Maintaining the Activity of Antibiotics in the Future

Jerome J. Schentag, Pharm D

Professor of Pharmacy

University at Buffalo

http://www.schentag-ce.com

Schentag@buffalo.edu

Antibiotic

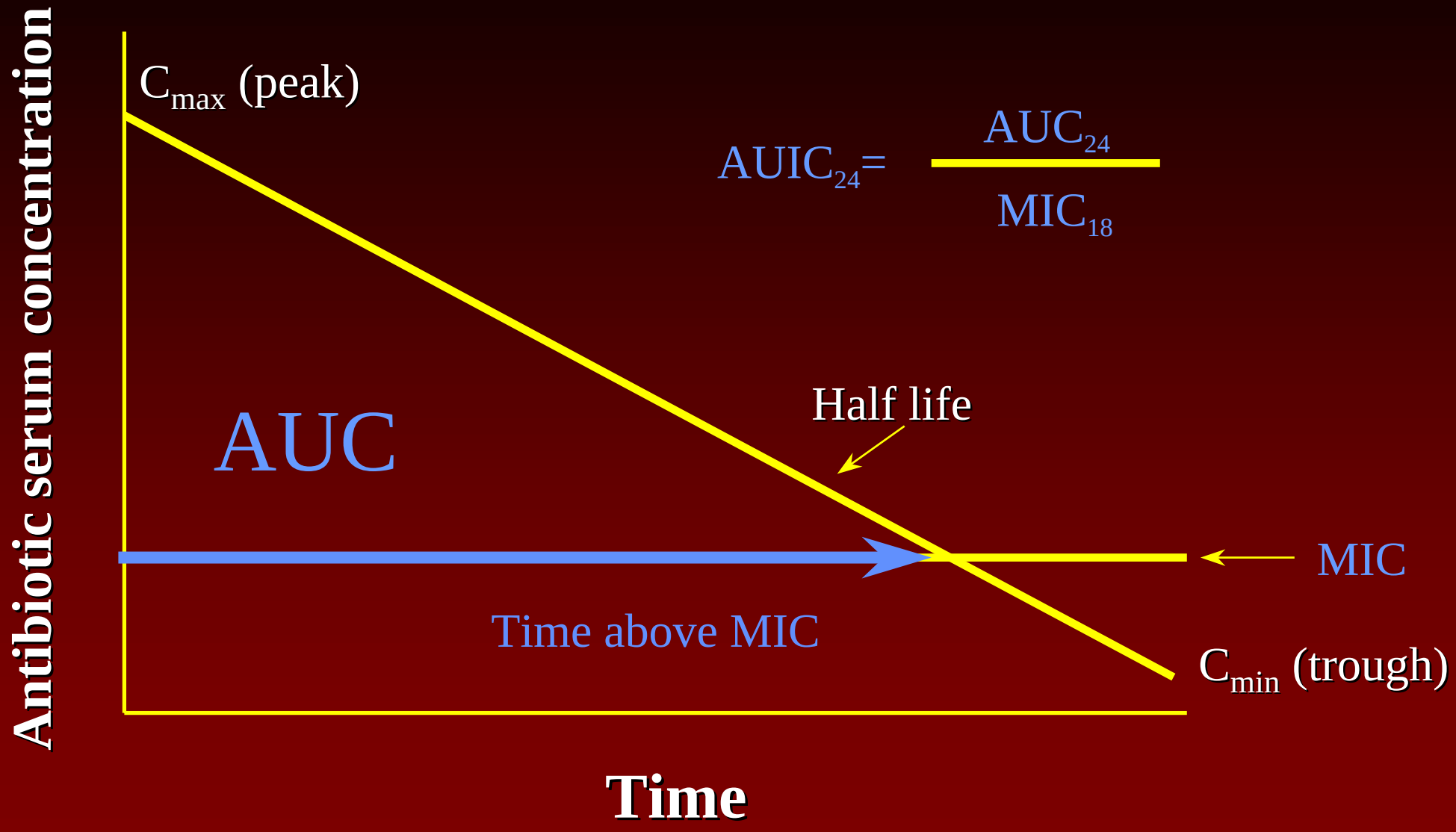
To understand what occurs inside the box, you have to do the math….

Infected Patient

Organism-MIC

Bacterial Eradication

Clinical Cure

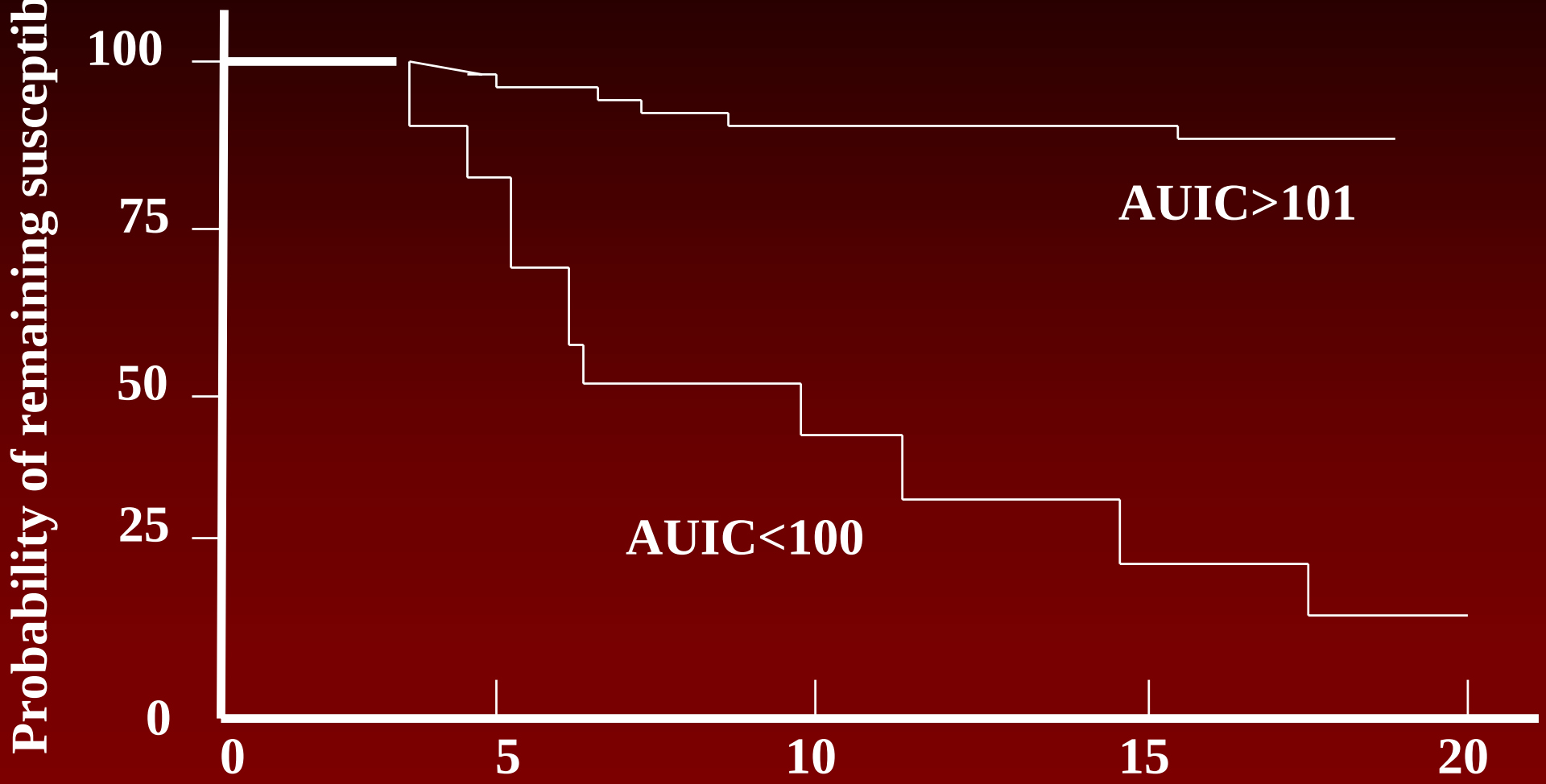

Antibiotic serum concentration
C_{max} (peak)
$AUIC_{24} = \frac{AUC_{24}}{MIC_{18}}$
AUC
Half life
MIC
Time above MIC
C_{min} (trough)
Time

Optimal PK and PD attributes in Humans

- **For optimal antimicrobial effect:**
  - **- C_{max} / MIC ratio should be >8 to 10**
  - **- AUC / MIC ratio should be > 125**
- **To minimize resistance development:**
  - **- AUC / MIC ratio should be >100**

AUIC vs Resistance

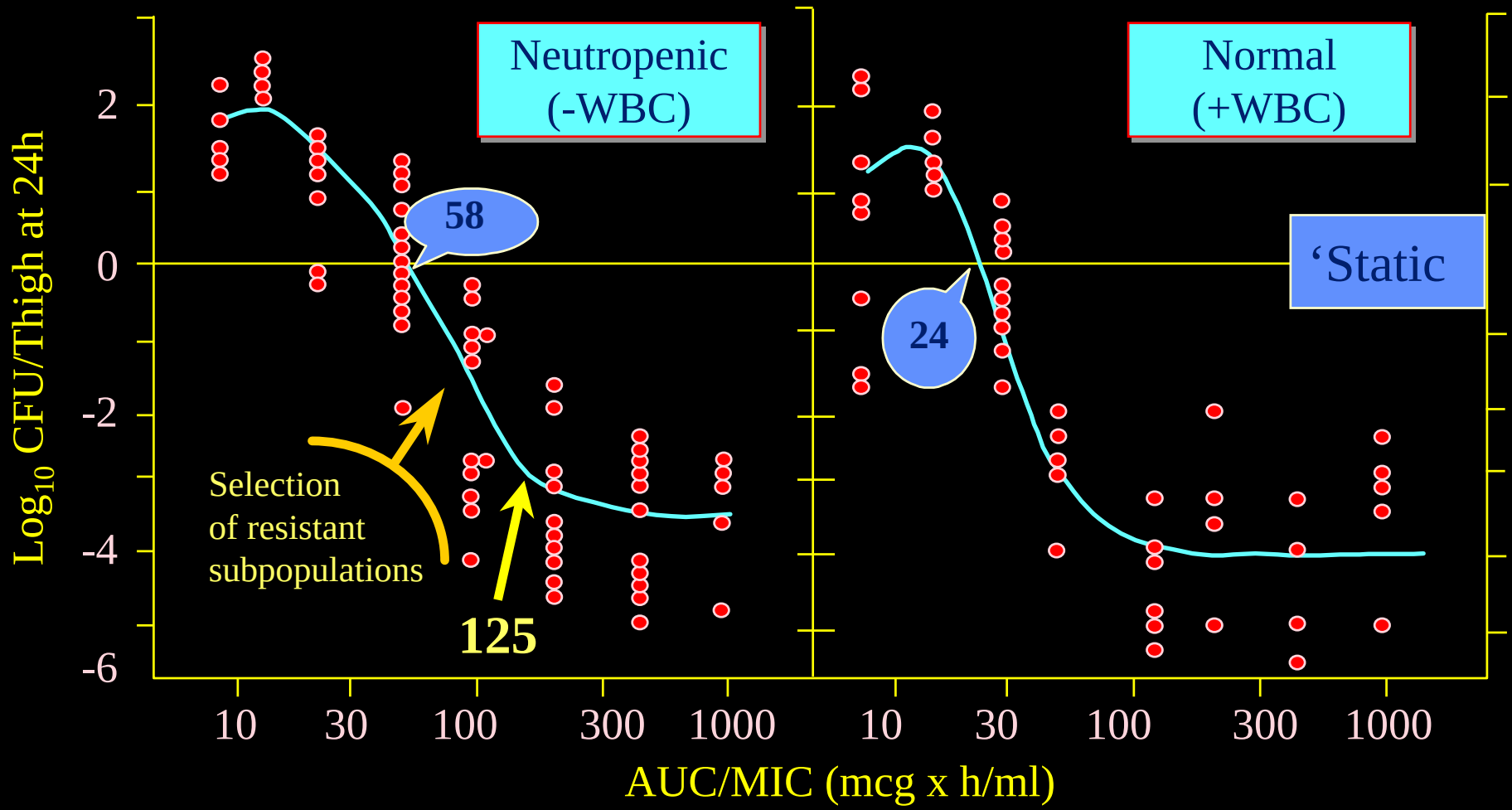
Thomas JK, Antimicrobial Agents Chemother. 42: 521-527, 1998.



Pharmacodynamic Predictors of Outcome in Gram-Positive Infections

- Less human data available compared to gram-negative infections
- Both Peak/MIC and AUC/MIC have been found to correlate with outcome
  - Animal infection models
  - *In vitro* infection models
  - Limited human data
- Optimal Peak/MIC 10-12.2 *(Preston et al. JAMA 1998;279: 125-129., Blaser et al.)*
- Partially protective AUC/MIC between 25-50; Optimal AUC/MIC for 100% cure ~ 100 *(Craig W.A.)*

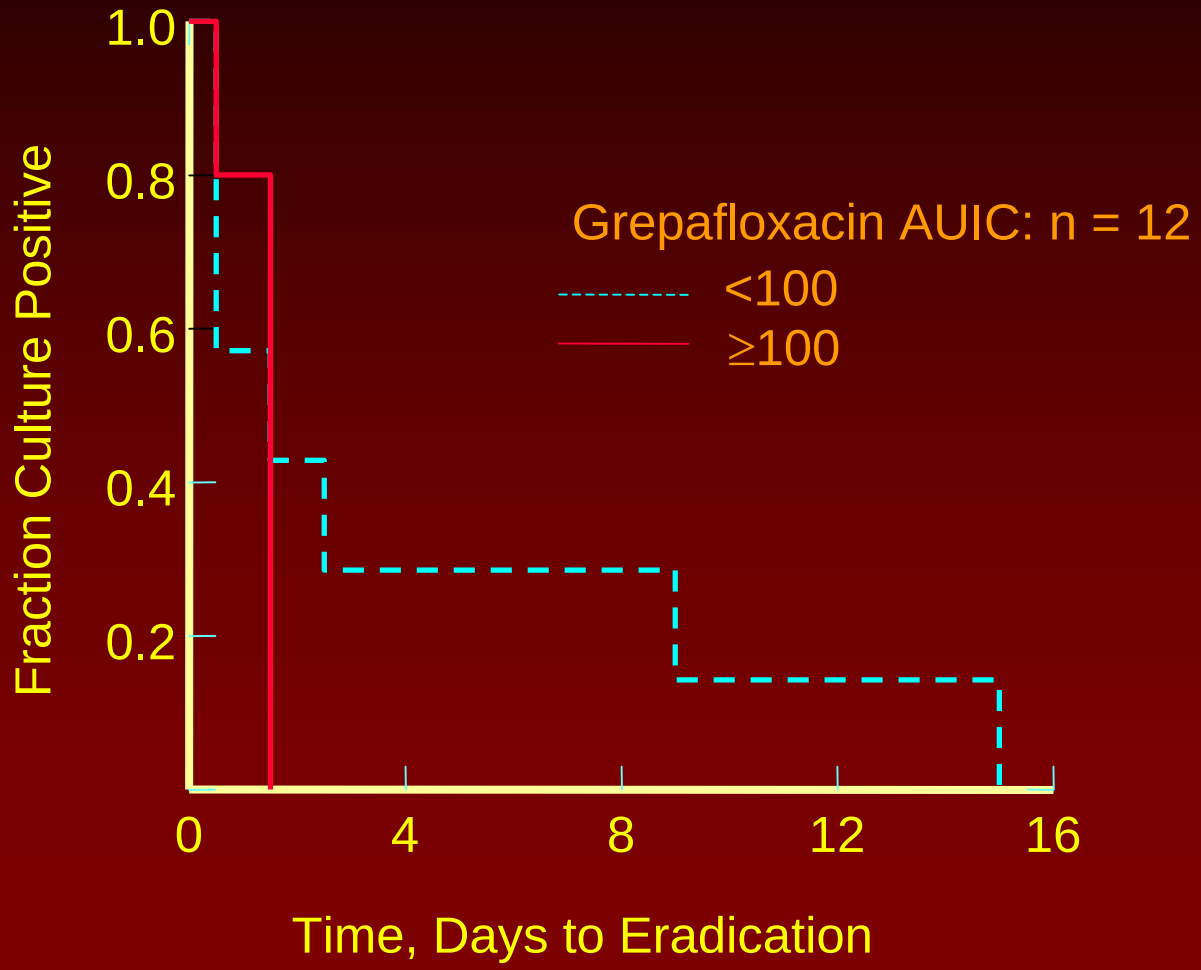
Relationship Between 24-h AUC/MIC Ratio and the Number of *S.pneumoniae* (7 strains) in the Thighs of Neutropenic and Normal Mice after 24-h Therapy with Levofloxacin



Vesga O and Craig W. ICAAC 1996

S. Pneumoniae - Grepafloxacin

Data source: Forrest et al JAC 40(supplA) 45-57, 1997



Schentag, Meagher, Forrest. Ann Pharmacotherapy 37: 1478-1488, 2003

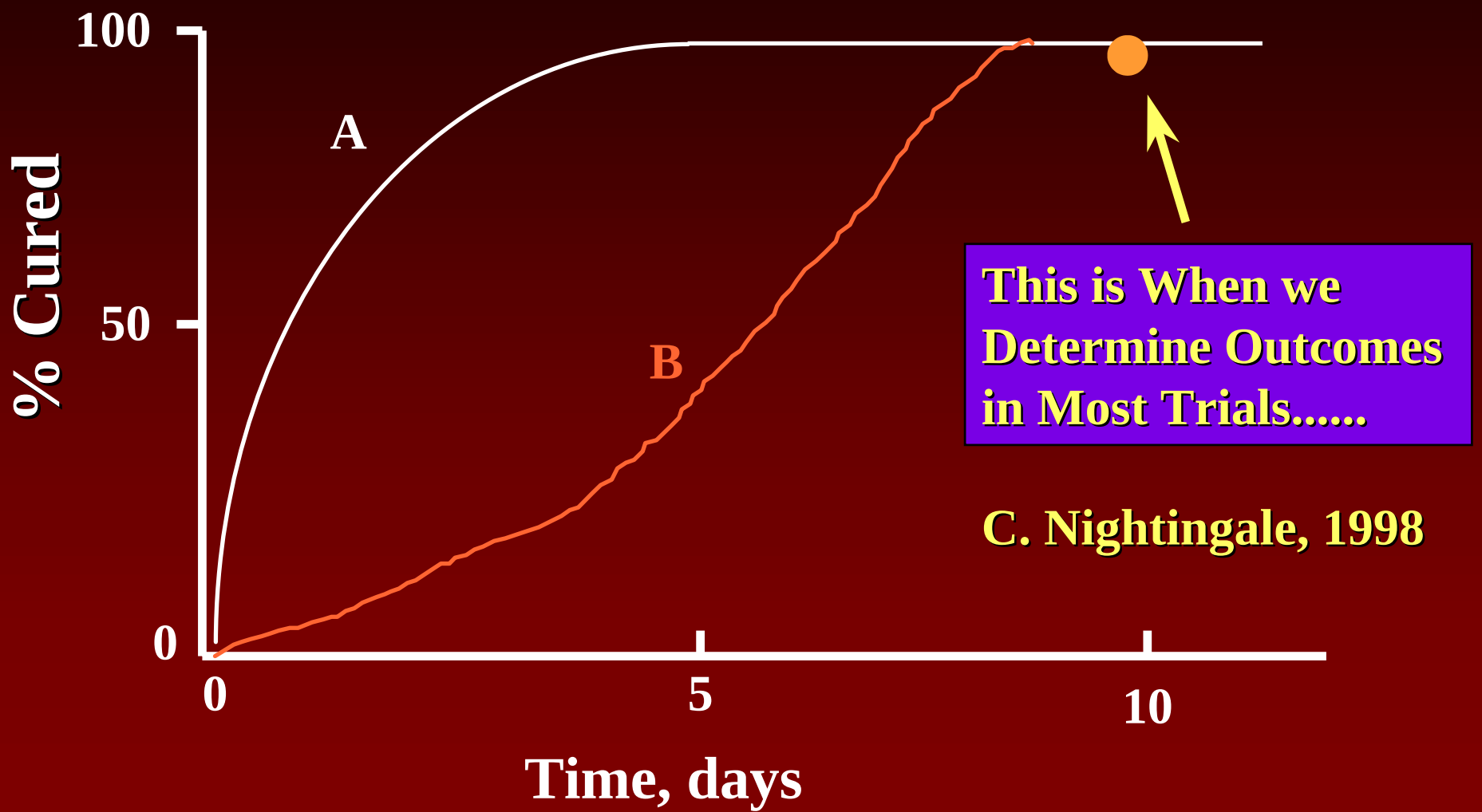
One AUIC value for All?

- Target value < 10, no measurable impact on whole bacterial populations (or sub-populations)
- Target value 25-50 selection pressure is highest at bacterio-static exposure in absence of WBCs
- Target value of 125 for efficacy
- Target value of 100 for resistance protection
- Target value of 250 for rapid concentration dependent killing

Why do these human data differ from those of animal models or in vitro?

- Serial cultures usually reveal a higher target AUIC than endpoint-presumed eradication (*S.pn* Example)
  - (100 for Grepa *vs.* 33 for Ambrose with Gati-Levo)
- Working with eradication (in patients) vs. microbial suppression (in animals or in vitro)
  - 'cidal targets in humans vs 'static targets in animals
- More difficult to kill bacteria in patients, requires a higher AUIC target? (actually, no proof of this..)
- Longer term endpoints than 24hrs in humans, as compared to 24hrs only in vitro or in animals

Clinical Trials are Designed to Assure Equivalence....



Consequences of Low Overall FQ activity vs Spn

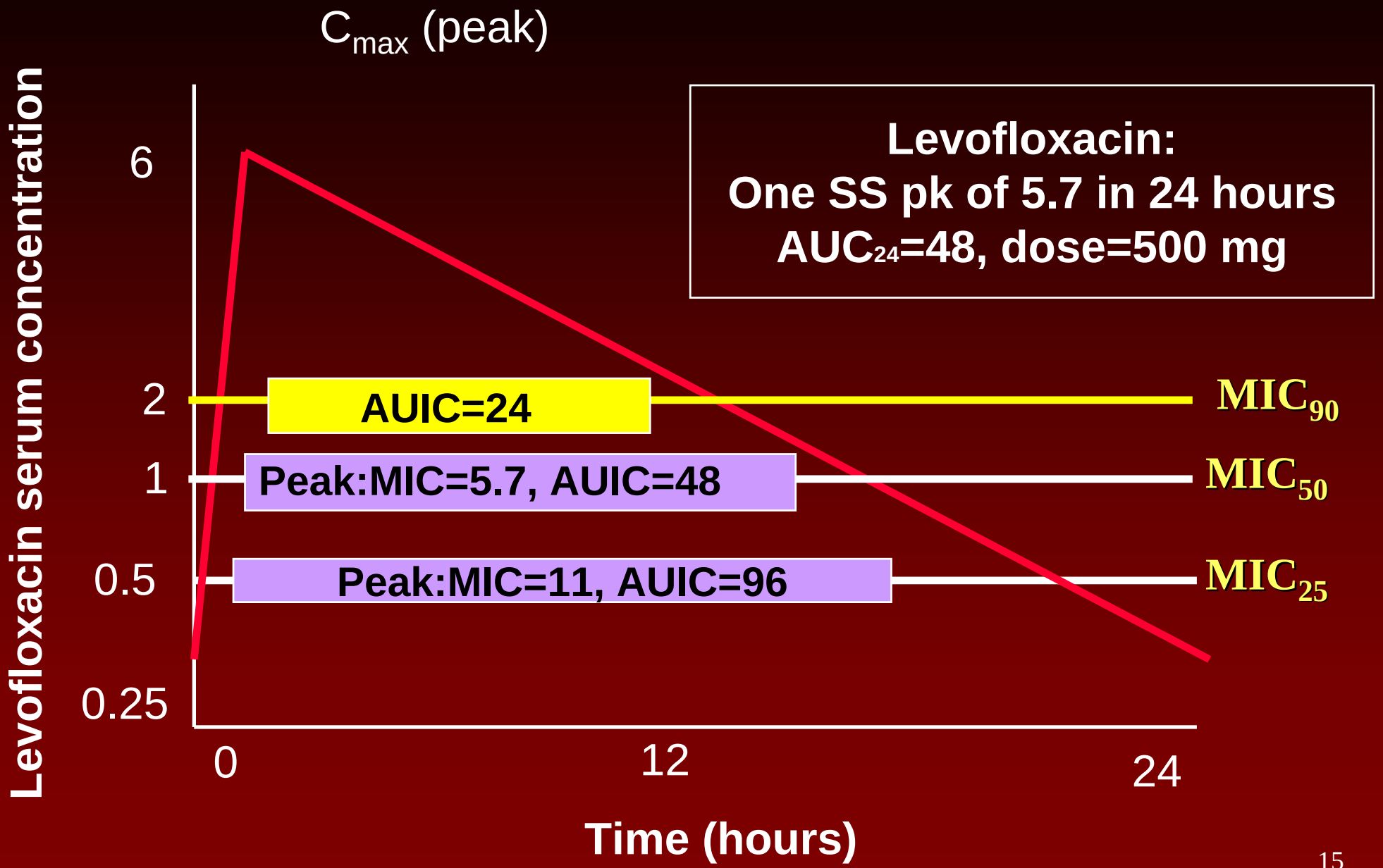
- Organism sub-populations are selected rather than eradicated
- Very slow decline in the numbers of organisms (i.e. bacteriostatic actions)
- Host defense must be intact to resolve the infection
- Residual colonization even in cured patients

Antibiotic Use And Resistance

- Antibiotics Select Resistant Organism Sub-populations, by Eradicating the Susceptible Majority Within Strains
- Resistant Sub-populations Proliferate while the Patient is treated, as They have a survival advantage when the antibiotic is present
- Selection is Linked to MPCs & AUICs

Emergence of *S. pneumoniae* resistance to fluoroquinolones

- **FQ resistance was not expected to cross react with resistance to Penicillins or Macrolides; recent studies in Canada show co-resistance in *S. pneumoniae* in spite of the different resistance mechanism.**
- **The True Scope of the selection problem is masked by high "breakpoints" for resistance. After Steady rises, MICs are now approaching the laboratory threshold values of 2-4 mcg/ml.**
  - **Because many of the older FQs produce low AUICs at this MIC value, the selected resistance that results from low AUICs has great potential to spread within communities.**
- **Selection of FQ resistance in *S. pneumoniae* may be linked to low AUIC FQs in the community...?**


C_{max} (peak)
Levofloxacin:
One SS pk of 5.7 in 24 hours
AUC_{24}=48, dose=500 mg
Levofloxacin serum concentration
6
2
1
0.5
0.25
AUIC=24
Peak:MIC=5.7, AUIC=48
Peak:MIC=11, AUIC=96
MIC_{90}
MIC_{50}
MIC_{25}
0
12
24
Time (hours)

AUIC 30-50

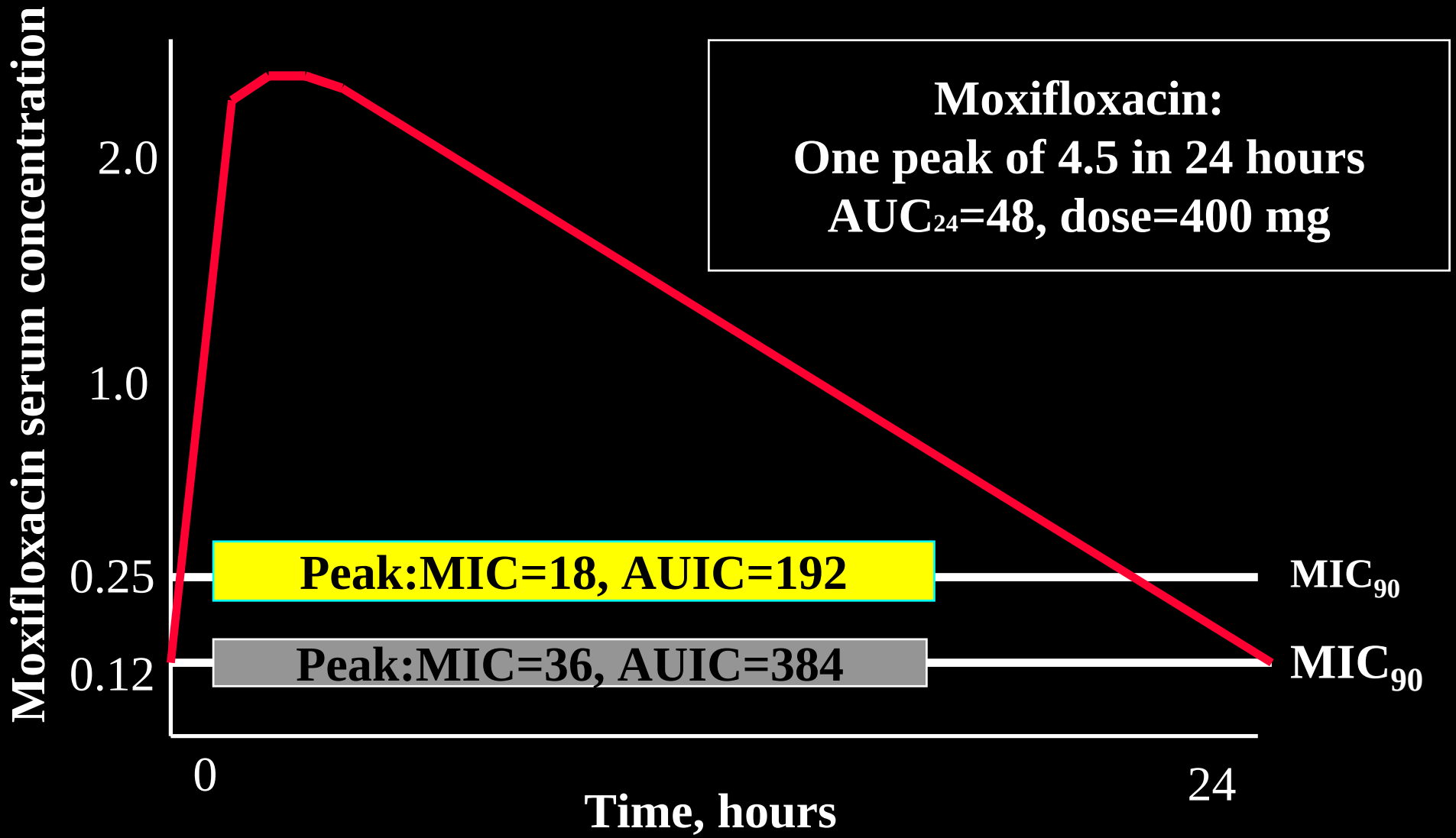
- **AUIC 30-50:**
  - Little to no killing in 7 days
  - Inoculum reduction, with reliance on host defense
  - Selection of resistant sub-populations, capable of surviving unless host defense can remove them.
  - Colonization of site with residual organisms

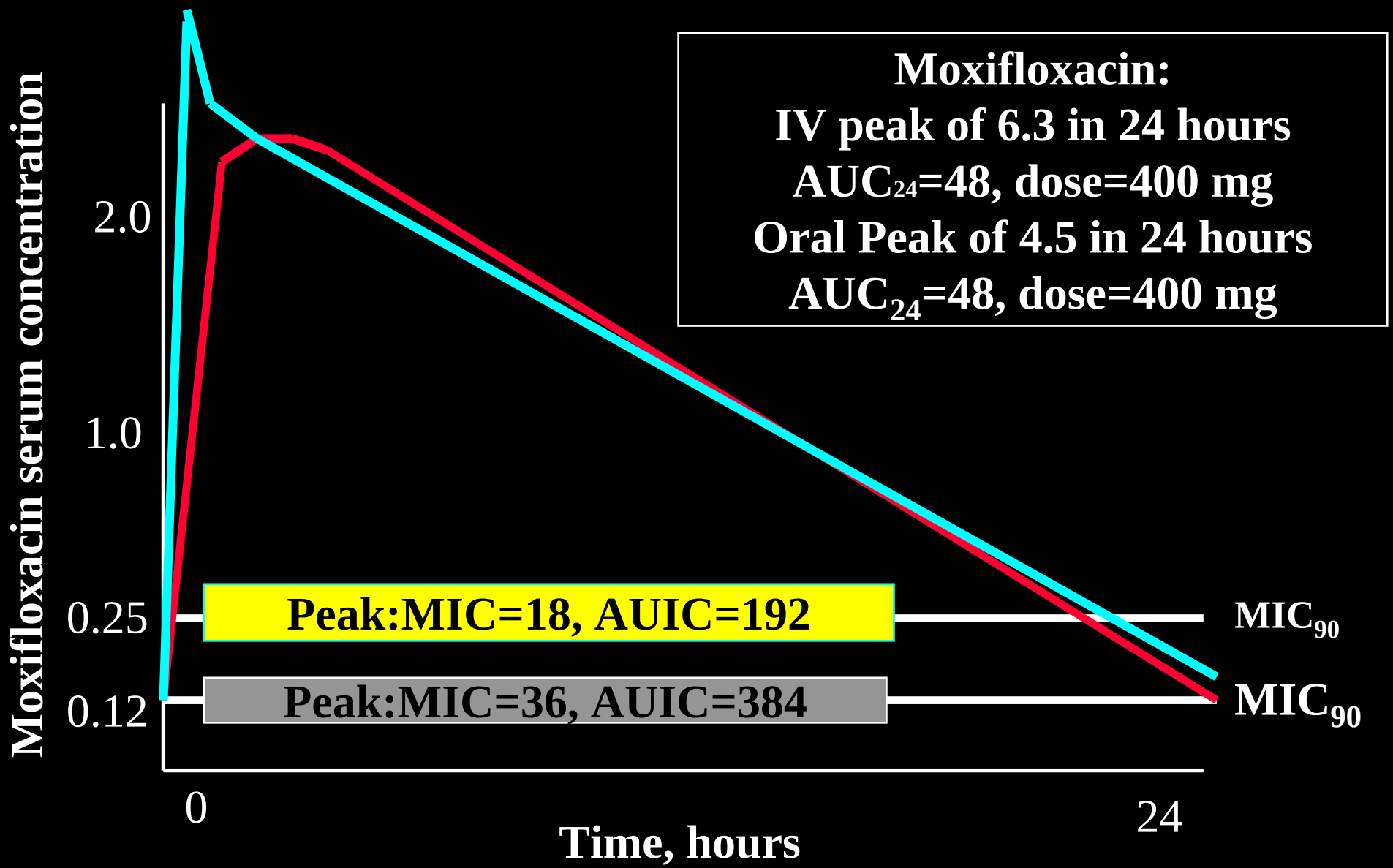
PK/PD vs FQ resistance

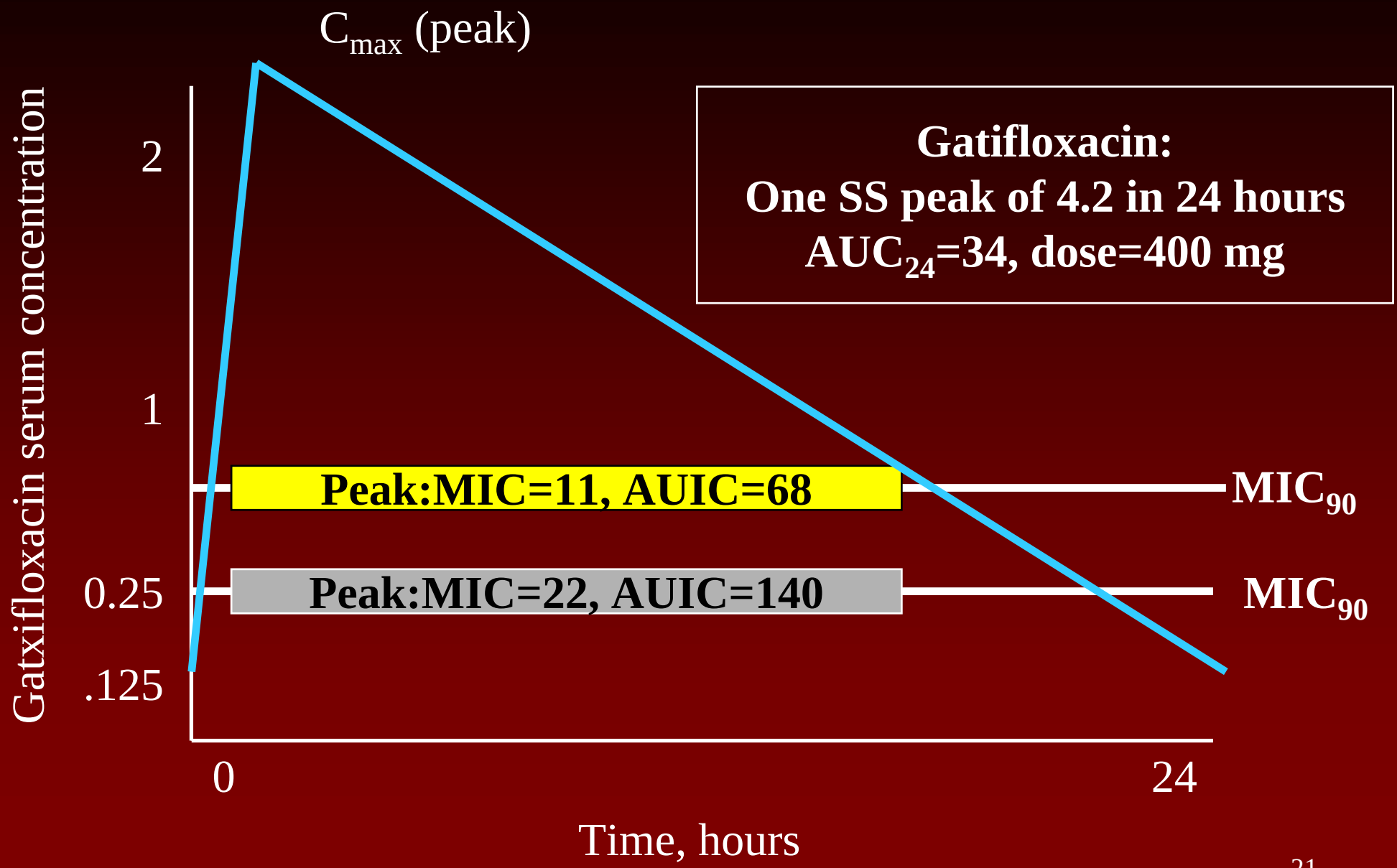
- **Low doses in relation to MIC (Low AUIC) are a potential problem in the development of *S. pneumoniae* resistance to the Weaker Quinolones**
- **Resistance to one, will cross over to all**
- **Increasing the dose (i.e. AUC) can solve the problem of Levofloxacin high MICs; Doses need to be increased to 500 bid to tid, if organism MICs are approaching 1.0-2.0 mcg/ml**
- **Might be better to use a more active FQ…**

AUIC > 250 vs AUIC 30-50

- **AUIC > 250:**
  - **One day Killing of S. pneumoniae (in vitro ~ 1hr killing)**
  - **killing of one step mutants, probably slower..**
  - **Faster (?) relief of S & S of infection**
  - **Shorter courses of therapy are possible, since 4-5 days after killing = Stop Treatment**


Moxifloxacin serum concentration
2.0
1.0
0.25
0.12
0
24
Time, hours
Moxifloxacin:
One peak of 4.5 in 24 hours
AUC24=48, dose=400 mg
Peak:MIC=18, AUIC=192
Peak:MIC=36, AUIC=384
MIC90
MIC90


Moxifloxacin:
IV peak of 6.3 in 24 hours
AUC24=48, dose=400 mg
Oral Peak of 4.5 in 24 hours
AUC24=48, dose=400 mg
Moxifloxacin serum concentration
2.0
1.0
0.25
0.12
Peak:MIC=18, AUIC=192
Peak:MIC=36, AUIC=384
MIC90
MIC90
0
24
Time, hours


C_{max} (peak)
Gatifloxacin:
One SS peak of 4.2 in 24 hours
AUC_{24}=34, dose=400 mg
Gatxifloxacin serum concentration
2
1
0.25
.125
Peak:MIC=11, AUIC=68
Peak:MIC=22, AUIC=140
MIC_{90}
MIC_{90}
0
24
Time, hours

Rapid Bacterial Eradication

- Ordinarily an advantage for an antibiotic
- Quick eradication leads to shorter courses of therapy, and lessens the risks of emergence of selected resistant organisms
- Fewer bugs around will mean symptom reduction sooner
- Shorter treatment courses are advantageous, if we assure rapid bacterial killing
  - β-Lactams and macrolides do not do this
  - Fluoroquinolones do, some more than others.

Fluoroquinolone resistance in *Pseudomonas aeruginosa*

- Why does Resistance follow the use patterns of some FQ antibiotics more than others?
  - Monopolistic use arguments?
- Principle of "marginal coverage"
  - Always the high MICs that develop resistance first among organisms
- Low AUIC (30-60) vs Resistance in *Pseudomonas aeruginosa*

FQ PK/PD for *P.aeruginosa*

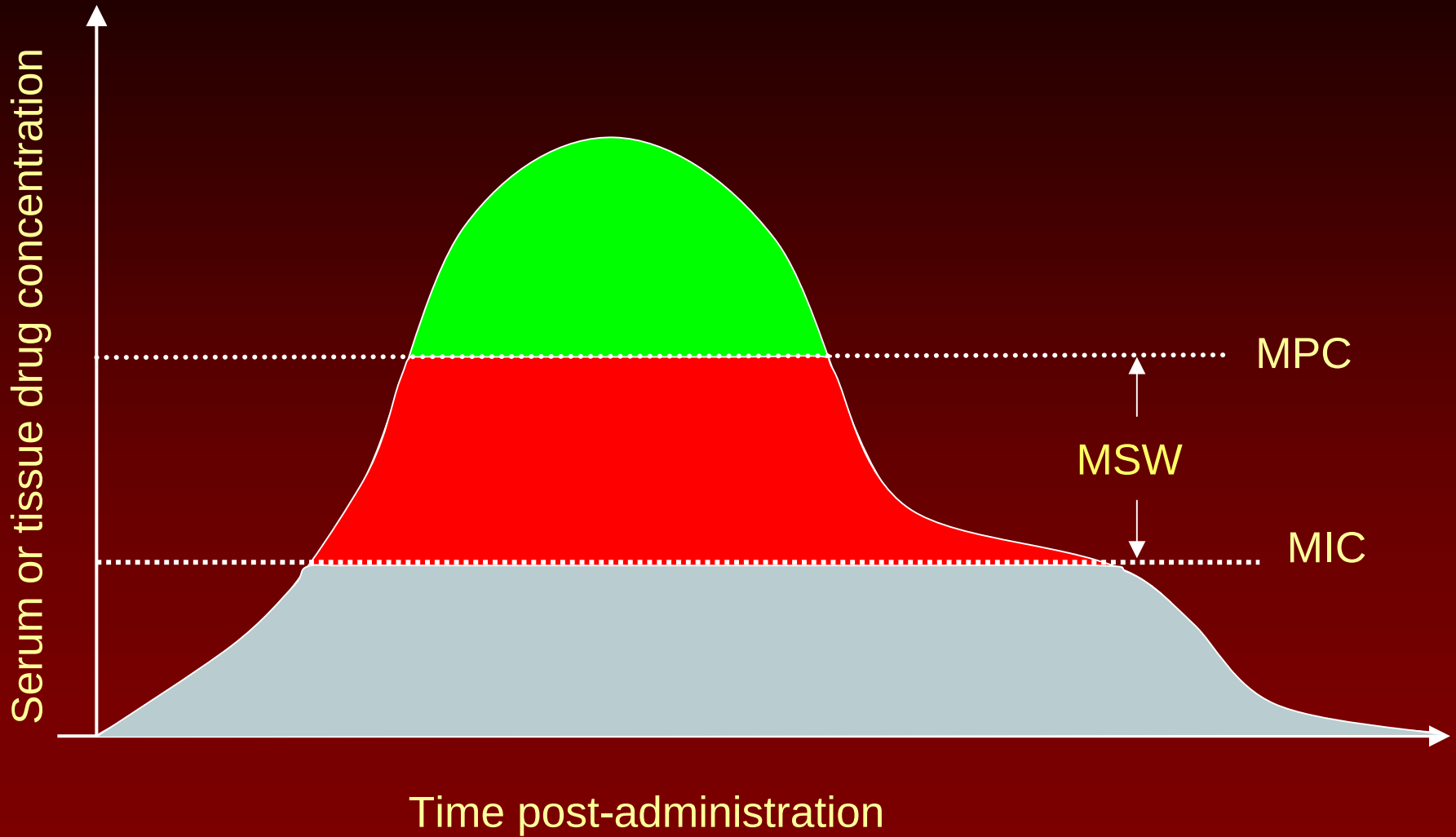
	Ciproflox	Levoflox	Moxiflox
Dose	750 BID or 400q8h	500 q24h	400 q24h
AUC_{24}	64	48	48
PsA MIC_{90}	0.5 mcg/ml	1.0 mcg/ml	4.0 mcg/ml
$AUIC_{24}$	128	48	12

MPC "window hypothesis"

- **Defined as the drug concentration range within which mutants are selectively enriched.**
  - **These ideas apply to a broad range of resistance problems**
  - **The mutant selection window hypothesis is relatively insensitive to individual resistance mechanisms**
  - **Once a small fraction of mutants is present, the issue is whether they will be enriched, not how they came into being.**
- **Traditional dosing regimens often place drug concentrations inside the window, such that a single mutation allows selective amplification of mutants.**

Discussions; Zhao, X. J Antimicrob Chemother 52: 731-733, 2003

Mutant Selection Window (MSW)



“MPC Window” vs “MIC Window”

- **First of all, why not just use MIC?**
  - **Zhao argues MPC correlates better with the MIC for resistant sub-populations than it correlates with the MIC for susceptible cells**
    - **Consider that MIC testing is an average of mostly susceptible populations, missing small numbers of sub-populations that have high MICs:**
      - **Beta lactamase producing enterobacter**
      - **Vancomycin insensitive MRSA (hetero-VISA)**
      - **FQ susceptible organisms with one step mutations**
- **Since AUIC is all about concentration in relation to susceptibility, can this concept of an AUIC window work as well or better than MPC window?**

Discussions; Zhao, X. J Antimicrob Chemother 52: 731-733, 2003

Emergence of resistant *S. pneumoniae*, in an in-vitro dynamic model that simulates Moxifloxacin concentrations inside and outside the mutant selection window: related changes in susceptibility, resistance frequency and bacterial killing

Stephen H Zinner, Irene Yu Lubenko, Deborah Gilbert, Kelly Simmons, Xilin Zhao, Karl Drlica, Alexander A Firsov.

Ref. J Antimicrob Chemother 52: 616-622, 2003

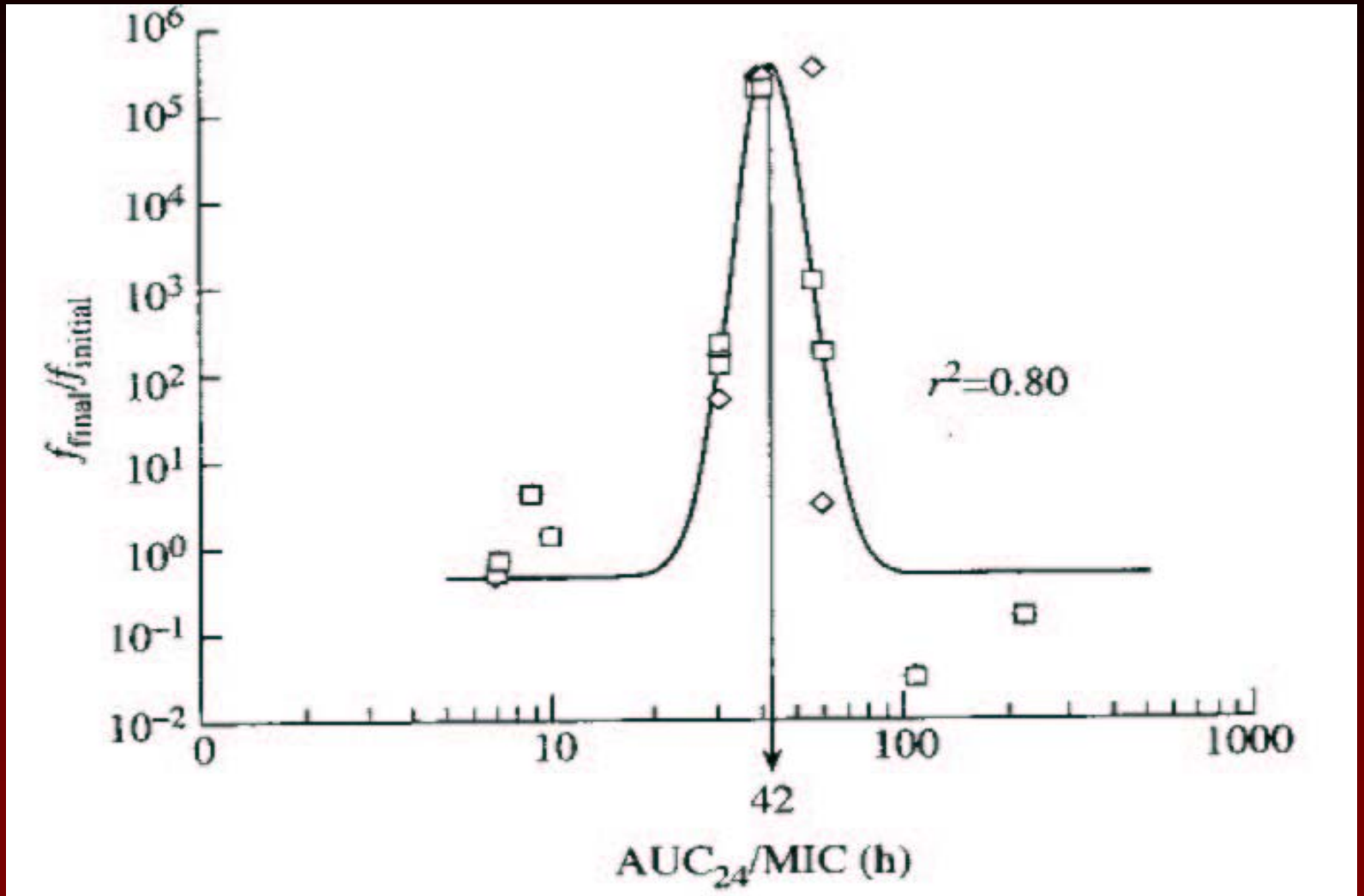


Figure 6. Effect of AUC_{24}/MIC on the increase in frequency of recovery of resistant mutants. Agar plates used to detect mutants contained either 4 × MIC

Zinner SH et al J Antimicrob Chemother 52: 616-622, 2003

Observations

- No selection of *S. pneumoniae* resistance at Moxifloxacin AUICs < 10 or >100
  - MIC was 0.1 and MPC was 0.5 for strain used
  - These data are consistent with clinical observations of selection windows: Thomas et al, AAC 1998
- Maximum selection of *S. pneumoniae* resistance at Moxifloxacin AUICs between 24 and 46.
- Data consistent with earlier studies of S. aureus selection windows for both Levofloxacin (31-61) and Moxifloxacin (Window was ~28 for selection)
  - Firsov. J Antimicrob Chemother 50: 533-539, 2002

Zinner SH et al J Antimicrob Chemother 52: 616-622, 2003

AUIC *vs.* MPC *vs.* "Windows"

- **Sorry this is getting more complicated, But:**
  - **You need a window on either MPC or AUIC if you wish to deal with BOTH eradication and resistance selection issues in the current literature and to conduct clinical trials.**
- **MPC will determine concentration dependent selection but not concentration dependent killing**
- **AUICs apply for either selection or killing, but you need 4 values to cover the possibilities:**
  - **< 10 for no effect on bacterial populations**
  - **> 24 to <80-100 for prediction of high selection risk**
    - **both time and concentration-dependent killing ABXs**
  - **~ 125 for MAX time-dependent killing rates**
  - **≥ 250 for MAX concentration-dependent killing rates**

Characterization of the Onset and Consequences of Pneumonia due to Fluoroquinolone-susceptible or –resistant *Pseudomonas aeruginosa*

Paladino JA, Sunderlin JL, Forrest A, Schentag JJ.

J Antimicrob Chemother 52: 457-463, 2003

P. aeruginosa Study Objectives

- **Characterize the specific PRIOR antibiotic regimens given to patients who subsequently develop LRTI from *P. aeruginosa***
- **Determine the AUIC of regimens preceding FQ-S and FQ-R *P. aeruginosa* isolates**
- **Characterize the regimens of patients treated for FQ-S and FQ-R *P. aeruginosa*, and assess outcomes of treatment**

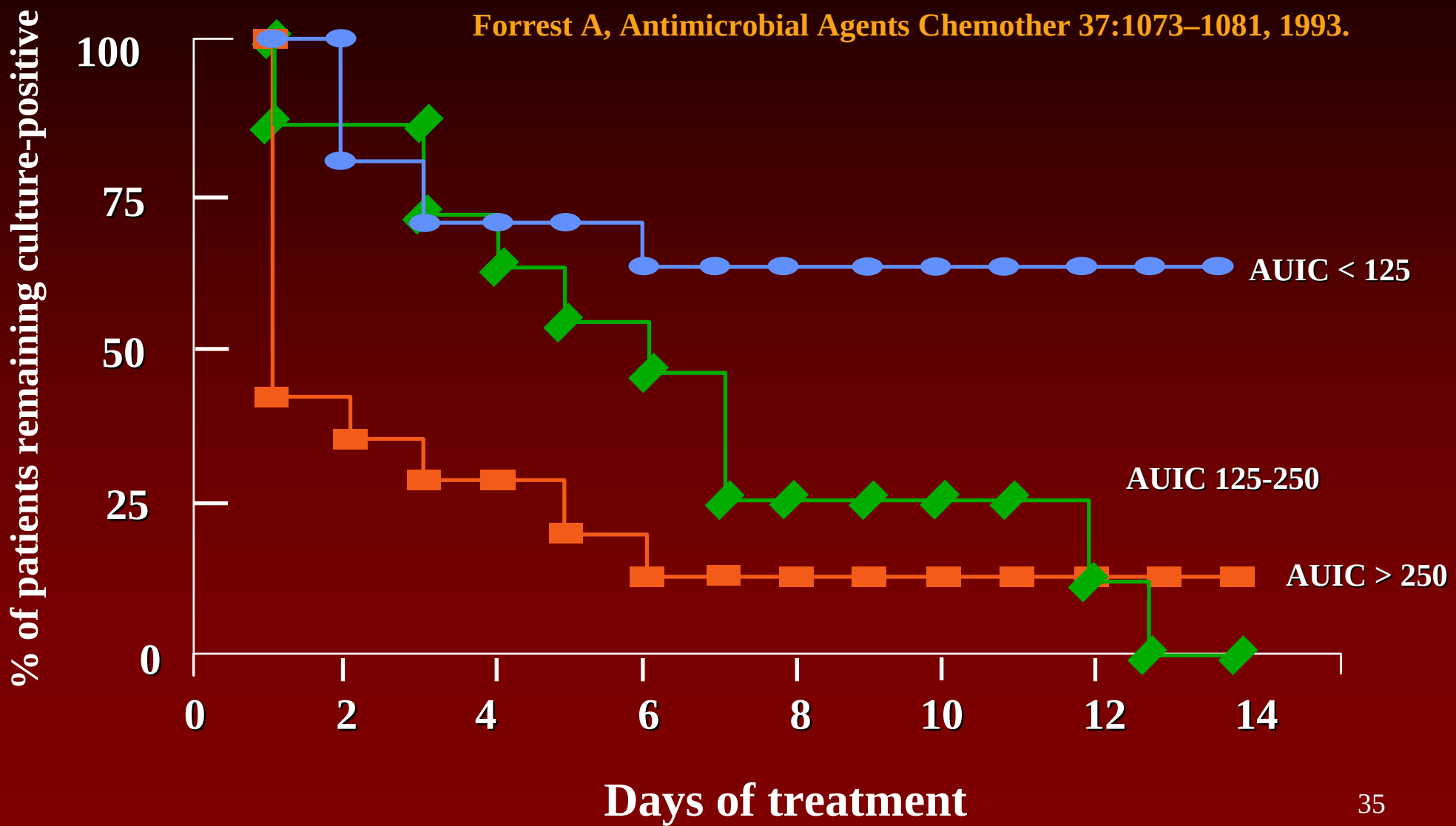
J Antimicrob Chemother 52: 457-463, 2003

Results: 50 FQ-S *vs.* 50 FQ-R LRTI

- **Cases of *P. aeruginosa* LRTI from 14 hospitals**
- **Patients with FQ-R had more often received a FQ ($p<0.027$) and this was more often Levofloxacin ($P<0.0001$).**
- **Prior FQ AUIC in FQ-S was 169; Prior FQ AUIC in FQ-R was 58 ($P=0.001$)**
- **Subsequent TX of both groups at total (all abx) AUIC > 169 resulted in similar cures overall, but all patients had complicated courses and numerous antibiotics were used in treatment.**

Paladino JA et al JAC 52: 457-463, 2003

Ciprofloxacin: Eradication vs AUIC



Optimal PK and PD in Humans

- **For optimal antimicrobial effect:**
  - **- C_{max} / MIC ratio should be >8 to 10**
  - **- AUC / MIC ratio should be > 125**
- **To minimize resistance development:**
  - **- AUC / MIC ratio should be >100**
- **Easy to justify an AUC/MIC > 250 for FQs**
  - **– very rapid eradication of the pathogen**

The bugs obey the same rules, gram positive, gram negative, no difference to them……