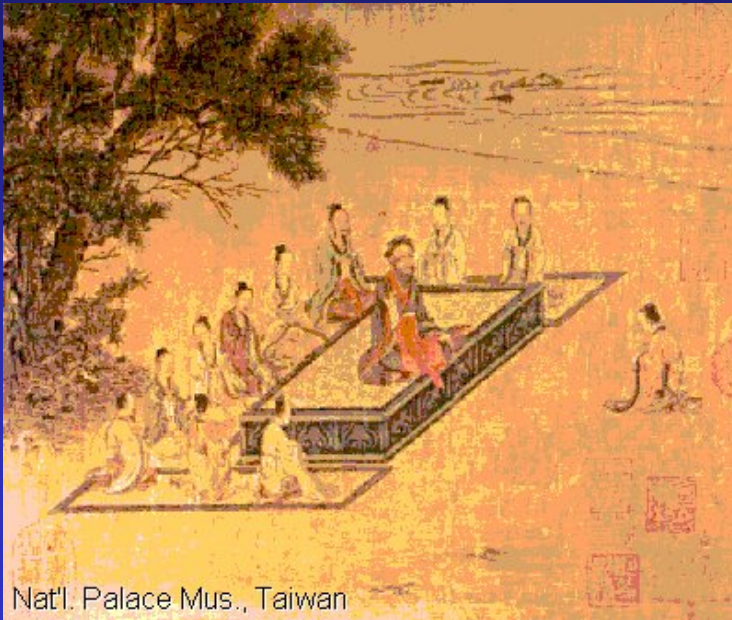


Asian PK/PD Educational Workshop

Welcome

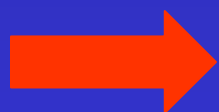


- Why is PK/PD important ?
- Who are we ?
- Programme of the Workshop

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



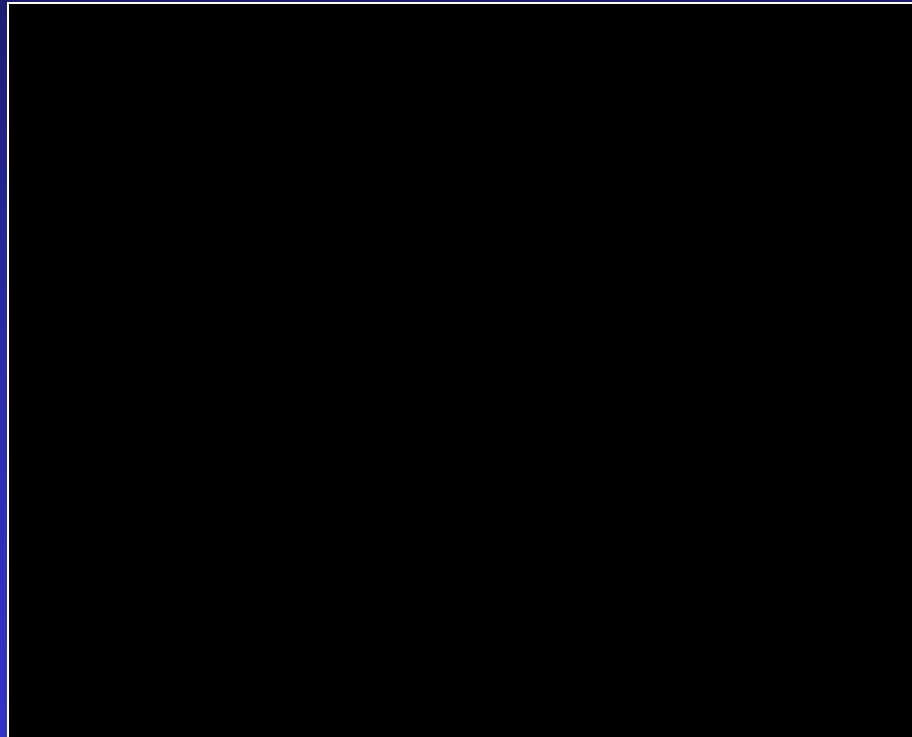
pharmacodynamics of antiinfective drugs was largely “*terra incognita*” 10 years ago

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 ?

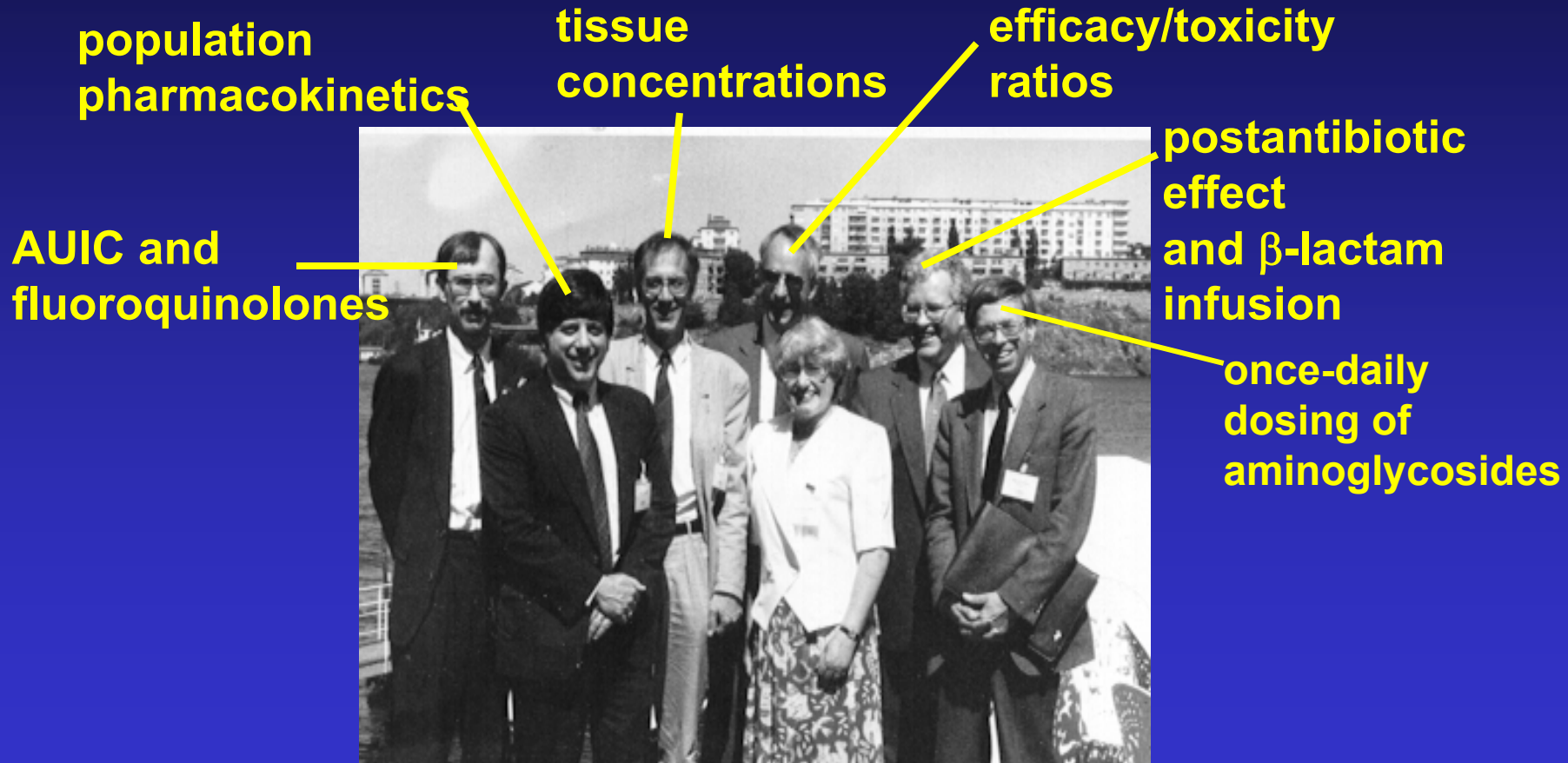


How did it start ?



**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 worldwide
(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>

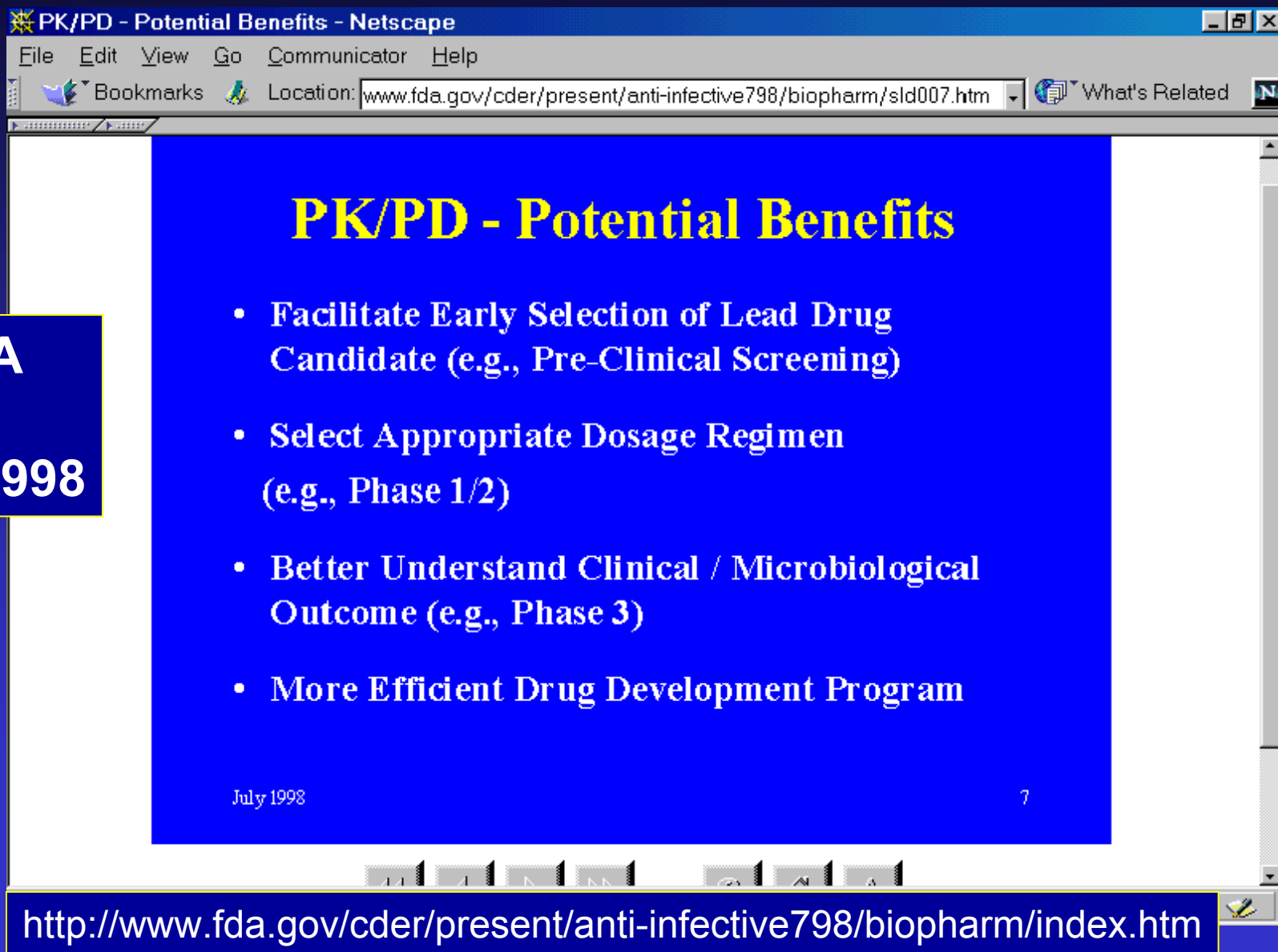


PK/PD since 1989 ...

- 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



The image shows a screenshot of a Netscape browser window. The title bar reads "PK/PD - Potential Benefits - Netscape". The address bar shows the URL "www.fda.gov/cder/present/anti-infective798/biopharm/sld007.htm". The main content area displays a blue slide with the following text:

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

At the bottom left of the slide, it says "July 1998". At the bottom right, there is a small question mark icon. Below the slide, the browser's status bar shows the URL "http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm".

PK /PD in action in the Regulatory in the USA

Back Forward Reload Home Search Netscape Print Security Shop Stop

Bookmarks Location: <http://www.fda.gov/cder/present/idsaphrma/default.htm> What's Related

Search Go

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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

<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 ...



The European Agency for the Evaluation of Medicinal Products

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**

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 ...

The screenshot displays the PubMed search interface. At the top, the PubMed logo and the National Library of Medicine (NLM) logo are visible. Below the logos, there are navigation tabs for 'Nucleotide', 'Protein', 'Genome', 'Structure', 'PMC', and 'Taxonomy'. A search bar contains the query 'pharmacodynamic* and antibiotic*', with a 'Go' button and a 'Clear' button. Below the search bar, there are links for 'Limits', 'Preview/index', 'History', 'Clipboard', and 'Details'. A second row of controls includes a 'Display' dropdown set to 'Summary', a 'Show' dropdown set to '20', a 'Sort' dropdown, and a 'Send to' dropdown set to 'Text'. A box highlights the text 'Items 1-20 of 872'. Below this, a list of search results is shown, with the first result highlighted by a red box:

1: [Ibrahim KH, Hovde LB, Ross G, Gunderson B, Wright DH, Rotschafer JC.](#)
Microbiologic effectiveness of time- or concentration-based dosing strategies in *Streptococcus pneumoniae*.
Diagn Microbiol Infect Dis. 2002 Nov;44(3):265-71.
PMID: 12493174 [PubMed - in process]

PK / PD in action for science and clinics

Resistance ...

The image shows a screenshot of the PubMed search interface. At the top, the PubMed logo is on the left, and the National Library of Medicine (NLM) logo is on the right. Below the logos, there are navigation tabs for Nucleotide, Protein, Genome, Structure, and PMC. A search bar contains the text "pharmacodynamic* and antibiotic* and resistance", which is highlighted with a red box. To the right of the search bar are "Go" and "Clear" buttons. Below the search bar, there are links for "Limits", "Preview/Index", "History", "Clipboard", and "Details". At the bottom of the interface, there are controls for "Display" (set to Summary), "Show:" (set to 20), "Sort", "Send to" (set to Text), and a red box highlighting the text "Items 1-20 of 239".

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.

Lancet Infect Dis 2002; 2: 593–604

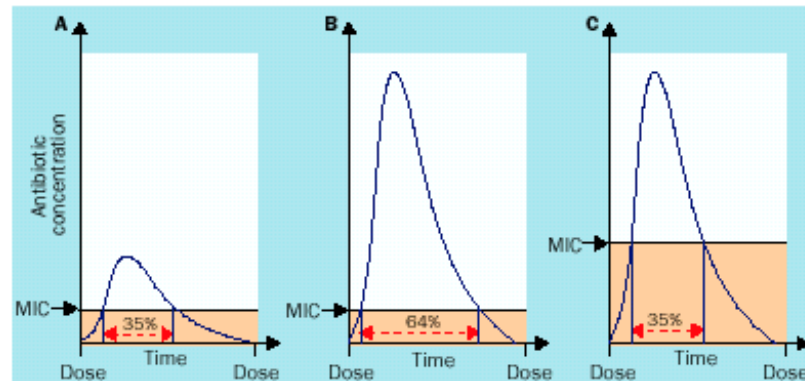


Figure 1. Relation of the free drug concentration at the site of infection to the minimal inhibitory concentration of the drug to the pathogen. (A) A β -lactam drug that achieves concentration above the MIC for <40% of the dosing interval is predicted to have a high rate of failure. (B) Another drug, 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.

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 nontypable *H influenzae* and *M catarrhalis*.^{13–18} Altogether, *S pneumoniae* and nontypable *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

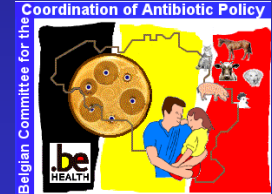
Professor of Pharmacology and Drug Development
Department of Pharmaceutical Sciences
Catholic University of Louvain, Brussels, Belgium

Where the hell could Belgium be ?



Somewhere here...

Paul M. Tulkens and PK/PD ...





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



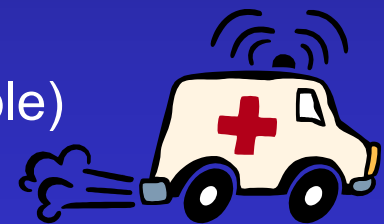
What you always wished to know but never dared to ask
because it seemed so basic ...
... and did not know how to begin with all that stuff ...

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