.0033$) (Table 5); a similar trend was noted for clindamycin among only isolates from the blood ($P=0.056$). Tetracycline susceptibility trended toward a significant decrease ($P=0.099$), though susceptibility increased over time for isolates in the blood. Azithromycin had a 14.4% increase ($P=0.13$), and erythromycin had a 4.2% decrease ($P=0.067$) in susceptibility during this time frame. While 7664 isolates were tested against erythromycin, only 749 were evaluated for azithromycin and cumulative susceptibility rates were similar.

For *S. mitis*, susceptibility decreased between 2010 and 2020 by ∼5%–10% for penicillin, erythromycin and tetracycline (Figure 2). However, the decrease was only significant for erythromycin, which displayed a 0.965 change in susceptibility rate each year among isolates from all sources ($P=0.011$) and a 0.942 rate change among *S. mitis* in the blood ($P=0.010$) (Table 6). In general, a robust trends analysis for many antibiotics

Table 4. Susceptibility rates for non-β-lactam antibiotics for *S. mitis* isolates from all culture sites obtained from VA Hospitals in the United States, 2010–20

	2010		2011		2012		2013		2014		2015		2016		2017		2018		2019		2020		Total (2010–20)	
	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*	% S	*n*
AZM[a]	22.2	9	42.1	19	28.6	14	50.0	20	42.9	14	50.0	4	26.7	15	38.5	26	38.5	13	42.1	19	16.7	6	37.7	159
CHL	97.9	47	98.0	49	96.4	56	98.8	84	97.0	66	100.0	48	98.0	49	98.4	61	100.0	48	100.0	43	100.0	22	98.4	573
CIP[a]	100.0	2	—	—	100.0	2	100.0	4	75.0	4	100.0	4	—	—	—	—	—	—	—	—	—	—	93.8	16
CLR[a]	—	—	—	—	—	—	—	—	—	—	72.7	11	0.0	1	—	—	—	—	—	—	0.0	1	61.5	13
CLI	86.0	86	89.6	77	87.1	93	83.2	167	84.1	170	85.7	175	84.3	178	81.1	196	78.8	179	83.7	202	84.3	159	83.8	1682
DAP[a]	—	—	100.0	1	—	—	—	—	—	—	—	—	100.0	1	—	—	100.0	1	—	—	—	—	100.0	3
ERY	43.0	93	40.9	66	39.8	83	42.9	161	41.8	184	41.8	170	33.5	164	33.0	188	31.5	165	33.5	191	32.9	149	37.1	1614
GAT[a]	—	—	100.0	2	33.3	3	100.0	4	83.3	6	100.0	3	100.0	1	—	—	—	—	100.0	1	0.0	1	81.0	21
GEN[a]	50.0	2	—	—	50.0	2	75.0	4	—	—	100.0	1	—	—	—	—	100.0	1	100.0	1	—	—	72.7	11
LVX	84.8	33	90.5	21	92.0	25	88.9	72	87.7	122	90.5	147	89.0	155	92.4	170	93.1	188	93.1	203	93.4	166	91.2	1302
LZD	100.0	14	100.0	30	100.0	27	100.0	45	100.0	56	100.0	81	99.1	106	100.0	97	100.0	120	99.3	151	100.0	102	99.8	829
MIN[a]	—	—	—	—	0.0	1	—	—	—	—	—	—	—	—	—	—	—	0	100.0	1	—	—	50.0	2
MXF[a]	100.0	3	100.0	15	100.0	14	85.7	14	100.0	1	100.0	1	94.1	17	94.3	35	94.7	38	95.5	88	96.7	60	95.5	286
NIT[a]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	100.0	3	100.0	1	100.0	4	100.0	8
Q/D[a]	80.0	5	50.0	18	61.5	13	84.6	13	90.0	10	—	—	—	—	—	—	—	—	50.0	2	—	—	68.9	61
RIF[a]	100.0	5	100.0	2	100.0	1	100.0	2	—	—	100.0	1	—	—	—	—	—	—	100.0	1	100.0	1	100.0	13
TET	77.4	53	78.3	46	71.4	42	70.4	71	64.7	167	60.8	181	59.4	180	59.1	203	65.5	206	65.3	222	63.5	159	64.2	1530
TGC[a]	—	—	100.0	1	—	—	—	—	—	—	—	—	100.0	1	100.0	25	100.0	18	100.0	56	100.0	45	100.0	146
SXT[a]	75.0	4	100.0	4	80.0	5	83.3	6	88.9	9	100.0	6	100.0	1	100.0	3	—	—	83.3	6	—	—	88.6	44
VAN	99.1	107	99.0	101	99.2	118	100.0	231	99.6	263	100.0	276	99.6	276	99.7	339	100.0	355	100.0	391	100.0	271	99.8	2728

S, susceptible; *n*, number of unique isolates; AZM, azithromycin; CHL, chloramphenicol; CIP, ciprofloxacin; CLR, clarithromycin; CLI, clindamycin; DAP, daptomycin; ERY, erythromycin; GAT, gatifloxacin; GEN, gentamicin; LVX, levofloxacin; LZD, linezolid; MIN, minocycline; MXF, moxifloxacin; NIT, nitrofurantoin; Q/D, quinupristin/dalfopristin; RIF, rifampicin; TET, tetracycline; TGC, tigecycline; SXT, trimethoprim/sulfamethoxazole; VAN, vancomycin.

[a]Antibiotics with fewer than 10 isolates (*n*) in at least 1 year.

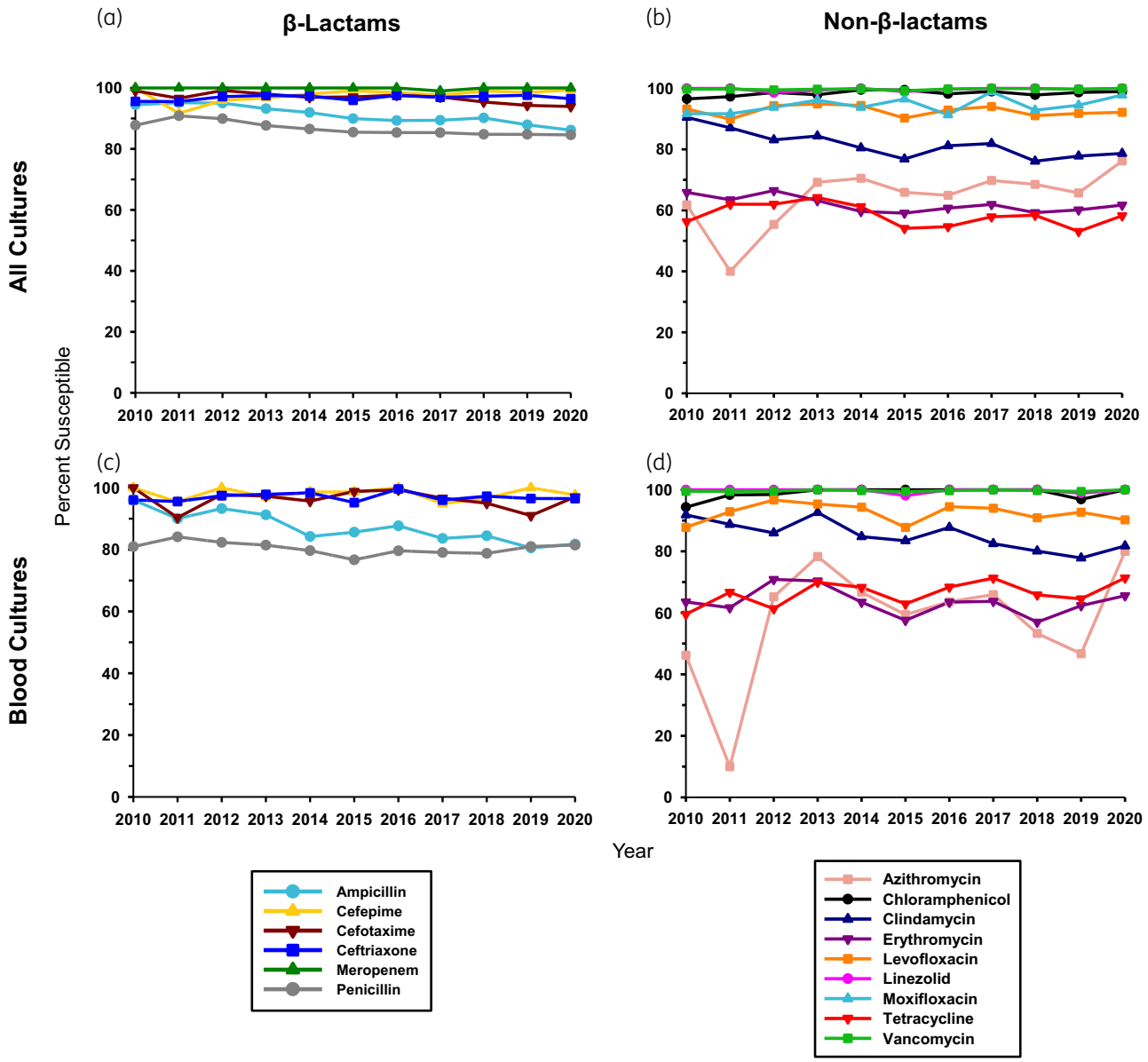

Figure 1. Changes in percentage susceptibility of non-speciated VGS isolates from all culture sites (a and b) and isolates from blood cultures (c and d) to β-lactams (a and c) and non-β-lactam antibiotics (b and d) between 2010 and 2020. Data are presented for antibiotics with $n \geq 10$ isolates for each year.

was not possible for *S. mitis* due to the smaller number of isolates tested.

Discussion

Antibiotic resistance is a global health threat and believed to contribute to 35 000 deaths every year in the United States.[13] VGS is an important cause of infective endocarditis, bacteraemia and odontogenic infections and can also cause pneumonia and meningitis.[14] Changes in resistance rates in VGS are important to consider since they may impact the efficacy of empirical treatment regimens. Further, susceptibility testing is not routinely performed for some infections that may be caused by VGS, such as odontogenic infections, which makes large-scale susceptibility patterns even more valuable for antibiotic selection. Thus, we assessed susceptibility patterns in VGS isolates from a large national database and evaluated susceptibility changes over time.

Previous studies have observed a relatively wide range of penicillin susceptibility rates for VGS. In a study that included 1152 VGS isolates collected between 1997 and 2000 from around the world, the penicillin susceptibility rate was 68.6%.[7] More recently, a study of 4164 *S. mitis* and *S. oralis* isolates collected in the Netherlands between 2013 and 2017 showed that 87.2%

Table 5. Trend analysis results for antibiotic susceptibility in non-speciated VGS isolates over time from 2010–20 using Poisson regression

	All culture sites		Blood cultures	
Antibiotic	rate change (95% CI)	*P* value	rate change (95% CI)	*P* value
Ampicillin	0.991 (0.980–1.002)	0.1008	0.985 (0.966–1.005)	0.1337
Azithromycin	1.025 (0.993–1.059)	0.1307	1.015 (0.956–1.078)	0.6334
Cefepime	1.003 (0.986–1.021)	0.7170	0.999 (0.967–1.032)	0.9389
Cefotaxime	0.995 (0.983–1.007)	0.4058	0.996 (0.974–1.019)	0.7287
Ceftriaxone	1.001 (0.994–1.008)	0.7920	1.000 (0.986–1.014)	0.9566
Chloramphenicol	1.001 (0.987–1.017)	0.8469	1.003 (0.976–1.030)	0.8326
Clindamycin	0.987 (0.978–0.996)	**0.0033**	0.986 (0.971–1000)	0.0564
Erythromycin	0.991 (0.982–1.001)	0.0674	0.992 (0.976–1.009)	0.3631
Levofloxacin	0.998 (0.988–1.009)	0.7424	0.998 (0.979–1.017)	0.7973
Linezolid	1.001 (0.986–1.015)	0.9430	1.000 (0.971–1.029)	0.9918
Meropenem	1.000 (0.969–1.031)	0.9870	—	—
Moxifloxacin	1.003 (0.978–1.028)	0.8319	—	—
Penicillin	0.994 (0.986–1.001)	0.0835	0.998 (0.985–1.010)	0.7198
Tetracycline	0.989 (0.976–1.002)	0.0994	1.007 (0.986–1.029)	0.4969
Vancomycin	1.000 (0.994–1.007)	0.9311	1.000 (0.989–1.012)	0.9723

Isolates were analysed from all culture sites together and for the subset of isolates from blood cultures. Antibiotics with $n \geq 10$ isolates tested for each year were included. Rate change indicates the change in susceptibility from year-to-year where values <1 mean that susceptibility is decreasing. Bold indicates significance at $P < 0.05$.

of isolates were susceptible to penicillin,[8] which was similar to the susceptibility rate in a smaller study of isolates from the United States and Europe.[10] Herein, the cumulative penicillin susceptibility rate when combining all species was 83.3% among 12 661 isolates (penicillin susceptibility for *S. mitis* = 71.0%, *S. oralis* = 80.9%, non-speciated VGS = 86.3%). Since most previous studies aggregated VGS isolates for analysis, differences in penicillin susceptibility rates between studies may in part be due to the differences in penicillin susceptibility among VGS species. Moet *et al.*[9] showed that *Streptococcus anginosus*, *Streptococcus constellatus*, *Streptococcus intermedius* and *Streptococcus mutans* had 88%–98% susceptibility to penicillin while *S. mitis*, *S. oralis*, *Streptococcus salivarius* and *Streptococcus sanguinis* only displayed 61%–75% susceptibility. Similar differences were also observed between these groups of VGS species for erythromycin susceptibility. The inter-species differences for penicillin and erythromycin are consistent with previous studies that tested antibiotics against VGS isolates from Taiwan and Korea.[15,16] In the present study, similar inter-species differences were observed. Penicillin and erythromycin susceptibilities were lower for *S. mitis* and *S. oralis* than non-speciated VGS. These data collectively support the potential value of identifying the VGS species in clinical microbiology laboratories to help optimize antibiotic selection.

Some antibiotics displayed a significant decrease in their susceptibility rate between 2010 and 2020 for VGS isolates including clindamycin (non-speciated VGS) and erythromycin (*S. mitis*) and a trend toward a significant decrease for penicillin (both). There have only been a few small studies that have also analysed antibiotic susceptibility trends over time for VGS. Prabhu *et al.*[17] previously noted decreases in susceptibility to each antibiotic they tested (clindamycin, erythromycin, penicillin, azithromycin, vancomycin and levofloxacin) for a small number of VGS isolates ($n = 50$) collected from patients with infective endocarditis about 20 years apart. The ∼10% decrease in clindamycin susceptibility we observed between 2010 and 2020 among VGS isolates is also concerning since this agent is sometimes prescribed empirically by dentists to treat odontogenic infections, which can be caused by VGS.[18] There are at least two potential explanations for the change in susceptibility over time: (i) the MICs of these drugs within VGS isolates are increasing (i.e. increased prevalence of resistance mechanisms); and (ii) the prevalence of more resistant VGS species is increasing among VGS isolates tested in VA Medical Centers. Resistance to clindamycin and erythromycin can both be caused by the same *erm*-encoded methylase, which modifies the ribosomal target binding site.[19] Non-susceptibility to penicillin in VGS is caused by mutations in the PBP binding site.[20] Though increases in the prevalence of more resistant VGS species cannot be ruled as a cause for the observed changes in non-speciated VGS over time, the decreases in susceptibility for *S. mitis* at least suggests that this is not the only explanation. Furthermore, there is little difference in the clindamycin susceptibility rates between VGS species in previous studies,[9] making it unlikely that changes in the distribution of species accounts for changes in clindamycin susceptibility rates over time we observed. Interestingly, among the subset of isolates from blood, a decrease in penicillin susceptibility was not observed for non-speciated VGS or *S. mitis* isolates. The cause of the difference between isolates from all culture sites (apparent decline in penicillin susceptibility over time) and those from blood (no apparent change) is not clear. Though, it is possible that there is a fitness cost that limits the ability for penicillin non-susceptible VGS isolates to cause infections in the blood.[21] Nonetheless, the declining susceptibility to these antibiotics within clinical isolates is

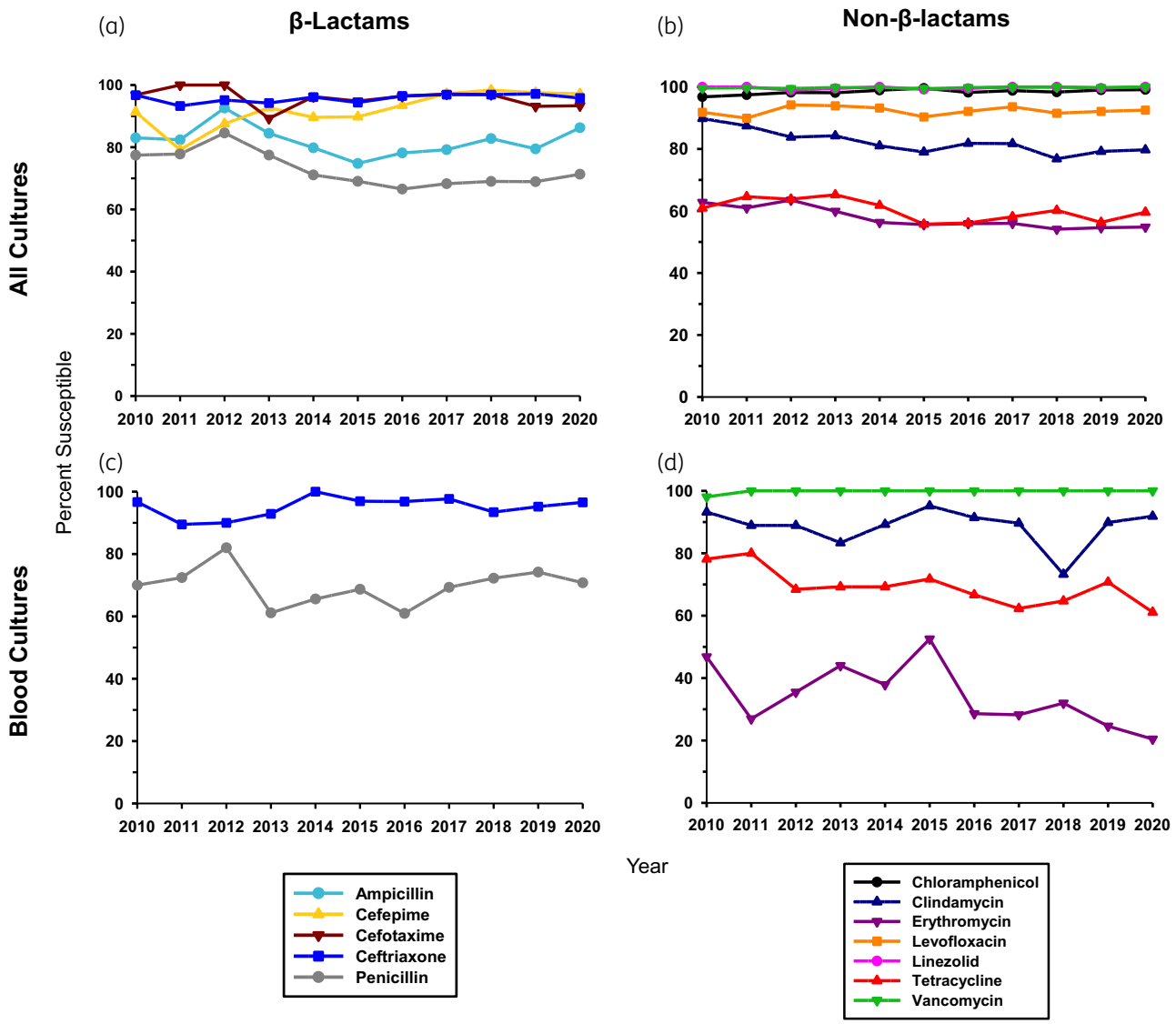

Figure 2. Changes in percentage susceptibility of *S. mitis* isolates from all culture sites (a and b) and isolates from blood cultures (c and d) to β-lactams (a and c) and non-β-lactam antibiotics (b and d) between 2010 and 2020. Data are presented for antibiotics with $n \geq 10$ isolates for each year.

worrisome and may impact the efficacy of empirical treatment of VGS infections.

There are several strengths to this project including the large isolate number, wide range of antibiotics included, and data separated by year to permit trend analyses. However, there are also some limitations. First, the study relies on susceptibility and resistance determinations by each clinical microbiology lab and numeric MICs were not available to verify accurate interpretation. However, we have previously found through manual chart review that there are very few susceptibility interpretation errors made using this approach.[22] Second, it is possible that some of the isolates without a species identification were *S. mitis* or *S. oralis* since each clinical microbiology laboratory may have had a different approach to identifying VGS isolates. Thus, differences in susceptibility between species in our study are somewhat difficult to interpret. However, these differences were drastic for a few antibiotics and warrant future study to determine if one species is more resistant than others. Third, it is possible that there was a selective testing bias since not every isolate was tested against every antibiotic. The large number of isolates included likely mitigates this concern for many of the antibiotics. Finally, it was not possible to differentiate isolates that caused infection from those that may have been colonizers. Thus, some of the changes in susceptibility over time may not apply to all isolates from all culture sites or types of infection.

In conclusion, we observed susceptibility rates of >90% for many clinically relevant antibiotics for VGS including ceftriaxone, meropenem, levofloxacin and vancomycin. Isolates identified as *S. mitis* had notably lower susceptibility rates to penicillins and macrolides. This difference in susceptibility suggests that it may

Table 6. Trend analysis results for antibiotic susceptibility in *Streptococcus mitis* isolates over time from 2010–20 using Poisson regression

	All cultures sites		Blood cultures	
Antibiotic	rate change (95% CI)	*P* value	rate change (95% CI)	*P* value
Ampicillin	1.002 (0.978–1.026)	0.8881	—	—
Cefepime	1.015 (0.983–1.048)	0.3644	—	—
Cefotaxime	0.998 (0.976–1.020)	0.8422	—	—
Ceftriaxone	1.003 (0.986–1.019)	0.7574	1.002 (0.974–1.031)	0.9092
Chloramphenicol	1.003 (0.974–1.032)	0.8570	—	—
Clindamycin	0.994 (0.976–1.012)	0.5239	0.995 (0.967–1.024)	0.7456
Erythromycin	0.965 (0.939–0.992)	**0.0112**	0.942 (0.899–0.986)	**0.0104**
Levofloxacin	1.008 (0.986–1.031)	0.4773	—	—
Linezolid	1.000 (0.974–1.026)	0.9816	—	—
Penicillin	0.985 (0.969–1.002)	0.0862	1.003 (0.975–1.033)	0.8190
Tetracycline	0.986 (0.963–1.009)	0.2413	0.981 (0.943–1.020)	0.3319
Vancomycin	1.001 (0.987–1.014)	0.9103	1.001 (0.978–1.024)	0.9465

Isolates were analysed from all culture sites together and for the subset of isolates from blood cultures. Antibiotics with $n \geq 10$ isolates tested for each year were included. Rate change indicates the change in susceptibility from year-to-year where values <1 mean that susceptibility is decreasing. Bold indicates significance at $P < 0.05$.

be beneficial to routinely define the species of VGS isolates in the clinical microbiology laboratory to better facilitate antibiotic selection. Of great concern, there was a significant trend toward decreased susceptibility to clindamycin for non-speciated VGS isolates and erythromycin for *S. mitis* isolates. There was also a trend toward decreased penicillin susceptibility (not statistically significant) among VGS isolates from all culture sites but not among the subset of isolates from the blood. Continuation of these trends could have important implications in the treatment of VGS infections and warrants continued monitoring. Empirical antibiotic selection must consider potential changes in VGS susceptibility patterns to maintain adequate clinical response rates.

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Transparency declarations

None to declare.

Disclaimer

The opinions expressed are those of the authors and do not represent those of the Department of Veterans Affairs or the US Government.

Supplementary data

Tables S1 to S5 are available as Supplementary data at *JAC-AMR* Online.

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