Antibiotic combinations *vs*. monotherapy in critical care

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Why do we wish to associate antibiotics ?

- enlarge the spectrum
  - empiric therapy in situations where the offending organism is unknown or largely uncertain
    - nosocomial infections in Intensive Care units in absence of pre-emptive sampling;
    - patient with infection from difficult to trace origin
  - suspicion of polymicrobial infection
  - patient with previous antibiotic therapy and suspected of infection with multi-mechanisms of resistance

accepted by everyone, but should be associated with step-down approaches, which is not alsways done …

- improve antibacterial efficacy
  - additive/synergistic effects
  - combination of complementary pharmacodynamic properties
  - addition of pharmacodynamic effects

open to much controversies related to *in vitro* ➔*in vivo* translation …

- reduce the rate and/or odds of emergence of resistance

something probably to think more and more about …

Enlarging the spectrum …

- CAP type 2 with co-morbidities
  - *S. pneumonia* + *H. influenzae* + an *"atypical"* organism
    - amoxicilin + clavulanic acid + macrolide …
    - but what about monotherapy with moxifloxacin / levofloxacin ?
- CAP type 3 or 4
  - *S. pneumonia* + *H. influenzae* + a Gram (-) organism
    - ceftriaxone + ciprofloxacin
    - but what about meropenem / imipenem …
- Nosocomial pneumonia (first 3 days of therapy)
  - *S. aureus* – many Gram (-) negative organisms – *P. aeruginosa* …
    - ceftazidime + amikacin
    - but perhaps meropenem/ imipenem …
    - add vancomycin in case of suspicion of MRSA ….
- Polytraumatized patient (empiric therapy)
  - skin flora + gut flora (including anaerobes…)
    - vancomycin, ceftazidime, metronidazole, aminoglycoside …

Improving antibiotic efficacy …

- synergy, antagonism and indifference

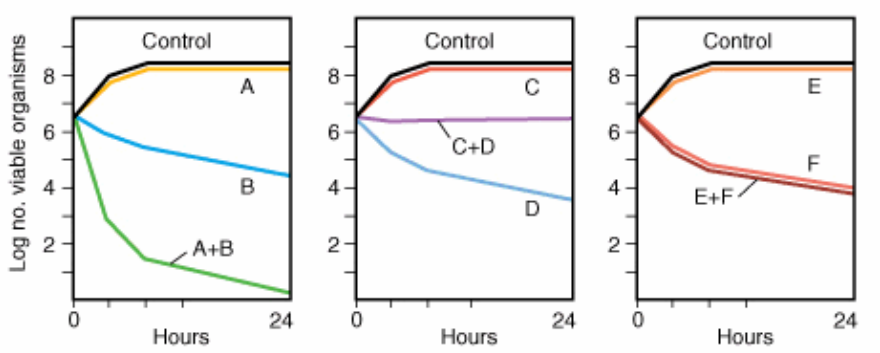
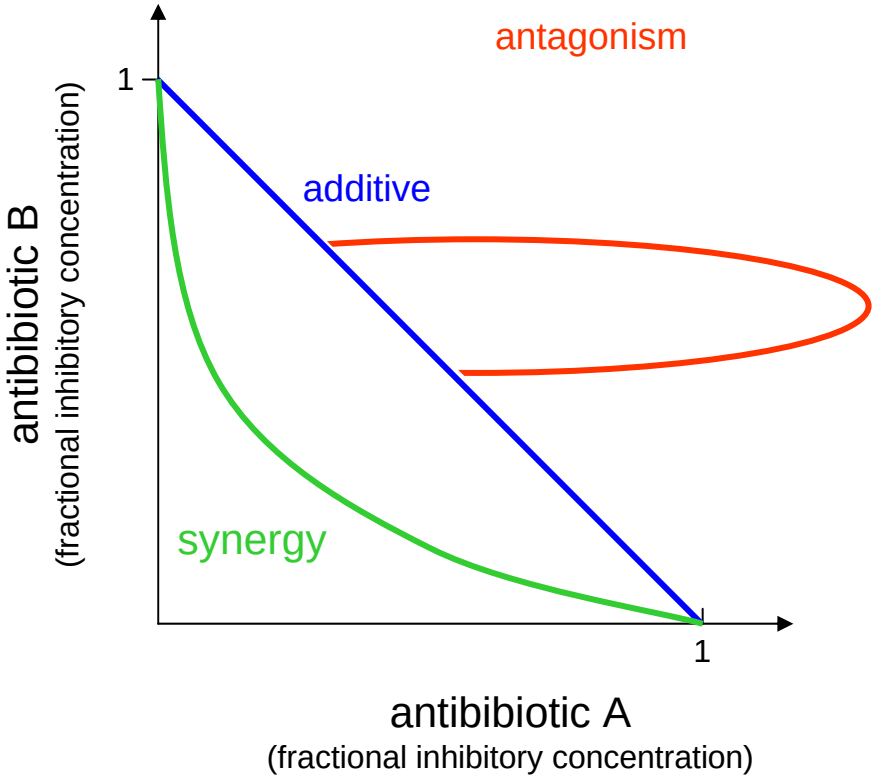


Figure 16-1 **Antibacterial effects of antibiotic combinations.** *Left:* Curve of A+B illustrates synergism (increased killing). *Center:* Curve of C+D illustrates antagonism (D is less effective when C is added). *Right:* Curve of E+F illustrates indifference, or additive effect (addition of E to F has no effect on F). *(From Moellering RC Jr. Use and abuse of antibiotic combinations. R I Med J. 1972;55:341.)*



FIC index = MIC (A+B) / MIC (A) + MIC (B+A) / MIC (B)

Is synergy important ?…

- probably critical for co-trimoxazole and synergistins (SYNERCID®)…

- for other antibiotics, clear in vitro evidence only for β-lactams plus aminoglycosides in poorly susceptible bacteria (true biochemical synergy) …

  ➔ potential applications in

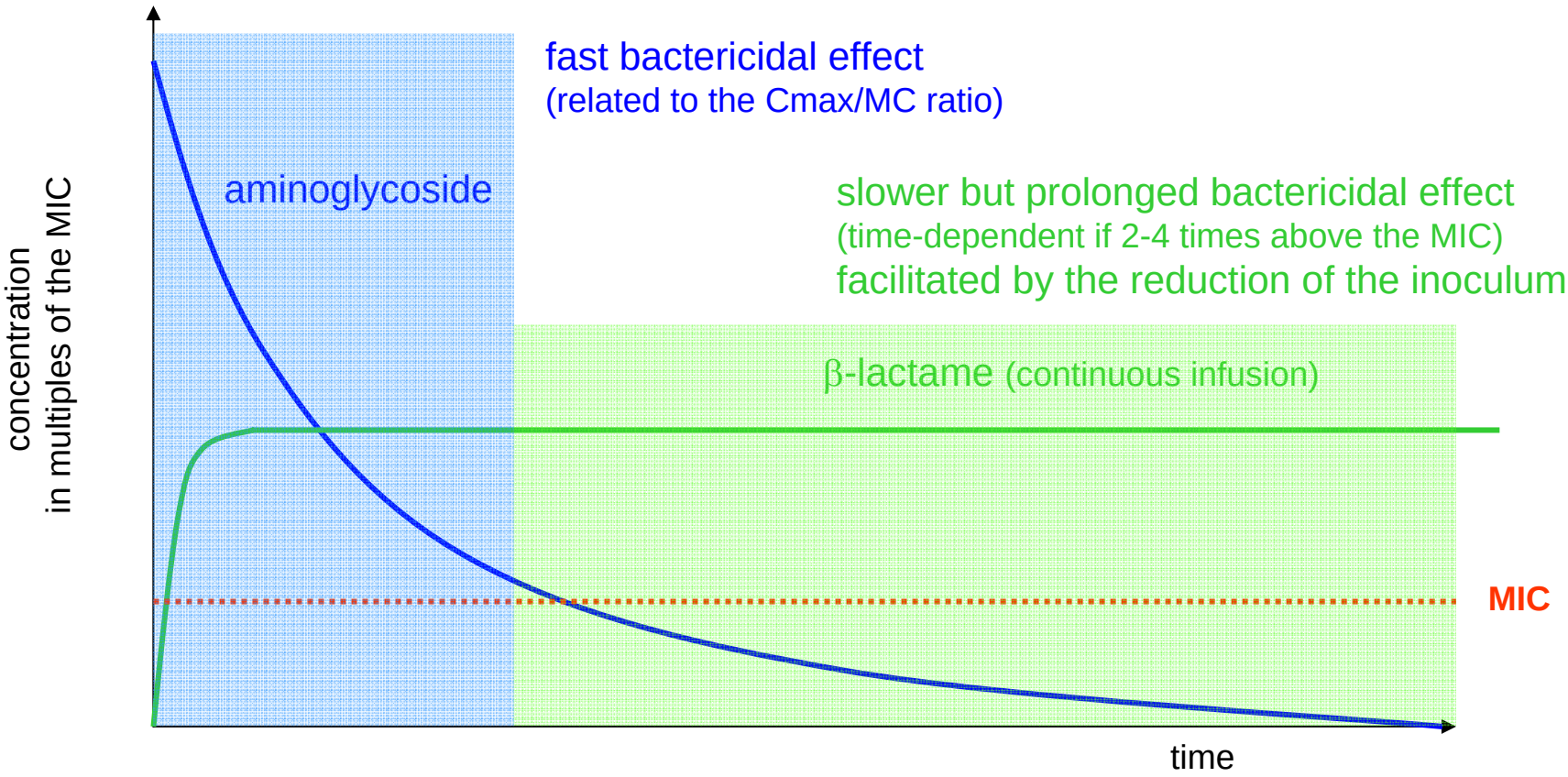
  - endocarditis (enterococci…; supported by clinical studies)
  - pseudomonal infections (only partially supported by clincical studies…
  - impaired host (neutropenia)

  most other antibiotics show indifference or antagonism… and the clinical significance of these is unclear and even doubtful (except for physical or chemical incompatibilities…)

Combination of useful pharmacodynamic properties

- time-dependent and concentration-dependent antibiotics

  ➔ β-lactams plus aminoglycosides …

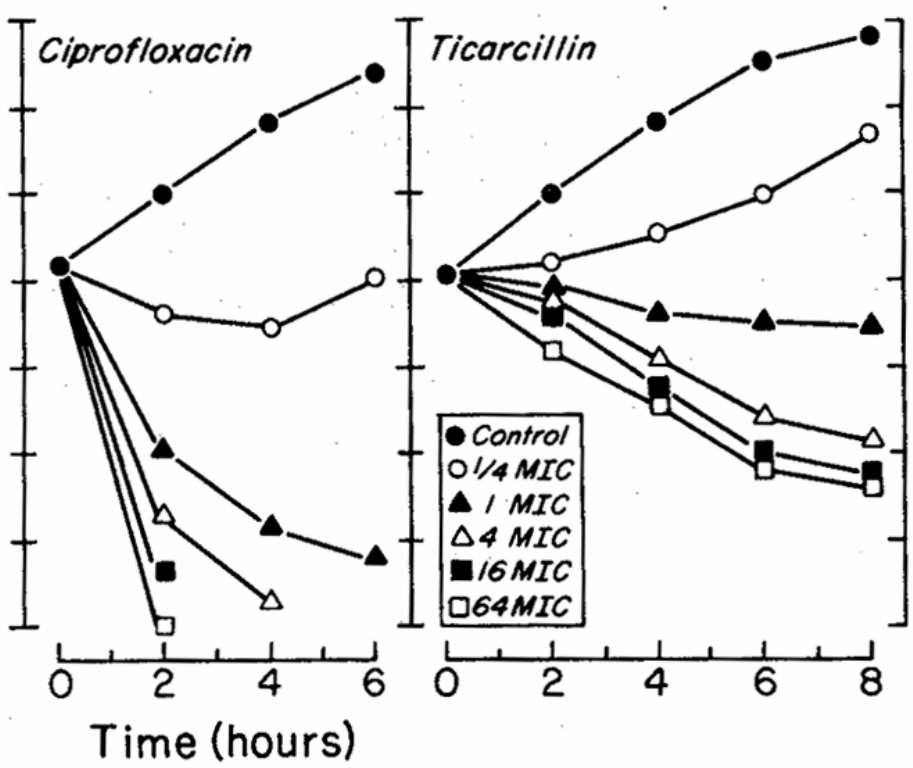


The rate of kill IS important…

A simple experiment …

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

quinolones … β-lactams …

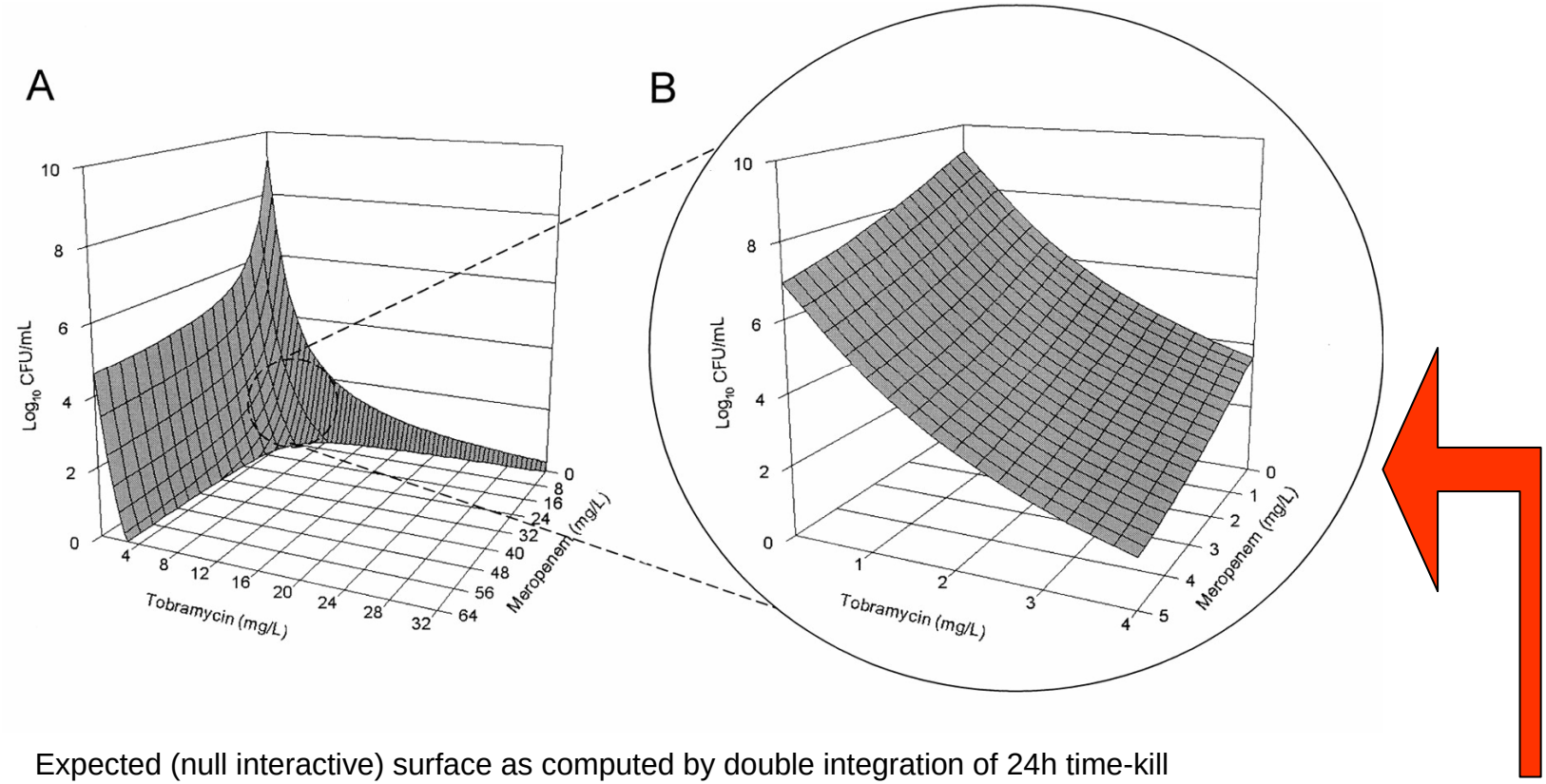


Fast … Slow …

Craig et al., 1998

Combination may be most useful when PK/PD indices are low

activities of meropenem alone and in combination (24) h for *P. aeruginosa* with MIC=1mg/L



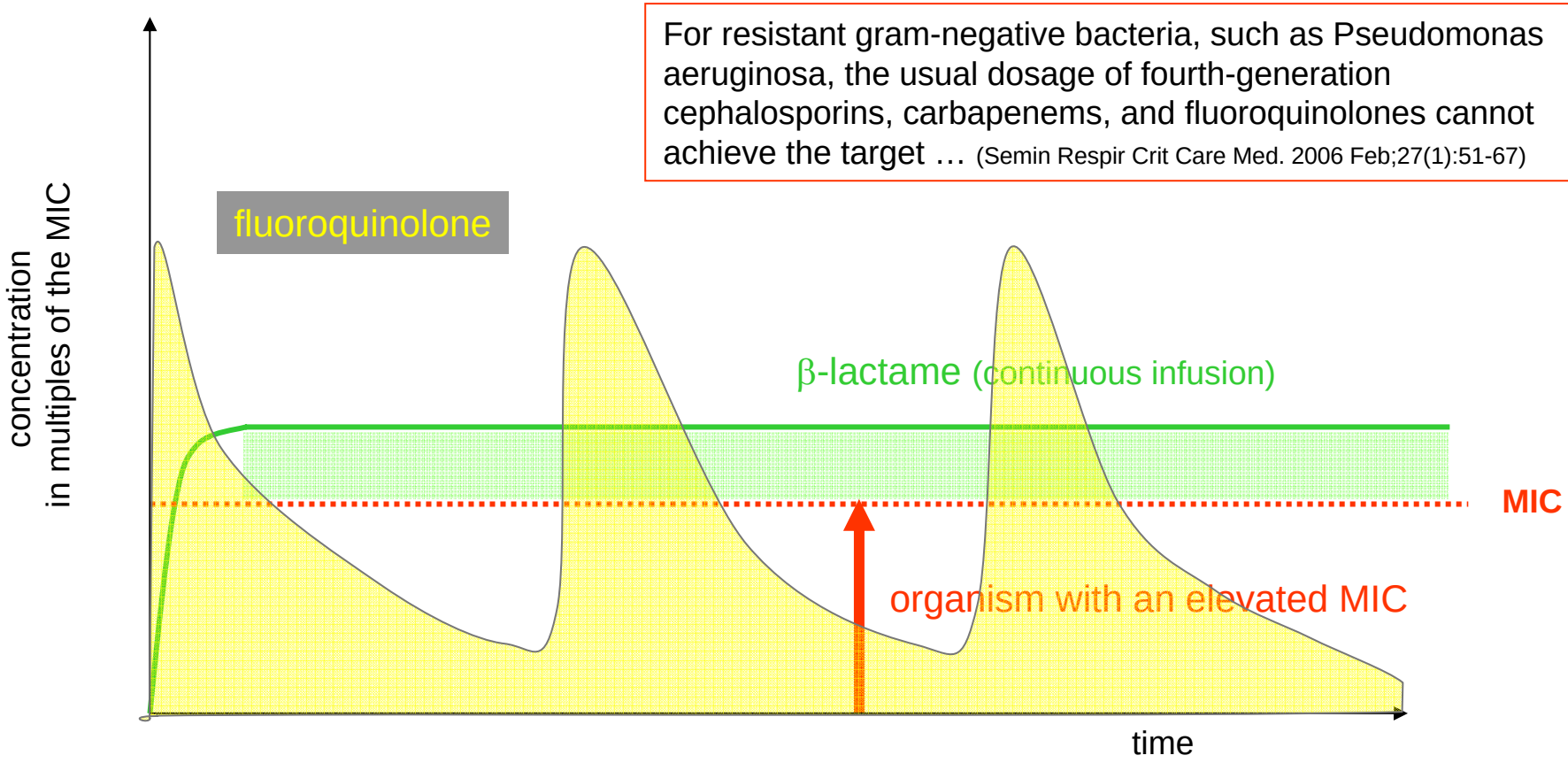
Expected (null interactive) surface as computed by double integration of 24h time-kill data concentration ranges:
(A) meropenem, 0 to 64 mg/liter, and tobramycin, 0 to 32 mg/liter
(B) meropenem, 0 to 5 mg/liter, and tobramycin, 0 to 4 mg/liter (B). → low MIC/ concentration ratios

Tam et al., Antimicrob Agents Chemother. 2004 Nov;48(11):4315-21.

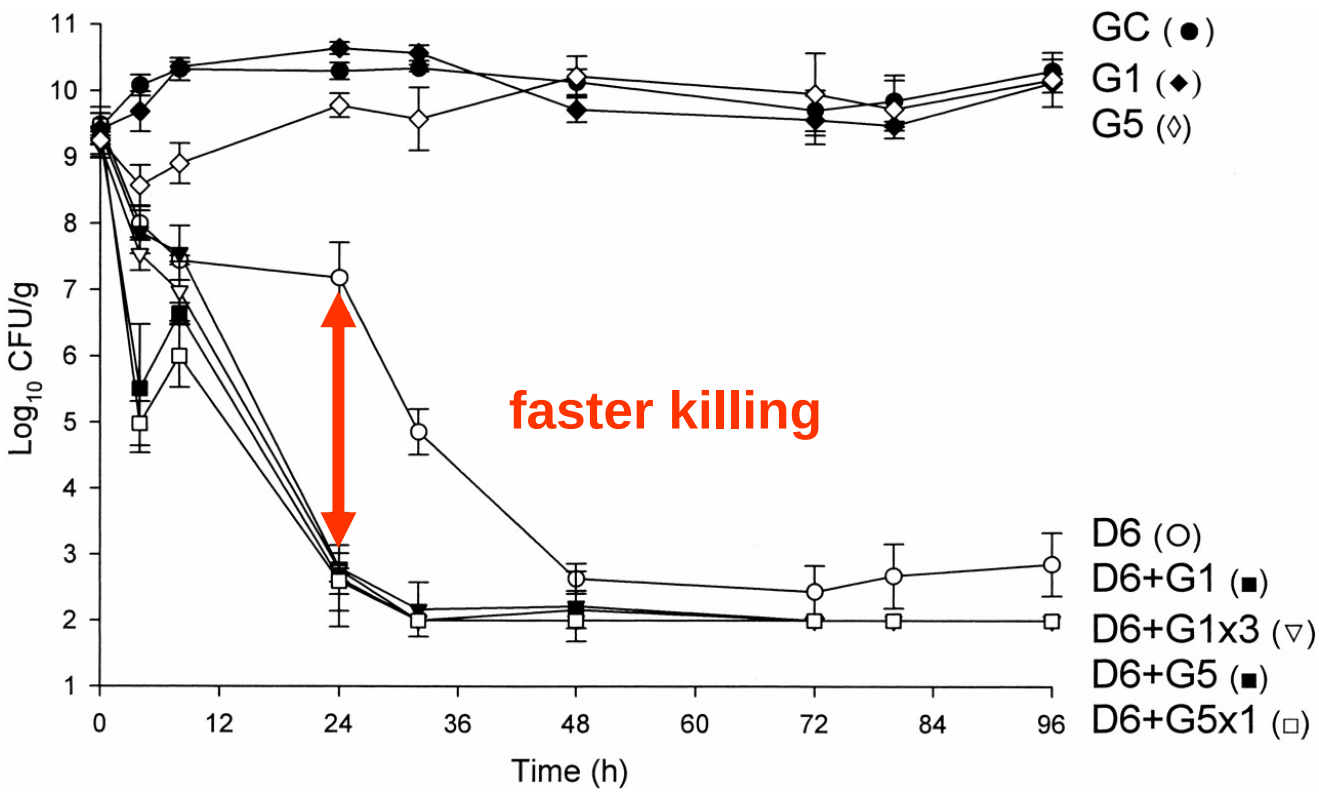
Combination of useful pharmacodynamic properties

- addition of pharmacodynamic parameters
  - β-lactams plus fluoroquinolones …

For resistant gram-negative bacteria, such as Pseudomonas aeruginosa, the usual dosage of fourth-generation cephalosporins, carbapenems, and fluoroquinolones cannot achieve the target … (Semin Respir Crit Care Med. 2006 Feb;27(1):51-67)



Combination of bactericidal antibiotics …



Activities of daptomycin (6 mg/kg/day) alone and in combination with gentamicin versus MRSA 494.

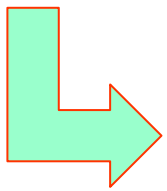
- GC, growth control; G1, gentamicin in 1-mg/kg doses q8h; G5, gentamicin in 5-mg/kg doses q24h;
- D6, daptomycin in 6-mg/kg doses given q24h;
- D6 + G1x3, daptomycin plus gentamicin (three 1-mg/kg doses); D6 + G5x1, daptomycin plus gentamicin in one 5-mg/kg dose.

Tsuji & Rybak, Antimicrob Agents Chemother. 2005 Jul;49(7):2735-45 (In vitro pharmacodynamic infection model).

Combination of pharmacodynamic indices ?

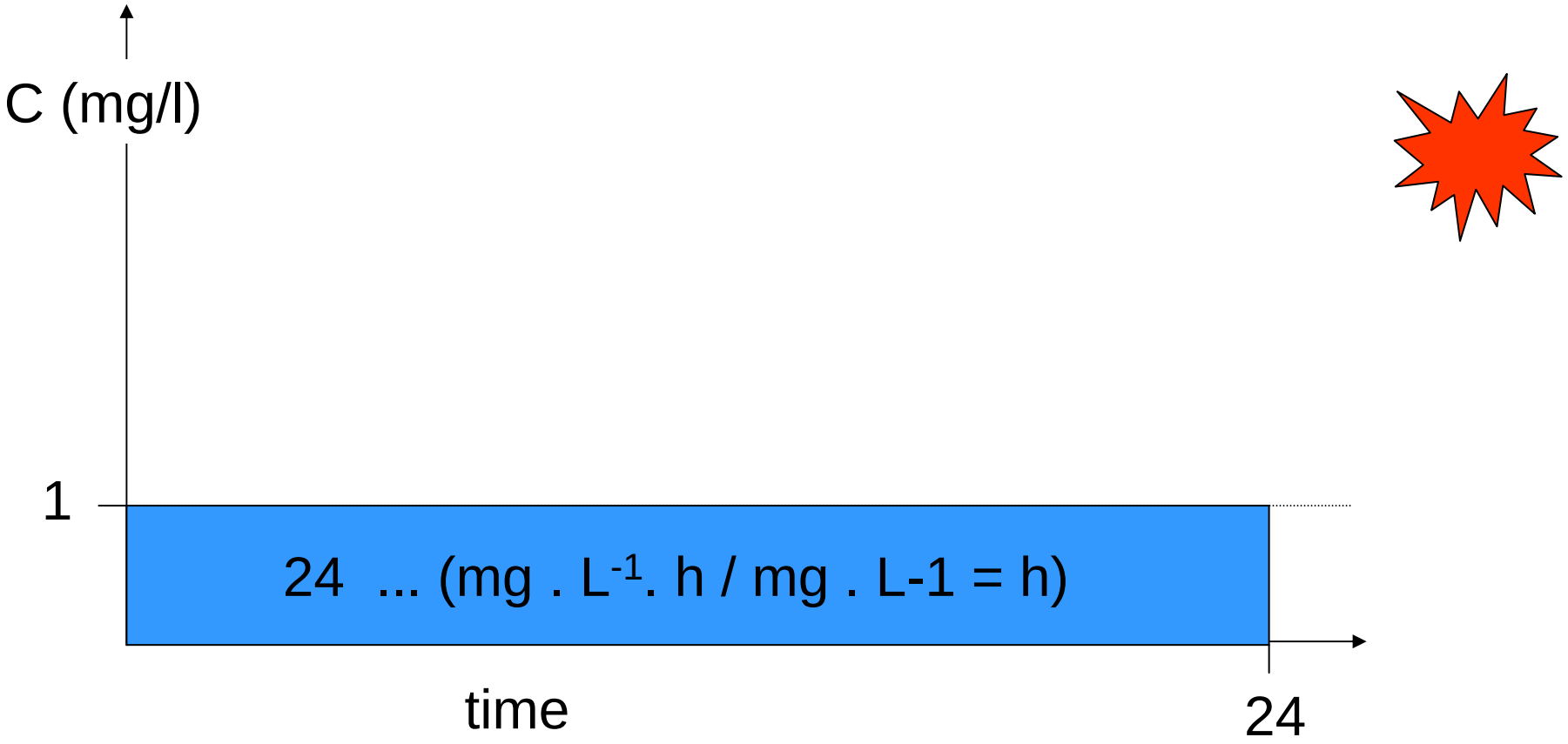
- limitations:
  - can pharmacodynamic indices be simply added ?
    - AUC_{24h}/MIC drug A + AUC_{24h}/MIC drug B ?
    - AUC_{24h}/MIC drug A + time > MIC drug C ?
    - C_{max}/MIC drug D + time > MIC drug B ?
  - can we use a surrogate common pharmacodynamic index ?
    - AUC_{24h}/MIC ?

      hint: if you do NOT use different schedules,
      C_{max}/MIC, AUC_{24h}/MIC, and time > MIC are co-variates
      and are directly interrelated…



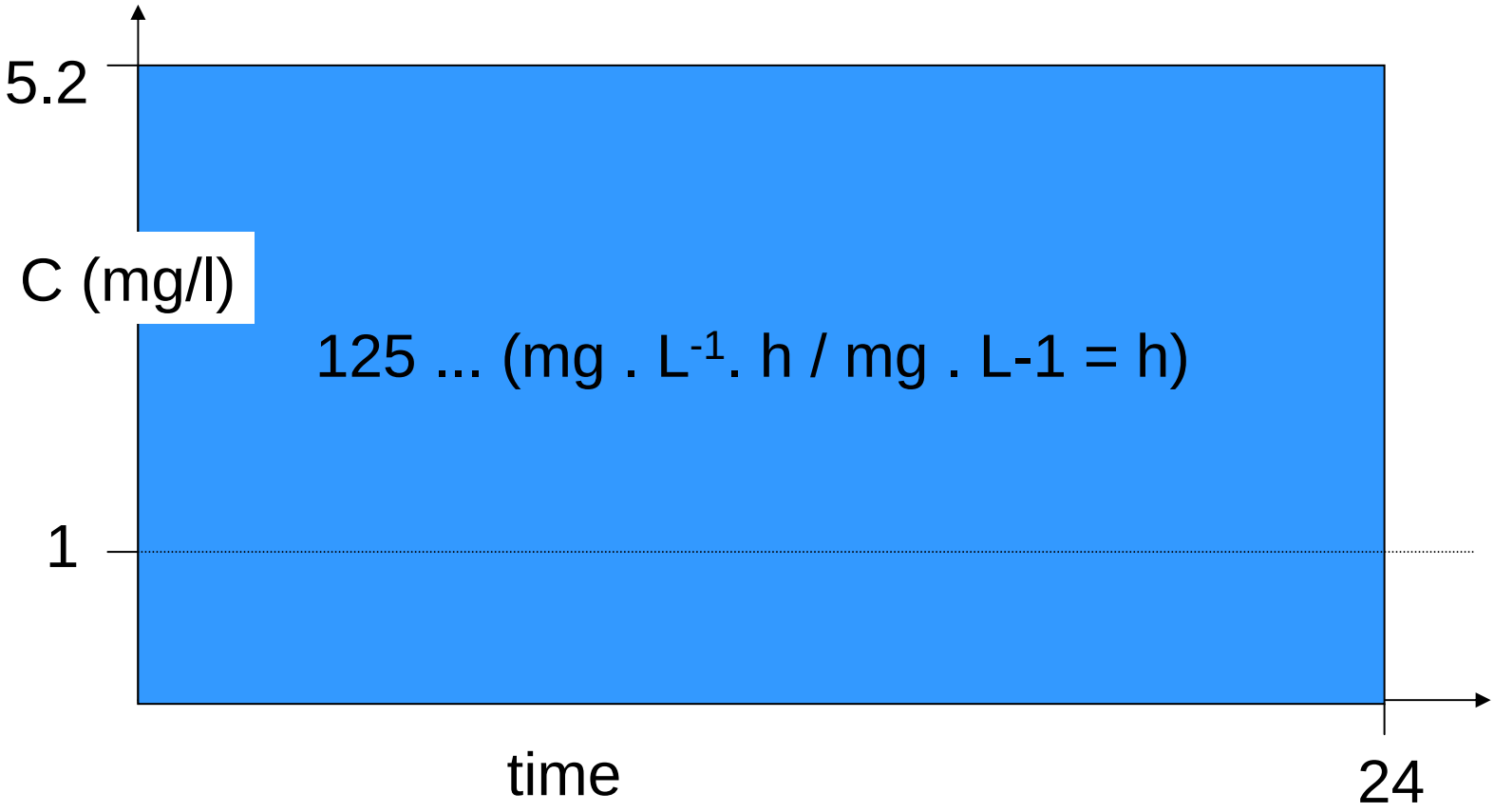
Please, follow the demonstration at the blackboard in order not to get confused …

What is a AUC/MIC ?



What is a AUC/MIC ?

You want an AUC/MIC = 125 ...

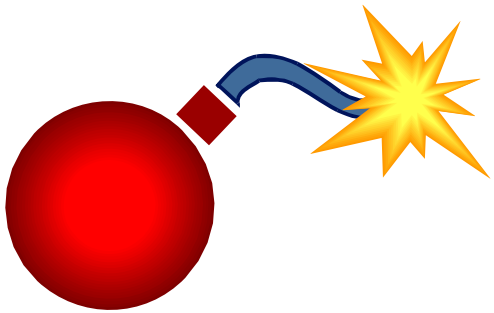


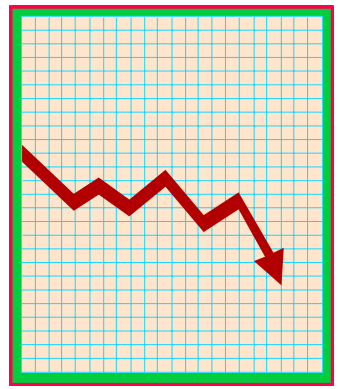
A simple rule...

24h-AUC/MIC =

- 30 ➔ 1.25 x MIC for 24h
- 125 ➔ 5.2 x MIC for 24h
- 400 ➔ 16 x MIC for 24h

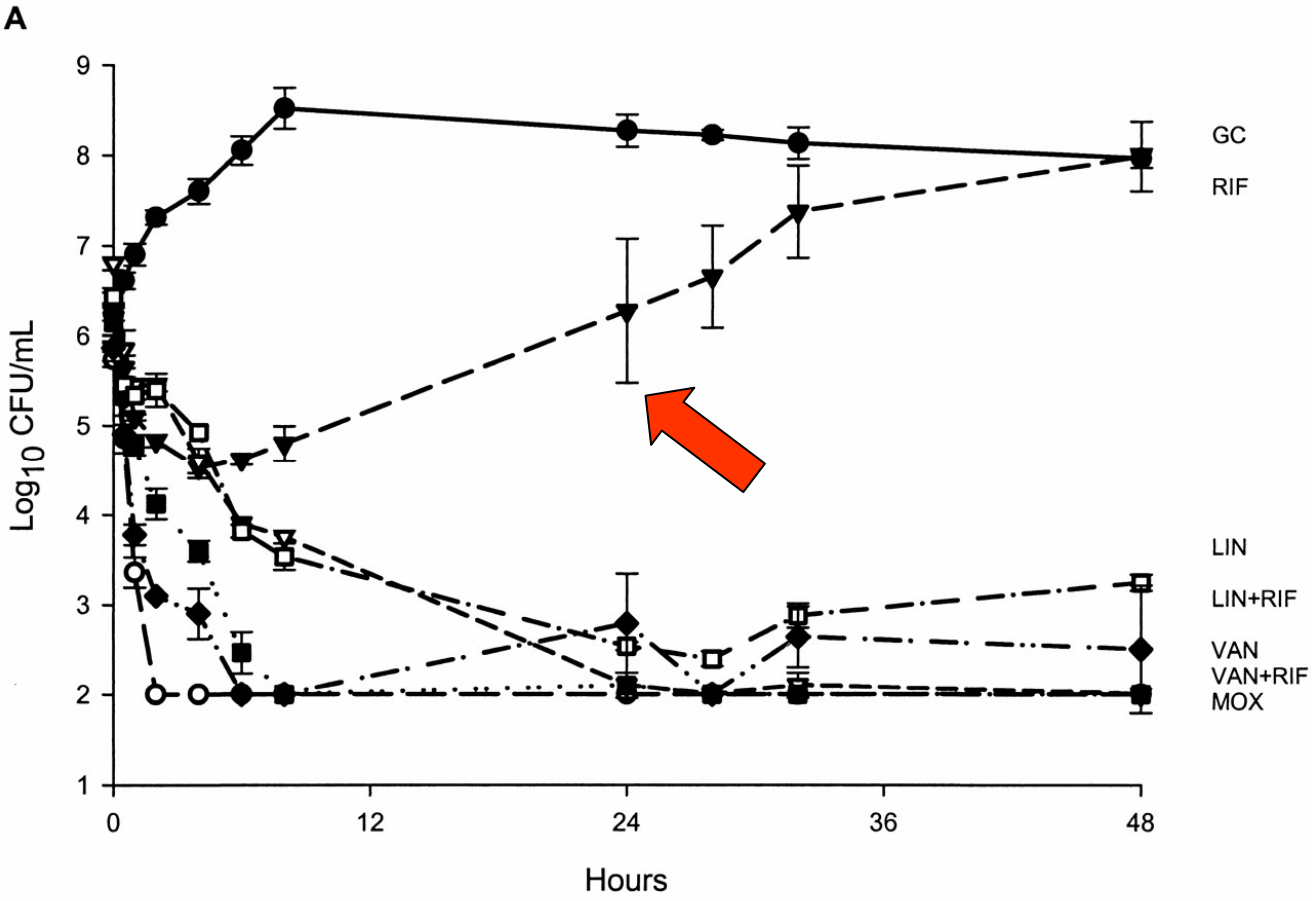
Résistance...





Reducing the rate / odds of resistance ?

Failure of rifampicin to eradicate *S. pneumoniae* …

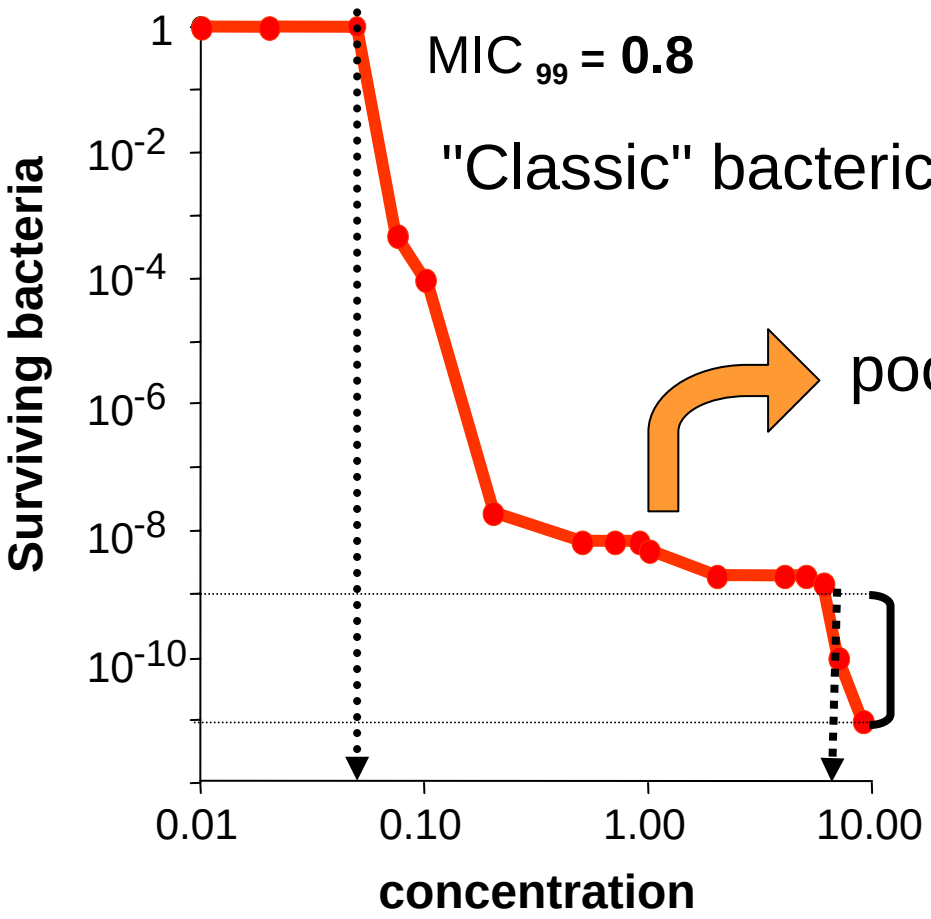


Cha & Rybak, Antimicrob Agents Chemother. 2003 Jun;47(6):1984-7.

Simulations of activities against *S. pneumoniae* clinical isolate 79.

GC, growth control;
RIF, rifampin;
LIN, linezolid;
VAN, vancomycin;
MOX, moxifloxacin.

Mutant Prevention Concentration …



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

"Classic" bactericidal effect

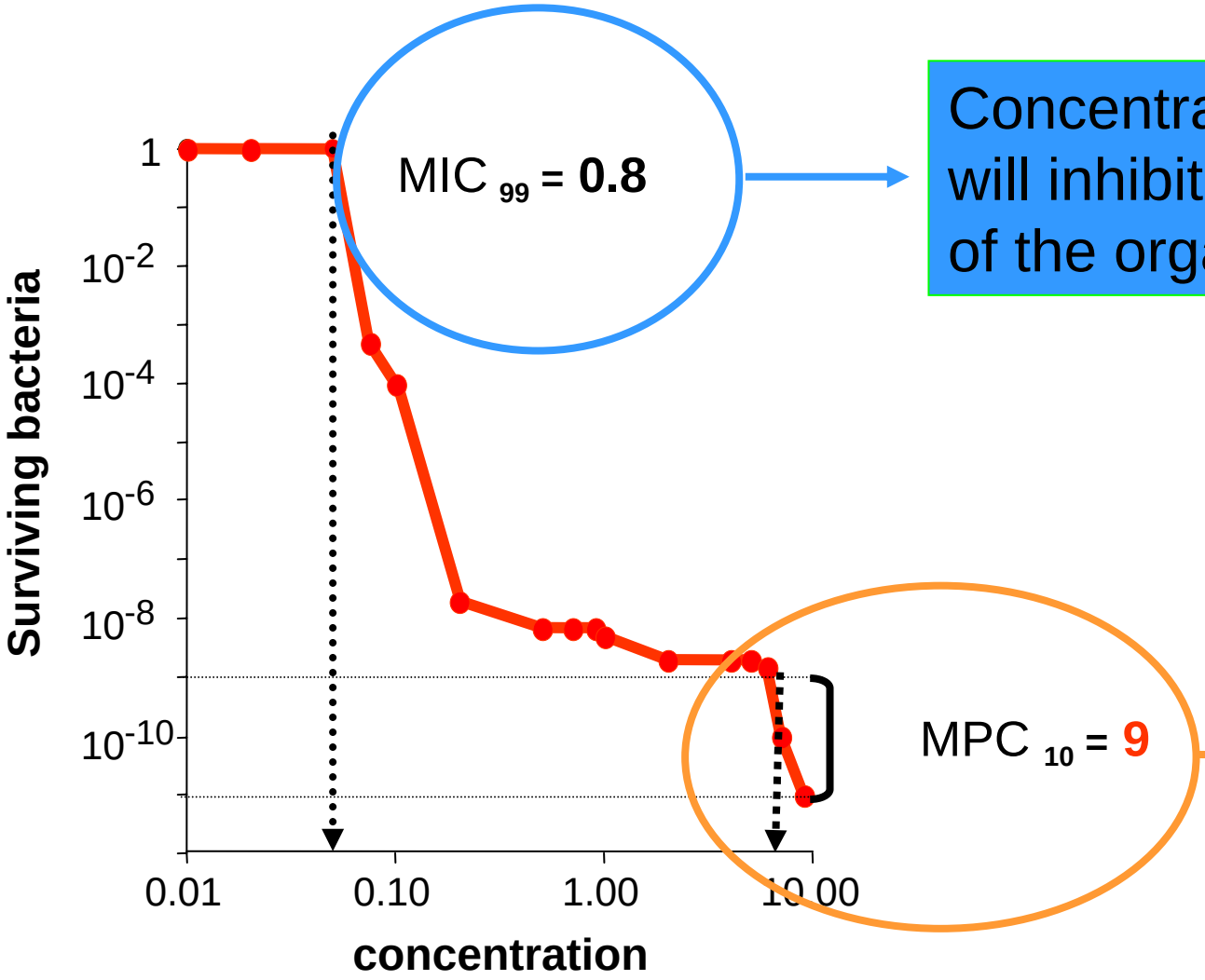
poorly sensitive organisms…

Elimination of resistant organisms

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

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

Mutant Prevention Concentration …

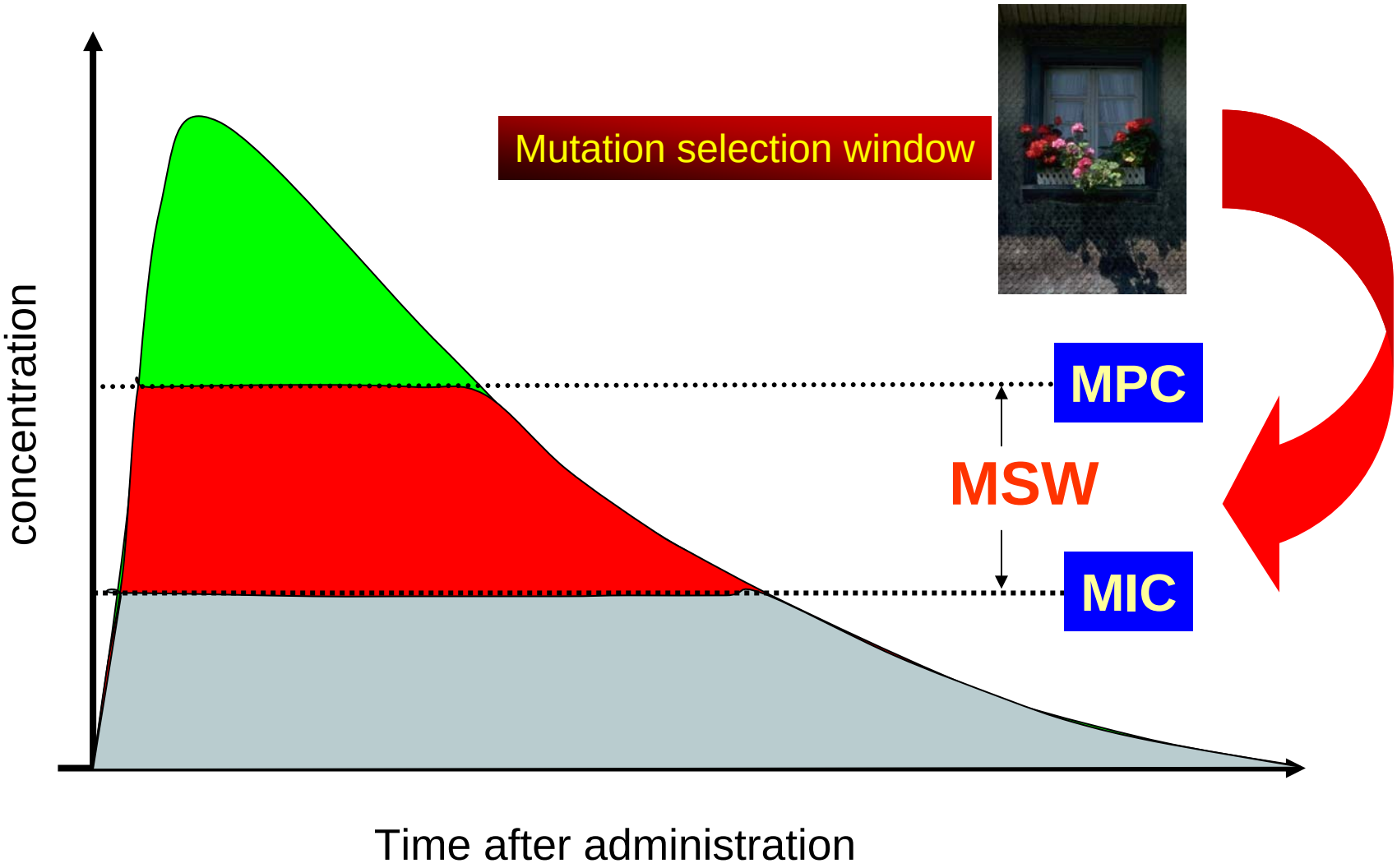


Concentration which will inhibit the majority of the organisms

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 (and to the Cmax)?

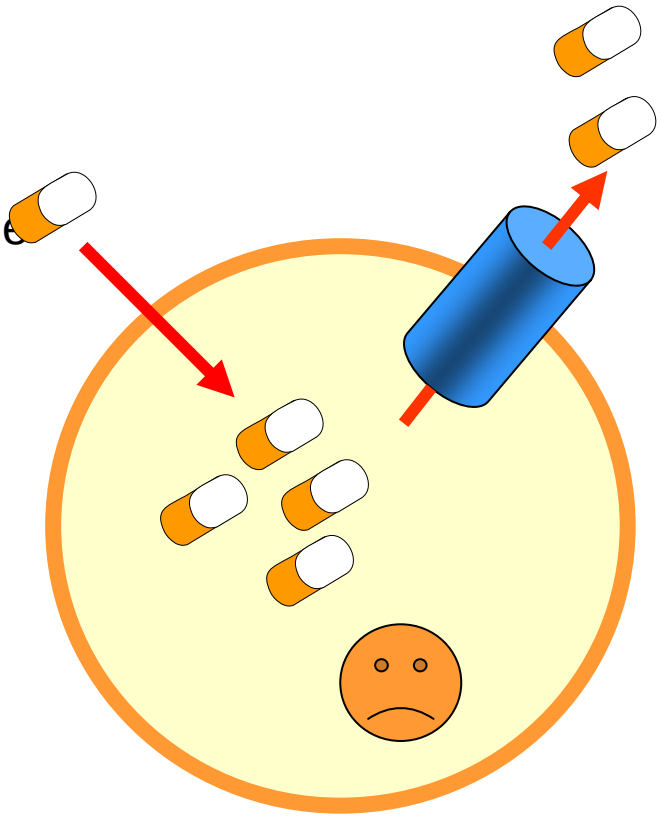
Molecule	MIC	MPC		C_{max}
levoflox. (500 mg)	1	8		≈ **6**
moxiflox. (400 mg)	0.25	1		≈ **4**

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

The MPC is (practically) about 4-10 x the MIC …
and the MIC can be used as a guide …

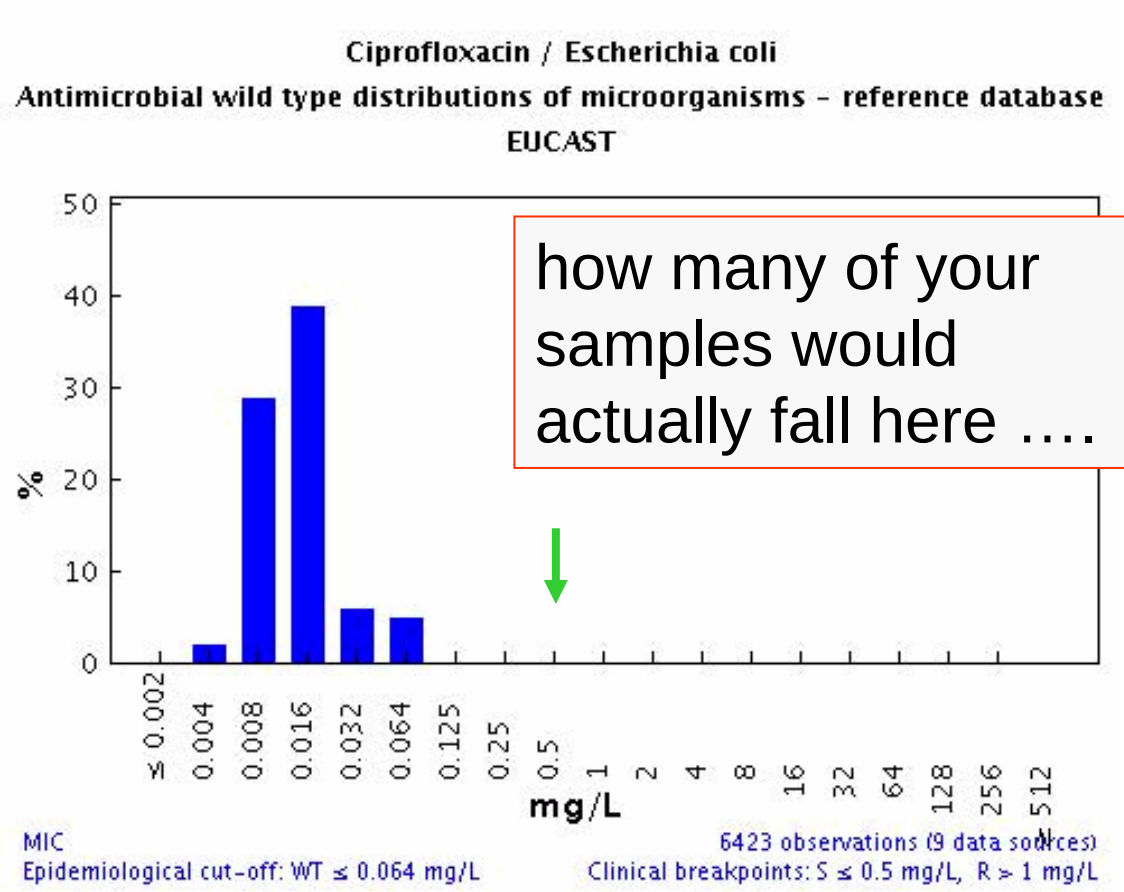
Efflux and MIC ?

- 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 …



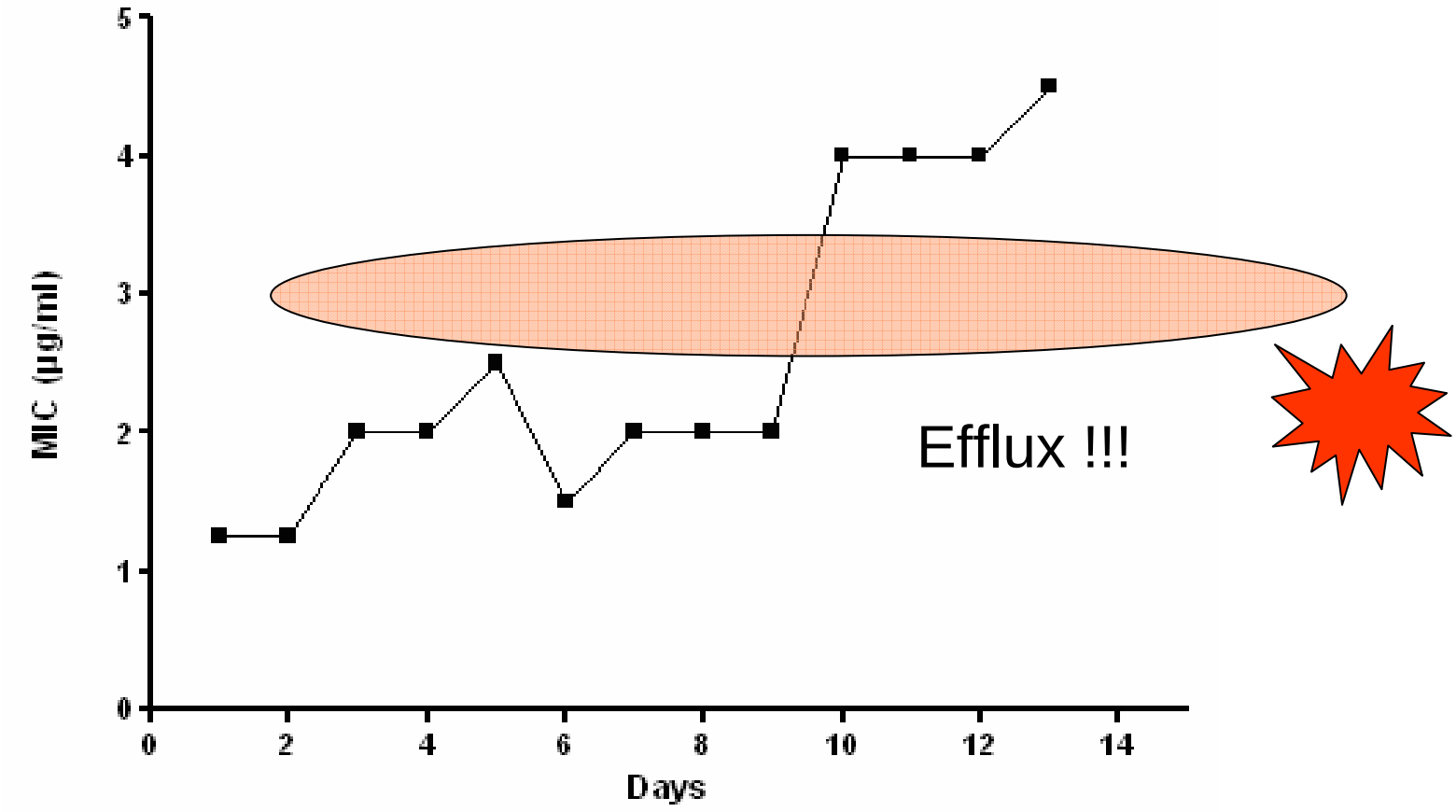
Van Bambeke et al.
J Antimicrob Chemother. 2003;51:1055-65.

Why is MIC important for detecting efflux ?



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

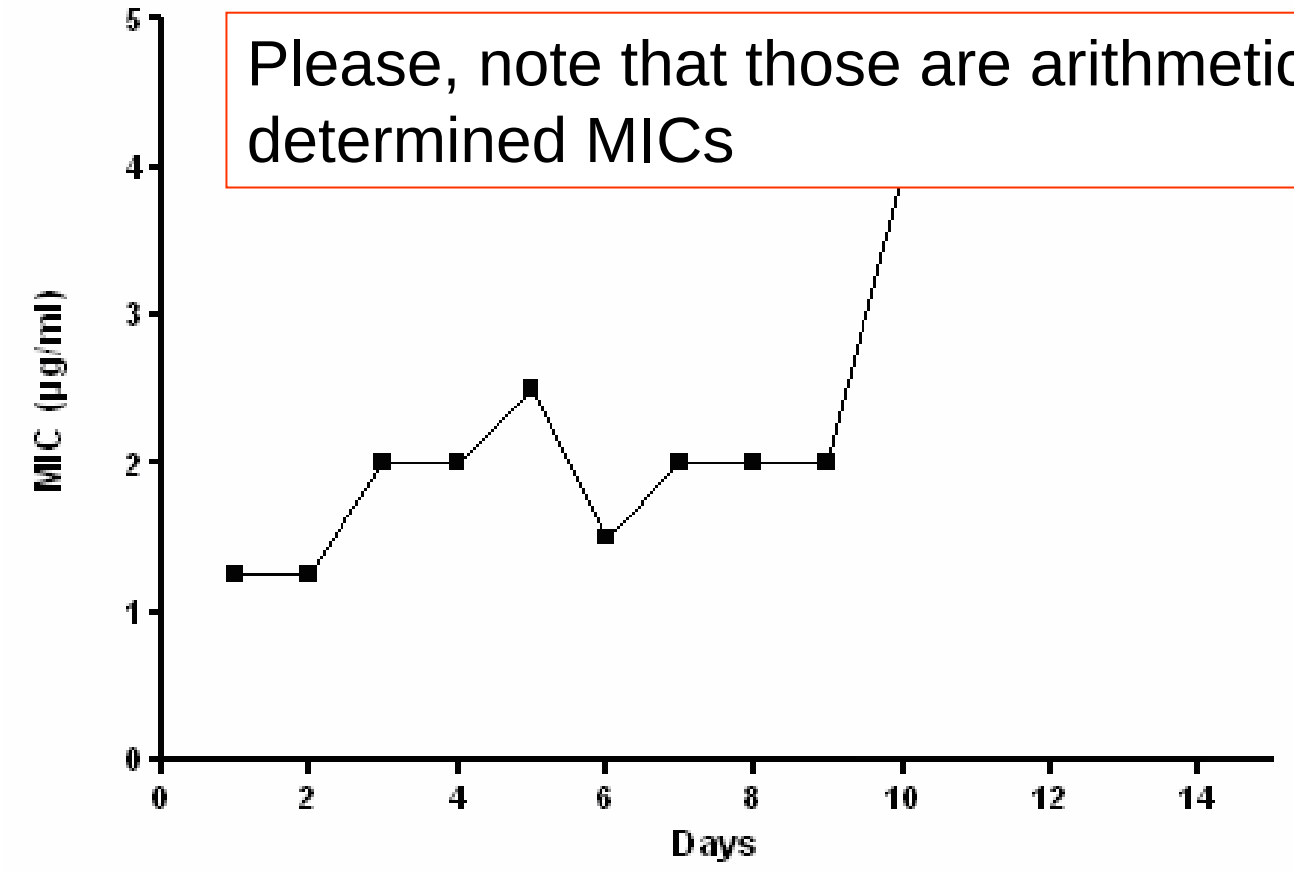
Efflux and *S. pneumoniae*



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 MICobserved each day

Avrain et al., 7th ECC, 2005

Efflux and *S. pneumoniae*



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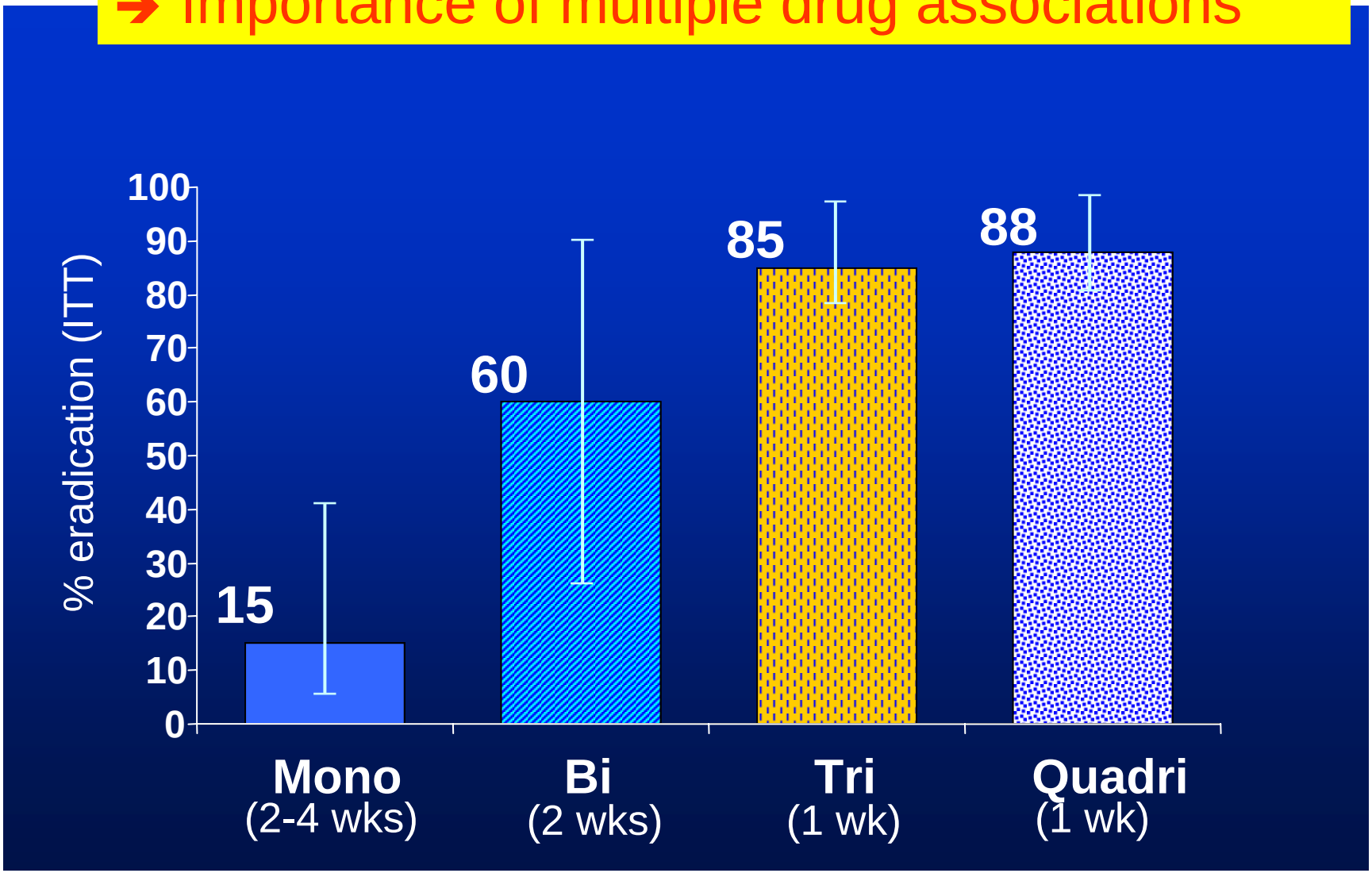
Avrain et al., 7th ECC, 2005

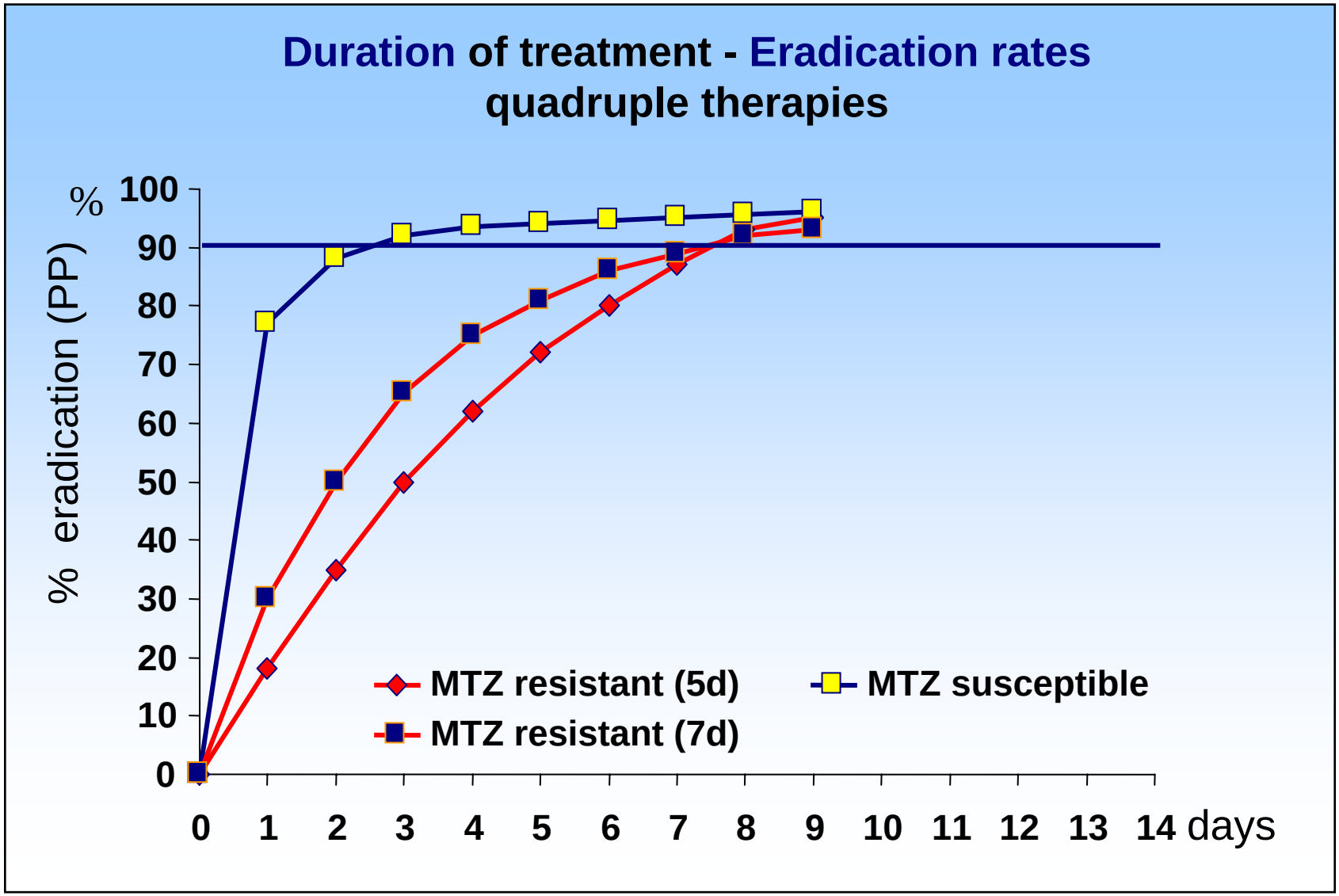
Heteroresistance and MIC: the case of vancomycin ?

Combination: the *Helicobacter pylori* paradigm

➔ Importance of multiple drug associations



Combination: the *Helicobacter pylori* paradigm



Combination …

- seems a logical approach for optimizing therapy;
- has received a lot of attention from microbiologists, but clinical data remain scanty and controversial except for a defined number of clear-cut situations;
- still lacks sound, detailed pharmacodynamic rulings for efficacy;
- should not be neglected … as a useful approach IF step down therapy is part of your procedures (if not, try to implement it …);
- should not be implemented for reasons of toxicity only … (this was not developed but is open to discussion…)