Antibiotics in 2005:
Which one do we need to use and when ?

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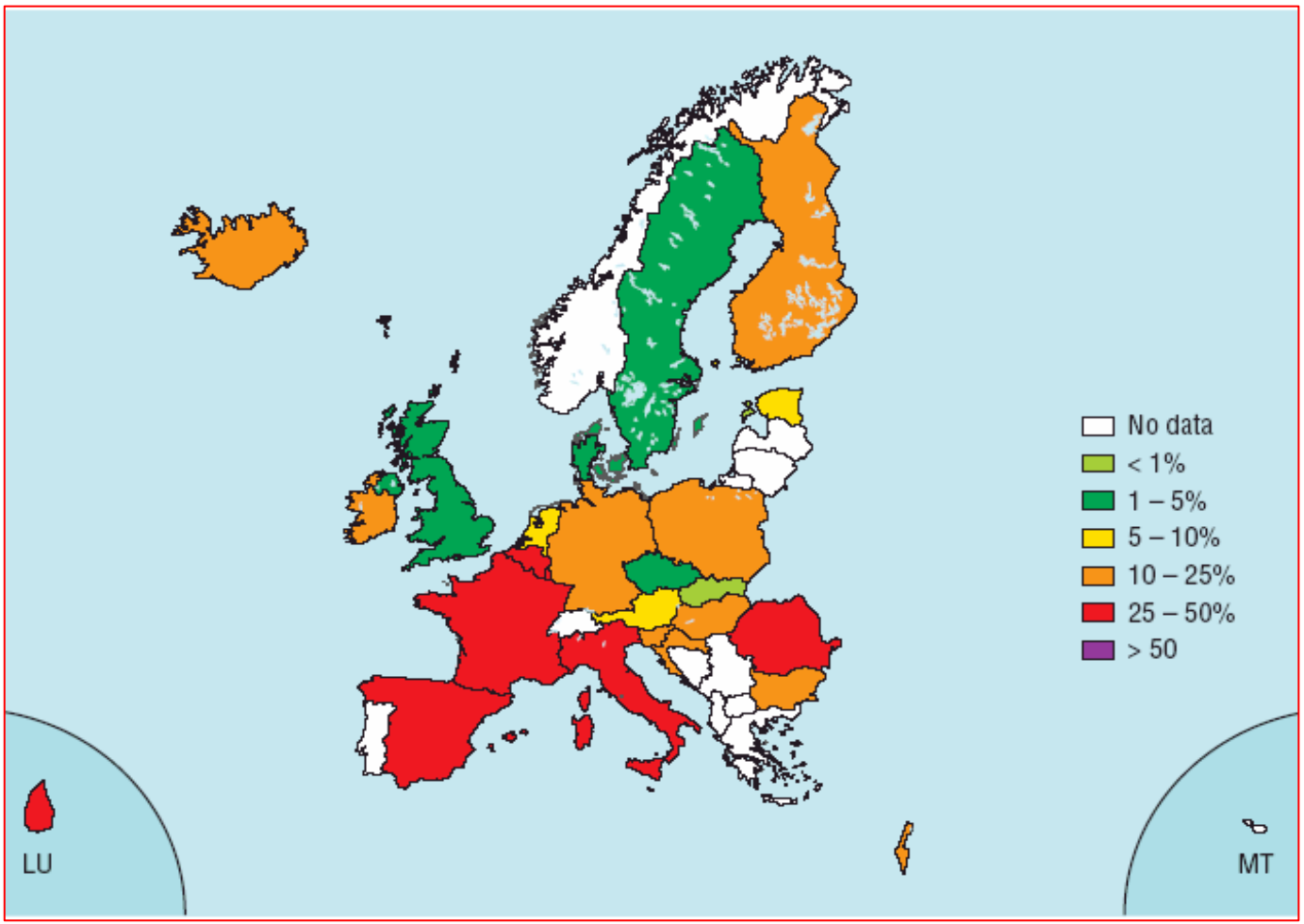
- rising resistance in key respiratory pathogens !
- use antibiotics sparingly and rationally !
- important differences between antibiotics (PK/PD, rate of kill, Mutant Prevention Concentration) beyond simple MICs vs key pathogens …
- best agent first to minimize resistance and better outcomes
- can we also reduce health care costs ?

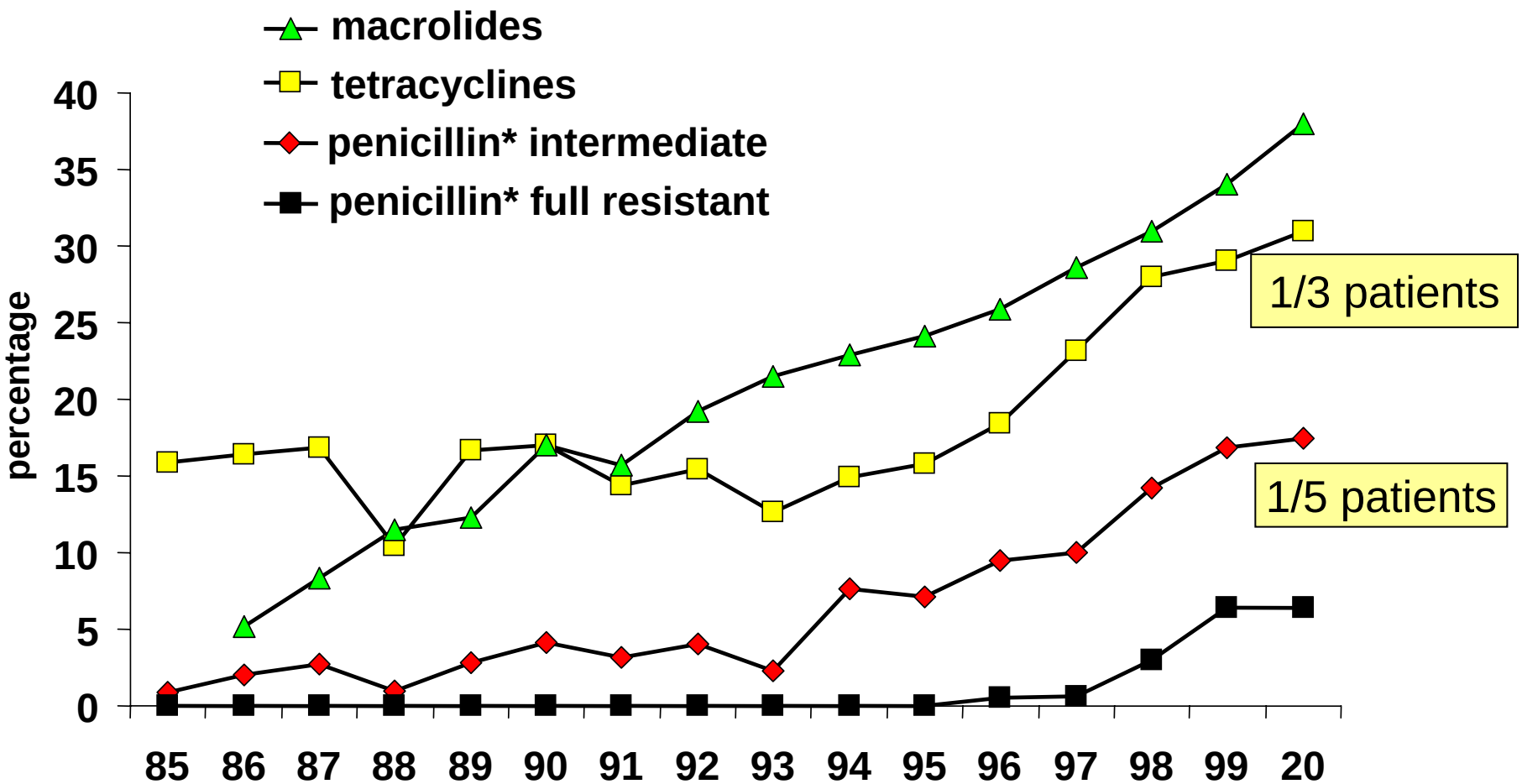
Resistance in Europe …

Resistance of *S. pneumoniae* (invasive isolates) to erythromycin* in 2003



* = all macrolides (clarithromycin, roxithromycin…), and azalides (azithromycin), but not ketolides (telithromycin)

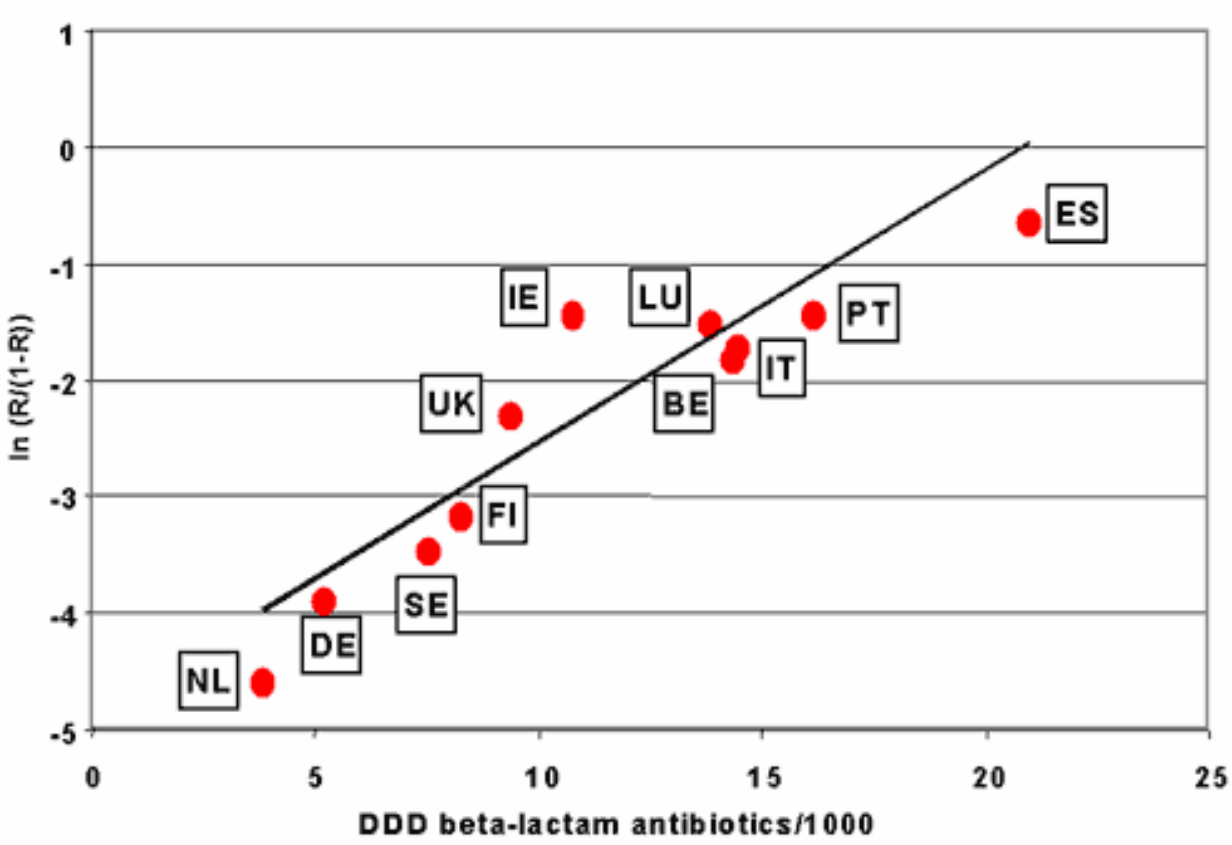
Trends of Resistance (Belgian data) …



* all β-lactams (= penicillins, cephalosporins, …)

Belgian Reference Laboratory for pneumococci, Leuven, 2000

Is there a relationship between (widespread) use and resistance ?



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

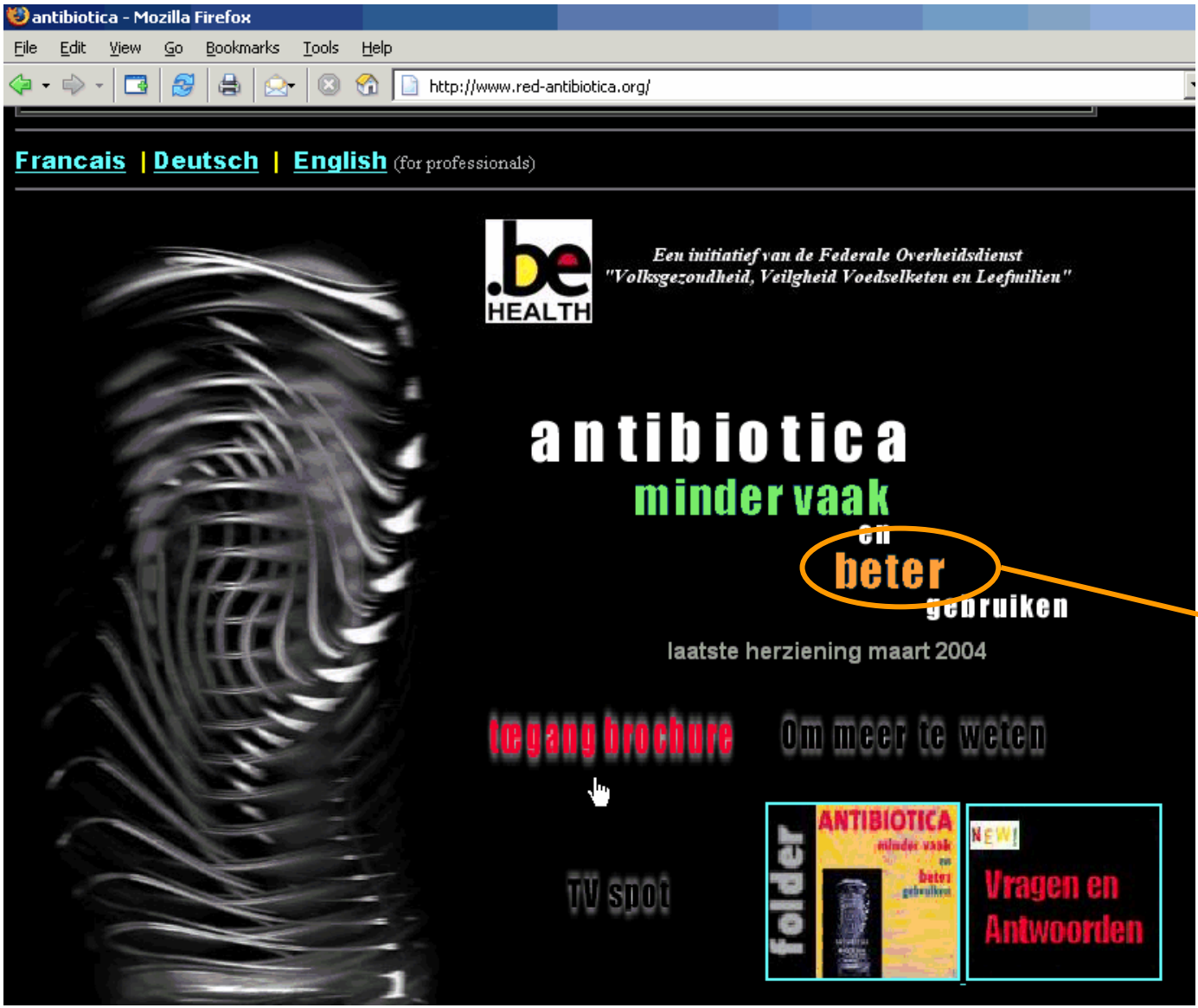
- **resistance data are from 1998 to 1999; antibiotic sales data 1997.**
- **DDD = defined daily doses**

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

Use antibiotics with caution … Belgian antibiotic campaigns

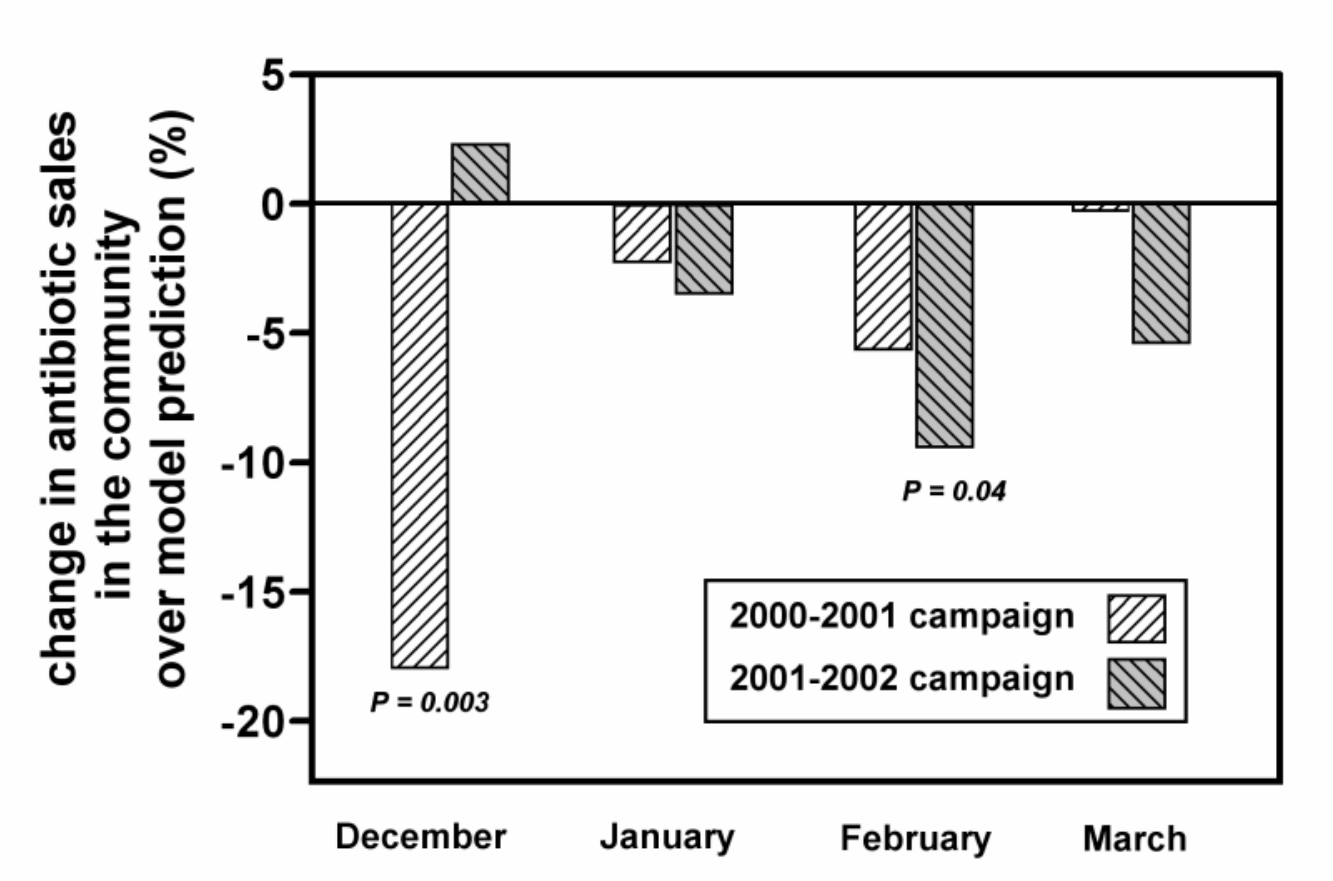
less…

Use antibiotics with caution … Belgian antibiotic campaigns



and better …

Success of public campaigns …

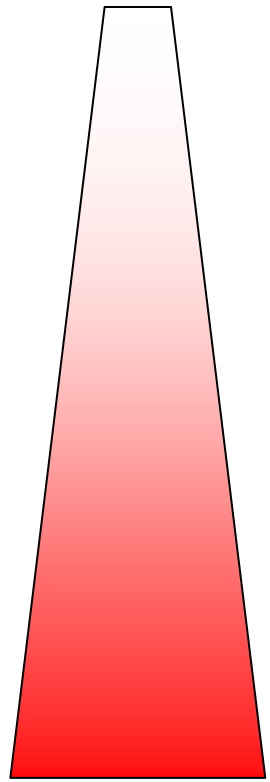


- significant reduction of AB prescriptions (sales = prescriptions in Belgium) during the influenza epidemic periods
- no significant-side effect detected
- cost-effective for public health

from Bauraind *et al.*, JAMA 2004; 292:2468-70;
more details on http://www.antibiotiques.org/english/

What is "better" ?

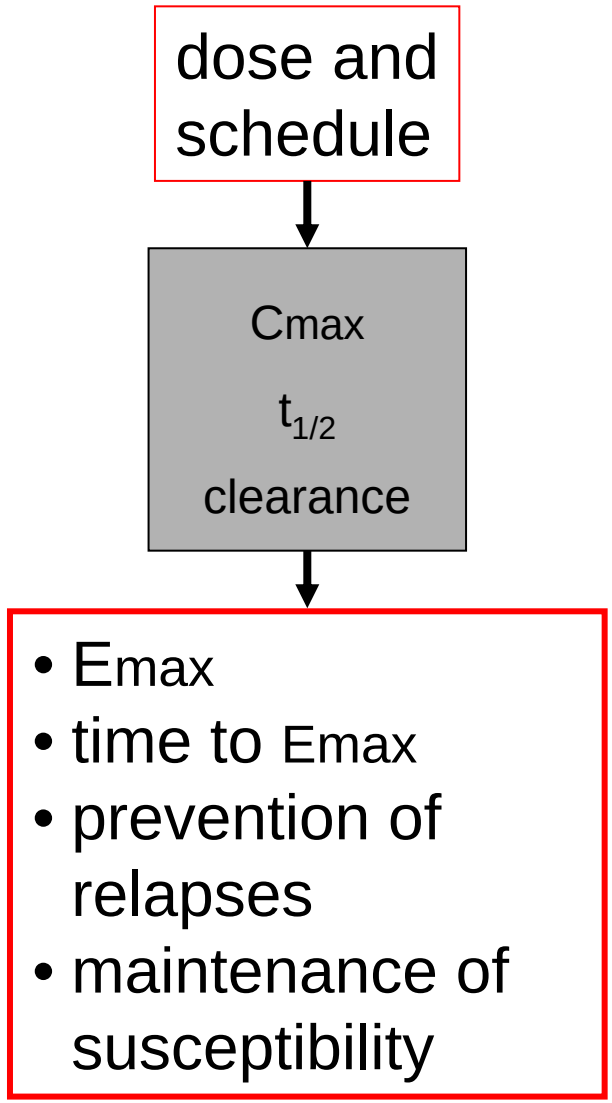
- to be globally efficacious
  - ➔ **pharmacodynamics (PK/PD)**
- to act fast
  - ➔ **rate of killing**
- to avoid selection of resistance
  - ➔ **"mutant prevention concentration"**



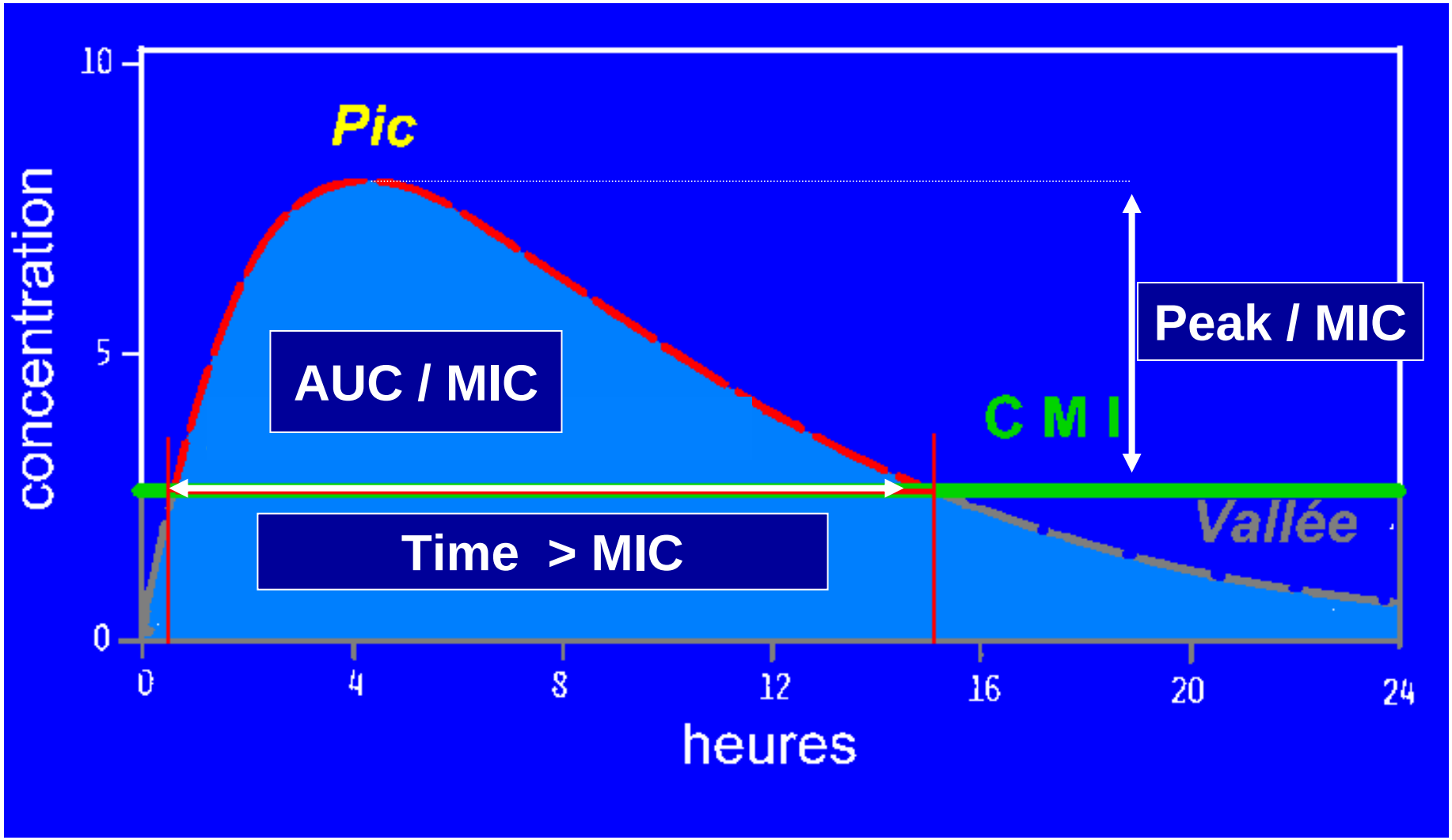
What is Pharmacokinetics / Pharmacodynamics (PK/PD) ?

- Pharmacokinetics:
  what the body does to the drug
  - ➔ absorption, distribution, serum and tissue levels elimination, …

- Pharmacodynamics (of AB):
  what the drug does to the bacteria
  - ➔ static vs. bactericidal effect, rate of kill, eradication, prevention of resistance….



From Pharmacokinetics to Pharmacodynamics of AB …



The 3 main groups of antibiotics

after W.A. Craig, 2000; revised 2003)

AB	PK/PD parameter	Action
β-lactams	time above MIC	stay above the MIC as needed
macrolides, tetracyclines…	AUC/MIC	give a sufficient daily dose …
quinolones	peak/MIC and AUC/MIC	obtain a sufficient peak and give a sufficient total daily dose

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000;
revised accord. to Craig, Infect. Dis. Clin. N. Amer., 17:479-502, 2003

To be effective …

You choose a β-lactam …

- give it several times a day (3 to 4 times), or use an "*extended release*" form;
- adjust the dose to meet the decrease in susceptibility of *S. pneumoniae* (from 0.5 to 2 or even 4 g/daily);
- add clavulanic acid (or use a 2d generation cephalosporin like cefuroxime) in case you suspect a **β-lactamase producing** organism *;
- do not anticipate activity against organisms causing "atypical pneumonia" and related syndromes **.

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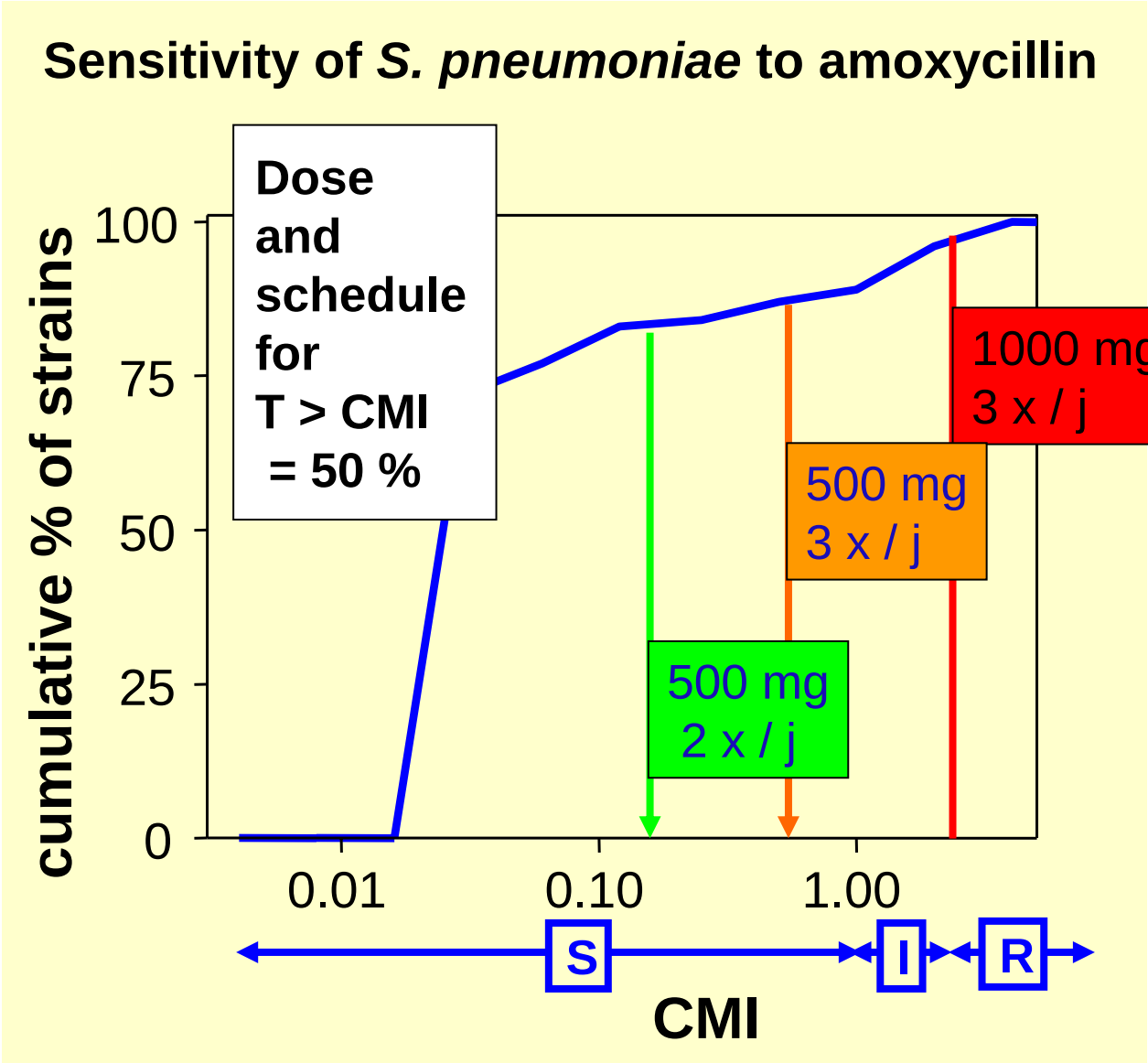
* *Haemophilus influenzae*, *Moraxella catarrhalis*, …

** *Legionella pneumophila*, *Chlamydia pneumoniae*, *Mycoplasma spp*.

Dosing amoxycilline for respiratory tract infections in Belgium



MIC data: J. Verhaegen et al., 2001

To be effective …

You decide to try a fluoroquinolone …

- no problems with penicillin-insensitive *S. pneumoniae* or with pathogens causing "atypical pneumonia" *,**

BUT you need …

- to get a peak large enough (10 x the MIC);
- to look for an AUC/MIC of at least 100
- to remain above the Mutant Prevention Concentration (MPC)
- try to stay away from efflux pumps…

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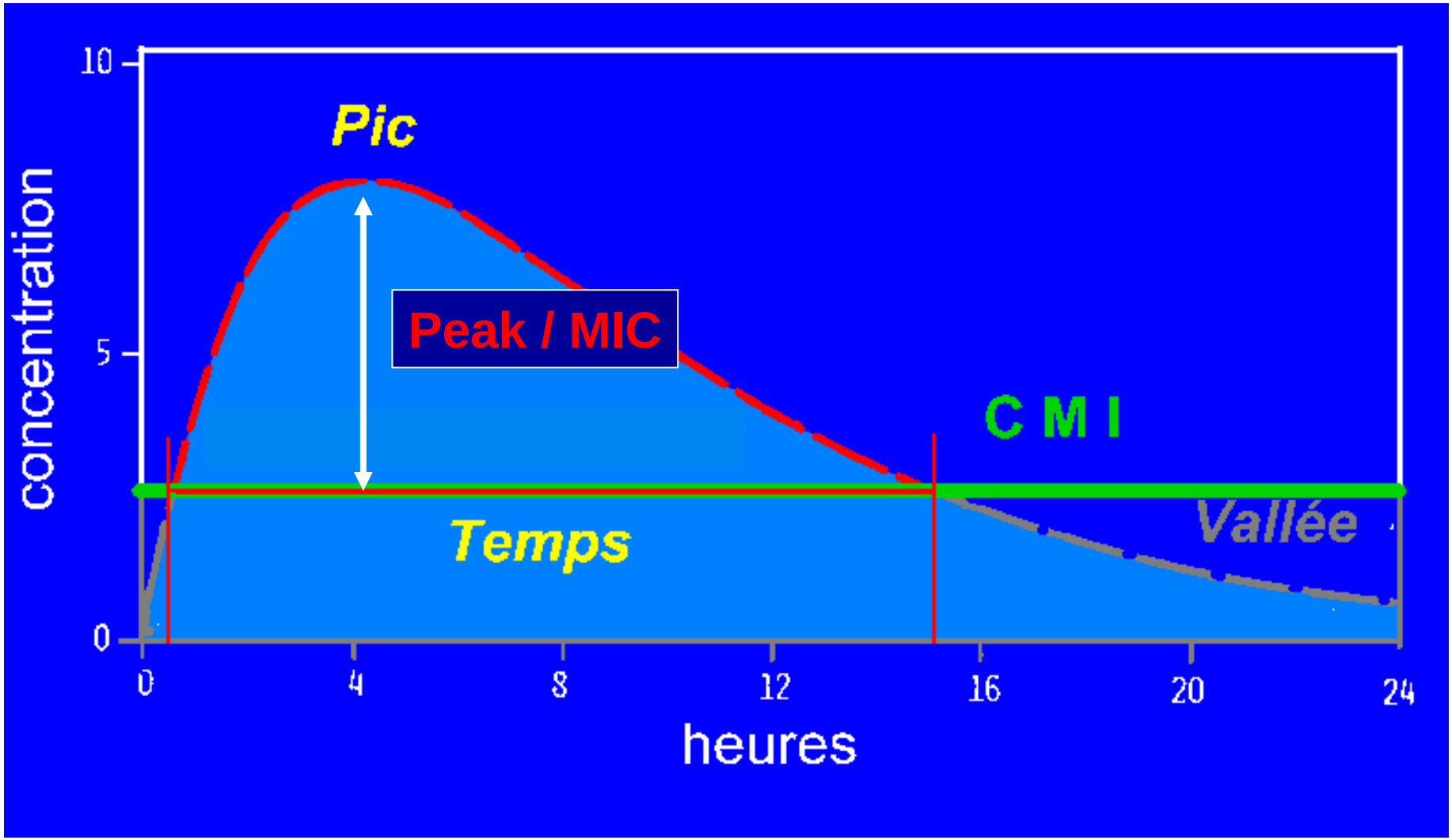
* *Haemophilus influenzae*, *Moraxella catarrhalis*, …

** *Legionella pneumophila*, *Chlamydia pneumoniae*, *Mycoplasma spp*.

What do you mean by "PEAK /MIC > 10" and "AUC / MIC > 100"



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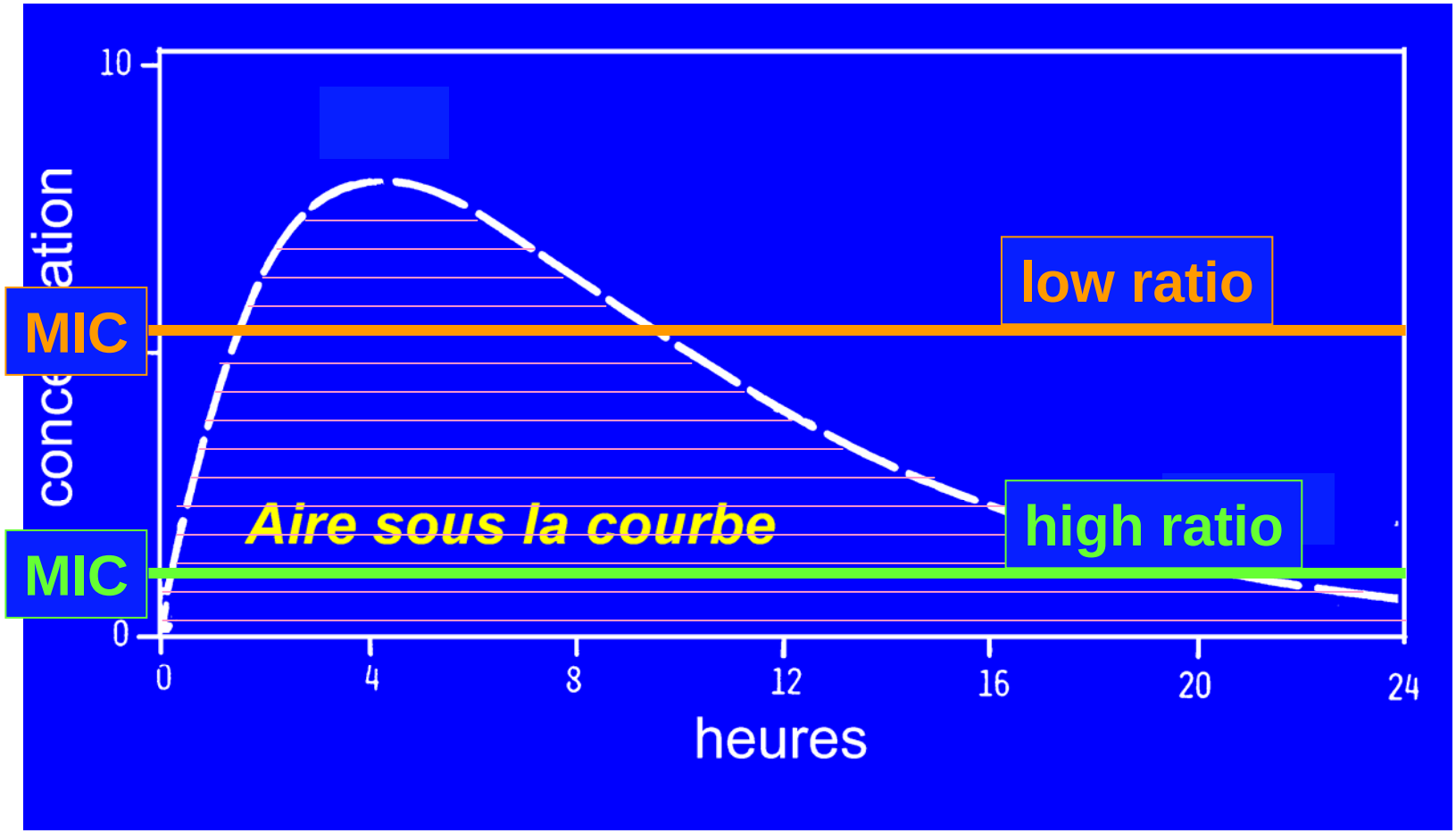
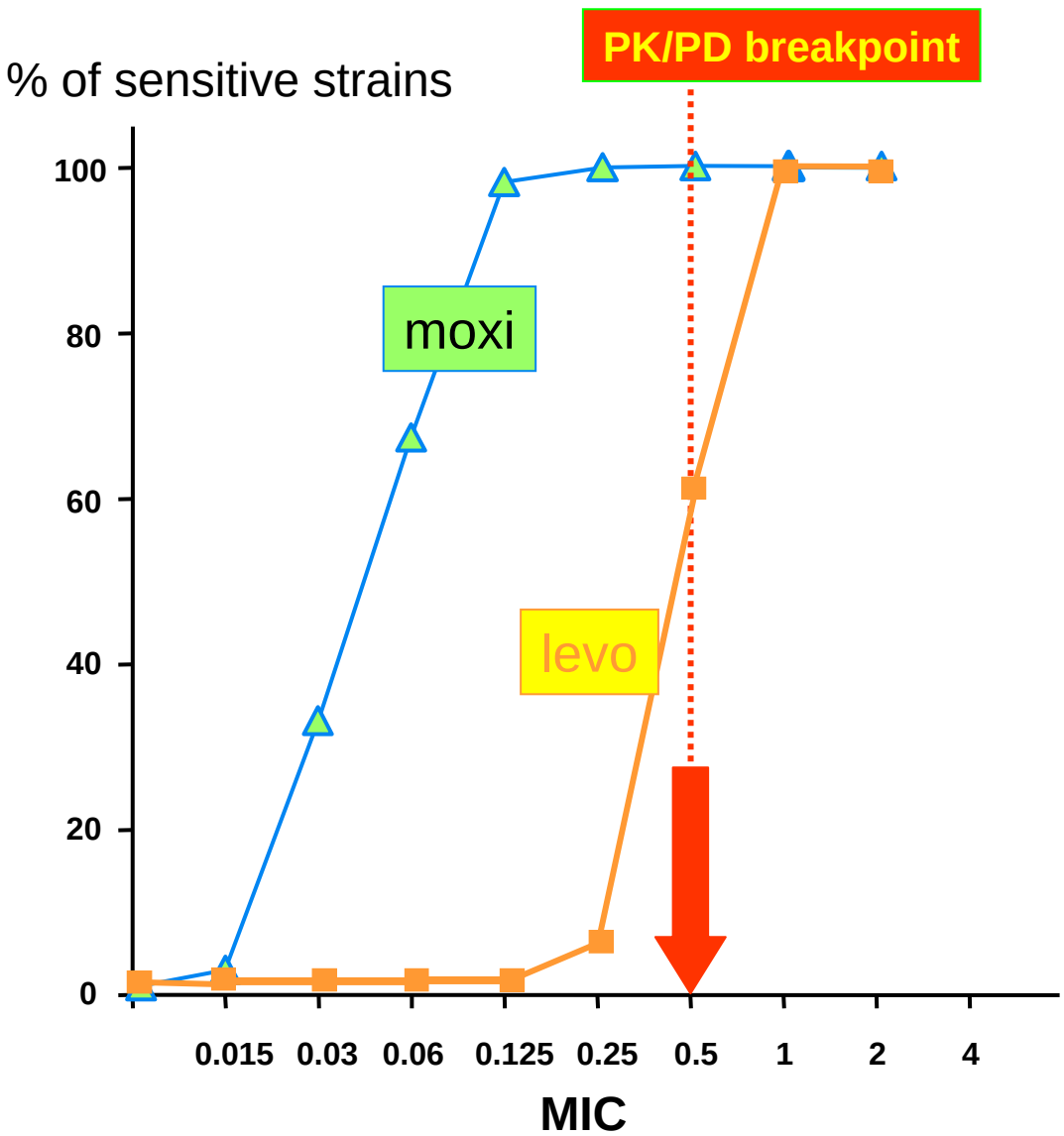


AUC_{24h} = dose / clearance

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

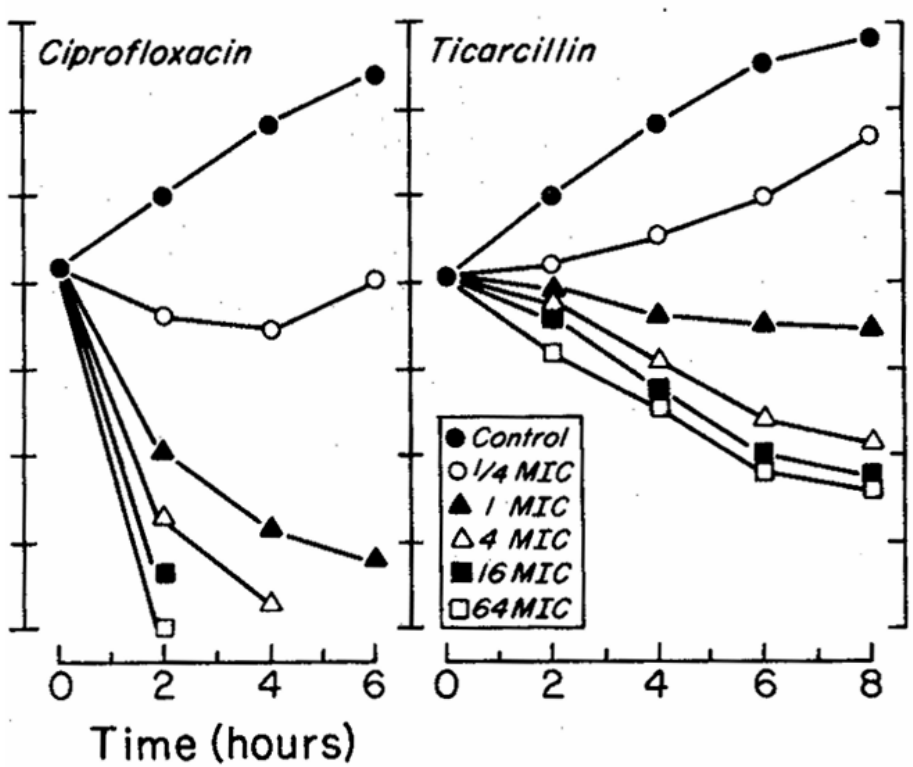
MIC data: J. Verhaegen et al., 2003

The rate of kill may also be important…

A simple experiment …

- put bacteria in broth
- add antibiotic at increasing concentrations
- look at the reduction of the inoculum

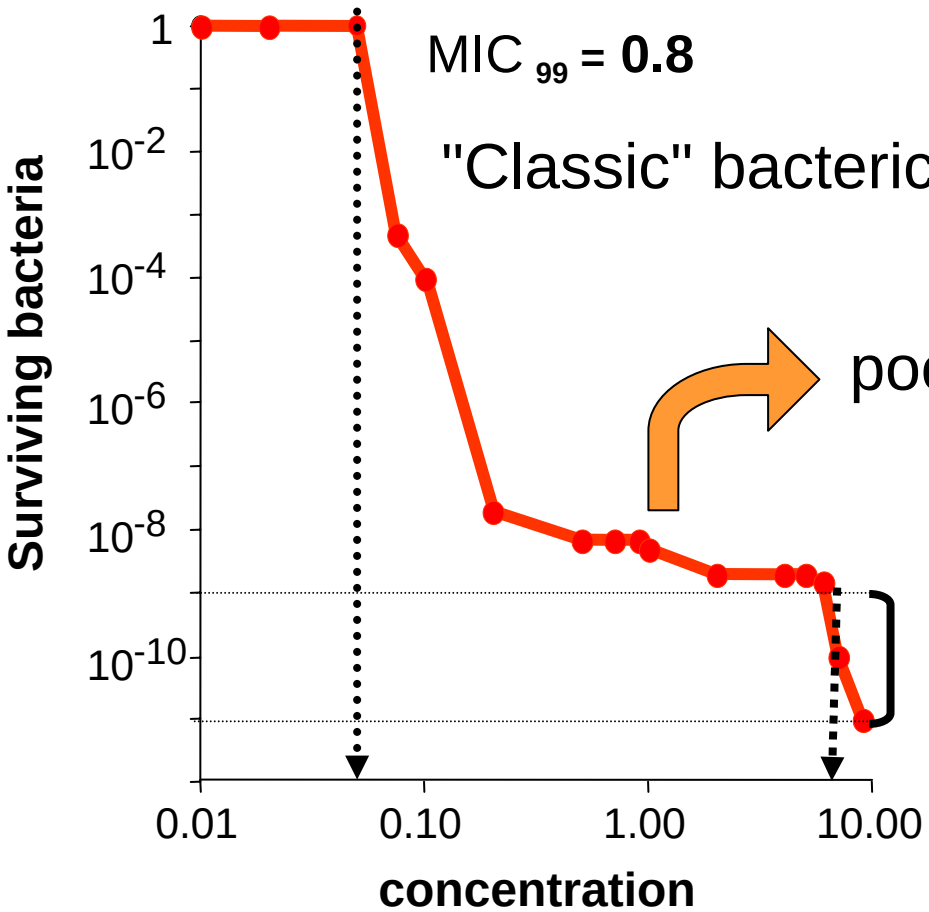
quinolones … β-lactams …



Fast … Slow …

Craig et al., 1998

Mutant Prevention Concentration …



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

"Classic" bactericidal effect

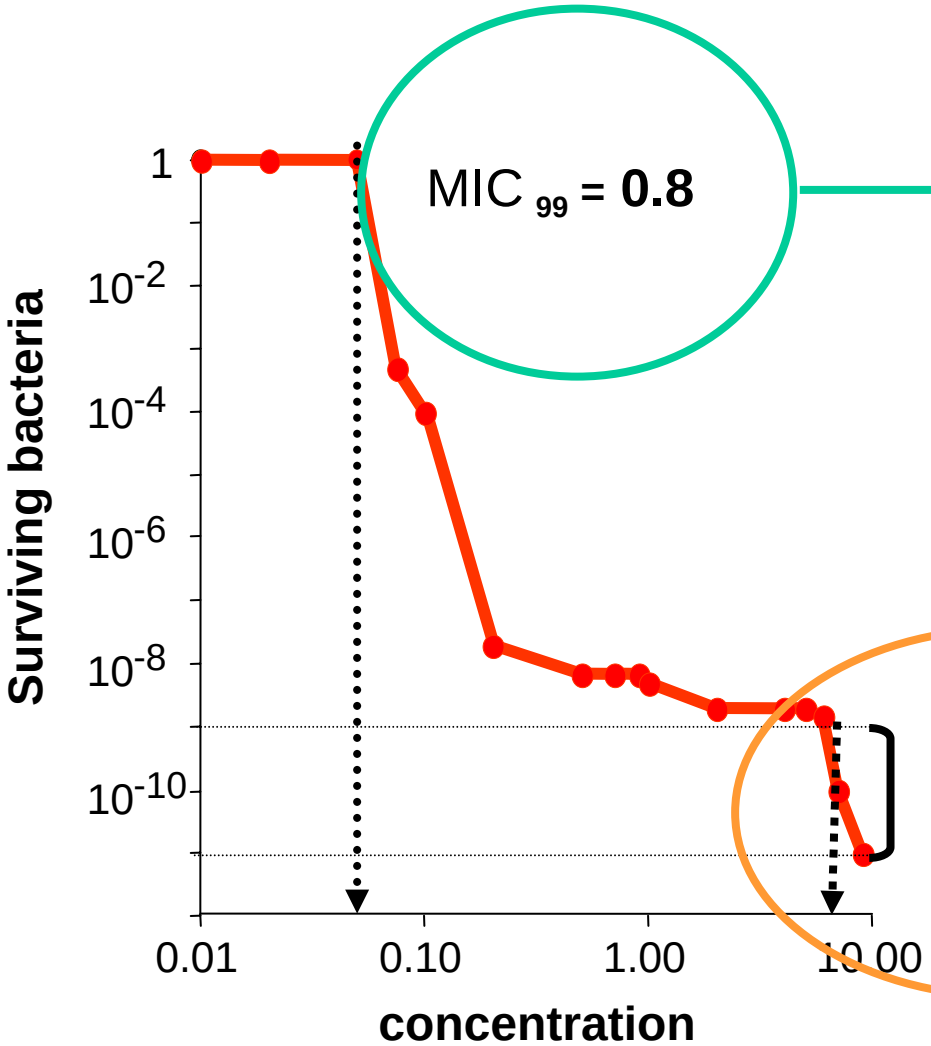
poorly sensitive organisms…

Elimination of resistant organisms

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

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

Mutant Prevention Concentration …

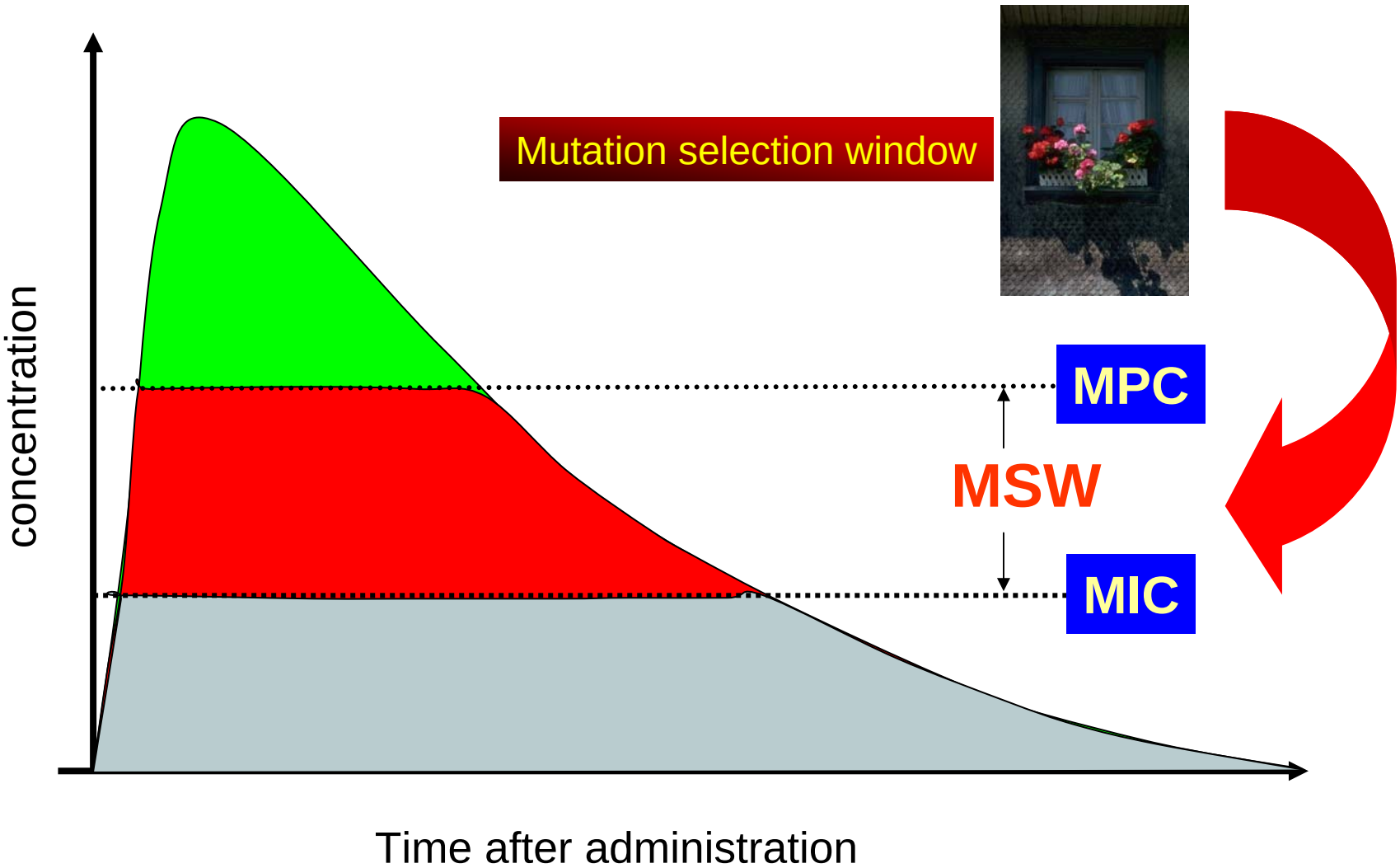


Concentration which will inhibit the majority of the organisms

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

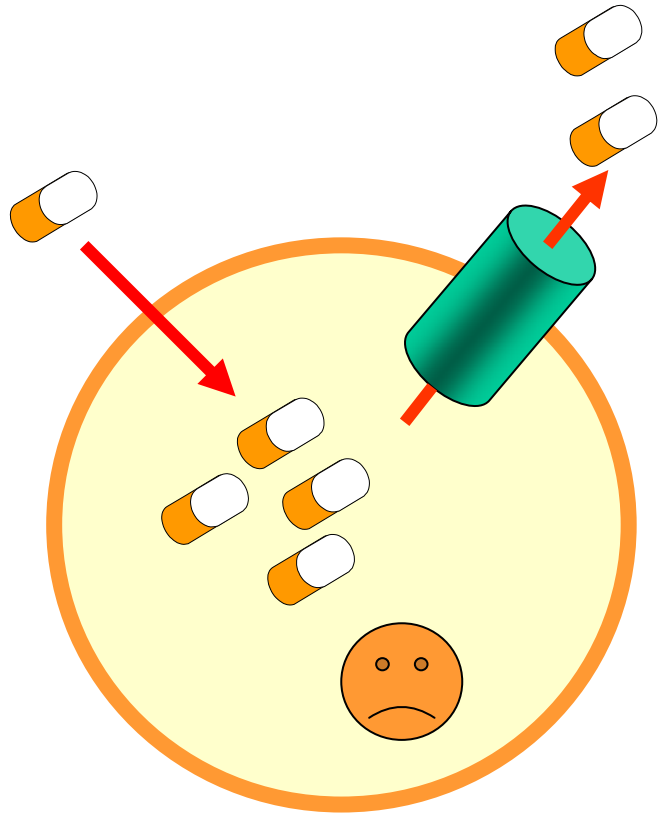
Which are the MPC values compared to
- MIC for *S. pneumoniae*
- C_{max} for a standard dose ?

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

Efflux ?

- universal mechanism for cell protection against membrane-diffusing agents
- many drugs diffuse though membranes and become opprtunistic substrates of efflux pumps
- for AB, efflux decreases the amount of drug in bacteria and impairs activity, favouring selection of less sensitive organisms
- but recognition by efflux varies widely among closely related drugs e.g. levofloxacin >> moxifloxacin



- Van Bambeke et al. J Antimicrob Chemother. 2003;51:1055-65.
- Mesaros et al. Tijdschrift voor Geneeskunde (2005) 61:1407-1417
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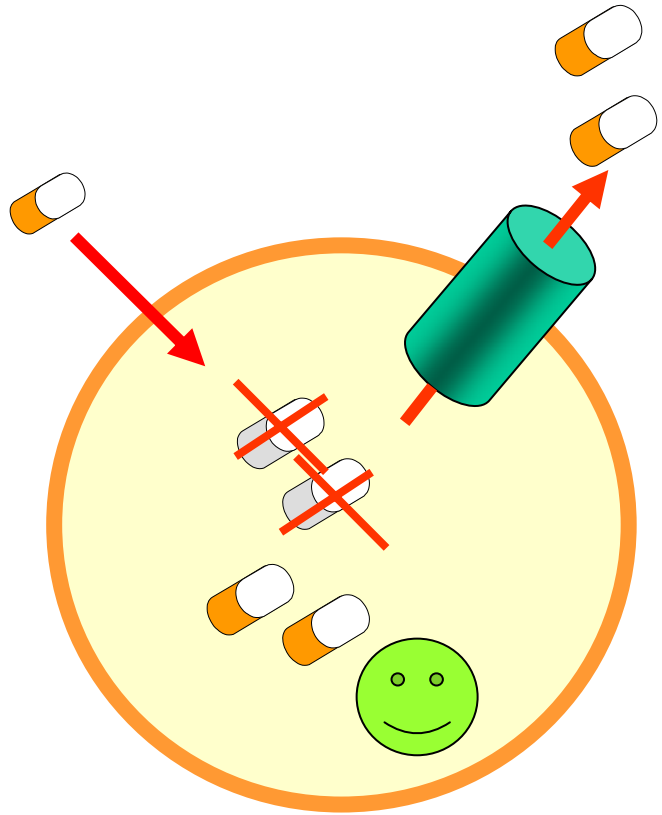

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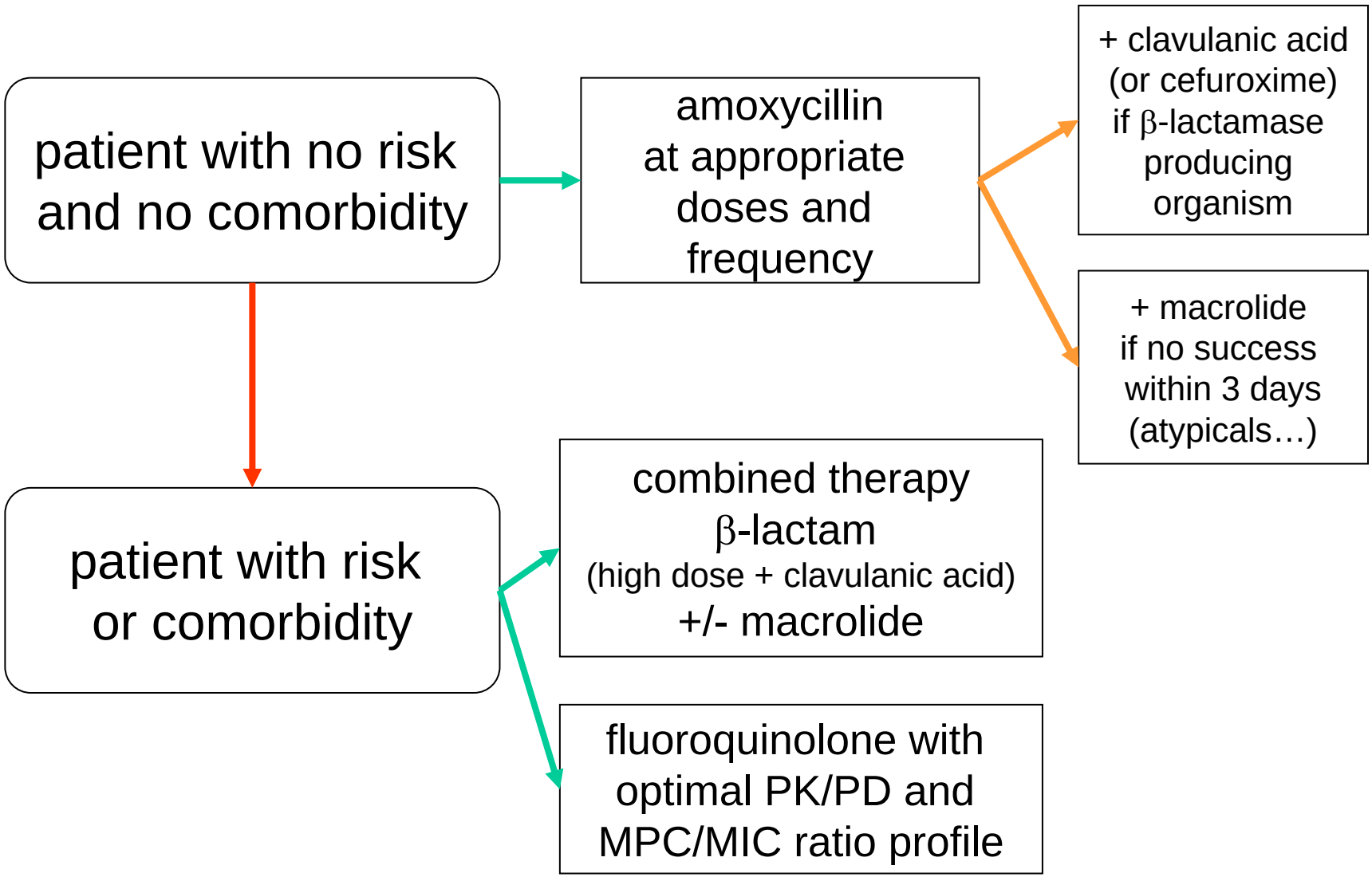
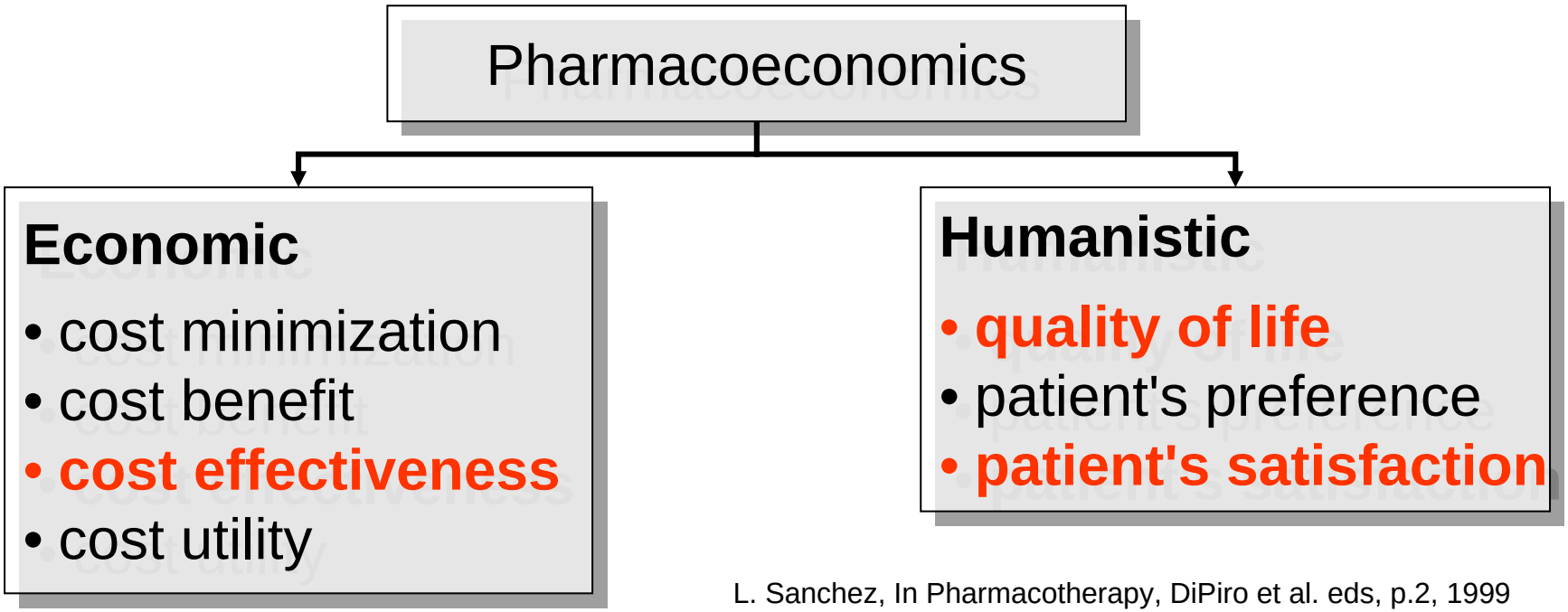
A rational and (correctly) conservative approach for respiratory tract infections… *



* adapted from Belgian IDAB CAP guidelines – limited to CAP 1, 2, and 3

And what about health care costs ?



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

- Pharmacoeconomics of antibiotics in Europe is still largely underdeveloped (and 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

To conclude …

Quinolones in 2005: an update

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ABSTRACT

Quinolones are one of the largest classes of antimicrobial agents used worldwide. This review considers the quinolones that are available currently and used widely in Europe (norfoxacin, ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin) within their historical perspective, while trying to position them in the context of recent and possible future advances based on an understanding of: (1) their chemical structures and how these impact on activity and toxicity; (2) resistance mechanisms (mutations in target genes, efflux pumps); (3) their pharmacodynamic properties (AUC/MIC and C_{max}/MIC ratios; mutant prevention concentration and mutant selection window); and (4) epidemiological considerations (risk of emergence of resistance, clonal spread). Their main indications are examined in relation to their advantages and drawbacks. Overall, it is concluded that these important agents should be used in an educated fashion, based on a careful balance between their ease of use and efficacy vs. the risk of emerging resistance and toxicity. However, there is now substantial evidence to support use of the most potent drug at the appropriate dose whenever this is required.

Keywords Ciprofloxacin, pharmacodynamics, quinolones, resistance, review, toxicity

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