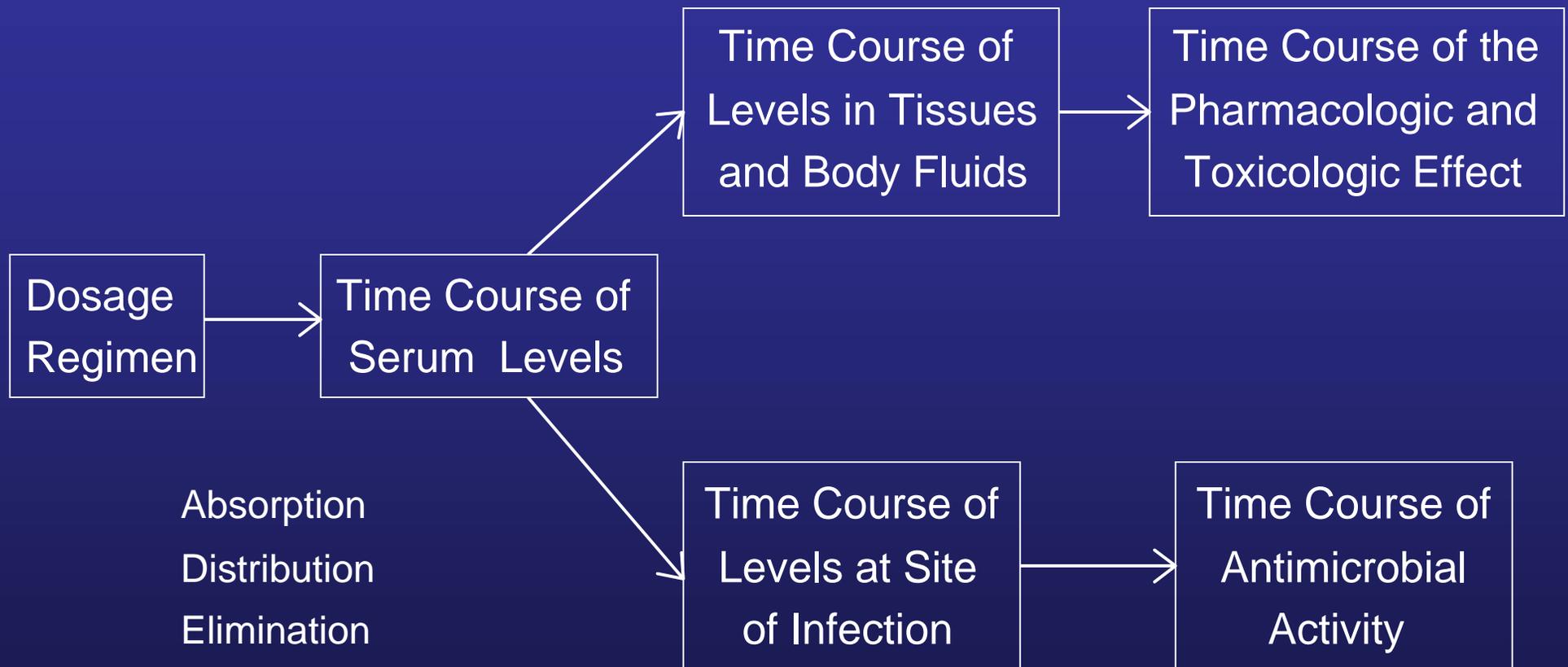


**Importance of Time Above MIC for  
In-Vivo Activity of Augmentin  
and Other Beta-Lactams in  
Acute Otitis Media**

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# Pharmacology of Antimicrobial Therapy



**Pharmacokinetics**

**Pharmacodynamics**

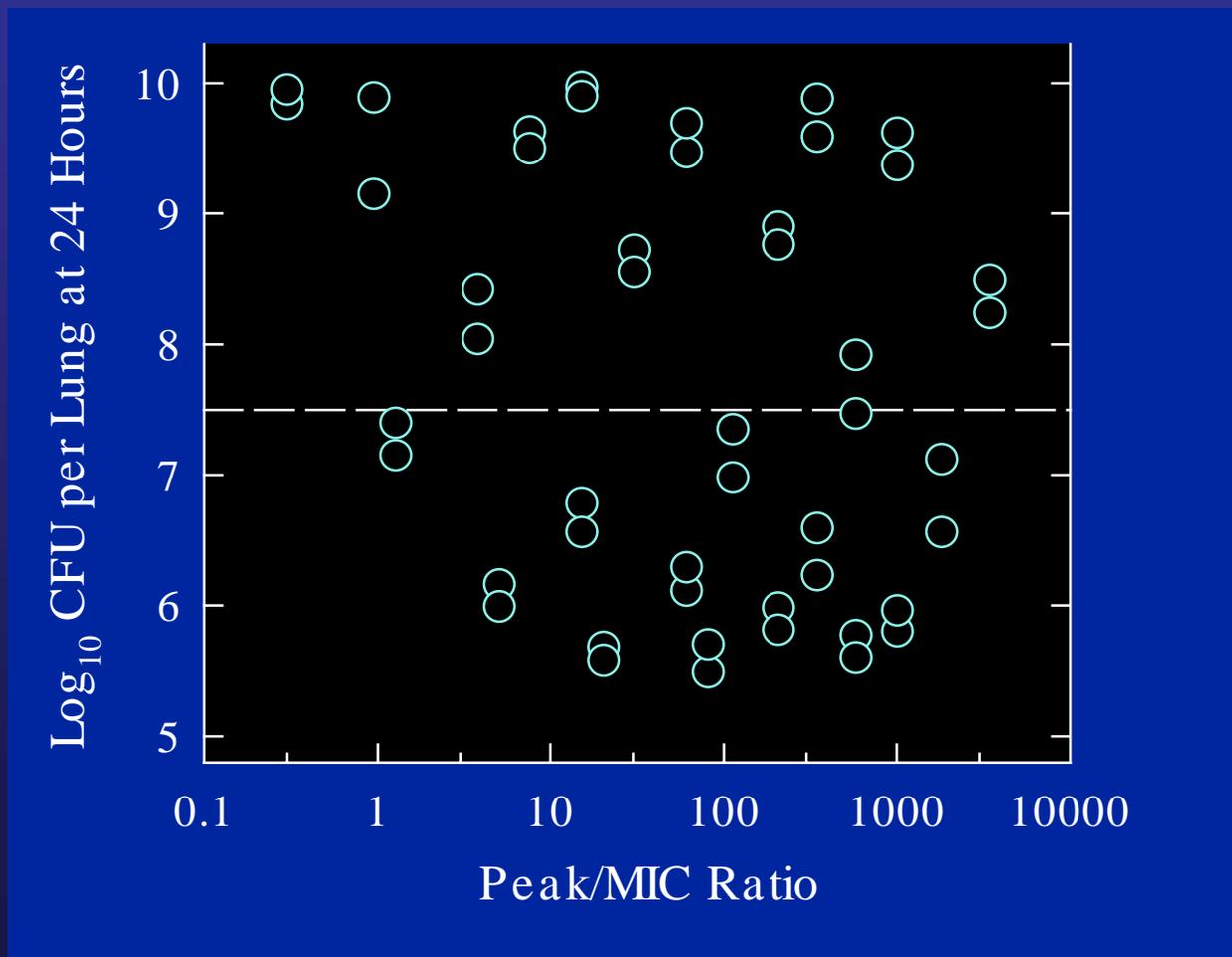
# Parameters of Antimicrobial Activity

- **Potency:**
  1. MIC
  2. MBC
- **Time Course of Activity:**
  1. Rate of killing and effect of increasing concentrations
  2. Persistent effects (postantibiotic effect, postantibiotic sub-MIC effects, postantibiotic leukocyte enhancement)

# Pattern of Antimicrobial Activity for Amoxicillin and Other $\beta$ -Lactams

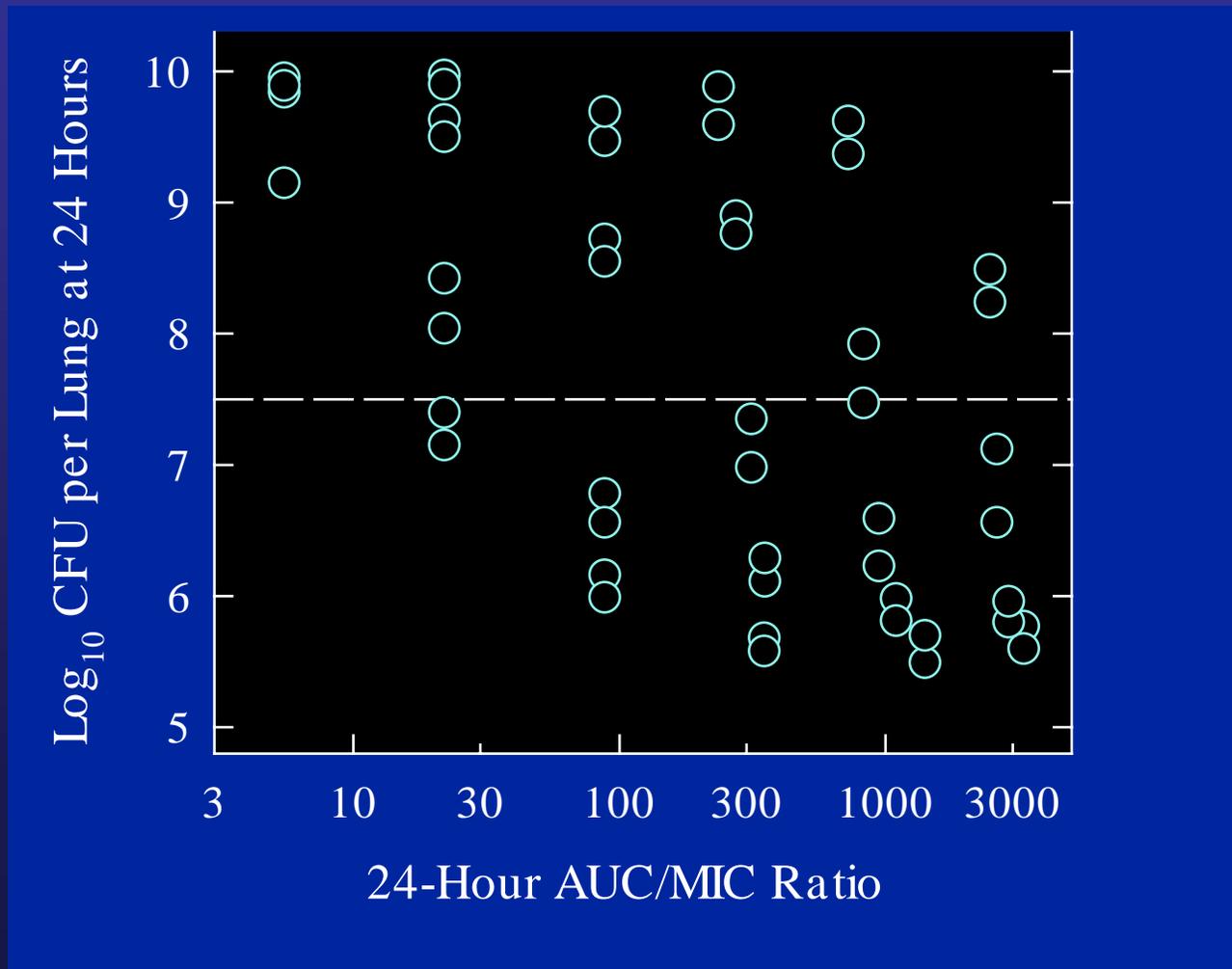
- Time-dependent killing and minimal to moderate persistent effects
- Goal of dosing regimen: optimize duration of exposure
- Time Above MIC major parameter correlating with efficacy

# Relationship Between Peak/MIC Ratio and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model

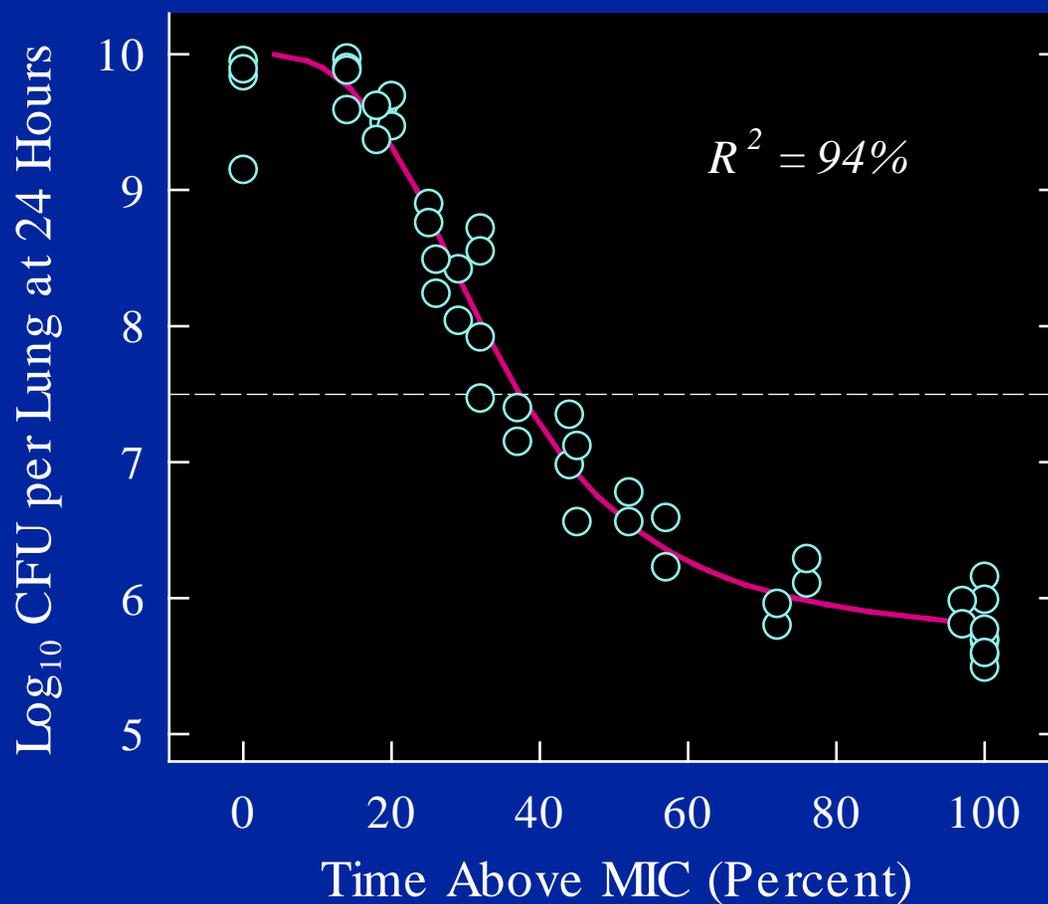


Craig CID, 1998

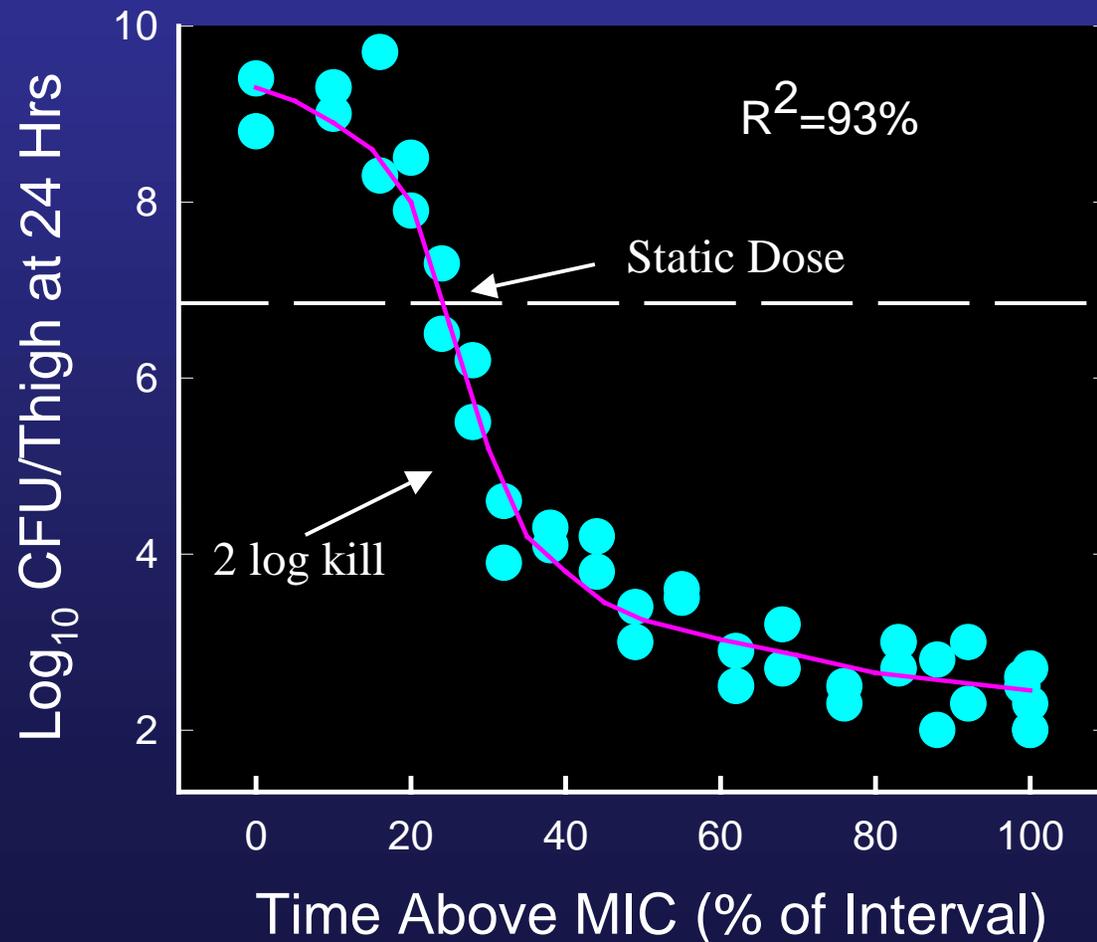
# Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model



# Relationship Between Time Above MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model



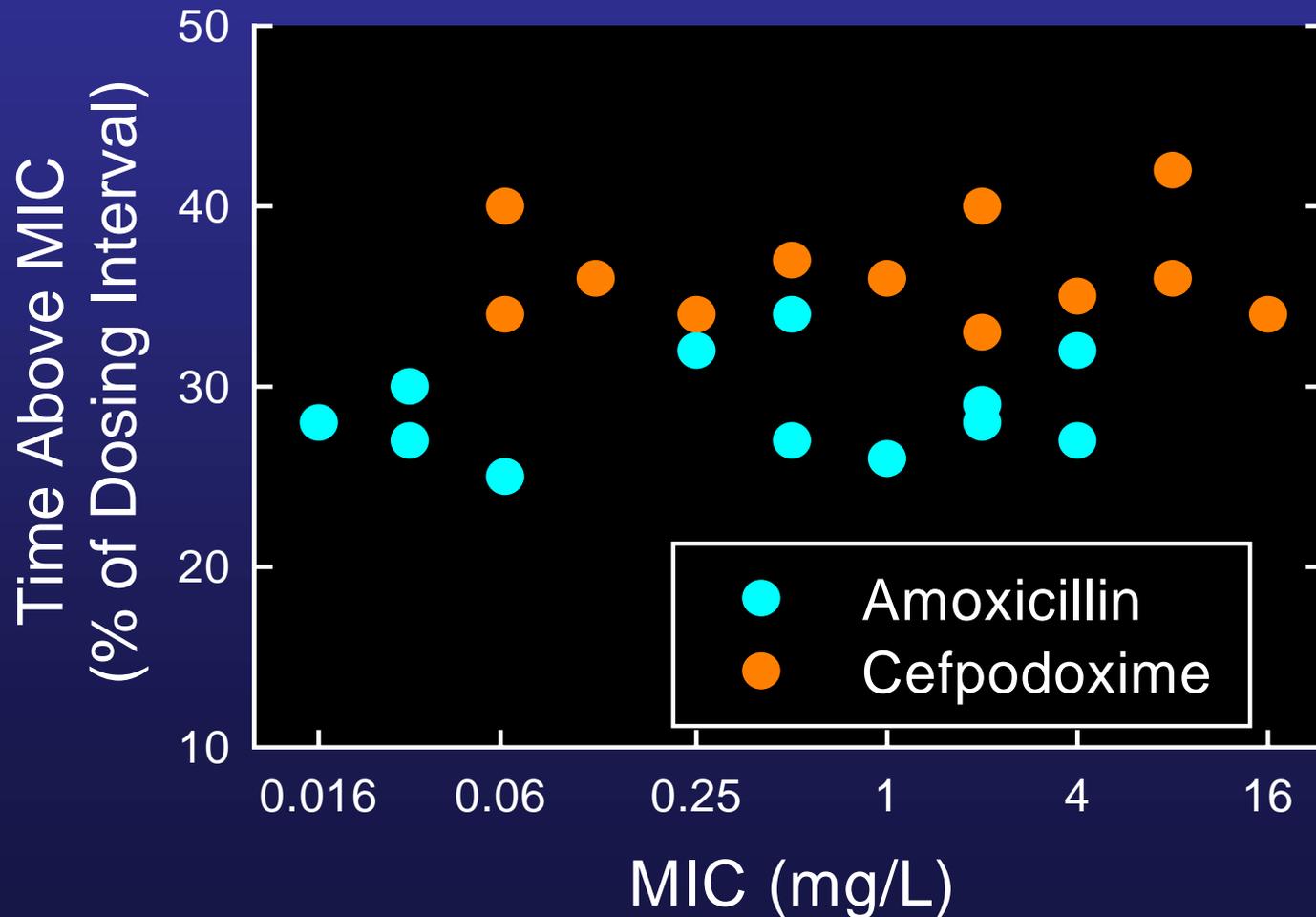
# Relationship Between Time Above MIC and Efficacy for Amoxicillin against *Streptococcus pneumoniae* in a Murine Thigh-Infection Model



## Time Above MIC for $\beta$ -Lactams

- Is the magnitude of the parameter required for efficacy the same in different animal species including humans? **YES**
- Does the magnitude of the parameter vary with:
  1. the dosing regimen? **NO**
  2. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)? **NO**
  3. different drugs within the same class? **Penicillins less than cephalosporins; no difference within groups providing free, unbound drug levels are used**
  4. different organisms including resistant strains ? **FOR SOME; no difference for penicillin-resistant pneumococci**

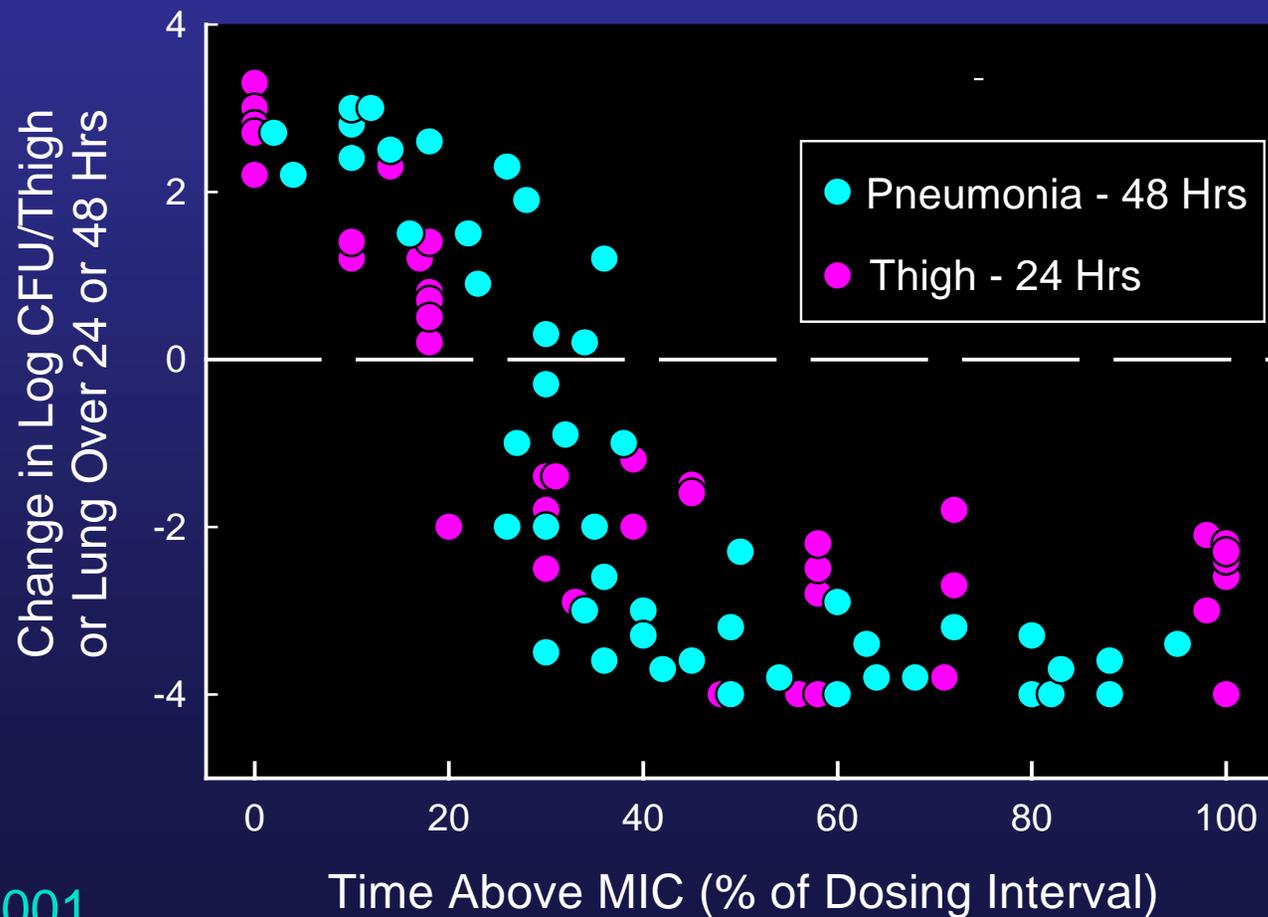
# Relationship Between MIC and T>MIC for Amoxicillin & Cefpodoxime with strains of *S. pneumoniae*



# Time Above MIC: $\beta$ -Lactams

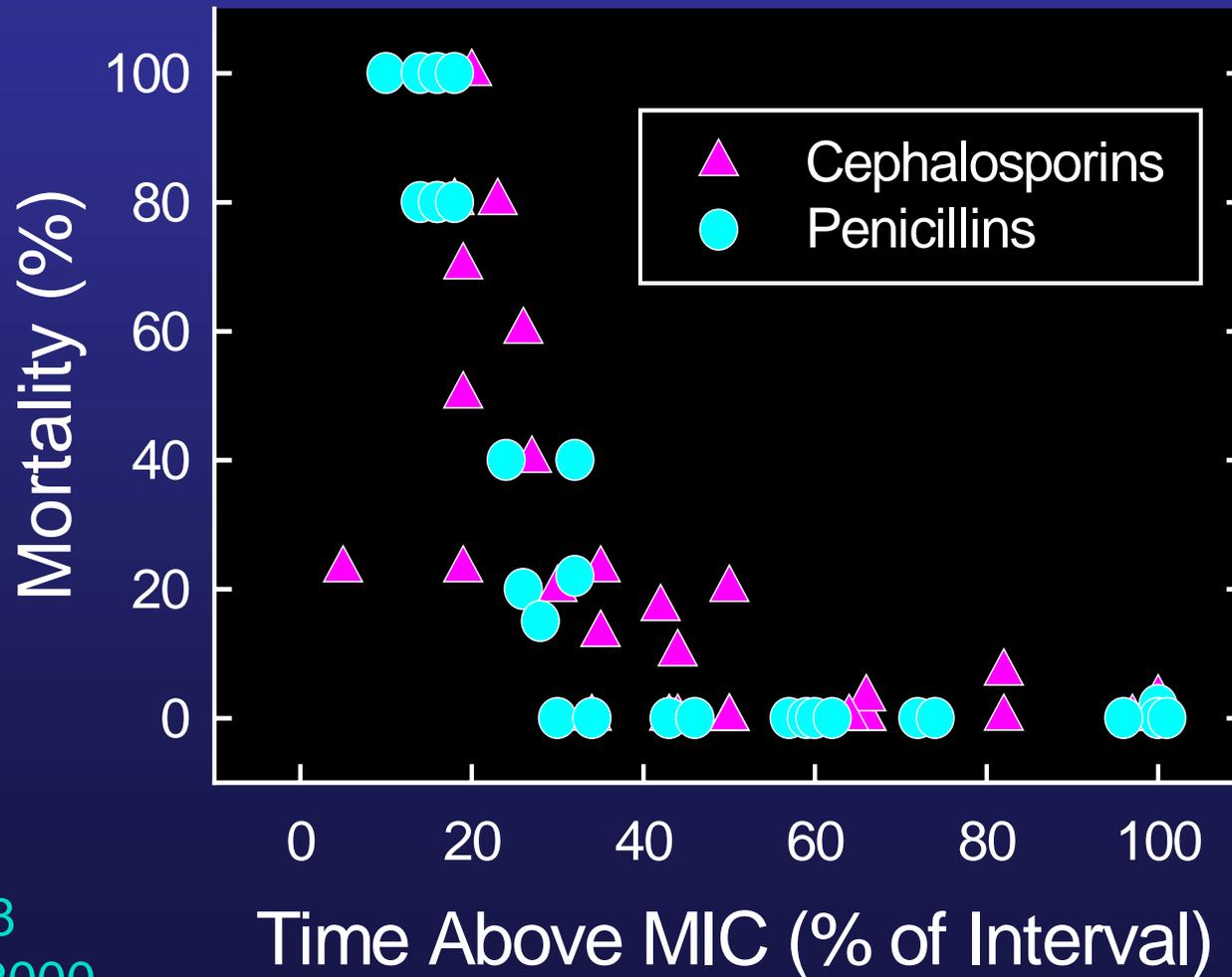
- T>MIC (% of dosing interval) required for the static dose against most organisms in neutropenic mice vary from 25-35% for penicillins and from 30-45% for cephalosporins
- The presence of neutrophils reduces the T>MIC required for efficacy by 5-10%
- Free drug levels of penicillins and cephalosporins need to exceed the MIC for 35-50% of the dosing interval to produce maximum survival

# Relationship Between T>MIC and Efficacy for Amoxicillin against *Streptococcus pneumoniae* in Murine Pneumonia and Thigh-Infection Models



Craig CID, 2001

# Relationship Between Time Above MIC and Efficacy in Animal Infection Models for *S. pneumoniae*



Craig CID, 1998  
Nickolau AAC 2000

# Time Above MIC vs Efficacy in Acute Otitis Media and Acute Sinusitis

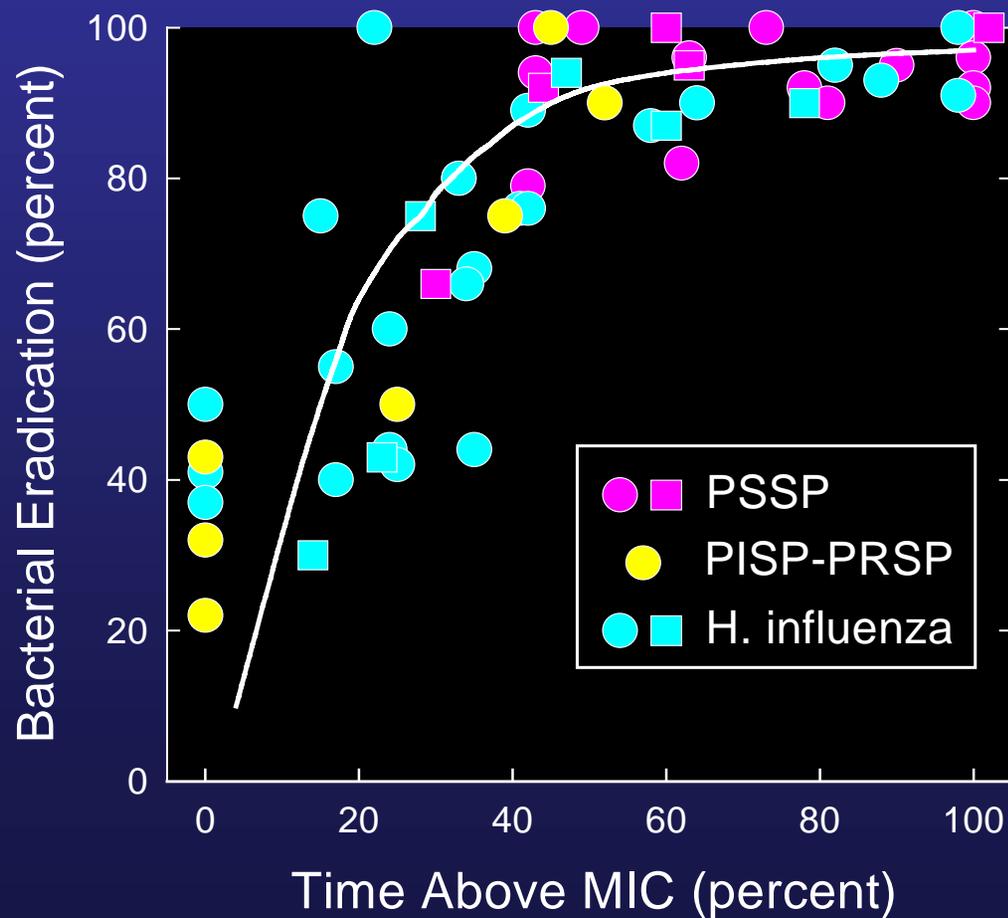
- Bacteriologic cure for different beta-lactams against *S. pneumoniae* and *H. influenzae* from double tap studies in acute otitis media and acute maxillary sinusitis
- Time above MIC calculated from serum levels and MICs for different organisms

Craig & Andes, *Pediatr Infect Dis J*, 1996

Dagan et al studies

Gwaltney & Scheld studies

# Relationship Between T>MIC and Bacterial Eradication with Beta-Lactams in Otitis Media (Circles) and Maxillary Sinusitis (Squares)



## General Conclusions

Time above MIC is the important determinant of activity for  $\beta$ -Lactams against major respiratory pathogens, including penicillin-resistant pneumococci

Studies in acute otitis media and sinusitis demonstrate a good correlation between the time above MIC required for bacteriologic cure of pneumococci and the time above MIC required for a 2 log kill or 90-100% survival in animal infection models

# What Does Theory Predict for the 90/6.4/day Formulation of Augmentin?

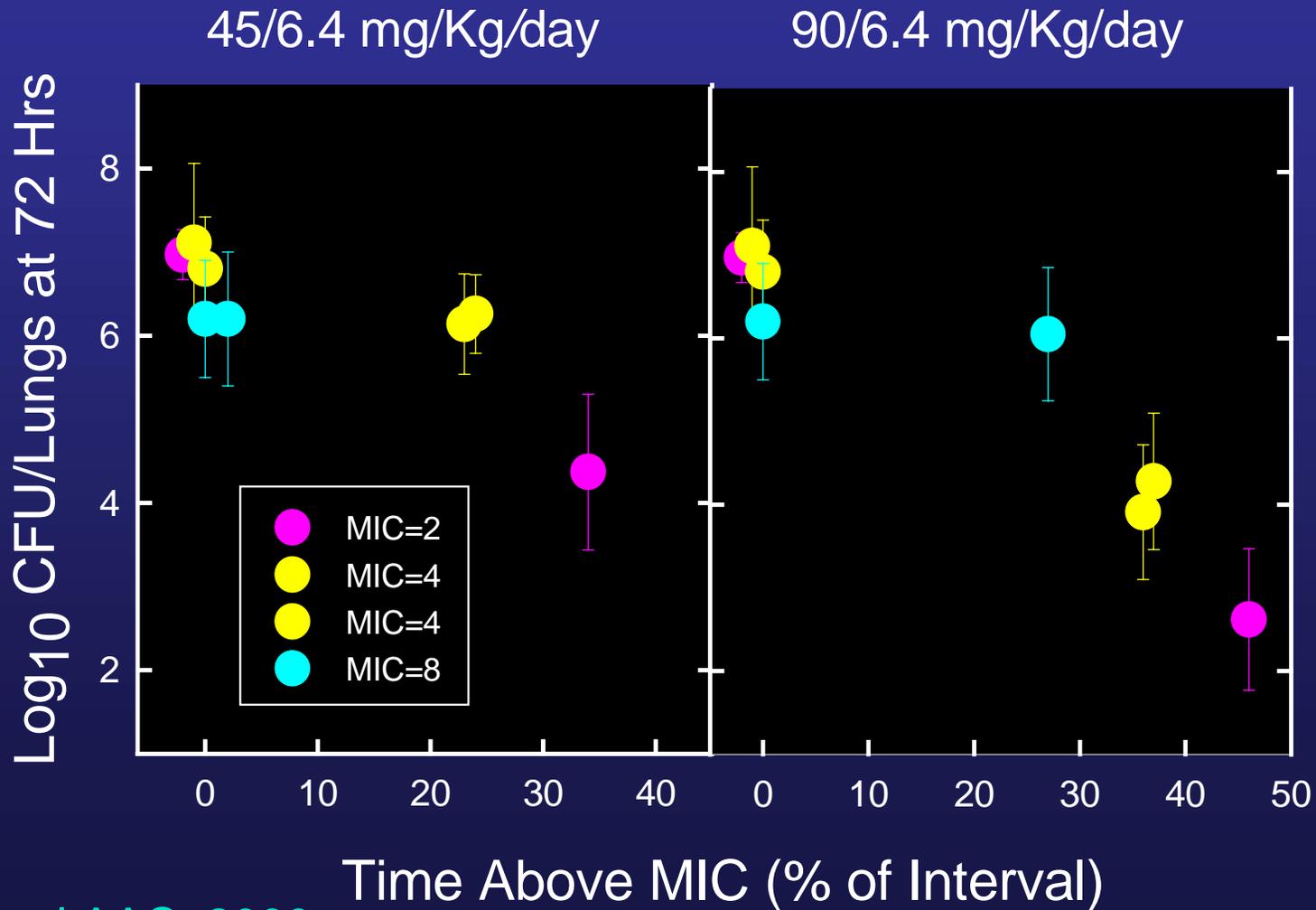
## Animal Data:

- Pneumonia study in rats with simulation of human pharmacokinetics

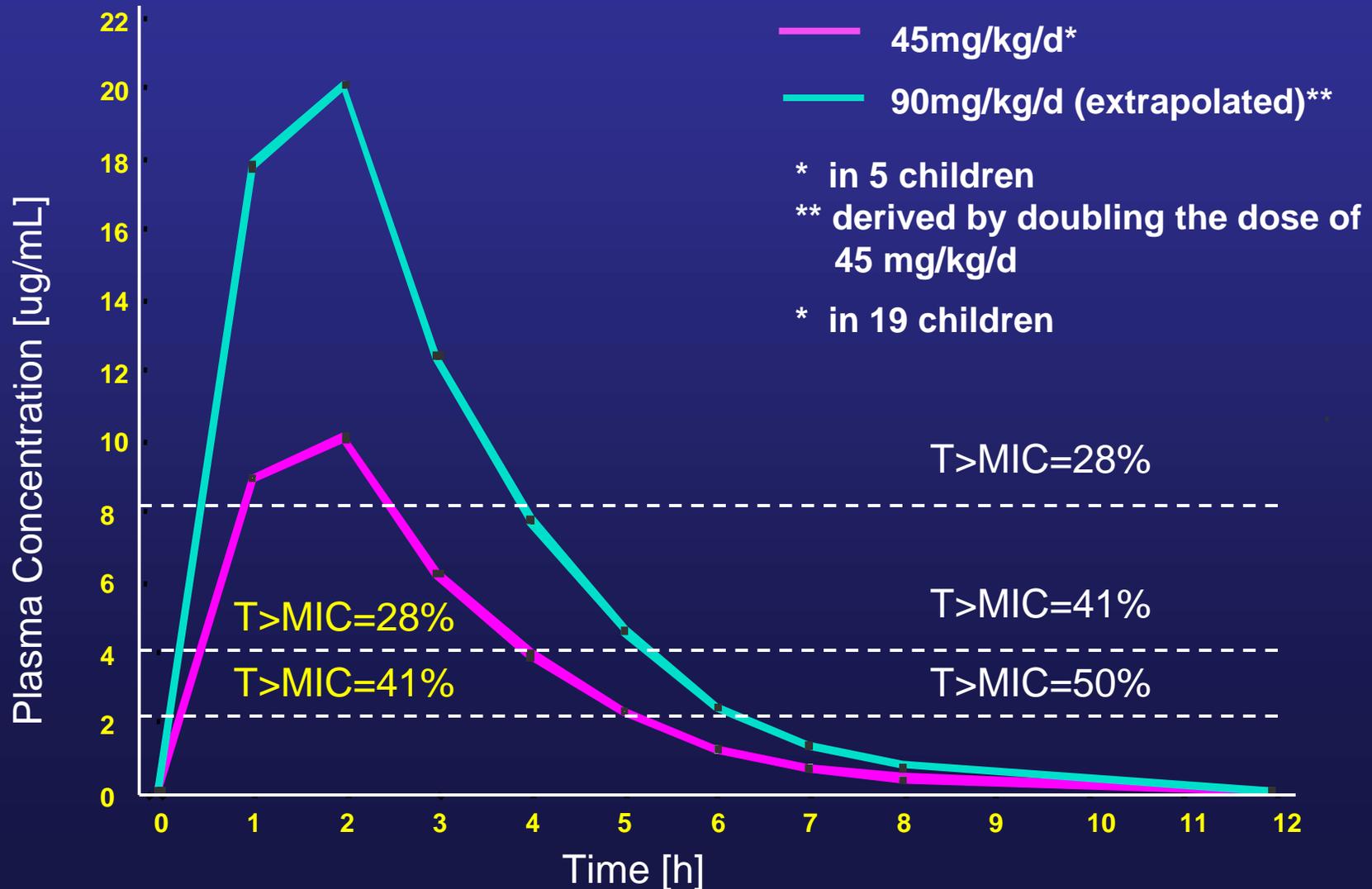
## Pharmacokinetic Data:

- Extrapolated data from 5 children that received 45/6.4 mg/Kg/day
- Recent study in 18 children that received 90/6.4 mg/Kg/day (mean age 5 years and range in age from 0.3-11 years)

# Efficacy of Simulated Human Concentrations of Amoxicillin/Clavulanate in Pneumococcal Respiratory Tract Infections in Rats



# DAILY 45 MG/KG Q12 VS 90 MG/KG Q12



# Mean amoxicillin plasma-concentration profile following administration of Augmentin 600 suspension (45/3.2 mg/kg) to paediatric patients (n=18)

