

PK/PD of Antibiotics in relation to resistance

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ISAP

International Society of Anti-Infective Pharmacology

Founded in 1991

Optimal antibiotic dosage

```
graph TD; A[Optimal antibiotic dosage] --- B[Efficacy]; A --- C[Toxicity]; A --- D[Resistance];
```

Efficacy

Toxicity

Resistance

Optimal antibiotic dosage

```
graph TD; A[Optimal antibiotic dosage] --- B[Efficacy]; A --- C[Toxicity]; A --- D[Resistance]; style D fill:#ff0000,stroke:#ff0000,stroke-width:2px;
```

Efficacy

Toxicity

Resistance

Question:

Can the PK/PD and dosage of antibiotics influence the emergence of antibiotic resistance ?

Optimal antibiotic dosage

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graph TD; A[Optimal antibiotic dosage] --- B[Efficacy]; A --- C[Toxicity]; A --- D[Resistance];
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Efficacy

Toxicity

Resistance

Question:

Can the PK/PD and dosage of antibiotics influence the emergence of antibiotic resistance ?

YES!

Optimal antibiotic dosage

```
graph TD; A[Optimal antibiotic dosage] --- B[Efficacy]; A --- C[Toxicity]; A --- D[Resistance];
```

Efficacy

Toxicity

Resistance

Question:

Can general predictions be drawn from current data on what antibiotic dosage regimen would minimize emergence of resistance while preserving efficacy and without increasing toxicity ?

Optimal antibiotic dosage

```
graph TD; A[Optimal antibiotic dosage] --- B[Efficacy]; A --- C[Toxicity]; A --- D[Resistance];
```

Efficacy

Toxicity

Resistance

Question:

Can general predictions be drawn from existing data on what antibiotic dosage regimen would minimize emergence of resistance - while preserving efficacy and without increasing toxicity ?

NO !

What is resistance?

- *Genotype*
The bacteria carry certain resistance elements
- *Phenotype*
The bacteria has an increased MIC in comparison with the wild type
- *Clinical*
The bacteria are able to multiply in humans in the presence of drug concentrations achievable during therapy

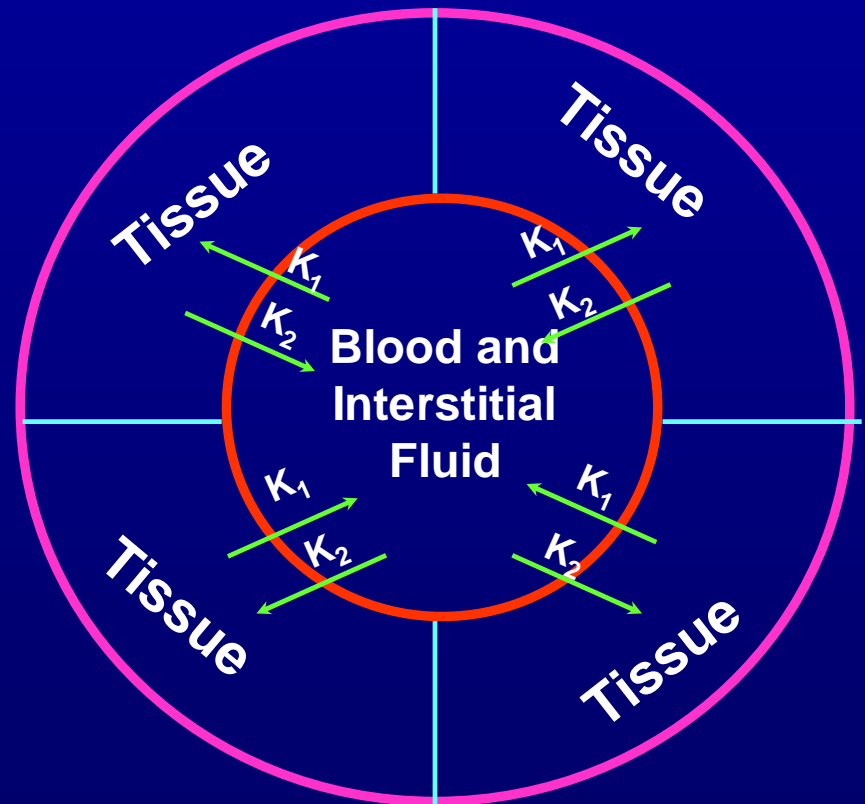
In vitro data vs resistance

- Resistance mechanisms detected *in vitro* must be the same as expressed *in vivo*
- Inoculum *in vitro* vs the site of infection
- Pharmacokinetics *in vitro* vs in the human body

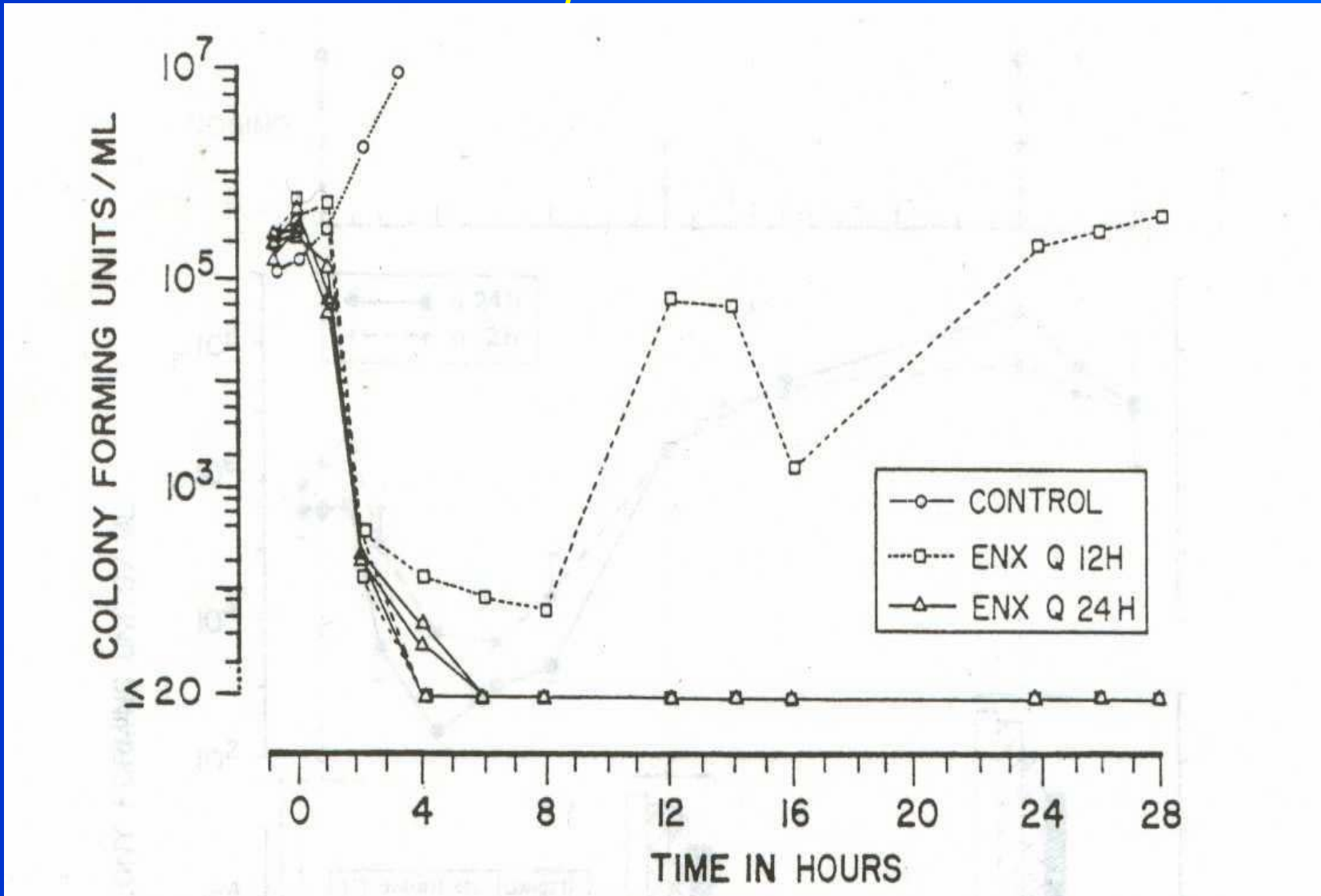
Ecological compartments

- *Oropharyngeal*
- *Skin*
- *Peri-urethral*
- *Faecal*
- *Intracellular*

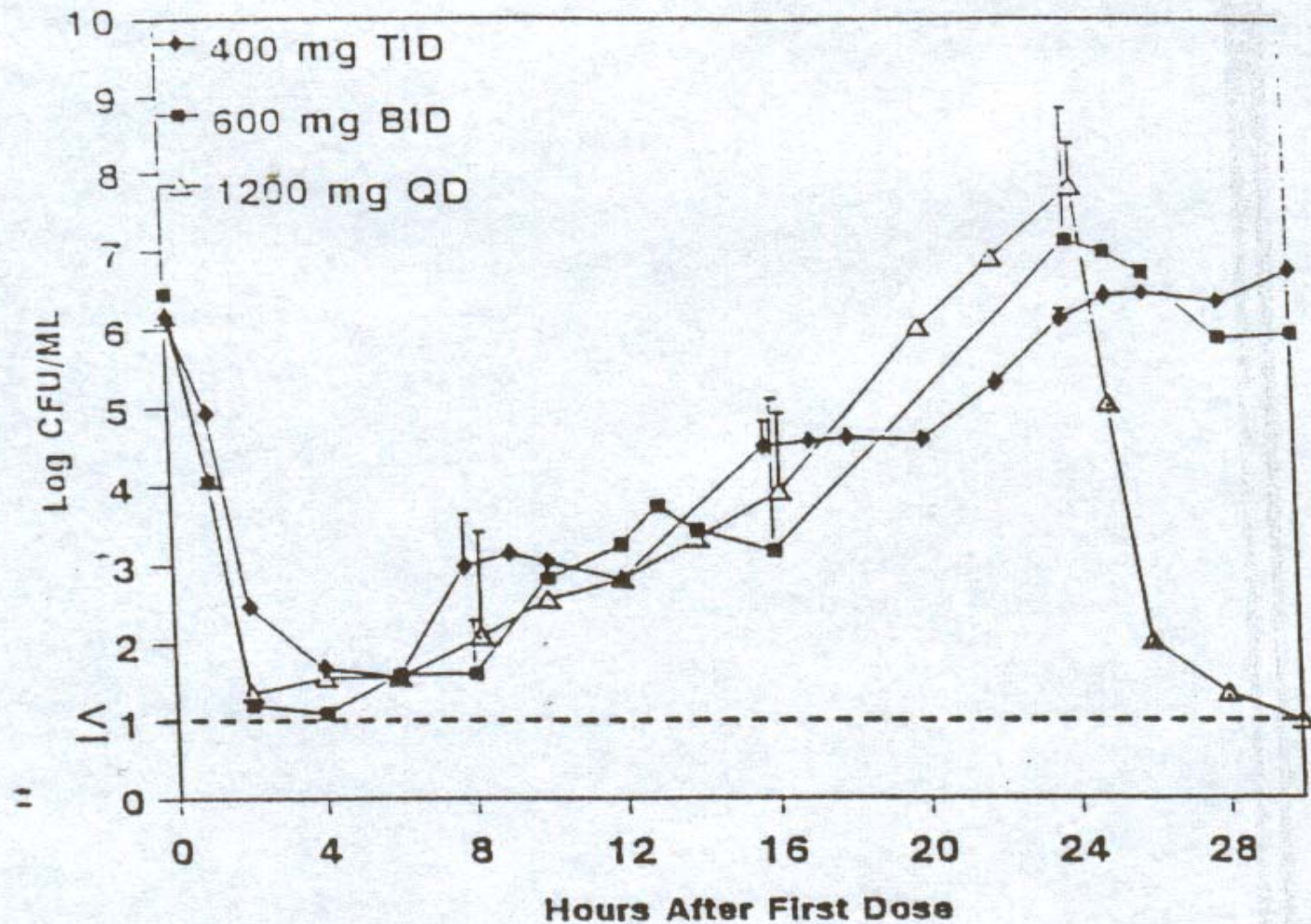
Multicompartment pharmacokinetics



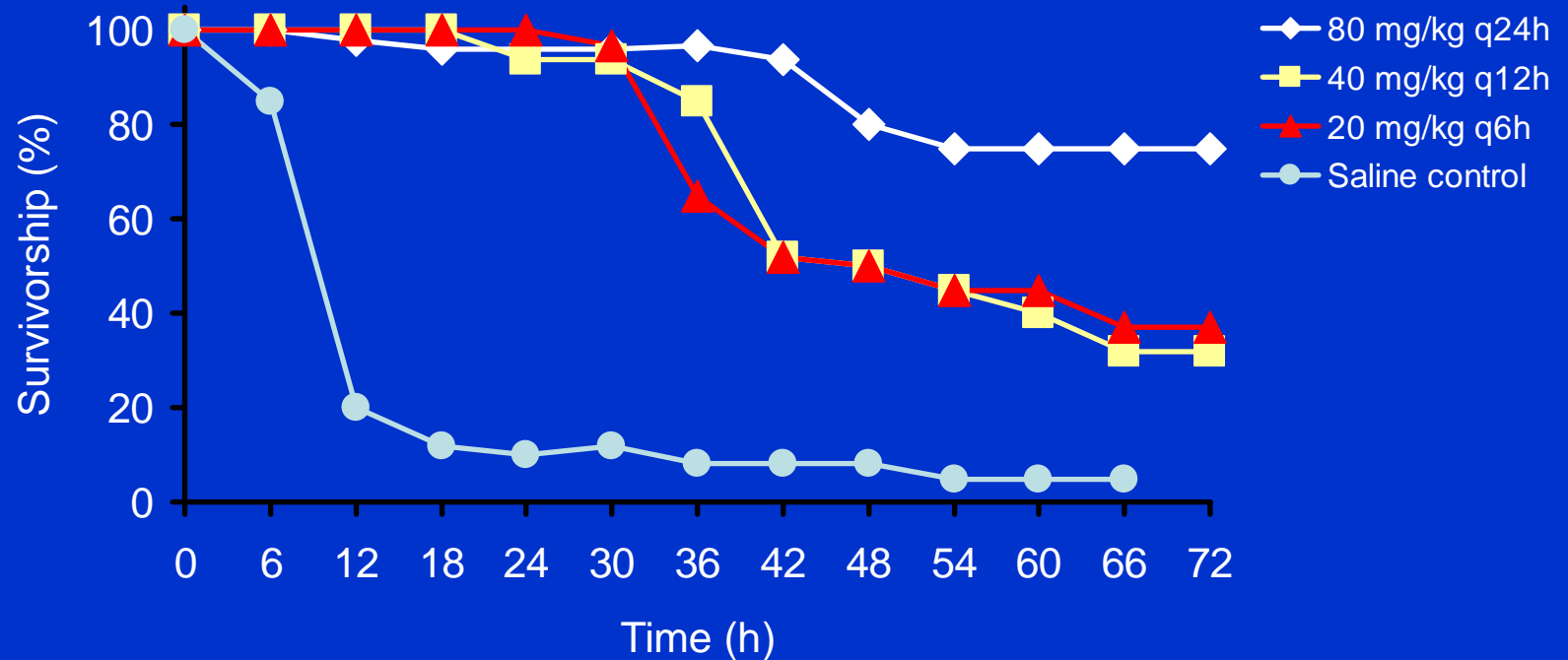
Bactericidal activity of two enoxacin regimens against *K.pneumoniae*

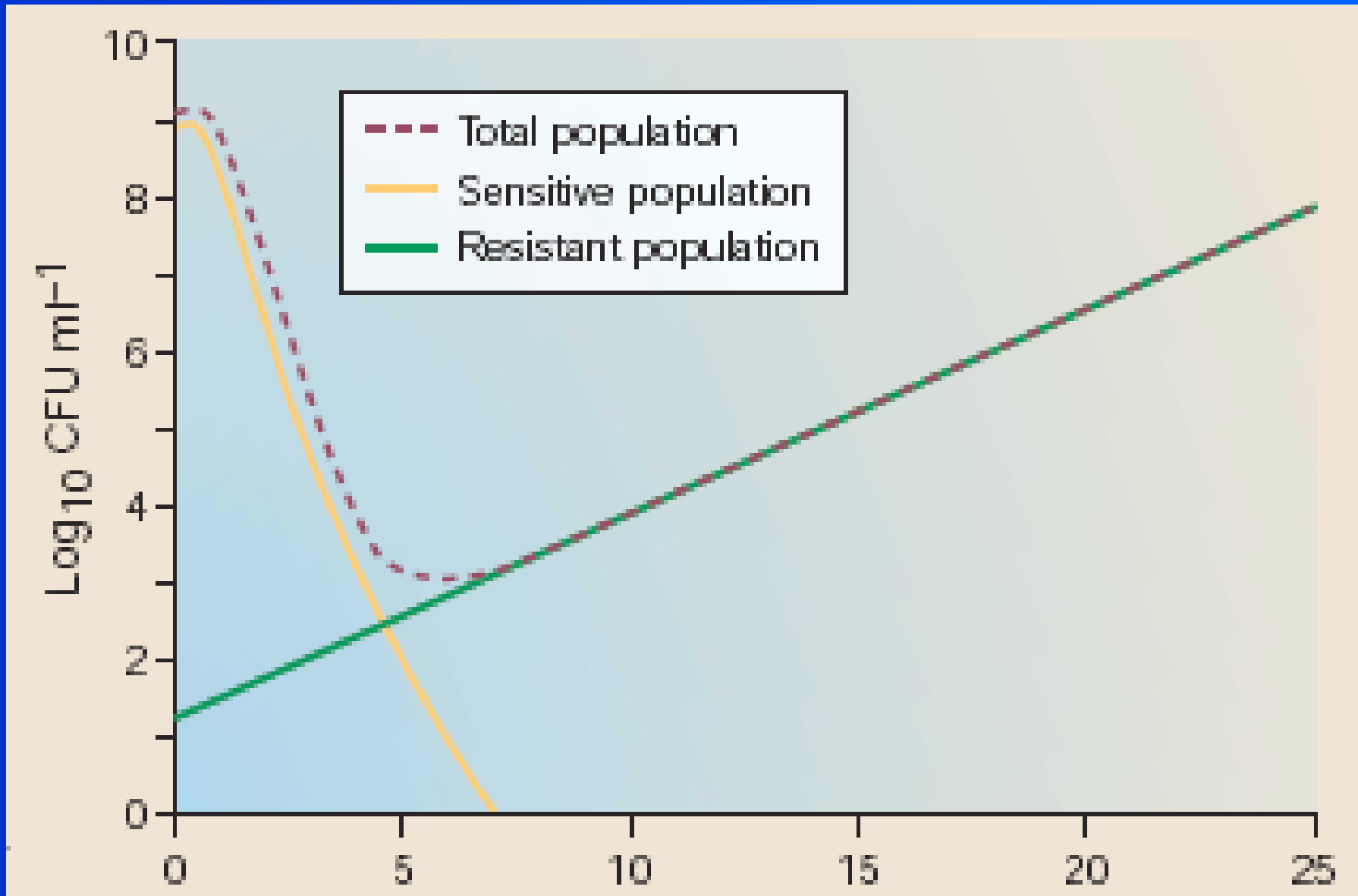


Killing of *P.aeruginosa* at three different dosage regimens of ciprofloxacin



Lomefloxacin Therapy for *Pseudomonas* Sepsis in Neutropenic Rats: Effect of Dose Fractionation (N=50/Group)





**Mutant Preventive
Concentration (MPC)**

**Mutant Selective
Window (MSW)**

MIC and MPC in theory

MIC

Antibiotic concentration that prevents the growth of susceptible bacteria

A measure of the Majority of the Population

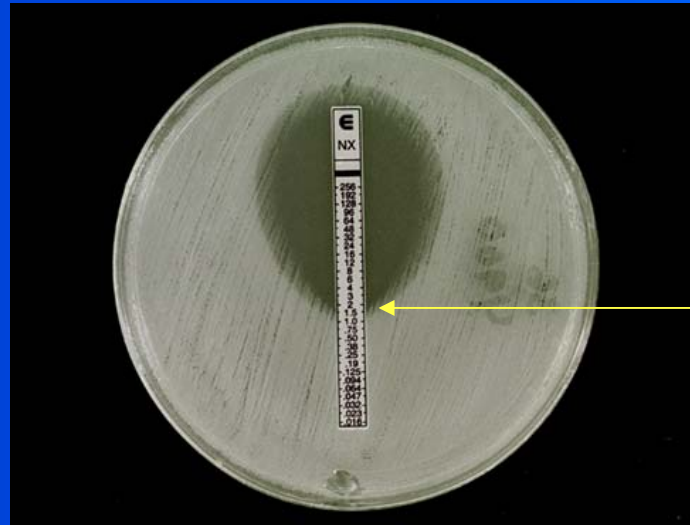
MPC

Antibiotic concentration that prevents the growth of single-step resistant mutant

A measure of the Most Resistant Part of the Population

MIC and MPC in practice

MIC (Etest)



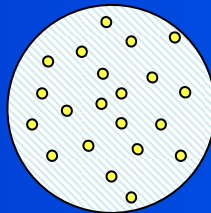
Cells 0.5 McFarland
16-18 hrs, 37°C

MIC

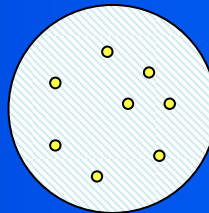
MPC

Dong, Zhao, Domagala, Drlica
AAC, 43: 1756-1758, 1999

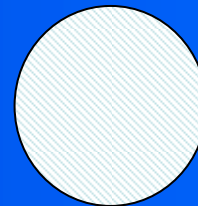
0.1 µg/ml



0.3 µg/ml



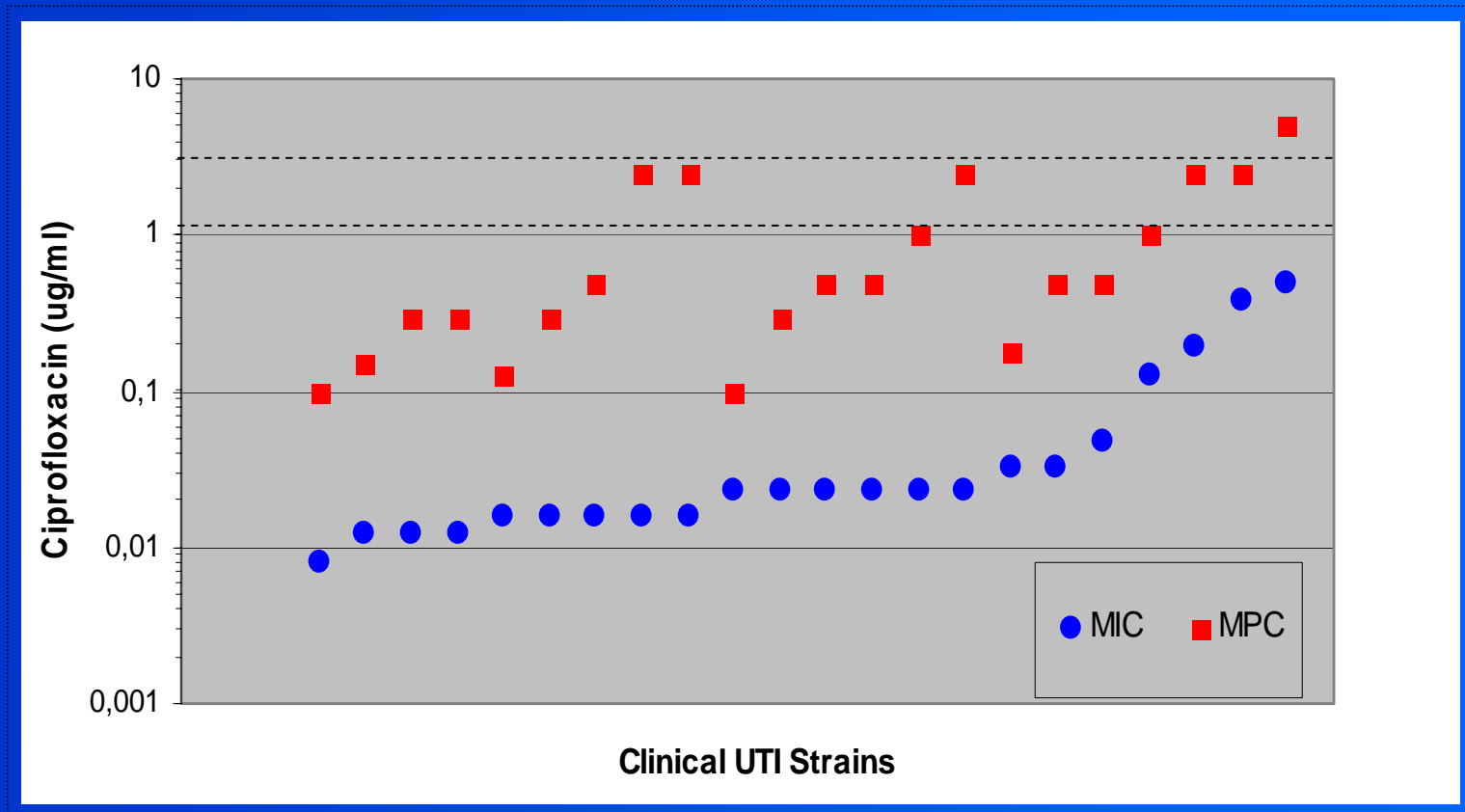
0.5 µg/ml



Cells $\geq 10^{10}$
48 hrs, 37°C

MPC

22 Sensitive Clinical UTI E.coli isolates



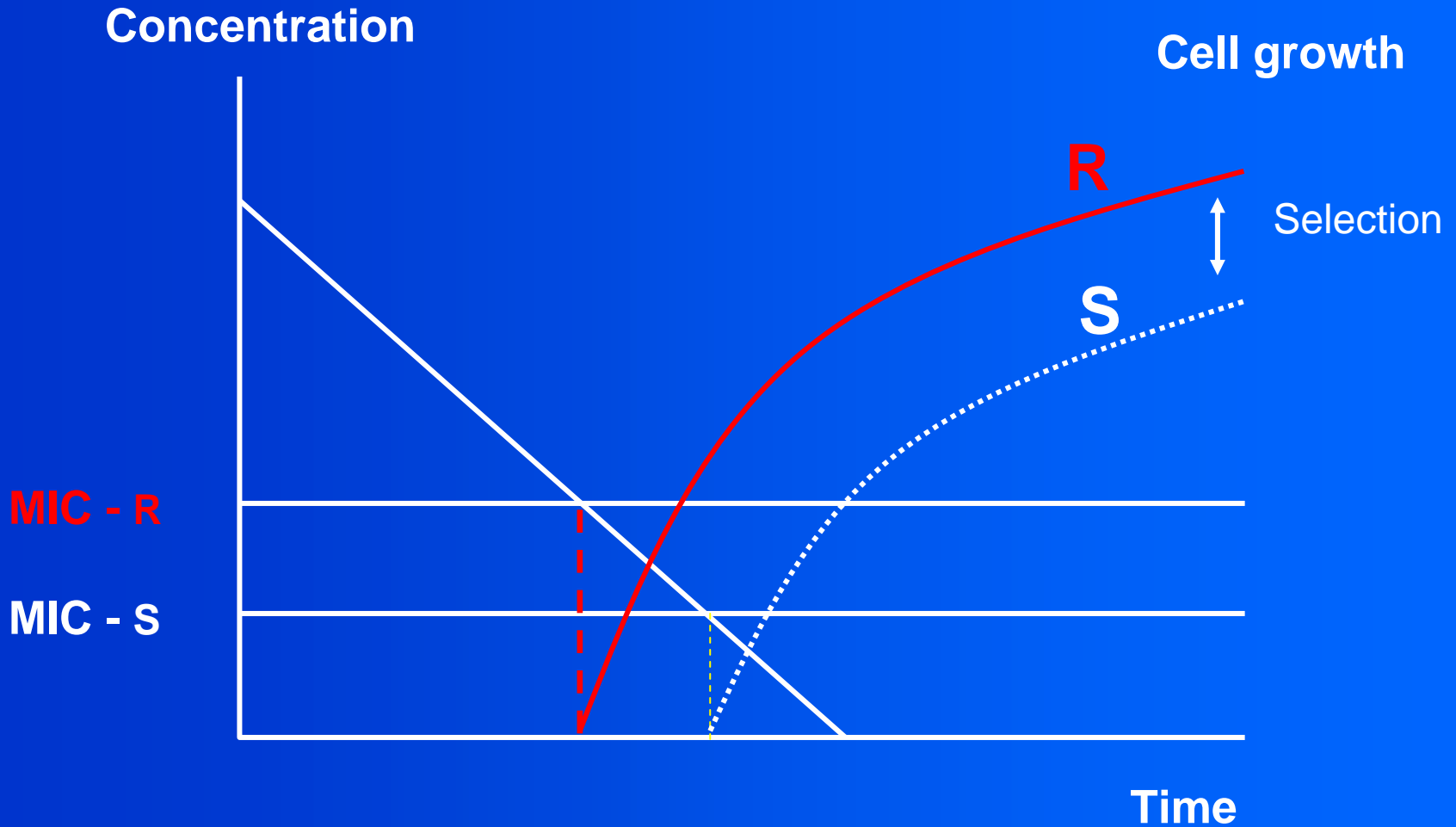
Marcusson et al , JAC, accepted for publication

MPC

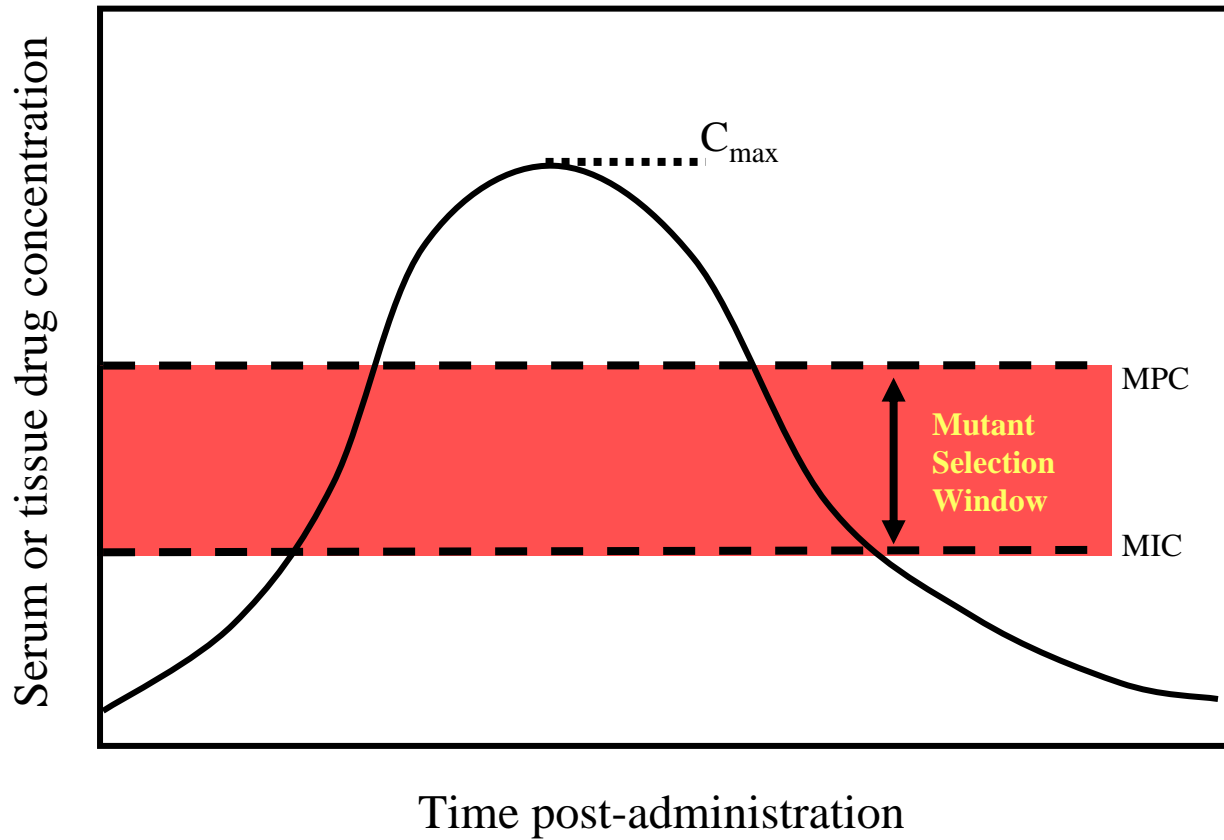
- The concept has similarities to agar dilution MICs. Both are measured at static concentrations
- The last decade has clearly shown that the MIC alone is not predictive for outcome. MIC has to be related to dosing regimens, pk and PK/PD indices
- It is not logical to use the MPC as a primary parameter

PK/PD and resistance

Mutant selective window (MSW)



The concept of Mutant Selective Window



PD and resistance: Endpoints

- Regrowth of the population- increase in MICs
- Change in the number of resistant bacteria during the experiment e.g. time zero vs time X
(culture on antibiotic containing plates)
- AUC of the population analysis profile
(serial plating on antibiotic plates during the experiments)
- Specific measuring of the susceptible and resistant population
(competition assay using selective markers)

Pharmacodynamic indices used in resistance studies

C_{max} / MIC

$T > MPC$

C_{max} / MPC

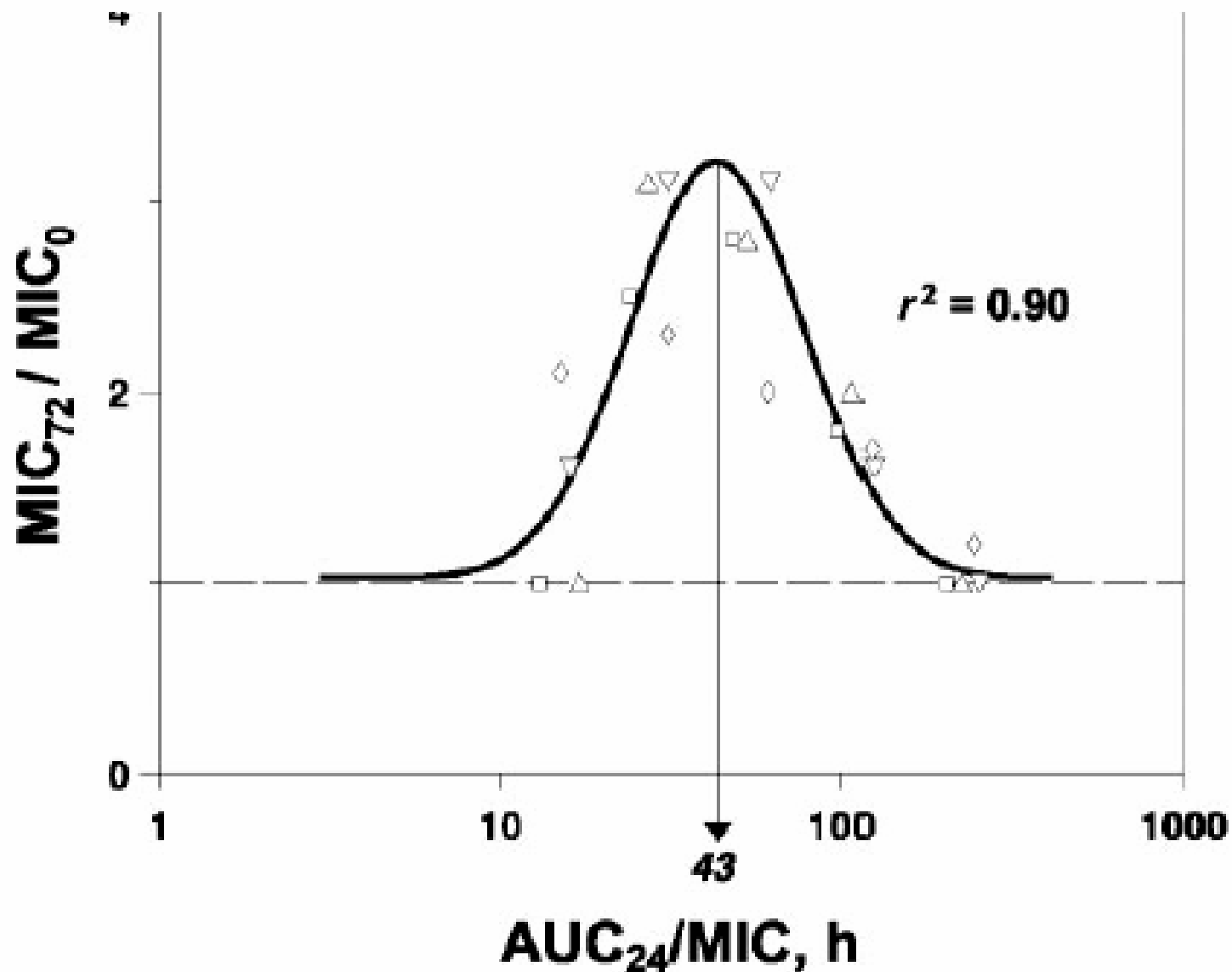
T_{MSW}

AUC / MIC

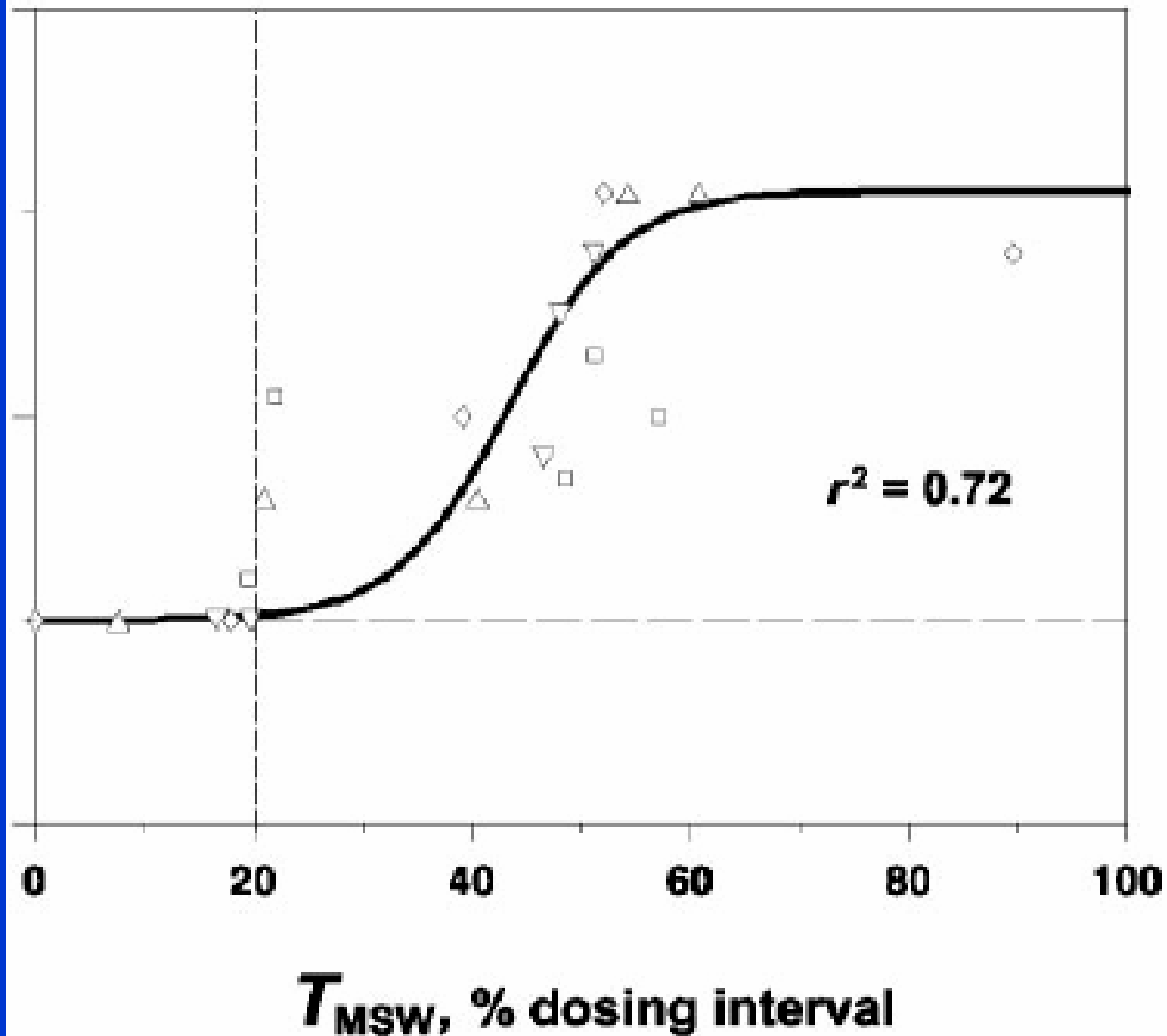
AUC_{MSW}

AUC / MPC

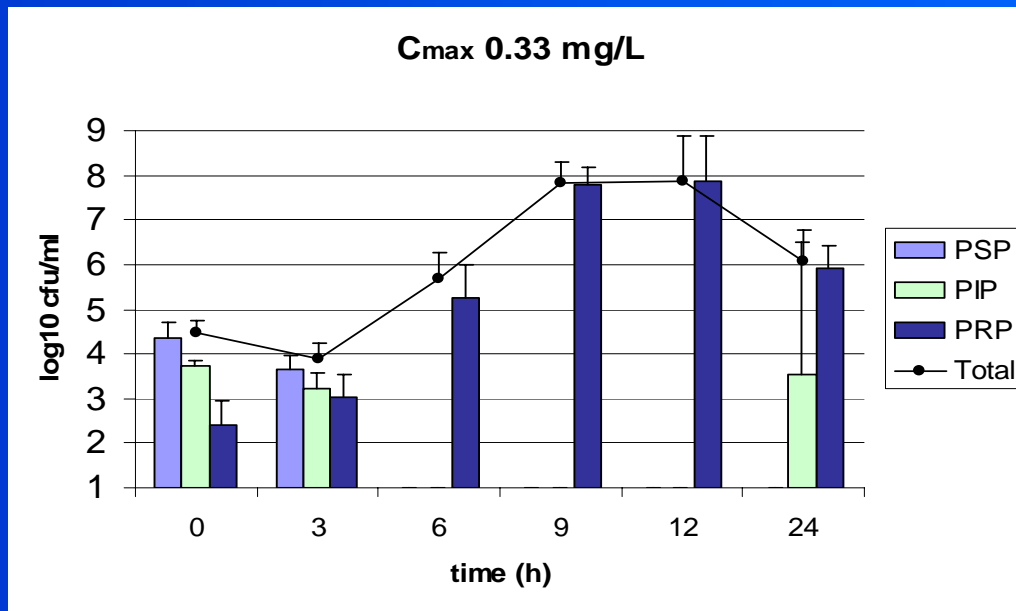
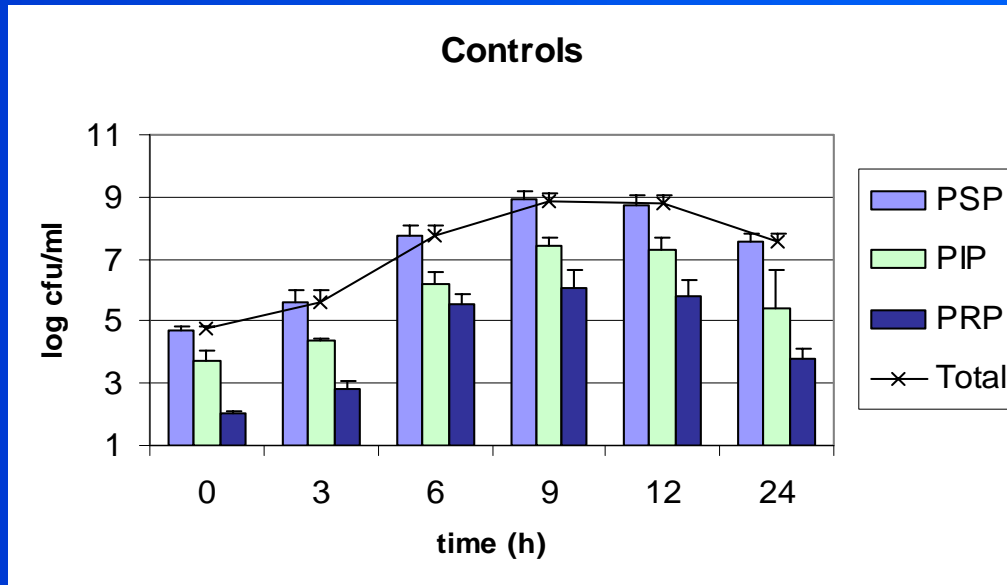
In Vitro Pharmacodynamic Evaluation of the Mutant Selection Window Hypothesis Using Four Fluoroquinolones against *Staphylococcus aureus*



MIC_{T2} / MIC₀



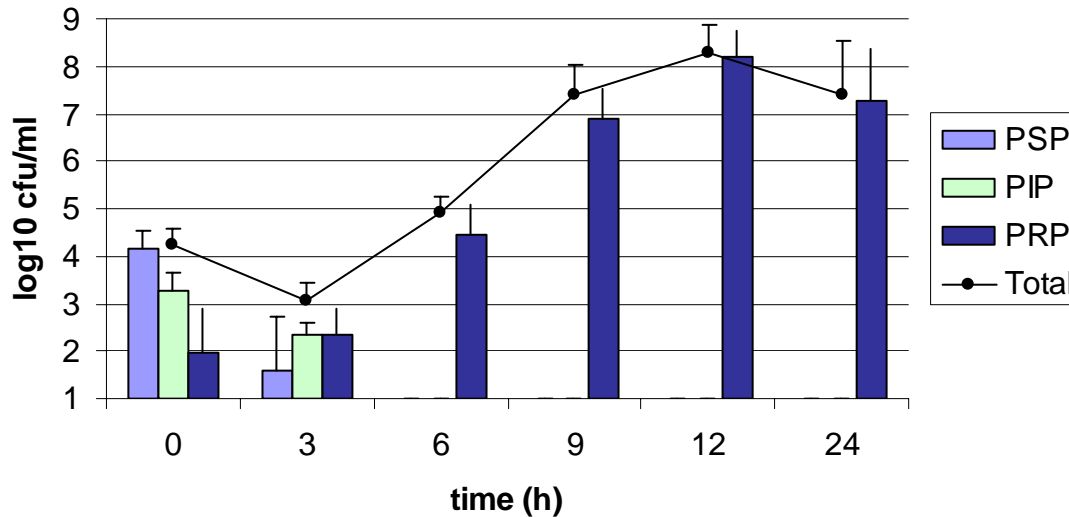
Pharmacodynamics of Penicillin G vs *S.pneumoniae* with different susceptibility for penicillin



T>MIC
PSP 46%
PIP 6%
PRP 0%

Odenholt et al
 AAC 47,518,2003

C_{max} 1.5 mg/L



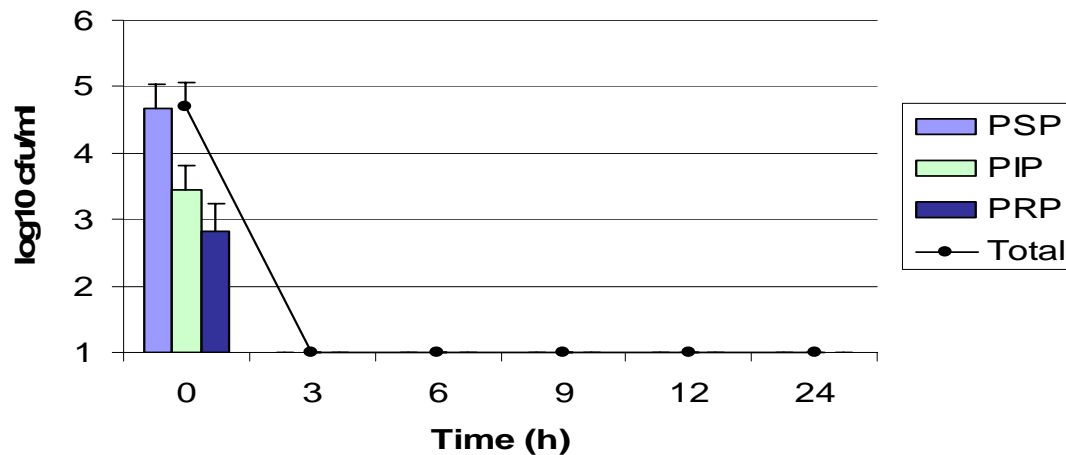
T > MIC

PSP 75%

PIP 38%

PRP 0%

C_{max} of 53.5 mg/L



T > MIC

PSP 100%

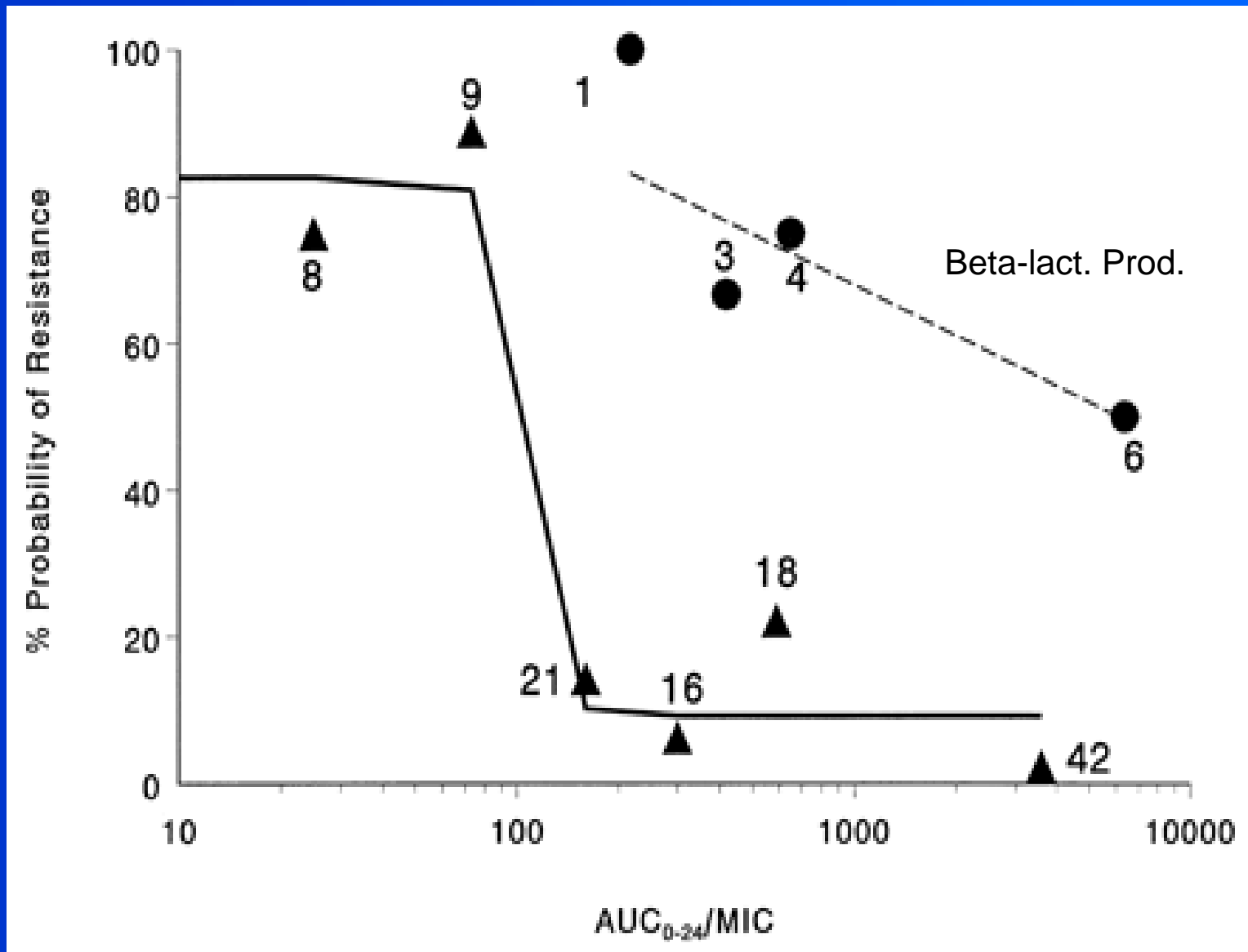
PIP 100%

PRP 48%

Pharmacodynamic Evaluation of Factors Associated with the
Development of Bacterial Resistance in Acutely
Ill Patients during Therapy

- Retrospective, including 4 earlier studies
- 107 acutely ill patients, 128 pathogens, 5 antimicrobial regimens.
- PK and MICs for every individual patient
- Pharmacodynamic (PD) models probability of developing bacterial resistance.

- Overall, in 32 of 128 (25%) resistance developed during therapy.
- AUC[0-24]/MIC was as a significant predictor.
- This relationship was observed across all treatments and within all organism groupings, with the exception of beta-lactamase-producing gram-negative organisms



Major risk factors for emergence of antibiotic resistance during therapy

- Mutation frequency / size of inoculum
- Biological fitness cost and cost compensation
- Selective antibiotic concentrations

Inoculum : 10^9 CFU

Mutation frequency

No of mutants

10^{-5}

10^4

10^{-8}

10^1

Conclusions

- Certain dosage regimens are clearly associated with a risk for selective enrichment of a resistant subpopulation
- The selective pressure varies between bacterial species, antibiotics, and resistance mechanisms
- The pharmacodynamic indices to minimize resistance will vary due to the infectious site, bacterial species, antibiotics, and resistance mechanisms

Conclusions

- Studies on prevention of resistance should be initiated early in drug development

Preferred properties:

- Low mutation rate
- High fitness cost of mutants
- Narrow MSW?

- ISAP should take the initiative on an international conference on PK/PD vs resistance including methodological issues, interpretation of current data, and research agenda needed