Use of antibiotics in clinical practice:
One selected topics:
1. Pharmacodynamics/ Pharmacokinetics (including breakpoints)
2. Guidelines (example: Community acquired pneumonia)

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology & Center for Clinical Pharmacy
Louvain Drug Research Institute,
Catholic University of Louvain
Brussels, Belgium

http://www.facm.ucl.ac.be

Thái Nguyên National General Hospital

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Do we have a problem ?

Obituary

J.-M. Ghuysen

This man discovered the mode of action of penicillins

Ann. Rev. Biochem. 1979. 48:73–101

USE OF MODEL ENZYMES IN THE DETERMINATION OF THE MODE OF ACTION OF PENICILLINS AND Δ^3-CEPHALOSPORINS[1]

Jean-Marie Ghuysen, Jean-Marie Frère, Mélina Leyh-Bouille, Jacques Coyette, Jean Dusart, and Martine Nguyen-Distèche

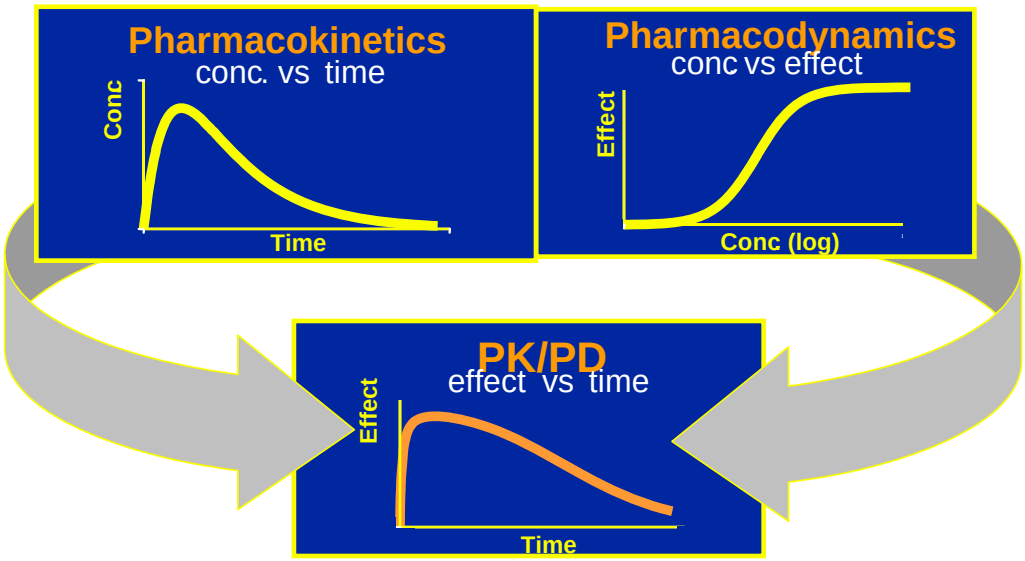
Service de Microbiologie, Faculté de Médecine, Institut de Botanique, Université de Liège, 4000 Sart Tilman, Liège, Belgium

and died from invasive pneumococcal infection …

http://www.cip.ulg.ac.be/newsite/pdf/jmghuysen.pdf

What is my goal ?

- Discuss with you two ways to improve antibiotic treatment (with pneumonia as an example)

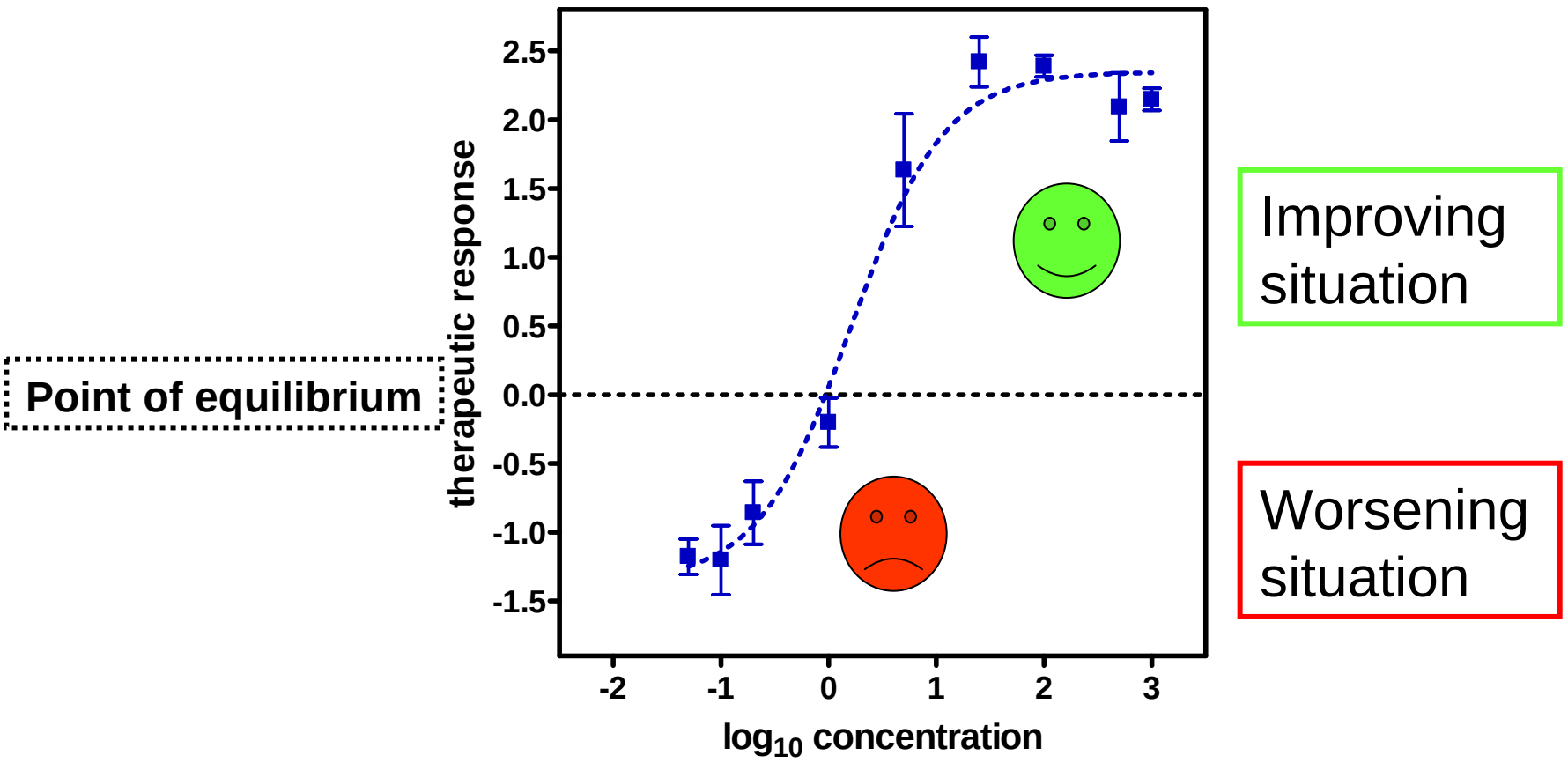


- Give a few comments about usefulness of a clinical pharmacist (example with vancomycin)

Part 1: Optimising treatment based on PK/PD principles

In a nutshell…

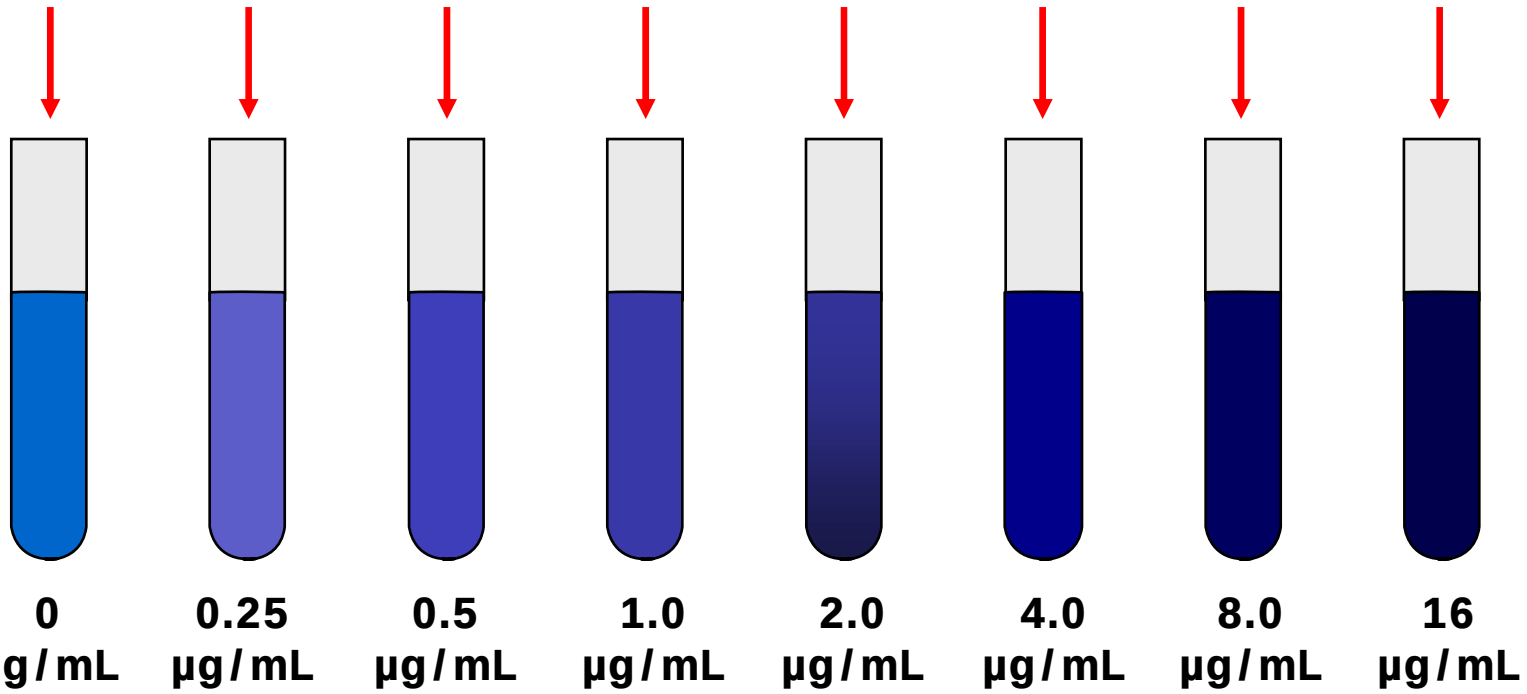
The dose must be adapted to the goal…



In a nutshell…

The target is the bacteria = MIC

Known quantity of bacteria placed into each tube

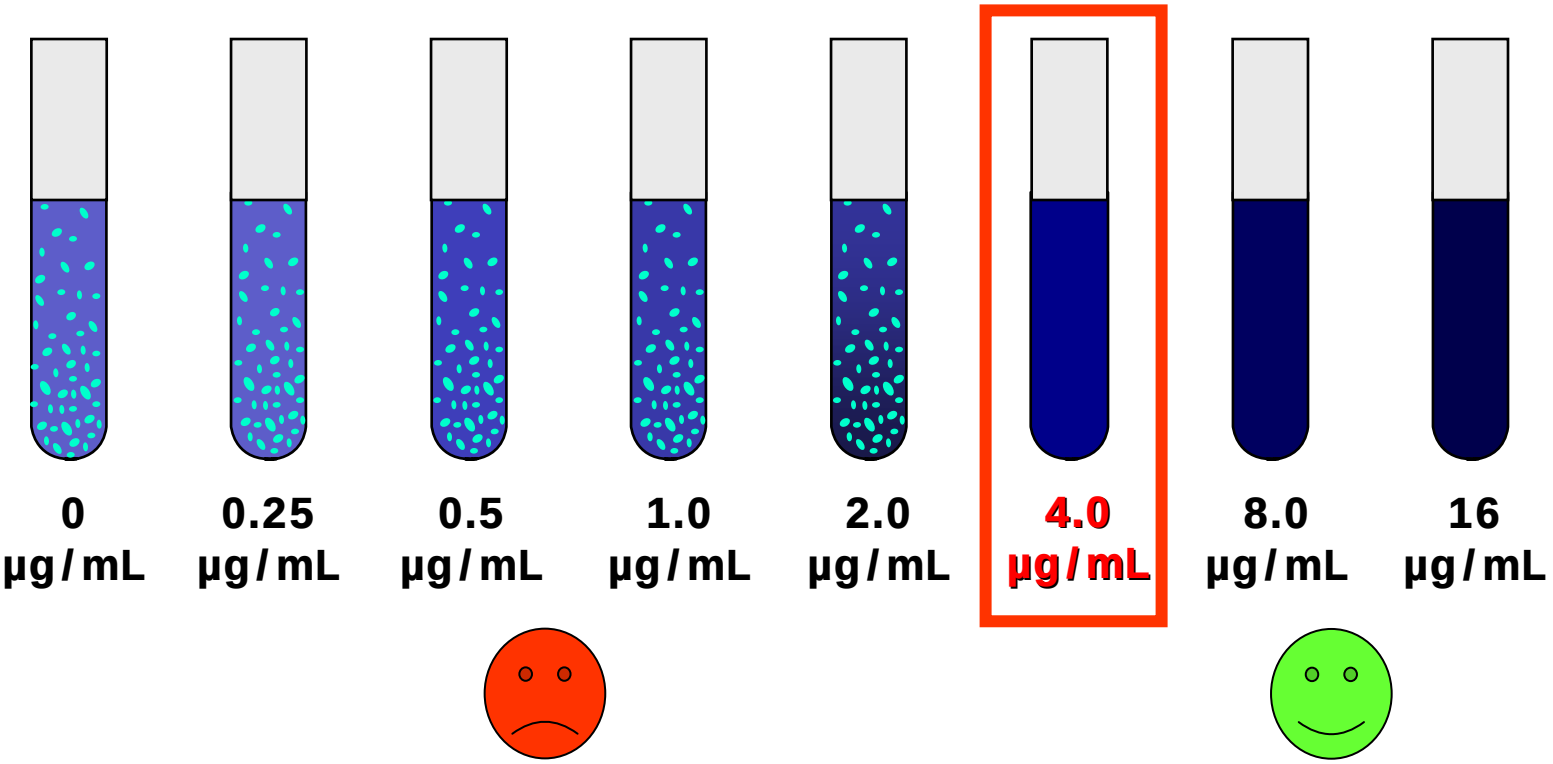


In a nutshell…

The target is the bacteria = MIC

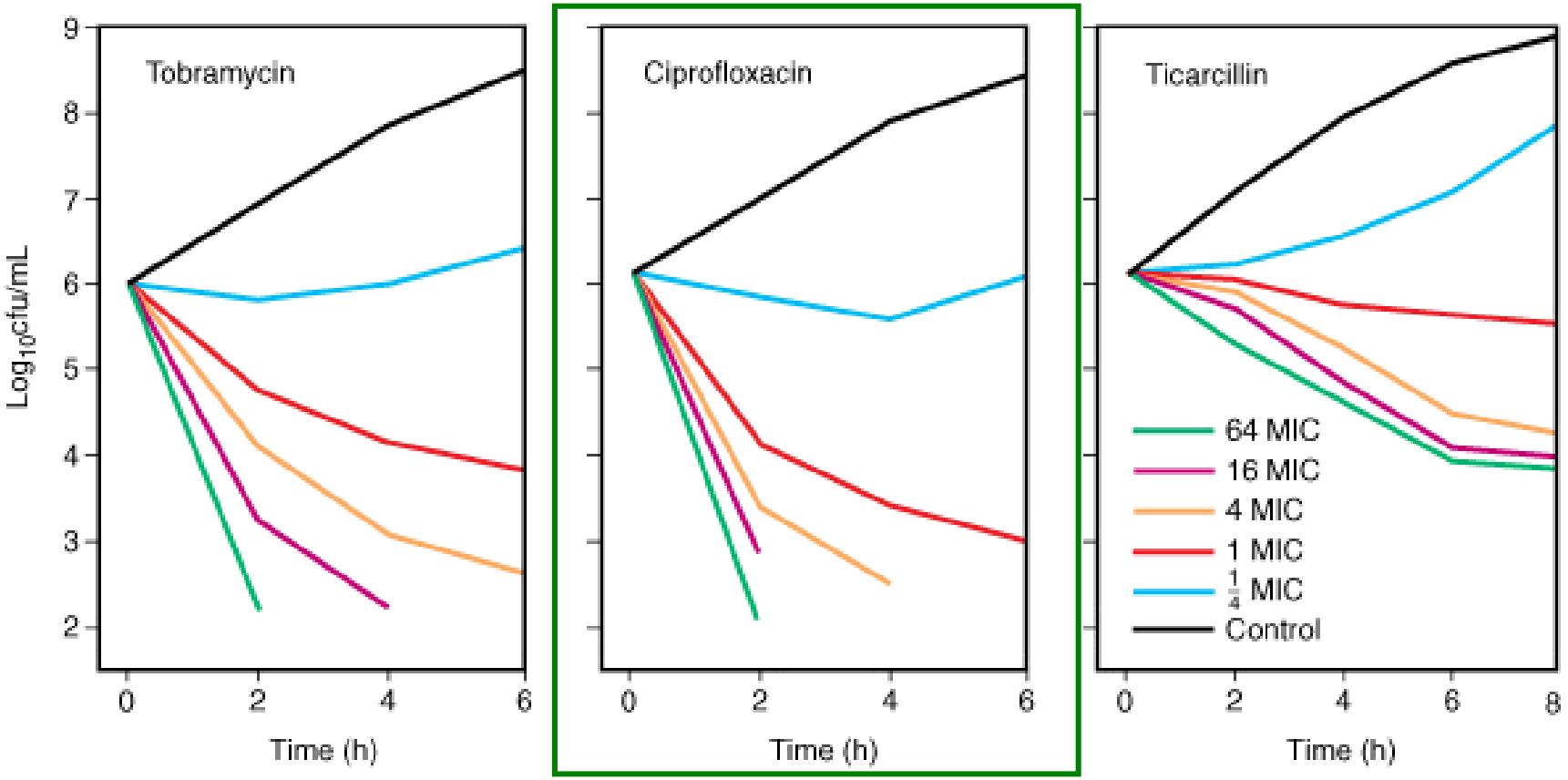
24h later…

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



A first comparison: in vitro kill curves vs MIC

conc. dependent

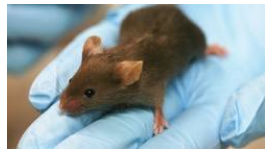


Time kill curves for *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one fourth to 64 times the minimum inhibitory concentration.
(From Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: A review. Scand J Infect Dis. 1990;74:63–70.)

First conclusions

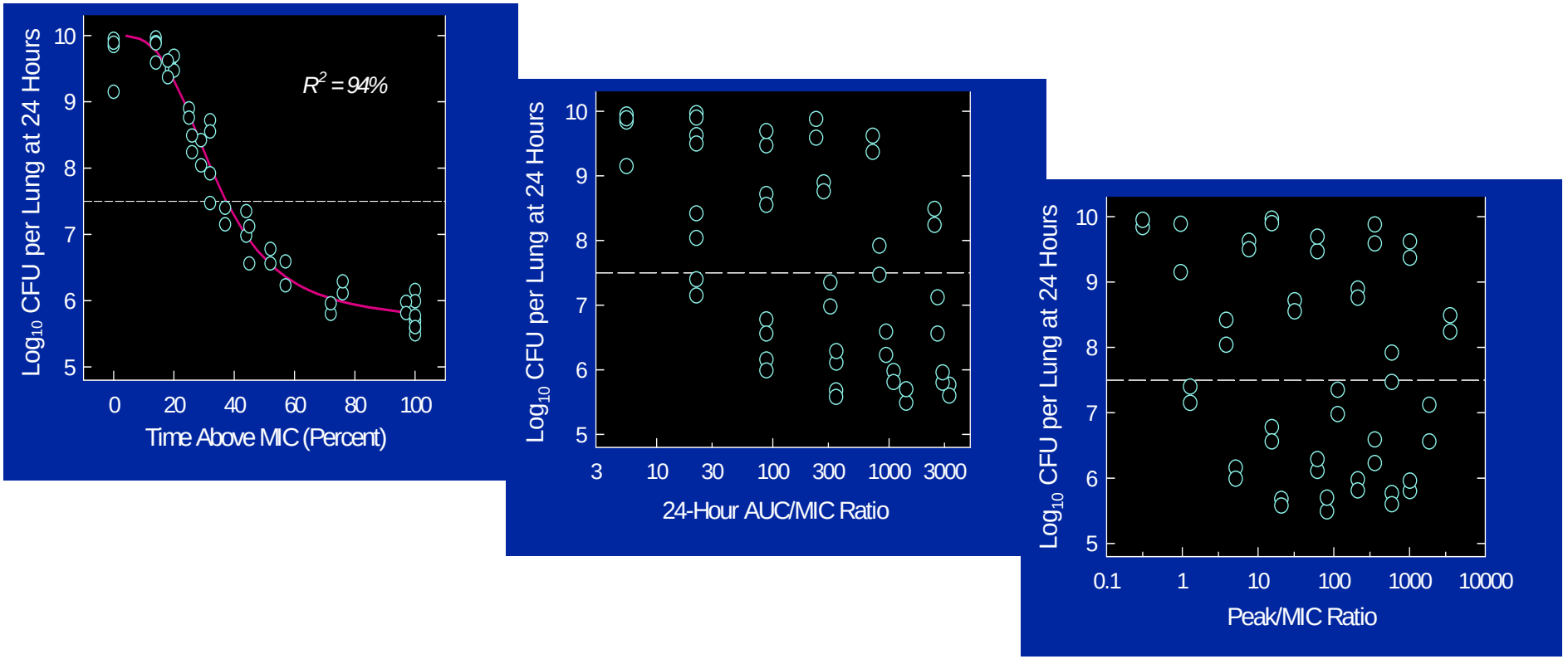
Considering their pharmacokinetics in humans

- β-lactams appear as **"time-dependent"** antibiotics because their serum concentrations is almost always > MICs …
  if you administer them several times a day (most have only short serum half-lives)
- Fluroquinolones and aminoglycosides are primarily **"concentration-dependent"** antibiotics as their bactericidal effect increases in proportion to their C_{max}/MIC ratio.



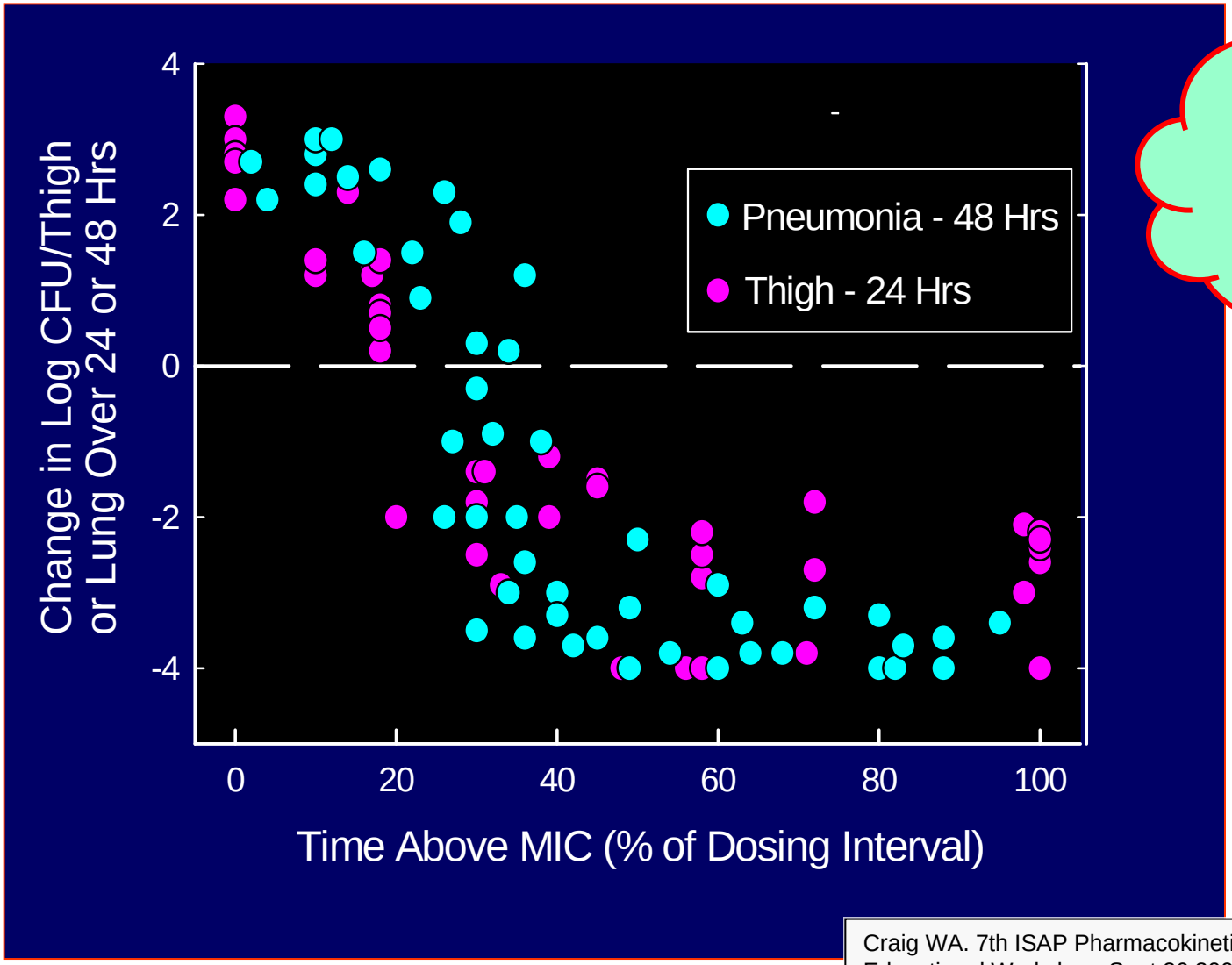
PK/PD in animals: β-lactams

1. For β-lactams, time > MIC is the only key index for efficacy



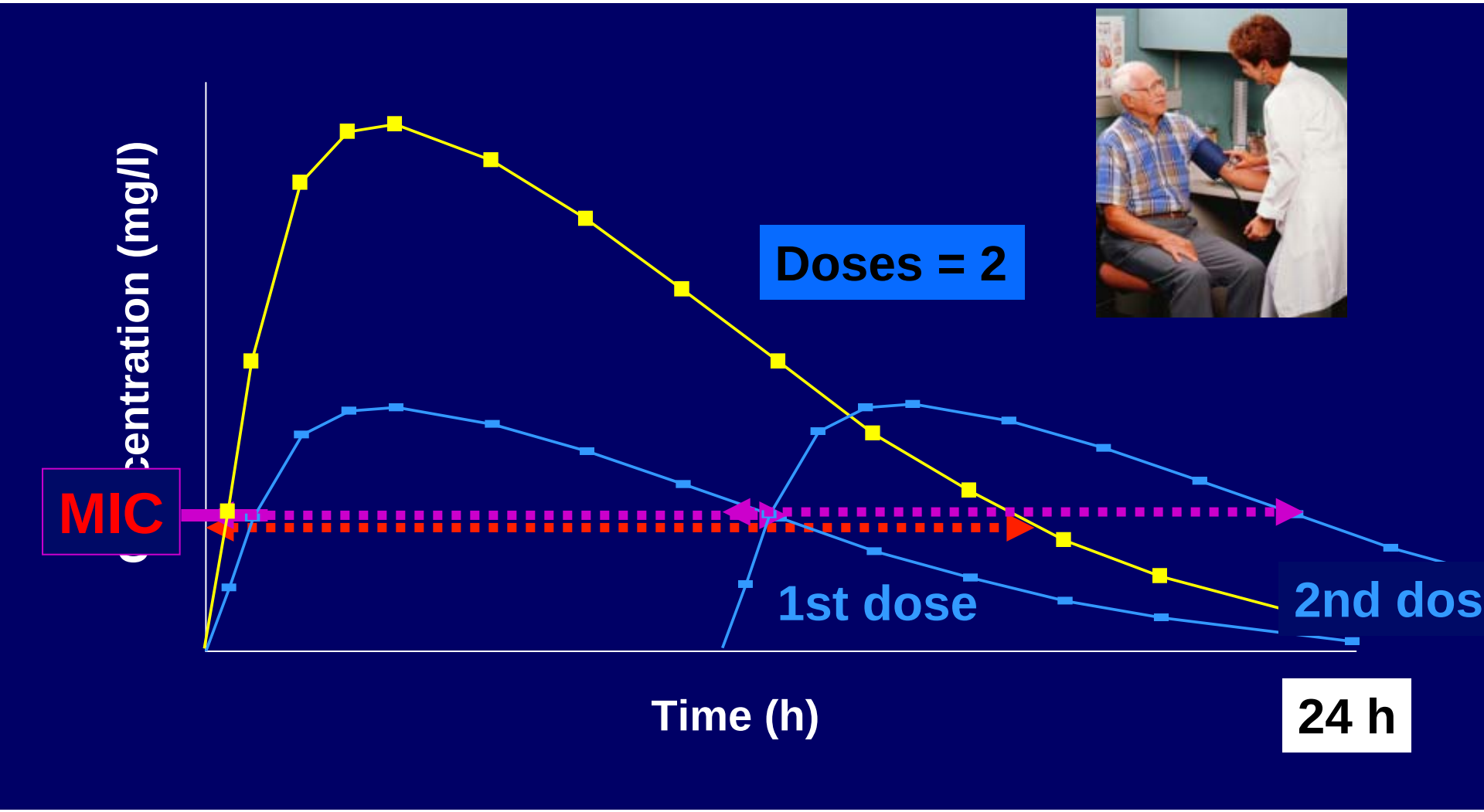
Correlation of PK/PD Indices with Efficacy of Cefotaxime against Klebsiella pneumoniae in a Murine Pneumonia Model (W.A. Craig – ISAP workshop – Stockholm, Sweden, 2000)

Relationship between T>MIC and efficacy of amoxicillin against *S. pneumoniae* in rat pneumonia and murine thigh infection models



Craig WA. 7th ISAP Pharmacokinetics/Pharmacodynamics (PK/PD) Educational Workshop. Sept 26 2001, San Diego, CA.

Oral penicillins: How to increase "Time > MIC" ?



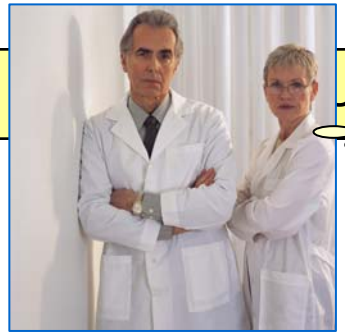
The next problem... (of many)

Clinicians tend to ask only (and clinical microbiologists to provide only) ‘S (susceptible) – I (intermediate susceptible) – R (resistant)’ answers based on accepted breakpoints…

But what is a breakpoint?

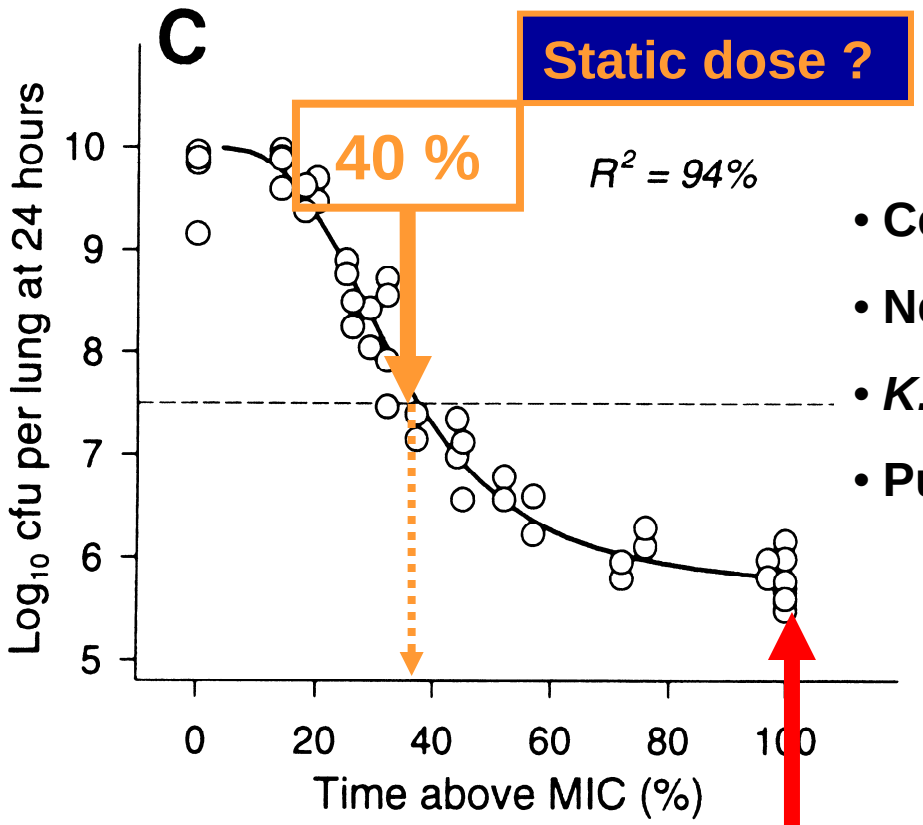
Using USA (NCCLS / CLSI) breakpoints was not a real help for the patient ...

cefotaxime vs. *E. coli*		**S≤ / R**
BSAC	United Kingdom	2 / ≥4
CA-SFM	France	4 / >32
CRG	The Netherlands	4 / >16
DIN	Germany	2 / ≥16
NWGA	Norway	1 / ≥32
SRGA	Sweden	0.5 / ≥2
NCCLS	U.S.A.	8 / ≥64



Is 64 mg/L really "susceptible" ?

The next problem: Is 40% T >MIC sufficient?



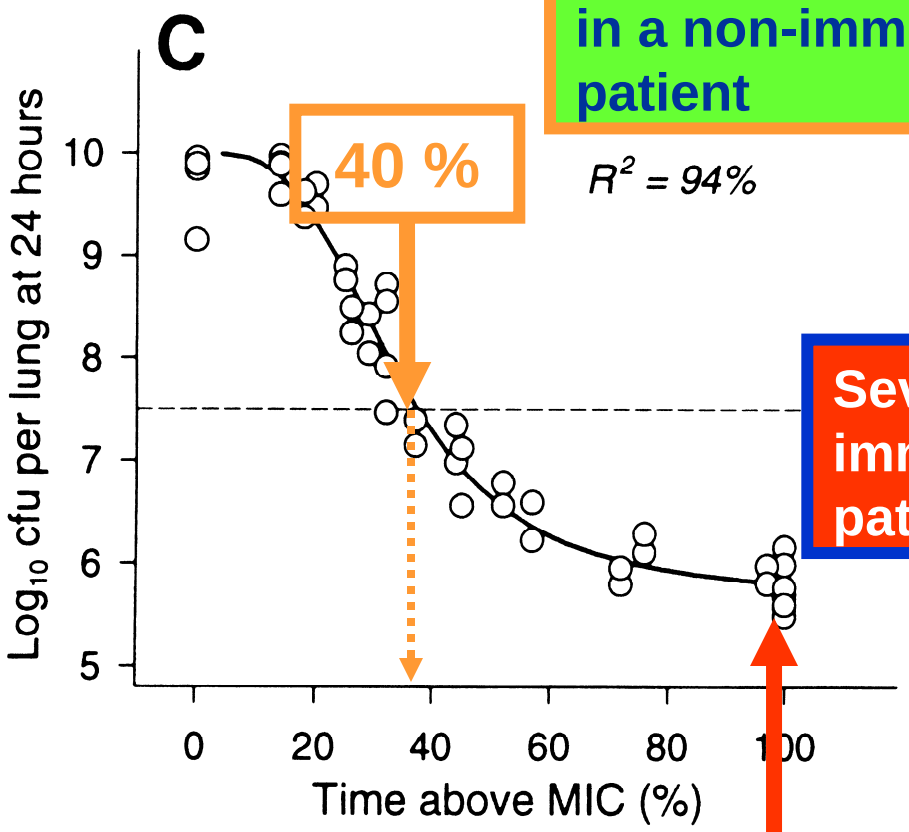
- Cefotaxime
- Neutropenic mice
- *K. pneumoniae*
- Pulmonary infection

100% – Maximal effect?

- Data: W.A. Craig, 2d ISAP Educational Workshop, Stockholm, Sweden, 2000 (see also Intern. J. Antimicrob. Agents 19 (2002) 261-268)
- Interpretation: P.M. Tulkens, ICAAC - ISAP PK/PD Workshop - Clinical Implications of PK/PD Modelling, Chicago, IL, 2005

Here is a proposal ...

Moderately severe infection in a non-immunosuppressed patient



Severe infection in immunosuppressed patient

100%?

- Data: W.A. Craig, 2d ISAP Educational Workshop, Stockholm, Sweden, 2000 (see also Intern. J. Antimicrob. Agents 19 (2002) 261-268)
- Interpretation: P.M. Tulkens, ICAAC - ISAP PK/PD Workshop - Clinical Implications of PK/PD Modelling, Chicago, IL, 2005

And the other antibiotics...

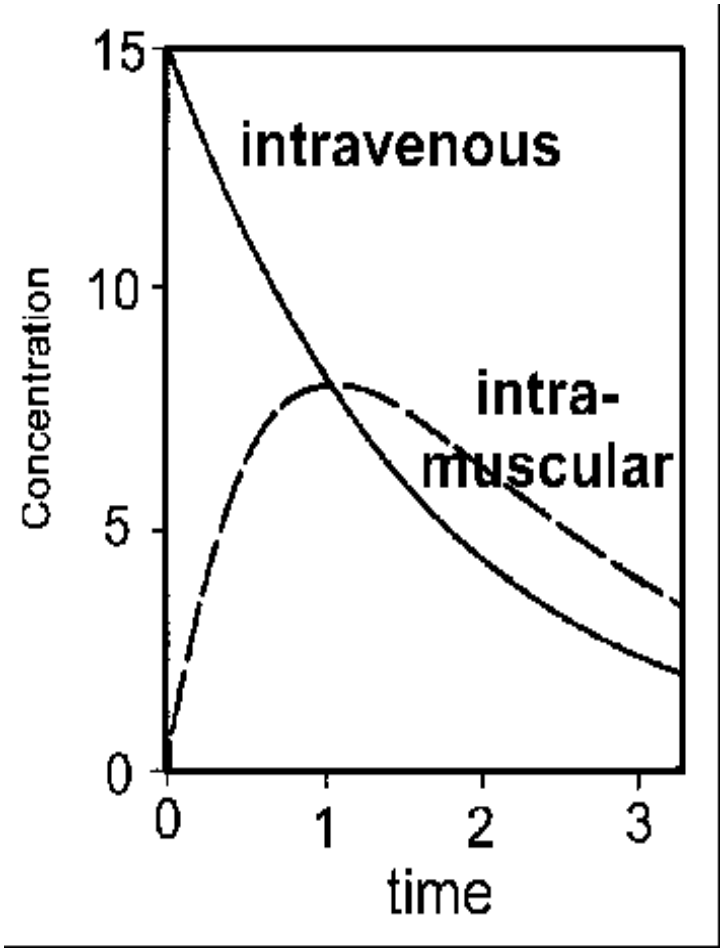
- Only β -lactams are fully time-dependent

- Other antibiotics are divided in two groups
  - those that are "C_{max}/MIC-dependent":
    - aminoglycosides and fluoroquinolones (partially)
  - those "AUC_{24h}/MIC-dependent":
    - most other antibiotics

Aminoglycosides: get a peak !

Aminoglycosides: get a peak !

Peak/MIC > 8



1. **Appropriate mode of administration**

⇨ **IV route**

2. **Calculation of the necessary peak value**

⇨ **minimal peak: = MIC x 8**

3. **Calculation of the adequate dosis**

⇨ **peak = dosis / Vd**

⇨ **dosis = peak x Vd**

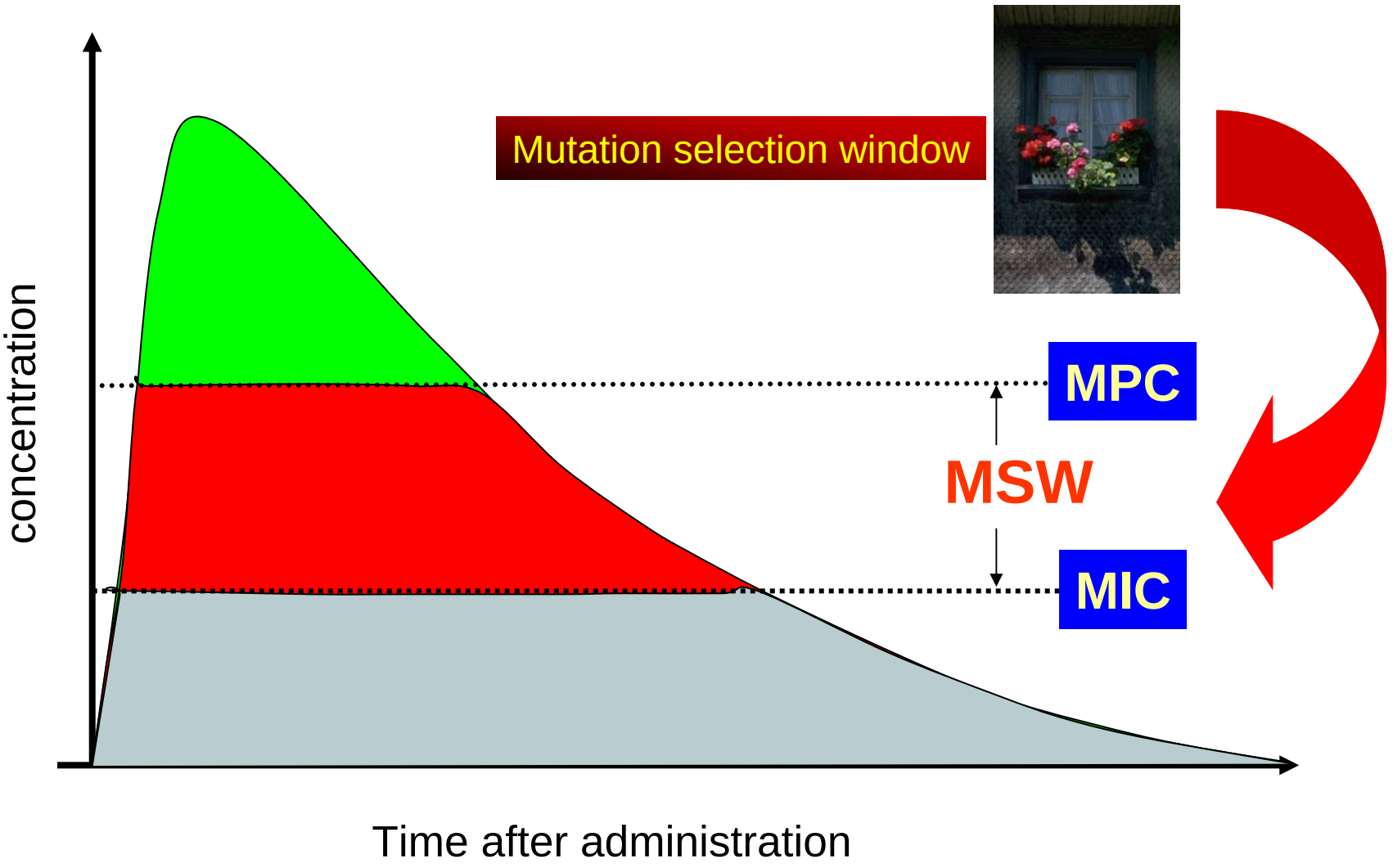
⇨ **dosis = MIC x 8 x Vd**

Aminoglycosides...

- optimize the peak !
  - must reach 8-10 x the MIC
  - use intravenous only (in 30 min)
  - use once-daily (full dose in one administration)
    - to increase efficacy
    - to reduce toxicity (associated with elevated through levels) [1]

[1] not shown here but ask questions

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



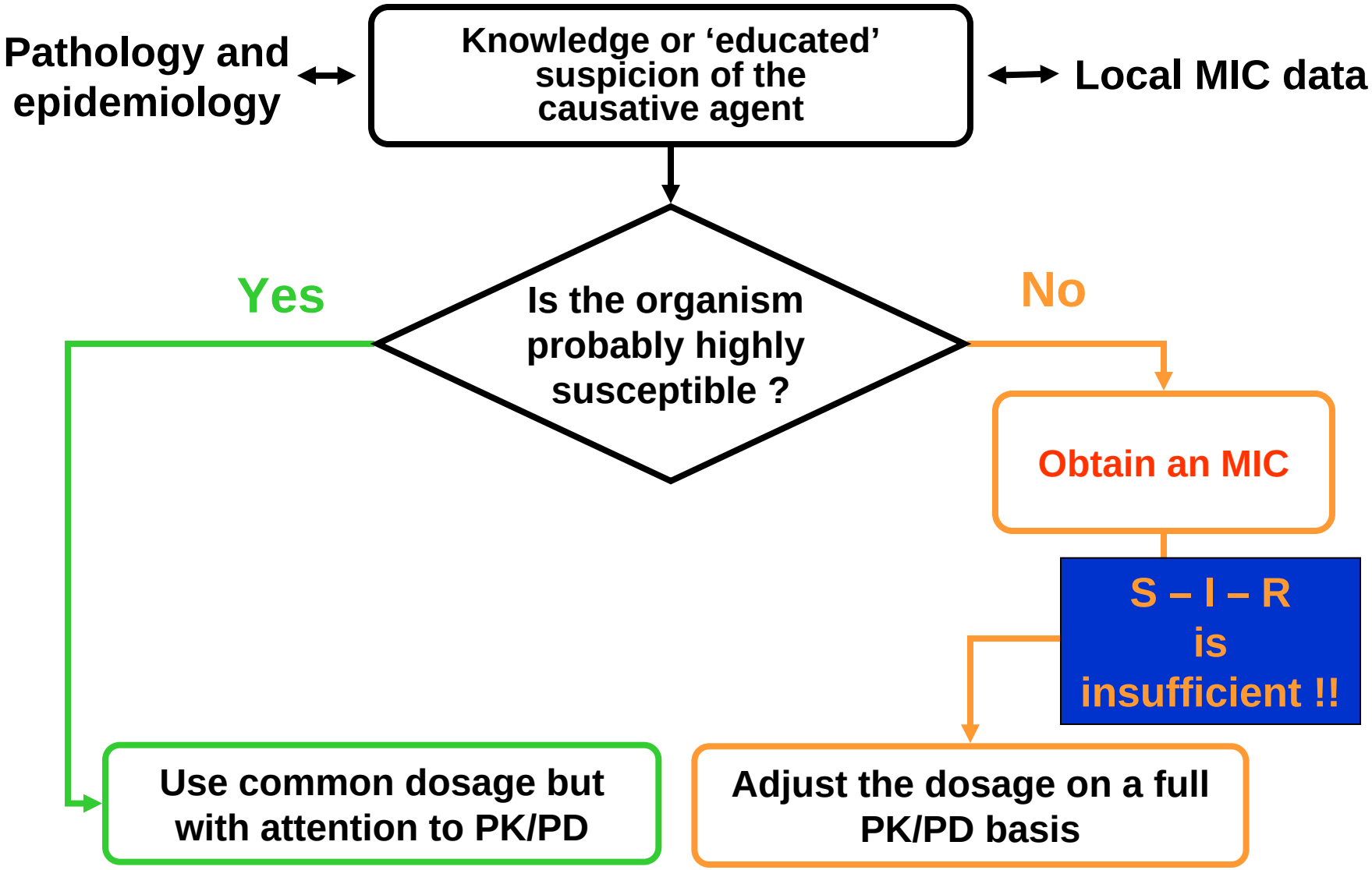
concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

For all other antibiotics, optimize the AUC_{24h}/MIC ratio

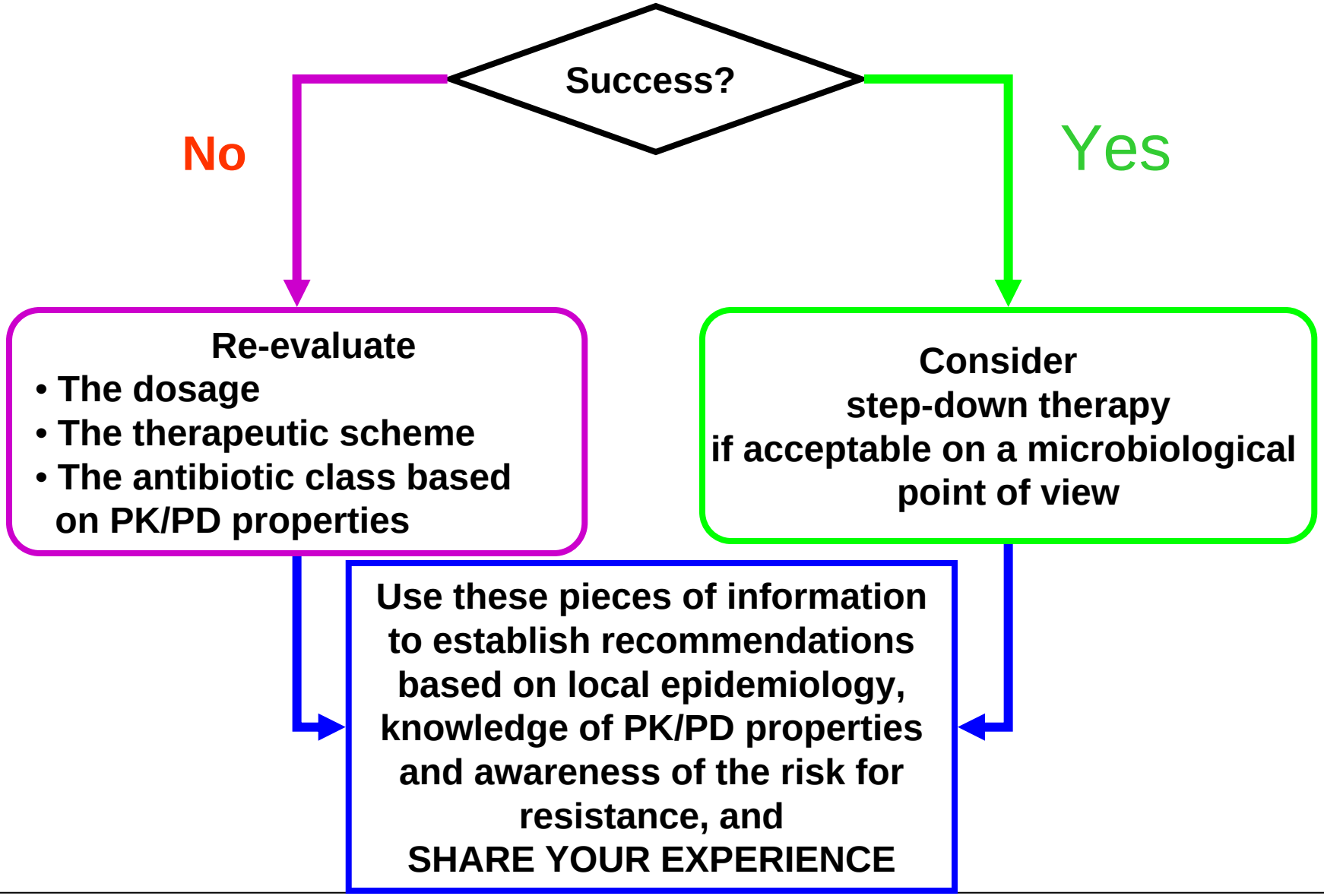
Simple rules:

- AUC = (dose x bioavailability) / clearance
- **Dose:** this is what you give...
- **Bioavailability:** this is what is absorbed by the patient
- **Look for a daiy dose that is sufficient for the MIC_{90}**
  (check EUCAST web site and rational documents)
  (low doses will promote the selection of resistance)

A clinical algorithm or a path to success…



A clinical algorithm (followed)…



Conclusions … or what do you need to consider for any antibiotic…

- **For the microbiologist:** Know and inform about susceptibility data in YOUR clinical/community environment
  - ➔ MICs are best….; use the methodology that suits your needs (CLSI, EUCAST, other…) but make interpretation based on EUCAST breakpoints

- **For the clinician:** use all available information (AUC *, peak *) and/or frequency of administration (time *) to make sure the drug your prescribe will be effective against the organisms you are fighting ...

- **For both and the pharmacists:** re-examine at regular intervals whether the choices made remain appropriate for YOUR patients… with the drug and the dose that were prescribed.

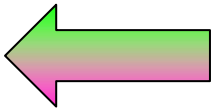
- **For all of you:** ***"New"*** antibiotics are not necessarily superior and may even be risky if the highest MIC they can safely cover is too close from the upper limit of the wild type population…

* get this information from your pharmacist, the literature, EUCAST, and industry …

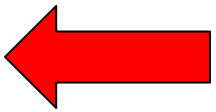
Part 2: Setting guidelines for treatment optimization

Guidelines: content and goals

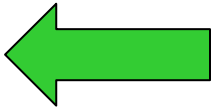
- Modern clinical guidelines should identify the **most valuable evidence** and integrate this knowledge to build **optimized decisions trees** that should be applicable to the **majority of patients**, while being sufficiently flexible to accommodate a sufficient level of **individual variation**



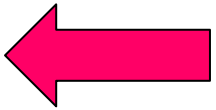
- But guidelines are also often seen as a mean to **standardize medical care** with 2 potential consequences/goals:



  - to **raise quality of care** while *reducing the risks* to patients



  - to achieve the **best balance between cost and medical efficacy** (broadly speaking)



The AGREE instrument

- Originally developed through a grant from the European Union
- Published in its version 1 in 2001
- Updated as version 2 in 2010 (translations available in French and Chinese)

http://www.agreetrust.org/

The 6 main domains

AGREE II INSTRUMENT

I. Domain 1. Scope and Purpose

II. Domain 2. Stakeholder Involvement

III. Domain 3. Rigour of Development

IV. Domain 4. Clarity of Presentation

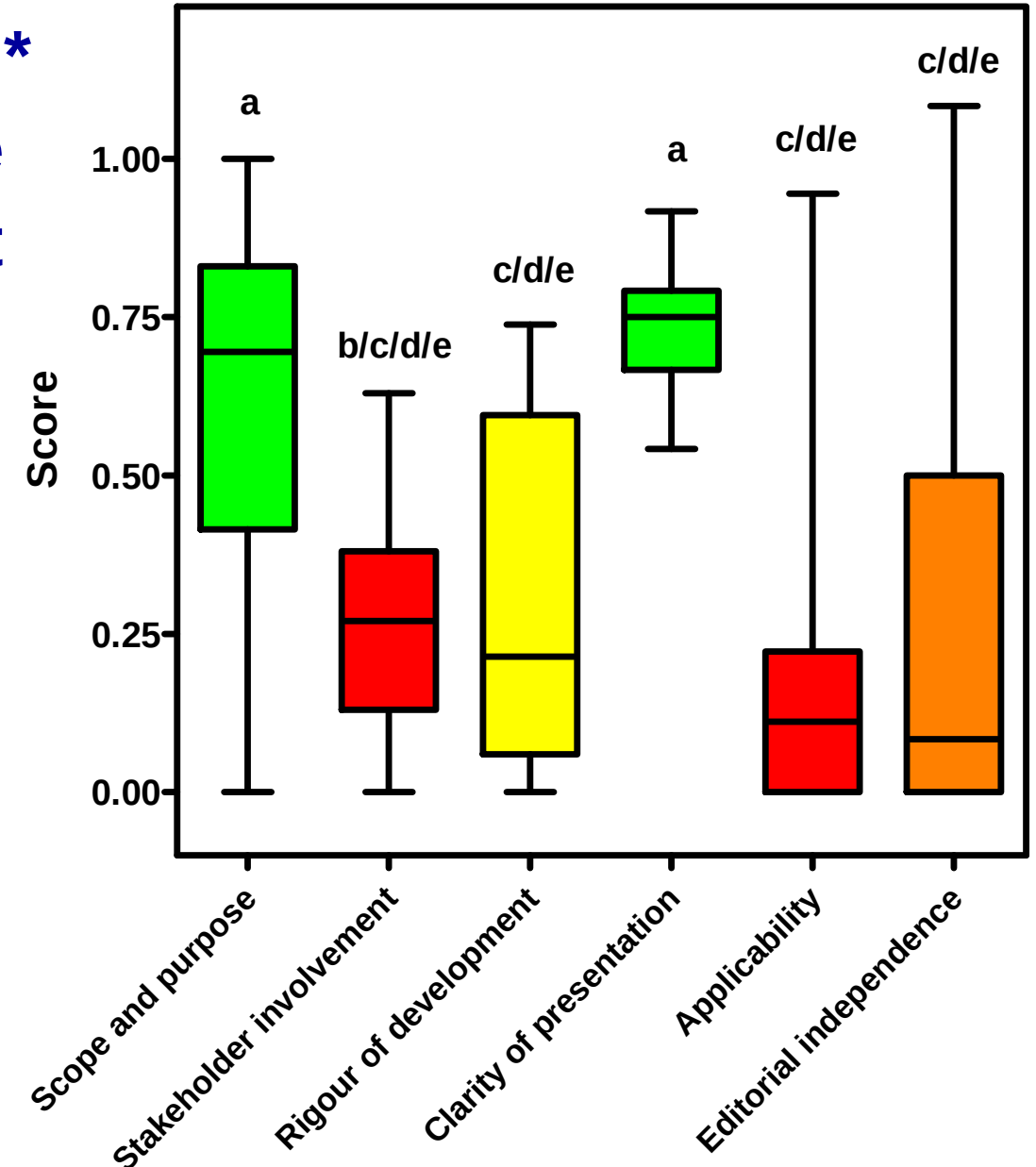
V. Domain 5. Applicability

VI. Domain 6. Editorial Independence

***A**ppraisal of **G**uidelines **R**esearch and **E**valuation – developed through an EU-funded research project and available on http://www.agreetrust.org/

Analysis of 30 CAP * guidelines with the AGREE Instrument

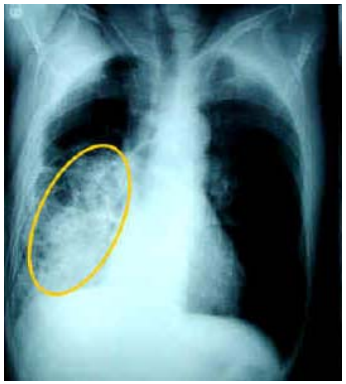
* CAP: community acquired pneumonia



- Mean scores presented as 'boxes and whiskers' (lowest to highest with 25 -75% and median.
- Scores of domains with different letters are significantly different from each other (Kruskal-Wallis test with Dunn's Multiple Comparison Test)

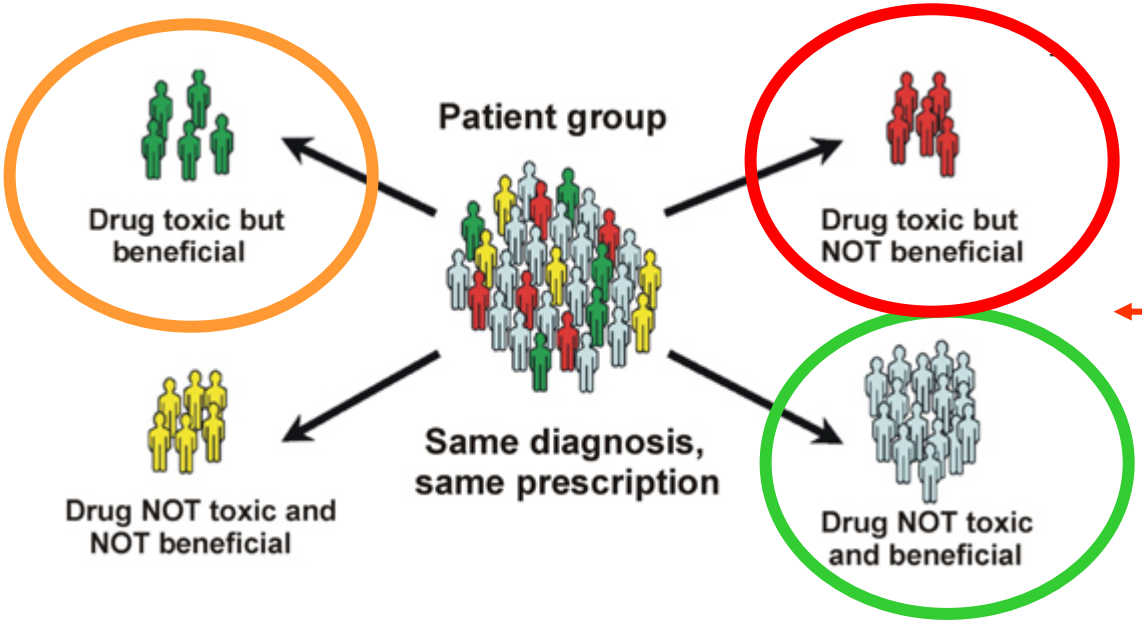
Carbonnelle *et al.*, in preparation

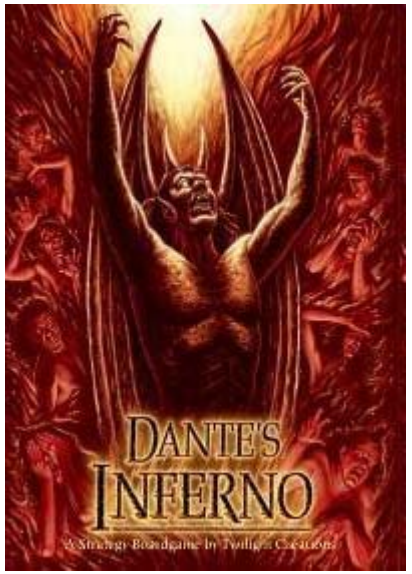
But what about side effects…



therapy ?

side effects ?





All antimicrobials have associated risks

Conclusions so far:

- All antimicrobials used in RTI are associated with known toxicities
- The main point will be the recognition of patients at risk (exclusions)
- The next point will be a correct evaluation of the benefit / risk ratio in the **specific environment** and for the **specific patient**

Never say that …

and check for specific risks

RTI: respiratory tract infection

The 3 major "points for attention" in guidelines

Are they not too dogmatic ?

Are they geared to the REAL patient ?

Are they regularly updated and modernized ?

Conclusions (and food for thought)

- Guidelines are **interesting** and most probably **useful**
- Their writing is a **difficult exercise** and their implementation is a long journey (unsurprisingly)… that **never ends** (no surprise either) …
- They MUST remain open to accommodate for **local** and special situations, with the primary emphasis on **epidemiology** and the second on **real patients**…
- At the end of the day, it will be the doctor's choice, but that choice MUST be rational and based on **best evidence applied to the patient**
- Societal responsibility (in this case, the **emergence of resistance**) should not be ignored*
- Economic responsibility is also important, although the acquisition costs of antibiotics are MUCH lower than those of many other drugs*

***Not addressed in this lecture but do ask questions…**

Disclosures

Financial support from

- the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
- *Université catholique de Louvain* for personal support
- Commercial Relationships:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics…
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - Belgian Transparency and Reimbursement Committees
  - Participation to EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones