MONTE CARLO SIMULATION
A Tool for Decision Support

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MONTE CARLO SIMULATION
Objectives

- To provide a brief history of Monte Carlo simulation
- To illustrate how Monte Carlo simulation works
- To review an example in which Monte Carlo simulation was used to evaluate dosing regimens for use in Phase 2/3 clinical trials
- To review the role of Monte Carlo simulation in PK-PD target attainment analysis for supporting *in vitro* susceptibility breakpoints
- To review a few commonly asked technical questions regarding the conduct of Monte Carlo simulations

MONTE CARLO SIMULATION
Early History

- Named after a city in Monaco where roulette remains a common game of chance
  - The roulette wheel may be viewed as a simple random number generator!
- Early history may predate the 17th century

Georges Buffon

Buffon's original form was to drop a needle of length L at random on grid of parallel lines of spacing D.

For L less than or equal D we obtain

P(needle intersects the grid) = 2 • L / *PI* • D

If we drop the needle N times and count R intersections we obtain:

P = R / N,

***PI* = 2 • L • N / R • D**

MONTE CARLO SIMULATION
Development as a Research Tool

- The name, "Monte Carlo simulation" and modern development as a scientific tool dates from World War II
- Important contributors to this development included Nicholas Metropolis, John von Neumann, and Stanislaw Ulam
- Work involved the direct simulation of the probabilistic problems associated with random neutron diffusion in fissile materials

John von Neumann

MONTE CARLO SIMULATION

Application to Anti-Infective Drug Development

George Drusano

Paul Ambrose

- Introduced to the infectious disease community by Drusano (presented to CDER, FDA in 1998)[1] and Ambrose[2]
- Currently, applications of Monte Carlo simulation include the following:
  - Evaluations of the adequacy of dosing regimens
  - Estimation of susceptibility breakpoints
  - Pharmacoeconomic studies

1. Drusano GL, Preston SL, Hardalo C, Hare R, Banfield C, Andes D, Vesga O, Criag WA. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. Antimicrob Agents Chemother. 2001; 45:13-22.
2. Ambrose PG, Richarson MA, Quintiliani R, Nightingale CH. Cost-effectiveness analysis of alternative antibiotic therapies for hospitalized patients with community-acquired pneumonia. 32nd Annual ASHP Midyear Clinical Meeting. Atlanta, Georgia, December 1997.

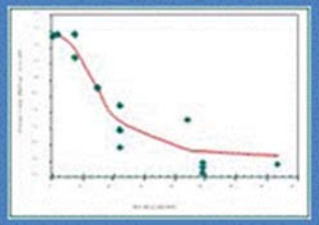
PK AND PK-PD SIMULATION INPUTS
Points to Consider

- Pharmacokinetics
  - PK data can be obtained from Phase 1 or Phase 2-3 population analyses and may focus on special patient populations of interest
  - Important to consider sources of PK variability including protein binding, body size, range of clearing organ function and other variables
- PK-PD relationships for efficacy
  - PK-PD targets for efficacy are typically obtained from non-clinical models of infection early in drug development or clinical data once Phase 2/3 data are collected
  - Need to consider protein binding for optimal translation of non-clinical data
  - Important to consider likelihood distributions for MIC data

ANTI-INFECTIVE DOSE SEELECTION

An Integrative Strategy

Pharmacodynamics



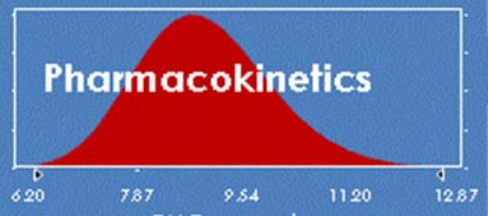
Infection models

Clinical Data

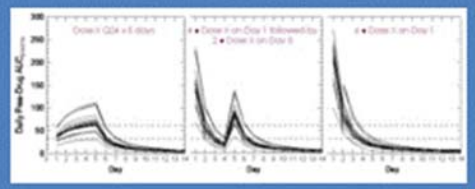
Efficacy
&
Safety

**Dose Justification,
MIC Breakpoint Justification,
Clinical Trial Simulation,
and more**

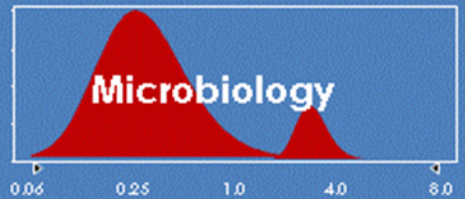
Pharmacokinetics



Modeling & Simulation

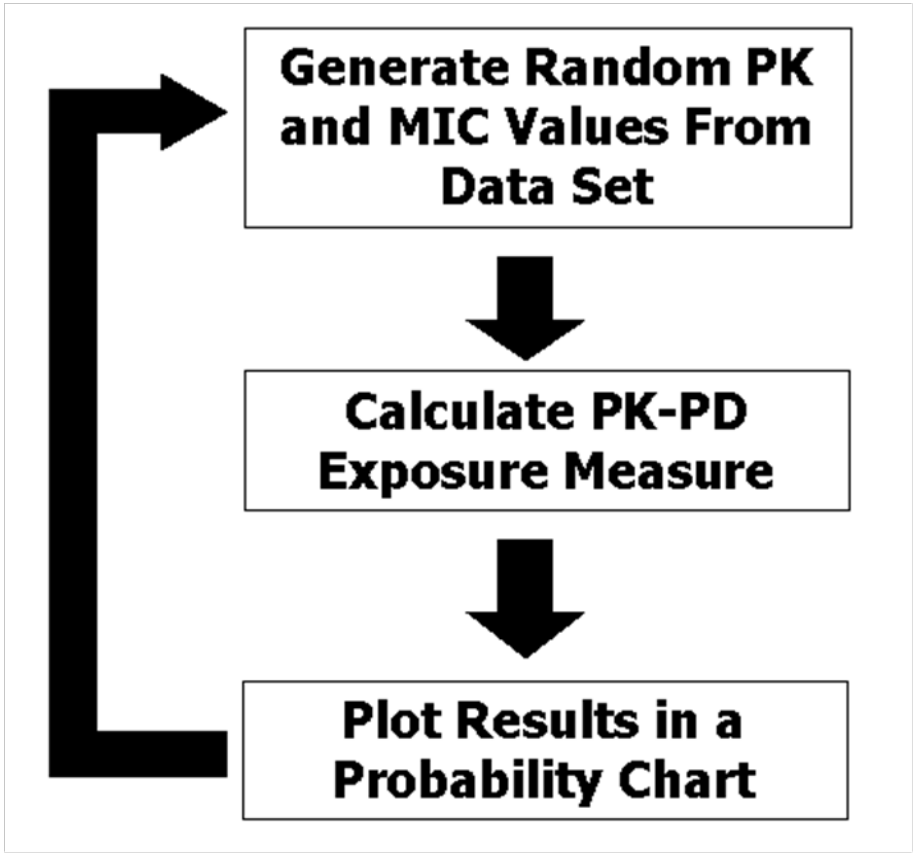


Microbiology



National Surveillance

MONTE CARLO SIMULATION
Example of a PK-PD Application



Dudley MN, Ambrose PG. Pharmacodynamics in the study of drug resistance and establishing in vitro susceptibility breakpoints: ready for prime-time. Current Opinion in Microbiology 2000;3:515-521

CASE STUDY 1
Doripenem Dose Selection

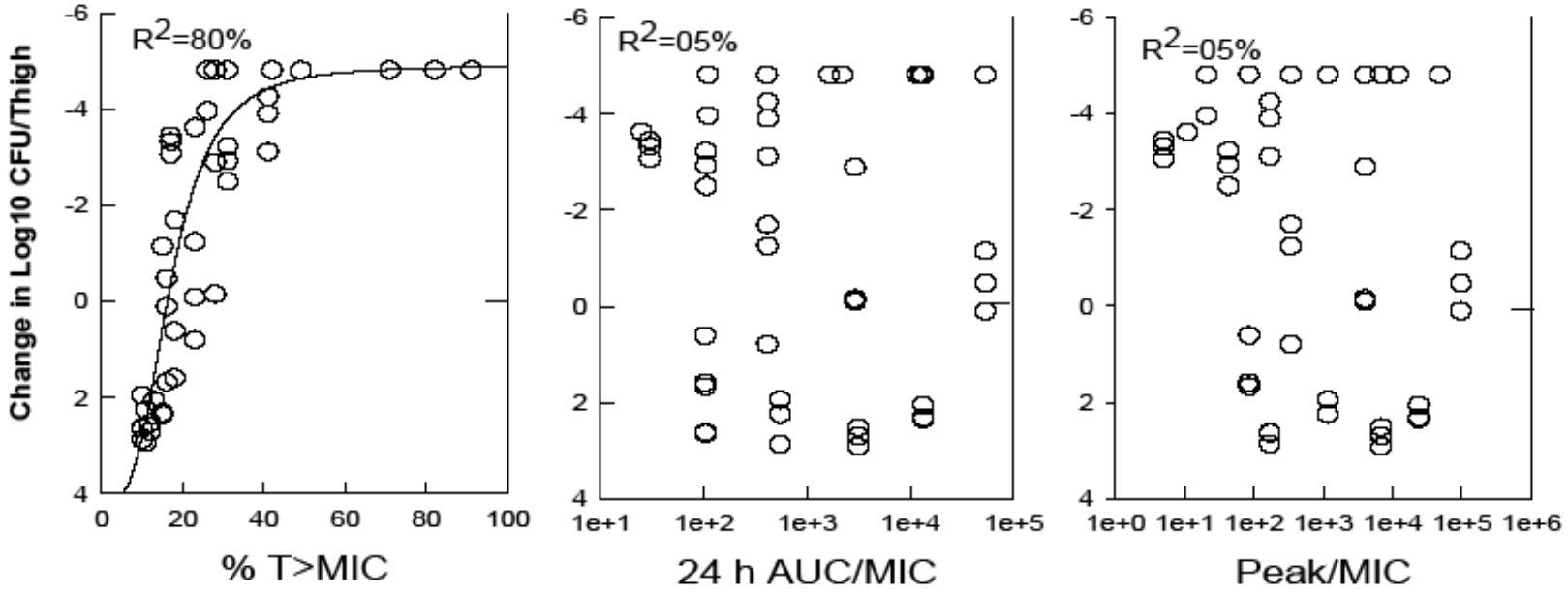
- In 2003, the safety and pharmacokinetics of doripenem were evaluated in a Phase 1 study of healthy normal volunteers[1]
- Doripenem's spectrum of *in vitro* microbiological activity included Enterobacteriaceae and *P. aeruginosa*
- Given this activity, Phase 2/3 clinical development plans included complicated urinary tract and intra-abdominal infections and hospital-acquired pneumonia indications
- In preparation for a FDA End-of-Phase 2a meeting, Monte Carlo simulations were used to discriminate between doripenem dose regimens

Thye D, Kilfoil T, Leighton A, Wikler M. Doripenem: A phase 1 study to evaluate safety, tolerability and pharmacokinetics in a western healthy volunteer population. 2003 ICAAC, Abstract A-21.

CASE STUDY 1

Identification of the PK-PD Goal of Therapy

Doripenem Against *Streptococcus pneumoniae*

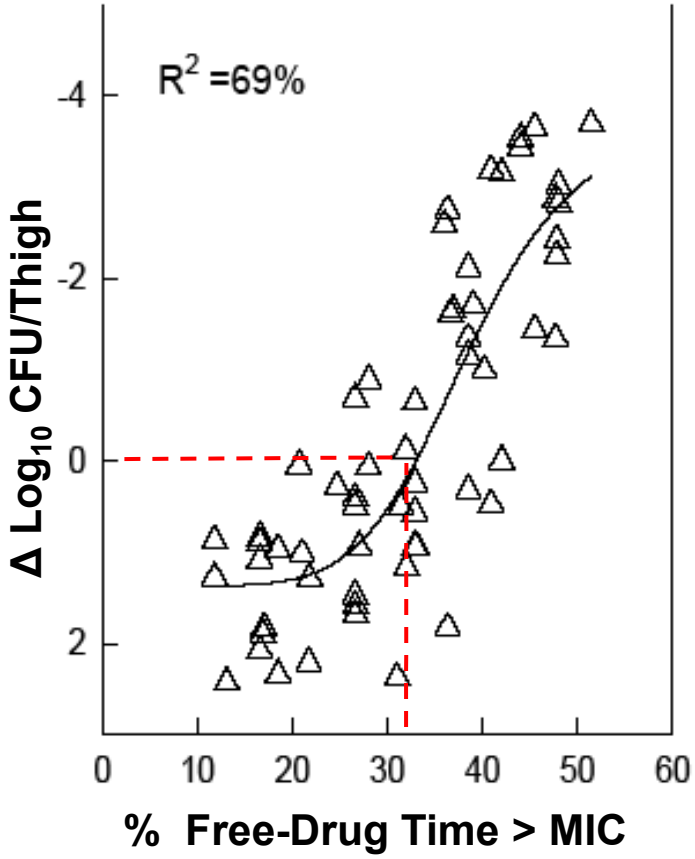


Andes DR and Craig WA. Pharmacodynamic activity of doripenem against multiple bacteria in a murine-thigh infection model. 2003 ICAAC, Abstract A-308

CASE STUDY 1

Identification of the PK-PD Goal of Therapy

Doripenem Against Gram-Negative Bacilli



- Given that the effectiveness of doripenem killing can increased by maximizing % T>MIC, an important question is, "How long is long enough?"
  - Depends upon the organism
    - Steptococci < Staphylococci < Gram-negative bacilli
  - Depends upon the target patient population

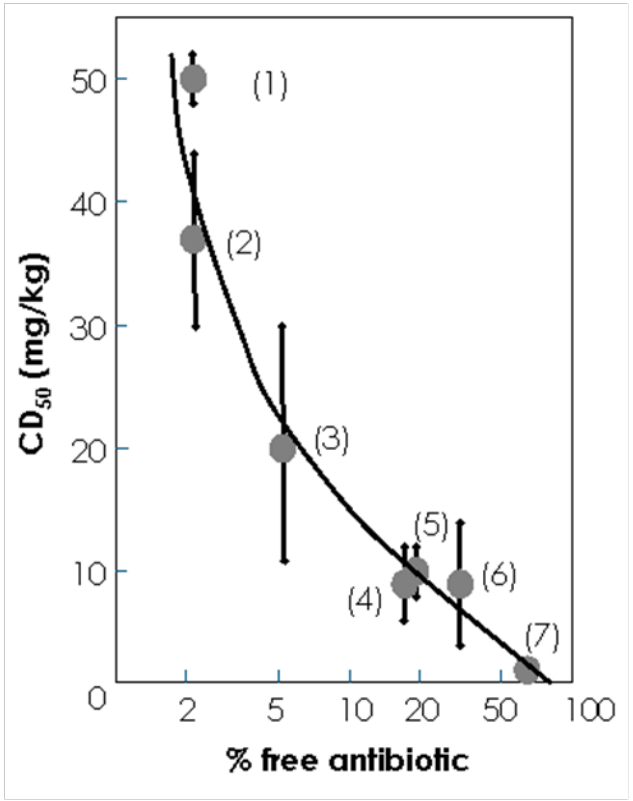
Andes DR and Craig WA. Pharmacodynamic activity of doripenem against multiple bacteria in a murine-thigh infection model. 2003 ICAAC, Abstract A-308

CASE STUDY 1
Evaluation of Protein-Binding

Since doripenem protein-binding is low (8.1%) and independent of concentration, the impact of protein binding can be assessed by evaluating other β-lactam agents

Free- vs. Total-Drug and Animal Survival

Drug	MIC (mg/L)	% bound	Peak (mg/L)	$T_{1/2}$ (hr)
1	0.25-0.5	98	3.1	0.3
2	0.25-0.5	98	4.3	0.2
3	0.25-0.5	95	5.0	0.3
4	0.25-0.5	81	2.9	0.3
5	0.25-0.5	79	4.5	0.2
6	0.25-0.5	71	3.7	0.2
7	0.25-0.5	36	5.1	0.1

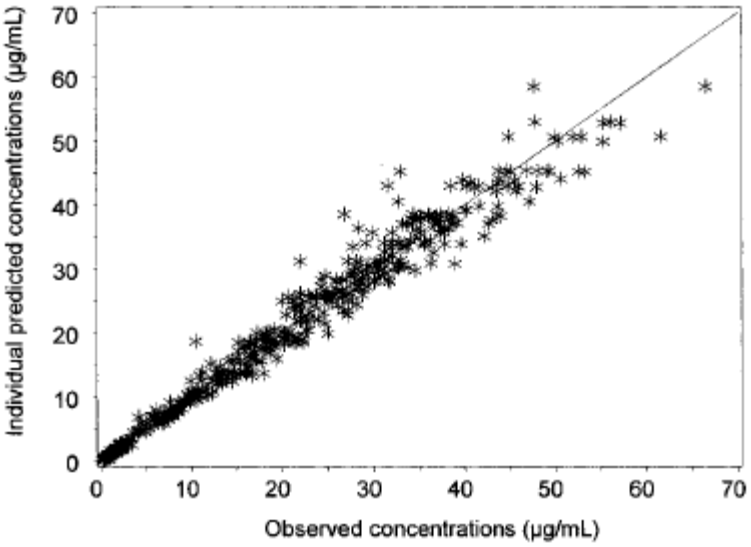


Merrikin DJ, Briant J, Rolinson GN. Effect of protein binding in antibiotic activity *in vivo*. J Antimicrob Chemother 1983;11:233-38.

CASE STUDY 1
Phase 1 Population PK Model

When using healthy volunteer data to make inferences about patient populations, it is important to account for limited variance

Parameter	Population Mean Estimate	Interindividual Variability (% CV)
CL (L/hr)	14.5	13%
Vc (L)	9.4	14%
Vp (L)	5.9	10%
Q (L/hr)	9.7	

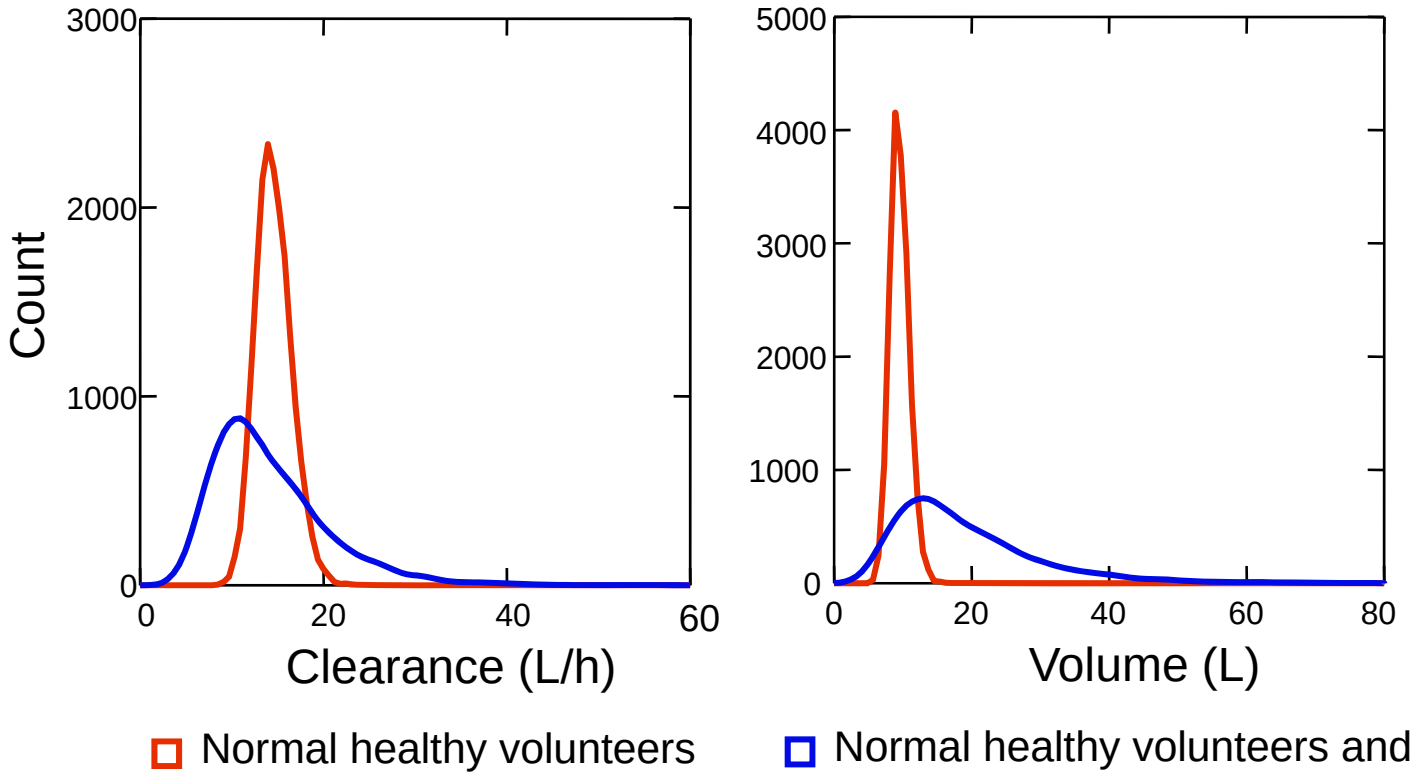


Predicted Cp	Residual Variability
1000 ng/mL	21%
> 5000 ng/mL	11%

Terminal Phase $T_{1/2} \approx 1$ hr

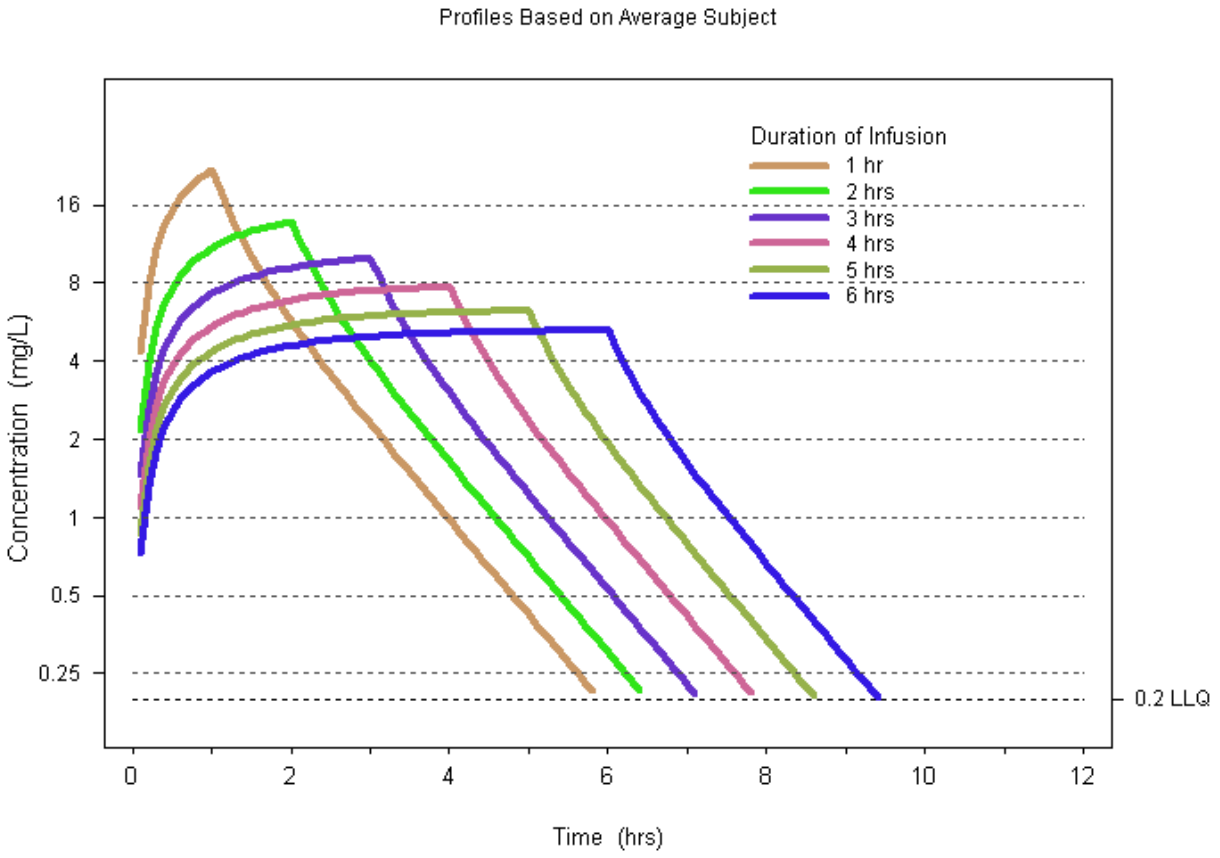
Bhavnani SM., Hammel JP, Cirincione BB, Wikler MA, Ambrose PG. Use of pharmacokinetic-pharmacodynamic target attainment analyses to support Phase 2 and 3 dosing strategies for doripenem. Antimicrob Agents Chemother 2005; 49:3944-3947.

DORIPENEM CASE STUDY
Impact of PK Variability



Parameter	Phase 1 population		Phase 1 and 2 populations	
	Population Mean Estimate	Interindividual Variability (% CV)	Population Mean Estimate	Interindividual Variability (% CV)
CL (L/hr)	14.5	**13.2%**	12.9	**42.9%**
Vc (L)	9.43	**14.4%**	16.7	**53.4%**

PROLONGED INFUSION
Optimizing Doripenem % T>MIC



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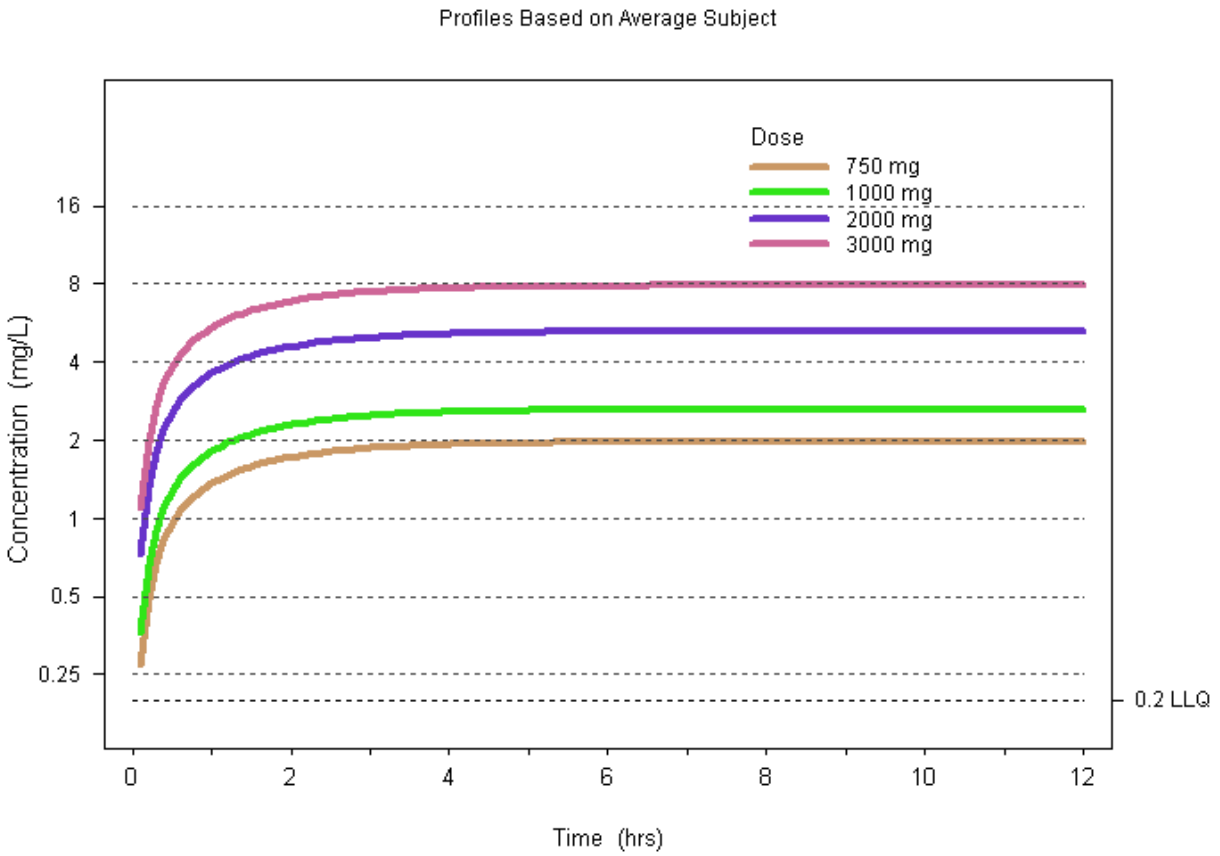
PROLONGED INFUSION
Optimizing Doripenem % T>MIC



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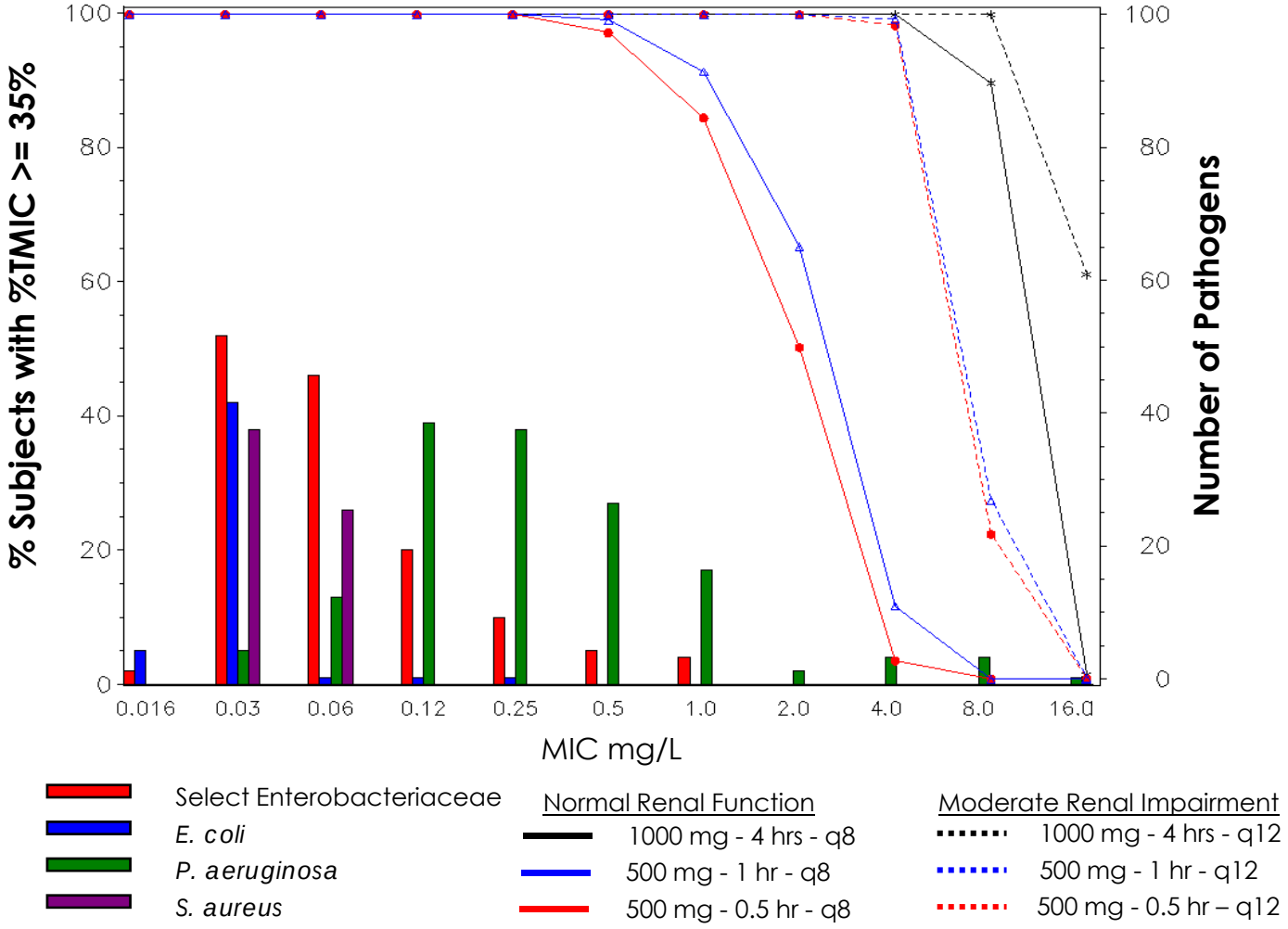
DORIPENEM

PK-PD Target Attainment by MIC



Van Wart SA, Andes DR, Ambrose PG, Bhavnani SM. Pharmacokinetic-pharmacodynamic modeling to support doripenem dose regimen optimization for critically ill patients. Diagn. Microbiol. Infect. Dis. 2009; 63:409-414.

CASE STUDY 1
Doripenem Dose Selection Conclusions

- Doripenem 500 mg Q8h as a 1 hour infusion in patients with normal renal function provided > 90% PK-PD target attainment up to a MIC value of 1 mg/L
- Administration of the same regimen as a prolonged infusion (over 4 hours) provided 90% PK-PD target attainment for MIC values ≤ 4 mg/L
  - Such a regimen allows for coverage of more resistant organisms such as *P. aeruginosa*
- These data suggested that doripenem 1000 mg Q8h as a 4 hour infusion (with adjustments for renal function) would be appropriate for study in sicker patients (e.g., hospital-acquired pneumonia)

Van Wart SA, Andes DR, Ambrose PG, Bhavnani SM. Pharmacokinetic-pharmacodynamic modeling to support doripenem dose regimen optimization for critically ill patients. Diagn. Microbiol. Infect. Dis. 2009; 63:409-414.

CASE STUDY 2
Issue Before the CLSI

- MIC breakpoints of 0.5, 1, and 2 mg/L for susceptible, intermediate, and resistant non-meningeal infections initially were in place for both ceftriaxone and cefotaxime against *Streptococcus pneumoniae*
- The manufacturer of ceftriaxone submitted robust data supporting a MIC breakpoint change to 1, 2, and 4 mg/L; significantly less data were available for cefotaxime
- Historically both agents have been treated as therapeutic alternatives
- Different breakpoints for each agent were likely to be problematic for clinical laboratories

CEFTRIAXONE (1 GM Q 24 Hrs)
Probability of PK-PD Target Attainment

	PK-PD Target (T>MIC)				
MIC	30%	40%	50%	60%	
0.25	100	100	100	100	
0.5	100	100	100	100	S?
1.0	100	100	99.4	92.9	
2.0	99.0	87.1	58.0	25.0	I?
4.0	65.6	8.4	0.8	0.1	R?
Entire MIC Dist.	99.1	98.4	97.3	96.0	
PCN-S	100	100	100	100	
PCN-I	100	100	99.0	97.8	
PCN-R	97.0	94.8	89.6	83.9	

Dudley MN, Ambrose PG. Monte Carlo Simulation of new cefotaxime, ceftriaxone and cefepime susceptibility breakpoints for *S. pneumoniae*, including strains with reduced susceptibility to penicillin. 2002 ICAAC, Abstract 635.

CEFOTAXIME (1 GM Q 8 Hrs)
Probability of PK-PD Target Attainment

	PK-PD TARGET (T>MIC)				
MIC	30%	40%	50%	60%	
0.25	100	99.9	99.2	96.4	
0.5	100	99.4	97.0	88.6	S?
1.0	99.8	98.0	88.9	71.4	
2.0	99.7	89.7	67.1	40.8	I?
4.0	90.3	61.9	29.2	11.2	R?
Entire MIC Dist.	99.8	99.0	96.2	92.5	
PCN-S	100	100	99.9	99.7	
PCN-I	99.5	98.4	95.7	90.0	
PCN-R	98.2	93.1	82.3	63.1	

Dudley MN, Ambrose PG. Monte Carlo Simulation of new cefotaxime, ceftriaxone and cefepime susceptibility breakpoints for *S. pneumoniae*, including strains with reduced susceptibility to penicillin. 2002 ICAAC, Abstract 635

CEFOTAXIME (1 GM Q 12 Hrs)
Probability of PK-PD Target Attainment

	PK-PD TARGET (T>MIC)				
MIC	30%	40%	50%	60%	
0.25	99.9	96.4	82.4	60.6	
0.5	98.9	88.6	64.5	38.6	S?
1.0	94.0	71.4	39.4	17.1	
2.0	78.6	40.8	14.6	4.0	I?
4.0	41.5	11.2	1.9	0.4	R?
Entire MIC Dist.	98.8	94.0	85.7	80.3	
PCN-S	99.9	99.9	99.1	95.7	
PCN-I	98.5	93.2	77.6	61.9	
PCN-R	89.7	68.0	40.2	18.6	

Dudley MN, Ambrose PG. Monte Carlo Simulation of new cefotaxime, ceftriaxone and cefepime susceptibility breakpoints for *S. pneumoniae*, including strains with reduced susceptibility to penicillin. 2002 ICAAC, Abstract 635.

CASE STUDY 2
CLSI Determination

- The CLSI Subcommittee on Antimicrobial Susceptibility Testing voted to increase the susceptibility breakpoints for ceftriaxone and cefotaxime by one dilution
- The new cefotaxime breakpoint for non-meningeal pneumococcal infections was established with the proviso that a dosage regimen of at least 1 g every 8 hours (or pediatric equivalent) was assumed to be administered
- This determination represented the first CLSI interpretive-dose qualification of a susceptibility breakpoint for a fixed-dose antibacterial agent in humans

EVALUATION OF SIMULATIONS
Commonly Asked Questions

1. Are simulated parameter distributions relevant given the source and sample size for input data?
2. For the case studies described, what are the common sources of variability that should be taken into account for similar such simulations?
3. When should a full versus major diagonal covariance matrix be utilized when simulating PK and/or PK-PD parameters?
4. What are the considerations for the sample size of a simulation?

EVALUATION OF SIMULATIONS
Commonly Asked Questions

1. Are simulated parameter distributions relevant given the source and sample size for input data?
   - It is important to compare the mean, variance and shape between source and simulated data for all input PK, PK-PD and demographic parameters
   - If the variability for PK and demographic parameters is tighter (as is the often the case with normal volunteer or special populations), smaller sample sizes for source data may be reasonable and/or all that is available; important to guard against "simulating the world from small samples"
   - However in such appropriate cases, an empirically broader magnitude of parameter variability (based on what is expected for a given target patient population) can be imposed; inferences to target populations will be thus more applicable

EVALUATION OF SIMULATIONS
Commonly Asked Questions

2. For the case studies described, what are the common sources of variability that should be taken into account for similar such simulations?
    - It is important to account for the most impressive sources of variability when constructing simulations
    - Sources of PK variability typically include body size, age, creatinine clearance for renally eliminated drugs, and other PK covariates
    - Sources of PK-PD variability may include immune status, comorbidities, bacterial species, and others

EVALUATION OF SIMULATIONS
Commonly Asked Questions

3. When should a full versus major diagonal covariance matrix be utilized when simulating PK and/or PK-PD parameters
    - Use of only population standard deviations (hence a major diagonal covariance matrix) may lead to falsely broad parameter distributions
    - Oftentimes, only mean and standard deviations for parameters are available
    - Use of a full covariance matrix is most important when the degree of correlation between input parameters is modest to high

EVALUATION OF SIMULATIONS
Commonly Asked Questions

4. What are the considerations for the sample size of a simulation?
    - Simulations of larger numbers of subjects are no more difficult to program than simulations of small numbers, and computers are currently fast and getting faster, so there typically are not reasons to constrain sample size
    - Generally, the more complex the distribution shapes or number of inputs, the larger the sample size required[1]
    - Larger simulations (e.g., 5, 000 to 10, 000 subjects) for the types of examples discussed in this lecture allow for stabilization of variance in the far tails of the distribution (> standard deviations)

Ambrose PG, Bhavnani SM, Rubino CM, Jones RN, Drusano GL. Susceptibility breakpoint decision support: Use of Monte Carlo Simulation and bootstrapping to establish minimum bacterial isolate sample size. 2005 ICAAC, Abstract A-1834.

THANK YOU FOR YOUR ATTENTION