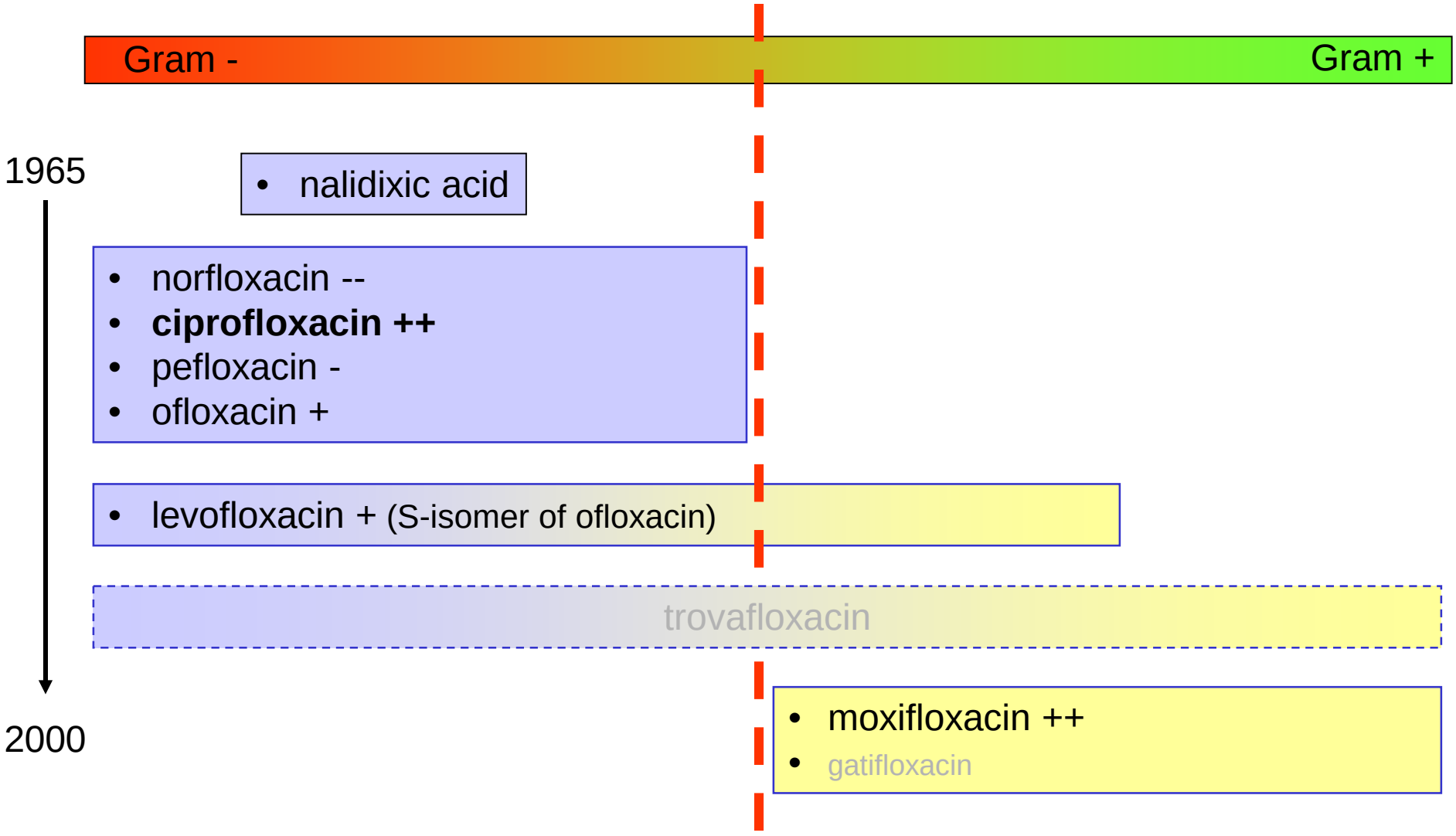
Fluoroquinolones

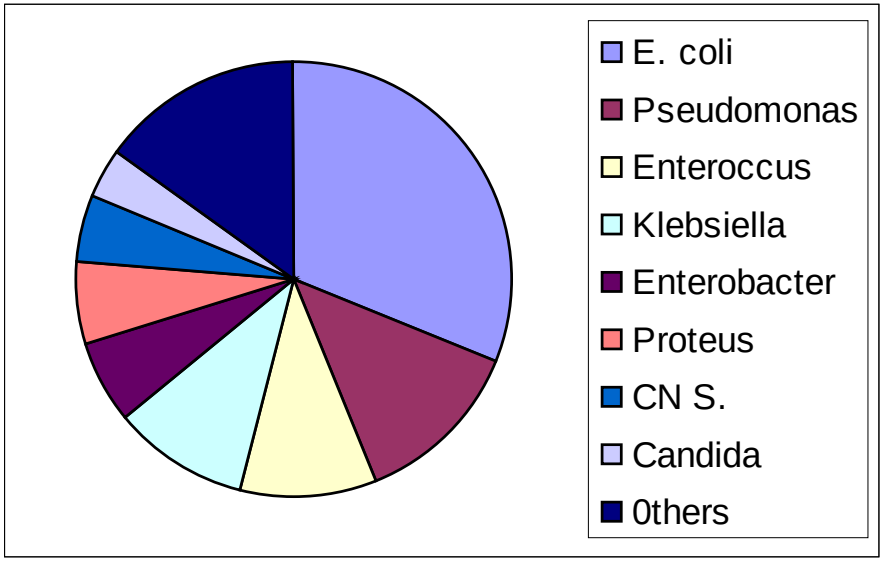
Which (fluoro)quinolones ?



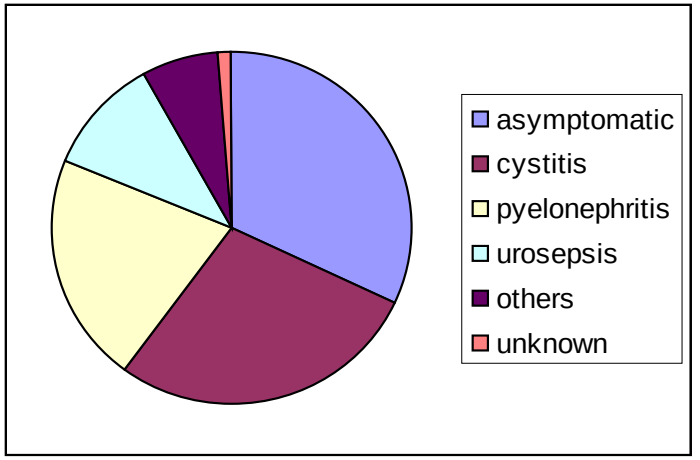
Fluoroquinolones in urology

Organisms and resistance in nosocomial urological specimens …

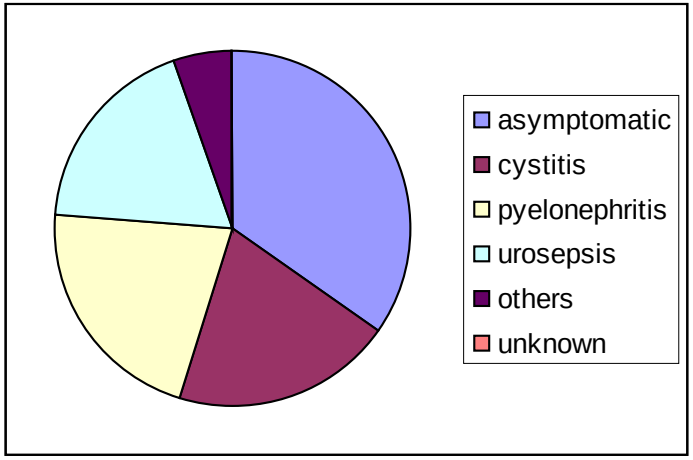
Distribution of microbial species in 486 patients with nosocomially acquired urinary tract infection



E. coli

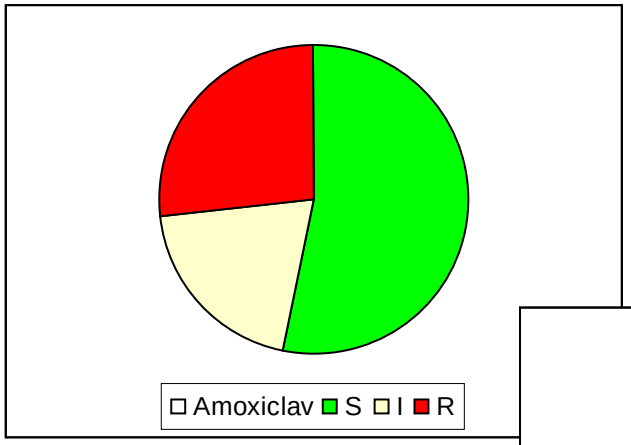


P. aeruginosa



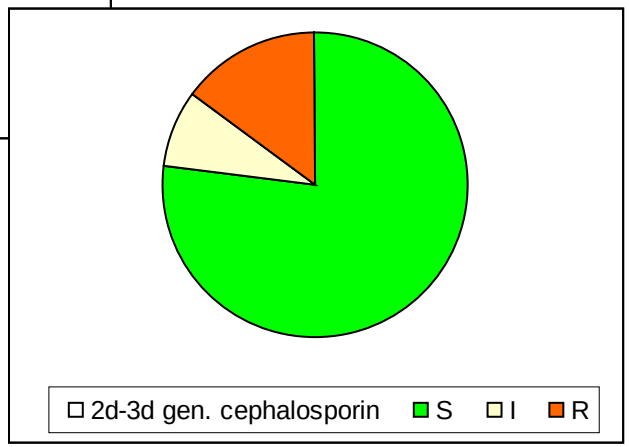
Johansen et al. Intern. J. Antimicrob. 2006; 28,Suppl.1:91-107
A study from the European Society of Infections in Urology (ESIU)

Organisms and resistance in nosocomial urological specimens …

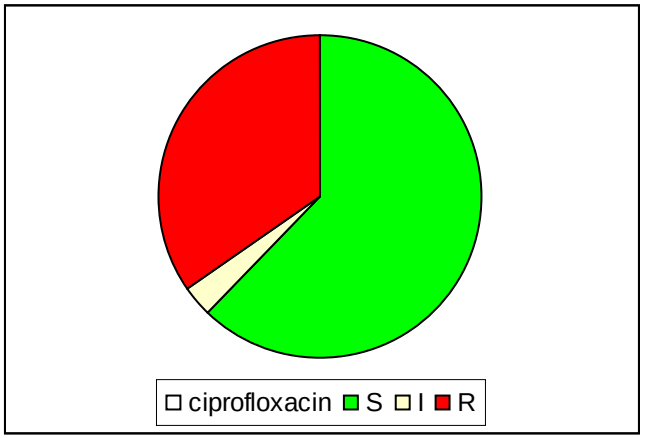


to amoxiclav

Resistance of *E. coli*



to 2d/3d gen. cephalosp.



to ciprofloxacin

Johansen et al. Intern. J. Antimicrob. 2006; 28,Suppl.1:91-107
A study from the European Society of Infections in Urology (ESIU)

Thus, we are facing a problem… and looking for a solution …

- Resistance rates are strong arguments for a critical antimicrobial policy
- Empiric therapy has to be initiated rapidly but culture must be taken before.
- Adjustment is important …
- Prophylaxis and treatment must be based on a continuous surveillance in Urology departments.
- Collaboration between urologists and microbiologists is decisive for good infection control.
- Facilities for preliminary culture of pathogens inside the urological ward may be useful

Johansen et al. Intern. J. Antimicrob. 2006; 28,Suppl.1:91-107
A study from the European Society of Infections in Urology (ESIU)

Where do we go from now ?

- Understand what quinolones are ?
- Are they causing more resistance ?
- What could be their limits
- What do guidelines say ?
- Do we use too much ?

Main useful pharmacological properties and drawbacks ?

On the positive side

- bactericidal
- concentration (C_{max}) and dose (24h-AUC)-dependent, allowing for rational fine tuning of the therapy including against resistant strains, based on simple rules for posology…
  - ➔ C_{max}/MIC > 10; 24h-AUC/MIC > 125
- good tolerance in general
- excellent bioavailability (rapid oral switch possible…)

On the negative side

- a few side effects that require attention (tendinitis, CNS, ...) and incompatibility with divalent traivalent cations (Ca_{++}, Al^{+++})
- emergence of resistance
  - target mutation (relatively easy ...)
  - unanticipated cross-resistances due to efflux…
  - breakpoints (limits of susceptibility) have been set historically to high (NCCLS), are better with EUCAST, but still need attention

Quinolones side effects...

Table 3. Main side-effects of quinolones that contribute to the limitation of their use, the frequency observed, and the populations at risk

Side-effect	Quinolone	Frequency	Population at risk
Genotoxicity			Pregnant women
Gastrointestinal effects (nausea, vomiting > diarrhea)	Fleroxacin, sparfloxacin, grepafloxacin[a]	> 10%	
	Others	2–8% [243]	
Skin reaction: phototoxicity	Sparfloxacin[a], fleroxacin[a], lomefloxacin[a], Bay 3118[a]	> 10% [244]	
	Others	< 2.5%	Cystic fibrosis [245]
Skin reactions: rash	Clinafloxacin[a]	4% [243]	
	Gemifloxacin	2.8% [246]	Young women
Chondrotoxicity	Pefloxacin[a]	14% [247]	Children, pregnant women
	Others	1.5% in children (ciprofloxacin [248])	
Tendinitis	Pefloxacin[a]	2.7% [249]	Elderly, especially if on corticosteroid therapy [250]
	> Levofloxacin/ofloxacin ≥ ciprofloxacin > Others [252,253]	0.4%	Athletes in training [251]
Minor CNS effects	Trovafloxacin	2–11% dizziness	Elderly [254]
Major CNS effects	Levofloxacin	0.026% confusion, alteration in mentation and affect [243]	Co-administration of NSAID or of inhibitors of CYP 450 [255]
	Fleroxacin[a] [256]	8% insomnia [257]	
Cardiovascular effects	Sparfloxacin[a] (9–28 ms)	2.9%	Female gender
	Grepafloxacin[a] (10 ms)		Co-administration of other drugs (prolonging QTc interval or inhibiting CYP 450 metabolism)
	Moxifloxacin (6 ms)		
	Levofloxacin (3 ms)[b]		
	Gatifloxacin (2.9 ms)		
	Gemifloxacin (2.6 ms) [246,258–260]		Heart disease [254]
Minor hepatic effects (transaminase elevation)	Grepafloxacin	12–16% transaminase elevation [243]	
	Others	< 3% [261]	
Major hepatic effects	Trovafloxacin[a]	0.006% [243]	Treatment duration > 14 days [262]
Hypoglycaemia	Clinafloxacin[a]		Co-administration of oral hypoglycemic agents [264]
	Gatifloxacin		
	Levofloxacin (one fatal case [263]		
Haematological toxicity	Temofloxacin[a]	0.02% haemolysis, thrombocytopenia, renal failure [256]	
CYP 450 inhibition	Enoxacin[a], clinafloxacin[a] [256] > ciprofloxacin > lomefloxacin, ofloxacin > levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin [262]		

[a]Side-effects have contributed to the withdrawal or limitation in use.
[b]Further studies have been requested from the manufacturer, as recent pharmacovigilance reports document a significant increase of the QTc interval, mainly in patients with concurrent medical conditions or other medications [243,265]; see also [266] for a recent study in the province of Varese, Italy, using prescription data on all incident users of several antibacterial and anti-arrhythmic drugs during the period July 1997 to December 1999.
NSAID, non-steroidal anti-inflammatory drug; CNS, central nervous system.

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

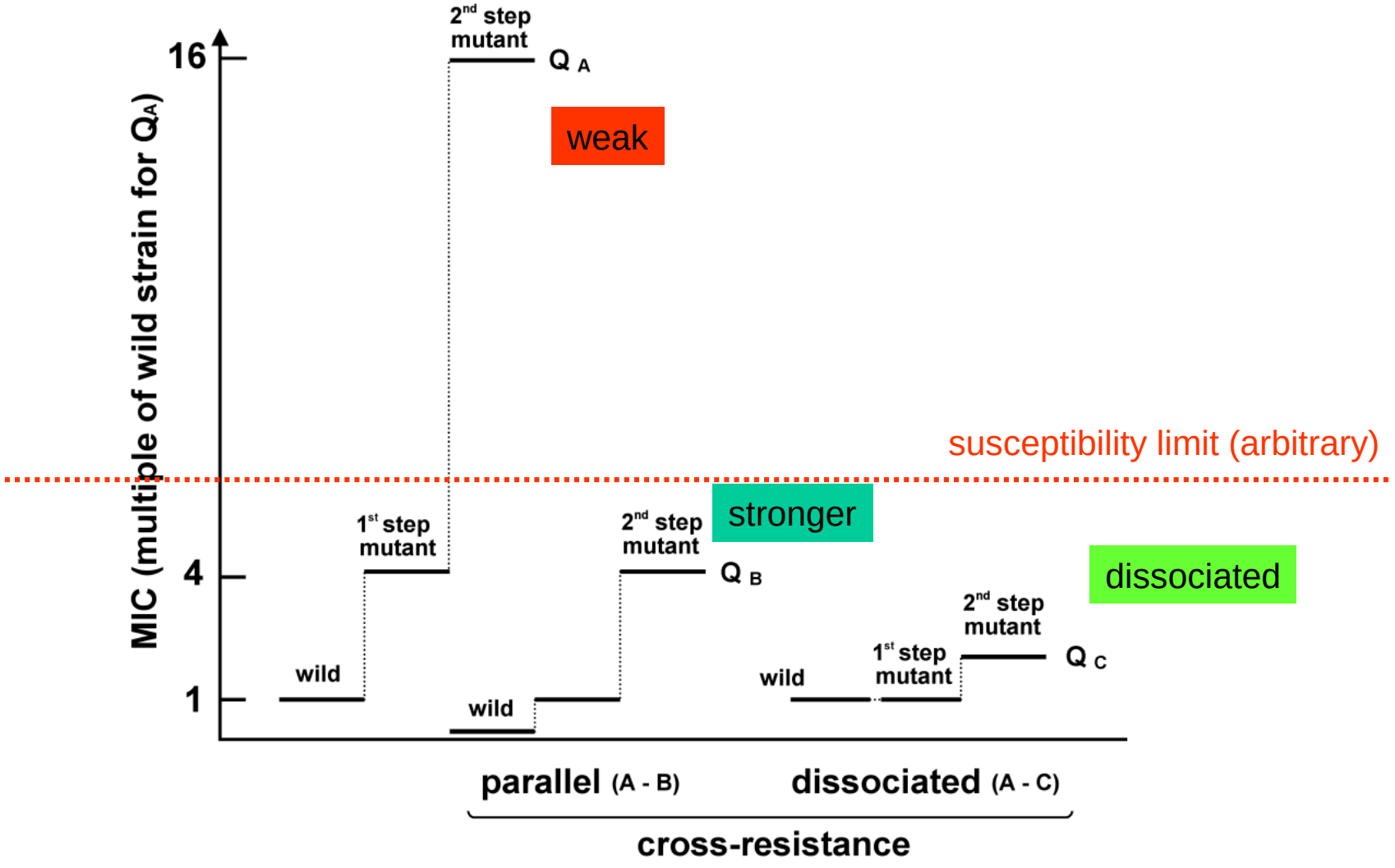
Quinolones side effects...: which are the populations (really) at risk ?

- pregnant women and children
- elderly, especially with corticoid therapy
- athletes in training (beware of the runners...)
- co-administration of NDSAIDs or drugs known for potential of $CytP_{450}$ interactions
- heart disease
- patients receiving neutralization anti-acids (Ca++/ Mg++ / Al+++) or Fe++

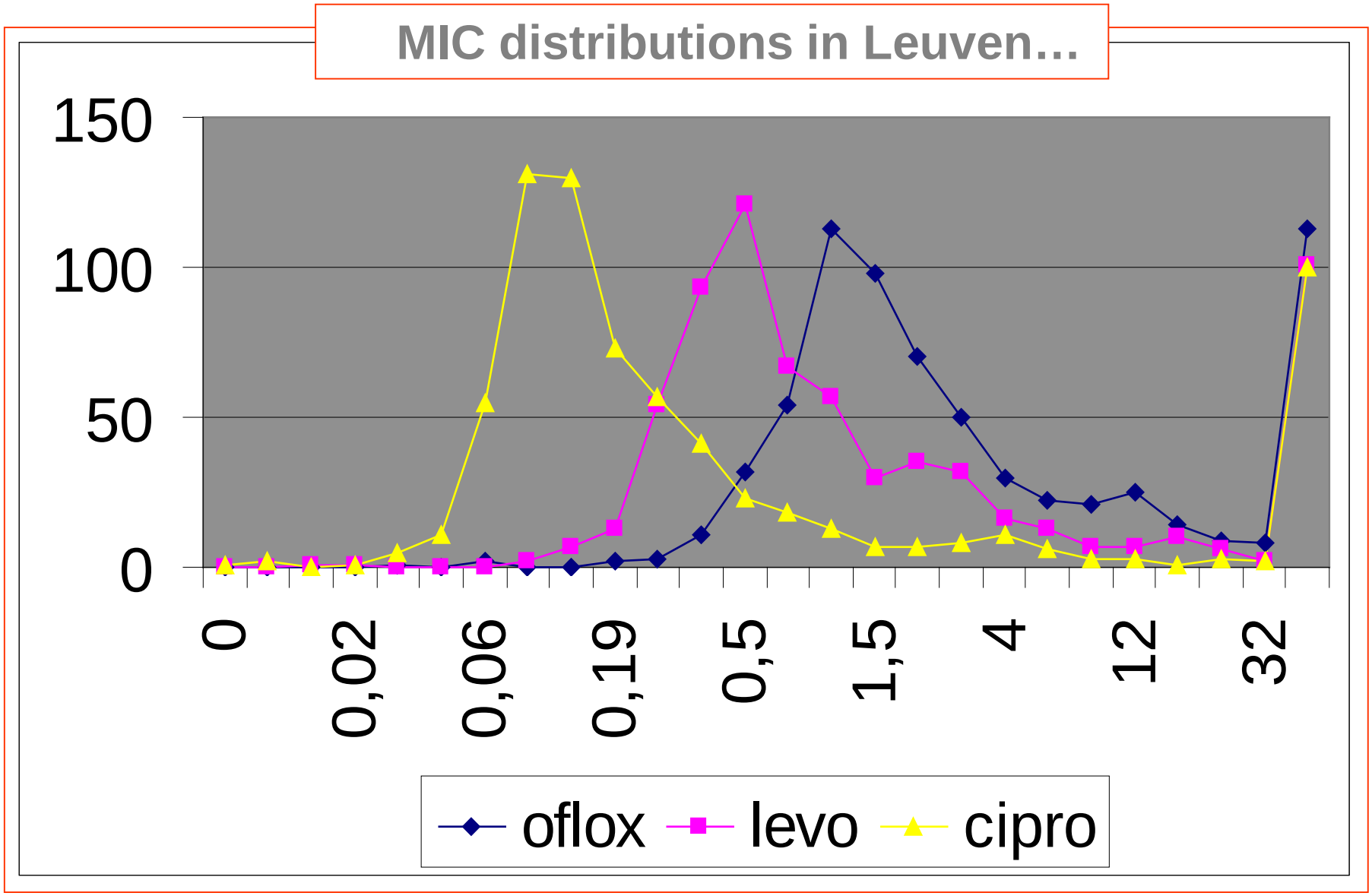
Resistance…

- long thought to be restricted to chromosomic mutations of the targets (DNA gyrase / topoisomerase)
  - high frequency of spontaneous mutations (10^{-7})
  - but limited horizontal and interbacterial spread …
- but, later on, observed in relation to decreased accumulation
  - loss of porins in Gram (-) bacteria
  - (over)expression of efflux
- now, seen through plasmidic-associated mechanisms (QnR)
  - risk of rapid horizontal spread …
- and very recently though fluoroquinolone-modifying enzymes !!
  (clinical significance still uncertain…)

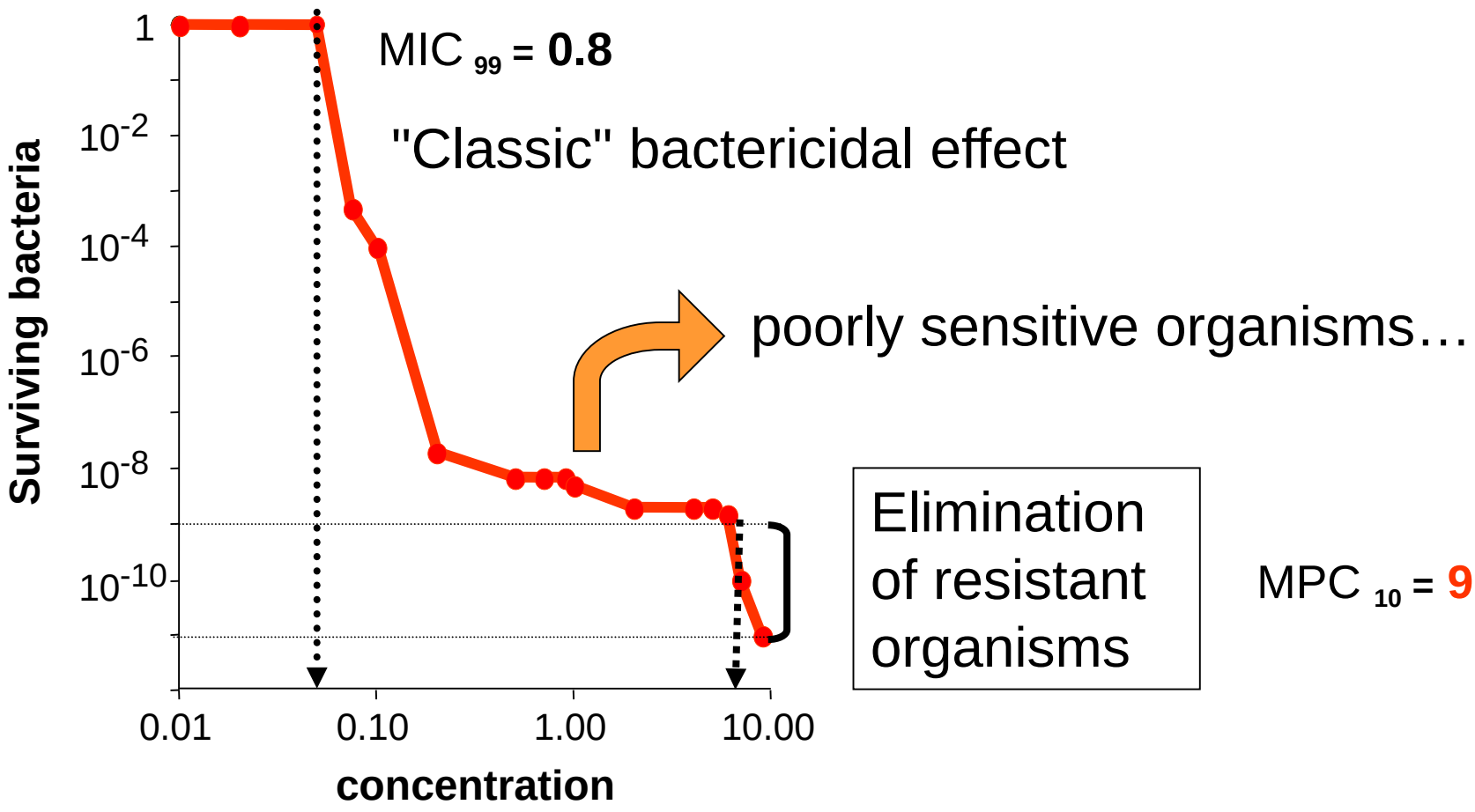
Resistance by target mutation: parallel and dissociated resistance and strong-versus weak fluoroquinolones



Application: look at MIC distributions where YOU are … to find "weak" quinolones

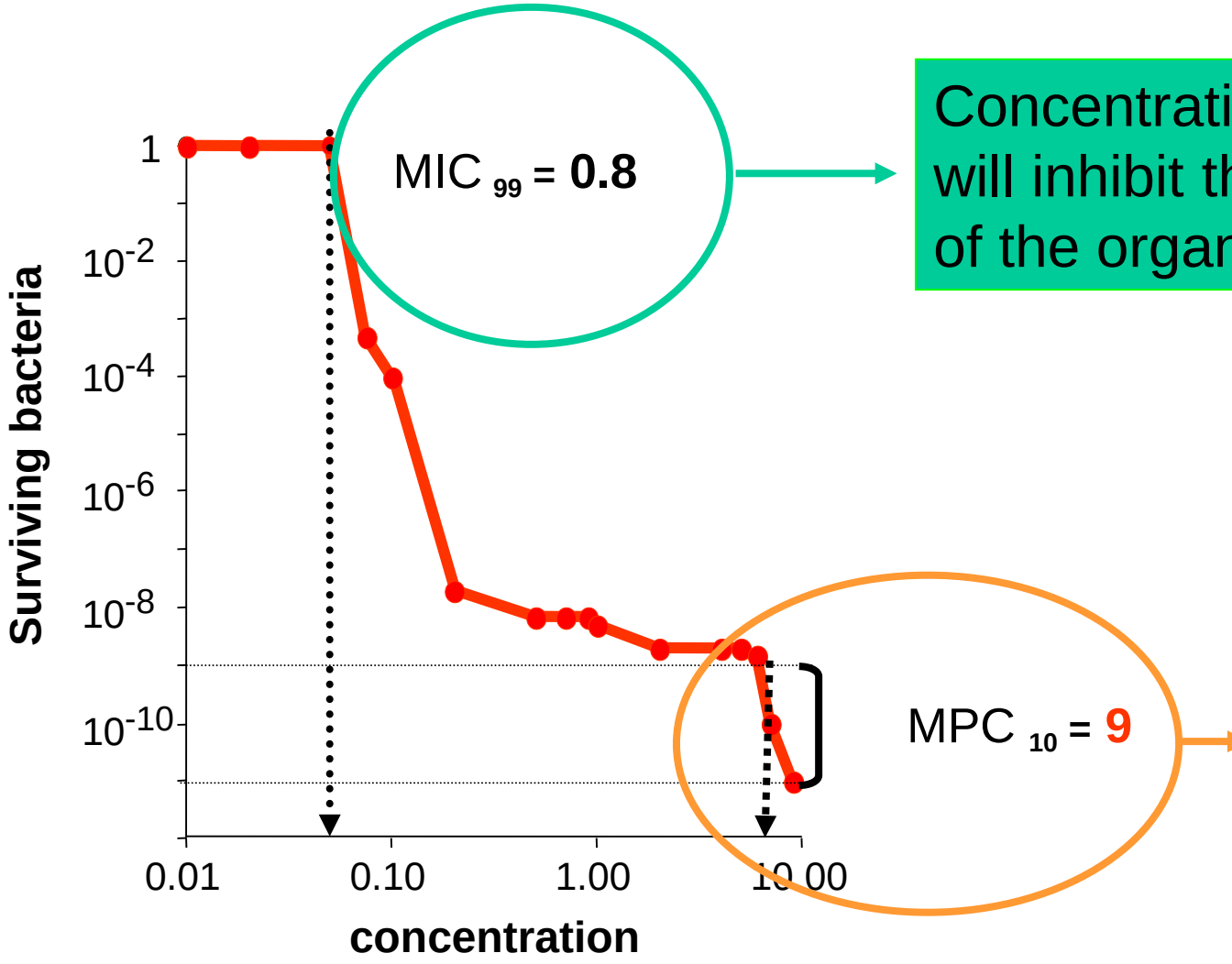


Mutant Prevention Concentration …



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

Mutant Prevention Concentration …

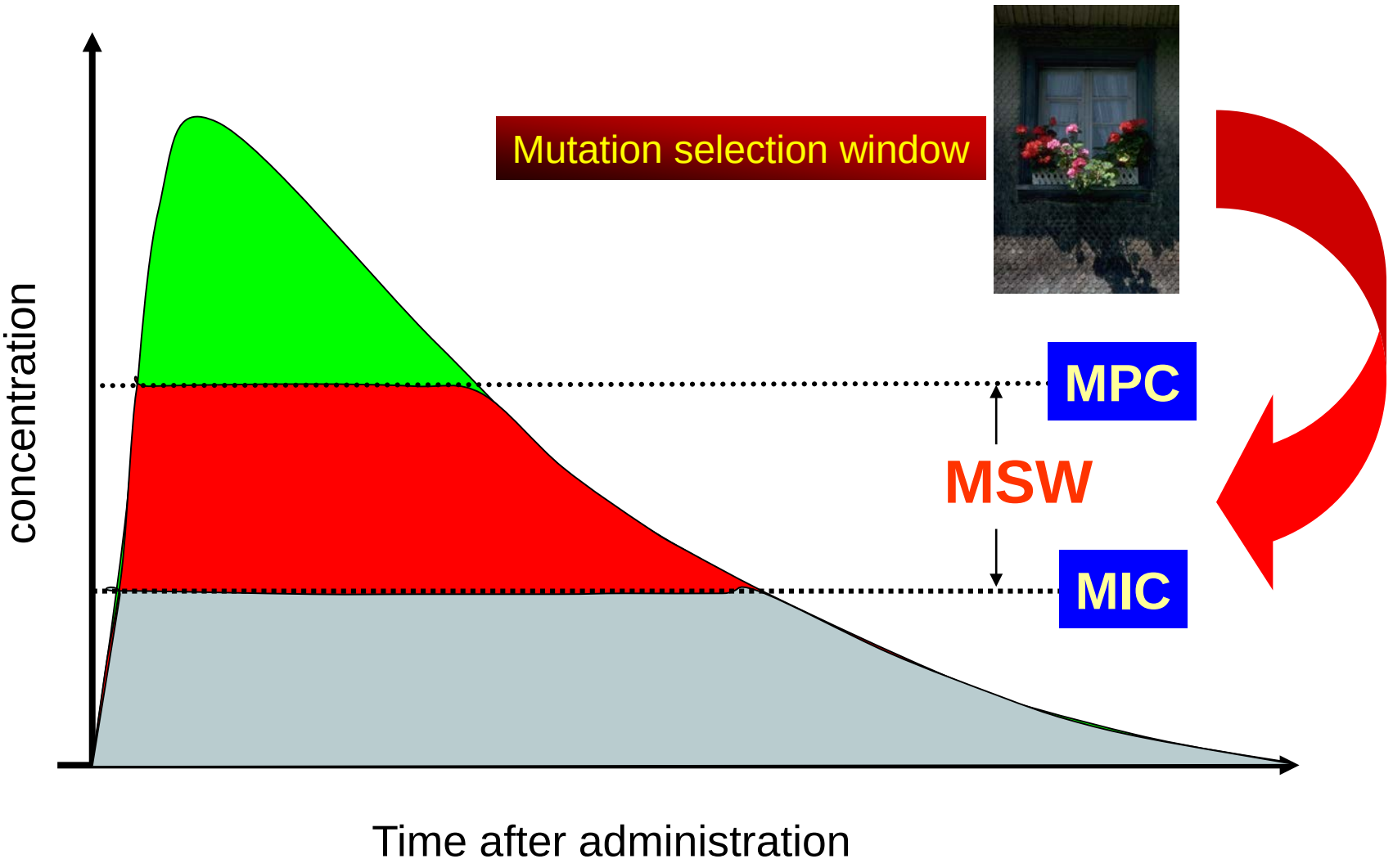


Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

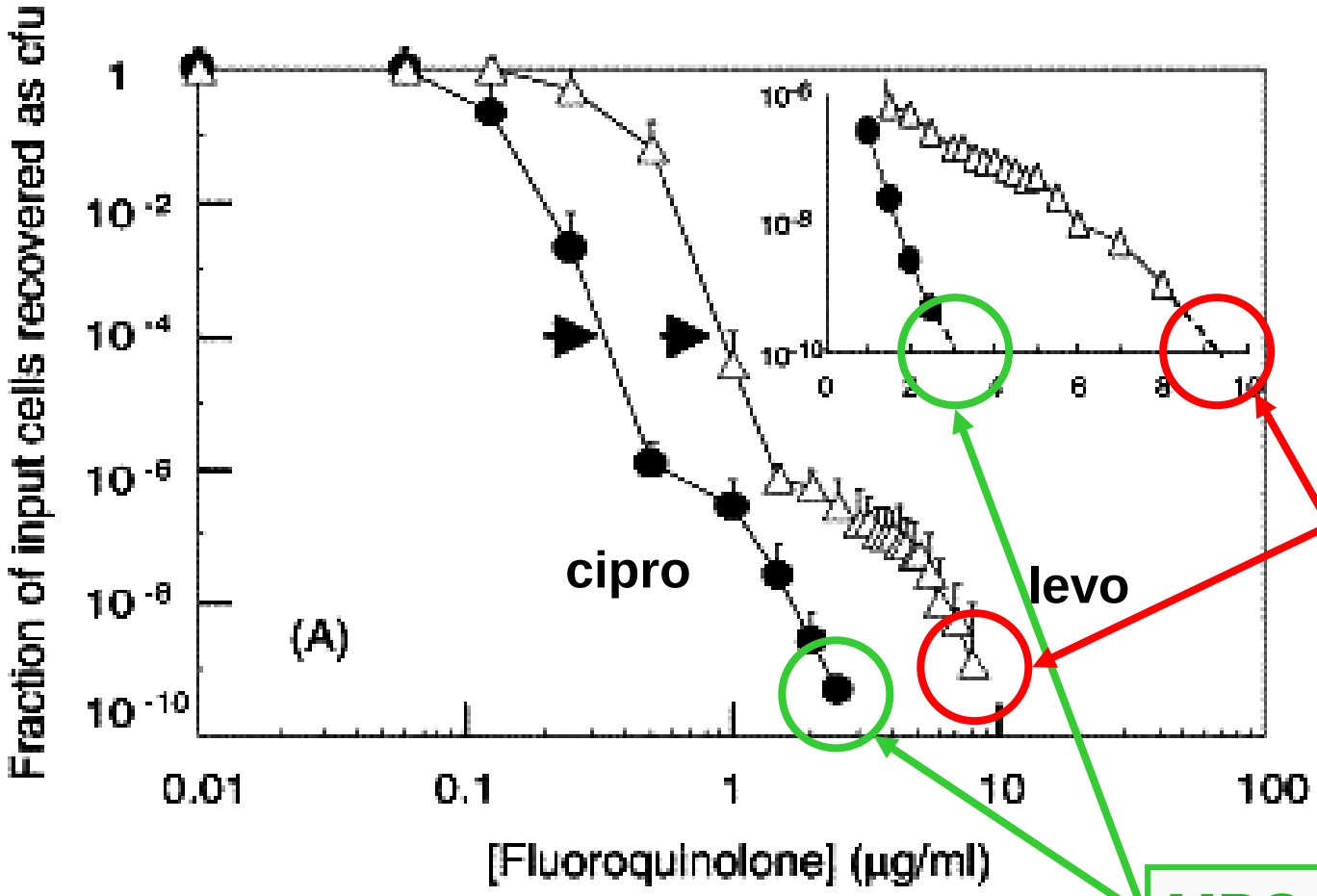
Dong *et al*; AAC 43:1756-1758

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



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

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



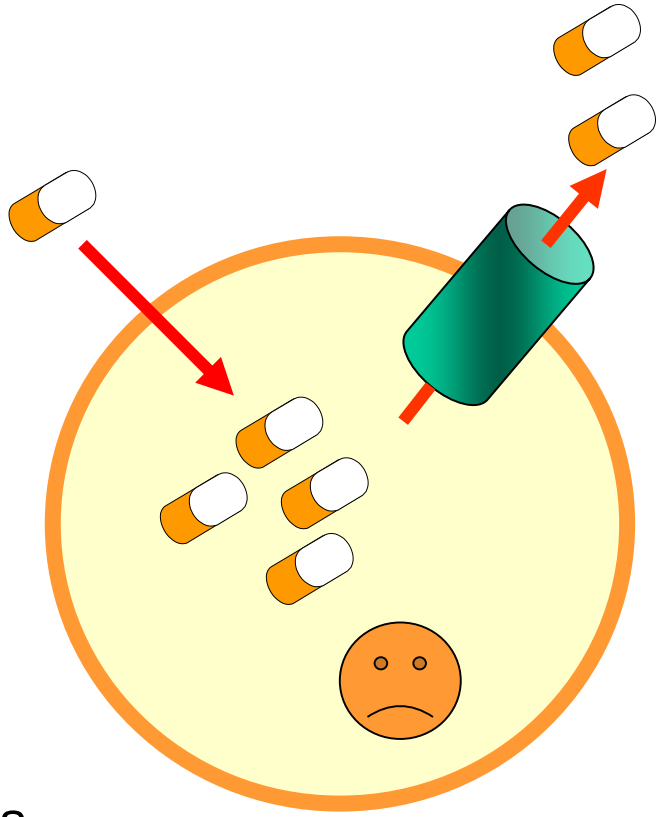
MPC levo = 9.5
(Cmax ~ 5 µg/ml

MPC cipro = 3
Cmax ~ 2.5 µg/ml

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

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

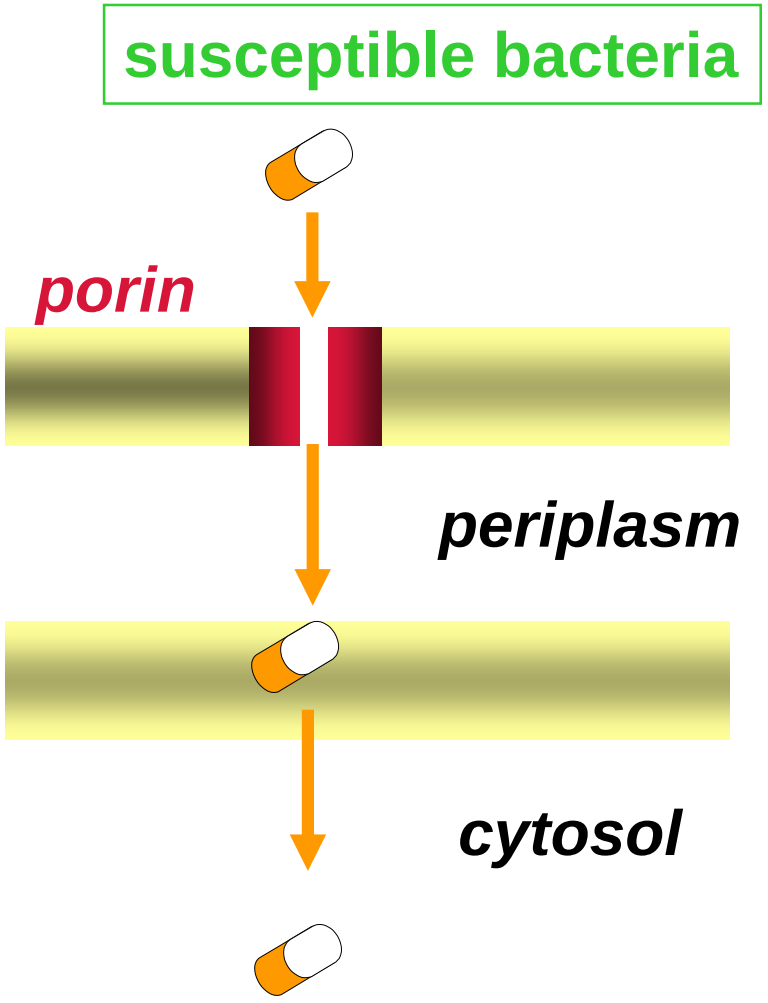


➔ the increase in MIC is modest and often leaves the strain categorized (falsely …) as "sensitive"…

➔ true MIC determination may, therefore, become more and more critical …

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

How does efflux work (Gram - bacteria) ?



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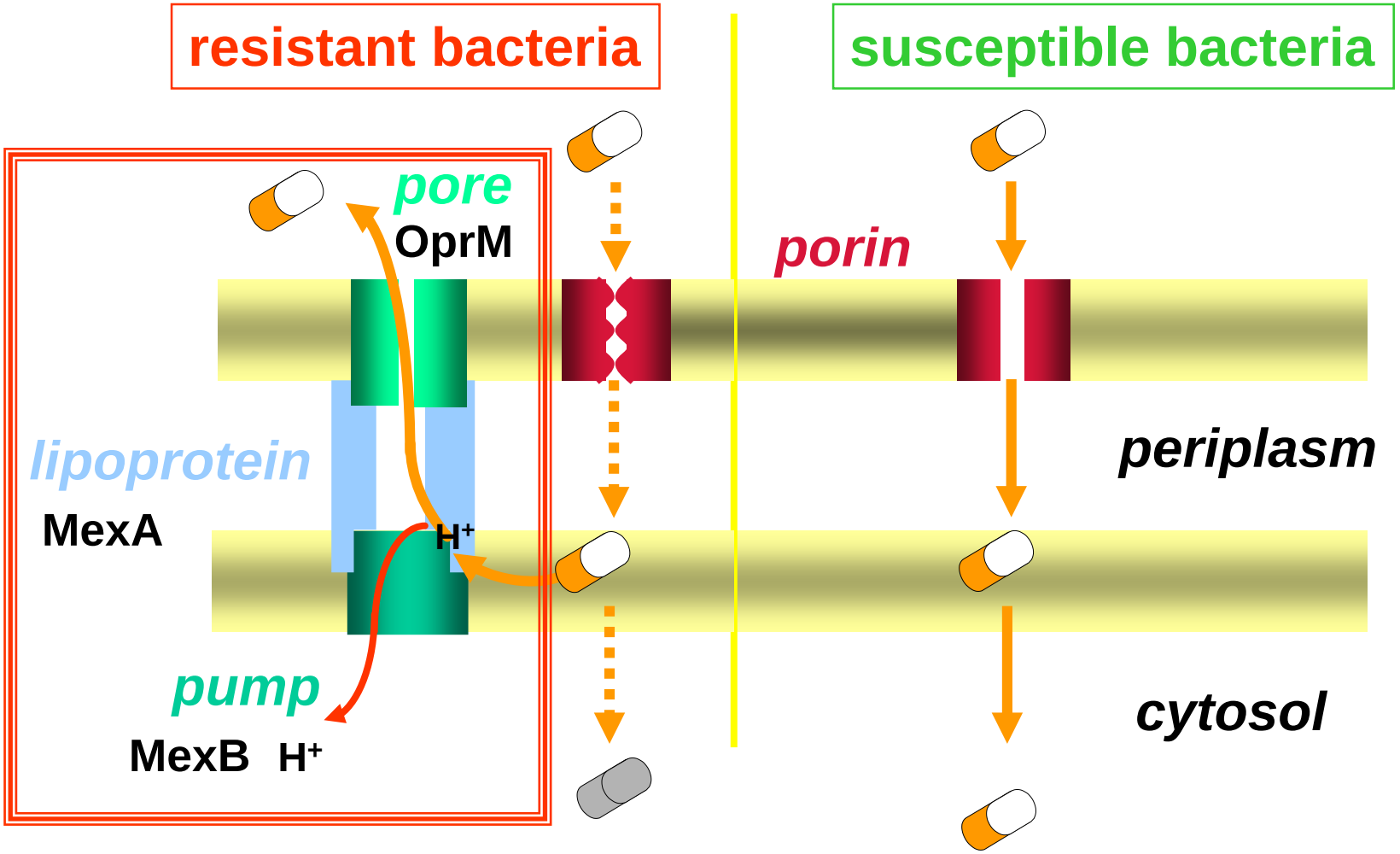
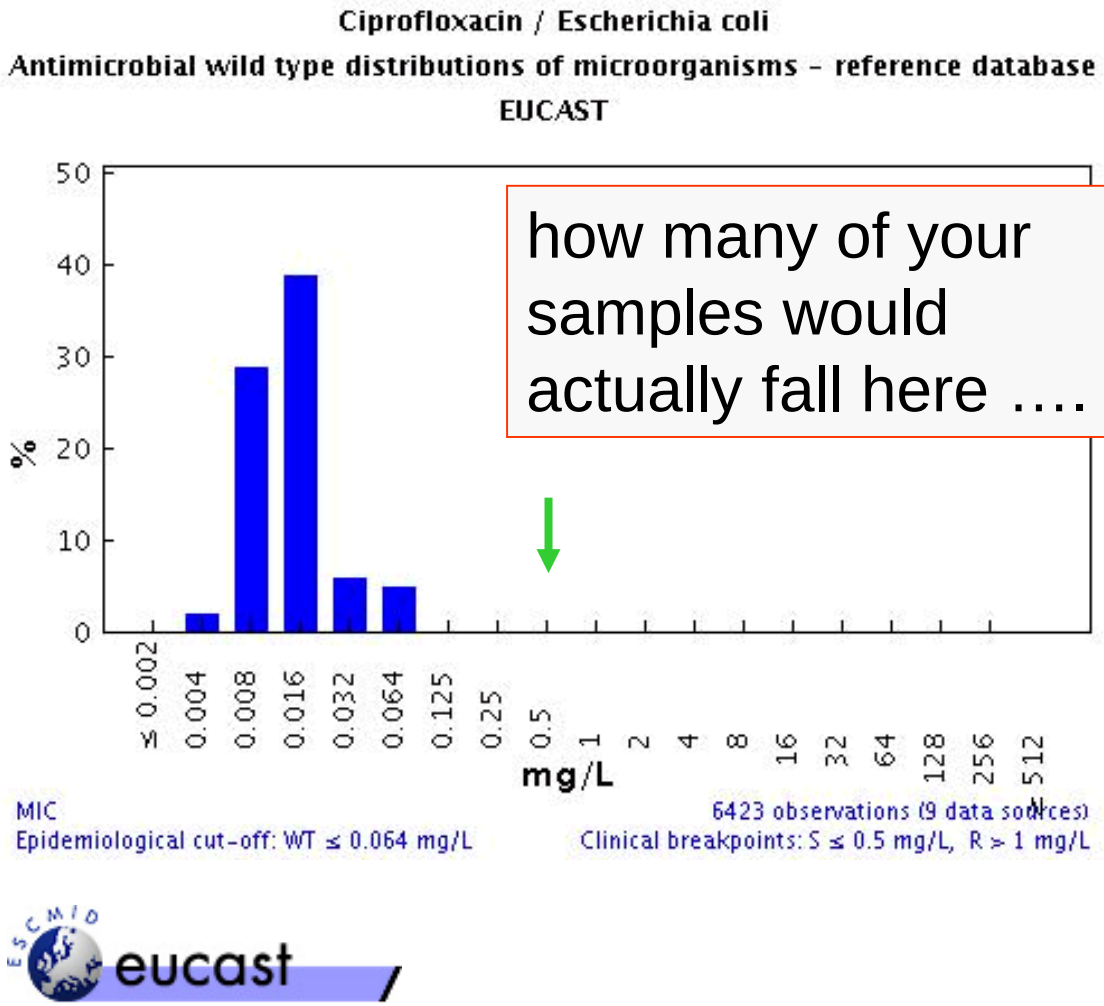


expressed in wild-type strains!

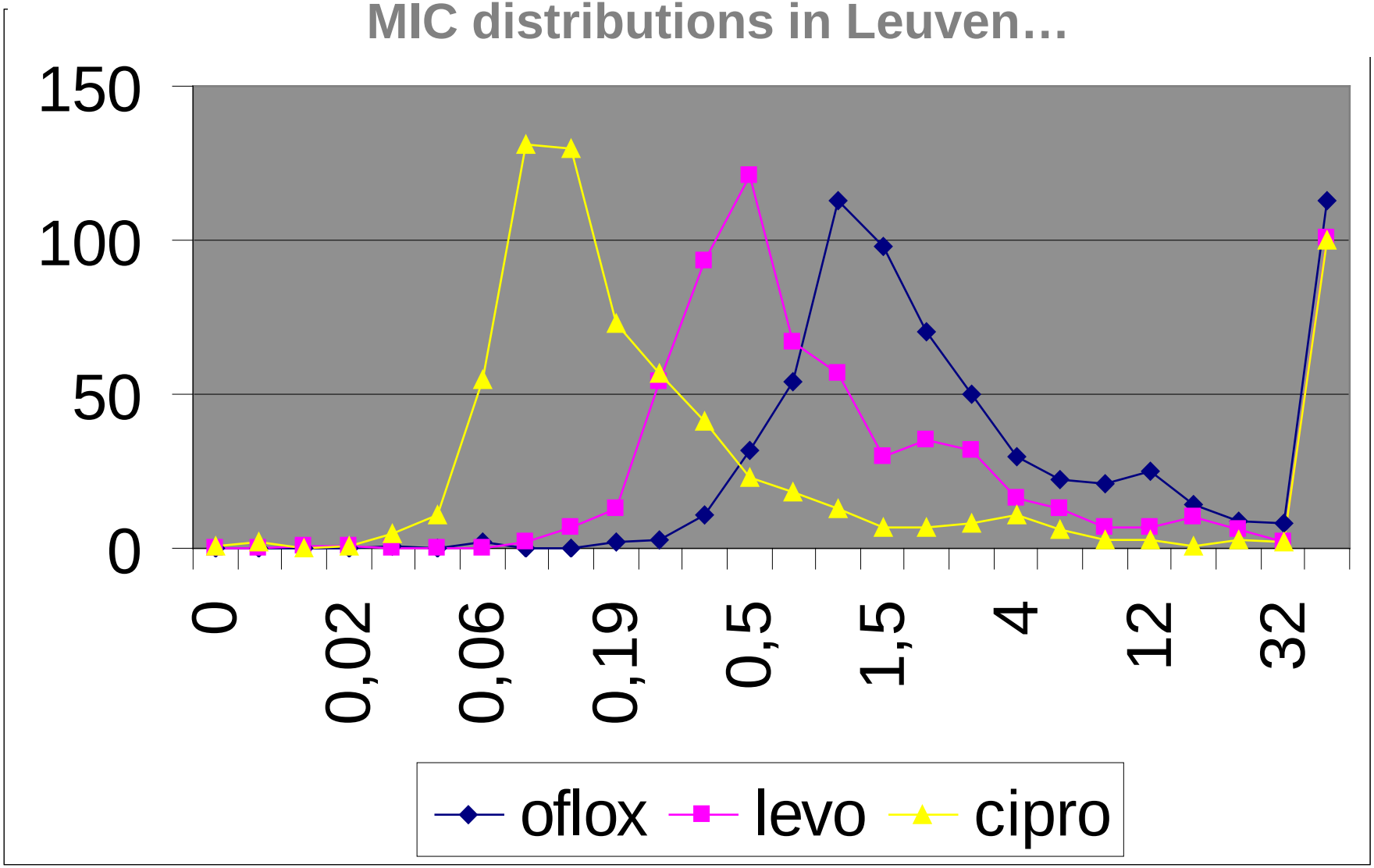
Why do you need to detect efflux ?



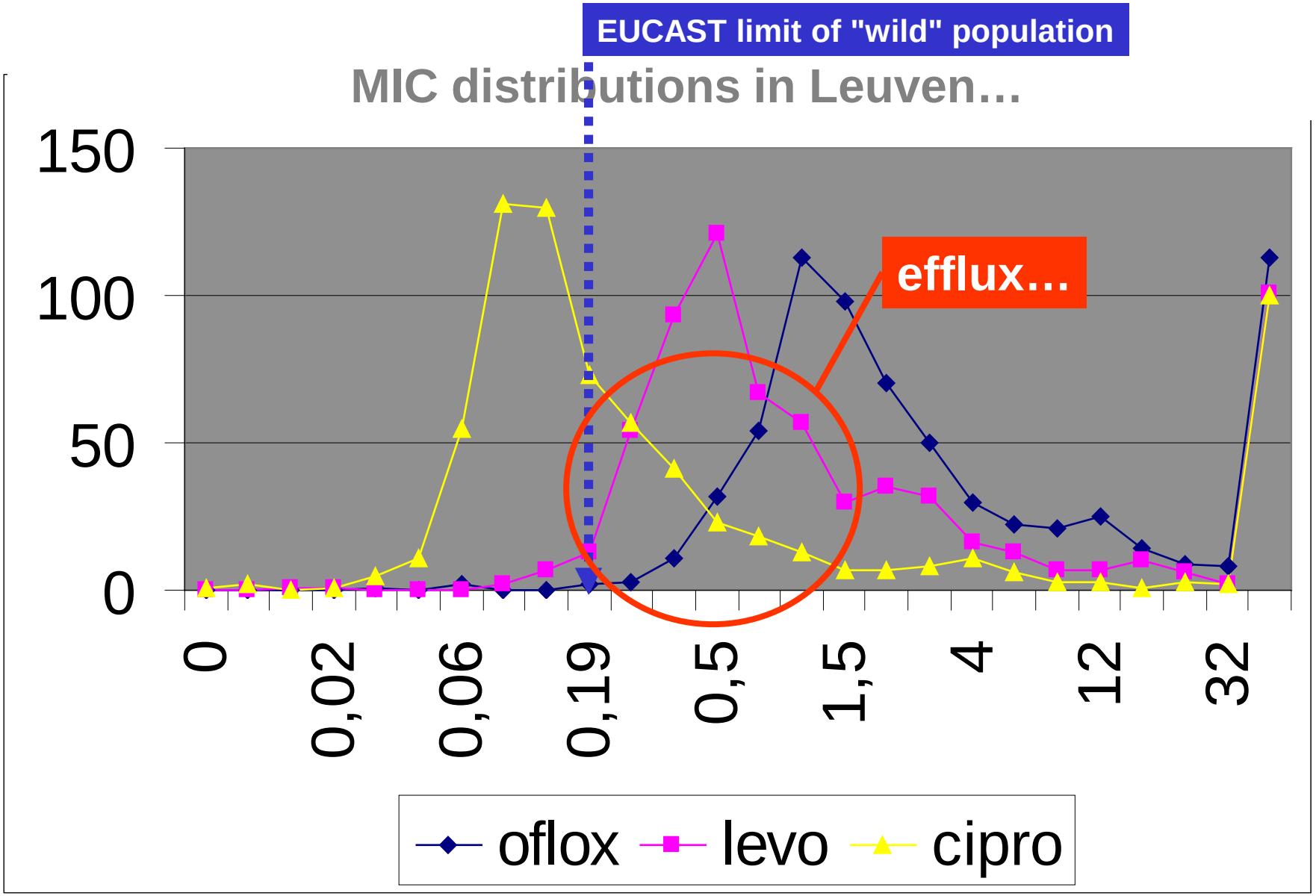
how many of your samples would actually fall here ….

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

Application: look at MIC distributions where YOU are …

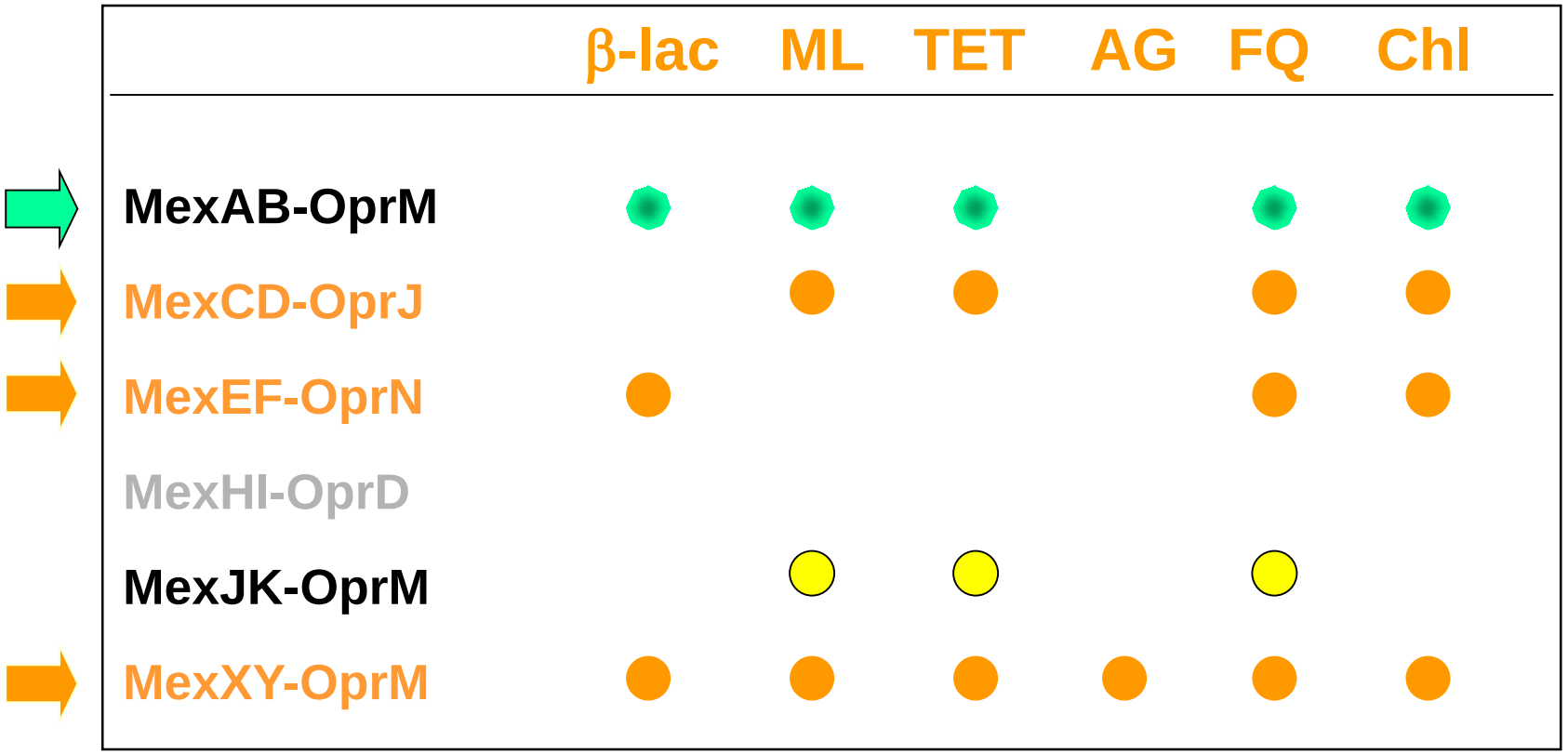


Application: look at MIC distributions where YOU are …



Why does efflux cause cross-resistance ?

(example with *P. aeruginosa*)



constitutive expression

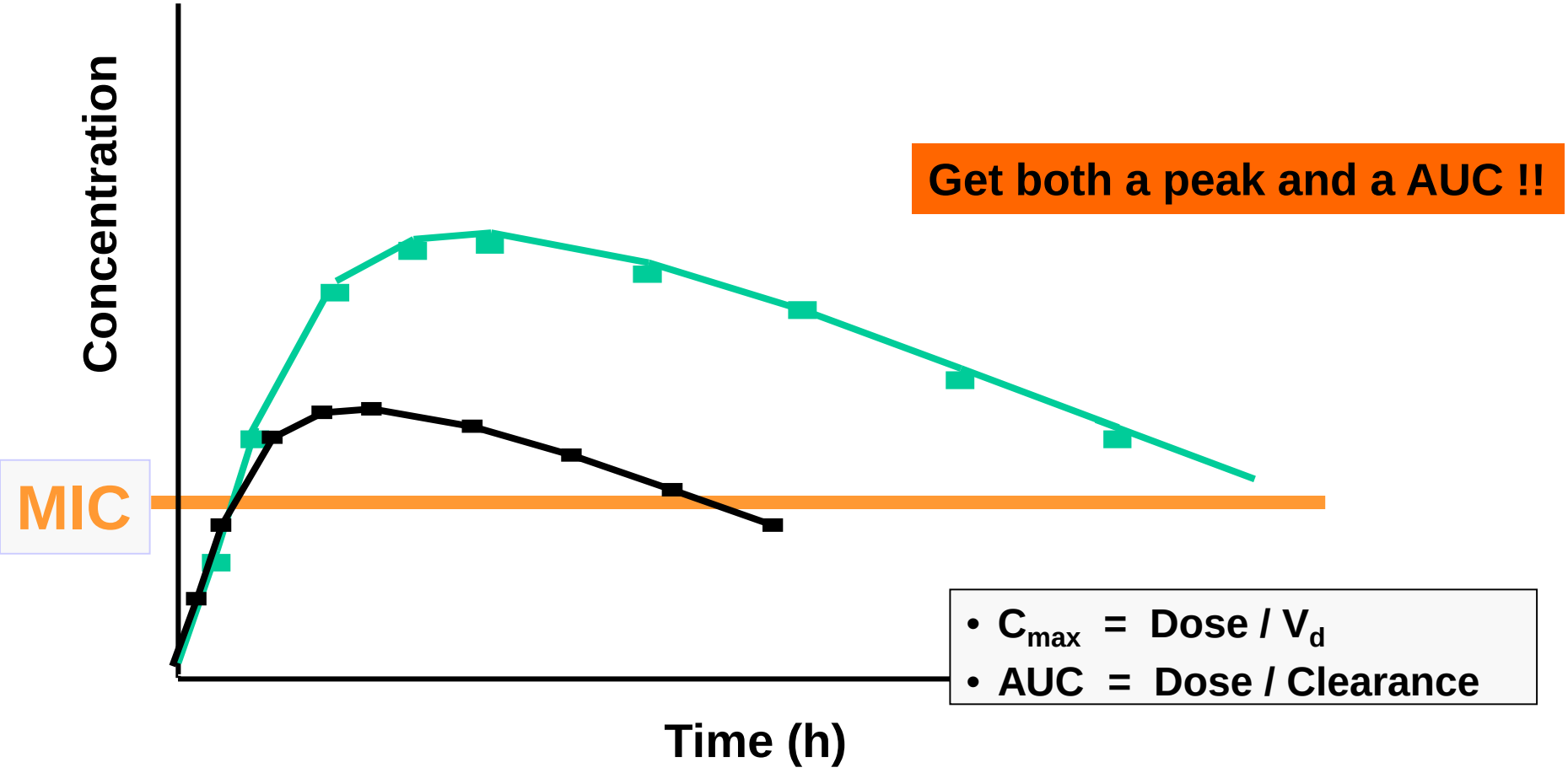
inducible expression

Van Bambeke et *al*. JAC (2003) 51:1055-65; Aeschlimann, Pharmacotherapy (2003) 23:916-24

Fluoroquinolones: get a peak and an AUC !

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

C_{max}/MIC ⇒ should be > 10



Application: choose a strong quinolone and use low enough break-points … or better … ask for an MIC and use PK/PD …

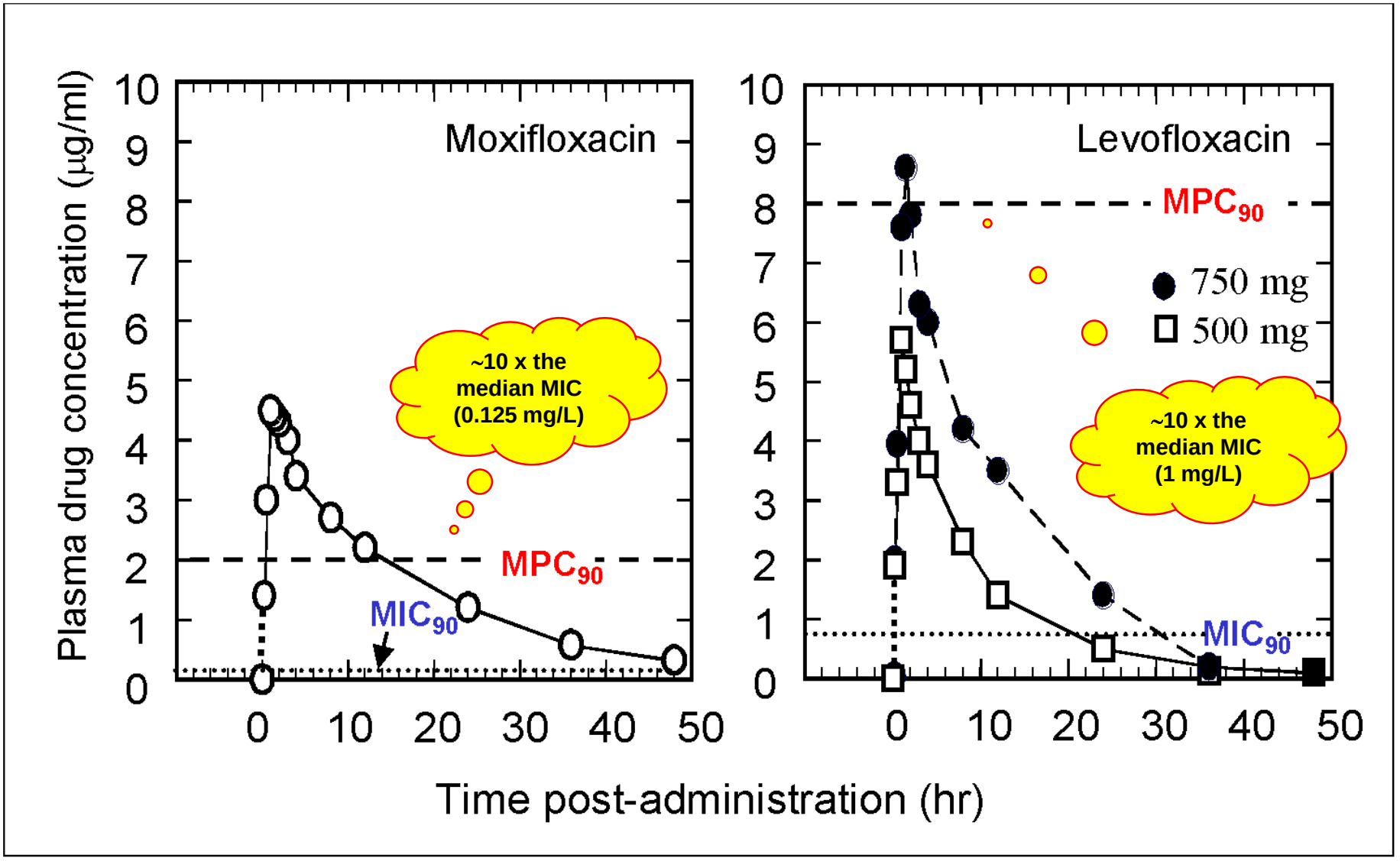
Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (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

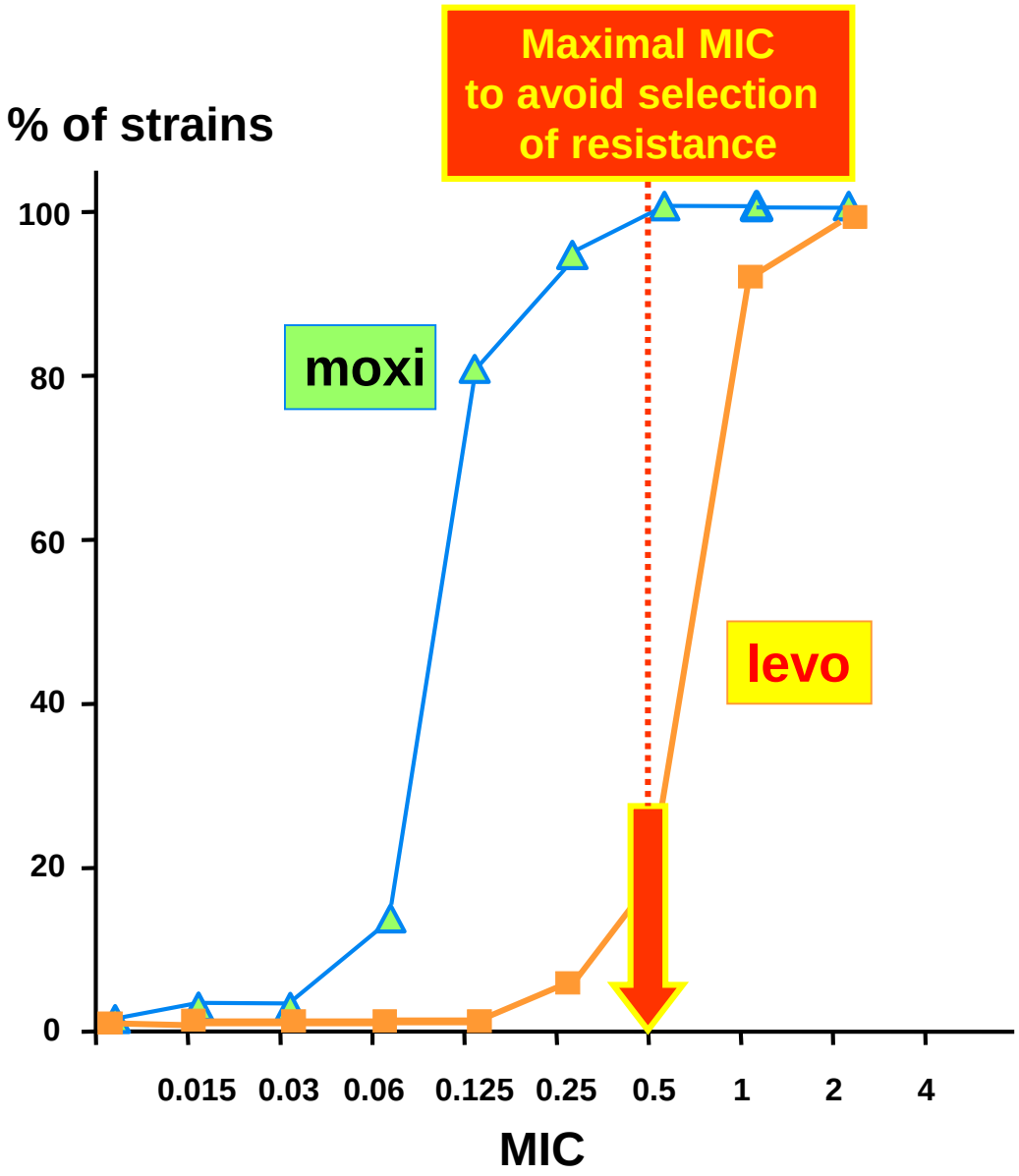
Fluoroquinolones downsides in a (scientific) nutshell and how to cope with them

- true risk of emergence of resistance
  - ➔ have local epidemiological surveys
  - ➔ have cultures and susceptibility data (MIC) for all isolates in difficult situations
  - ➔ dose appropriately ...
  - ➔ use potent (not weak) quinolones...
  - ➔ do not use if not needed...
- a few side effects
  - ➔ avoid populations at risk

MPC: moxifloxacin *vs* levofloxacin



Pharmacokinetics and "resistance" breakpoint *vs.* MIC



resistance breakpoint
- **AUC/MIC = 100**
- **peak/MIC = 10**

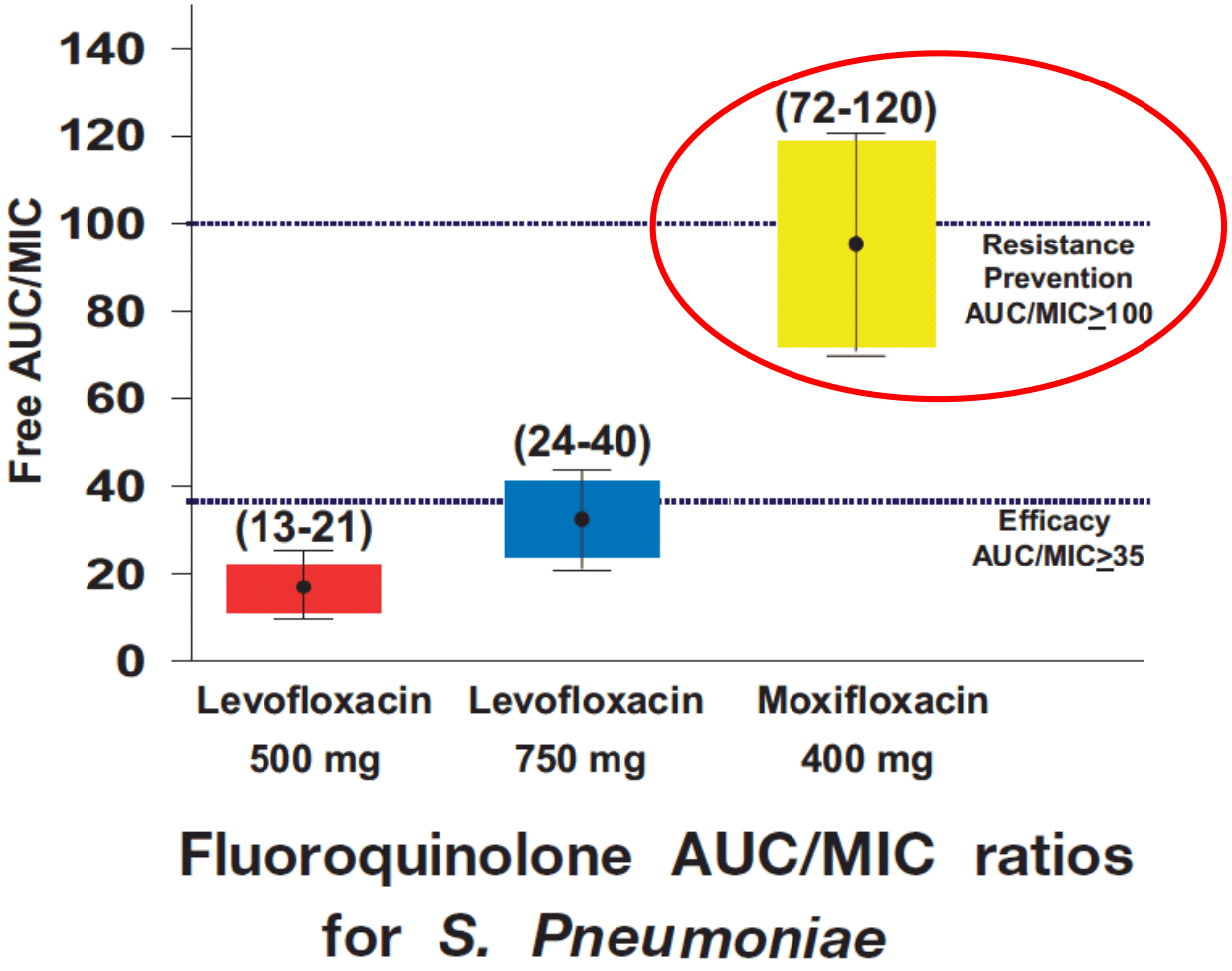
Levofloxacin 500 mg 1X / day
- **AUC [(mg/l)xh] 47**
- **peak [mg/l] 5**
- **➔ MIC_{max} ~ 0.5**

Moxifloxacin 400 mg 1X / day
- **AUC [(mg/l)xh] 48**
- **peak [mg/l] 4.5**
- **➔ MIC_{max} ~ 0.5**

MIC data: EUCAST MIC distributions (wild type)
PK data: US and EU labelling (typical values)

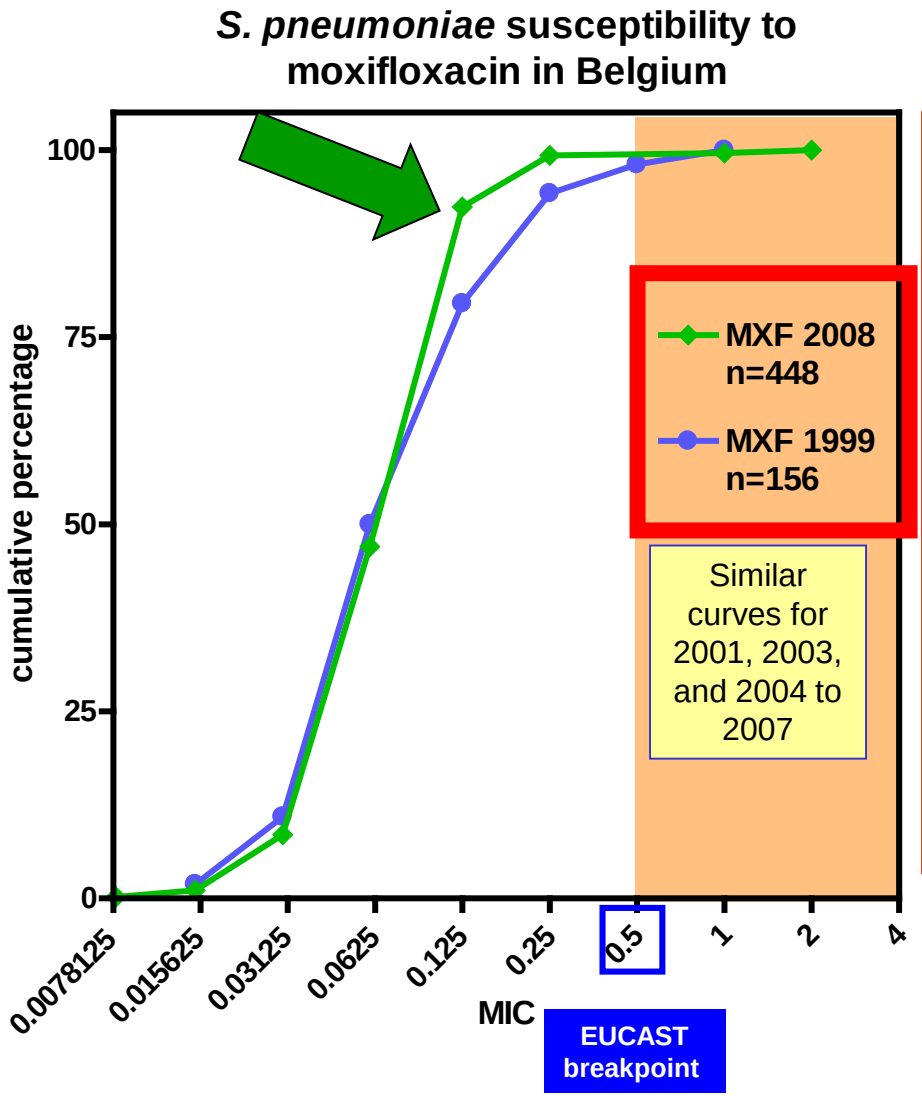
What differentiates fluoroquinolones ?

Results with *S. pneumoniae*



Would this cause less emergence of resistance ?

Moxifloxacin MIC's against *S. pneumoniae* in Belgium from 1999 to 2008 *

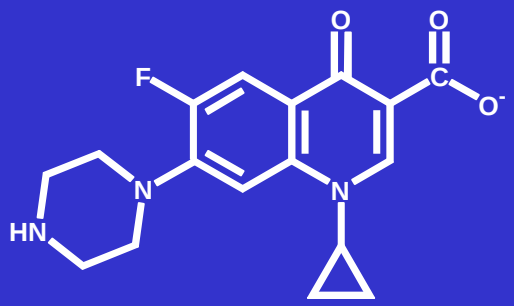


- Extract from the data of a national collection based on annual surveys made by the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates [https://www.wiv-isp.be/Programs/communicable-infectious-diseases/Pages/EN-BacterialDiseases.aspx?pflg=1033] and presented at the 19th ECCMID. May, 16-19 2009, Helsinki (Vanhoof *et al* abstract no. O467 [http://www.blackwellpublishing.com/eccmid19/abstract.asp?id=74082; last visited: 2 may 2014])
- See also
  - Vanhoof *et al* Acta Clin Belg. 2006;61:49-57
  - Vanhoof *et al* Pathol Biol (Paris) 2010;58:147-151)
- Confirmed in an independent study for the period 2004-2009 (Simoens *et al* Antimicrob Agents Chemother 2011;55:3051-3)
- Similar distribution for blood-stream isolates from patients with clinically confirmed diagnostic of CAP in 2007-2010 (Lismond *et al* Int J Antimicrob Agents. 2012;39(3):208-216)

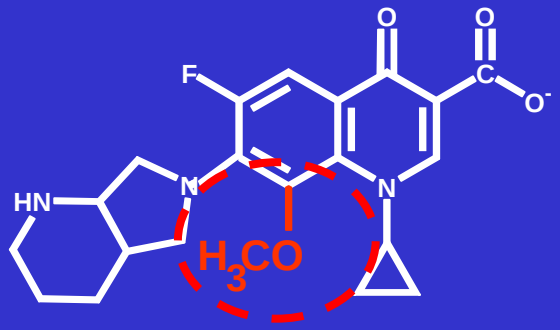
*** Moxifloxacin was introduced in 2001 and became the almost only fluoroquinolone used for RTI since 2004 in Belgium**

Is there a molecular basis for a lesser emergence of resistance with moxifloxacin ?

A C8-methoxy group lowers the MPC for an N-1-cyclopropyl-f luoroquinolone"



ciprofloxacin



moxifloxacin

FULL PRESCRIBING INFORMATION

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria.

https://www.merck.com/product/usa/pi_circulars/a/avelox/avelox_pi.pdf
Last accessed: 8/2/2015

PK/PD et résistance: application aux fluoroquinolones

Preventie van resistentie en doeltreffendheid:

- piek / MIC > 10
  (om de MPC te bereiken)
- AUC / MIC > 100
  (niet volledig immuuncompetente patiënt)

pieken en bruggen …

Nota: dit kan ook het geval zijn door te lage AUC_{24h} voor

- vancomycine (selectie van zogenaamd "hetero-VISA")
- tigecycline en macroliden (over-expressie of efflux pompen)

AUC_{24h} / MIC = 125 en Piek / MIC > 10 als limietwaarden voor de gevoeligheid aan FQ

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]
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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

Resistance: la dernière frontière ?

Application of a mathematical model to prevent in vivo amplification of antibiotic-resistant bacterial populations during therapy

Nelson Jumbe,[1,2] Arnold Louie,[1] Robert Leary,[3] Weiguo Liu,[2] Mark R. Deziel,[1] Vincent H. Tam,[1] Reetu Bachhawat,[2] Christopher Freeman,[2] James B. Kahn,[4] Karen Bush,[5] Michael N. Dudley,[6] Michael H. Miller,[2] and George L. Drusano[1]

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[3]San Diego Supercomputer Center, University of California, San Diego, San Diego, California, USA
[4]Ortho-McNeil Pharmaceutical, Raritan, New Jersey, USA
[5]Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey, USA
[6]Essential Therapeutics Inc., Mountain View, California, USA

Jumbe *et al.* J Clin Invest. 2003;112:275-85 - PMID: 12865415

Resistance… *The last frontier ?*

Application of a mathematical model to prevent
in vivo amp
bacterial po

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Karen Bush,[5] Mi

[1]Ordway Research Instit
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[4]Ortho-McNeil Pharma
[5]Johnson & Johnson Ph
[6]Essential Therapeutics

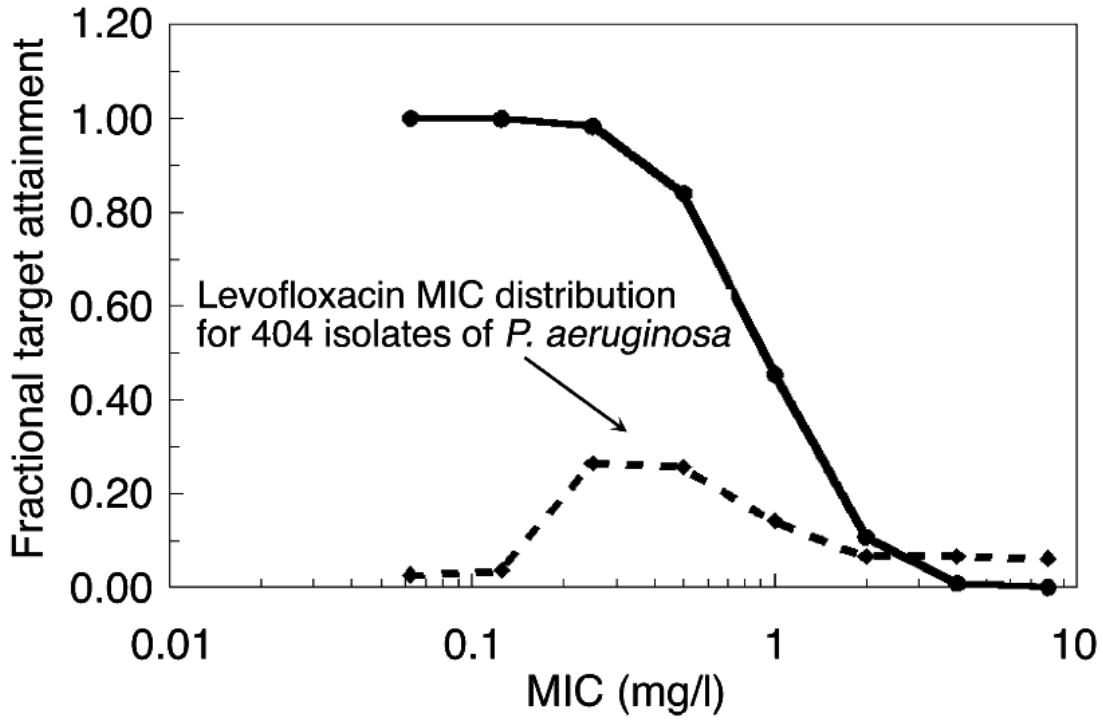

Figure 6

Target-attainment analysis. The fraction of 10,000 simulated subjects that attained an AUC/MIC ratio of 157:1 (target for suppression of resistance) is displayed as a function of the MIC for a distribution of 404 isolates of *P. aeruginosa*.

Jumbe *et al.* J Clin Invest. 2003;112:275-85 - PMID: 12865415

Resistance… *The last frontier ?*

Application of a mathematical model to prevent
in vivo amp
bacterial po

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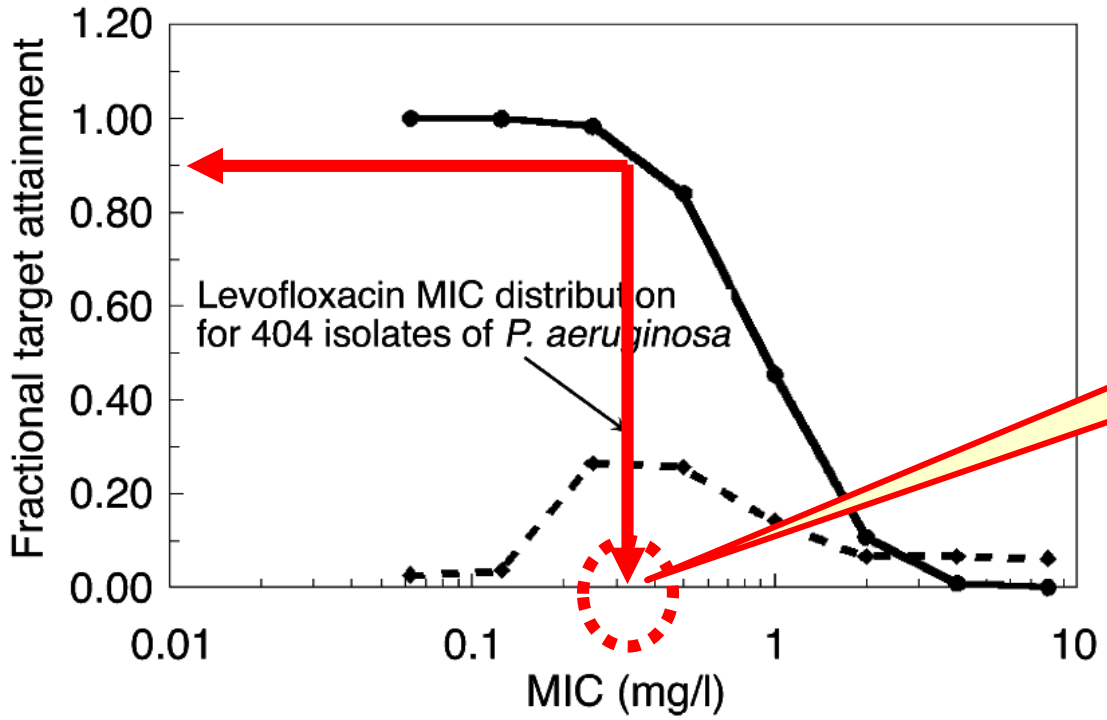

Figure 6

Target-attainment analysis. The fraction of 10,000 simulated subjects that attained an AUC/MIC ratio of 157:1 (target for suppression of resistance) is displayed as a function of the MIC for a distribution of 404 isolates of *P. aeruginosa*.

breakpoint: 0.3 mg/L

Jumbe *et al.* J Clin Invest. 2003;112:275-85 - PMID: 12865415

Resistace… *The last frontier ?*

EUCAST Clinical Breakpoint Tables v. 7.1, valid from 2017-03-10

Pseudomonas spp.

Fluoroquinolones	MIC breakpoint (mg/L)	
	S ≤	R >
Ciprofloxacin[1]	0.5	0.5
Levofloxacin[2]	1	1

Table 2B-1
Pseudomonas aeruginosa
M02 and M07

Table 2B-1. (Continued)

Antimicrobial Agent	MIC Interpretive Criteria (µg/mL)		
	S	I	R
FLUOROQUINOLONES			
Ciprofloxacin	≤ 1	2	≥ 4
Levofloxacin	≤ 2	4	≥ 8

Le problème est qu'un breakpoint "résistance" de 0.3 mg/L pour la lévofloxacine est **BEAUCOUP PLUS BAS** que les breakpoints de l'EUCAST ou même du CLSI (qui concernent l'efficacité)