New antimicrobials

Paul M. Tulkens

Françoise Van Bambeke

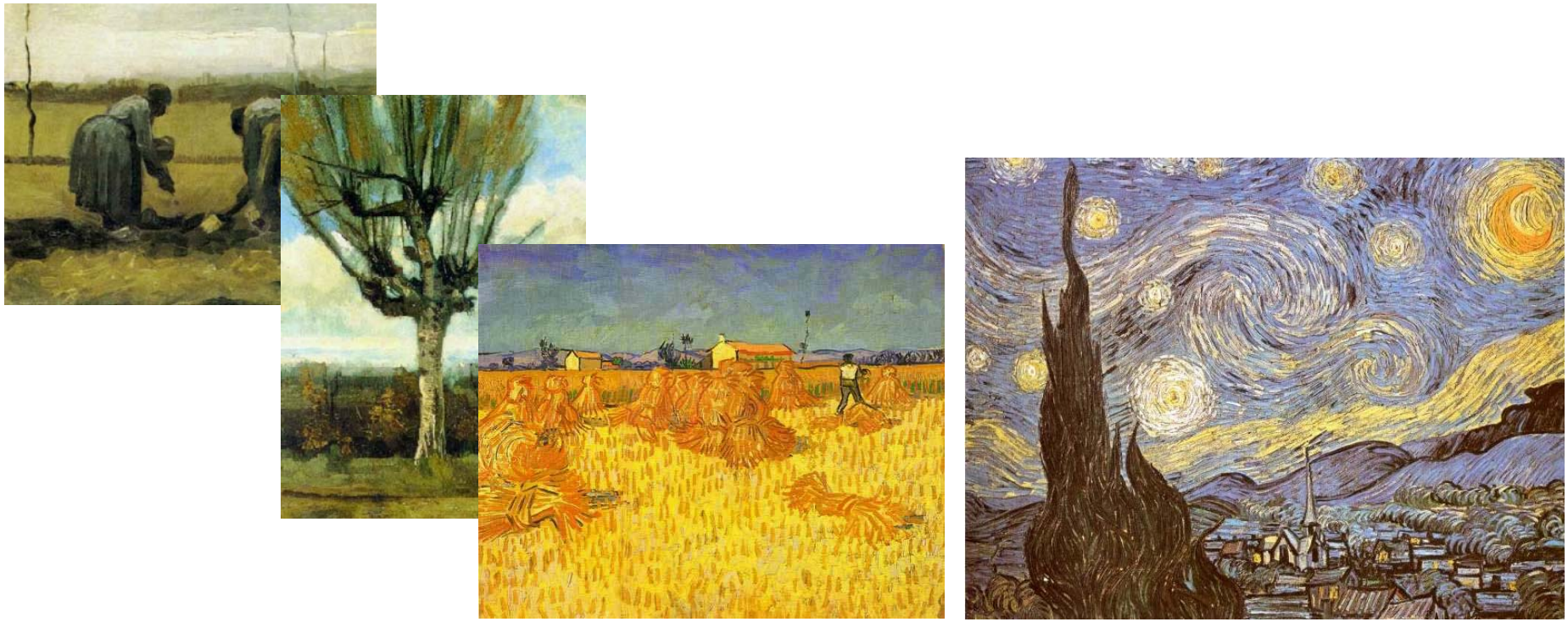
Unité de pharmacologie cellulaire et moléculaire

& Louvain Drug Research Institute

***Université catholique de Louvain*, Brussels, Belgium**

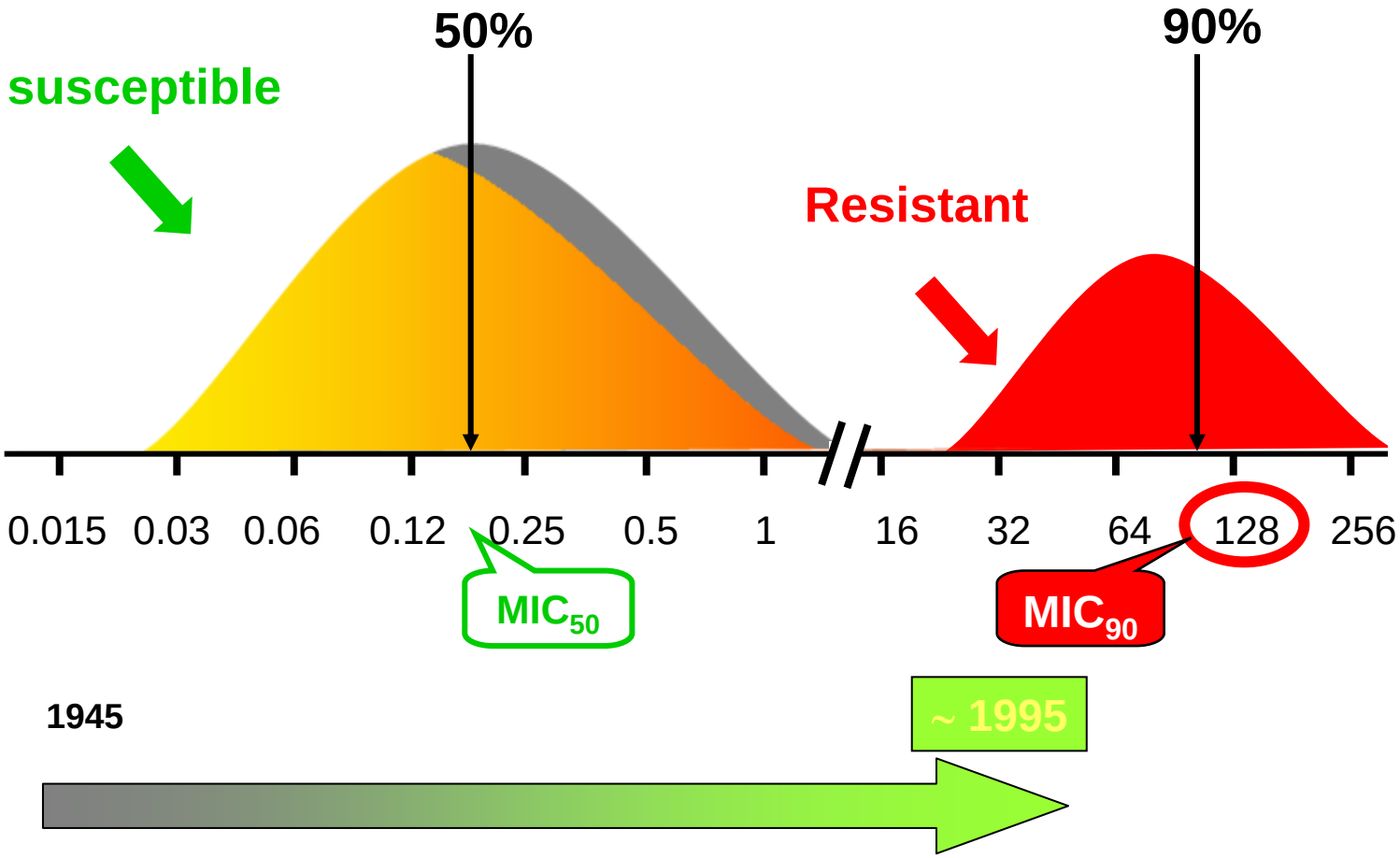
Slides are available on http://www.facm.ucl.ac.be

Why do we need new antimicrobials ?



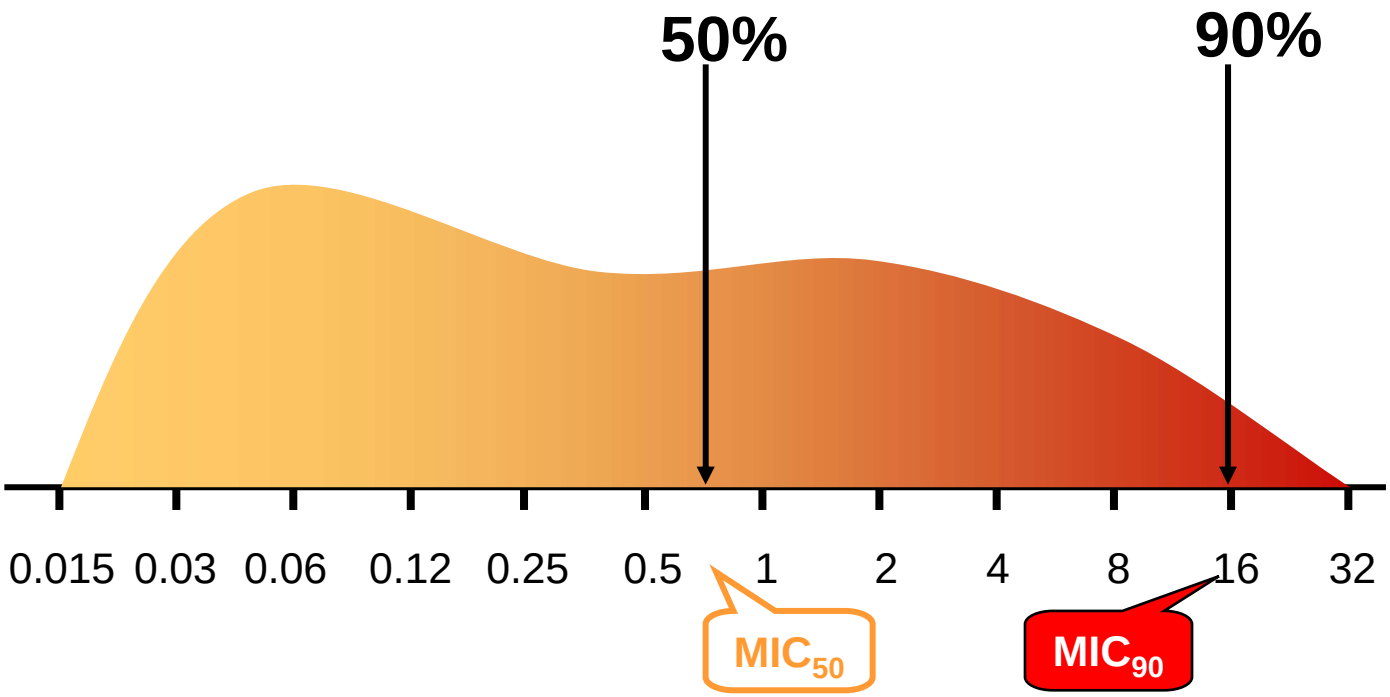
1945 **~ 1995** **2009**

Easy resistance …



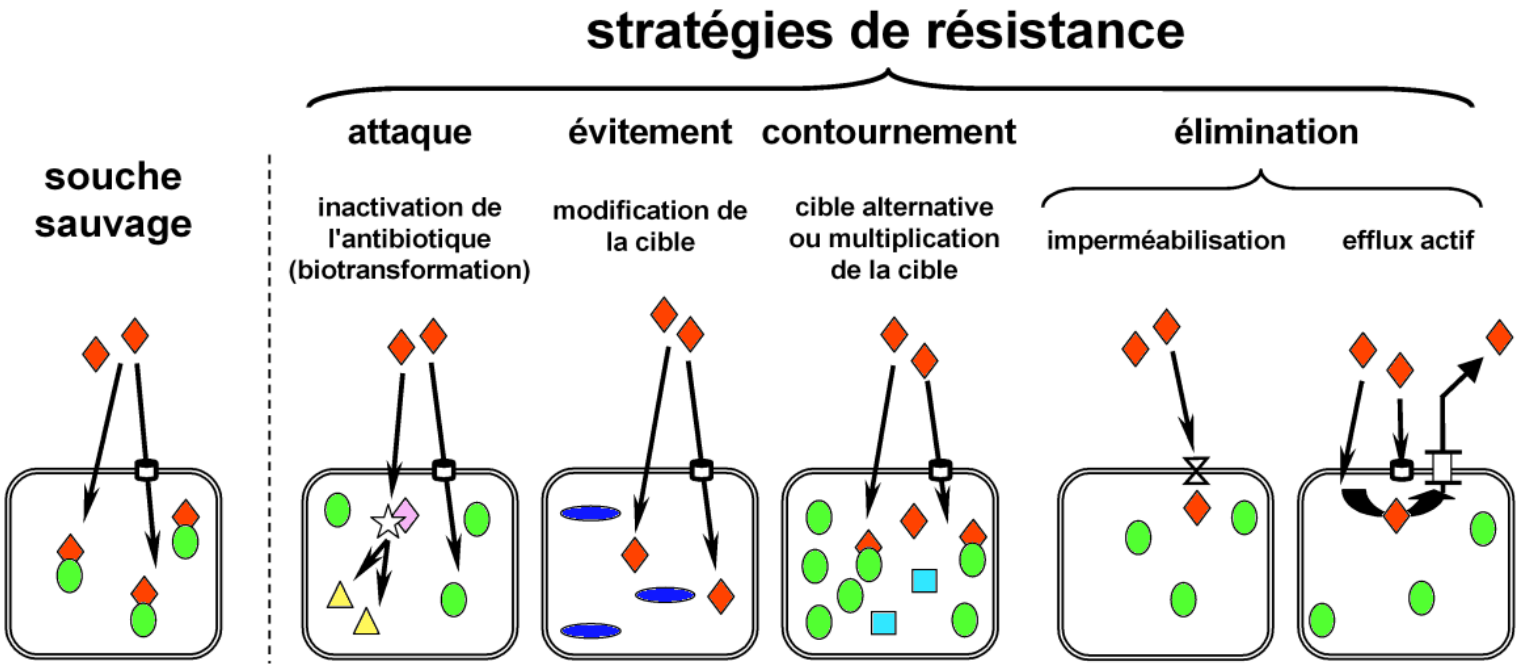
A more difficult situation …

Multiplicity of mechanisms



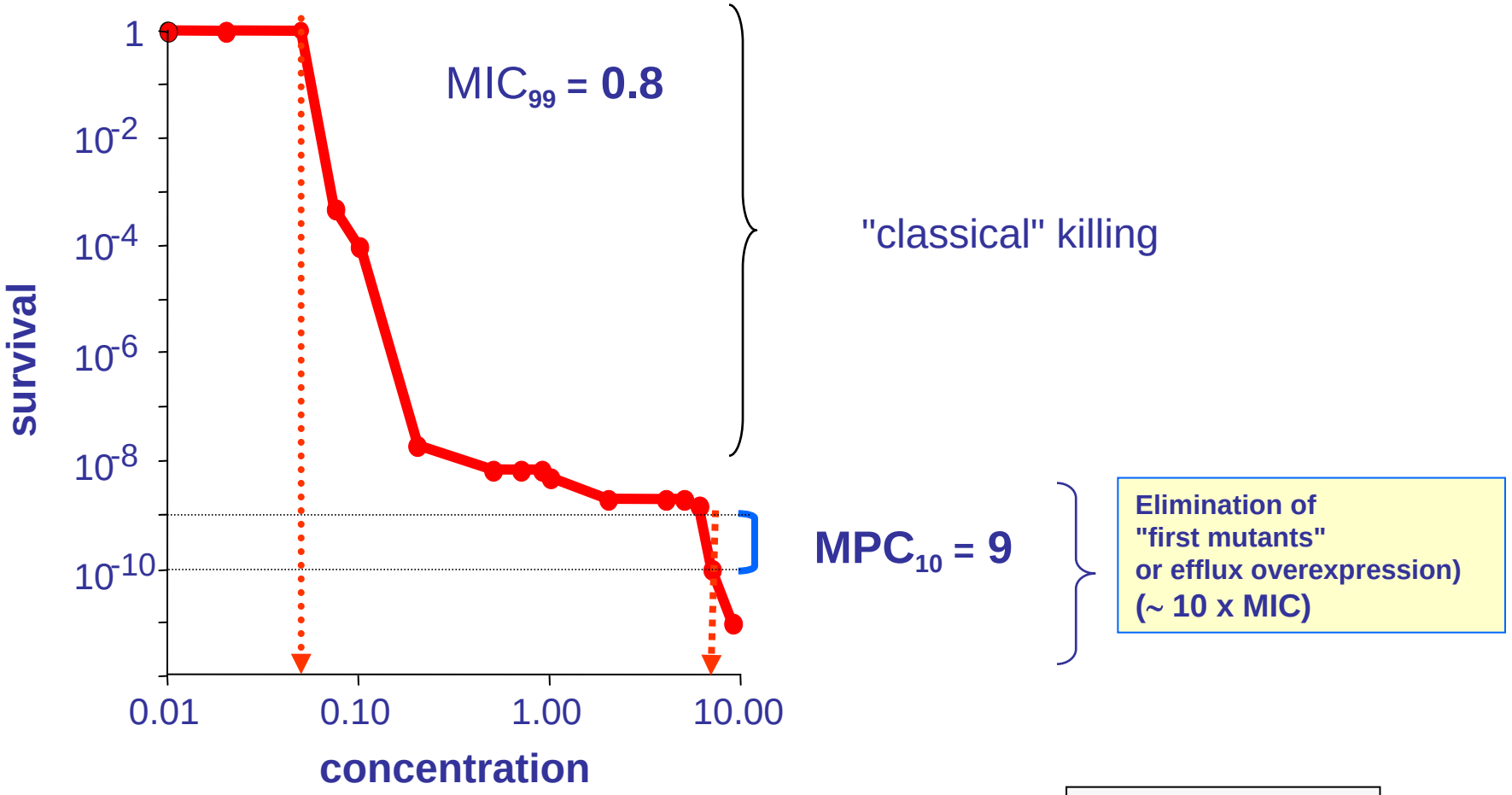
2009

A large number of mechanisms…



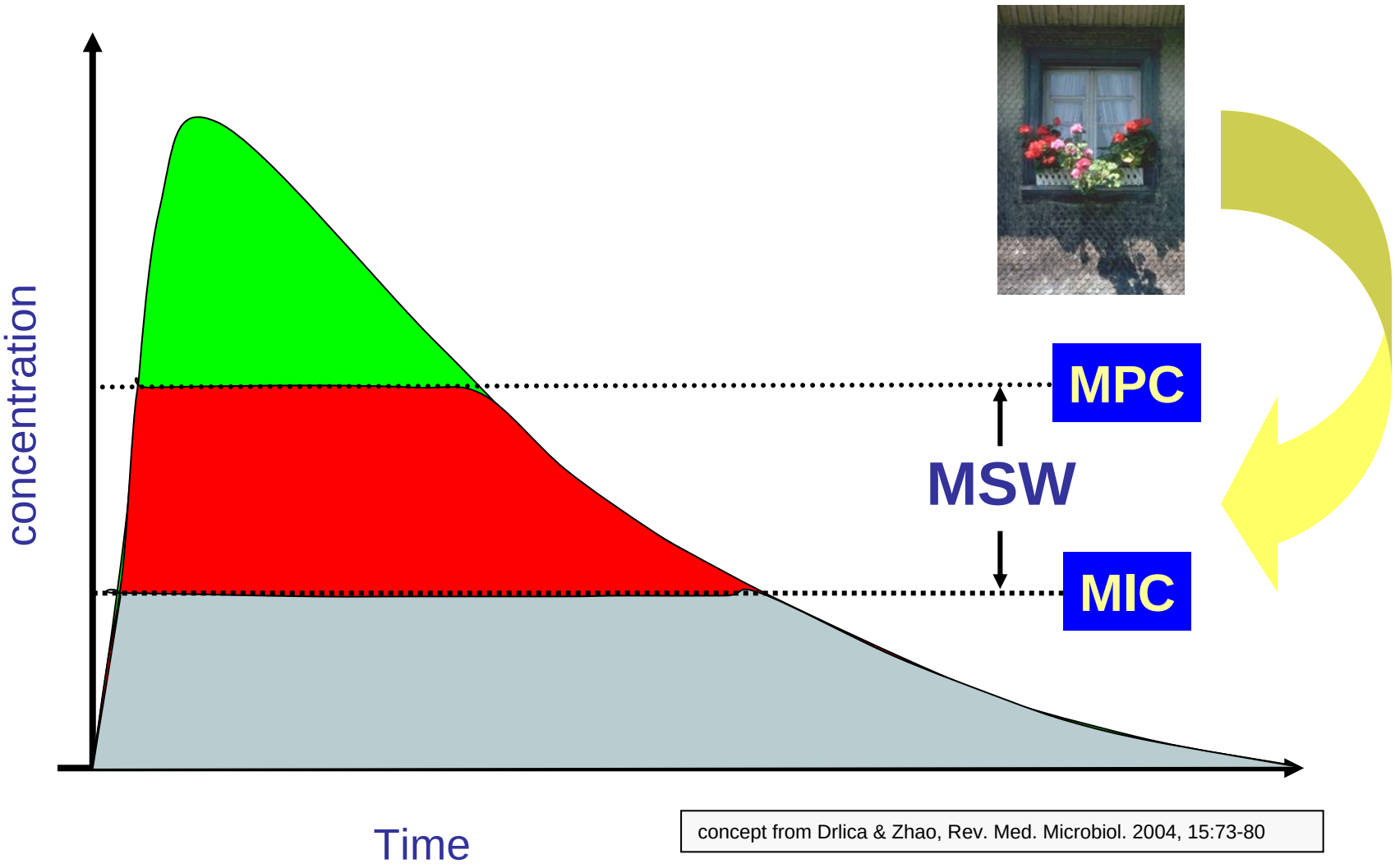
Populations of decreased susceptibility

- Well known for *S. pneumoniae* (and, more recently with *S. aureus* [VISA])
- Rediscovered under the the acronym "MPC" (***M**utation **P**revention **C**oncentration*) for fluoroquinolones with *Mycobacteriae* (and since then, with several other microrganisms)



Dong *et al*; AAC 43:1756-1758

The concept of "Selection/Induction Window"



concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

New antibiotics and new forms

- Registered in the EU (EMEA) and the U.S.A. (FDA)

- Daptomycin - http://www.emea.europa.eu/humandocs/Humans/EPAR/cubicin/cubicin.htm
- Tigecycline - http://www.emea.europa.eu/humandocs/Humans/EPAR/tygacil/tygacil.htm
- Doripenem - http://www.emea.europa.eu/humandocs/Humans/EPAR/doribax/doribax.htm

- Not yet registered in the EU but perhaps…

- Ceftobiprole (Basilea / Johnson & Johnson; available in Canada and Switzerland)
- Telavancin (Theravance / Astellas; may become available in the U.S.A.)
  Oritavancin (The Medicines Company; uncertain status)
- Gemifloxacin (Oscient Pharm. / Menarini; available in the U.S. but not in the E.U.)

- Probably not registered in any near future

- Dalbavancin ("on hold")
- Iclaprim (rejected by FDA)

- Inhalation forms (cystic fibrosis)

Daptomycin: historical landmarks….

1987 **1993** **1997**

Discovery of daptomycin as a novel anti-Gram + lipopeptide

In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.
Eliopoulos *et al*, **1986** Antimicrob. Agents Chemother. 30, 532-5

Development halted

- lack of efficacy
- toxicity

*"Lilly was not satisfied with the overall clinical results observed with the **twice-daily** dosing regimen utilized in these studies"*

Taking over by CUBIST

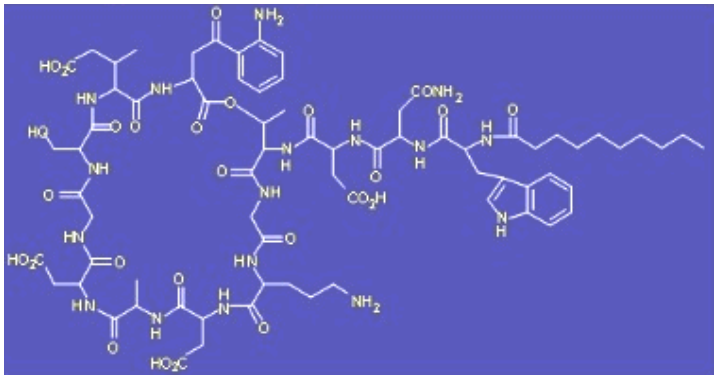
or *"pharmacodynamics in action ….."*

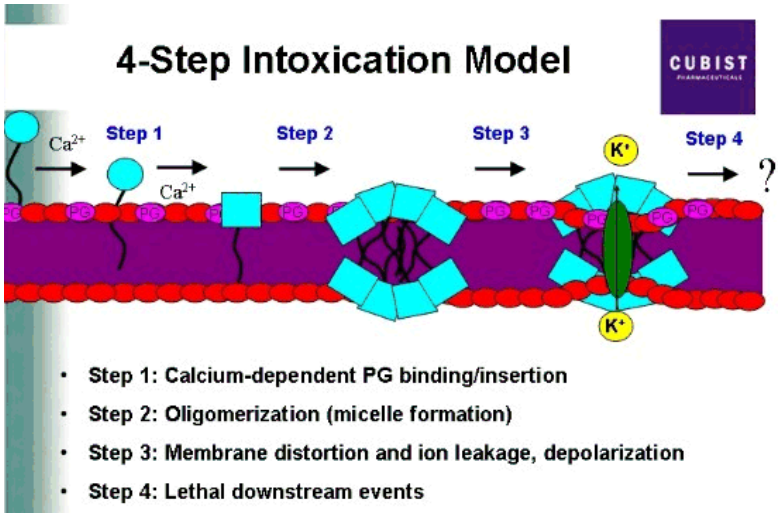
Once-daily dosing in dogs optimizes daptomycin safety.
Oleson *et al*, **2000**, AAC. 44:2948-53.

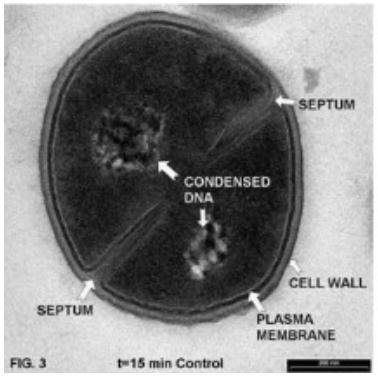
Daptomycin dose-effect relationship against resistant gram-positive organisms.
Cha *et al*, **2003,** AAC 47:1598-603

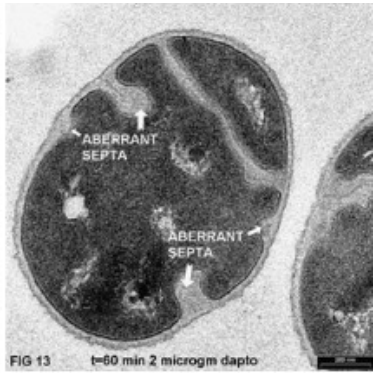
Daptomycin …

- very bactericidal (membrane destabilization; no need of proteinaceous receptor !) and potent (MIC *S. aureus* = 0.5mg/L)
- BUT intrinsically inactive against Gram(-) due to LPS protection
- spare mammalian cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes
- now registered in Europe for complicated skin and soft tissue infections
  (potential issues:
  - limited no. of clinical studies (only equivalence !);
  - safety (myopathy);
  - lack of Gram(-) coverage (no empiric treatment possible);
  - price (about 3-4 x vancomycin …)





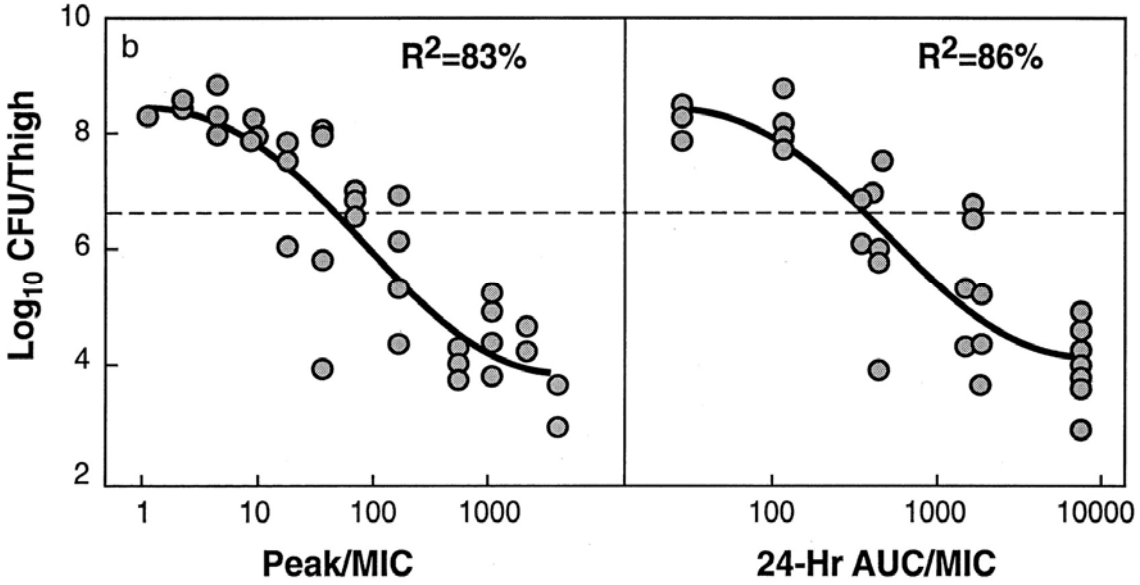




J. Silverman, 45thICAAC, 2005

PK/PD of daptomycin - animal models

Mouse thigh - *S. aureus*



Efficacy for
- Peak/MIC > 60-100
- AUC/MIC > 400-550 (total concentr.)

Safdar *et al.*, AAC (2004) 48:63

PK/PD of daptomycin - application to humans

dose and route of administration	compartment	AUC	AUC/MIC (1 mg/L)
4 mg/kg iv (registered dose)	serum	417	417
	inflamm. exsudate	318	318
6 mg/kg iv	serum	747	747

Dose adjustment if creatinine clearance < 30 ml/min

EUCAST breakpoint:
1 mg/L

Wise *et al.*, AAC (2002) 46:31-3
Dvorchik *et al.*, AAC (2003) 47:1318-23

Launching daptomycin…

1987 1993 1997 **2003-2006**

Registration

FDA : 2003

Europe : 2006

Indications in Europe

- **complicated skin and soft tissues infections with Gram (+)**

Efficacy up to an MIC of 1 mg/L

- **bacteremia**
- **endocarditis**
- **complicated urinary tract infections**

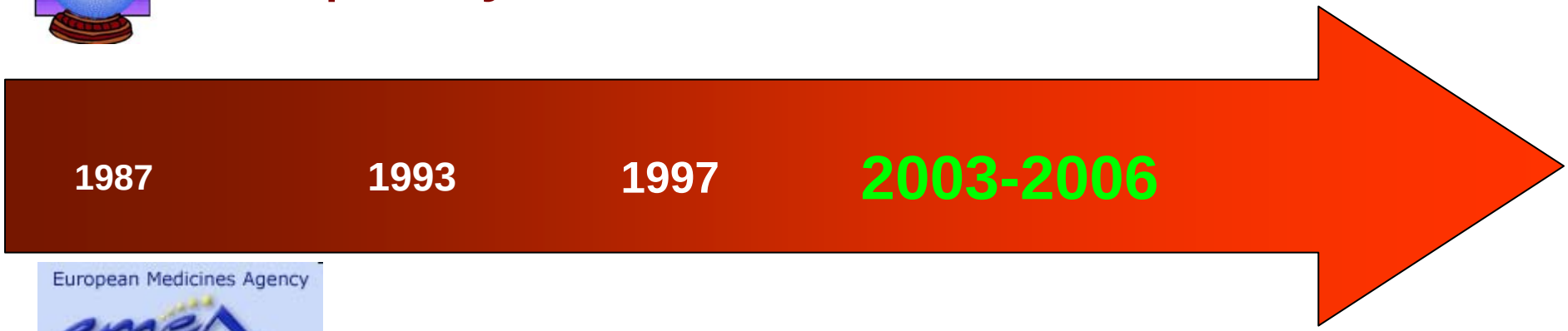
Lack of efficacy :

- **pneumonia (neutralization by the surfactant)**
- **VISA strains (no access to target)**

Only available as intravenous form !

Carpenter & Chambers CID (2004) 38: 994-1000

Daptomycin: where are we in EU ?



European Medicines Agency

emea

4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).

- Complicated skin and soft-tissue infections (cSSTI).
- Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Daptomycin and children in EU ?

1987 1993 1997 **2003-2006**

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Children and adolescents (< 18 years old)

Due to the lack of data on safety and efficacy Cubicin is not recommended for use in children and adolescents (< 18 years of age). See also section 5.2.

Children and adolescents (< 18 years of age)

Pharmacokinetic profiles were obtained following single intravenous administration of daptomycin 4 mg/kg in paediatric patients with proven or suspected Gram-positive infection, divided into three age groups (2-6 years, 7-11 years and 12-17 years). The pharmacokinetics of daptomycin following a single 4 mg/kg dose in adolescents aged 12-17 years are generally similar to those of healthy adult subjects with normal renal function with trends towards lower AUC and C_{max} in adolescents. In the younger age groups (2-6 years and 7-11 years), exposure (C_{max} and AUC) and elimination half-life for the same mg/kg dose were reduced compared with adolescents.

Daptomycin: were are going to ?

1987 1993 1997 **2003-2006** 2009…

While emerging resistance is rare, the scatter of reports in settings with high bacterial loads is of concern.[32]

To minimize the risk, three steps are advised:

first to explore the potential for higher dosage, guaranteeing levels above a 'mutant prevention concentration';

secondly, to recognize patients where surgical debridement is warranted;

and thirdly, to prevent cross-infection with resistant organisms.

Limited registry and volunteer data suggest that it may be possible to use daptomycin at significantly higher doses than the present 4–6 mg/kg, but side effects remain to be evaluated in large-scale clinical trials.

Livermore DM. J Antimicrob Chemother. 2008;62 Suppl 3:iii41-iii49.

Tigecycline: historical landmarks …

1993 **1999**

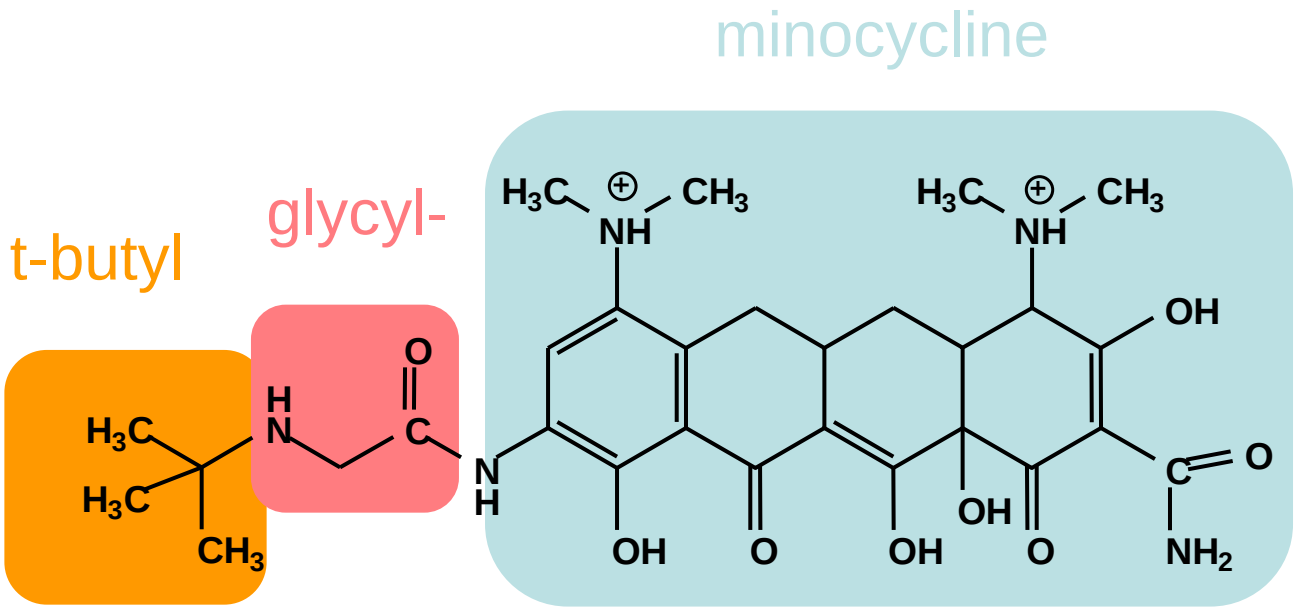
Disvovery of glycylcyclines as a novel class of antibiotics

In vitro and in vivo antibacterial activities of the glycylcyclines, a new class of semisynthetic tetracyclines.
Testa *et al.* Antimicrob Agents Chemother. **1993** 37:2270-7

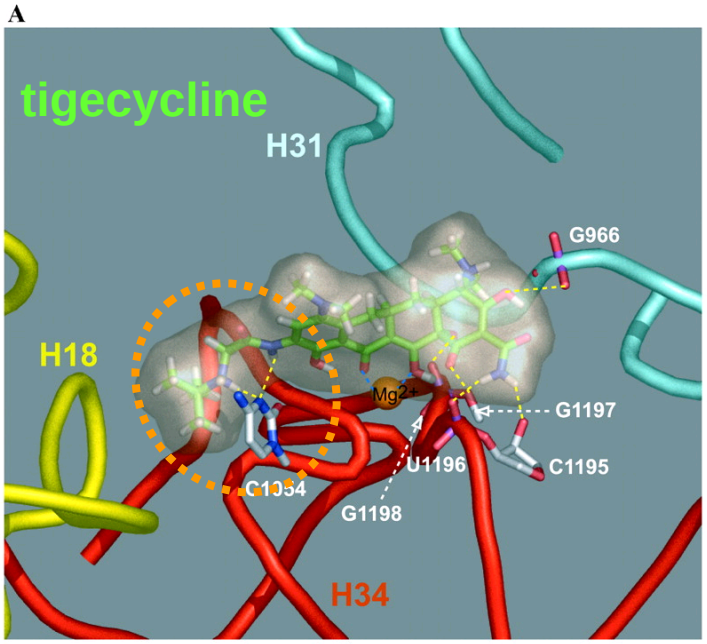
Demonstration of the spectrm of activity and candidate selection

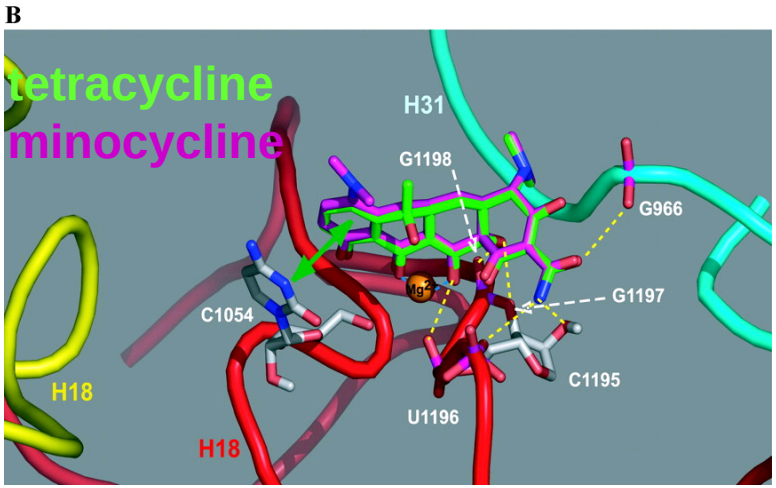
***In vitro* and *in vivo* antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).**
Petersen *et al.* **(1999)** Antimicrob Agents Chemother. 43:738-44.

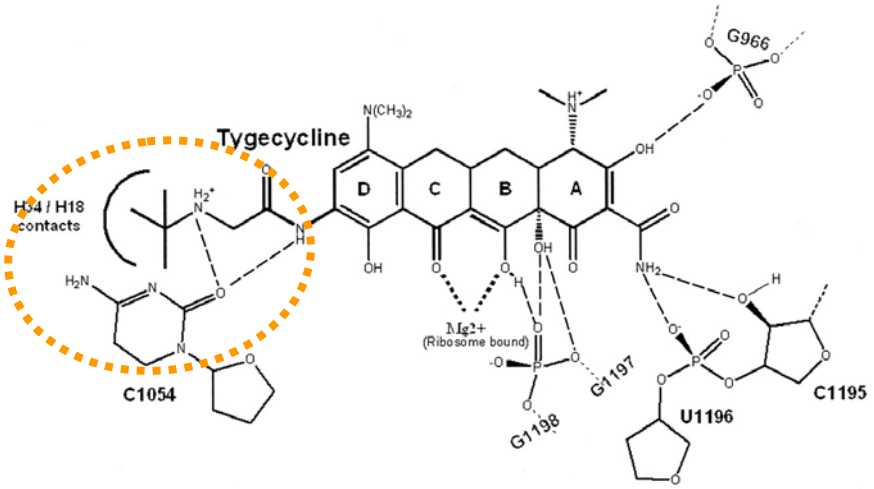
Tigecycline: chemical structure



Mode of action of tigecycline







- same binding site as tetracyclines in ribosome 16S RNA; additional interaction site
- Unaffected by resistance due to
  - ribosomal protection
  - Tet efflux pumps;
- But remains susceptible to broad spectrum efflux pumps of Gram(-) (MexXY in *P. aeruginosa*)

Olson *et al.*, AAC (2006) 50:2156-66

Tetra- and glycyl-cyclines: activity and resistance

species	phenotype	tetracycline	minocycline	tigecycline
E. coli	susceptible	1	1	0.25
	Efflux (Tet)	> 32	16	0.5
	Ribosomal protection	> 32	> 32	0.25
S. aureus	susceptible	0.12	0.06	0.25
	Efflux (Tet)	> 32	0.25	0.5
	Ribosomal protection	> 32	4	0.25

Petersen et al., AAC (1999) 43:738-44

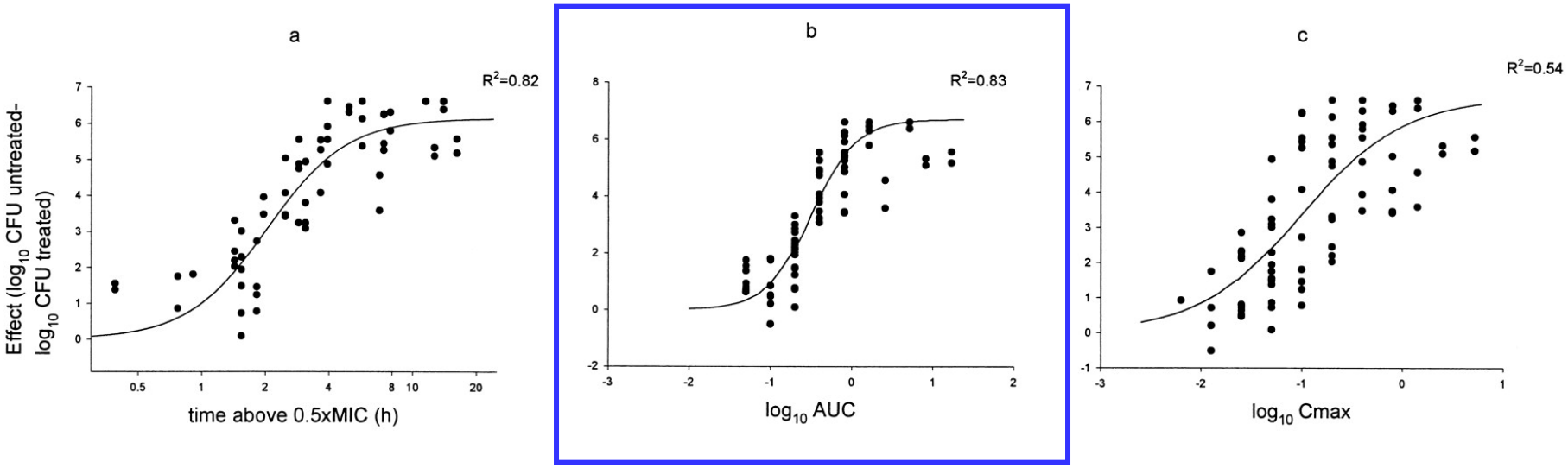
Tigecycline: pharmacokinetics

	tissue	AUC_{24h} (mg.h/L)	serum/tissue AUC ratio
Single dose: 100 mg	bile	2815	537
	bladder	120	23
	colon	17.3	2.6
	lung	9.19	2
	bone	2.05	0.4
	synovial fluid	1.68	0.31
	CSF	0.46	0.11
100 mg + 6x50 mg q12h	ELF	4.54	1.31
	alveolar MΦ	268	77.5

Rodvold, JAntimicrob Chemother (2006) 58:1221-9
Conte et al., Int J Antimicrob Agents (2005) 25:523-9

PK/PD of tigecycline – animal models

Mouse thigh - *S. pneumoniae*



Efficacy for AUC_{24h}/MIC of
- 1-5 (free fraction)
- ~ 10-50 (total conc.)

van Ogtrop *et al.,* AAC (2000) 44:943-9

PK/PD of tigecycline - application to humans

Table 1. Pharmacokinetic data for tigecycline *

Parameter	Pharmacological studies		Efficacy studies
	100 mg	50 mg	50 mg
C_{max} (mg/L)			
30-min infusion	1.45 ± 0.32	0.87 ± 0.23	0.80 ± 0.46
60-min infusion	0.90 ± 0.27	0.63 ± 0.10	0.49 ± 0.28
C_{min} (mg/L)	NA	0.13 ± 0.08	0.16 ± 0.09
Total body clearance (L/h)	21.8 ± 8.9	23.8 ± 7.8	19.9 ± 8.1
$T_{1/2}$ (h)	27.1 ± 14.3	42.4 ± 35.3	NA
$AUC_{24\ h}$ (mg/L.h)	NA	4.70 ± 1.70	5.85 ± 2.48
AUC_{∞} (mg/L.h)	5.19 ± 1.86	NA	NA
Fraction unbound (%)	13–29	13–20	NA
Volume of distribution (L)	568 ± 244	639 ± 307	NA

NA, not available.

* registration data

Tigecycline EUCAST breakpoints

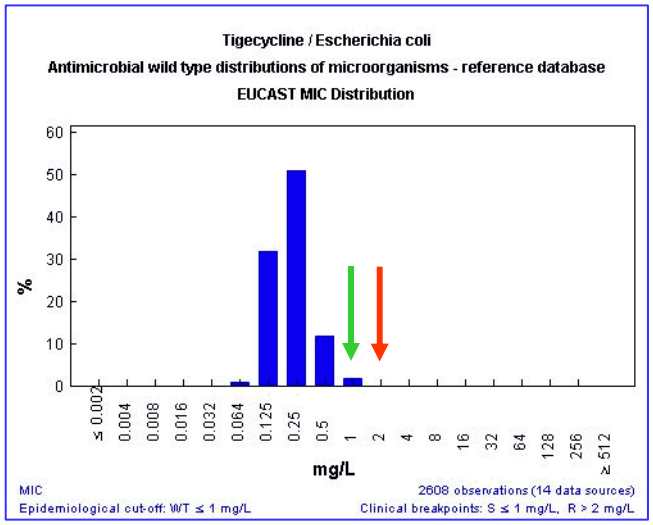
Tetracyclines - EUCAST clinical MIC breakpoints 2008-06-19 (v 2.2)

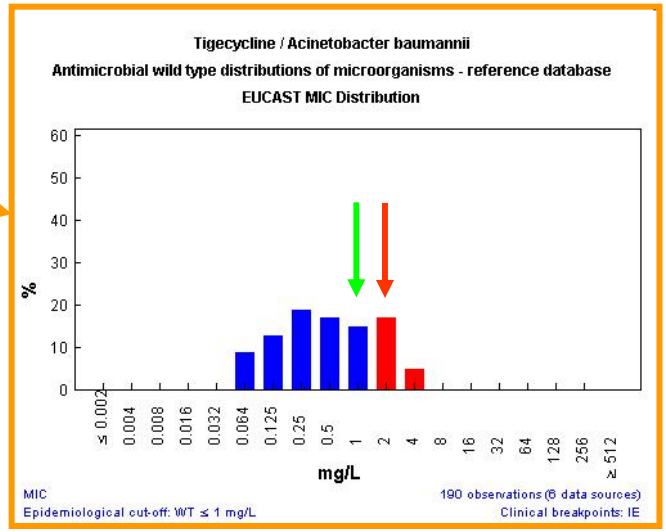
Tetracyclines Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.		Species-related breakpoints (S≤/R>)				
		Enterobac-teriaceae	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*
Tigecycline	RD	1/2[E]	IE	0.5/0.5[F,G]	0.25/0.5[G]	0.25/0.5[G]

E. The S/I and I/R breakpoints were increased to avoid dividing wild type MIC distributions of relevant species.

F. The S/I breakpoint was increased to avoid dividing wild type MIC distributions of relevant species.

G. Strains with MIC values above the S/I breakpoint are very rare or not yet reported.





Launching tigecycline in EU

1993 → **2005-6**

European Medicines Agency

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4.1 Therapeutic indications

Tygacil is indicated for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Paediatric patients
Tygacil is not recommended for use in children and adolescents below 18 years due to the lack of data on safety and efficacy (see sections 5.2 and 4.4).

Tigecycline and children in the EU

1993 **2005-6**

European Medicines Agency

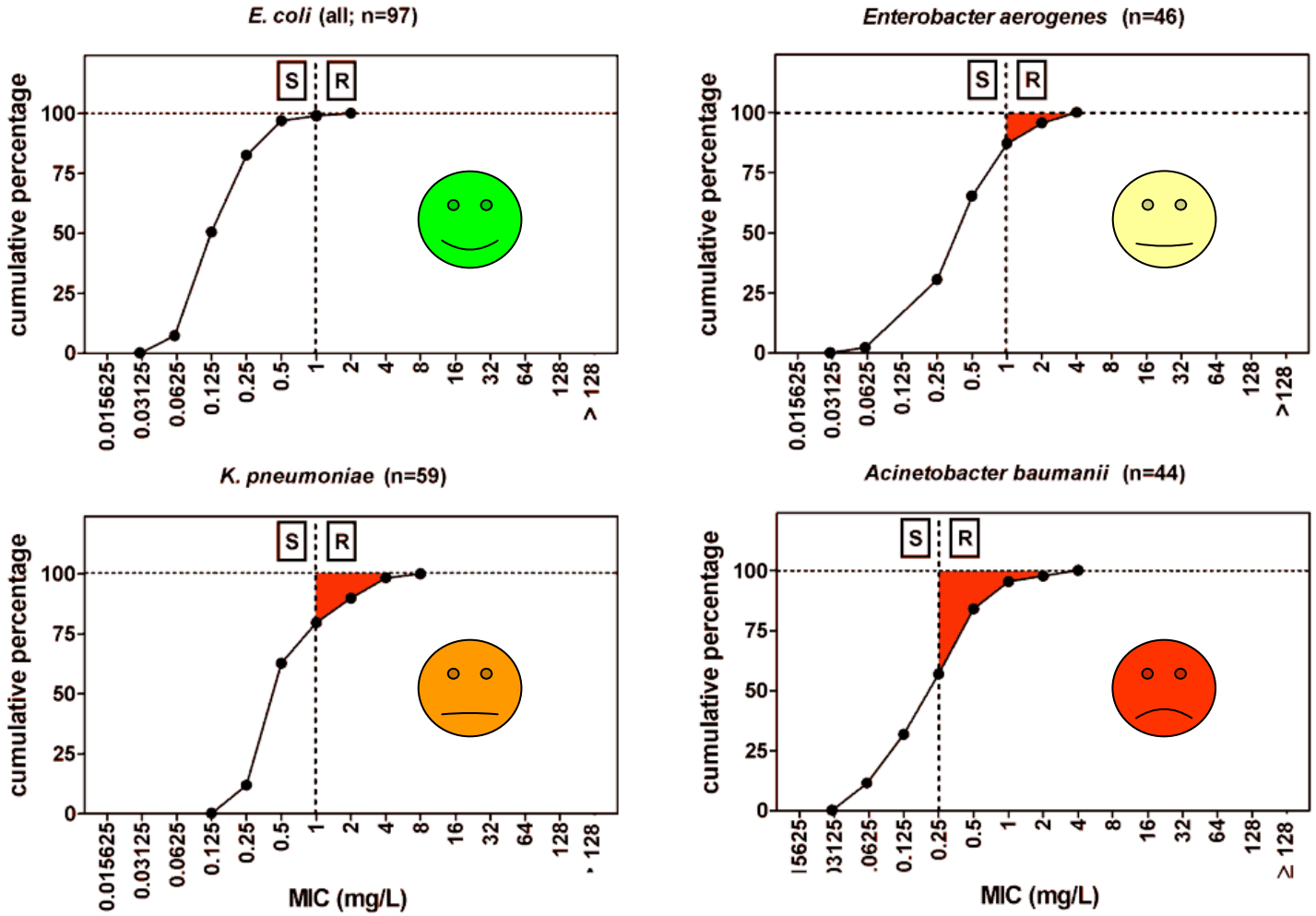
Results of studies in rats with tigecycline have shown bone discolouration. Tigecycline may be associated with permanent tooth discolouration in humans if used during tooth development (see section 4.8).

Tygacil should not be used in children under 8 years of age because of teeth discolouration, and is not recommended in adolescents below 18 years due to the lack of data on safety and efficacy (see sections 4.2 and 4.8).

Paediatric Patients
The pharmacokinetics of tigecycline in patients less than 18 years of age has not been established (see section 4.2).

Tigecycline: what can you do (as in Belgium) ?

MIC distributions in Belgium *



* survey performed in 2006

Tigecycline: where do we go ?

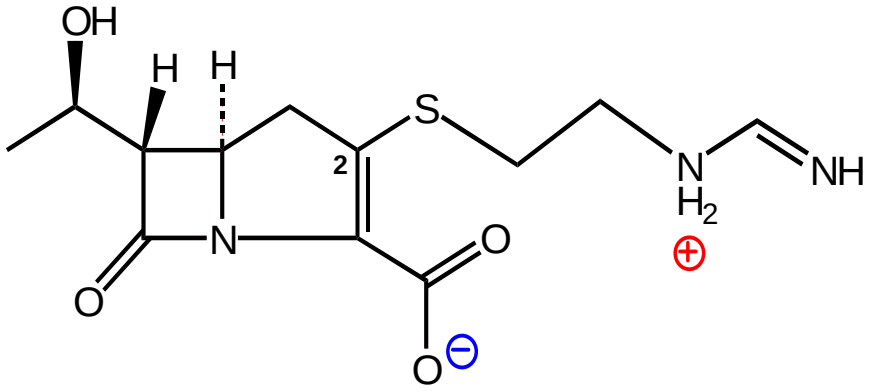
1993 **2005-6** **2009…**

- only agent that really expands our current armamentarium against Gram (-) (but NOT *Pseudomonas*) AND also MRSA …
- clinical success in abdominal infections (after excluding *P. aeruginosa* and/or *Proteus*) and skin and soft tissue infections (MRSA)
  - ➔ surveillance of susceptibilities ! (↗ of efflux pumps expression)
  - ➔ potential use in infections due to ESBL+ entrobacteriaceae
- BUT failure in nosocomial pneumonia…
- AND major unknown (so far) for children *…

☞ **a limited weapon in the hospital armamentarium…**

* pediatric studies are ongoing and/or proposed to Regulatory Authorities

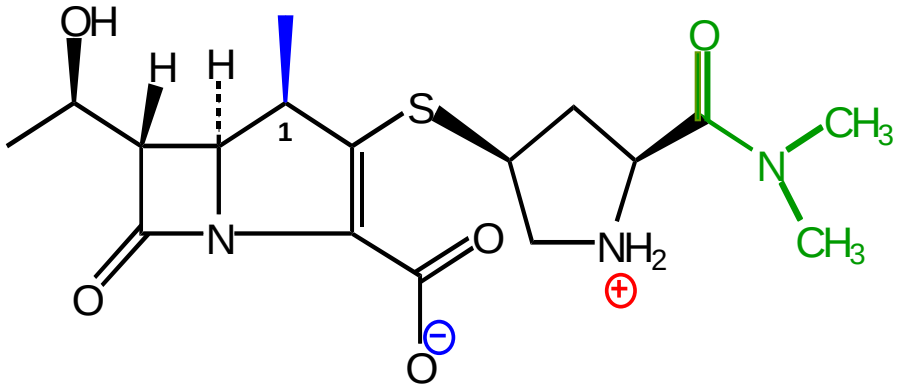
Doripenem…



imipenem (MSD 1977)

C2-(aminomethylideneamino)ethylsulfanyl

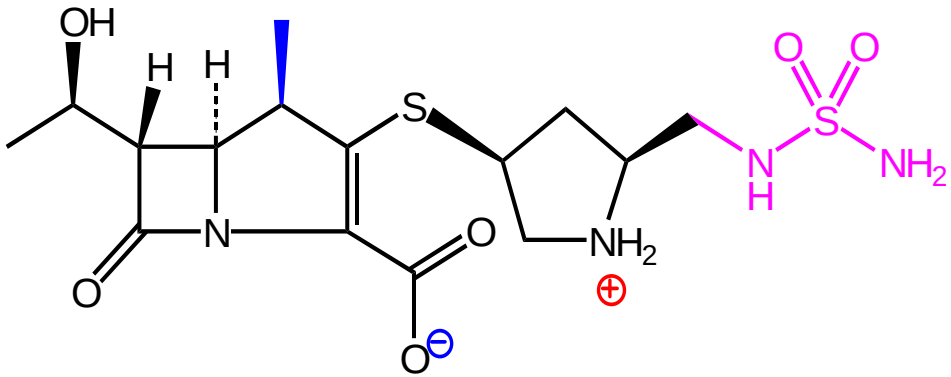
must be associated with cilastatine
to avoid hydrolysis and liberation of nephrotoxic compounds (renal dehydropeptidase)



meropenem (Sumimoto 1987)

1β-methyl, C2-pyrrolidylthio-dimethylcarbamoyl

protection against renal dehydropeptidase by addition of a methyl substituant in position 1



doripenem (Shionogi 1993)

1β-methyl, C2-pyrrolidylthio-sulfamoylaminomethyl

β-lactams are time-dependent …

but how long ?

"*un peu de tout…*"

various pathogens

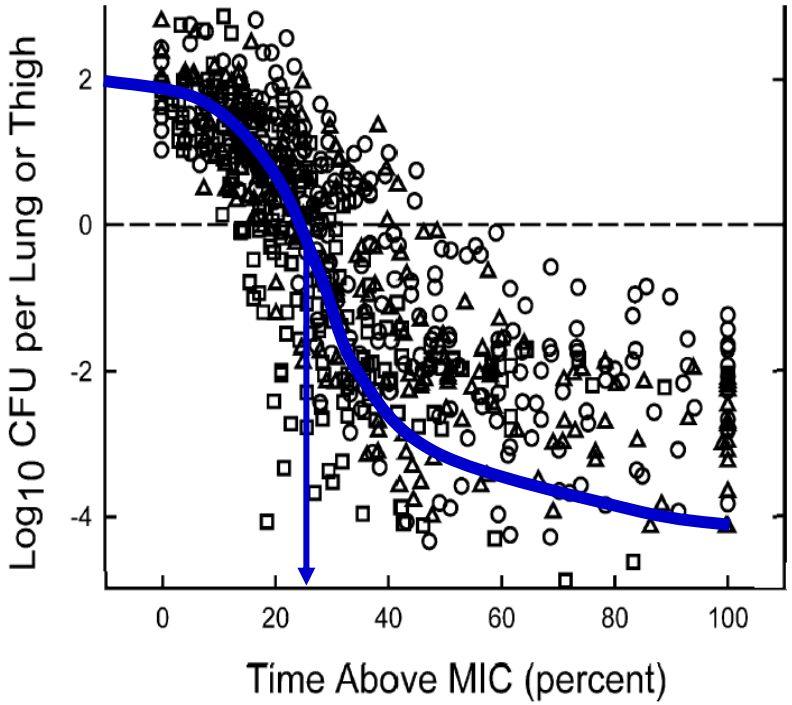


Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

Andes & Craig Int. J. Antimicrob. Agents 2002, 19: 261-268

doripenem

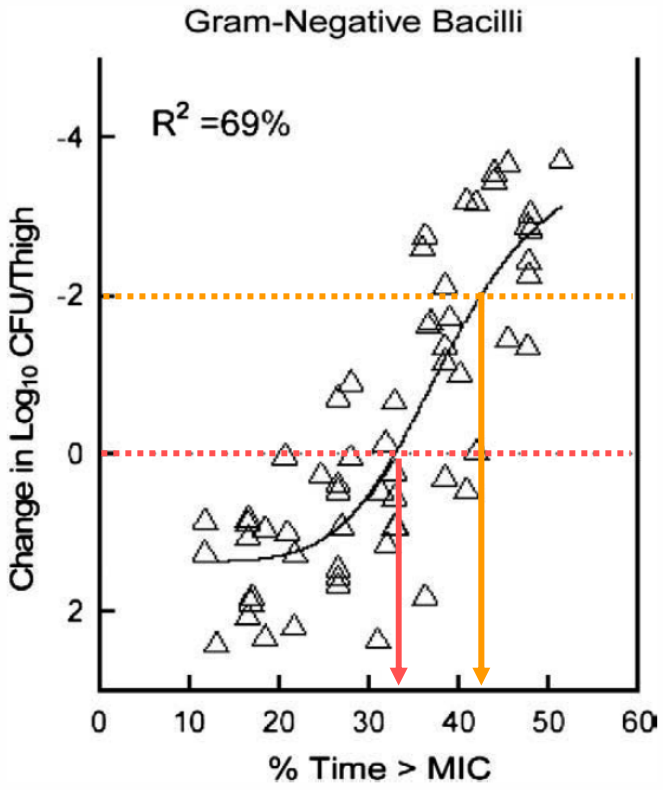


Fig. 4. Relationship between doripenem exposure, as measured by % Time > MIC, and response in a neutropenic murine-thigh infection model involving Gram-negative bacteria.

Van Wart et al., Diagn Microbiol Infect Dis. (2009) 63:409-414

Comparative PK profile of doripenem in volunteers

Single dose PK

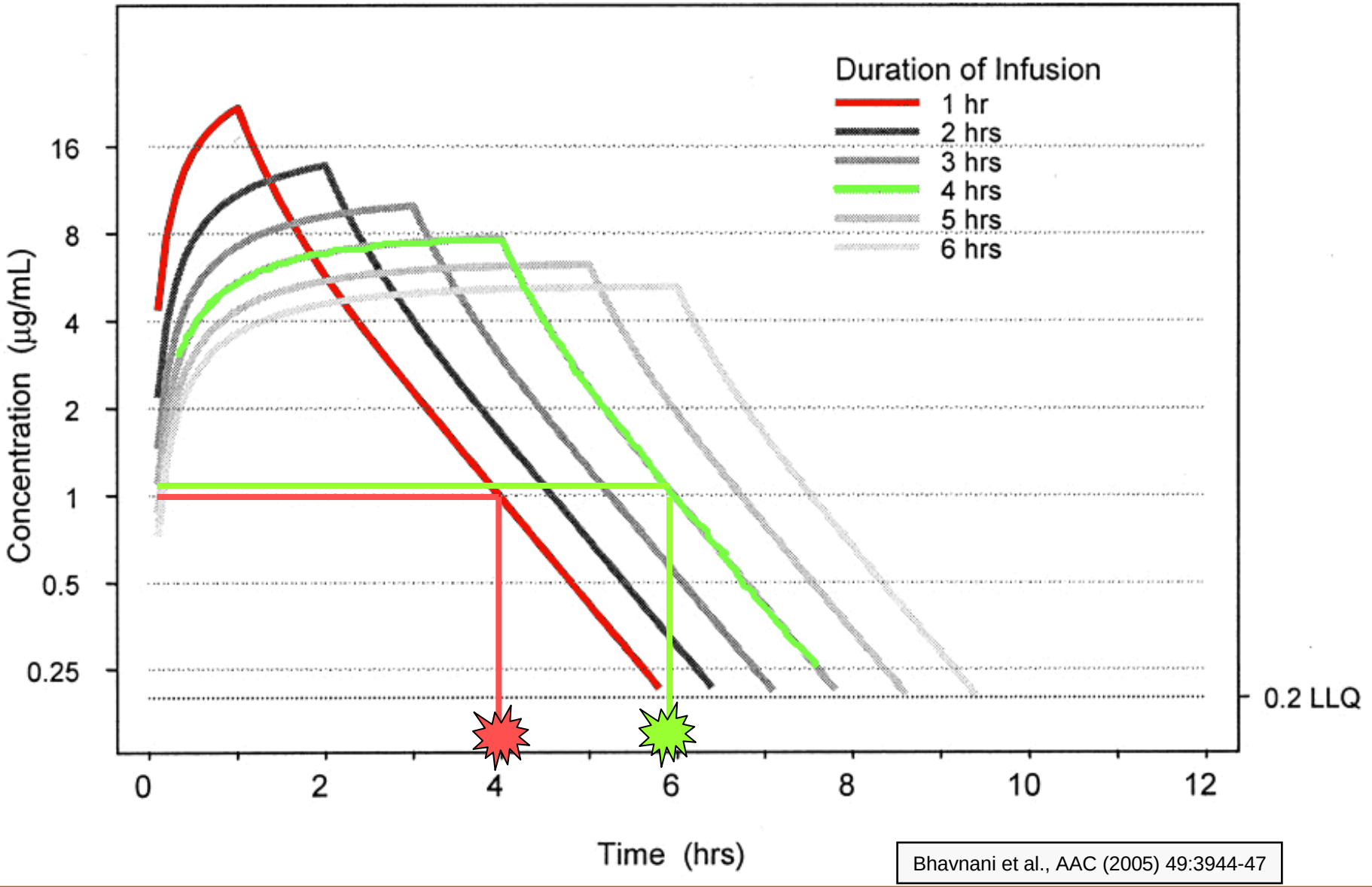
parameter	DOR	MEM	
	(500 mg)	(500 mg)	(1g)
C_{max} (mg/L)	20.2	26	50-60
Prot. binding (%)	8.9	2	
AUC (mg.h/L) – 8 h	44.1	27.2-32.4	66.9-77.5
$T_{½}$ (h)	0.93	1	

Elimination of doripenem is primarily via the renal route

- Dosage adjustment is necessary in patients with moderate and severe renal impairment; AUCs of doripenem and of the microbiologically inactive ring-opened metabolite are substantially increased in patients who require haemodialysis compared with healthy subjects
- the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment.

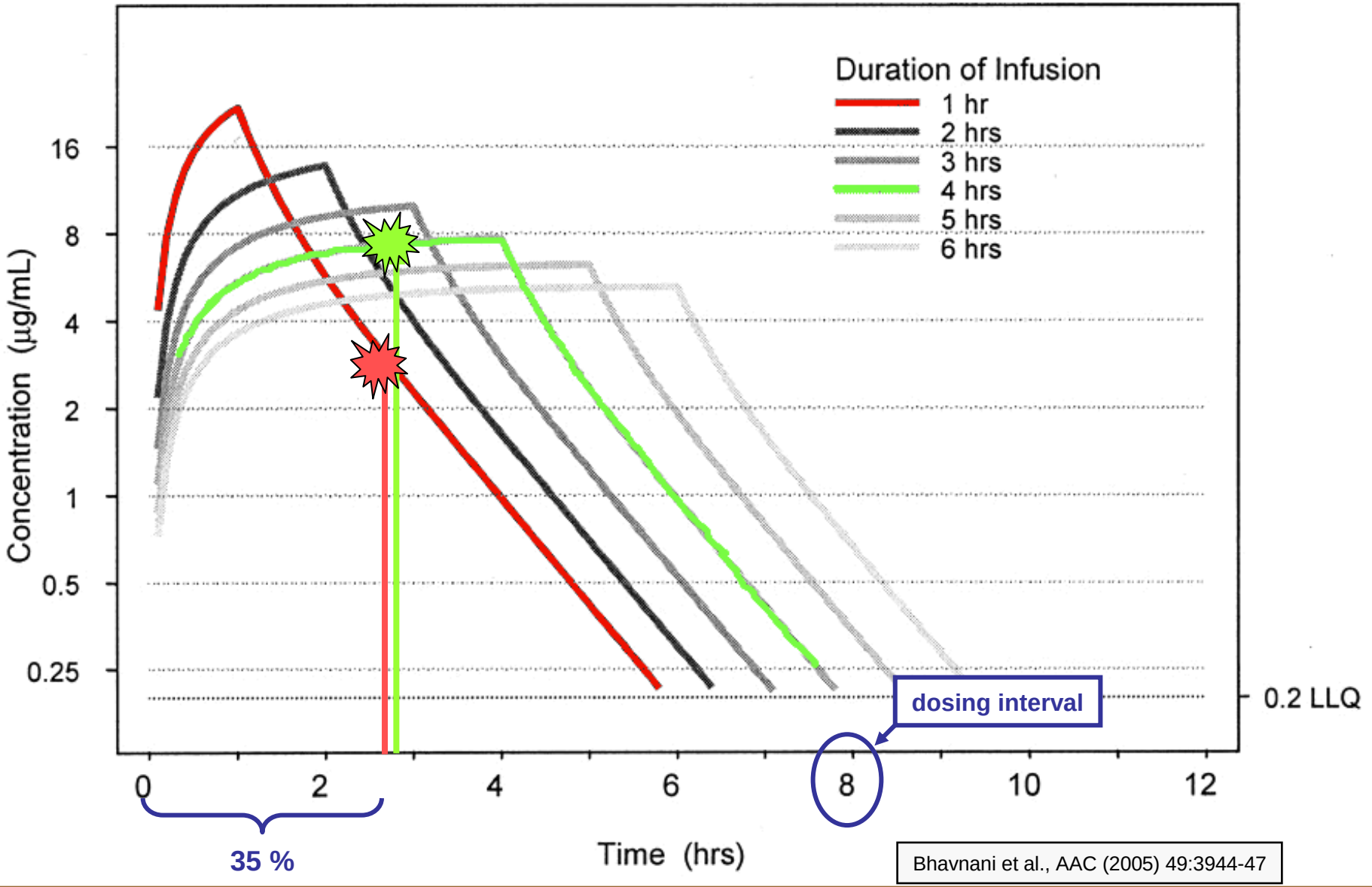
Zhanel et al., Drugs (2007) 67:1027-52

Doripenem: improvement of *f* T > MIC by means of prolonged infusion



Bhavnani et al., AAC (2005) 49:3944-47

Doripenem: prolonged infusion allow to cover higher MICs for a *f* T > MIC of 35 %



Bhavnani et al., AAC (2005) 49:3944-47

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST PK/PD evaluation

Specific target attainment rates for organisms obtained in the phase 3 clinical studies

	Dosing regimens used					
	500 mg, q8h, 1 h infusion			500 mg, q8h, 4 h infusion		
Species specific target attainment	**25% T>MIC**	**30% T>MIC**	**35% T>MIC**	**25% T>MIC**	**30% T>MIC**	**35% T>MIC**
Enterobacteriaceae	99.88	99.82	**99.72**	1	99.9	99.9
Non-Enterobacteriaceae	92.34	90.13	87.83	93.96	93.69	93.3
Pseudomonas aeruginosa	91.42	88.96	86.41	93.25	92.95	92.51
Acinetobacter spp.	82.13	80.95	78.99	82.26	82.2	82.16
Other gram-negative	99.43	98.01	**96.06**	02	100.02	100.01
***Haemophilus* spp.**	100	99.97	**99.88**	0	100	100
Enterococcus faecalis	76.79	62.42	50.79	90.61	89.4	87.18
***S. aureus* Oxa-S**	100	100	**99.99**	0	100	100
Streptococcus pneumoniae	100	99.91	**99.7**	.	100.	100.
Streptococcus spp. (other than *S. pneumoniae)*	99.81	99.66	99.54	99.96	99.96	99.93
Other gram-Positive	90.13	89.74	89.02	90.08	90.05	90.03
All Anaerobes	97.75	97.26	96.66	98.09	98	97.89

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST PK/PD evaluation

Specific target attainment rates for organisms obtained in the phase 3 clinical studies

	Dosing regimens used					
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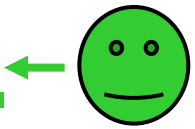

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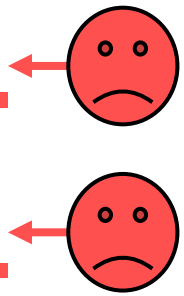


In press – not final

EMEA registration

Pharmacokinetic/pharmacodynamic relationship

Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of doripenem exceeds the MIC (%T>MIC) of the infecting organism has been shown to best correlate with efficacy in pre-clinical pharmacokinetic/pharmacodynamic (PK/PD) studies. Monte Carlo simulations using pathogen susceptibility results from completed phase 3 trials and population PK data indicated that the %T>MIC target of 35% was achieved in greater than 90% of patients with nosocomial pneumonia, complicated urinary tract infections and complicated intra-abdominal infections, for all degrees of renal function.

Extending the infusion time of Doribax to 4 hours maximizes the %T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. In seriously ill patients or those with an impaired immune response, a 4-hour infusion time may be more suitable when the MIC of doripenem for the known or suspected pathogen(s) has been shown or is expected to be > 0.5 mg/l, in order to reach a target attainment of 50% T>MIC in at least 95% of the patients (see section 4.2). Monte Carlo simulations supported the use of 500 mg 4-hour infusions every 8 hours in subjects with normal renal function for target pathogens with doripenem MICs ≤ 4 mg/l.

DORIBAX® Summary or Product Characteristics (EMEA)

EMEA registration

Breakpoints *

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Non species related Staphylococci	S ≤1 mg/l and R >4 mg/l inferred from the methicillin breakpoint
Enterobacteriaceae	S ≤1 mg/l and R >4 mg/l
Acinetobacter spp.	S ≤1 mg/l and R >4 mg/l
Pseudomonas spp.	S ≤1 mg/l and R >4 mg/l
Streptococcus spp. other than *S. pneumoniae*	S ≤1 mg/l and R >1 mg/l
S. pneumoniae	S ≤ 1 mg/l and R >1 mg/l
Enterococci	"inappropriate target"
Haemophilus spp.	S ≤ 1 mg/l and R >1 mg/l
N. gonorrhoeae	IE (insufficient evidence)
Anaerobes	S ≤1 mg/l and R >1 mg/l

* clinical data are fully taken into account in the EUCAST breakpoint setting !

DORIBAX® Summary or Product Characteristics (EMEA)

Why limiting the infusion to 4h ?

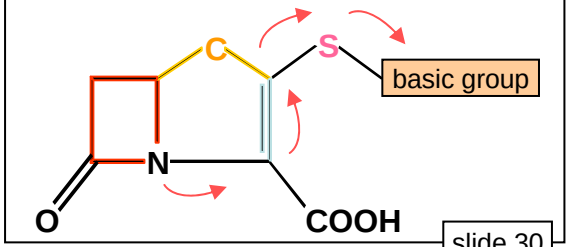
TABLE 3. Time during which β-lactams remains >90% stable at the highest concentration tested (see Table 1)

Drug(s)	Time (h, min)[a] at:	
	37°C	25°C
Aztreonam	>24	ND
Piperacillin	21, 40	~30
Piperacillin + tazobactam	>24	⩾72[b]
Azlocillin	>24	⩾72[b]
Mezlocillin	14	46, 30
Ceftazidime	8	24
Cefepime	13	20, 30
Cefpirome	7, 15	23, 40
Imipenem + cilastatin	2, 45	3, 30
Meropenem	1, 50	5, 15
Faropenem	>24	~80

[a] Decays were monitored for 24 h; the slope was calculated by linear regression and used to determine the 90% stability time point. All data were rounded to the closest 15-min value. ND, not determined.

[b] 90% stability for at least 72 h, but the slope was too weak to calculate the 90% intercept value with accuracy from the 24-h decay data.

because they carry an aminated side chain in C2 (nucleophilic)



carbapenems are much less stable than other β-lactams !

Viaene et al., AAC 2002; 46:2327-2332

Doripenem and children ?

European Medicines Agency

4.1 Therapeutic indications

Doribax is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- Nosocomial pneumonia (including ventilator–associated pneumonia)
- Complicated intra-abdominal infections
- Complicated urinary tract infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

FDA

----------USE IN SPECIFIC POPULATIONS----------

- Dosage adjustment is required in patients with moderately or severely impaired renal function (2.2, 12.3)
- DORIBAX® has not been studied in pediatric patients. (8.4)

Other novel antibiotics (pipeline…)

Ceftobiprole (Basilea / Johnson & Johnson)

- first cephalosporin with anti-MRSA action (is also active against *P. aeruginosa*)
- 2 X 750 mg ou 3 x 500 mg … (limited because of toxicity ?)
- "*target attainment rate*" : MIC of 4 mg/L (EUCAST breakpoint)
- submitted for "complicated skin and soft tissue infections" in EU and in the USA but no decision expected before end of 2009
- failure in nosocomial pneumonia (reason still unclear ?)

- Telavancin (Theravance / Astellas)
  - first lipoglycopeptide with FDA "near approval"; status uncertain in EU (safety issues)
  - very bactericidal (but Gram + ONLY); once-daily dosing
  - trend towards superiority in "complicated skin and soft tissue"
  - success in nosocomial pneumonia (*S. aureus*)

- Oritavancin (The Medicines Company)
  - lipopeptide very active against Gram +, with activity against SCV [incl. cystic fibrosis] and biofilm
  - very long half-life and large cellular accumulation
  - uncertain future (new phase 3 study requested by the FDA; no EMEA decision)

MIC of novel anti-Gram (+) antibiotics and EUCAST breakpoints

organism	ceftobiprole (4/4)	telavancin (1/1)**	oritavancin (0.125/0.25)**	vancomycin (2/2)**
MSSA	0.12-1	0.25/0.5	0.25/0.5	1/1
MRSA	0.25-4	0.25/0.25	0.25/0.5	1/1
VISA	0.5-2	0.5-1	1/1	**4/4**
VRSA	1-2	**2-4**	0.5	**16**
S. pneumo Pen non-S	0.25-1 *	≤ 0.06/≤ 0.06	≤0.002/0.004	≤ 0.25/≤ 0.5
Enteroc. Van S	0.064-16 *	0.12/0.5	0.12/0.5	1/2
Enteroc. Van R	*	**4-16**	0.03	**16**

* no EUCAST breakpoint set (insufficient evidence)
** draft (submitted for consultation)

Pillar et al., JAC (2008)61:595-602; Ge et al., AAC (2008) 52:3398-404; Draghi et al.,AAC (2008) 52:2383-2388; ICAAC (2008) C1-146,150,151; Lemaire et al. AAC (2009) Mar 16. [Epub]

Drugs with a (still) more incertain future ?

- **Fluoroquinolones**
  - **gemifloxacin**: very low MICs but unfavourable pharmacokinetics
    registered in the US but not (yet ?) in EU
  - **garenoxacin**: tolerance and commercial issues (U.S.).
  - **gatifloxacin**: restrictions imposed in the US; not available in EU

- **anti MRSA β-lactams**
  - **ceftaroline**: low MICs than ceftobiprole but less favorable pharmacokinetics ($t_{1/2}$ ↘)

- **glycopeptides**
  - **dalbavancin**: very long half life ($t_{1/2}$ ~ 7 days); no useful activity against VRSA and doubtful against VISA
    development on hold…

- **trimethoprim derivatives**
  - **iclaprim**: "impossible" pharmacokinetics; inferior to linezolid in phase 3 trials; further development uncertain…

A few words about inhaled antimicrobials …

Obvious applications in cystic fibrosis

- **TOBI** ® (nebulized tobramycin) since 1999
- **azithromycin-lysine** (AZLI)
  ("*In patients with CF, PA airway infection, moderate-to-severe lung disease, and no recent use of antipseudomonal antibiotics or azithromycin, 28-day treatment with AZLI significantly improved respiratory symptoms and pulmonary function, and was well tolerated*" – Chest. 2009 May;135(5):1223-32).
- **tobramycin inhaled powder** (TIP)
  (under development - Int J Pharm. 2009 Jan 5;365(1-2):162-9)
- **ARIKACE** ® (liposomal amikacin; under development - J Aerosol Med Pulm Drug Deliv. 2008 Sep;21(3):245-54)
- inhaled **ciprofloxacin** (Bayer-Schering) and **levofloxacin** (Mpex)
- **fosfomycin / tobramcyin** combinations (Gilead)

❖ and a novel approach:
KB001 (Kalobios) : monoclonal antibody for treatment of *Pseudomonas aeruginosa* lung infections.