

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

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The situation in the early 90's ...

- anti-infective drug dosing was largely irrational or not based on sound 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

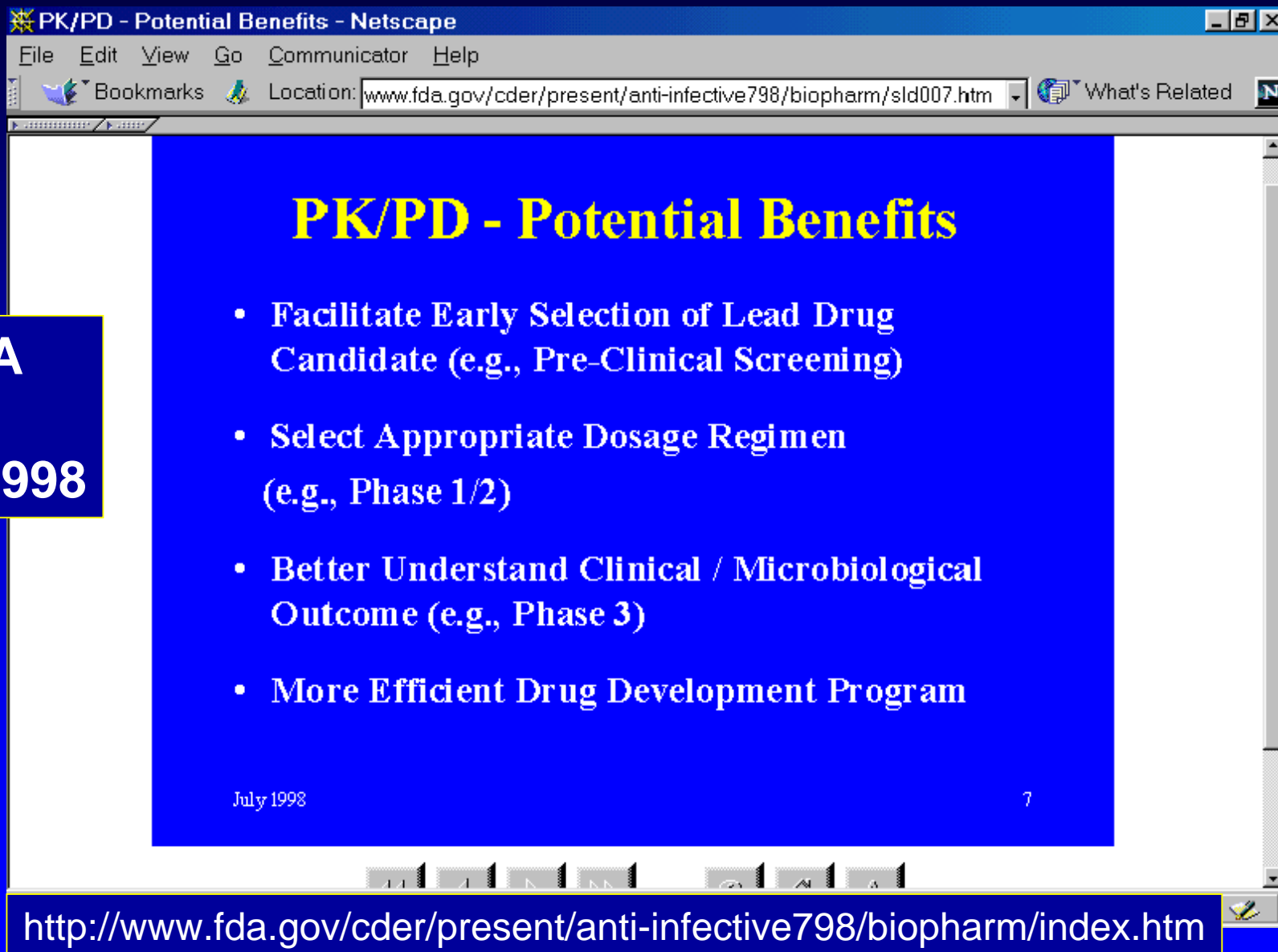
PK/PD of antiinfectives : what has been done ?

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



The screenshot shows a Netscape browser window with the title "PK/PD - Potential Benefits - Netscape". The address bar contains the URL "www.fda.gov/cder/present/anti-infective798/biopharm/sld007.htm". The main content area displays a slide with a blue background and yellow text. The slide title is "PK/PD - Potential Benefits". Below the title is a bulleted list of four points. At the bottom left of the slide is the date "July 1998" and at the bottom right is the number "7". The browser's status bar at the bottom shows the URL "http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm".

PK/PD - Potential Benefits

- Facilitate Early Selection of Lead Drug Candidate (e.g., Pre-Clinical Screening)
- Select Appropriate Dosage Regimen (e.g., Phase 1/2)
- Better Understand Clinical / Microbiological Outcome (e.g., Phase 3)
- More Efficient Drug Development Program

July 1998 7

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

PK /PD in action in the Regulatory in the USA

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IDSA/PhRma/FDA Working Group Meeting November 19-20, 2002

- [Agenda](#)
- Minutes [Day1](#) and [Day 2](#)

IDSA/PhRma/FDA Working Group Mtg. Presentations:

1. [Clinical Trials of Anti-Infectives for Highly Resistant Microorganisms](#) by Richard P. Wenzel, M.D., M.Sc.
2. [Drug Development for Resistant Pathogens](#) by Francis P. Tally, M.D.
3. [Developing Drugs for the Treatment of Infections due to Resistant Pathogens](#) by Edward Cox, M.D., M.P.H.
4. [Use of PK/PD to Facilitate Development of Drugs for Treatment of Resistant Pathogens](#) by William A. Craig, M.D.
5. [Use of PK/PD to Facilitate Development of Drugs for Treatment of Resistant Pathogens](#) by James A. Poupard, Ph.D.
6. [Exposure-Response: Application to Antimicrobial Drug Development](#) by Philip Colangelo,

Document: Done

FDA

November 2002

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

PK /PD in action in the Regulatory in Europe

**EMA
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 ...



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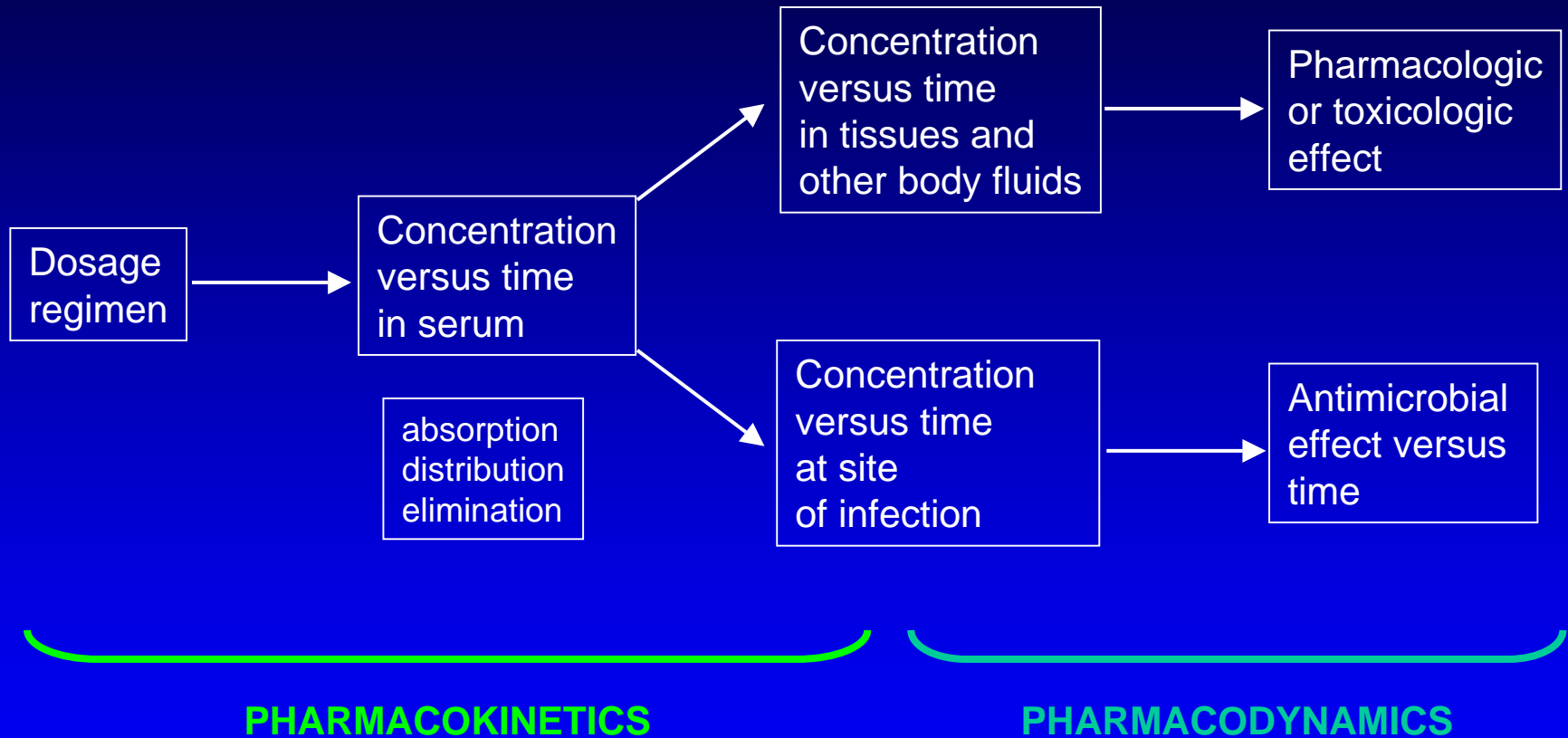
25 March 1999
EMEA/9880/99, Rev. 1

EMEA Discussion Paper on Antimicrobial Resistance

London, 27 July 2000
CPMP/EWP/2655/99

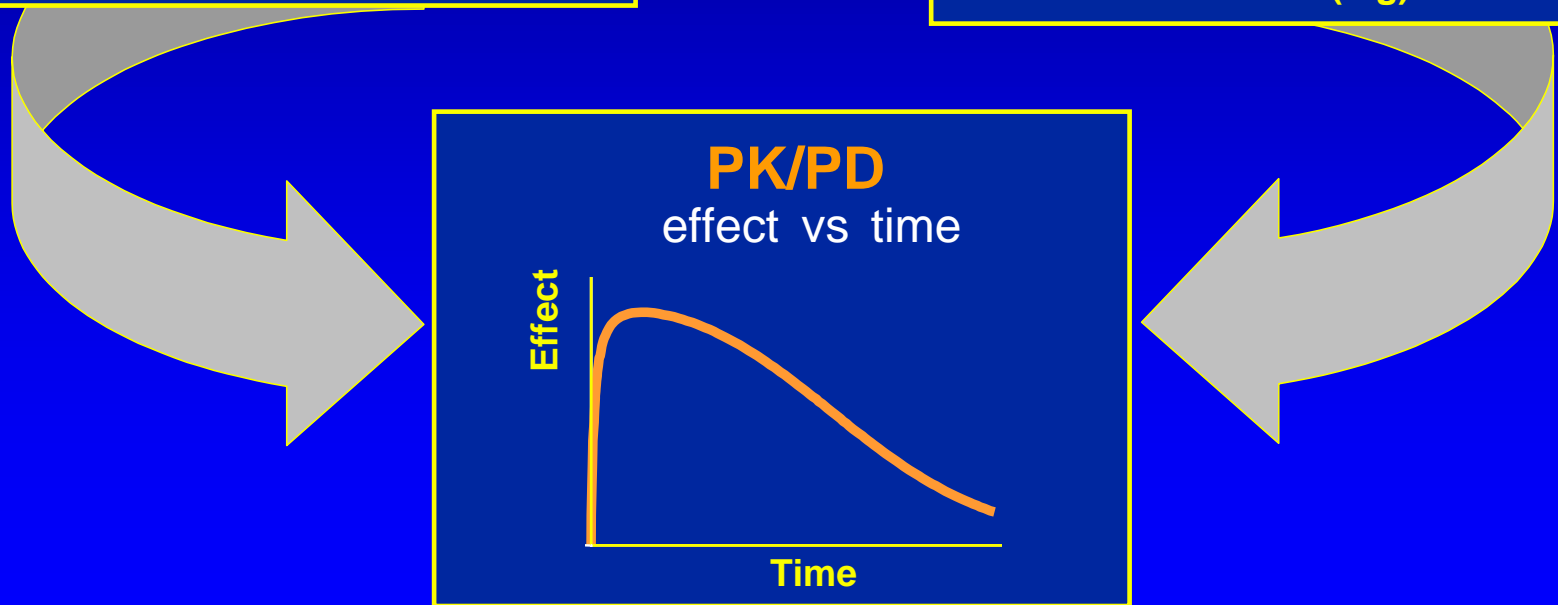
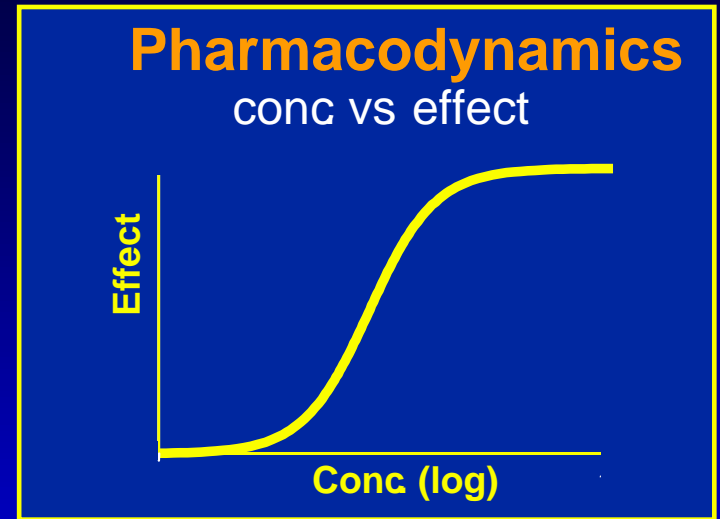
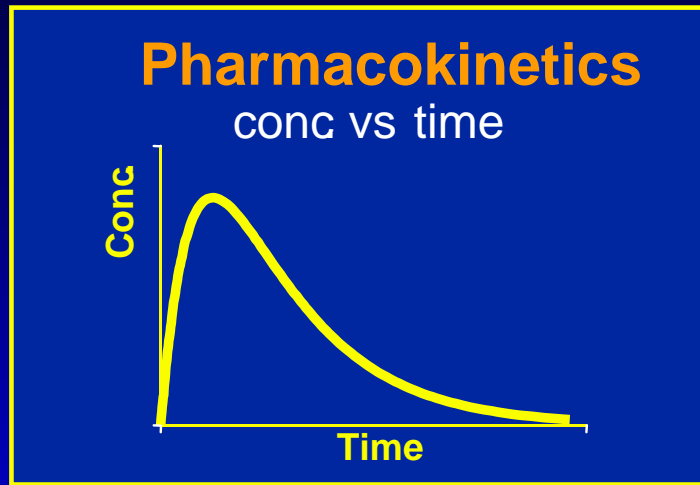
**POINTS TO CONSIDER ON PHARMACOKINETICS AND
PHARMACODYNAMICS IN THE DEVELOPMENT OF
ANTIBACTERIAL MEDICINAL PRODUCTS**

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

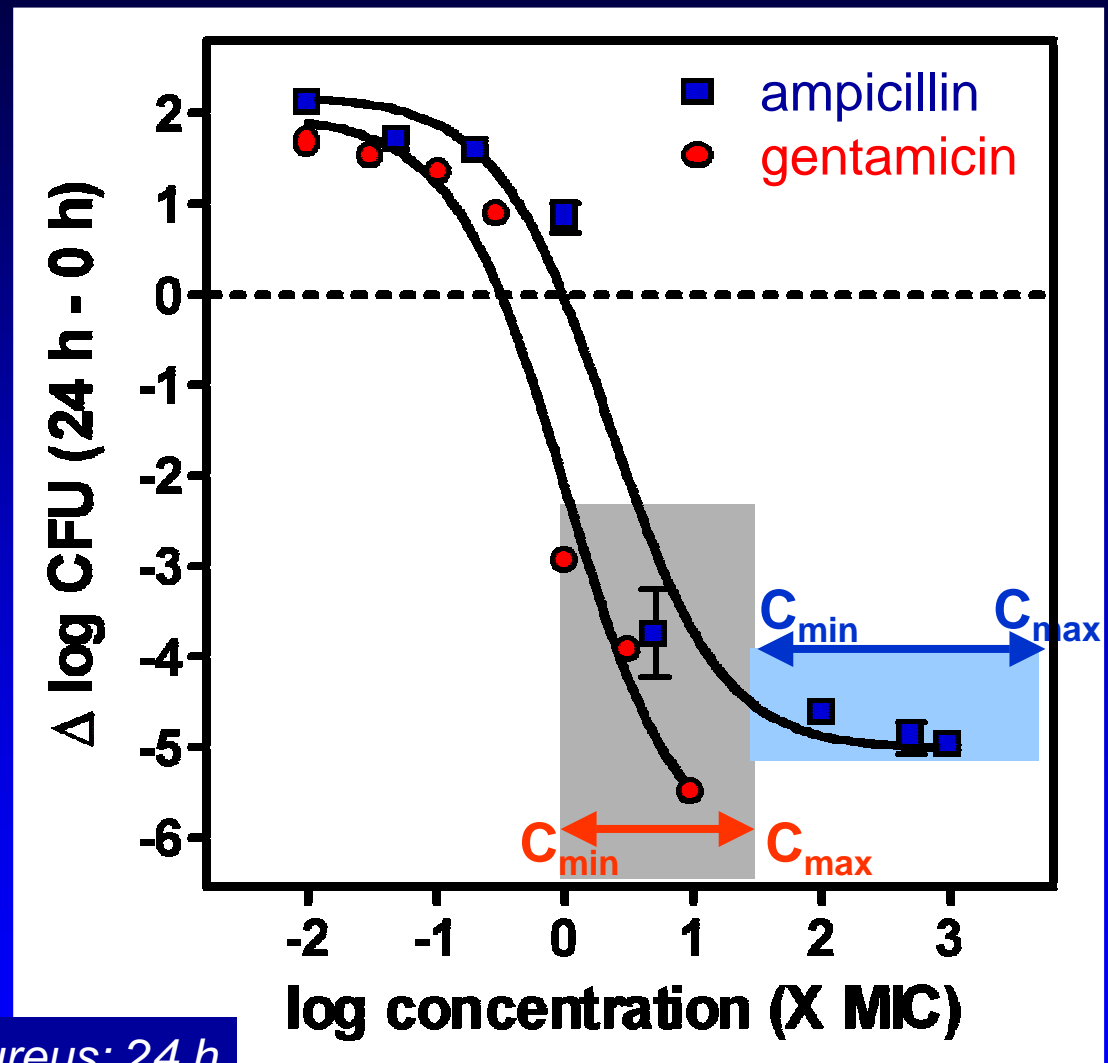
Available antibiotic can be divided in 3 groups

- 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 depends 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 persistent 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

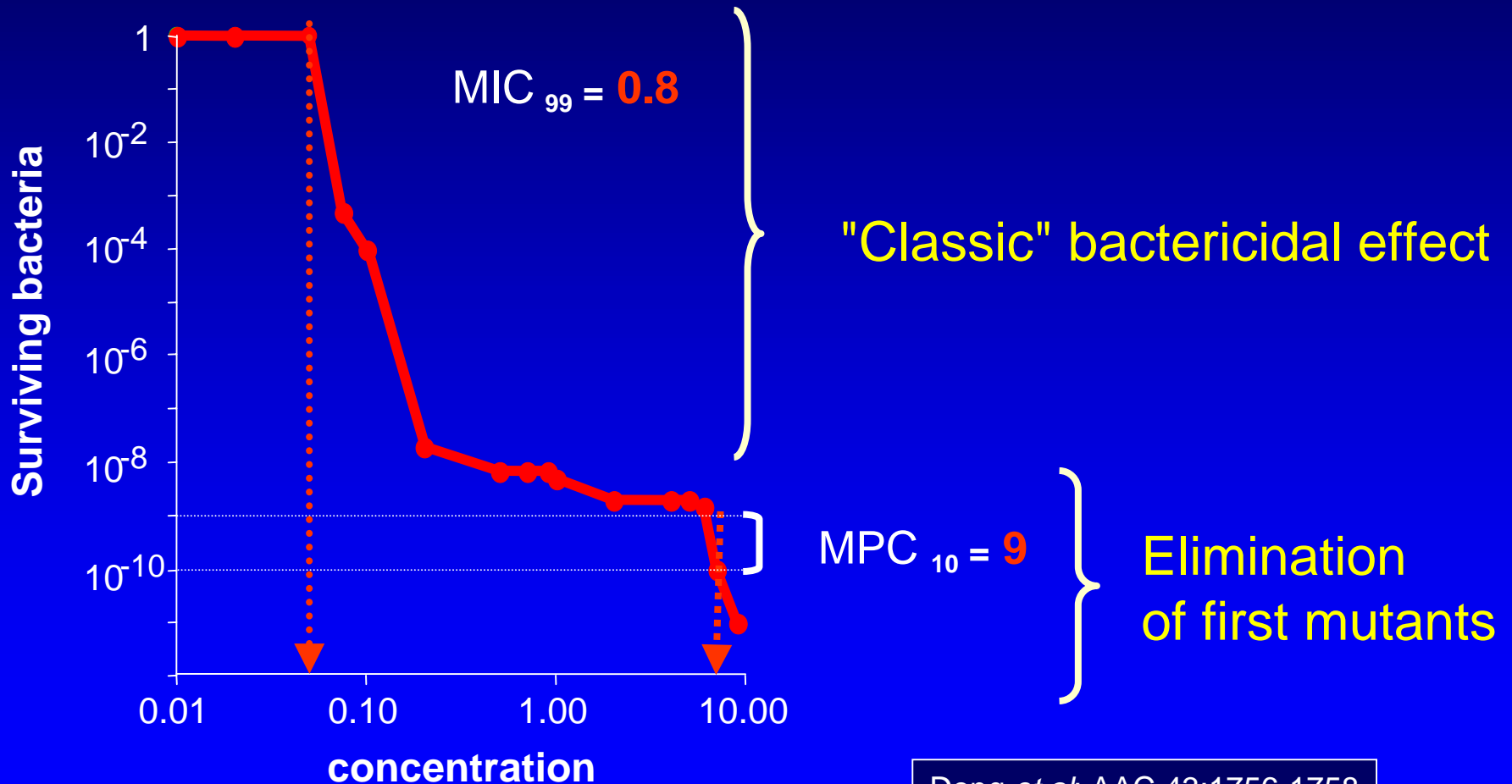
Some achievements:

- **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 ...

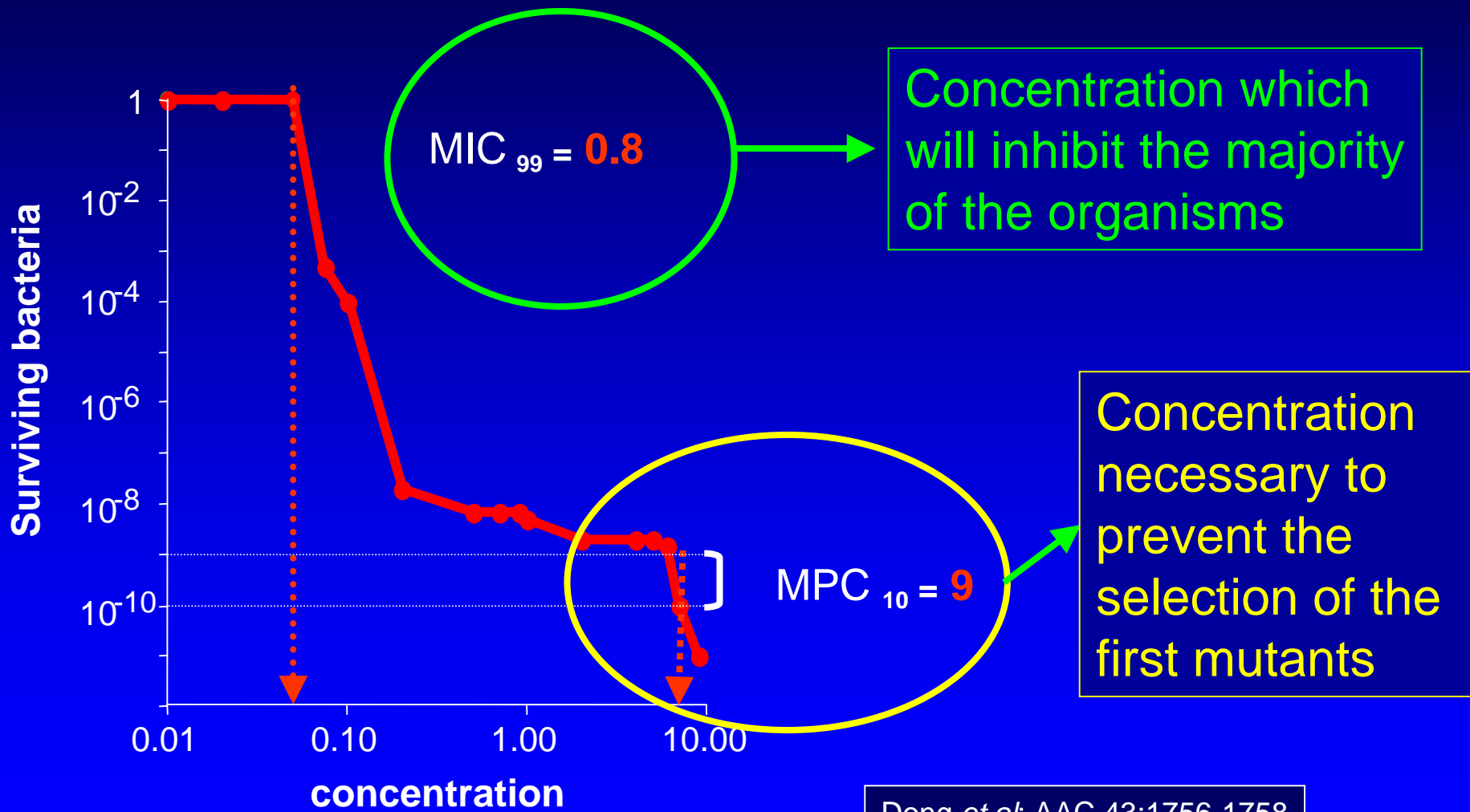
Mutant Prevention Concentration ...

Bactericidal effect of a FQ towards *Mycobacterium bovis*



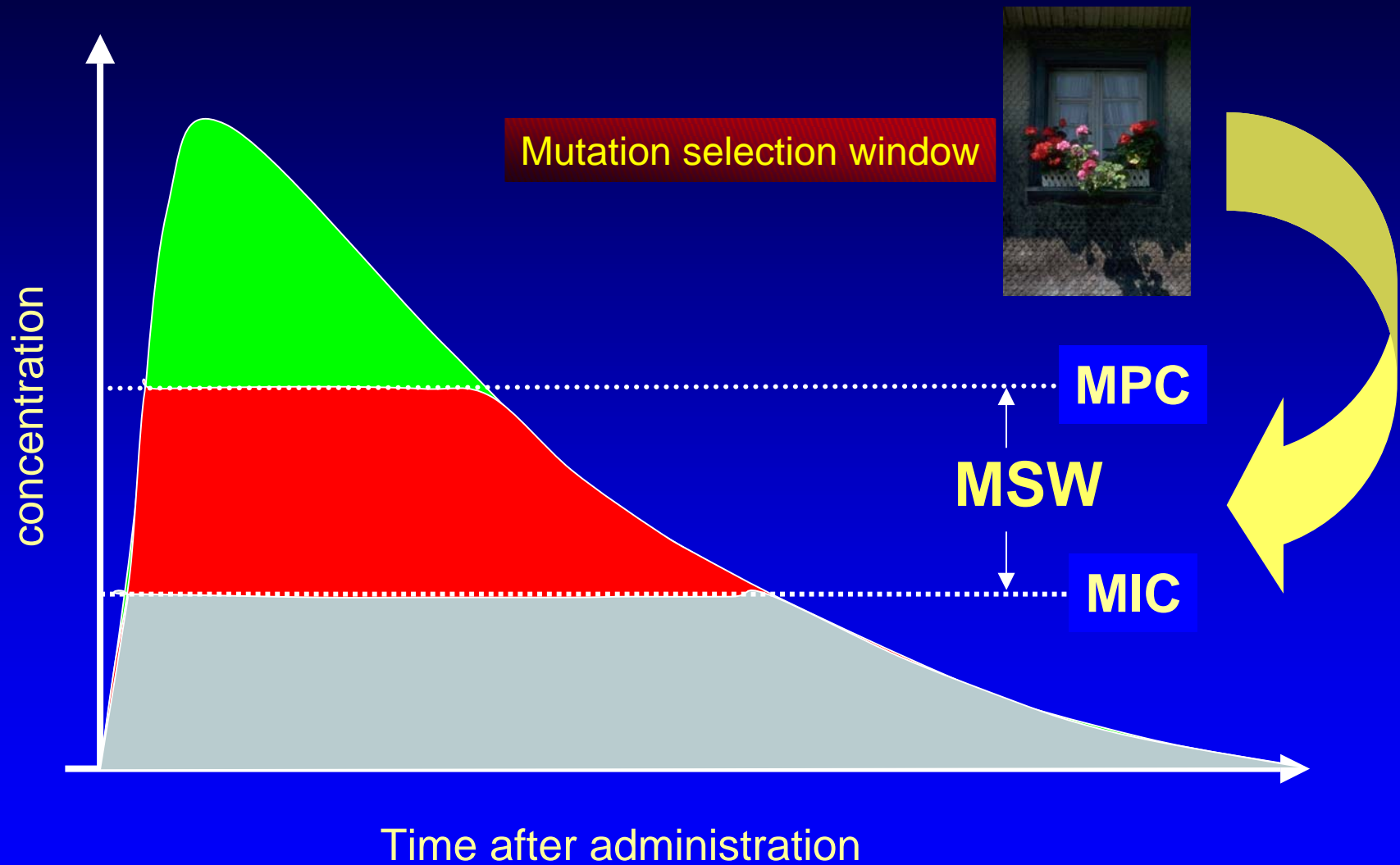
Dong *et al*; AAC 43:1756-1758

Mutant Prevention Concentration ...



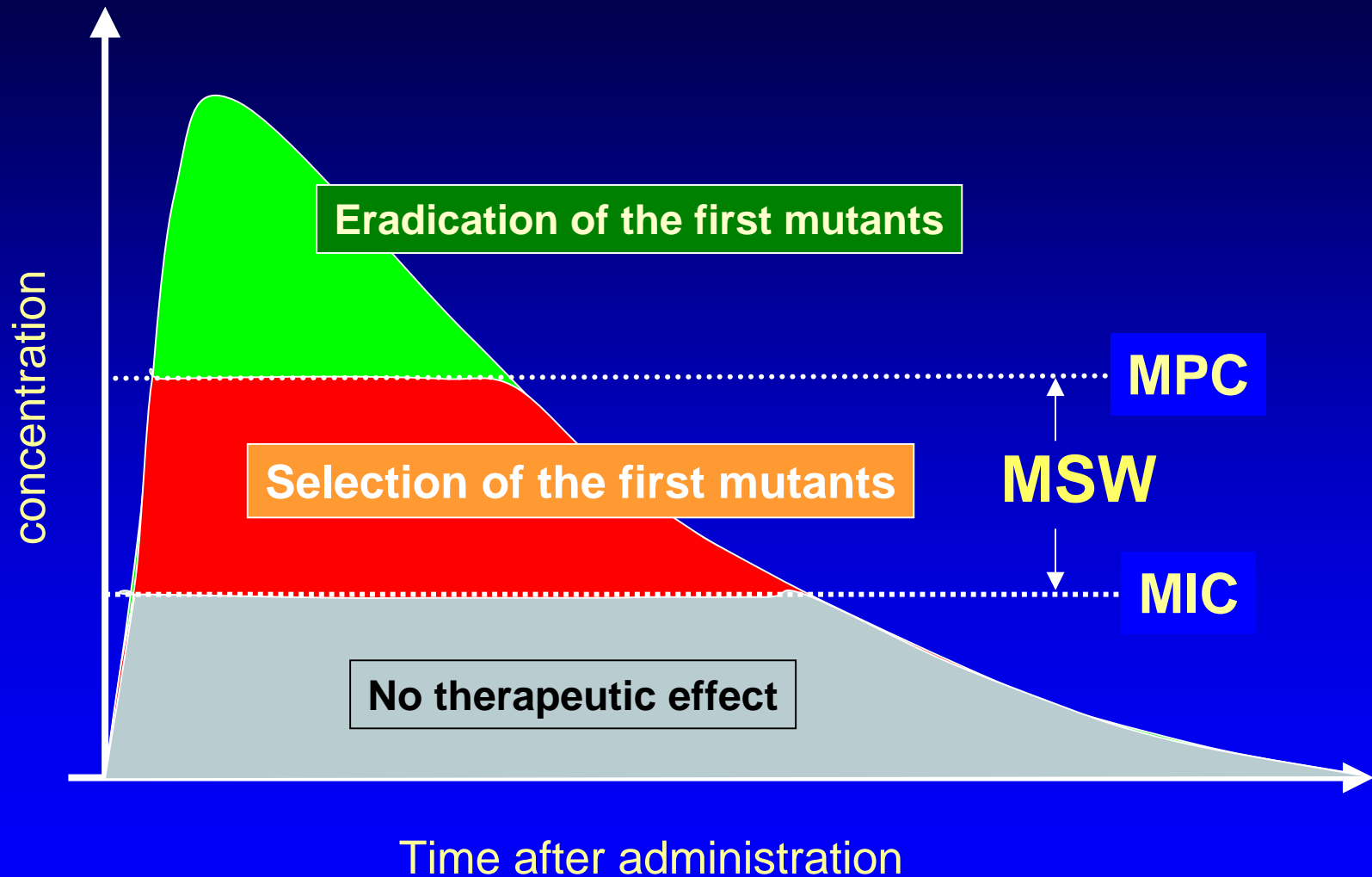
Dong *et al*; AAC 43:1756-1758

"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 ...

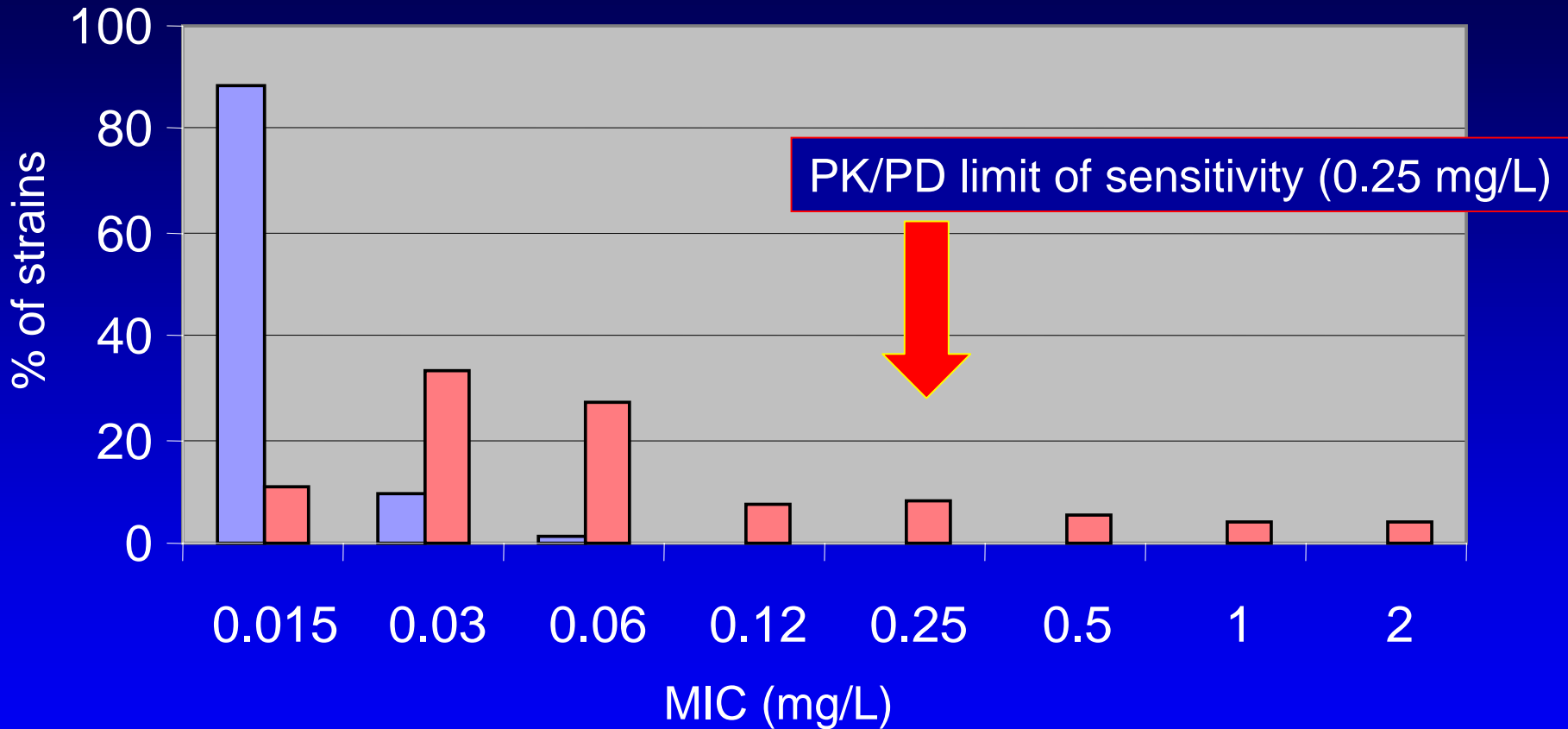
Drug	Typical daily dosage ^a	Typical PK values		Proposed PK/PD upper limit of sensitivity ($\mu\text{g/ml}$) for	
		C_{max} in mg/L total/free (dose)	$\text{AUC}_{24 \text{ h}}$ ($\text{mg} \times \text{h/L}$) total/free	Efficacy ^b	Prevention of resistance ^c
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	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...

■ Ery-S ■ Ery-r



MIC₉₀ for Ery-s strains: < 0.06 ...

But MIC₉₀ 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