Asian PK/PD Educational Workshop

PK/PD and resistance

or

How shall we tackle with the future...

Why would PK/PD be important for the prevention of resistance ?

- rate and intensity of the bactericidal effects → Dead bacteria never get resistant
- minimizing the potential for acquisition and/or emergence of mechanisms of resistance → How you kill might be important ...
- dealing with populations of decreased susceptibility → Creating a a safety margin...

Why would PK/PD be important for the prevention of resistance ?

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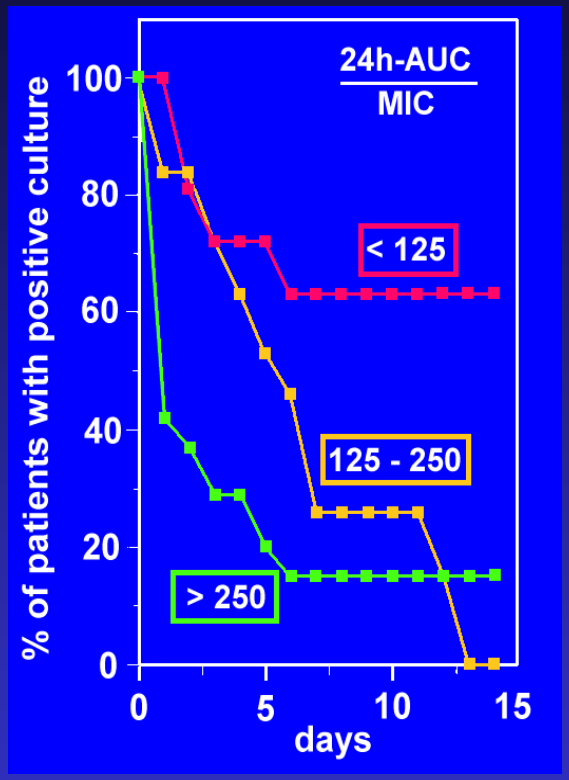
Dead bacteria never get resistant

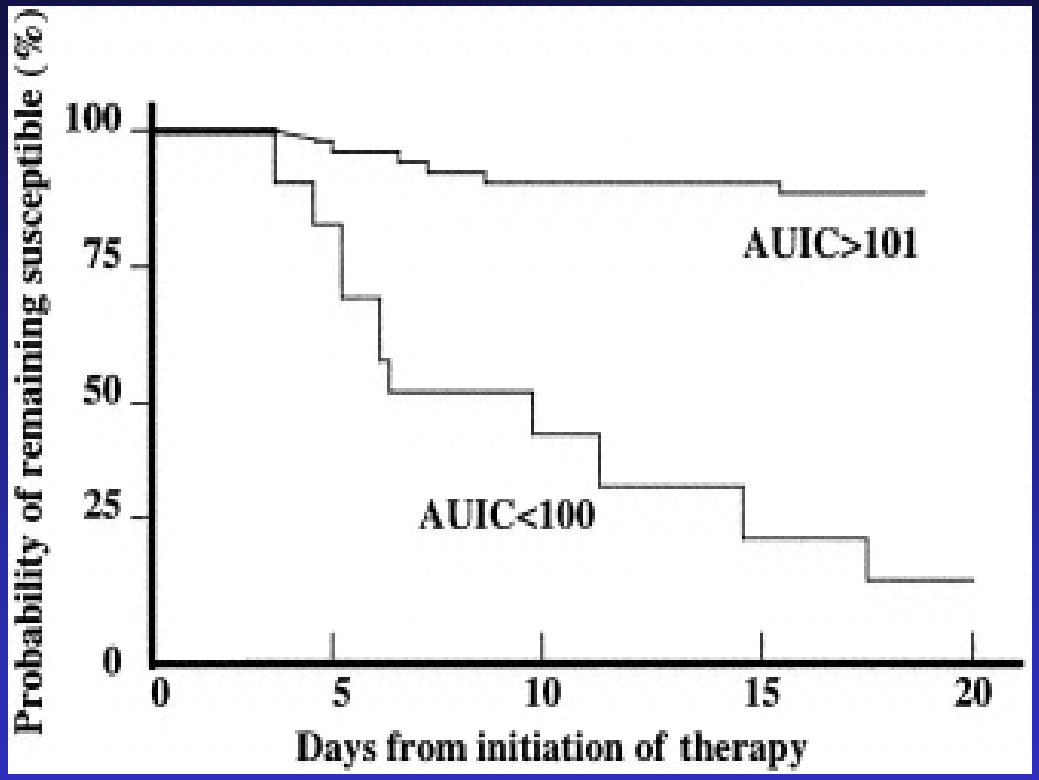
PK/PD and resistance : importance of the rate of bactericidal effect

- **less time for the bacteria**
  - **to acquire mechanisms of resistance**
  - **to build (or let the host build) barriers that will impair antibiotic access to its target**
- **better cooperation with the mechanism of resistance of the host**

Resistance and 24h AUC/MIC *in vivo* ...

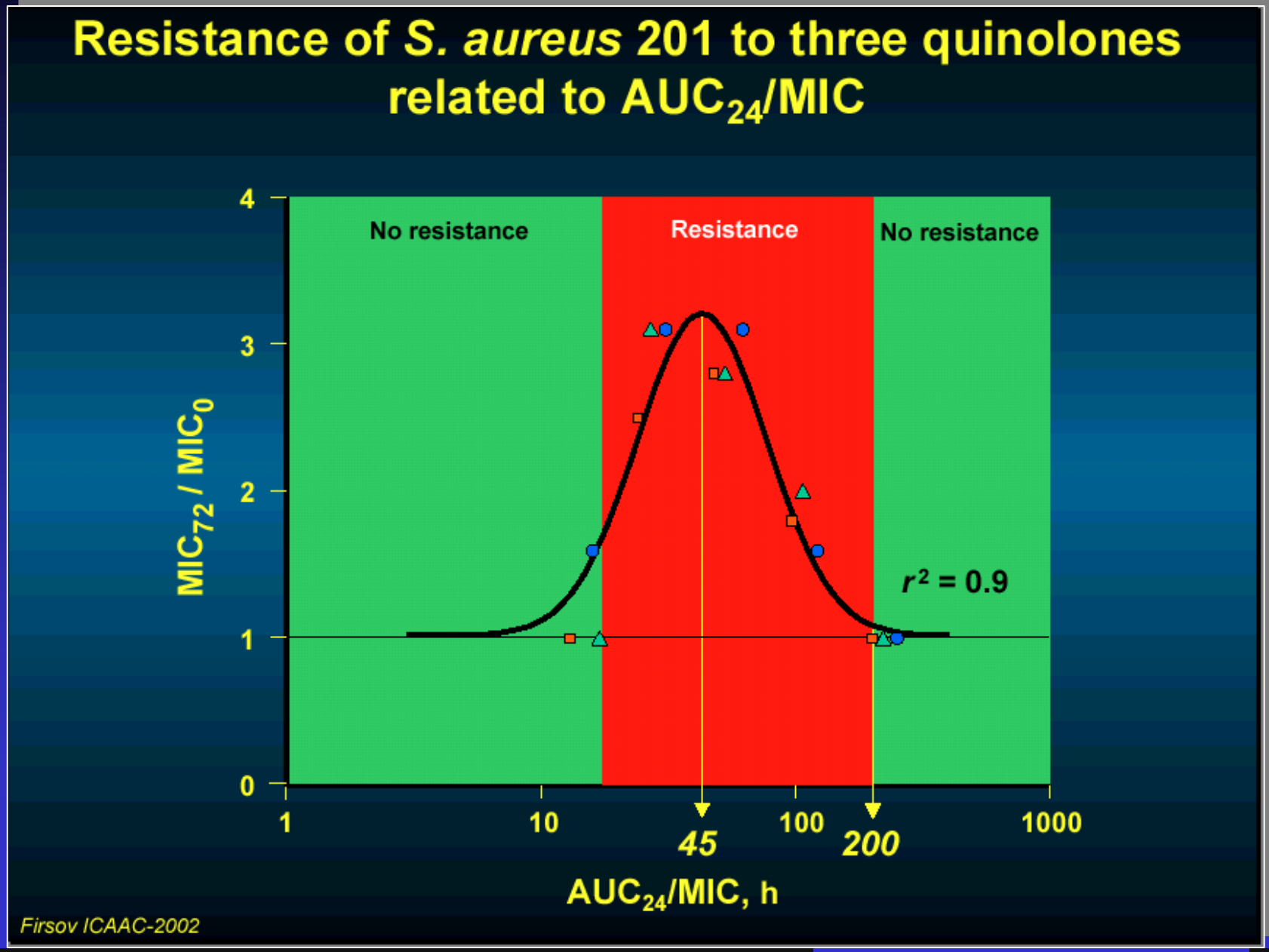


The 1993 study of Forrest *et al*. shows that a 24h AUC/MIC ratio for ciprofloxacin causes a slow clearance of bacteria



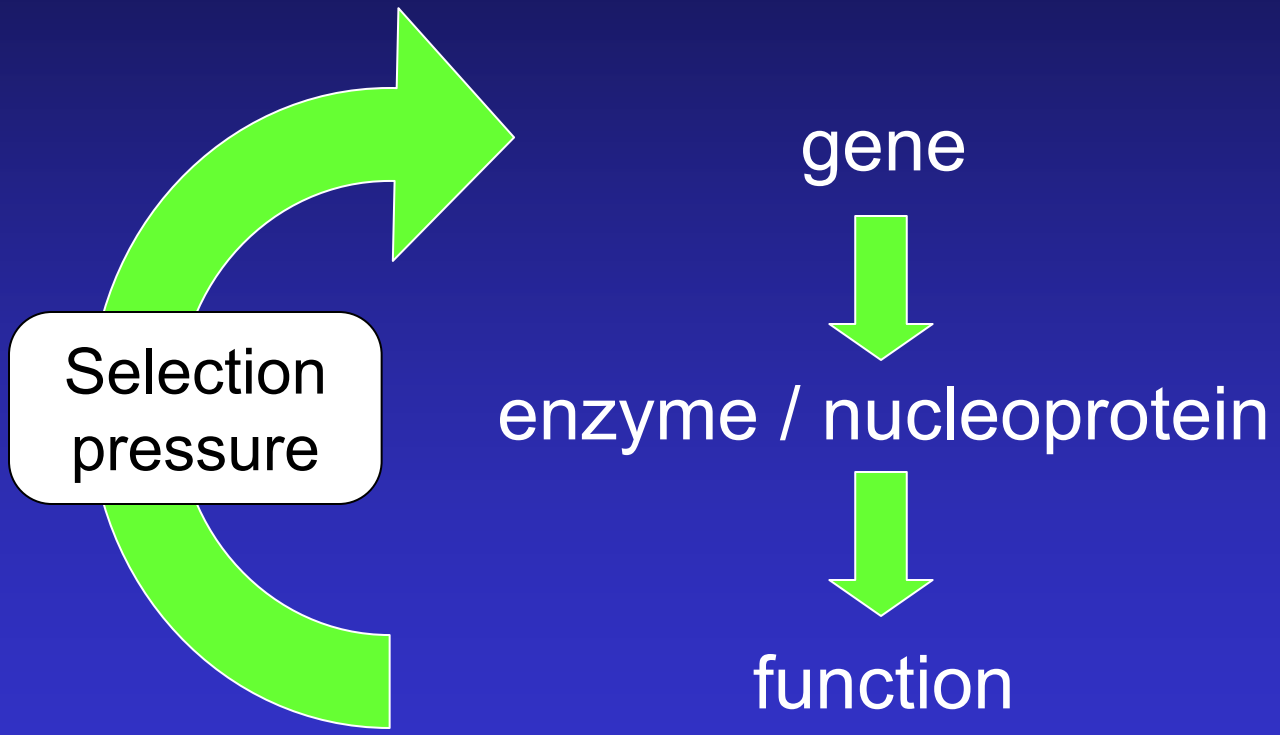
A 1998 study by the same group (Thomas JK, et al., AAC 42:521–7) shows that the risk of getting resistant is related to a 24h AUC/MIC ratio of < 100

Resistance and 24h AUC / MIC *in vitro*



Why would the rate of bactericidal effect be critical ?

A simple application of Darwin's concepts ...



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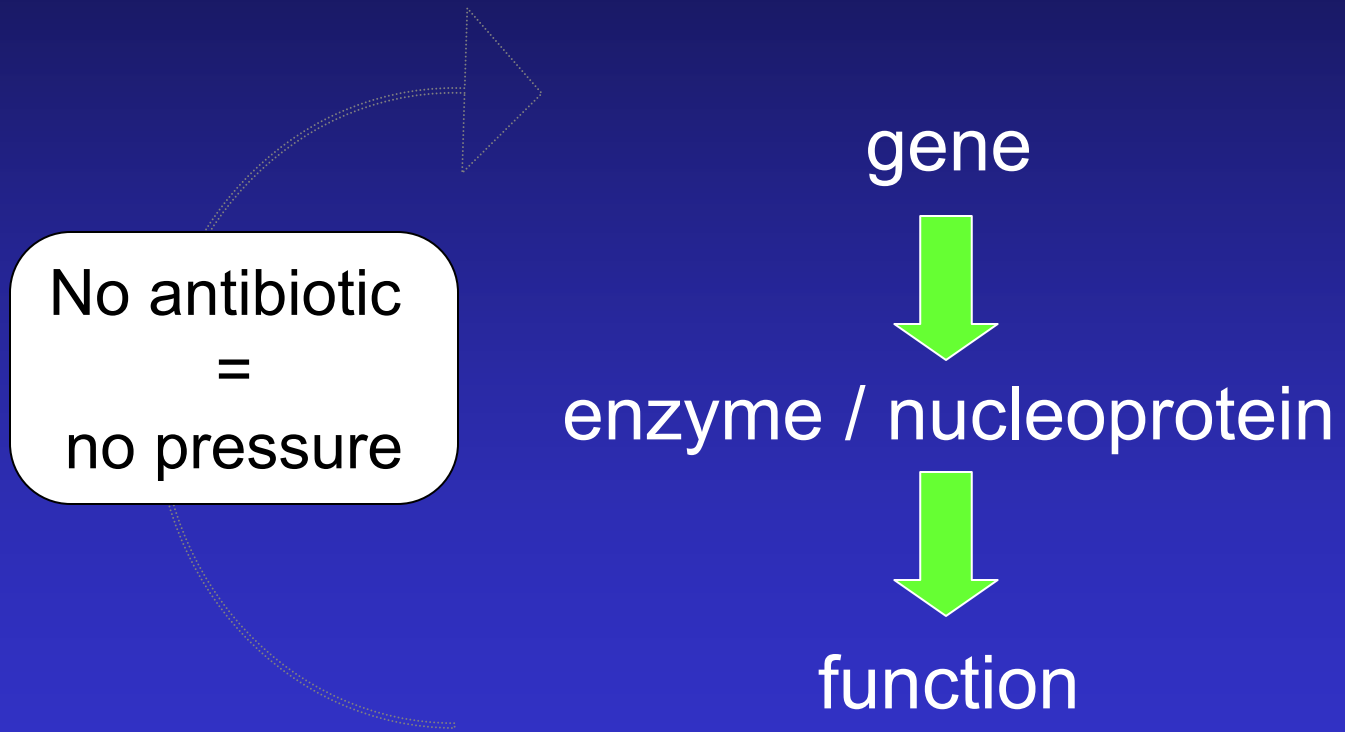

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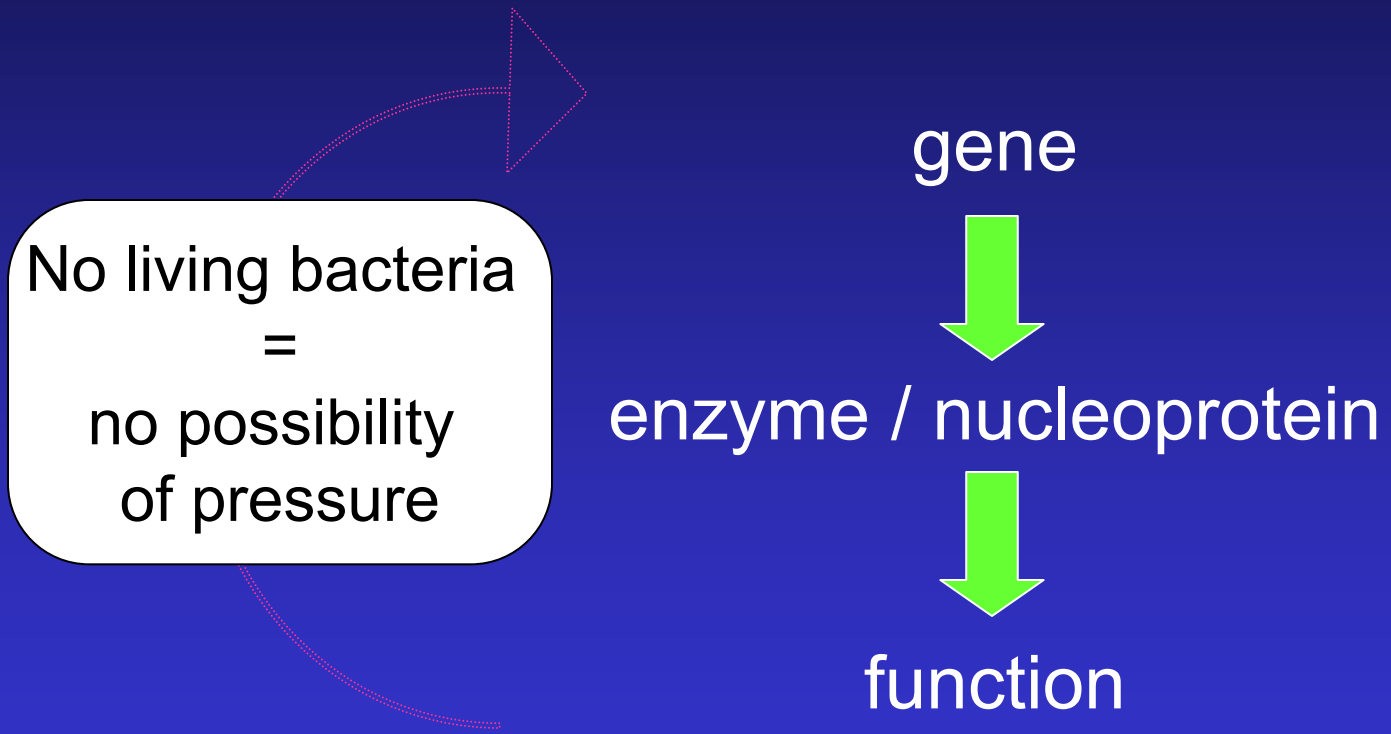

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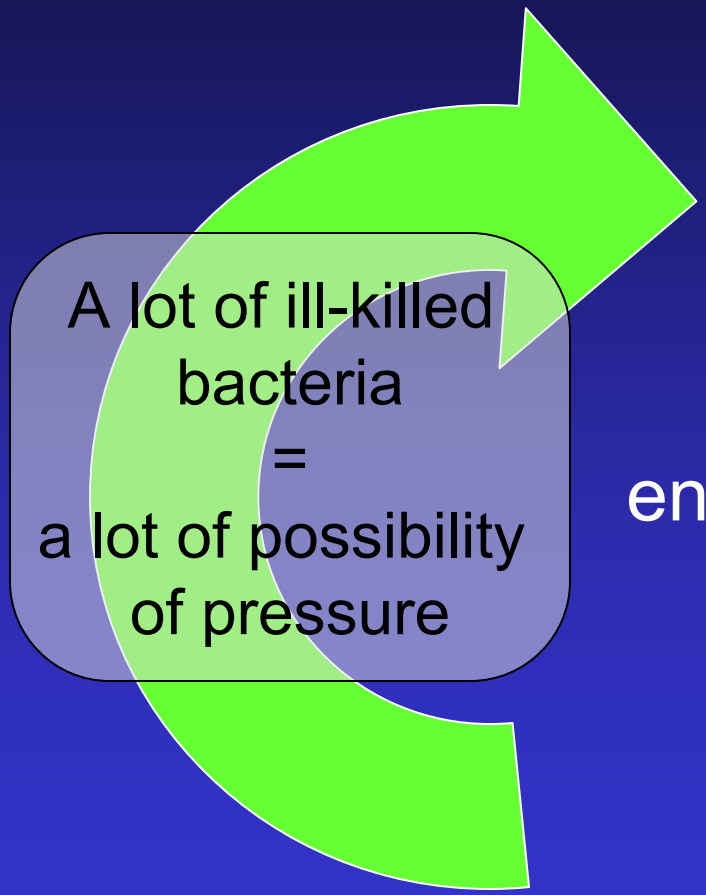

gene

enzyme / nucleoprotein

function

Why would PK/PD be important for the prevention of resistance ?

- rate and intensity of the bactericidal effects
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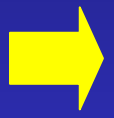
- dealing with populations of decreased susceptibility



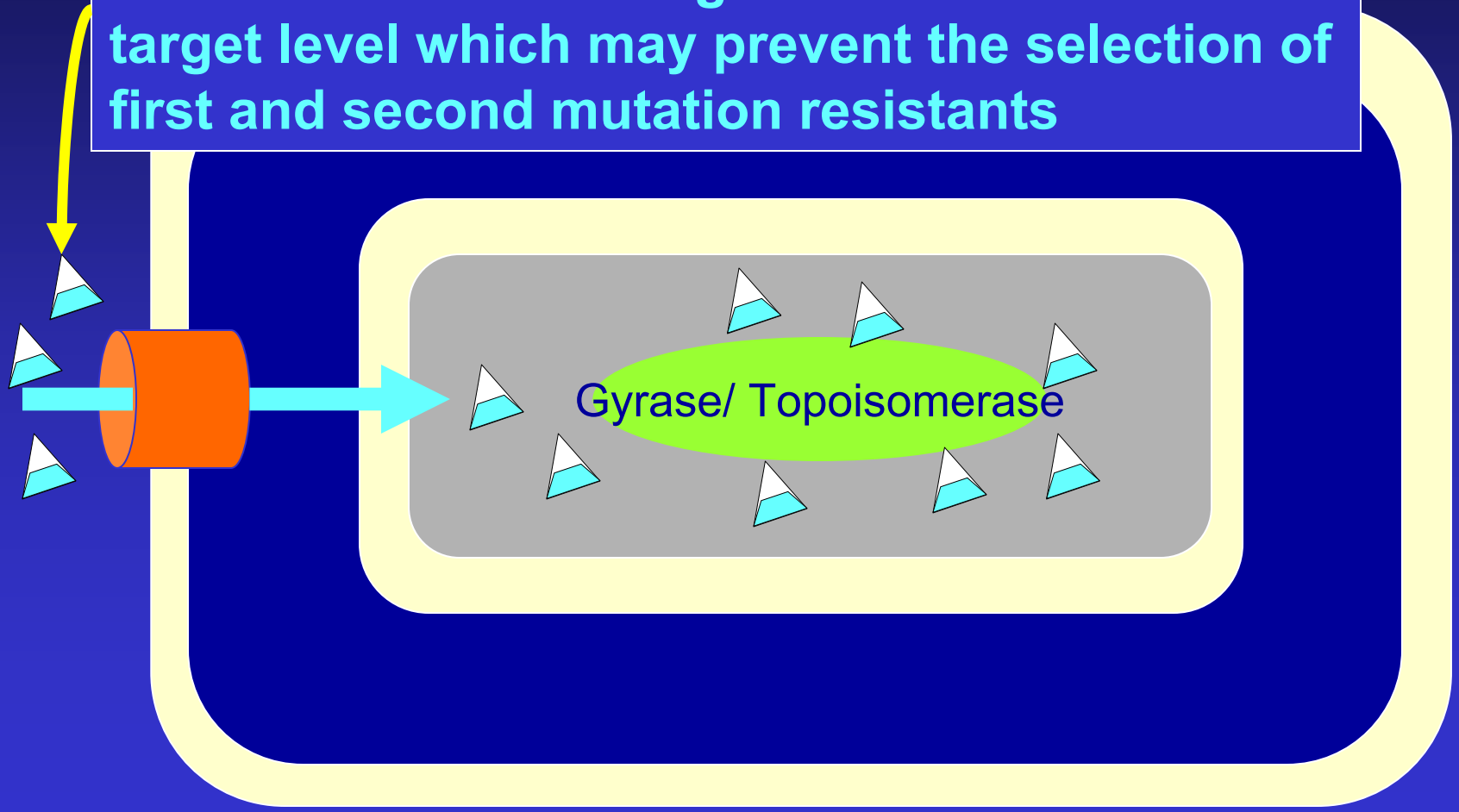
How you kill might be important ...

The bacterial efflux pumps may defeat a good PK ...

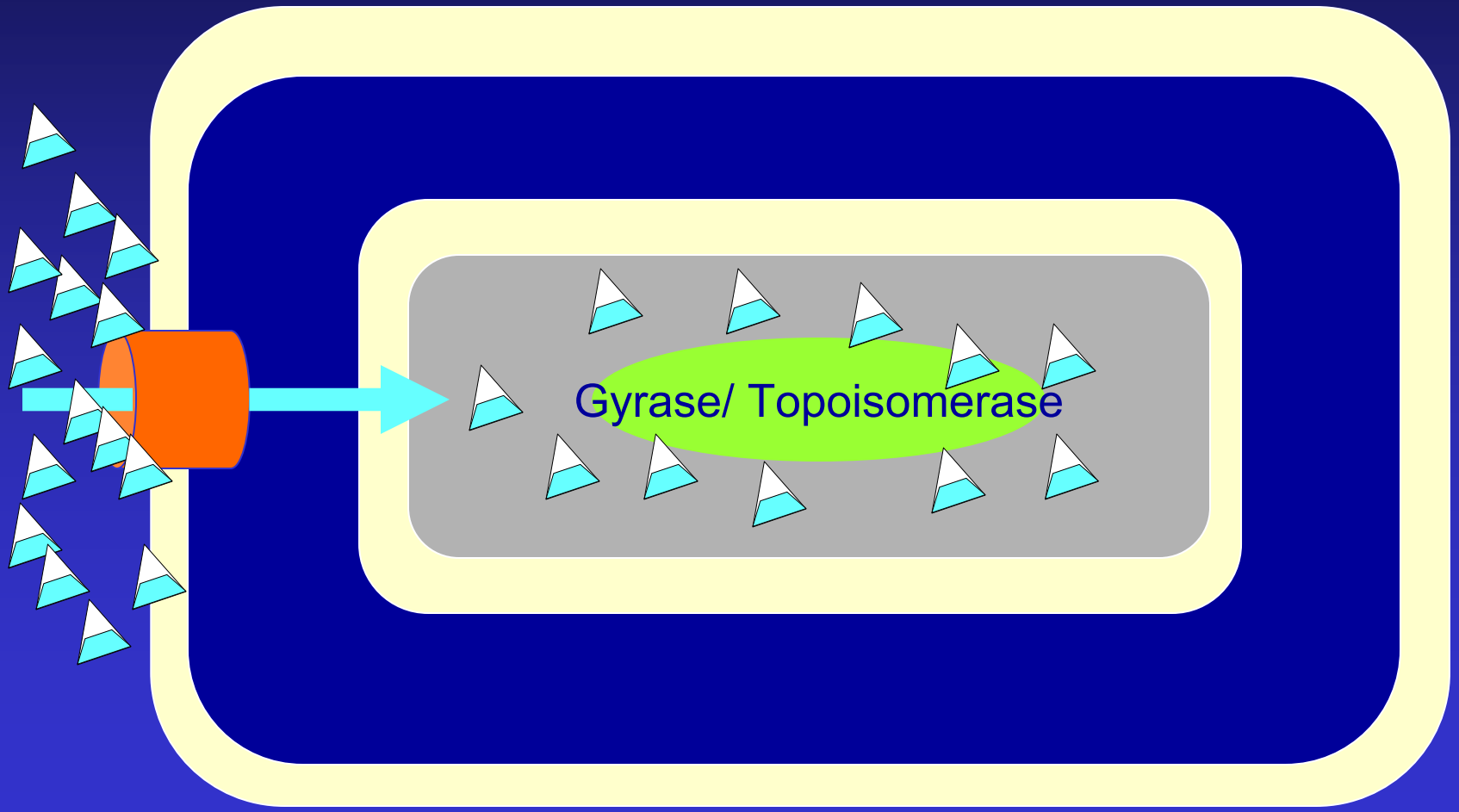
- by decreasing the intrabacterial concentration of the antibiotic and resulting in subinbitory concentrations and thereby favouring the possibility of mutations or acquisition of mechanims of resistance
- by allowing the development of multiple resistance

Efflux and selection of resistance to FQ

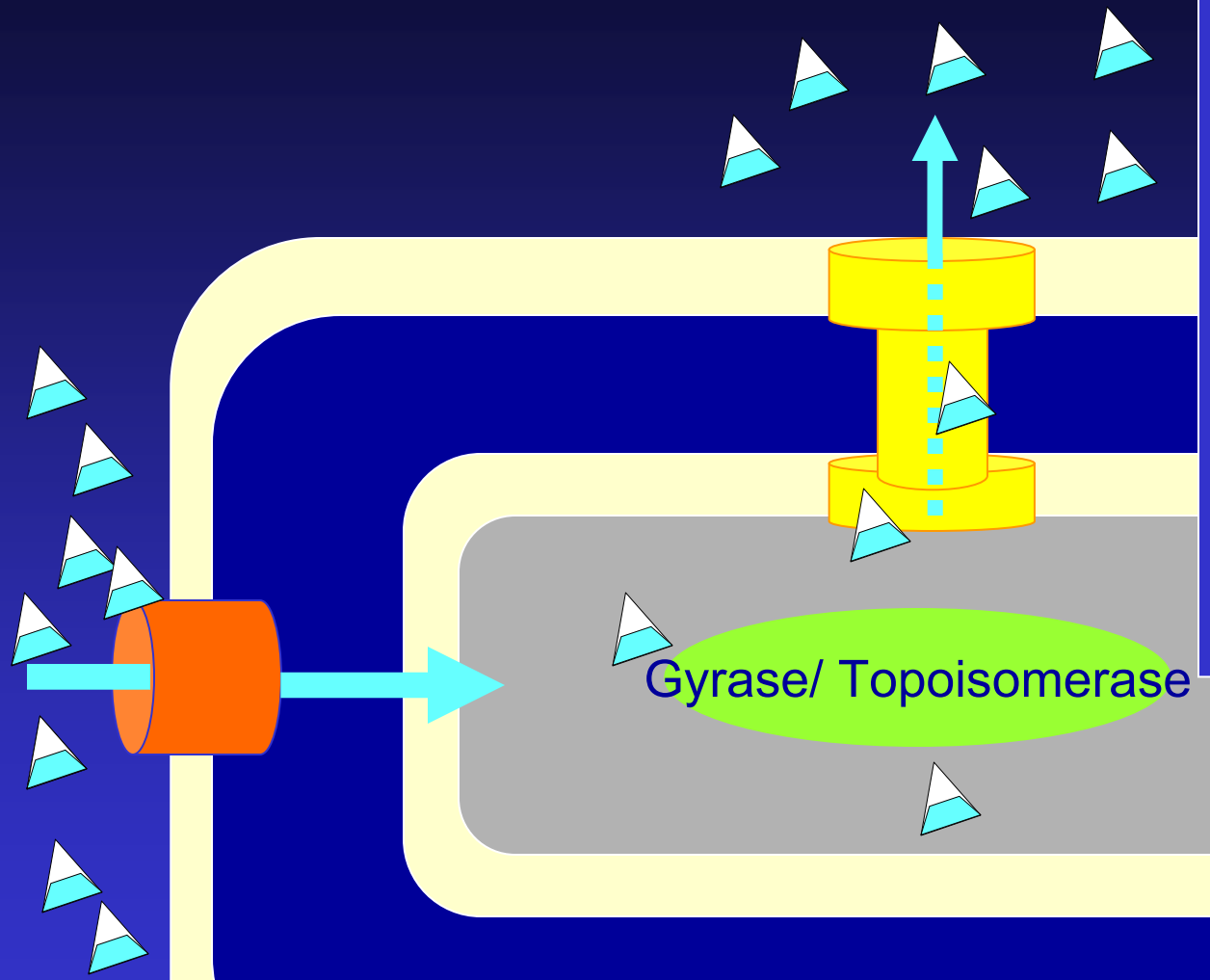
A certain serum AUC and a certain serum peak will determine the drug concentration at the target level which may prevent the selection of first and second mutation resistants



Efflux and selection of resistance to FQ



Efflux and selection of resistance to FQ



Efflux pumps will reduce the concentration at the level of the target and thereby favor the selection of target mutants!

Efflux and selection of resistance

Frequency of Levofloxacin-resistant mutants in *Pseudomonas aeruginosa*

Pump status	LVX MIC	Frequency of LVX-resistant mutants
WT	0.25	2×10^7 - 4×10^7

Wild P. aeruginosa show both a relatively high MIC and a high frequency of resistant mutants

Lomovskaya *et al*,
AAC (1999) 43:1340-1346

Efflux and selection of resistance

Frequency of Levofloxacin-resistant mutants in *Pseudomonas aeruginosa* if deleting the efflux pump operons

Pump status	LVX MIC	Frequency of LVX-resistant mutants
WT	0.25	2×10^7 - 4×10^7
Δ mexAB-oprM	0.015	
Δ mexCD-oprJ	0.25	
Δ mexEF-oprN	0.25	
Δ mexAB-oprM;Δ mexEF-oprN	0.015	
Δ mexCD-oprJ; Δ mexEF-oprN	0.25	
Δ mexAB-oprM; Δ mexCD-oprJ	0.015	
Δ mexAB-oprM; Δ mexCD-oprJ; Δ mexEF-oprN	0.015	

Lomovskaya *et al*,
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The MIC falls to low values ...

Efflux and selection of resistance

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Δ mexCD-oprJ	0.25	2×10^7 - 4×10^7
Δ mexEF-oprN	0.25	2×10^7 - 4×10^7
Δ mexAB-oprM;Δ mexEF-oprN	0.015	2×10^7 - 10^7
Δ mexCD-oprJ; Δ mexEF-oprN	0.25	2×10^6
Δ mexAB-oprM; Δ mexCD-oprJ	0.015	1×10^9
Δ mexAB-oprM; Δ mexCD-oprJ; Δ mexEF-oprN	0.015	**$<1 \times 10^{11}$**

Lomovskaya *et al,* AAC (1999) 43:1340-1346

AND the selection of mutants in FQ target becomes undetectable when ALL pumps are disrupted

Efflux and multi / cross-resistance in pathogenic bacteria

1 bacteria → several pumps → multiresistance

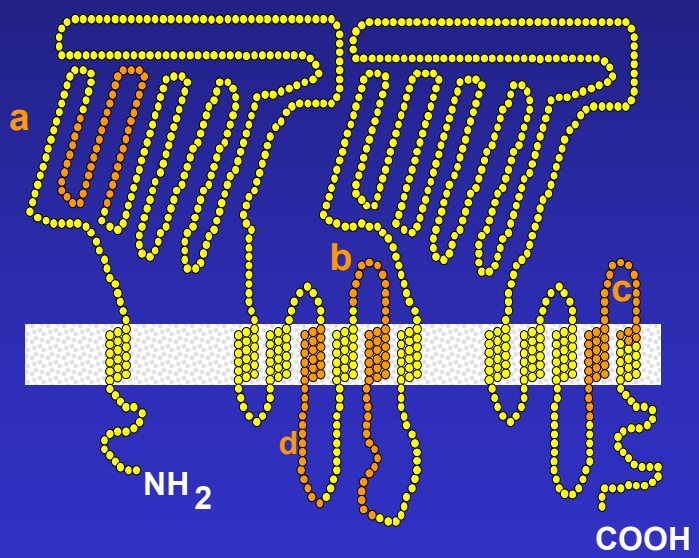
1 pump → several classes of antibiotics → crossresistance

1 class of antibiotics → several pumps → efficacy of inhibitors ?

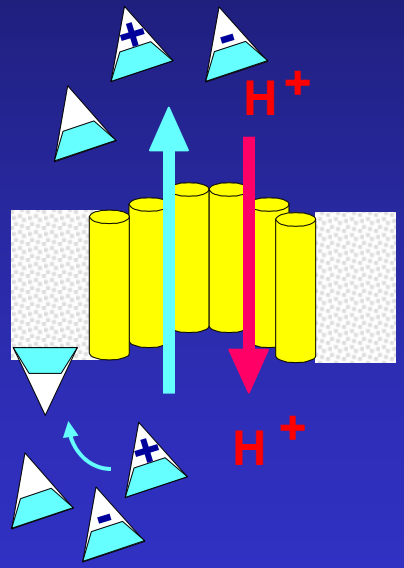
Most frequent antibiotic-pumps in procaryotes (1/2)

- **R**esistance **N**odulation **D**ivision (Gram -)

TOPOLOGY



MECHANISM



proton antiport

ANTIBIOTICS

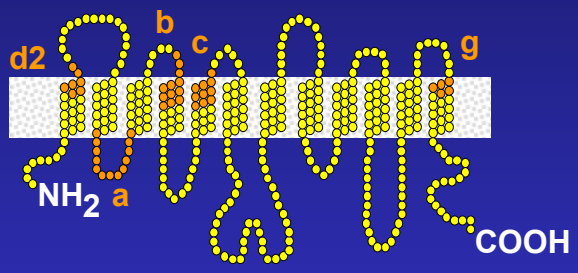
- tetracyclines
  fluoroquinolones
  erythromycin
  rifampicin
- β-lactams
  fluoroquinolones
  fusidic acid
- chloramphenicol
- aminoglycosides

Most frequent antibiotic-pumps in procaryotes (2/2)

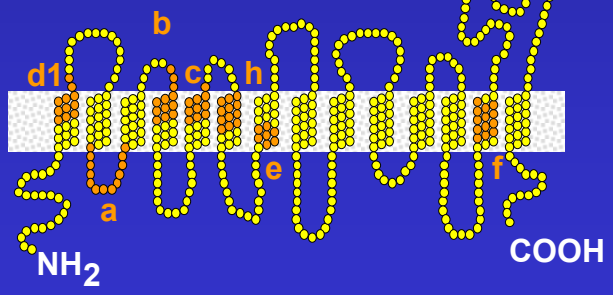
- **Major Facilitator Superfamily (Gram + and -)**

TOPOLOGY

12 TMS



14 TMS



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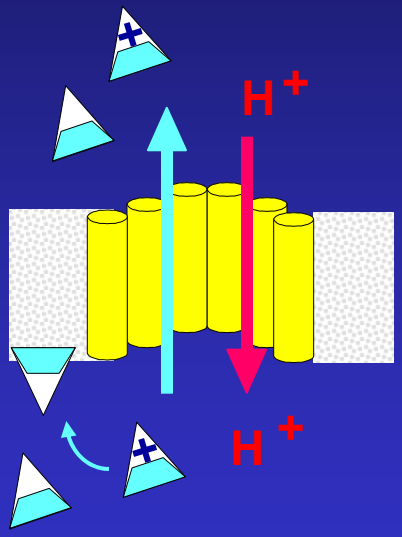


proton antiport

ANTIBIOTICS

tetracyclines
fluoroquinolones
macrolides
lincosamides
rifampicin
pristinamycin

chloramphenicol

aminoglycosides

The Mutant-prevention concentration (MPC) (1/3)

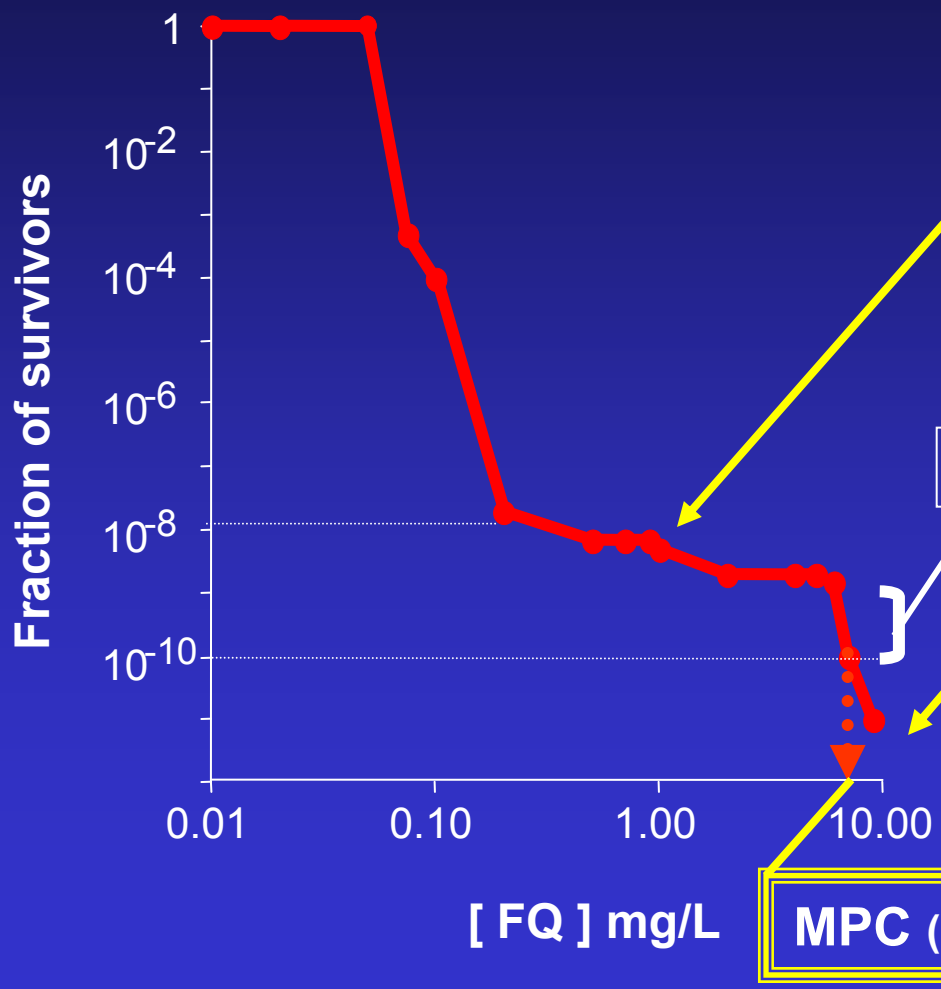
Effect of fluoroquinolone concentration on selection of resistant mutants of Mycobacterium bovis BCG and Staphylococcus aureus

Dong YZ, Zhao XL, Domagala & Drlica-K

Antimicrob. Agents Chemother. 43 : 1756-1758, 1999

- Mycobacterium bovis BCG and Staphylococcus aureus
- increasing concentrations of fluoroquinolones
  - a sharp drop, followed by a plateau and
  - a second sharp drop.

Bactericidal activity of FQs against *M. bovis*



The plateau region correlates with the presence of first-step resistant mutants.

Mutants are not recovered at concentrations above those required for the second sharp drop, …

thereby defining a Mutant Prevention Concentration (MPC).

Mutant-prevention concentration (MPC) (2/3) ...

Effect of fluoroquinolone concentration on selection of resistant mutants of Mycobacterium bovis BCG and Staphylococcus aureus

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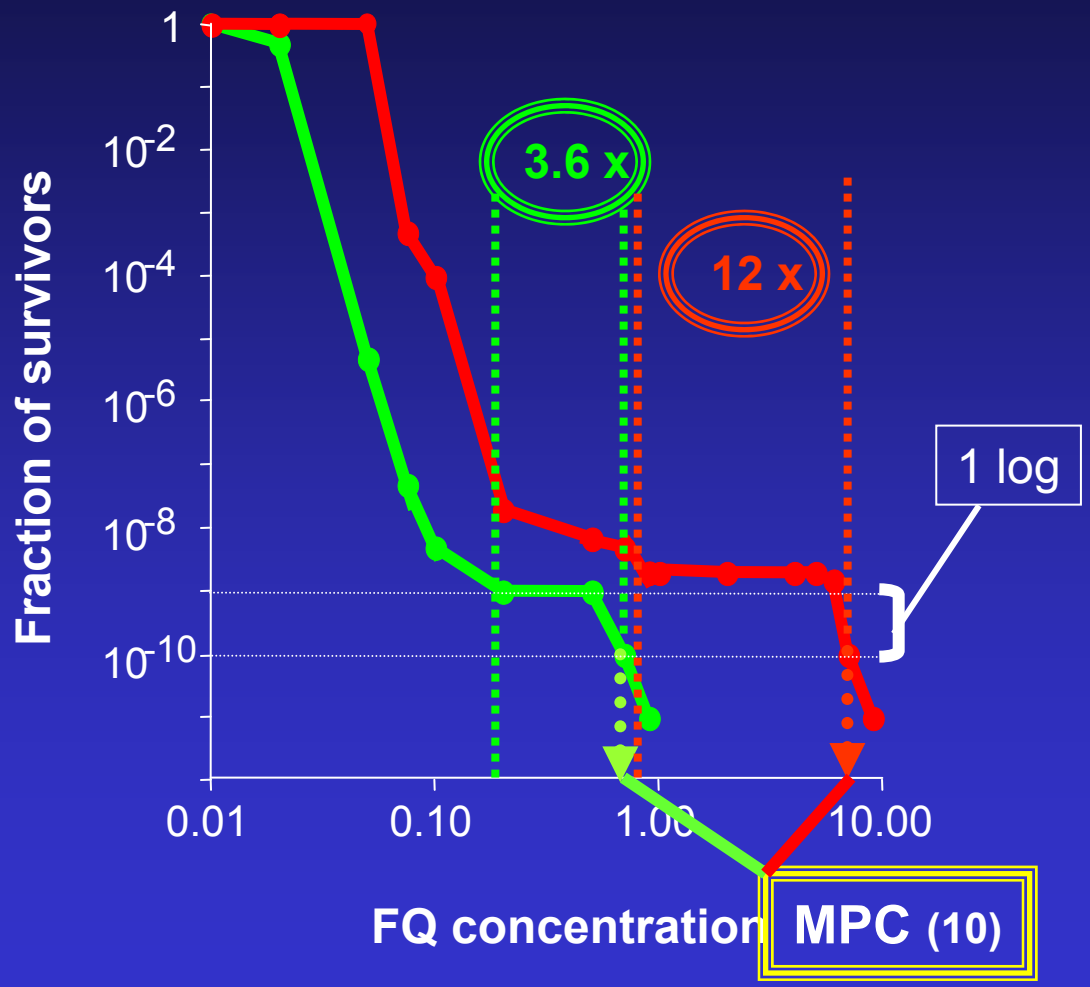
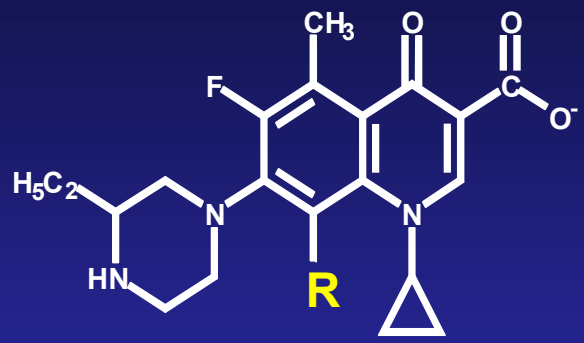
The mutant prevention concentration (MPC) is about 10 times larger larger than the MIC99 for most FQ

BUT, a C-8-methoxy group lowers the MPC for N-1-cyclopropyl fluoroquinolones

Role of the C8-methoxy in decreasing MPC

Bactericidal activity of FQs against *Mycobaterium bovis*





	PD160793	PD161148
	R = OCH_3	R = H
MIC 99	0.25	0.8
MPC 10	0.9	9
MPC/MIC	3.6	12

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

Peak concentrations as a tool to prevent emergence of resistance (MPC): using " PK / PD acceptable " MICs

Drug	Dosage (mg/24h)	C_{max} (mg/L)	"PK/PD Bkpt" (mg/L)	expect. MPC
norfloxacin	800	2.4 *	0.2	~ 2.4
ciprofloxacin	500	2.4 *	0.2	~ 2.4
ofloxacin	400	3-4.5 *, +	0.4	~ 4.8
levofloxacin	500	5-6 *, +	0.8	~ 9.6
moxifloxacin	400	4.5 *	0.4	~ 1.4

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®
\+ first dose to equilibrium

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* US prescrib. inf. (a

\+ first dose to equilibr

This is the C_{max} you'd like to obtain

® and AVELOX®

Why would PK/PD be important for the prevention of resistance ?

- rate and intensity of the bactericidal effects
- minimizing the potential for acquisition and/or emergence of mechanisms of resistance
- dealing with populations of decreased susceptibility

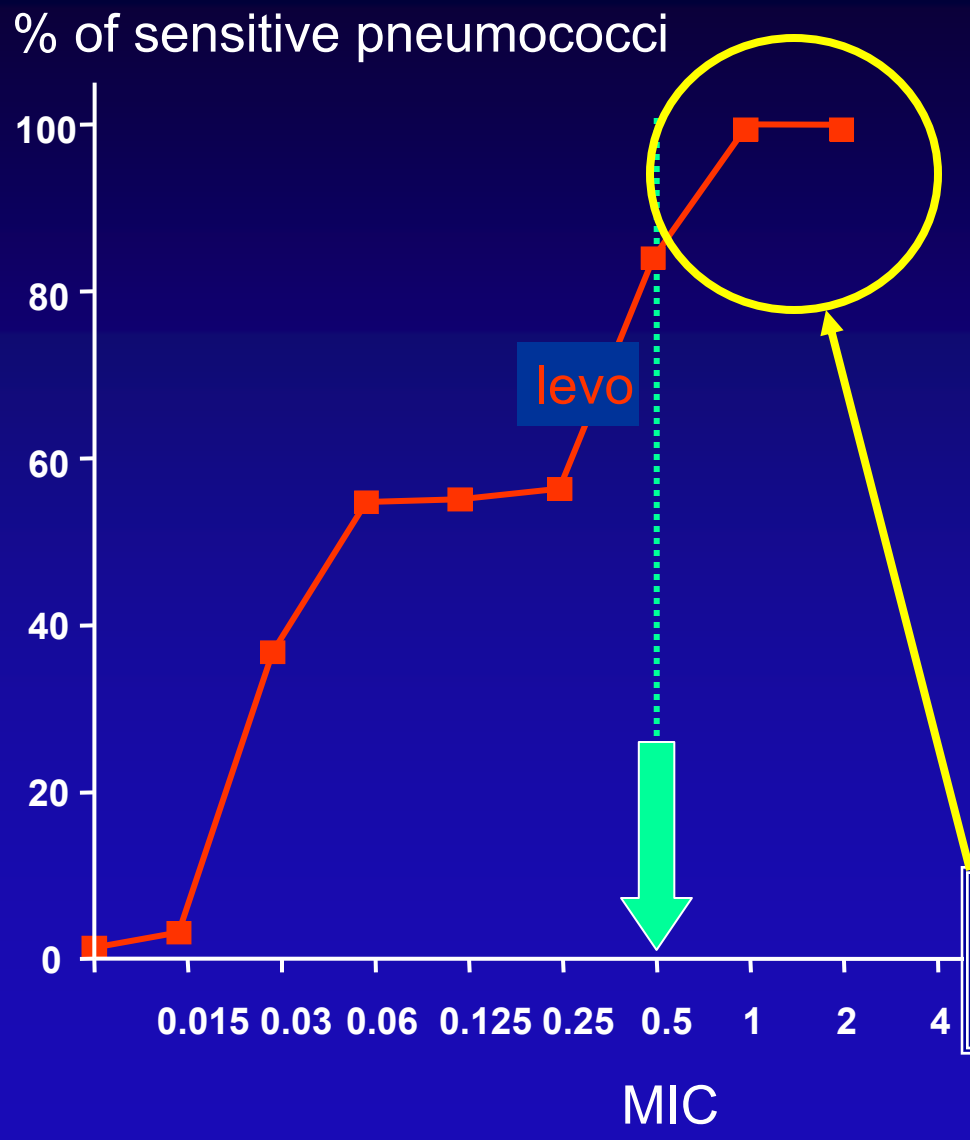
Creating a a safety margin...

Breakpoint issues ...

Drug	Dosage (mg/24h)	PK/PD Bkpts (mg/L) AUC/MIC (24h)	peak / MIC	NCCLS Bkpts*
norfloxacin	800	0.1	0.2	< 4
ciprofloxacin	500	0.1	0.2	< 1
ofloxacin	400	0.2-0.4	0.3 - 0.4	< 2
levofloxacin	500	0.4	0.4 - 0.5	< 2
gatifloxacin	400	0.3	0.4	< 2
moxifloxacin	400	0.4	0.4	< 2

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®

How to apply this a given country (Belgium) ?



Levofloxacin 500 mg

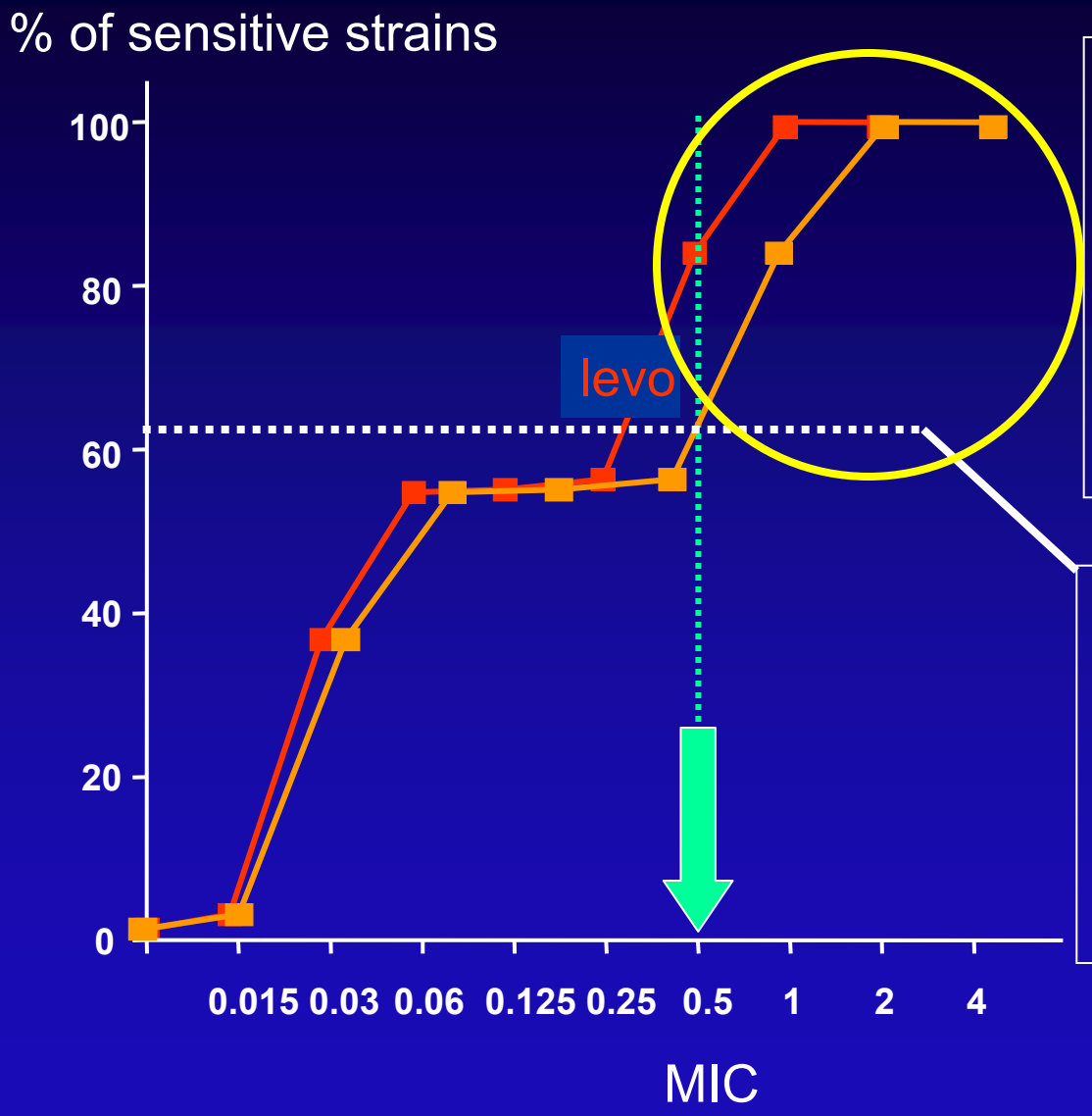
1X /day

- AUC [(mg/l)xh] 47
- peak [mg/l] 5
  - MIC_{max} AUC < 0.5
  - MIC_{max} peak < 0.5

you are left with 20 % of non covered bacteria !!

MIC data: J. Verhaegen et al., 2001

Why do we fear rapid emergence of large resistance to levofloxacine in Belgium ?



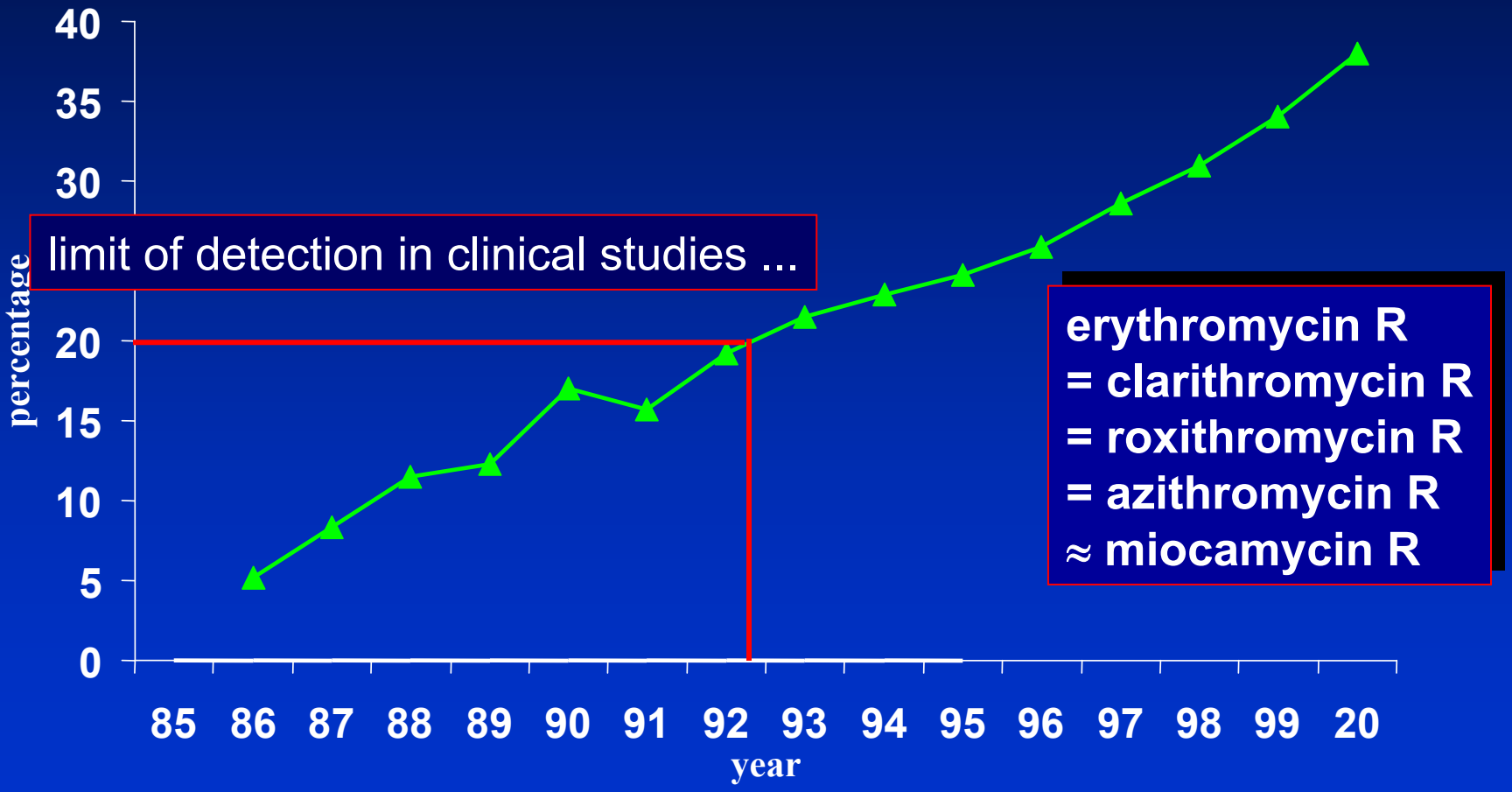
Resistance to FQ occurs easily
and rapidly by
- single-step mutation
- express. of efflux pumps

➔ increase of MICs by 1 or 2 dilutions

One dilution increase will be enough to cause
~ 40 % of strains to have MICs > 0.5 mg/L for levofloxacin

Why would telithromycin be potentially interesting in a given area (example = Belgium) ?

Evolution of resistance of S. pneumoniae to erythromycin

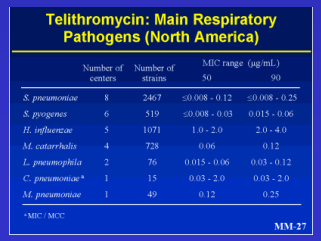


Reference laboratory for pneumococci, Louvain

Pharmacodynamics of telithromycin (as based on FDA submission; april 2001)

Organism	MIC_{90}	C_{max}/MIC_{90max}	AUC_{24h}/MIC_{90max}
S. pneumoniae	< 0.008 - 0.25	7.6	33.2
S. pyogenes	< 0.015 - 0.06	31.6	138
H. influenzae	2.0 - 4.0	0.475	2.075
M. catarrhalis	0.12	15.8	69.1
L. pneumophila	0.03 - 0.12		
C. pneumoniae	0.03 - 2		
M. pneumoniae	0.25		

Activity will be good for MIC≤ 0.25 mg/L, but may become problematic for higher MICs

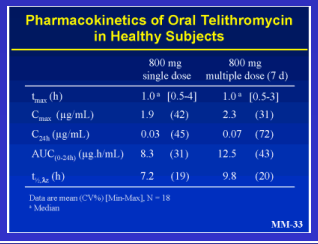


Telithromycin: Main Respiratory Pathogens (North America)

	Number of centers	Number of strains	MIC range (μg/mL) 50	90
S. pneumoniae	8	2467	≤0.008 - 0.12	≤0.008 - 0.25
S. pyogenes	6	519	≤0.008 - 0.03	0.015 - 0.06
H. influenzae	5	1071	1.0 - 2.0	2.0 - 4.0
M. catarrhalis	4	728	0.06	0.12
L. pneumophila	2	76	0.015 - 0.06	0.03 - 0.12
C. pneumoniae [a]	1	15	0.03 - 2.0	0.03 - 2.0
M. pneumoniae	1	49	0.12	0.25

[a] MIC / MCC

MM-27



Pharmacokinetics of Oral Telithromycin in Healthy Subjects

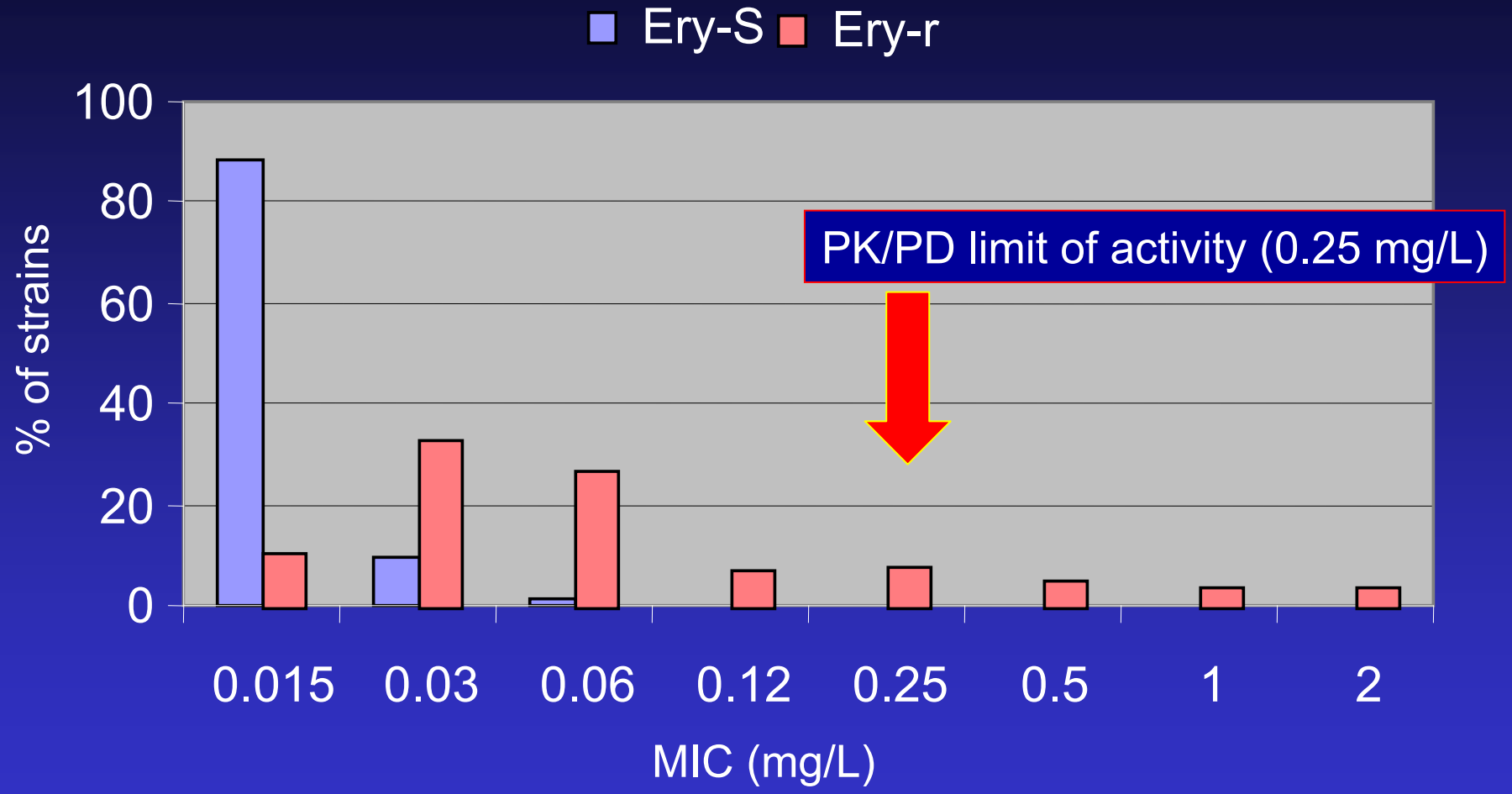
	800 mg single dose		800 mg multiple dose (7 d)	
t_{max} (h)	1.0 [a]	[0.5-4]	1.0 [a]	[0.5-3]
C_{max} (μg/mL)	1.9	(42)	2.3	(31)
C_{24h} (μg/mL)	0.03	(45)	0.07	(72)
$AUC_{(0-24h)}$ (μg.h/mL)	8.3	(31)	12.5	(43)
$t_{1/2z}$ (h)	7.2	(19)	9.8	(20)

Data are mean (CV%) [Min-Max], N = 18
[a] Median

MM-33

http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/

But why do we also fear a rapid resistance to telithromycin in Belgium ?

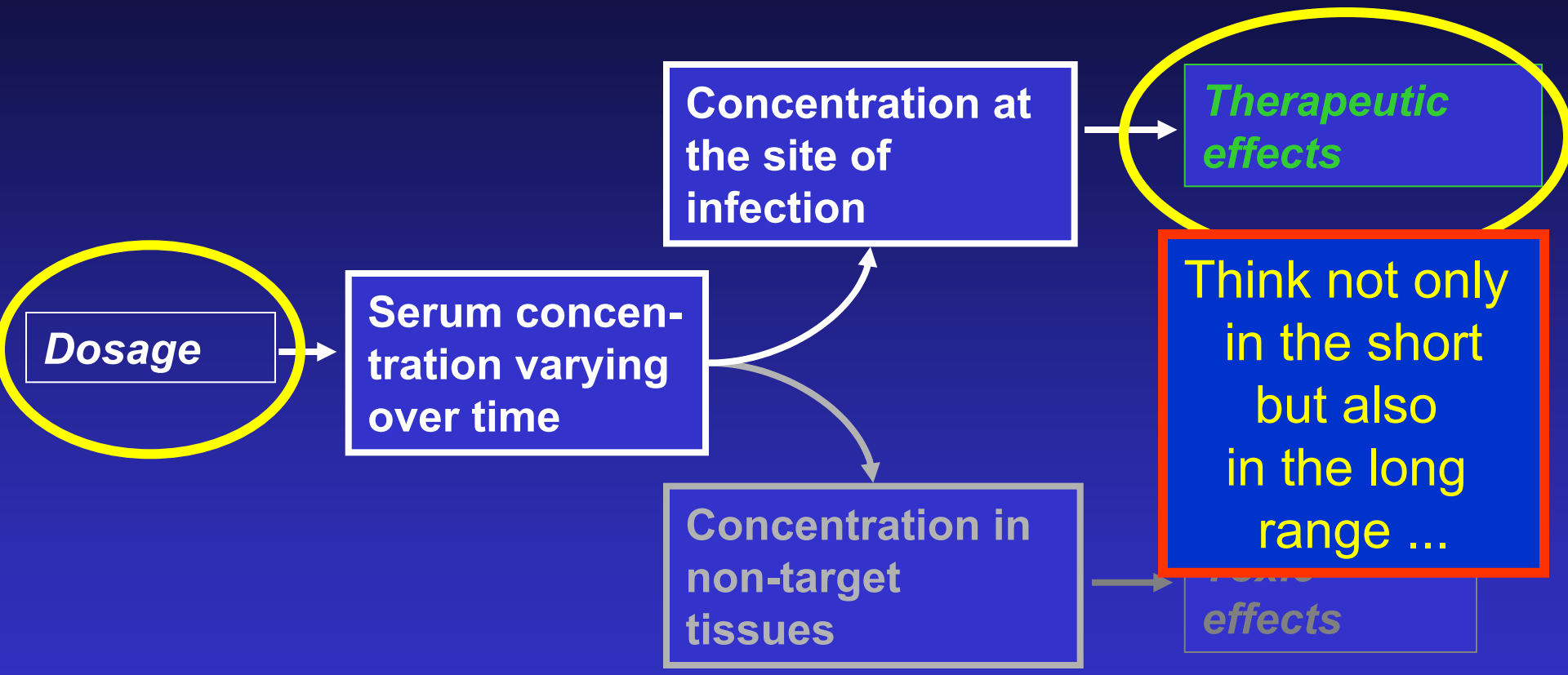


MIC_{90} for Ery-s strains: < 0.06 ...

But MIC_{90} for Ery-r strains: 0.25-0.5 ...

Verhaegen & Verbist, Acta Clin. Belg. 2001, 56: 351

This is where we are now ...



This is where Regulators and many others wish us to go ...

Dosage → **Serum concentration varying** → **Concentration at the site of infection** → ***Therapeutic effects***

Think not only in the short but also in the long range ...