Dose and Schedule Choices to Suppress Emergence of Resistance

G.L. Drusano, M.D.
Co-Director
Ordway Research Institute

Co-Investigators

Arnold Louie, M.D.

Mark Deziel, Ph.D., Deceased

James McSharry, Ph.D.

Henry S. Heine, Ph.D.

Co-Investigators

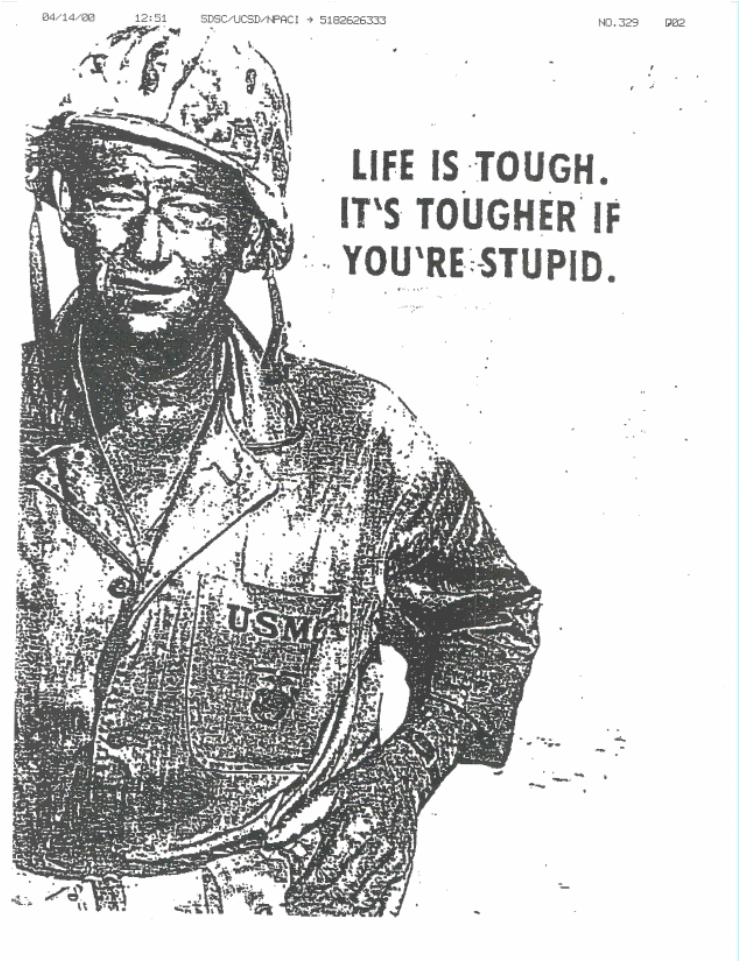
Paul Ambrose, Pharm.D.

Sujata Bhavnani, Pharm.D., M.S.

Dose and Schedule Choices to Suppress Emergence of Resistance

- We live in an age when nosocomial pathogens are rapidly becoming resistant to many or all classes of our antimicrobial agents
- For a variety of reasons, new agents with different targets to treat these organisms have not been forthcoming
- We, therefore need to find a way to preserve our currently available agents and, when new agents come online, to preserve their utility – **we need to be smarter!**

Dose and Schedule Choices to Suppress Emergence of Resistance

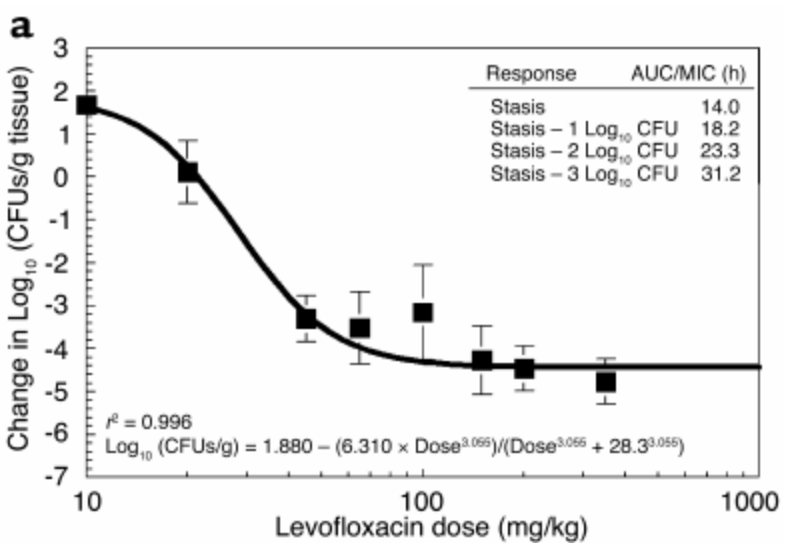


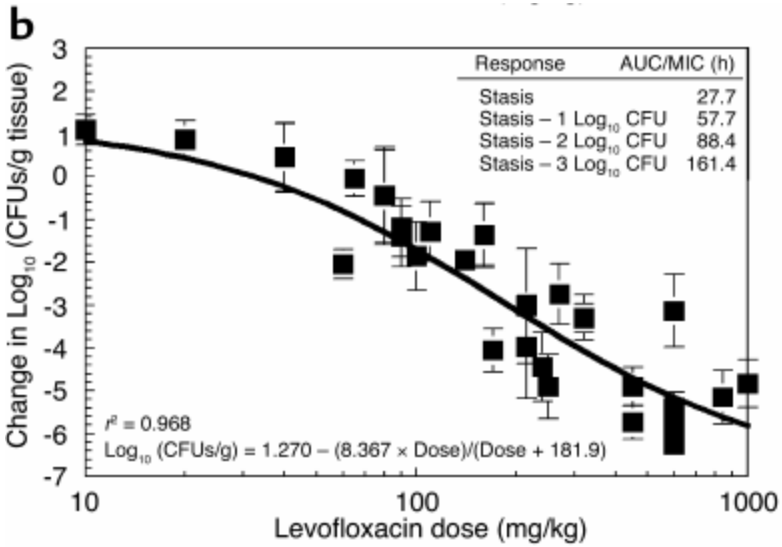
Dose and Schedule Choices to Suppress Emergence of Resistance

Pre-Clinical to Phase I/II: Delineation of Exposure-Response

This will examine the intensity of drug therapy

P. aeruginosa outcome studies





Jumbe et al J Clin Invest 2003;112:275-285

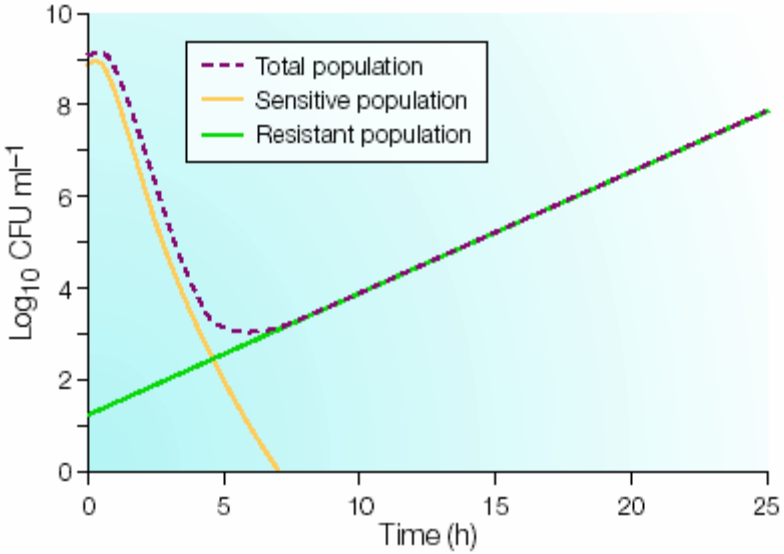
Dose and Schedule Choices to Suppress Emergence of Resistance

Pre-Clinical to Phase I/II: What about Resistance?

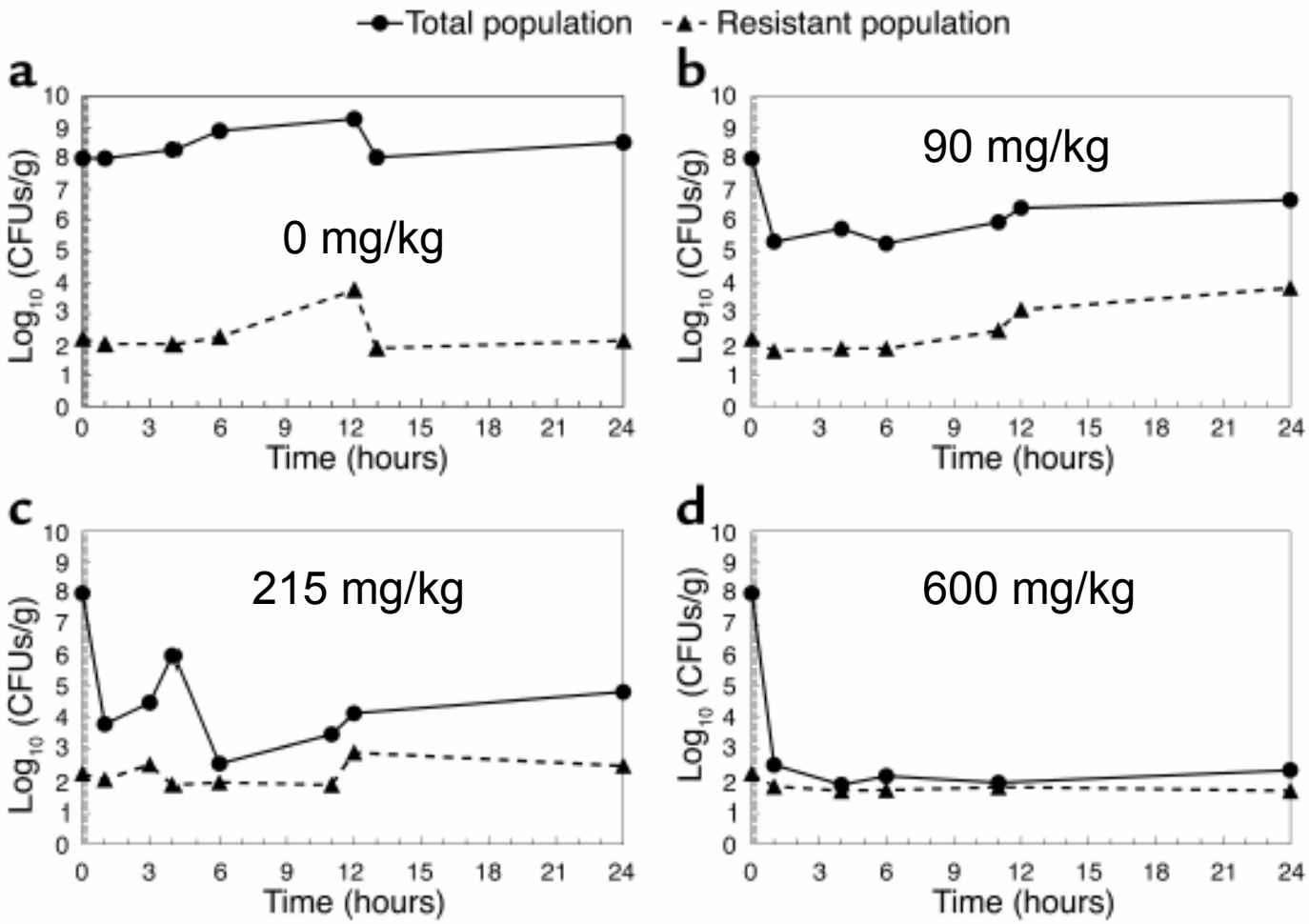
What intensity can suppress resistance?

Levofloxacin and *Pseudomonas aeruginosa* in a Mouse Thigh Infection Model

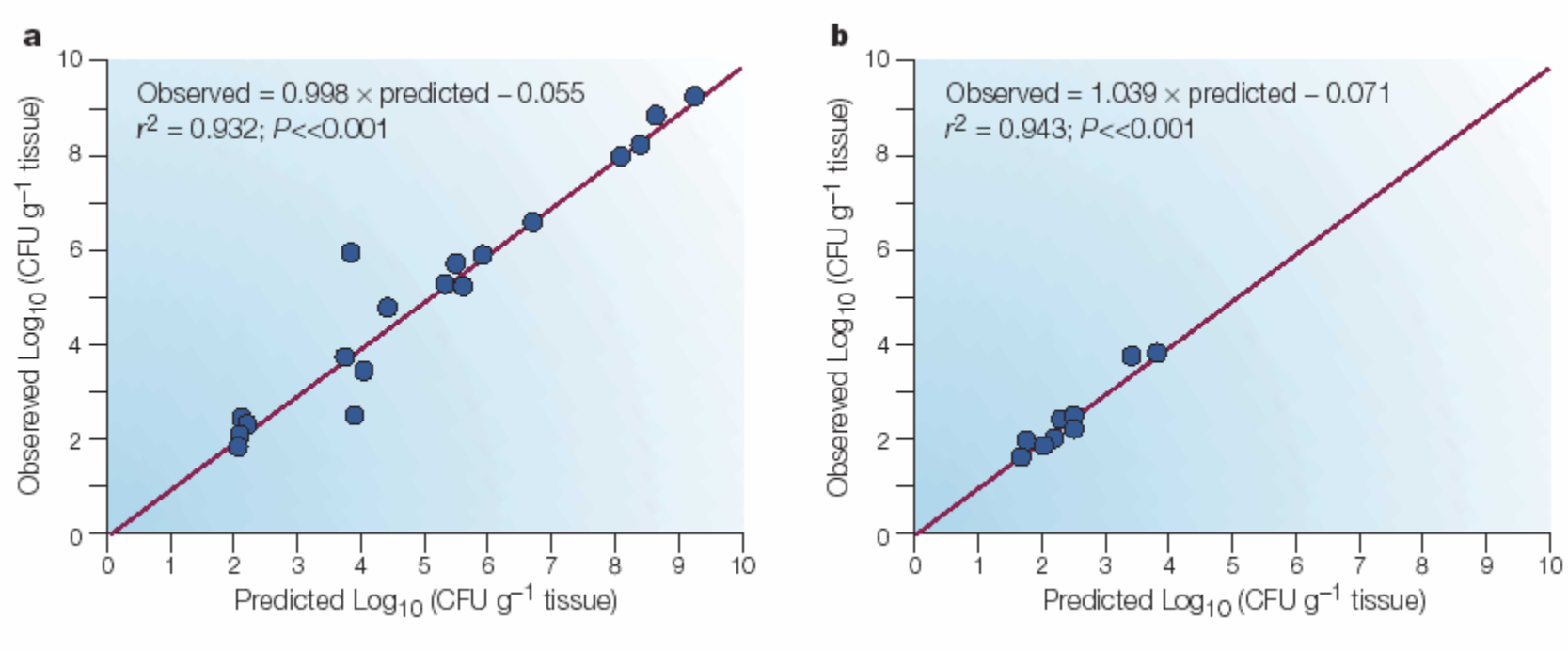
Can a drug exposure be identified that will prevent the resistant subpopulation from taking over the total population?



Drusano GL. Nat Rev Microbiol 2004;2:289-300

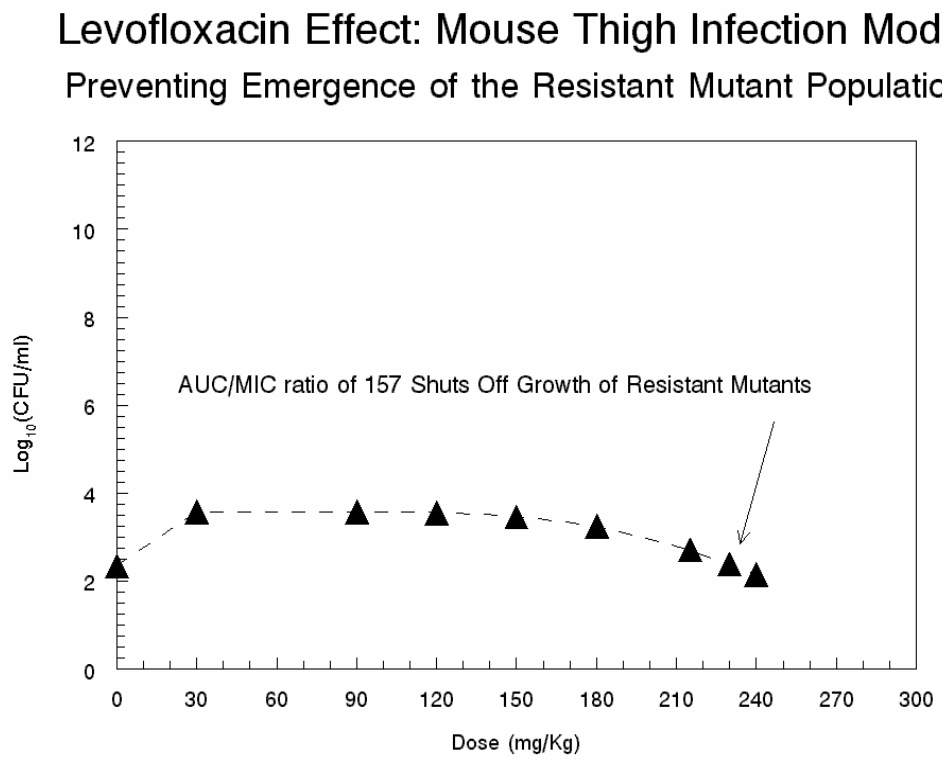


Jumbe et al J Clin Invest 2003;112:275-285

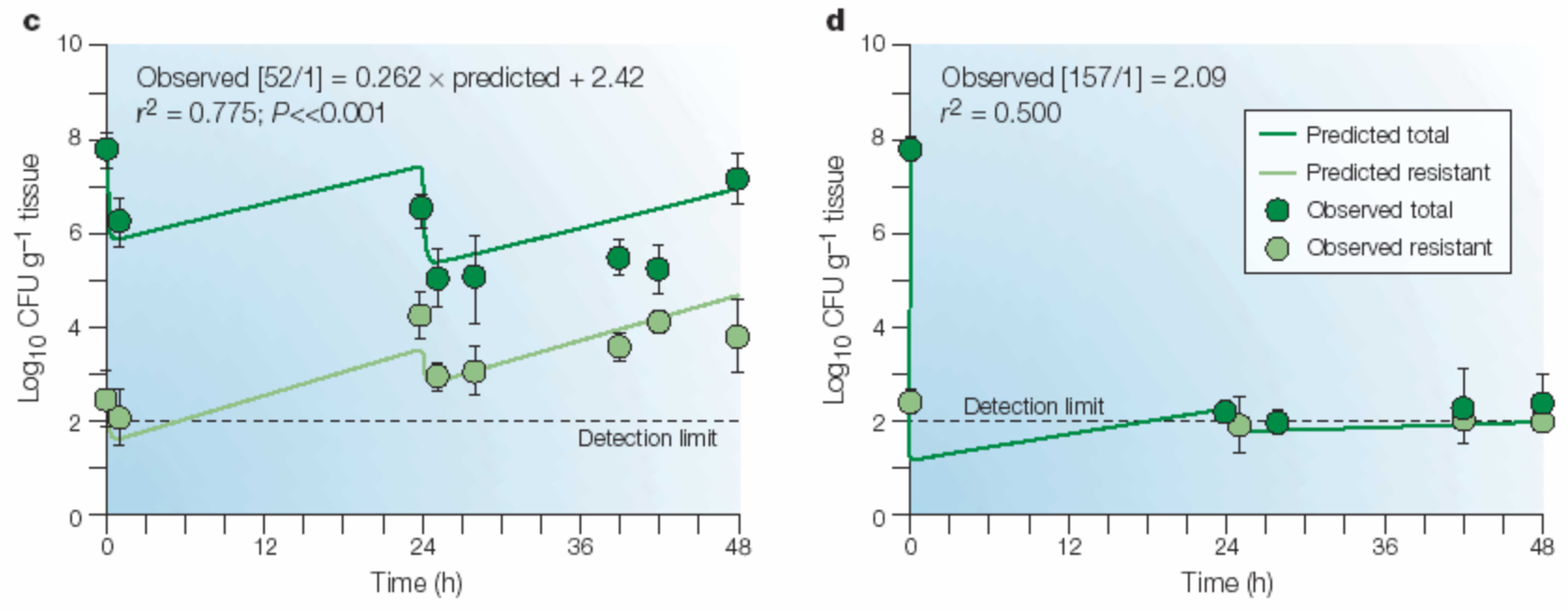


Jumbe et al J Clin Invest 2003;112:275-285
Drusano GL. Nat Rev Microbiol 2004;2:289-300

Dose and Schedule Choices to Suppress Emergence of Resistance



Jumbe et al J Clin Invest 2003;112:275-285
Drusano GL. Nat Rev Microbiol 2004;2:289-300

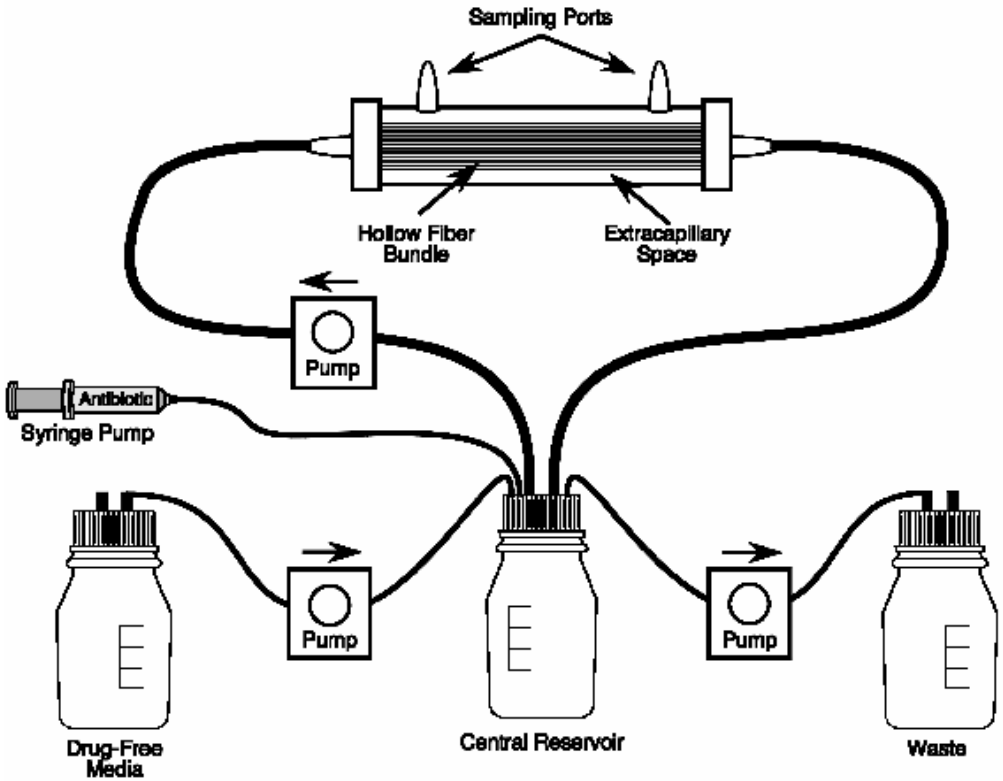


Jumbe et al J Clin Invest 2003;112:275-285
Drusano GL. Nat Rev Microbiol 2004;2:289-300

Dose and Schedule Choices to Suppress Emergence of Resistance

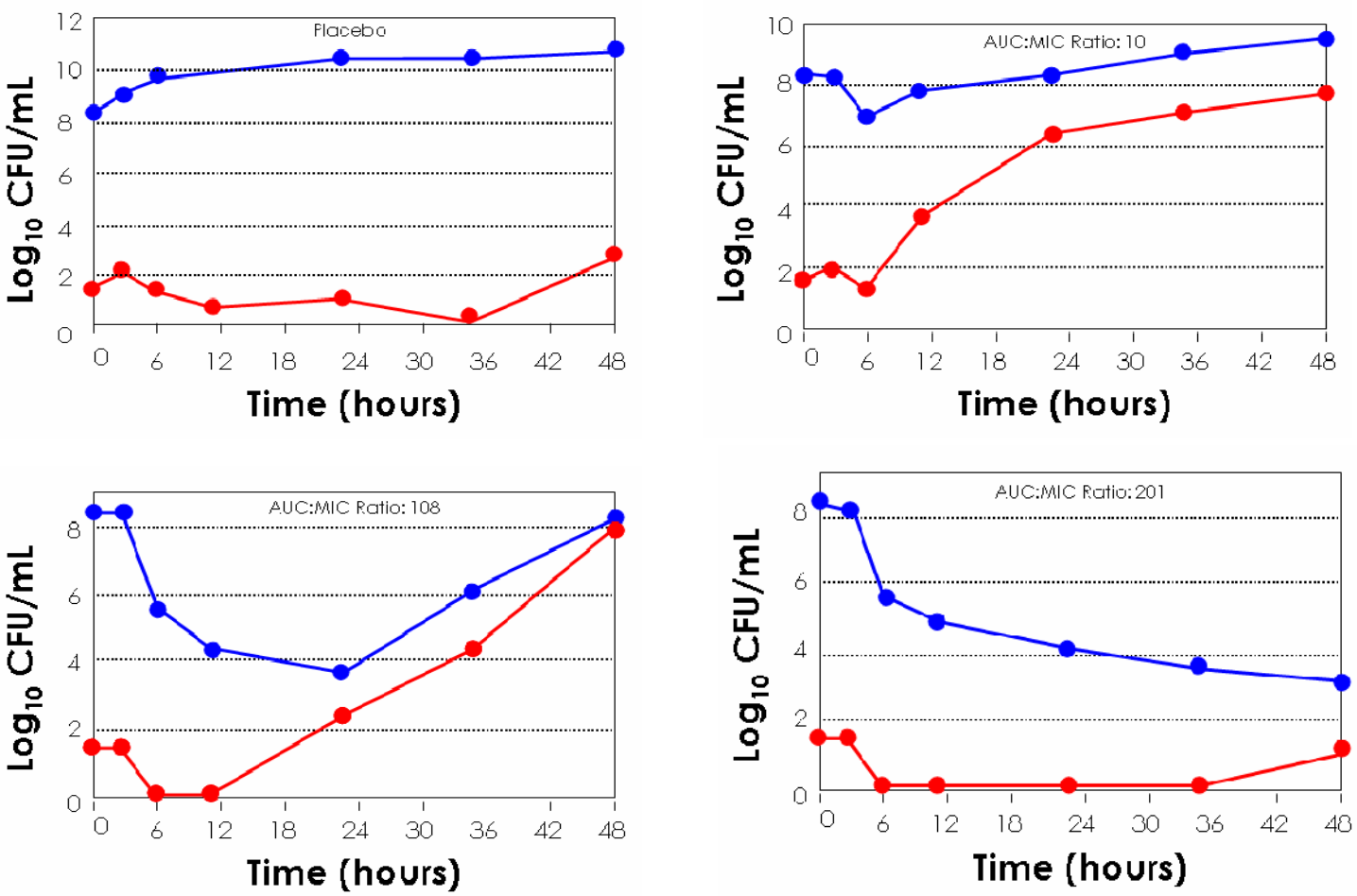
Pre-Clinical to Phase I/II: What about Resistance?
Can this be done *in vitro*?

Dose and Schedule Choices to Suppress Emergence of Resistance



The hollow fiber model was described by Blaser and Zinner and employed extensively by Dudley

Dose and Schedule Choices to Suppress Emergence of Resistance

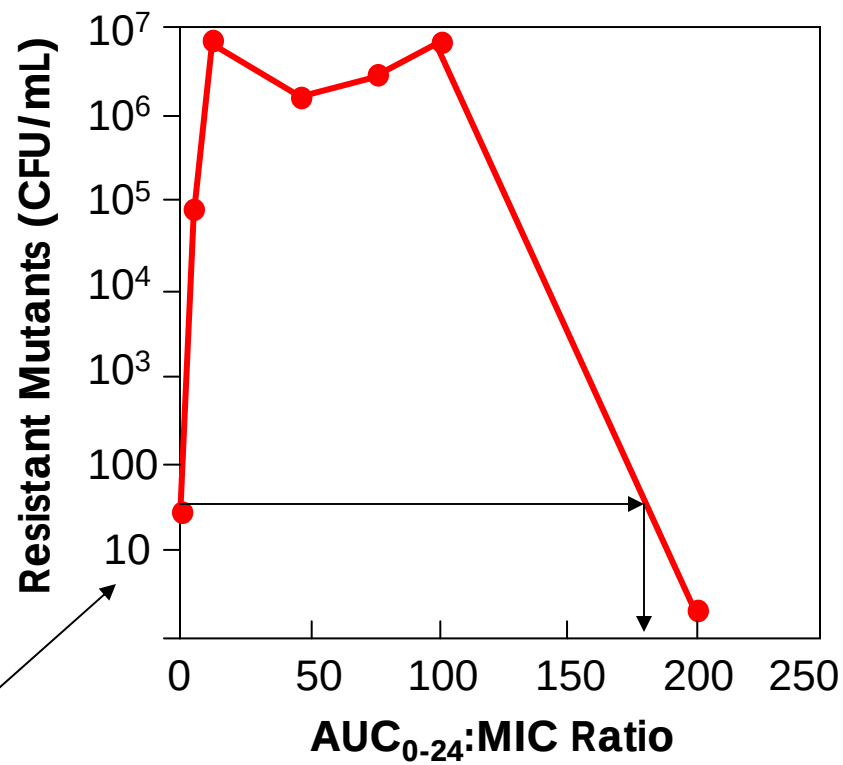


Tam V et al. Bacterial-population responses to drug selective pressure: Examination of garenoxacin's effect on *Pseudomonas aeruginosa*. J Infect Dis 2005;192:420-428

Dose and Schedule Choices to Suppress Emergence of Resistance

P. aeruginosa - Prevention of Amplification of Resistant Subpopulation

- The amplification of the resistant sub-population is a function of the AUC/MIC ratio
- The response curve is an inverted “U”.
- The AUC/MIC ratio for resistant organism stasis is circa 185/1

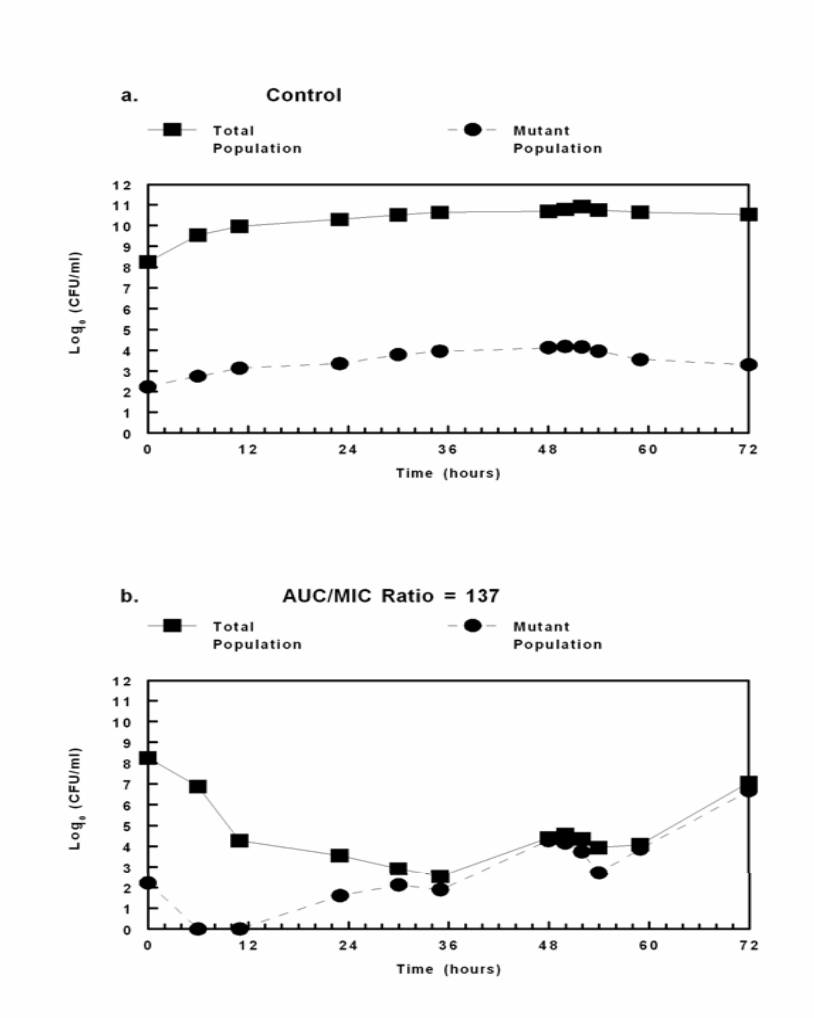


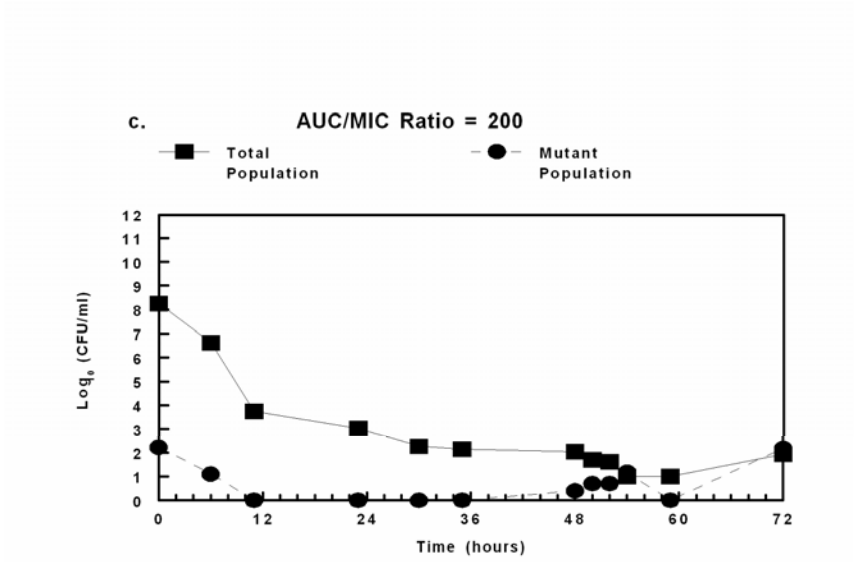
Resistant organisms at baseline

All other data points represent resistant organism counts at 48 hours of therapy

Dose and Schedule Choices to Suppress Emergence of Resistance

Propspective Validation Study





Tam V et al. Bacterial-population responses to drug selective pressure: Examination of garenoxacin's effect on *Pseudomonas aeruginosa*. J Infect Dis 2005;192:420-428

Dose and Schedule Choices to Suppress Emergence of Resistance

- Please note that the animal model had a breakpoint of 157 for resistance suppression
- Levofloxacin is 30% bound in the mouse
- Free drug target is (0.7 x 157) = 110
- The *in vitro* system developed a target exposure of 190, which is free drug; the *in vitro* system has no immune function
- Andes and Craig (AAC 2002;46:1665-1670) showed making mice G-penic increased the exposure target by 1.5 – 2.0 fold
- These *in vitro* data are consistent with the Craig findings

BRIDGING TO THE CLINIC

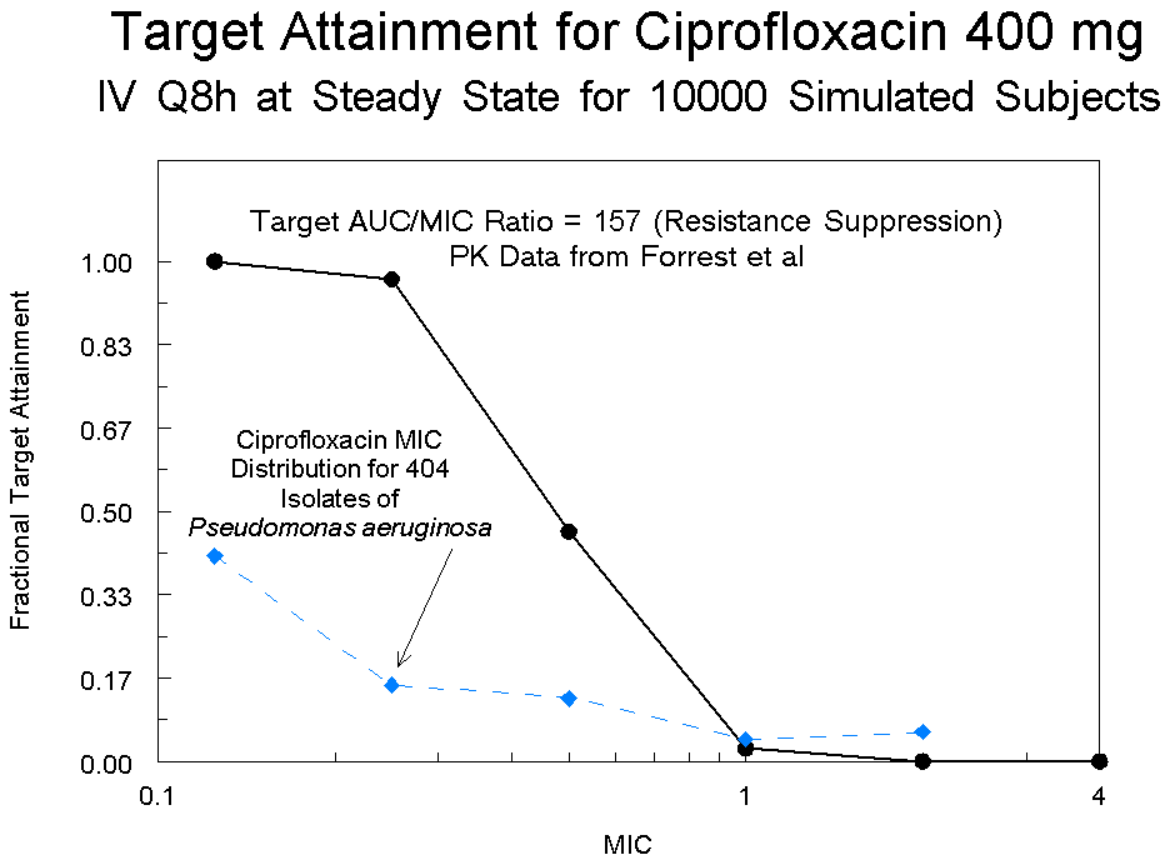
Correlation with Pre-Clinical Models

Do These Concordant Animal and Hollow Fiber Model Findings Correlate with Suppression of Resistance in the Clinic?

PK-PD TARTGET ATTAINMENT

Ciprofloxacin Against P. aeruginosa

Use of Monte Carlo Simulation



Taking the expectation demonstrates an overall target attainment of 62% and a predicted emergence of resistance rate of 38%

MONTE CARLO SIMUATION

Is It Predictive?

- Peloquin studied 200 mg IV Q 12 h of ciprofloxacin in nosocomial pneumonia - *P aeruginosa* resistance rate 70% (7/10 - pneumonia only) - 77% (10/13 - all respiratory tract)
- MCS (resistance suppression target) predicts emergence of resistance in 75%
- Fink et al studied ciprofloxacin in nosocomial pneumonia (400 mg IV Q 8 h) - *P aeruginosa* resistance rate 33% (12/36)
- MCS at this dose and schedule predicts suppression in 62% and emergence of resistance in 38%

Peloquin et al Arch Int Med 1989;1492269-73

Fink et al AAC 1994;38:547-57

PK-PD INFECTION MODELS
Lessons Learned

- We have shown that we can identify drug exposures that will suppress emergence of resistance in an animal model
- The hollow fiber infection model identifies an exposure that is 70% larger, because of the absence of immune function
- These predictions are validated in two different clinical trials with two different doses and schedules

Dose and Schedule Choices to Suppress Emergence of Resistance

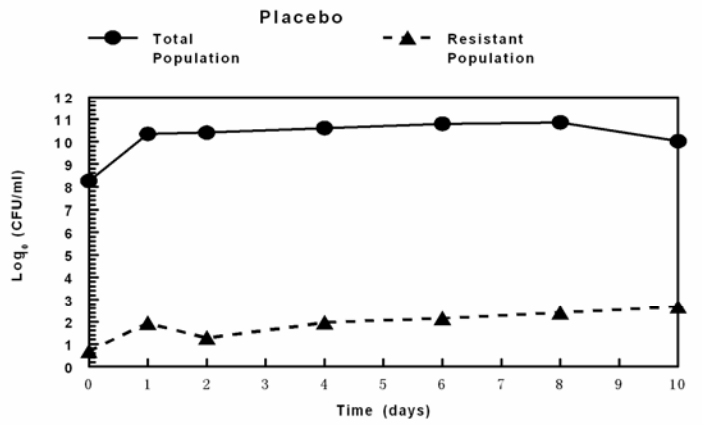
Pre-Clinical to Phase I/II: Does Therapy Duration Affect Resistant Sub-Population Amplification?

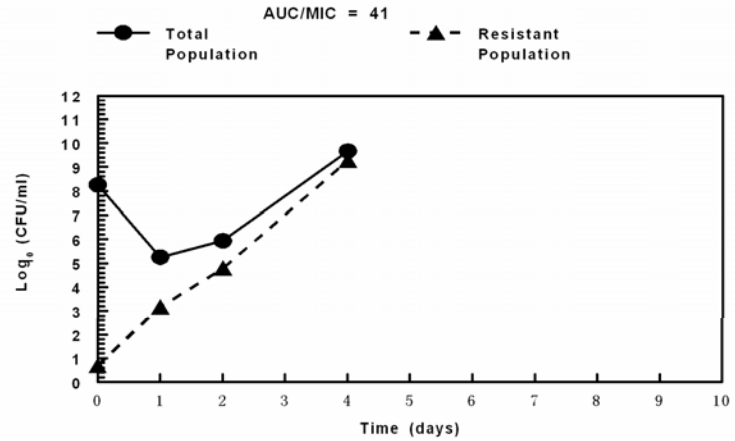
DURATION OF THERAPY

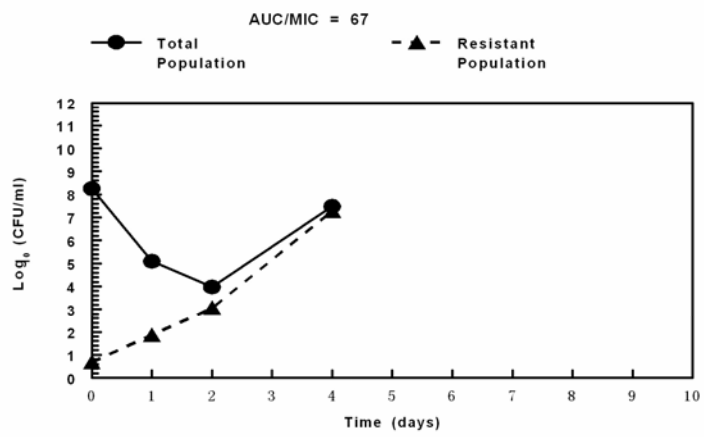
Impact on Resistance Amplification

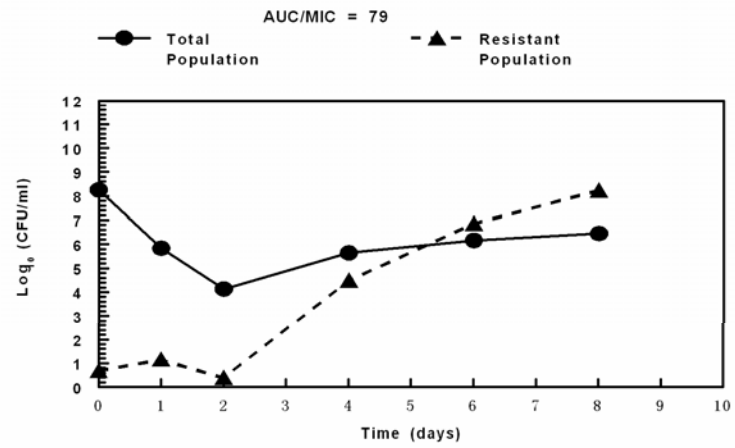
- We examined a quinolone against *Staphylococcus aureus* to determine the impact of duration of therapy on amplification of resistant subpopulations
- We were able to demonstrate that exposures that produce maximal kill rates do not, of necessity, suppress resistant subpopulations, making therapy duration very important

Garenoxacin Dose-Ranging Study



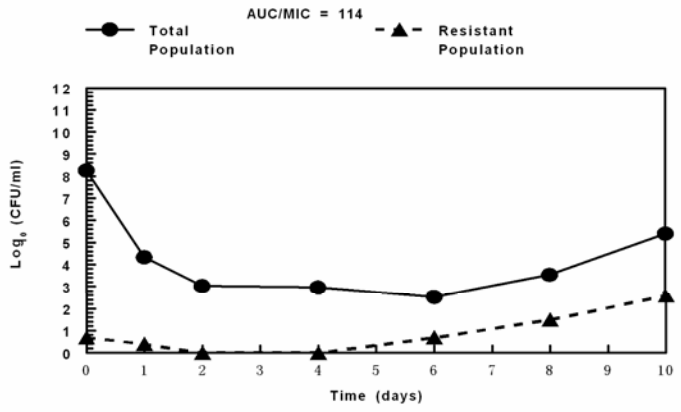


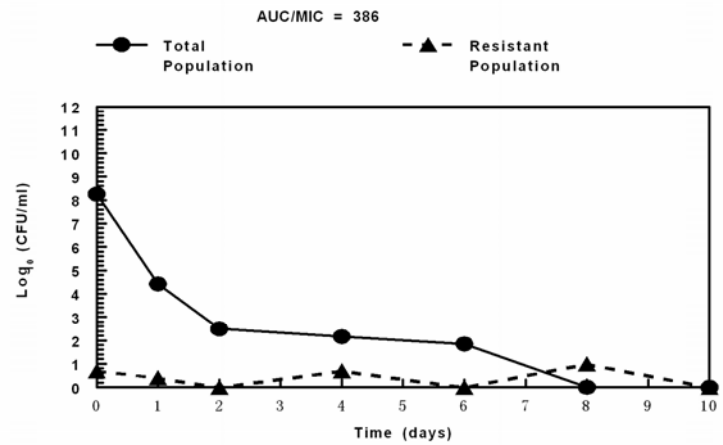


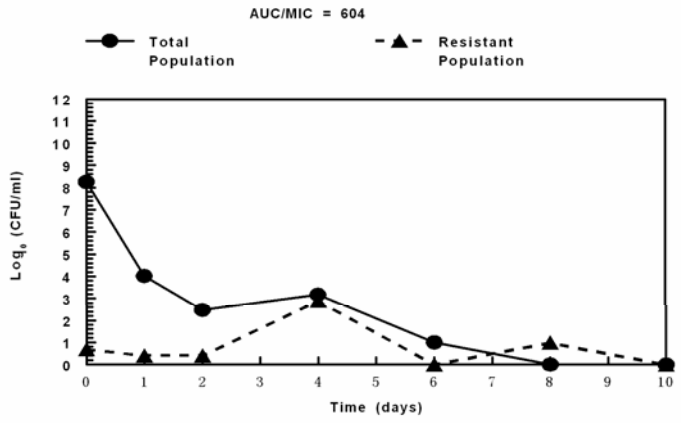


In Press, J Infect Dis

Garenoxacin Dose-Ranging Study







In Press, J Infect Dis

DURATION OF THERAPY

Impact on Resistance Amplification

- We modeled these data to obtain estimates of exposures that would:
  1. Maximally kill the organism, but not suppress resistance
  2. Suppress resistance
- The first regimen was an AUC/MIC ratio of 100
- The second was an AUC/MIC ratio of 280

Garenoxacin Prospective Validation Study

- Hypotheses to be tested in a prospective validation experiment:

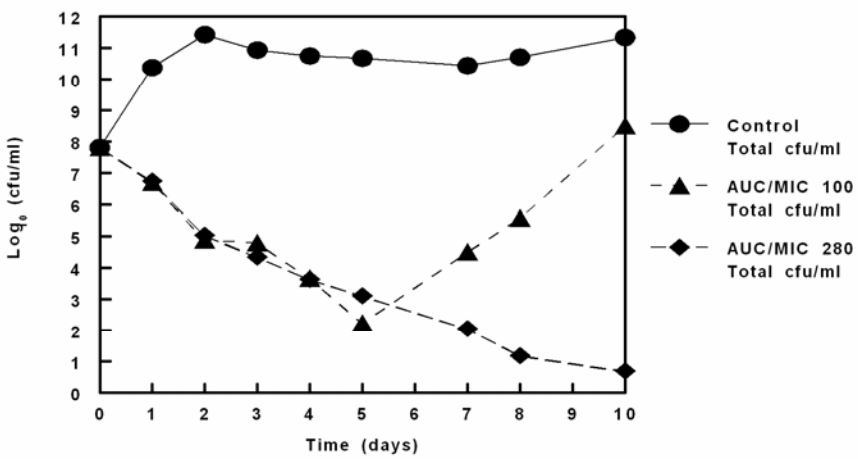
  1) The higher-intensity regimen will drive the colony counts down by circa 5-6 $\log_{10}$ (CFU/ml) by 5 days of therapy

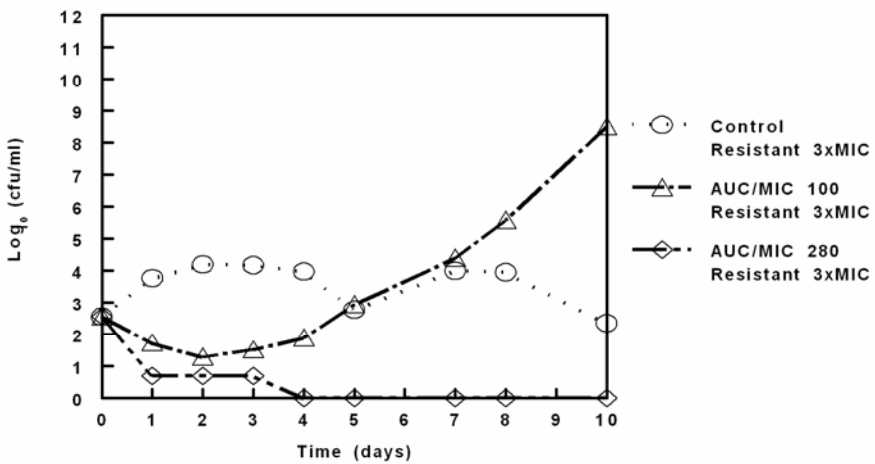
  2) The lower-intensity regimen will be similar to the intense regimen for 4 days as regards total colony counts

  3) The higher-intensity regimen will suppress resistance for the full 10 days of therapy

  4) The lower-intensity regimen will allow resistant organism amplification after day 4

Garenoxacin Prospective Validation Study





In Press, J Infect Dis

DURATION OF THERAPY

Impact on Resistance Amplification

- The prospective validation demonstrated that both regimens killed at the same rate and extent for 5 days
- HOWEVER, the smaller AUC/MIC allowed resistant population amplification after day 4
- The larger regimen prevented resistance through 10 days
- All hypotheses were prospectively validated

DURATION OF THERAPY

Impact on Resistance Amplification

- The longer therapy goes, the higher the drug exposure that is required to suppress resistance
- Lesson learned:
  ***Go in with high intensity therapy to suppress resistance**
  ***Stop quickly**

WHAT IS IT THAT WE WANT TO DO?

Response Hierarchy

Desired Endpoint	Required Exposure Intensity
Extinction endpoint	
Resistance subpopulation endpoint	
Traditional endpoints	

From a PK-PD perspective, if we want to decrease resistance, we need to realize that the use of traditional clinical trial endpoints are insufficient for the task

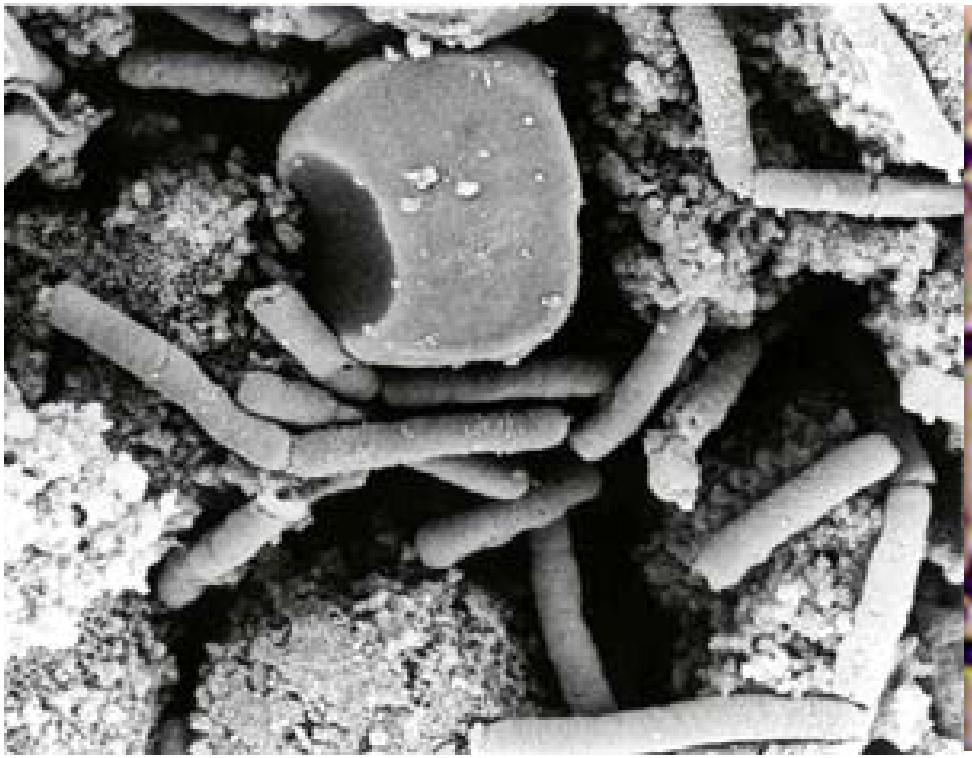
Dose and Schedule Choices to Suppress Emergence of Resistance

- There is not enough time to talk about extinction endpoints (Streptococcal pharyngitis, *Mycobacterium tuberculosis*, etc)
- We have examined suppression of resistance and learned that drug doses need to be chosen in a way that achieve drug exposures that will suppress amplification of resistant sub-populations for the vast majority of patients
- In this way we can preserve those drugs we have and protect new additions to our armamentarium

Dose and Schedule Choices to Suppress Emergence of Resistance

- We have seen (last night) data for new developments on the therapeutics front for biodefense pathogens
- We can examine this with the hollow fiber system, as well
- The following data were developed eith the support of 1 PO1 AI060908-01A1 “Choosing Drug Doses for Biodefense Pathogens”

Anthrax



Anthrax

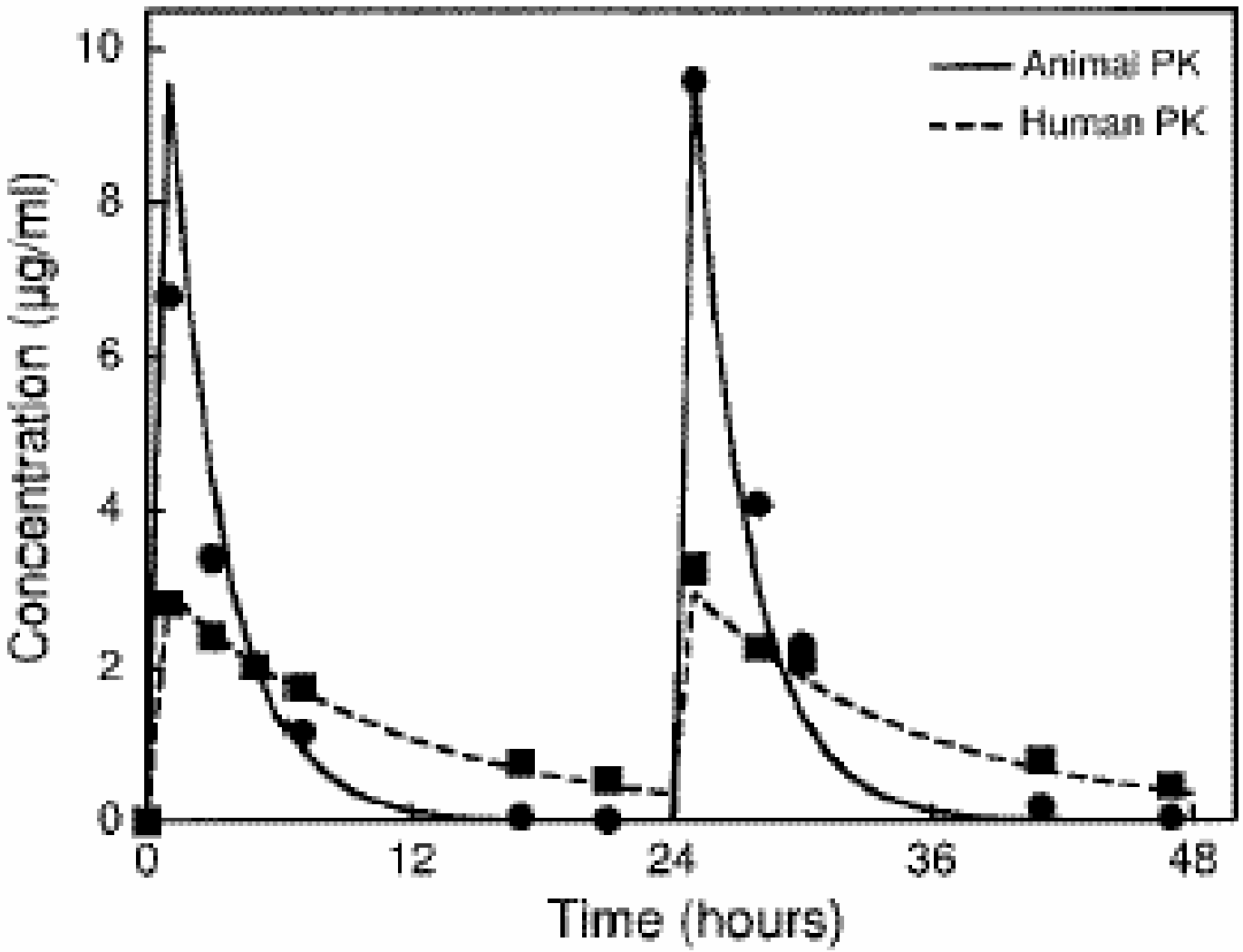
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2005, p. 5099–5106 Vol. 49, No. 12
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.12.5099–5106.2005
Copyright © 2005, American Society for Microbiology. All Rights Reserved.

Effective Antimicrobial Regimens for Use in Humans for Therapy of *Bacillus anthracis* Infections and Postexposure Prophylaxis†

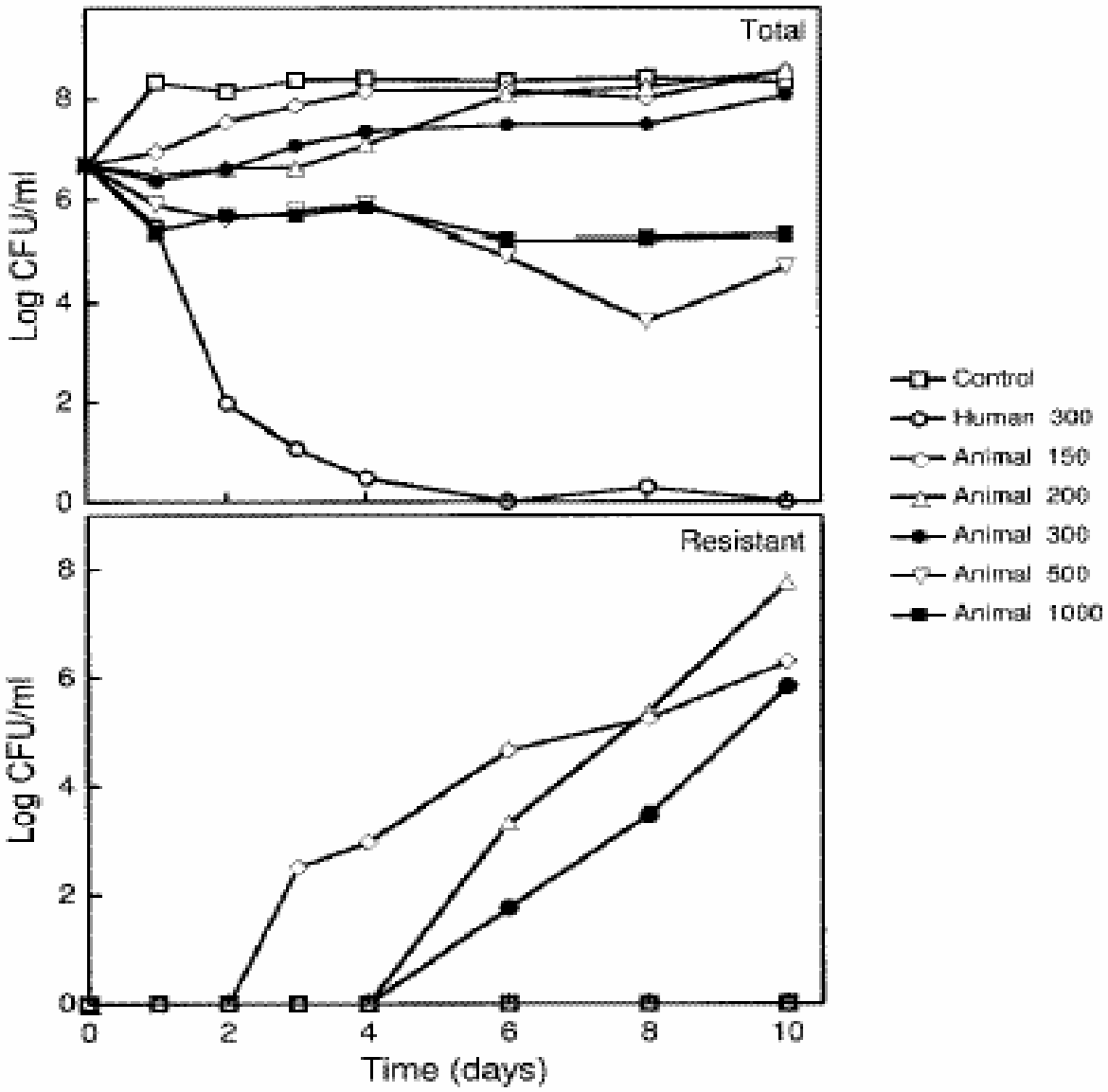
Mark R. Deziel,[1]‡ Henry Heine,[2] Arnold Louie,[1] Mark Kao,[3] William R. Byrne,[2] Jennifer Basset,[2] Lynda Miller,[2] Karen Bush,[3] Michael Kelly,[3] and G. L. Drusano[1]*

Ordway Research Institute, Albany, New York[1]; United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland[2]; and Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, New Jersey[3]

Anthrax Therapy

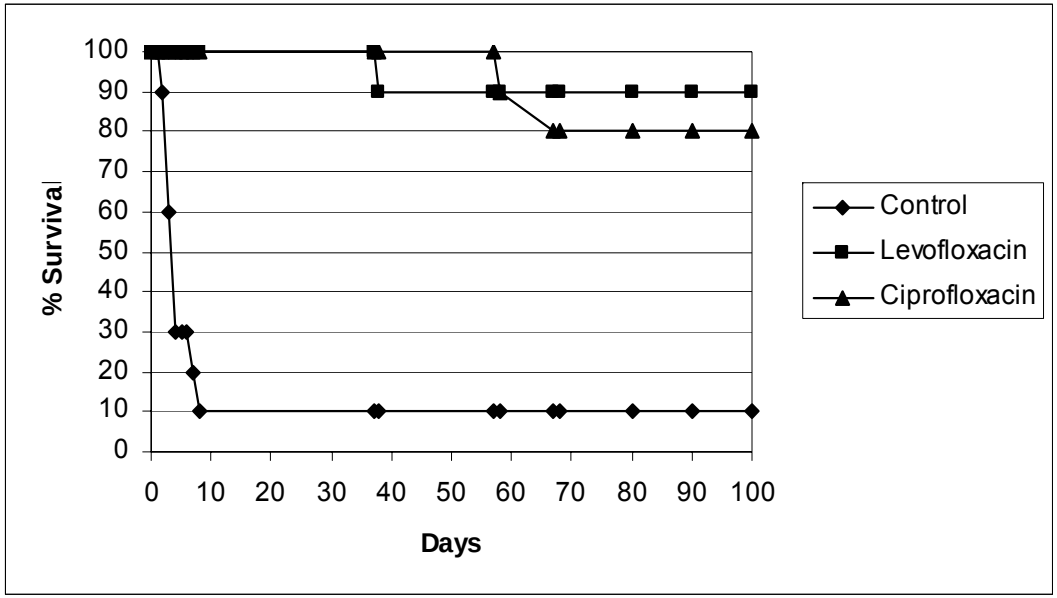


Anthrax Therapy



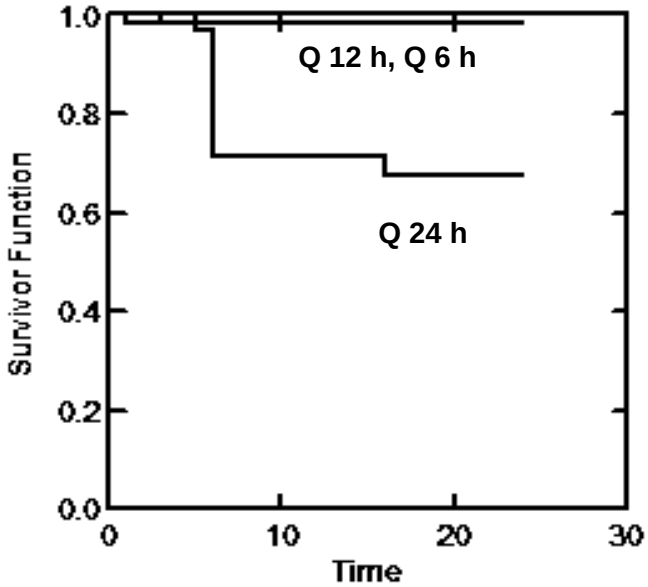
Anthrax Therapy

Rhesus Monkey Challenge



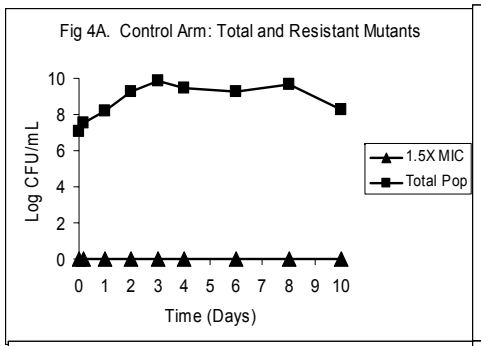
Kao, et al. AAC 2006;50:3535-3542

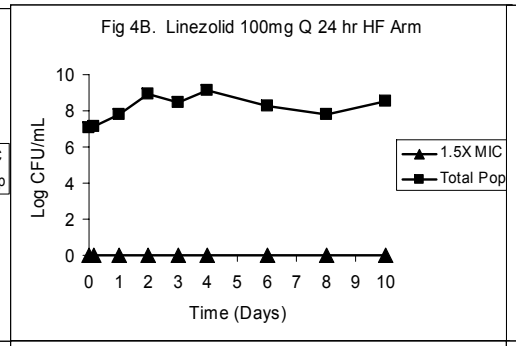
Mouse Challenge

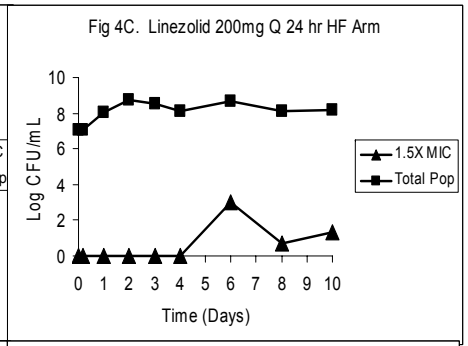


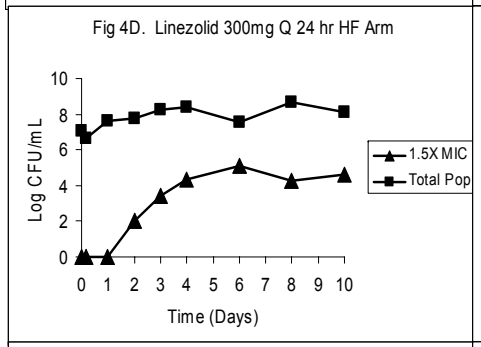
Deziel, MR et al. AAC 2005;49:5099-5106

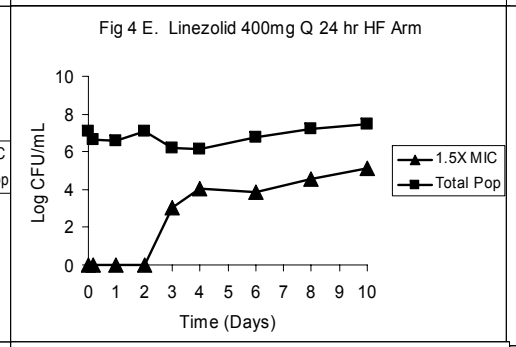
Anthrax Therapy

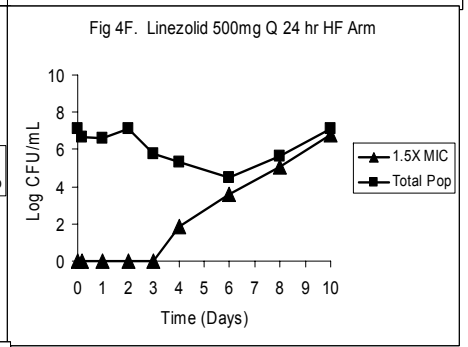


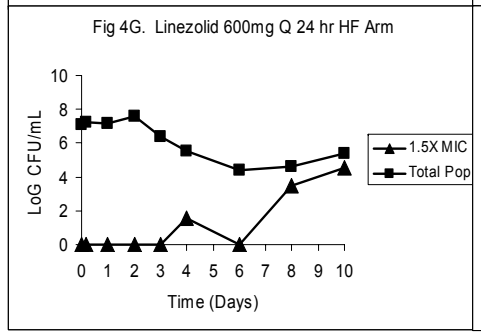


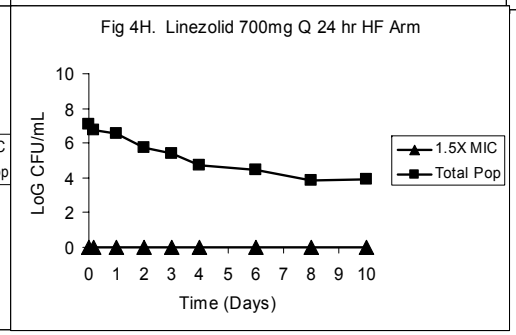




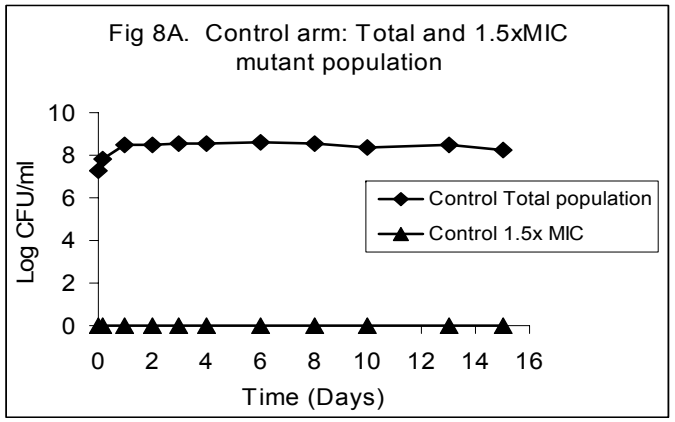


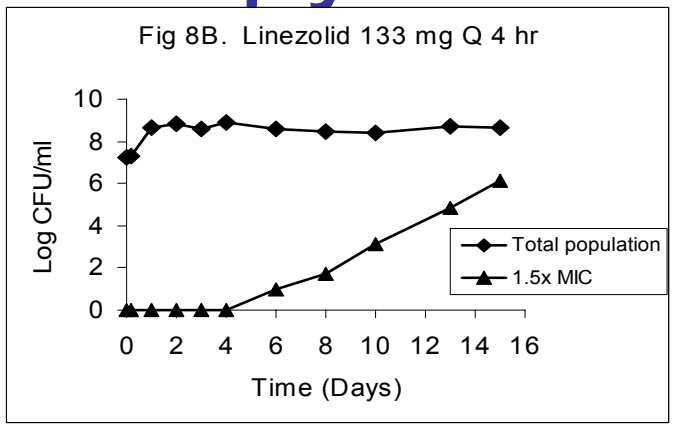


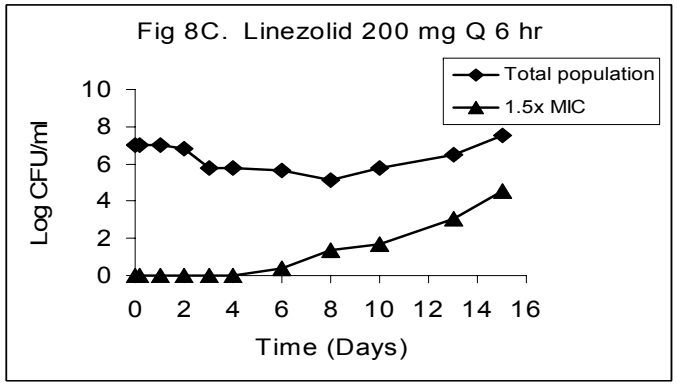


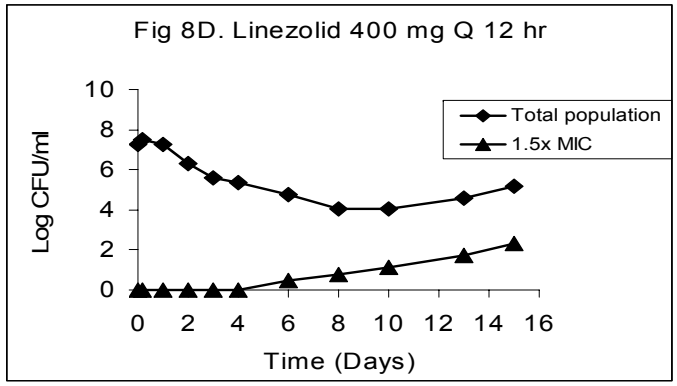


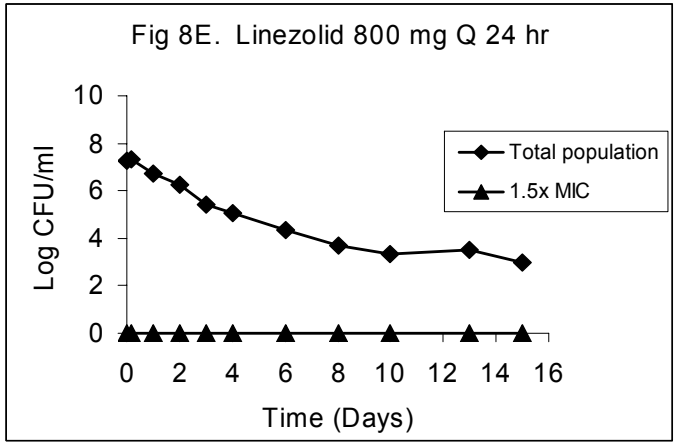
Anthrax Therapy







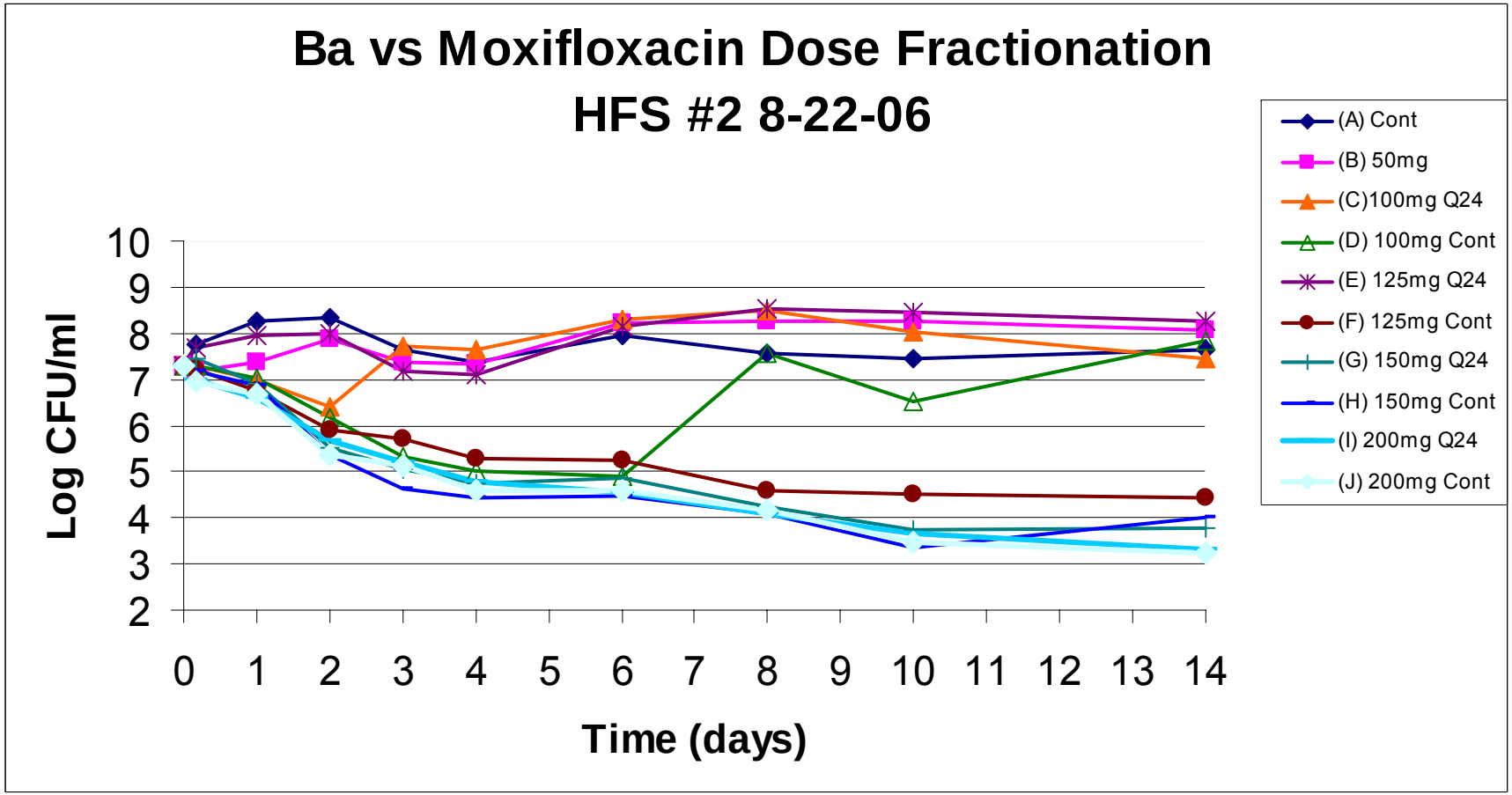




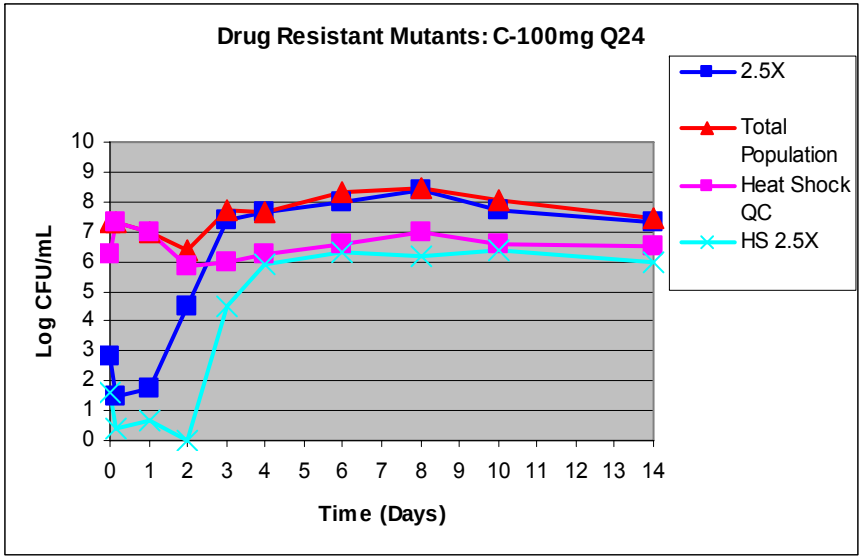
Anthrax Therapy

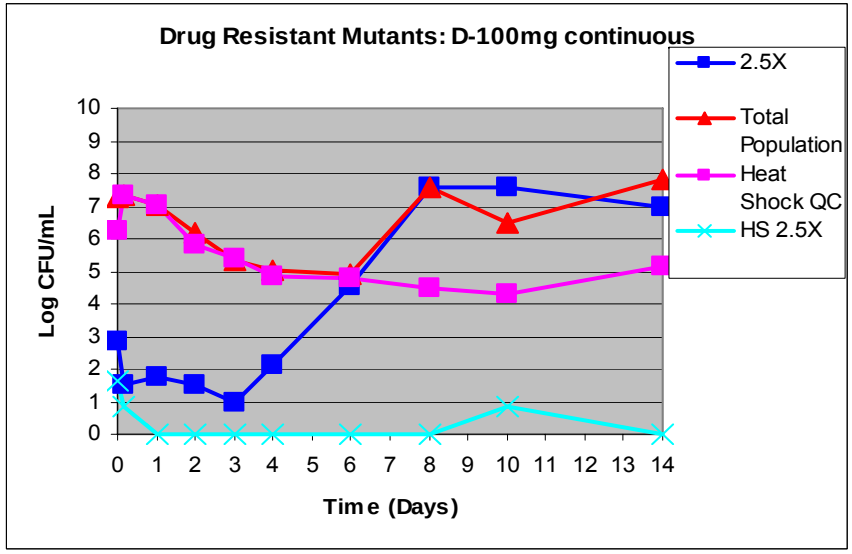
- So, for linezolid, once-daily dosing is actually better and suppression of resistance correlates best with Peak/MIC ratio
- Currently, we are examining linezolid's effect on toxin production in comparison to fluoroquinolones (In cipro we trust?)

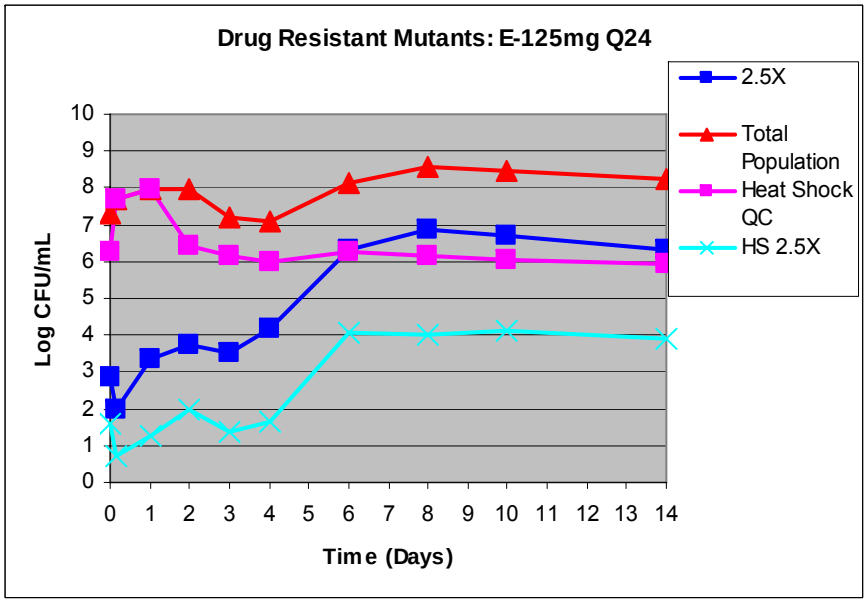
Anthrax Therapy

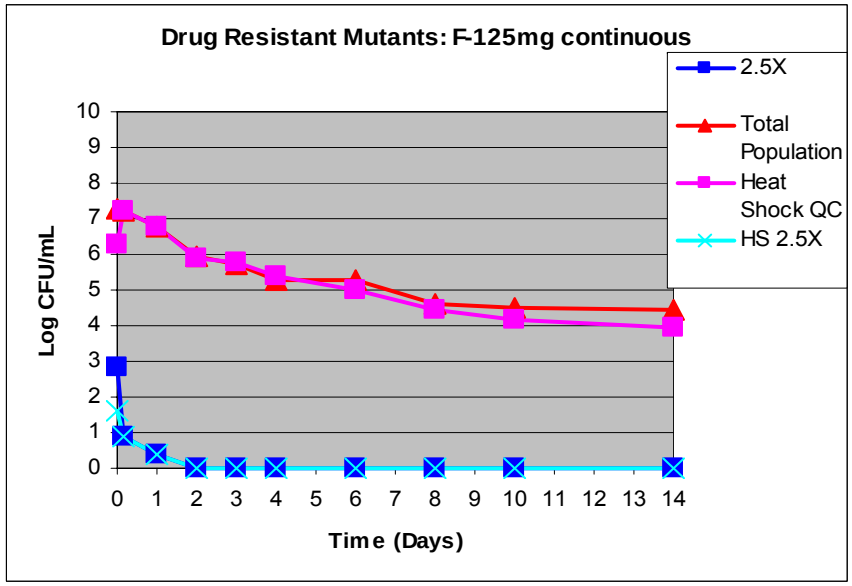


Anthrax Therapy

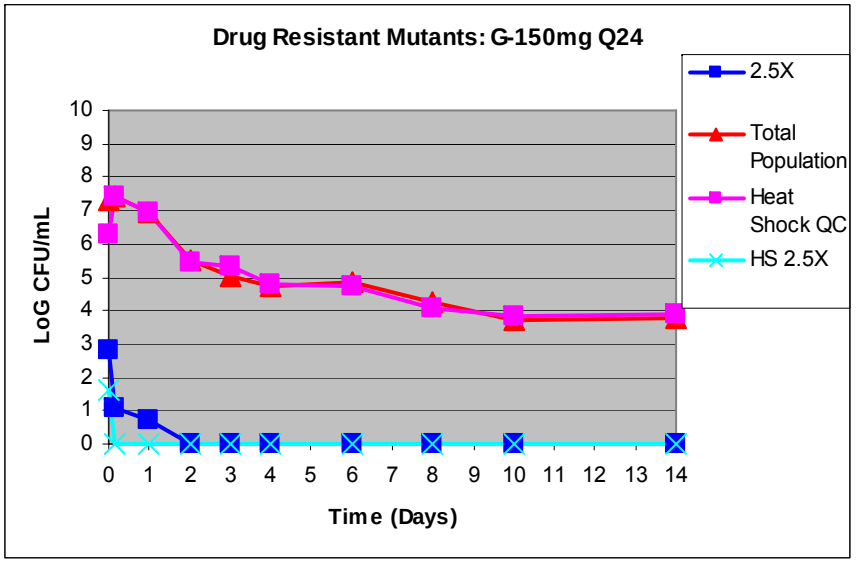


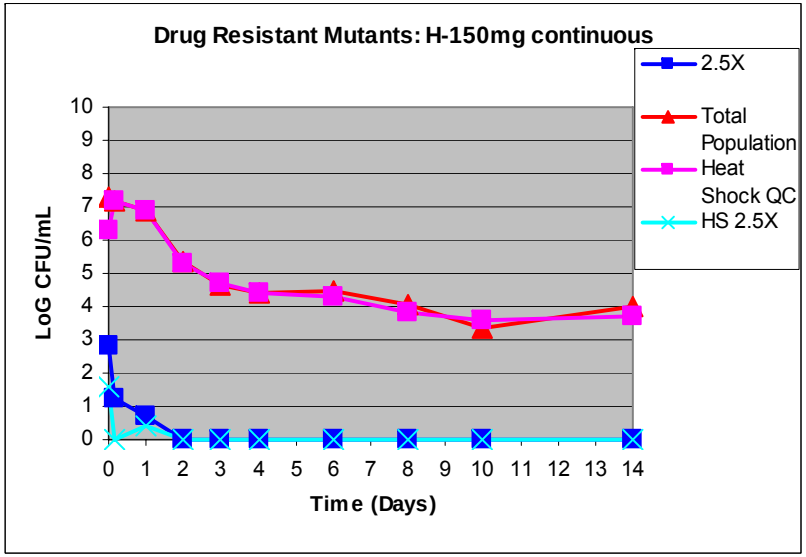


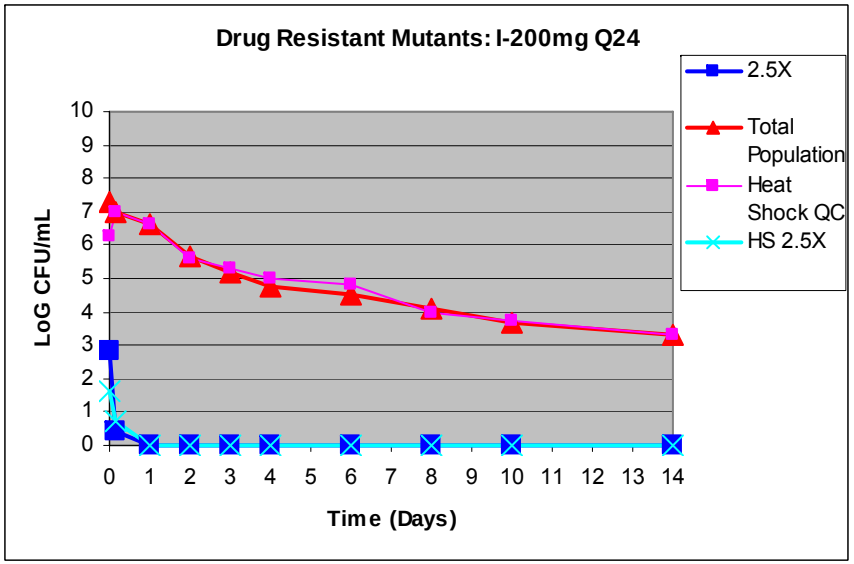


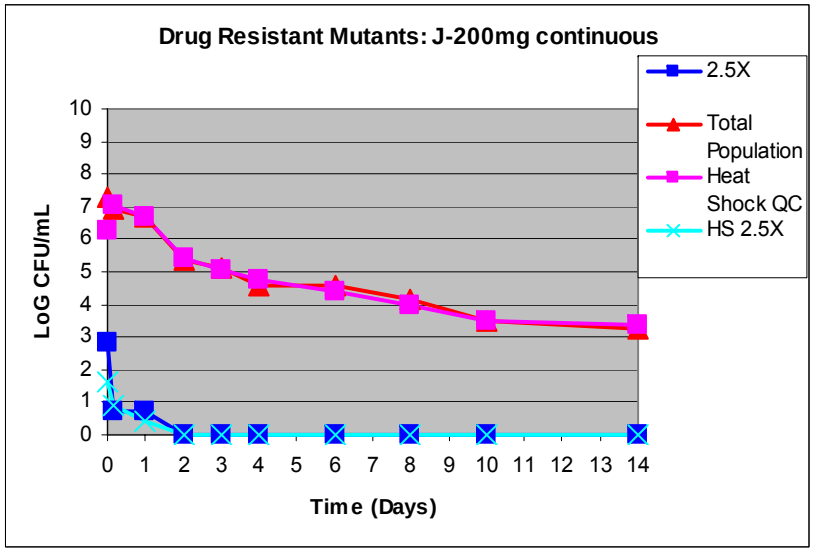


Anthrax Therapy





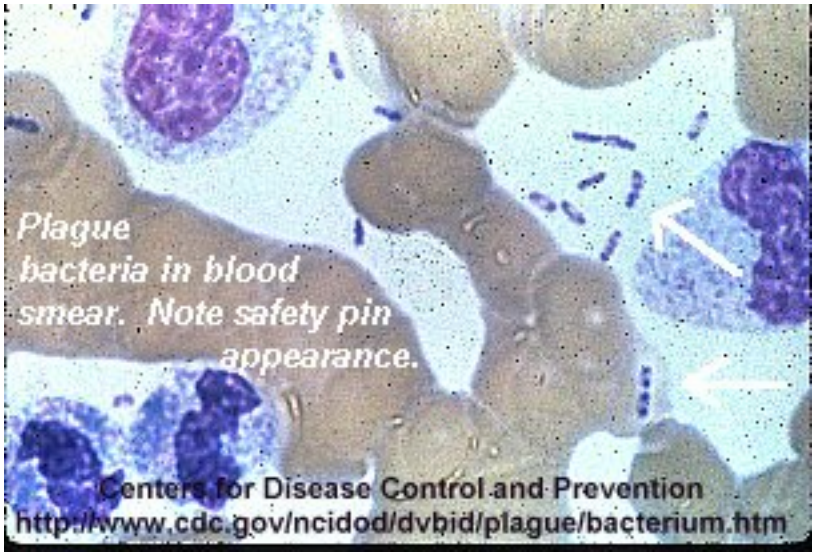




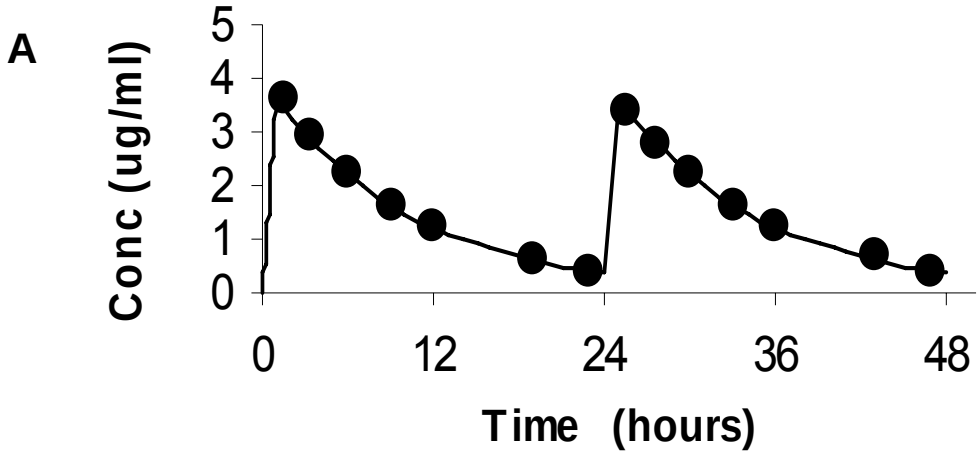
Anthrax Therapy

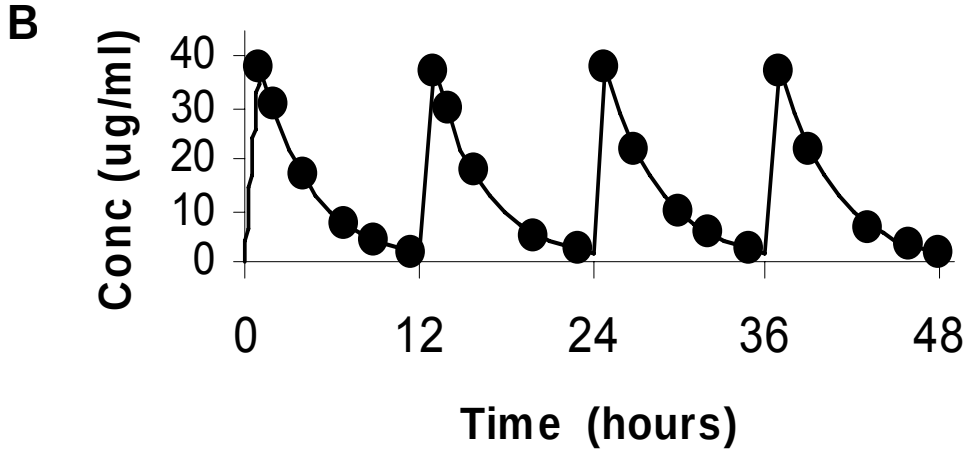
- Here, continuous infusion suppresses resistance best (very different from linezolid)
- There is considerable and very complex trafficking from vegetative phase to spore and back, with resistant organisms sometimes amplifying in spore phase

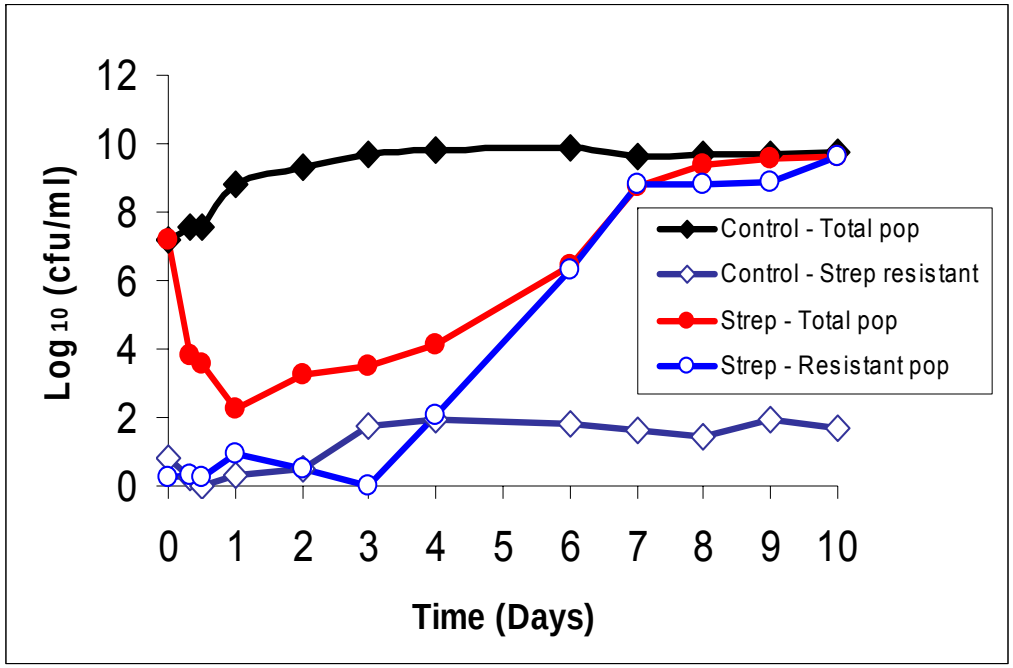
Plague

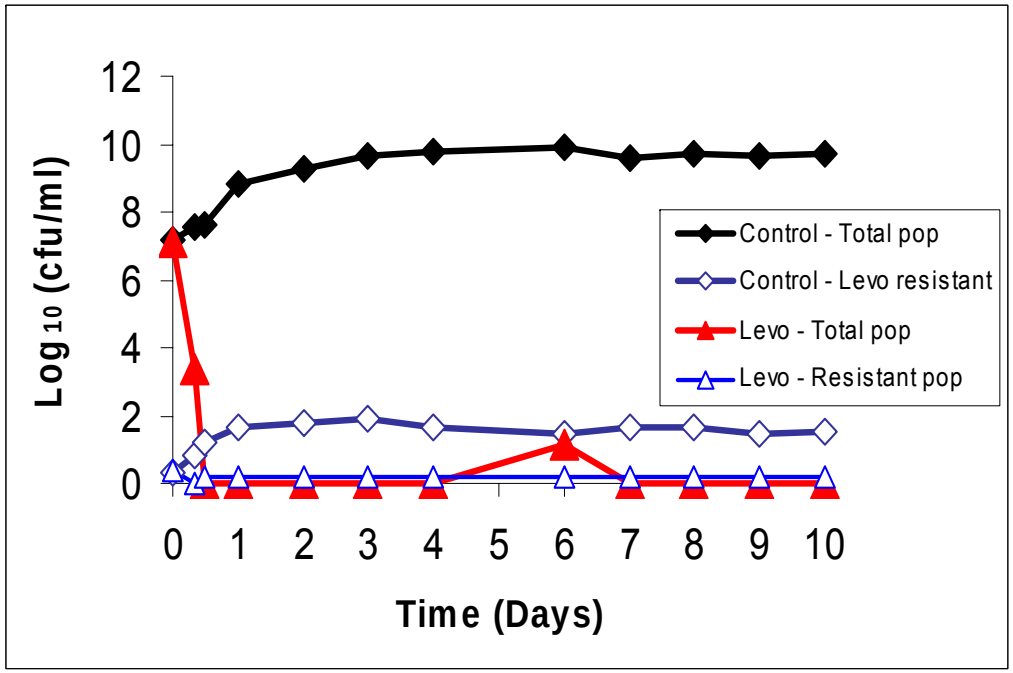

Plague
bacteria in blood
smear. Note safety pin
appearance.
Centers for Disease Control and Prevention
http://www.cdc.gov/ncidod/dvbid/plague/bacterium.htm

Plague Therapy

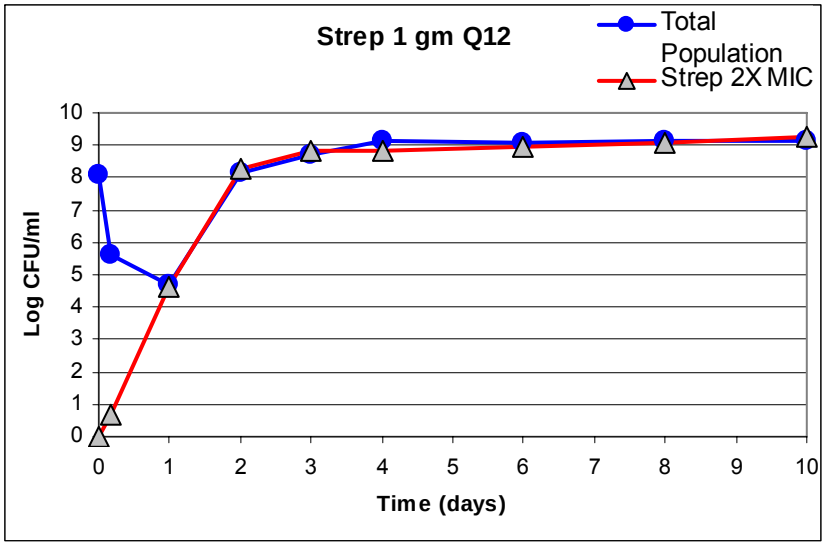


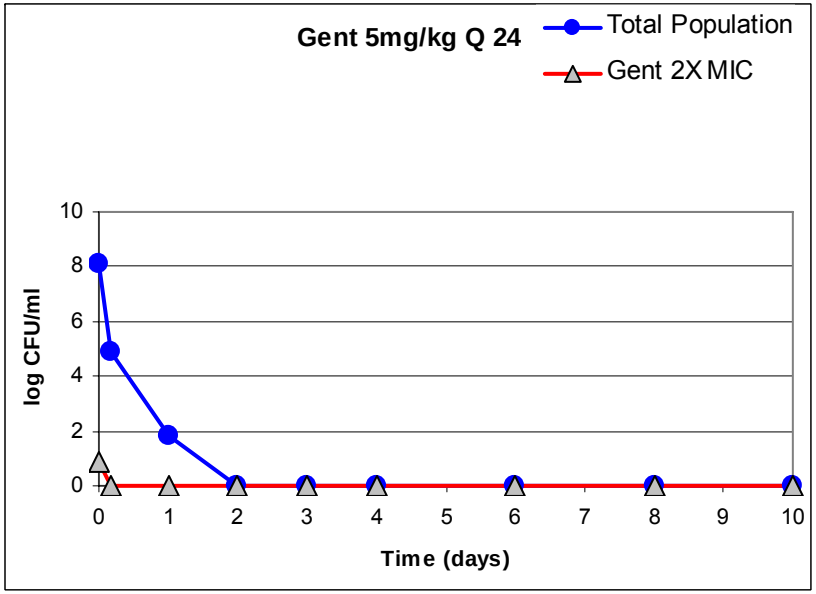



12
10
8
6
4
2
0
Log 10 (cfu/ml)
0 1 2 3 4 5 6 7 8 9 10
Time (Days)
Control - Total pop
Control - Strep resistant
Strep - Total pop
Strep - Resistant pop

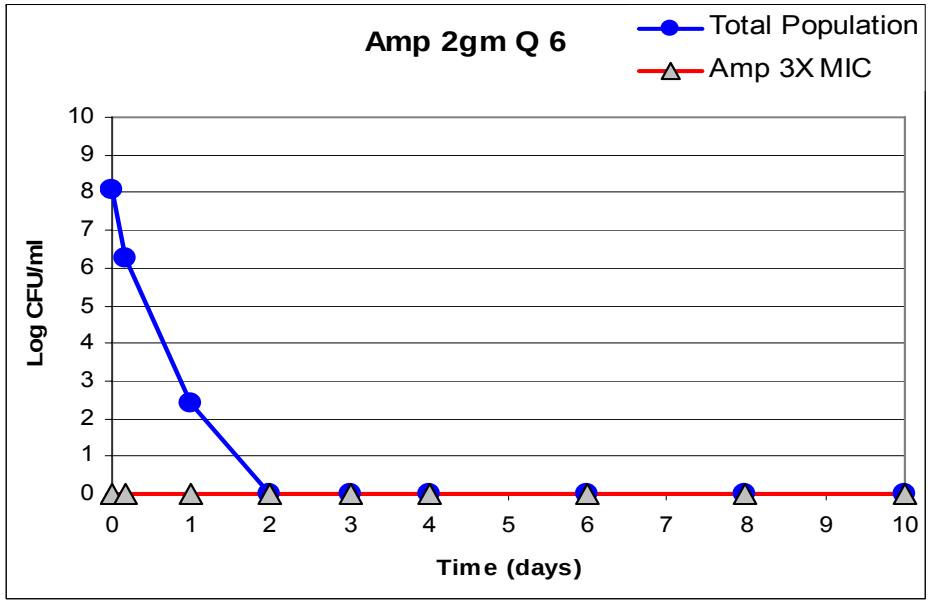

12
10
8
6
4
2
0
Log 10 (cfu/ml)
0 1 2 3 4 5 6 7 8 9 10
Time (Days)
Control - Total pop
Control - Levo resistant
Levo - Total pop
Levo - Resistant pop

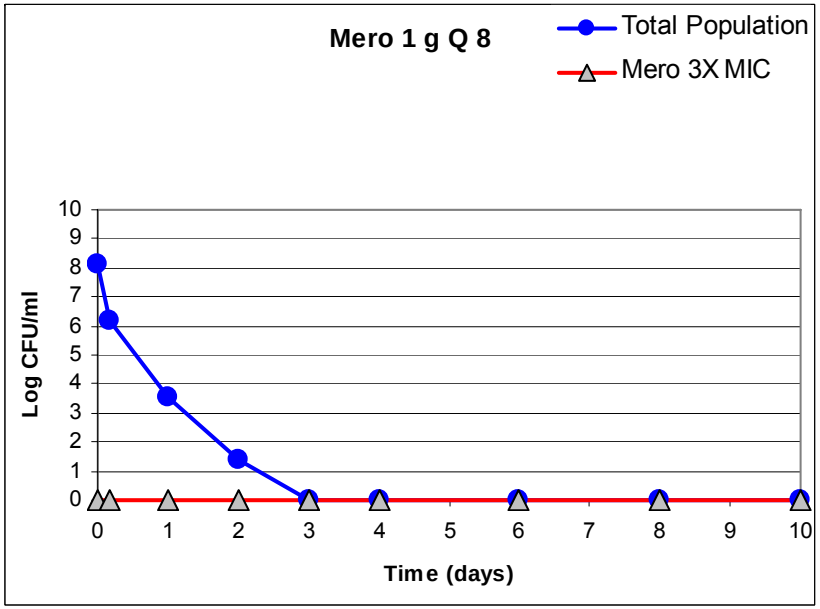
Plague Therapy

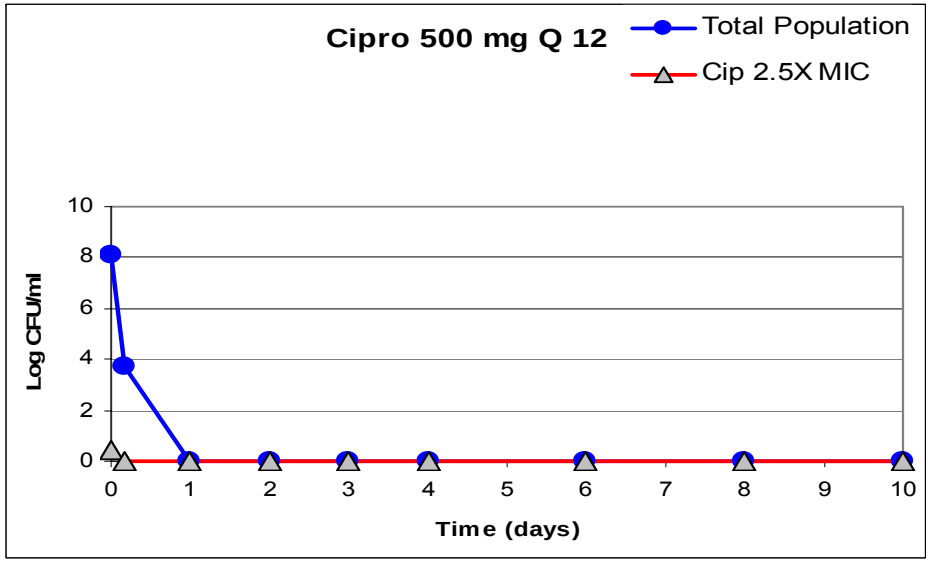


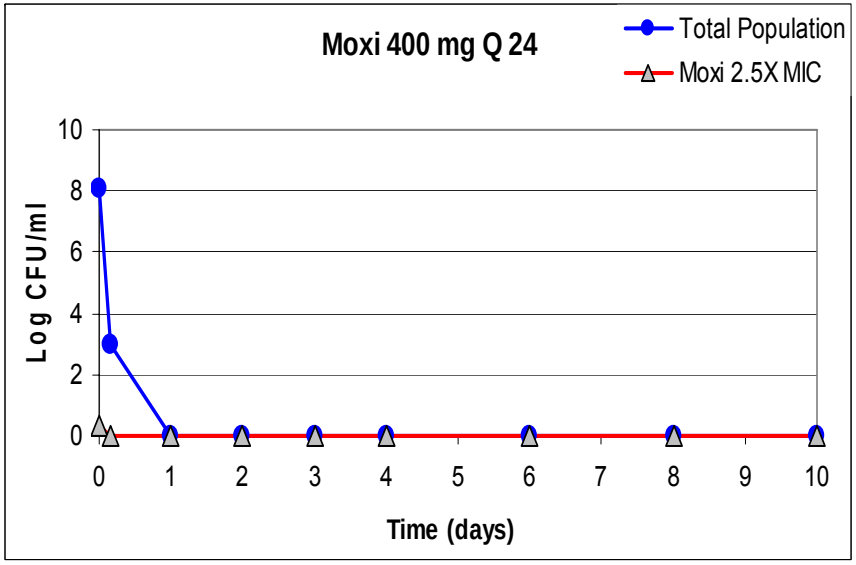


Plague Therapy









Plague Therapy

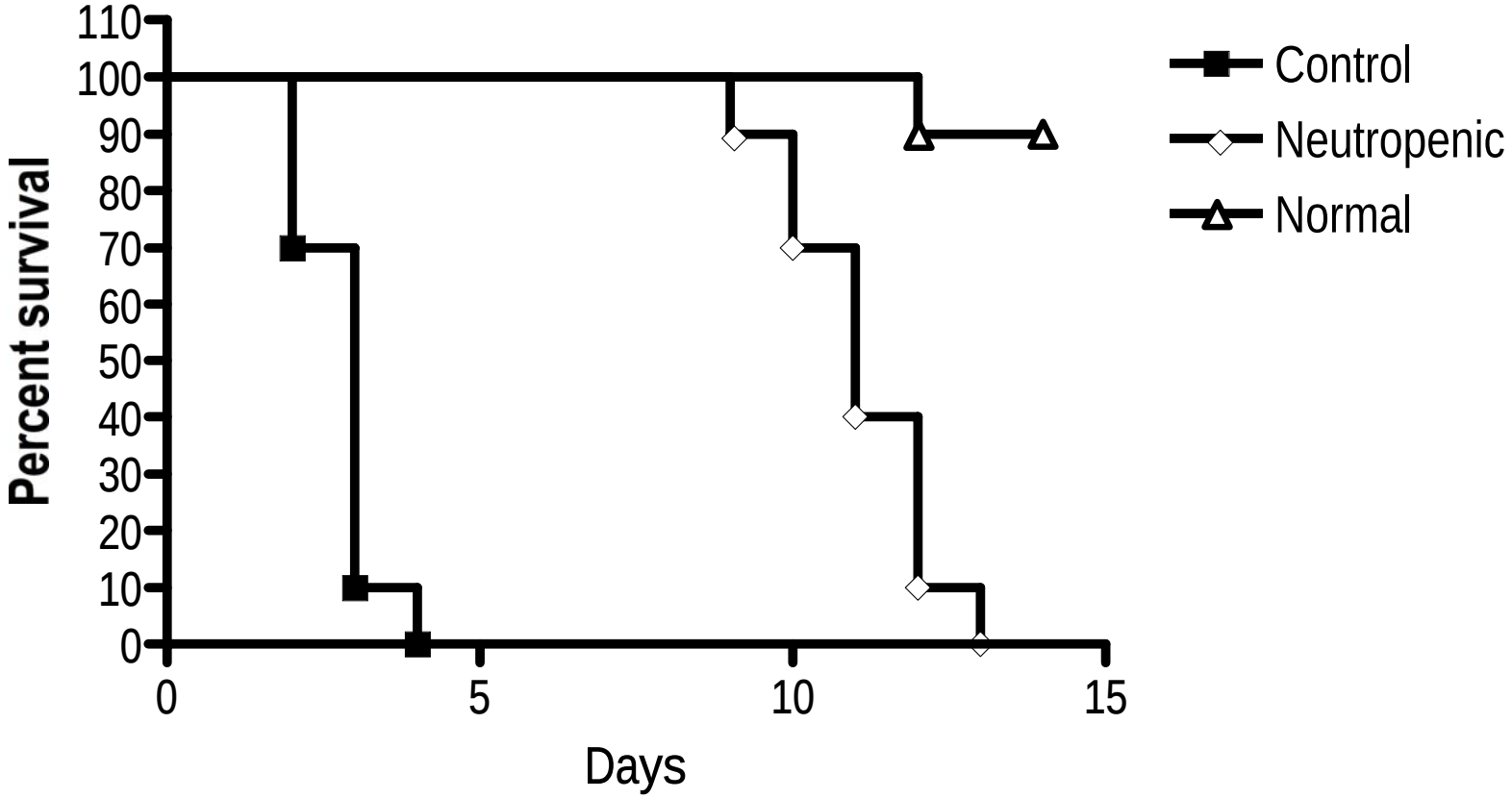
- Streptomycin caused significant kill, but emergence of resistance followed
- Seen with Dr. Louie's previous experiments
- Not seen with gentamicin
- Streptomycin-resistant mutants NOT cross-resistant to gentamicin
- This implies that the mutation was in the S12 protein
- Resistance CAN occur with gentamicin (respiratory transport chain mutation)

Plague Therapy

- Fluorquinolones look great
- So do β-lactams, but animal models have not borne this out in the past (see WR Byrne's paper in AAC)
- We will examine these issues in Dr. Heine's animal model
- Also, Program asked us to examine doxycycline and another protein synthesis inhibitor (gentamicin), which we did in the animal model

Plague Therapy

Survival Balb/c-Co92 Y.P. Challenge, Doxycycline Q6 40mg/kg



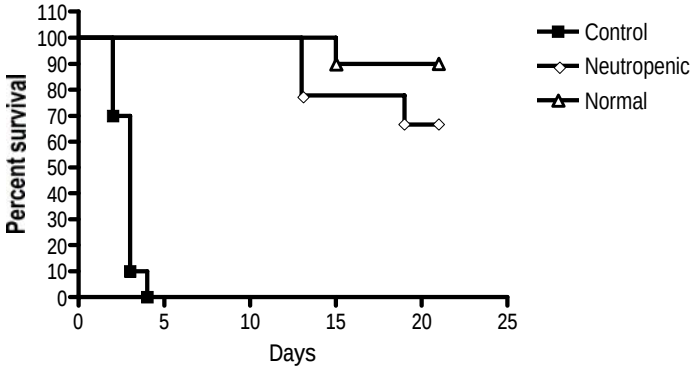
Statistically: Normal vs Neutropenic p = 0.000025

Control vs Neutropenic p = 0.000007

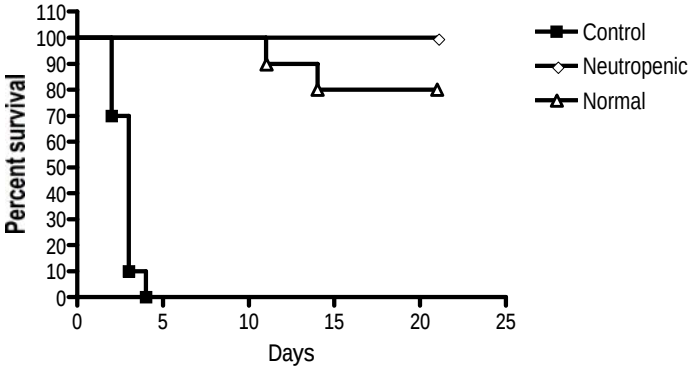
P values are NOT adjusted for multiple comparisons

Plague Therapy

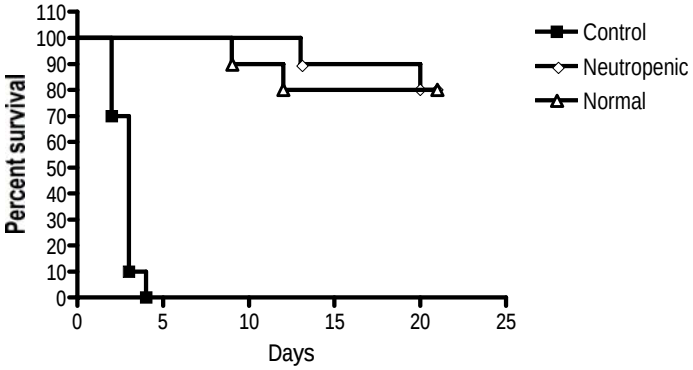
Survival Balb/c-Co92 Y.P. Challenge, Gentamicin Q6 12mg/kg



Survival Balb/c-Co92 Y.P. Challenge, Gentamicin Q12 24mg/kg

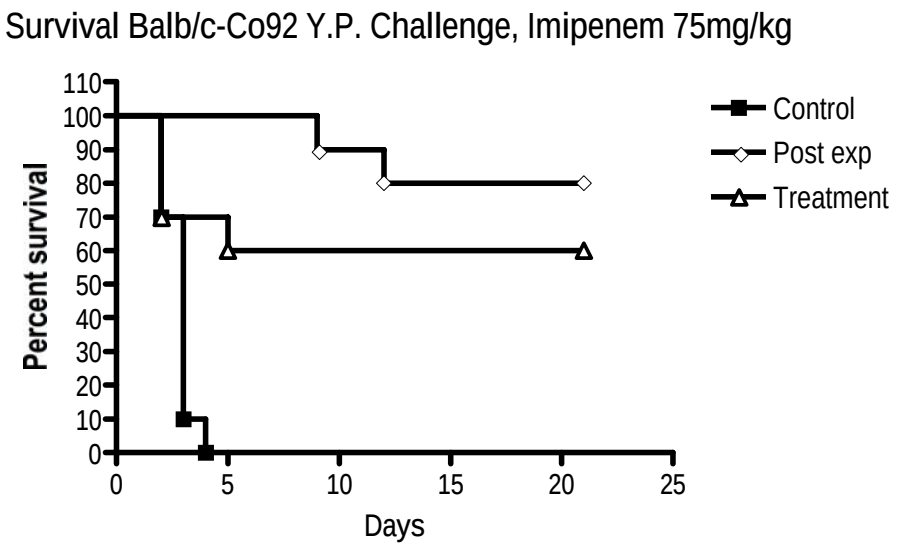


Survival Balb/c-Co92 Y.P. Challenge, Gentamicin QD 48mg/kg

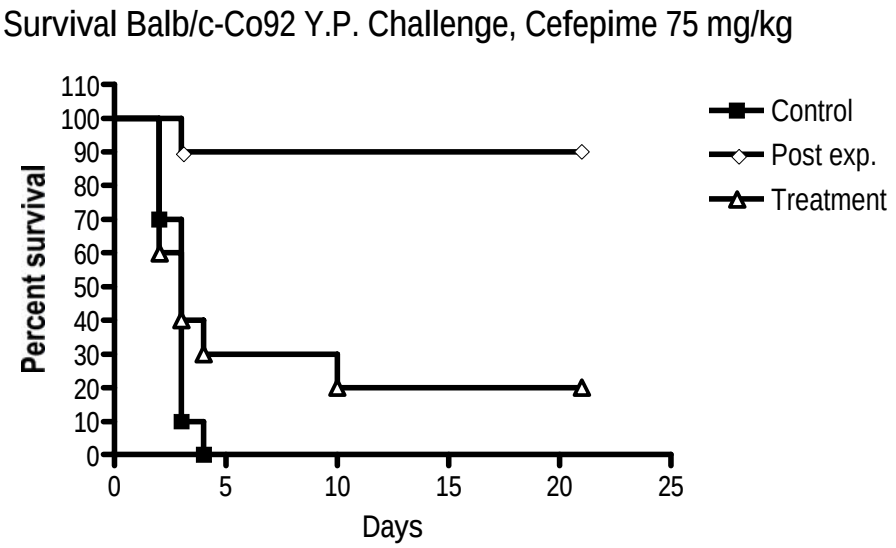


Statistically: Neutropenic vs Normal NS

Plague Therapy



Statistically: PEP vs Treatment = NS
Control vs Treatment = 0.008
P values are NOT adjusted for multiple comparisons



Statistically: PEP vs Treatment p = 0.0015
Control vs Treatment NS
P values are NOT adjusted for multiple comparisons

Plague Therapy

- Doxycycline requires an intact immune system
- Gentamicin does not
- Gentamicin effect is AUC/MIC driven as evidenced by being able to be given once daily, even with murine PK
- Gentamicin is better than streptomycin at suppressing resistance (may be a biofitness issue for S-12 protein versus electron transport chain enzyme mutation)
- B-lactams may have an issue with endotoxin release (carbapenems better)

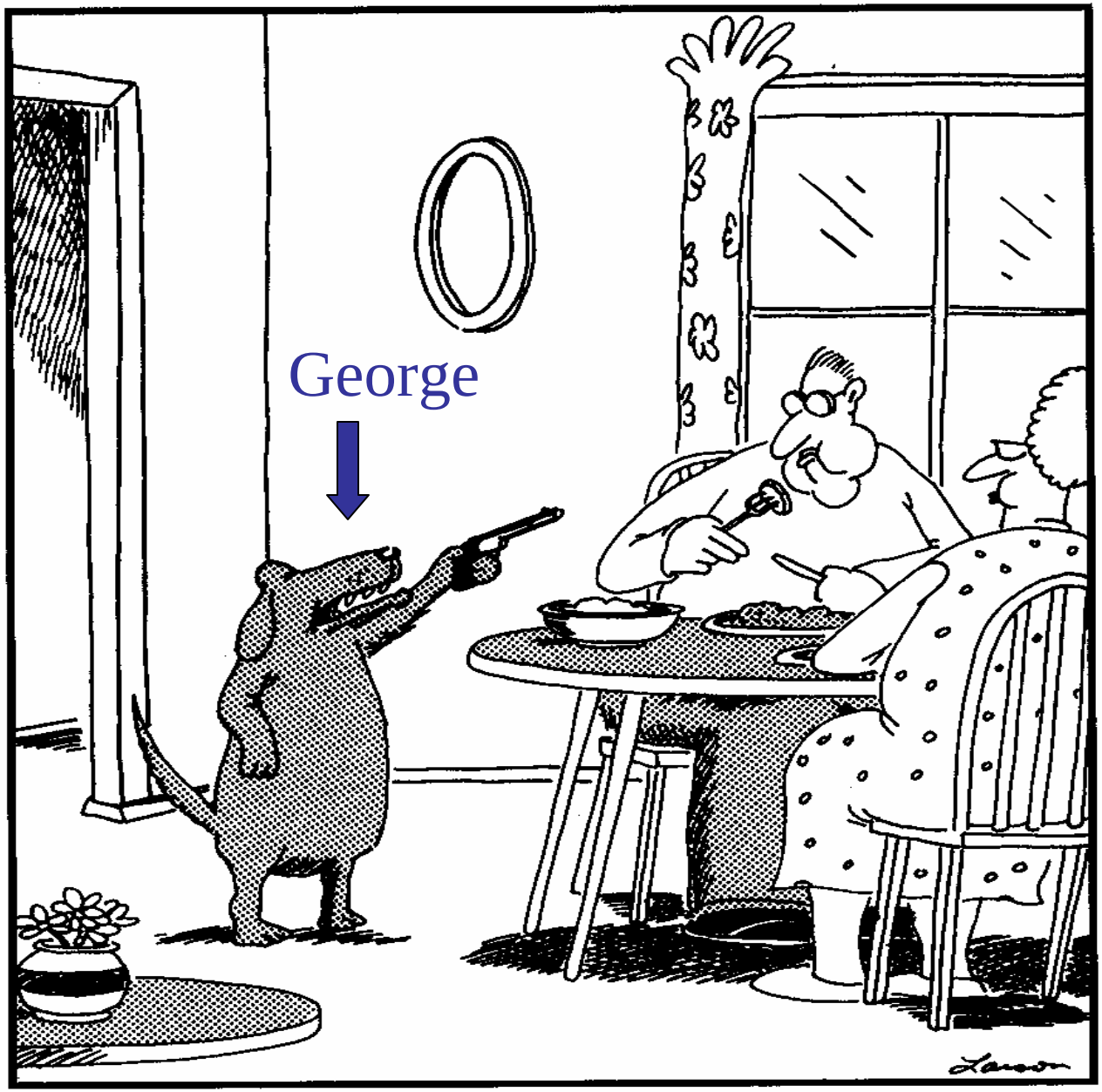
Anthrax and Plague Therapy

- So, the same sort of issues addressed with nosocomial pathogens can also be addressed for bioterror pathogens, both in the Hollow Fiber System and in animal models

Dose and Schedule Choices to Suppress Emergence of Resistance

I have been trying to interest the anti-infective community in antimicrobial pharmacodynamics for almost a quarter of a century, certainly without notable success.

WELL!



"Hey, bucko . . . I'm *through* begging."

Dose and Schedule Choices to Suppress Emergence of Resistance

Thank You for Your Attention!