# An Overview of Pharmacokinetic-Pharmacodynamic modelling

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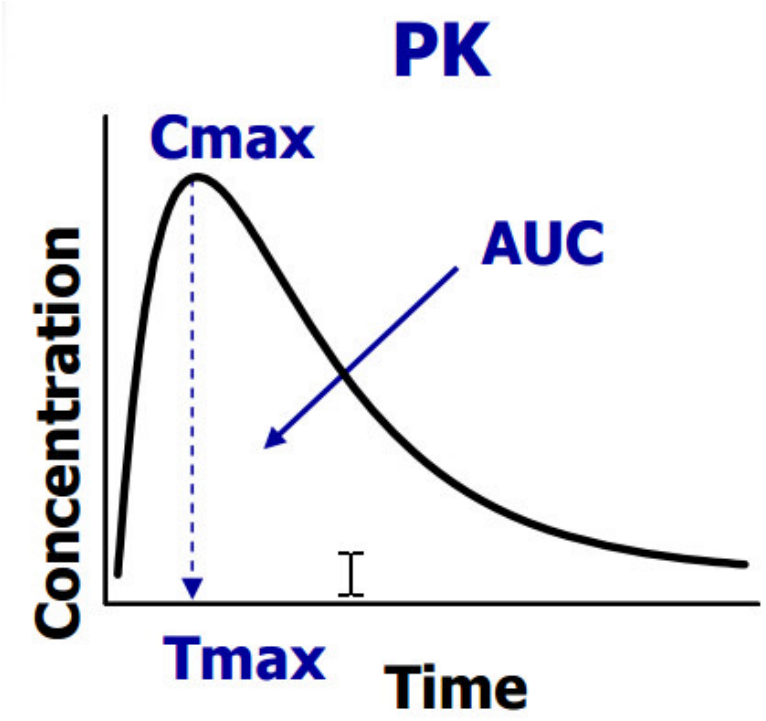
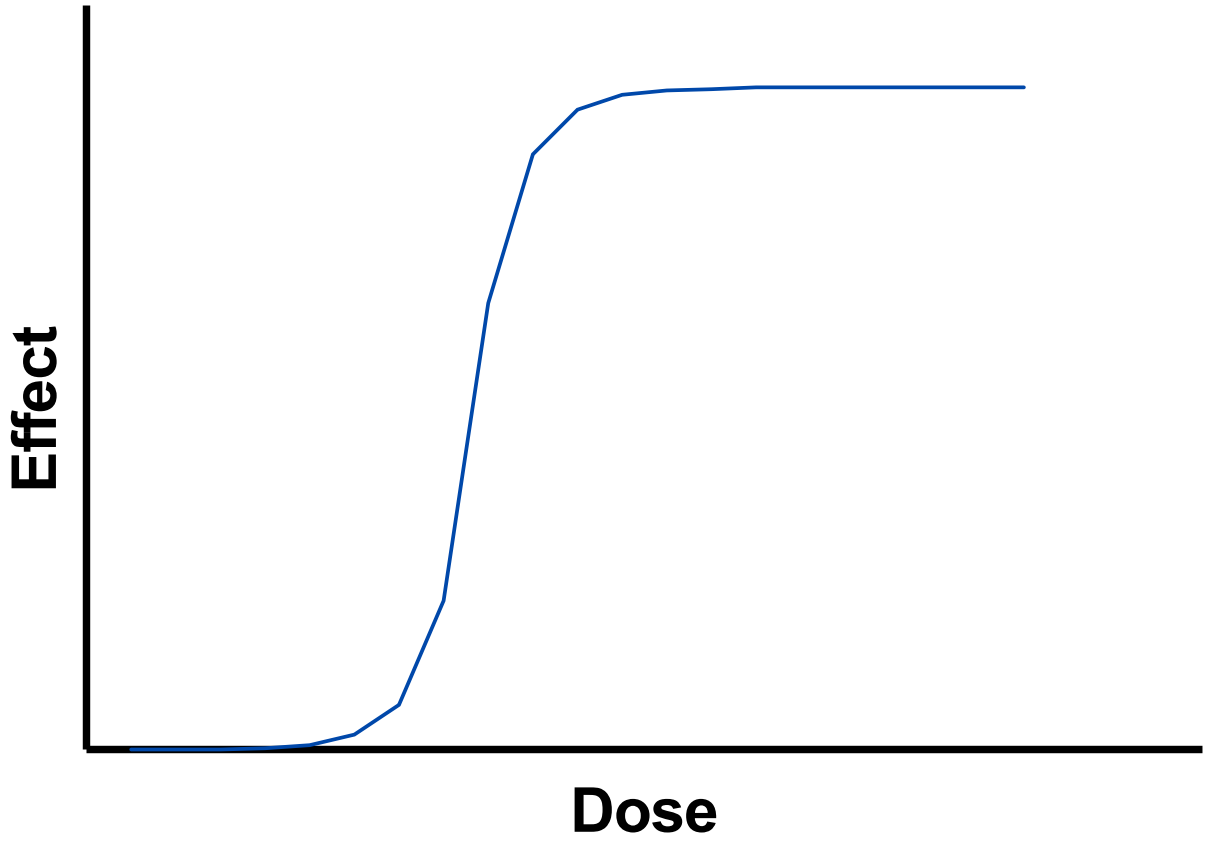
# A few basic definitions

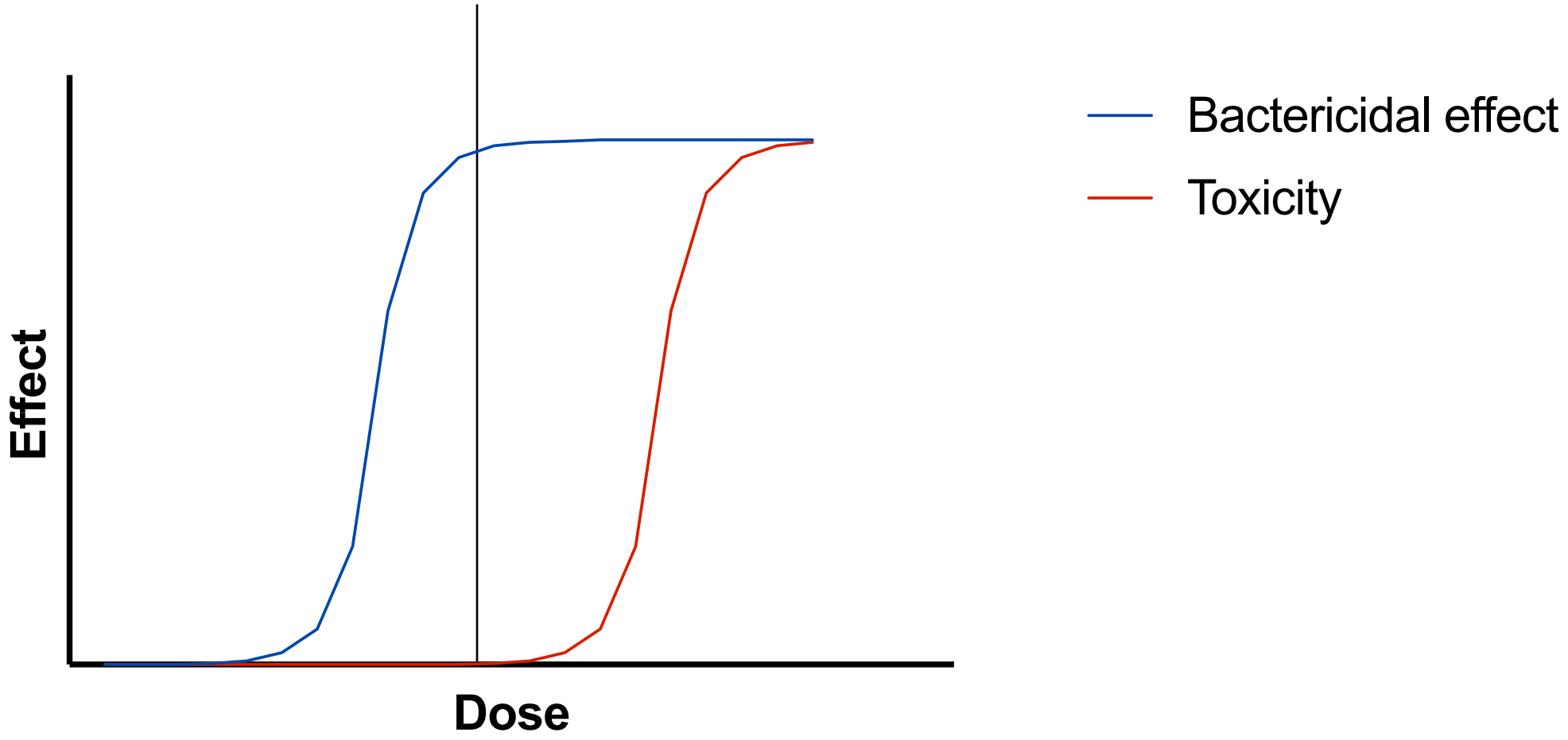
**Pharmacokinetics –** What a human (or animal) body does to a drug

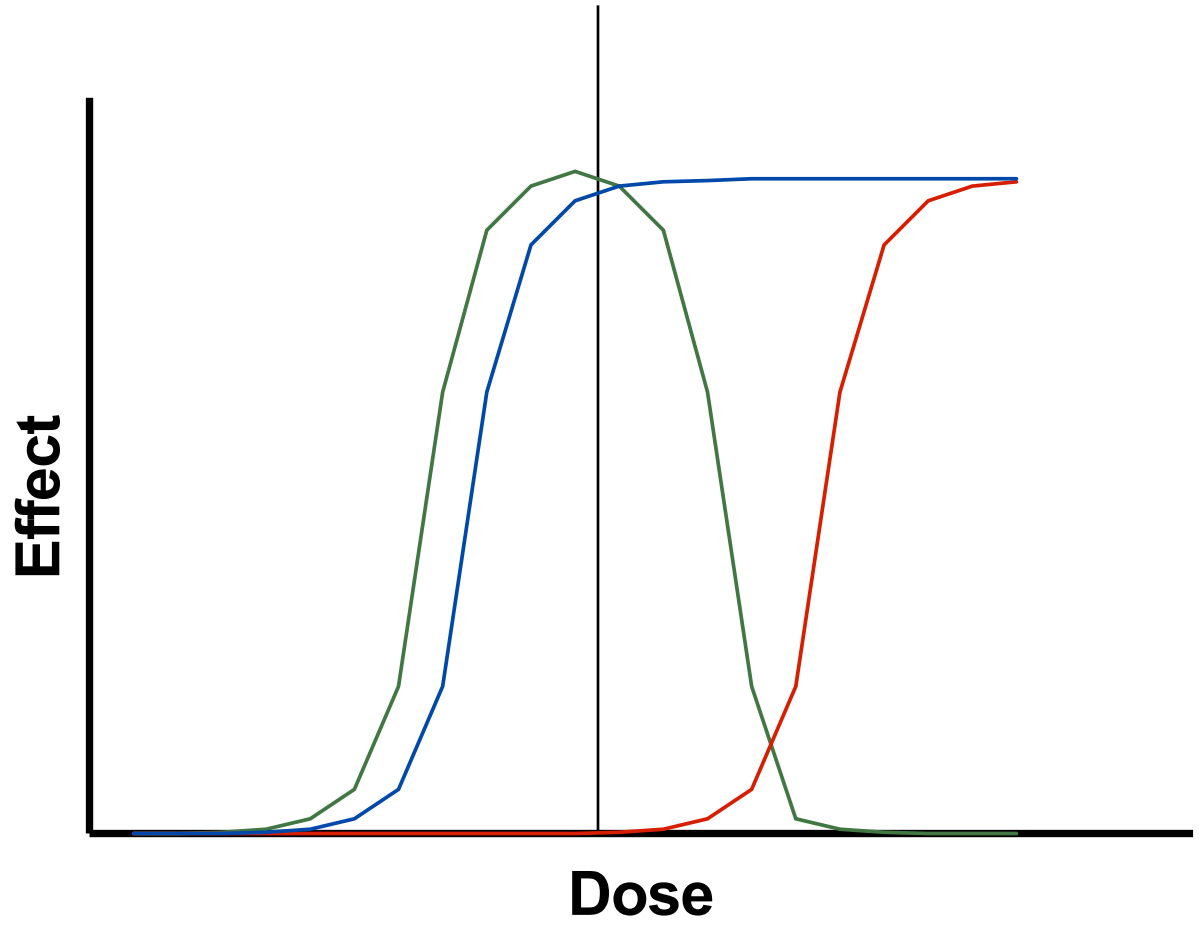


# A few basic definitions

**Pharmacodynamics –** What a drug does to the ‘body’ (whether the host or the pathogen)


Effect
Dose


Effect
Dose
Bactericidal effect
Toxicity



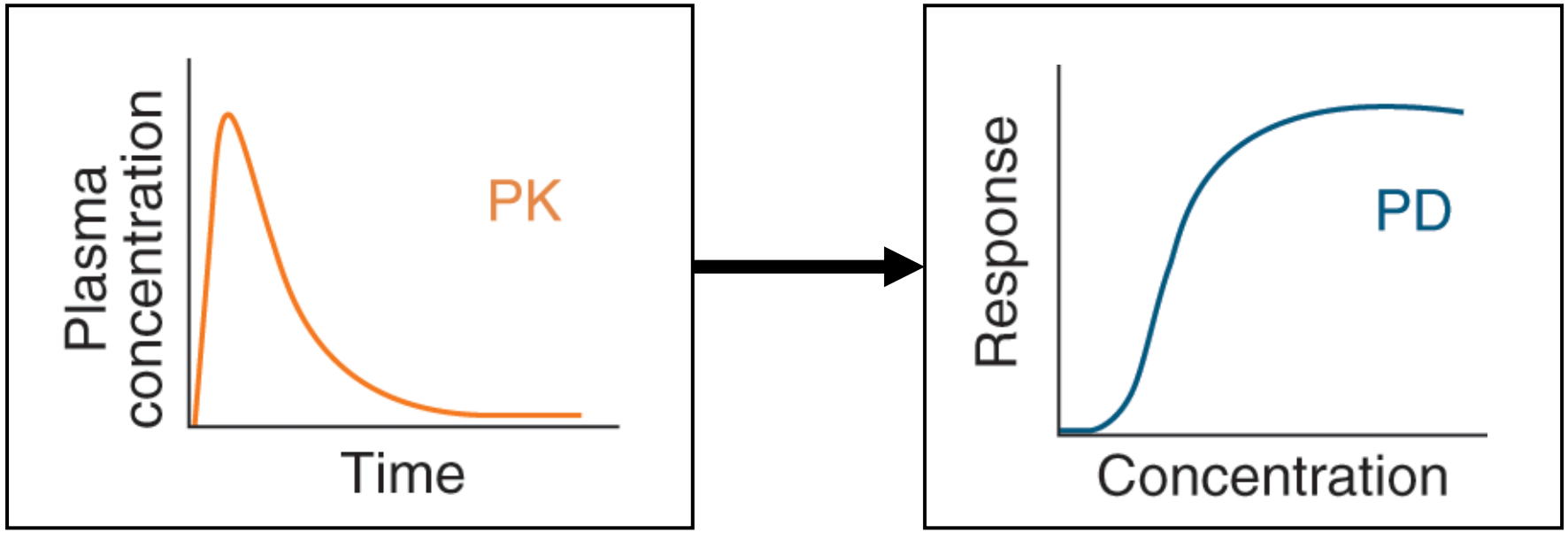

Bactericidal effect

Toxicity

Antimicrobial Resistance

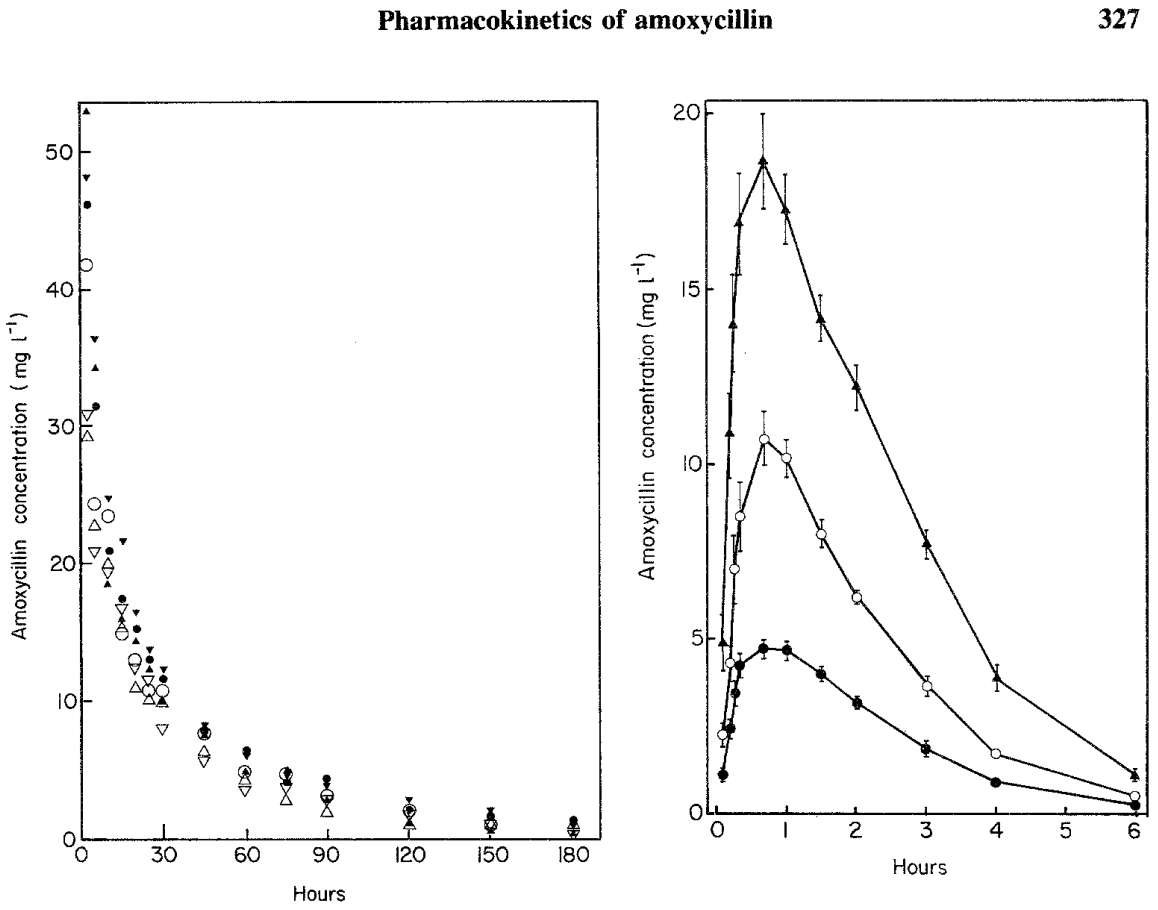
# A few basic definitions

**PK-PD modelling –** A structural model and mathematical equations that describe the dynamic concentration of a drug in a given compartment and the effects of the drug in that compartment.



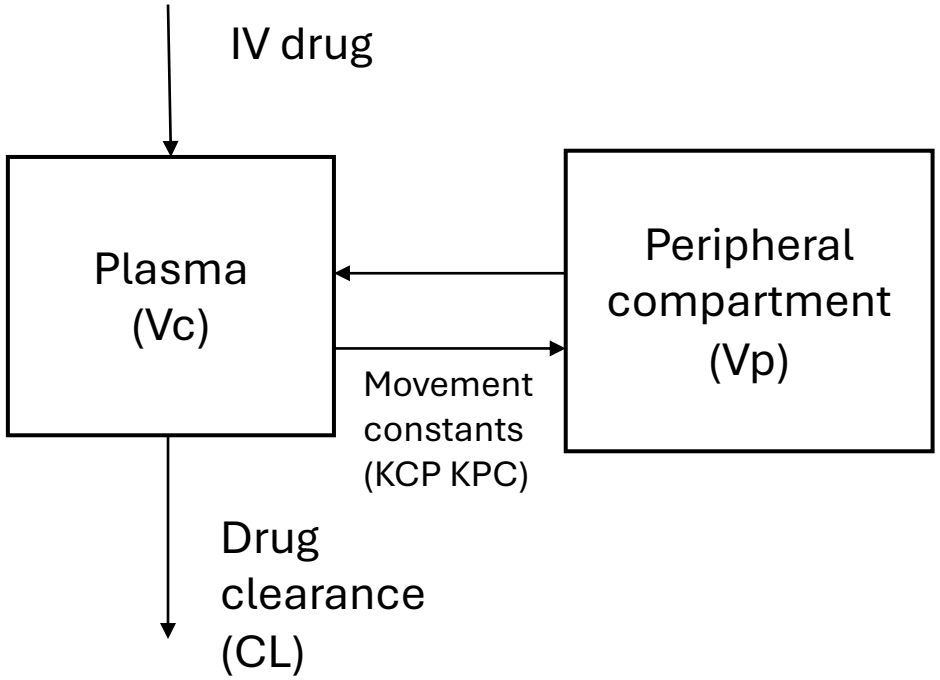
# Pharmacokinetics

# Tradition antimicrobial pharmacokinetics




*Hill et al, Journal of Infection 1980* ***2****, 320-332*

# Population Pharmacokinetic modelling



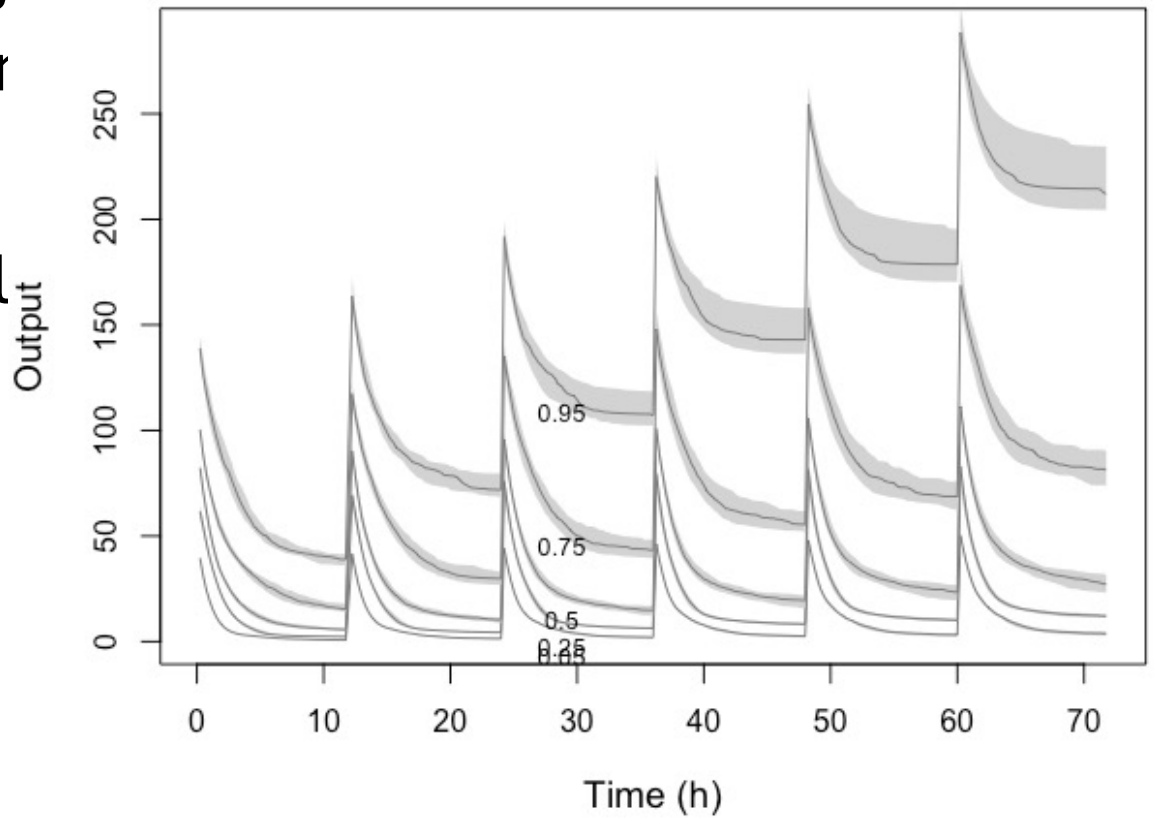

Vc = x * (y*body weight) * (z*age)

CL = x * (y*renal function) * (z*liver function)

# PopPK modelling

Allows inc t may affect the
drug pharr unction)

Can simul mits



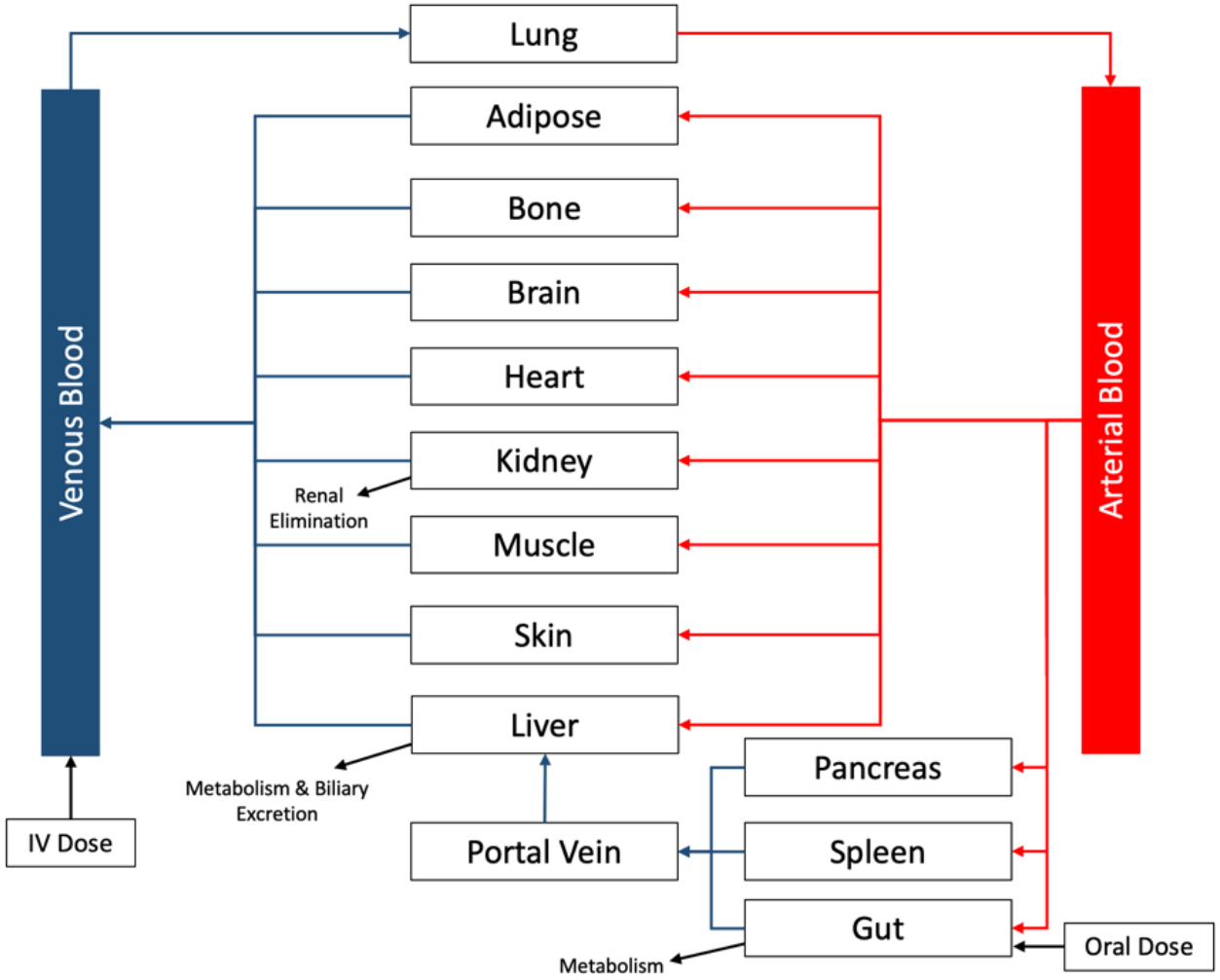
# However…

PopPK models only as good as the available PK data, and most PK data is from healthy (usually male) Caucasian volunteers

Limitations in extrapolation of prediction to

- Certain demographics (ethnicities, age)
- Co-morbidities (e.g. Renal and liver disease)
- Certain medical contexts (e.g. Pregnancy, critical illness)
- Body sites beyond that sampled (e.g. bone, CNS)

# Physiology-based PK modelling




Uses physiological, biochemical and anatomical insights of the body

with

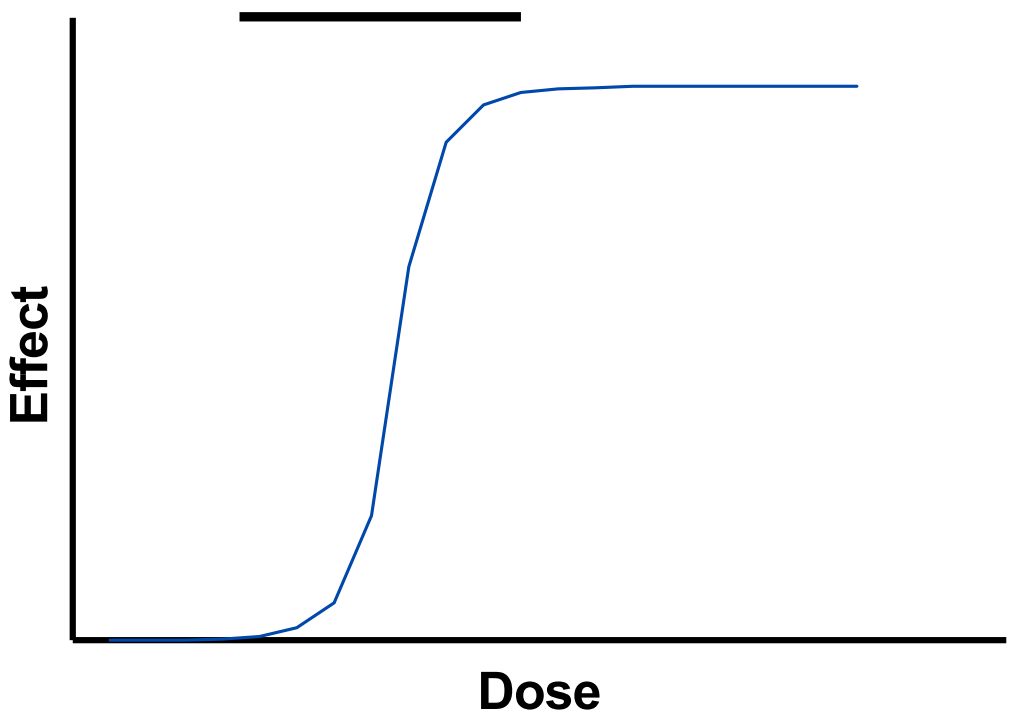
Phys-chemical and pharmacological properties of drug to predict pharmacokinetics

Can predict:

1. Drug concentrations in particular tissues
2. Variations of pharmacokinetics with different special populations
3. Interactions of drugs not tested in combination
4. Predict human pharmacokinetics for molecules in  early drug development)

# Pharmacodynamics

# Pharmacodynamic modelling




$$\frac{dX}{dt} = X * (Kg * (1 - \frac{X}{POPmax}) - \frac{Kk * \left(\frac{X}{\frac{\overline{V}}{E50}}\right)^{H}}{(1 + \left(\frac{X}{\frac{\overline{V}}{E50}}\right)^{H})})$$

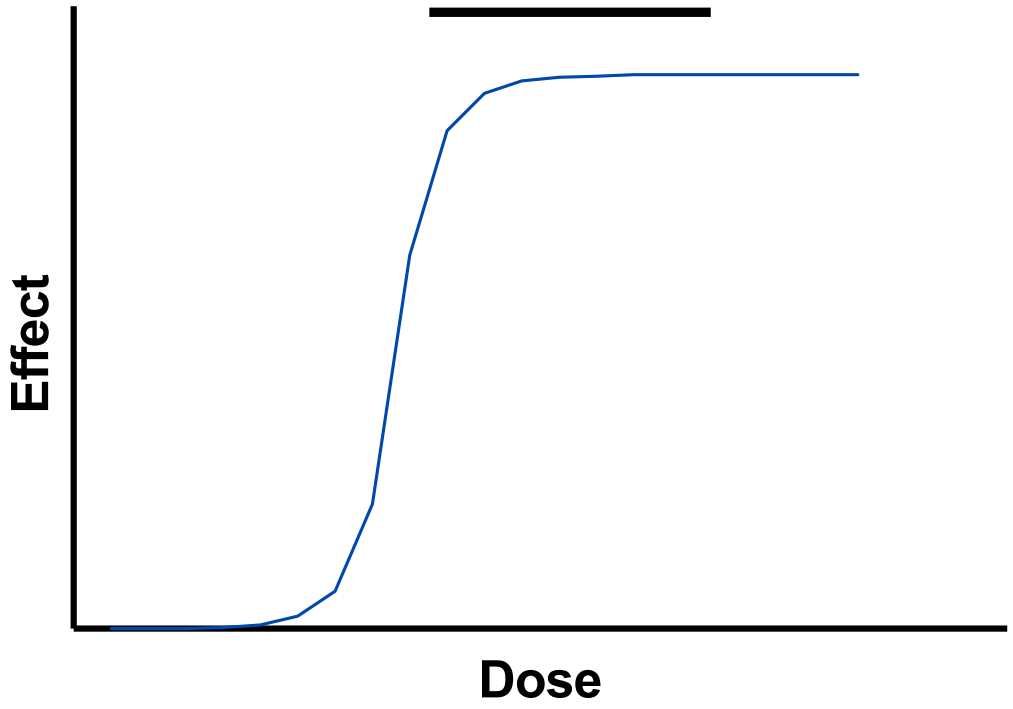
Where X = bacterial population

# Pharmacodynamic data from Humans

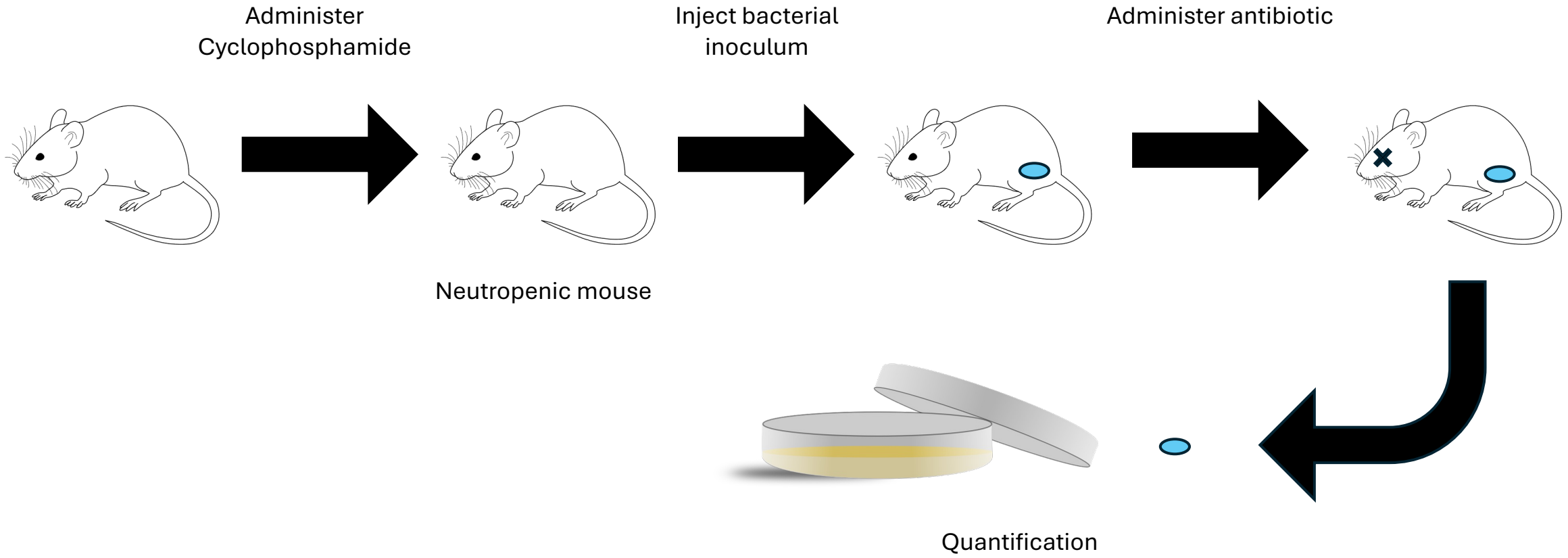
In theory, most ideal situation

However

- Data usually either categorical (e.g. mortality, microbiology success) or use of surrogates (e.g. inflammatory markers)
- Cannot measure effect for sub-maximal effect (ethically, at least)



# Neutropenic mouse model



# Neutropenic mouse model

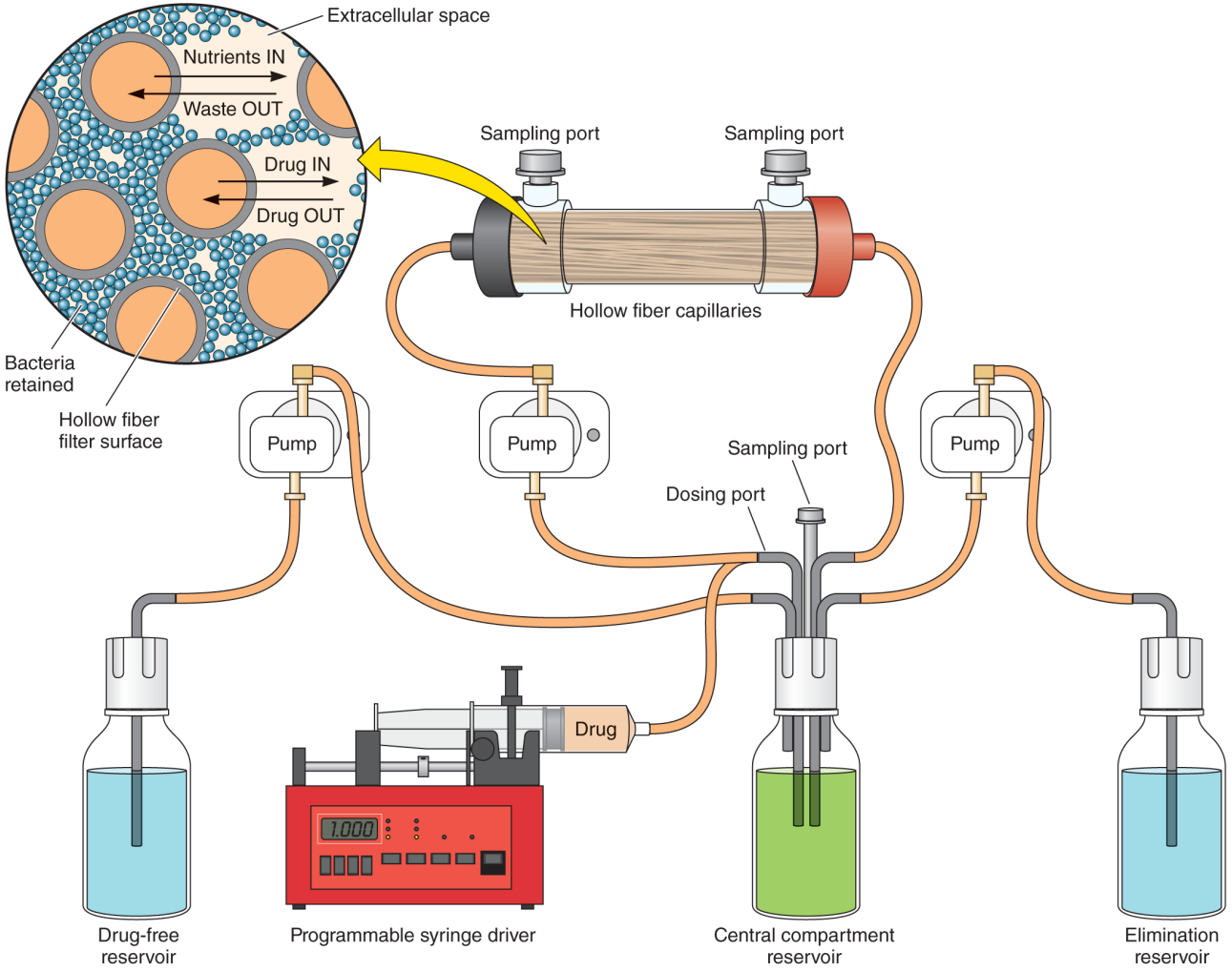
## Benefits

- Standardised and reproducible
- Lots of experience with the model
- Conclusions readily translate to humans
- Cornerstone of PK/PD target definition

## Limitations

- Resistance is almost never measured
- Mice usually cannot survive for >24-48h
- Mice are small, and therefore small inoculum
- Differences in animal PK and physiology

# Hollow Fibre infection model



# Hollow Fibre infection model

## Benefits

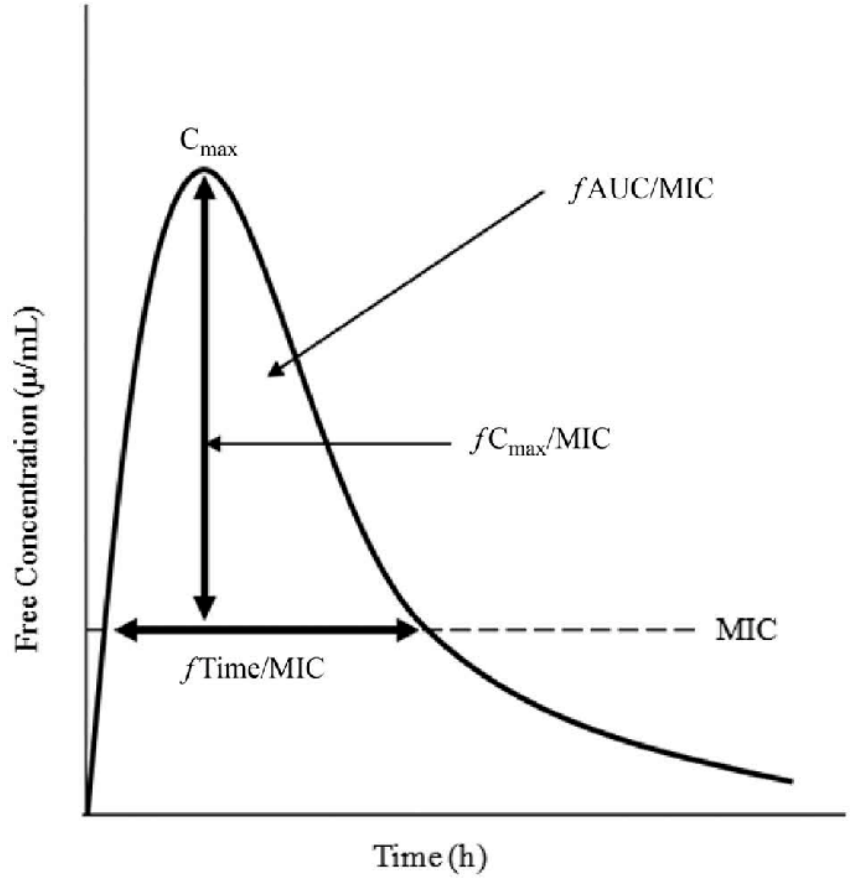
- Can examine resistance
- Can use high inoculum infections over a long period of time
- No use of animals
- Can use whichever PK profile you like

## Limitations

- Expensive
- Cannot replicate holistic tissue partitioning
- Lacks physiological context (protein binding, immune effectors etc.)
- Lack of track record with translation to humans

# PK/PD model outcomes

1. Define the relevant pharmacodynamic index



# PK/PD model outcomes

2. Define the pharmacodynamic target index for e.g. bacterial stasis, 1-log bacterial kill or suppression of emergence of resistance

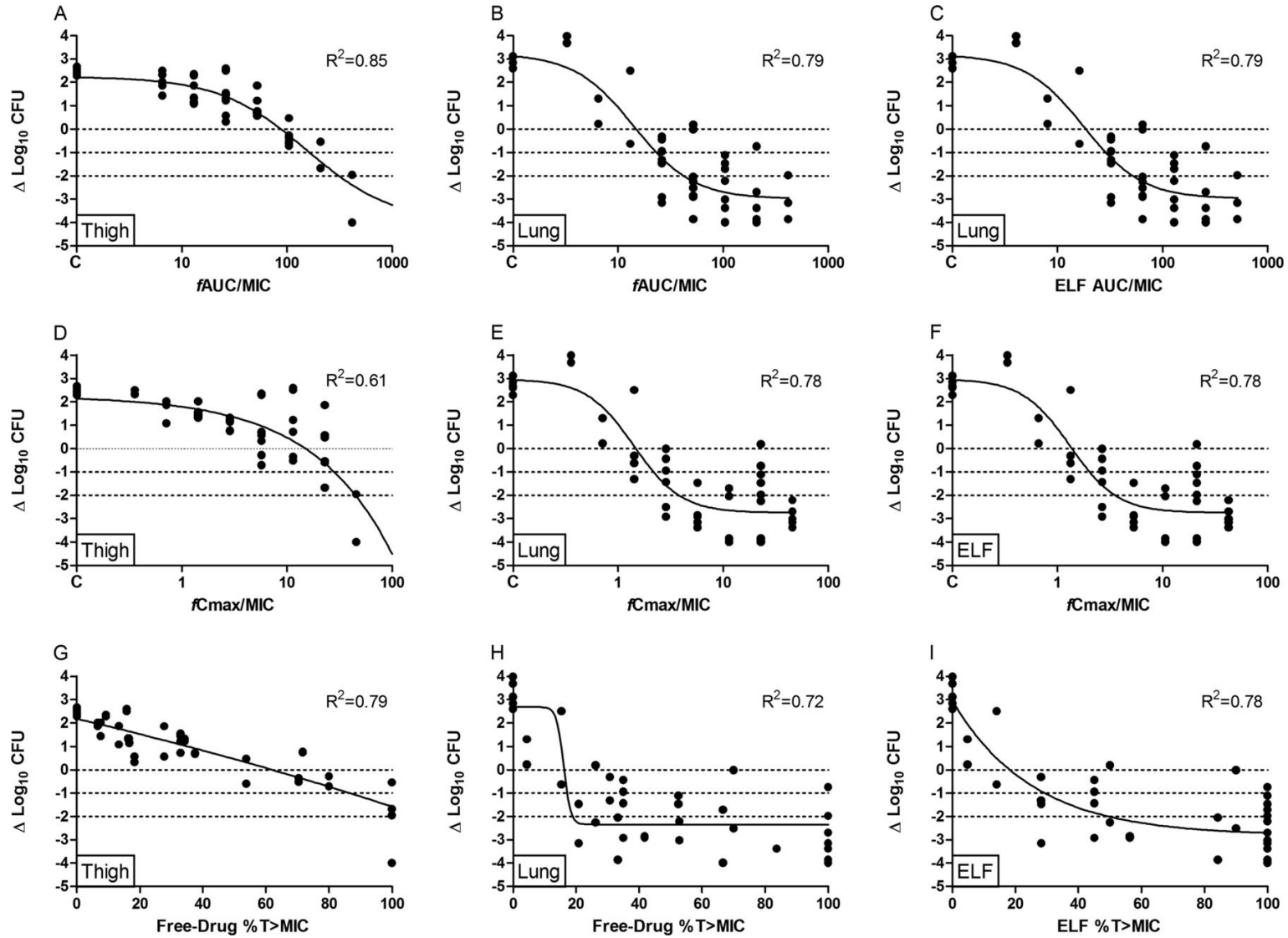
e.g.

Cmax:MIC > 10

AUC:MIC >200

%Time above MIC >50%

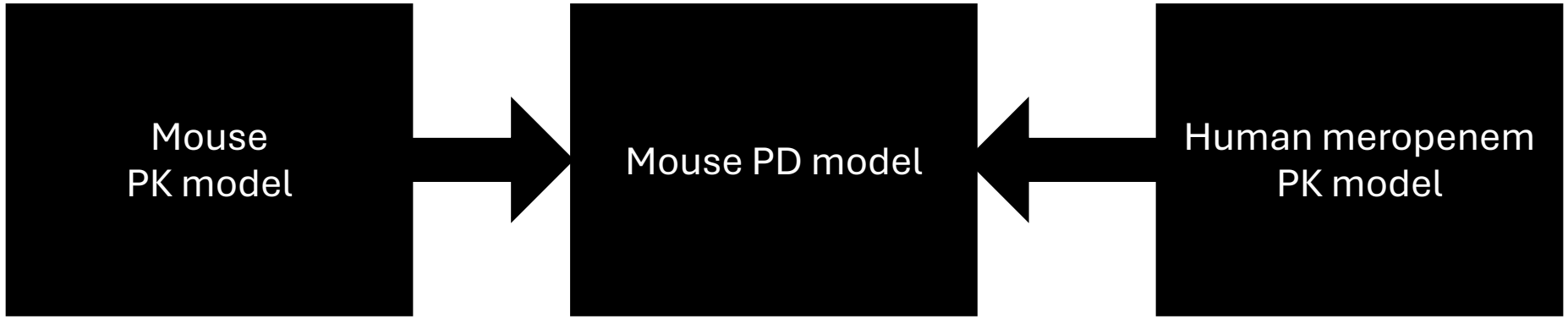
…and define regimen in humans that meets them




*Melchers et al, AAC, 2018*

# PK/PD model outcomes

3. Simulate pharmacodynamic outcome in humans.

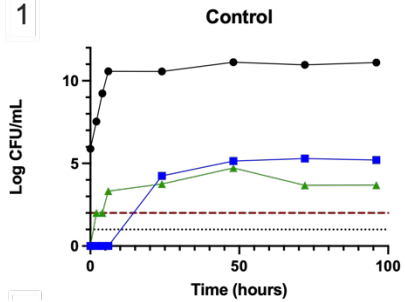


# PK/PD model outcomes

4. Characterise pharmacodynamic interactions of drugs

i.e. Determine if drugs are synergistic or antagonistic for both bactericidal effect and emergence of resistance

1




Total Counts  Flomoxef resistance counts  Fosfomycin resistant counts  Limit of detection (total counts)  Limit of detection (resistant counts)

# In summary…

This whole process underpins optimal dose selection of antimicrobials

# Some big limitations…

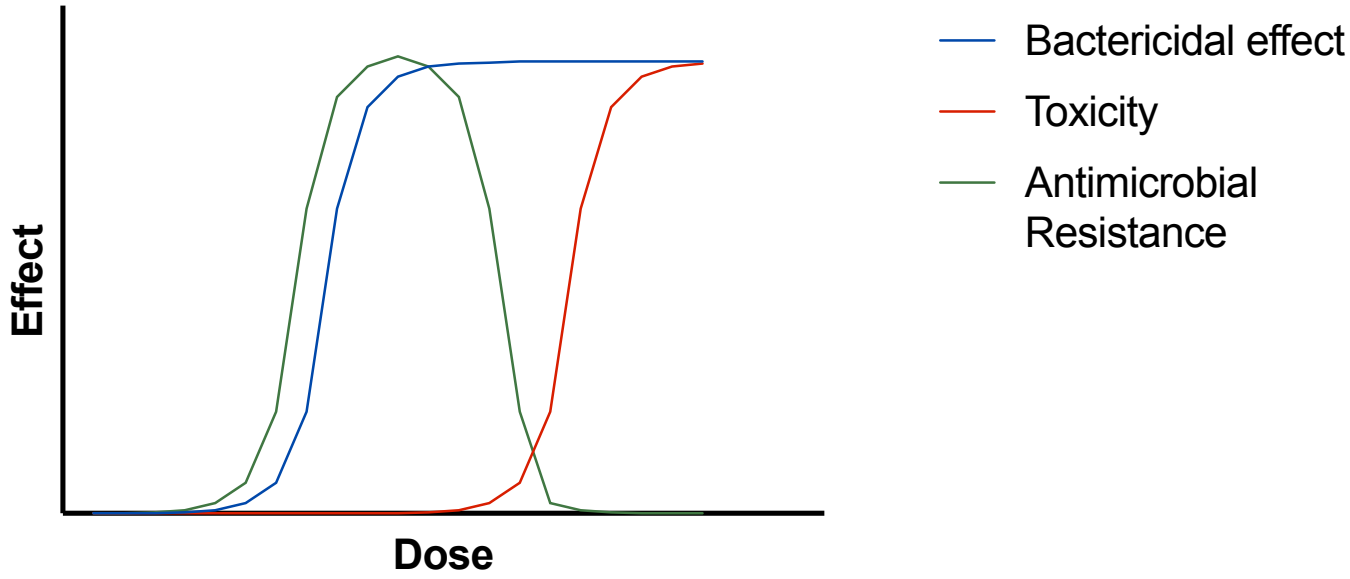
1. **Human pharmacokinetics is often poorly characterised and/or from a limited population**
   - Early antimicrobials not modelled well (if at all)
   - Data largely from (usually male) Caucasian healthy volunteers
   - Data often lacking from specific demographics and patient groups

2. **Pharmacodynamics for bactericidal effect typically not characterised well for many antibiotics**
   - Particularly older (and more frequently used antibiotics)

   e.g. amoxicillin, flucloxacillin
   - Particularly in certain infection sites

## 3. Pharmacodynamics for antimicrobial resistance often not characterised at all

- Drugs are not dosed appropriately to prevent emergence of resistance
- Includes newly developed drugs
- Arguably is the main reason for antimicrobial resistance



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Antimicrobial Chemotherapy | Review

# Challenges for global antibiotic regimen planning and establishing antimicrobial resistance targets: implications for the WHO Essential Medicines List and AWaRe antibiotic book dosing

Nada Reza,[1,2] Alessandro Gerada,[1,2] Katharine E. Stott,[1,2] Alex Howard,[1,2] Mike Sharland,[3] William Hope[1,2]

4. **There are lot of assumptions built in**
   - Translatability from *in vivo* / *in vitro* platform
   - The true ‘MIC’
   - Extrapolation of pharmacodynamics to other strains/species

5. **Resource and time intensive**
   - A PK/PD experimental package for a single drug-bug combination will take 6+ months and cost £100,000s
   - Impossible to keep up with evolving microbiology
   - Impossible to cover every drug-bug combination

# Possible solutions

1. Just need to do more of everything
2. Utilise novel *in silico* options e.g. PBPK modelling
3. Greater PK data availability
4. Regulatory input (for antimicrobial resistance emergence)
5. Rethink of how we examine pharmacodynamics
   - Better ways to use human pharmacodynamic data?
   - Better measures of antimicrobial susceptibility than MIC?

Thank you