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 bacteremia 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.

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Penicillin G and ceftiraxone are primary treatment options for bacteremia 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 Strepptococcus mitis, Strepptococcus 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, ceftiraxone, 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 analyses. Analyses were performed for antibiotics with 10 isolates/antibiotic since susceptibility testing was not performed for every antibiotic against each isolate (Table S1).

### 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 1: β-lactam susceptibility rates for non-speciated VGS isolates from all culture sites obtained from VA Hospitals in the United States, 2010–2020

| Year | AMX% | AMC% | AMP% | SAM% | CFZ% | FEP% | CTX% | CRO% | IPM% | MEM% | OXA% |
|------|------|------|------|------|------|------|------|------|------|------|------|
| 2010 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2011 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2012 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2013 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2014 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2015 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2016 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2017 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2018 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2019 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |
| 2020 | 100% | 100% | 94.5% | 84.2% | 100% | 100% | 99.1% | 95.6% | 100% | 100% | 84.2% |

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, ceftiraxone, 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 analyses. Analyses were performed for antibiotics with 10 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, 2010–2020

| Year | AZM | CHL | CIP | CLR | CLI | DAP | ERY | GAT | GEN | LVX | LZD | MIN | MXF | Q/D | RIF | TET | TGC | SXT | VAN |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 2010 | 61.8 | 96.5 | 79.2 | 90.5 | 100.0 | 65.9 | 65.5 | 92.3 | 82.4 | 93.2 | 100.0 | 99.7 | 91.7 | 93.8 | 96.9 | 56.3 | 55.8 | 99.7 |
| 2011 | 40.0 | 173 | 57.7 | —— | 462 | 100.0 | 173 | 100.0 | 94.8 | 162 | 100.0 | 100.0 | 12 | 27 | 32 | 53.1 | 93.8 | 735 | 99.8 |
| 2012 | 35.4 | 219 | 54.0 | —— | 604 | 66.5 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2013 | 55.4 | 239 | 97.3 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2014 | 65.2 | 99.5 | 97.3 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2015 | 70.5 | 197 | 90.0 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2016 | 78.0 | 190 | 89.7 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2017 | 88.0 | 165 | 89.7 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2018 | 69.9 | 98.6 | 89.7 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2019 | 70.5 | 148 | 89.7 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |
| 2020 | 68.5 | 239 | 89.7 | —— | 622 | 65.2 | 183 | 100.0 | 94.8 | 265 | 100.0 | 100.0 | 36 | 55 | 38 | —— | 100.0 | 804 | 99.8 |

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; Q/D, quinupristin/dalfopristin; RIF, rifampicin; TET, tetracycline; TGC, tigecycline; SXT, trimethoprim/sulfamethoxazole; VAN, vancomycin.

*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, 2010–2020.

| Year | AMX | AMP | AMC | AMOX | AMPC | AMP-SAM | CFZ | FEP | CTX | CRO | CEF | IPM | MEM | OXA | PEN |
|------|-----|-----|-----|------|------|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 2010 | 88.0 | 81.6 | 91.7 | 88.7 | 97.2 | 87.8 | 98.4 | 98.0 | 97.8 | 86.3 | 98.2 | 97.7 | 97.7 | 98.4 | 97.7 |
| 2011 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2012 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2013 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2014 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2015 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2016 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2017 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2018 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2019 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |
| 2020 | 87.4 | 87.5 | 91.7 | 89.9 | 97.6 | 87.8 | 98.0 | 98.3 | 98.2 | 97.7 | 98.2 | 97.7 | 97.3 | 98.4 | 97.7 |

- **AMX**: amoxicillin
- **AMP**: ampicillin
- **AMC**: amoxicillin/clavulanate
- **AMOX**: amoxicillin/sulbactam
- **AMPC**: amoxicillin/penicillin
- **CFZ**: cefazolin
- **FEP**: cefepime
- **CTX**: cefotaxime
- **CRO**: ceftriaxone
- **CEF**: cefalotin
- **IPM**: imipenem
- **MEM**: meropenem
- **OXA**: oxacillin
- **PEN**: penicillin
- **%S**: percentage susceptible
- **%n**: percentage non-susceptible

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 commonly 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-specified 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-specified 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-specified 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-specified 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-specified 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 statistically 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, 2010–2020

|         | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | Total (2010–2020) |
|---------|------|------|------|------|------|------|------|------|------|------|------|-------------------|
| AZM     | 22.2 | 9.0  | 42.1 | 19.0 | 28.6 | 14.0 | 50.0 | 12.0 | 50.0 | 22.2 | 19.0 | 16.7 | 6.0  |
| CHL     | 97.9 | 47.0 | 98.0 | 49.0 | 96.4 | 56.0 | 98.8 | 84.0 | 97.0 | 66.0 | 100.0| 48.0  | 26.7 |
| CIP     | 100.0| 2.0  | 100.0| 2.0  | 100.0| 4.0  | 100.0| 4.0  | 100.0| 2.0  | 100.0| 2.0  |
| CLR     | 86.0 | 86.0 | 89.6 | 77.0 | 83.2 | 167.0| 84.1 | 170.0| 85.7 | 175.0| 84.3 | 178.0 |
| CLI     | 86.0 | 86.0 | 89.6 | 77.0 | 83.2 | 167.0| 84.1 | 170.0| 85.7 | 175.0| 84.3 | 178.0 |
| DAP     | 100.0| 1.0  | 120.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  |
| ERY     | 43.0 | 93.0 | 40.0 | 66.0 | 39.8 | 19.0 | 42.9 | 161.0| 41.8 | 184.0| 41.8 | 170.0 |
| GAT     | 100.0| 2.0  | 100.0| 2.0  | 100.0| 4.0  | 100.0| 4.0  | 100.0| 2.0  | 100.0| 2.0  |
| GEN     | 50.0 | 2.0  | 50.0 | 2.0  | 75.0 | 4.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  |
| LVX     | 84.8 | 33.0 | 90.5 | 21.0 | 92.0 | 25.0 | 88.9 | 72.0 | 87.7 | 122.0| 90.5 | 147.0 |
| LZD     | 100.0| 14.0 | 100.0| 30.0 | 100.0| 27.0 | 100.0| 45.0 | 100.0| 56.0 | 100.0| 81.0 |
| MIN     | 100.0| 0.0  | 0.0  | 0.0  | 1.0  | 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  |
| MXF     | 100.0| 3.0  | 100.0| 15.0 | 100.0| 14.0 | 100.0| 14.0 | 100.0| 1.0  | 100.0| 1.0  |
| NIT     | 100.0| 0.0  | 100.0| 0.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  |
| Q/D     | 80.0 | 5.0  | 50.0 | 18.0 | 61.5 | 13.0 | 84.6 | 13.0 | 90.0 | 10.0 | 100.0| 1.0  |
| RIF     | 100.0| 5.0  | 100.0| 2.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  |
| TET     | 77.4 | 53.0 | 78.3 | 46.0 | 71.4 | 42.0 | 70.4 | 71.0 | 64.7 | 167.0| 60.8 | 181.0 |
| TGC     | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  | 100.0| 1.0  |
| SXT     | 75.0 | 4.0  | 100.0| 4.0  | 80.0 | 10.0 | 83.3 | 5.0  | 88.9 | 9.0  | 100.0| 6.0  |
| VAN     | 99.1 | 107.0| 99.0 | 101.0| 99.2 | 118.0| 100.0| 231.0| 99.6 | 263.0| 100.0| 276.0 |

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.

aAntibiotics with fewer than 10 isolates (n) in at least 1 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.\(^1\)\(^3\) **VGS** is an important cause of infective endocarditis, bacteraemia and odontogenic infections and can also cause pneumonia and meningitis.\(^1\)\(^4\) 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%
of isolates were susceptible to penicillin, which was similar to the susceptibility rate in a smaller study of isolates from the United States and Europe. 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. 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. 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 *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. 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 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. 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. Non-susceptibility to penicillin in VGS is caused by mutations in the PBPD binding site. 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, 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. Nonetheless, the declining susceptibility to these antibiotics within clinical isolates is

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

| Antibiotic          | All culture sites | Blood cultures |
|---------------------|-------------------|----------------|
|                     | rate change (95% CI) | P value       | rate change (95% CI) | P value       |
| Amoxicillin         | 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        |
| Ceftiraxone         | 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 (0.971–1.000) | 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* ≥ 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.
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. 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
VGS susceptibility patterns from 2010 to 2020

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

| Antibiotic       | All cultures sites | Blood cultures |
|------------------|--------------------|---------------|
|                  | rate change (95% CI) | P value |
|                  | rate change (95% CI) | P value |
| Ampicillin       | 1.002 (0.978–1.026)  | 0.8881 |
|                 | 1.002 (0.974–1.011)  | 1.000 (0.974–1.031) |
|                 | 0.995 (0.967–1.024)  | 0.9092 |
| Cefepime         | 1.015 (0.983–1.048)  | 0.3644 |
|                 | 0.991 (0.966–1.010)  | 1.000 (0.978–1.028) |
|                 | 0.992 (0.969–1.015)  | 0.7456 |
| Ceftriaxone      | 0.998 (0.976–1.020)  | 0.8422 |
|                 | 0.998 (0.976–1.020)  | 0.8570 |
|                 | 0.993 (0.974–1.012)  | 1.019 (0.994–1.048) |
| Chloramphenicol  | 1.003 (0.986–1.019)  | 0.7574 |
|                 | 1.003 (0.974–1.032)  | 0.942 (0.899–0.986) |
|                 | 0.994 (0.976–1.012)  | 0.0104 |
| Clindamycin      | 0.965 (0.939–0.992)  | 0.0112 |
|                 | 0.965 (0.939–0.992)  | 0.9465 |
| Erythromycin     | 1.008 (0.986–1.031)  | 0.4773 |
|                 | 1.000 (0.974–1.026)  | 0.9816 |
| Linezolid        | 1.000 (0.974–1.026)  | 0.0862 |
|                 | 1.000 (0.974–1.026)  | 1.003 (0.975–1.033) |
| Penicillin       | 0.985 (0.969–1.002)  | 0.2413 |
|                 | 0.985 (0.969–1.002)  | 0.981 (0.943–1.020) |
| Tetracycline     | 0.986 (0.963–1.009)  | 0.9103 |
|                 | 0.986 (0.963–1.009)  | 1.001 (0.978–1.024) |

Isolates were analysed from all culture sites together and for the subset of isolates from blood cultures. Antibiotics with n ≥ 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
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Supplementary data
Tables S1 to S5 are available as Supplementary data at JAC-AMR Online.

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