



# MRSA treatment: does the future shine ?

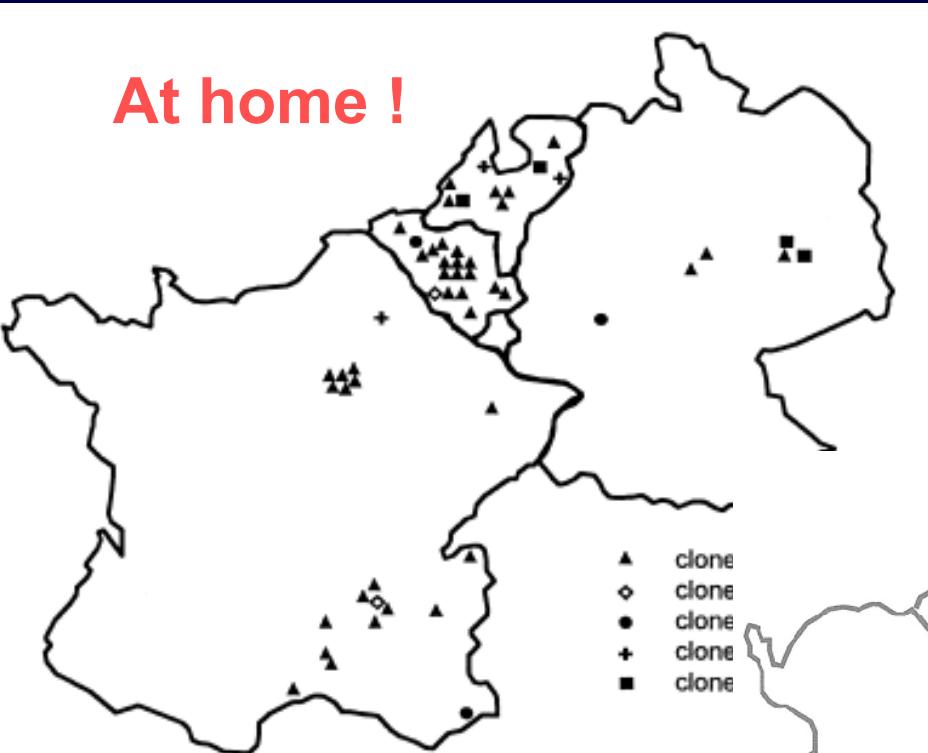
Françoise Van Bambeke & Paul M. Tulkens  
Unité de Pharmacologie cellulaire et moléculaire



UCL - Brussels

# MRSA : where are there ?

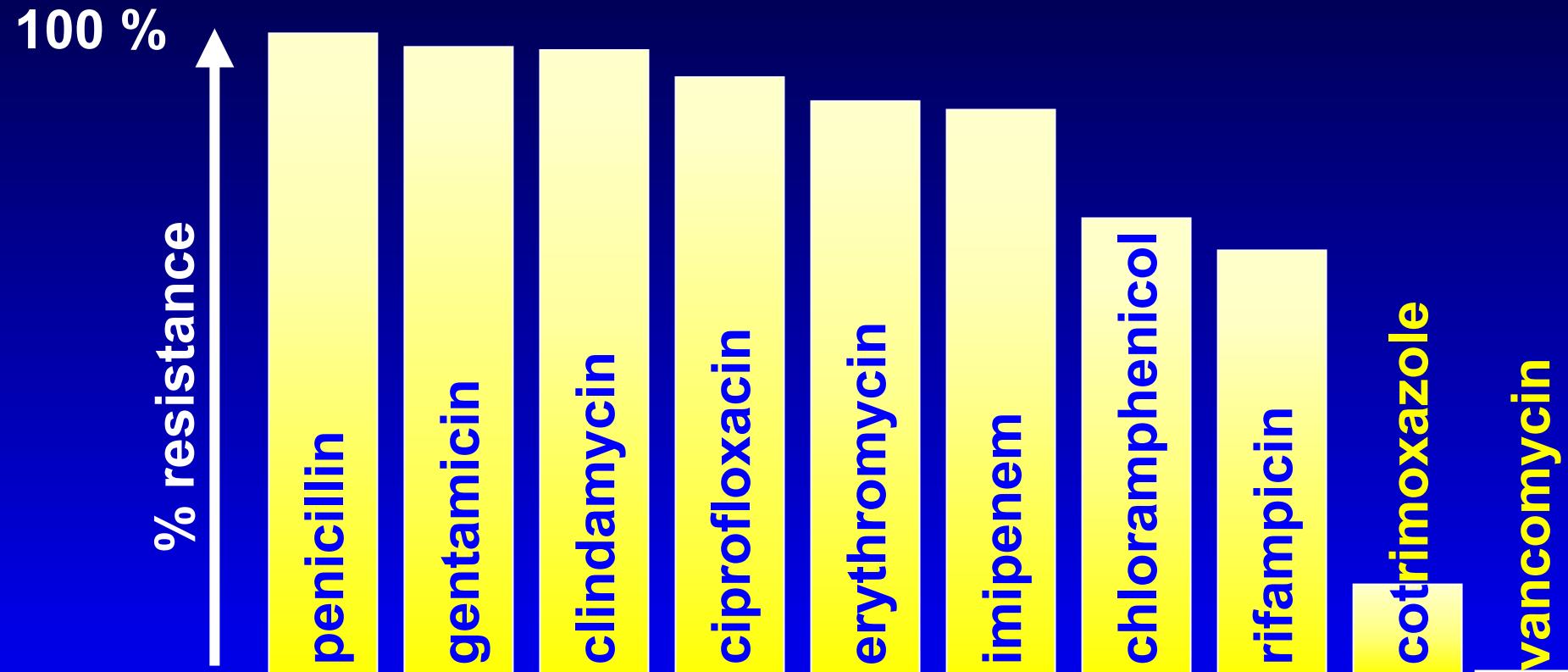
At home !



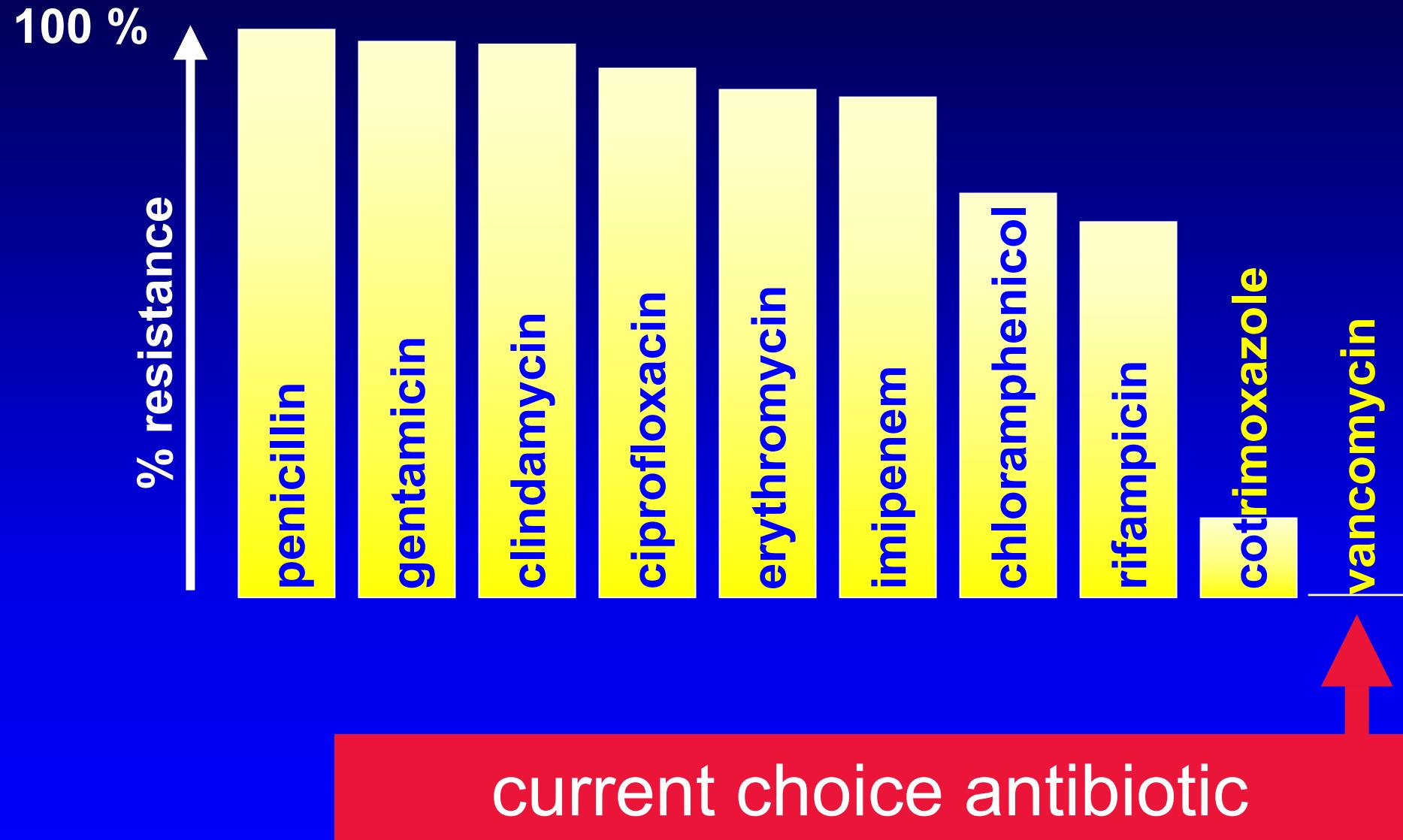
And here too!



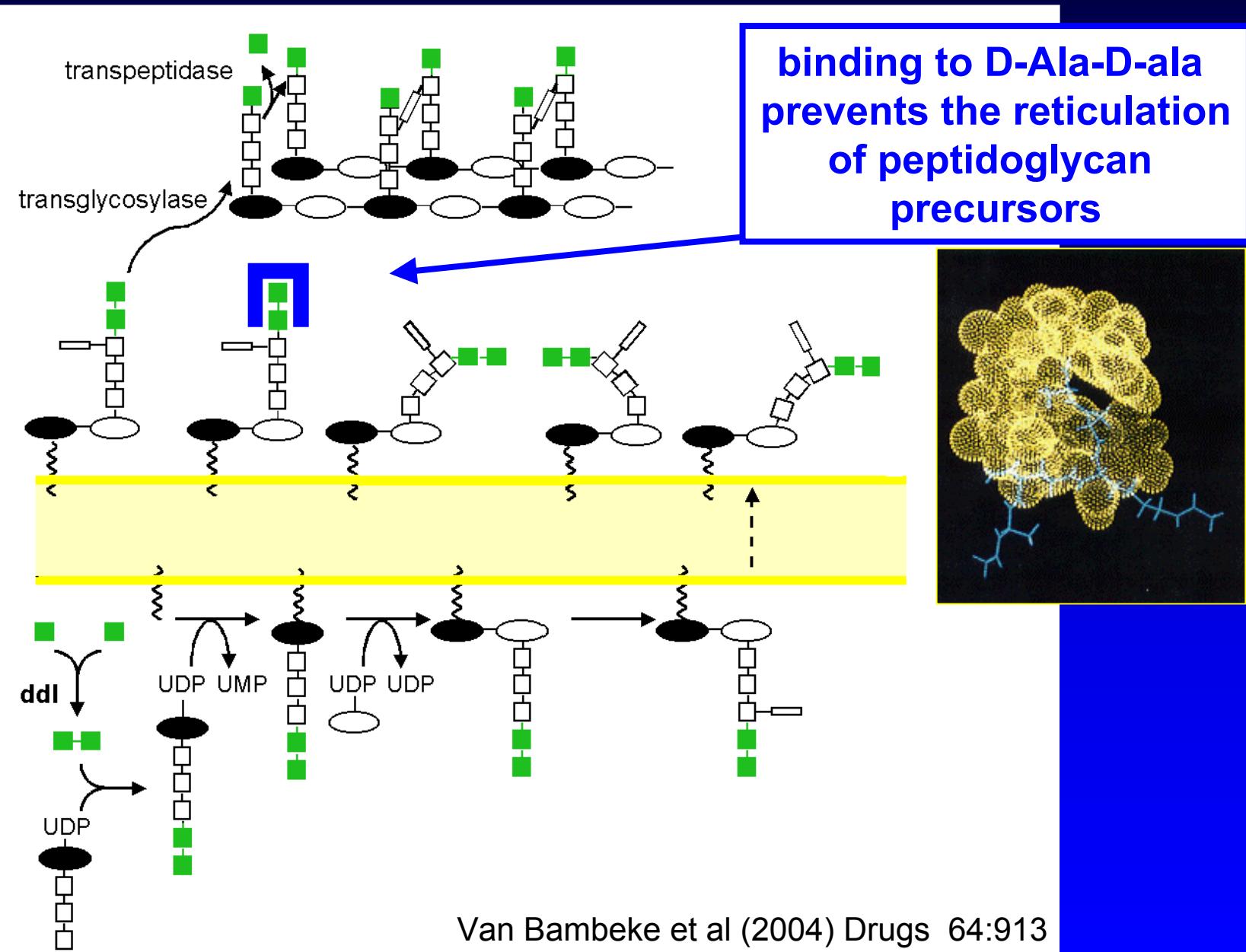
# MRSA : picture of resistance in Europe in 2000



# MRSA : picture of resistance in Europe in 2000



# Glycopeptide mechanism of action



# anti- MRSA : do we need something else ?



# anti- MRSA : do we need something else ?



**Methicillin-resistant *Staphylococcus aureus*  
clinical strain with reduced vancomycin  
susceptibility**

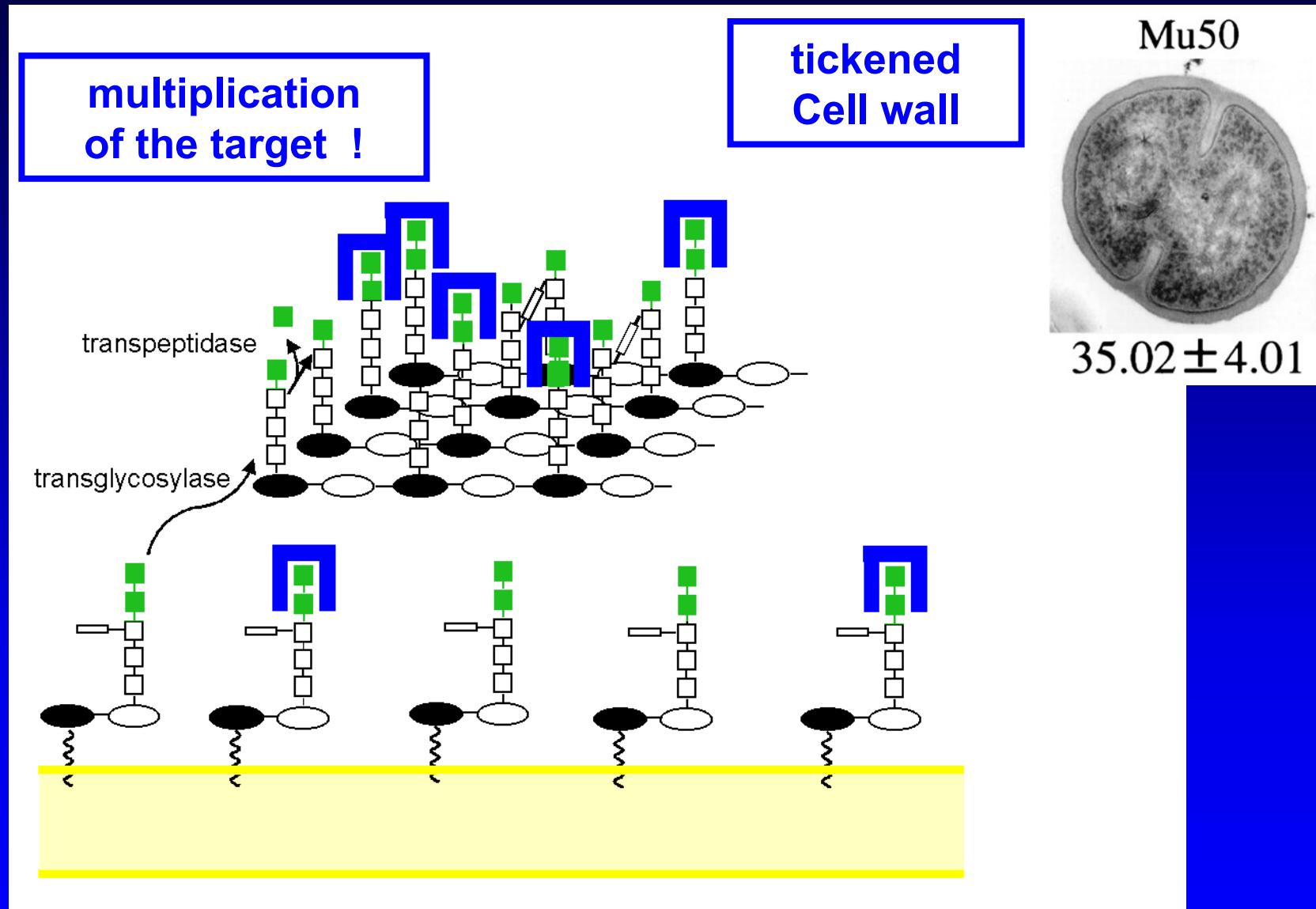
*J Antimicrob Chemother* 1997; **40**: 135–136

K. Hiramatsu<sup>a\*</sup>, H. Hanaki<sup>a</sup>, T. Ino<sup>b</sup>, K. Yabuta<sup>b</sup>,  
T. Oguri<sup>c</sup> and F. C. Tenover<sup>d</sup>

<sup>a</sup>Department of Bacteriology; <sup>b</sup>Department of Pediatrics, Juntendo University, Tokyo; <sup>c</sup>Clinical Laboratory, Juntendo Hospital, Tokyo, Japan; <sup>d</sup>Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA

	AB	MIC
AMP	64	
VAN	8	
GEN	128	
RIF	2048	
LVX	8	
TET	128	
SMX	0.125	
Q-D	0.5	
LZD	2	

# Resistance in staphylococci (GISA)



# Resistance in staphylococci (GISA)

already in Belgium

*Journal of Antimicrobial Chemotherapy* (2002) **50**, 383–391  
DOI: 10.1093/jac/dkf142

JAC

## Emergence of vancomycin-intermediate *Staphylococcus aureus* in a Belgian hospital: microbiological and clinical features

Olivier Denis<sup>1\*</sup>, Claire Nonhoff<sup>1</sup>, Baudouin Byl<sup>2</sup>, Christiane Knoop<sup>3</sup>, Sophie Bobin-Dubreux<sup>4</sup> and Marc J. Struelens<sup>1</sup>

<sup>1</sup>Service de Microbiologie, <sup>2</sup>Unité d'Epidémiologie et d'Hygiène Hospitalière and <sup>3</sup>Service de Pneumologie,  
Hôpital Erasme, Université Libre de Bruxelles, 808 route de Lennik, 1070 Brussels, Belgium;  
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Received 13 May 2002; accepted 10 June 2002

# anti- MRSA : do we need something else ?



Second threat



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## ORIGINAL ARTICLE

### BRIEF REPORT

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Volume 348:1342-1347

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Number 14

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## Infection with Vancomycin-Resistant *Staphylococcus aureus* Containing the vanA Resistance Gene

Soju Chang, M.D., M.P.H., Dawn M. Sievert, M.S., Jeffrey C. Hageman, M.H.S., Matthew L. Boulton, M.D., Fred C. Tenover, Ph.D., M.P.H., Frances Pouch Downes, Dr.P.H., Sandip Shah, M.S., James T. Rudrik, Ph.D., Guy R. Pupp, D.P.M., William J. Brown, Ph.D., Denise Cardo, M.D., Scott K. Fridkin, M.D., for the Vancomycin-Resistant *Staphylococcus aureus* Investigative Team



42nd Annual



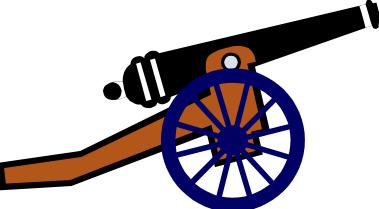
## MICs and kill kinetics of antibiotics against vancomycin resistant *Staphylococcus aureus* (VRSA) with vanA gene isolated at Penn State Hershey Medical Center

B. Bozdogan<sup>1</sup>, J. Chaitram<sup>2</sup>, P. C. Appelbaum<sup>1</sup>, C. Whitener<sup>1</sup>, F. A. Browne<sup>1</sup>, F. C. Tenover<sup>2</sup>

<sup>1</sup>Penn State Hershey Medical Center, Hershey, PA, <sup>2</sup>Centers for Disease Control and Prevention, Atlanta,

AB MIC

VAN	32
TEC	4



# anti- MRSA : weapons for tomorrow

<b>Oxazolidinones</b>	linezolid	marketed in Belgium
<b>Synergistins</b>	quinupristin/dalfopristin	marketed in US
<b>Lipopeptides</b>	daptomycin	marketed in US
<b>Glycopeptides</b>	oritavancin dalbavancin telavancin	phases II/III phases II/III phases II/III
<b>Glycylcyclines</b>	tigecycline PKT0796	phase III phase I
<b>Quinolones</b>	garenoxacin DQ-113	phase III investigational

# anti- MRSA : weapons for tomorrow

MRSA		
	vancomycin	0.25-2
<b>Oxazolidinones</b>	linezolid	1-8
<b>Synergistins</b>	Q/D	0.03-1
<b>Lipopeptides</b>	daptomycin	0.06-0.5
<b>Glycopeptides</b>	oritavancin dalbavancin telavancin	0.13-4 0.06-1 < 0.06-2
<b>Glycylcyclines</b>	tigecycline PKT0796	0.12-1 0.5
<b>Quinolones</b>	garenoxacin DQ-113	0.125-0.25 0.125

Slightly more active than Vanco

# anti- MRSA : weapons for tomorrow

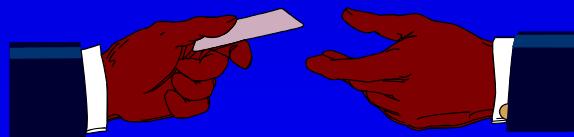
		VISA
	<b>vancomycin</b>	8
<b>Oxazolidinones</b>	linezolid	1-2
<b>Synergistins</b>	Q/D	0.25-0.25
<b>Lipopeptides</b>	daptomycin	0.5-1
<b>Glycopeptides</b>	oritavancin dalbavancin telavancin	1-8 2 2
<b>Glycylcyclines</b>	tigecycline PKT0796	0.06-1
<b>Quinolones</b>	garenoxacin DQ-113	0.5 0.25

Candiani JAC (1999) 44:179; Rybak AAC (2000) 44:1062; Petersen AAC (2002) 46:2595;  
Schmitz JAC (2002) 49:283-287; Konako AAC (2003) 47:3694; Pace AAC (2003) 47:3602

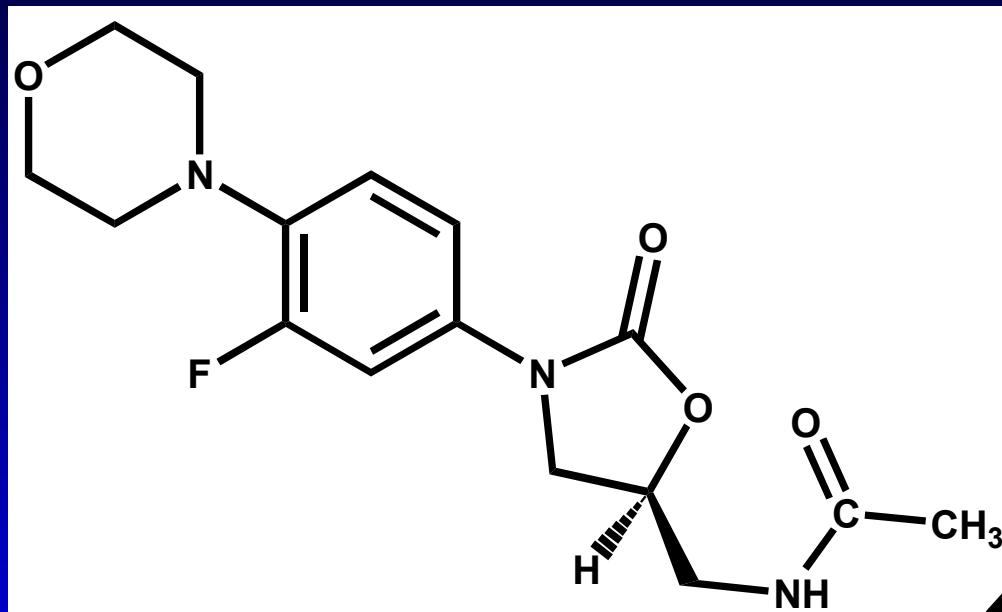
# New anti- MRSA :

1. A new life for old molecules :

change of owner , new breath ?



You said "New anti- MRSA" ?



Dupont



Upjohn

Linezolid (oxazolidinone)



Pharmacia



# **Linezolid: an historical perspective**

**Discovery of a new antibiotic class :**

**Oxazolidinones, a new class of synthetic antibacterial agents : in vitro and in vivo activities of DuP105 and DuP721.**

Slee et al; AAC. **1987**, 31: 1791-7.

**... an birth of a future drug:**

**Preparation of substituted oxazine - and thiazine oxazolidinone antibiotics.**

Barbachyn et al, **1995**, PCT Int. Appl. 37 pp. CODEN : PIXXD2 WO 9507271 A1 19950316).

# **Linezolid: an historical perspective**

**Linezolid identified as anti-MRSA:**

**In vitro activity of linezolid against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*.**

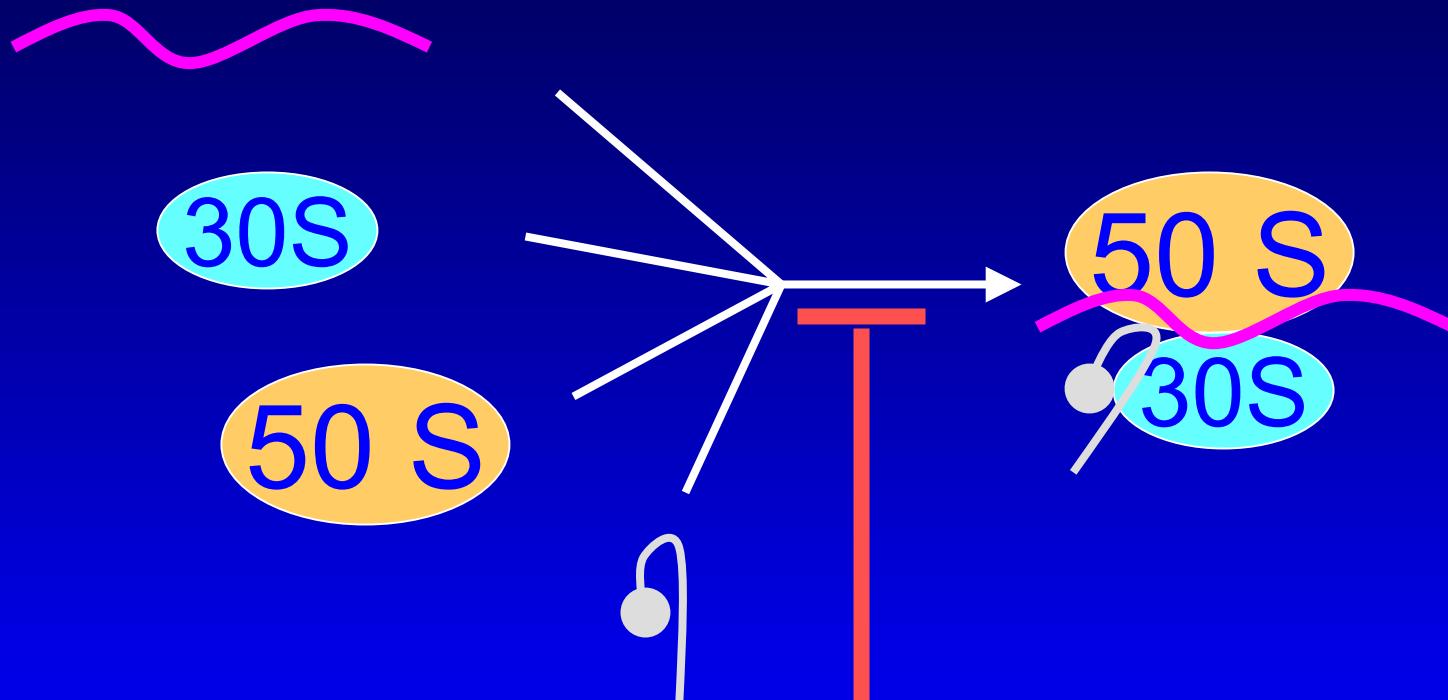
Patel et al, **1999** Diagn Microbiol Infect Dis., 34: 119-22.

**But very quickly ...**

**Linezolid resistance in a clinical isolate of *Staphylococcus aureus*.**

Tsiodras et al, Lancet. **2001** 358:207-8.

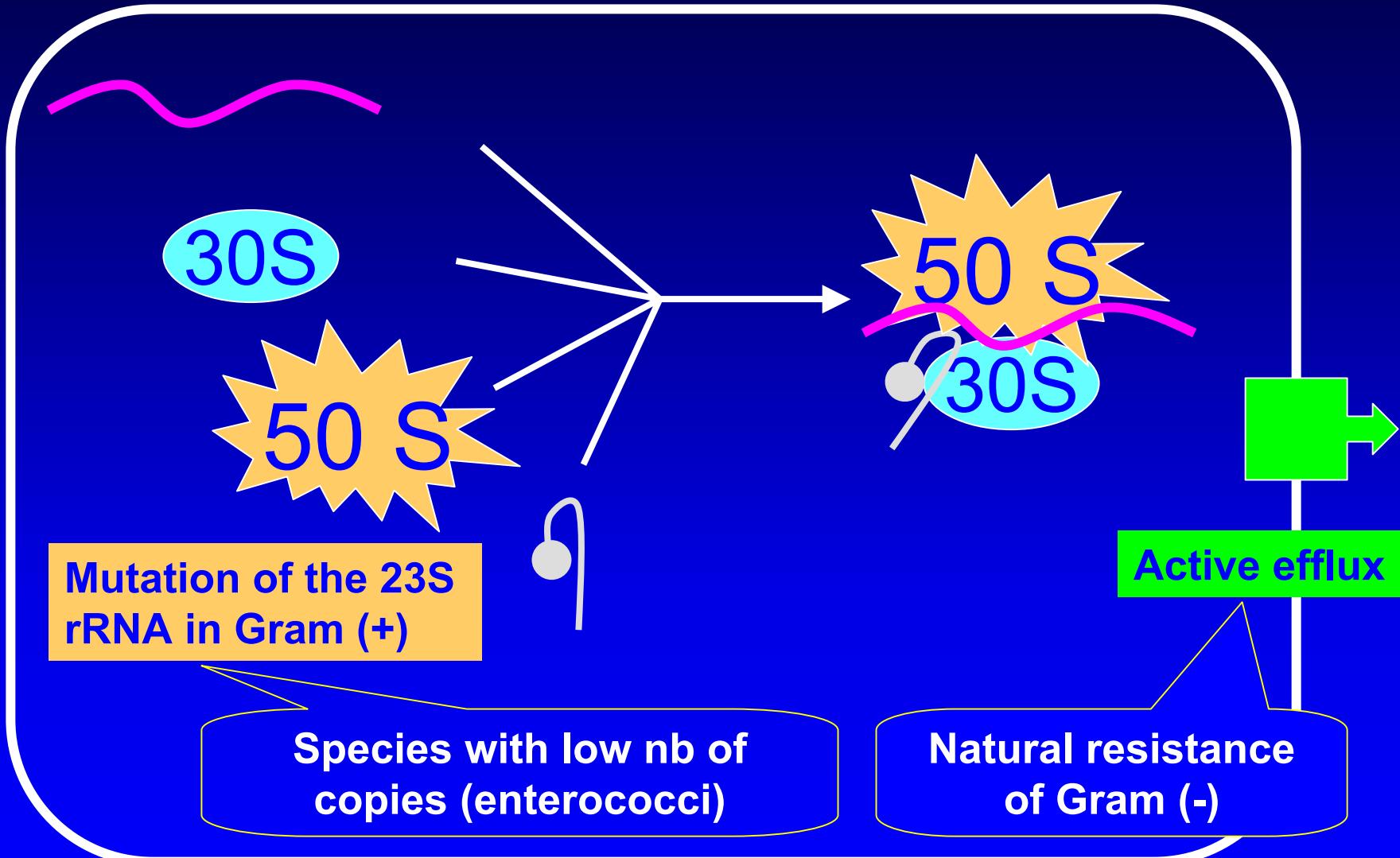
# Linezolid action and resistance



No cross-resistance  
with MLS

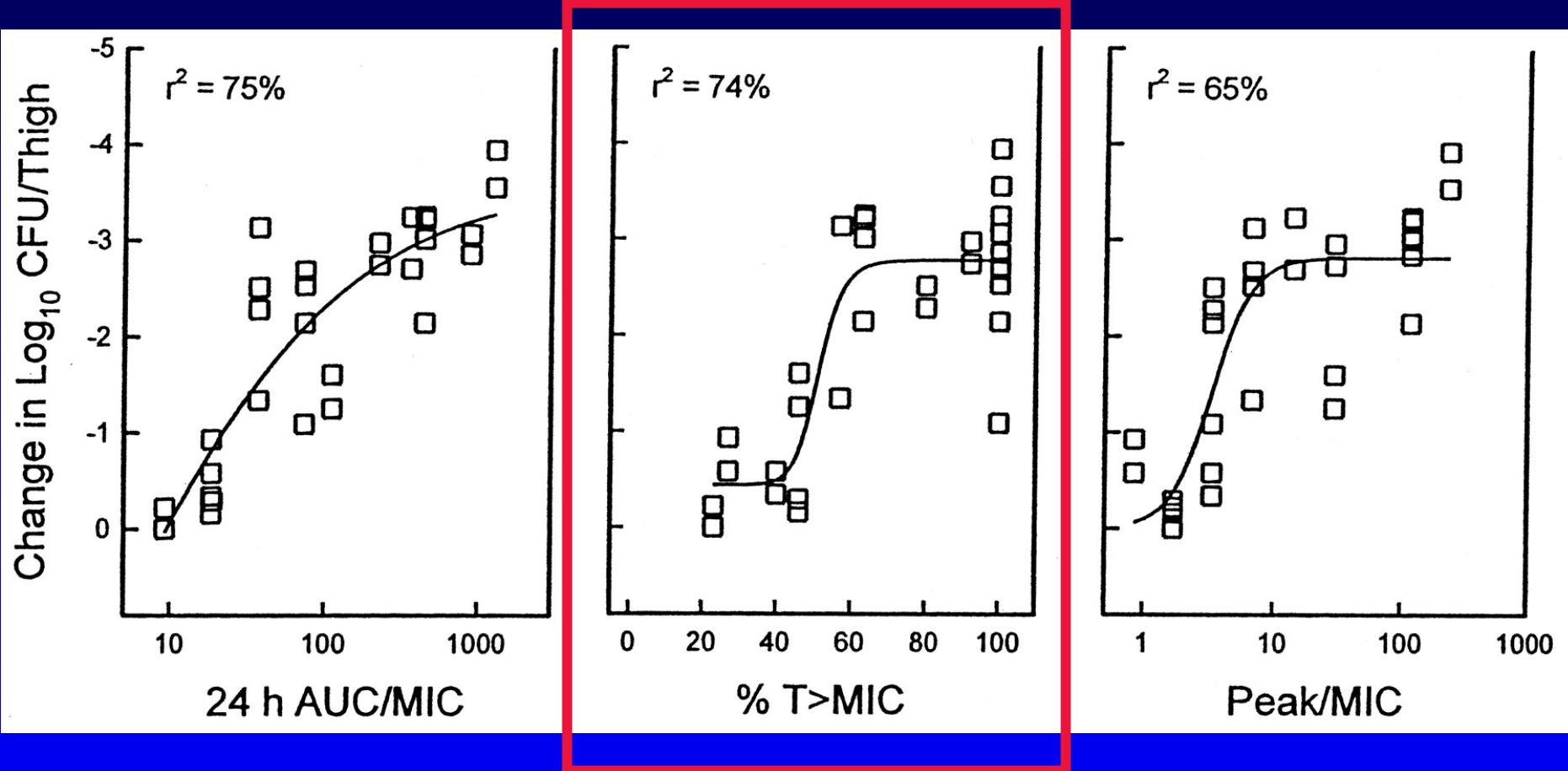
linezolid blocks the  
formation of the  
initiation complex

# Linezolid action and resistance



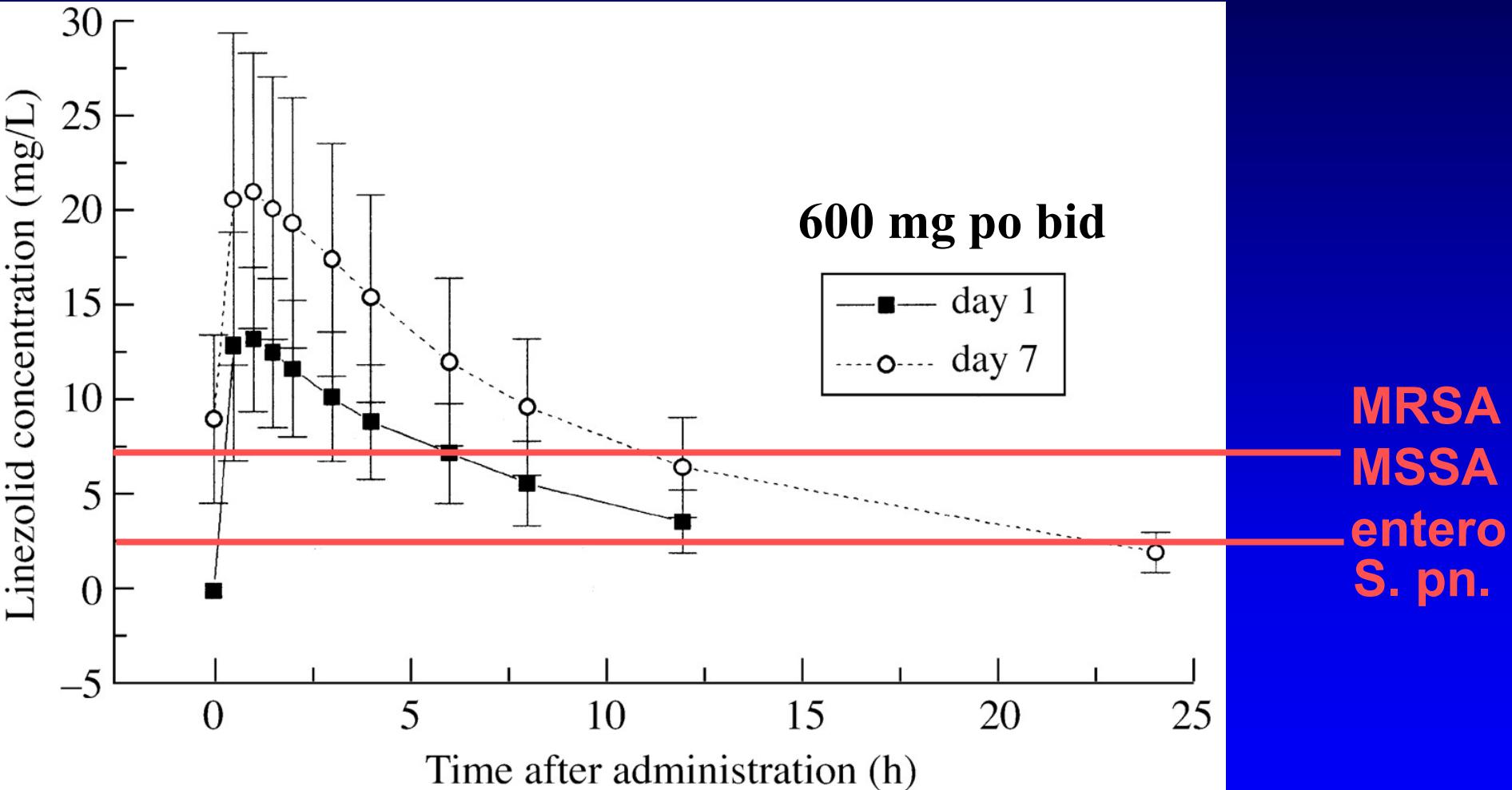
# Linezolid - PK / PD in vivo

MSSA model



Time – dependent BUT only < 3 log reduction !

# Linezolid - PK / PD in humans



# **Linezolid clinical use**

**Registered in Belgium for:**

- complicated skin and soft tissues infections by Gram (+)
- community acquired and nosocomial pneumonia

**BUT with severe restrictions for reimbursement ...**

<http://www.inami.be/other/fr/drug/medicalproducts/pdf/annex1-2-IV-20040401.pdf>

**Efficacy also demonstrated (in case reports) for:**

- Post-operative infections
- Meningitis
- Endocarditis
- Bacteriemia caused by vancomycin resistant strains

# Linezolid: Pros and Cons

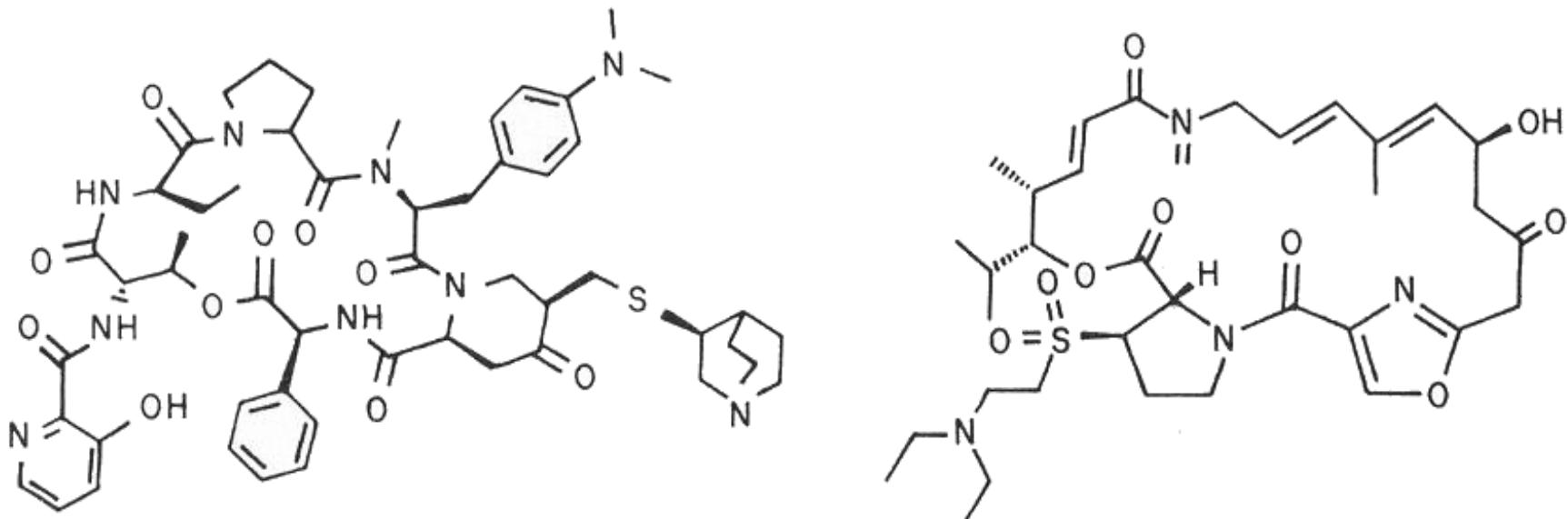
- Biodisponibility 100%
- Distribution in SNC  
bone

Efficacy of  
continuous infusion  
evaluated  
in animal models

Jacqueline (2002)  
AAC 46:3706

- Bacteriostatic
- MIC near PK/PD breakpoint
- resistance already selected
- Short half-life
- High price
- Toxicity
  - Gi disturbance
  - myelosuppression  
(> 2 weeks)
- interaction with IMAO inhib.

# New anti- MRSA : can we find better elsewhere ?



**Quinupristin/dalfopristin  
(synergistin)**



# **Quinupristin / Dalfopristin: an historical perspective**

**Synergistins do work ...in synergy ... since a long time ago!**

**Synergistic interaction of the streptogramins with the ribosome.**

Contreras & Vazquez, **1977**, Eur J Biochem/ FEBS 74, 549-51.

**But resistance mechanisms was already awaiting**

**Physical studies of a *Staphylococcus aureus* plasmid mediating resistance to streptogramins, lincosamins and aminoglycosides.**

Bouanchaud et al, **1977** Annales de microbiologie 128B, 431-7

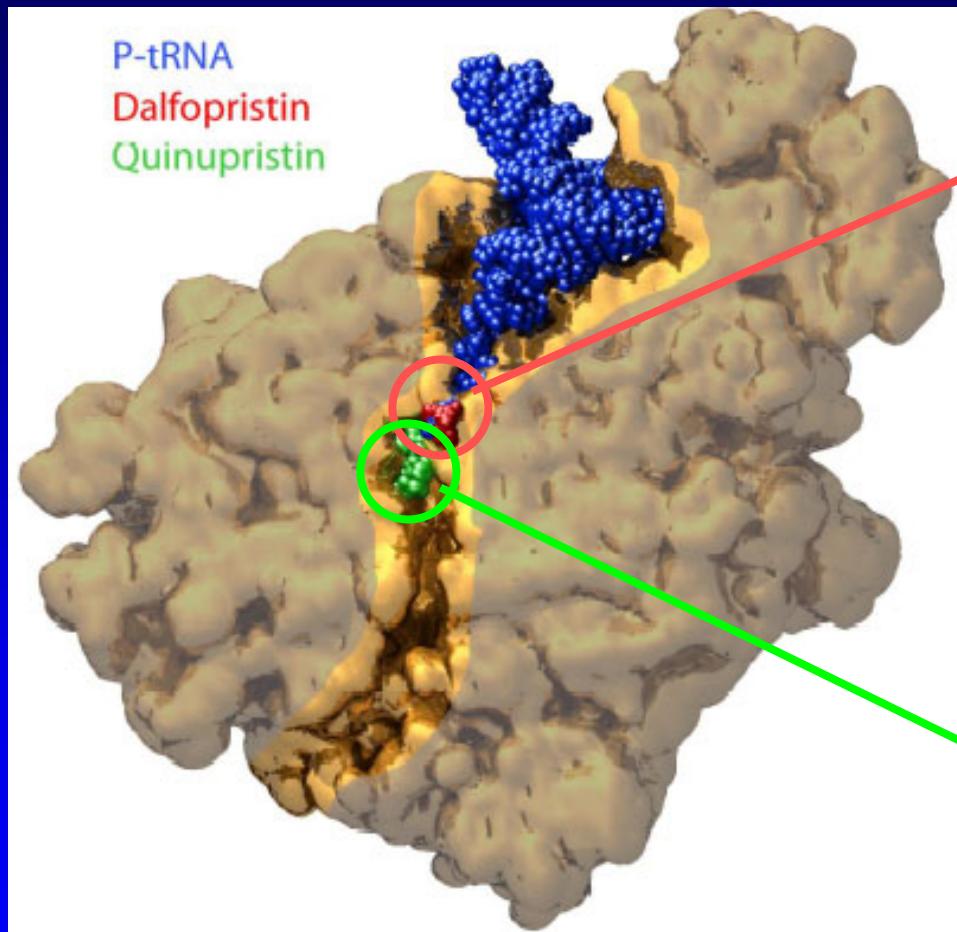
# **Quinupristin / Dalfopristin: an historical perspective**

**... and finding the winning combination took some time ...**

**Antimicrobial activity against *Staphylococcus aureus* of  
semisynthetic injectable streptogramins: RP 59500 and  
related compounds.**

Barriere et al **1992** JAC 30 Suppl A 1-8.

# Quinupristin/Dalfopristin action and resistance



$S_A$  blocks  
peptide bound  
formation

SYNERGY

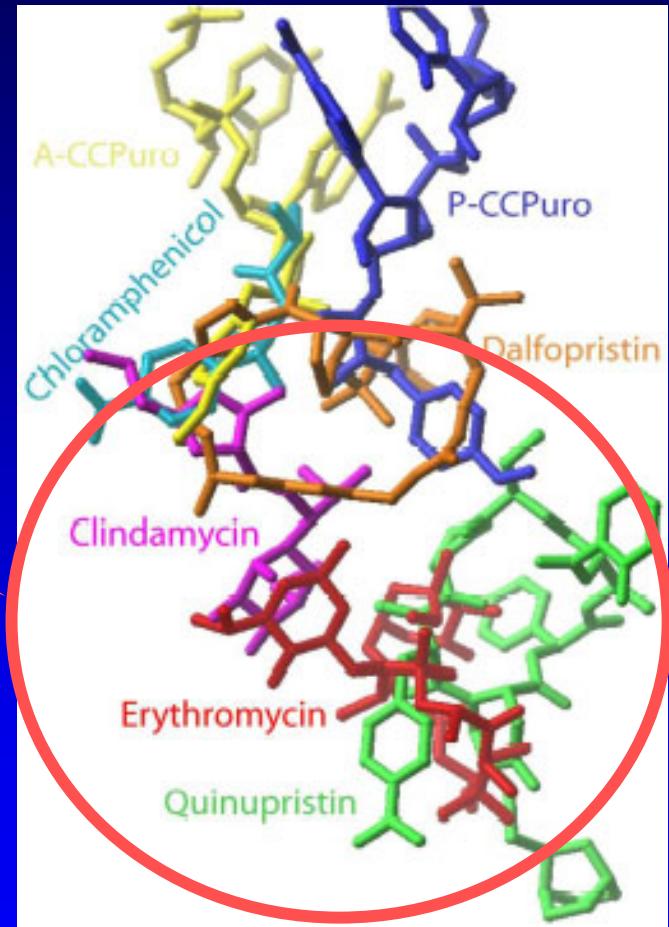
$S_B$  blocks  
the path of the  
nascent peptide

# Quinupristin/Dalfopristin action and resistance

## Resistance to quinupristin

- ribosomal methylation → cross-resistance MLS<sub>B</sub>

- enzymatic hydrolysis

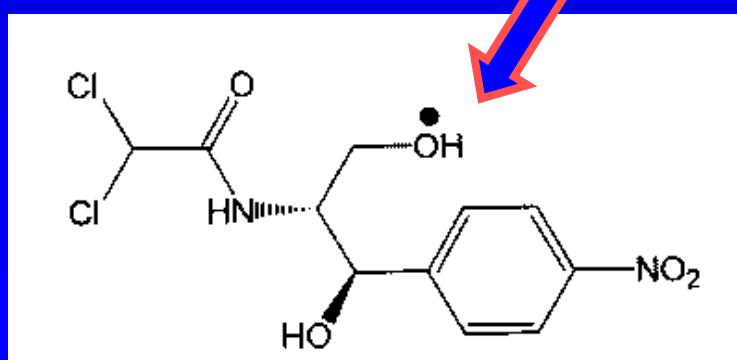
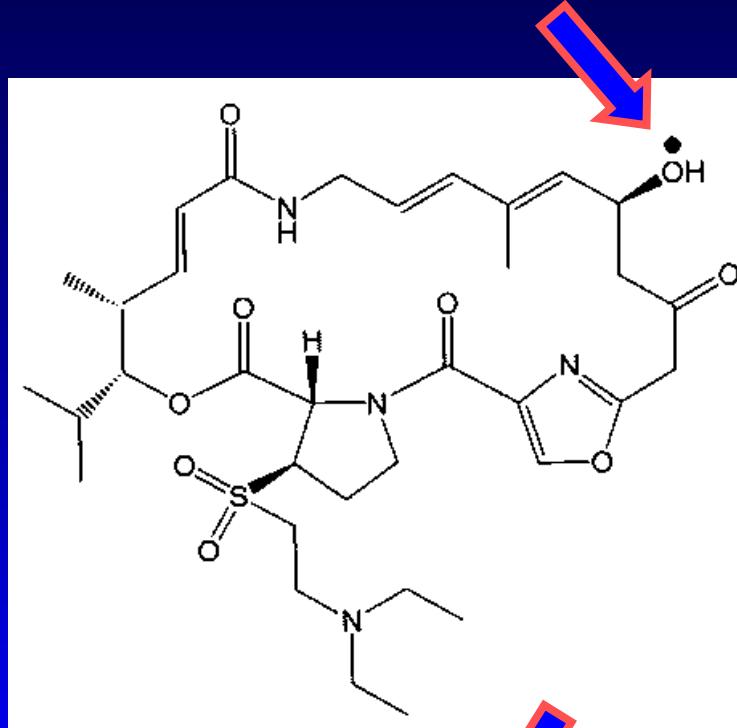


# Quinupristin/Dalfopristin action and resistance

## Resistance to dalfopristin

- enzymatic acetylation  
(enzymes related to chloramphenicol acetyltransferases)

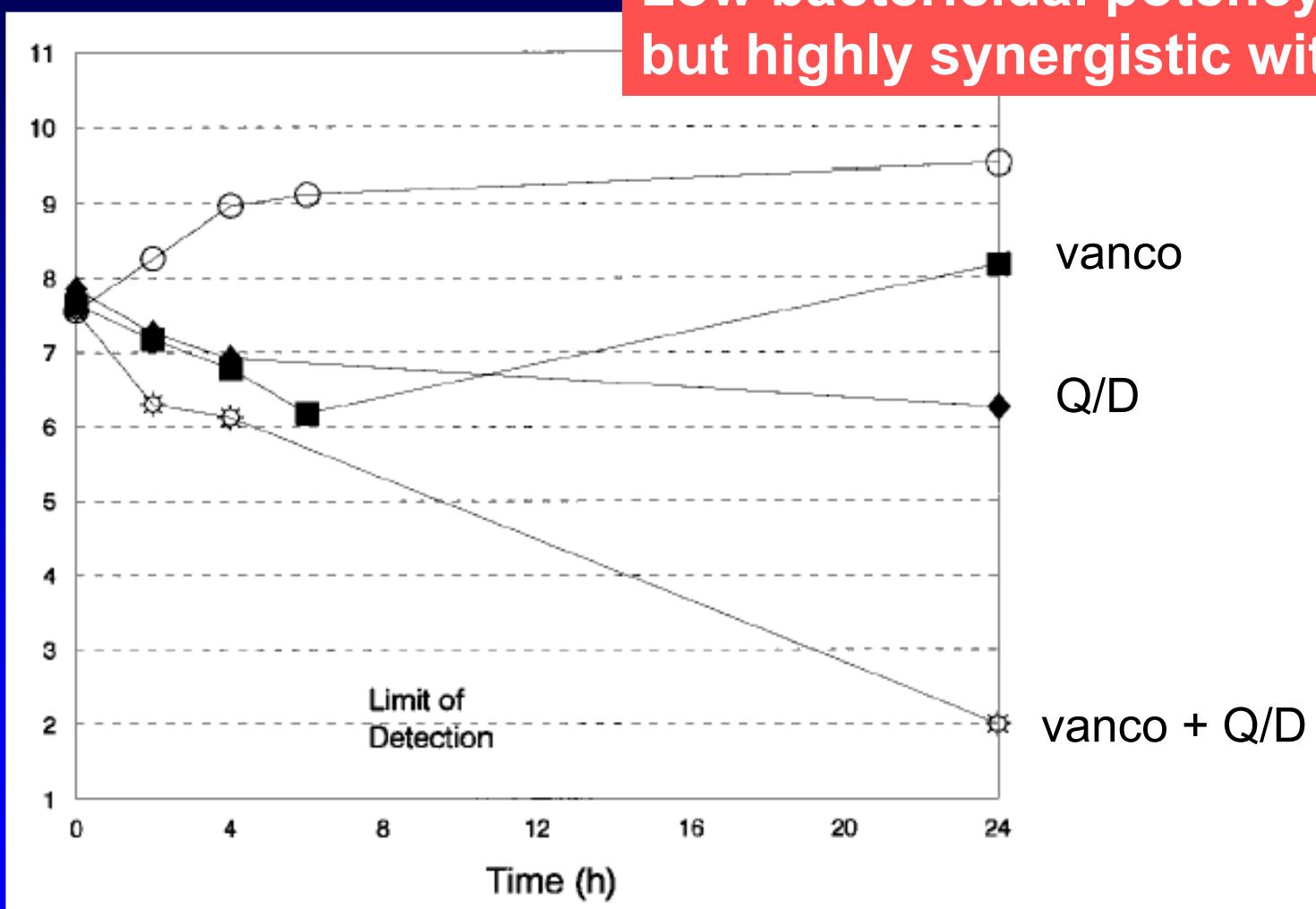
- efflux  
(intrinsic resistance in *E. faecalis*)



# Q/D - PK / PD in vitro

MRSA model

Low bactericidal potency  
but highly synergistic with vanco



# Q/D - PK / PD in humans

Dose (mg/kg)	AUC	MIC for AUC/MIC = 125	MIC MRSA
7.5 tid	7+11 = 18	0.14	0.03-1

MIC near the PK/PD breakpoint ...



failure possible ...



# Q/D clinical use

FDA approved for:

- complicated skin and soft tissues infections by MSSA/strepto
- bacteriemia due to Vanco-R *E. faecium*

Efficacy also demonstrated for:

- nosocomial pneumonia  
(= vanco; lower success if MRSA in both groups)

# Q/D: Pros and Cons

- highly active against VR *E. faecium*
- synergistic with other ABs

Efficacy of continuous infusion evaluated in in-vitro PD models

Ryback (1997)  
AAC 41:1359

numerous incompatibilities in perfusion

Rubinstein et al (1997)  
JAC 44:37

- poorly bactericidal against MRSA
- MIC near PK/PD breakpoint
- cross-resistance with ML
- bid or tid administration
- no oral route
- drug interactions (CYP450 3A4) caution with drugs prolonging QTc
- myalgia/arthralgia frequent
- high price
- not studied in children

# But where can I buy SYNERCID ® ?



In USA

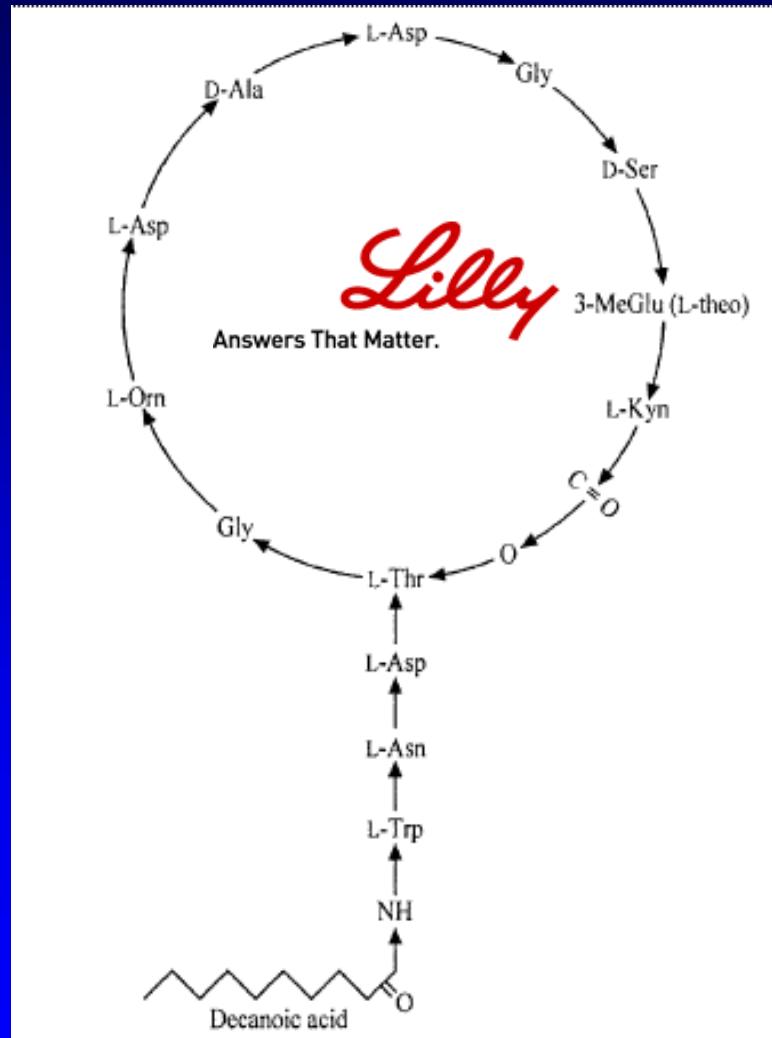
and, perhaps...



In Europe

# New anti- MRSA : another flashback ?

Daptomycin  
(lipopeptide)



# Daptomycin: an historical perspective

Finding a new antibiotic ....

**In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.**

Eliopoulos et al, **1986** AAC 30, 532-5 .

Belgian pioneers ...

**In vitro activity of LY146032, a new lipopeptide antibiotic, against gram-positive cocci.**

Verbist, **1987** AAC 31, 340-2

**Influence of LY146032 on human PMN in vitro.**

Van der Auwera et al, **1988**, JAC 21, 57-63

# Daptomycin: an historical perspective

But Lilly stops development in phase II in  
1993 for lack of efficacy ...



really

# **Daptomycin: an historical perspective**

**... But ...Daptomycin came back as a once-daily drug !!!**

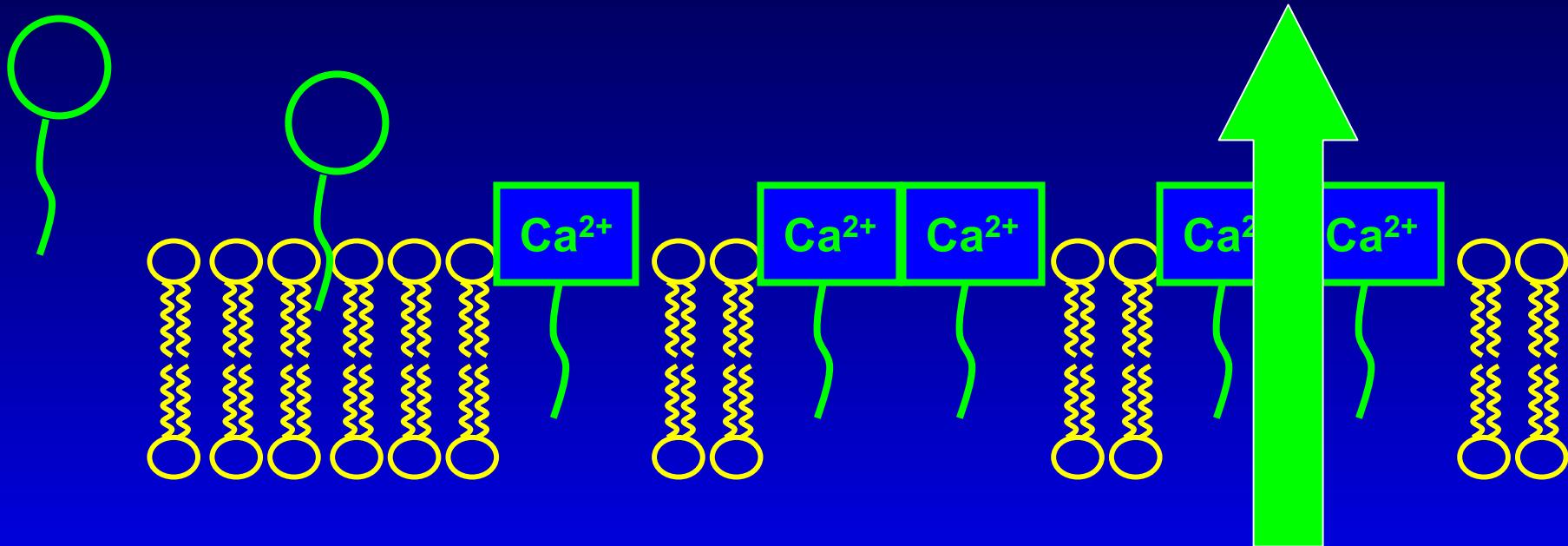
**Development of daptomycin for gram-positive infections.**  
Tally & DeBruin, **2000**, JAC 46:523-6.

**Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens.**  
Carpenter & Chambers, **2004**, Clin Infect Dis. 38:994-1000

**... thanks to PK/PD ...**

**Once-daily dosing in dogs optimizes daptomycin safety.**  
Oleson et al, **2000**, AAC. 44:2948-53.  
**Daptomycin dose-effect relationship against resistant gram-positive organisms.**  
Cha et al, **2003**, AAC 47:1598-603

# Daptomycin Action and resistance



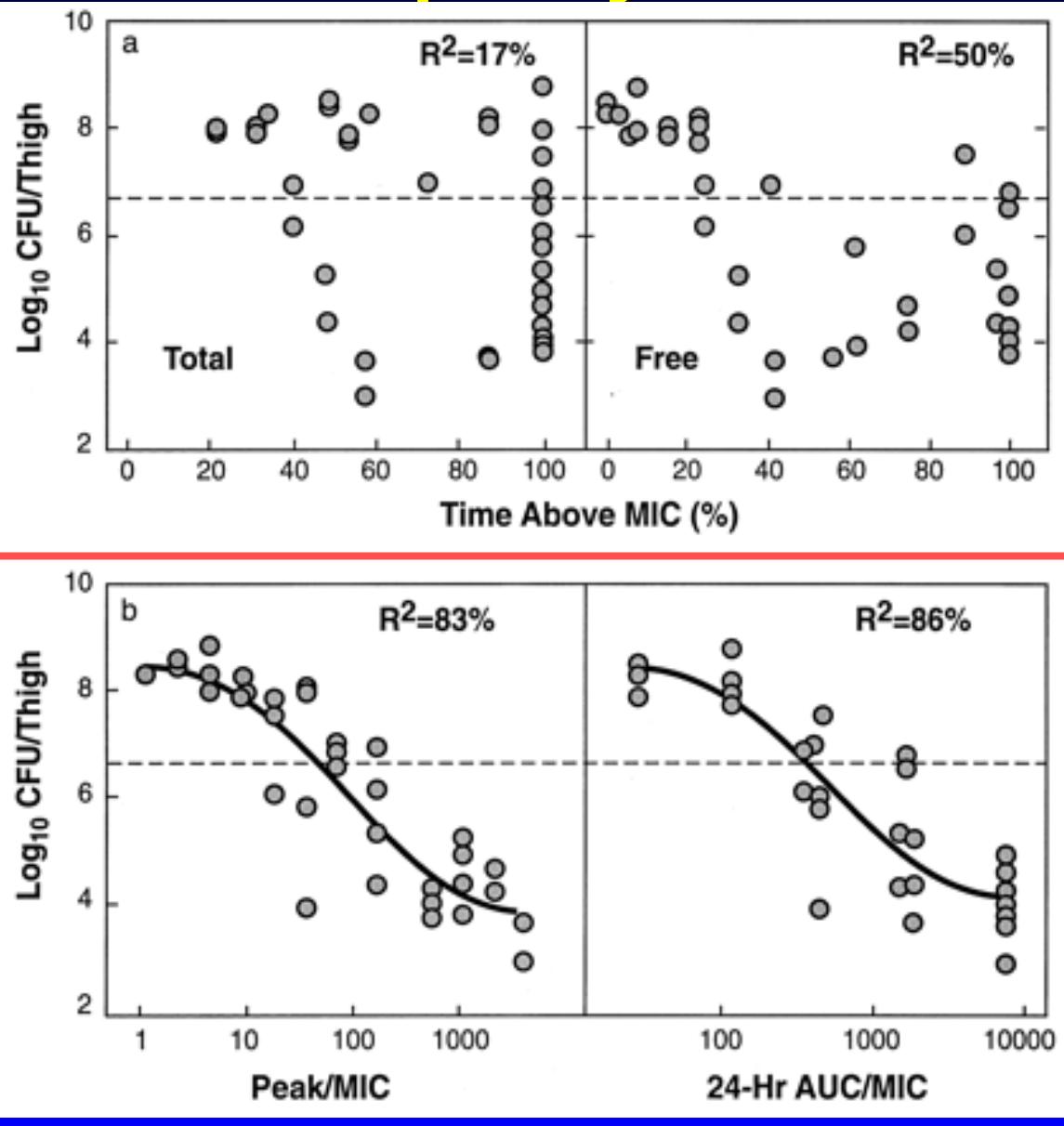
Resistance in 2/1000 subjects

From Phase II/III

(cubicin® package insert)

Mechanism ???

# Daptomycin in vivo PK/PD



conc-dependent  
activity

Peak/MIC > 60-100  
AUC/MIC > 400-550

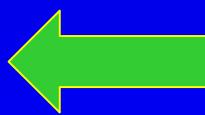
for *S. aureus*

# Daptomycin PK/PD in humans

Dose (mg/kg)	Cmax	MIC for Cmax/MIC = 60	AUC	MIC for AUC/MIC = 400	MIC MRSA
4	58	~ 1	500	~ 1	
6	100	~ 1.5	750	~ 2	0.06-0.5
8	133	~ 2	1130	~ 3	



success  
probable  
...



MIC  
↑  
PK/PD  
breakpoint ...

# Daptomycin clinical use

## FDA approved:

- complicated skin and soft tissues infections by Gram (+)

## Deceiving efficacy :

- community acquired pneumonia (inferiority to ceftriaxone)

## Efficacy in small trials ( 60 patients):

- complicated urinary tract infections

## Ongoing studies :

- bacteriemia and endocarditis by *S. aureus*



# Daptomycin: Pros and Cons

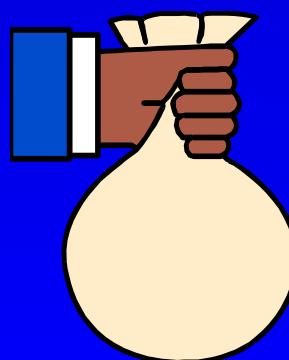
- bactericidal
- MIC < PK/PD breakpoint
- daily administration

- resistance already selected
- high price
- no oral route
- musculotoxic in animals  
    avoid combination with inhibitors  
    of HMGCoA reductase
- safety / efficacy not studied  
    in < 18 years

## New anti- MRSA :

2. novel molecules in an old class:

small companies do invest  
in glycopeptides



# New glycopeptides: historical perspective

Oritavancin LY33328:



**Reductive alkylation of glycopeptide antibiotics:  
synthesis and antibacterial activity.**

Cooper et al, **1996** J Antibiot (Tokyo). 49:575-81

Dalbavancin BI397:

**Amides of de-acetylglucosaminyl-deoxy  
teicoplanin active against highly glycopeptide-  
resistant enterococci. Synthesis and antibacterial  
activity.** Malabarba et al, **1994** J Antibiot (Tokyo) 47:  
1493-506



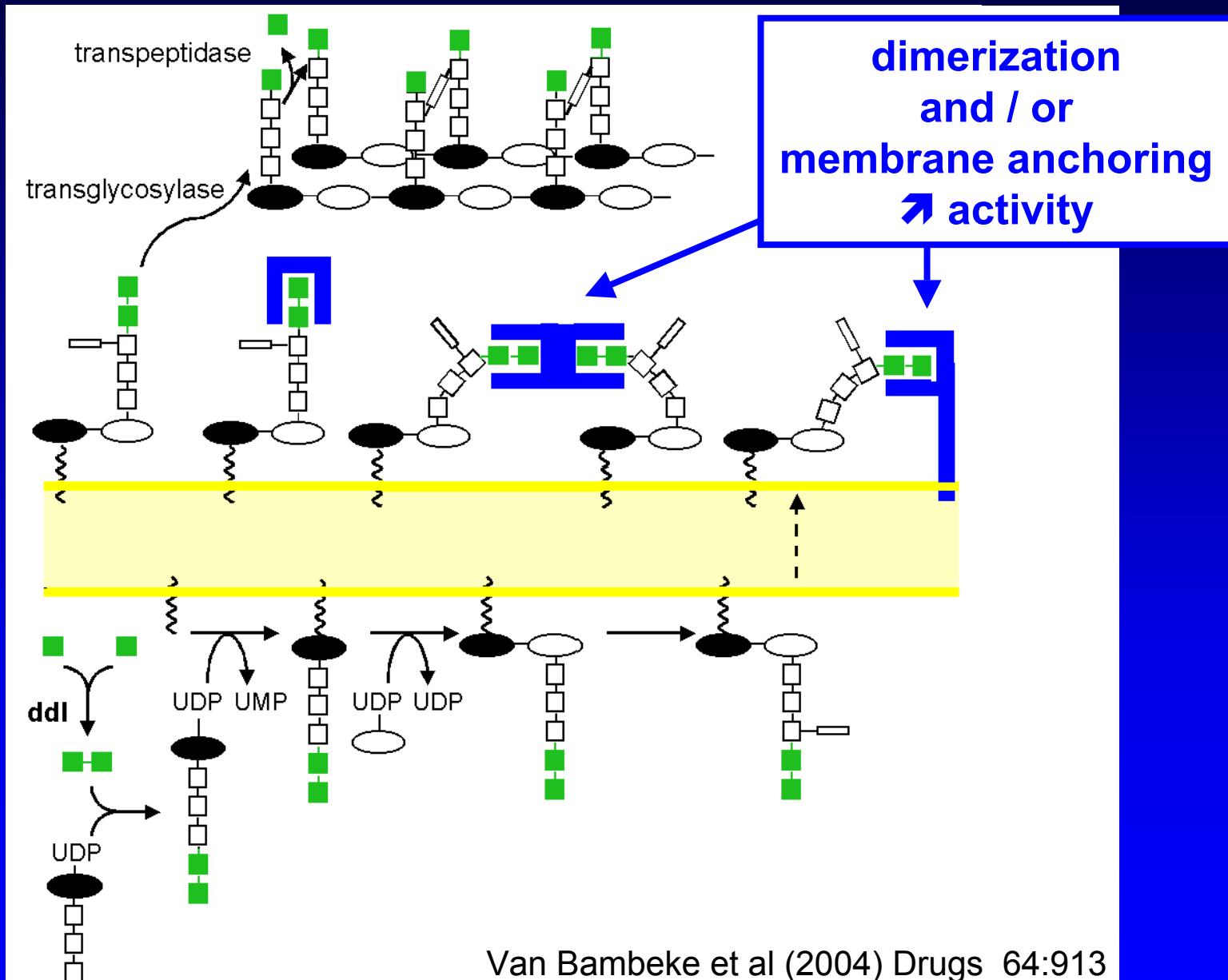
Telavancin TD-6424:

**Semi-synthetic glycopeptide antibacterials.**

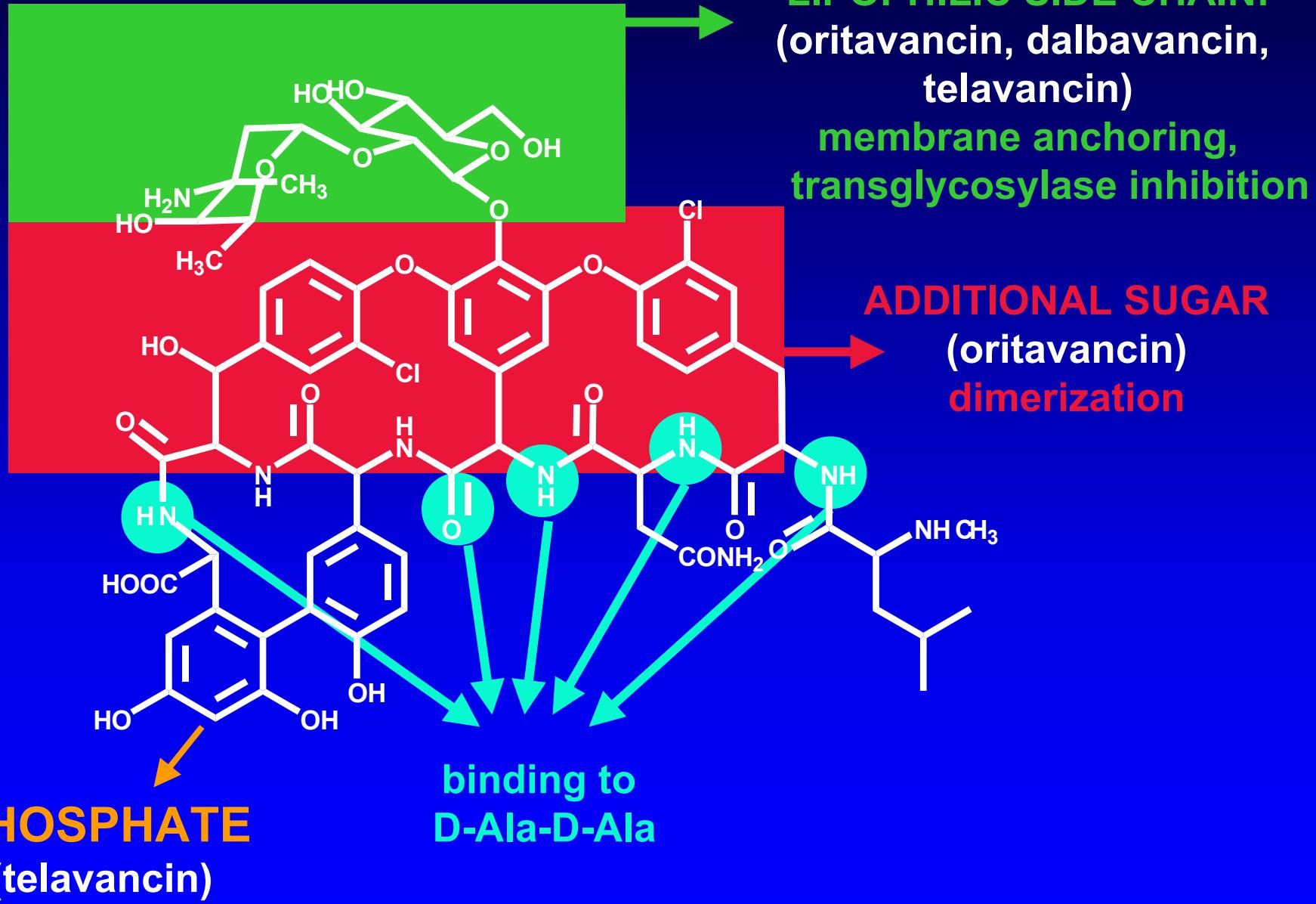
Judice & Pace, **2003**, Bioorg Med Chem Lett. 13:4165-8.



# Glycopeptide updated mode of action

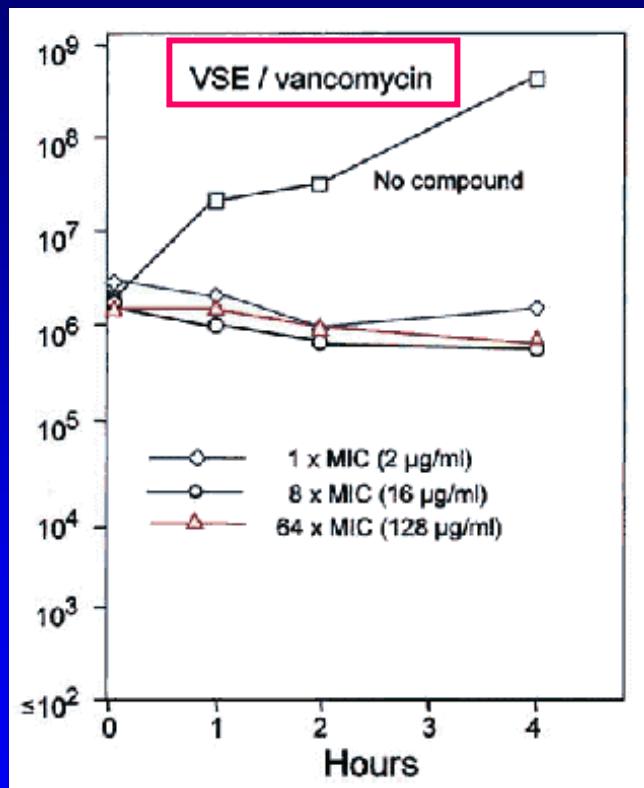


# Glycopeptide : what can we improve ?

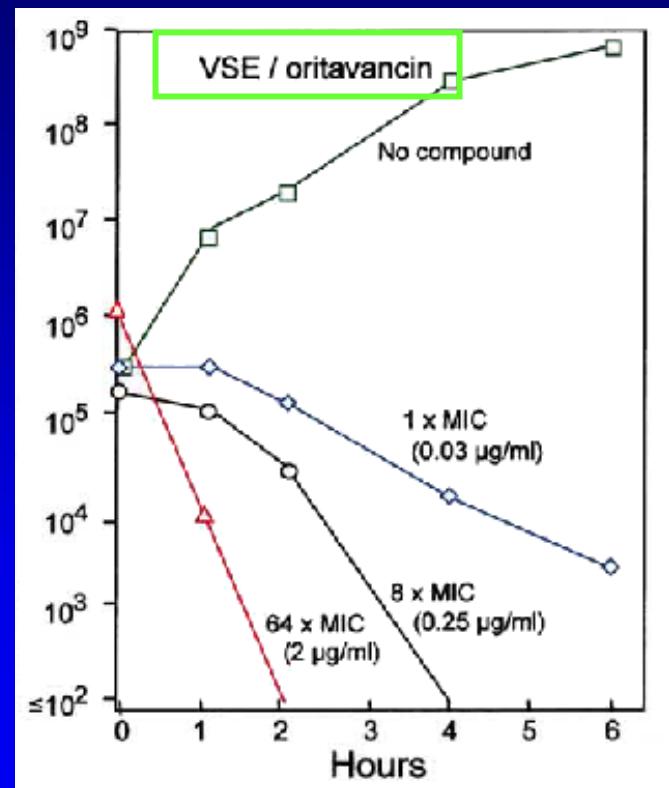


# New glycopeptides : in vitro PK/PD

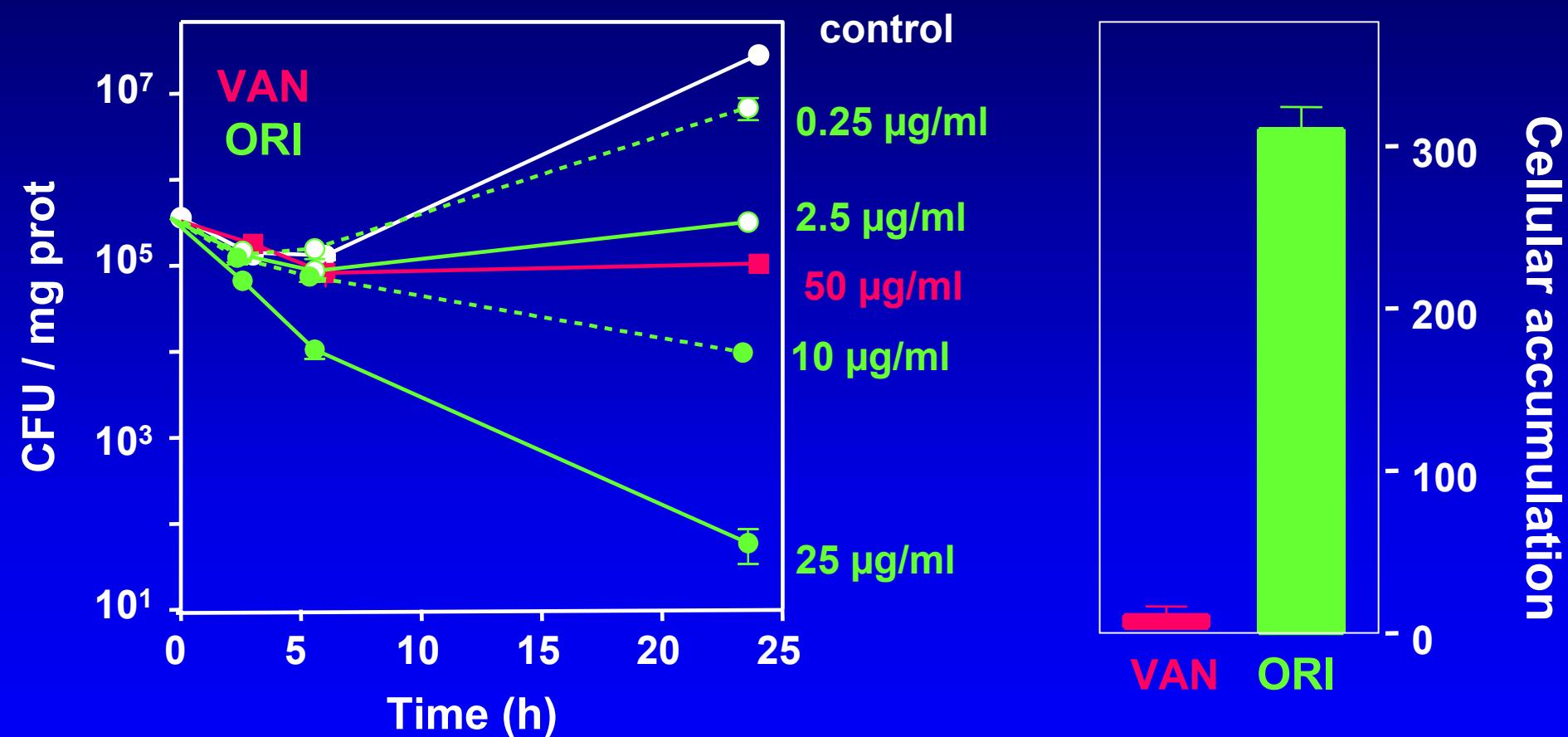
static effect



conc. dependent,  
bactericidal effect



# PK/PD properties of oritavancin in a model of *S.aureus* infected macrophages



# New glycopeptides : clinical experience

complicated skin and skin structure infection  
caused by Gram (+) including MRSA

(phase II/III; double blind, randomized)

517 pts

**Vancomycin 15 mg/kg bid  
3-7 days**

**followed by oral cephalexin  
10-14 days**

**Oritavancin 1.5-3 mg/kg qd  
3-7 days**

**SUCCESS :**  
**bacteriological**

**76 %**

**clinical**  
**with MRSA**

**80 %**

**80 %**

**=**

**74 %**

**76 %**

**74 %**

# New glycopeptides : clinical experience

complicated skin and skin structure infection  
caused by Gram (+) including MRSA

(phase II; controlled, randomized)

42 pts

**Vancomycin, ceftriaxone,  
cefazolin or clindamycin  
for 7-21 days**

**Dalbavancin  
15 mg/kg day 1  
+ 7.5 mg/kg day 8**

**SUCCESS :**  
**bacteriological**

**64 %**

**clinical**

**76 %**

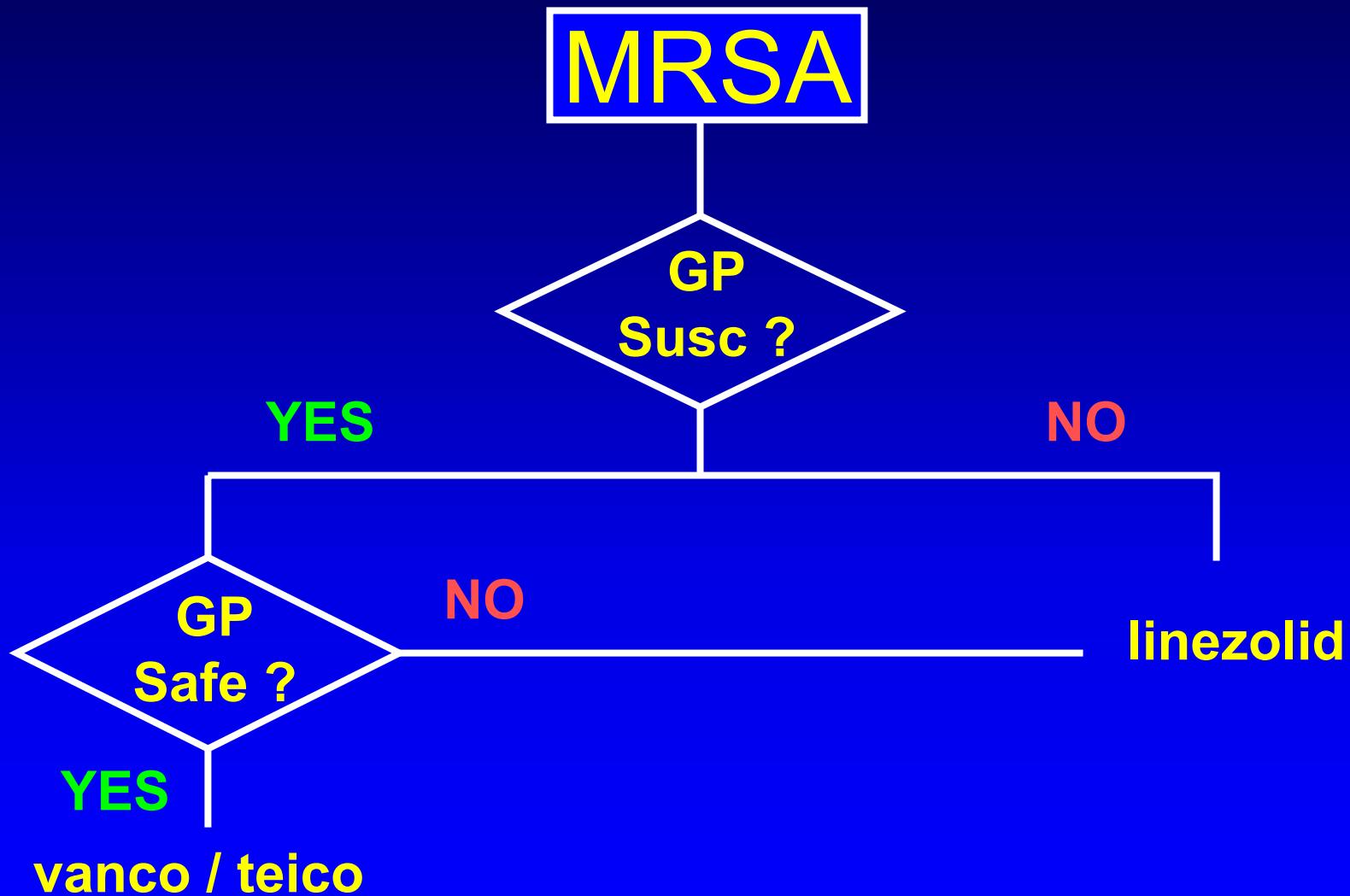
**73 %**

**94 %**

# New glycopeptides: Pros and Cons

- bactericidal including against VRE
- bactericidal against intracellular infections
- MIC < PK/PD breakpoint
- daily or weekly administration
- no oral route
- safety profile not yet established

# MRSA treatment : what to do in Belgium today?



# **MRSA treatment : any room for the coming molecules?**

**Quinupristin / dalfopristin ?**

**More useful for VRE than for MRSA  
→ no need so far in Belgium**

**Daptomycin ? New glycopeptides ?**

**May be useful in difficult situations (bactericidal)  
Clinical experience still lacking**

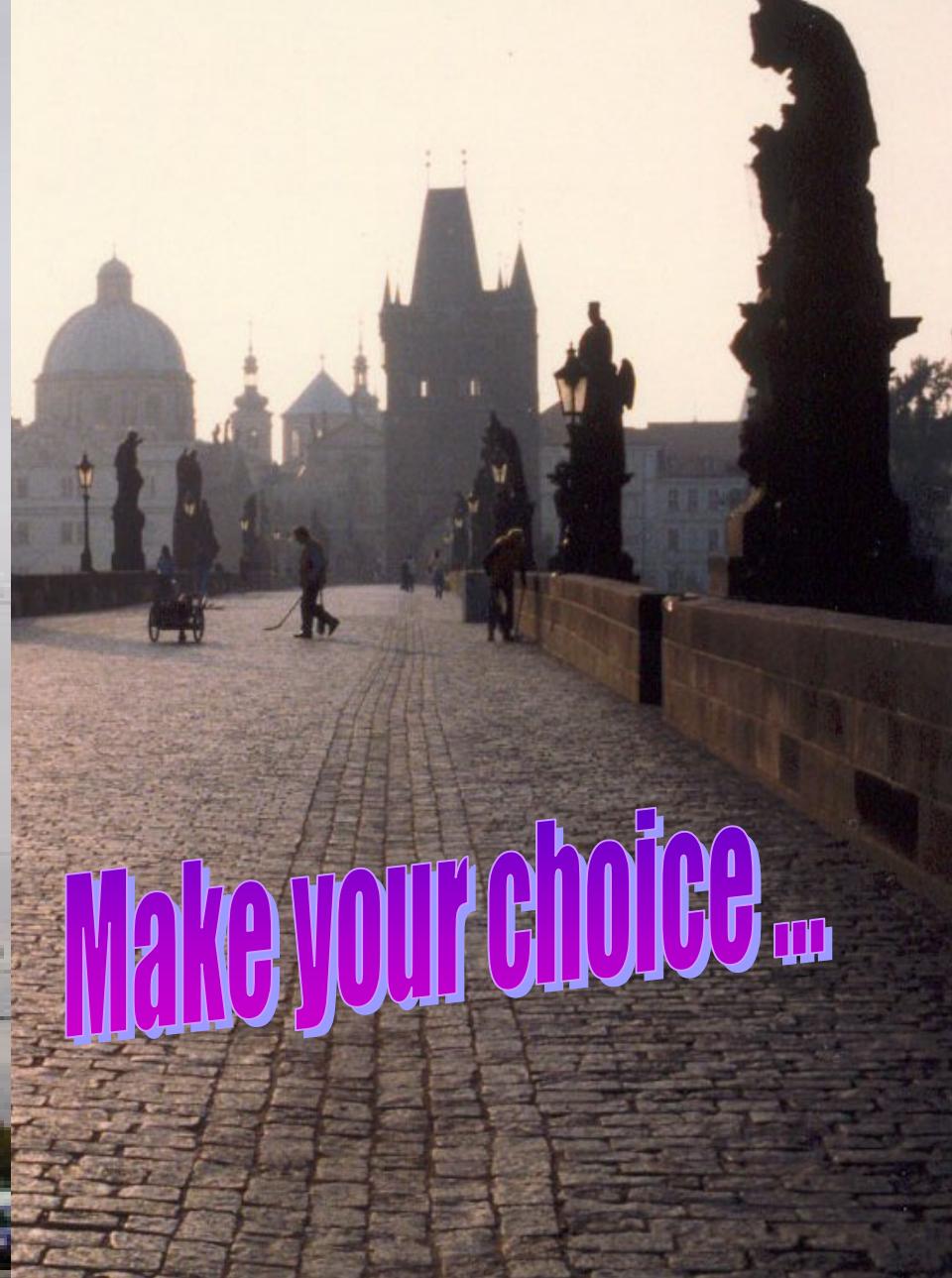
**BUT WE SHOULD USE THEM SPARINGLY  
TO AVOID RAPID SELECTION OF RESISTANCE**

**And all the other under development ?**

# Do we see the future backwards ?



# Do we see the future backwards ?



Make your choice...