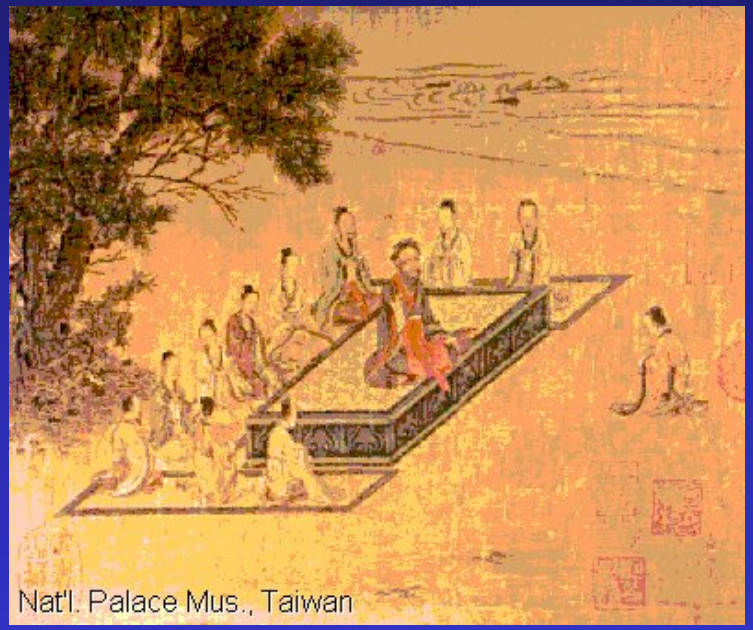
Asian PK/PD Educational Workshop

Welcome

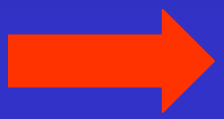


- Why is PK/PD important ?
- Who are we ?
- Programme of the Workshop

PK / PD of antiinfectives : where do we come from ?

The basics:

- **anti-infective drug usage has long been irrational or not scientifically based on a pharmacodynamic point of view**
  - **search for low doses for fear of toxicity**
  - **"errors" in drug dosages at registration**
  - **misunderstanding of "optimal schedules"**
- **pharmacokinetics was mostly used to establish "drug presence" rather than to correlate dosing with efficacy**



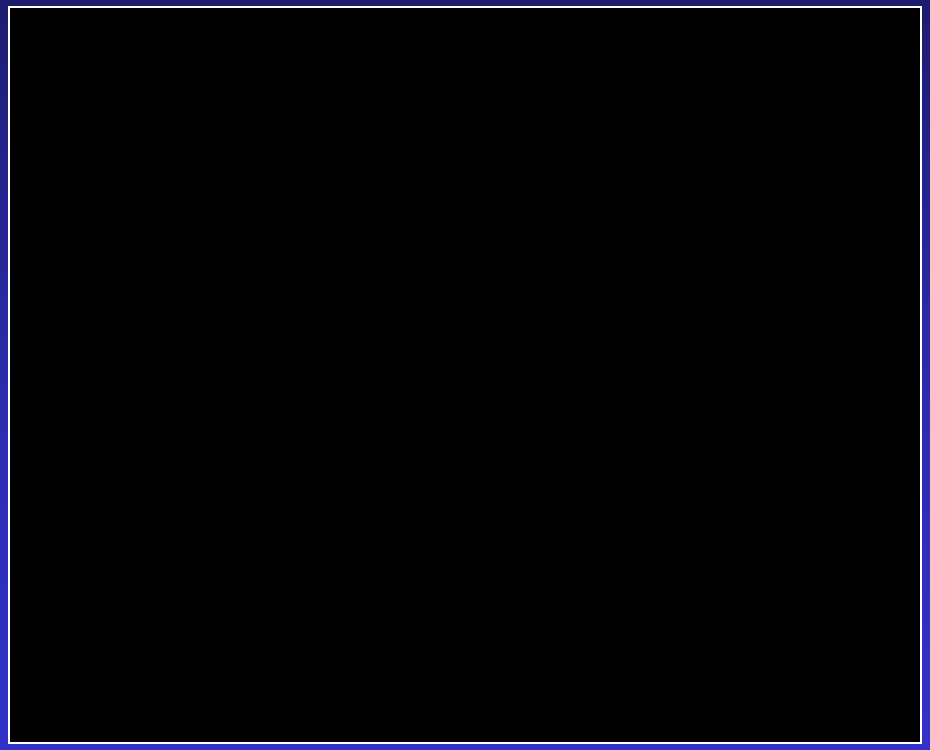
pharmacodynamics of antiinfective drugs was largely "*terra incognita*" 10 years ago

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 or glycopeptides *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**

How did it start ?



How did it start ?

A bunch of good guys met in Stockholm in 1989 ...

What did they think all about ?

PK/PD since 1989 ...

1991 : Creation of the International Society of Antiinfective Pharmacology

- incorporated in 1993 (Australia, now USA)
- 108 members wordwide
  (40% US, 40% Europe, 20% elsewhere)
  - academy
  - industry
- 11 independent symposia
- 11 co-sponsored symposia (ICAAC, ECCMID, …)
- 3 discussion symposia with Regulators
- 8 public educational workshops

http://www.isap.org

PK/PD since 1989 ...

1994 ... : organization of sessions on pharmacodynamics at the major international meetings (ICAAC, ECCMID, etc…)

1995 … : Introduction of PK/PD considerations in the drug development and registration process ...

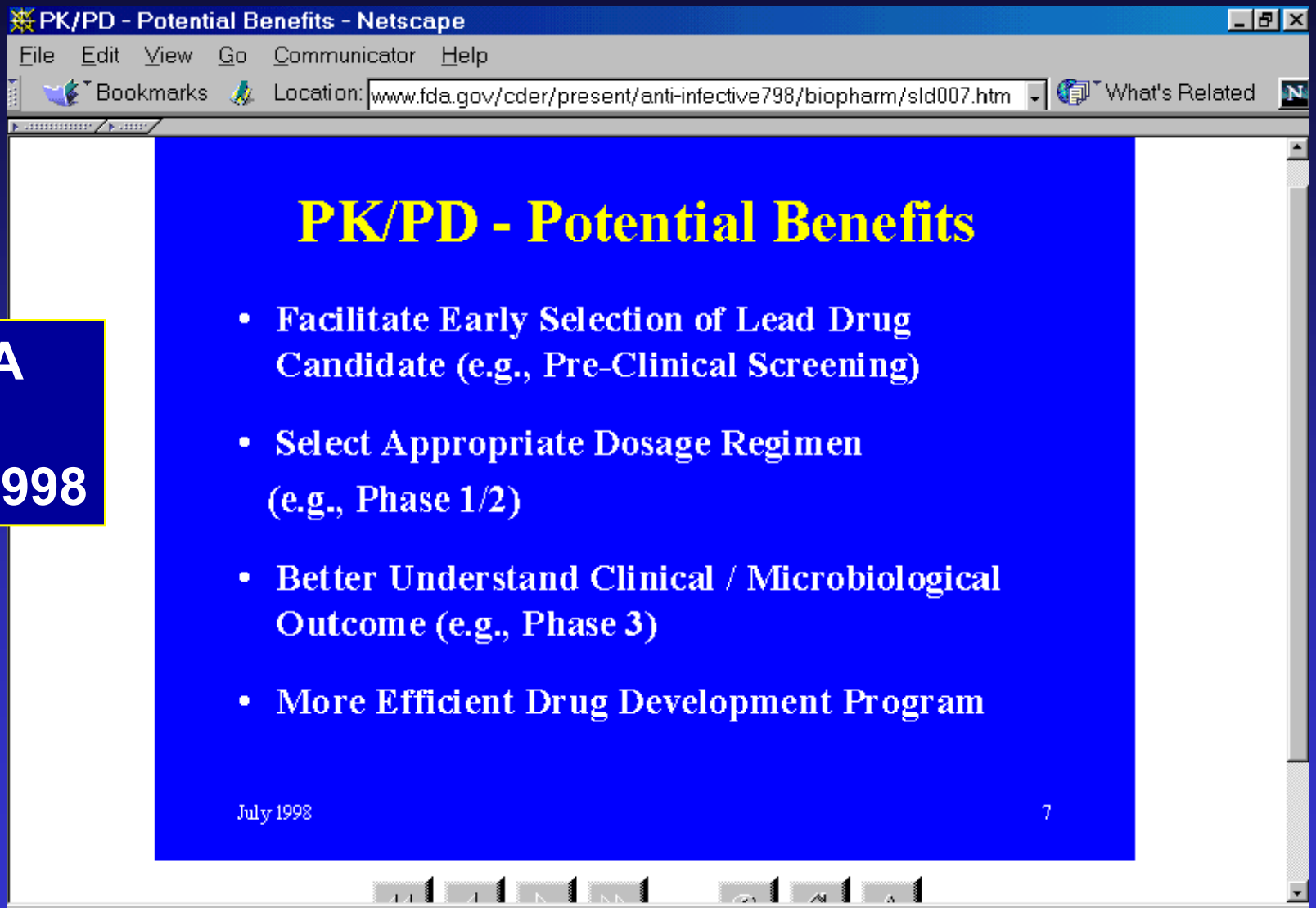
1998 … : PK/PD considerations introduced in clinical investigations and daily clinical activities ...

now …. : PK/PD considerations begin to be used to define optimal reimbursement schemes in some European countries …

PK /PD in action in the Regulatory in the USA

FDA

July 1998

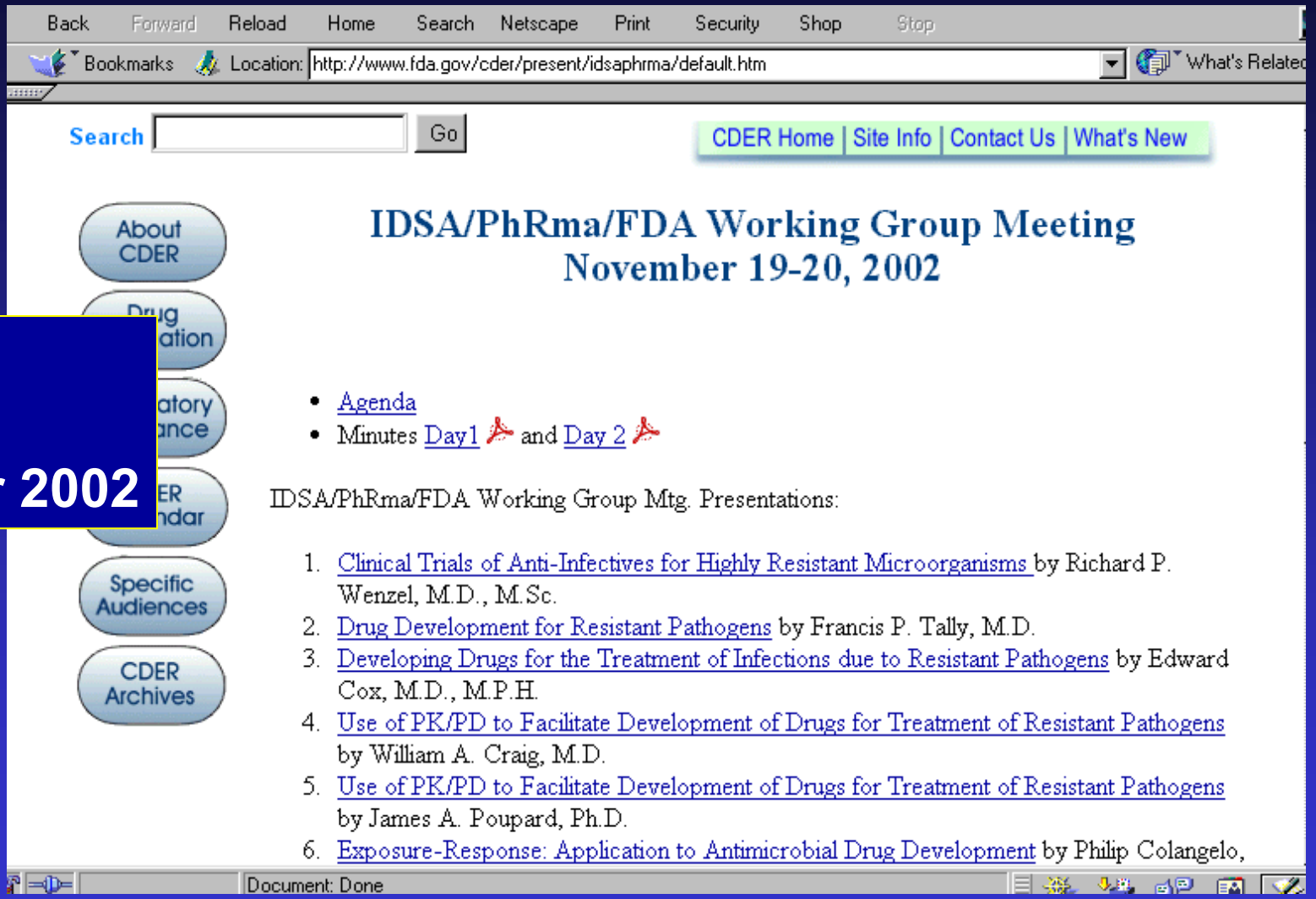


http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm

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.

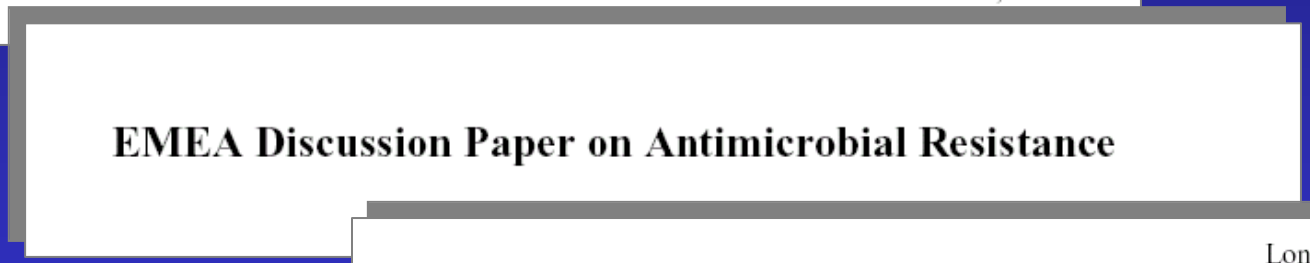
A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

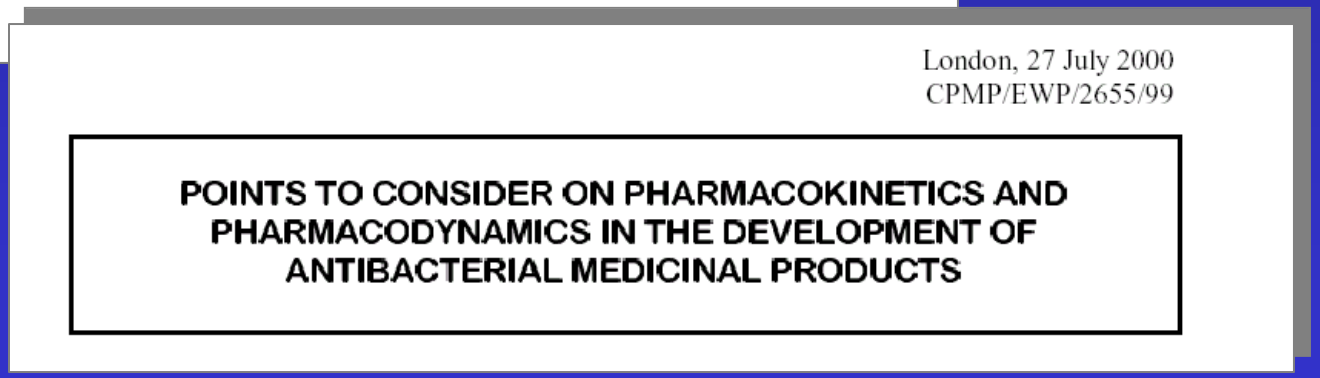
The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties… "

---

* Committee for Proprietary Medicinal Products

Publications of the EMEA ...





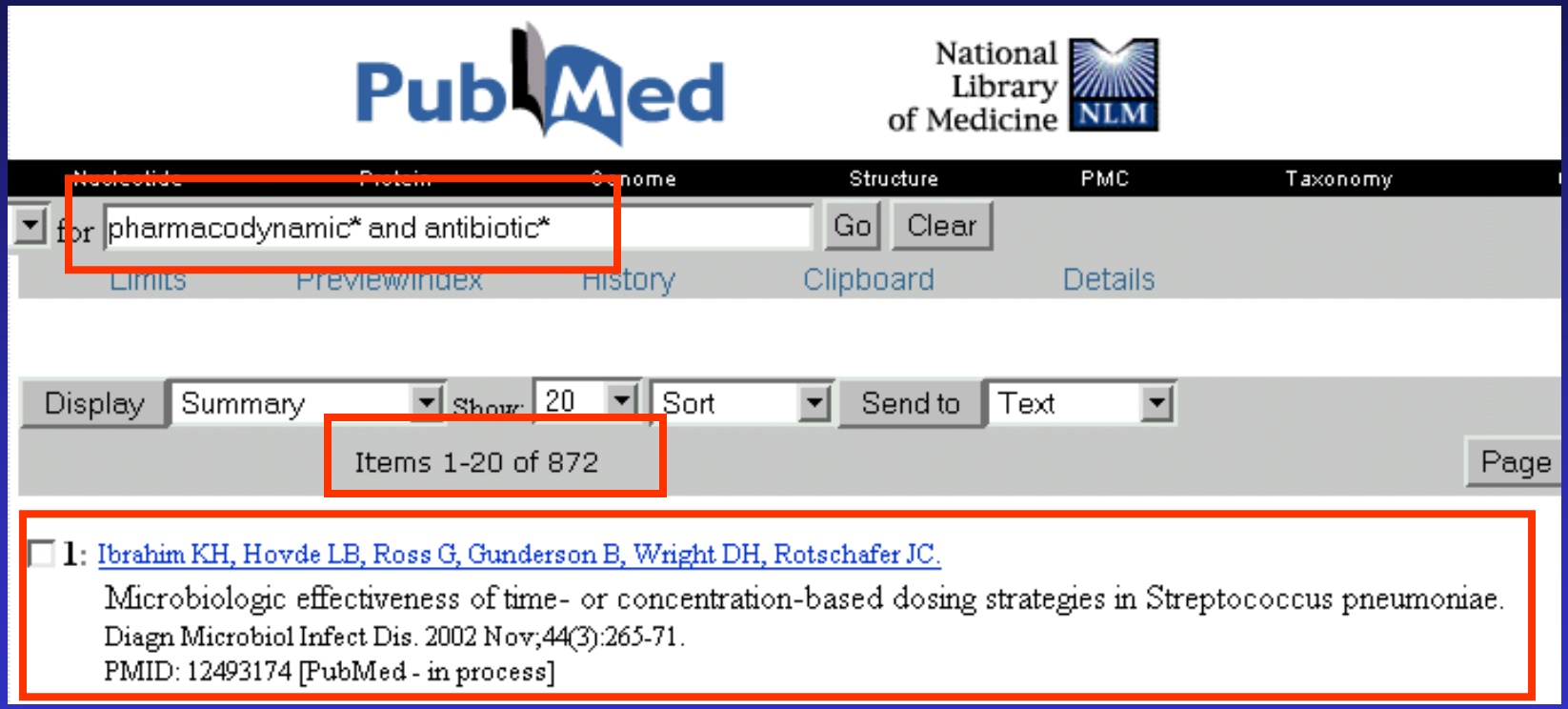
PK / PD in action for science and clinics

Some achievements:

- **once-daily dosing of aminoglycosides registration or reregistration in several 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**
- **continuous infusion of beta-lactams brought to clinical trials**

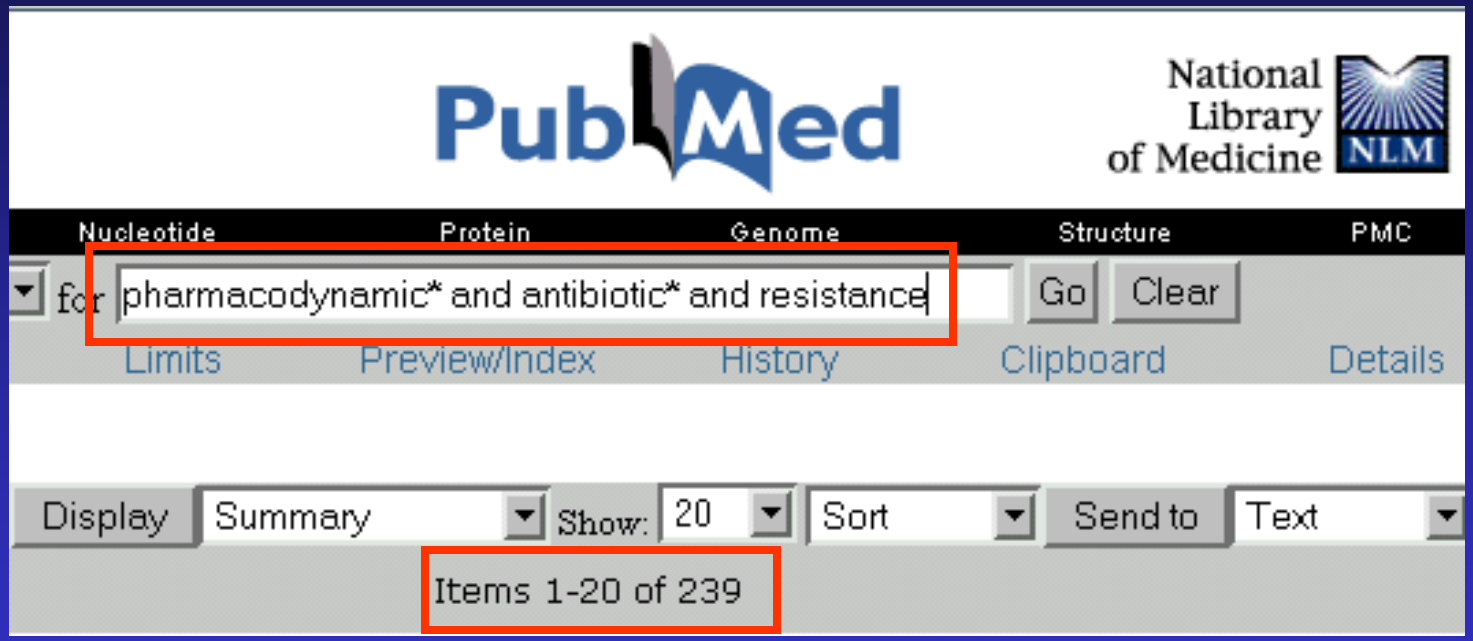
PK / PD in action for science and clinics

Publications ...



PK / PD in action for science and clinics

Resistance ...



PK / PD in action for science and clinics

Resistance and simple clinical situations ...

Bacterial eradication in the treatment of otitis media

Ron Dagan and Eugene Leibovitz

Drugs differ in their ability to eradicate various pathogens from the middle-ear cavity during acute otitis media (AOM), and these differences clearly affect clinical outcome. Outcome is derived from differences in the association between concentrations of the drugs at the site of infection and the antimicrobial effect (termed pharmacodynamics). These differences are even more marked in the present era of antimicrobial resistance. However, since AOM is a self-limiting disease in most cases, difference in clinical outcome is more difficult to ascertain than that of bacteriological outcome, which is measured within 3–5 days. A favourable clinical outcome regardless of the bacteriological effect of the drug can result in false optimism when less-effective antibiotic drugs are used. Inappropriate study design and manipulation of clinical results add to this confusion. In this review we attempt to highlight the evidence regarding bacteriological response to antibiotics in AOM and to draw attention to potential flaws that may mislead clinicians.

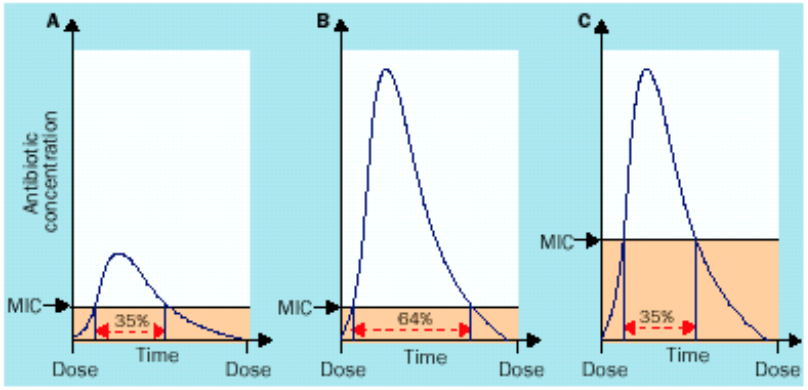


Figure 1. Relation of the free drug concentration at the site of infection to the minimal inhibitory concentration of the drug to the pathogen. (A) A β-lactam drug that achieves concentration above the MIC for <40% of the dosing interval is predicted to have a high rate of failure. (B) Another drug, if administered against the same organisms as in curve A, will show a high rate of eradication, since its concentration at the site of infection exceeds 40–50% of the dosing interval. (C) By increasing the MIC, the pathogen that was easily eradicated under the condition presented in curve B will not be eradicated if the concentrations of the same drug as in curve B does not exceed 40% of the dosing interval.

Lancet Infect Dis 2002; **2:** 593–604

exudates worldwide and causes roughly 40% of episodes of otitis media.[2] However, in some recent studies, *H influenzae* was more common than *S pneumoniae* in AOM.[10–12] *S pneumoniae* may be a more virulent pathogen than non-typable *H influenzae* and *M catarrhalis*.[13–18] Altogether, *S pneumoniae* and non-typable *H influenzae* constitute in most studies more than 80% of all AOM pathogens, and thus bacterial eradication of these two organisms is the key

So, why have we agreed to come here ?

We'll try to answer ...

Education …

Education …

Education …

Please, be interactive and DO ask questions

But, before we begin, who are we ?

Michael R. Jacobs, MD, PhD
Professor of Pathology and Medicine,
Case Western Reserve University, Cleveland, Ohio, USA

Director of Clinical Microbiology
University Hospitals of Cleveland, Cleveland, Ohio, USA

Paul M. Tulkens, MD, PhD
Professor of Pharmacology and Drug Development
Department of Pharmaceutical Sciences
Catholic University of Louvain, Brussels, Belgium

Where the hell could Belgium be ?

Paul M. Tulkens and PK/PD ...

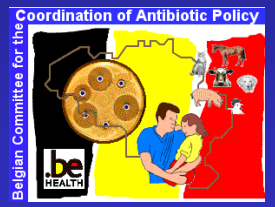
- **Scientific activities**
  - toxicology of aminoglycosides
  - intracellular infection
  - introducing new modes of AB administration to the clinics

→ **the once-a-day concept (1985-1990)**

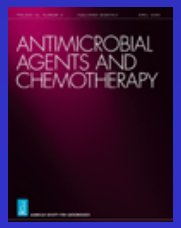
→ • present AB
• new derivatives

→ **β-lactams by continuous infusion**

- **Belgian and EU Regulatory activities**
  - Adviser to the Registration Commission (for AB)
  - Member of the National Commission for Drug Reimbursement
  - Member of the National Committee for the Coordination of the Antibiotic Policy



- **International activities**
  - Founding member and Past-President of ISAP
  - Editorial Board of Antimicrobial Agents and Chemotherapy



Programme, please ...

Morning sessions:

- Basic introduction to microbiological parameters
  M. Jacobs
- The general concepts of pharmacokinetics
  P.M. Tulkens
- Pharmacokinetics as applied to animal and in vitro models
  M. Jacobs
- The general concepts of pharmacodynamics
  P. M. Tulkens

What you always wished to know but never dared to ask because it seemed so basic …
… and did not know how to begin with all that stuff ...

Programme, please ...

Afternoon sessions:

- Pharmacodynamics as applied to animal models, or how to discover PK/PD parameters [P.M. Tulkens]
- PK/PD models for selected antibiotics [M. Jacobs]
- New approaches in PK/PD (drug transport, intracellular infections, difficult-to-reach areas) [P.M. Tulkens]
- Regulatory aspects and Population-based approaches [M. Jacobs]
- Resistance and PK/PD [P.M. Tulkens]
- Applications to practical situations (RTI as an example) [M. Jacobs]

How to (really) go from basic science to your daily (and future !!) activities