

# Farmacokinetiek en farmacodynamiek van antibiotica: wat heeft de afgelopen halve eeuw ons geleerd?



**Paul M. Tulkens**, MD, PhD  
Een van de Stichters en  
vorige voorzitter van ISAP (1998-2000)

Emeritus Hoogleraar  
*Pharmacologie cellulaire et moléculaire*  
*Louvain Drug Research Institute*  
*Health Sciences Sector*  
*Université catholique de Louvain*  
Brussel, België



17e SWAB symposium: "Uitersten in antimicrobiële therapie" - 30 juni 2016 - Utrecht

# Disclosures

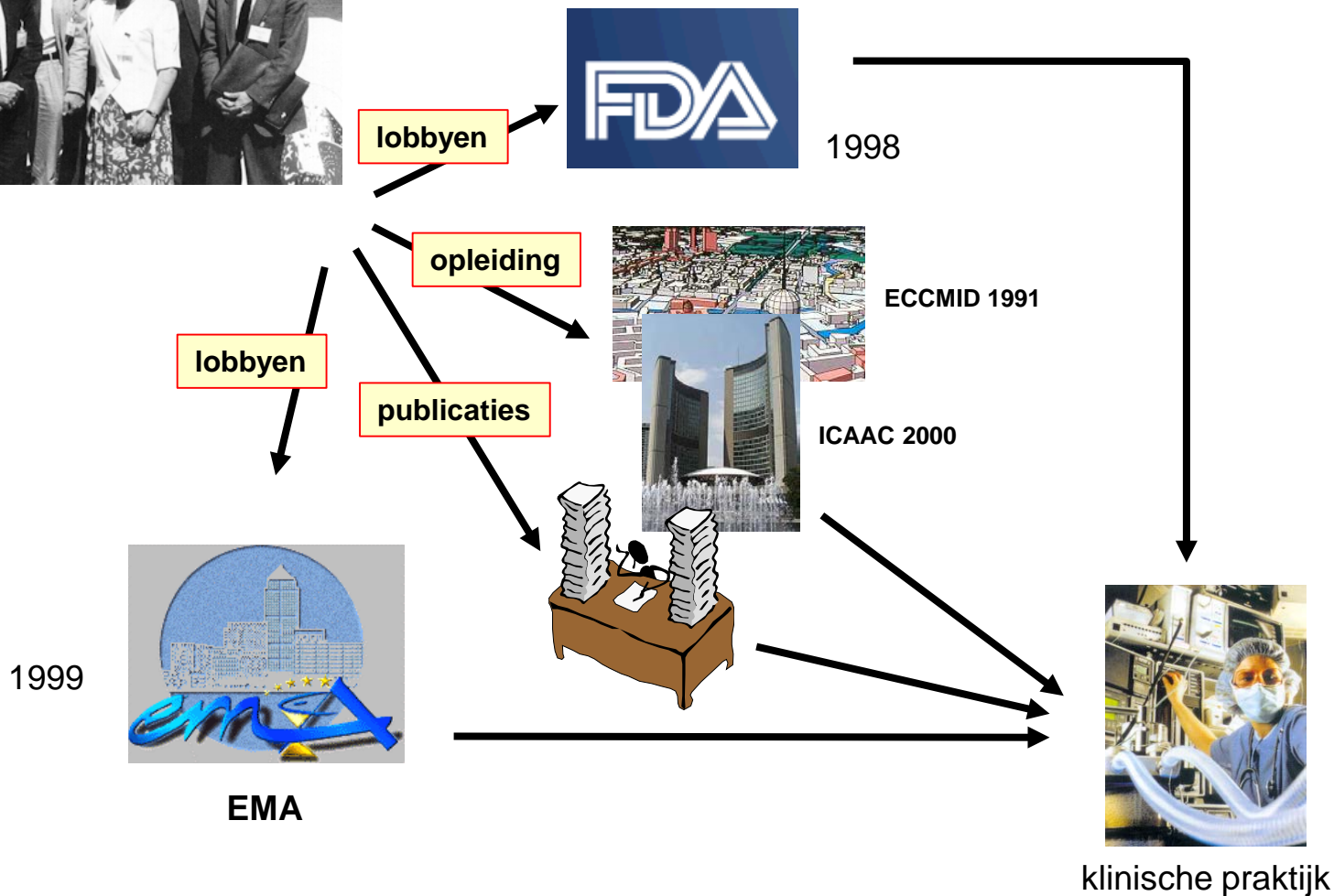
## (those who paid for our PK research and talks)

- Onderzoekssubsidies
  - Industrie: Cempra, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Melinta, Debiopharm, Eumedica
  - Publiek: *Fonds de la Recherche Scientifique (F.R.S.-FNRS)*, Belgische Federale Overheidsdienst "Volksgezondheid", *Région Wallonne*, *Région Bruxelloise/Brusselse Gewest*, Europese Unie (FP7 en JPIAMR)
- Spreker honoraria
  - Industrie: Bayer, GSK, OM-Pharma, Vifor, Dong A,
  - Publiek: Opleidingsprogramma Antibioticabeleid Vlaanderen
- Adviesraden en/of besluitvormingsorganen
  - Industrie: Bayer, Trius, The Medicines Company
  - Publiek: *US National Institutes of Health (grant reviewing)*; *EUCAST General Assembly and Steering committee*; *European Medicines Agency (as external expert)*; Belgische Commissie voor tegemoetkoming van geneesmiddelen; *Belgian Antibiotic Policy Coordination Committee (BAPCOC)*; *EU program "DRIVE AB" governance (new economical framework for antibiotics)*

# Waar zal ik over spreken?



Vanuit  
Stockholm  
in 1989 ...



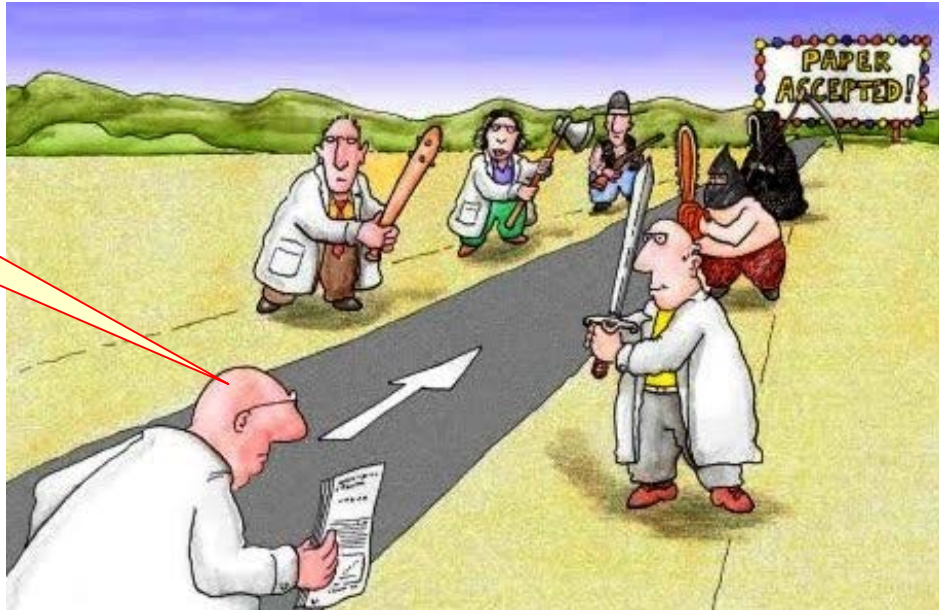
# Disclaimer ...

- Dit is een persoonlijke blik ...
- Ik heb zeker veel punten gemist en veel van de belangrijkste acteurs vergeten...
- Het meeste van wat ik zal tonen is op openbare documenten gebaseerd ... wat betekent dat de werkelijkheid anders zou kunnen zijn ...
- Met dank aan Johan Mouton voor de vele suggesties...

Dias beschikbaar op <http://www.facm.ucl.ac.be/> → Lectures → in het Nederlands

# Publicaties

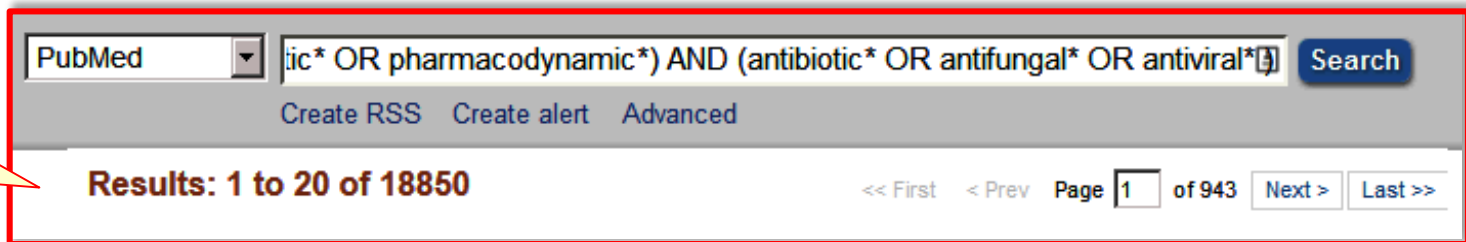
Vaak de aarde weg !



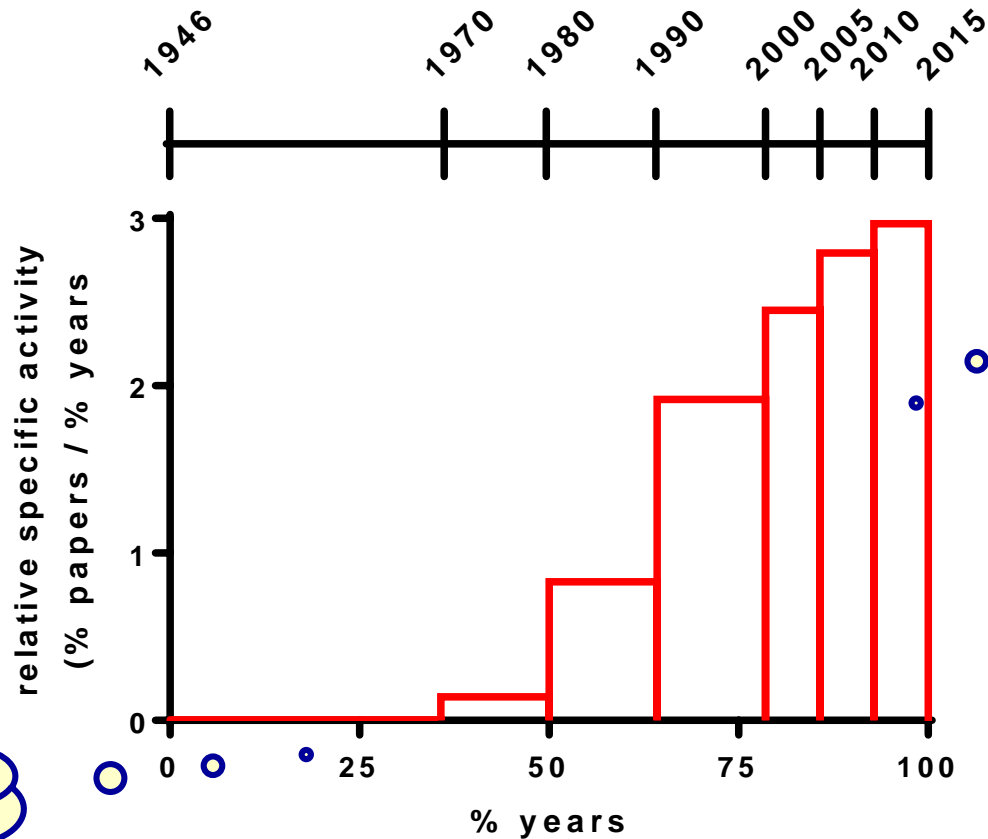
Maar probeer dit

(pharmacokinetic\* OR pharmacodynamic\*) AND (antibiotic\* OR antifungal\* OR antiviral\* )

En U krijgt dat



# Publicaties vanaf 1946 tot 2015 \*

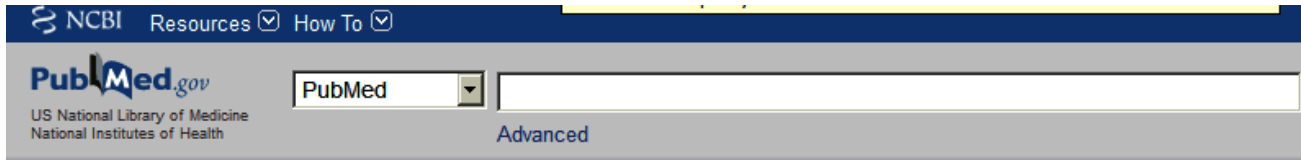


911  
artikels/jaar

20  
artikels/jaar

\* PubMed search using (pharmacokinetic\* OR pharmacodynamics\*) AND (antibiotic\* OR antiviral\* OR antifungal\*)

# Publicaties: één van de eerste



Abstract ▾

Mod Hosp. 1952 Oct;79(4):108-18.

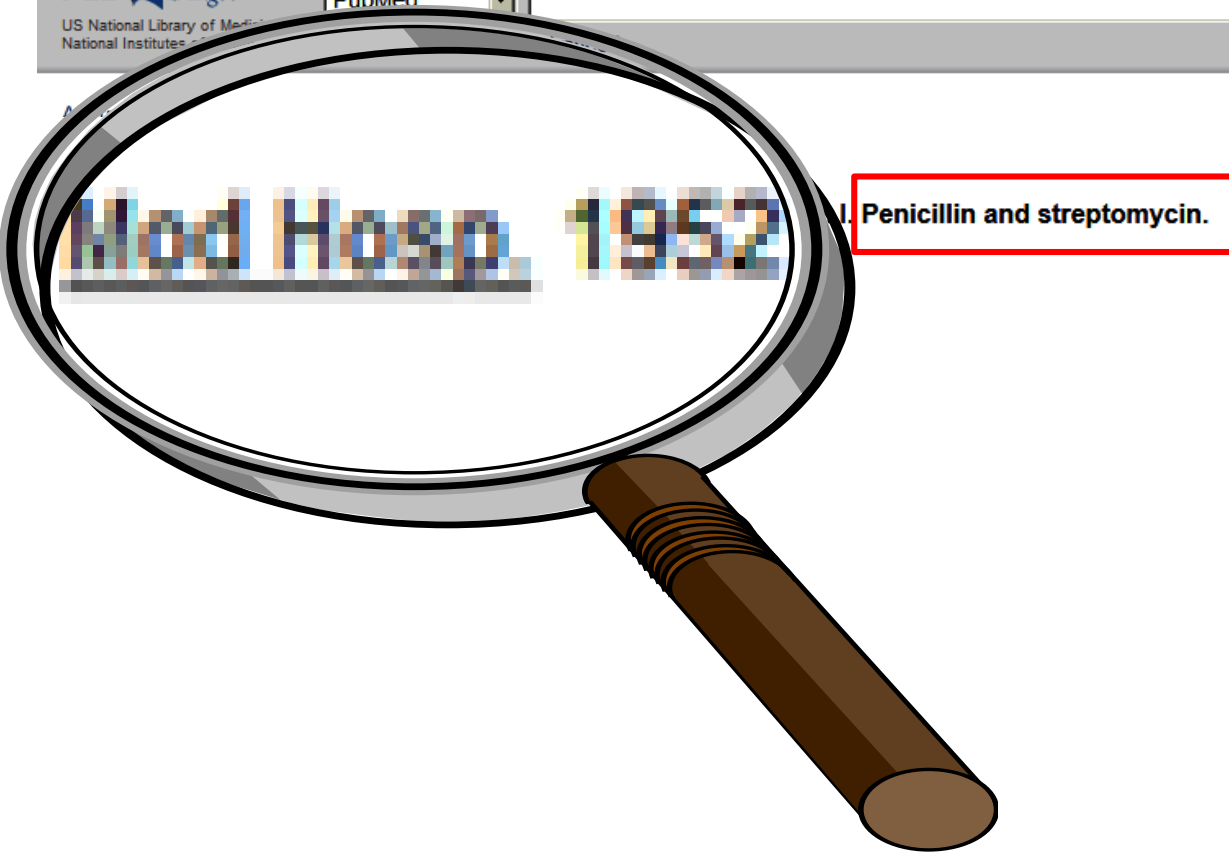
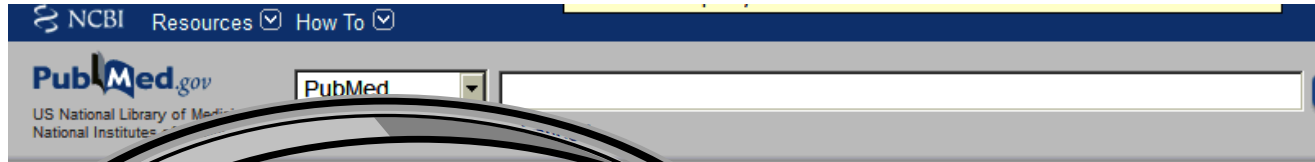
**The antibiotics; pharmacodynamics and principles of therapy. I. Penicillin and streptomycin.**

SHERROD TR.

PMID: 12992961 [PubMed - indexed for MEDLINE]

\* PubMed search using (pharmacokinetic\* OR pharmacodynamics\*) AND (antibiotic\* OR antiviral\* OR antifungal\*)

# Publications from the earliest ...



\* PubMed search using (pharmacokinetic\* OR pharmacodynamics\*) AND (antibiotic\* OR antiviral\* OR antifungal\*)



# Publications from the earliest ...



## *Notes and Abstracts*

Prepared by the Committee on Pharmacy and Therapeutics  
University of Illinois College of Medicine, Chicago 12

# ***THE ANTIBIOTICS: Pharmacodynamics and Principles of Therapy***

## **I. PENICILLIN AND STREPTOMYCIN**


\* PubMed search using (pharmacokinetic\* OR pharmacodynamics\*) AND (antibiotic\* OR antiviral\* OR antifungal\*)

# Publicaties ... tot drie van de laatste

## Extended-Interval Aminoglycoside Use in Cystic Fibrosis Exacerbation in Children and Young Adults: A Prospective Quality Improvement Project

Khalid H. Safi, MD<sup>1</sup>, Justina M. Damiani, PharmD, BCPS<sup>1</sup>, Julie Sturza, MPH<sup>1</sup>, and Samya Z. Nasr, MD, CPI<sup>1</sup>

Received February 2, 2016. Received revised February 2, 2016. Accepted for publication February 3, 2016.

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DOI: 10.1177/2333794X16635464  
gph.sagepub.com  


Int J Clin Pharm  
DOI 10.1007/s11096-016-0334-1



RESEARCH ARTICLE

## Evaluation of an alternative extended-infusion piperacillin-tazobactam dosing strategy for the treatment of gram-negative infections

Erin M. Winstead<sup>1</sup> · Patrick D. Ratliff<sup>2</sup> · Ryan P. Hickson<sup>3</sup> · Joseph E. Mueller<sup>4</sup> · William R. Judd<sup>2</sup>

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© Springer International Publishing 2016



Antimicrobial Agents  
and Chemotherapy

Antimicrob Agents Chemother 2016;60:3921–3933



## Colistin and Polymyxin B Dosage Regimens against *Acinetobacter baumannii*: Differences in Activity and the Emergence of Resistance

Soon-Ee Cheah,<sup>a</sup> Jian Li,<sup>a</sup> Brian T. Tsuji,<sup>b</sup> Alan Forrest,<sup>b,c</sup> Jürgen B. Bulitta,<sup>a,d</sup> Roger L. Nation<sup>a</sup>

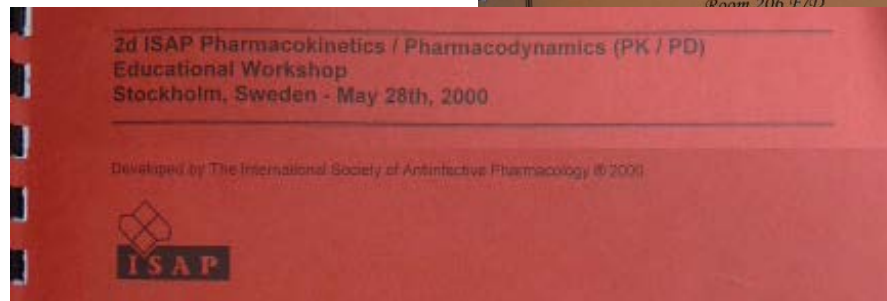
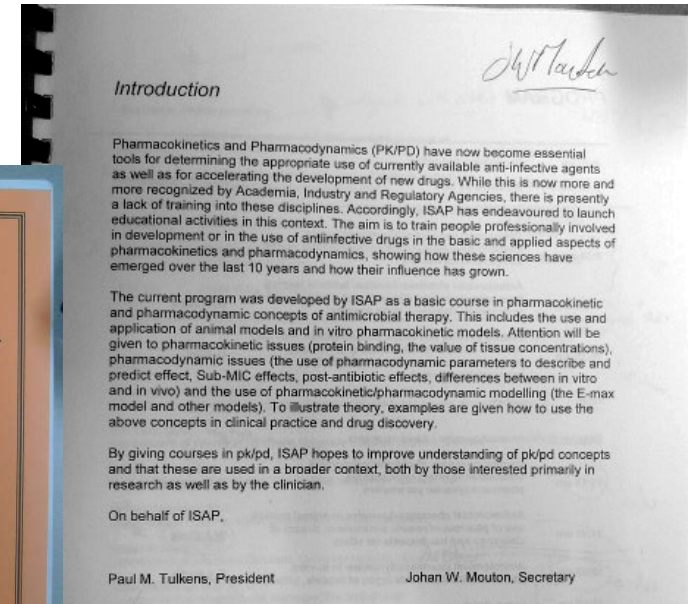
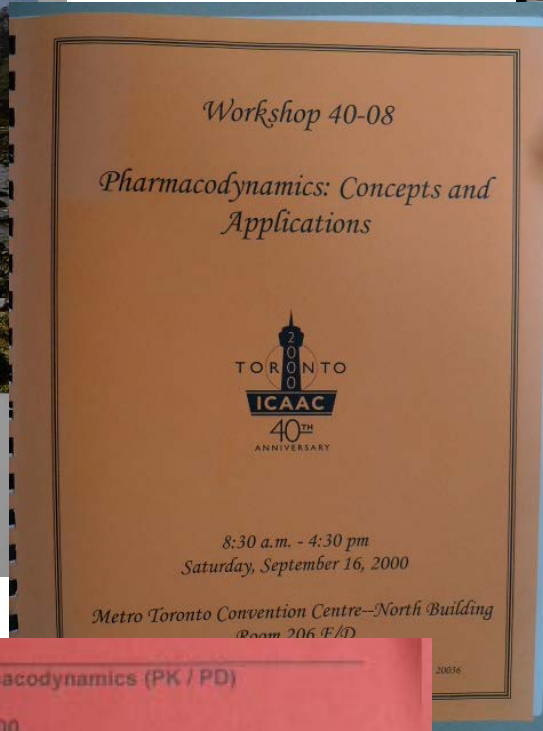
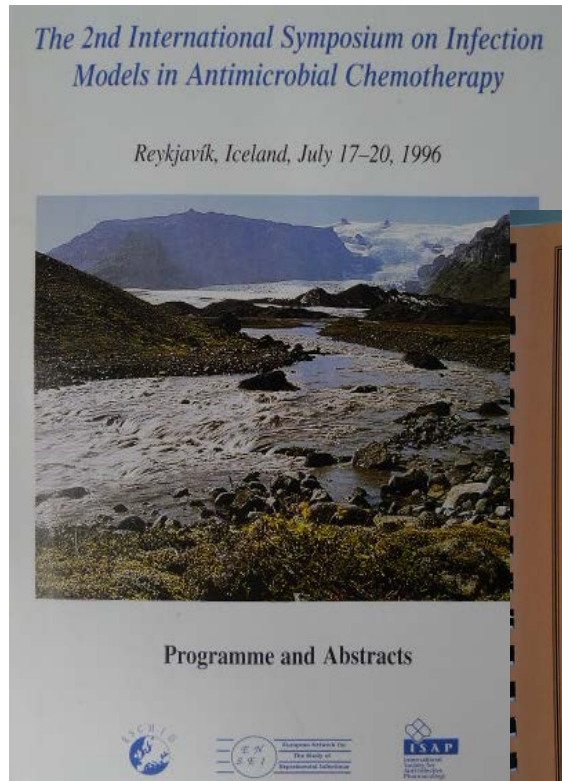
Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), Parkville, Victoria, Australia<sup>a</sup>; Laboratory of Antimicrobial Pharmacodynamics, Department of Pharmacy Practice, University of Buffalo, Buffalo, New York, USA<sup>b</sup>; Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, North Carolina, USA<sup>c</sup>; Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, Florida, USA<sup>d</sup>

\* PubMed search using (pharmacokinetic\* OR pharmacodynamics\*) AND (antibiotic\* OR antiviral\* OR antifungal\*)

# Eerste successen

- Publiceren over de farmacokinetiek / farmacodynamiek van antibiotica is uitgegroeid van een niche niveau tot een zeer populair topic...
- De grote hoeveelheid van wetenschappelijke gegevens heeft toegestaan om de PK/PD parameters van de meeste antibiotica te definiëren ... en te verspreiden via workshops en tekstboeken...
- Maar speciale populaties, specifieke toepassingen, en de relatie met resistentie moeten nog verder bestudeerd worden ...

# Sommige vroege workshops \*



vanuit de persoonlijke collectie van J.W. Mouton

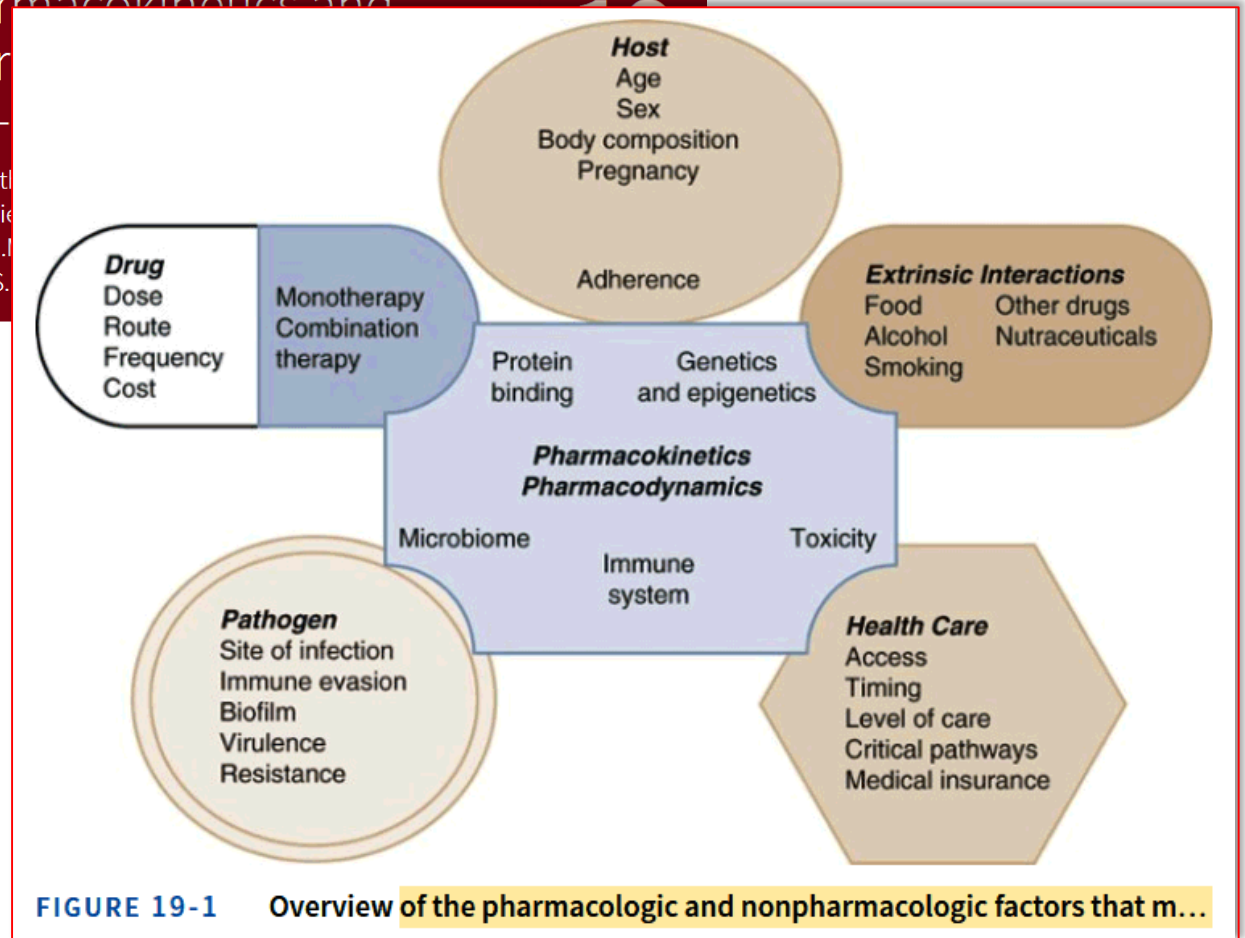
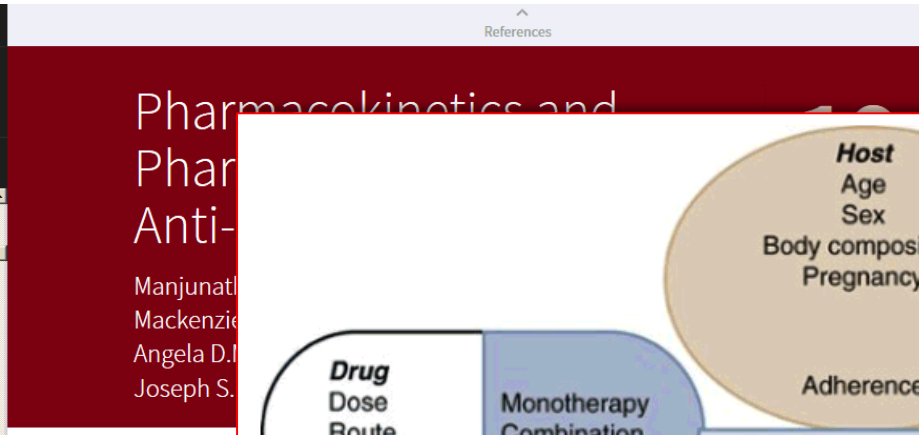
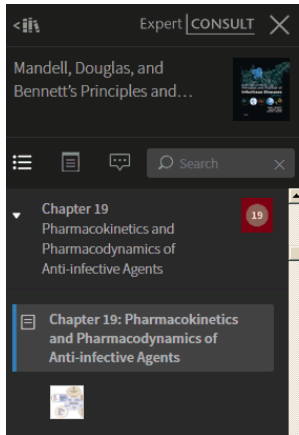
# Tekstboeken



8<sup>th</sup> Edition (2015)

( available on line at <https://expertconsult.inkling.com/read/mandell-douglas-bennetts-infectious-diseases-8> )

# Tekstboeken



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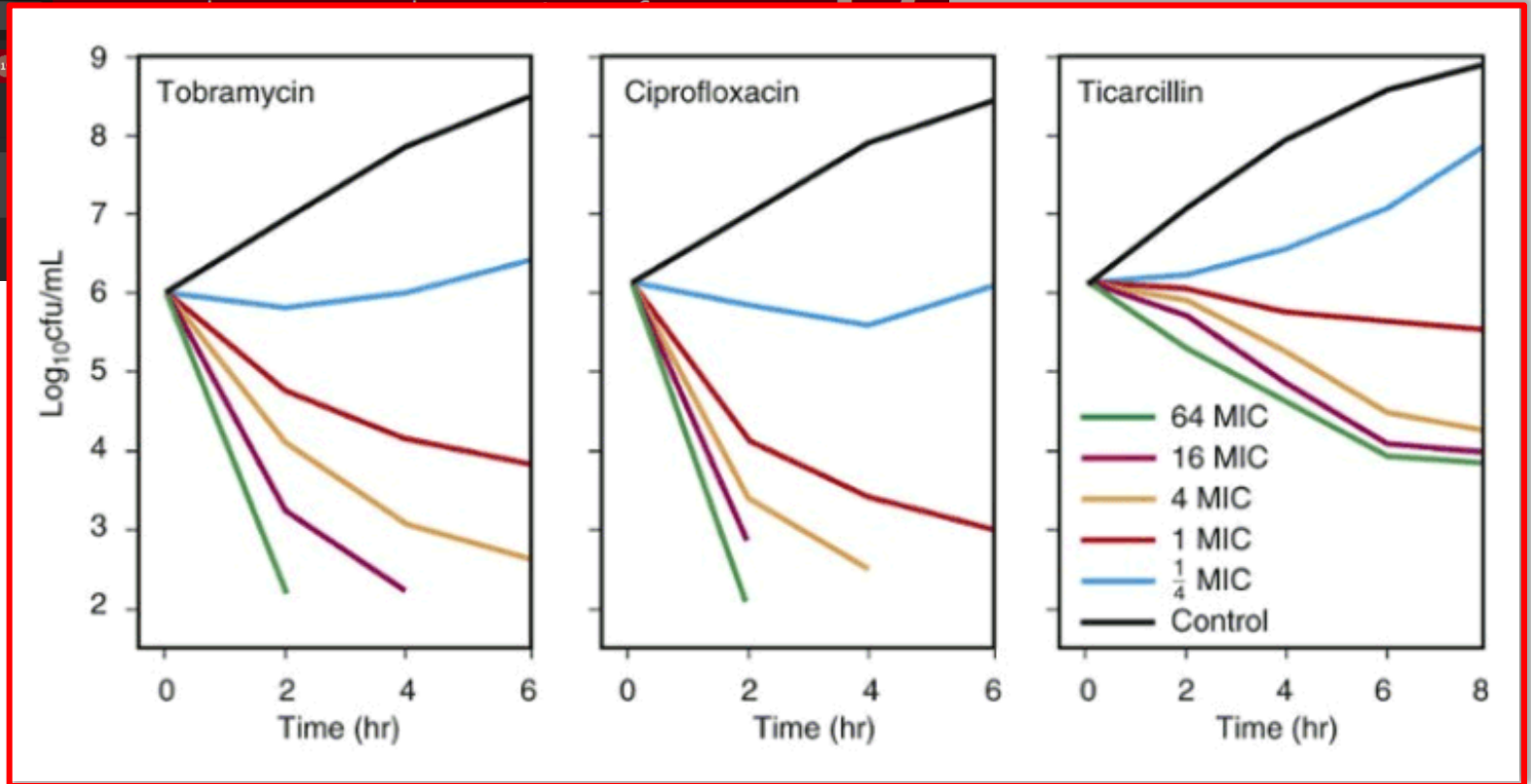
Expert CONSULT

Mandell, Douglas, and Bennett's Principles and...

Chapter 19  
Pharmacokinetics and Pharmacodynamics of Anti-infective Agents

Chapter 19: Pharmacokinetics and Pharmacodynamics of Anti-infective Agents

## Pharmacokinetics and 19



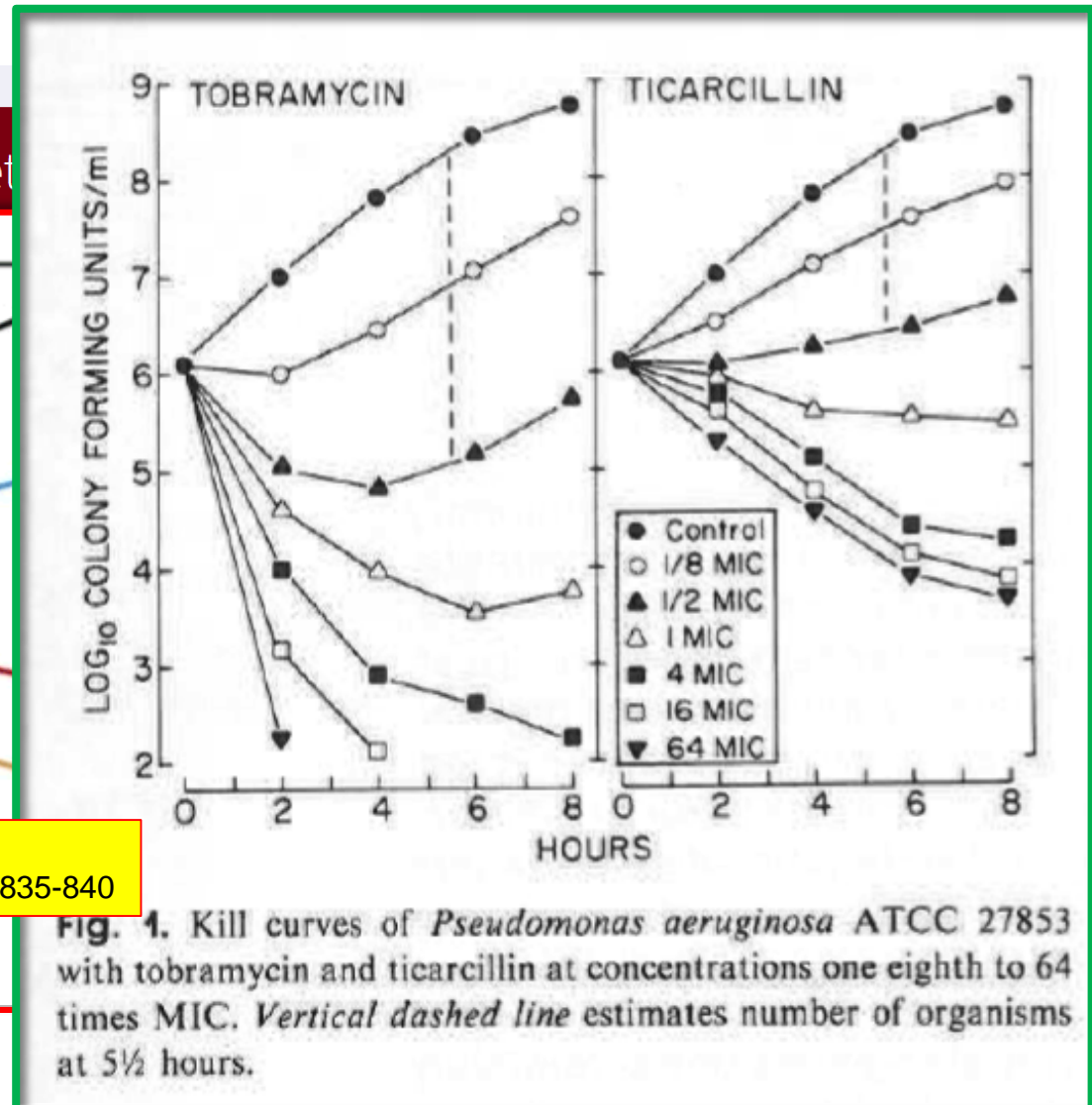
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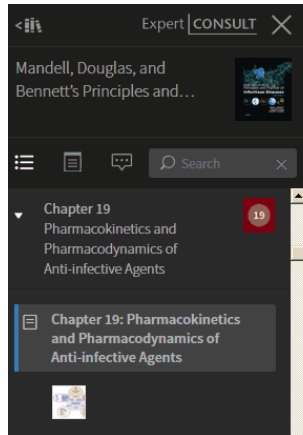


**Originele publicatie:**  
Vogelman & Craig (1986) Journal of Pediatrics 108:835-840





# Tekstboeken



**Concentration-Dependent Killing Agents**

**19**

**Time-Dependent Killing Agents**

**Postantibiotic Effect**

**Higher-Dose Extended-Interval Dosing**

**Continuous-Infusion and Extended-Infusion Regimens**

**Dose-Refinement Considerations**

# En boeken

Een zeer  
goed boek

Designed as a reference on the application of pharmacokinetic-pharmacodynamic principles for the optimization of antimicrobial therapy, namely pharmacotherapy, and infectious diseases.

...integration of pharmacokinetics with pharmacodynamics for all major classes of antibiotics, and the translation of in vitro and animal model data to basic research and clinical situations in humans.

[https://books.google.be/books/about/Fundamentals\\_of\\_Antimicrobial\\_Pharmacokinetics.html?id=i\\_G8BAAAQBAJ&source=kp\\_cover&redir\\_esc=y&hl=en](https://books.google.be/books/about/Fundamentals_of_Antimicrobial_Pharmacokinetics.html?id=i_G8BAAAQBAJ&source=kp_cover&redir_esc=y&hl=en)

Alexander A. Vinks · Hartmut Derendorf  
Johan W. Mouton *Editors*

## Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics

 Springer

# Wat kennen we vandaag over determinanten van de activiteit van de meeste antibiotica ?

1.  $\beta$ -lactam antibiotica zijn tijdsafhankelijk ... en frequente toediening (of zelfs continu infuus) is de beste manier (op PK/PD basis)

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1992, p. 2577-2583  
0066-4804/92/122577-07\$02.00/0  
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Vol. 36, No. 12

## MINIREVIEW

### Continuous Infusion of $\beta$ -Lactam Antibiotics

WILLIAM A. CRAIG<sup>1,2,3\*</sup> AND STEVEN C. EBERT<sup>3,4</sup>

*Department of Medicine<sup>1</sup> and School of Pharmacy,<sup>3</sup> University of Wisconsin, Madison, Wisconsin 53792;  
Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin  
53705<sup>2</sup>; and Department of Pharmacy, Meriter Hospital, Madison, Wisconsin 53715<sup>4</sup>*

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- Maar monitoring is essentieel omdat serum spiegels onvoorspelbaar zijn...

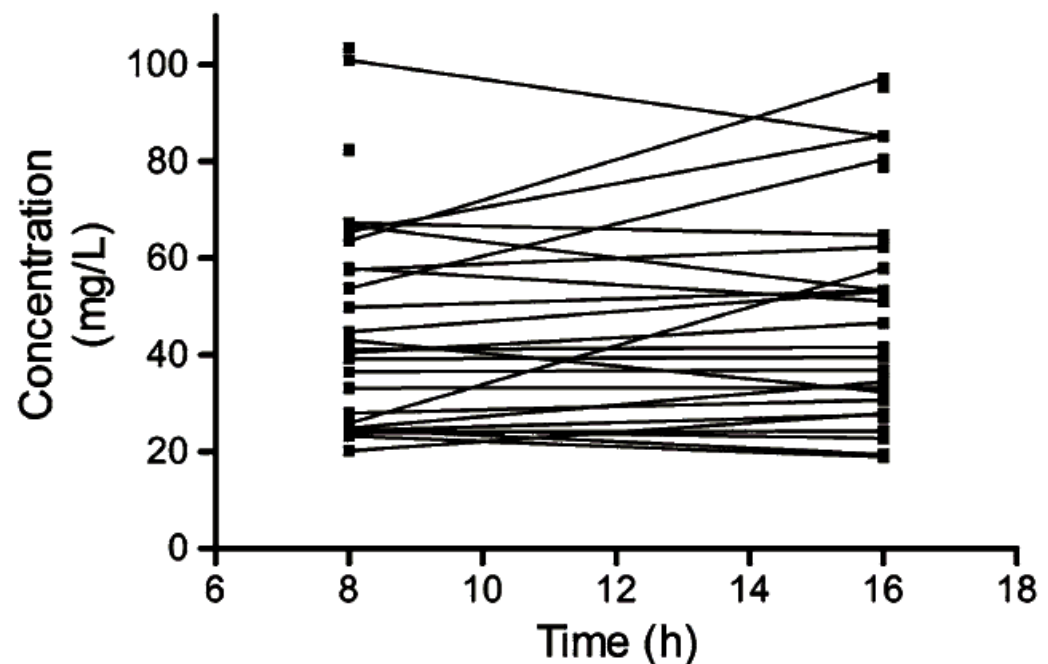
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Vol. 36, No. 12

**Fig. 10.4** Concentrations of ceftazidime during continuous infusions of ceftazidime (4.5 g/day) in patients on the ICU. Unpublished data from Mouton and Vinks (2007)



Muller & Mouton, Continuous Infusion of Beta-lactam Antibiotics In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinck, H. Derendorf & JW Mouton eds, Springer, 2014, p 223-256

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Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin  
53705<sup>2</sup>; and Department of Pharmacy, Meriter Hospital, Madison, Wisconsin 53715<sup>4</sup>*

- Maar monitoring is essentieel omdat serum spiegels onvoorspelbaar zijn...
- En we kunnen (moeten ?) bespreken wat de benodigde  $C_s$ /MIC-ratio is (of  $C_{min}$  ?)

# Wat kennen we vandaag over determinanten van de activiteit van de meeste antibiotica ?

## 1. $\beta$ -lactam antibiotica zijn tijdsafhankelijke ... en frequente toediening (of e

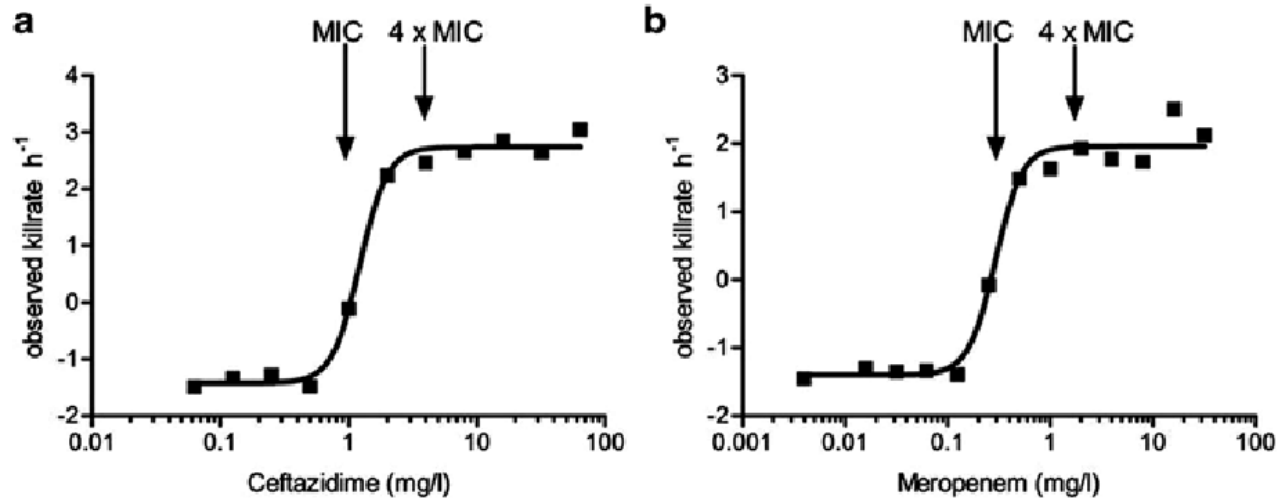
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Department of Medicine<sup>1</sup>,  
Department of Medicine  
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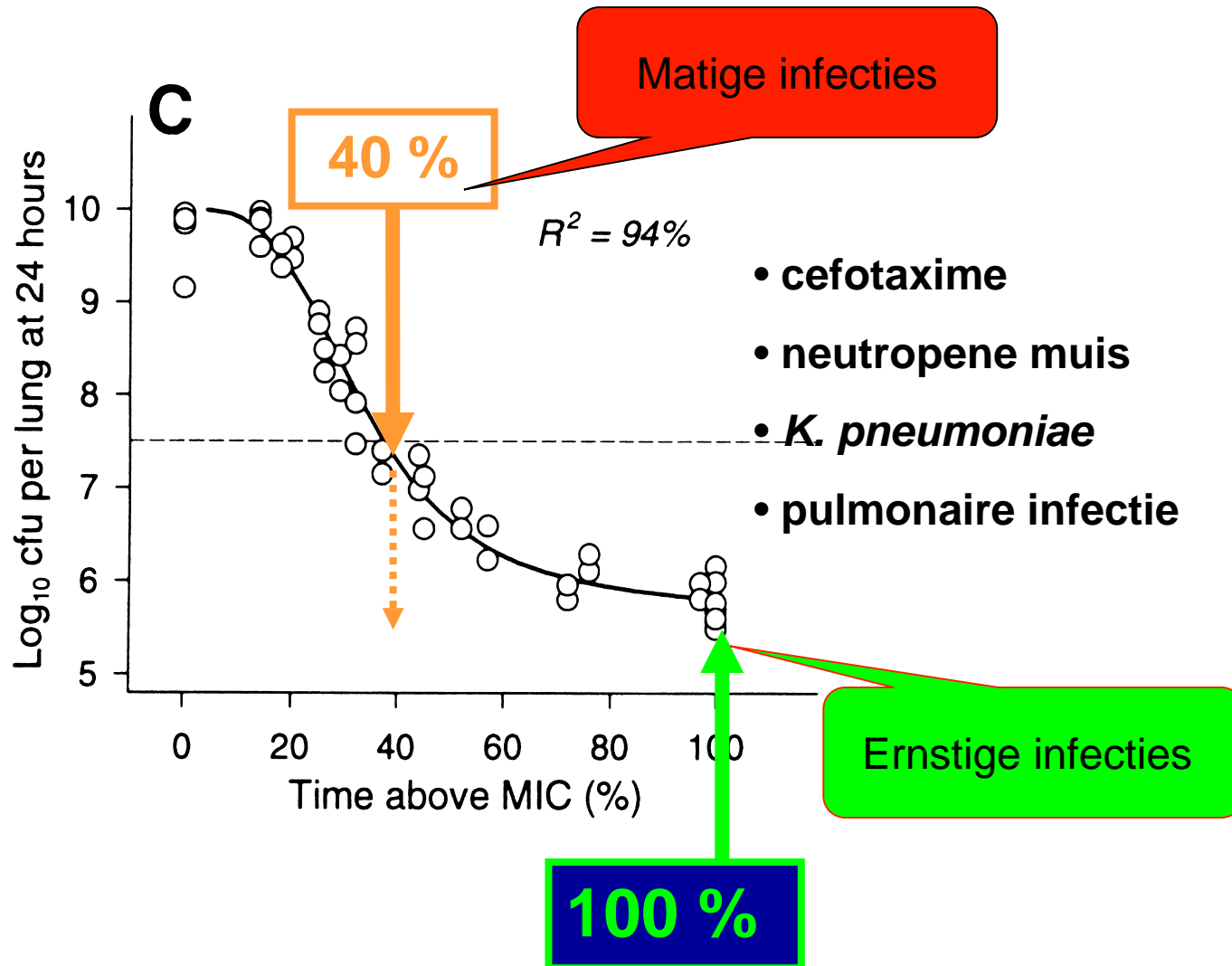
- Maar monitoren van de  
spiegels on

- En we kunnen  
benodigde C



**Fig. 10.2** Relationship between concentration of ceftazidime (a) and meropenem (b) and kill rate. The relationship follows a Hill type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within 2–3 twofold dilutions. The maximum kill rate is attained at around 4×MIC. Figure modified from Mouton and Vinks (2005b, 2007). Reproduced from Mouton JW, Vinks AA. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics: the minimum inhibitory concentration versus stationary concentration. Clin Pharmacokinet. 2005;44(2):201–10 with permission from Adis (© Springer International Publishing AG [2005]. All rights reserved

# β-lactams met de conventionele toediening





# Naar optimalisatie van $\beta$ -lactam toediening...

*J Antimicrob Chemother* 2016; **71**: 196–207  
doi:10.1093/jac/dkv288 Advance Access publication 3 October 2015

**Journal of  
Antimicrobial  
Chemotherapy**

## **Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort**

**Mohd H. Abdul-Aziz<sup>1</sup>, Jeffrey Lipman<sup>1,2</sup>, Murat Akova<sup>3</sup>, Matteo Bassetti<sup>4</sup>, Jan J. De Waele<sup>5</sup>, George Dimopoulos<sup>6</sup>, Joel Dulhunty<sup>1,2</sup>, Kirsi-Maija Kaukonen<sup>7</sup>, Despoina Koulenti<sup>1,6</sup>, Claude Martin<sup>8,9</sup>, Philippe Montravers<sup>10</sup>, Jordi Rello<sup>11</sup>, Andrew Rhodes<sup>12</sup>, Therese Starr<sup>2</sup>, Steven C. Wallis<sup>1</sup> and Jason A. Roberts<sup>1,2\*</sup> on behalf of the DALI Study Group†**

<sup>1</sup>Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia; <sup>2</sup>Departments of Intensive Care Medicine and Pharmacy, Royal Brisbane and Women's Hospital, Brisbane, Australia; <sup>3</sup>Department of Infectious Diseases, School of Medicine, Hacettepe University, Ankara, Turkey; <sup>4</sup>Infectious Diseases Division, Azienda Ospedaliera Universitaria Santa Maria della Misericordia, Udine, Italy; <sup>5</sup>Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium; <sup>6</sup>Department of Critical Care, Attikon University Hospital, Athens, Greece; <sup>7</sup>Department of Anesthesiology and Intensive Care Medicine, Helsinki University Central Hospital, Helsinki, Finland; <sup>8</sup>Anesthésie réanimation, Hospital Nord, Marseille, France; <sup>9</sup>AzuRea Group, Paris, France; <sup>10</sup>Département d'Anesthésie Réanimation, Centre Hospitalier Universitaire Bichat-Claude Bernard, AP-HP, Université Paris VII, Paris, France; <sup>11</sup>CIBERES, Vall d'Hebron Institut of Research, Universitat Autònoma de Barcelona, Barcelona, Spain; <sup>12</sup>St George's Healthcare NHS Trust and Department of Intensive Care Medicine, St George's University of London, London, UK

# Naar optimalisatie van $\beta$ -lactam toediening...

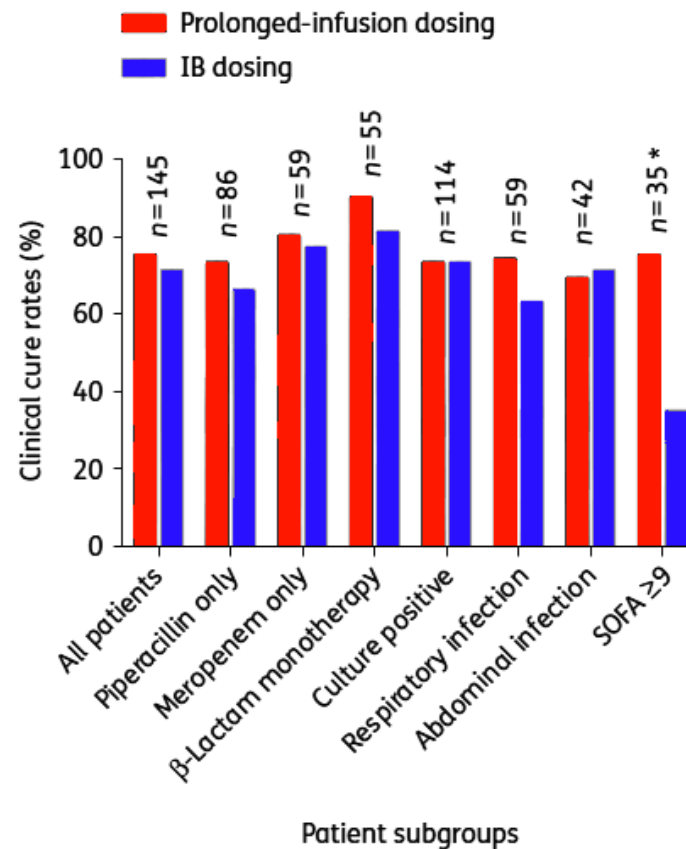
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## Is prolonged infusion of piperacillin/tazobactam in critically ill patients associated with improved pharmacodynamic and patient outcomes? Defining Antibiotic Levels in Intensive Care

Mohd H. Abdul-Aziz<sup>1</sup>, Jeffrey Lipman<sup>1,2</sup>, Murat Akova<sup>3</sup>, Matt Joel Dulhunty<sup>1,2</sup>, Kirsi-Maija Kaukonen<sup>7</sup>, Despoina Koulenti<sup>1,6</sup>, Andrew Rhodes<sup>12</sup>, Therese Starr<sup>2</sup>, Steven C. Wallis<sup>1</sup> and Jas

<sup>1</sup>Burns Trauma and Critical Care Research Centre, The University of Queensland, St. George's Hospital, Brisbane, Australia; <sup>2</sup>Department of Pharmacy, Royal Brisbane and Women's Hospital, Brisbane, Australia; <sup>3</sup>Department of Infectious Diseases, Hacettepe University, Ankara, Turkey; <sup>4</sup>Infectious Diseases, Azienda Ospedaliera, Udine, Italy; <sup>5</sup>Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium; <sup>6</sup>Department of Critical Care Medicine, Attikon University Hospital, Athens, Greece; <sup>7</sup>Department of Anesthesiology, Helsinki University Central Hospital, Helsinki, Finland; <sup>8</sup>Anesthésie réanimation, Hôpital Nord, Marseille, France; <sup>9</sup>Anesthésie Réanimation, Centre Hospitalier Universitaire Bichat-Claude Bernard, Paris, France; <sup>10</sup>Department of Intensive Care Medicine, St George's Hospital, London, UK; <sup>11</sup>Department of Intensive Care Medicine, St George's Hospital, London, UK; <sup>12</sup>Department of Intensive Care Medicine, St George's Hospital, London, UK

## Prolonged-infusion versus intermittent-bolus dosing of $\beta$ -lactams



**Figure 3.** Clinical cure rate comparison between prolonged-infusion and IB dosing for patients who received antibiotics for treatment of infections, stratified according to subgroups. An asterisk indicates a significant difference between prolonged-infusion and IB dosing ( $P < 0.05$ ). n, number of patients in the subgroup.

# En monitoring van $\beta$ -lactams komt eraan !!



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Contents lists available at [ScienceDirect](#)

International Journal of Antimicrobial Agents

journal homepage: <http://www.elsevier.com/locate/ijantimicag>

Review [International Journal of Antimicrobial Agents 46 \(2015\) 367–375](#)

## Assays for therapeutic drug monitoring of $\beta$ -lactam antibiotics: A structured review

Mieke Carlier<sup>a,b,\*</sup>, Veronique Stove<sup>a</sup>, Steven C. Wallis<sup>c</sup>, Jan J. De Waele<sup>b</sup>,  
Alain G. Verstraete<sup>a</sup>, Jeffrey Lipman<sup>c,d</sup>, Jason A. Roberts<sup>c,d,e</sup>

<sup>a</sup> Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium

<sup>b</sup> Department of Critical Care Medicine, Ghent University, Ghent, Belgium

<sup>c</sup> Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, Queensland, Australia

<sup>d</sup> Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

<sup>e</sup> Institute of Translational Medicine, University of Liverpool, Liverpool, UK

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## International Journal of Antimicrobial Agents

journal homepage

M. Carlier et al. / International Journal of Antimicrobial Agents 46 (2015) 367–375

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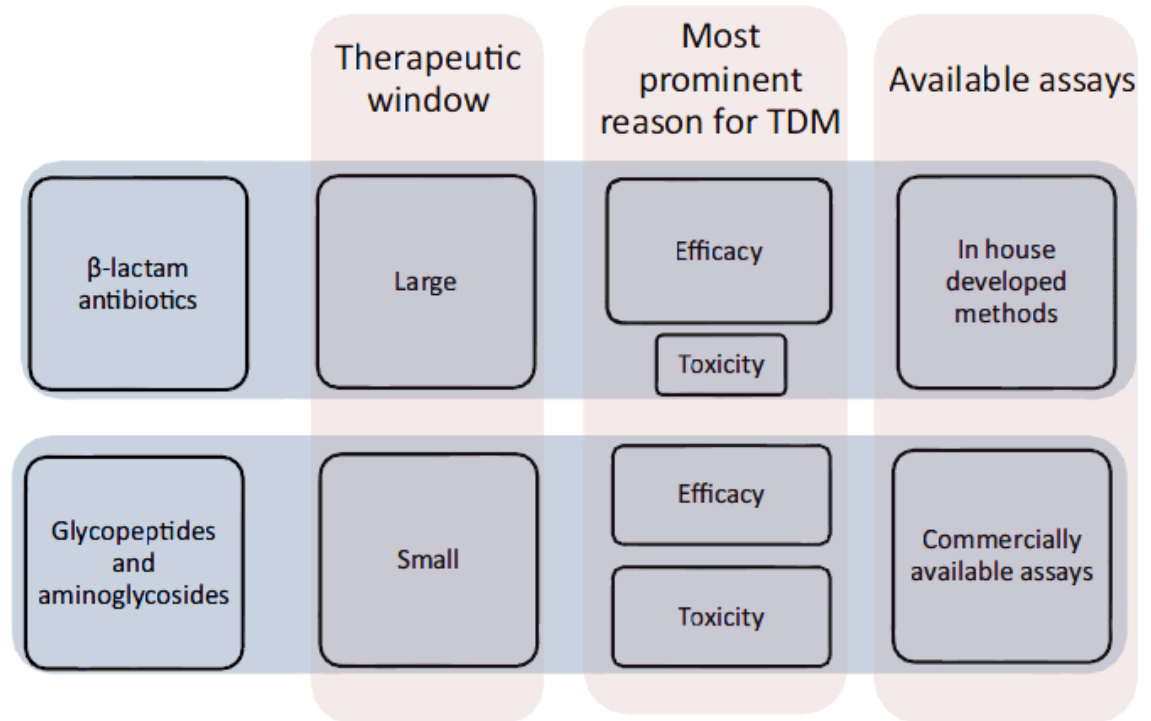
<sup>a</sup> Department of Clinical Chemistry, Microbiology and Immunology

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<sup>c</sup> Burns, Trauma and Critical Care Research Centre, University of Liverpool

<sup>d</sup> Department of Intensive Care Medicine, Royal Brisbane and

<sup>e</sup> Institute of Translational Medicine, University of Liverpool, Liverpool



**Fig. 1.** Comparison of therapeutic drug monitoring (TDM) of  $\beta$ -lactam antibiotics with that of aminoglycosides and glycopeptides.

# $\beta$ -lactams in de toekomst

Pas de dosering aan op een volledige PK / PD basis **en blijf de vrije bloedspiegels volgen**

**in intensieve zorgen, VLUIG veranderende situatie !**

## Maar wat hebben we nodig?

- een snelle en betrouwbare bepaling van de **serum vrije fractie** ...
- resultaten die **beschikbaar** zijn binnen de **periode van de medische shift !**
- een duidelijke omschrijving van het gewenste doel voor de werkzaamheid ... en het voorkomen van het ontstaan van resistentie ...  
→  **$C_{\min}$  (of  $C_{SS}$ ) = 4 x de MIC ?**
- een duidelijke definitie van de maximale doses zonder onaanvaardbare toxiciteit (convulsies ...) ...  
→  **$C_{\max} <$  dan voor een conventionele wijze van toediening ?**
- een algoritme dat de volgende dosis op basis van de populatie PK, maar ook op basis van echte gegevens van de vorige toediening berekent is ...  
→ **adaptieve PK / PD modelling ...**

# Wat kennen we vandaag over determinanten van de activiteit van de meeste antibiotica ?

2. aminoglycosiden zijn concentratieafhankelijk en moeten eenmaal daags toegediend worden voor verhoogde werkzaamheid en mogelijke vermindering van toxiciteit

*Journal of Antimicrobial Chemotherapy* (1989) **24**, 281–293

## Review

### Determinants of efficacy and toxicity of aminoglycosides

H. Mattie<sup>a</sup>, W. A. Craig<sup>b</sup> and J. C. Pechère<sup>c</sup>

<sup>a</sup>University Hospital, Department of Infectious Diseases, Bldg 1, C5-P, PO Box 9600, 2300 RC Leiden, The Netherlands; <sup>b</sup>William S. Middleton Memorial Veterans' Hospital, 2500 Overlook Terrace, Madison WI 53705, USA; <sup>c</sup>Department of Microbiology, Centre Médicale Universitaire, 9, Avenue de Champel, 1211 Geneva, Switzerland

# Wat kennen we vandaag over determinanten van de activiteit van de meeste antibiotica ?

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*Journal of Antimicrobial Chemotherapy*

## Determinants of efficacy

H. Mattie<sup>a</sup>, W.

<sup>a</sup>University Hospital, Department of  
2300 RC Leiden, The Netherlands  
Hospital, 2500 Overlook Terrace  
Microbiology, Centre Médicale Un

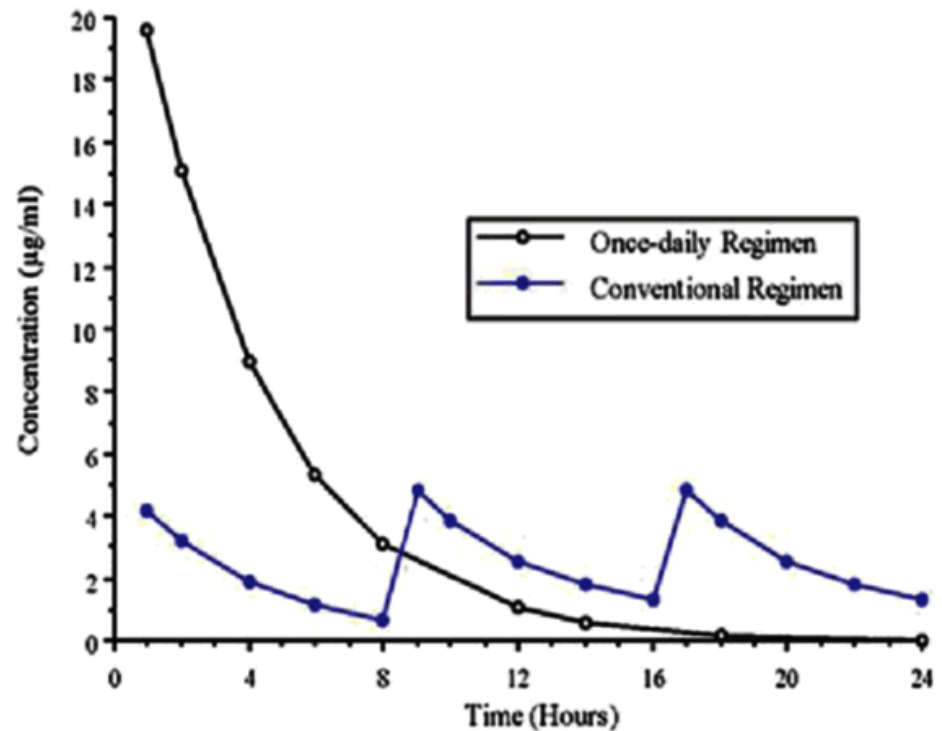
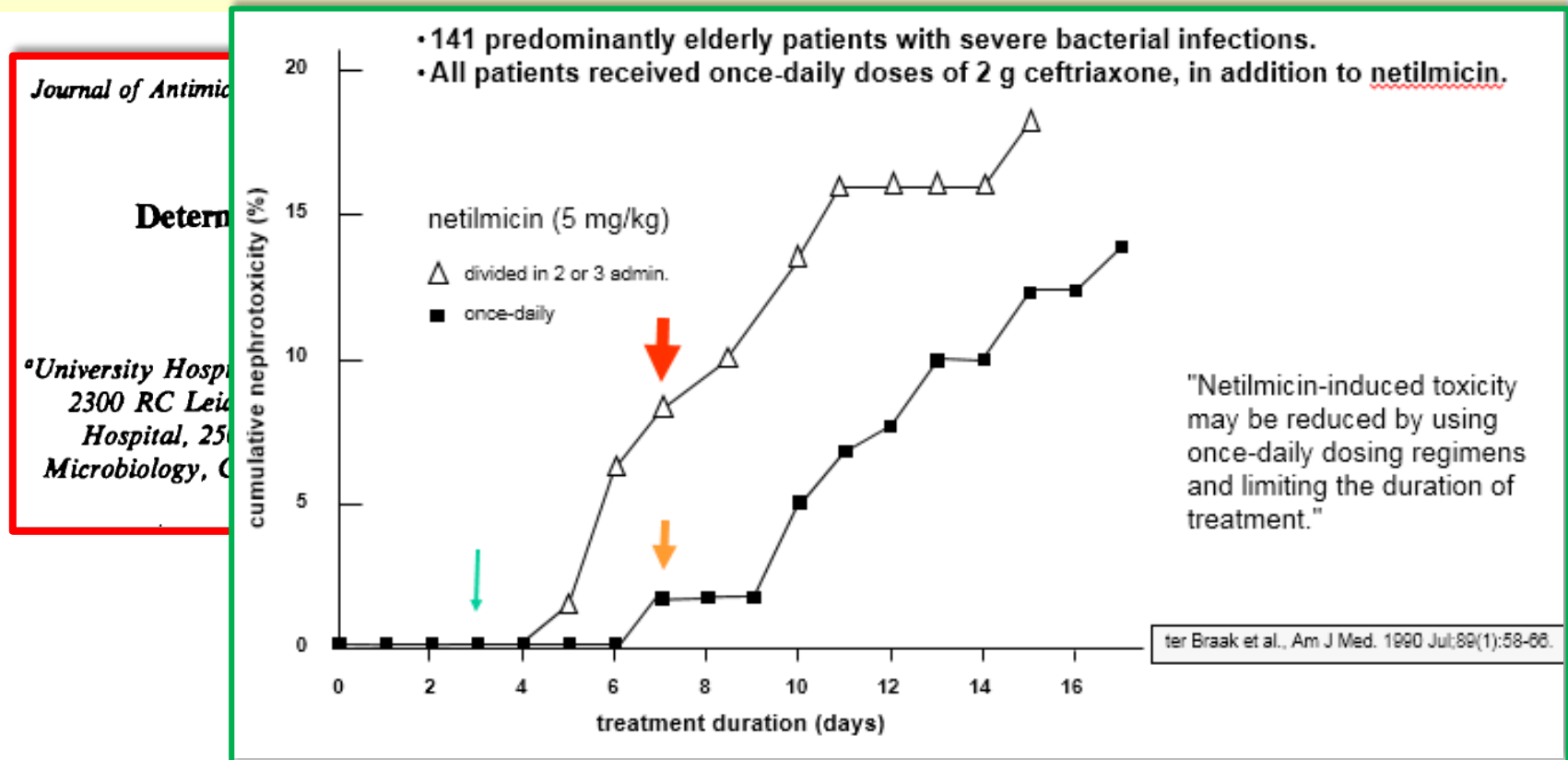


Fig. 9.1 Concentration-time profile comparison of conventional q8h intermittent dosing versus the once-daily daily administration technique

# Wat kennen we vandaag over determinanten van de activiteit van de meeste antibiotica ?

## 2. aminoglycosiden zijn concentratieafhankelijk en moeten eenmaal daags toegediend worden voor verhoogde werkzaamheid en mogelijke vermindering van toxiciteit





# Wat kennen we vandaag over determinanten van de activiteit van de meeste antibiotica ?

## 3. fluorochinolonen moeten een voldoende $AUC_{24h}/MIC$ -ratio bereiken (125?) voor effectiviteit tegen Gram-negatieve bacteriën...

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993, p. 1073-1081  
0066-4804/93/051073-09\$02.00/0  
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Vol. 37, No. 5

### Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

ALAN FORREST, DAVID E. NIX, CHARLES H. BALLOW, THOMAS F. GOSS,  
MARY C. BIRMINGHAM, AND JEROME J. SCHENTAG\*

*Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209-1194*

Received 19 February 1992/Accepted 5 February 1993

# Wat kennen we vandaag over determinanten van de activiteit van de meeste antibiotica ?

## 3. fluoroquinolonen moeten een voldoende $AUC_{24h}/MIC$ -ratio bereiken (125?) voor effectiviteit tegen Gram-negatieve bacteriën...

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1993  
0066-4804/93/051073-09\$02.00/0  
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### Pharmacodynamics of Serum Concentrations

ALAN FORREST, DAVID E. ...  
MARY C. BIRMI ...  
*Center for Clinical Pharmacy Research,  
Buffalo, New York 14260  
Millard Fillmore*

Received 1993

1078 FORREST ET AL.

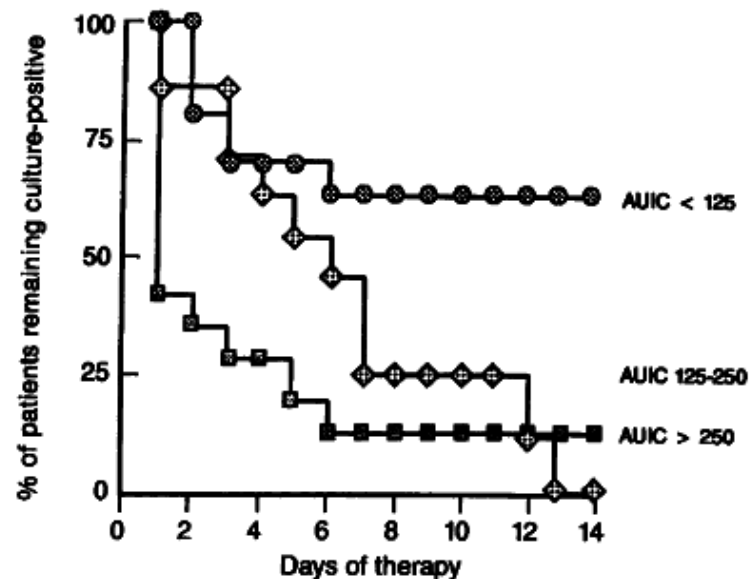


FIG. 5. Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ( $P < 0.005$ ).

# Amerikaanse breekpunten voor fluorochinolonen waren veel te hoog !

Table 2. Pharmacokinetic parameters used for proposing PK/PD based limits of sensitivity and conditions favouring the prevention of emergence of resistance for most common organisms and systemic infections, together with the breakpoints set by European and American ad-hoc organisations

Drug	Typical daily dosage <sup>a</sup>	Typical PK values		Proposed PK/PD upper limit		Breakpoints (mg/L) <sup>d</sup>	
		C <sub>max</sub> in mg/L total/free (dose)	AUC <sub>24 h</sub> (mg × h/L) total/free	Efficacy <sup>b</sup>	Prevention of resistance <sup>c</sup>	EUCAST (S/R)	NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	≤0.5/>1	≤4/8/>16
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤0.5/>1 (≤0.125/>2)	≤1/2/>4
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤0.5/>1 <sup>f</sup> (≤0.125/>4)	≤2/4/8
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤1/>2 (≤2/>2)	≤2/4/8
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤0.5/>1 (≤0.5/>0.5)	≤1/2/4

binnenkort meer over  
breekpunten en resistentie

# Tweede successen ...



Registratie



Breekpunten

# Vandaag worden ALLE nieuwe antibiotica met PK/PD beoordeeld voor registratie

## In Verenigde Staten (FDA)

The screenshot shows the FDA website's search interface. At the top, the FDA logo and the text "U.S. Food and Drug Administration" are visible, along with the tagline "Protecting and Promoting Your Health". A search bar is present with the text "Search FDA" and a magnifying glass icon. Below the search bar, there are navigation tabs for "Home", "Food", "Drugs", "Medical Devices", "Radiation-Emitting Products", "Vaccines, Blood & Biologics", "Animal & Veterinary", "Cosmetics", and "Tobacco Products". The search results section is highlighted with a red box and contains the text "Search Results" and "Showing 1 - 10 of about 248 for PK/PD antibiotics".

U.S. Department of Health and Human Services

**FDA** U.S. Food and Drug Administration  
Protecting and Promoting Your Health

A to Z Index | Follow FDA | En Español

Search FDA

Home > Search

**Refine Search Results**

**FILTER BY TOPICS**

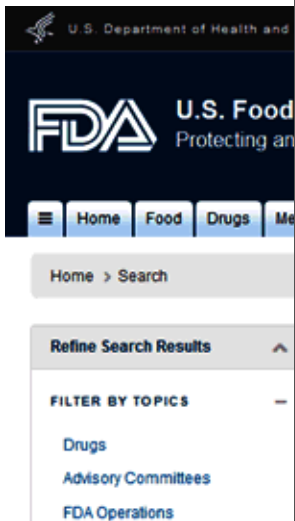
- Drugs
- Advisory Committees
- FDA Operations

PK/PD antibiotics

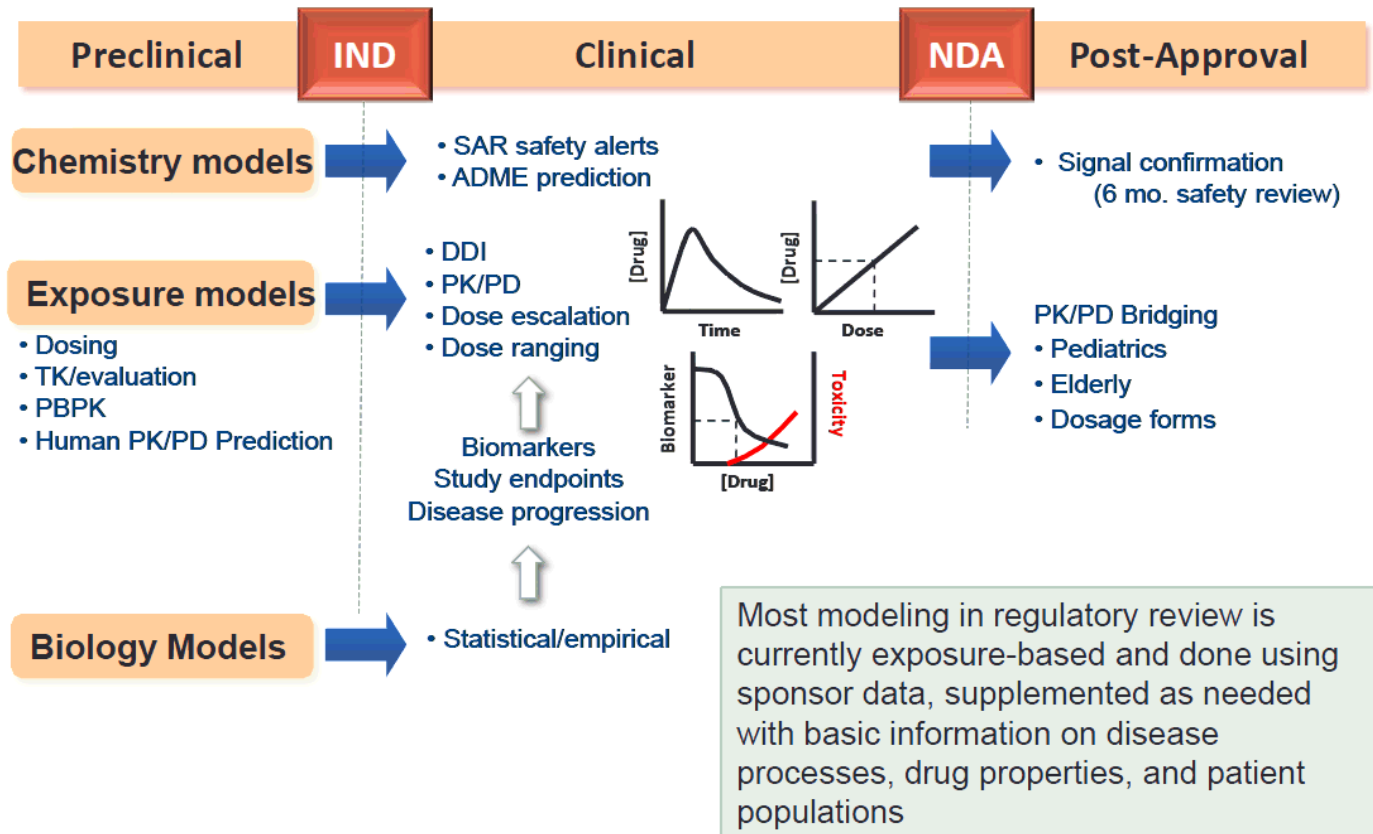
**Search Results**  
Showing 1 - 10 of about 248 for PK/PD antibiotics

# Vandaag worden ALLE nieuwe antibiotica met PK/PD beoordeeld voor registratie

In Verenigde



## Model-Based Drug Development Today



Courtesy of T. Colatsky

<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm344417.pdf>

# Vandaag worden ALLE nieuwe PK/PD beoordeeld voor

## In Verenigde Staten (FDA)

The screenshot shows the FDA website's search interface. At the top, the FDA logo and 'U.S. Food and Drug Administration' are visible. Below the navigation bar, a search bar contains the text 'PK/PD antibiotics'. To the left, a 'Refine Search Results' sidebar is open, showing 'FILTER BY TOPICS' with options for 'Drugs', 'Advisory Committees', and 'FDA Operations'. Below the search bar, a 'Search Results' box indicates 'Showing 1 - 10 of about 248 for PK/PD antibiotics'. The search results area is currently empty.



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

www.fda.gov

## Antibiotics

- Microcosmic/ongoing innovation
- Large, empirical NI trials to evaluate efficacy in MDR generally not feasible
- New methods to assess antibiotic efficacy (mechanistic extrapolation; IVIVC and modeling; PK/PD extrapolation; animal models)
- CDER Antibiotic Drug Development Task Force

<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm344417.pdf>

# Vandaag worden ALLE nieuwe antibiotica met PK/PD beoordeeld voor registratie

In Europa



An agency of the European Union

 EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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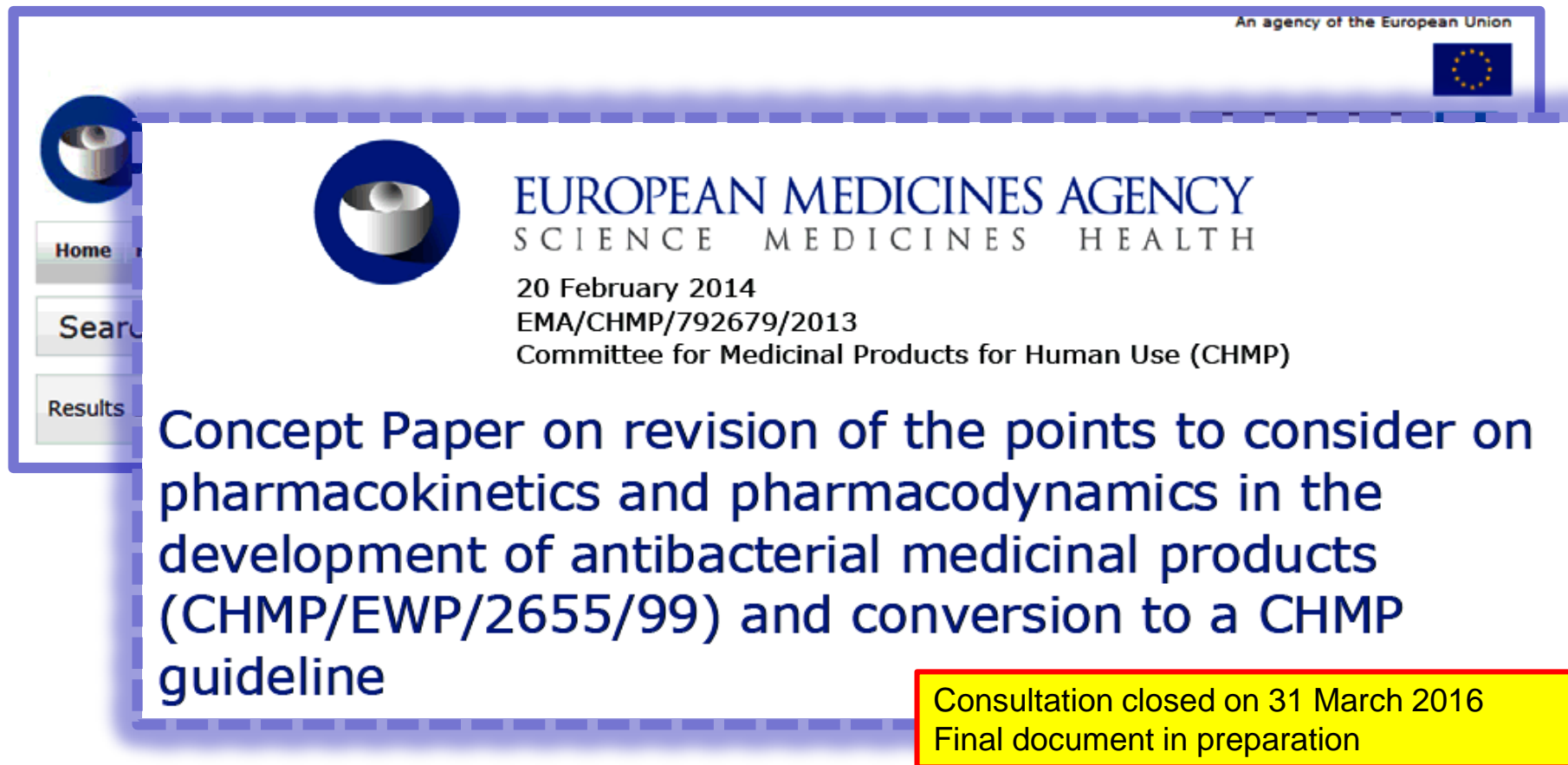
Search [Advanced Search](#)

Results **1 - 10** of about **435** for "**PK/PD antibiotics**". Search took **0.09** seconds.




# Vandaag worden ALLE nieuwe antibiotica met PK/PD beoordeeld voor registratie

In Europa



An agency of the European Union



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

20 February 2014  
EMA/CHMP/792679/2013  
Committee for Medicinal Products for Human Use (CHMP)

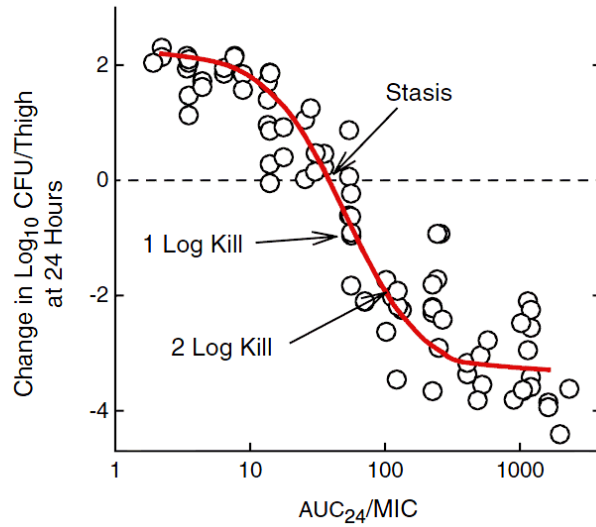
Concept Paper on revision of the points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CHMP/EWP/2655/99) and conversion to a CHMP guideline

Consultation closed on 31 March 2016  
Final document in preparation

Home  
Search  
Results

# Breekpunten...

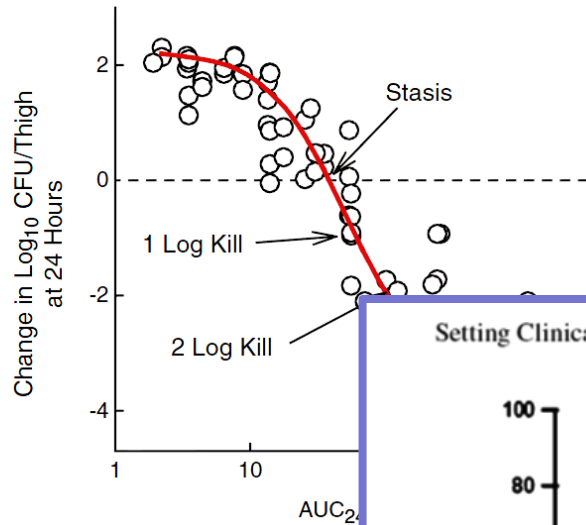
**Fig. 2.6** Change in  $\log_{10}$  CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)



PK/PD parameters

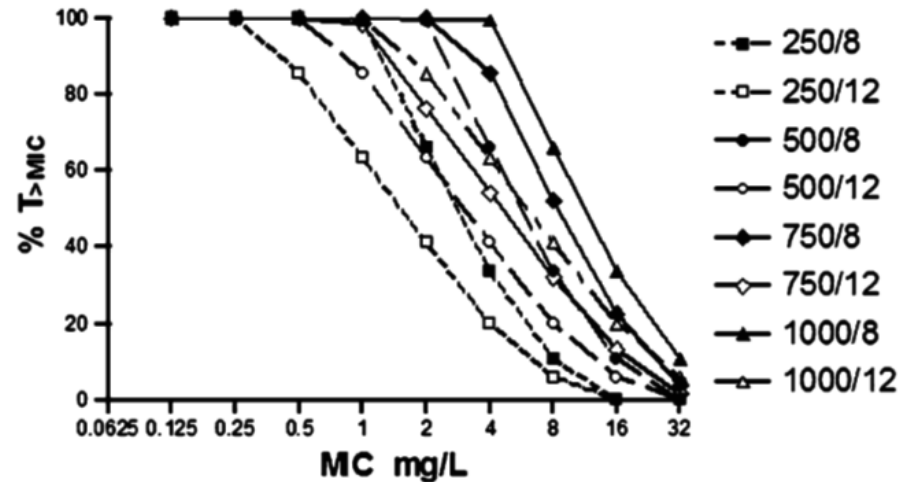
# Breakpoint setting...

**Fig. 2.6** Change in  $\log_{10}$  CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)



Target attainment rates

Setting Clinical MIC Breakpoints from a PK/PD Point of View...



**Fig. 3.2** Relationship between  $\%T > MIC$  and MIC for various dosing regimens of ceftibiprole. Illustrated is the close relationship between target MIC (usually the clinical breakpoint) and the dosing regimen. Adapted from Mouton et al. (2004)

# Modellering en voorspellen

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2001, p. 13-22  
0066-4804/01/\$04.00+0 DOI: 10.1128/AAC.45.1.13-22.2001  
Copyright © 2001, American Society for Microbiology. All Rights Reserved.

Vol. 45, No. 1

## Use of Preclinical Data for Selection of a Phase II/III Dose for Evernimicin and Identification of a Preclinical MIC Breakpoint

G. L. DRUSANO,<sup>1\*</sup> S. L. PRESTON,<sup>1</sup> C. HARDALO,<sup>2</sup> R. HARE,<sup>2</sup> C. BANFIELD,<sup>2</sup>  
D. ANDES,<sup>3</sup> O. VESGA,<sup>3</sup> AND W. A. CRAIG<sup>3</sup>

*Division of Clinical Pharmacology, Albany Medical College, Albany, New York<sup>1</sup>; Schering Plough Research Institute, Kenilworth, New Jersey<sup>2</sup>; and Division of Clinical Pharmacology, University of Wisconsin, Madison, Wisconsin<sup>3</sup>*

Received 22 November 1999/Returned for modification 26 April 2000/Accepted 1 September 2000

# Modelling en voorspellen

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2001, p. 13–22  
0066-4804/01/\$04.00+0 DOI: 10.1128/AAC.45.1.13–22.2001  
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Vol. 45, No. 1

## Use of Preclinical Data for Selection of a Phase II/III Dose for Evernimicin and Identification of a Preclinical MIC Breakpoint

Division of  
Kenilworth

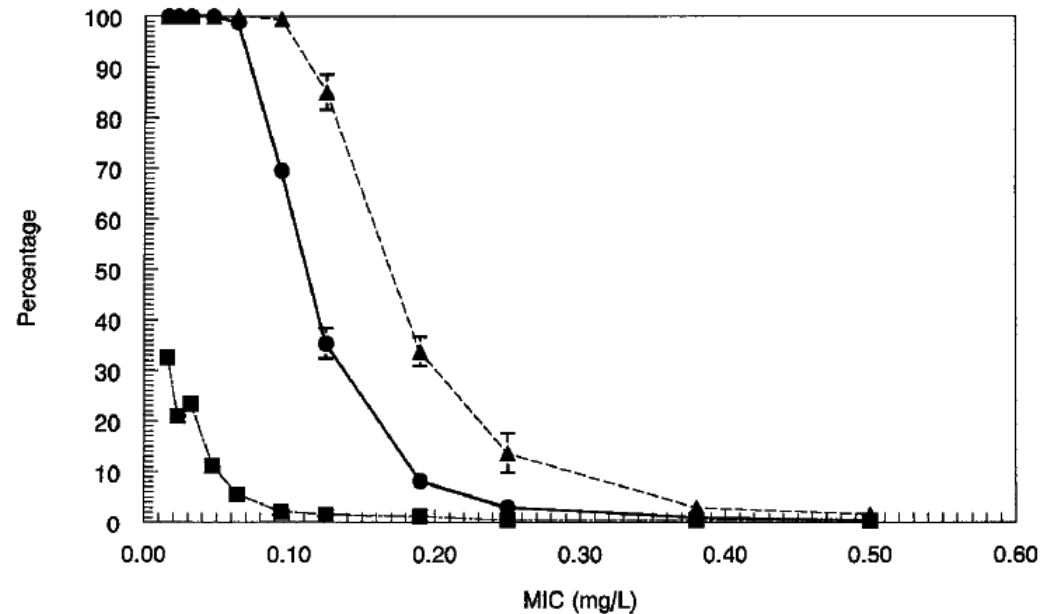
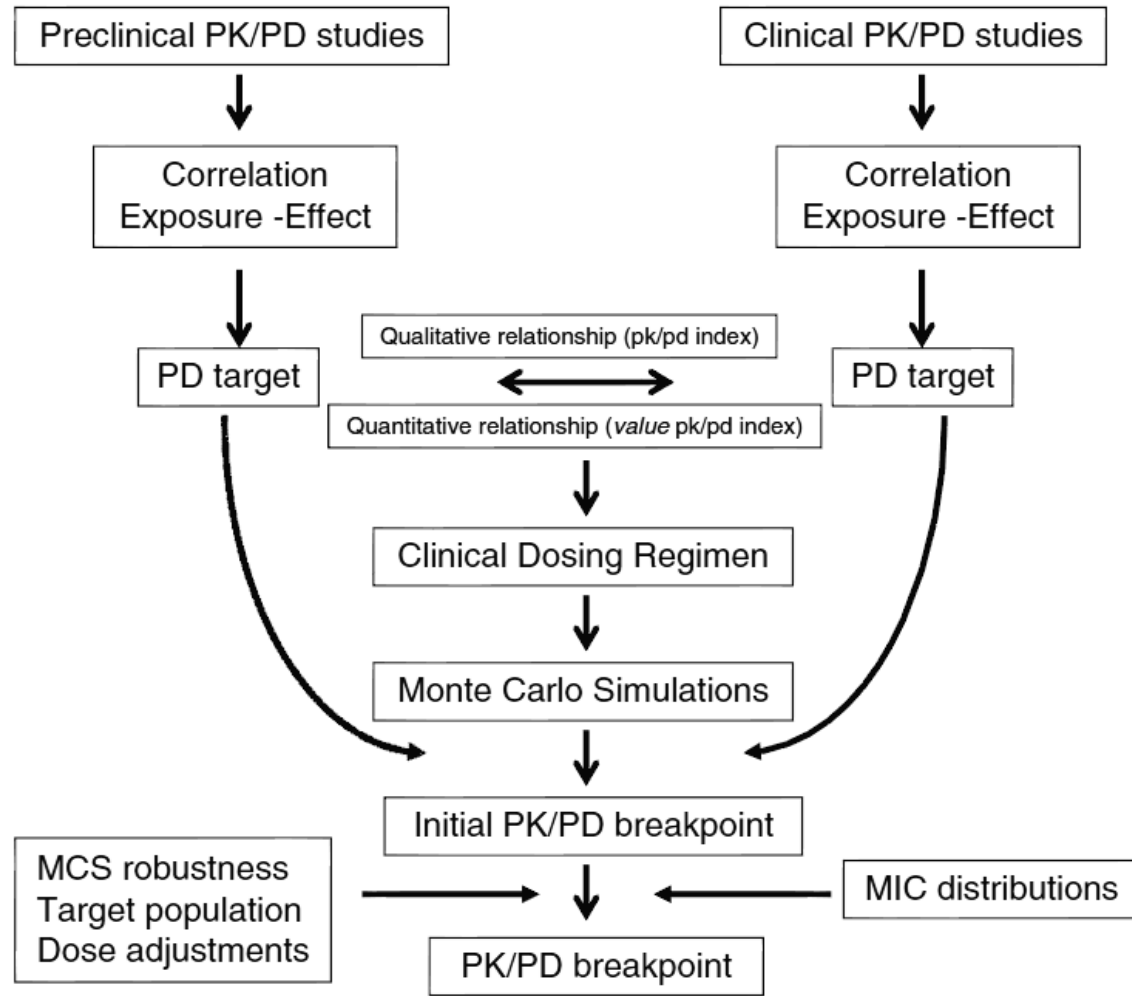


FIG. 4. Fractional attainment of the 90%  $E_{max}$  target for *S. pneumoniae* for the 6-mg/kg dose (●) and the 9-mg/kg dose (▲). The interval MIC distribution information is included (■).

# Breakpoint instelling: de EUCAST weg



**Fig. 3.4** Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

# Waar zijn we nu ?



# Wat moeten we nu doen \*

- **"oude antibiotica" herontdekken**  
→ belangrijk voor regelgevende instanties MAAR weinig belangstelling van farmaceutische bedrijven ...
- **geïndividualiseerde therapie**  
→ Volg het pad ... samen met het ontwikkeling van snelle diagnose en gevoeligheidsbepaling...
- **toxicodynamiek**  
→ kunnen we beter doen, maar de mechanismen zijn complex en voor elke farmacologische klasse specifiek ....
- **preventie van resistentie**  
→ dit kan de echte uitdaging worden

\* persoonlijke opvattingen



# Oude antibiotica ?



# Oude antibiotica ?



ESCMID Conference on Reviving Old Antibiotics



## Optimisation of therapy in Gram-negative infections

[https://www.escmid.org/research\\_projects/escmid\\_conferences/past\\_escmid\\_conferences/reviving\\_old\\_antibiotics/](https://www.escmid.org/research_projects/escmid_conferences/past_escmid_conferences/reviving_old_antibiotics/)

temocillin

fosfomycin

nitrofurantoin

mecillinam

cefoxitin

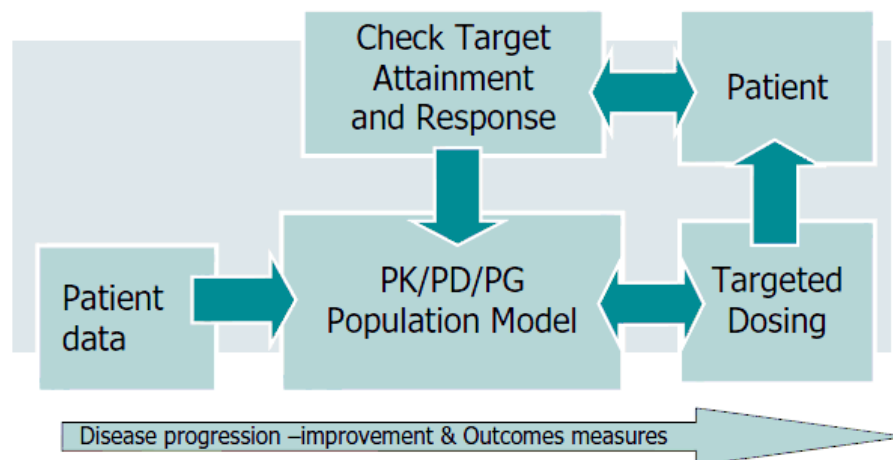
colistin

minocyclin

chloramphenicol

fusidic acid

# Geïndividualiseerde therapie



**Fig. 6.5** Schematic representation of the target-controlled model-based individualized dosing strategy. A clinical pharmacokinetics program with a patient-specific population model describing absorption, distribution, and elimination of the antibiotic in relation to patient-specific parameters is used. Patient data and desired target concentrations are entered into the system. Next, a model-based loading dose and maintenance regimen required to optimally achieve the target concentrations is determined. This regimen is administered to the patient and subsequent concentration measurement(s) are used as feedback to check target attainment and update the model and/or design a new dosing regimen, if required. *PK* pharmacokinetics, *PD* pharmacodynamics, *PG* pharmacogenetics

# Geïndividualiseerde therapie



## Clinical Vignette 12.1: TDM of Vancomycin Administered by Continuous Infusion

A 21-year-old student has developed subacute meningitis and peritonitis in the presence of a ventriculoperitoneal shunt that was placed for hydrocephaly that developed following removal of a brain tumor. He has a fever of 38.9 °C, headache, and severe abdominal pain.

His length is 187 cm and his weight is 67 kg. The cerebrospinal fluid (CSF) WBC count is  $>2.0 \times 10^9/\text{ml}$  and the Gram stain shows Gram positive cocci in clusters.

Empirical therapy with vancomycin is started at a loading dose of 15 mg/kg and a daily dose of 30 mg/kg/day by i.v. continuous infusion (CI). In practice, two syringes of 1 g are administered over 12 h with an infusion pump. Both *S. aureus* MSSA (MIC 1 µg/mL) and coagulase-negative staphylococci (MIC 2 µg/mL) are cultured from the CSF. The shunt is removed and a ventricular external drain is placed. Vancomycin 10 mg is given once intraventricularly.

A vancomycin serum level on Day 3 is 15 µg/mL. The daily CI vancomycin dose is increased to 2,250 mg (two syringes of 1,225 mg) and in the subsequent days target serum levels of 20 µg/mL are reached.

Because of the CI, each serum level sample is a correct one, regardless of the time of sampling, and adjustments of dosing are easily achieved in this neurosurgical department.

# Toxicodynamiek

Een nieuw inzicht voor de aminoglycosiden ....

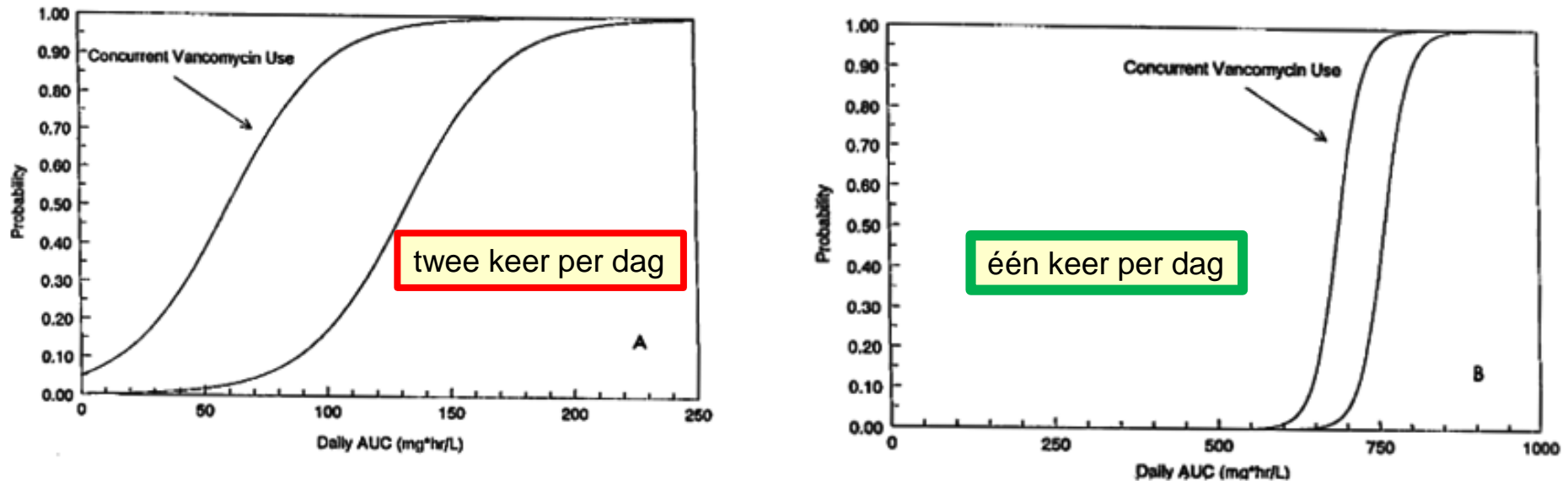
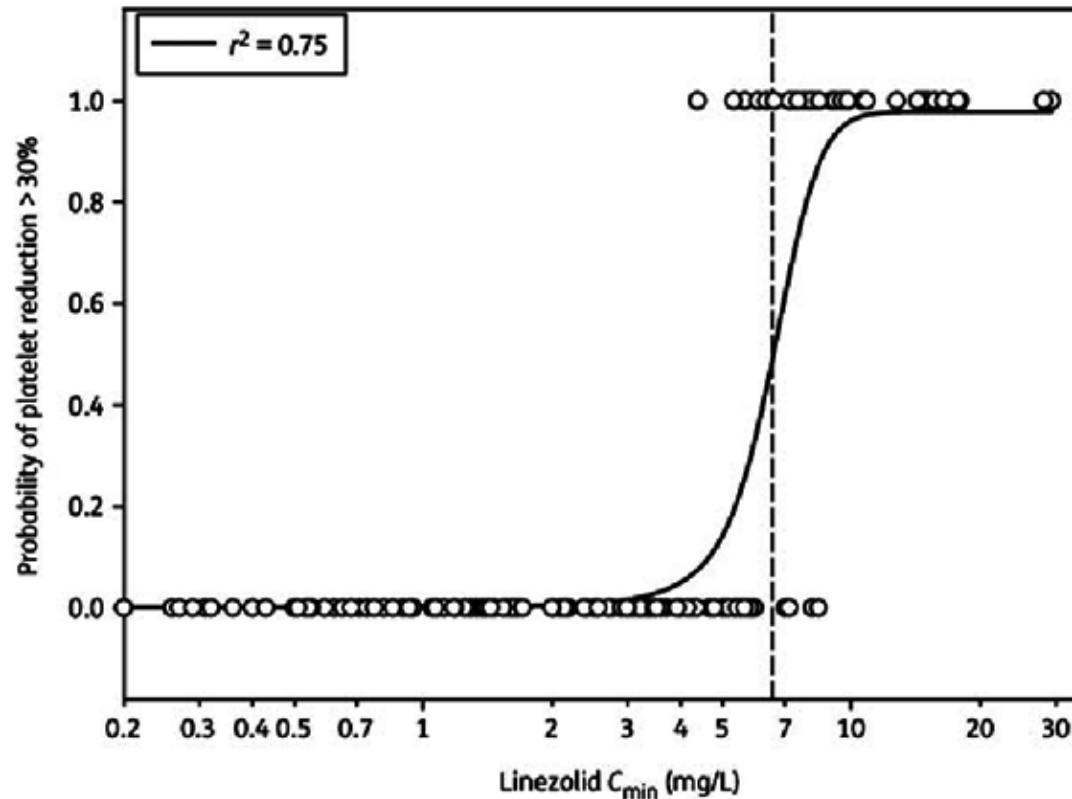


FIG. 1. (A) Curve of probability of development of aminoglycoside nephrotoxicity for patients receiving the drug on a twice-daily basis as estimated by multivariate logistic regression analysis. The probability rises as a function of increasing daily exposure to aminoglycoside, as indexed to the AUC. Concurrent vancomycin use provides a marked increase in the probability of nephrotoxicity for equivalent exposure to aminoglycosides, as indexed to the daily AUC. (B) Once-daily administration shifts the curves of probability of nephrotoxicity as influenced by daily aminoglycoside AUC to the right.

# Toxicodynamiek

En met linezolid ....



**Fig. 16.13** Linezolid  $C_{\min}$  and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the  $C_{\min}$  observed over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the  $C_{\min}$  value predicting 50 % probability of thrombocytopenia

Theuretzbacher U, PK/PD of Oxazolidinones In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinck, H. Derendorf & JW Mouton eds, Springer, 2014, p 401-443

# Toxicodynamics

## Modelling linezolid toxiciteit



## Clinical Population Pharmacokinetics and Toxicodynamics of Linezolid

Lauren M. Boak,<sup>a\*</sup> Craig R. Rayner,<sup>a,b</sup> M. Lindsay Grayson,<sup>c,d</sup> David L. Paterson,<sup>e\*</sup> Denis Spelman,<sup>f</sup> Sharmila Khumra,<sup>c,h</sup> Blair Capitano,<sup>e\*</sup> Alan Forrest,<sup>g</sup> Jian Li,<sup>a</sup> Roger L. Nation,<sup>a</sup> Jurgen B. Bulitta<sup>a,g,h</sup>

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville campus), Parkville, Australia<sup>a</sup>; d3 Medicine LLC, Parsippany, New Jersey, USA<sup>b</sup>; Department of Medicine, Austin Hospital, Melbourne, Australia<sup>c</sup>; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia<sup>d</sup>; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA<sup>e</sup>; Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia<sup>f</sup>; School of Pharmacy and Pharmaceutical Sciences, SUNY at Buffalo, Buffalo, New York, USA<sup>g</sup>; Centre for Medicine Use and Safety, Monash University (Parkville campus), Parkville, Australia<sup>h</sup>

**Antimicrob Agents Chemother 2014;58:334–2343**

# Toxicodynamics

## Modelling linezolid toxiciteit

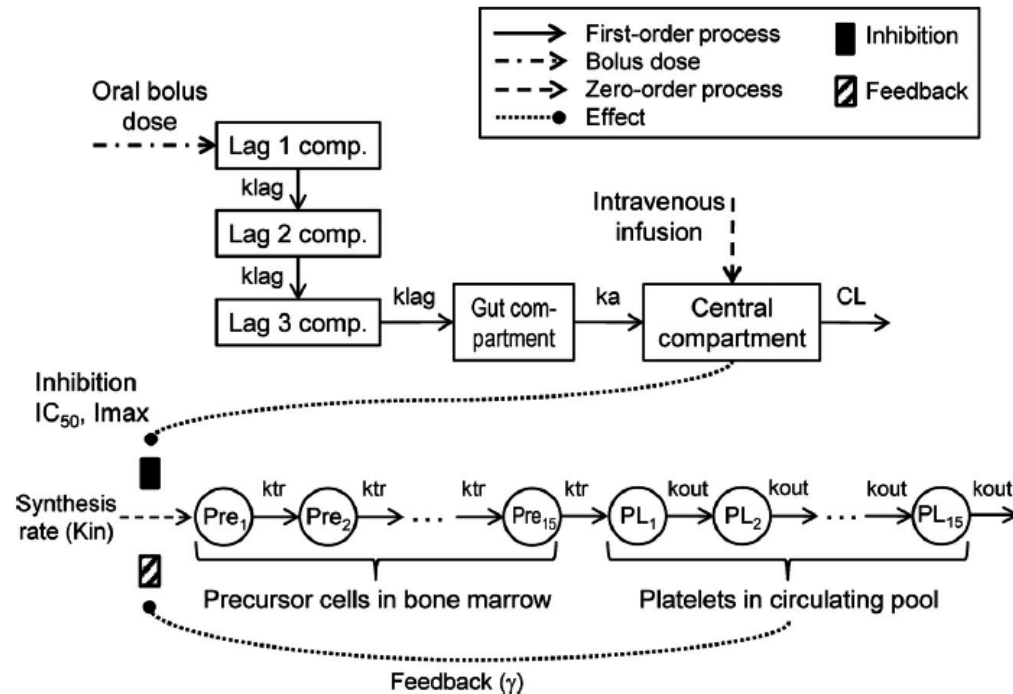
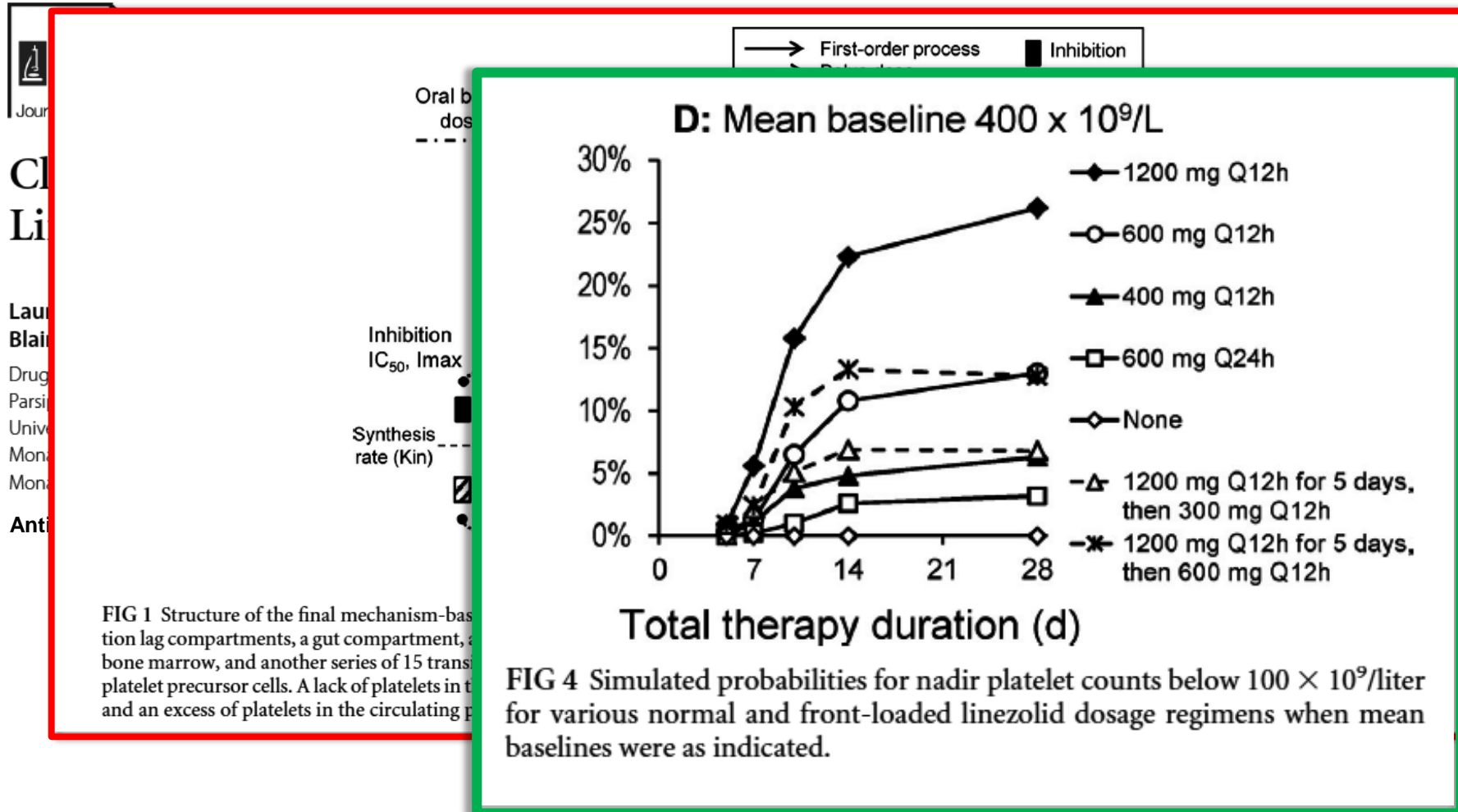


FIG 1 Structure of the final mechanism-based population pharmacokinetic/toxicodynamic model. The pharmacokinetic model is comprised of three absorption lag compartments, a gut compartment, and a central compartment. One series of 15 transit compartments was used to describe platelet precursor cells in the bone marrow, and another series of 15 transit compartments to describe platelets in the circulating pool. Platelets displayed a feedback effect on the synthesis of platelet precursor cells. A lack of platelets in the circulating pool compared to the platelet count at steady state caused a stimulation of platelet precursor synthesis, and an excess of platelets in the circulating pool caused an inhibition of platelet precursor synthesis.



# Toxicodynamics

## Modelling linezolid toxiciteit



# Resistentie:

## Hoe kunnen we er tegen vechten

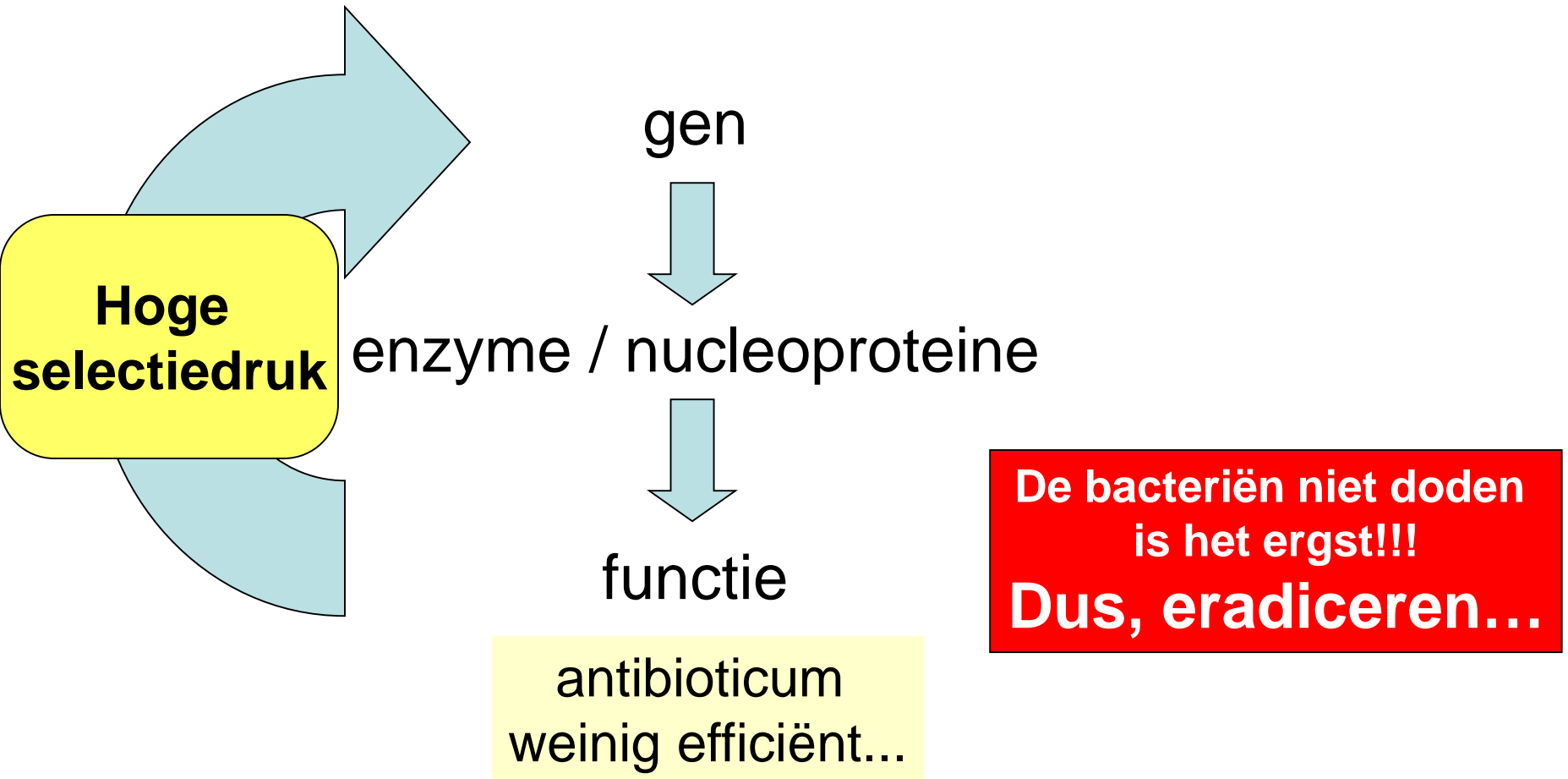


- Eradiceren
  - Mutaties
  - Effluxpompen
- Concentratie die mutaties en/of efflux voorkomt
- En in de praktijk (voorbeeld met chinolonen)...

# De vier reden om te eradiceren...

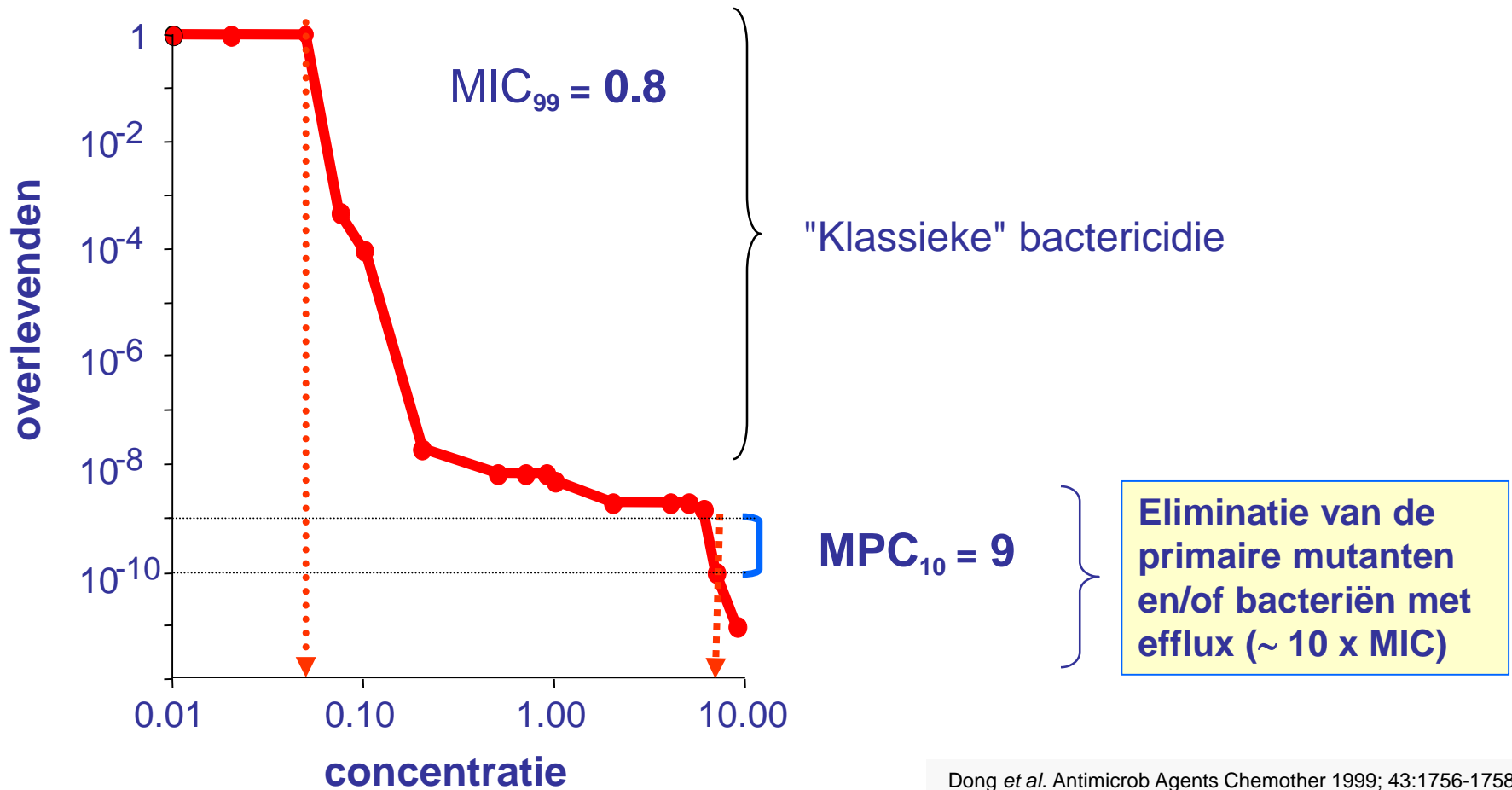
- Dode bacteriën muteren niet meer...  
(eenvoudige toepassing op de principes van Darwin...)
- Als ze dood zijn kunnen ze hun buur niet meer gaan contamineren...  
(basisprincipe van acties in de epidemiologie...)
- Hoe dan ook, als Pasteur gelijk heeft (en hij heeft gelijk...), moet men de ziekteverwekker niet uitschakelen om te genezen?  
(fysiopathologisch principe van infectieziekten...)
- Wenst u niet dat uw patiënt veel sneller geneest en voor goed?  
(een tevreden patiënt is er één die niet terugkomt... voor hetzelfde probleem)

# Selectie van mutanten: de rol van antibiotica...

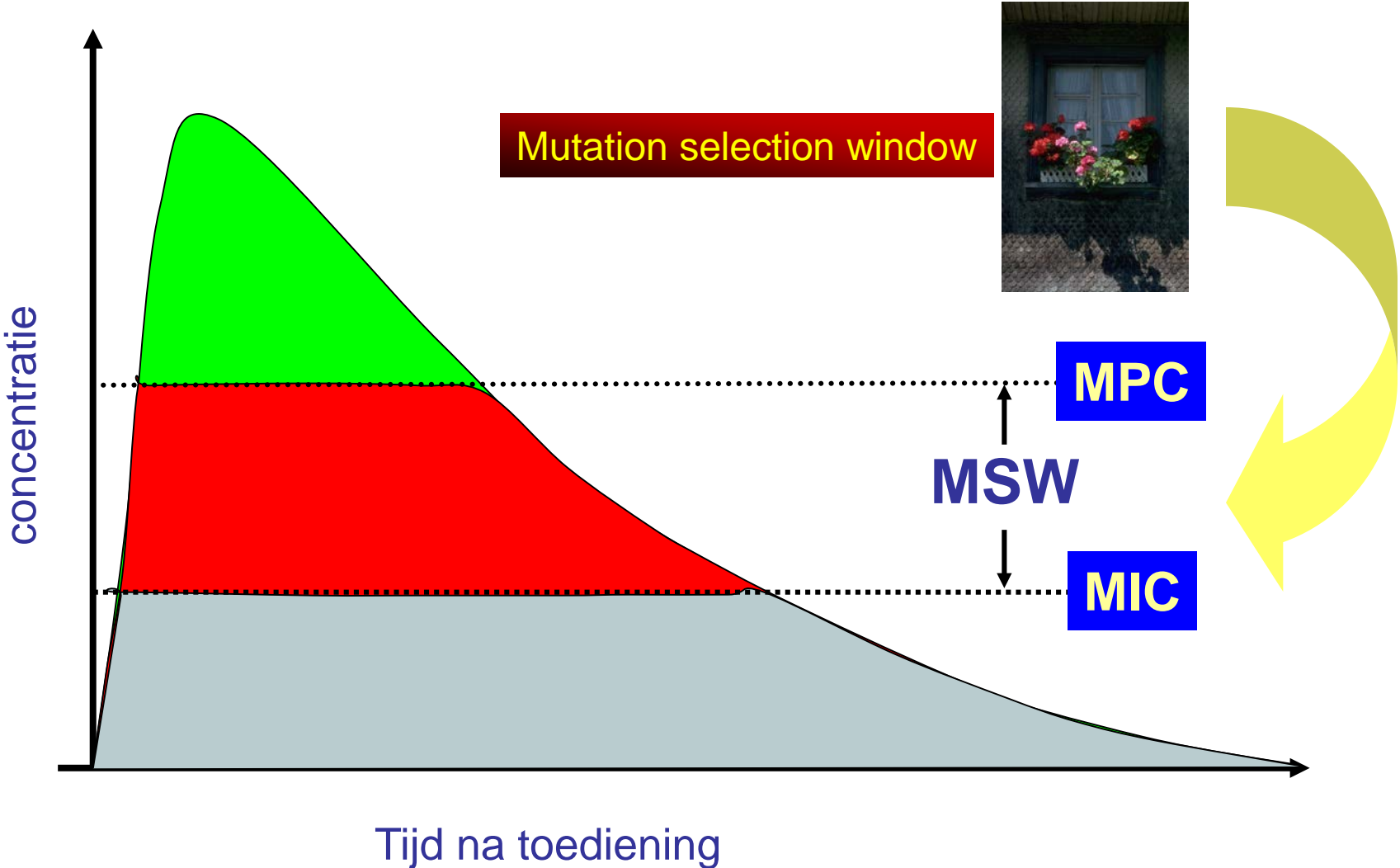


# Concentratie die mutaties / efflux voorkomt... (Mutation Preventing Concentration [MPC])

Voorbeeld: bactericide werking van een FQ tegenover *Mycobacterium bovis*

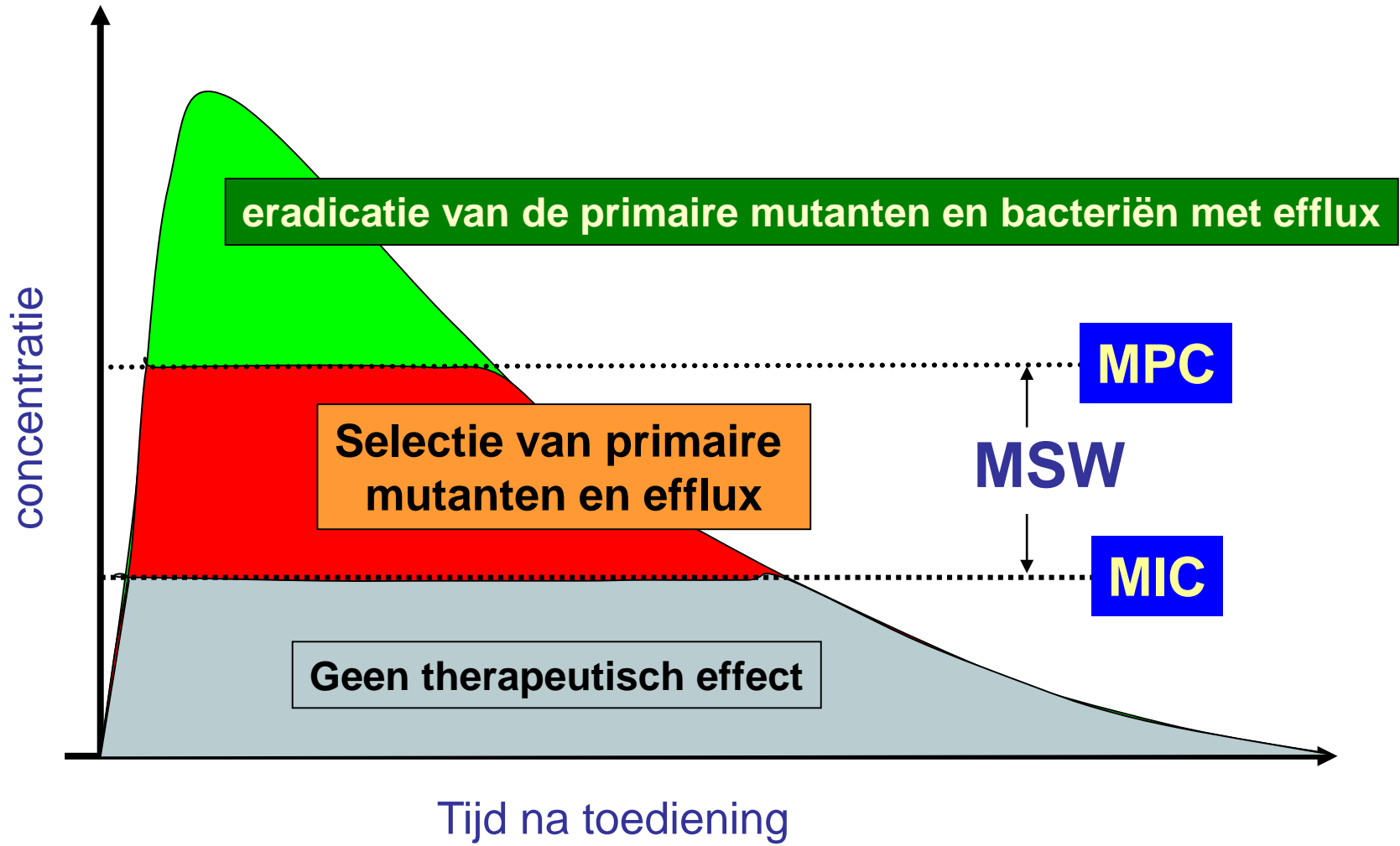


# Venster waarbinnen selectie van mutaties en efflux plaatsvindt...



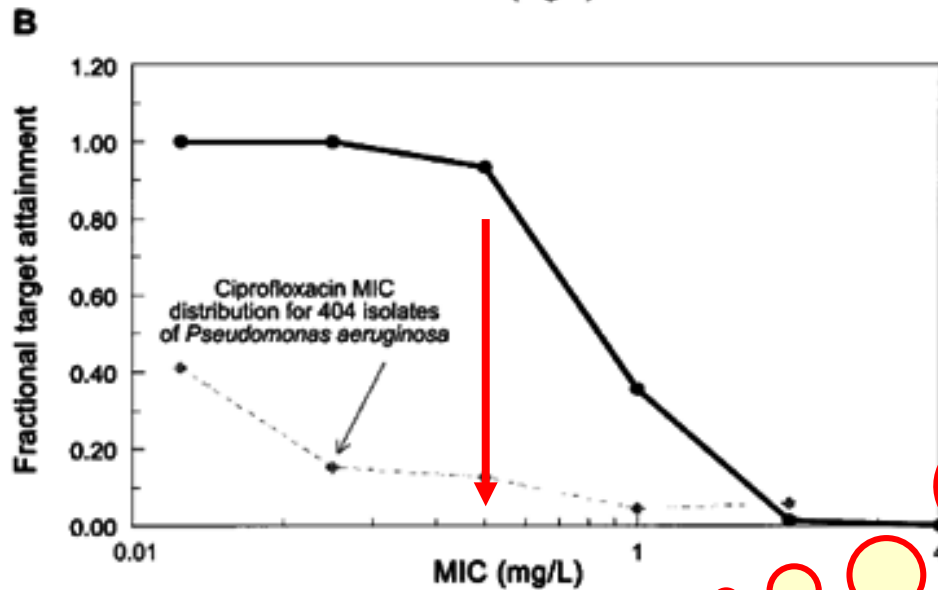
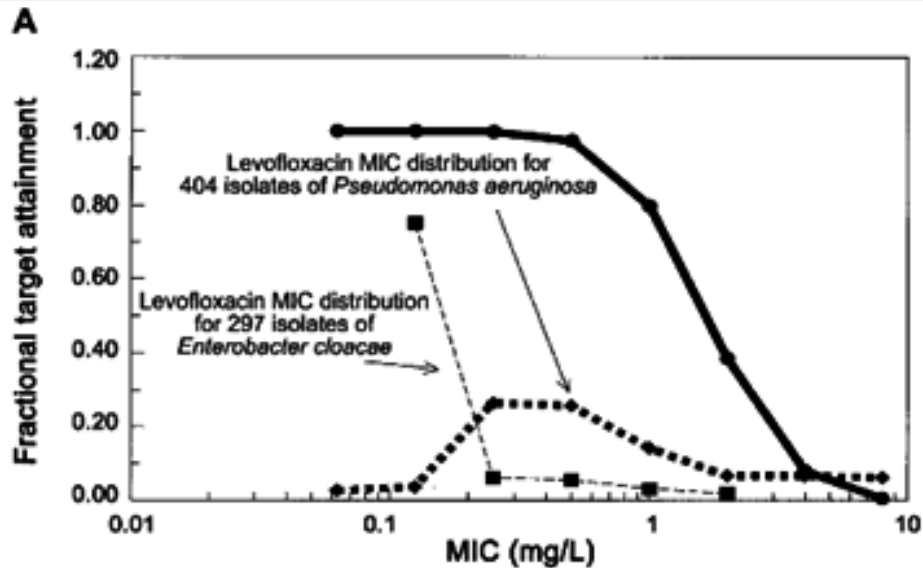
concept overgenomen van Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

# Venster waarbinnen selectie van mutaties plaatsvindt...



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

# Resistentie... *The last frontier* ?



De fluoroquinolonen saga:  
"target attainment rate" om  
resistentie voor te komen

het probleem is dat het  
"resistentie" breekpunt VEEL  
lager zal worden dan de  
CLSI en/of EUCAST  
doeltreffendheid breekpunten

...



# Maar wie heeft dit gedaan ?



maar er waren  
vele anderen ....

**The right  
team,  
folks ...**

# Ik heb (zeker) veel belangrijke punten vergeten...

stel dus  
maar  
vragen !



Dias beschikbaar op <http://www.facm.ucl.ac.be/> → Lectures → in het Nederlands