

General concepts of pharmacodynamics

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Pharmacodynamics – why?

- To optimise the treatment of patients
 - Better and faster cure / improvement
 - Less adverse reactions

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- To reduce the risk for ecological unwanted effects
 - Resistance developments
 - Selections for other microorganisms

Ecological unwanted effects

- **Resistance developments**

JL Martinez et al. Antimicrob Agent Chemother 2000;44:1771-1777.

- **Seldom in the infective microorganisms**

DN Fish et al. Pharmacotherapy 1995;15:279-291.

JK Thomas et al. Antimicrobial Agent Chemother 1998;42:521-527.

- **Often in the normal microflora**

N Høiby. J Antimicrob Chemother 2000;46:Suppl.1:59-62.

R Dagan et al. J Antimicrob Chemother 2001;47:129-140.

----many studies----

- **Selection of unwanted microorganisms**

- **Always?**

F Baquero et al. J Chemother 1999;suppl.1:35-43.

----we all know about Candida, Clostridium difficile, Enterococci, etc. ----

Pharmacodynamics – why?

- To optimise the treatment of patients
 - Better and faster cure / improvement
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- To reduce the risk for ecological unwanted effects
 - Resistance developments
 - Selections for other microorganisms
- Cost-effectiveness ?

Antibiotic effects

- Effects:
 - On the infectious microorganisms
 - Bactericidal or bacteriostatic effect
 - Inhibition of toxinproduction
 - Resistance development
 - On the normal flora
 - Resistance development
 - Selection of unwanted microroganisms
 - On the host
 - Survival
 - Adverse effects, - toxicity, allergy

Antibiotic effects in the following

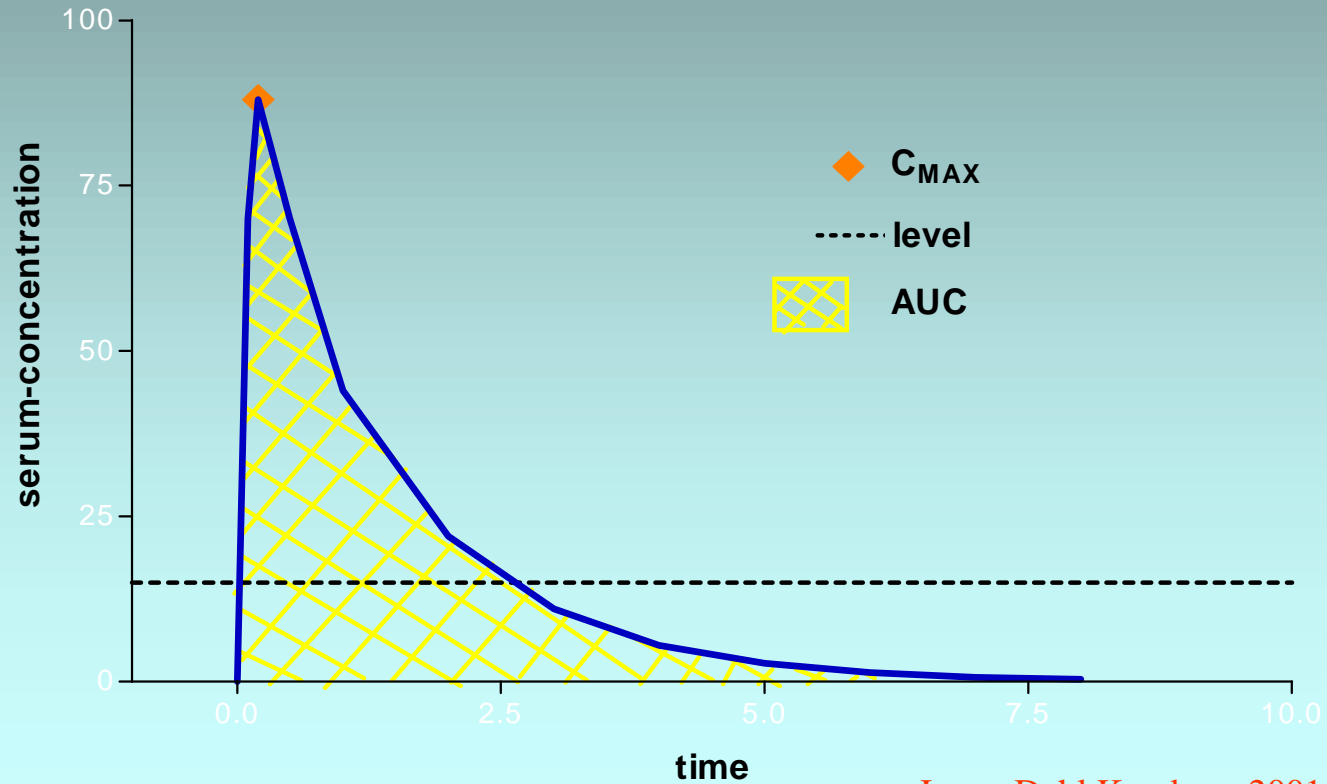
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Definitions

- Pharmacokinetics:
 - What the body does to the drug
 - concentration \sim time
- Pharmacodynamics:
 - What the drug does to the body (microorganisms)
 - effect \sim $\log(\text{dose})$

Definitions

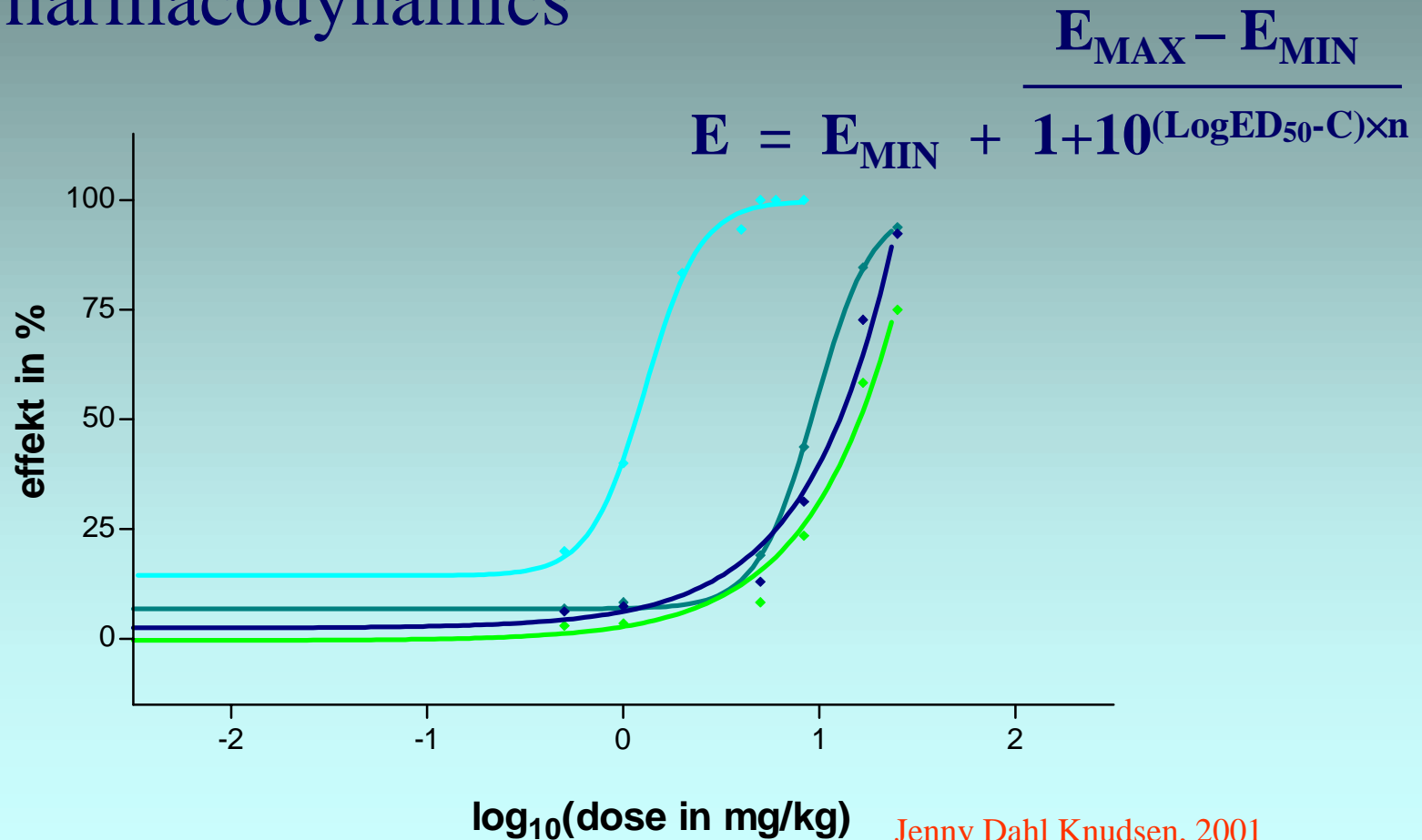
Pharmacokinetics



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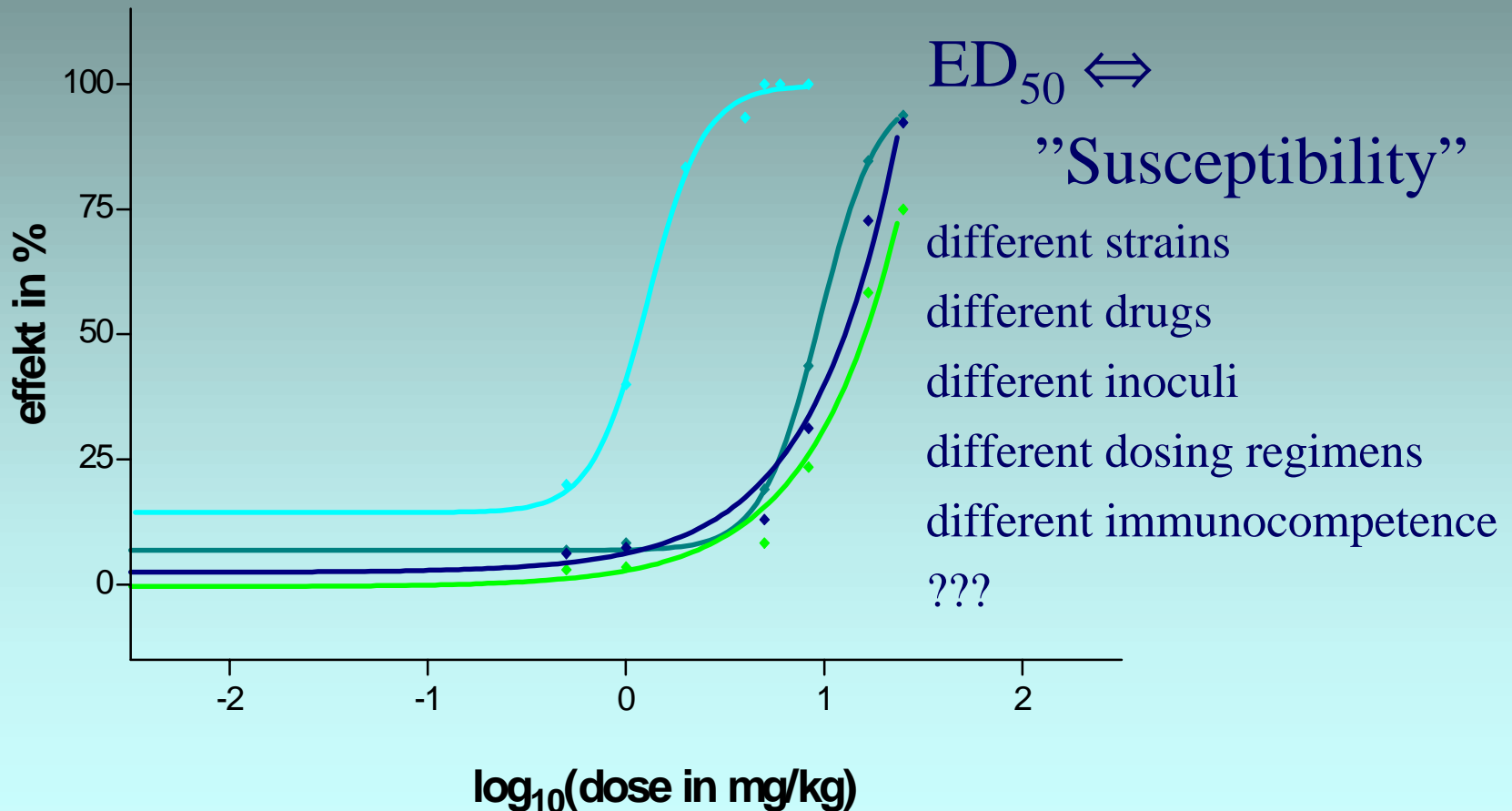
Definitions

Pharmacodynamics



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Dose-response-relationships



Pharmacodynamics

- Correlations between the pharmacokinetic parameters and effect are expected to be universal for all susceptible microorganisms

$$E \sim T_{>MIC} \text{ or } T_{>MBC}$$

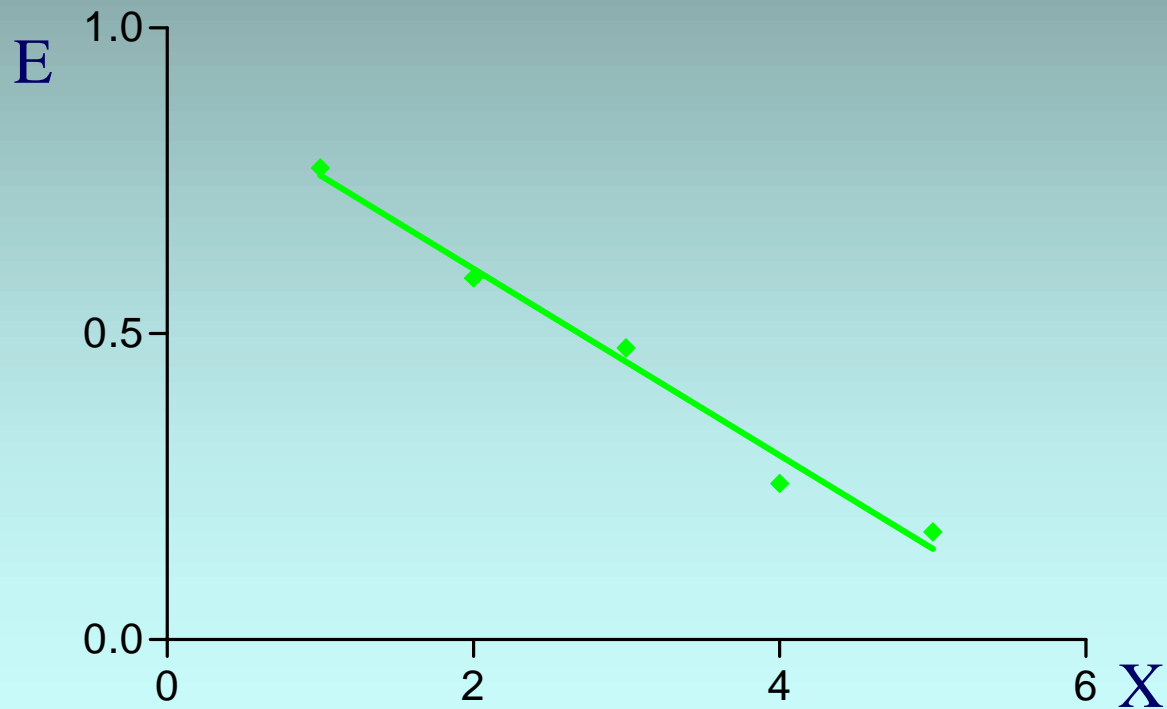
$$E \sim C_{MAX} \text{ or } C_{MAX}/MIC$$

$$E \sim AUC \text{ or } AUC/MIC$$

$$E_X : Z \sim Y; Q \sim W; \text{ etc.}$$

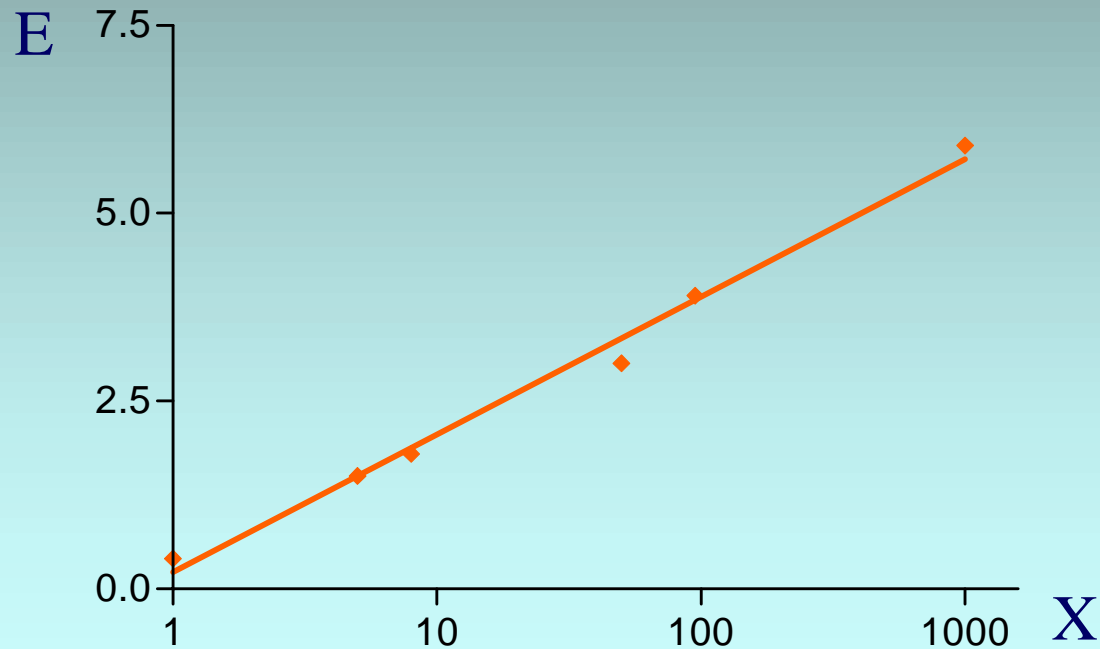
Linear model

$$E = \alpha \times X + \beta$$



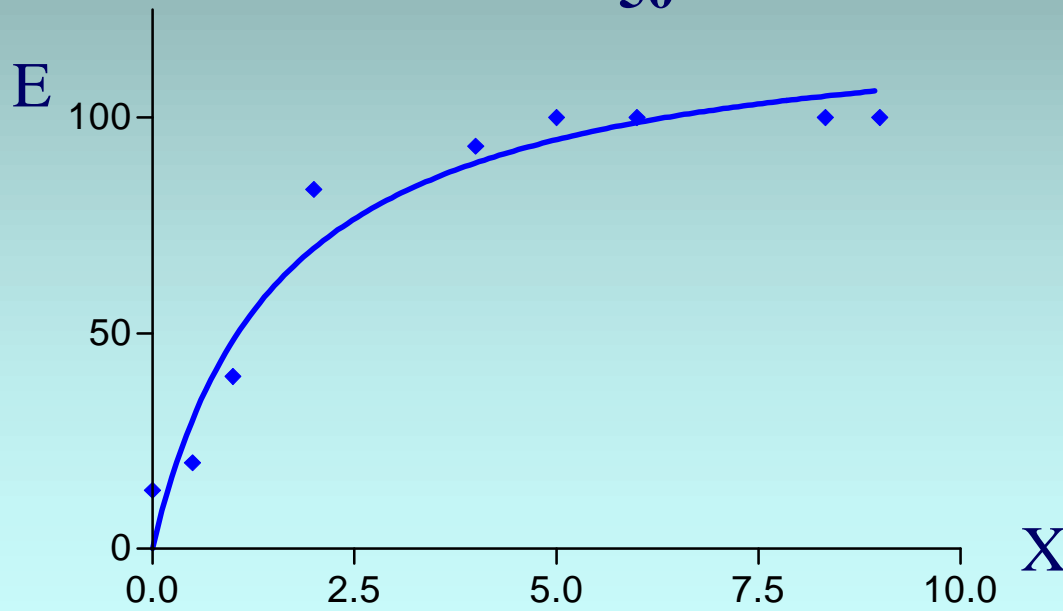
Log-linear model

$$E = \alpha \times \log X + \beta$$



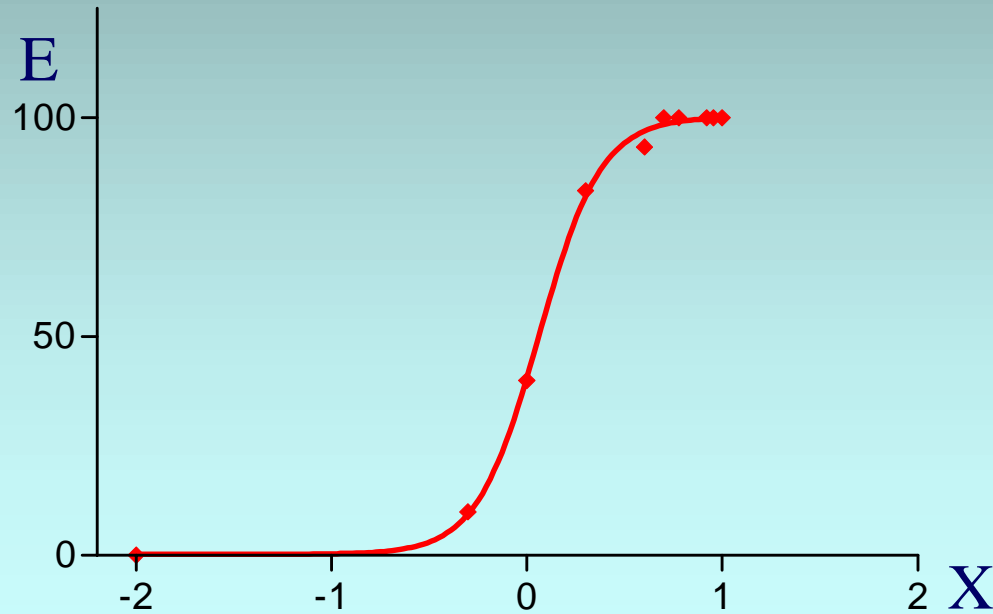
E_{MAX} -model

$$E = \frac{E_{MAX} \times X}{ED_{50} + X}$$



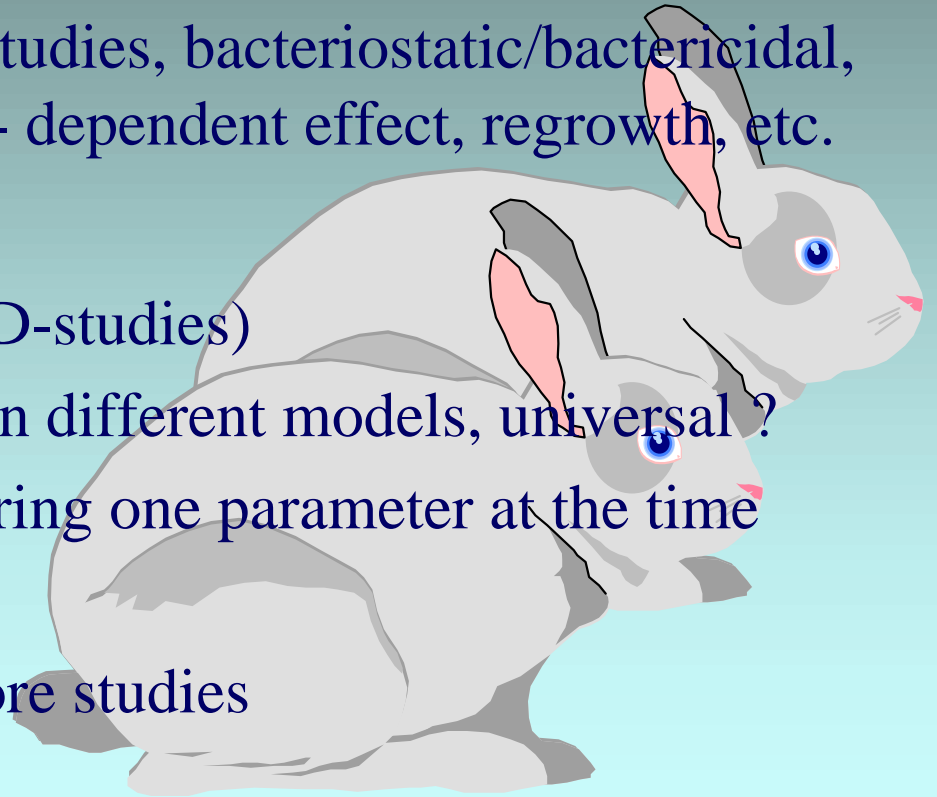
Sigmoid model (variable slope)

$$E = E_{\text{MIN}} + \frac{E_{\text{MAX}} - E_{\text{MIN}}}{1 + 10^{(\text{LogED}_{50} - X) \times n}} \approx \frac{E_{\text{MAX}} \times X^n}{\text{ED}_{50}^n + X^n}$$

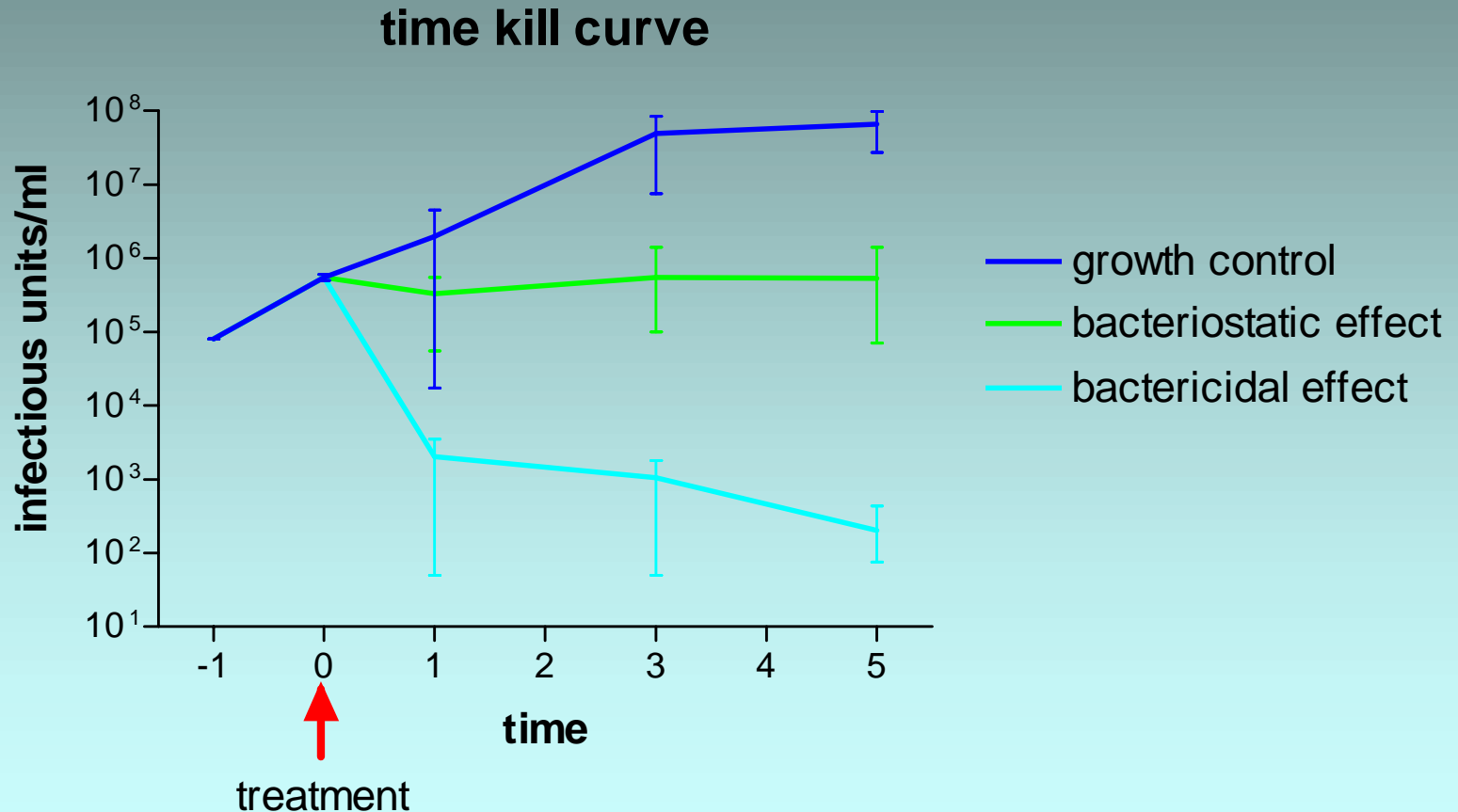


Predictive parameters

- In vitro studies
 - MIC/MBC, time-kill-studies, bacteriostatic/bactericidal, concentration- or time- dependent effect, regrowth, etc.
- In vivo studies
 - Animal models (PK/PD-studies)
 - Numerous studies in different models, universal ?
 - advantage of exploring one parameter at the time
 - Human studies
 - always need for more studies



Effect on microorganisms



How to identify the predictive parameter(s) in vivo

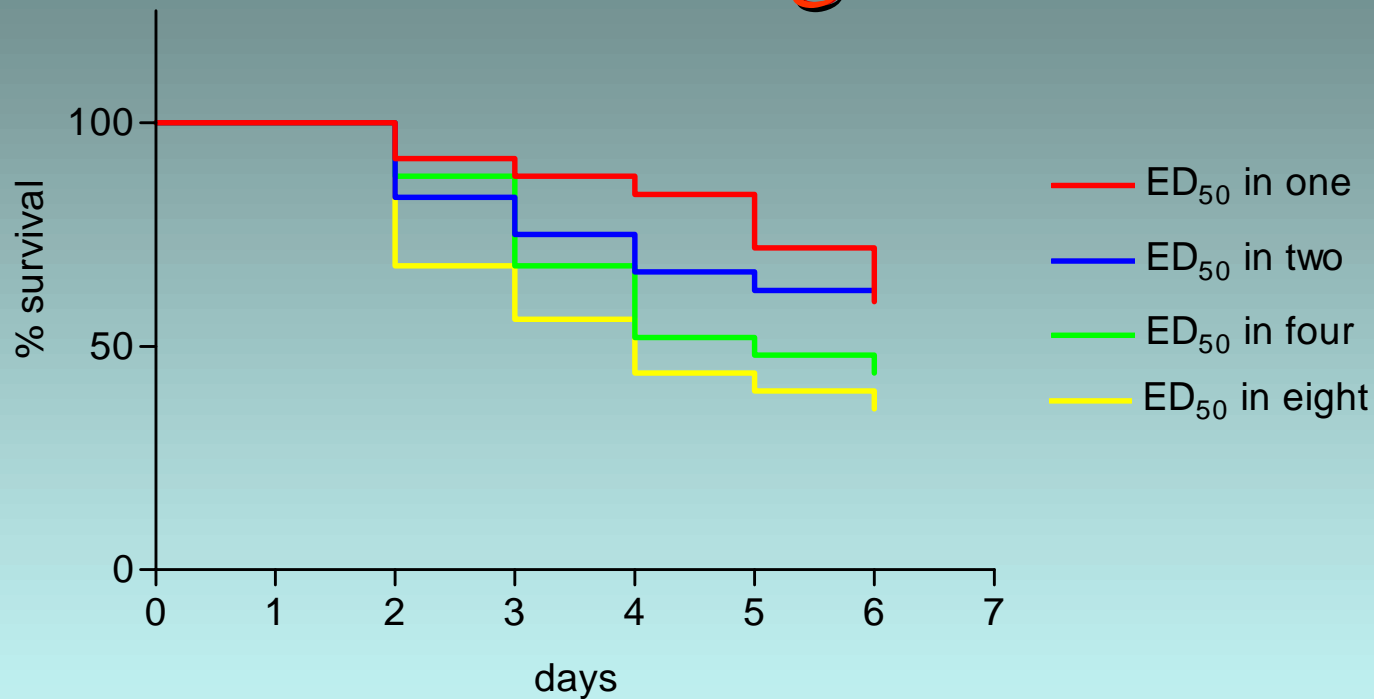
- Explore the correlation between effect and various PK/PD parameters:
 - One drug, one microorganism, many dosing regimens
 - One drug, many microorganisms, one dosing regimen
 - More drugs from the same class of antibiotics, one or more organisms, one or more dosing regimens
- Study the PK/PD parameters at a certain effect
 - The PK/PD parameters at ED_{50} for many organisms and one drug



Parameters with dosing

<i>parameter</i>	<i>Many small doses</i>	<i>Few large doses</i>
C_{MAX}	minimal	maximal
$T_{>MIC}$	longer	shorter
AUC	same	same
PAE	disappear	maximal
PASME	maximal	minimal
Vd	same	same

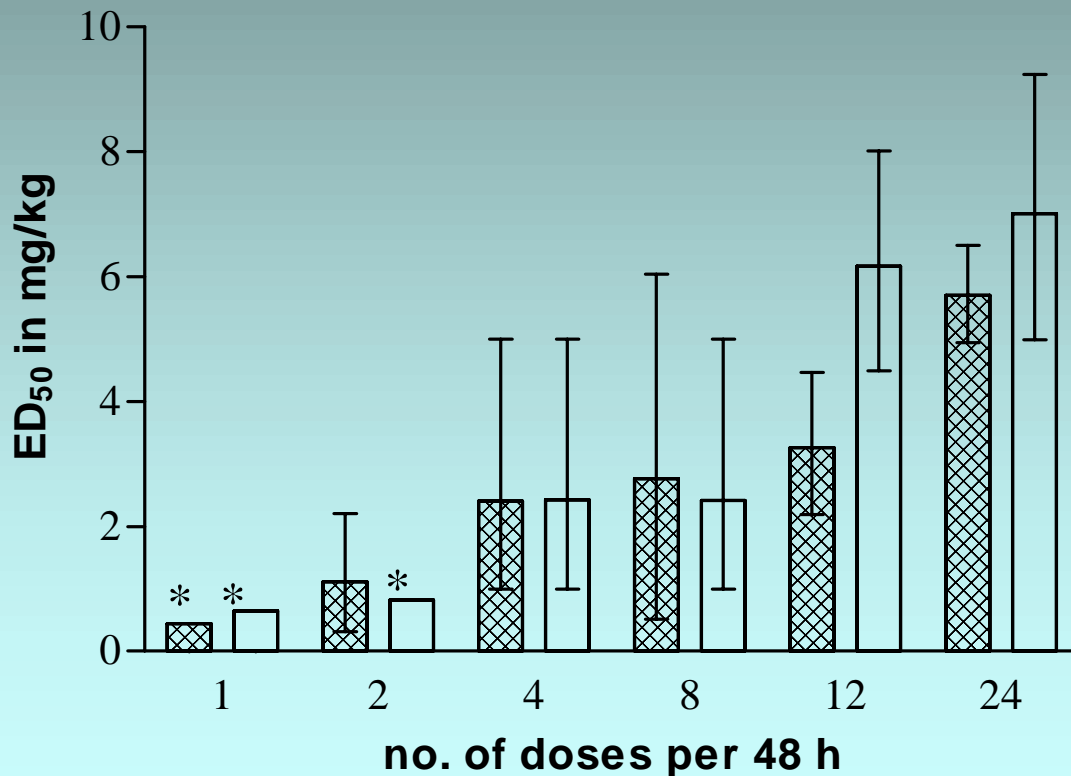
Azithromycin, one pneumococcus, different regimens



The ED₅₀ dose was used in different regimens

JG den Hollander et al. AAC 1998;42:377-382.

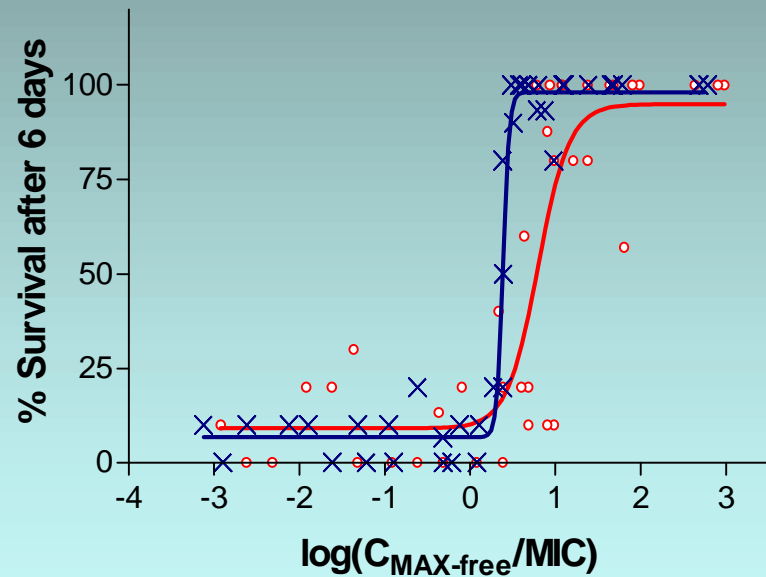
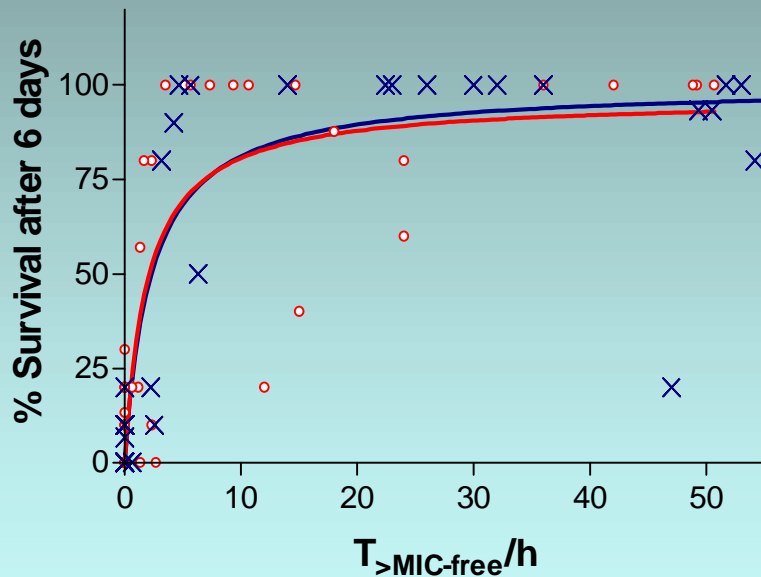
Teicoplanin and vancomycin, one pneumococcus, many dosing regimens



Teicoplanin and vancomycin against a pneumococcus in immunocompetent mice

JD Knudsen et al. AAC 2000;44:1247-1254.

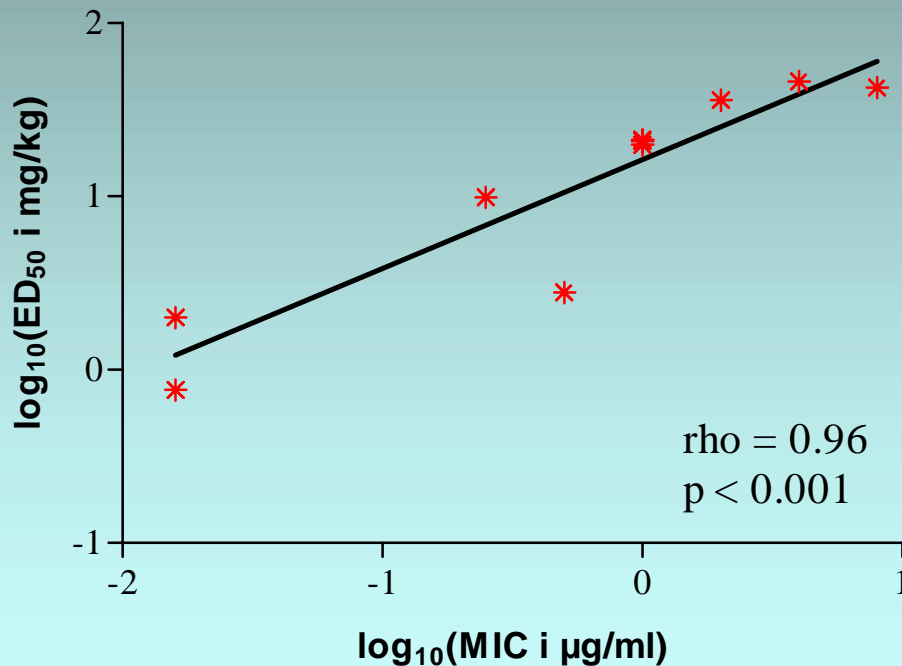
Teicoplanin and vancomycin II



JD Knudsen et al. AAC 2000;44:1247-1254.

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Penicillin-G, ten pneumococci, many dosing regimens



Determination of ED₅₀s and the correlation to MICs

For each ED₅₀ the PK/PD parameters were measured/calculated:

$T_{>\text{MIC}}$: 42 (24-60) min

$C_{\text{MAX}}/\text{MIC}$: 38 (9-96)

AUC/MIC : 27 (7.3-72) h

JD Knudsen et al. AAC
1995;39:1253-1258.

Future focus on PK/PD

To optimise the dosing regimens for different infectious diseases

To optimise the use of old well known drugs especially with focus on intermediate resistant microorganisms

To optimise the dosing regimens for new drugs to enhance the chances of success in treatments and to reduce the risk of failures and development of resistance

