Temporal and Geographic Variation in Antimicrobial Susceptibility and Resistance Patterns of Enterococci: Results From the SENTRY Antimicrobial Surveillance Program, 1997–2016

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Background. The SENTRY Antimicrobial Surveillance Program was established in 1997 and presently encompasses more than 750,000 bacterial isolates from over 400 medical centers worldwide. Among these pathogens, enterococci represents a prominent cause of bloodstream (BSIs), intra-abdominal (IAIs), skin and skin structure, and urinary tract infections (UTIs). In the present study, we reviewed geographic and temporal trends in Enterococcus species and resistant phenotypes identified throughout the SENTRY Program.

Methods. From 1997 to 2016, a total of 49,491 clinically significant enterococci isolates (15 species) were submitted from 298 medical centers representing the Asia-Pacific (APAC), European, Latin American (LATAM), and North American (NA) regions. Bacteria were identified by standard algorithms and matrix-assisted laser desorption ionization—time of flight mass spectrometry. Susceptibility (S) testing was performed by reference broth microdilution methods and interpreted using Clinical and Laboratory Standards Institute/US Food and Drug Administration and European Committee on Antimicrobial Susceptibility Testing criteria.

Results. The most common Enterococcus species in all 4 regions were Enterococcus faecalis (64.7%) and E. faecium (29.0%). Enterococci accounted for 10.7% of BSIs in NA and was most prominent as a cause of IAIs (24.0%) in APAC and of UTIs (19.8%) in LATAM. A steady decrease in the susceptibility to ampicillin and vancomycin was observed in all regions over the 20-year interval. Vancomycin-resistant enterococci (VRE) accounted for more than 8% of enterococcal isolates in all regions and was most common in NA (21.6%). Among the 7615 VRE isolates detected, 89.1% were the VanA phenotype (91.0% EFM) and 10.9% were VanB. Several newer antimicrobial agents demonstrated promising activity against VRE, including daptomycin (99.6%–100.0% S), linezolid (98.0%–99.6% S), oritavancin (92.2%–98.3% S), tedizolid (99.5%–100.0% S), and tigecycline (99.4%–100.0% S).

Conclusions. Enterococci remained a prominent gram-positive pathogen in the SENTRY Program from 1997 through 2016. The overall frequency of VRE was 15.4% and increased over time in all monitored regions. Newly released agents with novel mechanisms of action show promising activity against VRE.

Keywords. enterococci; SENTRY; surveillance; VRE.

Enterococcus species currently represent the second and third most frequently observed pathogens responsible for health care–associated infections (HAIs) in the United States and Europe (EUR), respectively [1, 2]. In a recent survey (2011–2014) conducted by the National Healthcare Safety Network (NHSN) at the US Centers for Disease Control and Prevention (CDC), enterococci ranked second among antimicrobial-resistant pathogens associated with HAIs: first among pathogens associated with central line–associated bloodstream infections (CLABSIs), second among causes of surgical site infections (SSIs), and third among catheter-associated urinary tract infections [2]. Over the past 3 decades, enterococci have emerged from being considered benign commensal bacteria of low virulence to medically important multidrug-resistant (MDR; resistant to 3 or more classes of agents) HAI pathogens that are considered a serious public health threat [3–5].

Enterococci are natural colonizers of the human and animal gastrointestinal tract and are notable for their ability to survive in harsh environments [3]. Most enterococci are intrinsically resistant to aminoglycosides and many β-lactam agents (cephalosporins), and some species, such as Enterococcus faecium, have acquired a variety of genetic determinants that confer resistance to several antimicrobial classes, including chloramphenicol, tetracyclines, macrolides, lincosamides, glycopeptides, fluoroquinolones, and rarely some of the newly introduced agents...
such as linezolid, daptomycin, and quinupristin-dalfopristin [3, 5–12].

Trends toward an increasing prevalence of MDR enterococci as HAI pathogens have been observed [2]. Data from the 2011–2014 NHSN survey revealed that 42.5% of CLABSIs and 19.1% of SSIs due to enterococci in US medical centers were vancomycin resistant (VRE) [2]. The occurrence and spread of VRE have been documented worldwide [3, 10]. In 2011–2012, the European CDC reported VRE prevalence ranging from 3.6% to 31% in several European countries [1]. VRE has been reported in South America, Asia, and Australia, emphasizing the global occurrence of VRE in the health care environment [3, 13–20].

The majority of enterococcal infections are caused by Enterococcus faecalis and E. faecium, and until a few decades ago, E. faecalis comprised 80%–90% of the isolates [21]. More recent reports have described the emergence and dissemination of E. faecium isolates that are resistant to vancomycin and aminoglycosides (high-level resistance [HLAR]), which precludes using this combination as a standard therapy [3, 9, 22].

The leading factors responsible for VRE include the increased use of vancomycin for treatment of infections caused by methicillin-resistant Staphylococcus spp. coupled with intra- and interhospital dissemination of resistant clones [20, 23, 24]. VRE infections occur most commonly among at-risk patients, such as those in intensive care units, on hemodialysis, in nursing homes, those who are immunocompromised, or those being treated with selected antimicrobial agents, such as broad-spectrum cephalosporins, and are typically preceded by gastrointestinal tract colonization [3, 25–28]. VRE infections are also associated with additional morbidity, mortality, and treatment expense, especially for patients with confounding risk factors due to the reduced number of therapeutic options and potentially greater pathogenicity of these strains acquiring virulence genes [3, 5, 8, 9, 13, 20, 28–30]. VRE infections in hospitals are often clonal, with the epidemic–virulent clonal complex (CC)–17 lineage of E. faecium disseminated worldwide [3, 20, 22, 24, 31].

The epidemiology of VRE and other forms of enterococcal infection has been described in numerous single-center, sentinel, and population-based surveys conducted throughout the world [2, 5, 10, 13–19, 22, 24, 31, 32]. However, the dynamic nature of VRE trends in the United States and elsewhere suggests that this issue still merits considerable monitoring and surveillance attention [3, 5, 10, 24, 33].

The SENTRY Antimicrobial Surveillance Program is a global program that has been conducted for 20 years (1997–2016) and collects consecutive invasive and noninvasive Enterococcus spp. isolates from hospitals located in North America (NA), EUR, Latin America (LATAM), and the Asia-Pacific region (APAC) each calendar year. Enterococcus spp. isolates are evaluated for susceptibility against various antimicrobial agents used clinically to treat and prevent VRE [10, 24, 33–36]. Applying modern methods for species identification, antimicrobial susceptibility testing, and characterizing antibacterial resistance mechanisms provides a level of standardization and clarity that makes these observations very useful in the ongoing fight against antimicrobial resistance [3, 10, 24, 34, 35, 37].

Previous SENTRY Program publications from 1997 to the present have reported broad geographic trends in the isolation of various Enterococcus species from clinical specimens and the accompanying rates of antimicrobial resistance in the United States and globally [10, 24, 33, 35–42]. The present summary focuses on the geographic and temporal variations in the frequency of the Enterococcus species causing VRE and the associated antimicrobial resistance profiles using the extensive SENTRY Program database from 1997 to 2016. Specifically, this includes results for 49,491 isolates of Enterococcus species from 298 medical centers in 43 nations worldwide. This report discusses the occurrence of enterococcal infections by species and site of infection as well as the occurrence of VRE isolates and their resistance characterizations. Trends in susceptibility to a variety of established and newly introduced antimicrobials in each geographic region are also reported.

METHODS

Study Design

The SENTRY Program was initiated in early 1997 to investigate longitudinal trends in antimicrobial resistance and the frequency of pathogen occurrence. Five major objectives address the most common types of infection in a prevalence-style format: Objective A, bloodstream infections (BSIs); Objective B, community-acquired respiratory tract infections caused by Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, and Moraxella catarrhalis; Objective C, pneumonias in hospitalized patients (PIHP); Objective D, skin and skin structure or wound infections (SSSIs); and Objective E, urinary tract infections (UTIs). In addition, intra-abdominal infections (IAIs) were monitored from 2005 through 2016. Consecutive isolates (1 per patient infection episode) were forwarded to the regional monitoring sites for reference quantitative antimicrobial susceptibility testing and confirmation of organism identification. More than 750,000 isolates, including 49,491 enterococci, have been processed from 1997 through 2016 (Table 1).

Participants and Monitors

Three reference laboratories acted as monitoring sites during the 1997–1999 interval: the University of Iowa College of Medicine, Iowa City, Iowa (NA and LATAM for 1997–1999 and EUR for 1999); Utrecht University, Utrecht, Netherlands (EUR for 1997–1998); and the Women’s and Children’s Hospital, Adelaide, Australia (APAC for 1998–1999). Beginning in 2000, all isolates were referred to the central monitoring laboratory, JMI Laboratories (North Liberty, IA).
Participating sites varied in number by region: 162 sites (25,206 isolates) in the NA region; 18 sites (4,755 isolates) in the LATAM region; 65 sites (16,054 isolates in Europe, Israel, and Turkey) in the EUR region; and 53 sites (3,476 isolates) in the APAC region.

Organisms

Participating institutions identified isolates using methods routinely employed at the submitting laboratory, which include the use of Vitek, MicroScan, API, and AuxaColor systems supplemented with classical methods for bacterial identification. Isolates were submitted to the monitoring laboratory that confirmed identification by morphological, biochemical, and molecular methods. From 2012 to 2016, isolate identity was confirmed by matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker, Billerica, MA). Isolates that could not be identified by either phenotypic or proteomic methods were identified using sequence-based methods [10, 24, 33, 35, 37, 41].

Antimicrobial Agents

Representatives from all clinically important antimicrobial classes have been tested (ampicillin, penicillin, erythromycin, vancomycin, teicoplanin, chloramphenicol, doxycycline, gentamicin, streptomycin, ciprofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole [TMP-SMZ]), as well as newer compounds such as linezolid, quinupristin-dalfopristin, daptomycin, tedizolid, telavancin, dalbavancin, oritavancin, and tigecycline. Antimicrobials were obtained from their US manufacturer or representative.

Antimicrobial Susceptibility Testing

Isolates were susceptibility tested by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (CLSI) M07 document [43] and using reference 96-well panels manufactured by JMI Laboratories or acquired from Thermo Fisher (Cleveland, OH). Quality assurance was performed by concurrently testing CLSI-recommended quality control (QC) reference strains (Staphylococcus aureus ATCC 29213, E. faecalis ATCC 29212, and S. pneumoniae ATCC 49619). All QC results were within published acceptable ranges. Clinical breakpoints approved by the US Food and Drug Administration, CLSI [44], and/or the European Committee on Antimicrobial Susceptibility Testing [45] were applied for all tested agents. The vancomycin-resistant phenotypes (VanA and VanB) were defined as follows: VanA, resistant to vancomycin (minimum inhibitory concentration [MIC], >4 mg/L) and teicoplanin (MIC, >8 mg/L); VanB, resistant to vancomycin (MIC, >4 mg/L) but susceptible (MIC, ≤8 mg/L) to teicoplanin [44].

RESULTS

Nationwide surveillance programs, such as the SCOPE Program [46, 47], have provided data on nosocomial enterococcal BSIs, and the NHSN system [2, 48] also provides national data on various types of nosocomial infections due to enterococci. The SENTRY Program has documented occurrence rates for 49,491 enterococci isolates by site of infection (BSI, PIHP, SSSI, IAI, and UTI) and is the only surveillance system that analyzes data on a broad geographic scale that includes NA, EUR, LATAM, and the APAC region. During the study period (1997–2016), a total of 765,388 strains were processed by SENTRY Program participants (373,452 from NA, 236,911 from EUR, 77,314 from LATAM, and 77,711 from the APAC region), 6.5% of which were Enterococcus spp. (Table 1).

Table 1 shows the occurrence rates of enterococcal infections by site of infection within each geographic region. Enterococci accounted for 10.7% of BSI isolates in NA. The lowest rates of enterococcal infections among BSIs occurred in LATAM and APAC (5.0 and 5.1%, respectively). The highest detected rate of enterococcal UTIs was in LATAM (19.8%), followed by APAC (17.7%) and EUR (16.7%). The highest rates of IAI due to enterococci were observed in the APAC (24.0%) and LATAM (23.5%) regions.

The frequencies of reported Enterococcus species isolates by geographic region are listed in Table 2. Of the 15 species identified in the survey, E. faecalis was the most prevalent, ranging from 62.8% of enterococci isolated in EUR to 74.1% in LATAM. E. faecium, the species in which vancomycin resistance is most prevalent, was the second most commonly identified species in all geographic regions. The proportion of E. casseliflavus and E. gallinarum isolates (species intrinsically less susceptible to vancomycin) continued to be low across all geographic regions.
(range, 0.4%–1.4%). Identification to the species level was not performed for 0.5%–4.6% of the isolates reported.

The frequency of the VanA (resistant to vancomycin and teicoplanin) [44] and VanB (resistant to vancomycin but susceptible to teicoplanin) [44] phenotypes in each region is shown in Table 3. Among 49,491 isolates of enterococci, 13.7% exhibited a VanA phenotype (range, 6.7% [APAC] to 20.0% [NA]) and 1.7% showed a VanB phenotype (range, 0.9% [LATAM] to 2.6% [APAC]). There were 6788 VanA isolates (91.0% E. faecium), 827 VanB isolates (75.3% E. faecium), and 702 VanC (E. gallinarum and E. casseliflavus) isolates (Table 2). Whereas the frequency of VanA E. faecium varied considerably among the different regions (64.7% in NA to 19.0% in EUR), the rate of VanB E. faecium was consistently low (range, 3.6% [NA] to 7.5% [LATAM]) across all 4 regions (Table 3). Only 2.5% of E. faecalis isolates were resistant to vancomycin (1.9% VanA and 0.6% VanB), with little variation among the regions (Table 3). High-level resistance to streptomycin (HLR-strep; MIC, >1024 mg/L) was detected in 40.7% of E. faecium (19.4% [APAC], 19.5% [NA], 26.9% [LATAM], and 61.6% [EUR]) and 23.0% of E. faecalis (12.5% [APAC], 18.5% [NA], 27.8% [LATAM], and 28.1% [EUR]; data not shown) isolates. Resistance to ampicillin was 89.8% among E. faecium (81.6% [LATAM], 89.6% [NA], 90.8% [EUR], and 91.6% [APAC]; data not shown) and 0.4% among E. faecalis (0.1% [APAC], 0.3% [NA], 0.4% [EUR], and 0.7% [LATAM]; data not shown) isolates.

Antimicrobial susceptibility trends of the enterococcal strains tested are shown in Table 4. A decline in the susceptibility to ampicillin and vancomycin was seen over time in all geographic regions. Although neither doxycycline (range, 23.8%–55.2% susceptible) nor tetracycline (range, 24.9%–43.9% susceptible) was very active, this level of activity was maintained in all regions except NA, where susceptibility declined. Linezolid, an oxazolidinone, maintained a high level

![Table 2](https://example.com/table2.png)

| Enterococcus Species | North America (n = 29,206) | Europe (n = 16,054) | Latin America (n = 47,755) | Asia-Pacific (n = 34,78) | Total Number of Isolates |
|----------------------|-----------------------------|---------------------|-----------------------------|--------------------------|-------------------------|
| E. avium             | 0.8                         | 0.8                 | 1.8                         | 1.2                      | 447                     |
| E. casseliflavus      | 0.5                         | 0.5                 | 0.4                         | 1.0                      | 256                     |
| E. cecorum           | 0.0                         | <0.1                | 0.0                         | 0.0                      | 1                       |
| E. devriesei         | 0.0                         | 0.0                 | <0.1                        | 0.0                      | 1                       |
| E. durans            | 0.2                         | 0.5                 | 0.3                         | 0.2                      | 158                     |
| E. faecalis          | 64.2                        | 62.8                | 74.1                        | 64.0                     | 32,015                  |
| E. faecium           | 28.4                        | 32.6                | 18.4                        | 31.3                     | 14,360                  |
| E. gallinarum        | 0.8                         | 0.0                 | 1.4                         | 0.8                      | 446                     |
| E. gallinarum        | <0.1                        | 0.0                 | 0.0                         | 0.0                      | 1                       |
| E. hirae             | 0.1                         | 0.2                 | 0.3                         | 0.3                      | 89                      |
| E. italicus          | 0.0                         | <0.1                | 0.0                         | 0.0                      | 1                       |
| E. malodoratus       | 0.0                         | 0.0                 | <0.1                        | 0.0                      | 1                       |
| E. munditii          | <0.1                        | 0.0                 | <0.1                        | <0.1                     | 3                       |
| E. raffinosus        | 0.3                         | 0.0                 | <0.1                        | 0.7                      | 137                     |
| E. thailandicus      | <0.1                        | <0.1                | 0.0                         | 0.0                      | 2                       |
| Undetermined         | 4.6                         | 1.6                 | 3.2                         | 0.5                      | 1573                    |

![Table 3](https://example.com/table3.png)

| Organism/Organism Group | Asia-Pacific | Europe | Latin America | North America | Total |
|-------------------------|--------------|--------|---------------|---------------|-------|
| Enterococcus spp., No. (%) | 3476         | 16,054 | 4755          | 25,206        | 49,491 |
| Vancomycin-susceptible (≤4 mg/L) | 3135 (90.2) | 14,626 (91.1) | 4249 (89.4) | 19,544 (77.5) | 41,554 (84.0) |
| Vancomycin-resistant (VanA) | 232 (6.7)   | 1095 (6.8)  | 426 (9.0)    | 5035 (20.0)   | 6788 (13.7)  |
| Vancomycin-resistant (VanB) | 89 (2.6)    | 279 (1.7)   | 44 (0.9)     | 415 (1.6)     | 827 (1.7)    |
| Enterococcus faecium, No. (%) | 1089        | 5229    | 876           | 7166          | 14,360 |
| Vancomycin-susceptible (≤4 mg/L) | 780 (71.8)  | 3990 (76.3) | 517 (59.1) | 2268 (31.6)  | 7555 (52.6) |
| Vancomycin-resistant (VanA) | 227 (20.8)  | 992 (19.0)  | 323 (36.8)   | 4637 (64.7)   | 6179 (43.0)  |
| Vancomycin-resistant (VanB) | 82 (7.5)    | 246 (4.7)   | 36 (4.1)     | 259 (3.6)     | 623 (4.3)    |
| Enterococcus faecalis, No. (%) | 2225        | 10,078  | 3524          | 16,188        | 32,015 |
| Vancomycin-susceptible (≤4 mg/L) | 2213 (99.5) | 9942 (98.6) | 3413 (96.8) | 15,631 (96.6) | 31,199 (97.5) |
| Vancomycin-resistant (VanA) | 5 (0.2)     | 103 (1.0)   | 103 (0.0)    | 398 (2.5)     | 609 (1.9)    |
| Vancomycin-resistant (VanB) | 7 (0.3)     | 33 (0.3)    | 8 (0.2)      | 156 (1.0)     | 204 (0.6)    |
Table 4. Trends in Antimicrobial Susceptibility of All Tested Enterococci in Each Monitored Region for 1997–2016: SENTRY Program

| Region | Time Period | No. of Isolates | AMP<sup>a</sup> | CHL<sup>b</sup> | TET<sup>c</sup> | LZD | VAN <sup>d</sup> |
|--------|-------------|----------------|----------------|----------------|----------------|-----|---------------|
| NA     | 1997–2000   | 4195           | 79.2           | 82.3           | 37.1           | 96.6| 87.6          |
| NA     | 2001–2004   | 3685           | 75.7           | 88.2           | 38.2           | 99.5| 82.7          |
| NA     | 2005–2008   | 6509           | 68.2           | 89.7           | 37.8           | 99.2| 72.5          |
| NA     | 2009–2012   | 6130           | 69.6           | NT             | 24.6           | 99.4| 71.8          |
| NA     | 2013–2016   | 4867           | 76.9           | NT             | 24.9           | 99.6| 79.0          |
| EUR    | 1997–2000   | 1593           | 83.8           | 67.9           | 33.8           | 98.8| 96.6          |
| EUR    | 2001–2004   | 2196           | 78.7           | 74.1           | 40.1           | 99.9| 96.1          |
| EUR    | 2005–2008   | 4759           | 67.4           | 74.5           | 43.9           | 99.8| 90.6          |
| EUR    | 2009–2012   | 4144           | 64.8           | NT             | 38.2           | 99.7| 87.7          |
| EUR    | 2013–2016   | 3362           | 64.7           | NT             | 33.1           | 99.7| 90.1          |
| LATAM  | 1997–2000   | 491            | 95.5           | 69.0           | 34.2           | 95.7| 98.4          |
| LATAM  | 2001–2004   | 560            | 86.2           | 72.3           | 31.1           | 100.0| 94.5         |
| LATAM  | 2005–2008   | 1825           | 83.9           | 73.1           | 40.1           | 99.8| 88.7          |
| LATAM  | 2009–2012   | 1326           | 80.2           | NT             | 41.6           | 99.9| 87.3          |
| LATAM  | 2013–2016   | 553            | 78.1           | NT             | 43.8           | 99.6| 83.5          |
| APAC   | 1997–2000   | 528            | 83.0           | 75.2           | 33.5           | 97.0| 99.4          |
| APAC   | 2001–2004   | 590            | 73.1           | 75.6           | 36.4           | 100| 96.3          |
| APAC   | 2005–2008   | 952            | 66.4           | NT             | 37.2           | 99.6| 86.2          |
| APAC   | 2009–2012   | 988            | 67.9           | NT             | 33.4           | 99.5| 87.0          |
| APAC   | 2013–2016   | 4128           | 65.8           | NT             | 33.7           | 99.5| 86.4          |

Abbreviations: AMP, ampicillin; APAC, Asia-Pacific region; CHL, chloramphenicol; EUR, Europe; LATAM, Latin America; LZD, linezolid; NA, North America; NT, not tested; TET, tetracycline; VAN, vancomycin.

<sup>a</sup>Criteria as published by Clinical and Laboratory Standards Institute 2018 [44].

<sup>b</sup>The results of ampicillin susceptibility tests may be used to predict susceptibility to amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam among non-β-lactamase-producing enterococci and imipenem for E. faecalis [44].

<sup>c</sup>Chloramphenicol was tested against isolates collected during 1997–2005.

<sup>d</sup>Organisms that are susceptible to tetracycline are also considered susceptible to doxycycline and minocycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline, minocycline, or both [44].

of activity (>95.0%) in all regions over the monitored 20-year period.

Although the frequency of infections due to VRE has been shown to increase in many areas of the world, resistance may vary within a given nation or region, supporting the need for ongoing surveillance and applying strict infection prevention practices [3, 10, 33]. Recent data from Europe found that although the rate of VRE infections has increased, the prevalence may vary as much as 10-fold across different countries [1, 49]. At the outset of the SENTRY Program in 1997–1999, considerable variation was exhibited in the frequency of VRE infections among geographic regions within the United States, with higher numbers of infections in the Northeast and North Central states compared with the Western and Southern states [33]. These differences have been muted over time; however, VRE remains most common in the Northeast (29.2% of all enterococcal infections), compared with 22% in the Midwest and South and 18.4% in the West (data not shown). Given the predominance of vancomycin-resistant E. faecium in the United States and clonal spread due to CC-17 causing inter- and intrahospital transmission of a hospital-adapted pathogen, it is not surprising that less variability is found currently in US VRE rates [3, 10, 20, 24].

An important aspect of any antimicrobial surveillance program is longitudinality [50–52]. By conducting surveillance of specific pathogens across many years, one can assess the emergence of specific strains or species and discover changes in the antimicrobial susceptibility profiles of the organisms [10, 20, 24, 50, 51]. Furthermore, when longitudinal surveillance encompasses a broad geographic distribution, one may eventually develop a useful picture of regional, national, or even global trends or shifts in species distribution and antimicrobial resistance [10, 20, 50]. Thus, over the 20-year duration of the SENTRY Program, it is clear that the frequency of VRE (VanA and VanB only) as a cause of enterococcal infection has increased incrementally in all 4 of the monitored global regions (Figure 1). In the early years of the SENTRY Program (1997–2000), VRE was relatively uncommon (0.0%–3.0%) in all monitored regions except for NA (10.3%); however, the frequency of VRE increased in all regions through 2012. The decline in VRE in recent years (2013–2016) in EUR and NA (Figure 1) is likely due to regional and national emphasis on the prudent use of vancomycin and applying infection prevention (IP) efforts directed at controlling methicillin-resistant S. aureus and VRE [10, 53]. The global spread of the hospital-derived CC-17 VRE, coupled with less intensive IP efforts, continues to account for
the progressive increases in VRE in the APAC and LATAM regions [10, 20, 24]. Clearly, VRE has become a global threat to the care of hospitalized individuals and must be addressed by enhanced antimicrobial stewardship and IP efforts. Also, the prudent application of novel and newer agents with potent activity against these MDR pathogens appears to be more necessary [3, 9, 10, 12, 20, 22, 54].

As resistance to vancomycin is usually accompanied by multiple resistance to other antimicrobial agents such as macrolides, tetracyclines, and fluoroquinolones, the activity of alternative therapeutic agents for VRE infections was evaluated. Table 5 lists, by region, the MIC\textsubscript{50} and MIC\textsubscript{90} values and percentage of isolates susceptible for 9 antimicrobial agents tested against VRE (VanA and VanB) in the SENTRY Program. Notably, most older agents (ampicillin, doxycycline, piperacillin-tazobactam) were largely inactive and contribute to the MDR nature of \textit{E. faecium} and \textit{E. faecalis} worldwide.

The emergence of VRE has prompted the clinical development of several novel and modified antimicrobial compounds with potent activity against most VRE strains, including the oxazolidinones (linezolid and tedizolid), the lipopeptides or lipoglycopeptides (oritavancin, dalbavancin, and telavancin), and a glycyclcline (tigecycline) [6, 9, 10, 22]. In contrast to the older agents (ampicillin and tetracycline) shown in Table 5, linezolid, tedizolid, daptomycin, oritavancin, and tigecycline were all highly active (92.2\%–100.0\% susceptible) against the VRE from the SENTRY Program and, in most cases, were more active than quinupristin-dalfopristin, especially those from EUR and LATAM (Table 5). Among these agents, daptomycin, linezolid, oritavancin, quinupristin-dalfopristin, and tedizolid are indicated for treatment of infections due to VRE, whereas telavancin and tigecycline are not approved for the treatment of VRE [6]. In contrast to oritavancin, neither dalbavancin (4.2\% susceptible at the CLSI \textit{E. faecalis} vancomycin-susceptible breakpoint of ≤0.25 mg/L) nor telavancin (1.8\% susceptible...
Potency and Spectrum of 9 Selected Antimicrobial Agents Tested Against 7615 Vancomycin-Resistant (VanA and VanB Phenotypes) Enterococcal Isolates in the SENTRY Program, 1997–2016

| Antimicrobial Agent | NA (n = 5450) | EUR (n = 1374) | LATAM (n = 470) | APAC (n = 321) |
|---------------------|---------------|----------------|-----------------|---------------|
| Ampicillin<sup>a</sup> | >8/≥8 (10.5) | >8/≥8 (10.0) | >8/≥8 (22.8) | >8/≥8 (3.4) |
| Tetracycline<sup>b</sup> | >8/≥8 (35.6) | ≤4/≥8 (57.5) | ≤4/≥8 (64.7) | ≤4/≥8 (62.3) |
| Tigecycline | ≤0.12/≤0.12 (99.2) | ≤0.12/≤0.12 (99.5) | ≤0.12/≤0.12 (99.3) | 0.12/0.25 (99.4) |
| Daptomycin | 2/2 (99.6) | 2/2 (100.0) | 1/2 (100.0) | 2/4 (99.7) |
| Oritavancin<sup>c</sup> | 0.03/0.12 (92.3) | 0.015/0.06 (95.7) | 0.03/0.12 (92.2) | ≤0.008/0.06 (98.3) |
| Linezolid | 1/2 (98.0) | 1/2 (99.2) | 1/2 (99.6) | 1/2 (99.4) |
| Tedizolid<sup>d</sup> | 0.12/0.25 (99.5) | 0.12/0.25 (99.5) | 0.12/0.25 (100.0) | 0.12/0.25 (100.0) |
| Quinupristin-dalfopristin<sup>e</sup> | ≤0.5/≥2 (95.9) | 1/≥2 (83.5) | 1/≥2 (84.9) | 1/2 (92.4) |

Abbreviations: APAC, Asia-Pacific region; EUR, Europe; LATAM, Latin America; MIC, minimum inhibitory concentration; NA, North America.

<sup>a</sup>Critera as published by Clinical and Laboratory Standards Institute 2018 [44] and European Committee on Antimicrobial Susceptibility Testing 2018 (tigecycline only) [45].

<sup>b</sup>The results of ampicillin susceptibility tests may be used to predict susceptibility to amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam among non-β-lactamase-producing enterococci and imipenem for *E. faecalis* [44].

<sup>c</sup>Organisms that are susceptible to tetracycline are also considered susceptible to doxycycline and minocycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline, minocycline, or both [44].

<sup>d</sup>Susceptible breakpoint (MIC, ≤0.12 mg/L) for vancomycin-susceptible *E. faecalis* was applied to all vancomycin-resistant enterococci [44]. Enterococci that are susceptible to oritavancin (VanA) may be resistant to dalbavancin and/or telavancin.

<sup>e</sup>Susceptible breakpoint (MIC, ≤0.5 mg/L) for *E. faecalis* was applied to all vancomycin-resistant enterococci [44].

<sup>f</sup>Data for vancomycin-resistant *E. faecium* only.

at the CLSI *E. faecalis* vancomycin-susceptible breakpoint of ≤0.25 mg/L were active against VanA-VRE (data not shown). Dalbavancin (81.8% susceptible at the CLSI *E. faecalis* vancomycin-susceptible breakpoint of ≤0.25 mg/L) and telavancin (79.4% susceptible at the CLSI *E. faecalis* vancomycin-susceptible breakpoint of ≤0.25 mg/L) showed moderate activity against VanB-VRE (data not shown).

Enterococcal resistance has been described for quinupristin-dalfopristin and linezolid and more recently for daptomycin and tigecycline [6, 9, 22, 55–57]. In the context of the SENTRY Program, despite observing a low rate of linezolid resistance (1.6% of VRE), characterization of linezolid-resistant *E. faecalis* and *E. faecium* isolates revealed that alterations in 23S rRNA (G2576T mutations) were the dominant oxazolidinone resistance mechanism in *E. faecium*, whereas the plasmid-borne resistance gene optrA became more prevalent in *E. faecalis* [58]. Thus, data from the SENTRY Program continue to document the global dissemination of optrA-carrying *E. faecalis* isolates recovered from patients in countries beyond the APAC region, including China, Ireland, Sweden, and the United States [58]. As such, monitoring the emergence and spread of this resistance determinant at local and regional levels is important, especially due to the potential for *E. faecalis* bacteria to serve as a reservoir for spreading optrA to MDR pathogens (ie, *E. faecium*).

**DISCUSSION**

The SENTRY Antimicrobial Surveillance Program was designed to track antimicrobial resistance trends and the spectrum of microbial pathogens causing human infection on a global scale. The SENTRY Program has unique features that distinguish it from other excellent surveillance projects, such as the SCOPE Program [46, 47], the NHSN [2, 48], the European Antimicrobial Resistance Surveillance Network (EARS-Net) [49], and population-based surveillance programs conducted in the United States [5, 29], Australia [14], Canada [13, 16, 17], China [18], India [15], South Korea [59], Norway [60], and Taiwan [19]. Whereas these cited programs are usually based in a single country, may track only nosocomial infections, and/or rely primarily on a wide variety of susceptibility testing results/methods from participating centers, the SENTRY Program monitors nosocomial and community-onset infections on a global scale using validated reference identification and antimicrobial susceptibility testing methods in a central monitoring laboratory design, including central quality assurance [10, 24, 33, 35–42].

When the SENTRY Program began in 1997, VRE was an uncommon cause of HAI in most world regions except NA [33, 46]. Subsequently, VRE rates increased steadily in all geographic regions, as did resistance to commonly used anti-enterococcal antimicrobial agents such as penicillins (ampicillin and piperacillin-tazobactam) and tetracyclines and teicoplanin in EUR. The introduction of new agents with potent activity against VRE *E. faecium*, such as linezolid, tedizolid, daptomycin, and tigecycline, offers great promise in the treatment of VRE infections. However, the clinical data supporting their wide monotherapy use in severe, complicated infections are relatively limited, and the role of these new agents in the current armamentarium remains to be established [6, 9, 22, 54]. Each of these agents demonstrates excellent, often bactericidal, activity, and each agent inhibits more than 98.0% of VanA and VanB enterococci across all 4 monitored regions (Table 5). Moreover, the breadth and duration of the
SENTRY Program allows for the detection of emerging resistance to these agents, as they are employed throughout the world [10, 24, 37, 58]. As an example, despite the low frequency of resistance to oxazolidinones among *E. faecalis* and *E. faecium* isolates, the SENTRY Program confirmed the identification of phenotypically nonsusceptible strains and documented the presence of ribosomal mutations in both species as well as the plasmid-borne (eg, *opTRA*) resistance genes in *E. faecalis* from multiple geographic locations and numerous other oxazolidinone resistance mechanisms [58]. Implementing proteomic and molecular characterization of HAI pathogens, such as the enterococci in the context of a global surveillance program, allows detailed and accurate characterization of infecting strains that will be useful in defining resistance and evaluating new candidate agents for the prevention and/or treatment of these serious infections.

In comparing these data, it is important to realize that the results of most surveillance studies have potential biases that reflect the population surveyed, the method for data collection, and the underlying purposes for data collection [50, 51, 61–64]. Significant differences may exist regarding patterns of antimicrobial resistance and usage, and these differences are likely to affect the ability to compare data among different studies [50, 51, 61–64]. Thus, longitudinal surveillance (SENTRY Program) by the same reference methods and study sites is important in providing accurate estimates of trends in antibacterial and antifungal resistance [10, 24, 34, 35, 37, 65].

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