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Frequency and Antimicrobial Susceptibility Profile of Vancomycin-Resistant Enterococci from Latin America: A Report from the SENTRY Antimicrobial Surveillance Program (1997-2006)

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Objective: To evaluate the prevalence and susceptibility profile of vancomycin-resistant enterococci (VRE) in Latin America. VRE emerged nearly twenty years ago in the United States (USA) and rapidly disseminated in many USA hospitals; however, its prevalence seems to remain relatively low in Latin America.

Methods: As part of the SENTRY Antimicrobial Surveillance Program, a total of 2026 enterococci isolated between January 1997 and December 2006 from Latin American hospitals were studied. The susceptibility profile to nine antimicrobial agents was determined by CLSI broth microdilution methods and results interpreted according to CLSI document M100-S18 (2008).

Results: *E. faecalis* (78.2%) and *E. faecium* (12.7%) were the most frequently isolated species. Blood (42.0%) and urinary tract (16.0%) represented the most frequent body sites of infection. A total of 104 (5.1%) strains were identified as VRE, with 76.9% of them being isolated in Brazil. The VRE frequency increased from 0.0% (1997 and 1998) to 10.3% (2006), with an important increase after 2002. Although the numbers of *E. faecalis* and *E. faecium* exhibiting the VRE phenotype were similar, the percentage of vancomycin-resistant *E. faecium* (VR-EFM; 19.8%) was proportionally higher than vancomycin-resistant *E. faecalis* (VR-EF; 3.3%). A significant increase in VR-EFM isolates was detected in Brazil in 2006. VRE was most frequently isolated from bloodstream (46.2%). The antimicrobial susceptibility profile of VRE isolates is summarized in the table. Linezolid and tigecycline were the most active compounds tested against VRE. In contrast, the majority of VRE were resistant to teicoplanin (*vanA* pattern).

	VR-EF (53)			VR-EFM (51)		
Antimicrobial agent	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S
Ampicillin	4	16	86.8	>16	>16	2.0
Teicoplanin	>16	>16	3.8	>16	>16	5.9
Gentamicin (HL)	>1000	>1000	18.9	≤500	>1000	76.5
Streptomycin (HL)	≤1000	>2000	83.0	>2000	>2000	16.0
Quinupristin/dalfopristin	>2	>8	1.9	1	>2	69.0
Linezolid	1	2	100.0	1	2	100.0

Conclusions: An important increase in the frequency of VRE has been observed in Latin America and appears to be associated with the dissemination of endemic clones expressing the *vanA*. Linezolid and tigecycline were the only antimicrobials with broad activity against *Enterococcus* spp. independent of the species identification or glycopeptide phenotype.

INTRODUCTION

Enterococci are intrinsically resistant to many antimicrobial agents, including aminoglycosides, clindamycin, antistaphylococcal penicillins, cephalosporins, and most fluoroquinolones. Furthermore, the ability of enterococci to develop or acquire resistance to other agents is well recognized. Vancomycin and teicoplanin usually represent the initial therapeutic options for treatment of serious infections caused by ampicillin-resistant enterococci or for those affecting patients allergic to ß-lactam antibiotics. However, the clinical use of these antimicrobial agents has been impacted by the emergence and spread of vancomycin-resistant enterococci (VRE).

According to the United States (USA) Center for Disease Control and Prevention (CDC), the percentage of enterococcal isolates resistant to vancomycin reported by USA hospitals increased from 0.3% in 1989 to 28.5% of all isolates in 2003. The reported increases in VRE colonization and infection among hospitalized patients are of concern for several reasons. Infections due to VRE are usually associated with greater morbidity, mortality, lengths of stay and hospital costs than those due to vancomycin-susceptible enterococci, independent of co-morbidity conditions that may have led to the infection. In addition, the emergence of VRE limits therapeutic options for treatment of serious infections and serves as a potential source of vancomycin resistance genes that may transfer to other organisms, such as *Staphylococcus aureus*.

The objective of this study was to evaluate the prevalence and susceptibility profile of VRE in the Latin American hospitals participating in the SENTRY Antimicrobial Surveillance Program (1997-2006).

MATERIALS AND METHODS

Bacterial strains: Non-duplicate bacterial pathogens were collected during the first 10 years (1997-2006) of the SENTRY Program in Latin American medical centers. All isolates were identified at the participating institution by routine methodologies. Upon receipt at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), isolates were subcultured to ensure viability and purity. Confirmation of species identification was performed with the Vitek system (bioMerieux Vitek, St Louis, MO) or conventional methods, as required.

Medical centers: The participant medical centers included 13 cities in seven countries: São Paulo (1997-2006), Brasília (1999-2006) Florianópolis (1997-2006) and Porto Alegre (1999-2006) in Brazil; Buenos Aires and San Isidro in Argentina (1997-2006); Santiago in Chile (two sites, 1997-2006); Montevideo in Uruguay (1997); Medelin in Colombia (1997-2006); Mexico City (three sites, 1997-2001), Guadalajara (2004-2006), and Durango (2005-2006) in Mexico; and Caracas in Venezuela (1998-2004).

Susceptibility testing: *Enterococcus* spp. isolates were tested against several antimicrobial agents including tigecycline by microdilution methods using fresh Mueller-Hinton broth as recommended by the Clinical and Laboratory Standards Institute (CLSI M7-A7, 2006). Susceptibility results were interpreted according to CLSI document M100-S18 (2008) for all comparison agents. The tigecycline breakpoints were those established by the USA Food and Drug Administration (FDA) for *E. faecalis* (≤0.25 mg/L for susceptible). Concurrent quality control was performed using the following organisms: *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213.

RESULTS

- A total of 2,026 *Enterococcus* spp. isolates were collected from Latin American medical centers. *E. faecalis* was most prevalent (78.2%), followed by *E. faecium* (12.7%).
- Most *Enterococcus* spp. isolates were collected in Brazil (46.7%) followed by Argentina (18.2%), Mexico (14.9%) and Chile (13.1%) and were predominantly recovered from bloodstream infections (42.0%), followed by urinary tract (16.0%) and skin and soft tissue (13.0%).
- Overall, 104 (5.1%) *Enterococcus* spp. isolates were categorized as VRE with most being *E. faecium* (19.8%) compared to *E. faecalis* (3.3%).
- VRE isolates were more frequently isolated from bloodstream (46.2%) followed by skin and soft tissue (26.0%) and urine (23.1%).
- Tigecycline (MIC_{90}, 0.25 mg/L; 98.1% susceptible) and linezolid (MIC_{90}, 2 mg/L; 99.2% susceptible) were the most active agents against *Enterococcus* spp., independent of the species or glycopeptide resistance phenotype; tigecycline was eight-fold more potent than linezolid.
- Synergistic activity with aminoglycosides would be best achieved with streptomycin (83.0%) and gentamicin (77.0%) for vancomycin-resistant *E. faecalis* and *E. faecium* strains, respectively. Furthermore, 83.0% of vancomycin-resistant *E. faecium* were susceptible to chloramphenicol.
- The VRE frequency increased from 0.0% (1997 and 1998) to 10.3% (2006) during the study. An increase in the frequency of vancomycin-resistant *E. faecium* exhibiting the VanA phenotype was observed in 2006, mainly in one Brazilian medical center (Figures 1 and 2).

Table 1. Antimicrobial susceptibility profiles of *E. faecalis* and *E. faecium* isolates collected from the Latin American region (SENTRY Antimicrobial Surveillance Program, 1997-2006).

	E. faecalis (1,584)						*E. faecium* (258)					
	Vancomycin-resistant (53)			Vancomycin-susceptible (1,528)			Vancomycin-resistant (51)			Vancomycin-susceptible (194)		
Antimicrobial Agent	MIC_{50}[a]	MIC_{90}	%Susc.[b]	MIC_{50}	MIC_{90}	%Susc.	MIC_{50}	MIC_{90}	%Susc.	MIC_{50}	MIC_{90}	%Susc.
Ampicillin	4	16	86.8	1	4	98.9	>16	>16	2.0	>16	>16	40.7
Chloramphenicol	>16	>16	6.7	8	>16	70.9	8	16	83.0	8	16	82.0
Ciprofloxacin	>4	>4	3.8	1	>4	62.0	4	4	2.0	4	>4	16.5
Gentamicin (HL)[c]	>1000	>1000	18.9	≤500	>1000	72.9	≤500	>1000	77.0	≤500	>1000	66.0
Linezolid	1	2	100.0	2	2	99.3	1	2	100.0	1	2	100.0
Quinupristin/Dalfopristin	>2	>8	1.9	>2	8	1.8	1	>2	69.0	1	>2	66.0
Rifampicin	>2	>2	3.3	>2	>2	20.9	>2	>2	0.0	>2	>2	18.9
Streptomycin (HL)[d]	≤1000	>2000	83	≤1000	>2000	73.1	>2000	>2000	16.0	≤1000	>2000	52.1
Teicoplanin	>16	>16	3.8	≤2	≤2	99.9	>16	>16	5.9	≤ 2	≤2	100.0
Tigecycline	≤0.12	0.25	97.7	≤0.12	0.25	98.1	≤0.12	≤0.12	100.0	≤0.12	0.25	97.7

a. MIC values in mg/L.
b. CLSI (2008) or USA-FDA breakpoint criteria were applied.
c. High level gentamicin; testing range 500-1000 mg/L.
d. High level streptomycin; testing range 1000-2000 mg/L.

Figure 1. Yearly distribution of the vancomycin-resistance phenotype among *E. faecalis* and *E. faecium* isolates collected from Latin American hospitals (SENTRY Antimicrobial Surveillance Program, 1997-2006).

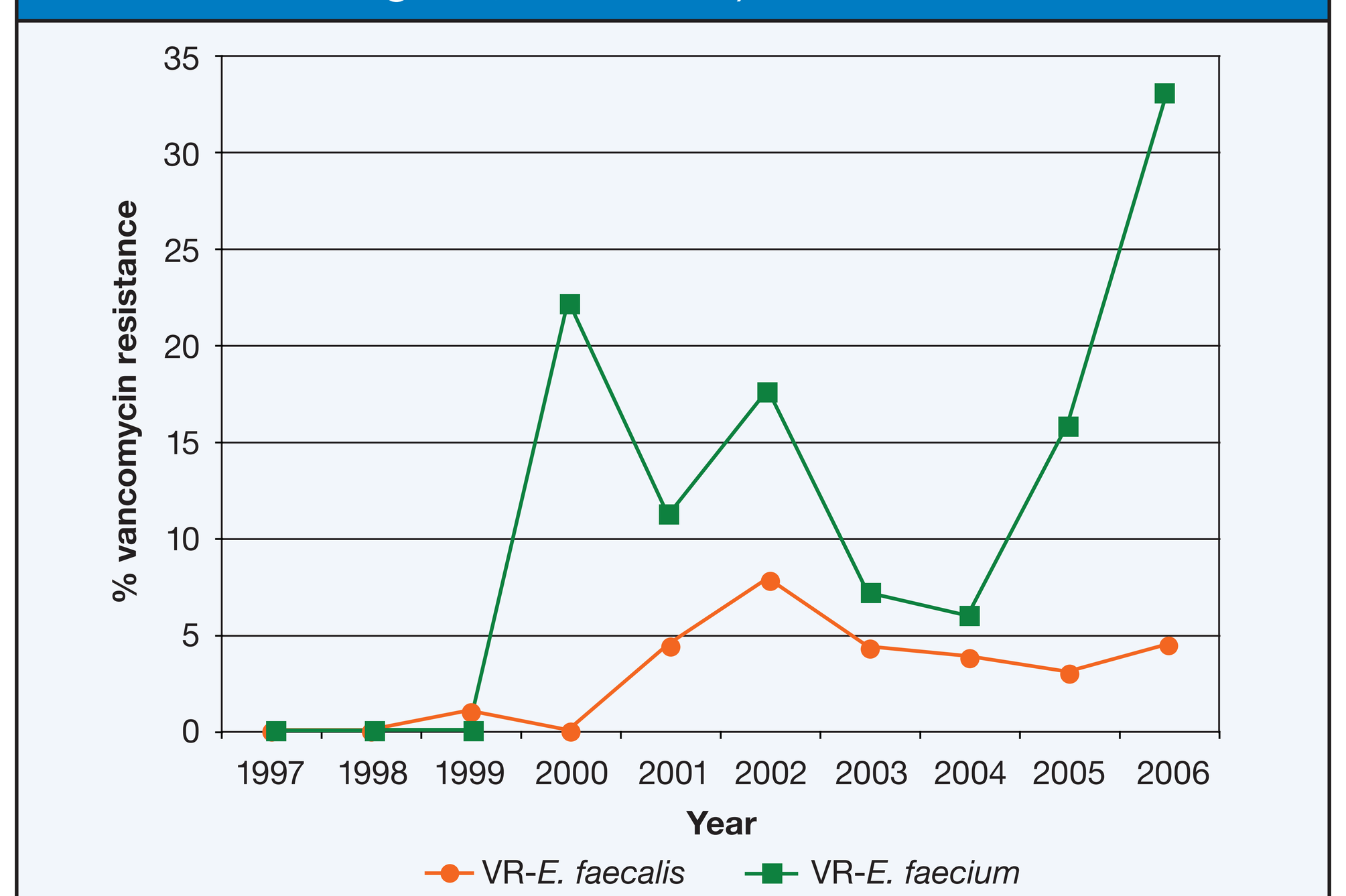
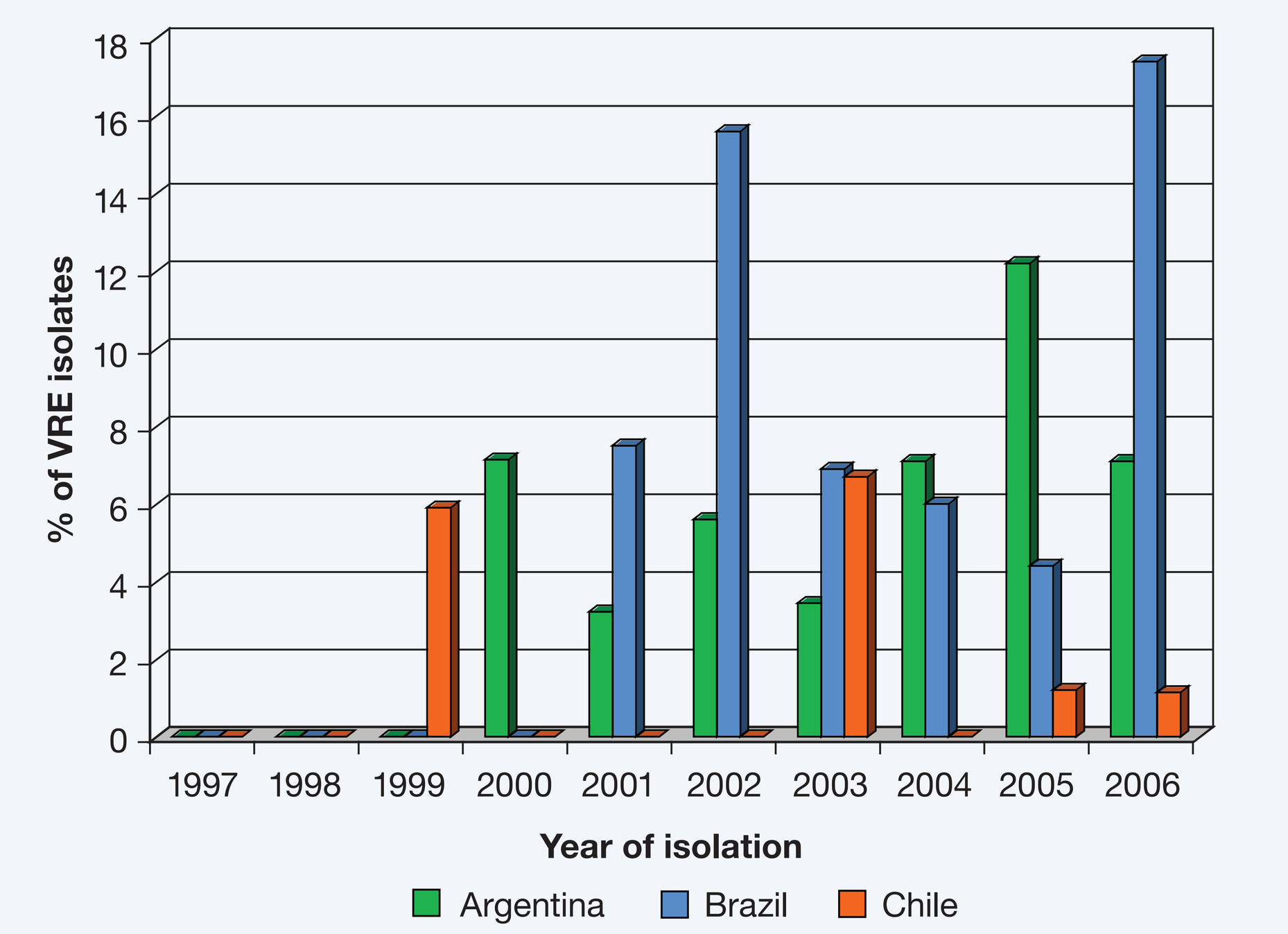


Figure 2. Yearly frequency of VRE by nation (SENTRY Antimicrobial Surveillance Program, 1997-2006).



CONCLUSIONS

- The frequency of vancomycin-resistant enterococci remained low until 2004, but rapidly increased in subsequent years (2005-2006).
- This rapid increase appeared to be associated with the dissemination of an endemic *vanA* clone in a single Brazilian institution.
- Tigecycline and linezolid may serve as alternative therapeutic options to the glycopeptides for treatment of serious enterococcal infections, given their spectrum of activity and potency against resistant strains.

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