Optimization of Dosing of Beta-lactams to Prevent Emergence of Resistance

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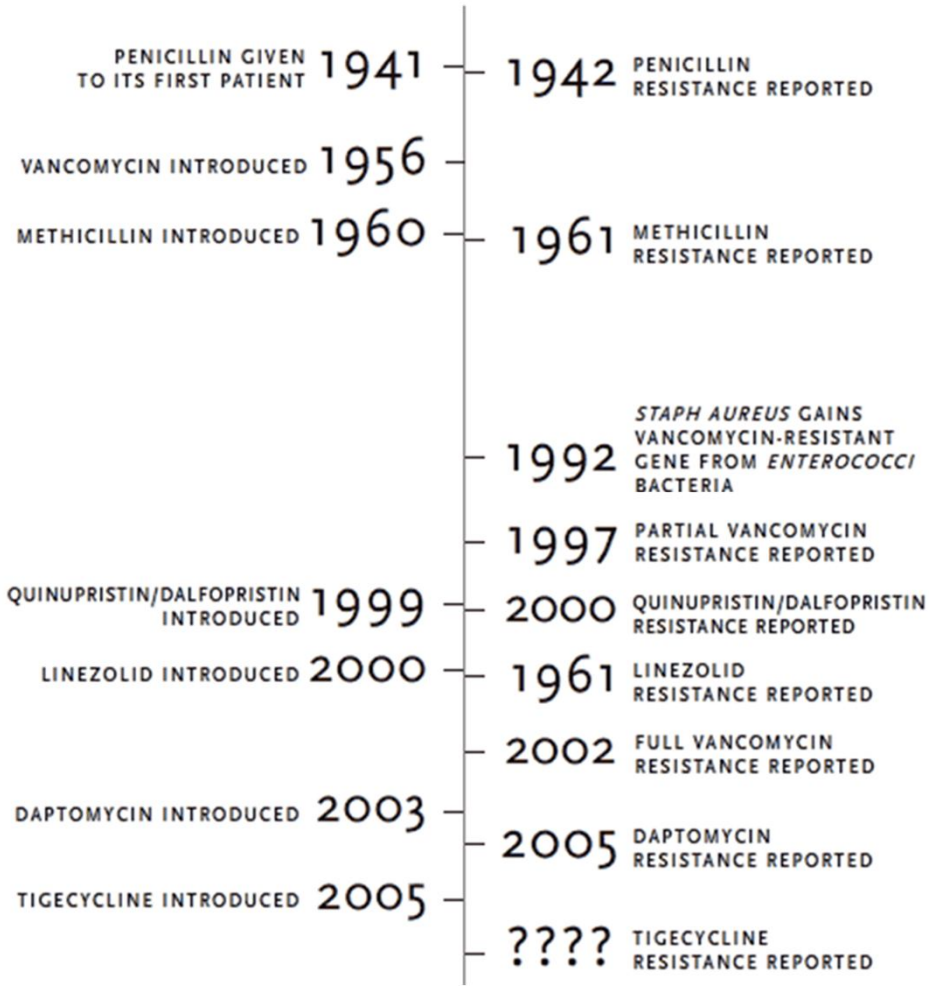
Antimicrobial Resistance

- Inevitable consequence
  - Unfavorable outcomes
  - Shorten drug lifespan
- Emergence likelihood
  - Predictable?
  - Delayed by strategies in drug (re-)development?

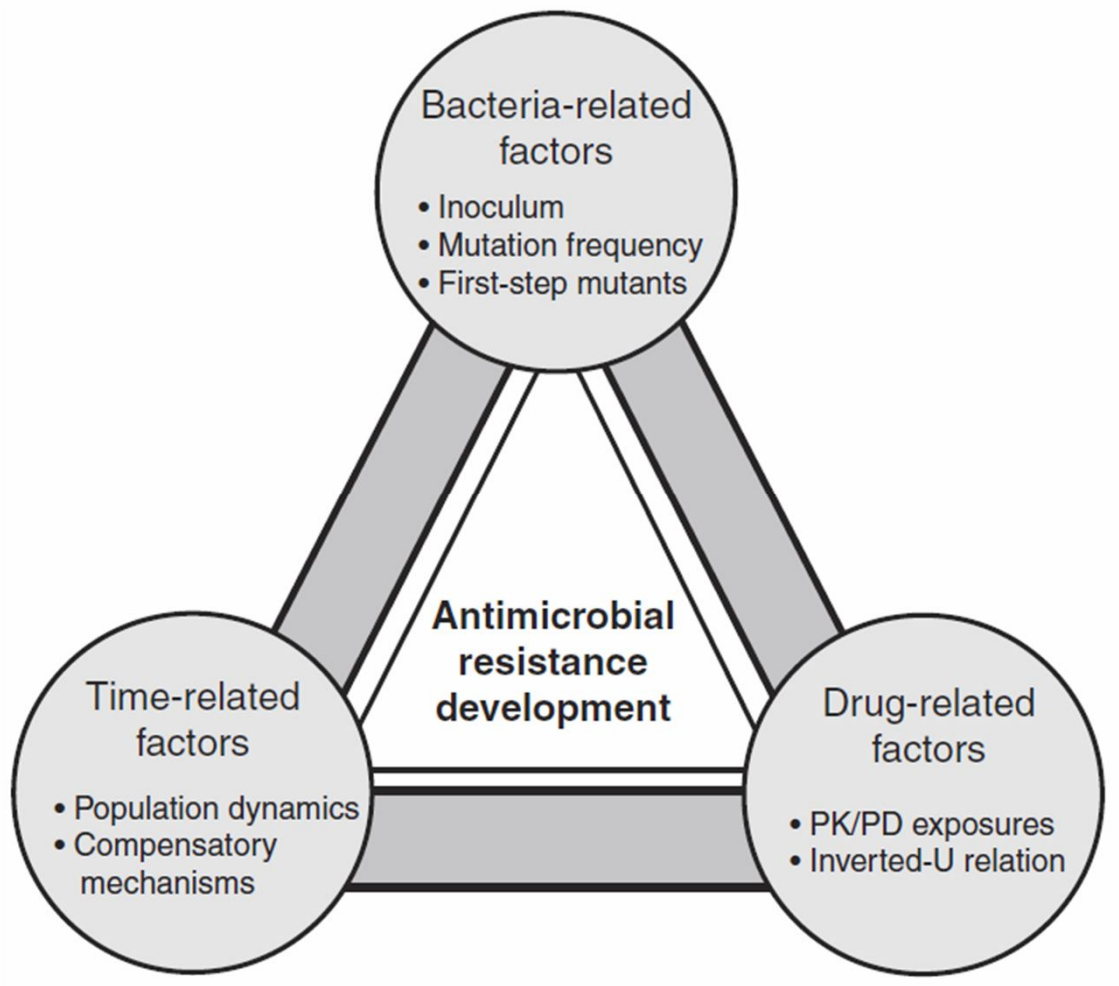


http://www.pbs.org/wgbh/nova/sciencenow/0303/04-arms-nf.html

Clinical Experience

- Ciprofloxacin
  - Multiple post-approval dose escalations
  - 100mg q12 → 200mg q12 → 400mg q12 → 400mg q8
- AN3365 (GSK 2251052)
  - Phase 2 study termination
  - “Microbiological findings of resistance on therapy”

Key Factors in Resistance Development

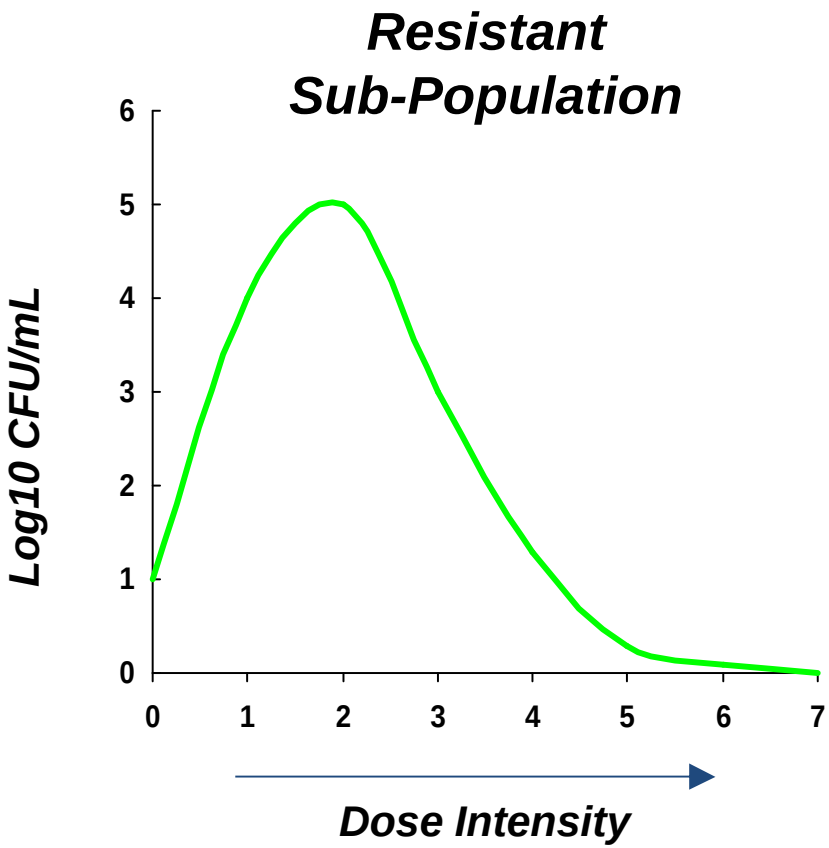


Singh R. Curr Opin Pharmacol 2011

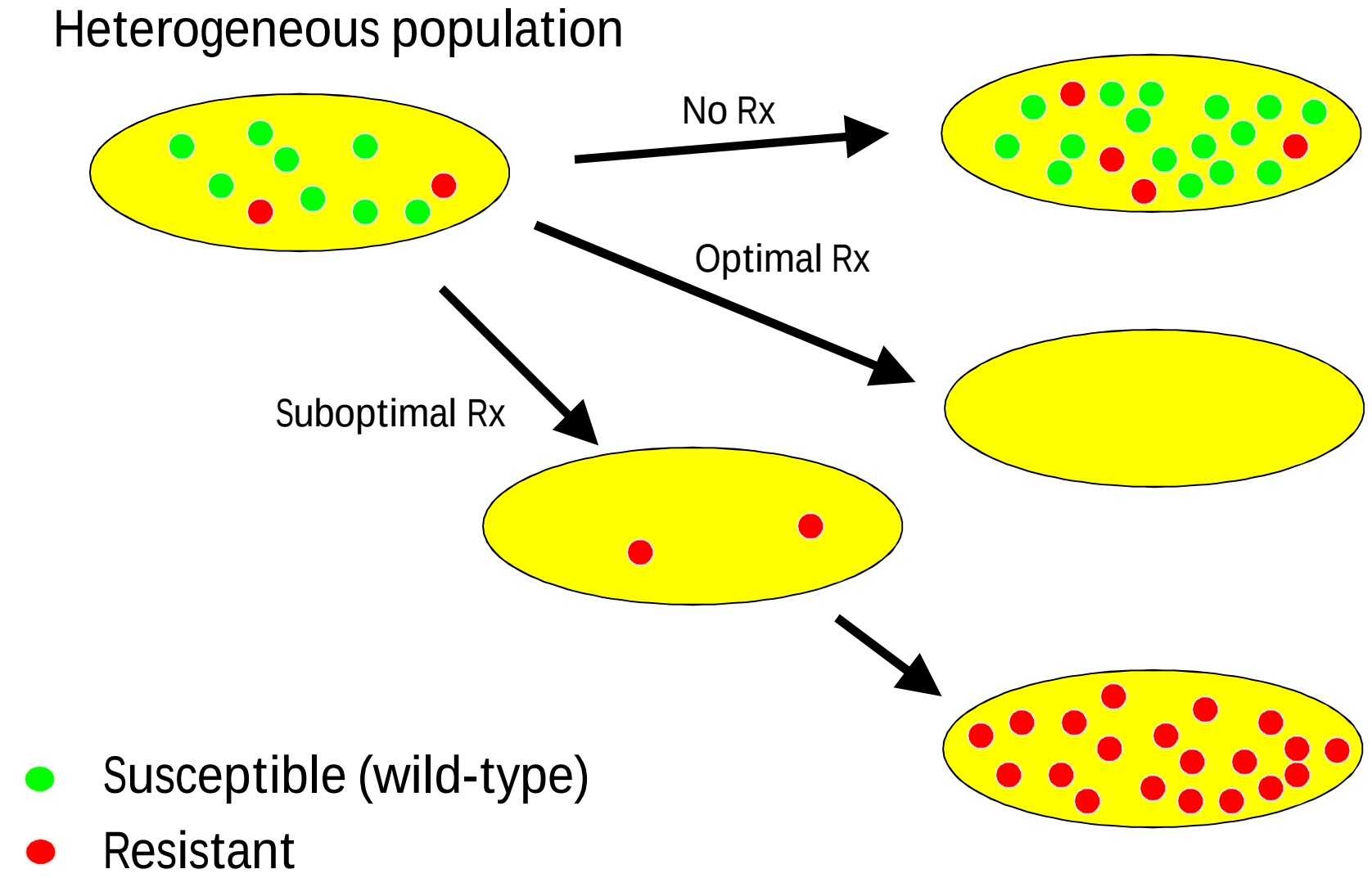
Resistance Counter-selection

‘Inverted-U’ Phenomenon

- Resistant sub-population rises initially & then declines with increasing drug exposure



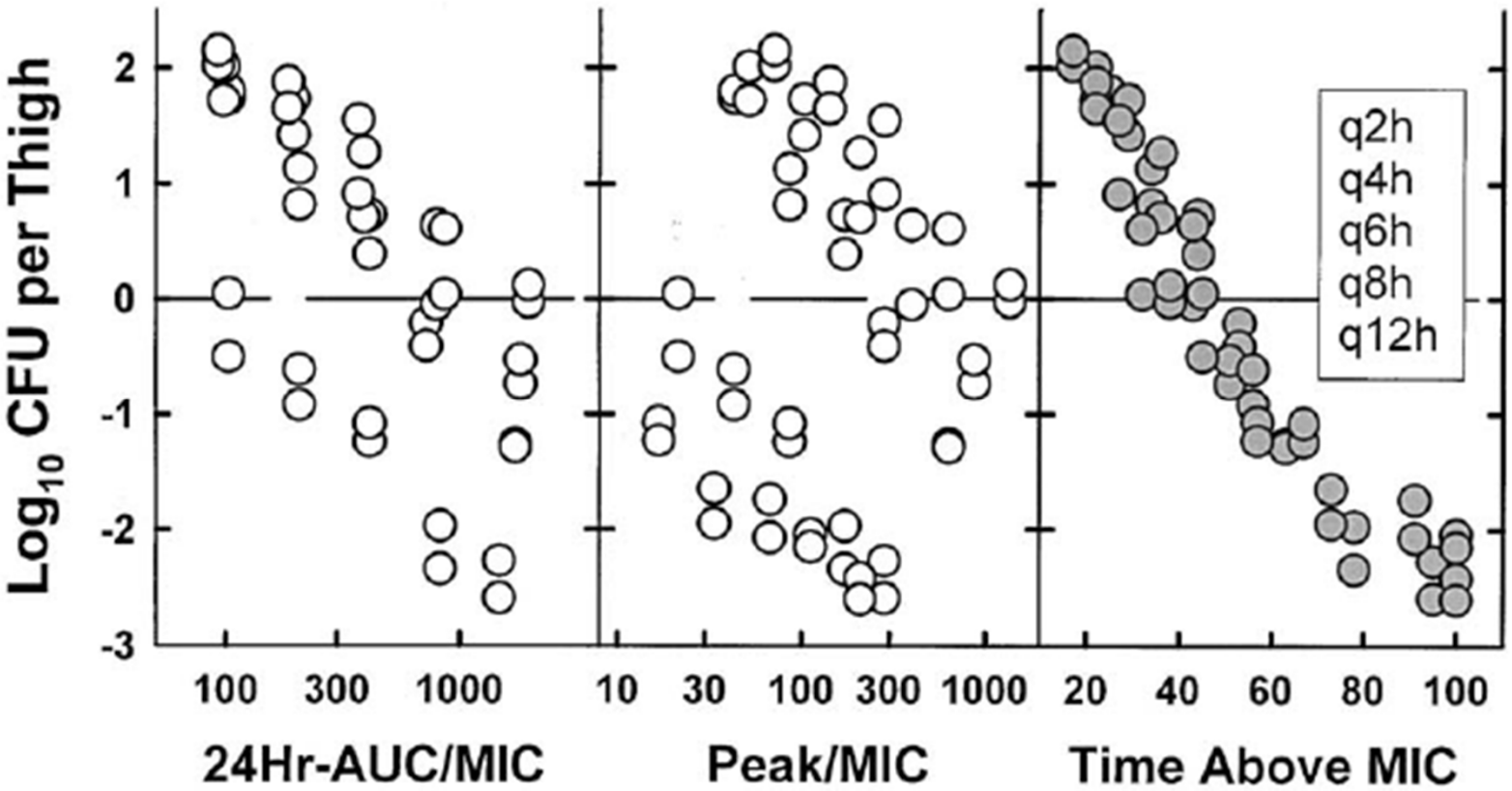
Tam VH. Antimicrob Agents Chemother 2007



Tam VH. In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics. Springer 2014

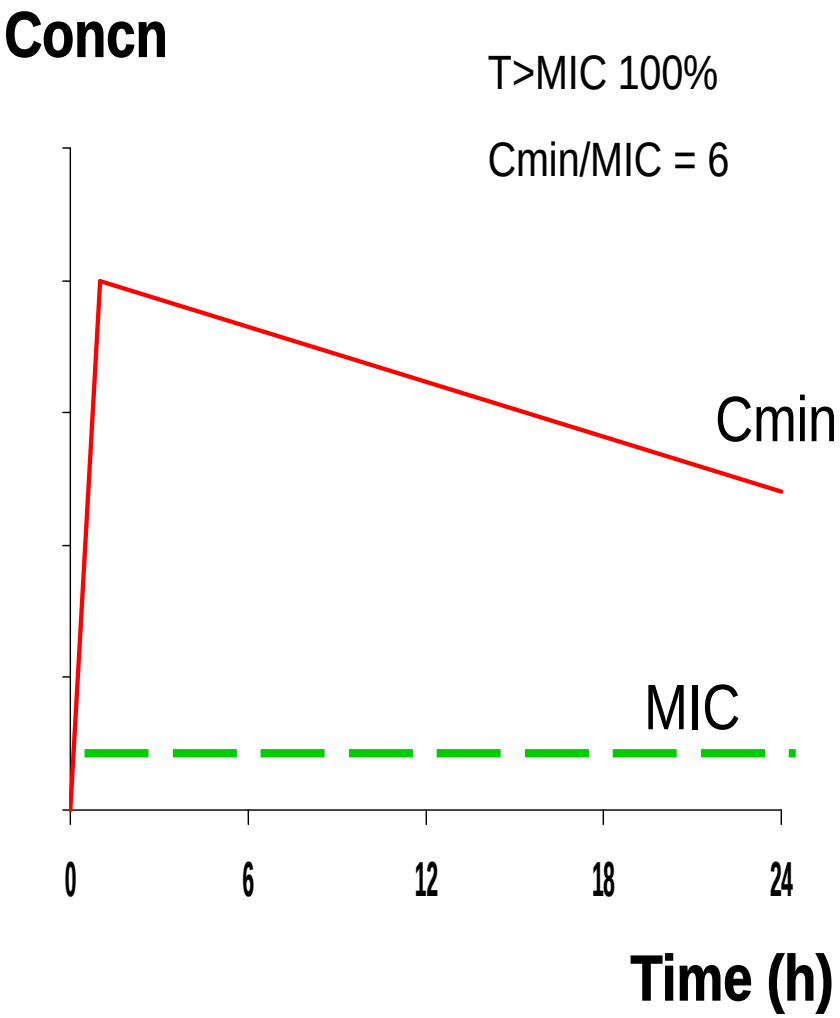
Beta-lactam Pharmacodynamics

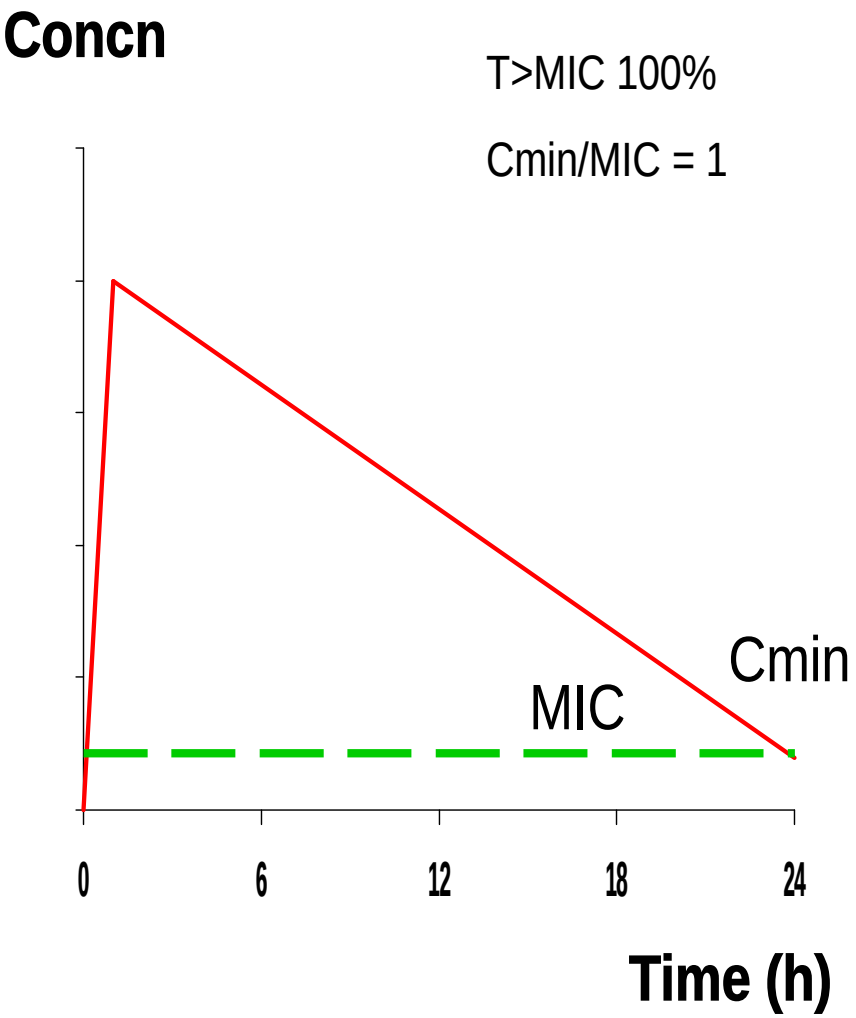
Ceftazidime vs *P. aeruginosa* (murine thigh infection model for 24h)



Craig WA. Infect Dis Clin North Am 2003

Ceiling Effect with %T>MIC

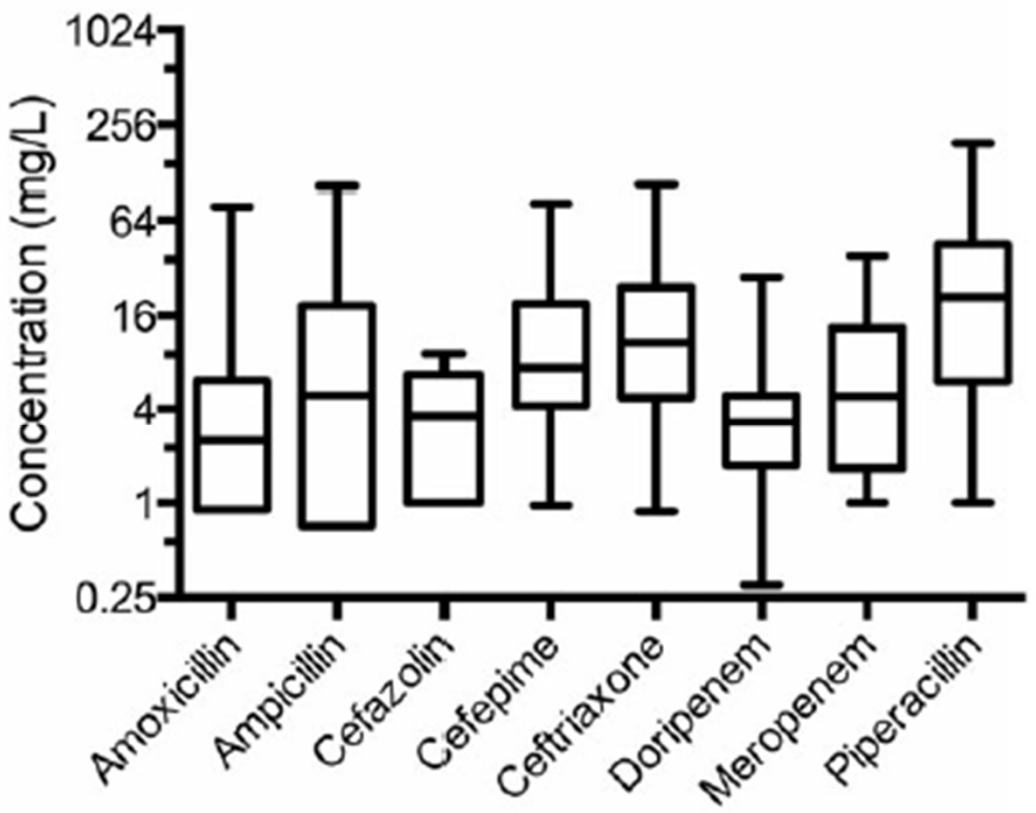




Studies correlating Cmin/MIC to Efficacy

Studies	Drug	Patients	Breakpoint
Tam 2012	Cefepime	Bacteremia	4.3
Li 2007	Meropenem	Lower RT Infection	5.0
MacVane 2014	Ceftazidime and cefepime	VAP	12.0
Aitken 2015	Cefepime	VAP	2.1

Wide Inter-subject Variability



Roberts JA. Clin Infect Dis 2014

Adopted PK/PD Targets

- Beta-lactam TDM - part of routine clinical care
- 9 ICUs in 7 countries

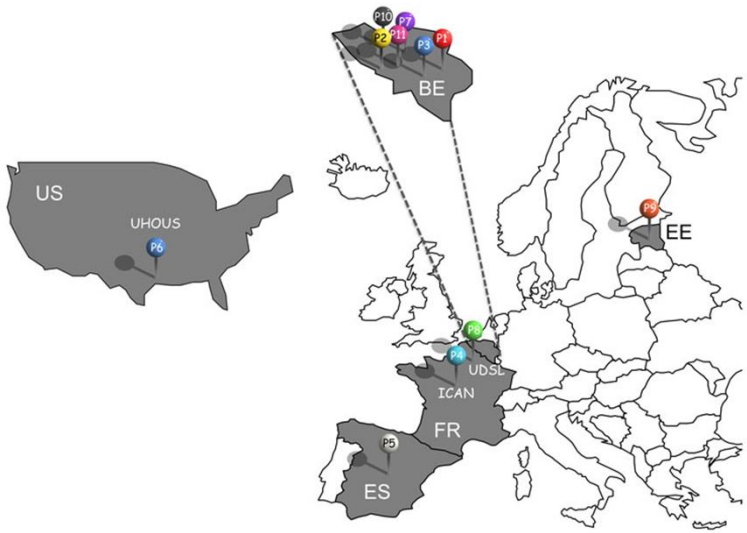
Target	Threshold fT > Target Exposure
1x MIC	100%
2-4x MIC	100%
4x MIC	40%
4x MIC	50%
4x MIC	70%
4x MIC	100%

Wong G. J Antimicrob Chemother 2014

MON4STRAT

Therapeutic Beta-Lactam Monitoring for Stratified Treatment of Hospital-acquired Pneumonia:

improved dose-dependent efficacy, decreased treatment duration, and prevention of emergence of resistance



11 partner institutions in 5 countries with complementary expertise

Funding from EU Framework Program for research, technological development and demonstration

Overarching Goals

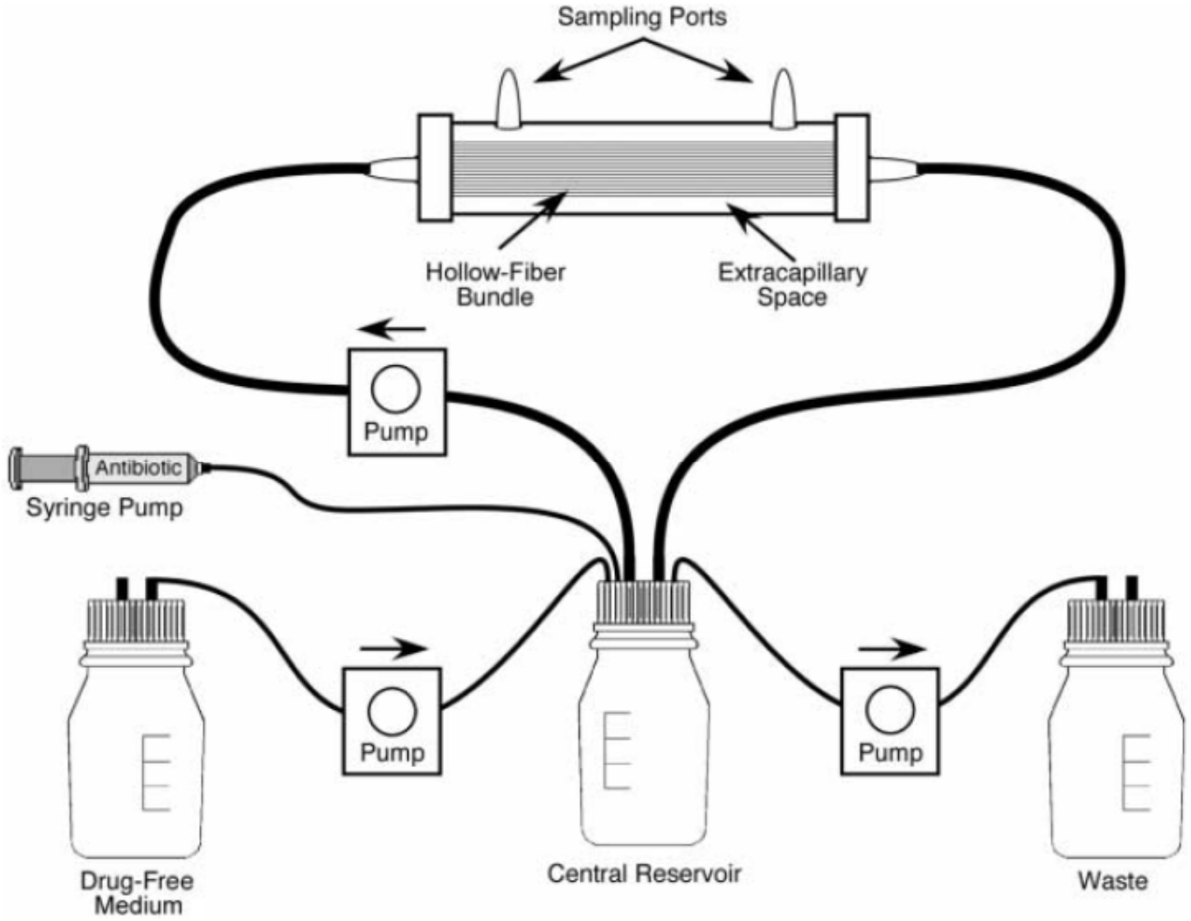
- Leveraging on past experience to advance the standard of medical care
- Prospective, randomized, controlled study
  - In 3 European clinical sites
- TDM guided dosing of beta-lactams
  - Benchtop device in ICU
  - Real time data for adaptive feedback design

Bacterial Isolates

Bacteria	Source	Cefepime (mg/l)	Ceftazidime (mg/l)	Meropenem (mg/l)	Resistance Mechanism
K. pneumoniae	Respiratory	0.25	0.5	0.06	Wild-type
K. pneumoniae	Urine	16	64	0.06	CTX-M15
P. aeruginosa	Respiratory	0.5	1	0.13	Wild-type
P. aeruginosa	Respiratory	16	64	0.25	↑AmpC

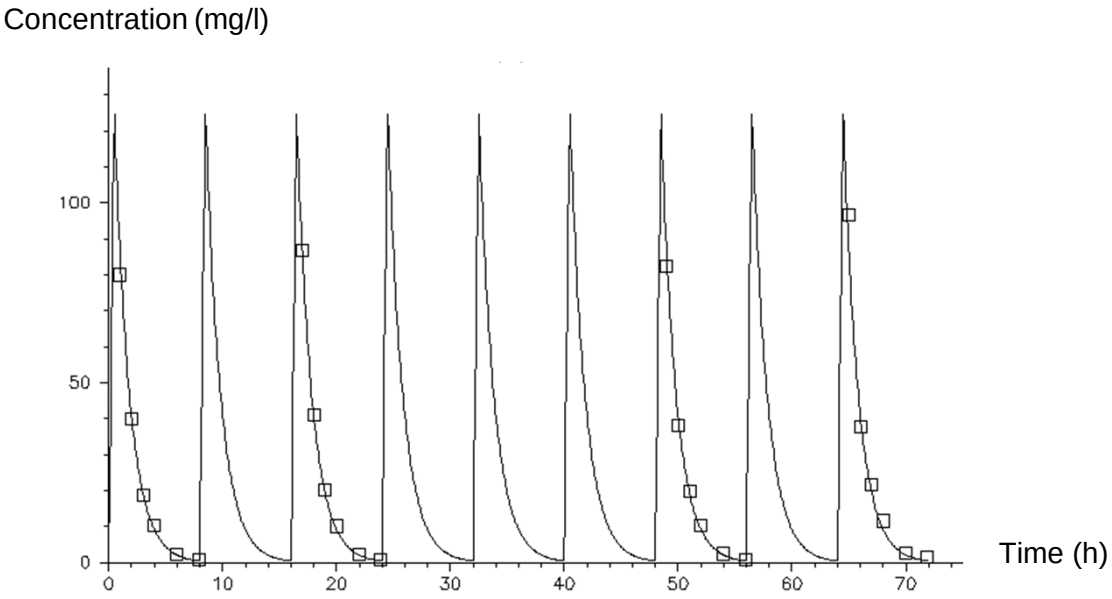
Resistant phenotype

Hollow-Fiber Infection Model



Tam VH. J Infect Dis 2007

PK Simulation in HFIM

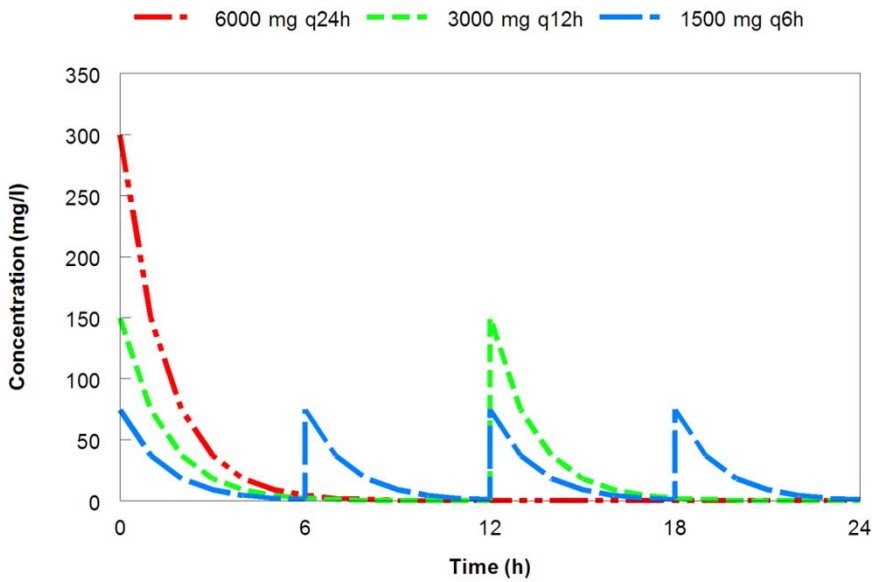


Target Cmax = 120 mg/l
Target half-life = 1 h
Target Cmin = 0.66 mg/l

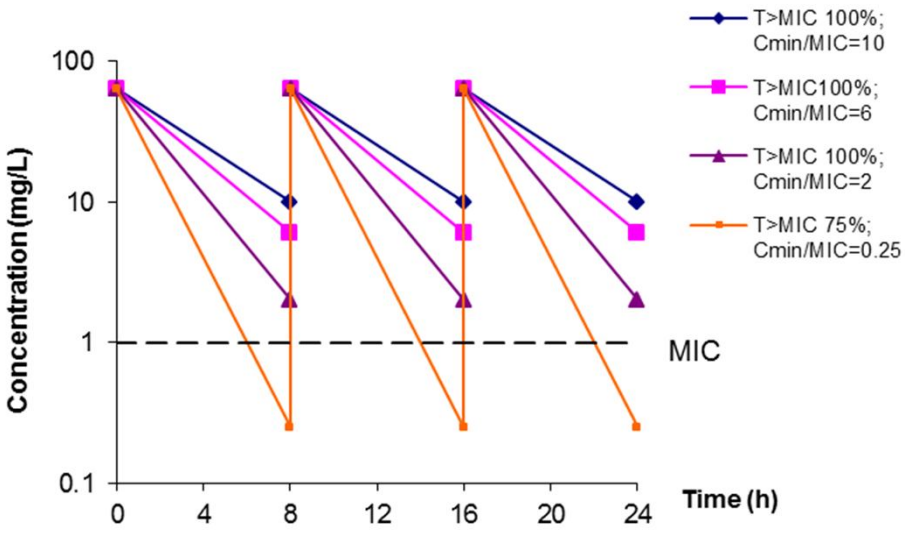
Open squares – observed concn
Solid line – best-fit model
R^2 = 0.991
Best-fit Cmax = 124 mg/l
Best-fit half-life = 0.93 h
Best-fit Cmin = 0.51 mg/l

- Simulation of meropenem 2g IV q8h (each dose given over 30 mins)

Dose-fractionation/ranging Design



Tam VH. PLoS Comput Biol 2011

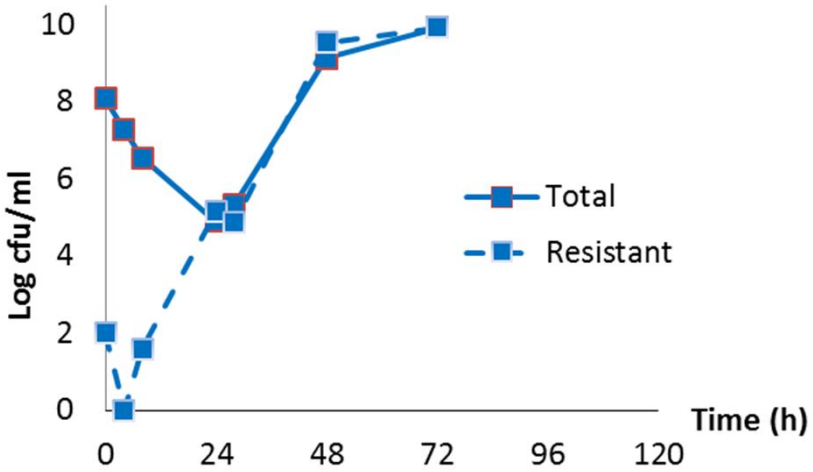


Tam VH. Antimicrob Agents Chemother 2005

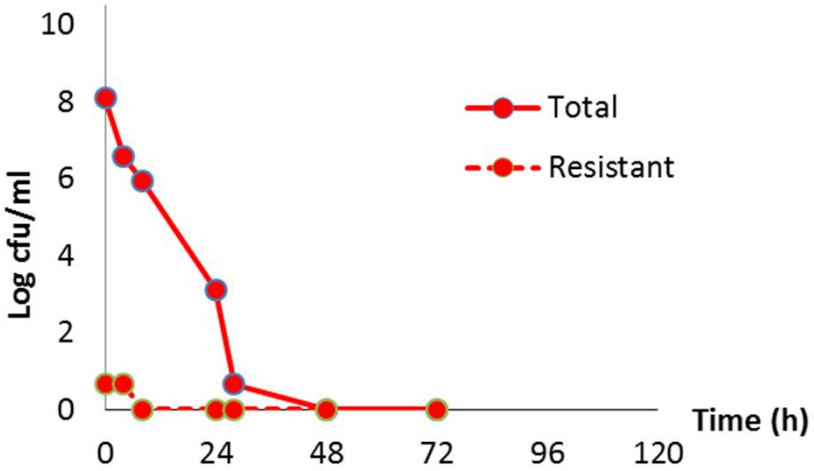
PK Simulation Parameters

Agent	Target Cmax (mg/l)	Cmax Range (mg/l)	Target $t_{1/2}$ (h)	$t_{1/2}$ Range (h)	N
Meropenem	120 (2g)	20-120	1	1-2	13
Cefepime	160 (2g)	120-560	2	1-4	10
Ceftazidime	120 (2g)	30-300	2	2	8

P. aeruginosa WT
Ceftazidime MIC = 1 mg/l



0.5g q8h
CAZ Cmin/MIC = 2.9

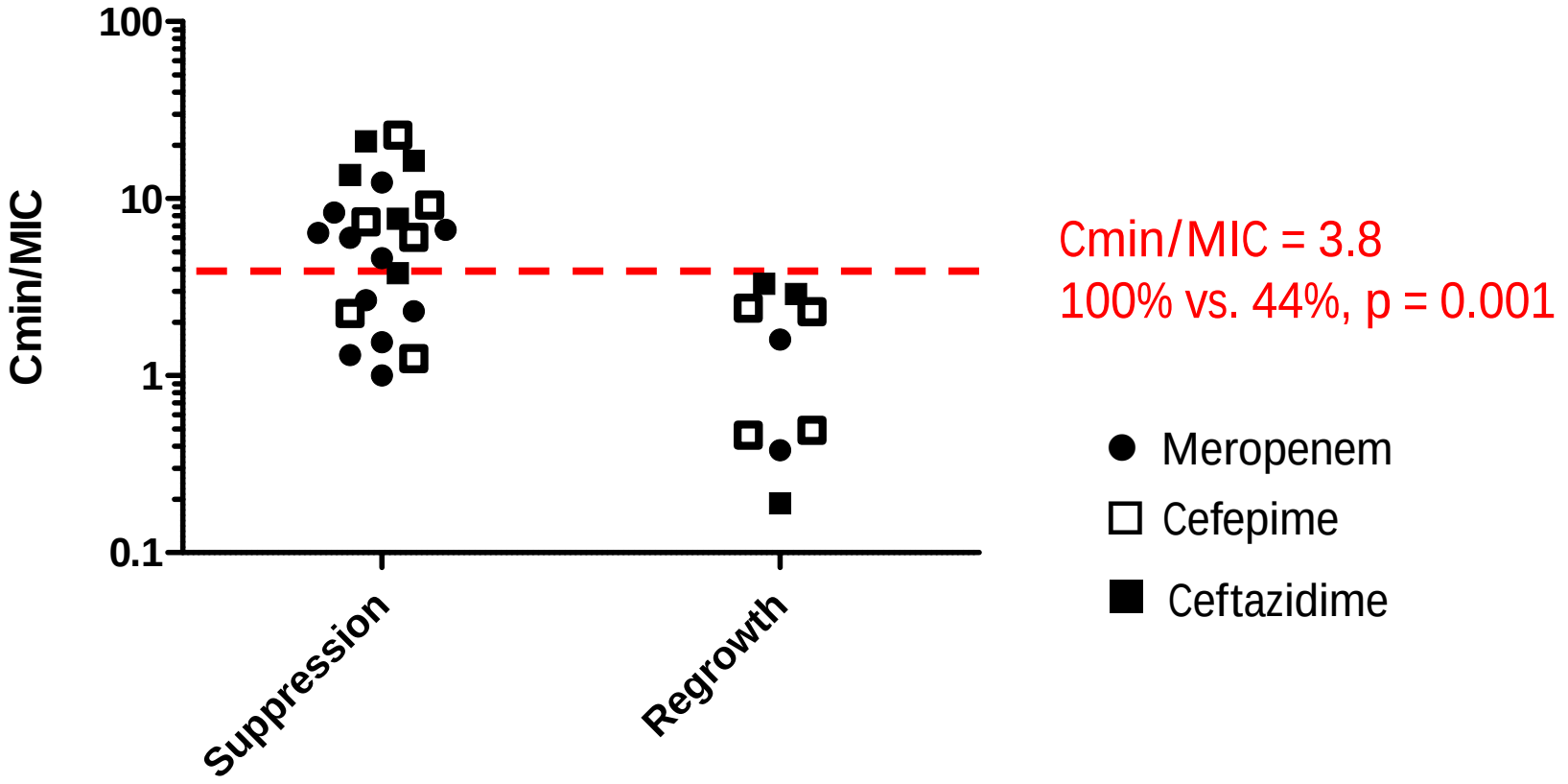


2g q8h
CAZ Cmin/MIC = 7.7

Overall Response

Agent	Suppression	Regrowth	N
Meropenem	11	2	13
Cefepime	6	4	10
Ceftazidime	5	3	8
Total	22	9	31

PK/PD Correlation - Targets



7.5 +/- 6.3 vs. 1.6 +/- 1.2, $p < 0.001$

Tam VH. J Antimicrob Chemother 2017 (in press)

Dosing Ladder (normal renal function)

- Balancing computation burden and practicality in ICU
- Patient-specific MIC
- Based on serial measurements and dosing escalations towards:
  - Target attainment (e.g., C_{min} >= 4xMIC) or
  - Highest dosing level

MEM Regimen	1g q8h (0.5h)	1g q8h (3h)	2g q8h (3h)	6g q24h (CI)	8g q24h (CI)*
ETA (4x 0.5 mg/l)	58.5%	69.0%	80.6%	100.0%	100.0%
ETA (4x 2 mg/l)	13.9%	20.9%	48.2%	96.9%	98.6%

Empiric (both groups) → Intervention group → TDM guided when MIC available

Conclusions

- Antimicrobial resistance
  - Inevitable consequence
  - Multi-factorial
- Emergence likelihood delayed by
  - Judicious use
  - Rational dosing strategies

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