The pharmacological and microbiological basis of PK/PD : why did we need to invent PK/PD in the first place ?

Paul M. Tulkens

- Cellular and Molecular Pharmacology Unit
  Catholic University of Louvain, Brussels, Belgium
- Founding member and past-president (1998-2000) of ISAP

www.facm.ucl.ac.be

www.isap.org

The situation in the early 90's …

- anti-infective drug doising was largely irrational or not based on sounds pharmacodynamics / toxicodynamics
  - search for low doses for fear of toxicity
  - “errors” in drug dosages at registration
  - misunderstanding of what is an optimal schedule and what it implies
- pharmacokinetics was mainly used to establish “drug presence” rather than to make true correlations with efficacy

PK/PD of antiinfectives : what has been done ?

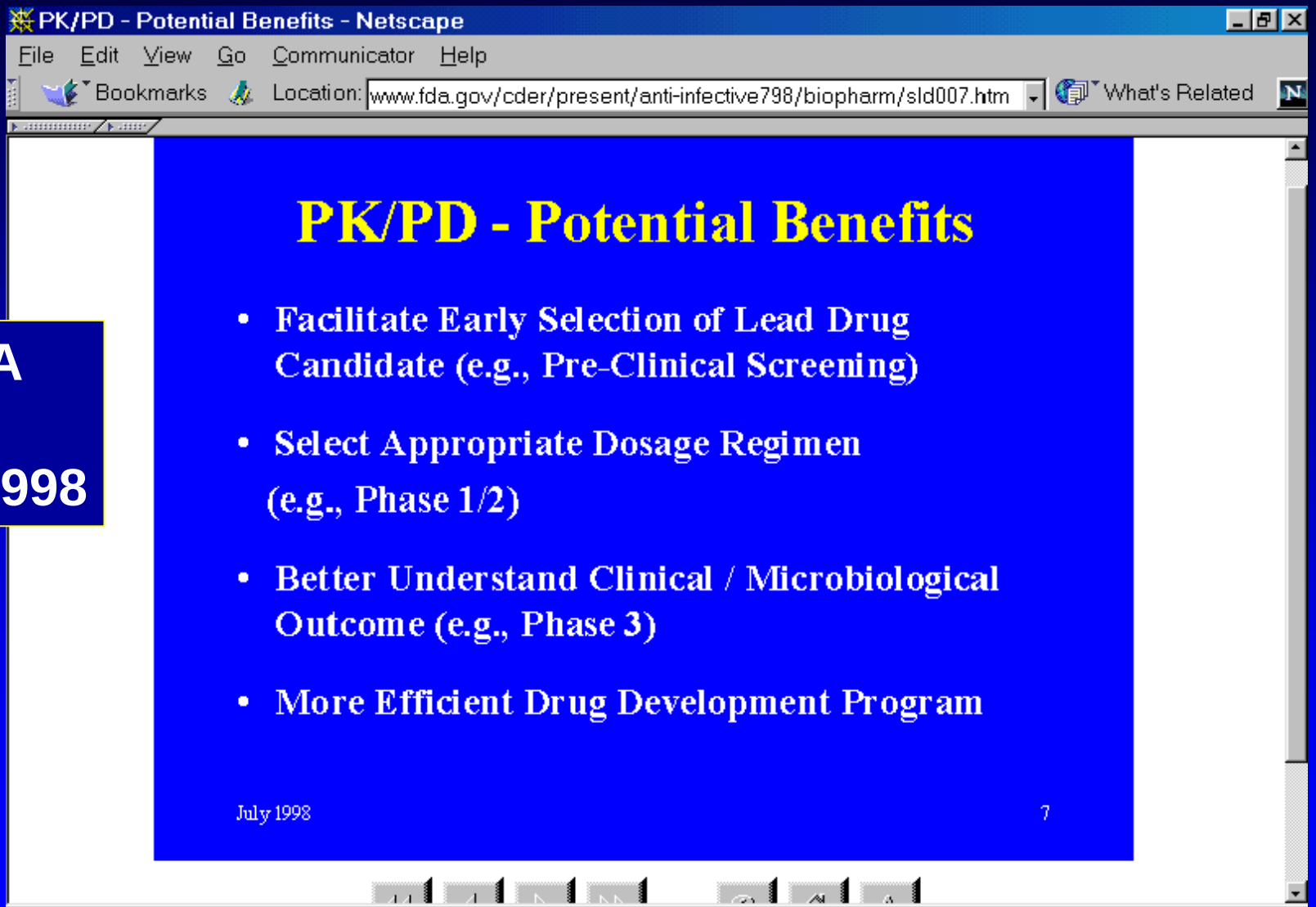
Over the last 10 years, three major concepts have emerged and proven useful :

- **dose-effect relationships are not the same for all anti-infectives**
  - **beta-lactams *vs.* fluoroquinolones or aminoglycosides**
- **integration of PK/PD within pre-clinical and early clinical development allows prediction of success or failure of new antimicrobials**
- **PK/PD may help in preventing the emergence of resistance**

PK /PD in action in the Regulatory in the USA

FDA

July 1998

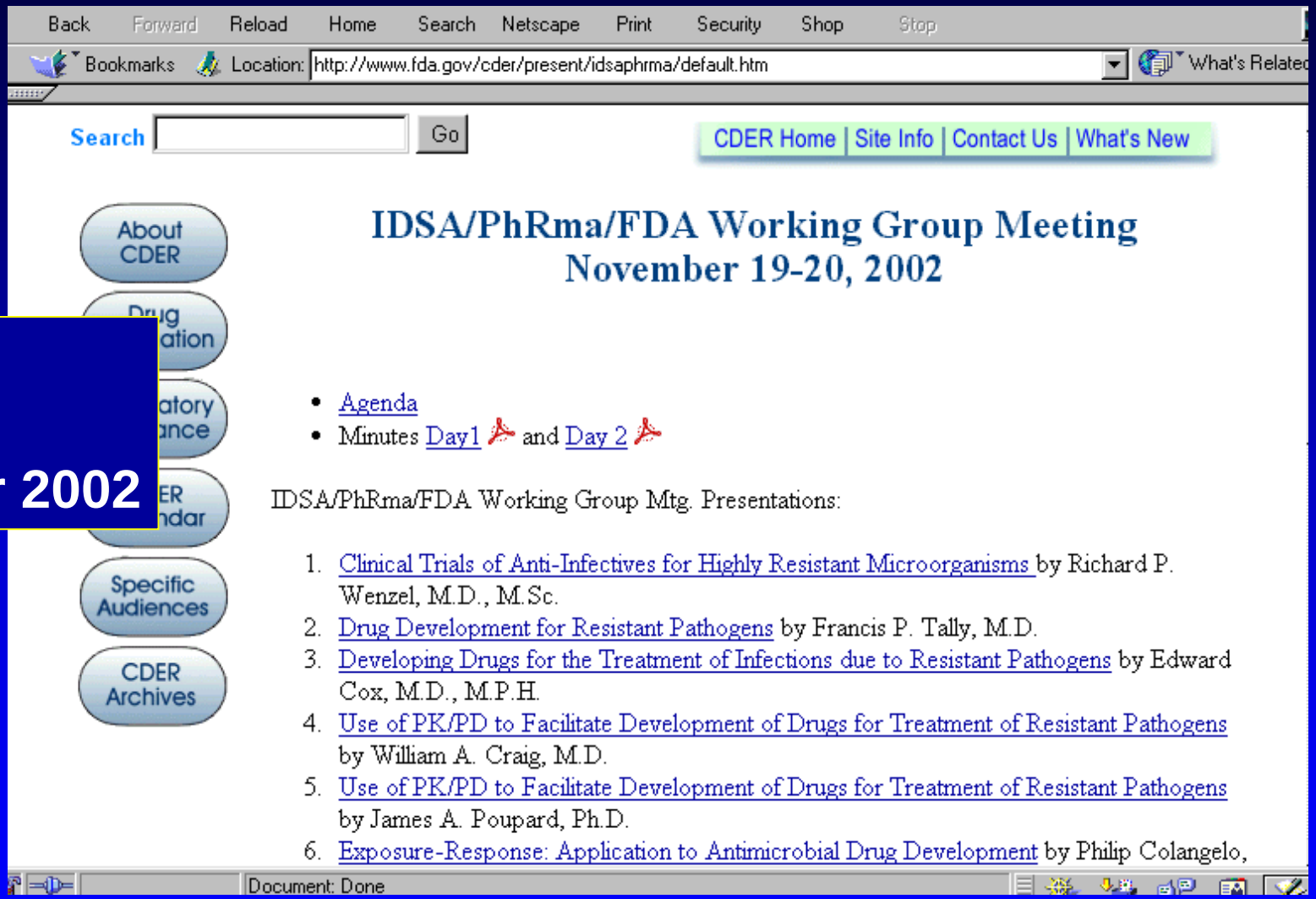


http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm

PK /PD in action in the Regulatory in the USA

FDA

November 2002



http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm

PK /PD in action in the Regulatory in Europe

EMEA
July 1999

" Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

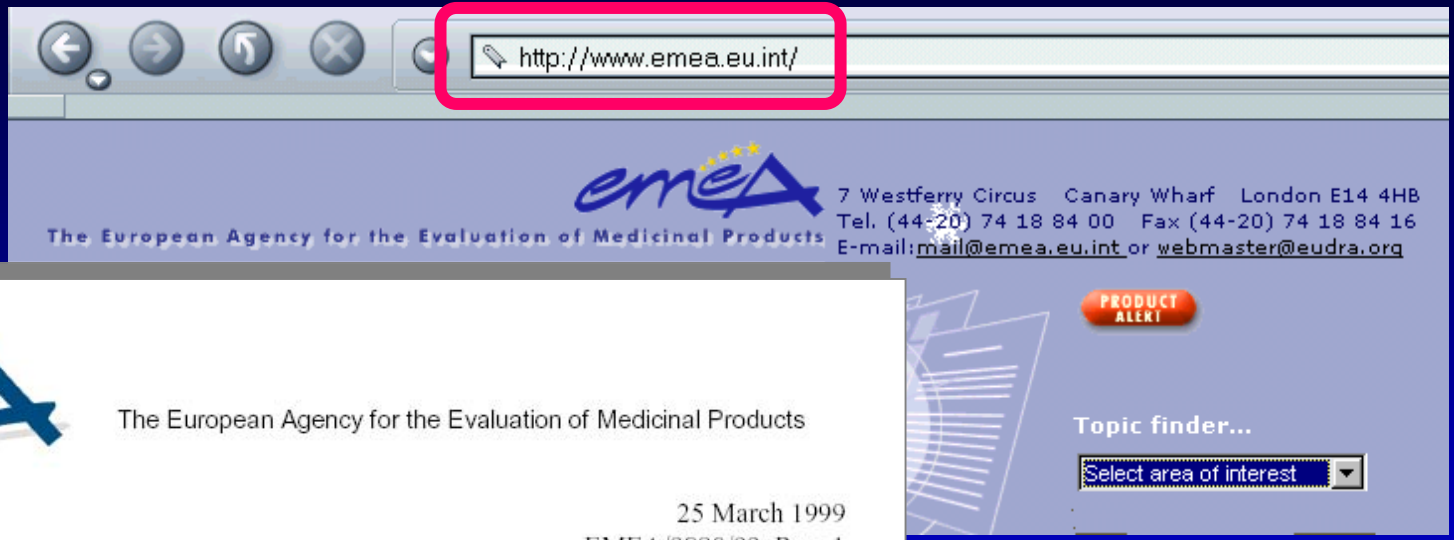
A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

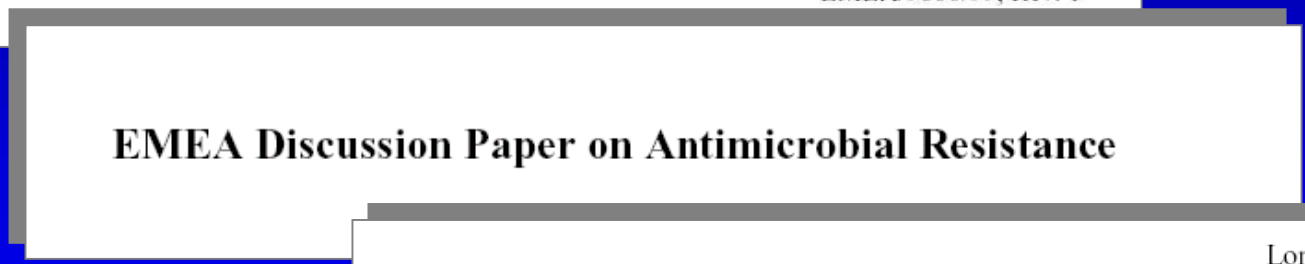
The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties… "

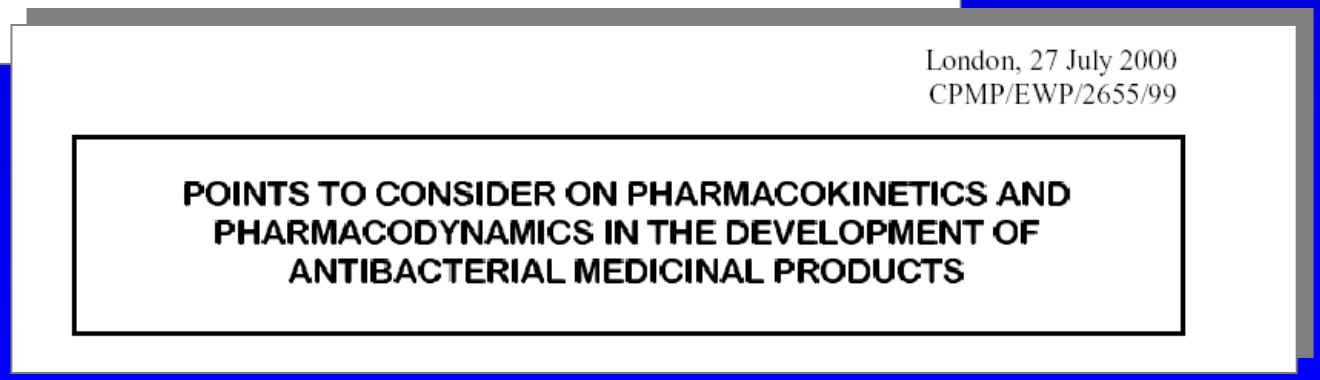
---

* Committee for Proprietary Medicinal Products

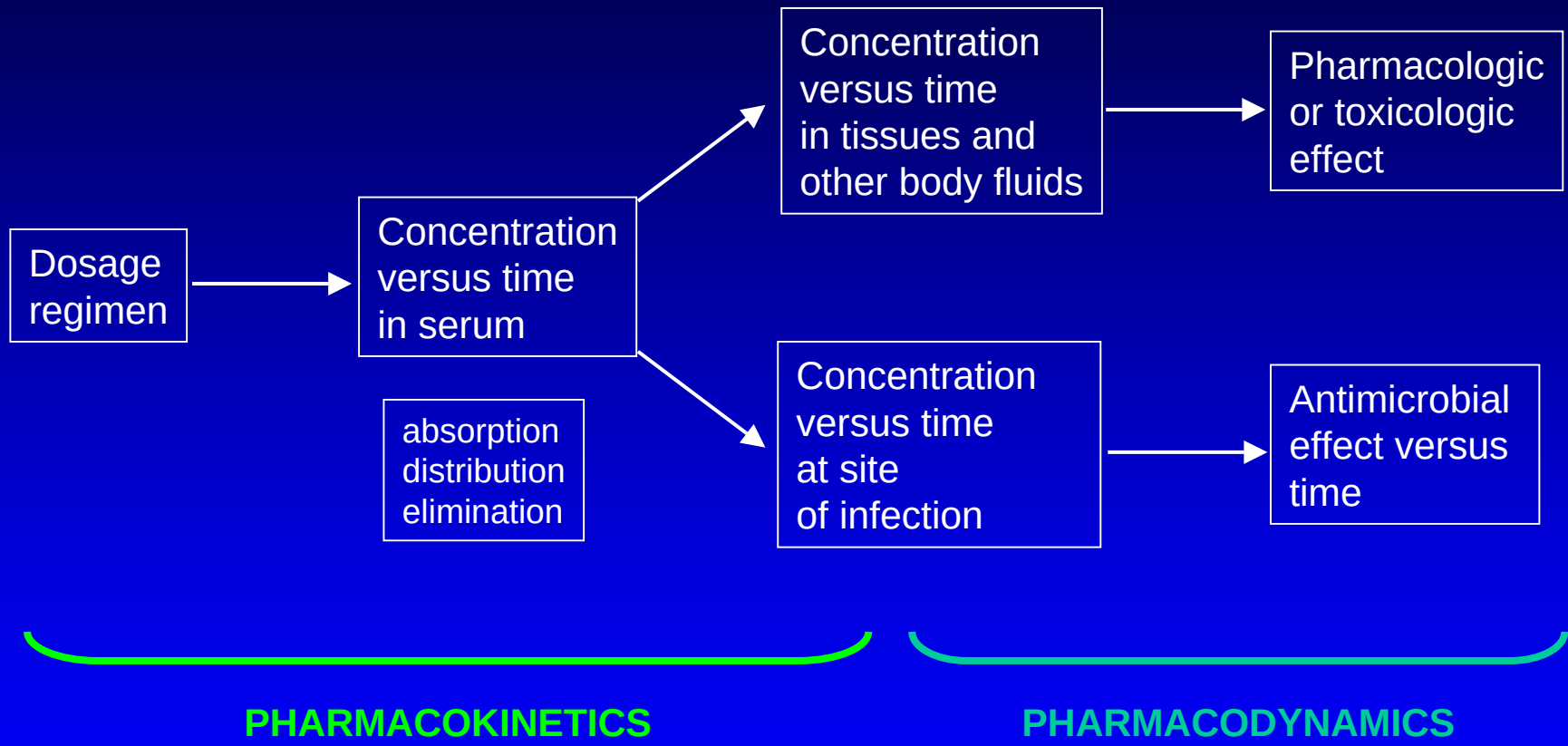
Publications of the EMEA ...





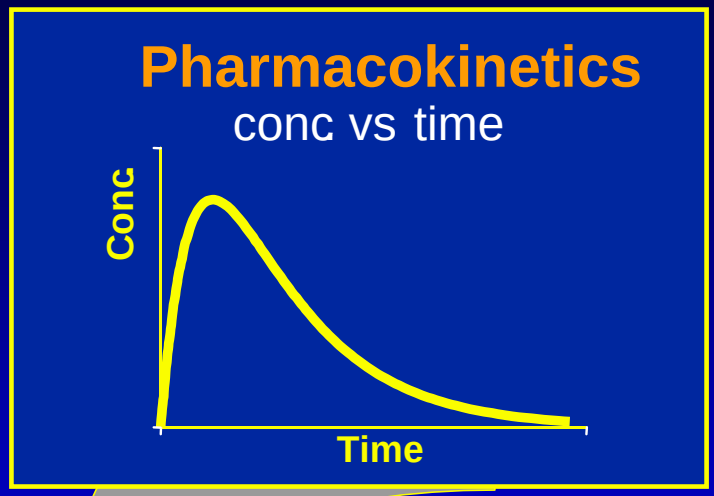


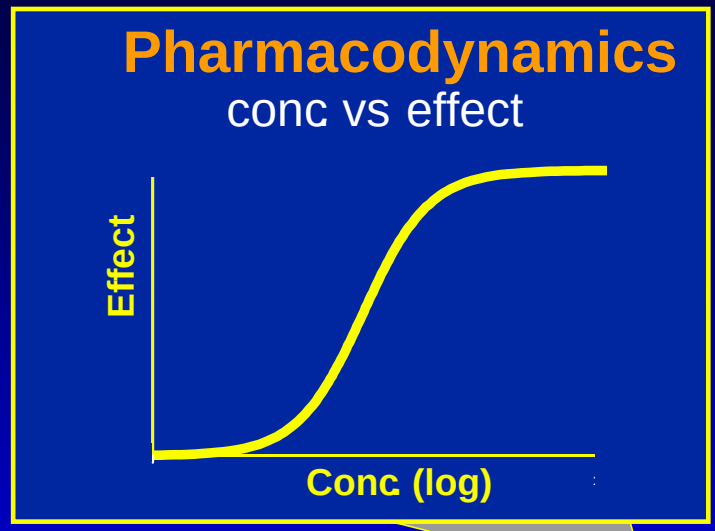
The basis of PK/PD

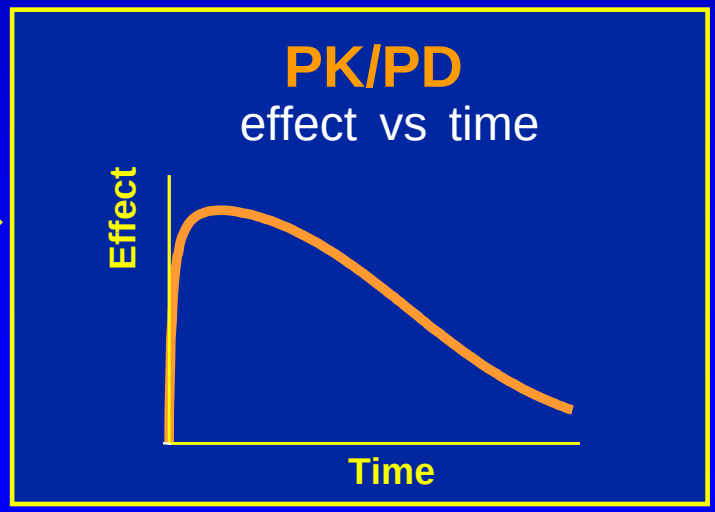


Craig (1998) CID 26:1-10

Moving from PK to PD …







Pharmacokinetic/ Pharmacodynamics in Drug Development and Evaluation

The combination of in vitro modelling, proper design of animal model experiments, and the willingness to obtain sparse pharmacokinetic information on patients in clinical trials allows an in depth understanding of which aspects of drug exposure are most closely linked to therapeutic outcome as well as to toxicity.

By providing such information to clinicians, drug therapy can achieve the goal of maximal therapeutic effect while engendering the lowest probability of encountering a drug exposure-related adverse event.

Main PK/PD properties of antibiotics

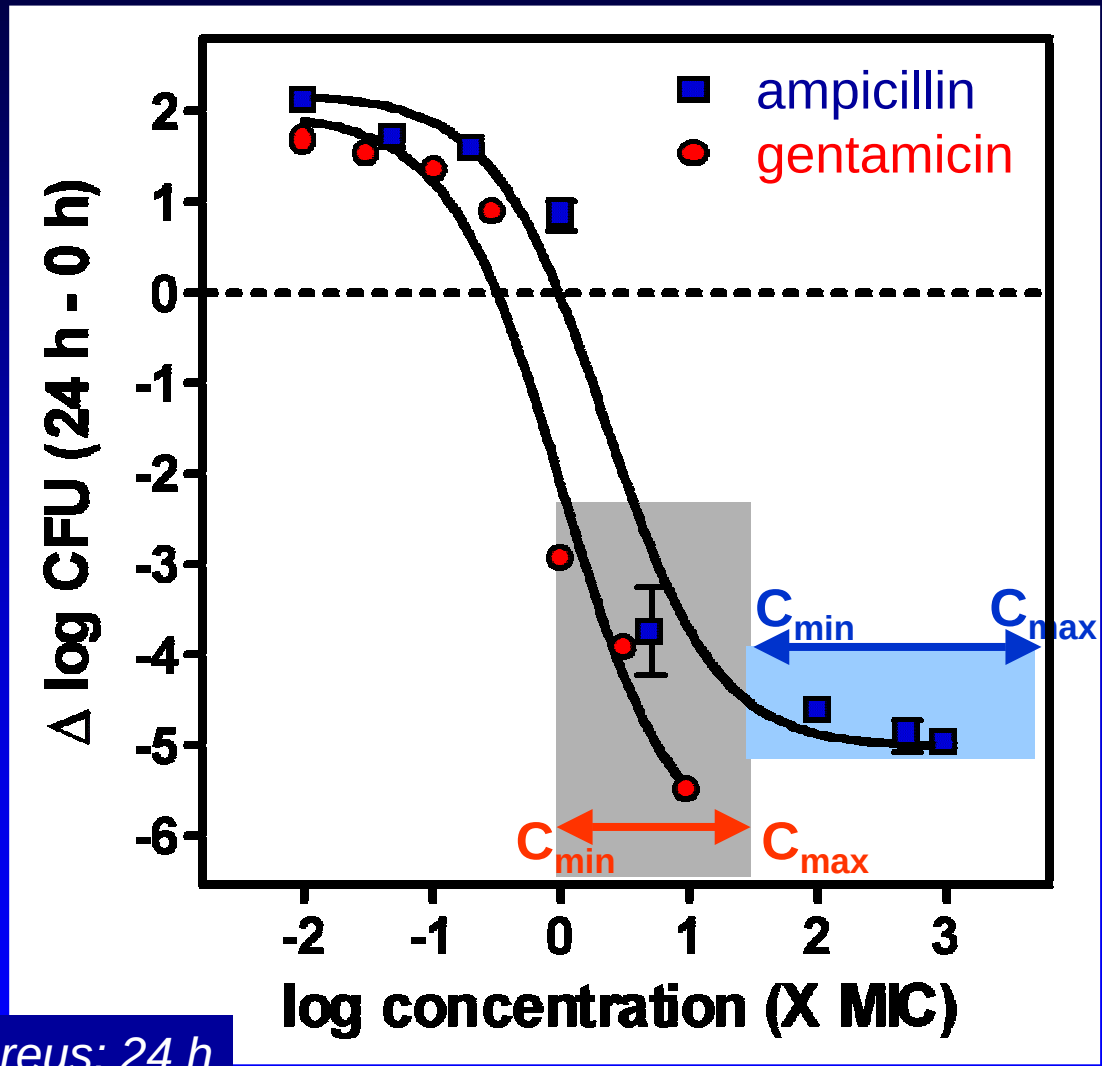
Available antibiotic can be divided in 3 groups

- time - dependent (T > MIC)
- AUC / MIC - dependent
- both AUC / MIC AND peak / MIC -dependent

Caveat: this applies to the "clinically-meaningful" concentration window only …

Clinically-meaningful concentration window …

All antibiotics are concentration-dependent, but it all dependent as how you look at them …



S. aureus; 24 h

Barcia-Macay *et al,* submitted; Lemaire *et al* (2005) JAC

Antibiotics Group # 1

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

1. Antibiotics with time-dependent effects and no or little persistent effects

AB	PK/PD parameter	Goal
β-lactams	Time above MIC	Maximize the exposure time

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

Antibiotics Group # 2

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

2. Antibiotics with time-dependent effects, with little or no influence of the concentration BUT with persistent effects

AB	PK/PD parameter	Goal
glycopeptides tetracyclines macrolides streptogramines fluconazole	**24h AUC / MIC ratio**	**Optimize the quantity of AB administered**

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

Antibiotics Group # 3

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

3. Antibiotics with concentration-dependent activity and with persistant effects (PAE)

AB	PK/PD parameter	Goal
aminoglycosides fluoroquinolones daptomycin	C_{max} / MIC **and** 24h AUC / MIC ratios	Optimize **both the peak** and the **quantity** of drug

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

PK / PD in action for the clinics

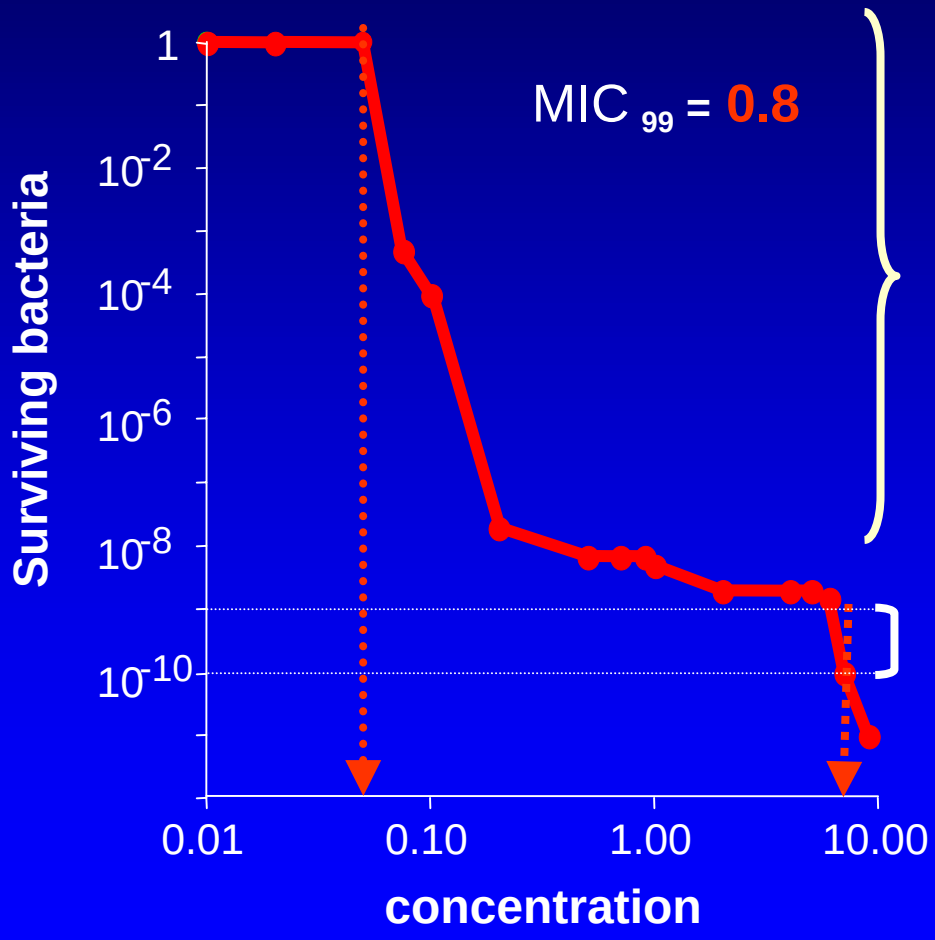
Some achievements:

- **once-daily dosing of aminoglycosides introduced in many countries**
  - **amikacin, netilmicin (from bid to qd)**
  - **isepamicin (registered essentially for qd dosing)**
- **24h AUC / MIC and C_{max} / MIC ratios used as guides for phase II / III trials, for treatment optimization and for registration of new antimicrobials**
  - **moxifloxacin**
  - **telithromycin**
- **dosage of beta-lactams adjusted to cover T > MIC in relation with the expected pathogen…**

PK/PD and resistance …

Mutant Prevention Concentration …

Bactericidal effect of a FQ towards *Mycobacterium bovis*

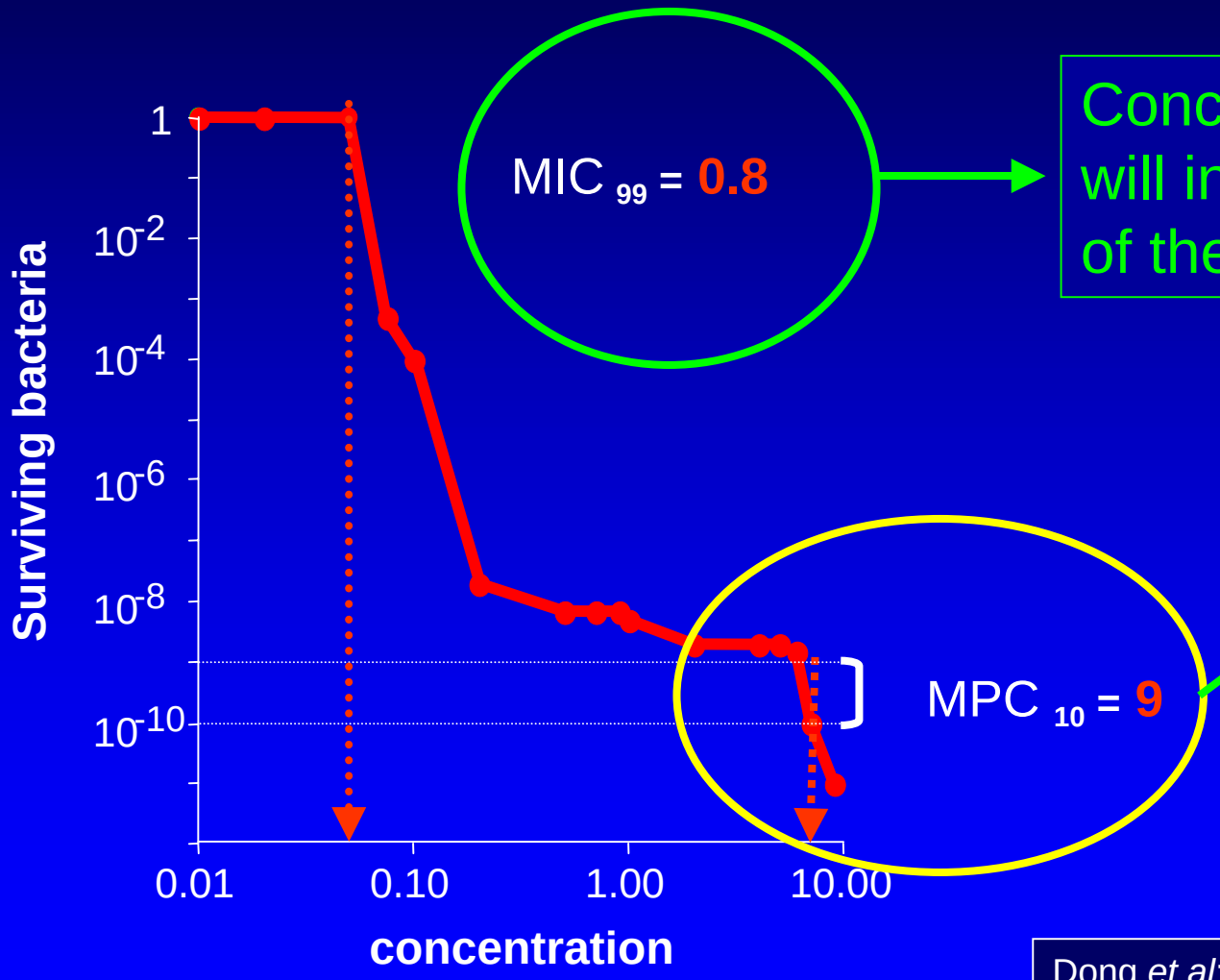


"Classic" bactericidal effect

Elimination of first mutants

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

Mutant Prevention Concentration …

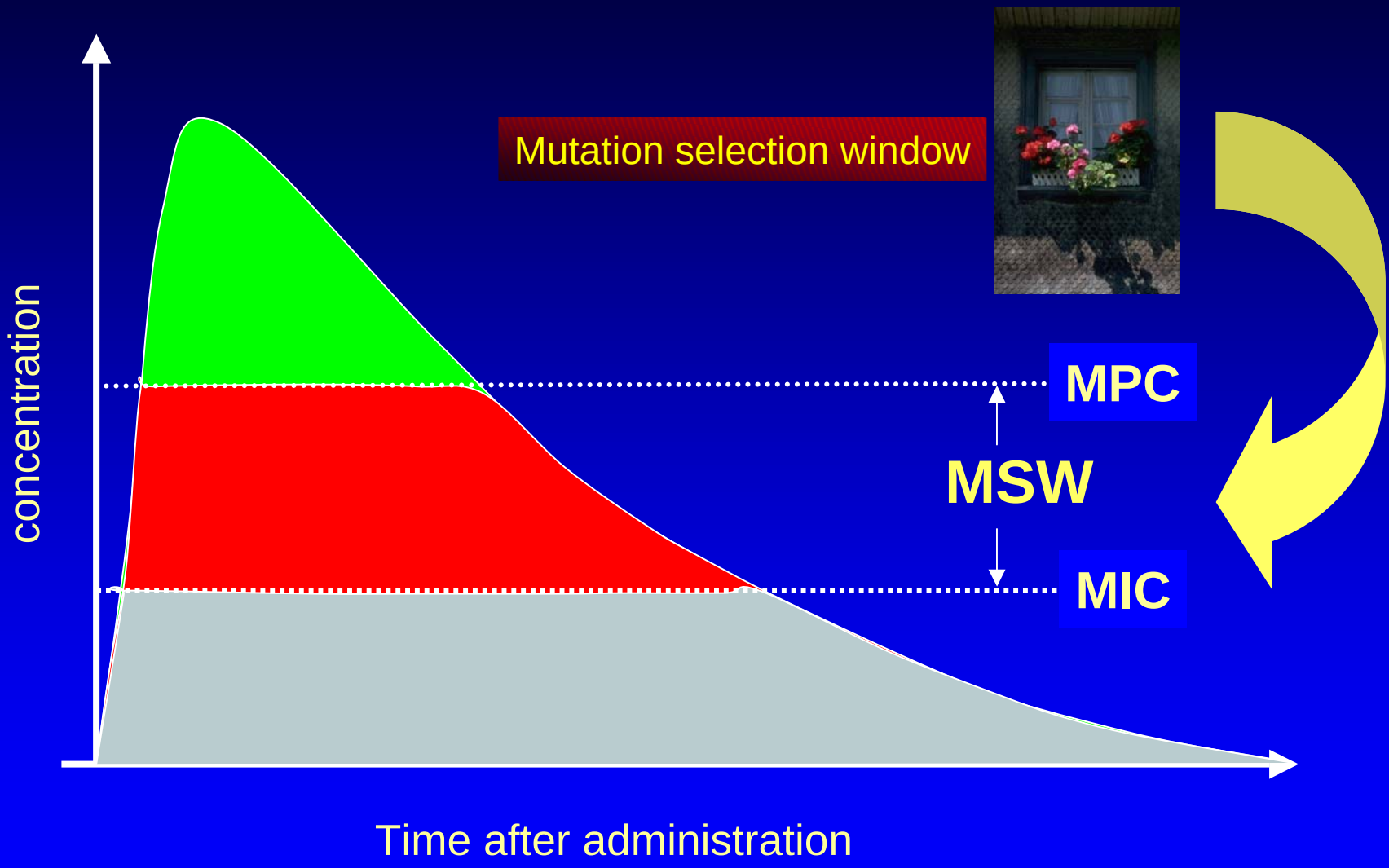


Concentration which will inhibit the majority of the organisms

Concentration necessary to prevent the selection of the first mutants

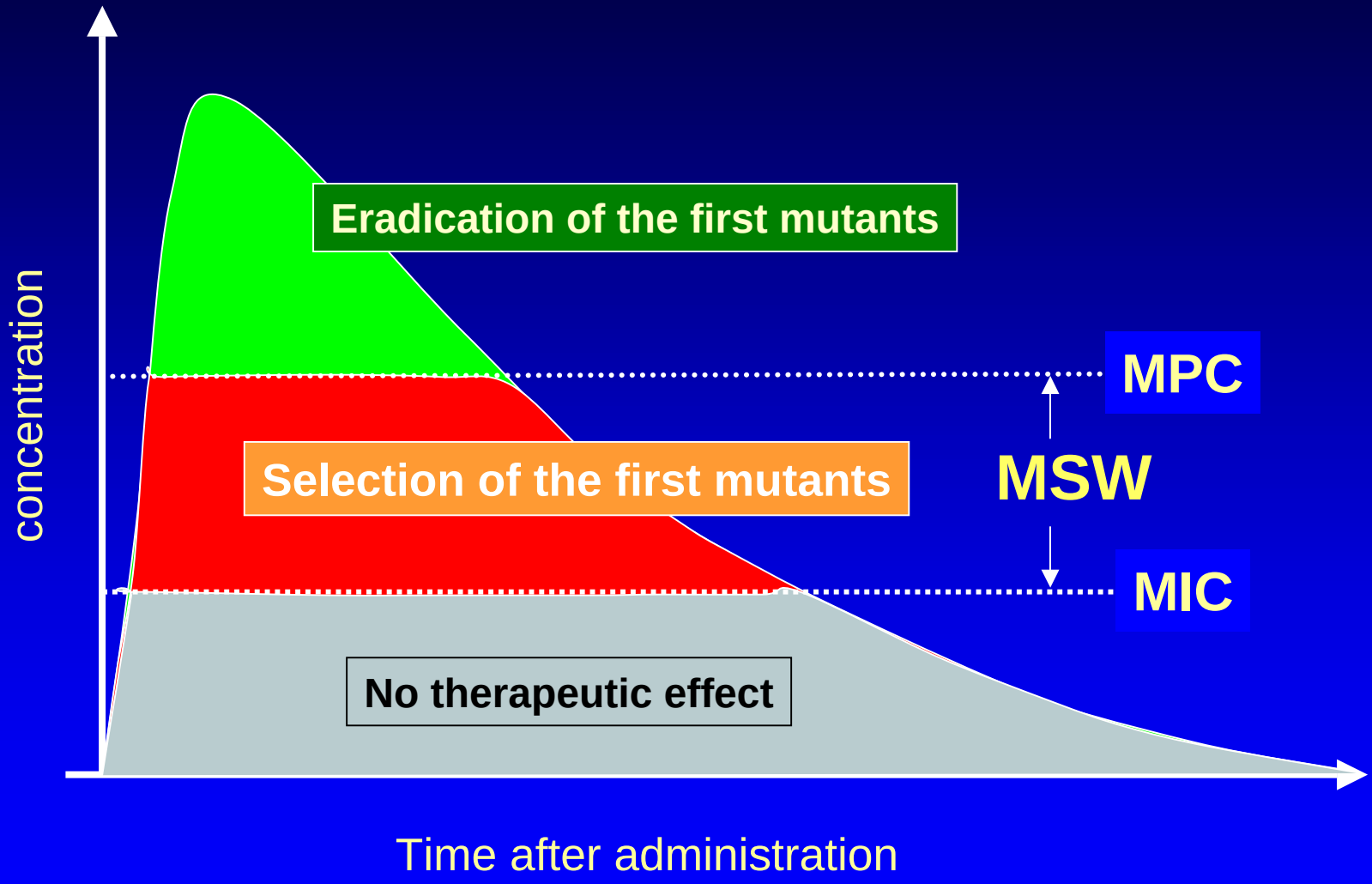
Dong *et al*; AAC 43:1756-1758

"Window" where selection of mutants takes place …



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

"Window" where selection of mutants takes place …



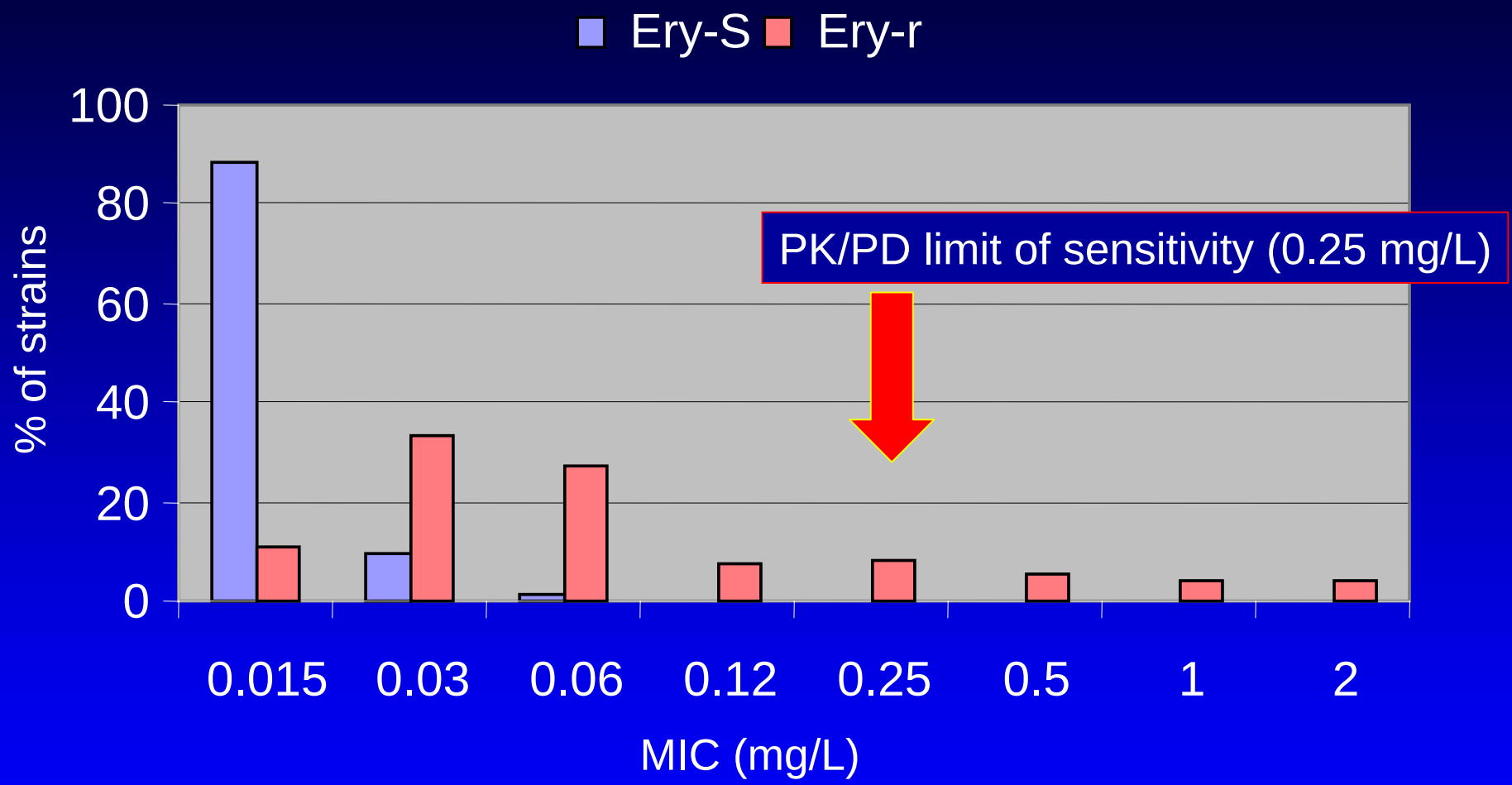
concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

Therefore, new breakpoints for 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]
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

Or, correct assessment of telithromycin…



MIC_{90} for Ery-s strains: < 0.06 ...

But MIC_{90} for Ery-r strains: 0.25-0.5 ...

Verhaegen & Verbist, Acta Clin. Belg. 2001, 56: 351

PK/PD in 2005 …

- Use if for efficacy …
- Consider it for avoiding resistance