Pharmacodynamics of antibiotics …

From what you already knew about
" ***optimizing activity*** " ...
to what you didn't dare to ask about
Emergence of Resistance...

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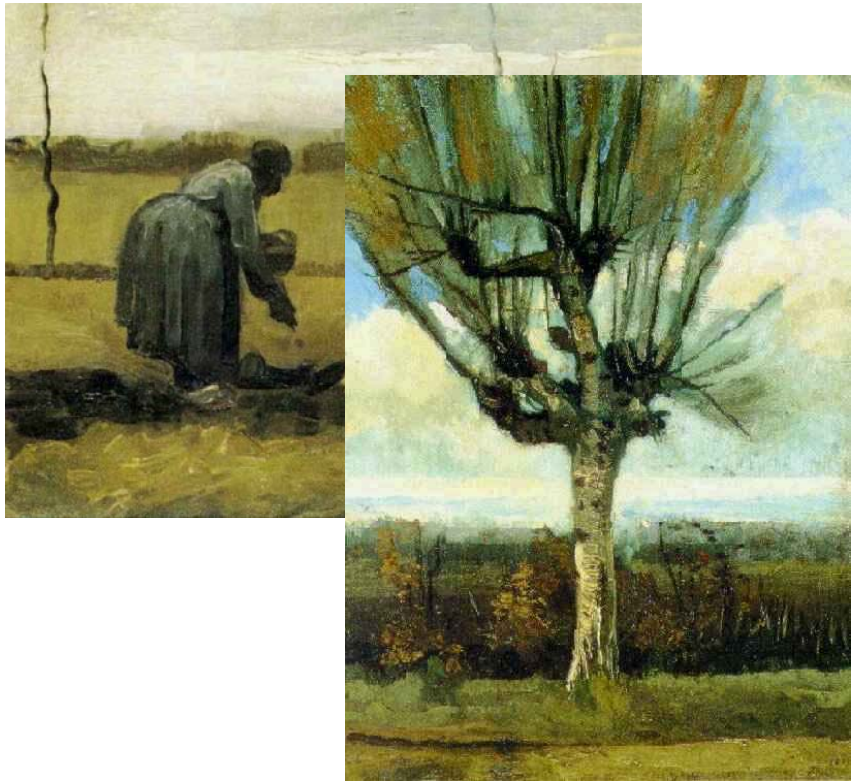
International Society for Anti-infective Pharmacology (ISAP)

Are antibiotics following a path to madness ?

discovery in soil bacteria and fungi

Are antibiotics following a path to madness ?



and then we all saw the blooming tree of semi-synthetic and totally synthetic antibiotics

Are antibiotics following a path to madness ?

and the General Surgeon told us
that the fighth was over

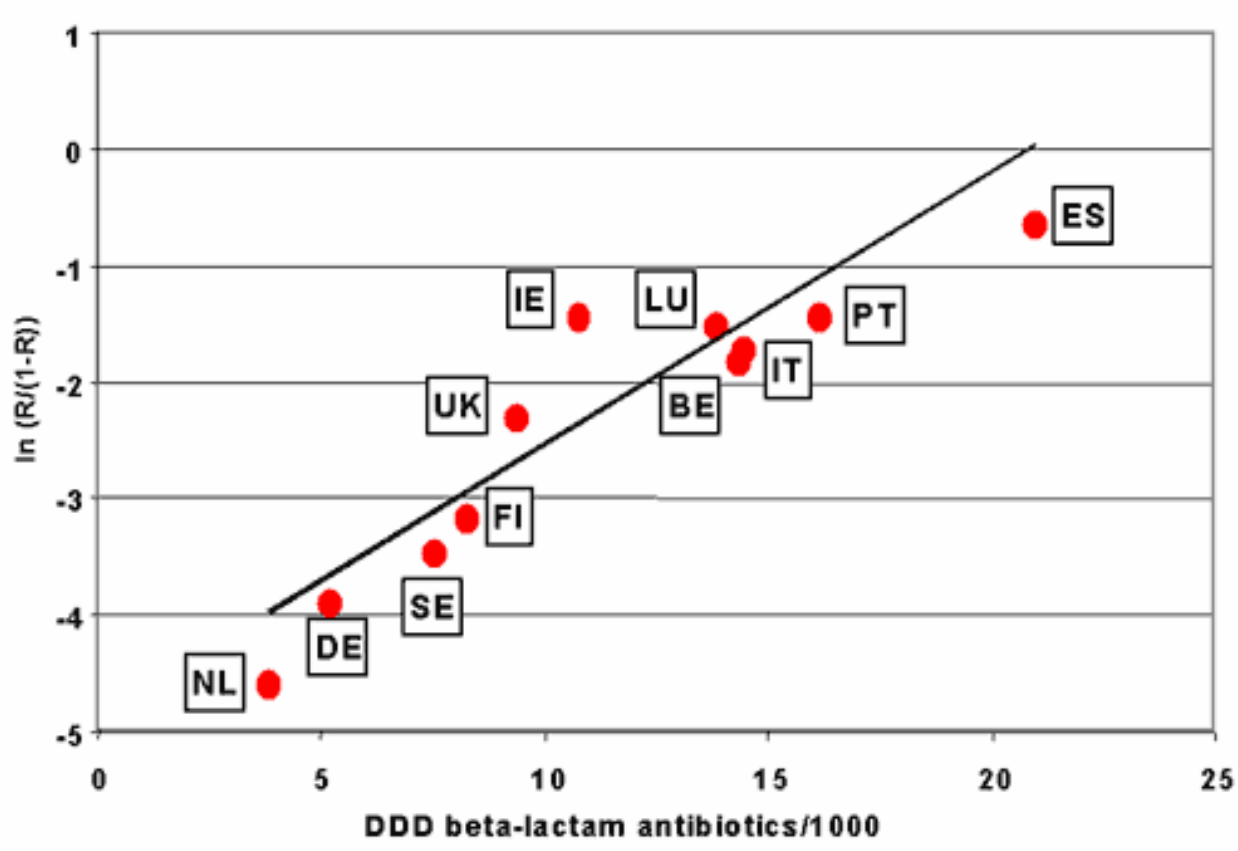
Are antibiotics following a path to madness ?

But…

Antibiotics and resistance...

- Rising resistance and correlation with antibiotic use …
- Did we use antibiotics in a rational way ? …
- What can we do beyond not using antibiotics ?
- Can this also reduce health care costs ? …

Overuse is one of the problems …



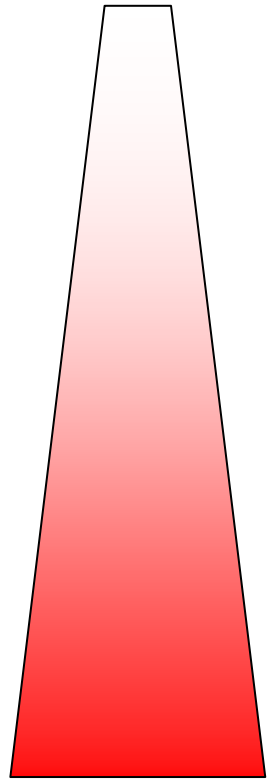
Risk of resistance to β-lactams among invasive isolates of *Streptoccus pneumoniae* regressed against outpatient sales of beta-lactam antibiotics in 11 European countries

- **resistance data are from 1998 to 1999; antibiotic sales data 1997.**
- **DDD = defined daily doses**

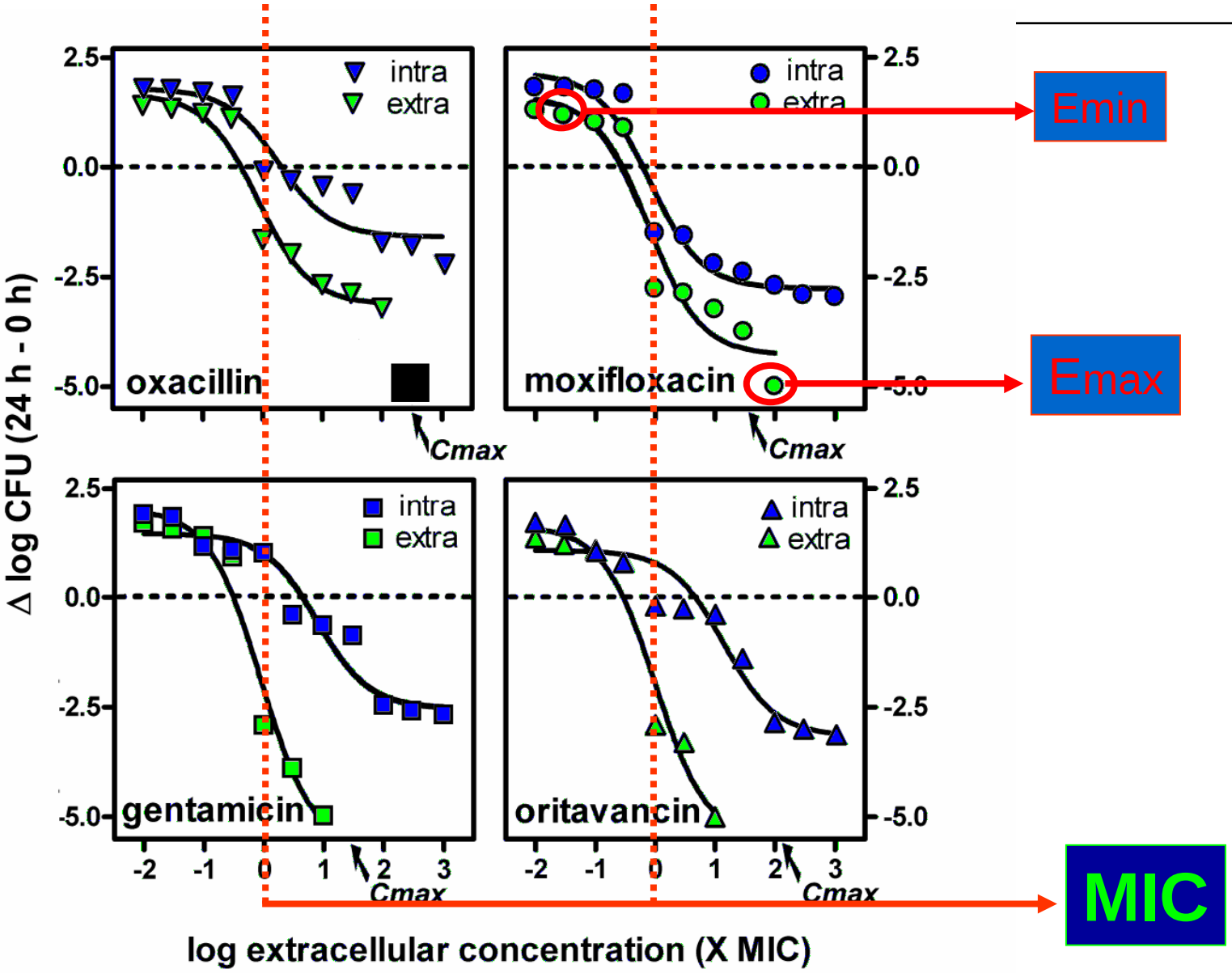
Bronzwaer SL, Cars O, et al. Emerg Infect Dis 2002 Mar;8(3):278-82

How can you be "better" ?

- be globally efficacious
  - ➔ **pharmacodynamics (PK/PD)**
- avoid selection of resistance
  - ➔ **decide on security margins …**
  - ➔ **invest in Mutant Prevention Concentration …**
  - ➔ **think about efflux …**

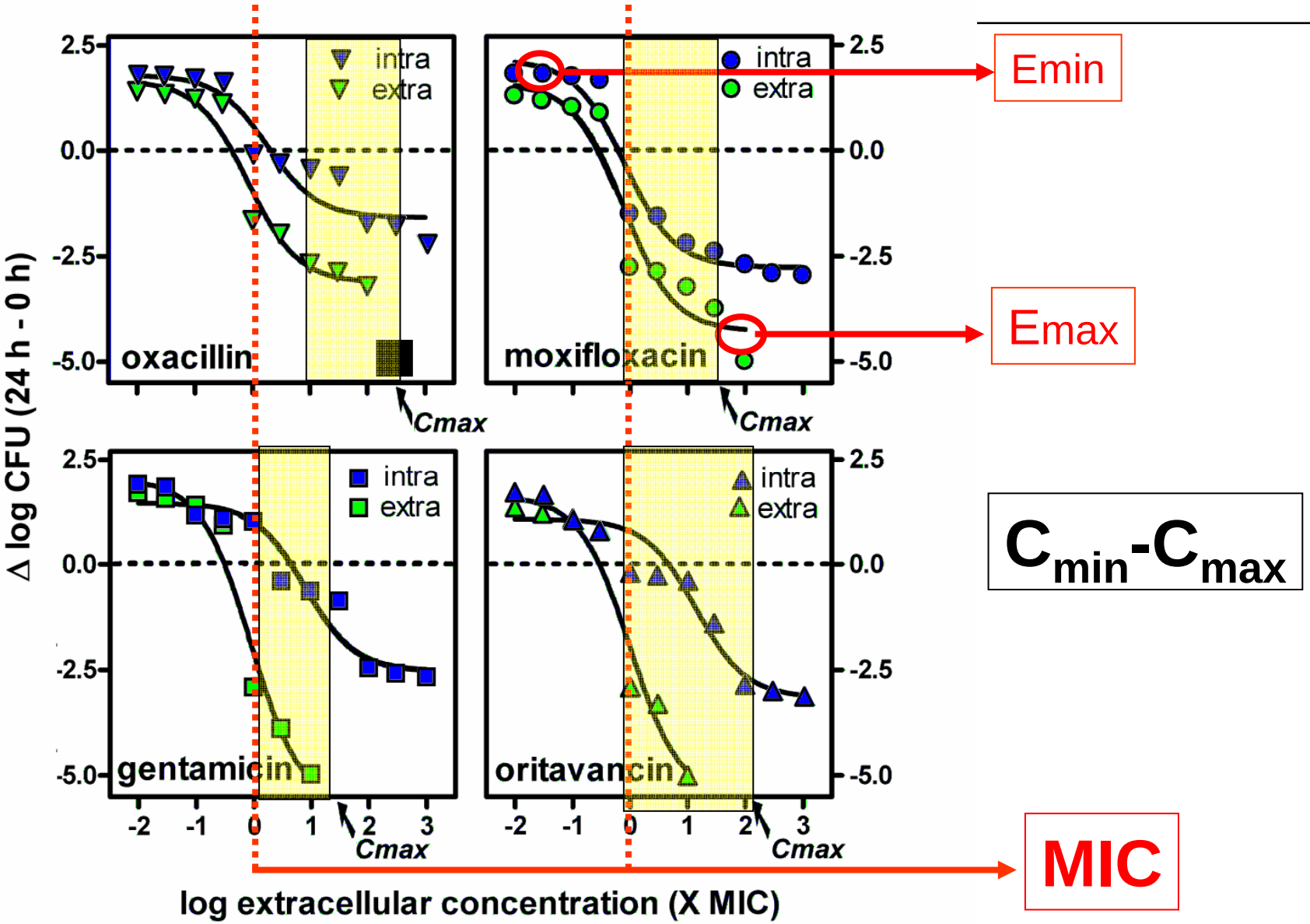


A few words about efficacy ...



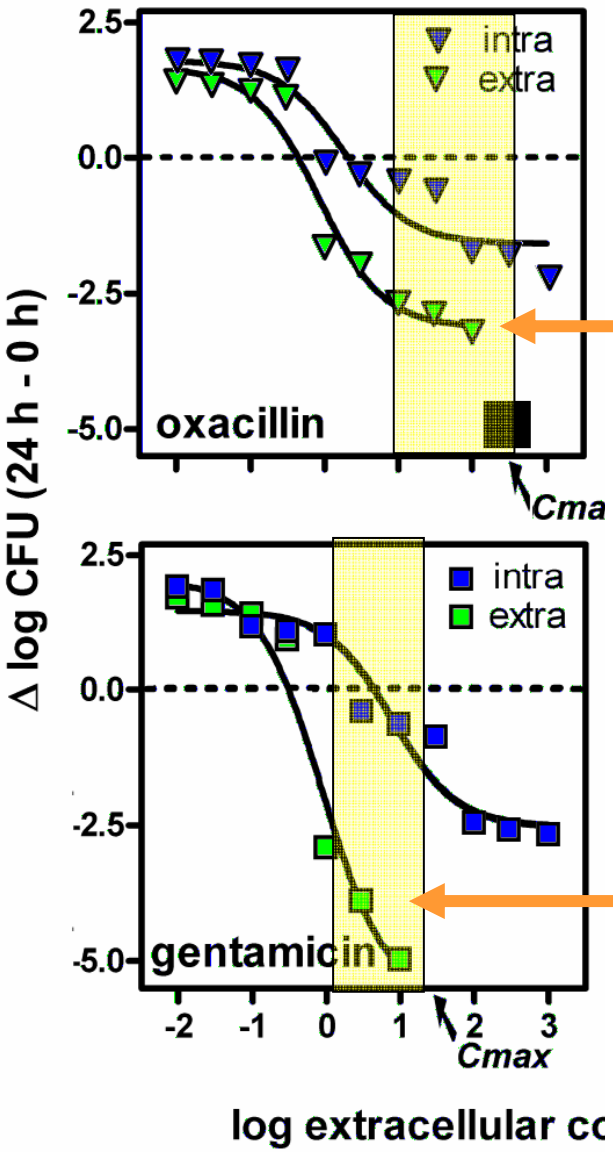
Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

And what if we put pharmacokinetics ?



Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

And what if we put pharmacokinetics ?



low concentration dependency

C_{min}-C_{max}

high concentration dependency

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

Conclusions so far ...

- Contrary to most beliefs, <u>all</u> antibiotics are concentration-dependent (like all other drugs);
- **but** is is all about at which serum concentration E_{max} will be obtained **and** how large it is (compared to untreated controls) ....

- If E_{max} is small and obtained at a **low concentration/MIC ratio** (relative to what you could reach in serum), all what you are left with is time ... and you get *in vivo* a **time-dependent antibiotic** (viz. β-lactams, vancomycin, ...)

  ➔ BEWARE ! If the MIC rises, you will need to increase the concentration to reach your (weak) E_{max} <u>or to use low breakpoints</u> if wishing to avoid clinical failures (viz. cephalosporins ...) ...

Breakpoints for cephalosporins and glycopeptides

eucast
European Antimicrobial Breakpoints

Clinical breakpoints
- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams
- Fluoroquinolones
- Aminoglycosides
- Glycopeptides
- Oxazolidones
- Macrolides, ketolides & clindamycin
- Tetracyclines, Tigecycline
- Chloramphenicol, daptomycin, dalfopristine/-quinopristine, fusidic acid, rifampicin
- Trimethoprim, sulfamethoxazole, co-trimoxazole, nitrofurantoin, fosfomycin.

EUCAST definitions of resistance & epidemiological cut off values

EUCAST principles for setting breakpoints

Information for companies

Cephalosporins

EUCAST clinical MIC breakpoints

Cephalosporins Click on antibiotic name to see wild type MIC distributions.		*Enterobac-teriaceae*[2]	*Pseudo-monas*[3]	Non-species related breakpoints[1] S≤/R>
Cefazolin	RD	--	--	1/2
Cefepime	RD	1/8	8/8	4/8
Cefotaxime	RD	1/2	--	1/2
Ceftazidime	RD	1/8	8/8	4/8
Ceftriaxone	RD	1/2	--	1/2
Cefuroxime	RD	8/8[5]	--	4/8

2006-03-31 (v 1.0)

Brand new !!

Carbapenem Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)				Non-species related breakpoints[1] S≤/R>
		Enterobac-teriaceae	*Pseudo-monas*	*Acineto-bacter*	*Gram-negative anaerobes*	
Ertapenem	RD	0.5/1	--	--	1/1[8]	0.5/1
Imipenem	RD	2/8[2]	4/8[6]	2/8	2/8	2/8
Meropenem	RD	2/8	2/8	2/8	2/8	2/8

Conclusions (2d part) ...

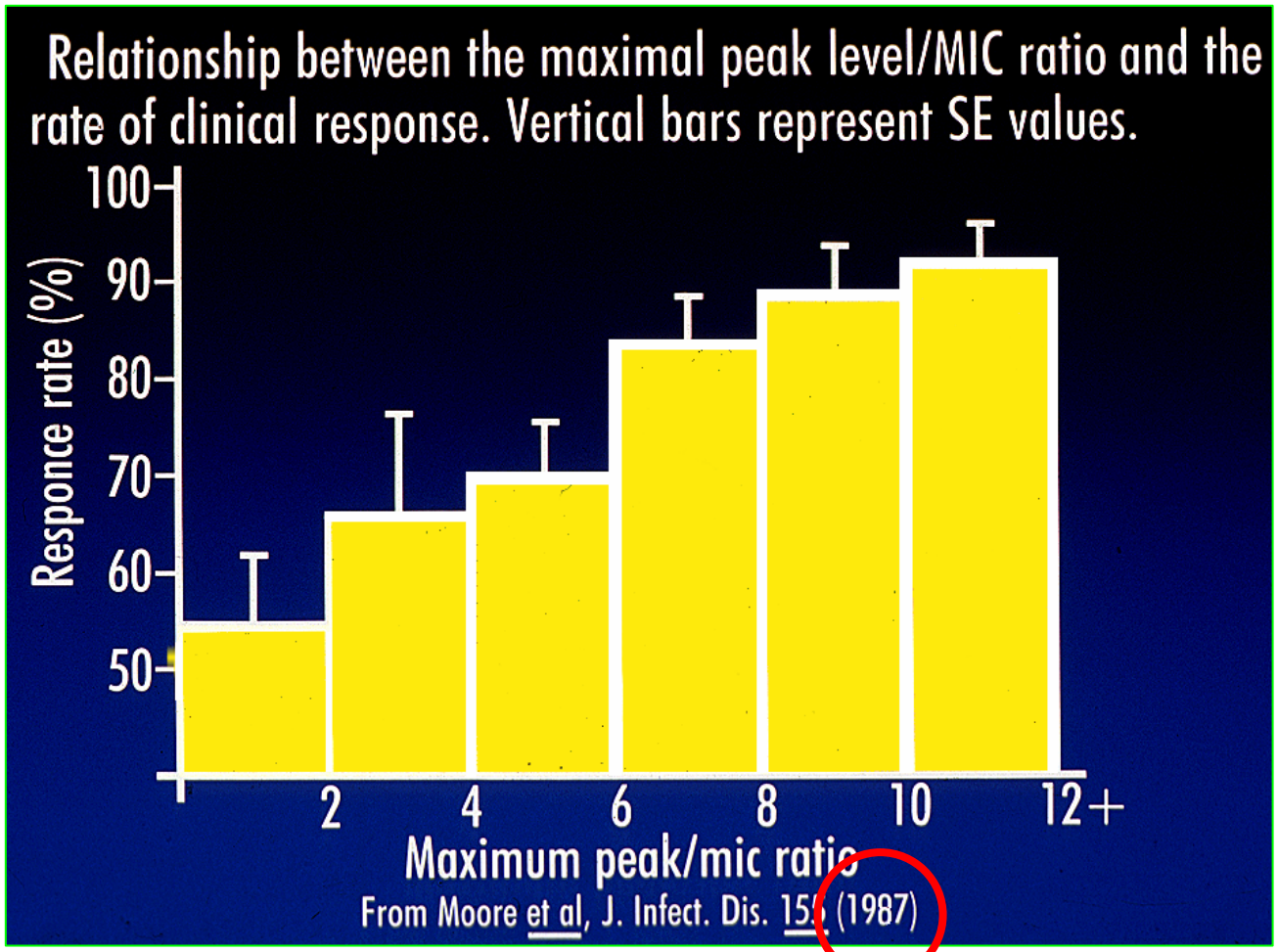
- If E_{max} is large and obtained at serum concentrations higher than the usual C_{max}/MIC ratio, you get *in vivo* a **concentration- and AUC-dependent antibiotic** (viz. fluoroquinolones...)

➔ BEWARE: the MIC of the offending organism is also critical ...

➔ increasing the C_{max}/MIC and the AUCMIC ratios will increase your effectiveness and may be the only way to act upon offending organisms with elevated MICs ...

➔ low Cmax/MIC and AUC/MIC ratios will lead to failures and emergence of resistance ...

After all, that was all known since 1987 ... for the good, old faithful aminoglycosides ...



Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration.

But it wasn't so for fluoroquinolones ...

Related Articles, Links

1: Rev Infect Dis. 1988 Jan-Feb;10 Suppl 1:S70-6.

Comparative activity of the 4-quinolones.

Phillips I, King A.

Department of Microbiology, United Medical School, Guy's Hospital, London, United Kingdom.

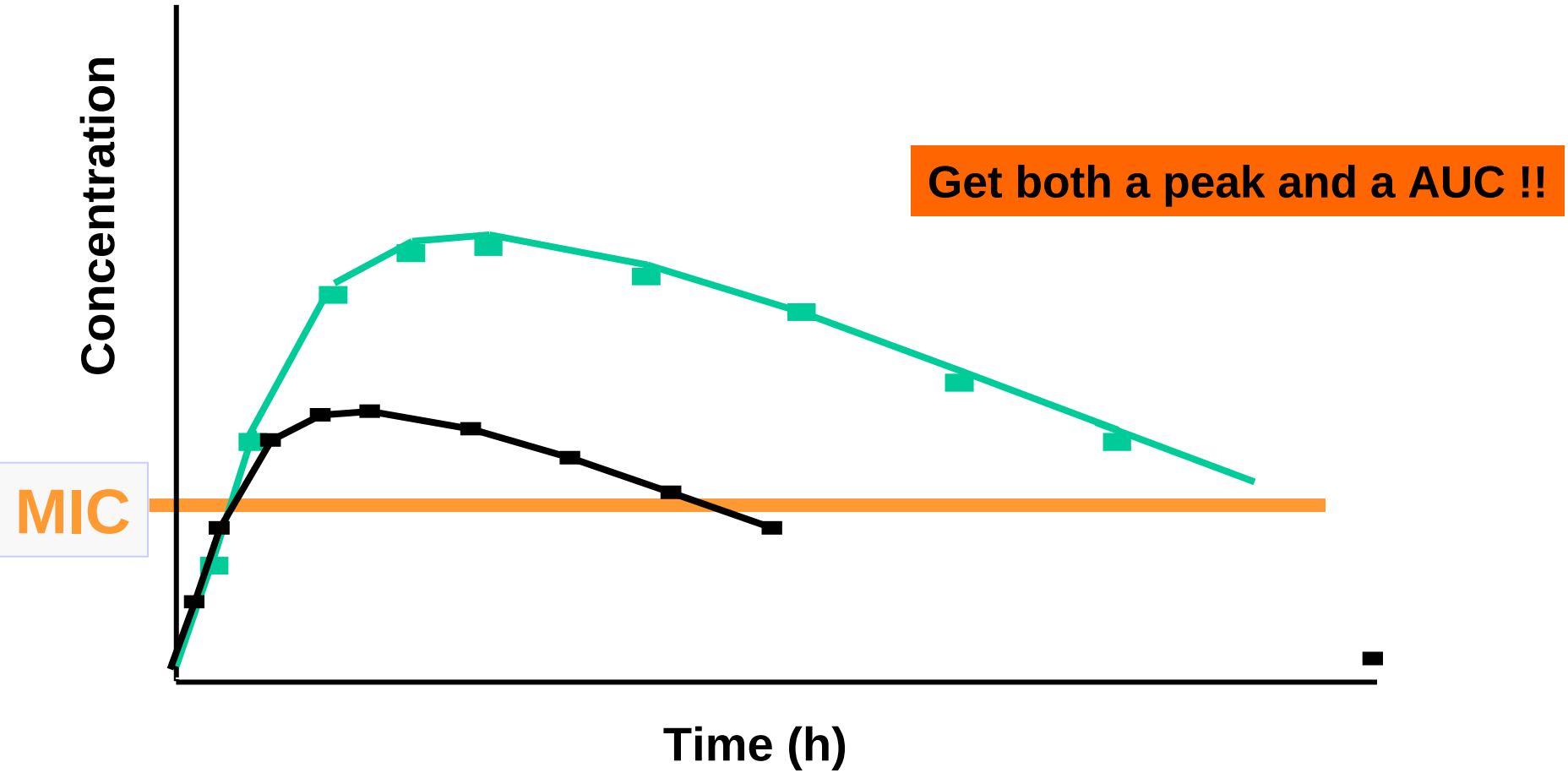
Minimal inhibitory concentrations (MICs) of the 4-quinolones ciprofloxacin, enoxacin, norfloxacin, ofloxacin, pefloxacin, difloxacin, A-56620, and CI-934 are consistent world-wide, with allowances for differences in acquired resistance. MICs of these drugs for Enterobacteriaceae correlate with those of nalidixic acid, but resistance to the quinolones is rare if a breakpoint of greater than 2 mg/L is accepted. Most intestinal pathogens are sensitive. Acinetobacter, Pseudomonas aeruginosa, and other Pseudomonas species except Pseudomonas maltophilia are usually sensitive. Ciprofloxacin is generally the most active of the 4-quinolones against these organisms. All of the new agents have antistaphylococcal activity, but that of norfloxacin and ofloxacin is borderline. Against streptococci,

with a Cmax at 1.5-2.5 mg/L ?

Fluoroquinolones: get a peak and an AUC !

in order to optimize: AUC_{24h}/MIC ➡ should be > 125 *

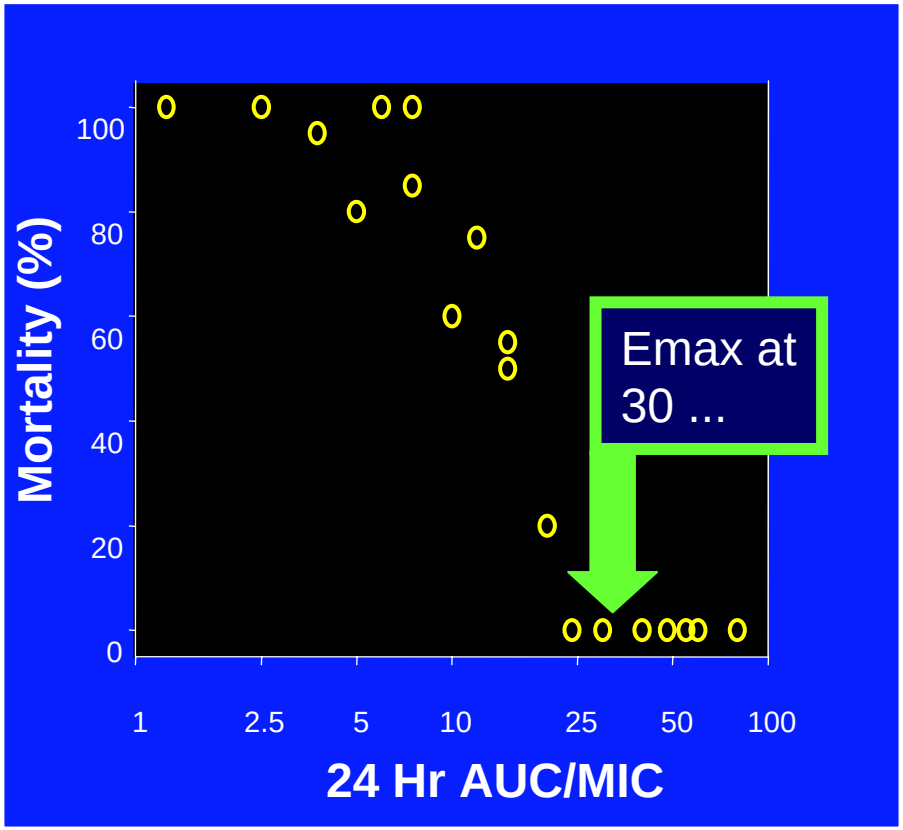
C_{max}/MIC ➡ should be > 10



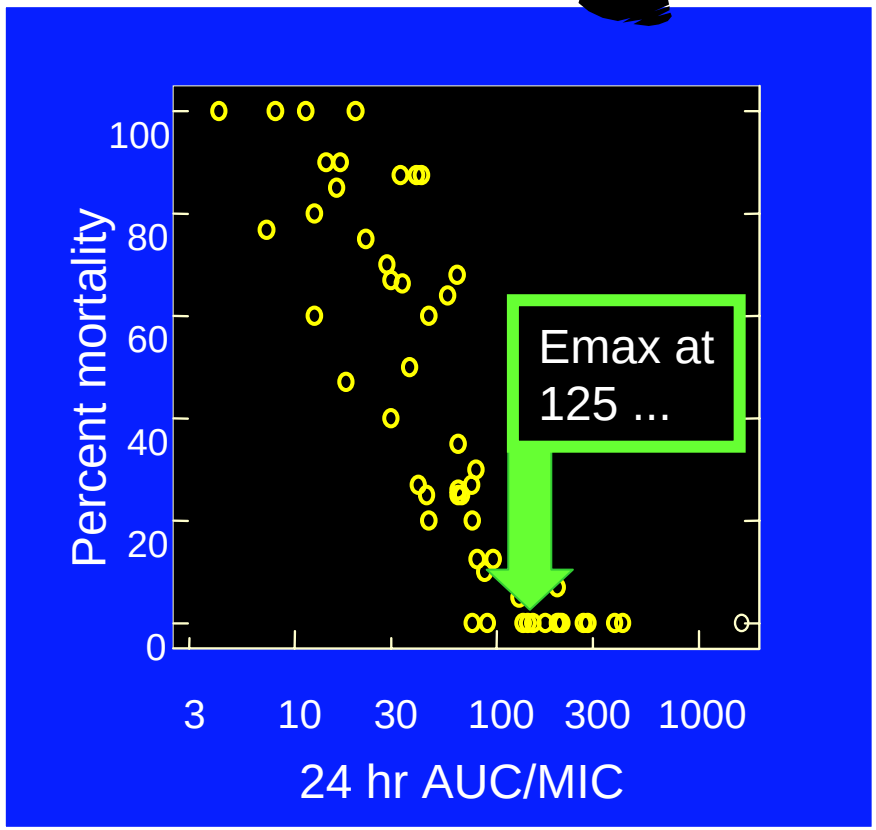
Get both a peak and a AUC !!

You said AUC/MIC >125 for Gram (+) ?

The saga of *S. pneumoniae* ...



non-neutropenic



neutropenic

You said Cmax/MIC ratio > 10 for Gram (+) ?

The saga of *S. pneumoniae* ...

Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. Preston et al., J.A.M.A., 1998 Jan 14;279(2):125-9

RESULTS (as presented by the authors)**:**

- 134 / 313 had both PK and MIC
- **clinical AND bacterial outcomes were related to peak/MIC**
  (logistic regression; $p < 0.001$)
- **results were favourable if peak / MIC > 12.2**

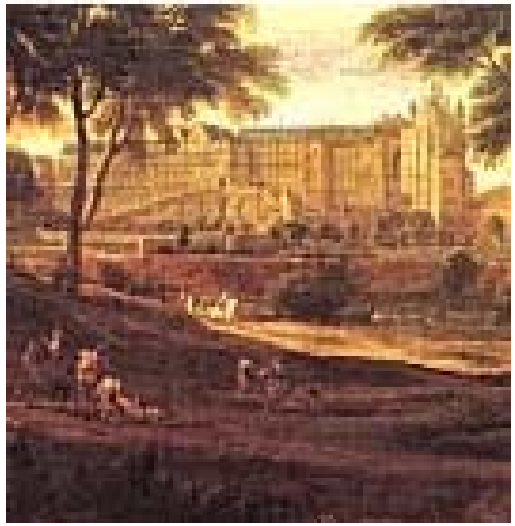
So, let us be Europeans ...
i.e. be cautious ... (aka not bold)

If you believe G. Drusano was telling you the truth when he said "I am a doctor"...

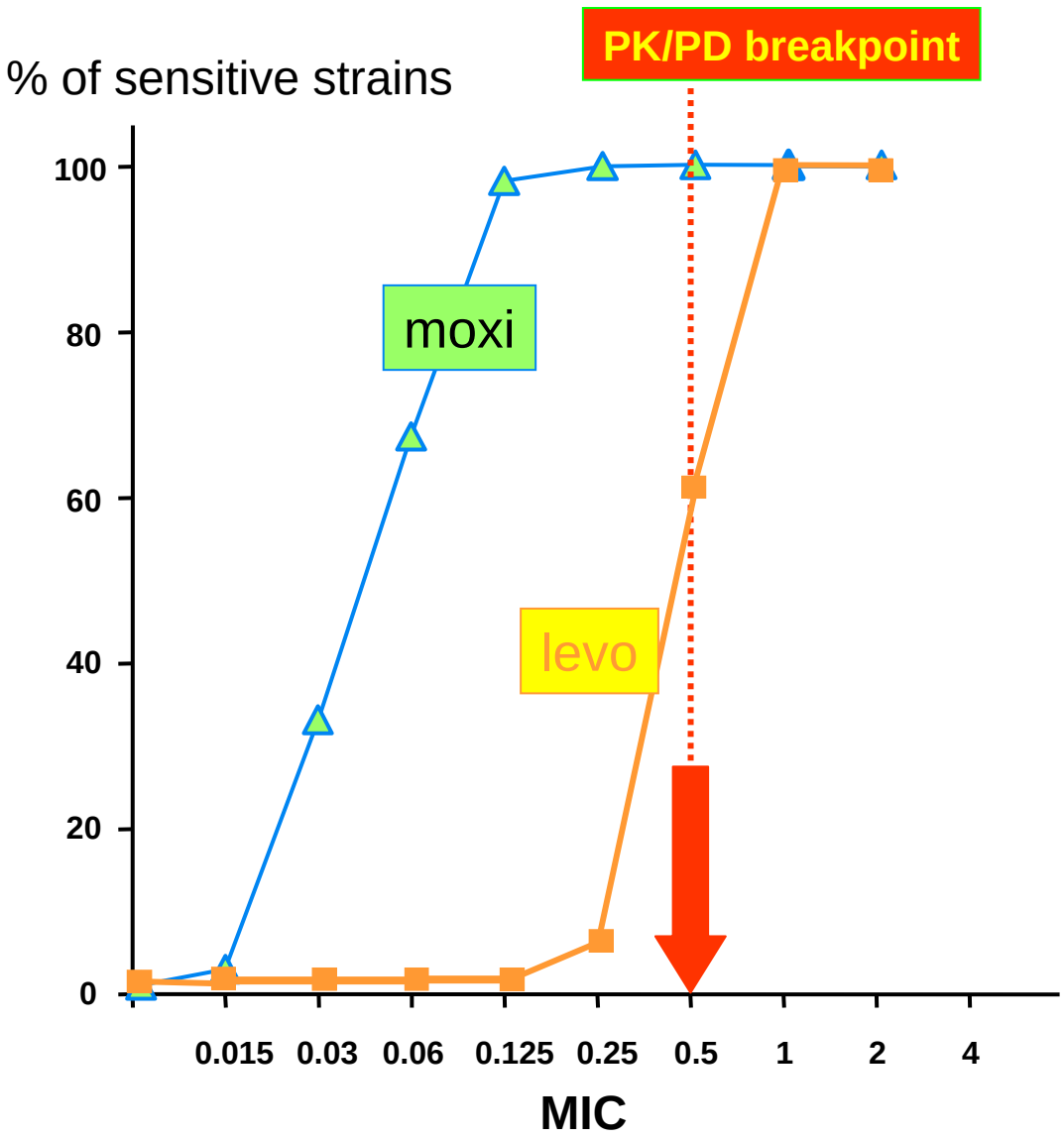
➔ peak / MIC > 10

If you believe your patient is not a healthy mouse … and think that J.J. Schentag is a knowledgeable PK/PD maniac...

➔ AUC_{24h} / MIC > 100



PK/PD in action …



Levofloxacin 500 mg 1X / jr

- AUC [(mg/l)xh] 47
- peak [mg/l] 5

➔ MIC_{max} < 0.5

Moxifloxacin 400 mg 1X /jr

- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5

➔ MIC_{max} < 0.5

MIC data: J. Verhaegen et al., 2003

Same exercise for the French pneumococci ...

J.W. Decousser et al. / International Journal of Antimicrobial Agents 20 (2002) 186–195

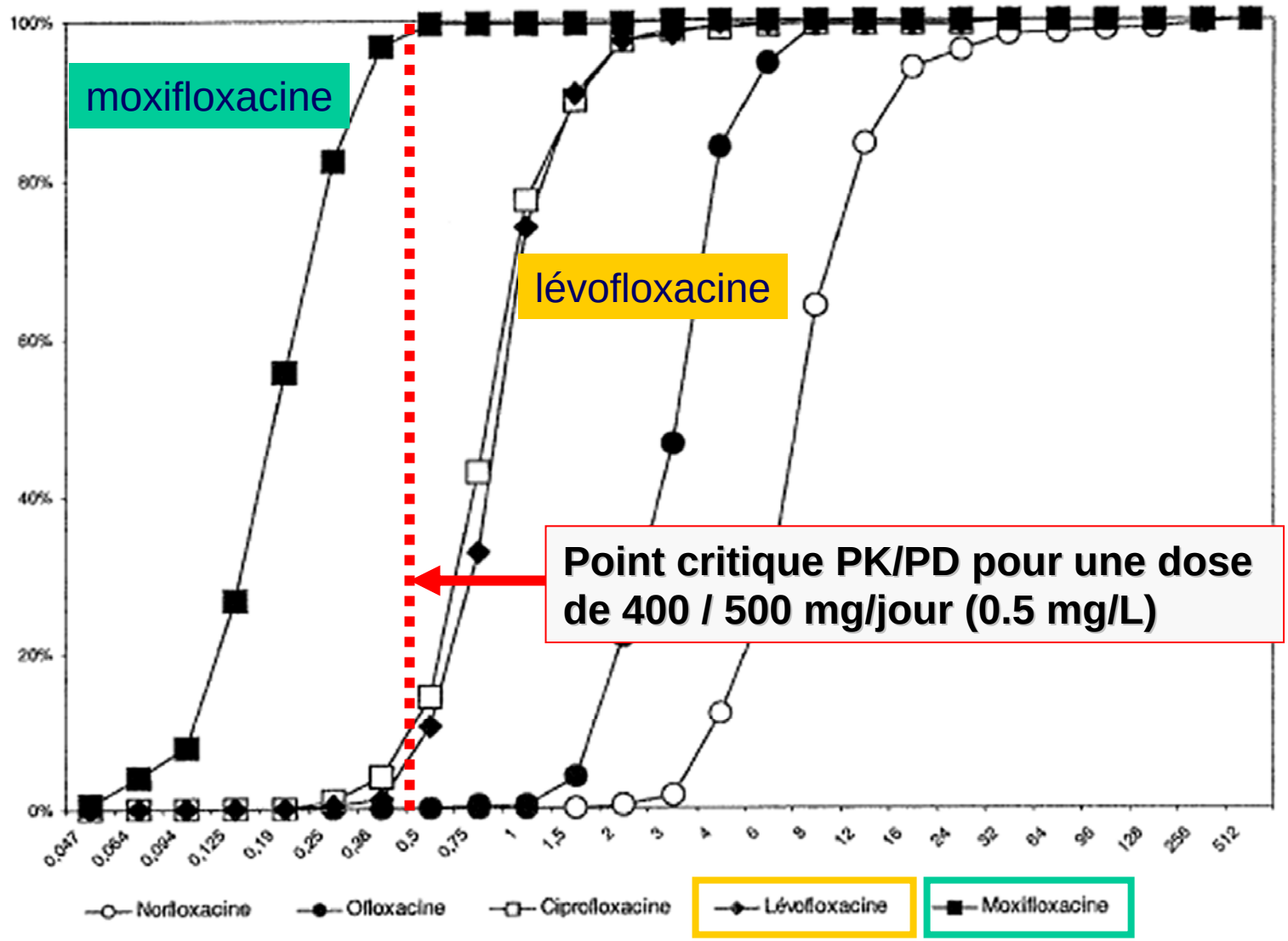
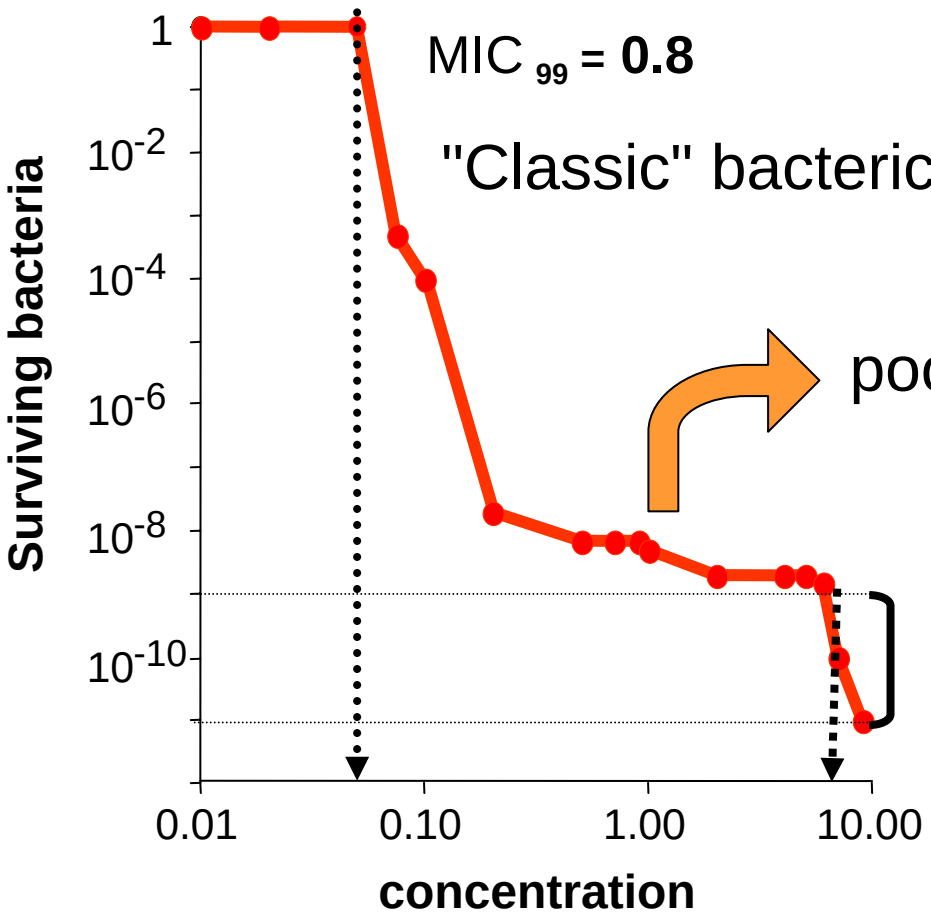


Fig. 1. Distribution of fluoroquinolone MICs for *S. pneumoniae* blood isolates.

But we need to invest in something new…

Mutant Prevention Concentration …



MIC $_{99}$ = **0.8**

"Classic" bactericidal effect

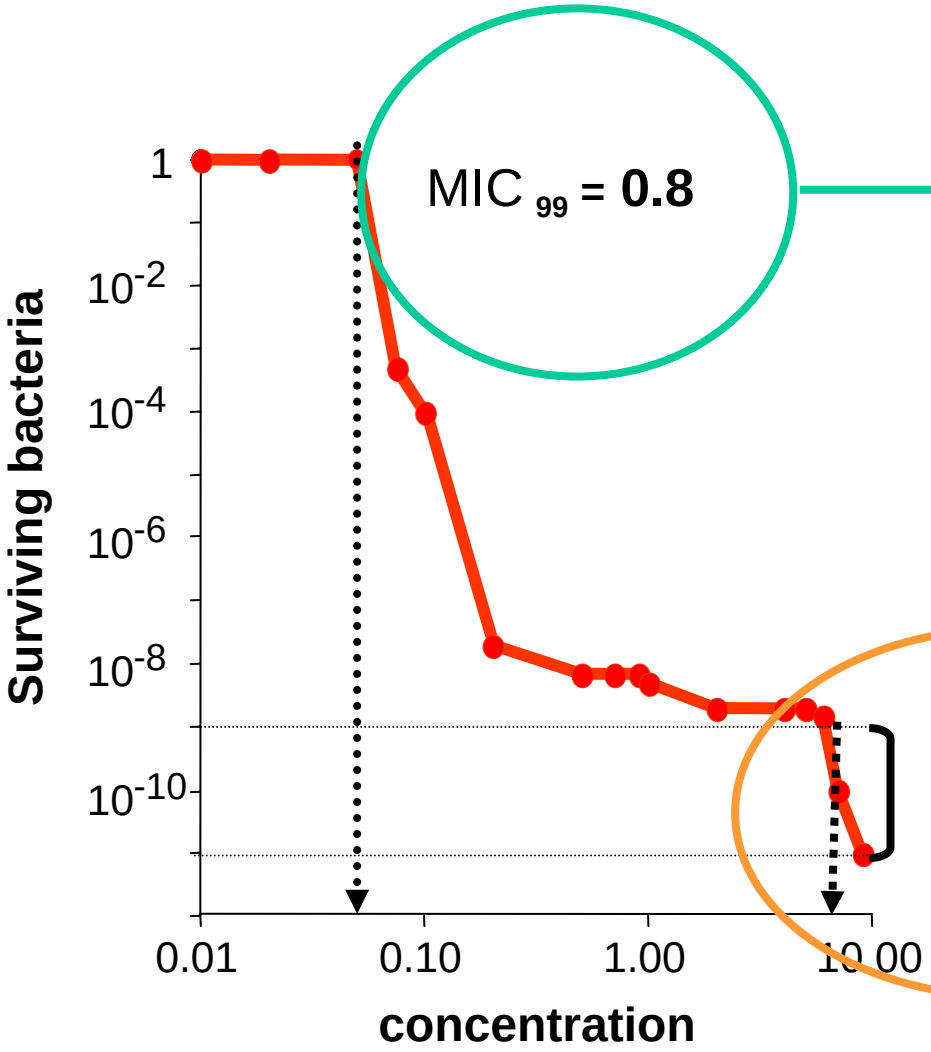
poorly sensitive organisms…

Elimination of resistant organisms

MPC $_{10}$ = **9**

Dong *et al:* AAC 1999; 43:1756-1758

Mutant Prevention Concentration …

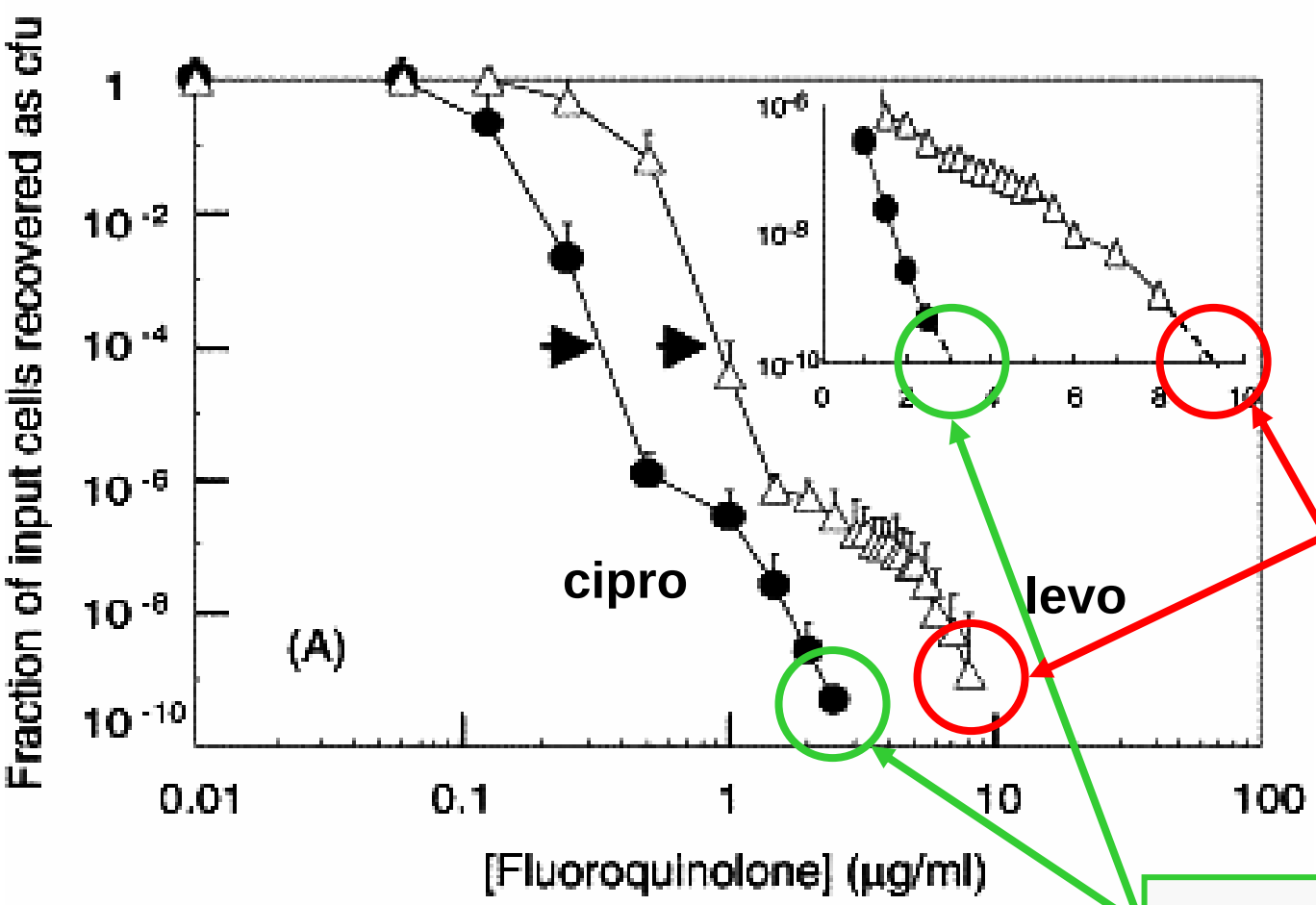


Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

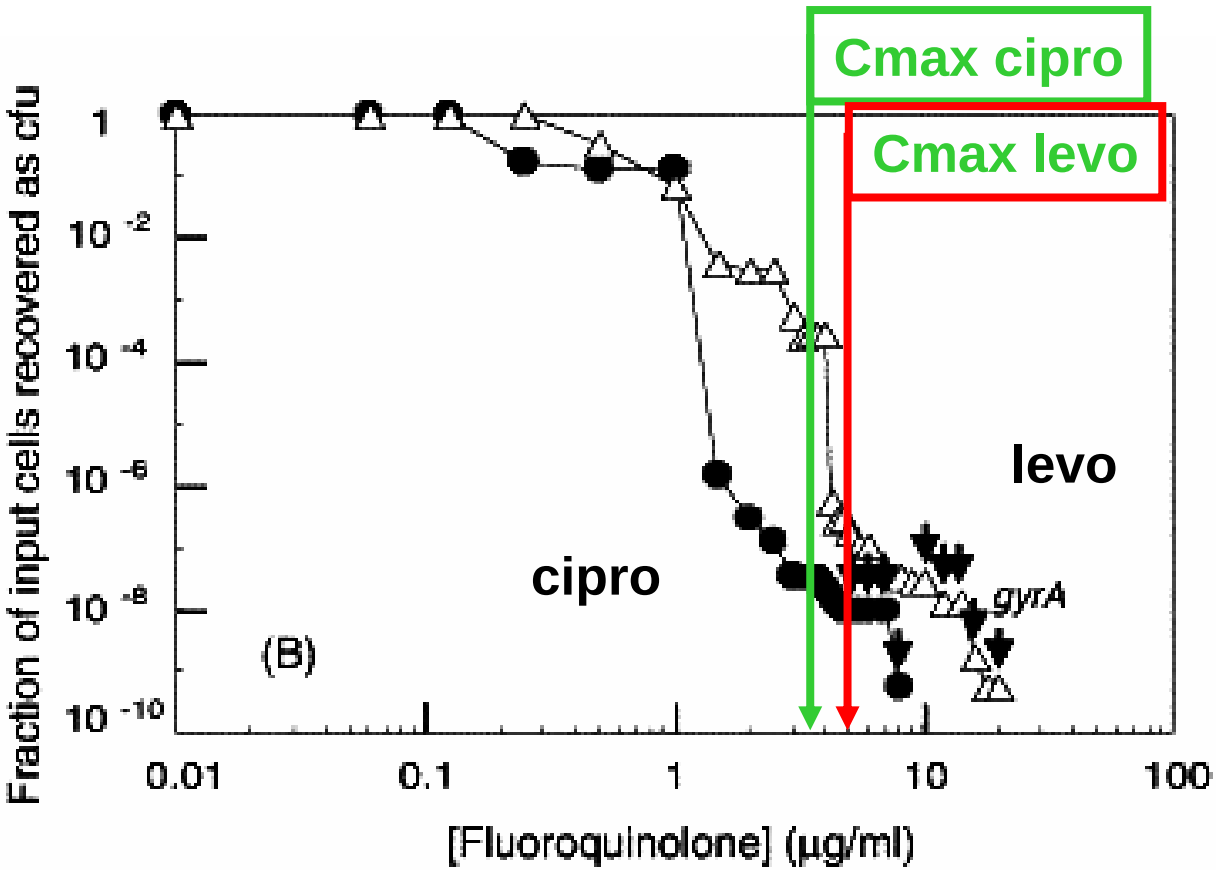
Dong *et al*; AAC 43:1756-1758

Mutant Prevention Concentration of ciprofloxacin and levofloxacin in *P. aeruginosa* (clinical isolates) with "normal" susceptibility (MIC = 0.33 and 0.9 mg/L) …



Hansen et al. I.J.Antimicrob. Agents 2006;27:120-124

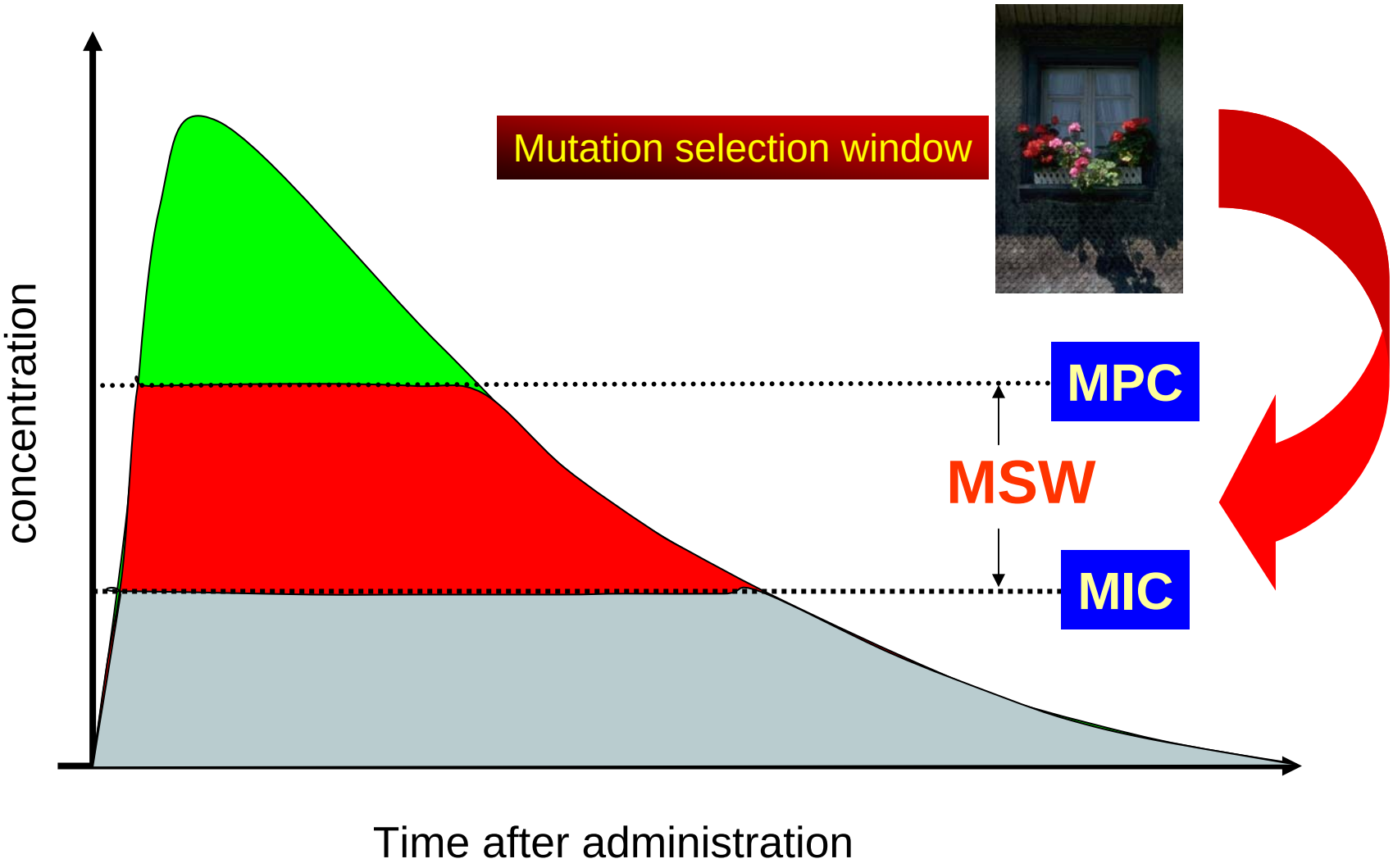
Mutant Prevention Concentration of ciprofloxacin and levofloxacin in a strain of *P. aeruginosa* with reduced susceptibility (MIC = 2 and 4 mg/L) …



Mutants !!
(T-83-I)

Hansen et al. I.J.Antimicrob. Agents 2006;27:120-124

"Window" where selection of mutants/resistants may take place …



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

Is this also true for S. *pneumoniae* ?

Molecule	MIC	MPC		C_{max}
levoflox. (500 mg)	1	8		≈ **6**
moxiflox. (400 mg)	0.25	1		≈ **4**

Adapted from D. Croisier, 2005, Bondeau et al., 2001, and Hansen et al, 2003

Is this all ?

Although fluoroquinolone resistance in *S. pneumoniae* isolates remains low, the opportunity for increased resistance exists as the use of fluoroquinolones for the treatment of respiratory tract infections rises. The potential for resistance formation should thus be considered when specific fluoroquinolones are selected for treatment. Including MPCs as part of a dosing strategy may be one means of limiting the selection of fluoroquinolone-resistant mutants and preserving this class of antibiotic.

MPCs obtained for *S. pneumoniae* isolates[a]

Isolate	Cipro	Gati	Gemi	Levo	Moxi
	MP_{MIC}	MP_{MIC}	MP_{MIC}	MP_{MIC}	MP_{MIC}
Wild-type GyrA and ParC, efflux negative					
2587	16	2	8	4	8
2663	8	8	16	4	8
2670	8	2	4	4	16
ParC Ser79Phe, wild-type GyrA, efflux negative					
4610	16	16	8	16	>16
14744	16	16	16	16	16
GyrA Ser81Phe, wild-type ParC, efflux negative					
1146	8	1	8	2	2
Efflux positive, wild-type GyrA and ParC					
15017	4	8	4	4	8
16072	4	4	4	2	4

[a] MP_{MIC} are given in multiples of the MIC of each drug.

H.J. Smith et al. Antimicrob. Agents Chemother.2004; 48: 3954-3958

A proposal for PK/PD based-breakpoints for fluoroquinolones...

Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

MIC and MPC: can the first tell about the second ?

TABLE 1. MPC/MIC ratios

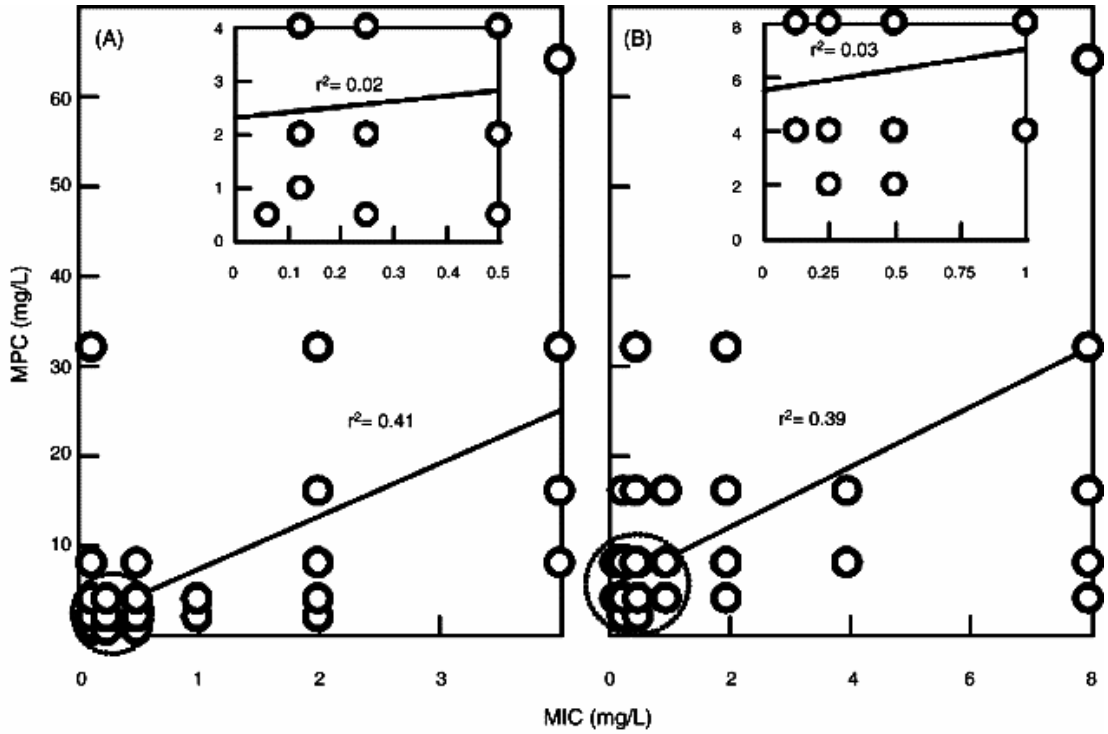
Isolate[a]	MPC/MIC [mg/liter (ratio)]	
	Levofloxacin	Moxifloxacin
Sp-S	4/1 (4)	2/0.25 (8)
Sp-NS	8/1 (8)	2/0.25 (8)
Sp-R	4/1 (4)	2/0.25 (8)
Hi-N	0.125/0.015 (8)	0.125/0.03 (4)
Hi-P	0.06/0.015 (4)	0.25/0.03 (8)
Mc-P	2/0.125 (16)	2/0.125 (16)

[a] Sp, *S. pneumoniae*; Hi, *H. influenzae*; Mc, *M. catarrhalis*;

Hermsen et al.
Antimicrob Agents Chemother. 2005 Apr;49(4):1633-5.

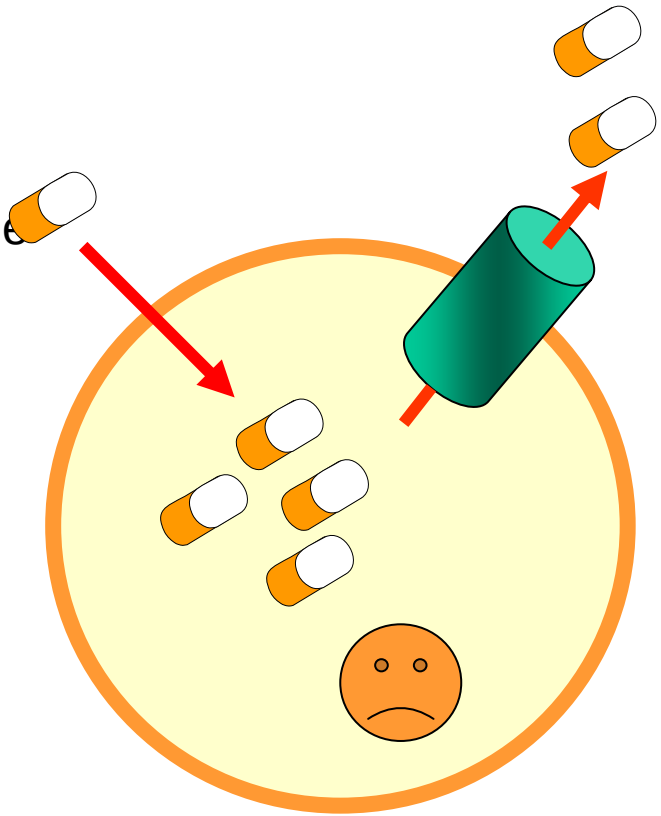
Hansen et al. I.J.Antimicrob. Agents 2006;27:120-124

See also: Drlica et al., Antimircob. Agents Chemother. 2006; 50:403-404



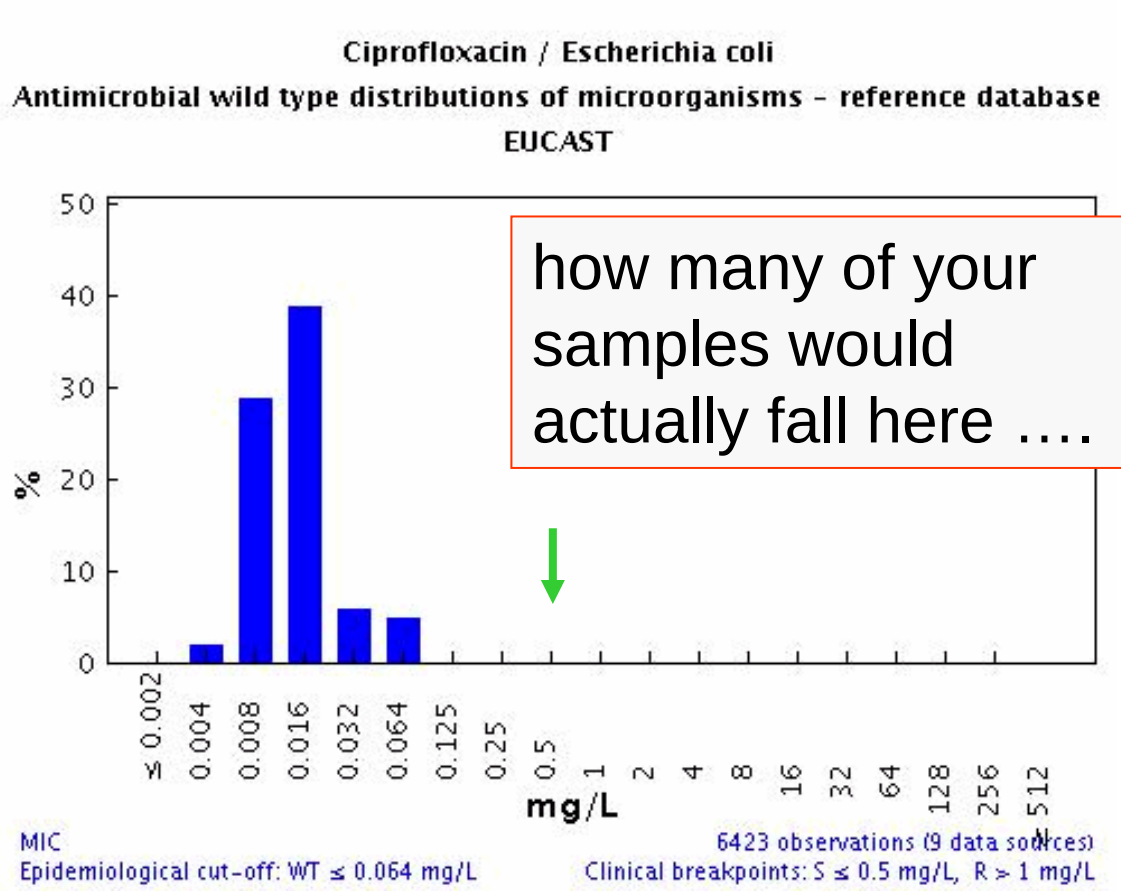
Efflux and MIC ?

- efflux is a universal mechanism for cell protection against membrane-diffusing agents
- many drugs diffuse though membranes and become opportunistic substrates of efflux pumps
- for AB, efflux decreases the amount of drug in bacteria and impairs activity, increasing the MIC …
- insufficient drug exposure favors the selection of less sensitive organisms
- but
  - recognition by efflux varies widely among closely related drugs
    (e.g. levofloxacin >> moxifloxacin)
  - the increase in MIC is modest and often leaves the strain categorized (falsely …) as "sensitive"…
- true MIC determination may, therefore, become more and more critical …



Van Bambeke et al.
J Antimicrob Chemother. 2003;51:1055-65.

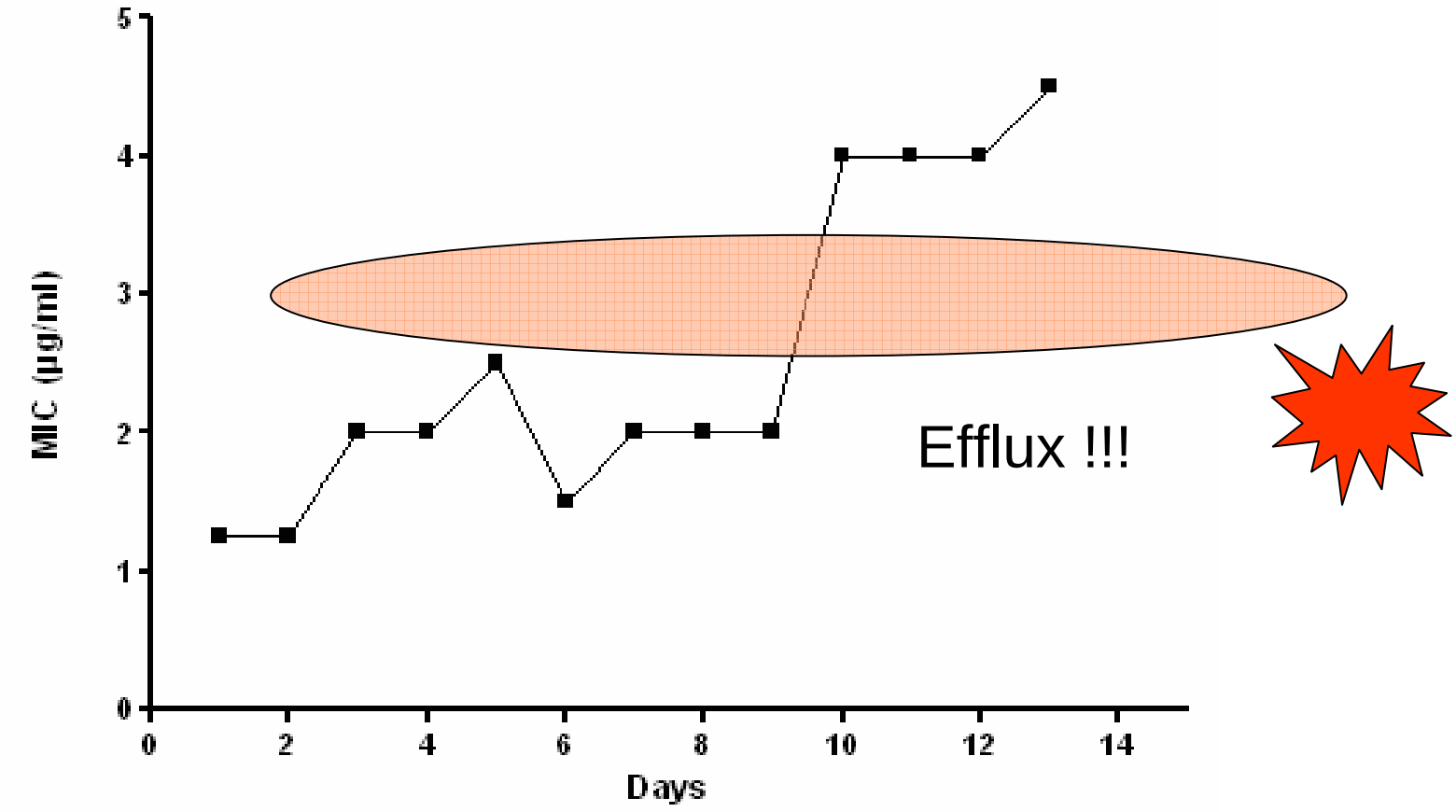
Why do you need to detect efflux ?



how many of your samples would actually fall here ….

But will be brought back to wild type distribution in the presence of efflux inhibitor ...

Efflux is in you backyard ..



Typical increase in MIC of *S. pneumoniae* (wild type) towards CIP upon sucessive 24h incubations in the presence of CIP at concentrations equal to half the MIC observed each day

Avrain et al., 7th ECC, 2005

And efflux favours resistance ...
if you have not a Cmax/MIC ratio > 8 ...

TABLE 2. Frequency of mutation of *S. aureus* ATCC 29213

Mutation frequency with ciprofloxacin at:		
4× MIC (1 μg/ml)	8× MIC (2 μg/ml)	16× MIC (4 μg/ml)
$>10^{-6}$	1.2×10^{-8}	$<10^{-9}$
1.3×10^{-8}	$<10^{-9}$	$<10^{-9}$
$<10^{-9}$	$<10^{-9}$	$<10^{-9}$

Kahn et al., Antimicrob Agents Chemother. 2006 Feb;50(2):810-2.

And efflux favours resistance ...
if you have not a Cmax/MIC ratio > 8 ...

TABLE 2. Frequency of mutation of *S. aureus* ATCC 29213

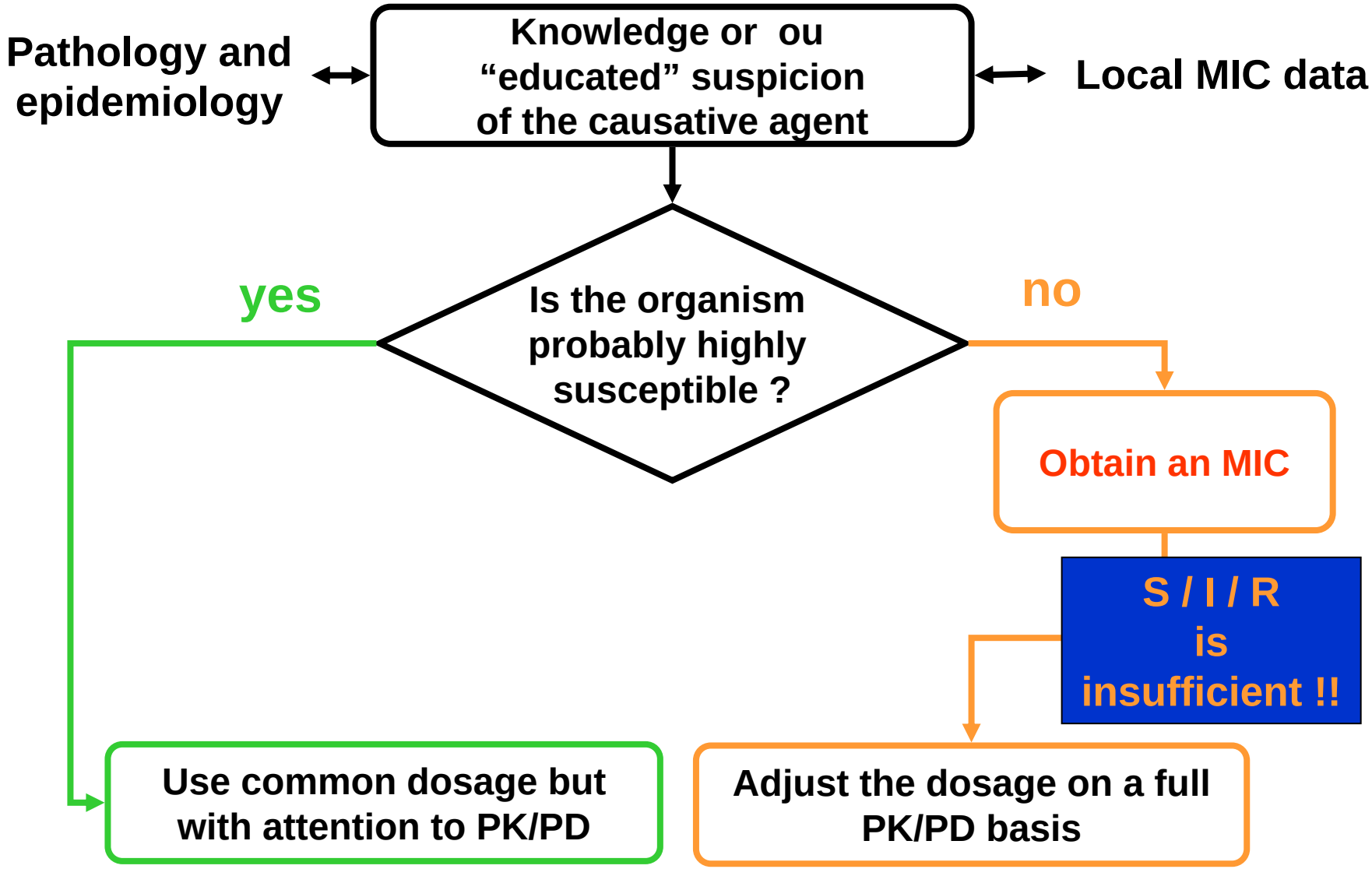
Piperine concn (μg/ml)	Mutation frequency with ciprofloxacin at:		
	4× MIC (1 μg/ml)	8× MIC (2 μg/ml)	16× MIC (4 μg/ml)
0	$>10^{-6}$	1.2×10^{-8}	$<10^{-9}$
25	1.3×10^{-8}	$<10^{-9}$	$<10^{-9}$
50	$<10^{-9}$	$<10^{-9}$	$<10^{-9}$

This is an efflux pump inhibitor ...

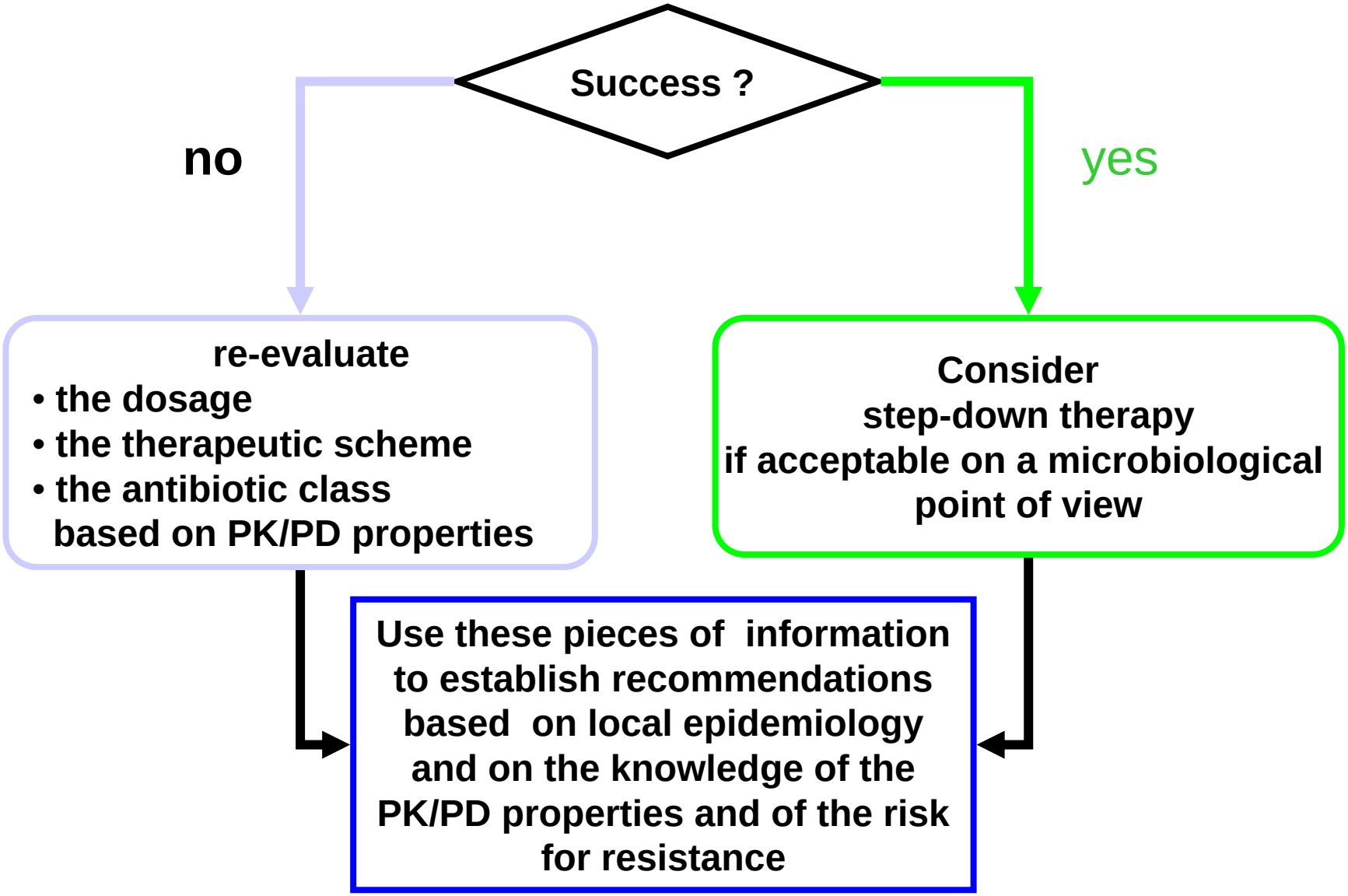
And see how it protects against the risk of mutation...

Kahn et al., Antimicrob Agents Chemother. 2006 Feb;50(2):810-2.

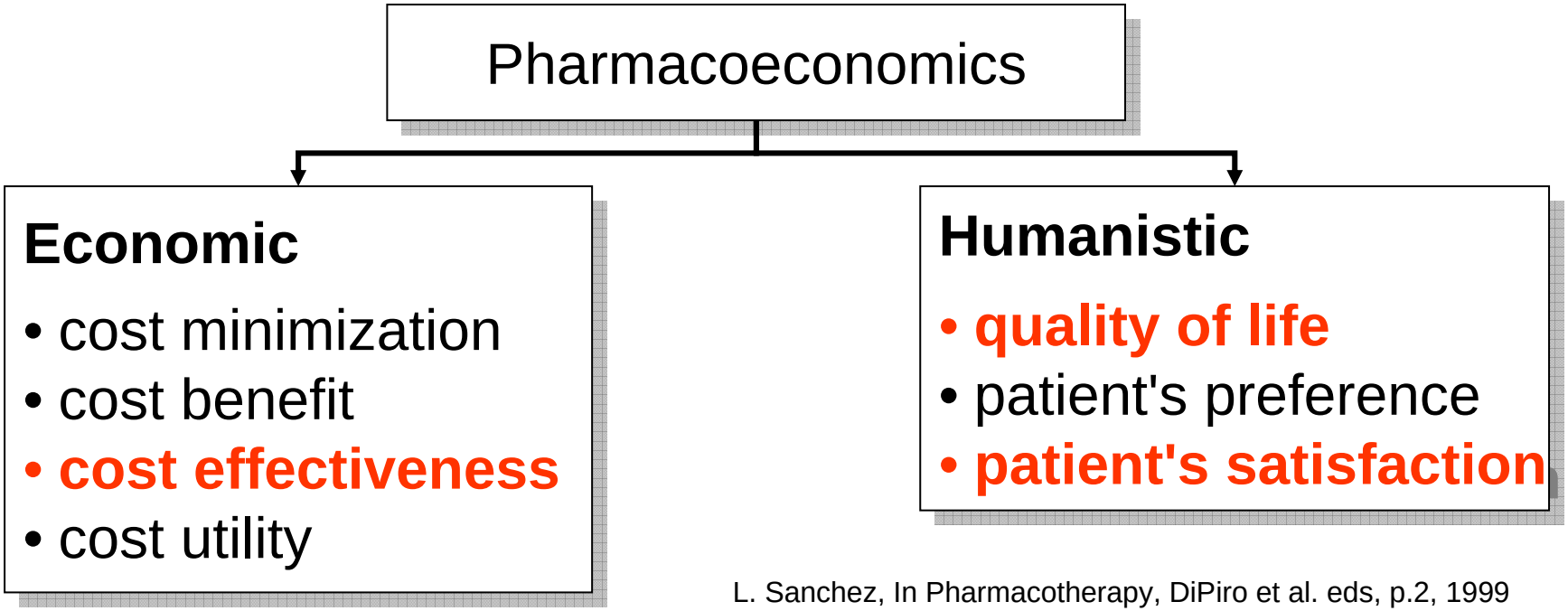
A clinical algorithm ...



A clinical algorithm (follow.) ...



And what about health care costs ?



L. Sanchez, In Pharmacotherapy, DiPiro et al. eds, p.2, 1999

- Pharmacoeconomics of antibiotics is still largely underdeveloped outside the USA (but US-based models cannot easily be applied);
- However, comparisons identifying differences in
  - amount of money needed to reach a given (better ?) clinical outcome;
  - expenses related to the same (or better) quality of life and patient's satisfaction;

  may already suggest interesting avenues for further fine-tuning therapeutic guidelines

Rational bases for the choice of an antibiotic

- Know your LOCAL epidemiology
  - ➢ obtain MIC distributions from your microbiologists…
- know the PK profile of the drugs you consider to purchase
  - ➢ aim at obtaining > 90 % efficacy against the organisms of interest (AUC, peak, time above MIC) with a standard dosage, ...
- include a safety margin (MPC …)
- Compare products on that basis first …
- Remember that
  - no antibiotic (if possible) is the best…
  - but that treatment failures (when treatment is needed) cost a lot … (so that cheap but 2d class antibiotics may not be a bargain...)

Please, act …

www.facm.ucl.ac.be

F. Van Bambeke, Pharm.
A. Spinewine, Pharm.
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