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Activity of Tigecycline Tested Against a Worldwide Collection of Vancomycin-Resistant Enterococci (VRE)

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Introduction

- *Enterococcus* spp. ranks 3rd as the pathogen causing bacteremia and cSSSI in North America and 4th in Europe (SENTRY Antimicrobial Surveillance Program)
- VRE occurrence rates have consistently increased over the last two decades, but with a wide geographic variation
- Tigecycline appears to be a potential treatment for VRE infections

Deshpande et al., DMID 2007; Florescu et al., JAC 2008; Sader et al., ICAAC 2007 [C2-1548].

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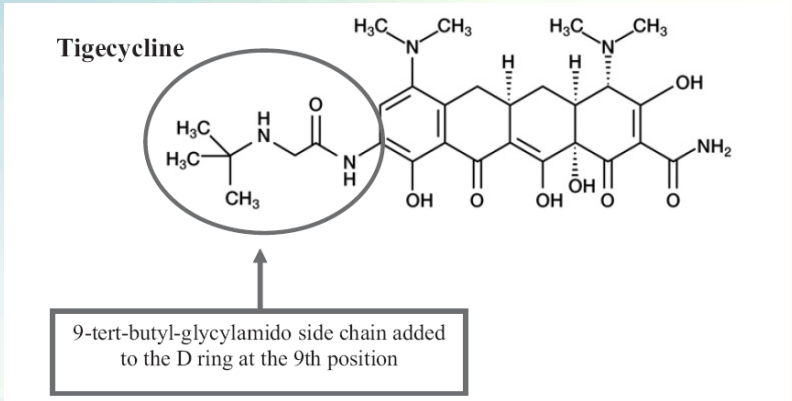
Introduction



- Tigecycline is the only compound of the glycylcycline class approved for clinical use
- Tigecycline has broad-spectrum of antimicrobial activity which includes many MDR Gram-negative and -positive organisms
- FDA approved indications include:
  - Complicated intra-abdmonial infection
  - Complicated skin and skin structure infection
  - Community-acquired bacterial pneumonia
- <u>Tigecycline is not currently approved by the FDA for the treatment of VRE infections</u>

French GL, J Chemother 2008; Paterson LR, IJAA 2008; Tygacil® Package Insert.

Objectives

- To evaluate the occurrence of VRE overtime in 4 geographic regions: North America, Europe, Asia-Pacific and Latin America

- To evaluate VRE susceptibility to tigecycline and antimicrobial agents currently used to treat enterococcal infections, regardless of regulatory indications

Material and Methods

- Unique patient isolates were consecutively collected according to the site of infection over the 2004-2008 period.

- 224 medical centers participated worldwide
  - North America: 95 (89 in the USA)
  - Europe: 35 (14 countries)
  - Asia-Pacific region: 82 (11 countries)
  - Latin America: 12 (5 countries)

Material and Methods

- **19,535 enterococcal isolates**
  - **13,262 *E. faecalis***
  - **6,273 *E. faecium***

- **Site of infection**
  - **Bloodstream: 50%**
  - **Skin and skin structure: 20%**
  - **Urinary tract: 20%**
  - **Others: 10%**

Results

Number of enterococcal strains by region

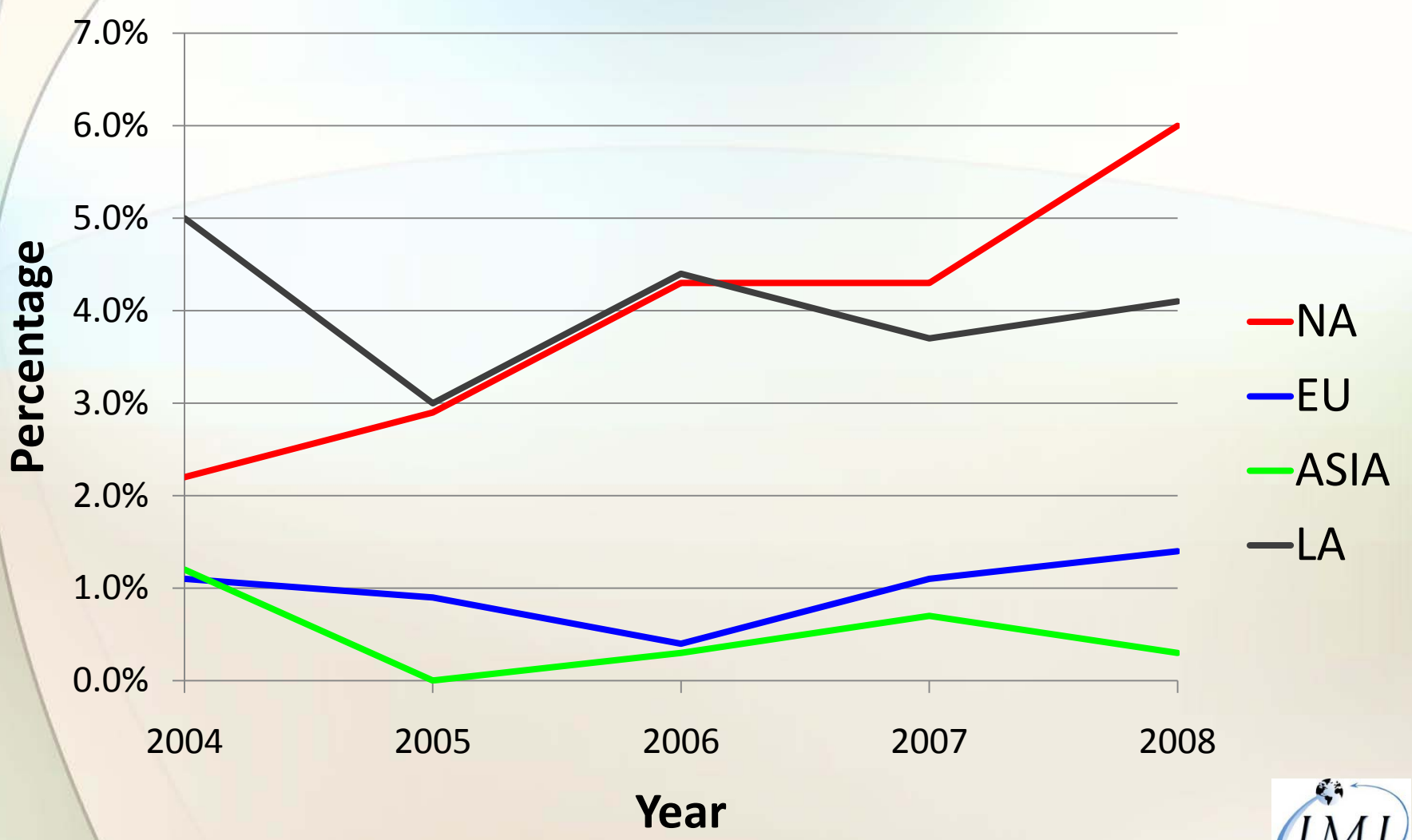
	No. of isolates (%)				
Organism	NA	EU	ASIA	LA	Overall
E. faecalis	5,910 (66.7)	4,064 (67.2)	1,563 (61.7)	1,725 (82.5)	13,262 (67.9)
E. faecium	2,952 (33.3)	1,982 (32.8)	972 (38.3)	367 (17.5)	6,273 (32.1)
Total	8,862	6,046	2,535	2,092	19,535

Results

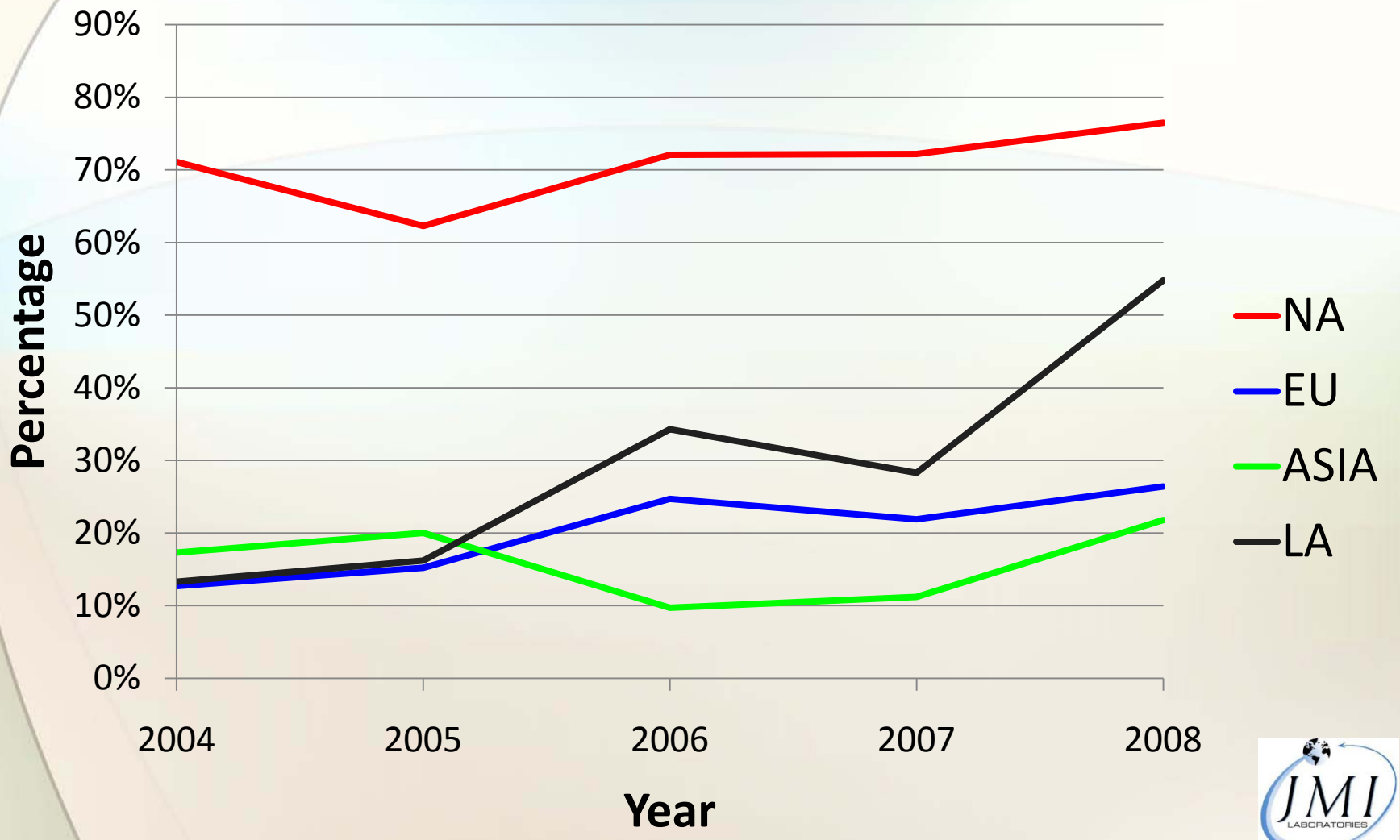
Vancomycin resistance rates by region

Organism	Vancomycin resistance rate (% with VanA phenotype)				
	NA	EU	ASIA	LA	Overall
E. faecalis	4.6 (66)	1.4 (90)	0.4 (43)	4.1 (97)	3.1 (74.6)
E. faecium	71.4 (97)	21.2 (79)	14.1 (88)	32.7 (95)	44.5 (93.3)

Vancomycin-resistant *E. faecalis*

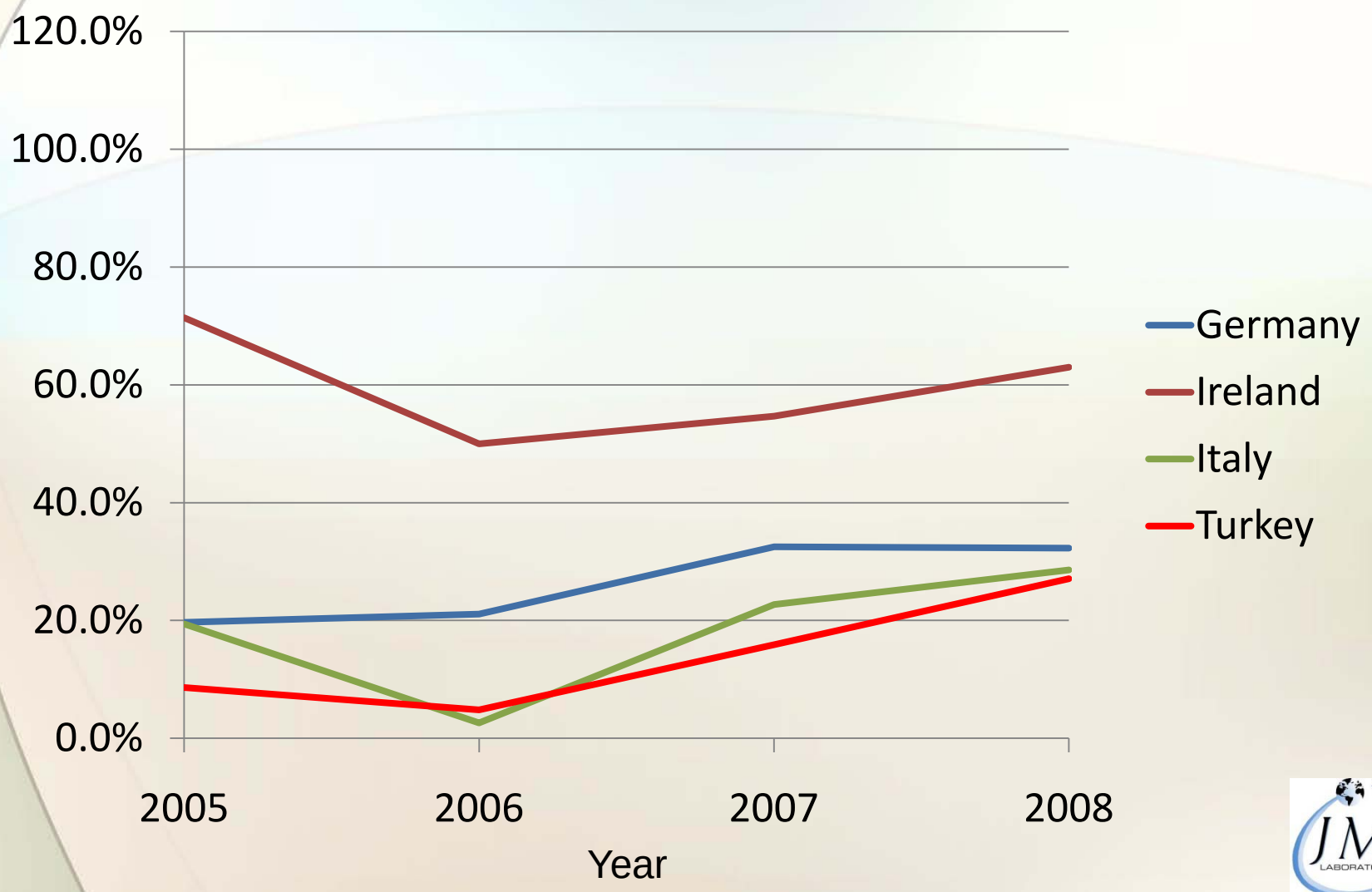


Vancomycin-resistant *E. faecium*



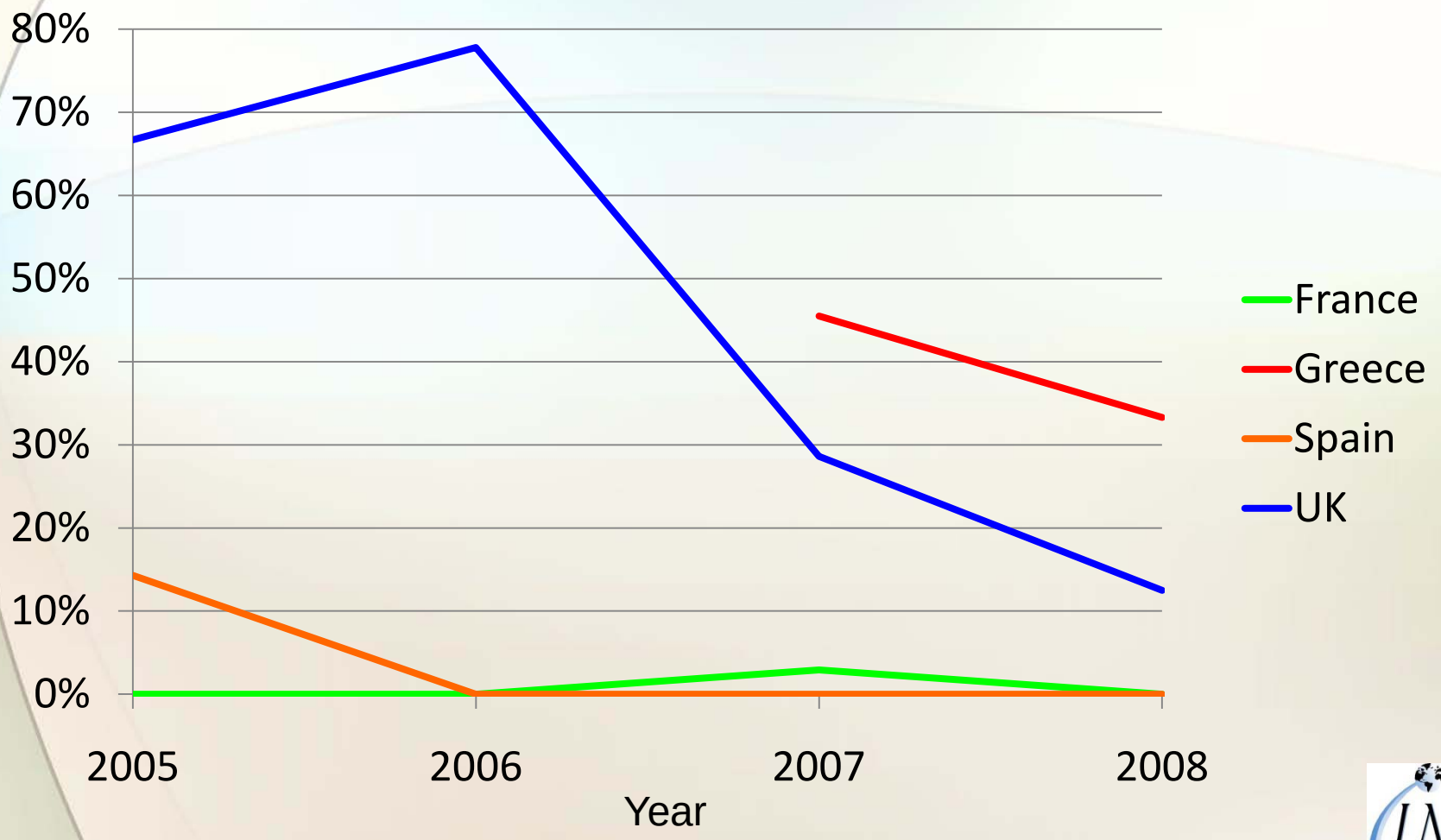
Vancomycin-resistant *E. faecium* in Europe

(Countries with increasing or high VRE rates in recent years)



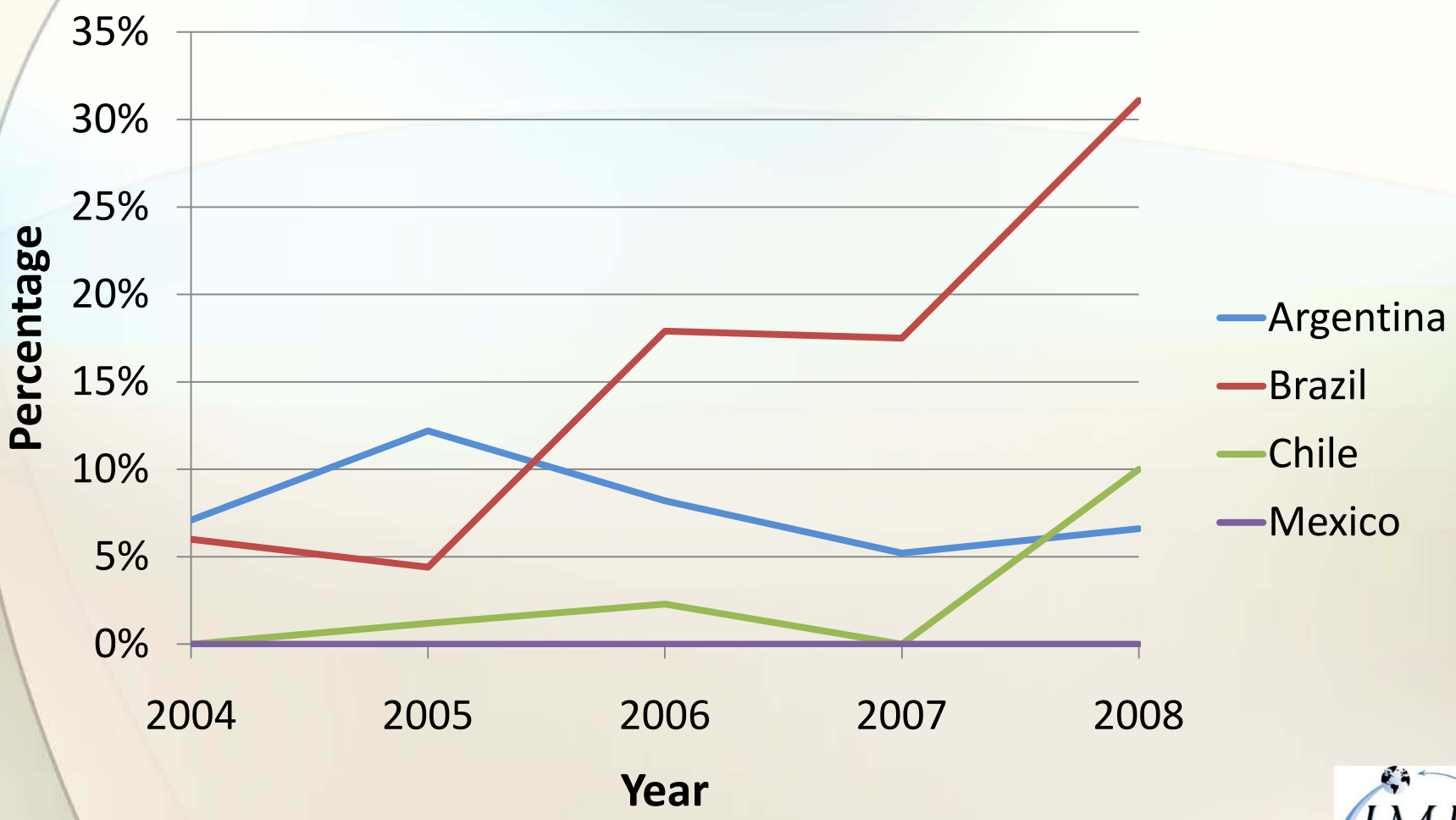
Vancomycin-resistant *E. faecium* in Europe

(Countries with decreasing or low VRE rates in recent years)



*** VRE was <u>not</u> detected in Sweden or Switzerland during the study period.**

VRE in Latin America*



*** Includes vancomycin-resistant *E. faecalis* and *E. faecium* combined**

Results

Comparison of in vitro activity for selected antimicrobial agents tested against vancomycin-resistant *E. faecalis* (410 strains)

Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible	% resistant
Tigecycline	0.12	0.25	97.6[a]	-
Minocycline	8	>8	40.9	22.7
Tetracycline	>8	>8	27.1	72.9
Ampicillin	≤2	4	97.3	2.7
Quin/dalfo	>2	>2	1.2	98.3
Gentamicin (HL)	>1000	>1000	23.5	76.5
Streptomycin (HL)	2000	>2000	46.8	53.2
Linezolid	1	2	98.8	1.2
Daptomycin	0.5	1	100.0	-
Teicoplanin	>16	>16	25.4	72.7
Vancomycin	>16	>16	0.0	100.0

a. According to USA-FDA breakpoint of ≤0.25 µg/ml for vancomycin-susceptible isolates.

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Results

Comparison of in vitro activity of selected antimicrobial agents tested against vancomycin-resistant *E. faecium* (2,794 strains)

Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible	% resistant
Tigecycline	0.06	0.12	99.5[a]	-
Minocycline	≤0.25	>8	67.0	16.5
Tetracycline	≤4	>8	59.3	40.0
Ampicillin	>16	>16	0.6	99.4
Quin/dalfo	0.5	1	92.7	3.6
Gentamicin (HL)	≤500	>1000	67.0	33.0
Streptomycin (HL)	2000	>2000	42.6	57.4
Linezolid	1	2	97.9	1.7
Daptomycin	2	4	99.9	-
Teicoplanin	>16	>16	6.7	83.8
Vancomycin	>16	>16	0.0	100.0

a. According to USA-FDA breakpoint of ≤0.25 µg/ml for vancomycin-susceptible isolates.

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Results

Activity of tigecycline tested against enterococci

Organism/phenotype (no. Tested)	No. of strains (cumulative %) inhibited at tigecycline MIC (µg/ml) of:					
	≤0.06	0.12	0.25[a]	0.5	1	2
E. faecalis						
All[b] (13,262)	4,430 (33.4)	8,922 (67.3)	4,023 (97.6)	310 (>99.9)	7 (100.0)	-
VanA[c] (306)	123 (40.2)	222 (72.6)	77 (97.7)	6 (99.7)	1 (100.0)	-
VanB[d] (104)	47 (45.2)	73 (70.2)	28 (97.1)	3 (100.0)	-	-
E. faecium						
All[b] (6,273)	3,535 (56.4)	5,585 (89.0)	631 (99.1)	49 (99.9)	7 (>99.9)	1 (100.0)
VanA[c] (2,607)	1,584 (60.8)	2,367 (90.8)	226 (99.5)	11 (99.9)	2 (>99.9)	1 (100.0)
VanB[d] (187)	94 (50.3)	161 (86.1)	26 (100.0)	-	-	-

a. USA-FDA susceptible breakpoint for vancomycin-susceptible *Enterococcus* spp.
b. Includes vancomycin-susceptible and -resistant strains.
c. VanA phenotype, e.g. isolates resistant to vancomycin and teicoplanin.
d. VanB phenotype, e.g. isolates resistant to vancomycin and susceptible to teicoplanin

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Conclusions

- VRE rates were very high in the USA and showed continuous increase over time
- VRE rates recently increased in Europe overall but with a great country-to-country variation:
  - Substantial increase was observed in Germany, Ireland, Italy and Turkey
  - A significant decreased occurred in Greece, Spain and UK (from 67 to 12% among *E. faecium*)
  - VRE was very low or nil in occurrence for France, Sweden and Switzerland

Conclusions

- Tigecycline activity against enterococci was not adversely affected by vancomycin resistance

- Tigecycline was among the most active agents tested against VRE and may represent an important therapeutic option for infections caused by this pathogen. Susceptibility rates for tigecycline were comparable to linezolid and daptomycin

Acknowledgments

- JMI Laboratories staff
- All participant medical centers worldwide

Thank you!