



UMC Utrecht

# Glycopeptide-resistant enterococci

Marc Bonten  
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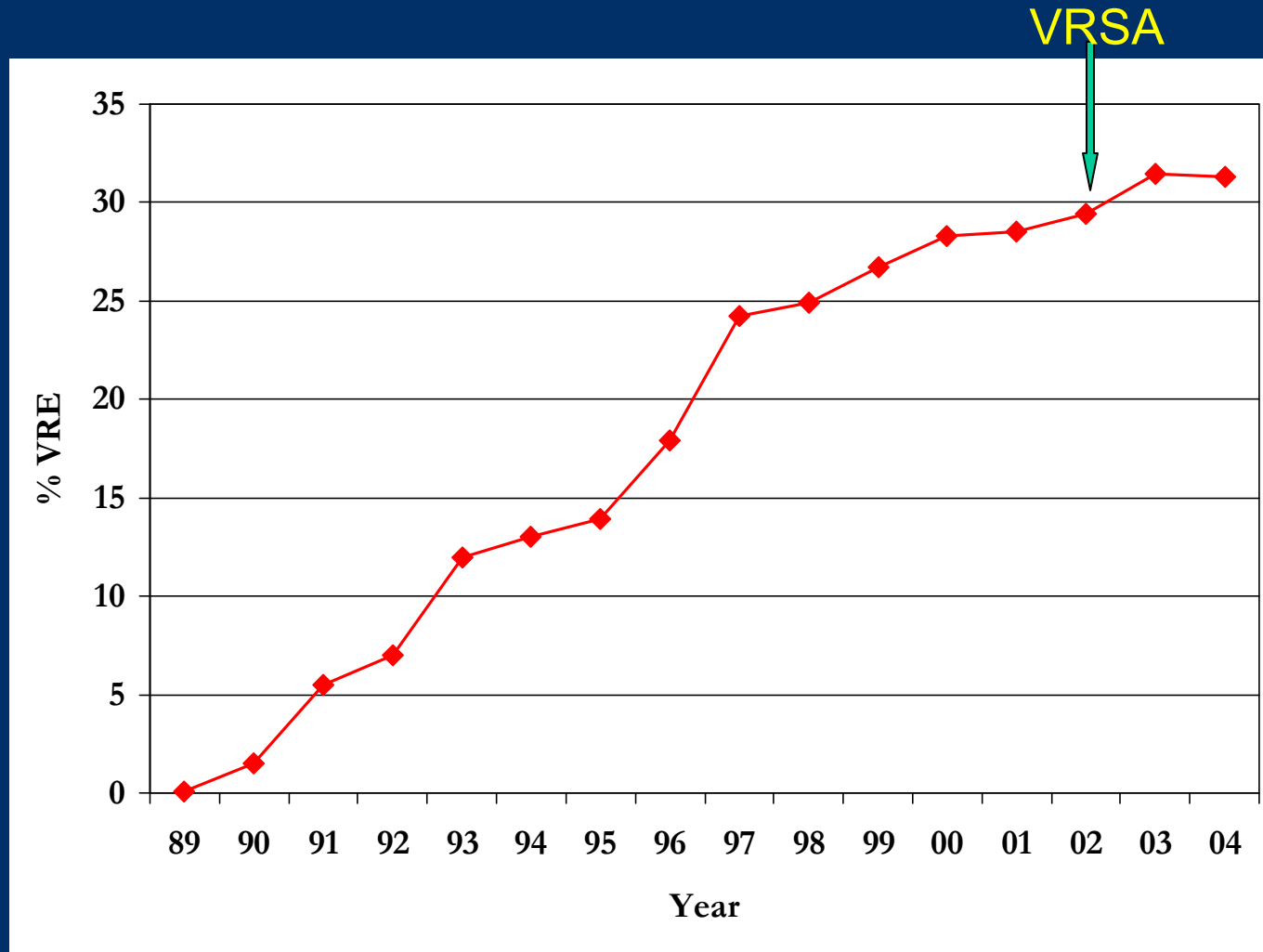
# Enterococci

- Enterococci are opportunistic nosocomial pathogens
- Not only found in humans but in a wide range of animals, including insects, plants and in the environment
- New developments the last two decades:
  - Changes in the ecology of enterococcal infections

# Developments in enterococcal ecology

- Typically: *E. faecalis* 90%/*E. faecium* 5-10%
- Late 1980s in US: Emergence of beta-lactam resistance among *E. faecium* clinical isolates
- In 1990s-2000: change in the *E. faecalis*/*E. faecium* ration among invasive isolates
- 1990-now in US: increase of VRE (*E. faecium*) prevalence in hospitals

# Rate of vancomycin-resistance in enterococcal bloodstream infections in US Intensive Care Units

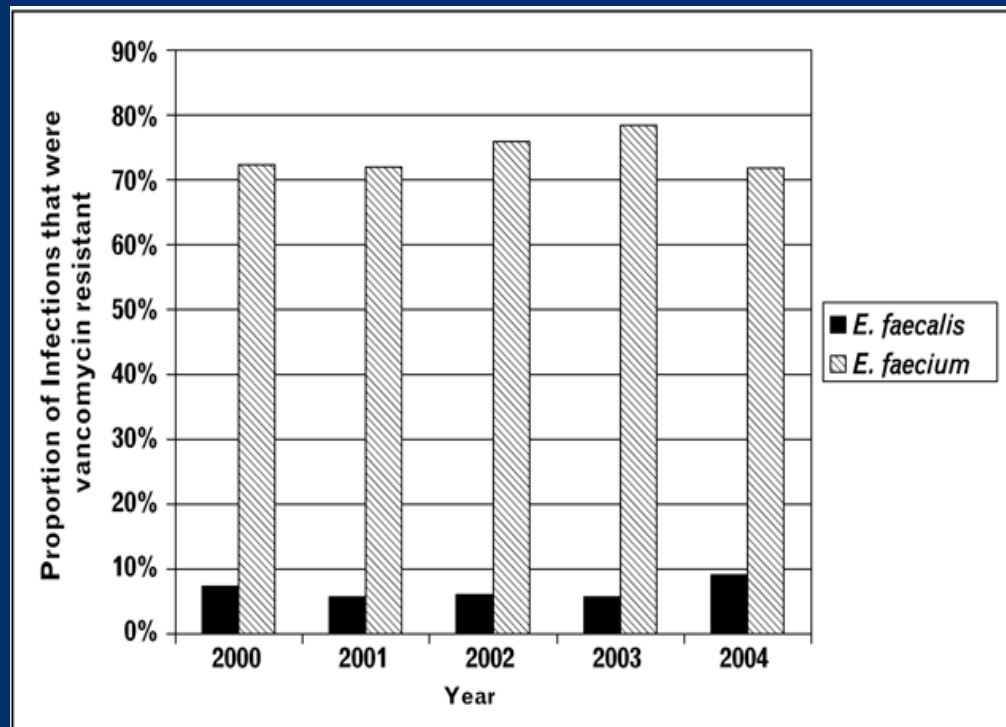


Source: NNIS

## Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Annual Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007

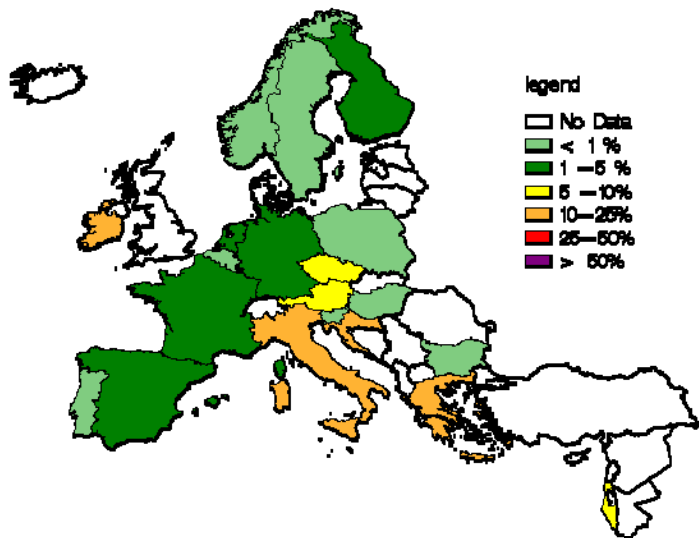
Pathogen	Overall <sup>a</sup>	
	No. (%) of pathogenic isolates	Rank
CoNS	5,178 (15.3)	1
<i>Staphylococcus aureus</i>	4,913 (14.5)	2
<i>Enterococcus</i> species		3
<i>E. faecalis</i>	1,177 (3.5)	
<i>E. faecium</i>	1,888 (5.6)	
NOS	1,028 (3.0)	
<i>Candida</i> species		4
<i>C. albicans</i>	2,295 (6.8)	
Other <i>Candida</i> spp. or NOS	1,333 (3.9)	
<i>Escherichia coli</i>	3,264 (9.6)	5
<i>Pseudomonas aeruginosa</i>	2,664 (7.9)	6
<i>Klebsiella pneumoniae</i>	1,956 (5.8)	7
<i>Enterobacter</i> species	1,624 (4.8)	8
<i>Acinetobacter baumannii</i>	902 (2.7)	9
<i>Klebsiella oxytoca</i>	359 (1.1)	10
Other	5,267 (15.6)	
Total	33,848 (100)	

# Proportion of VRE among Enterococcal ICU Isolates



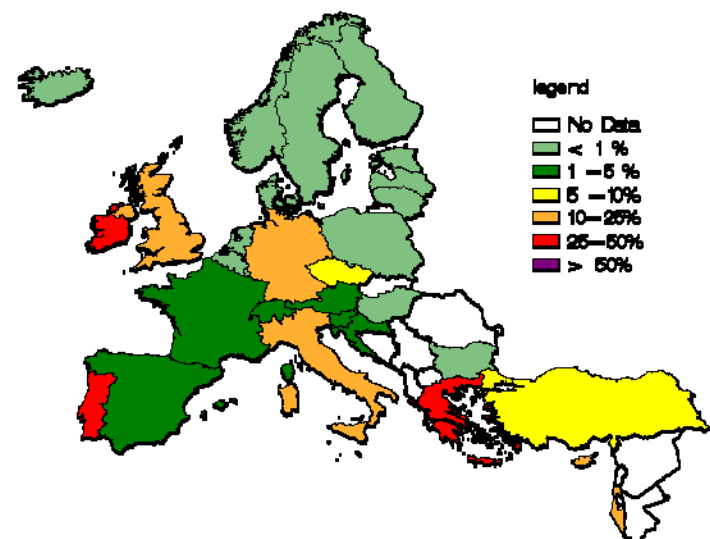
# Glycopeptide-resistant *E. faecium* in Europe

Proportion of Glycopeptide resistant *E. faecium* isolates in participating countries in 2002  
(c) EARSS



2002

Proportion of Glycopeptide resistant *E. faecium* isolates in participating countries in 2007  
(c) EARSS



2007

# Glycopeptide consumption (Wegener *et al.* 1994)

## Human:

- US (296 million): 11,460 kg
- F, GE, I, GB, NL (273 million): 2,256 kg

## Veterinary (Avoparcin as growth promoter):

- US: 0 kg?
- DK: 24,117 kg

# VRE outside hospitals (1997)

## Europe (Netherlands)

- Non-hospitalized persons: 8-12%
- Farm animals: 34-98%  
(Veal calves, pigs, poultry)
- Domestic animals: 16-48%  
(cats and dogs)

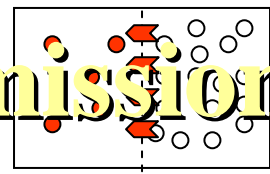
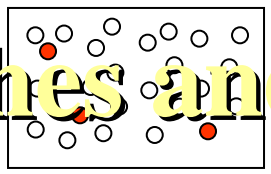
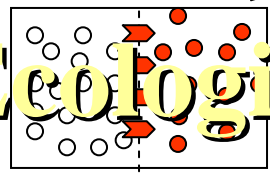
## US

- Virtually none

# Ecological niches and transmission routes

Avoparcin

Vancomycin

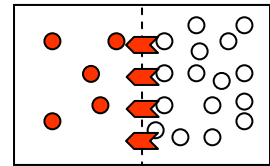
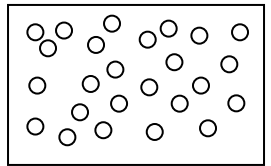
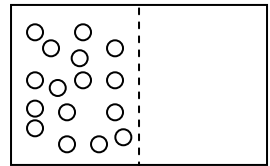


Animal reservoir

Community reservoir

Hospital reservoir

US

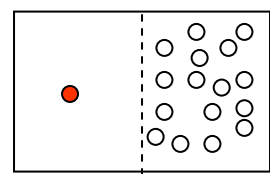
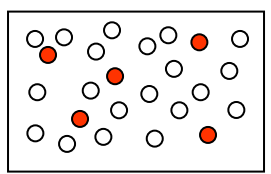
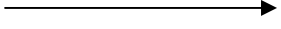
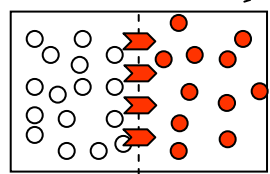


Animal reservoir

Community reservoir

Hospital reservoir

Europe



Animal reservoir

Community reservoir

Hospital reservoir

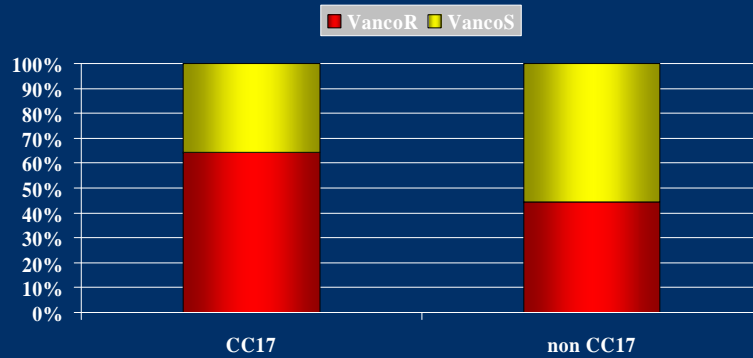


# What explains the ecological abundance of *E. faecium* CC-17 in hospitals?

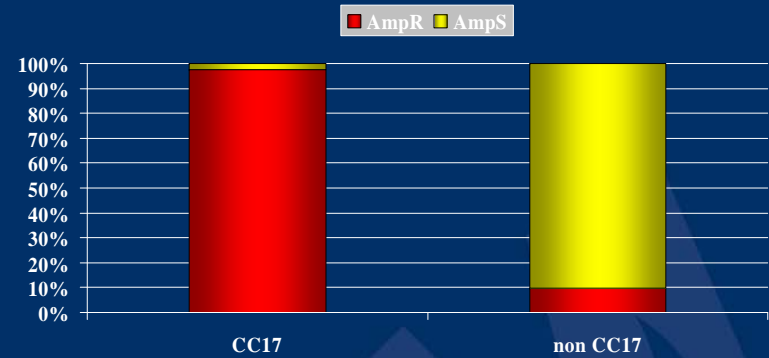
- Antibiotic resistance?
- Increased virulence?
- Other?

# Antibiotic resistance

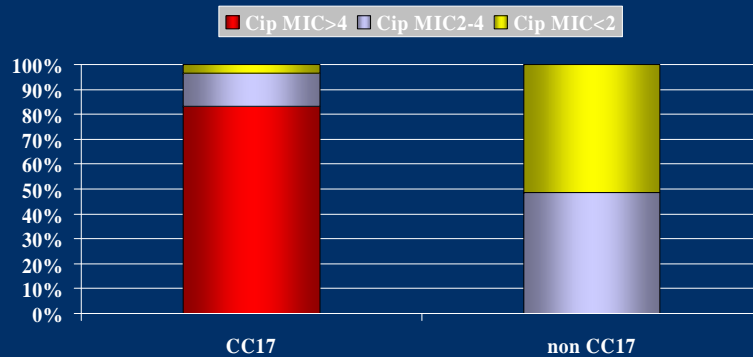
## Vancomycin



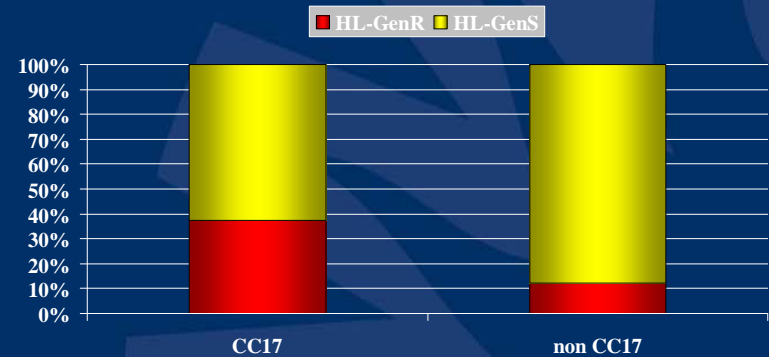
## Ampicillin



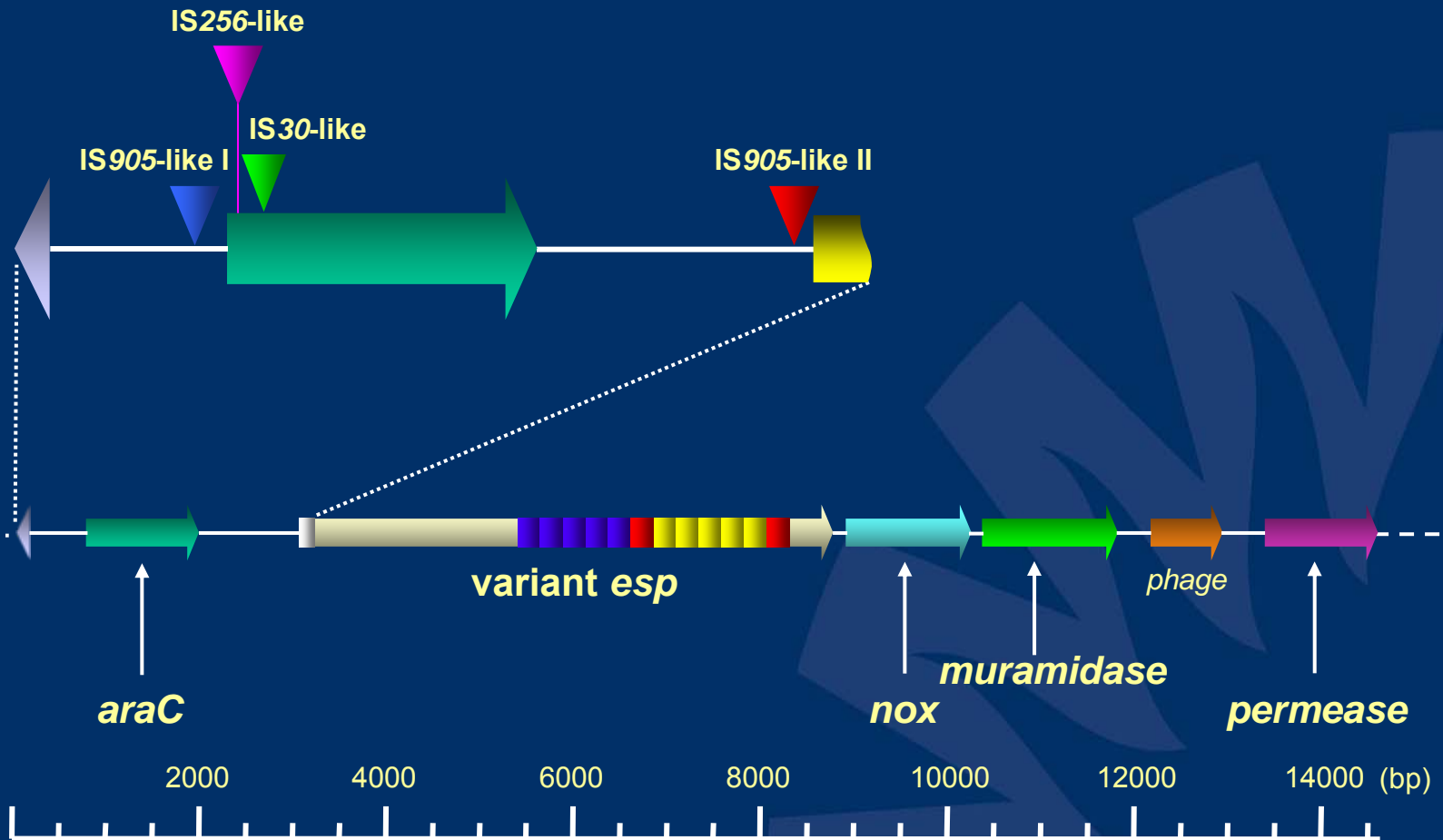
## Ciprofloxacin



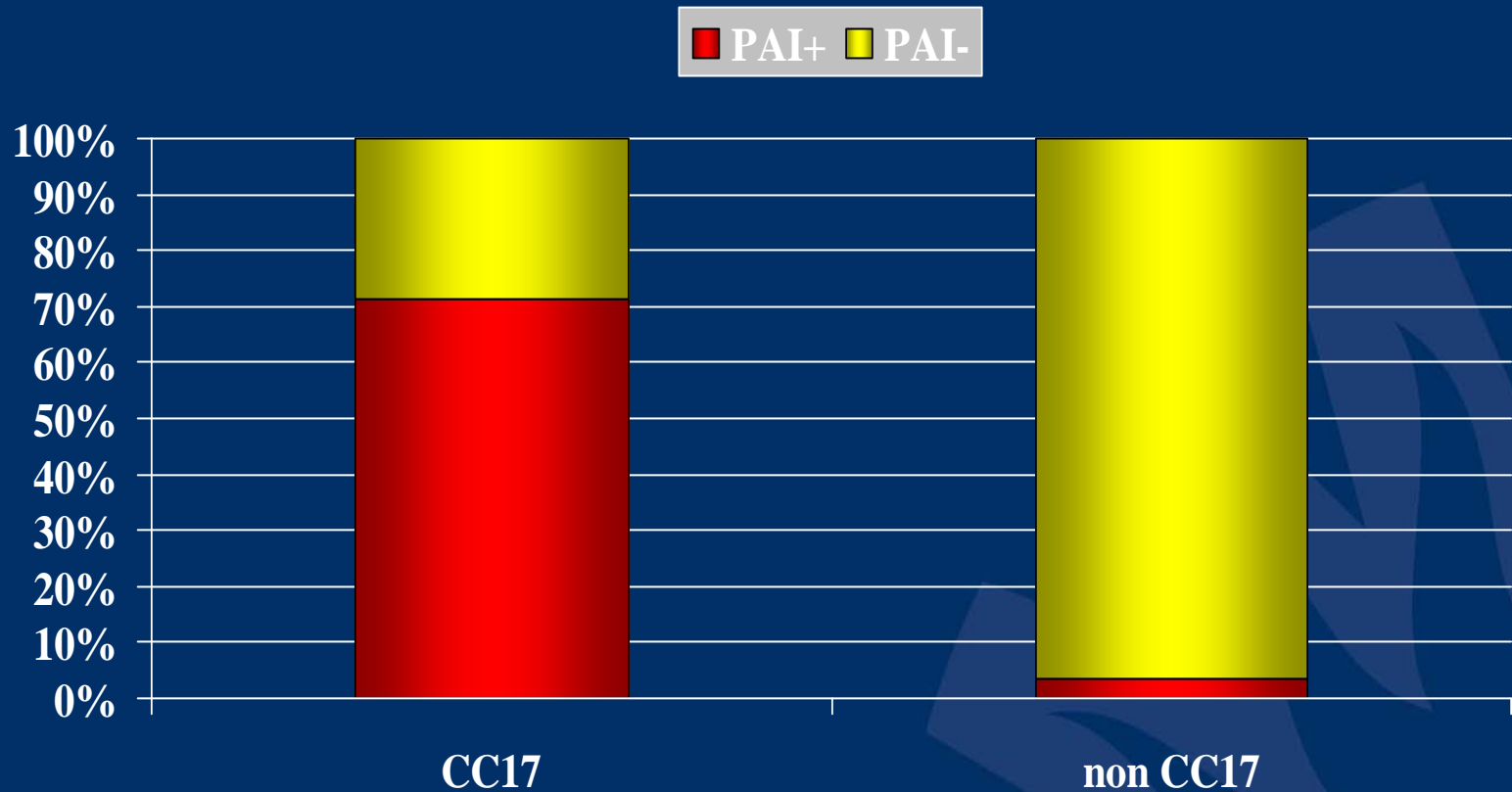
## Gentamicin



# A putative pathogenicity island in CC-17 *E. faecium*



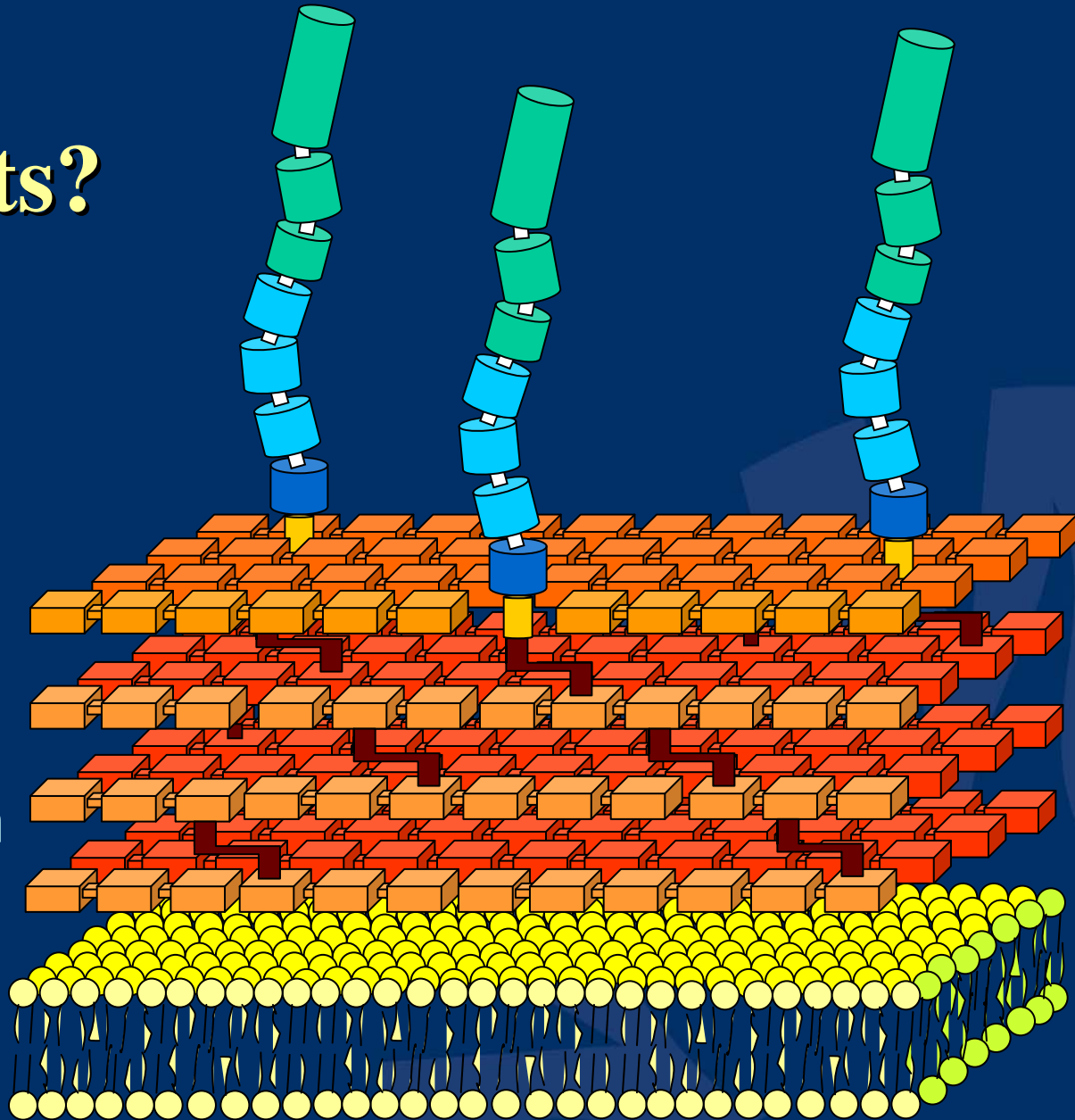
# Putative pathogenicity island: enriched in complex17



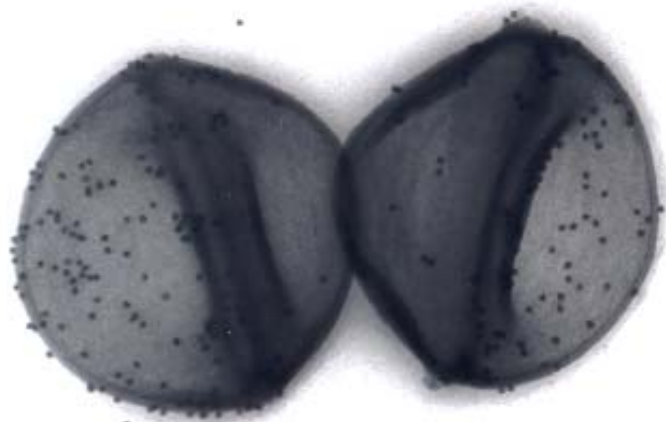
# Virulence determinants?

## Enterococcal Surface Protein (Esp)

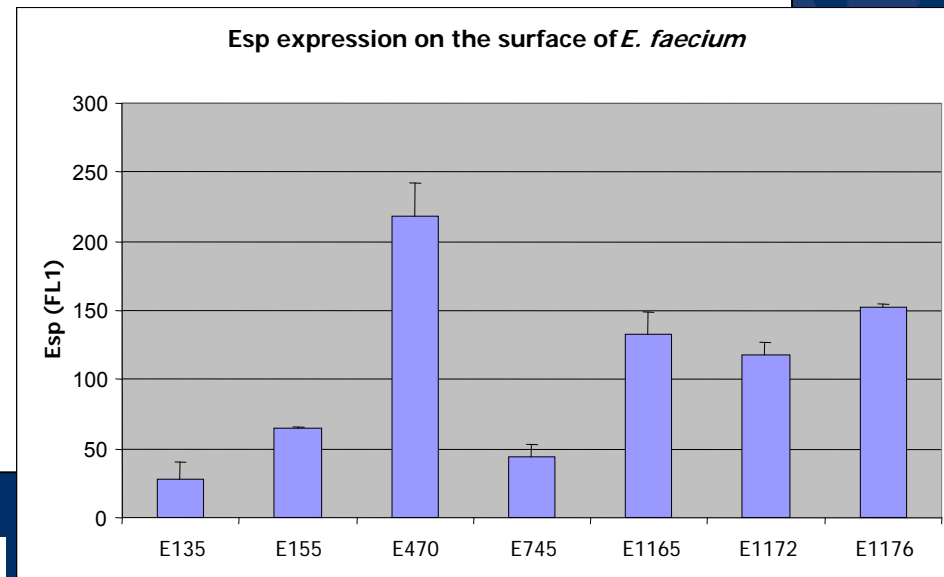
- In *E. faecalis*:
  - Biofilm formation
  - UT colonization



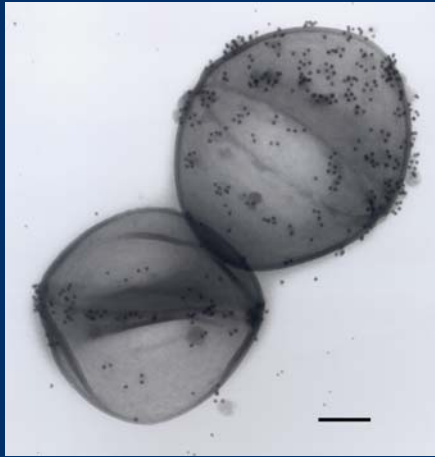
# Esp is expressed on the cell surface of *E. faecium*



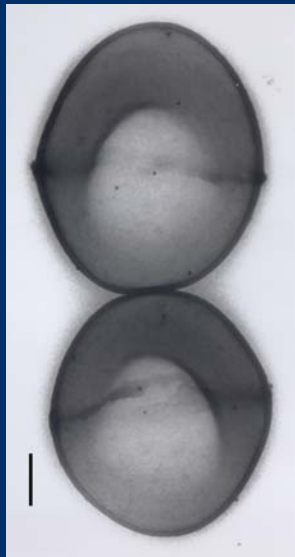
200nm 30.000X



# Esp is involved in biofilm formation



E1162



E1162Δesp

JOURNAL OF BACTERIOLOGY, Nov. 2007, p. 8233-8240  
0021-9193/07/\$08.00+0 doi:10.1128/JB.01205-07  
Copyright © 2007, American Society for Microbiology. All Rights Reserved.

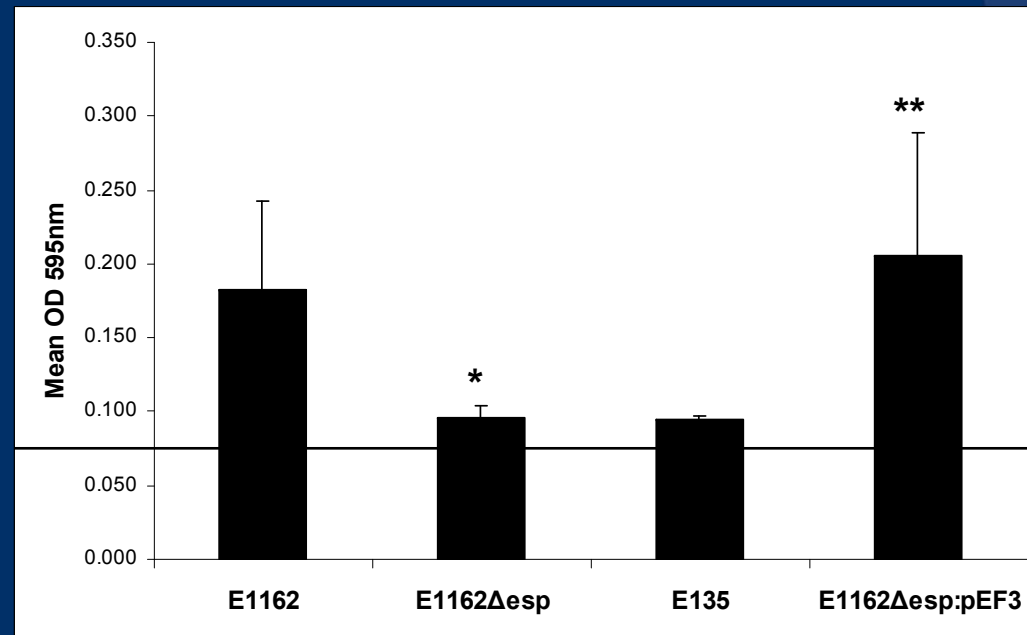
Vol. 189, No. 22

## Enterococcal Surface Protein Esp Is Important for Biofilm Formation of *Enterococcus faecium* E1162<sup>v</sup>

Esther Heikens,\* Marc J. M. Bonten, and Rob J. L. Willems

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Received 27 July 2007/Accepted 31 August 2007



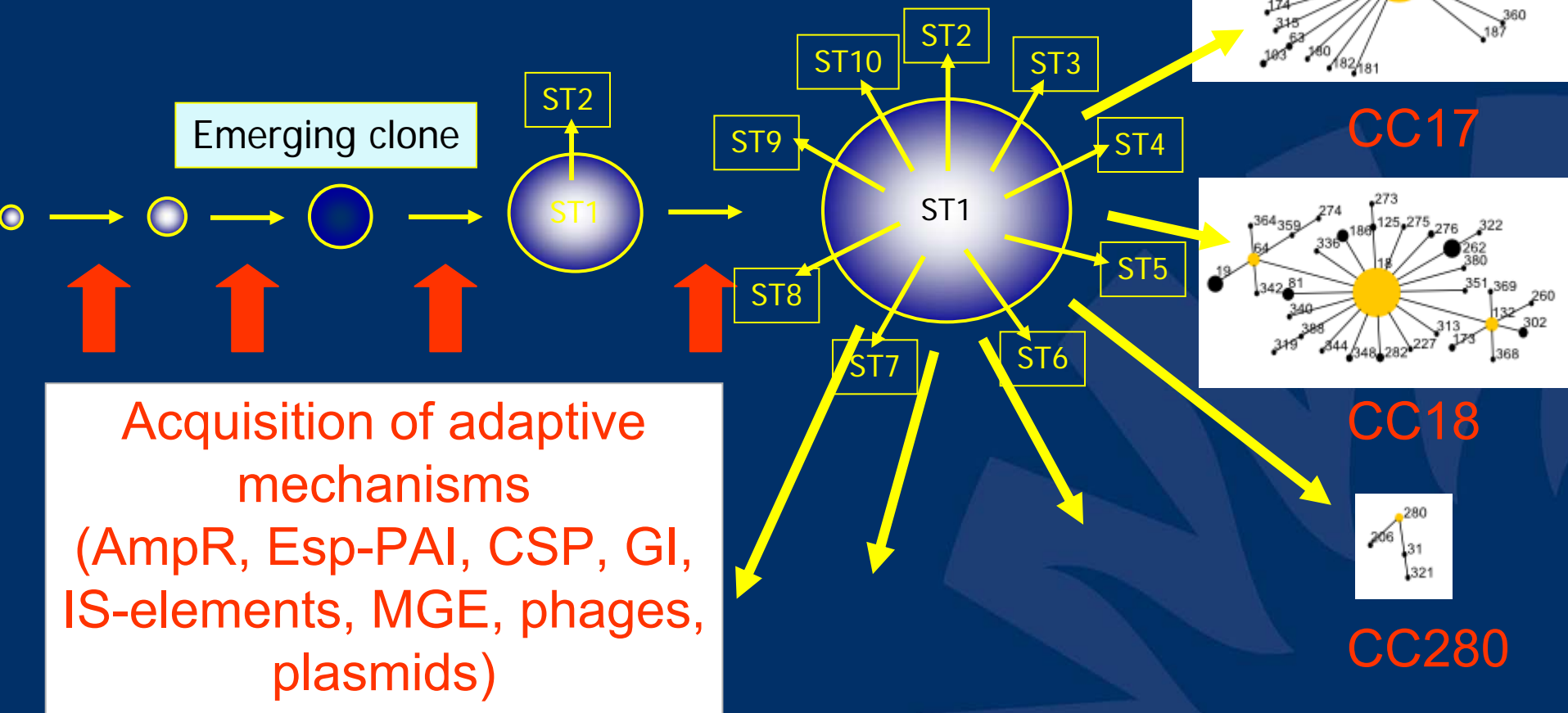
Background level

\* P<0.001, \*\* P<0.0005

# Whole genome approach: Identification of other CC-17 specific genes

- Comparative genomic hybridizations using a mixed whole genome array (9 *Efm*)
  - Hybridization with 97 isolates (CC17 and non-CC17)
  - 437 spots  $\geq$  80% specific for CC17

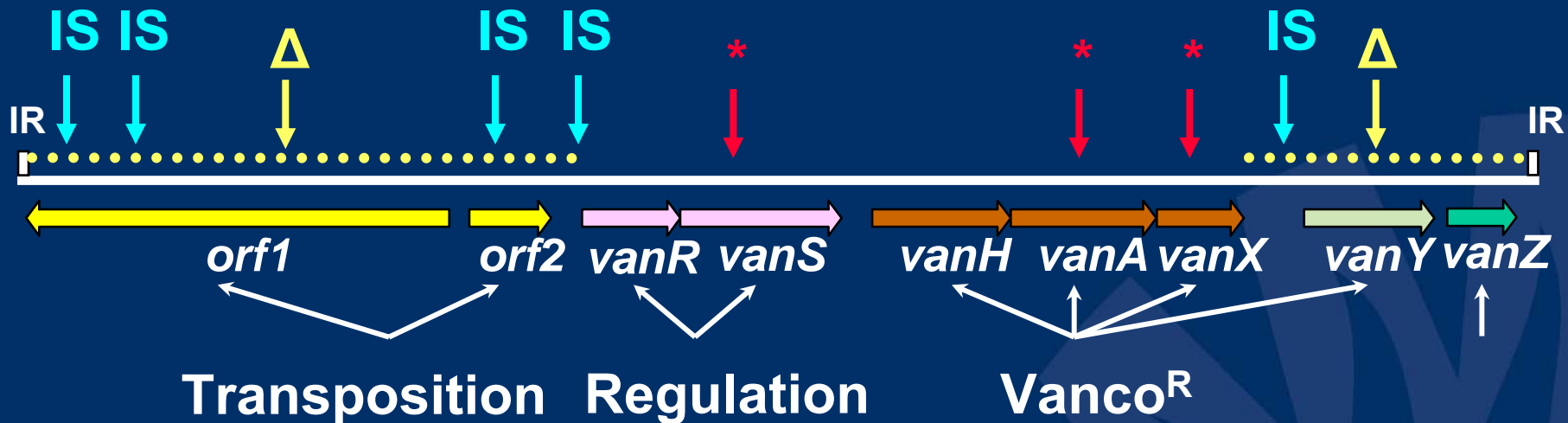
# Evolution of Hospital acquired *E. faecium* clones



# Conclusions on molecular epidemiology

- Not all *E. faecium* clones are identical!!
- *E. faecium* have evolved in distinct genetic “host-specific” lineages (Clonal Complexes)
- *E. faecium* isolates responsible for the majority of the hospital burden belong to several evolutionary and genetically distinct subpopulation/subspecies (for instance CC17), which have spread globally

# The vancomycin-resistance transposon Tn1546



**4 main types (47 Tn1546 sub-types)**

# Potential effects of antibiotics on antibiotic resistance prevalence (VRE)

- Selection after mutation
  - No role
- Selection after horizontal gene transfer (=transposon transfer)
  - Probably minor role
- Selection after cross-transmission
  - Overwhelming importance

# The association between antecedent vancomycin treatment and hospital-acquired VRE

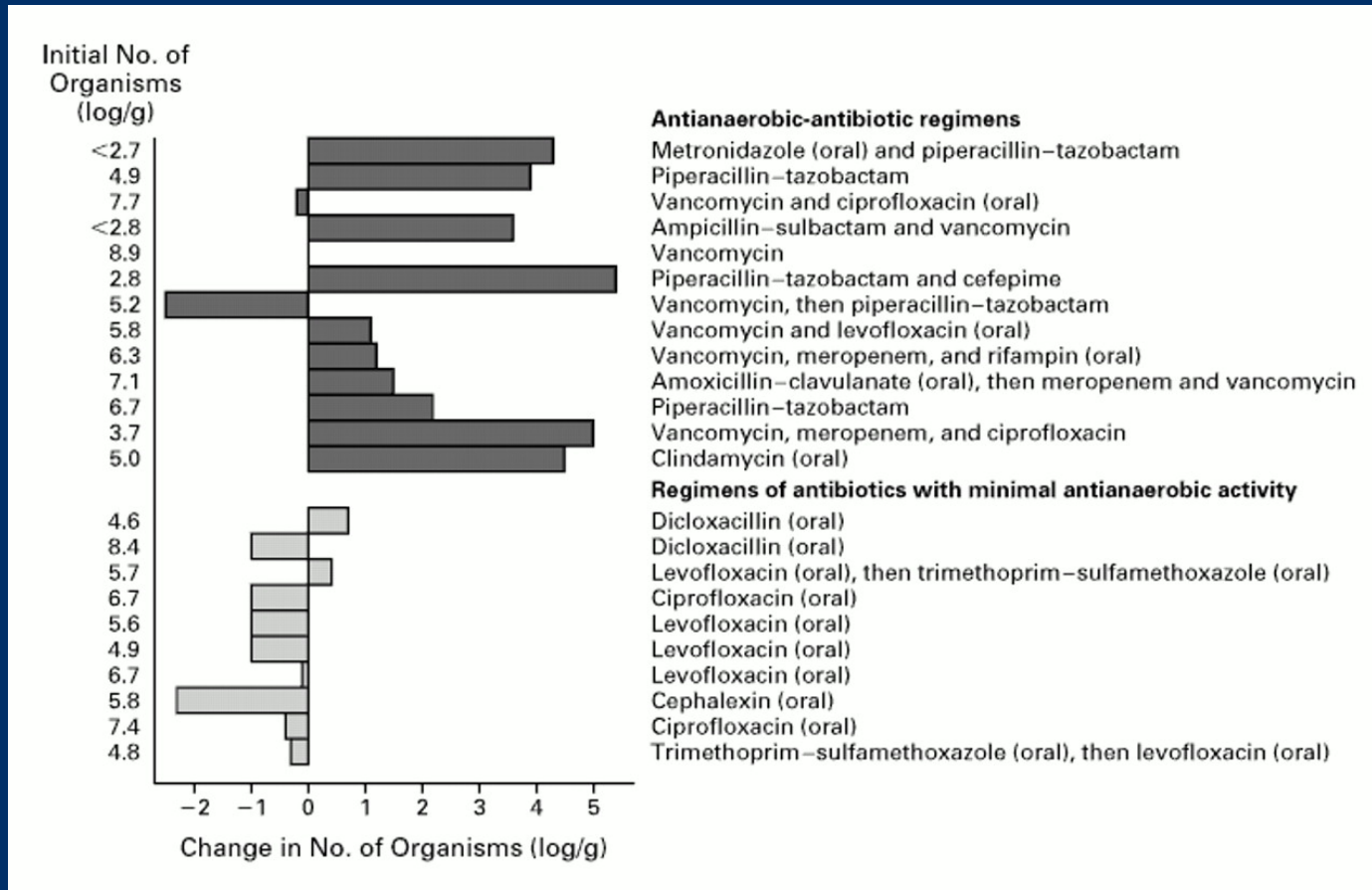
Carmeli, Samore and Huskins. *Arch Intern Med* 1999; 159: 2461-8

- Meta-analysis
- Case-control studies (n=20, in 15 reports) examining the association of vancomycin treatment and VRE
- 586 pts with VRE (61% Van) and 1249 controls (26% Van)
- Potential problems in studies
  - Selecting control group
    - VSE (n=5) or 'no VRE' (n=15)
  - Case patient identification
    - Clinical cultures (n=5), surveillance (n=6), acquisition (3)
  - Adjustment for length of hospitalization
    - Yes (n=5), no (n=10)
  - Publication bias
    - Funnel plot analysis

# The Odds ratios of vancomycin treatment

	Odds ratio
Pooled data of all studies heterogeneity $p < 0.001$	4.5 (3-6.9)
Selection of control group	
VSE	10.7 (4.8-23.8)
no VRE	2.7 (2-3.8)
Case patient identification	
clinical cultures	6.2 (3.2-12.2)
surveillance	3.3 (1.7-6.3)
acquisition	3.2 (1.7-5.9)
Adjustment for LOS	
no	3.1 (1.8-5.3)
yes	1.4 (0.74-2.6)
Publication bias	$P < .01$ (overrepresentation of small studies with high ORs)

# Effect on the Density of VRE in Stool of Therapy with Antianaerobic-Antibiotic Regimens in 13 Patients and Regimens of Antibiotics with Minimal Antianaerobic Activity in 10 Patients



Donskey C et al. N Engl J Med 2000;343:1925-1932



# VRE and mortality

- VRE infection as a prognostic marker for mortality
  - Overwhelming evidence
- VRE infection as an etiological factor for mortality
  - Hardly any (convincing) evidence
  - Excluding confounders (such as severity of underlying illness) is almost impossible

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# Epidemiology of colonisation of patients and environment with vancomycin-resistant enterococci

*Marc J M Bonten, Mary K Hayden, Catherine Nathan, Jean van Voorhis, Marian Matushek, Sarah Slaughter, Thomas Rice, Robert A Weinstein*

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Vol 348 } December 14, 1996

## VRE: The triple threat bug

Persistent colonizer of the gut, like multi-resistant Gram-negative rods

Persistent colonizer of the skin, like MRSA

Frequent colonizer of the inanimate environment, like *C. difficile*

# Chlorhexidine Gluconate to Cleanse Patients in a Medical Intensive Care Unit

*The Effectiveness of Source Control to Reduce the Bioburden of Vancomycin-Resistant Enterococci*

Michael O. Vernon, DrPH; Mary K. Hayden, MD; William E. Trick, MD; Robert A. Hayes, BSc; Donald W. Blom, RN; Robert A. Weinstein, MD; for the Chicago Antimicrobial Resistance Project (CARP)

Arch Intern Med. 2006;166:306-312

Prospective sequential-group single-arm clinical trial

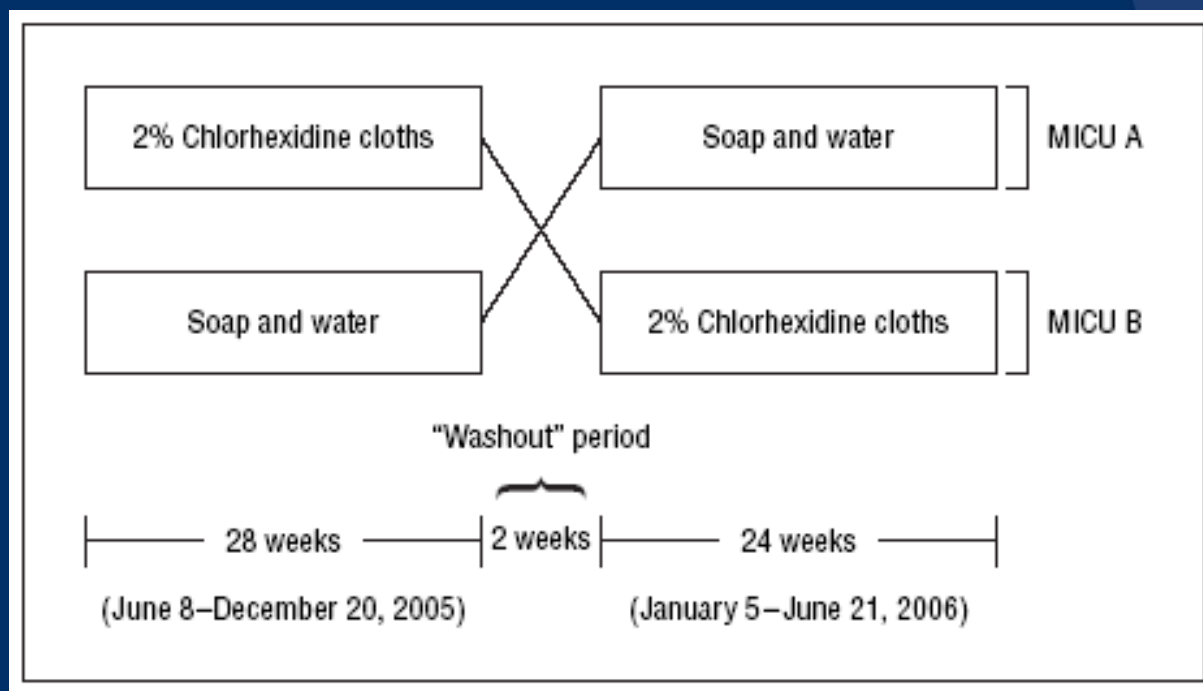
**Conclusion:** Cleansing patients with chlorhexidine-saturated cloths is a simple, effective strategy to reduce VRE contamination of patients' skin, the environment, and health care workers' hands and to decrease patient acquisition of VRE.



# Effectiveness of Chlorhexidine Bathing to Reduce Catheter-Associated Bloodstream Infections in Medical Intensive Care Unit Patients

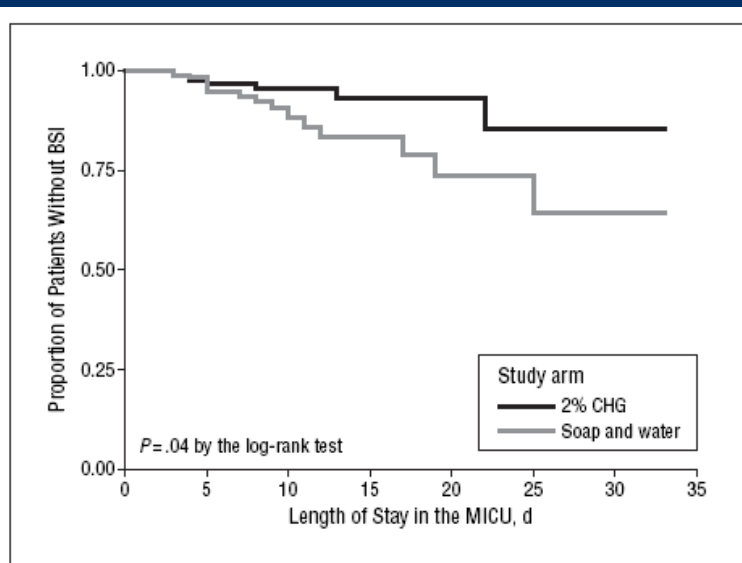
Susan C. Bleasdale, MD; William E. Trick, MD; Ines M. Gonzalez, MD;  
Rosie D. Lyles, MD; Mary K. Hayden, MD; Robert A. Weinstein, MD

Arch Intern Med. 2007;167(19):2073-2079



**Table 2. Comparison of Incidence of Infection by Method of Bathing Patients and Infection Category**

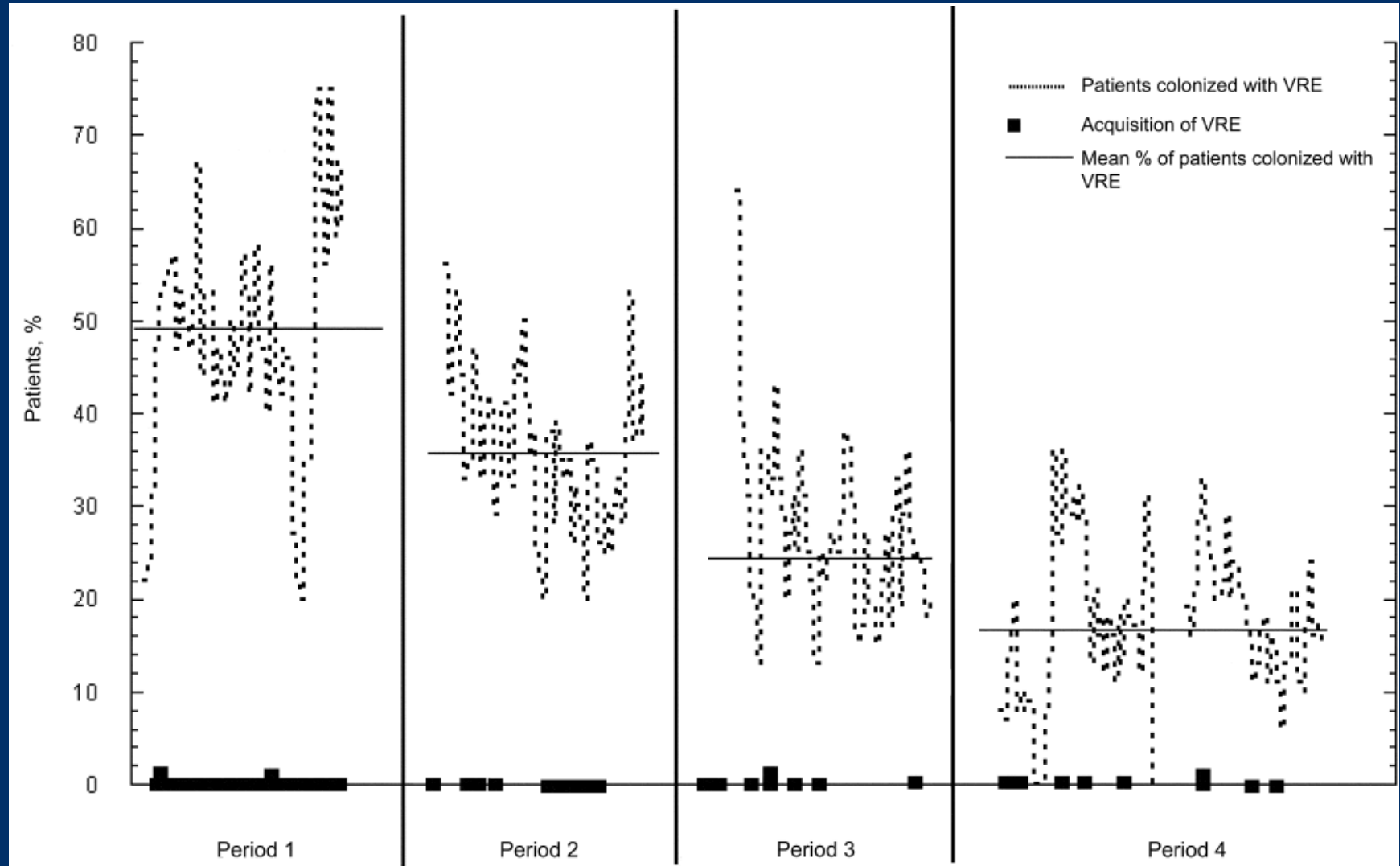
Infection Category	Bathing Method				Difference (95% CI)	P Value
	Soap and Water		2% CHG			
	Events	Rate <sup>a</sup>	Events	Rate <sup>a</sup>		
Primary BSI	22	10.4	9	4.1	6.3 (1.2 to 11)	.01
Contaminant	9	4.3	4	1.8	2.4 (-0.9 to 5.7)	.16
Clinical sepsis	9	4.2	16	7.2	-3.0 (-7.5 to 1.5)	.20
Urinary tract infection	17	8.0	13	5.9	2.1 (-2.8 to 7.1)	.41
Ventilator-associated pneumonia	15	6.8	18	7.8	-1.1 (-6.3 to 4.1)	.69
Secondary BSI	5	2.4	5	2.3	0 (-2.8 to 3.0)	.95
<i>Clostridium difficile</i> diarrhea	20	9.4	21	9.5	0 (-5.9 to 5.7)	.98



**Figure 2.** Kaplan-Meier survival curve for occurrence of bloodstream infection (BSI) by study arm. CHG indicates chlorhexidine gluconate; MICU, medical intensive care unit.

**Conclusions:** Daily cleansing of MICU patients with CHG-impregnated cloths is a simple, effective strategy to decrease the rate of primary BSIs.

# Effect of Improved Environmental Cleaning on Transmission of VRE



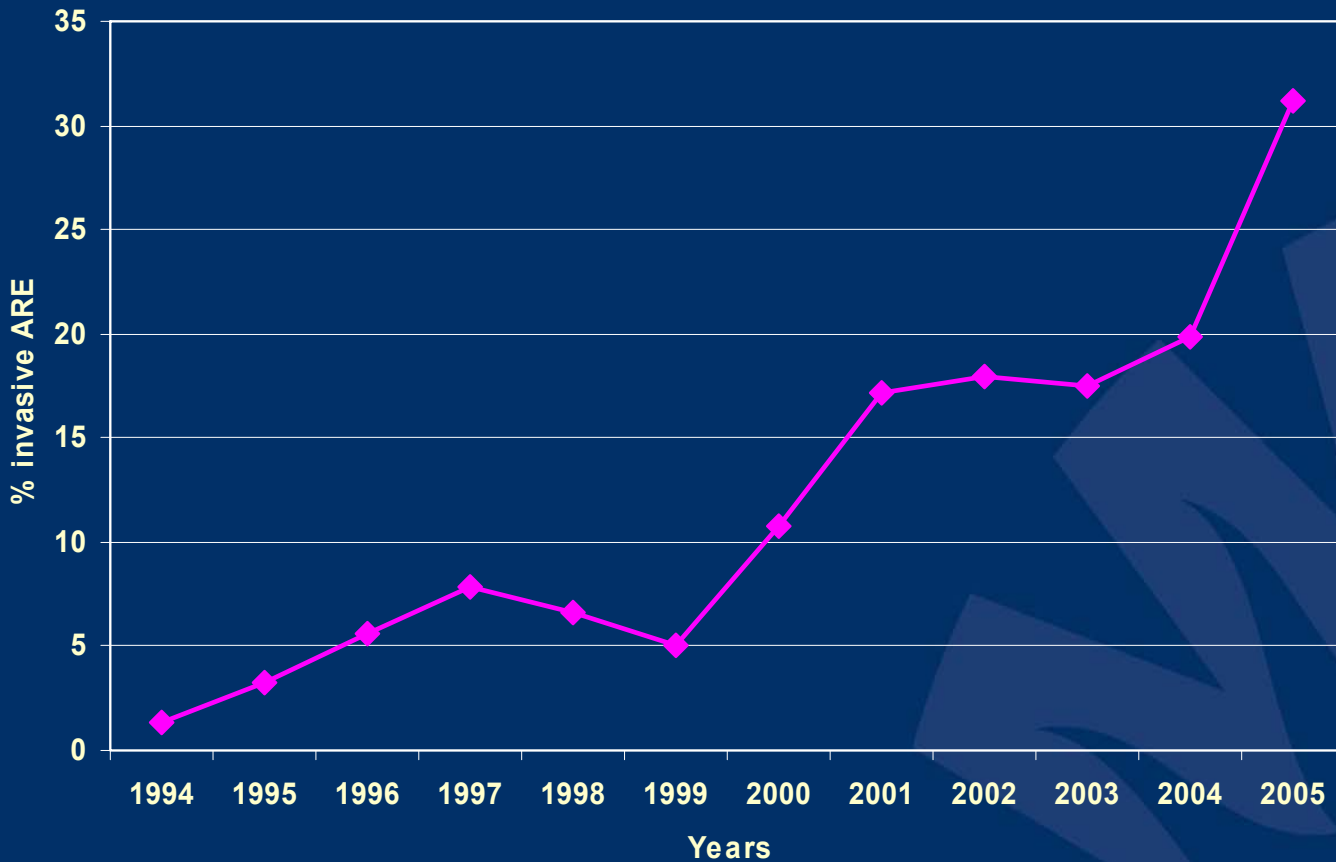
# Conclusions on prevention of VRE transmission and infection

- Transmission
  - Standard barrier precautions (including hand hygiene) are important
  - Environmental cleaning
  - Source reduction through skin decontamination with chlorhexidine
  - Modulation of antibiotics (?)
- Infections
  - Source reduction through skin decontamination with chlorhexidine
  - Reduction/modulation of antibiotics (?)

**If you don't have VRE!**

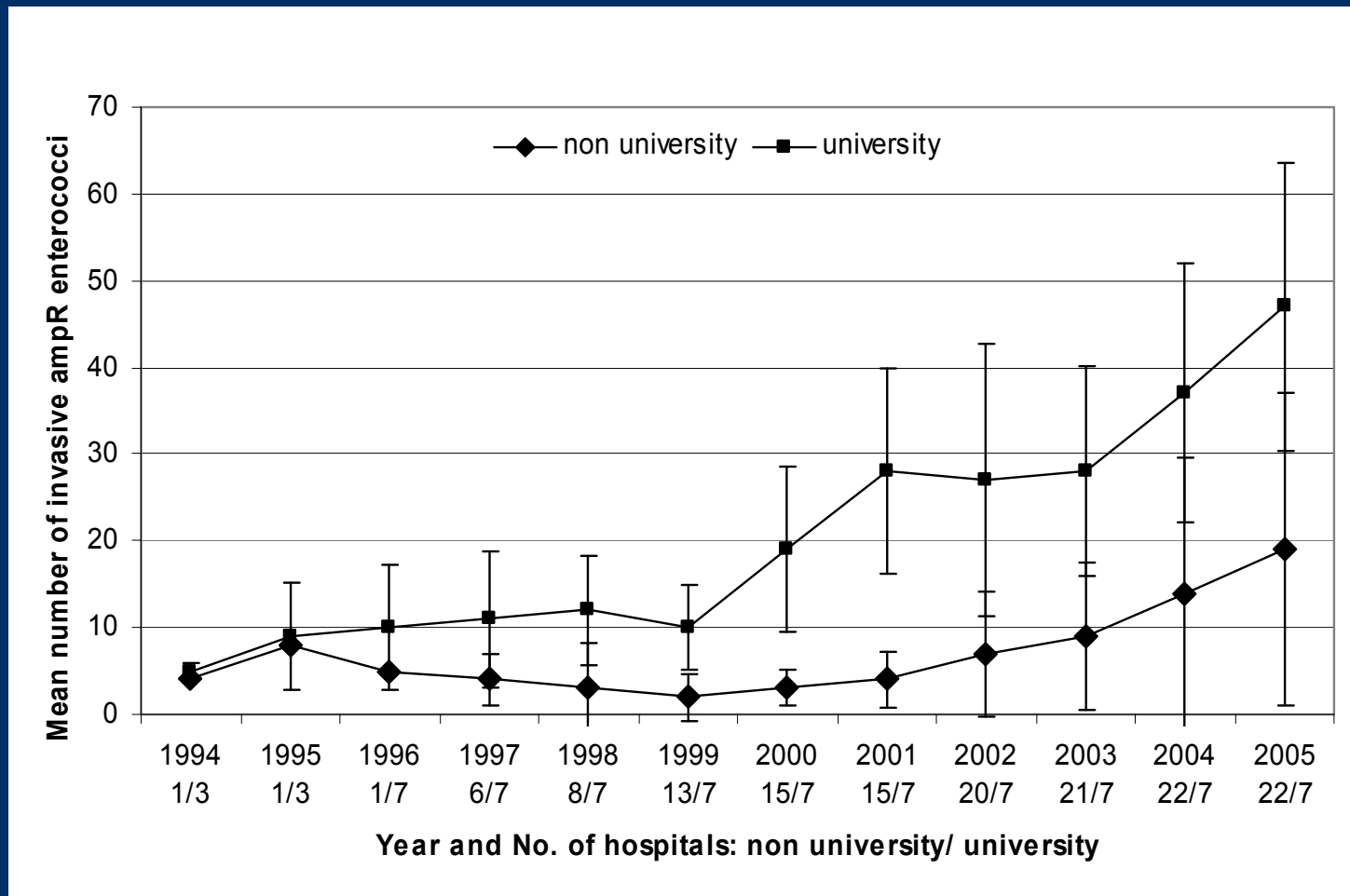
**Look for ampicillin-resistant  
E. faecium!**

# Proportion of invasive ARE from total number of invasive Enterococcus species in UMC Utrecht

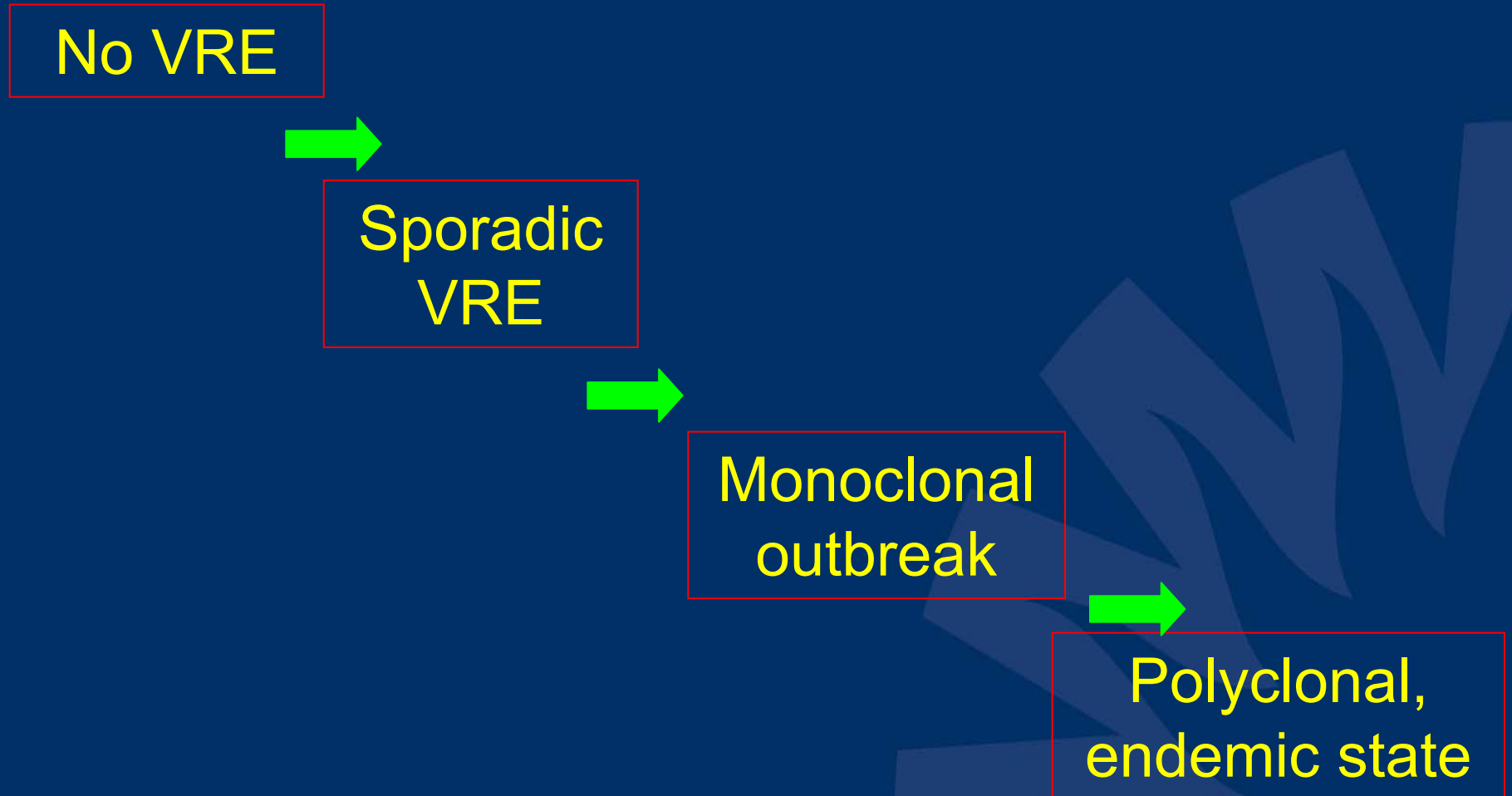


*Top et al. CMI 2007*

# Incidence of invasive Ampicillin-resistant enterococcal infections in Dutch hospitals



# Establishment of VRE Endemicity in Hospitals



# Establishment of ARE Endemicity in Hospitals

No ARE



Sporadic  
ARE

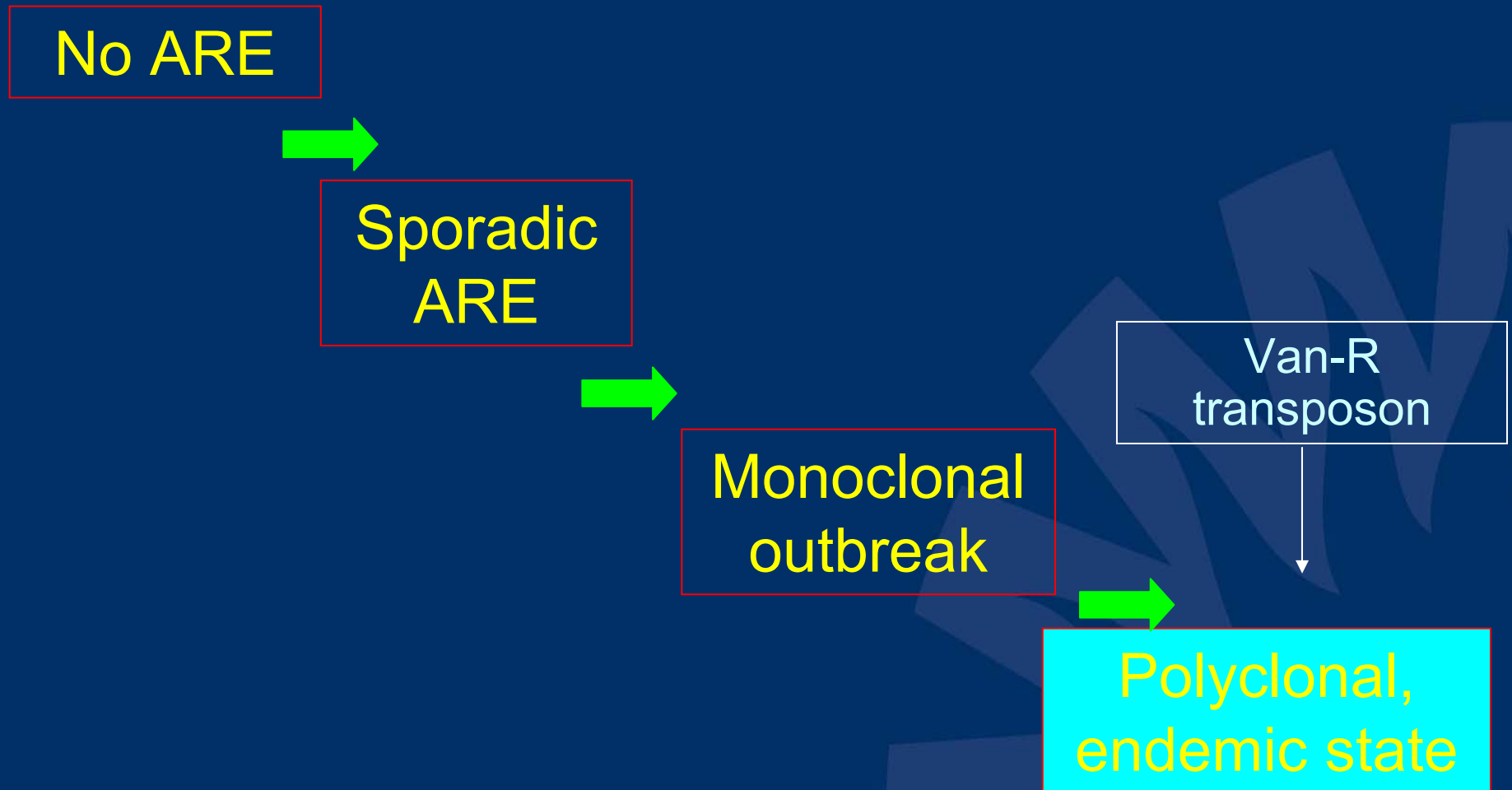


Monoclonal  
outbreak



Polyclonal,  
endemic state

# Establishment of ARE Endemicity in Hospitals



# “Approaches to Control multiresistant Enterococci: Studies on molecular ecology, horizontal gene transfer, fitness and prevention.”



Rob Willems

Janetta Top

Helen Leavis

Willem van Schaik

Marieke de Regt

Esther Heikens

Antoni Hendrickx

Robert Weinstein

Mary Haiden

