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

MA Pfaller[1], RE Mendes[1], M Cormican[2], RN Jones[1], RK Flamm[1]

[1]JMI Laboratories, North Liberty, Iowa, USA; [2] National University of Ireland, Galway, Galway, Ireland

Contact Information:
Michael A. Pfaller, MD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: mike-pfaller@jmilabs.com

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- The SENTRY Antimicrobial Surveillance Program was established in 1997 and presently encompasses over 700,000 bacterial isolates from over 300 medical centers worldwide
- Among the pathogens surveyed in the SENTRY Program, enterococci represent a cause of bloodstream (BSIs), intra-abdominal (IAIs), skin and skin structure (SSSIs), and urinary tract infections (UTIs)
- In the presented study, we review geographic and temporal trends in enterococci species and resistant phenotypes identified throughout the SENTRY Program

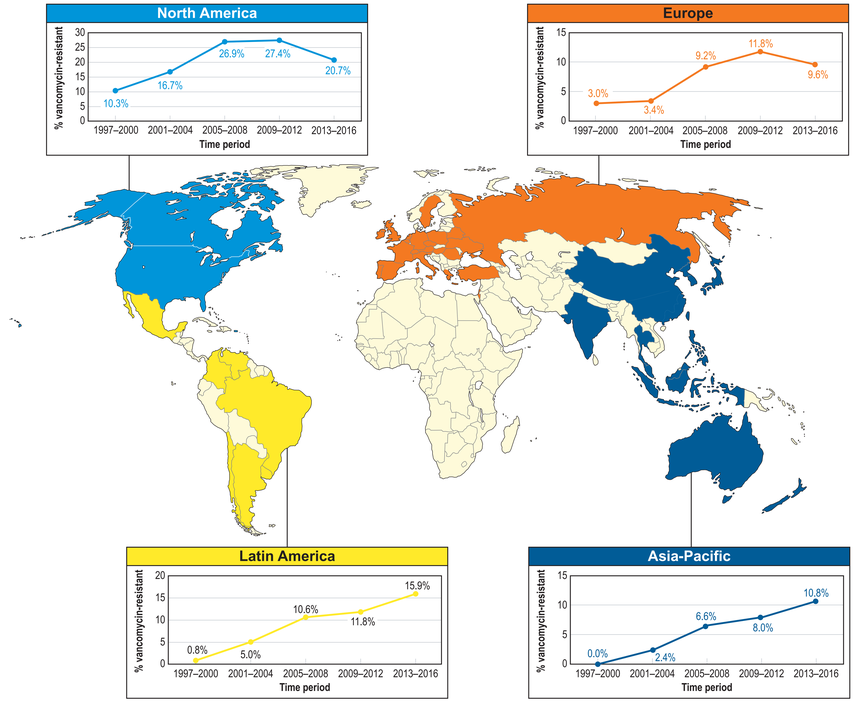
Materials and Methods

- Over 20 years, 51,866 clinically significant enterococci isolates (15 species, 6.6% of all isolates collected) were submitted from over 300 medical centers representing the Asia-Pacific (APAC), European (EUR), 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 at each site and confirmed at JMI Laboratories
  - Only 1 isolate per patient per infection episode was submitted
  - Infection types included bloodstream, pneumonia in hospitalized patients (PIHP), skin and skin structure, intra-abdominal, and urinary tract
- Susceptibility (S) testing was performed at JMI Laboratories by Clinical and Laboratory Standards Institute (CLSI) methods and results were interpreted using CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2018 criteria
- Antimicrobials tested were ampicillin, chloramphenicol, daptomycin (DAP), doxycycline, linezolid (LZD), oritavancin (ORI), piperacillin-tazobactam (P-T), quinupristin-dalfopristin, tedizolid (TZD), teicoplanin (TEC), tetracycline, tigecycline (TGC), and vancomycin (VAN)

Table 1. Incidence of *Enterococcus* species isolated from all monitored infections in the 4 geographic regions in the SENTRY Antimicrobial Surveillance Program (1997–2016)

	Incidence (%) among enterococcal isolates tested, by region			
***Enterococcus* species**	**North America (n=25,205)**	**Europe (n=16,054)**	**Latin America (n=4,755)**	**Asia-Pacific (n=5,852)**
E. avium	0.8	0.8	1.8	1.0
E. casseliflavus	0.5	0.5	0.4	0.9
E. cecorum	0.0	<0.1	0.0	0.0
E. devriesei	0.0	0.0	<0.1	0.0
E. durans	0.2	0.5	0.3	0.1
E. faecalis	64.2	62.8	74.1	60.9
E. faecium	28.4	32.6	18.4	35.1
E. gallinarum	0.8	0.9	1.4	0.9
E. gilvus	<0.1	0.0	0.0	0.0
E. hirae	0.1	0.2	0.3	0.3
E. italicus	0.0	<0.1	0.0	0.0
E. malodoratus	0.0	0.0	<0.1	0.0
E. mundtii	<0.1	0.0	<0.1	<0.1
E. raffinosus	0.3	0.1	<0.1	0.4
E. thailandicus	<0.1	<0.1	0.0	0.0
Undetermined	4.6	1.6	3.2	0.3

Figure 1. Frequency of vancomycin-resistant enterococci over time and geographic region



- VanA (nonsusceptible to VAN and TEC; CLSI, 2018), VanB (nonsusceptible to VAN but susceptible to TEC; CLSI, 2018), and VanC (*E. gallinarum* and *E. casseliflavus*) vancomycin-resistant (VRE) phenotypes were identified according to CLSI criteria
  - In this study, VRE is defined as VanA and VanB phenotypes only

Results

- The most common *Enterococcus* species in all 4 regions were *Enterococcus faecalis* (64.3%) and *E. faecium* (29.5%) (Table 1)
- Enterococci accounted for more than 10% of BSIs in NA and were the most prominent cause of IAIs (40.7%) and UTIs (24.4%) in APAC (Table 2)
- A steady decrease in antimicrobial susceptibilities was observed in all regions over the 20-year period (Table 3 and Figure 1)
  - VRE phenotypes accounted for more than 8% of isolates in all regions (1997–2016), except for APAC (6.3%), and were most common in NA (21.6%) (Figure 1)
  - Among 51,866 isolates of enterococci, 13.2% exhibited a VanA phenotype (range 4.6% [APAC] to 20.0% [NA]) and 1.6% showed a VanB phenotype (range 0.9% [LATAM] to 1.7% [APAC and EUR]) (Table 4)
  - Only 1.4% of isolates were a VanC phenotype (data not shown)
  - Over the 20-year duration of the SENTRY Program, the frequency of VRE as a cause of enterococcal infection has increased incrementally in all 4 of the monitored global regions (Figure 1)
- Several newer agents demonstrated promising activity against VRE, including DAP (99.6%–100.0%S), LZD (98.0%–99.6%S), ORI (92.2%–97.7%S), TZD (99.5%–100.0%S), and TGC (99.2%–99.5%S) (Table 5)
- Some trending analysis may have limitations due to inconsistent participation of certain countries, especially in the Asia-Pacific and eastern European regions

Table 2. Variations in the occurrence of enterococcal infections in hospitals contributing isolates to the SENTRY Antimicrobial Surveillance Program (1997–2016)

	No. of isolates per infection type, no. (%) enterococci				
Region	**BSI**	**PIHP**	**IAI**	**SSSI**	**UTI**
North America	136,766	66,012	4,450	74,943	31,832
	14,575 (10.7)	470 (0.7)	581 (13.1)	4,454 (5.9)	3,994 (12.5)
Europe	103,487	35,780	4,458	39,849	14,874
	8,398 (8.1)	631 (1.8)	766 (17.2)	2,943 (7.4)	2,489 (16.7)
Latin America	37,035	12,110	183	12,768	3,829
	1,867 (5.0)	187 (1.5)	43 (23.5)	1,246 (9.8)	757 (19.8)
Asia-Pacific	32,963	20,811	243	21,744	4,594
	1,818 (5.5)	177 (0.9)	99 (40.7)	988 (4.5)	1,119 (24.4)

NOTE: A total of 789,280 strains (51,866 enterococci [6.6%]) were analyzed over the 20 study years.
Abbreviations: BSI, bloodstream infection; IAI, intra-abdominal infection; PIHP, pneumonia in hospitalized patient; SSSI, skin and skin structure infection; UTI, urinary tract infection.

Table 3. Trends in antimicrobial susceptibility of all tested enterococci (51,866 isolates) in each monitored region for 1997–2016: SENTRY Antimicrobial Surveillance Program[a]

Region	Time period	No. tested	AMP	CHL	DOX	LZD	P-T	VAN
NA	1997–2000	4,195	79.2	82.3	51.8	96.6	79.0	87.6
	2001–2004	3,685	75.7	88.2	47.1	99.5	75.2	82.7
	2005–2008	6,509	68.2	89.7	49.4	99.2	67.8	72.5
	2009–2012	6,130	69.6	NT	43.7	99.4	69.4	71.8
	2013–2016	4,686	76.9	NT	41.5	99.6	76.6	79.0
EUR	1997–2000	1,593	83.8	67.9	46.0	98.8	87.7	96.6
	2001–2004	2,196	78.7	74.1	45.3	99.9	77.2	96.1
	2005–2008	4,759	67.4	74.5	45.5	99.8	67.0	90.6
	2009–2012	4,144	64.8	NT	49.1	99.7	64.4	87.7
	2013–2016	3,362	64.7	NT	47.2	99.7	64.4	90.0
LATAM	1997–2000	491	95.5	69.0	45.8	95.7	92.5	98.4
	2001–2004	560	86.2	72.3	43.4	100.0	76.2	94.5
	2005–2008	1,825	83.9	73.1	40.9	99.8	80.4	88.7
	2009–2012	1,326	79.9	NT	50.9	99.9	79.1	87.3
	2013–2016	553	78.1	NT	55.2	99.6	77.0	83.5
APAC	1997–2000	591	81.7	73.6	37.1	97.1	77.4	99.5
	2001–2004	590	73.1	75.6	43.4	100.0	71.5	96.3
	2005–2008	2,265	63.4	61.9	23.8	99.4	61.8	92.9
	2009–2012	1,868	65.1	NT	43.0	99.5	62.5	91.7
	2013–2016	538	64.5	NT	41.2	99.6	64.3	88.7

[a]Abbreviations AMP, ampicillin; APAC, Asia-Pacific; CHL, chloramphenicol; DOX, doxycycline; EUR, Europe; LATAM, Latin America; LZD, linezolid; NA, North America; NT, not tested; P-T, piperacillin-tazobactam; VAN, vancomycin
[a] Criteria as published by CLSI (2018) and EUCAST (2018; TZP only).

Table 4. Enterococcal isolates stratified by geography and vancomycin phenotype

Organism/organism group	Asia-Pacific	Europe	Latin America	North America	Total
***Enterococcus* spp.**	**5,852**	**16,054**	**4,755**	**25,205**	**51,866**
Vancomycin-susceptible (≤4 mg/L)	5,447 (93.1%)	14,626 (91.1%)	4,249 (89.4%)	19,544 (77.5%)	43,866 (84.6%)
Vancomycin-resistant (VanA)	271 (4.6%)	1,095 (6.8%)	426 (9.0%)	5,035 (20.0%)	6,827 (13.2%)
Vancomycin-resistant (VanB)	99 (1.7%)	279 (1.7%)	44 (0.9%)	415 (1.6%)	837 (1.6%)
Enterococcus faecium	**2,052**	**5,228**	**875**	**7,165**	**15,320**
Vancomycin-susceptible (≤4 mg/L)	1,701 (82.9%)	3,990 (76.3%)	517 (59.1%)	2,267 (31.6%)	8,475 (55.3%)
Vancomycin-resistant (VanA)	261 (12.7%)	991 (19.0%)	322 (36.8%)	4,637 (64.7%)	6,211 (40.5%)
Vancomycin-resistant (VanB)	88 (4.3%)	246 (4.7%)	36 (4.1%)	259 (3.6%)	629 (4.1%)
Enterococcus faecalis	**3,564**	**10,079**	**3,525**	**16,188**	**33,356**
Vancomycin-susceptible (≤4 mg/L)	3,542 (99.4%)	9,942 (98.6%)	3,413 (96.8%)	15,632 (96.6%)	32,529 (97.5%)
Vancomycin-resistant (VanA)	10 (0.3%)	104 (1.0%)	104 (3.0%)	398 (2.5%)	616 (1.8%)
Vancomycin-resistant (VanB)	11 (0.3%)	33 (0.3%)	8 (0.2%)	156 (1.0%)	208 (0.6%)

Table 5. Potency and spectrum of selected antimicrobial agents tested against 7,664 vancomycin-resistant enterococcal isolates in the SENTRY Antimicrobial Surveillance Program, 1997–2016

	$MIC_{50/90}$ in mg/L (% of tested isolates susceptible)[a]			
Antimicrobial agent	**North America (n=5,450)**	**Europe (n=1,374)**	**Latin America (n=470)**	**Asia-Pacific (n=370)**
Ampicillin	>8/>8 (10.5)	>8/>8 (10.0)	>8/>8 (22.8)	>8/>8 (5.1)
Daptomycin	2/2 (99.6)	2/2 (100.0)	1/2 (100.0)	2/4 (99.7)
Doxycycline	>4/>4 (49.8)	≤1/>4 (62.7)	≤1/>4 (67.6)	≤1/>4 (60.6)
Linezolid	1/2 (98.0)	1/2 (99.2)	1/2 (99.6)	1/2 (99.5)
Oritavancin[b]	0.03/0.12 (92.3)	0.015/0.06 (95.7)	0.03/0.12 (92.2)	≤0.008/0.06 (97.7)
Piperacillin-tazobactam	>16/>16 (10.2)	>16/>16 (9.4)	>16/>16 (18.9)	>16/>16 (4.9)
Quinupristin-dalfopristin[c]	≤0.5/1 (96.0)	1/2 (83.5)	1/2 (84.9)	1/1 (90.5)
Tedizolid[d]	0.12/0.25 (99.5)	0.12/0.25 (99.5)	0.12/0.25 (100.0)	0.12/0.25 (100.0)
Teicoplanin	>8/>8 (12.7)	>8/>8 (31.5)	>8/>8 (23.2)	>8/>8 (42.8)
Tigecycline	≤0.12/≤0.12 (99.2)	≤0.12/≤0.12 (99.5)	≤0.12/≤0.12 (99.3)	0.12/0.25 (99.5)

[a] Criteria as published by CLSI (2018) and EUCAST (2018; piperacillin-tazobactam and tigecycline only).
[b] Susceptible breakpoint (MIC, ≤0.12 mg/L) for vancomycin-susceptible *E. faecalis* applied to all VRE.
[c] Data for vancomycin-resistant *E. faecium* only.
[d] Susceptible breakpoint (MIC, ≤0.5 mg/L) for *E. faecalis* applied to all VRE.

Conclusions

- Enterococci remained a prominent pathogen over the 20 years of the SENTRY Program
- The frequency of VRE was 14.8% overall and increased over time in all regions
- Agents with novel mechanisms of action show promising activity against VRE

References

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