Application of PK/PD principles to RTIs

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Topics

- Examples of correlations between PK/PD predictions and outcome in human studies
  - Otitis media
  - Sinusitis
  - AECB
  - CAP
- Evaluation of new antibiotics
  - Quinolones
  - Telithromycin
- Development of PK/PD based MIC breakpoints

Outpatient Clinical Studies in Respiratory Tract Infections

- High rates of spontaneous resolution make it difficult to show differences in efficacy between agents
- The BEST objective measure of the effectiveness of an antibiotic is eradication of the pathogen from the site of infection
- Bacteriologic outcome studies are not often performed due to necessity for invasive procedures to obtain specimens
- Most studies are therefore designed to show equivalent clinical outcomes between established and new agents
- Inadequacies of agents studied are therefore often not apparent

Dagan R, et al. *Pediatr Infect Dis J.* 1998;17:776–782.

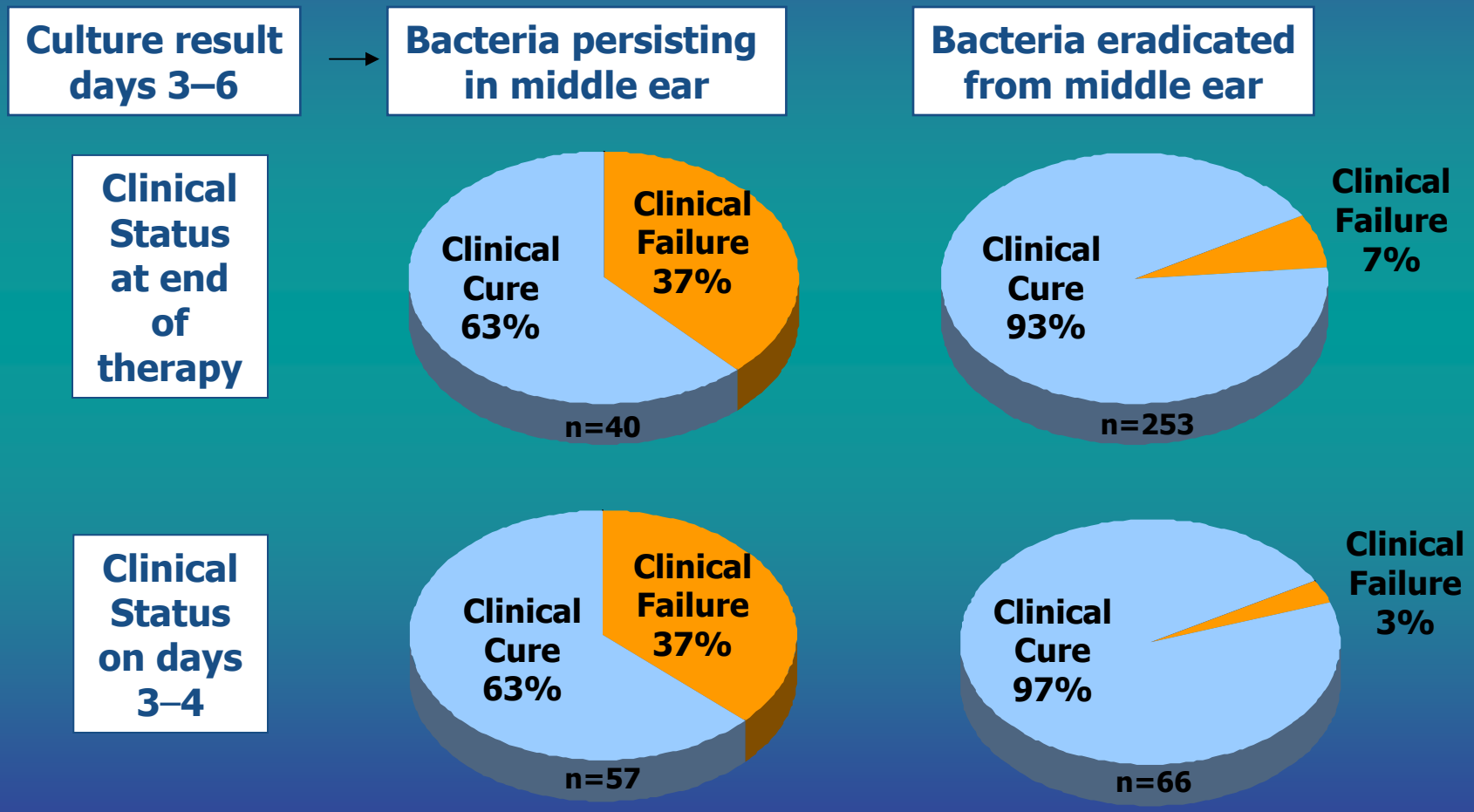
Choice of Antibacterial Therapy

- There is a need for
  - Statistically valid clinical studies
  - Accurate prediction of efficacy
  - Revised susceptibility breakpoints
  - Newer dosage regimens
  - Newer antibacterials

Outcomes in Trials of Antibacterial Drugs for AOM

- Measure of outcome
  - Clinical: Symptomatic improvement, or symptomatic and otoscopic improvement, etc.
  - Bacteriologic: Eradication of bacteria
  - Bacteriologic/Clinical: Clinical improvement plus eradication of bacteria in clinical failures
- Timing of outcome
  - During therapy
  - End of therapy
  - After therapy

Clinical versus Bacteriological Outcomes



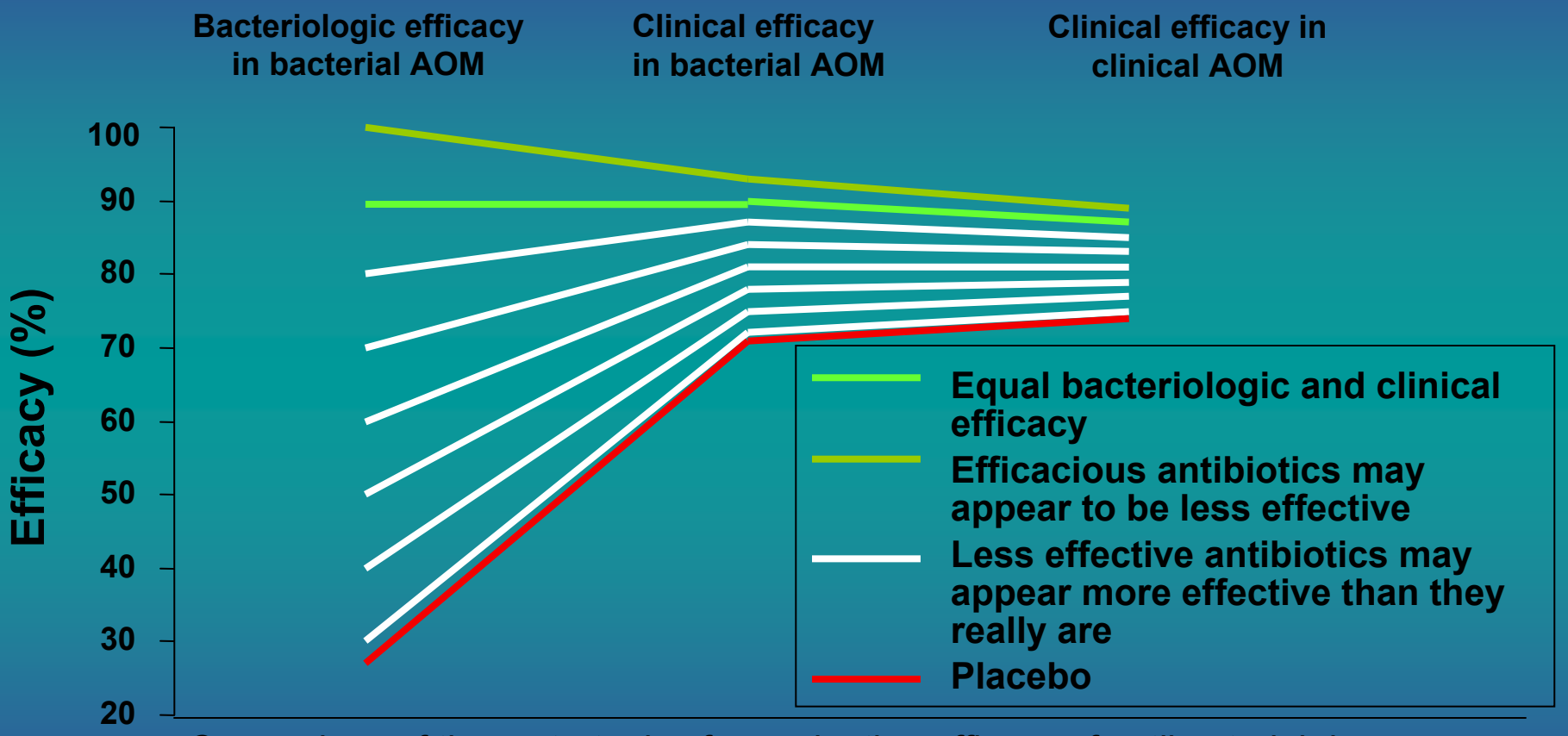
1. Adapted from Dagan R, et al. *PIDJ* 1998;17:776–782.
2. Adapted from Carlin SA, et al. *Pediatr* 1991;118:178–183.

Differentiating Between Antibiotics in AOM

- Bacteriologic outcome during therapy and clinical outcome at end of therapy have been shown to be the most useful time points to assess therapy
- Outcome by day 30 (Test-of-Cure) shows no relationship to treatment due to frequent new viral and bacterial infections
- Outcome is worse in patients with risk factors:
  - <2 years old
  - Prior AOM
  - Prior antibiotics
  - Daycare
  - Siblings

Dowell SF, et al. *Pediatr Infect Dis J.* 1999;18:1-9; Carlin SA, et al. *J Pediatr*. 1991;118:178-183; Klein JO. *Clin Infect Dis.* 1994;19:823–-833.

The Pollyanna Phenomenon

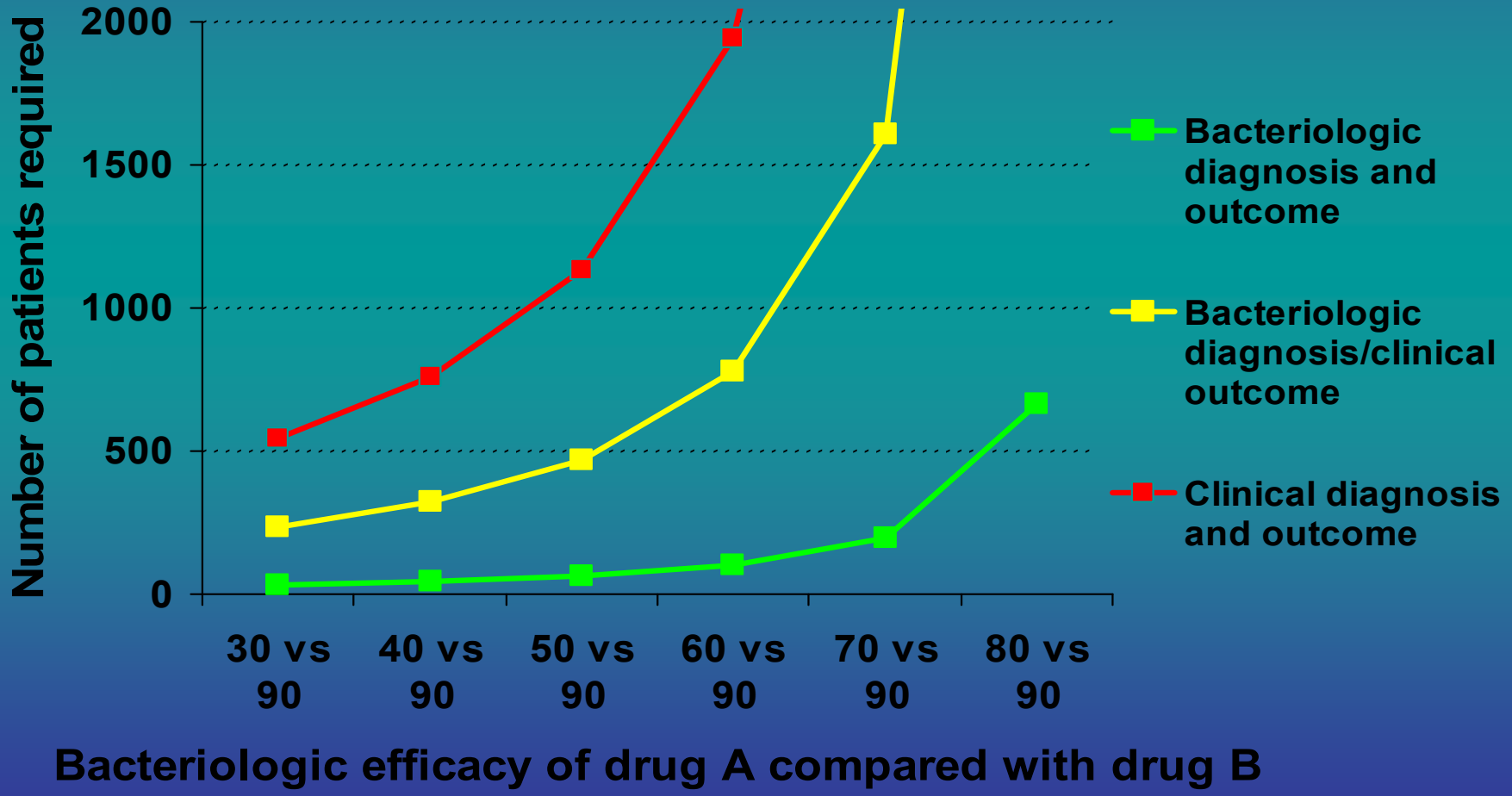


Comparison of three strategies for evaluating efficacy of antibacterial drugs for the treatment of AOM. For each hypothetical level of bacteriologic efficacy, calculated clinical efficacy rates are connected by solid line.

Marchant CD, et al. *J Pediatr* 1992;120:72–77.

Sample sizes required to detect differences between antibacterial drugs for acute otitis media

Comparison of bacteriologic versus clinical outcomes in trials of two drugs (half the patients would be in each arm of a study)

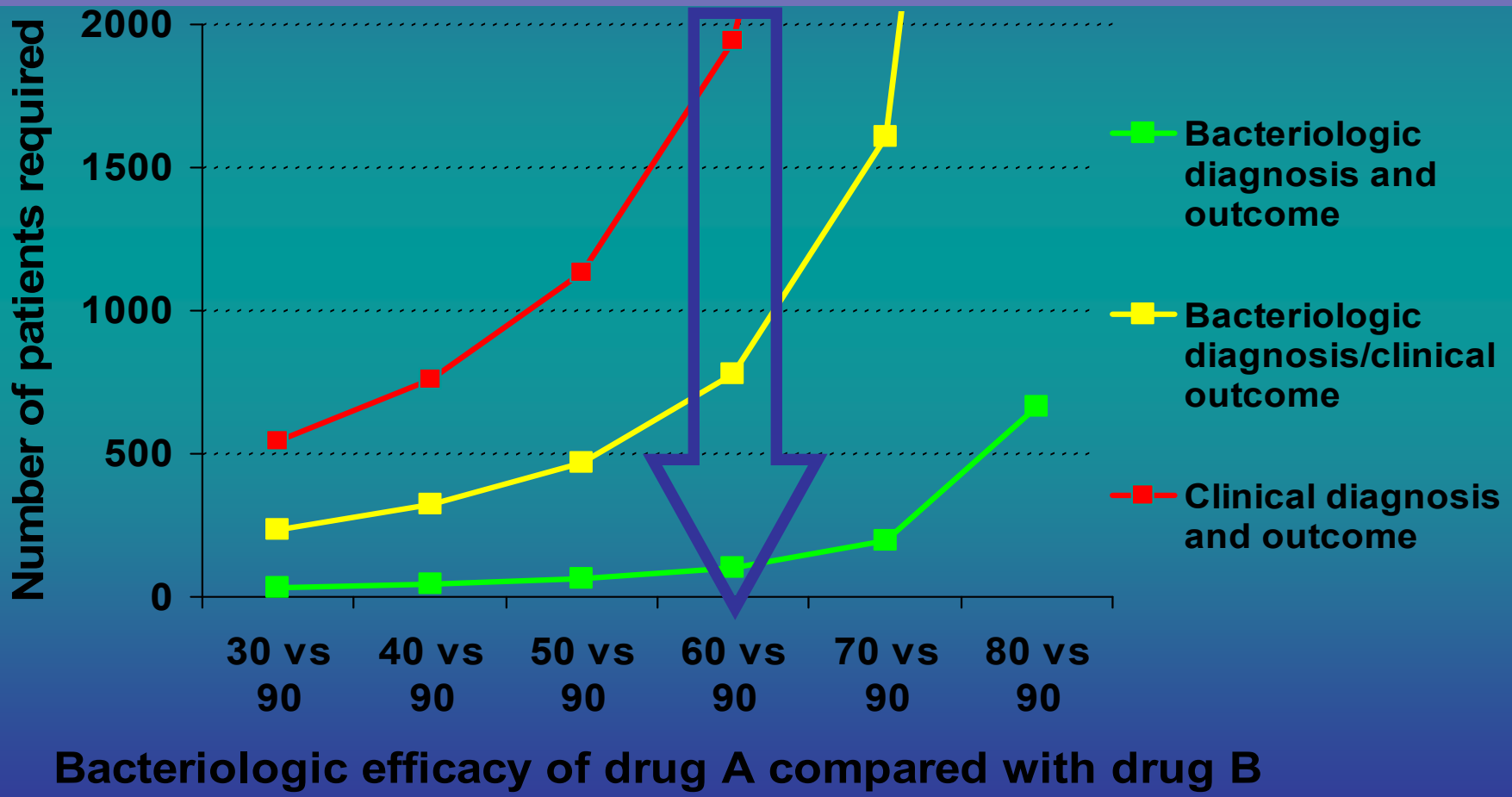


Marchant *et al*. *J Pediatr* 1992; **120**:72–77

Sample sizes required to detect differences between

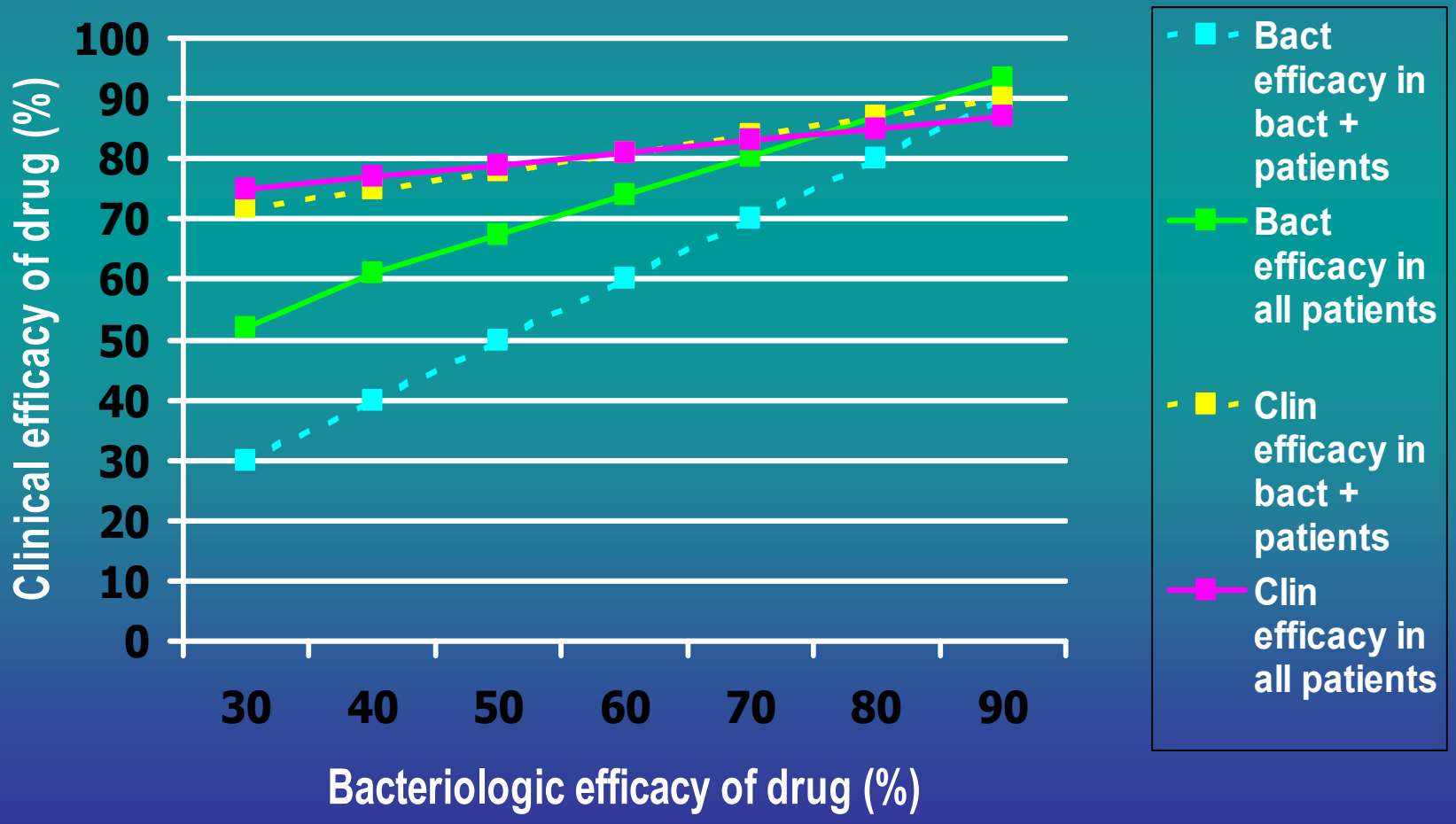
No. of patients required to detect 60 vs. 90% bacteriologic efficacy*:

- Clinical/clinical: 1934
- Bacterial/clinical: 780 bacteriologically evaluable
- Bacterial/bacterial: 100 bacteriologically evaluable



Marchant *et al. J Pediatr* 1992; **120**:72–77

Comparison of bacteriologic vs *clinical outcomes in AOM*



Marchant C. et al. *J Pediatr* 1992; **120**:72–77.

Theoretical Clinical Impact of Drug Efficacy in USA

Bacteriologic efficacy	Number of children with persistent symptoms on day 3–6 per million prescriptions	Number of children with persistent symptoms on day 3–6 per 20 million prescriptions
90%	20,000	400,000
70%	60,000	1,200,000
50%	100,000	2,000,000
30%	140,000	2,800,000

Based on Marchant CD, et al. *J Pediatr.* 1992;120:72–77.

Is *in vitro* Resistance Clinically Relevant?

- The correlation between antibacterial susceptibility and clinical outcome has been debated for decades
- Many variables can affect clinical outcome:
  - Severity of disease
  - Severe medical co-morbidity
  - Age of patient
  - Virulence of infecting pathogen
  - Bacterial load
  - PK/PD of antibacterial at site(s) of infection
  - Evolving new resistance mechanisms
  - Patient compliance

Bacteriologic Failure of Macrolide Therapy

- Numerous case reports with bacteriologic evidence for macrolide failure in patients infected with macrolide-resistant pneumococci
- Treatment failure documented with erythromycin, azithromycin, clarithromycin and josamycin
- Macrolide-resistant pneumococci cultured from blood and other normally sterile sites (children and adults)
- Pneumococcus with erythromycin MIC >8 μg/mL isolated from blood

Klugman KP, et al. *BMJ.* 1986;292:730.
Klugman KP. *Eur Resp J.* 2002;20(suppl 36):S1-S6.

24 Case Reports of Bacteriologic Failure of Macrolide Therapy of RTIs Caused By Drug-resistant Pneumococci

Agent	Site	MIC (µg/mL)
Erythromycin	Blood	>8
Erythromycin	Lung puncture	>8
Erythromycin	Lung puncture	>8
Erythromycin	Blood	>8
Erythromycin	Blood	>8
Erythromycin	Blood	>8
Erythromycin	Blood	>8
Clarithromycin	Blood	8
Clarithromycin	Blood	>8
Clarithromycin	Blood	>8
Clarithromycin	Blood	>8
Josamycin	Blood	>8
Josamycin	Blood	>8

Agent	Site	MIC (µg/mL)
Azithromycin	Blood	16
Azithromycin	Blood	8
Azithromycin	Blood	8
Azithromycin	Blood	>128
Azithromycin	Blood	8
Azithromycin	Blood	16
Azithromycin	Blood	16
Azithromycin	Blood	>8
Azithromycin	Blood	>8
Azithromycin	Blood	>8
Azithromycin	Blood	>8

Adapted from Klugman KP. *Eur Resp J.* 2002;20(suppl 36):S1-S6.

Case Reports of Macrolide-Resistant *S. pneumoniae* Bacteremia

	Patient 1	Patient 2	Patient 3	Patient 4
Presentation:	Pneumonia	Bronchitis	Pneumonia	AOM
Initial Therapy:	Azithromycin	Azithromycin	Clarithromycin	Azithromycin
	MIC µg/mL	**MIC µg/mL**	**MIC µg/mL**	**MIC µg/mL**
Penicillin	0.03 (S)	**0.4 (I)**	**0.25 (I)**	**0.5 (I)**
Ceftriaxone	0.12 (S)	0.2 (S)	0.12 (S)	0.12 (S)
Tetracycline	0.25 (S)	0.25 (S)	0.125 (S)	0.125 (S)
Erythromycin	**8 (R)**	**16 (R)**	**8 (R)**	**16 (R)**
Clindamycin	0.06 (S)	0.06 (S)	<0.016 (S)	0.06 (S)
Levofloxacin	1.0 (S)	0.5 (S)	1.0 (S)	0.5 (S)
Outcome:	Bacteremia	Bacteremia	Bacteremia	Bacteremia
Effective therapy:	Ceftriaxone + vancomycin; D/C pen V	Cefotaxime + azithromycin; D/C levofloxacin	Vancomycin	Ceftriaxone

Adapted from Kelley MA. *Clin Infect Dis.* 2000;31:1008-1011.

Case Reports of Macrolide-Resistant *S. pneumoniae* Bacteremia

Patient age:	8 mo	10 mo	44 yo	65 yo	52 yo
Presentation:	AOM	AOM	Cough, fever	Cough	Sinusitis, cough
Initial therapy:	TMP/SMX, cefixime, clarithromycin	Azithromycin	Azithromycin	Cephalexin, azithromycin,	Azithromycin
Site of isolation:	CSF, blood	CSF, blood	Blood, BAL	Blood, BAL	Blood
Outcome:	Meningitis Survived	Meningitis Survived	Bacteremia Survived	Pneumonia Survived	Pneumonia Survived
MICs (mg/mL):					
Penicillin	0.06 (S)	**0.12 (I)**	**2 (R)**	**1 (I)**	**2 (R)**
Cefotaxime/ ceftriaxone	0.12 (S)	0.06 (S) -	**1 (I)**	0.5 (S)	0.5 (S)
TMP/SMX	**4/80 (R)**	-	**8/152 (R)**	-	**4/76 (R)**
Erythromycin	**2 (I)**	**>256 (R)**	-	-	-
Azithromycin	**4 (R)**	-	**8 (R)**	**8 (R)**	**>128 (R)**
Clarithromycin	**1 (I)**	-	-	-	-
Clindamycin	≤0.12 (S)	-	0.25 (S)	-	**>256 (R)**
Cefixime	1	-	-	-	-
Levofloxacin	-	-	0.5 (S)	1 (S)	0.5 (S)

Reid R, et al. *Pediatr Infect Dis J*. 1995;14:1104-1105.
Jackson MA, et al. *Pediatr Infect Dis J*. 1996;15:1049-1051.
Fogarty C, et al. *Clin Infect Dis*. 2000;31:613-615.

Resistance Mechanisms of *S. pneumoniae:* Macrolides

- **Active efflux—M phenotype (*mef*)**
  - **Efflux pump associated with *mefE* gene**
  - **MICs in range of 1-32 µg/mL**
  - **Usually susceptible to clindamycin**
- **Target modification—MLS_B phenotype (*erm*)**
  - **Methylation of 23S ribosomal RNA blocks binding of macrolides/azalides**
  - **Ribosomal methylase encoded by *ermAM* gene**
  - **MICs >64 µg/mL**
  - **Resistant to Macrolides, Lincomycins (e.g., clindamycin) and Streptogramin B**

Shortridge VD, et al. *Diagn Microbiol Infect Dis.* 1996;26(2):73-78.
Roberts MC, et al. *Antimicrob Agents Chemother.* 1999;43(12):2823-2832.
Tait-Kamradt A, et al. *Antimicrob Agents Chemother.* 2000;44(12):3395-3401.
Johnston NJ, et al. *Antimicrob Agents Chemother.* 1998;42(9):2425-2426.

Bacteriologic Failure of Macrolide Therapy for *S. pneumoniae*

- Analysis of treatment failures documents a threshold for bacteriologic failure at an MIC of ~8 µg/mL
- Level unachievable for 50% of the dosing interval in patients treated with IV erythromycin
- Bacteriologically documented failures in patients infected with pneumococci expressing *mefE* resistance with MIC ≥8 µg/mL
- Level of MIC is more important predictor of clinical relevance of macrolide resistance than presence of *mefA* gene

Klugman KP. *Eur Respir J.* 2002;20:(suppl 36)S1-S6.
Kelley MA. *Clin Infect Dis.* 2000;31:1008.

Emergence of Macrolide-R During Therapy of Pneumococcal Pneumonia

- Case Report: 28-year old male (previously healthy)
  - 5-day history of cough/dyspnea; hypotension; hypothermia; rales; WBC 14,000 mm^3 (28% bands); RUL and RML infiltrates
  - *S. pneumoniae* cultured from sputum; negative blood culture
- Empirical therapy with 500 mg azithromycin IV
  - Condition improved rapidly; 4th day of treatment sudden deterioration; pneumococci isolated from BAL and pleural fluid
  - Ceftriaxone+vancomycin given but patient died (multi-organ failure)
- Initial isolate fully susceptible to all antibiotics tested including penicillin (MIC <0.016 µg/mL), clindamycin (MIC 0.008 µg/mL), azithromycin (MIC 0.008 µg/mL)
- Later isolate, although still susceptible to penicillin and clindamycin, resistant to azithromycin and quinupristin-dalfopristin (MICs 2 to 4 µg/mL)
- Not e*rm* or *mef*; insertion in gene of ribosomal protein L22

Musher DM, et al. *N Engl J Med*. 2002;346:630–631.

Case Reports: Clinical Failure of Levofloxacin in Patients with Quinolone-resistant *S. pneumoniae*

- **Levofloxacin treatment failure in pneumococcal pneumonia[1]**
  - **63-year-old male with community-acquired pneumonia (CAP); received levofloxacin for bronchitis days earlier**
  - **Levofloxacin started in hospital; persistent disease**
  - ***S. pneumoniae* (sputum) levofloxacin MIC >32 µg/mL; improved with ceftriaxone**
- **Three levofloxacin treatment failures of pneumococcal RTI[2]**
  - **Three cases of *S. pneumoniae* infection (CAP, chronic sinusitis, hospital-acquired pneumonia)**
  - **Baseline isolates from two patients were levofloxacin-R (MICs >4 to >32 µg/mL)**
  - **Two patients had significant history of prior fluoroquinolone use**
- **Levofloxacin failure in a patient with pneumococcal pneumonia[3]**
  - **53-year-old male with pneumococcal pneumonia and underlying comorbidities**
  - **Pen-S MIC 0.0023 µg/mL, but treated with levofloxacin due to local penicillin shortage**
  - **Levofloxacin-R MIC 6 µg/mL resulted in clinical failure**

1. Kuehnert MJ, et al. *Ann Intern Med.* 1999;131:312–313.
2. Fishman MA, et al. *39th ICAAC.* San Francisco, 1999; Abstract 825.
3. Empey PE, et al. *Ann Pharmacother.* 2001;35:687–690.

Characteristics of *S. pneumoniae* Isolated Before (b), During (d), or After (a) Therapy with Levofloxacin from Four Patients with CAP

Patient	Source and time	Serotype	MIC (μg/mL)			Amino acid substitution	
			LEVO	MOXI	GATI	PAR C	GYR A
1	Sputum-b	23F	1(S)	0.12(S)	0.25(S)	–	–
	Sputum-a	23F	8(R)	1(S)	2(I)	S79F	S81F
2	Sputum-b	6A	4(I)	0.25(S)	0.5(S)	S79F	–
	Sputum-d	6A	16(R)	4(R)	4(R)	S79F	S81F
3*	Blood-b	14	16(R)	4(R)	2(I)	S79F	S81Y
	Pleural fluid-d	14	16(R)	4(R)	2(I)	S79F and D83Y	S81Y
4*	Sputum-d	ND	16(R)	4(R)	8(R)	S79Y	E85K

* Prior fluoroquinolone exposure

Davidson R, et al. *N Engl J Med.* 2002;346:747–750.

Understanding Bacteriologic Failure Due to Penicillin Resistance in Invasive Pneumococcal Pneumonia

- **Azoulay-Dupuis[1]**
  - Primary determinant of decreased virulence might be the serotype, rather than acquired penicillin resistance (animal model)
- **Quach[2]**
  - Invasive infections caused by PRSP and PSSP do not differ in clinical presentation, morbidity or mortality in a pediatric population
  - PRSP associated with increased length of ICU stay
- **Moroney[3]**
  - Factors other than resistance, such as severity of illness at presentation have a stronger influence on pneumococcal pneumonia outcomes
- **Bedos[4]**
  - 465 patients with pneumococcal pneumonia (29% Pen-I and 10.5% Pen-R), majority treated with β-lactams. No significant difference in mortality between Pen-S (18%) and Pen-I and Pen-R (14%) groups
- **Klugman[5]**
  - Recent review of the available evidence suggests that penicillin and amoxicillin are not associated with bacteriologic failure in penicillin resistant pneumoccocal pneumonia

1. Azoulay-Dupuis E, et al. *Antimicrob Agents Chemother.* 2000;44:1575–1577; 2. Quach C, et al. *ICAAC.* 2000: Abstract 1862; 3. Moroney JF, et al. *Clin Infect Dis.* 2001;33:797–805; 4. Bedos JP, et al. *ICAAC.* 2001: Abstract L-851; 5. Klugman K. *Eur Respir J.* 2002;20(suppl 36):S1–S6.

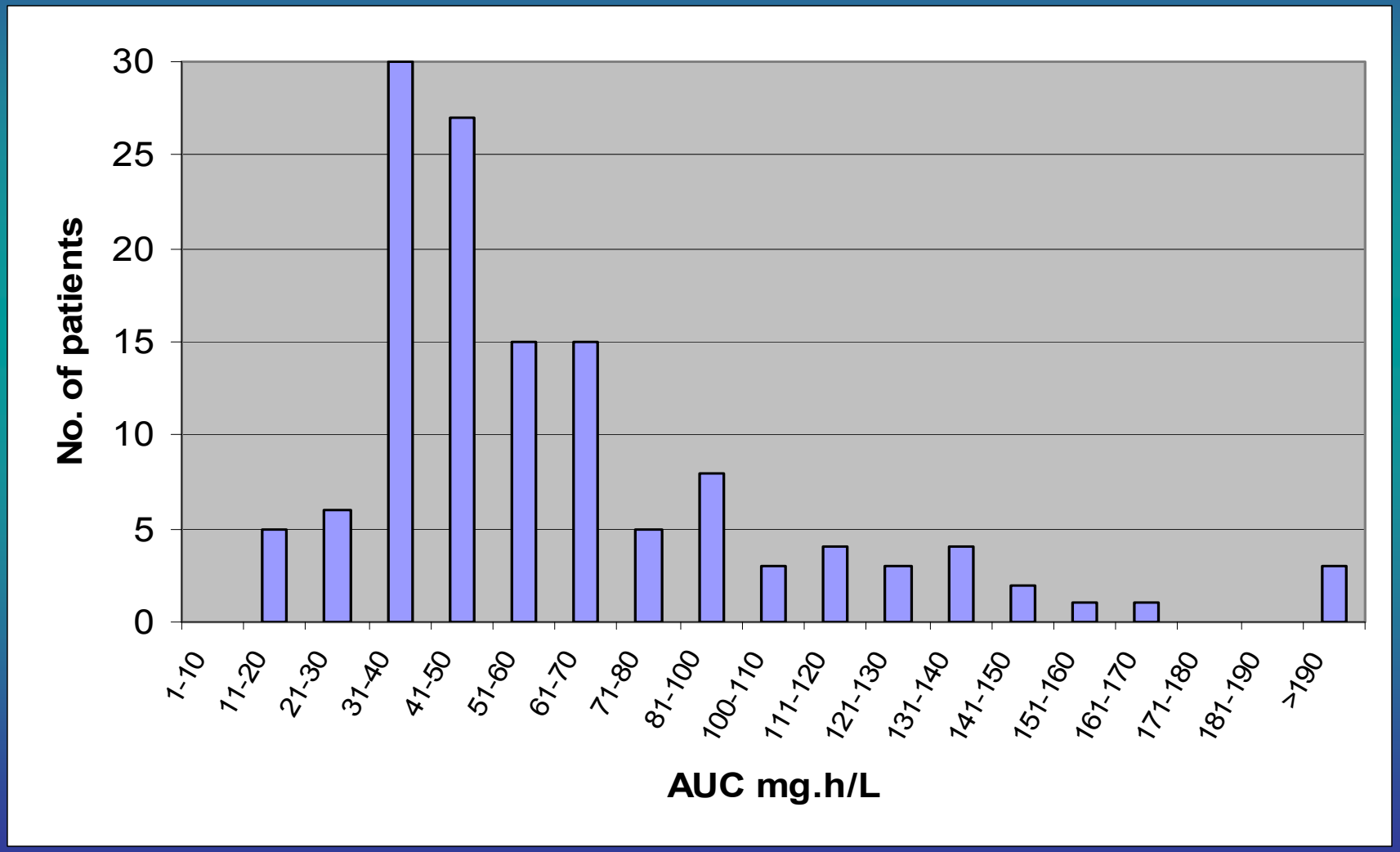
Levofloxacin pharmacodymanic study

- 134 hospitalized patients with culture-proven respiratory tract (N=100), skin/soft tissue (N=25) or complicated urinary tract (N=9) infections
- Commonest pathogens:
  - Streptococcus pneumoniae (N=21)
  - Staphylococcus aureus (N=15)
- Treated with IV levofloxacin 500 mg qd for 5-14 days
- Clinical (N=134) and bacteriological (N=116) outcomes followed

Preston SL, Drusano GL, Berman AL, Fowler CL,Chow AT, Dornseif B, Reichl V, Natarajan J, Corrado M. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 1998, 279:125-129

Levofloxacin AUCs

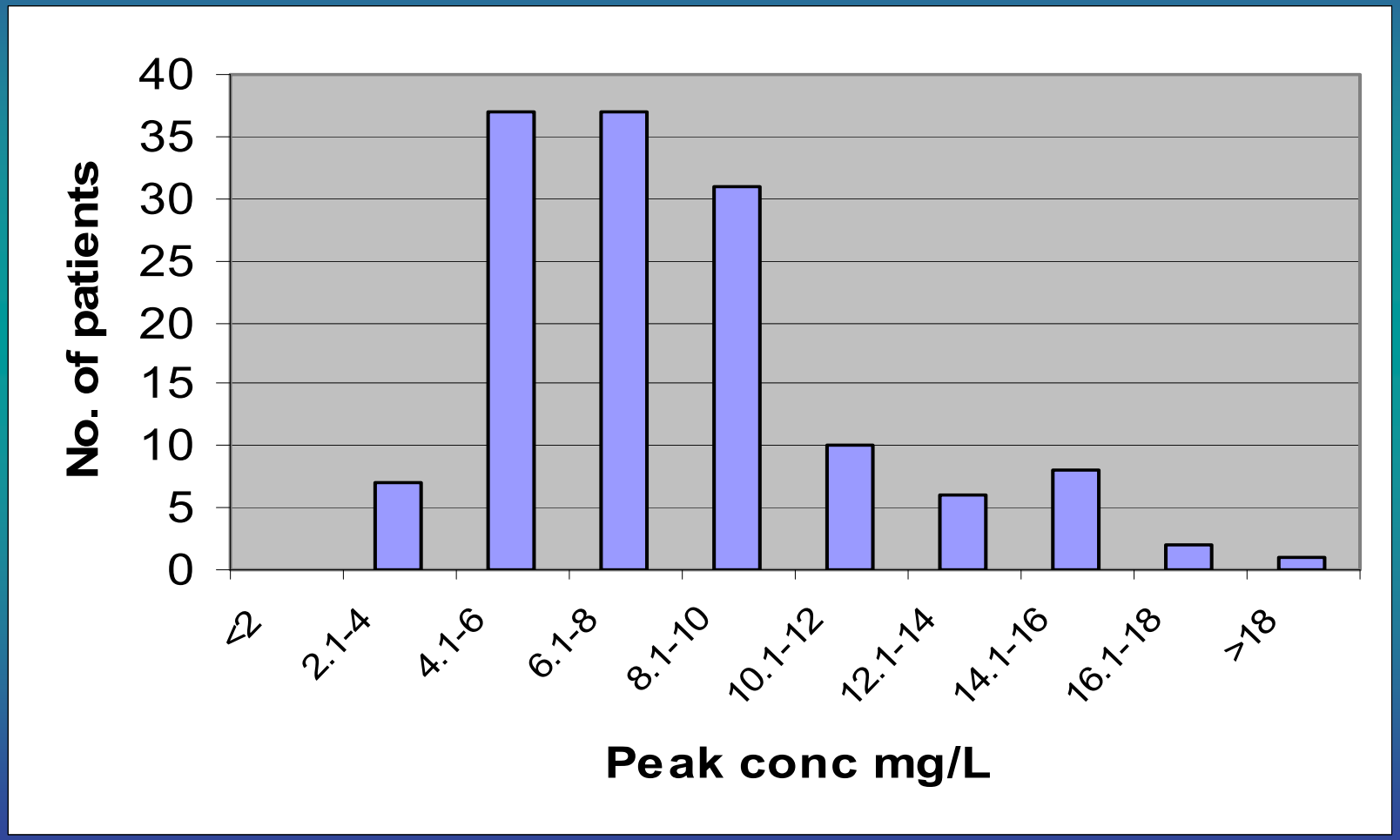
134 patients with resp, skin or urinary infections



Adapted from Preston et al., JAMA 1998, 279:125-129

Levofloxacin Peak Serum Concs.

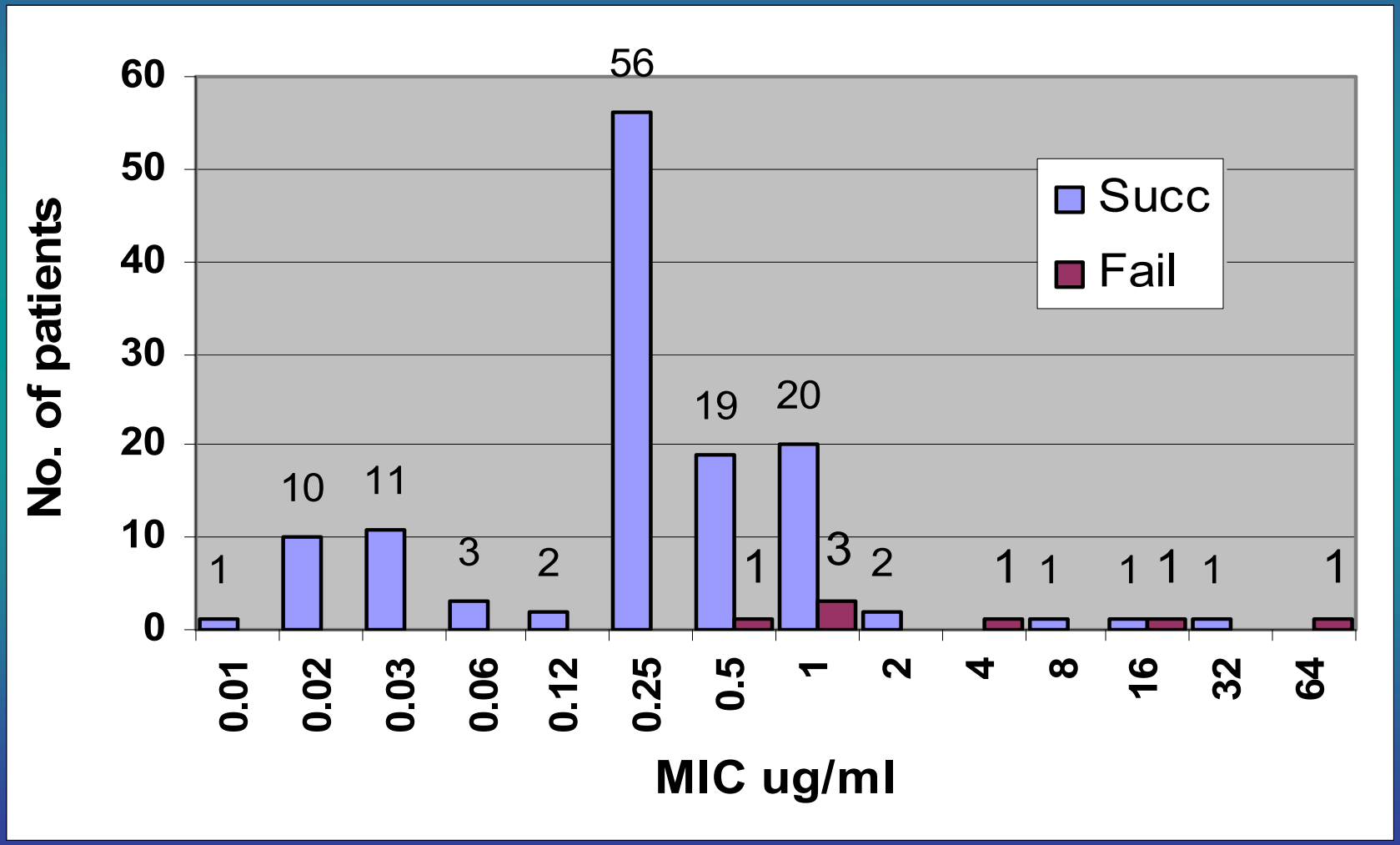
134 patients with resp, skin or urinary infections



Adapted from Preston et al., JAMA 1998, 279:125-129

Levofloxacin MICs

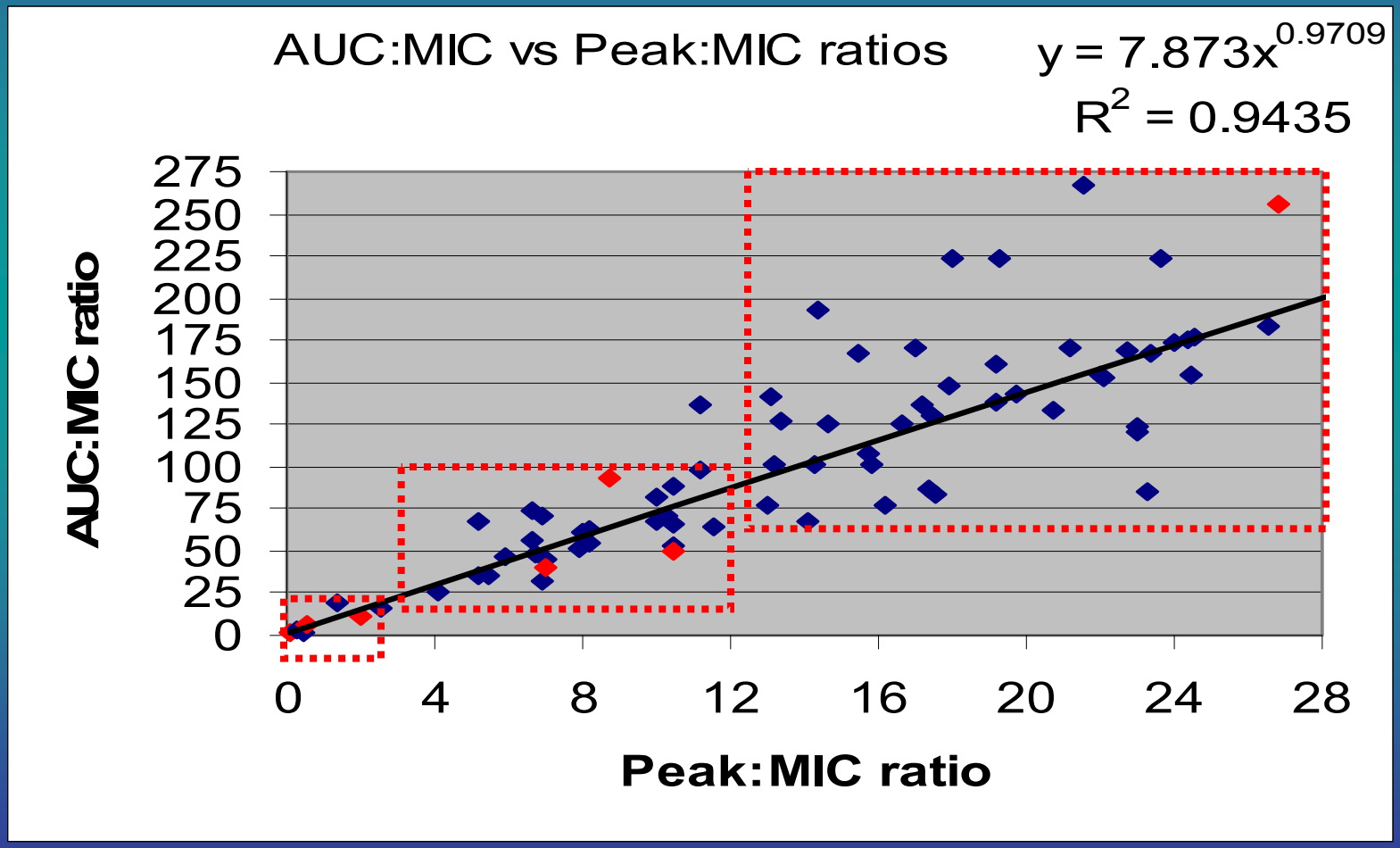
134 patients with resp, skin or urinary infections



Adapted from Preston et al., JAMA 1998, 279:125-129

Levofloxacin PK/PD vs. clinical outcome

134 patients with resp, skin or urinary infections



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Levofloxacin MICs vs. clinical outcome

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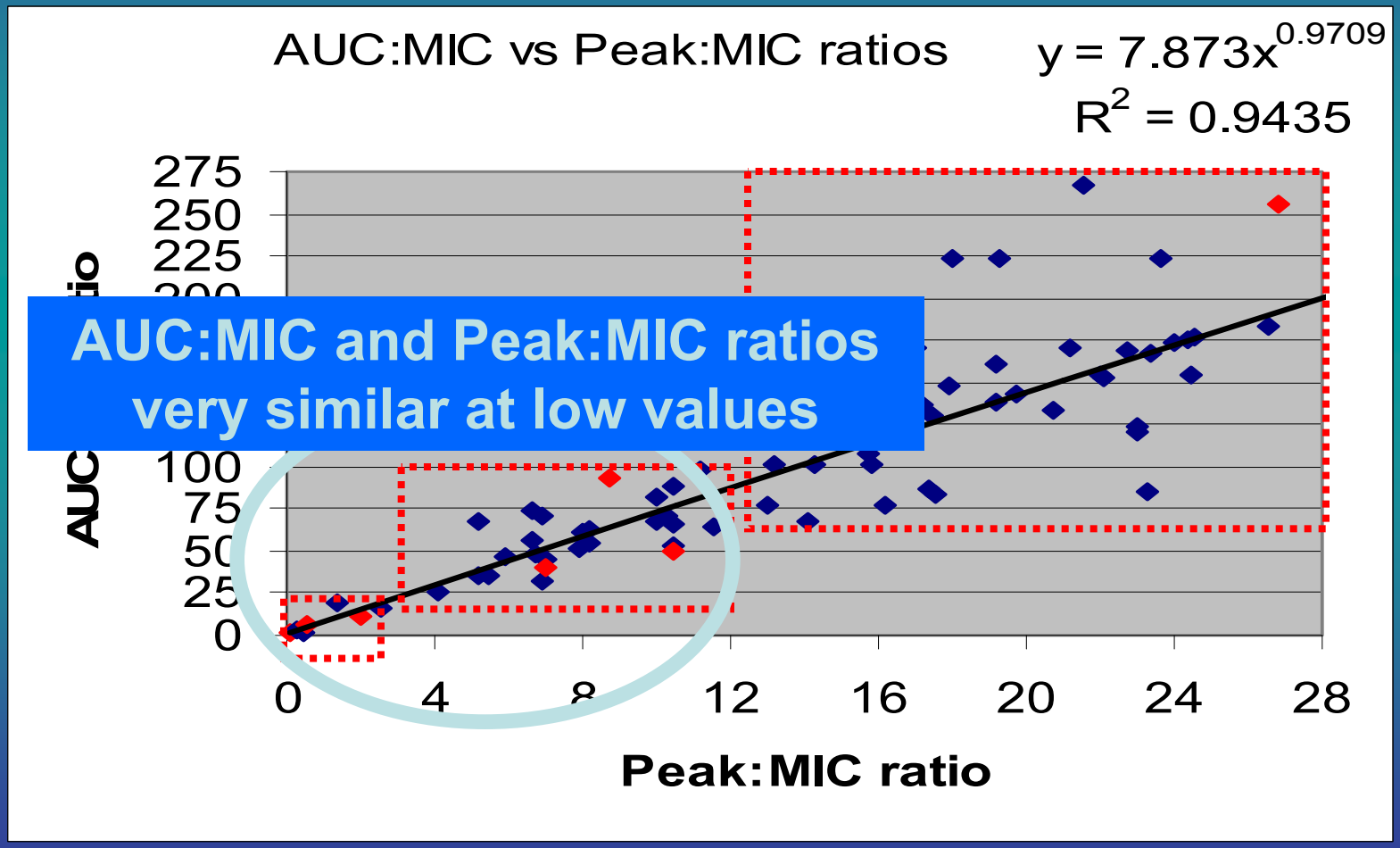
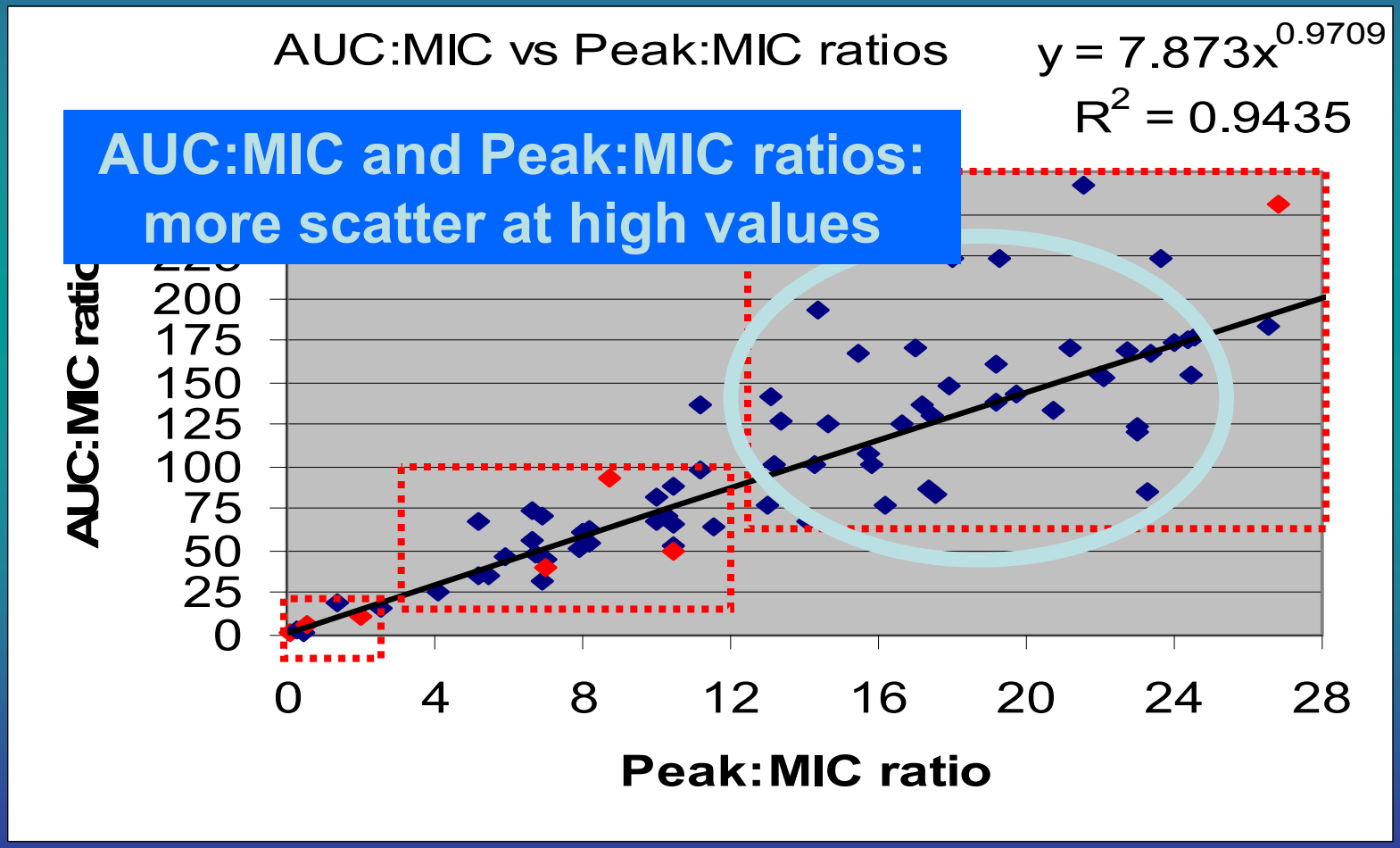


Adapted from Preston et al., JAMA 1998, 279:125-129 and published in Jacobs, M.R. (2001). Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. *Clinical Microbiology and Infection* 11, 589–96

Levofloxacin MICs vs. clinical outcome

134 patients with resp, skin or urinary infections



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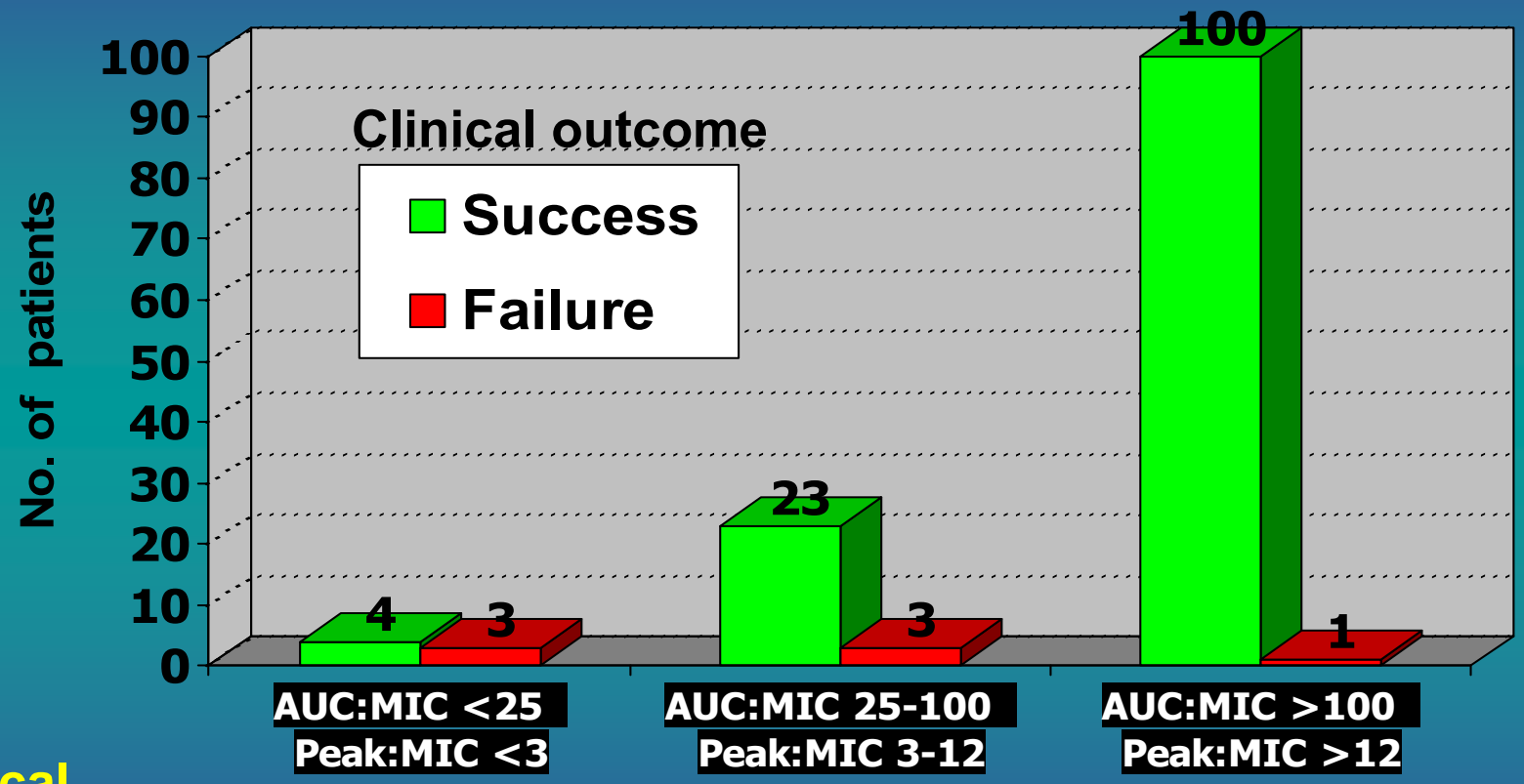
Levofloxacin PK/PD correlations with clinical outcome

134 hospitalized patients with respiratory tract, skin or complicated urinary tract infections treated with 500 mg qd for 5-14 days



Clinical failure rate **43%** **11.5%** **1%**

For AUC:MIC ratios <25 vs. >25, P=.003; for ratios <100 vs. >100, P=.001 (Fisher)

Adapted from Preston et al., JAMA 1998, 279:125-129 and published in Jacobs, M.R. (2001). Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. *Clinical Microbiology and Infection* 11, 589–96

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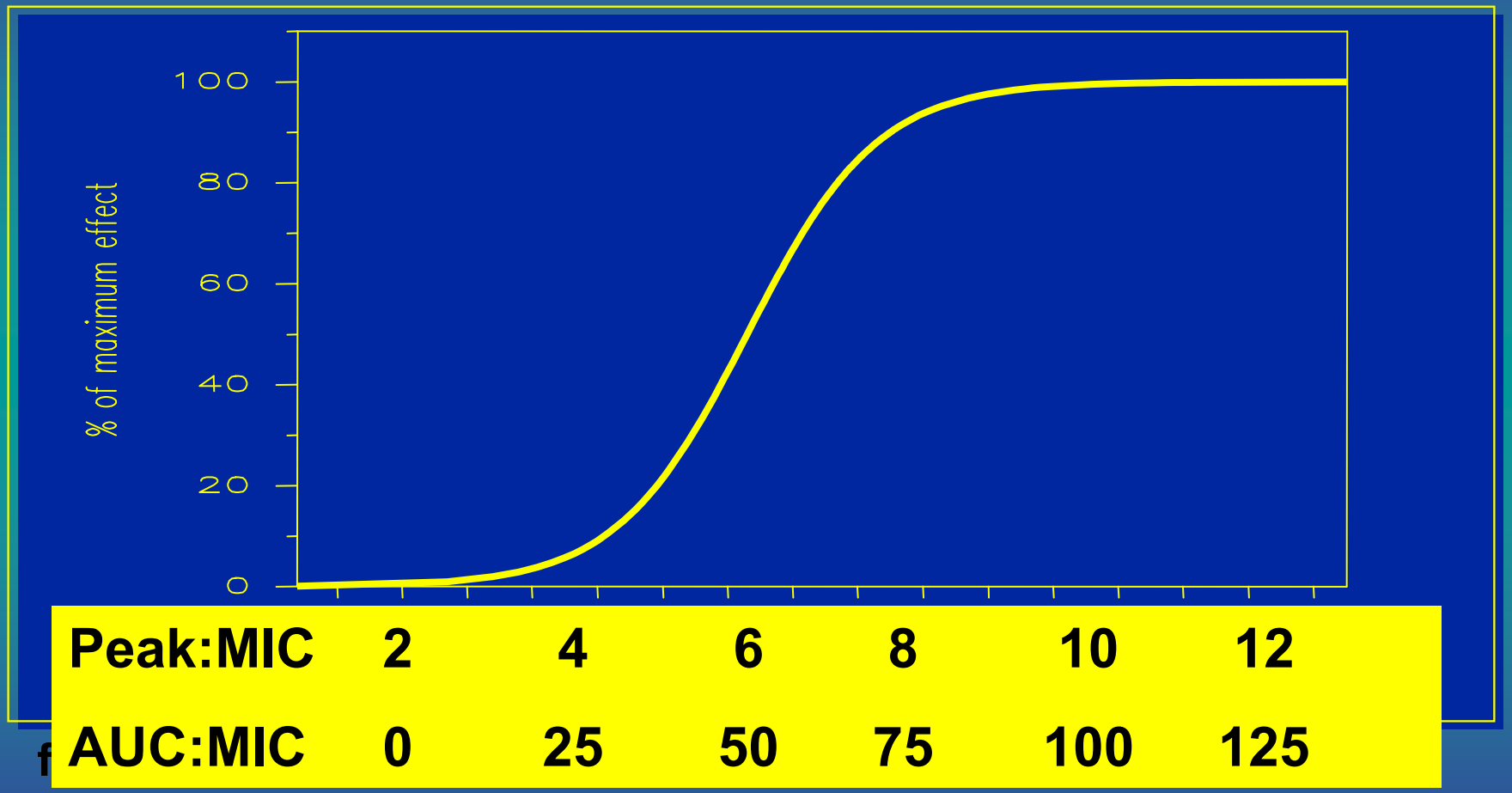


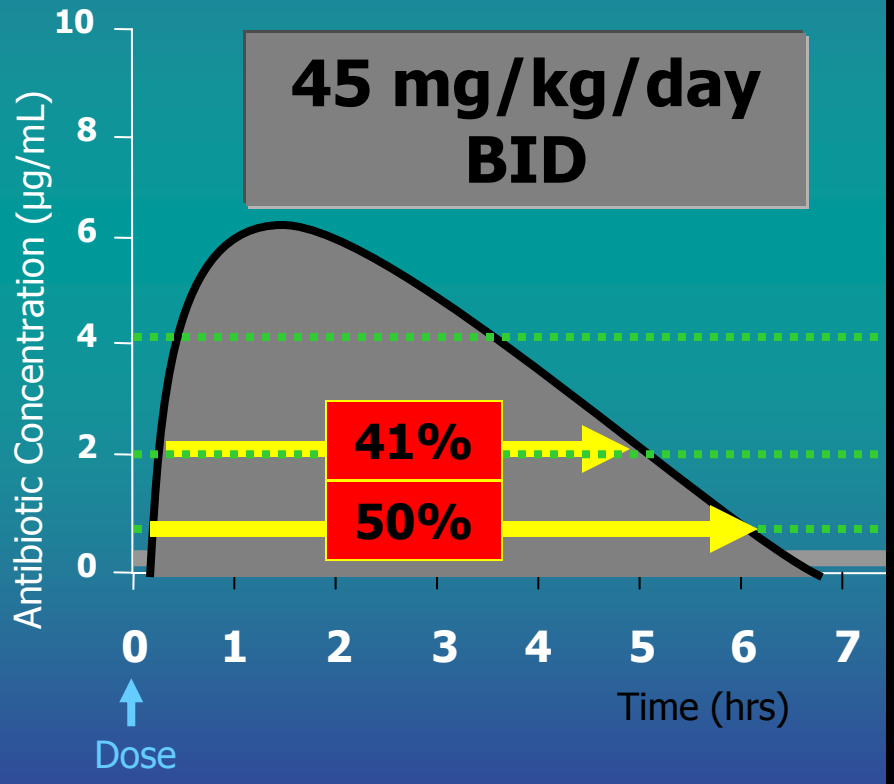
Adapted from Preston et al., JAMA 1998, 279:125-129 and published in Jacobs, M.R. (2001). Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. *Clinical Microbiology and Infection* 11, 589–96

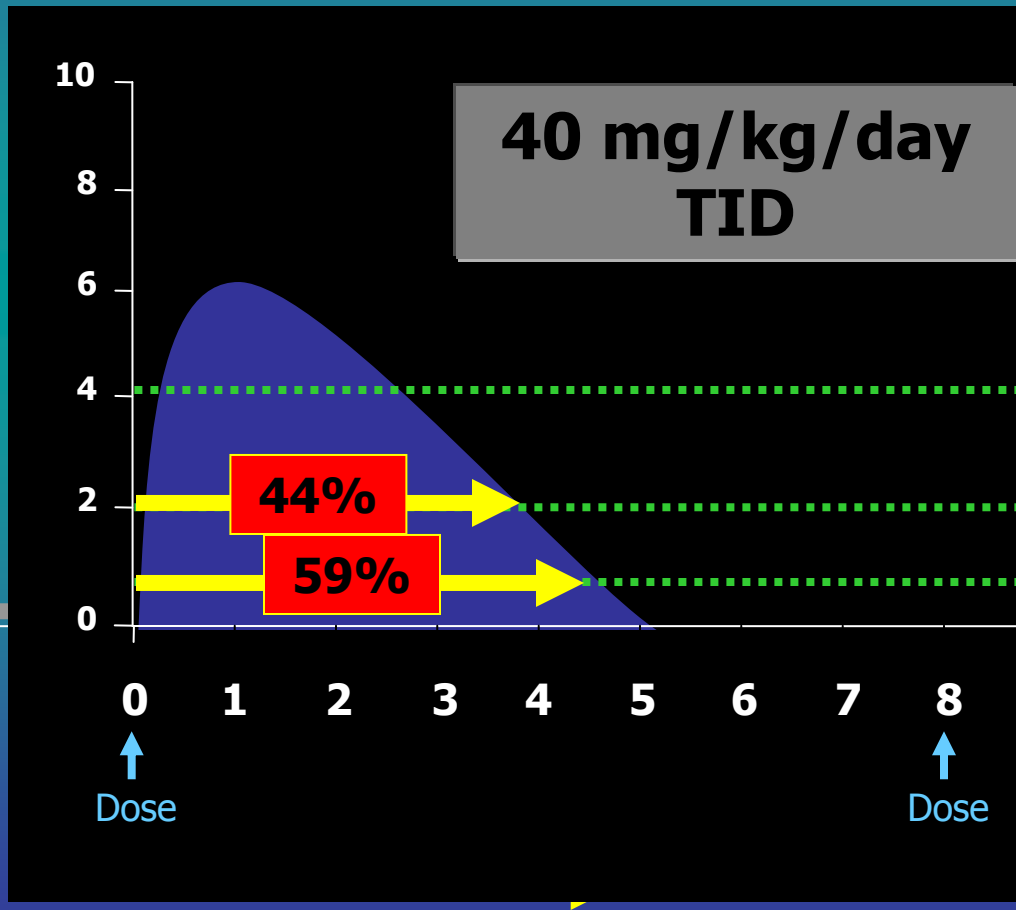
Optimizing PK/PD parameters

Amoxicillin: "Time above MIC"

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed at 12 h at 45 mg/kg/d and at 8 h at 40 mg/kg/d



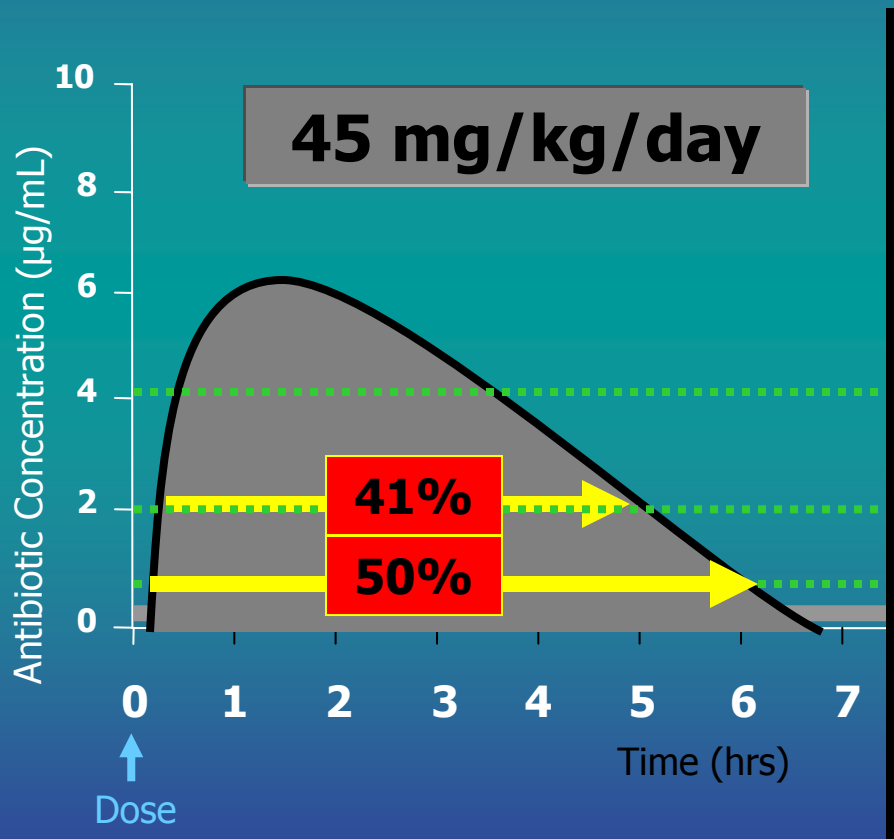


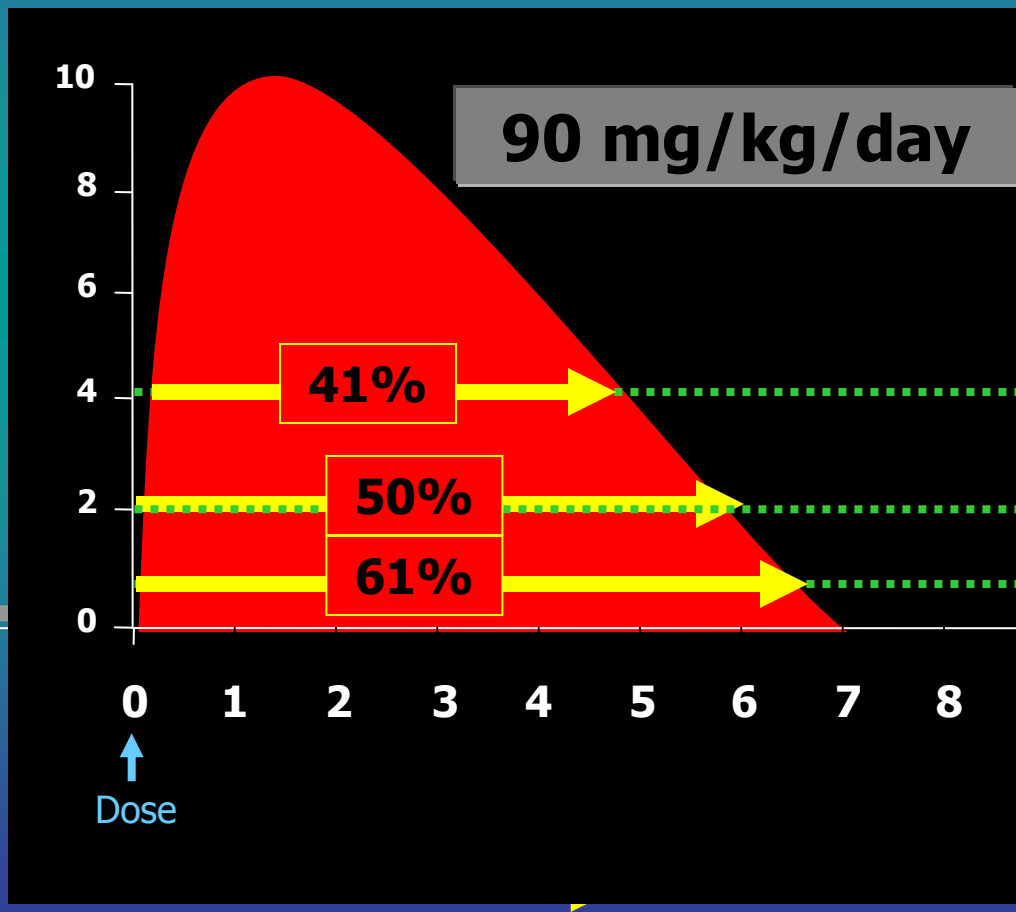
Adapted from Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg.* 2000;123:S1-S32; and Clive Kay, personal communication. GSK data on file

Amoxicillin: "Time above MIC"

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed every 12 hours at 45 and 90 mg/kg/d



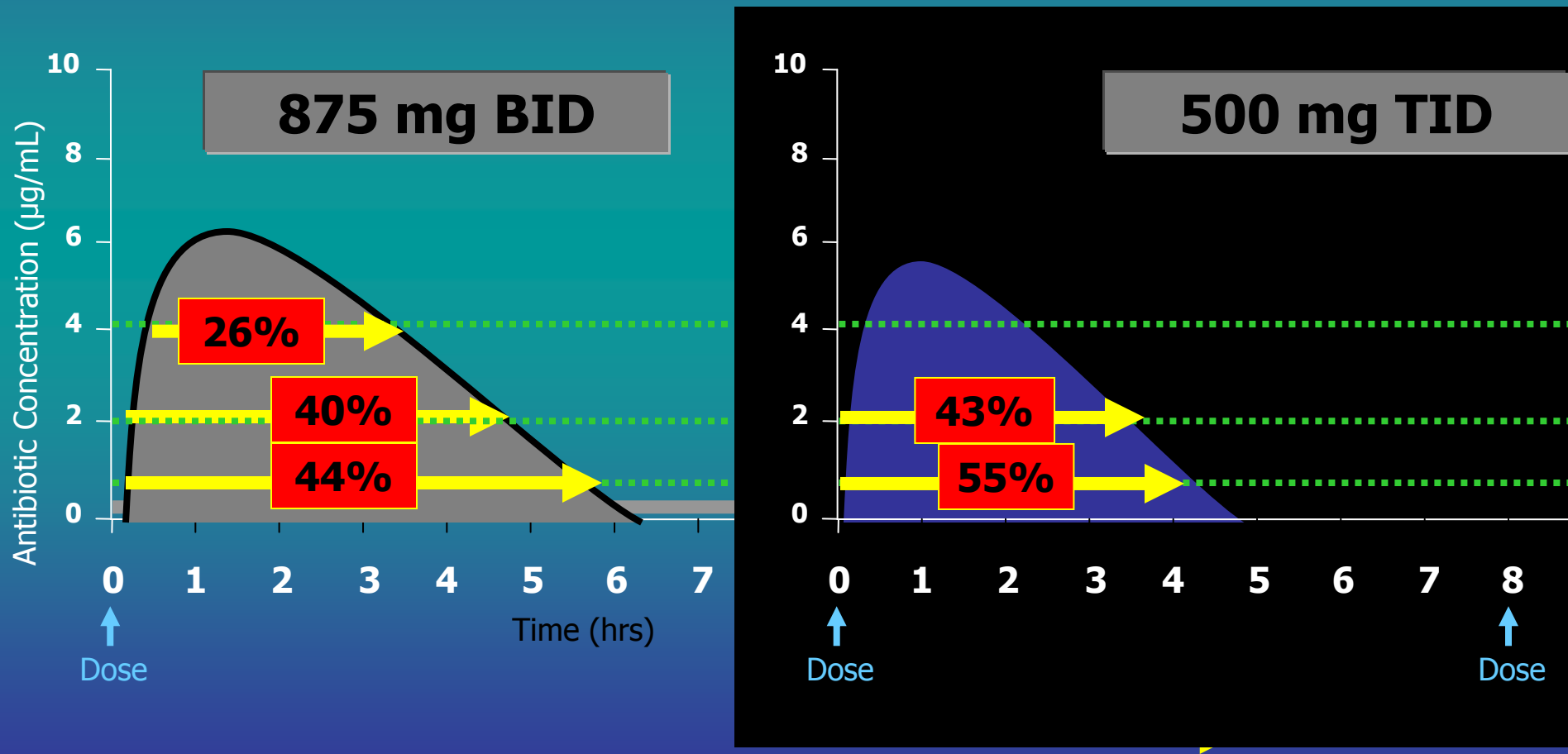


Adapted from Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg.* 2000;123:S1-S32; and Clive Kay, personal communication. GSK data on file

Amoxicillin: "Time above MIC"

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed at 12 h at 875 mg and at 8 h at 500 mg

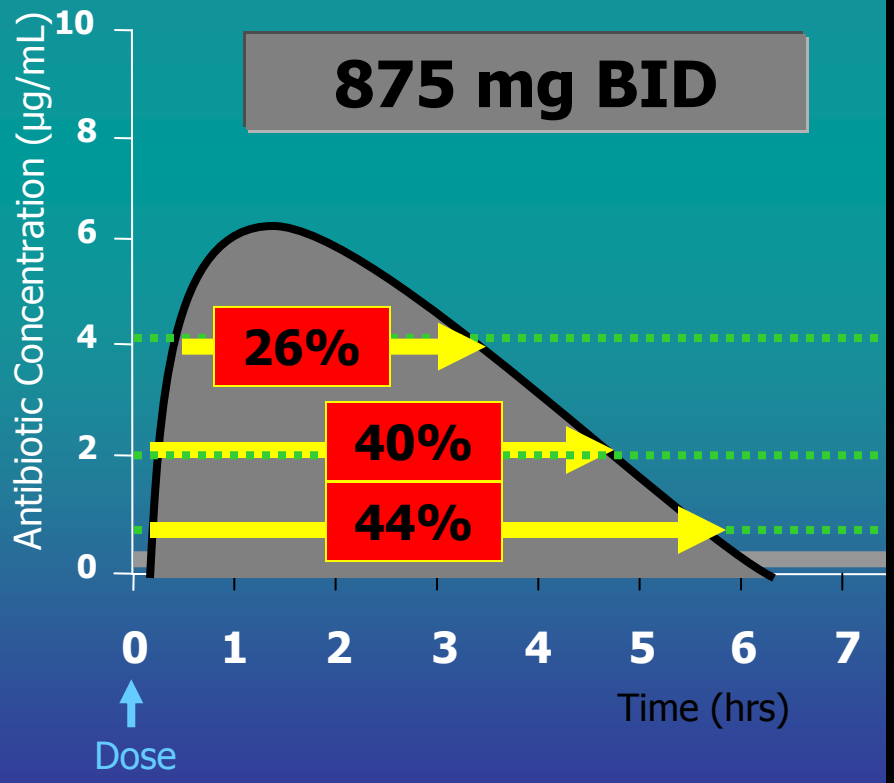


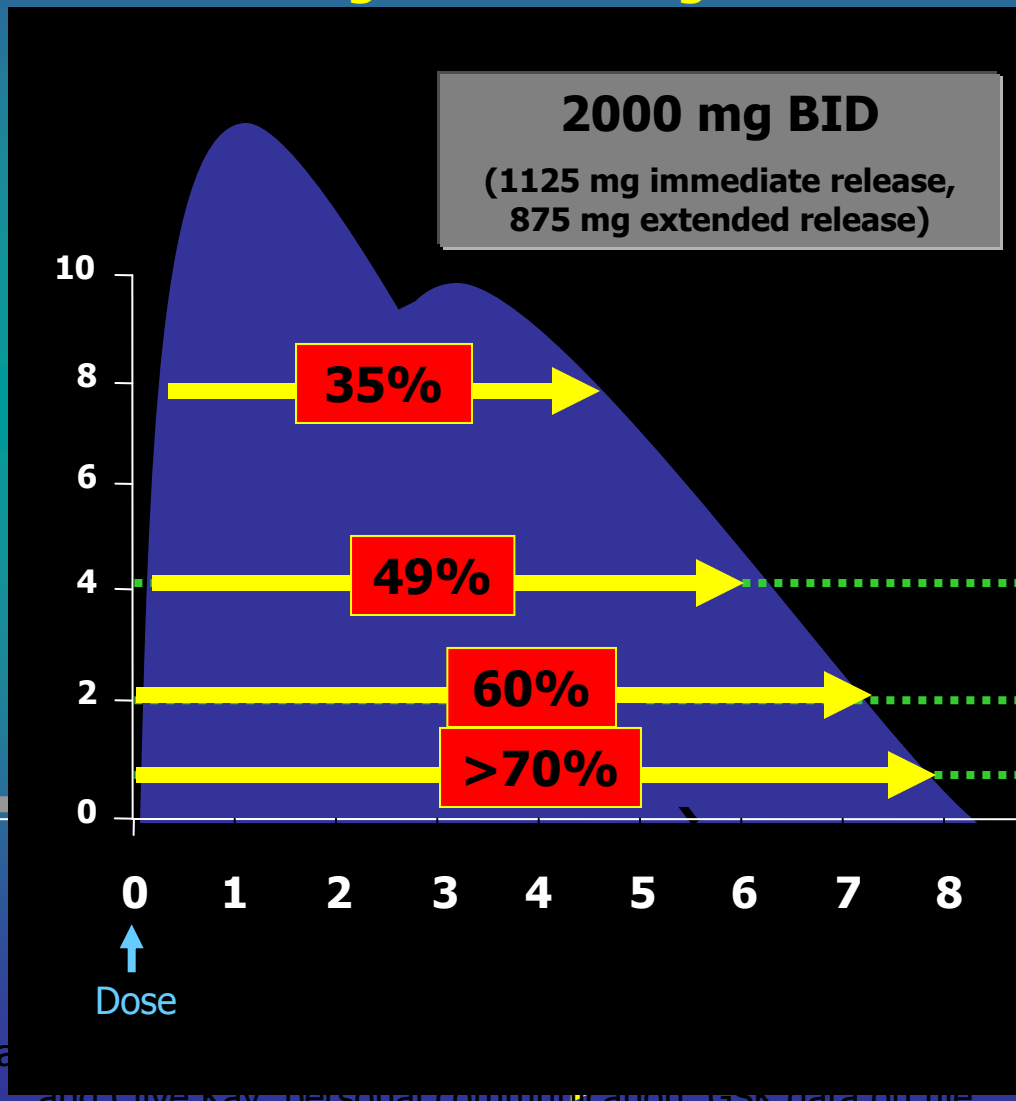
Adapted from Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg.* 2000;123:S1-S32; and Clive Kay, personal communication. GSK data on file

Amoxicillin: "Time above MIC"

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed at 12 h at 875 mg and 2000 mg

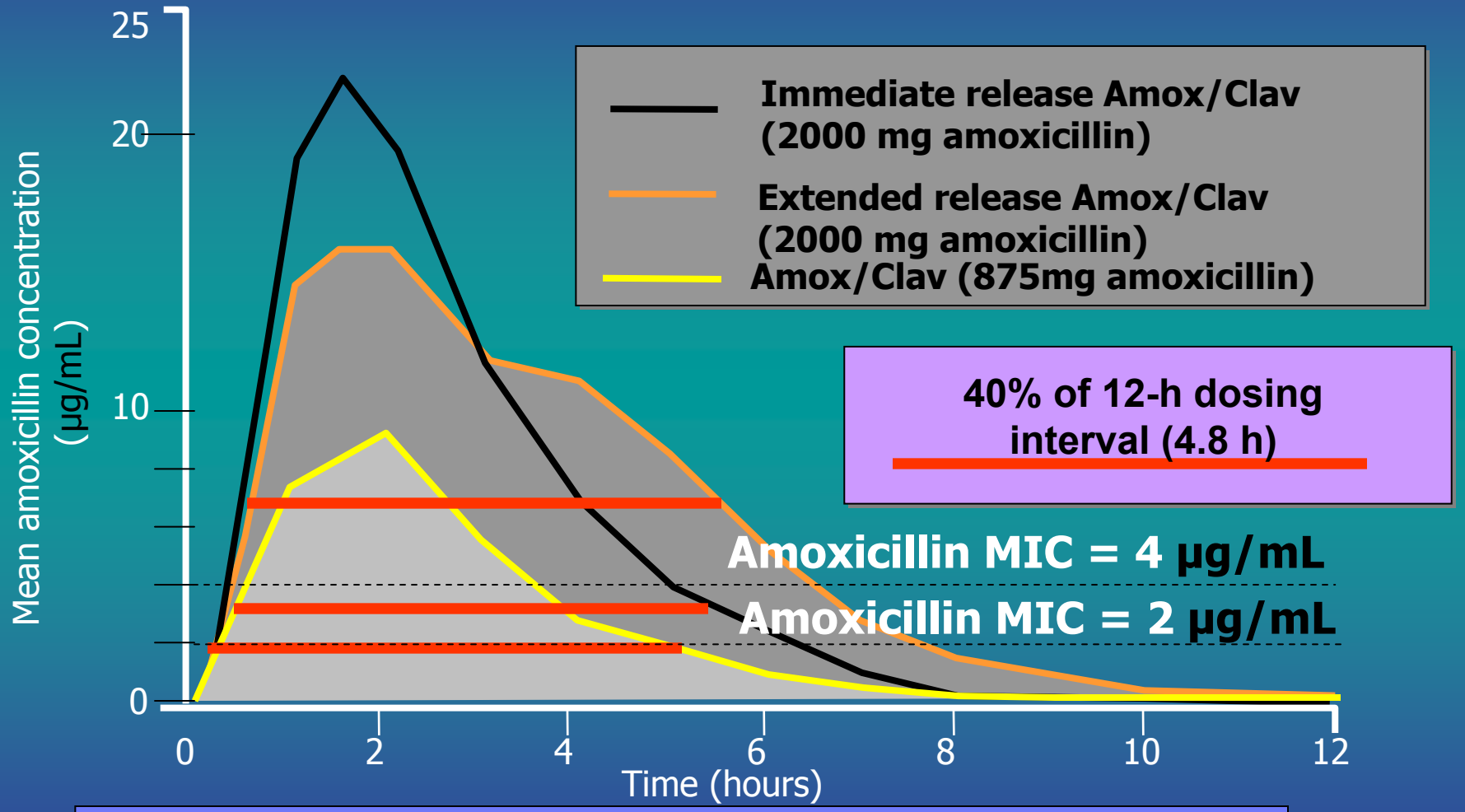




Adapted from Sinus and Allergy Health Pa

and Clive Kay, personal communication. GSK data on file

Extended-release amoxicillin-clavulanate (2000 mg amoxicillin per dose) vs. immediate release amoxicillin-clavulanate (875 and 2000 mg amoxicillin per dose)



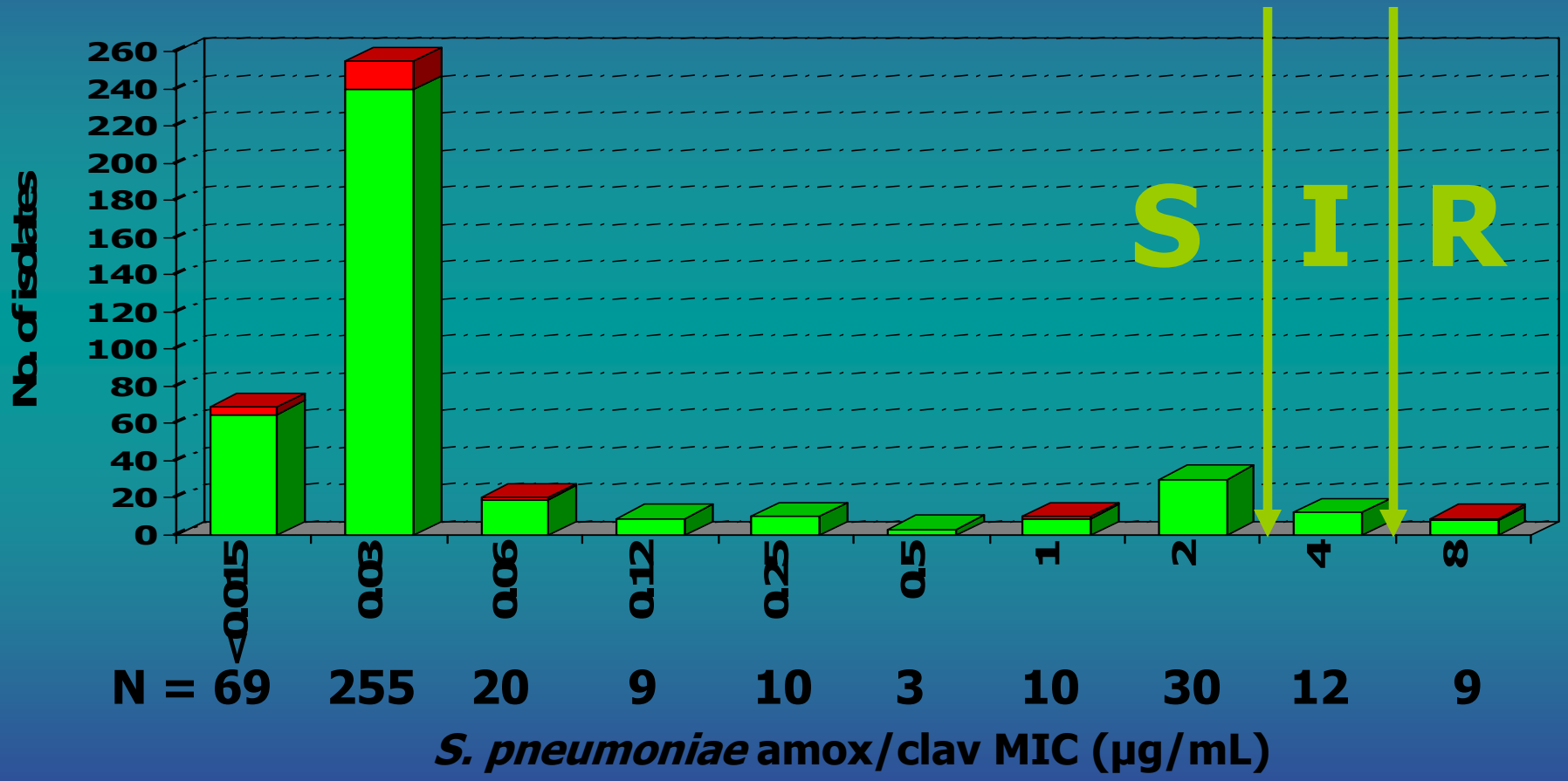
Extended release formulation cannot be duplicated by using immediate release amoxicillin/clavulanate plus extra amoxicillin

Adapted from Kaye CM, et al. *Clin Ther.* 2001;23:578-584

Extended release amoxicillin-clavulanate: Clinical Trials Design

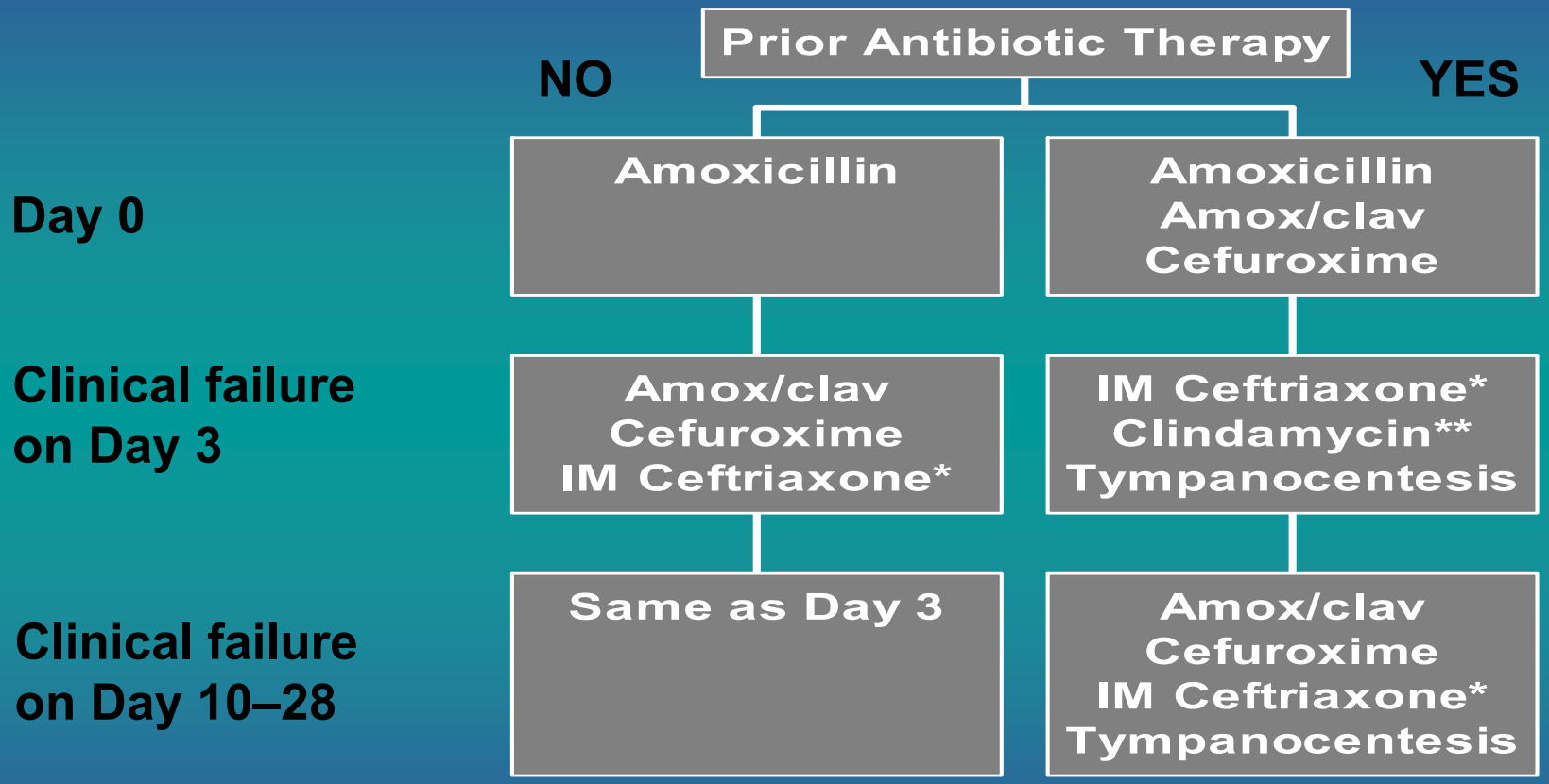
- Clinical program developed according to FDA *Guidance for Industry: Developing Antimicrobial Drugs–General Considerations for Clinical Trials* (Center for Drug Evaluation and Research, July 1998)
- Because large number of patients required to show clinical superiority, most comparative studies are designed to show noninferiority
- Most patients were therefore studied in noncomparative studies

Clinical Success and Bacteriologic Eradication at TOC for *S. pneumoniae* by Amox/Clav MIC: All Indications Combined (RTI)



GlaxoSmithKline, data on file.

Antimicrobial Recommendations for AOM



*Three doses on consecutive days.
**Not effective against *H. influenzae* or *M. catarrhalis*.
Dowell et al. *Pediatr Infect Dis J* 1999;18:1.

Antimicrobial Recommendations for AECB

Category	Probable Pathogen	Therapy
Group 1	Viral	Symptomatic
Group 2	*H. influenzae*, *S. pneumoniae*, *M. catarrhalis* possibly atypical organisms	Doxycycline, newer macrolide newer cephalosporins
Group 3 & 4	As above with the possible addition of *Pseudomonas* spp Enterobacteriaceae, and other gram-negative pathogens	Amoxicillin/clavulanate, fluoroquinolones*

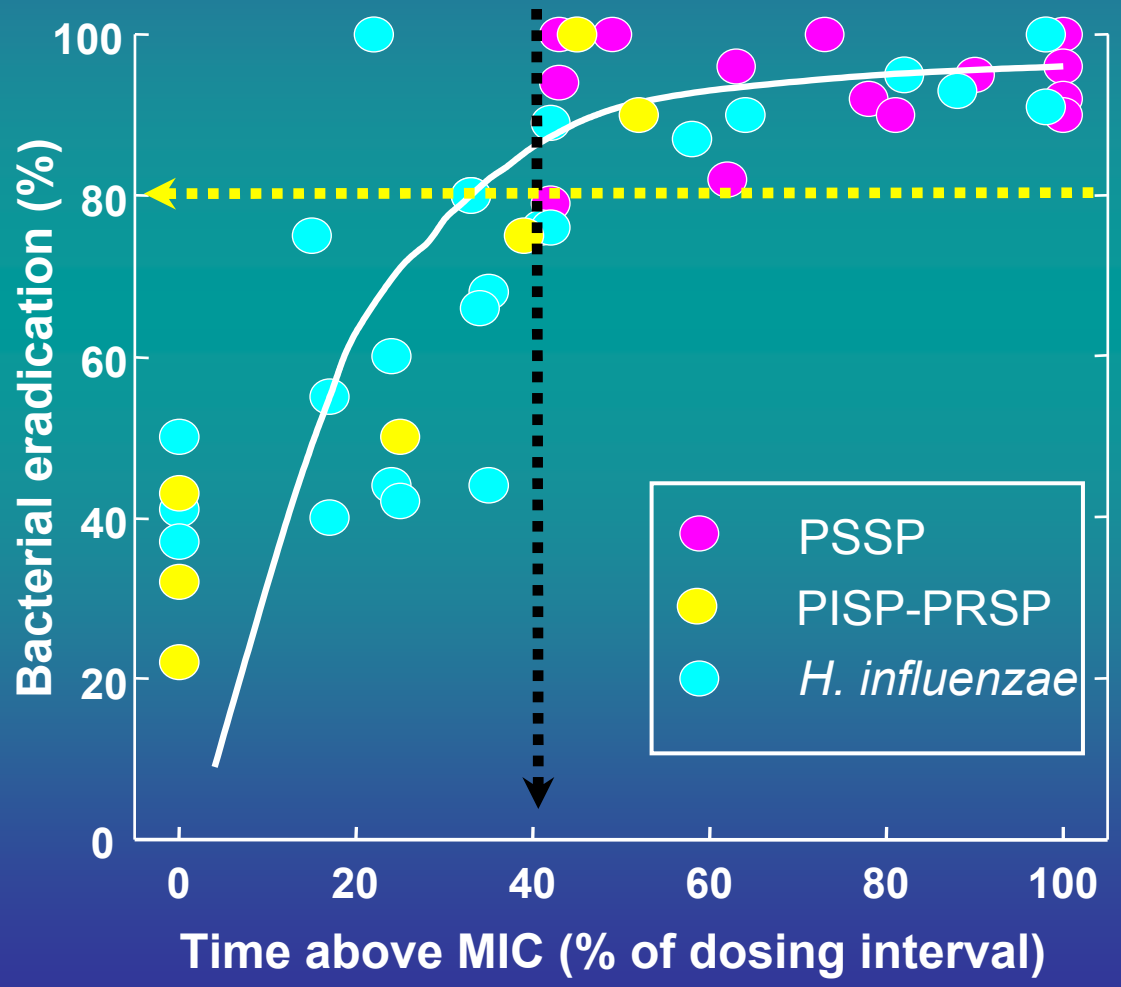
*If at risk for infection with *Pseudomonas* spp, use ciprofloxacin.

Balter et al. *Can Med Assoc J* 1994;151(suppl 10):5; Adams and Anzueto. *Semin Respir Infect* 2000;15:234.

Bacteriologic outcome studies

- AOM
- AECB

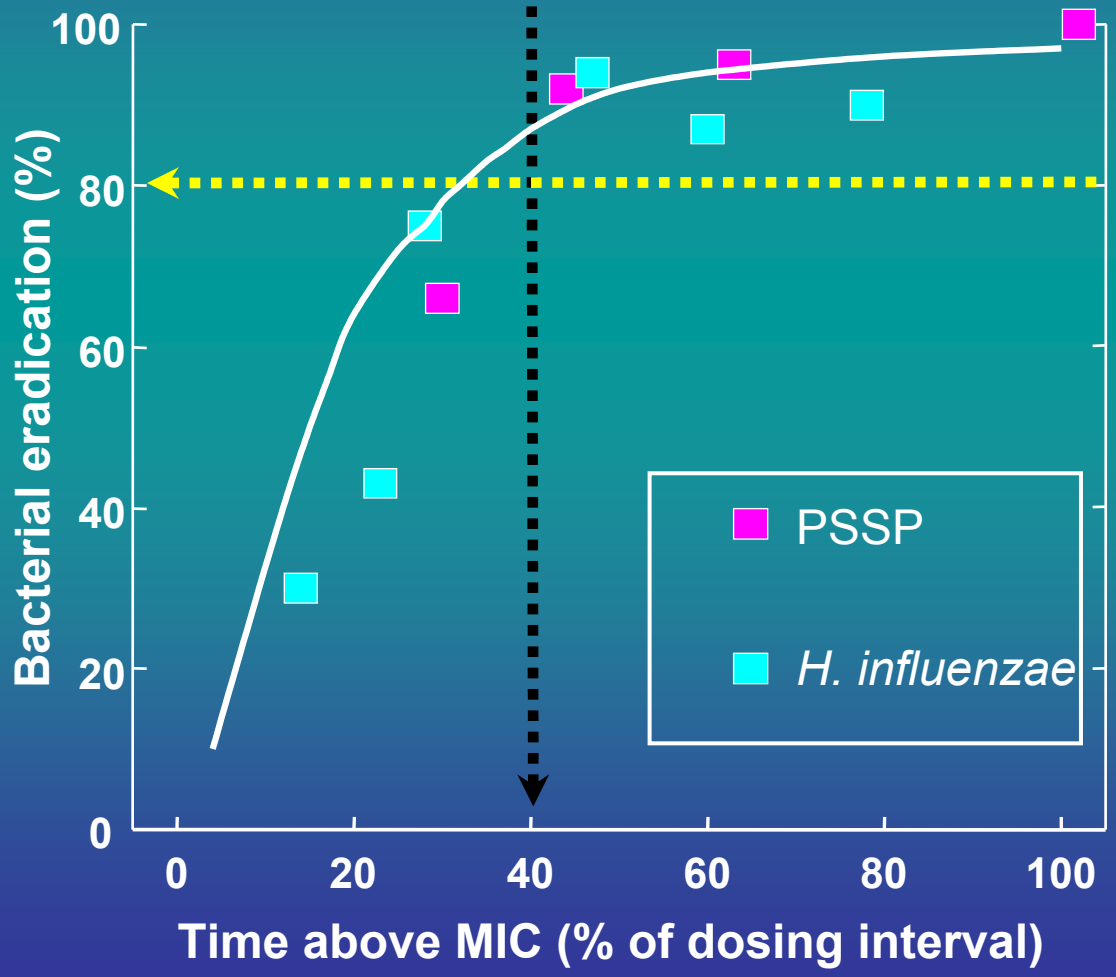
Relationship between Time above MIC and bacterial eradication with β-lactams in otitis media



Craig & Andes, Pediatr Infect Dis J, 1996

Dagan et al studies

Relationship between Time above MIC and bacterial eradication with β-lactams in maxillary sinusitis

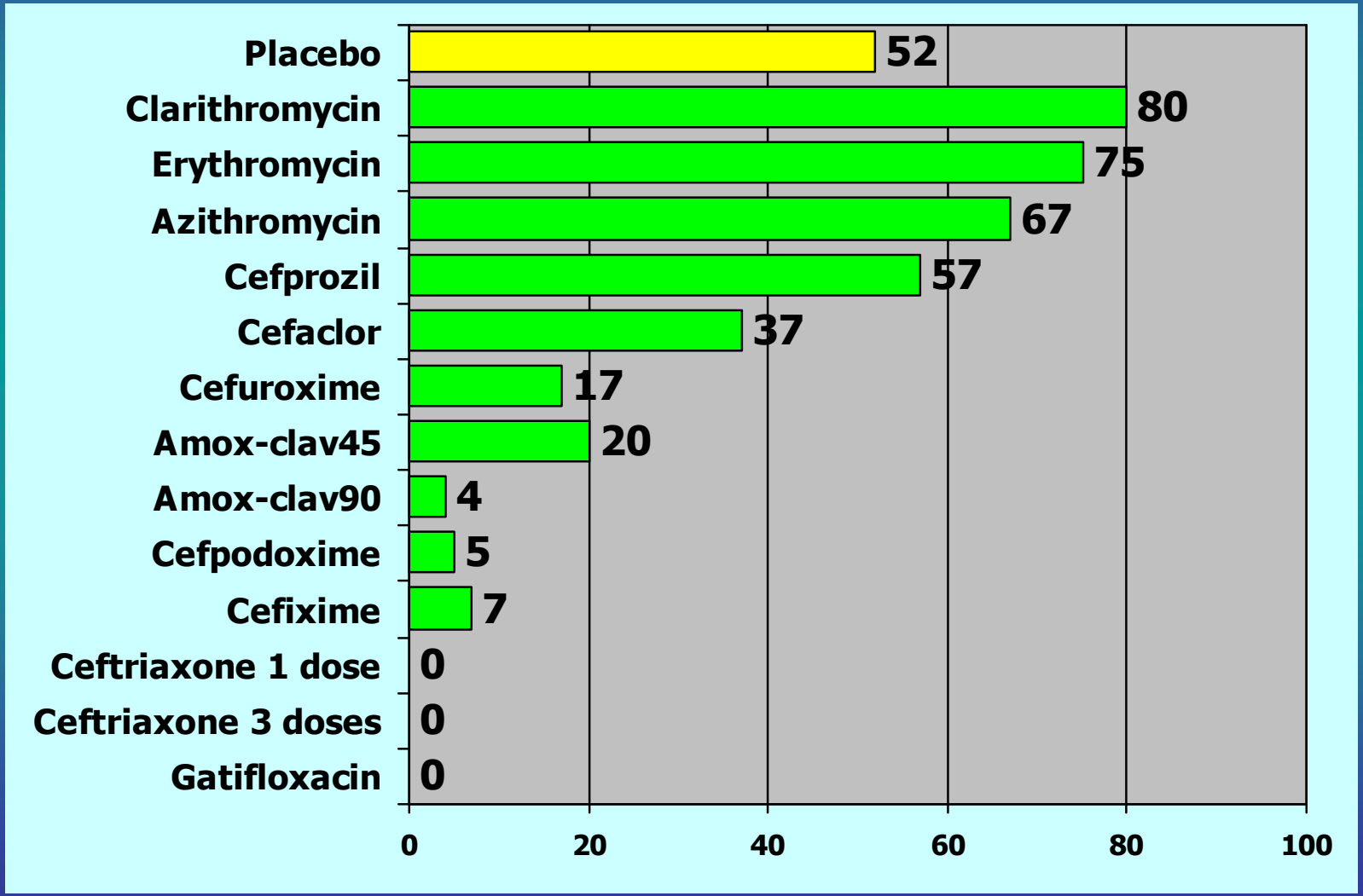


Craig & Andes, Pediatr Infect Dis J, 1996

Gwaltney & Scheld studies

Haemophilus influenzae: Bacteriological Failure Rates in AOM Studies (excl amox and SXT)

2nd Tympanocentesis Performed on Day 2-6 of treatment



Adapted from Klein CID 1992, 14(supp 2):209, Jacobs MR CMI 2001, 7:589, Dagan ICAAC 2001

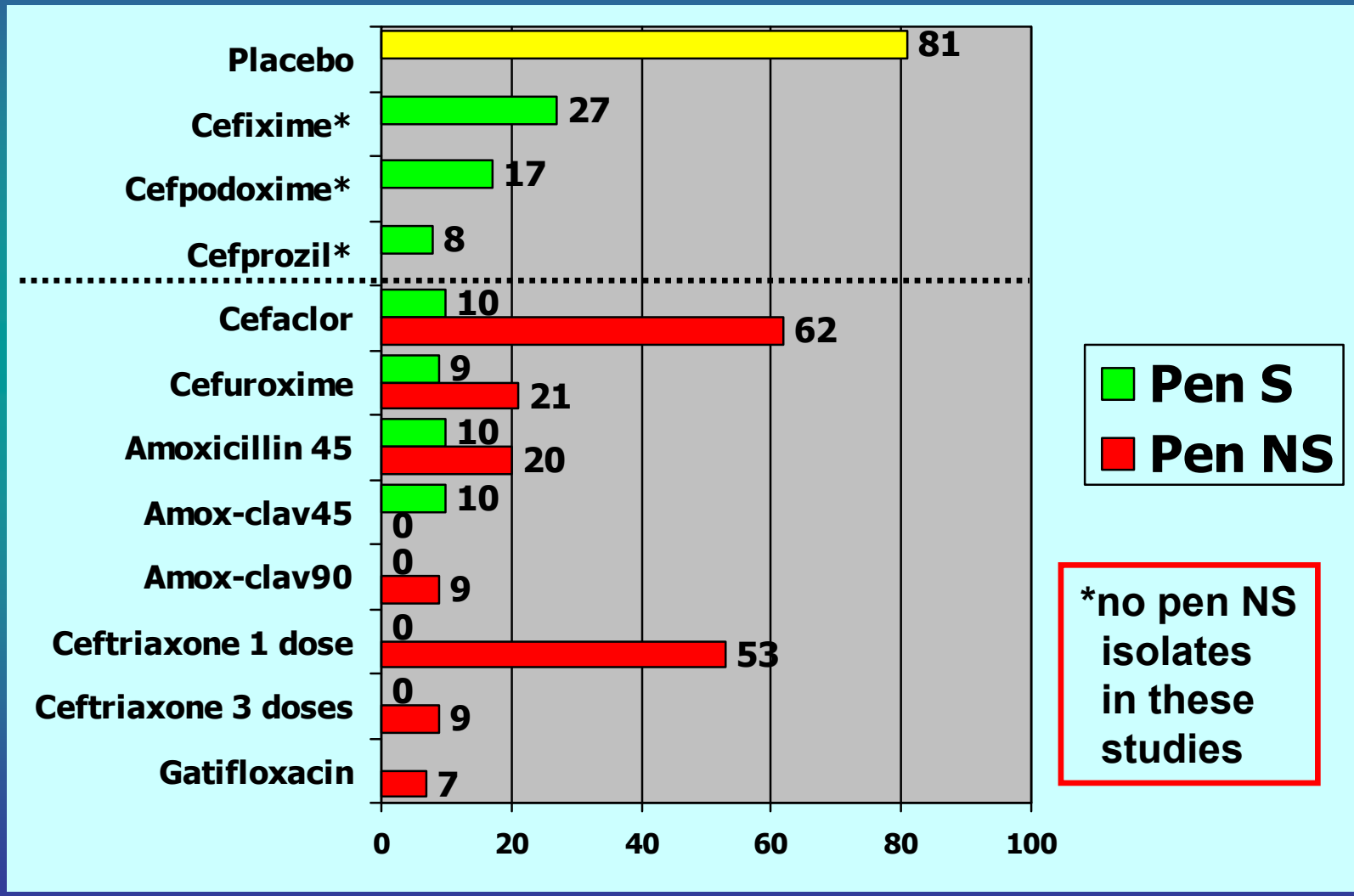
Haemophilus influenzae: Bacteriological Failure Rates in AOM Studies with Amoxicillin and SXT

2nd Tympanocentesis Performed on Day 2-6 of treatment

Adapted from Klein CID 1992, 14(supp 2):209, and Jacobs MR CMI 2001, 7:589

Streptococcus pneumoniae: Bacteriological Failure Rates in AOM Studies (excl. azithromycin and SXT)

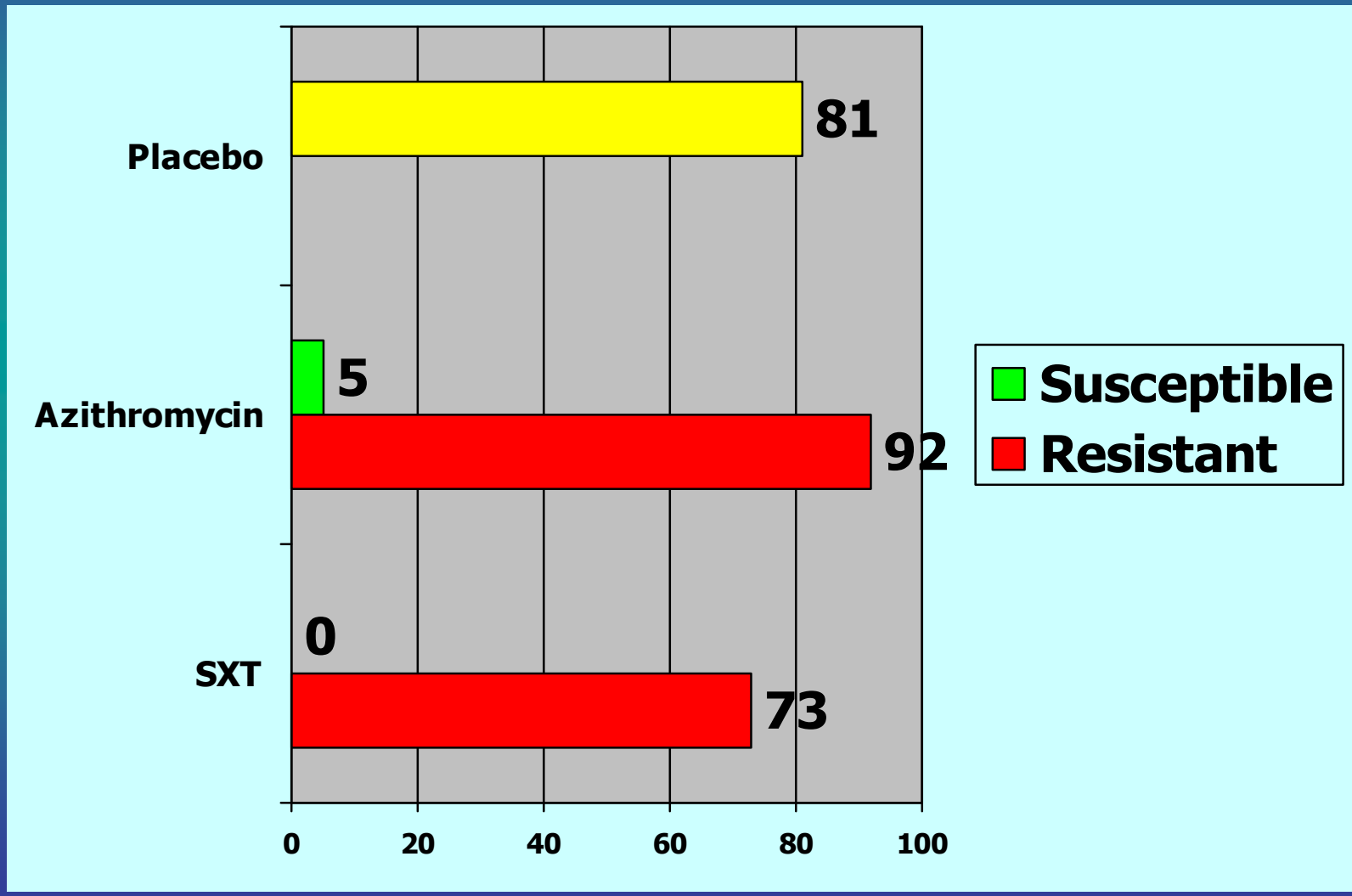
2nd Tympanocentesis Performed on Day 2-6 of treatment



Adapted from Klein CID 1992, 14(supp 2):209, and Jacobs MR CMI 2001, 7:589

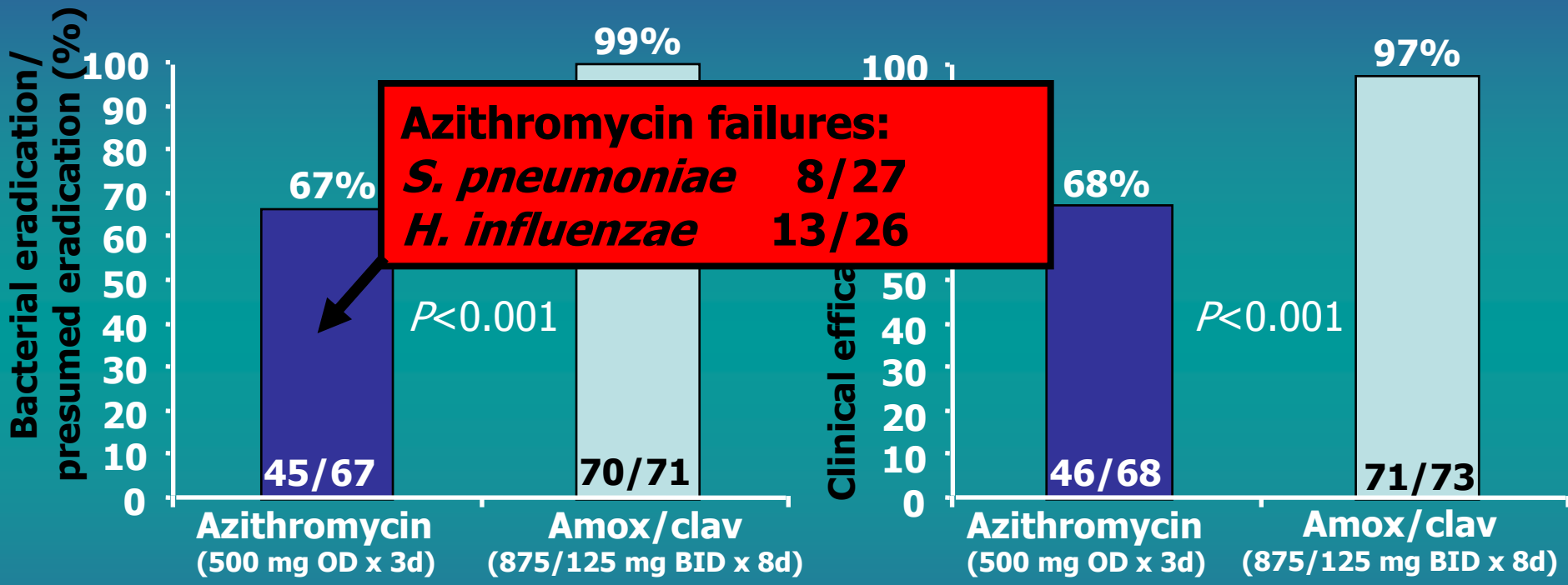
Streptococcus pneumoniae: Bacteriological Failure Rates in AOM Studies with Azithromycin and SXT

2nd Tympanocentesis Performed on Day 2-6 of treatment



Adapted from Klein CID 1992, 14(supp 2):209, and Jacobs MR CMI 2001, 7:589

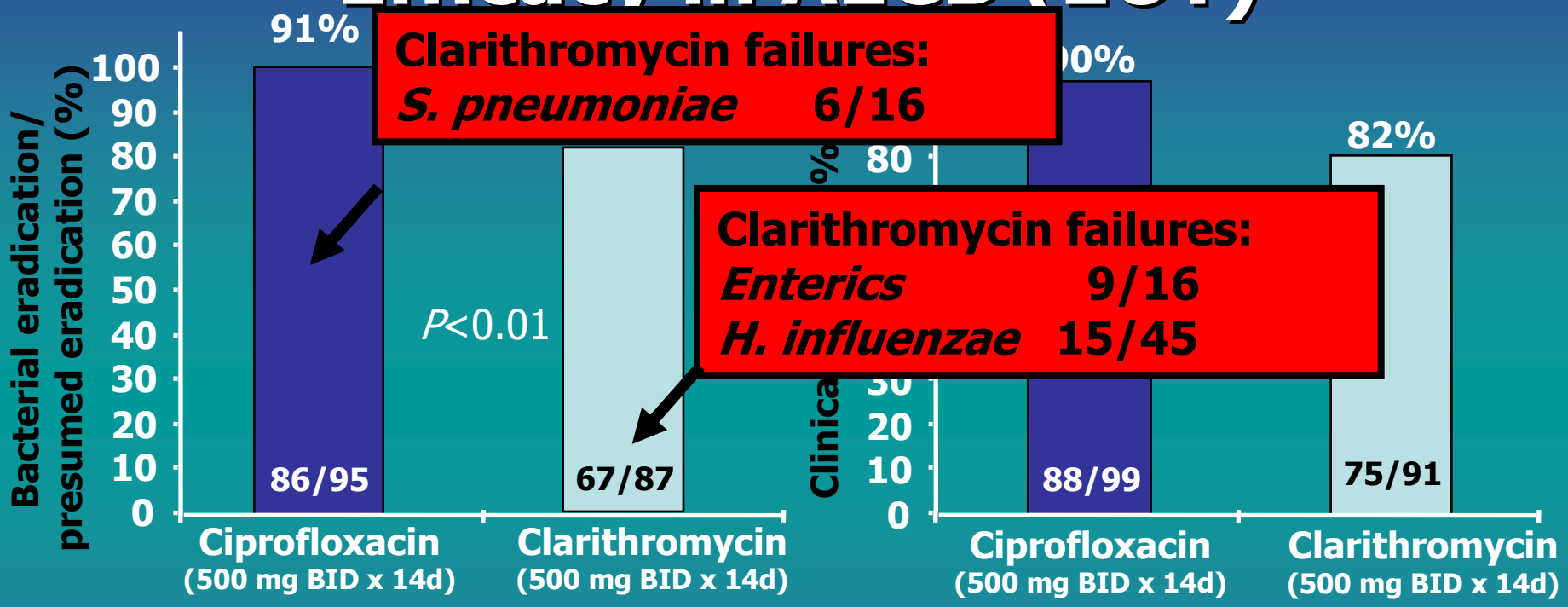
Bacterial Eradication and Clinical Efficacy in AECB (EOT)



Pre-therapy pathogens:	Amox/clav (N=96)	Azithromycin (N=79)
H. influenzae	16%	33%
S. pneumoniae	35%	34%

Adapted from Beghi G, et al. *J Chemother.* 1995;7:146-152.

Bacterial Eradication and Clinical Efficacy in AECB (EOT)



Pre-therapy pathogens:	Cipro (N=118)	Clarithro (N=103)
H. influenzae	38%	27%
M. catarrhalis	20%	23%
S. pneumoniae	14%	15%

Adapted from Chodosh S, et al. *Clin Infect Dis.* 1998;27:730-738.

MIC distributions of RTI pathogens

- MIC distributions can provide a basis for comparing susceptibilities of different bacterial species causing infections at the same sites
- MIC distributions can show if discrimination between isolates with different MICs is likely to be possible in clinical studies
- MIC distributions can be applied to clinically determined breakpoints to determine susceptibility of isolates

Amoxicillin

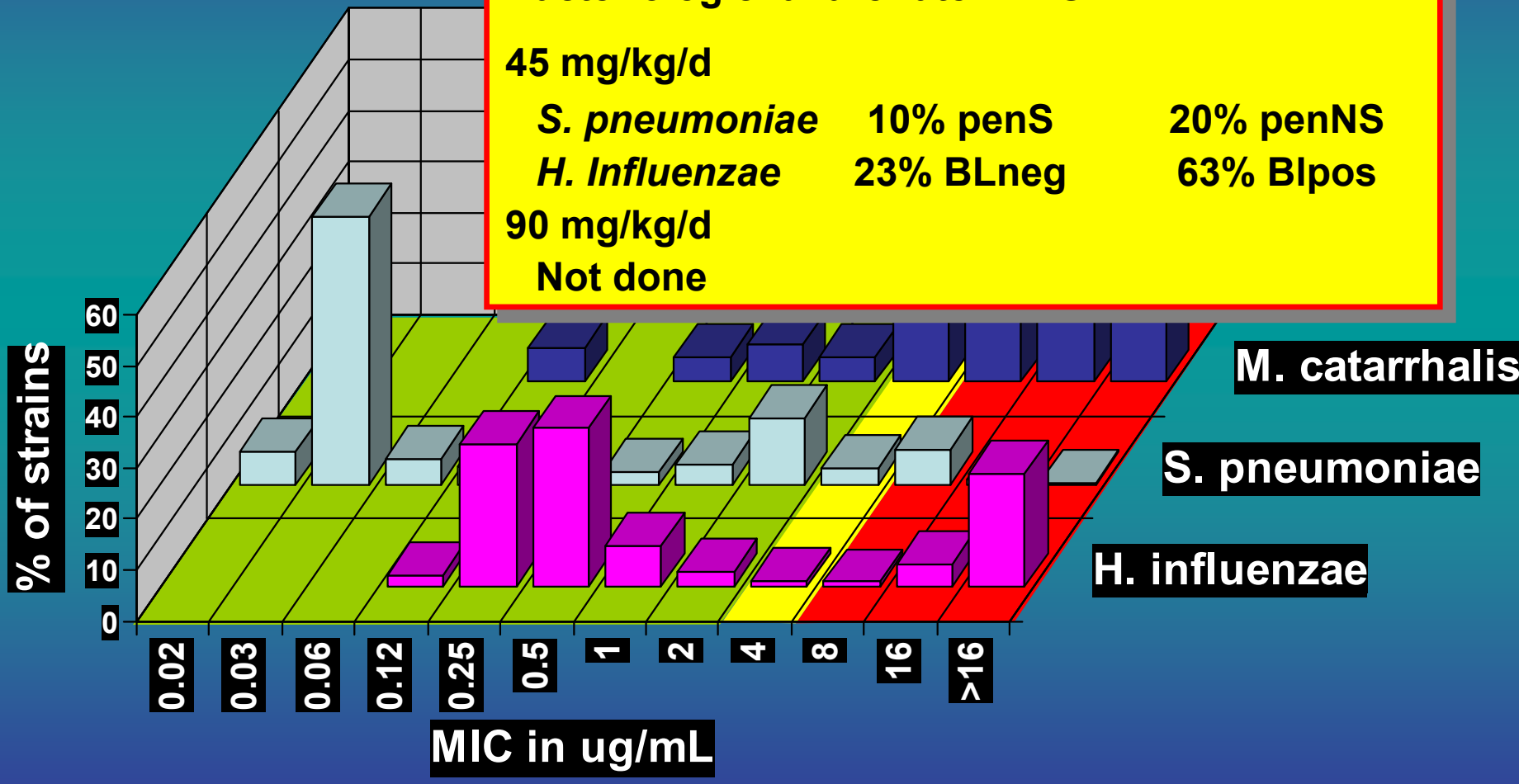
Bacteriologic failure rate in AOM:

45 mg/kg/d

S. pneumoniae	10% penS	20% penNS
H. Influenzae	23% BLneg	63% Blpos

90 mg/kg/d

Not done



Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* 2000 (n=206)

Amoxicillin-clavulanate

Bacteriologic failure rate in AOM:

45 mg/kg/d

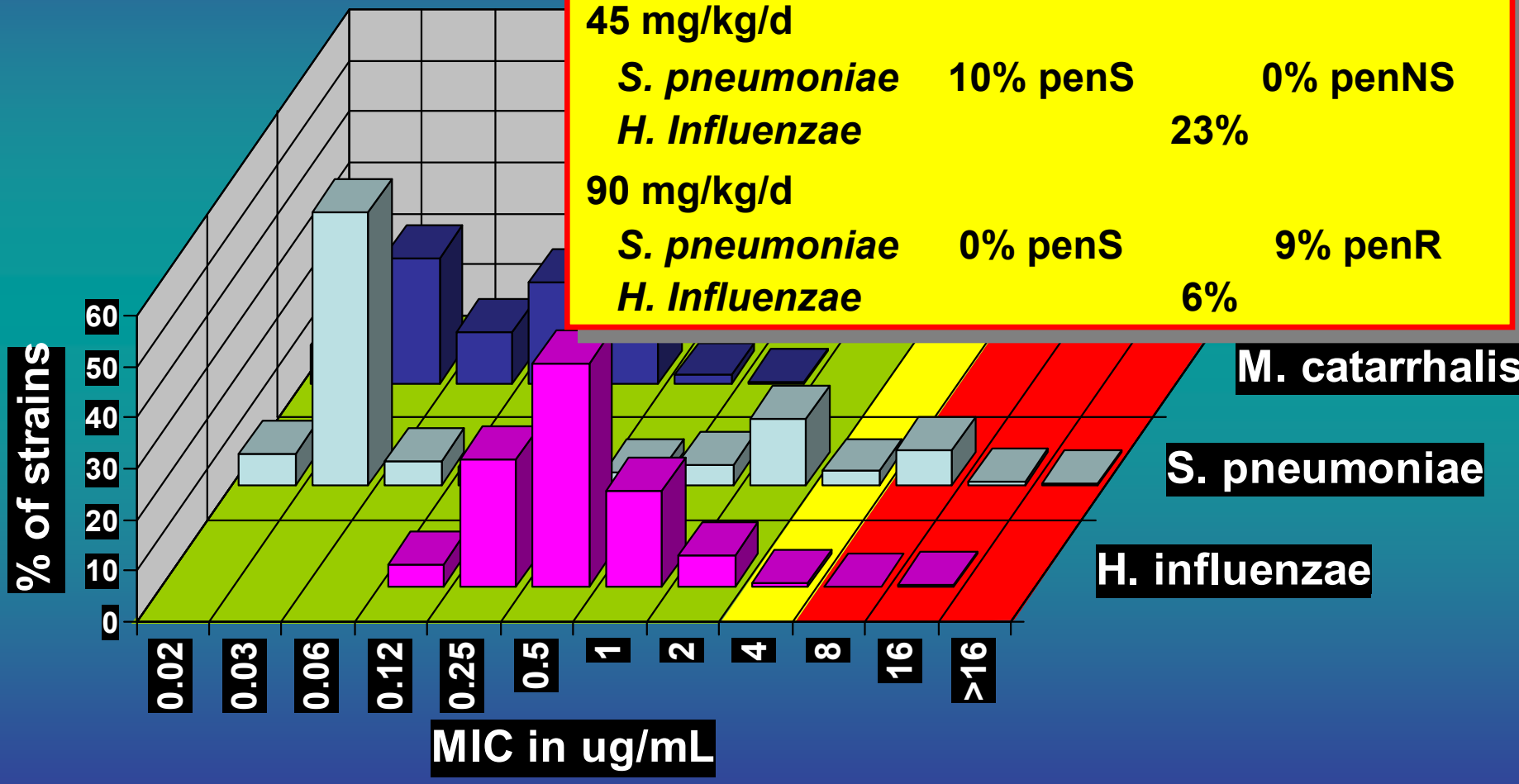
S. pneumoniae **10% penS** **0% penNS**

H. Influenzae **23%**

90 mg/kg/d

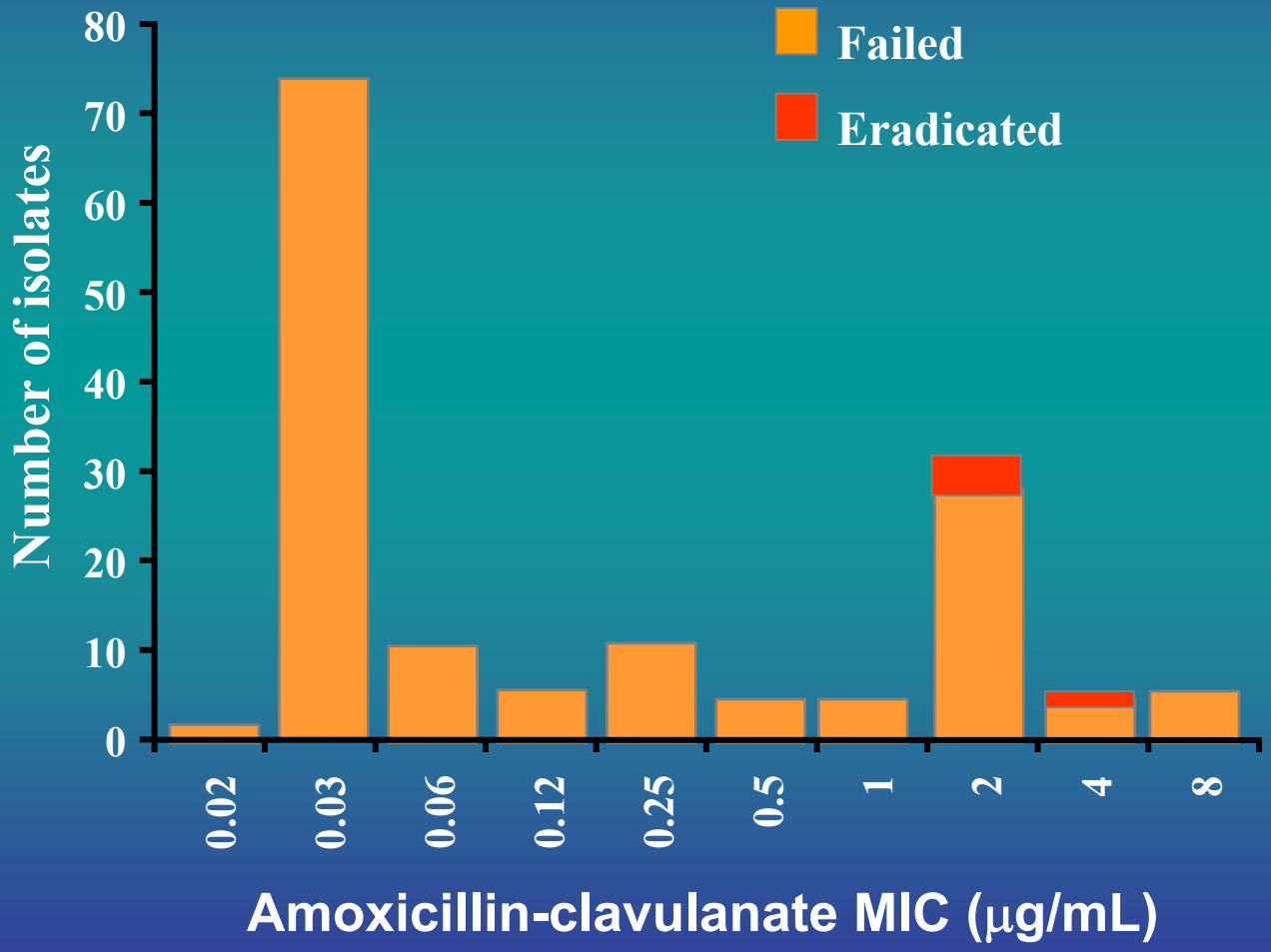
S. pneumoniae **0% penS** **9% penR**

H. Influenzae **6%**



Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *AugSR M. catarrhalis* (n=972)

Eradication of *S. pneumoniae* in AOM According to Amoxicillin-clavulanate MIC (N=149)



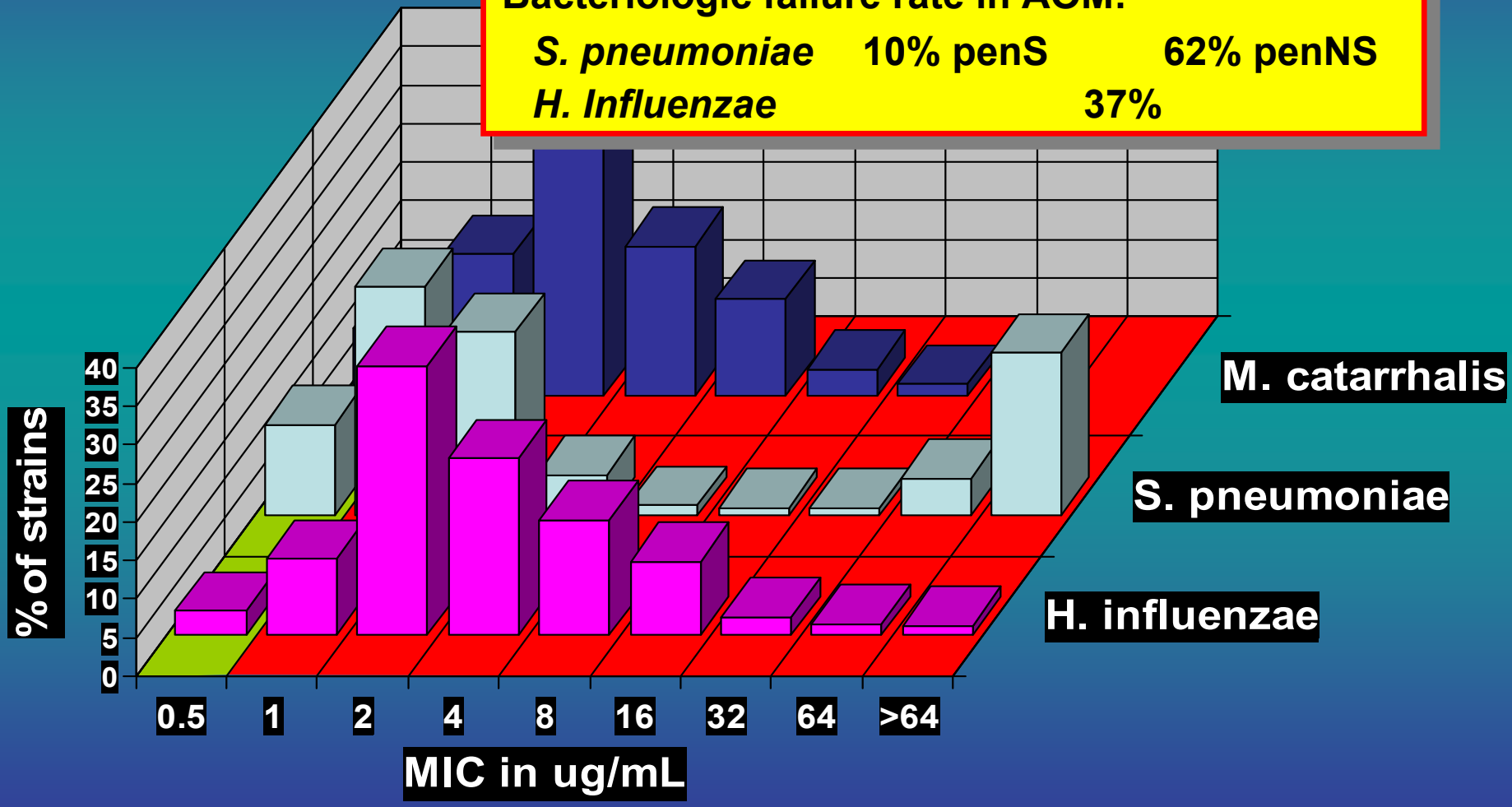
Dagan R, et al. *Pediatr Infect Dis J* 2001;20:829–837.

Cefaclor

Bacteriologic failure rate in AOM:

S. pneumoniae **10% penS 62% penNS**

H. Influenzae **37%**



Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* 2000 (n=206)

Ceftriaxone

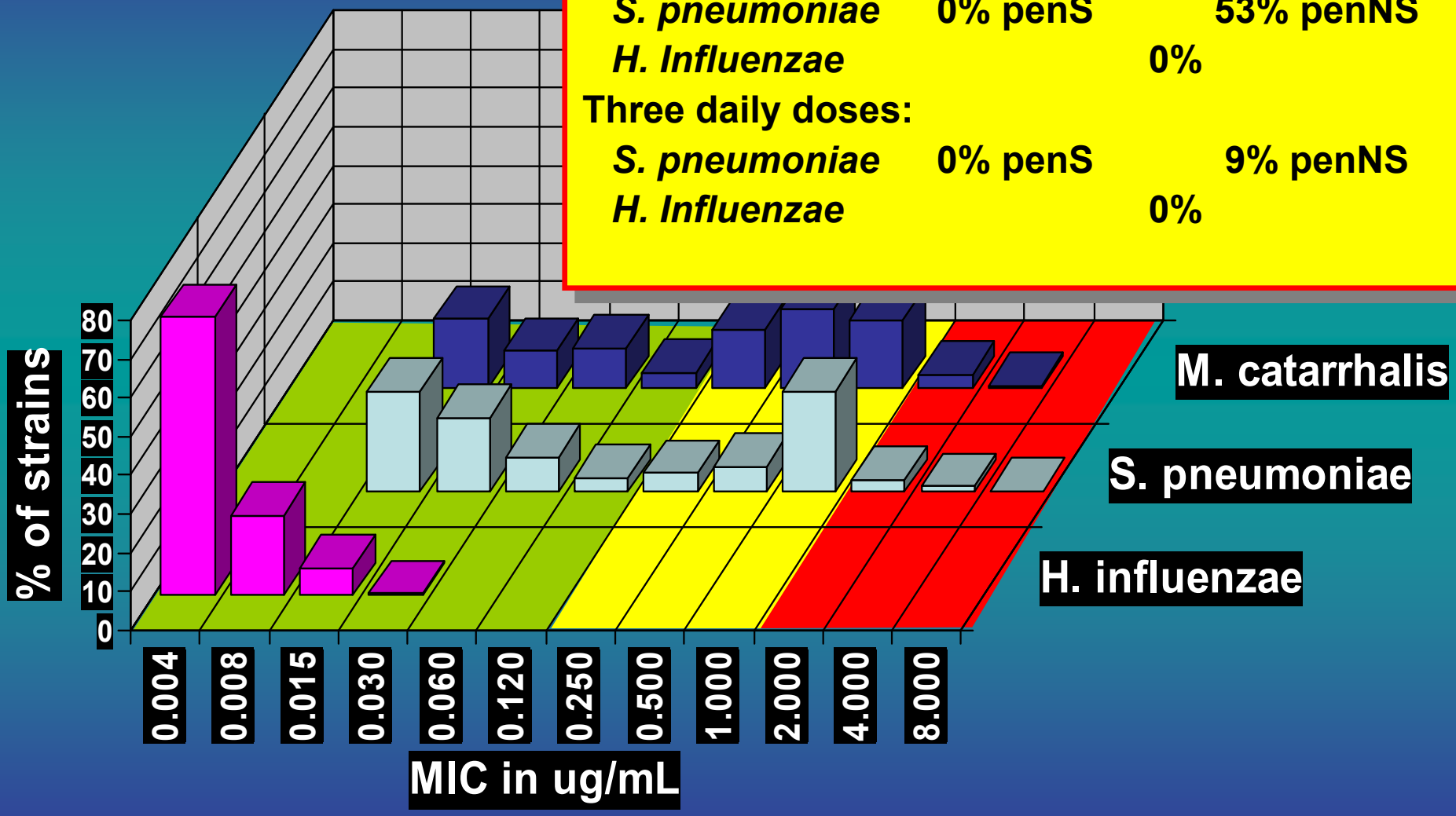
Bacteriologic failure rate in AOM:

One dose:

S. pneumoniae	0% penS	53% penNS
H. Influenzae	0%	

Three daily doses:

S. pneumoniae	0% penS	9% penNS
H. Influenzae	0%	



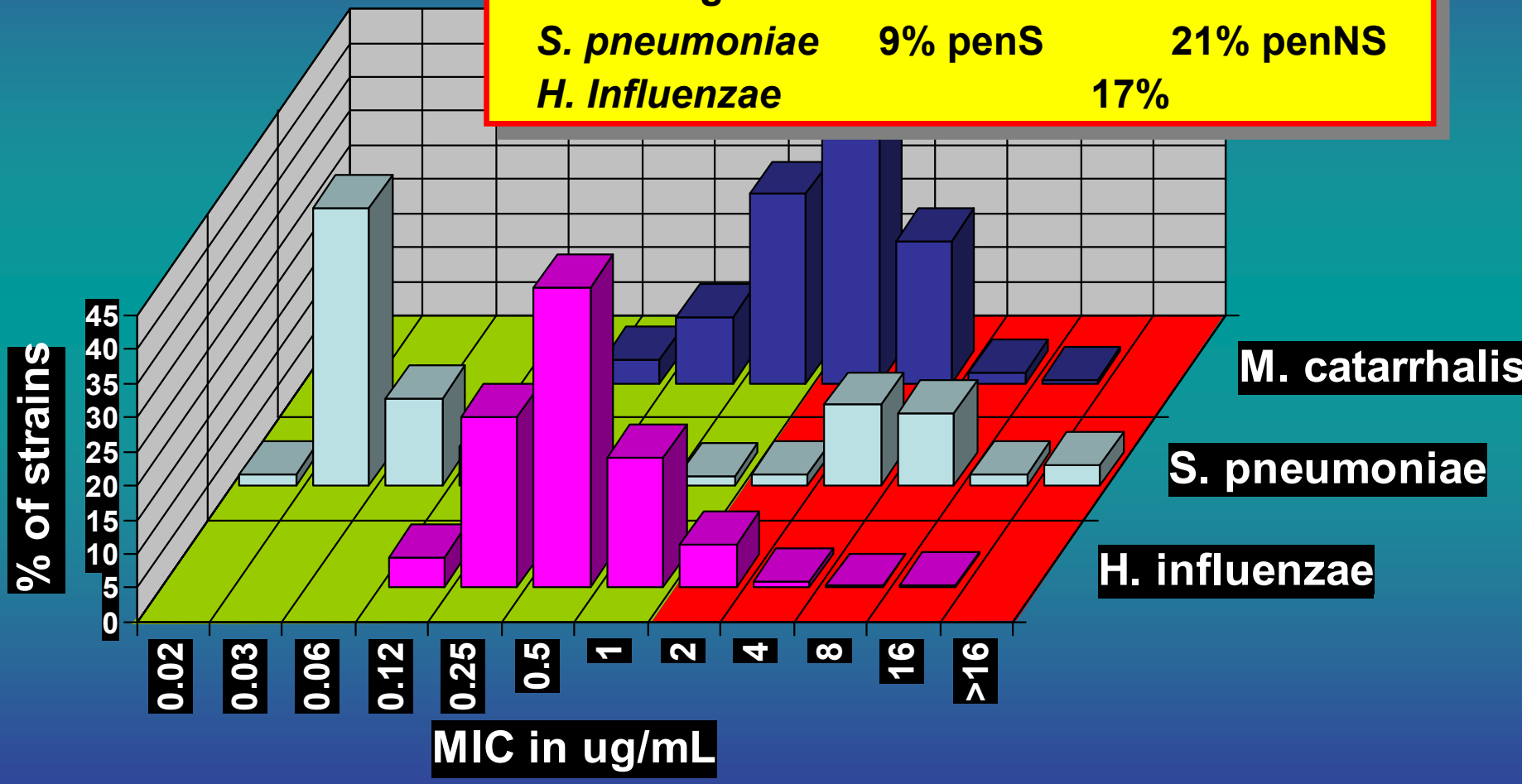
Adapted from Alexander Project 2000; GlaxoSmithKline, data on file.

Cefuroxime axetil

Bacteriologic failure rate in AOM:

S. pneumoniae **9% penS** **21% penNS**

H. Influenzae **17%**

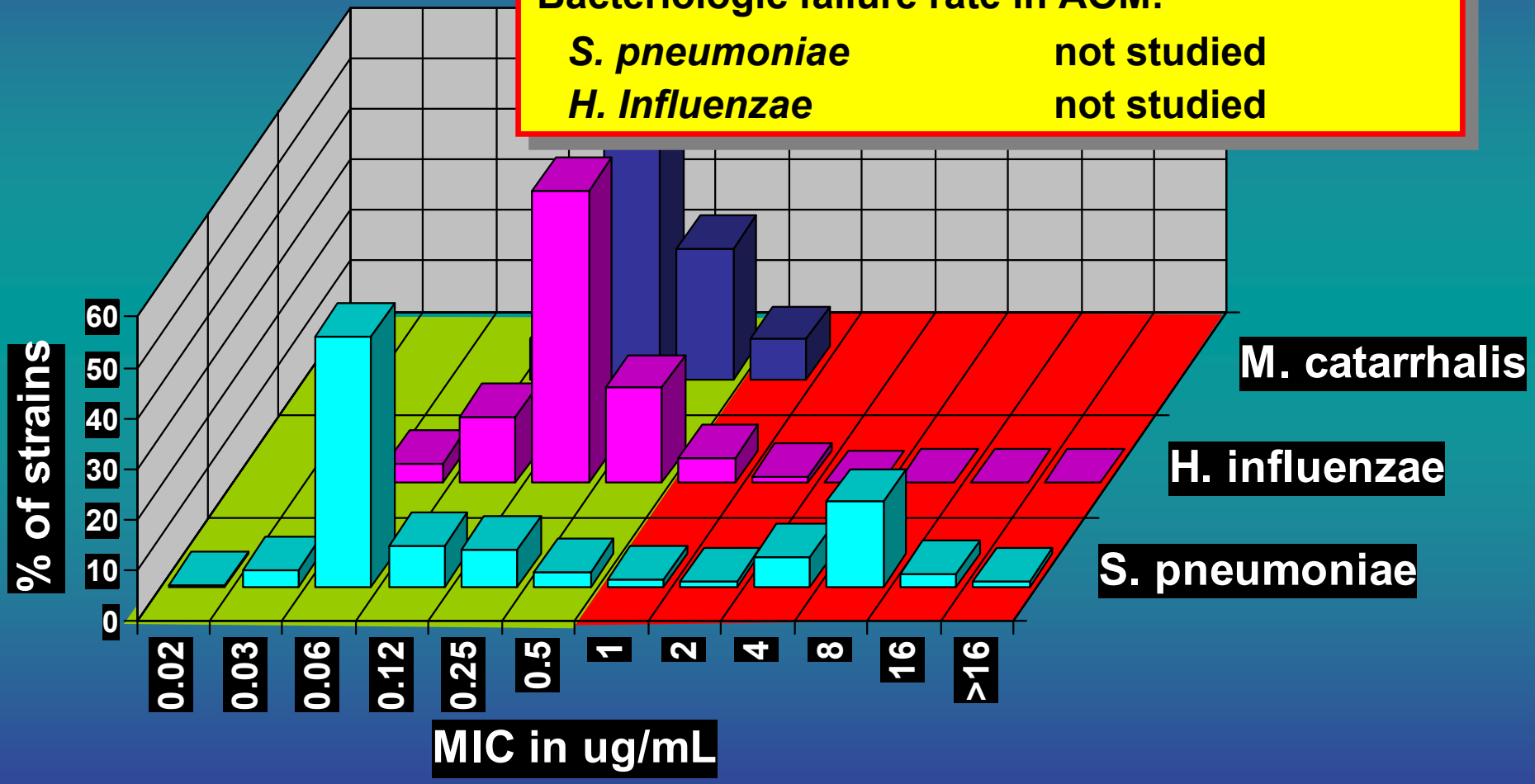


Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* 2000 (n=206)

Cefdinir

Bacteriologic failure rate in AOM:

S. pneumoniae	**not studied**
H. Influenzae	**not studied**

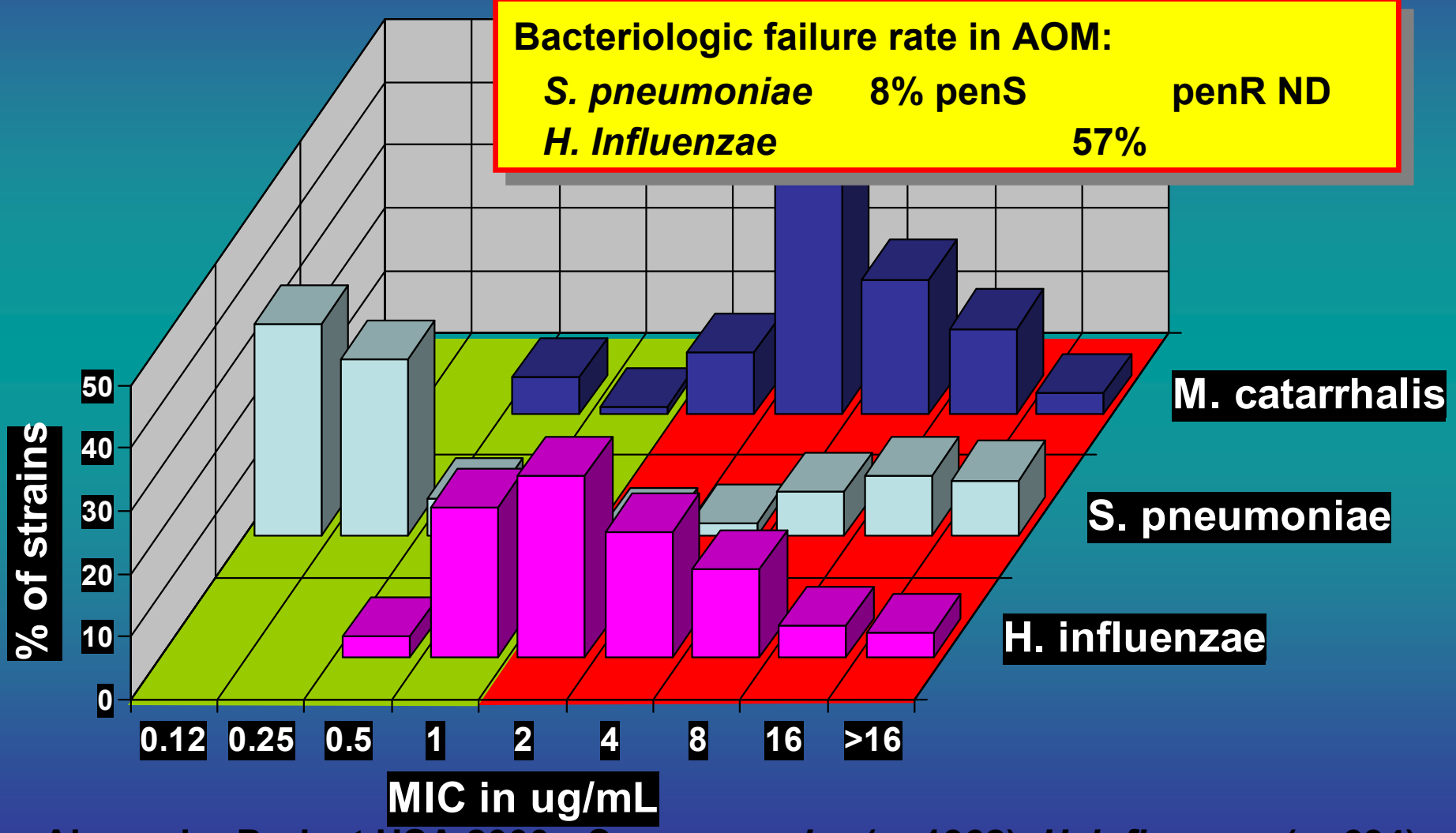


Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)

Cefprozil

Bacteriologic failure rate in AOM:

S. pneumoniae	8% penS	penR ND
H. Influenzae	57%	



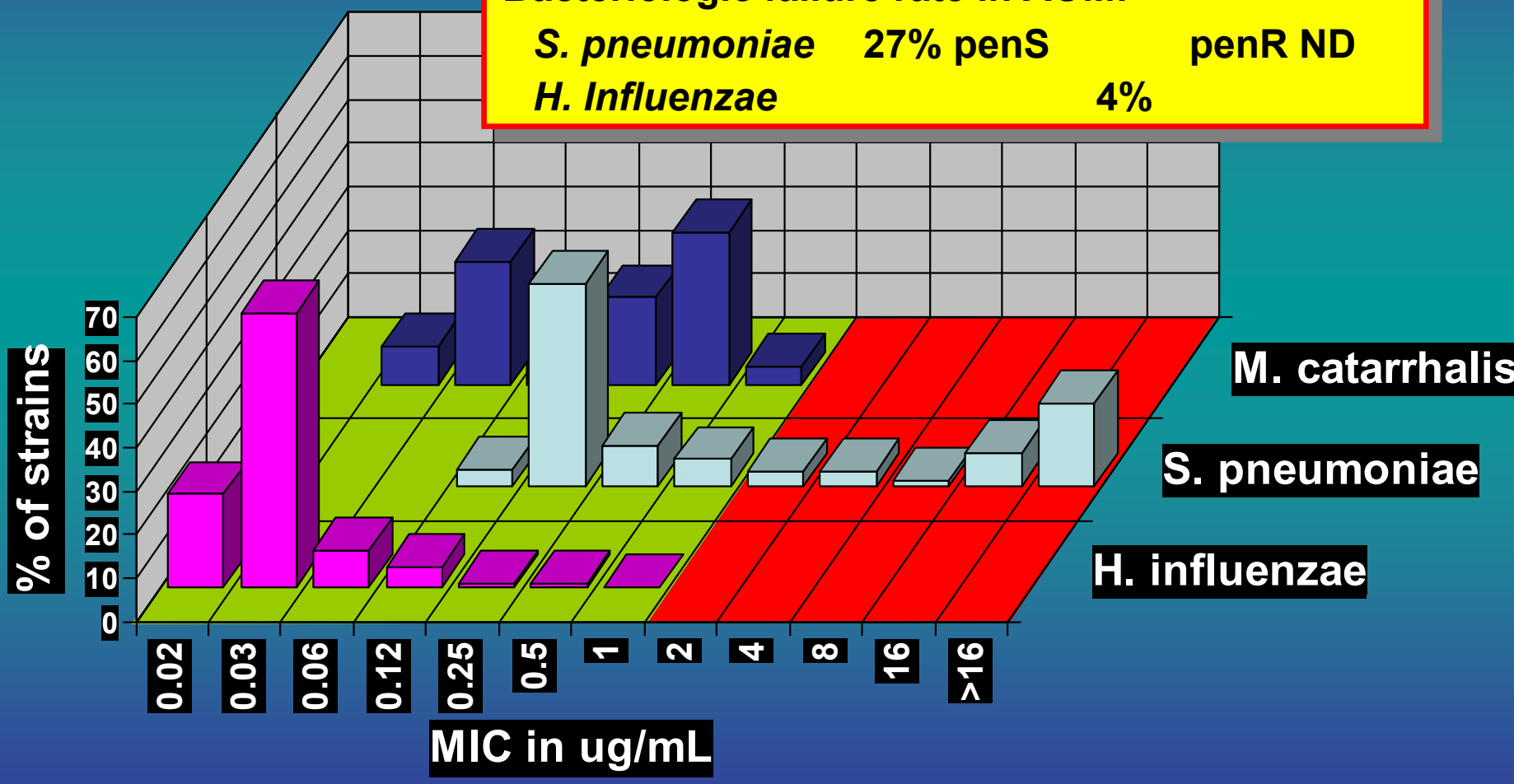
Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* 2000 (n=206)

Cefixime

Bacteriologic failure rate in AOM:

S. pneumoniae **27% penS penR ND**

H. Influenzae **4%**

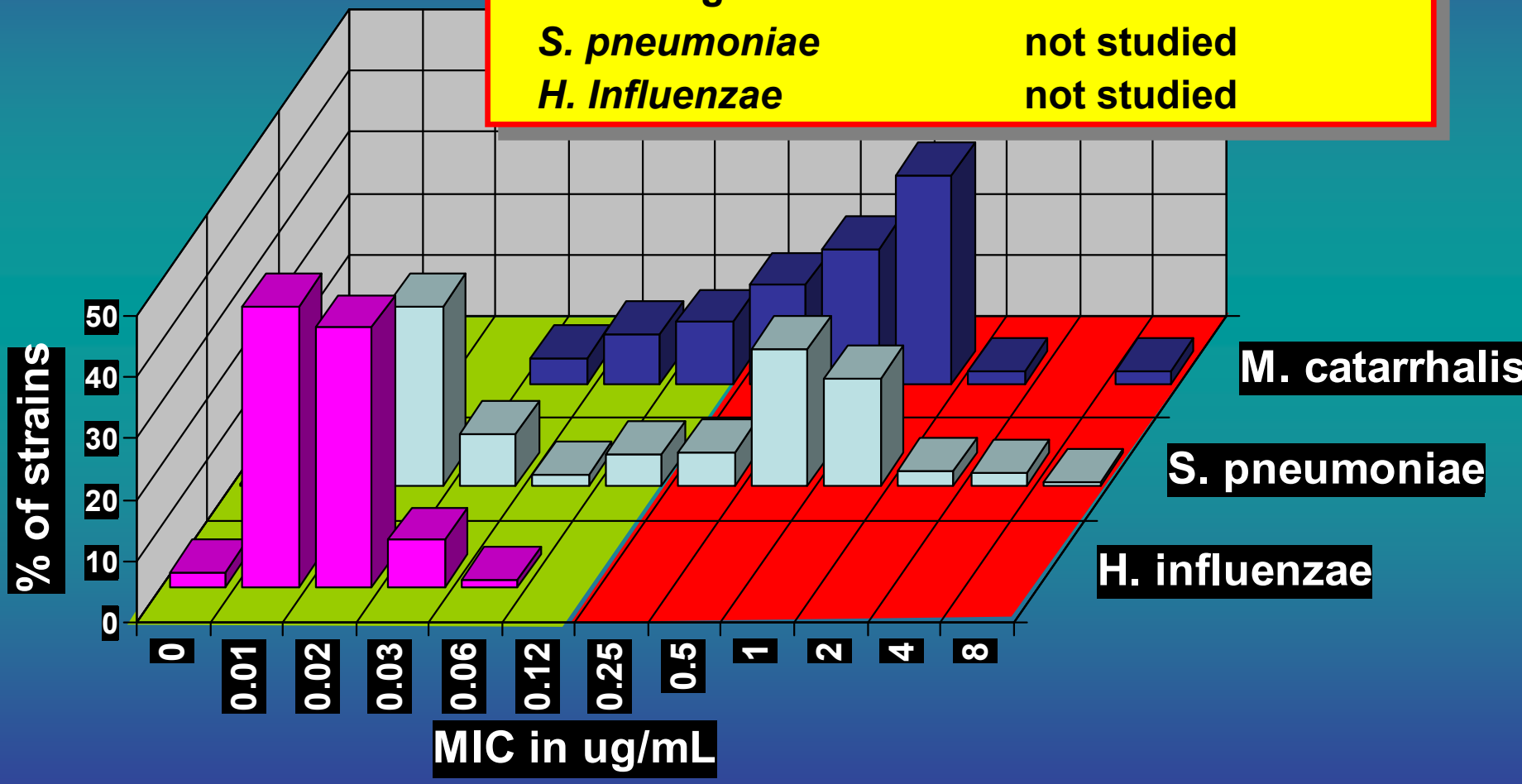


Alexander Project USA 2000: ***S. pneumoniae*** **(n=1362),** ***H. influenzae*** **(n=634),** ***M. catarrhalis*** **2000 (n=206)**

Cefditoren

Bacteriologic failure rate in AOM:

S. pneumoniae	**not studied**
H. Influenzae	**not studied**

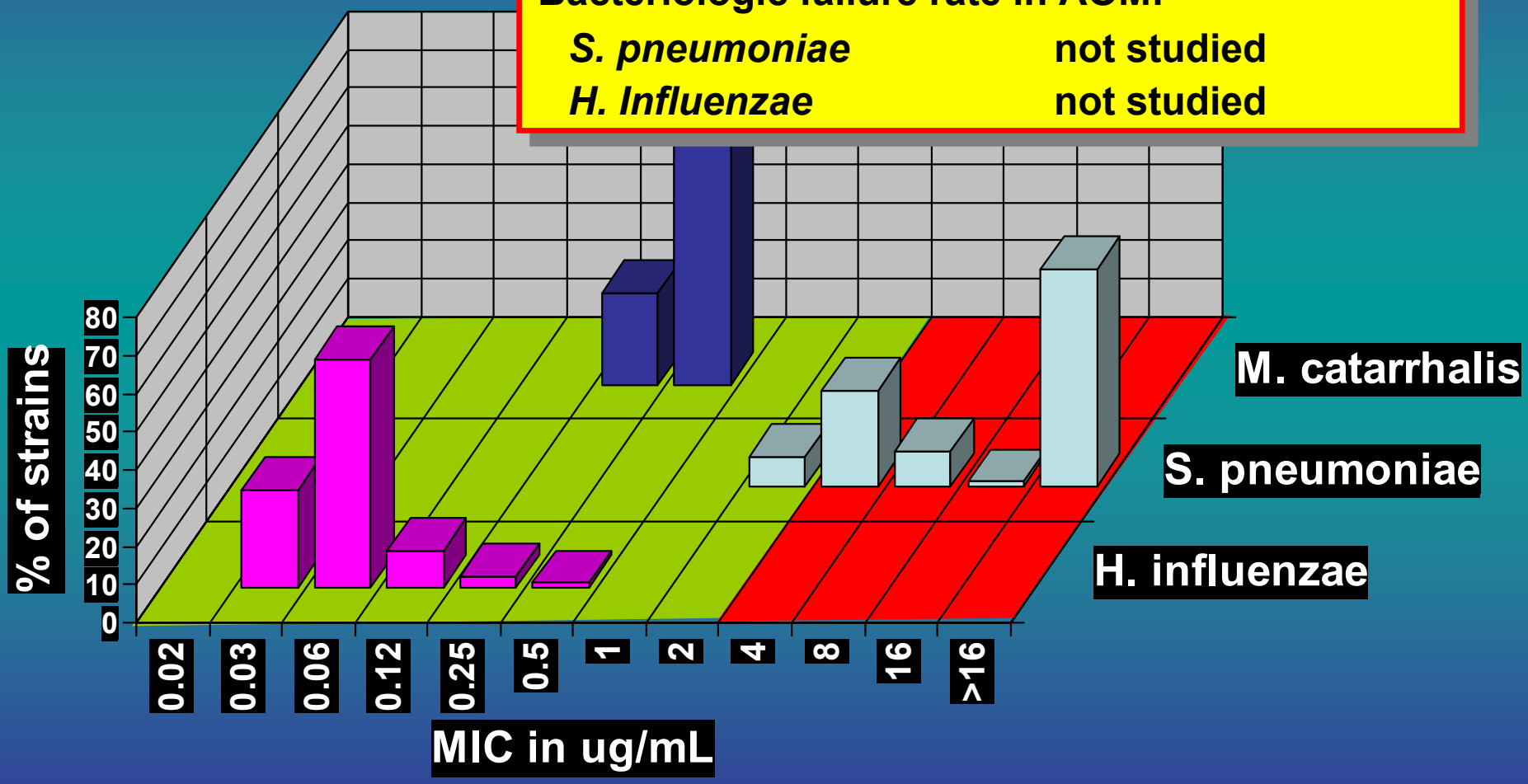


Adapted from Jacobs ICAAC 1997 abstr E103, Kelly ICAAC 1999 abstr 2323, and Spectracef Prescribing Information 2002

Ceftibuten

Bacteriologic failure rate in AOM:

S. pneumoniae	**not studied**
H. Influenzae	**not studied**

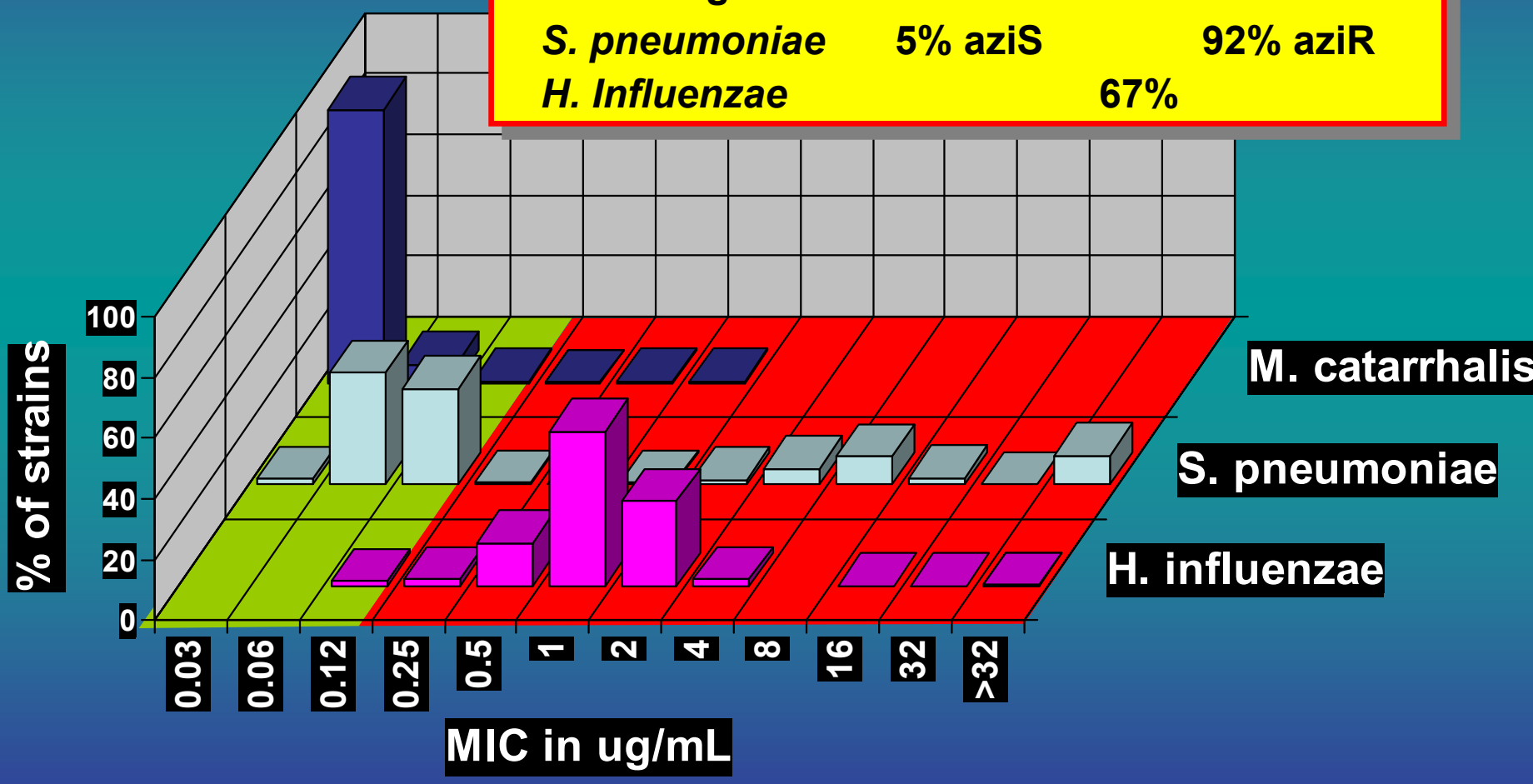


Adapted from Jacobs ICAAC 1997 abstr E103,
and Cedax Prescribing Information 2002

Azithromycin

Bacteriologic failure rate in AOM:

S. pneumoniae	5% aziS	92% aziR
H. Influenzae		67%

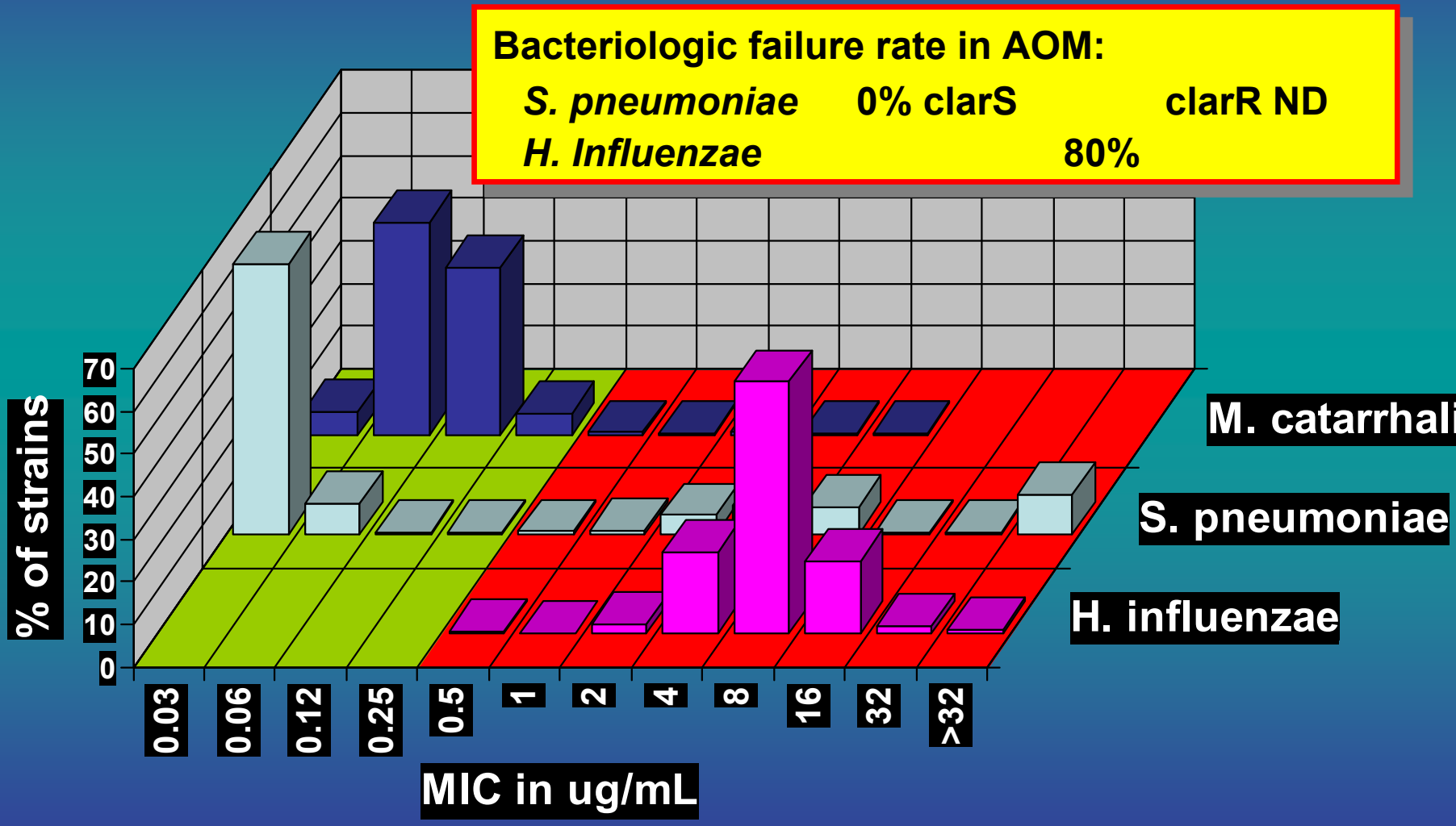


Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *AugSR M. catarrhalis* (n=969)

Clarithromycin

Bacteriologic failure rate in AOM:

S. pneumoniae	0% clarS	clarR ND
H. Influenzae		80%

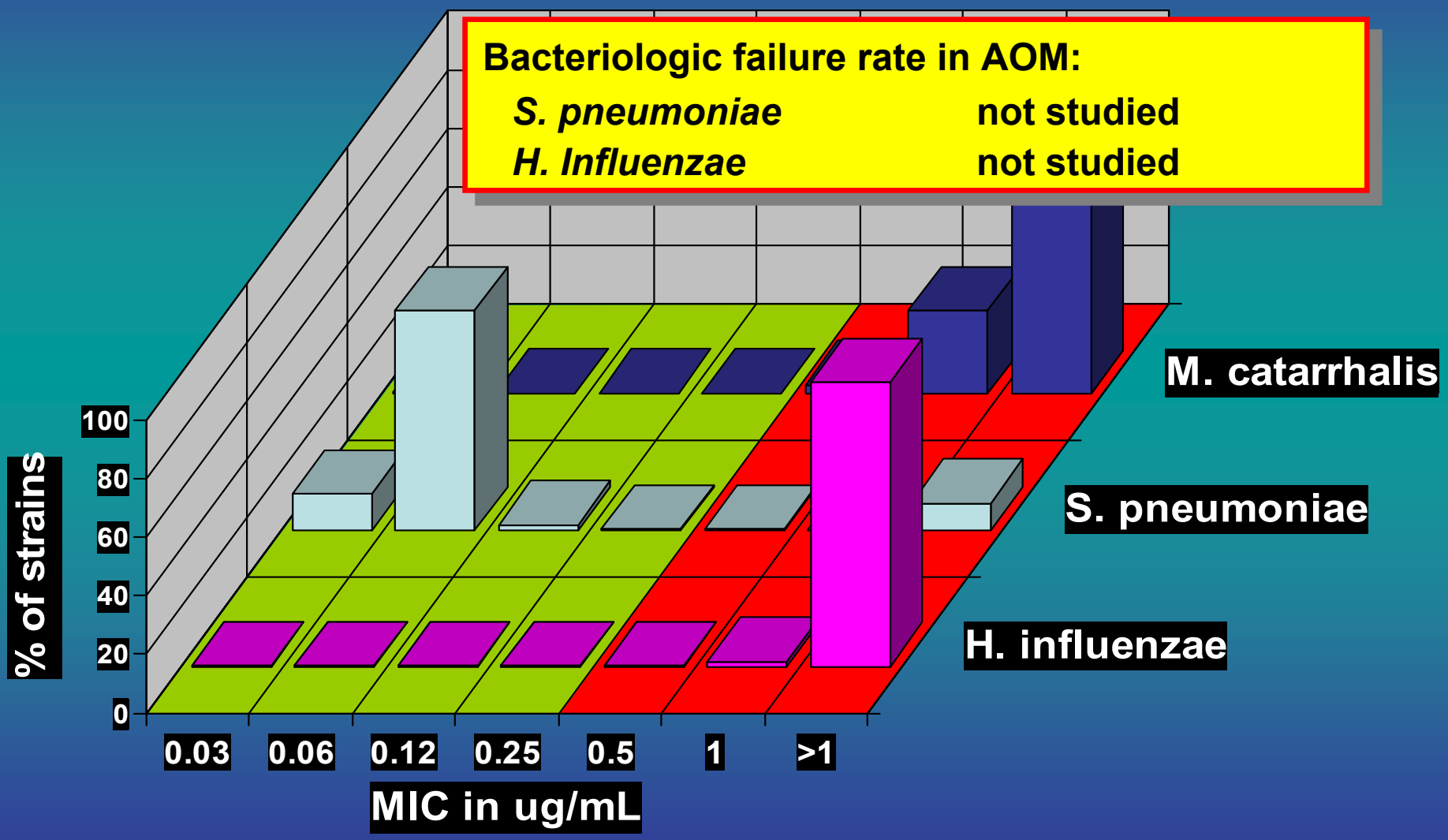


Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *AugSR M. catarrhalis* (n=969)

Clindamycin

Bacteriologic failure rate in AOM:

S. pneumoniae	not studied
H. Influenzae	not studied

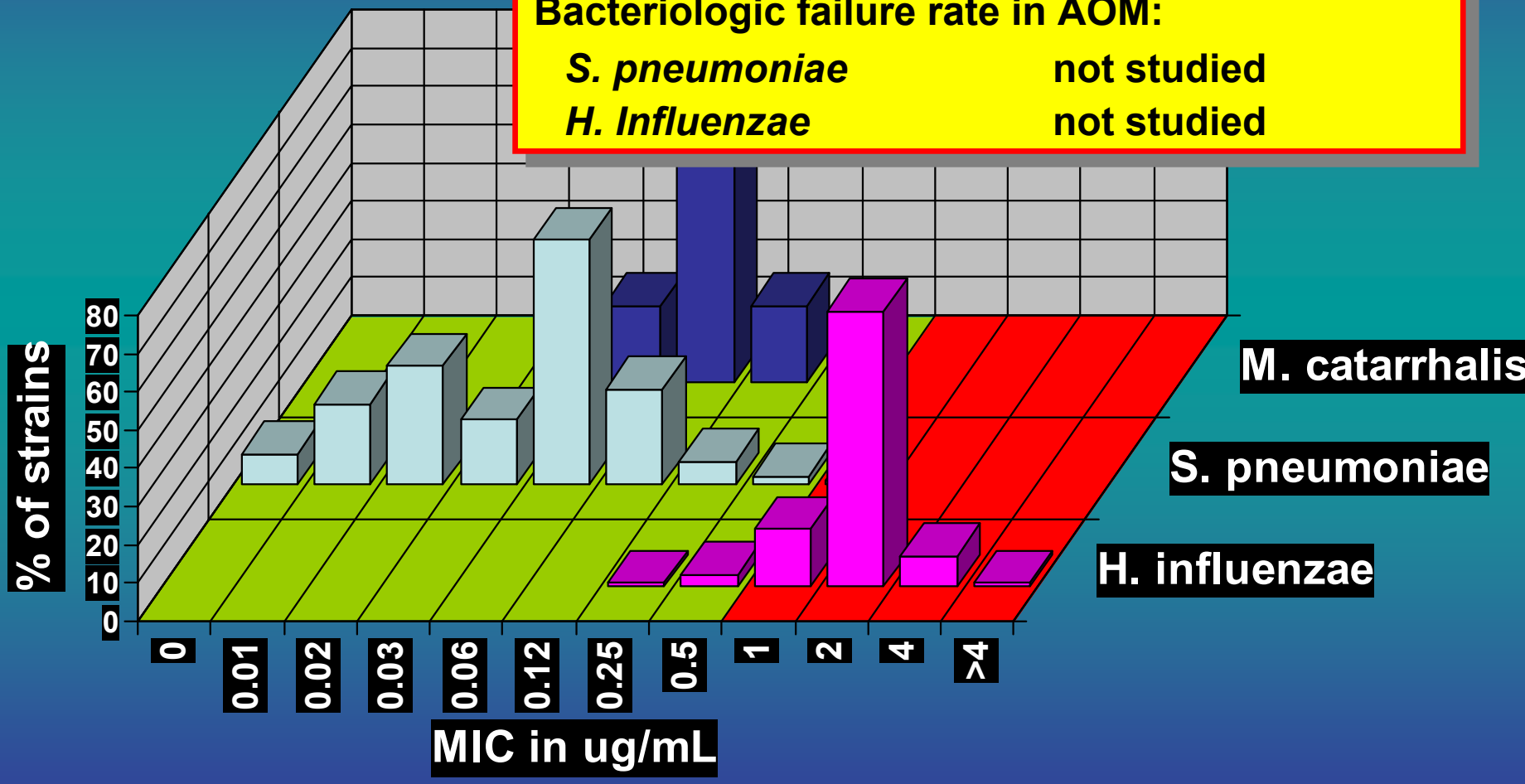


Alexander Project USA 2000: *S. pneumoniae* (n=1362)
AugSR H. influenzae (n=3793) *M. catarrhalis* 2000 (n=970)

Telithromycin

Bacteriologic failure rate in AOM:

S. pneumoniae	**not studied**
H. Influenzae	**not studied**

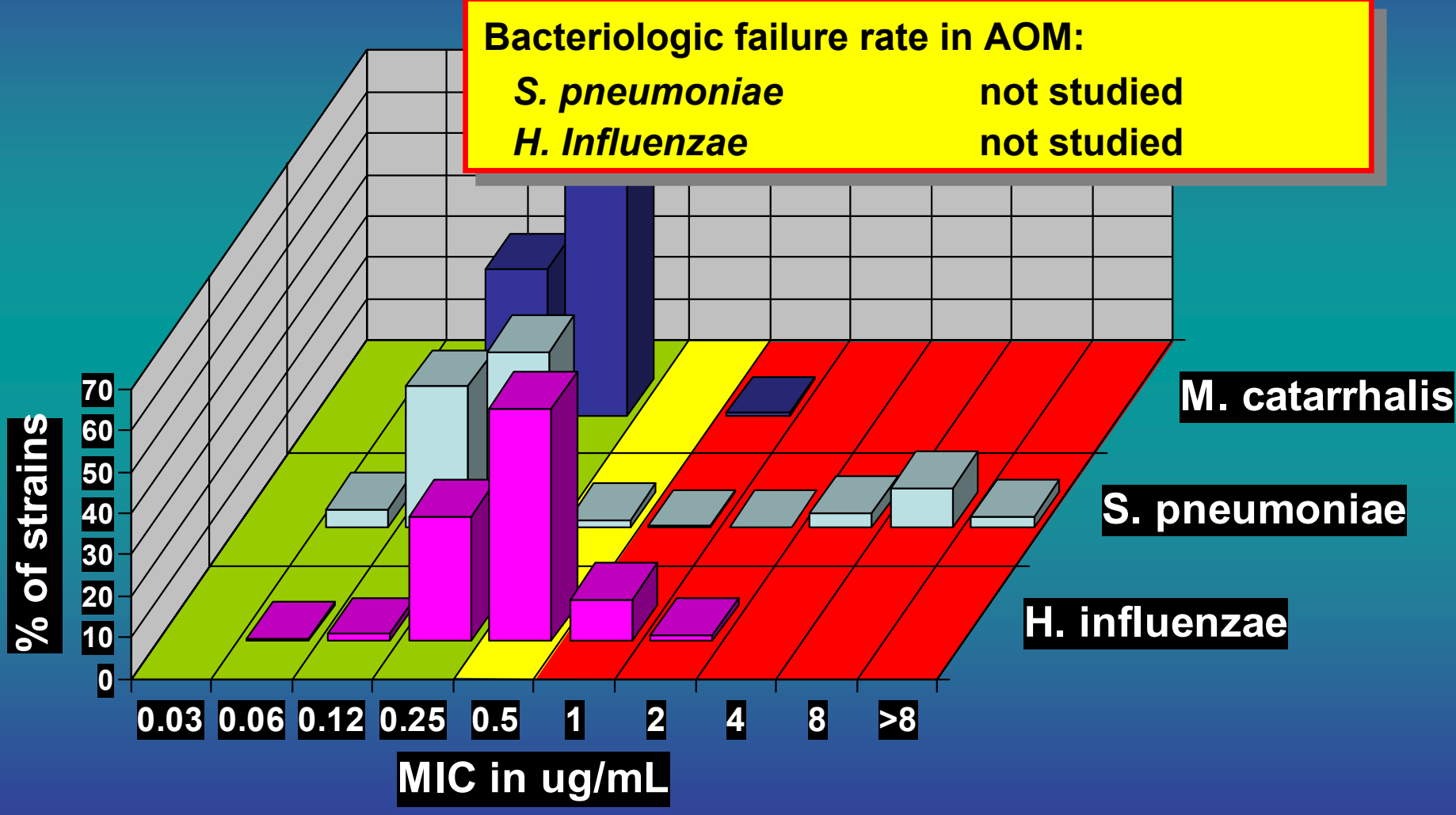


Nagai AAC 2002, 46:371-7; Pankuch AAC 1998, 42:3032-34

Doxycycline

Bacteriologic failure rate in AOM:

S. pneumoniae	**not studied**
H. Influenzae	**not studied**

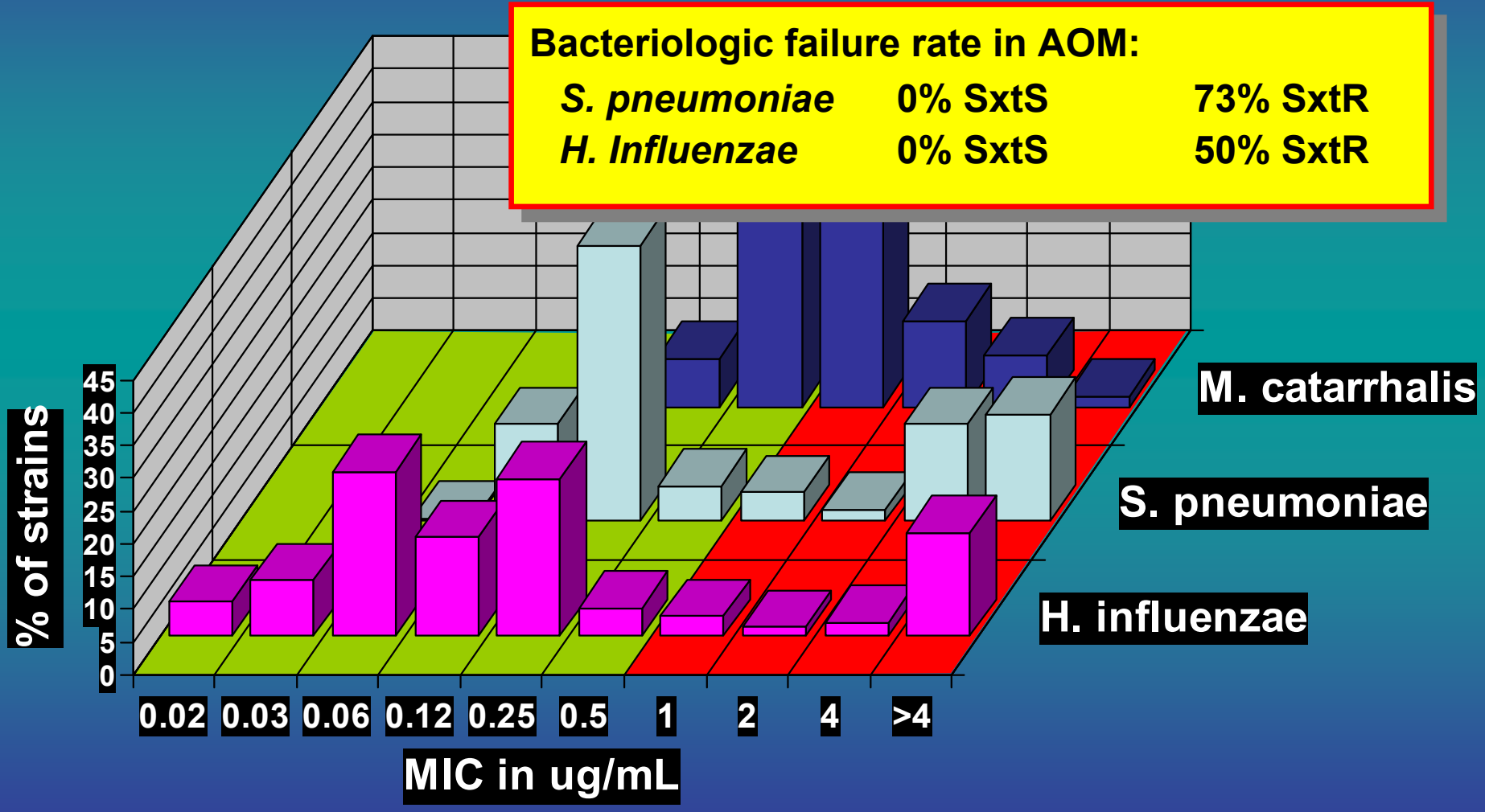


Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* 2000 (n=206)

Trimethoprim-sulfamethoxazole

Bacteriologic failure rate in AOM:

S. pneumoniae	0% SxtS	73% SxtR
H. Influenzae	0% SxtS	50% SxtR



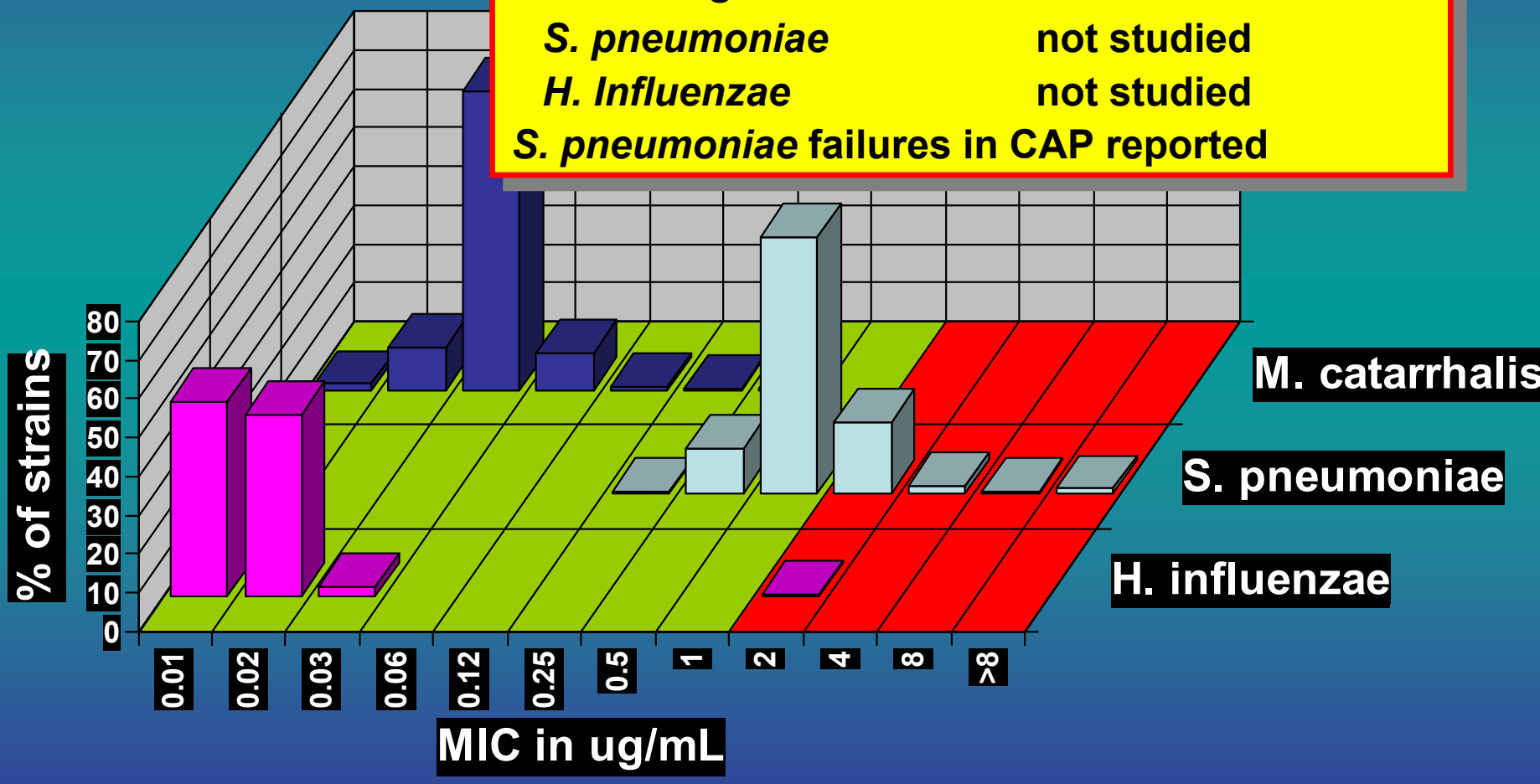
Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* AugSR (n=972)

Ciprofloxacin

Bacteriologic failure rate in AOM:

S. pneumoniae	not studied
H. Influenzae	not studied

***S. pneumoniae* failures in CAP reported**



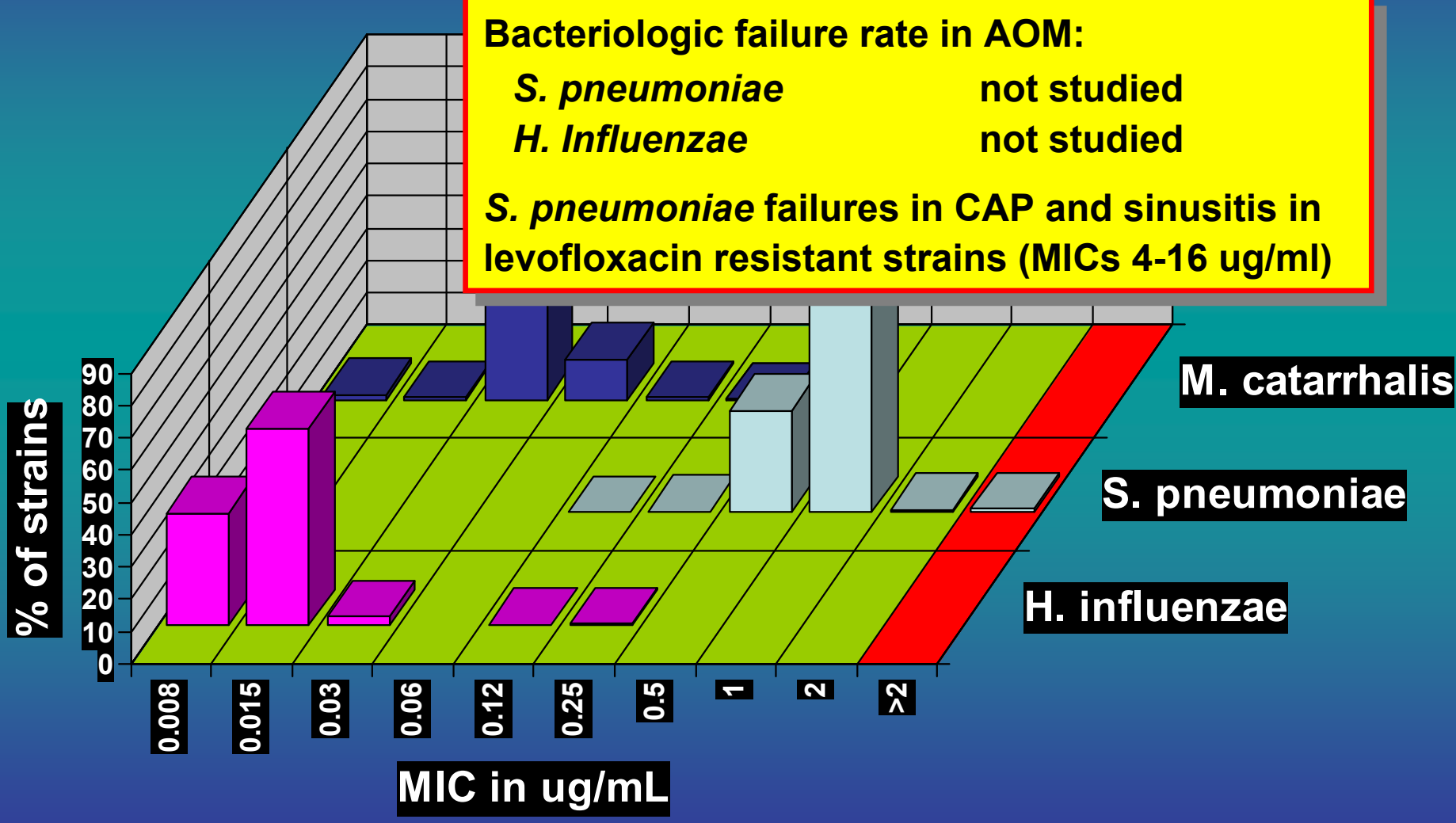
Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* AugSR (n=972)

Levofloxacin

Bacteriologic failure rate in AOM:

S. pneumoniae	not studied
H. Influenzae	not studied

***S. pneumoniae* failures in CAP and sinusitis in levofloxacin resistant strains (MICs 4-16 ug/ml)**

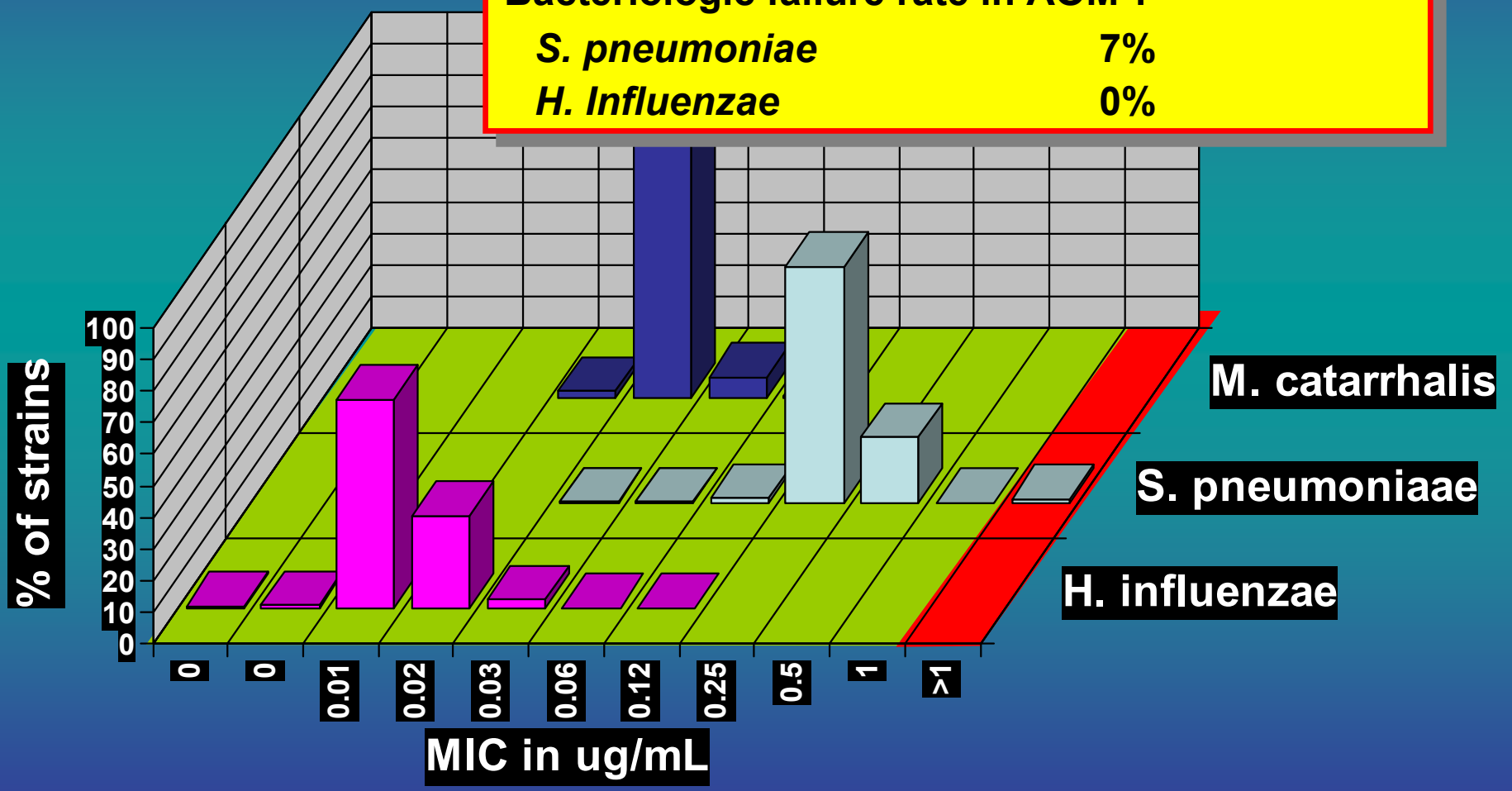


Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* AugSR (n=972)

Gatifloxacin

Bacteriologic failure rate in AOM*:

S. pneumoniae	**7%**
H. Influenzae	**0%**



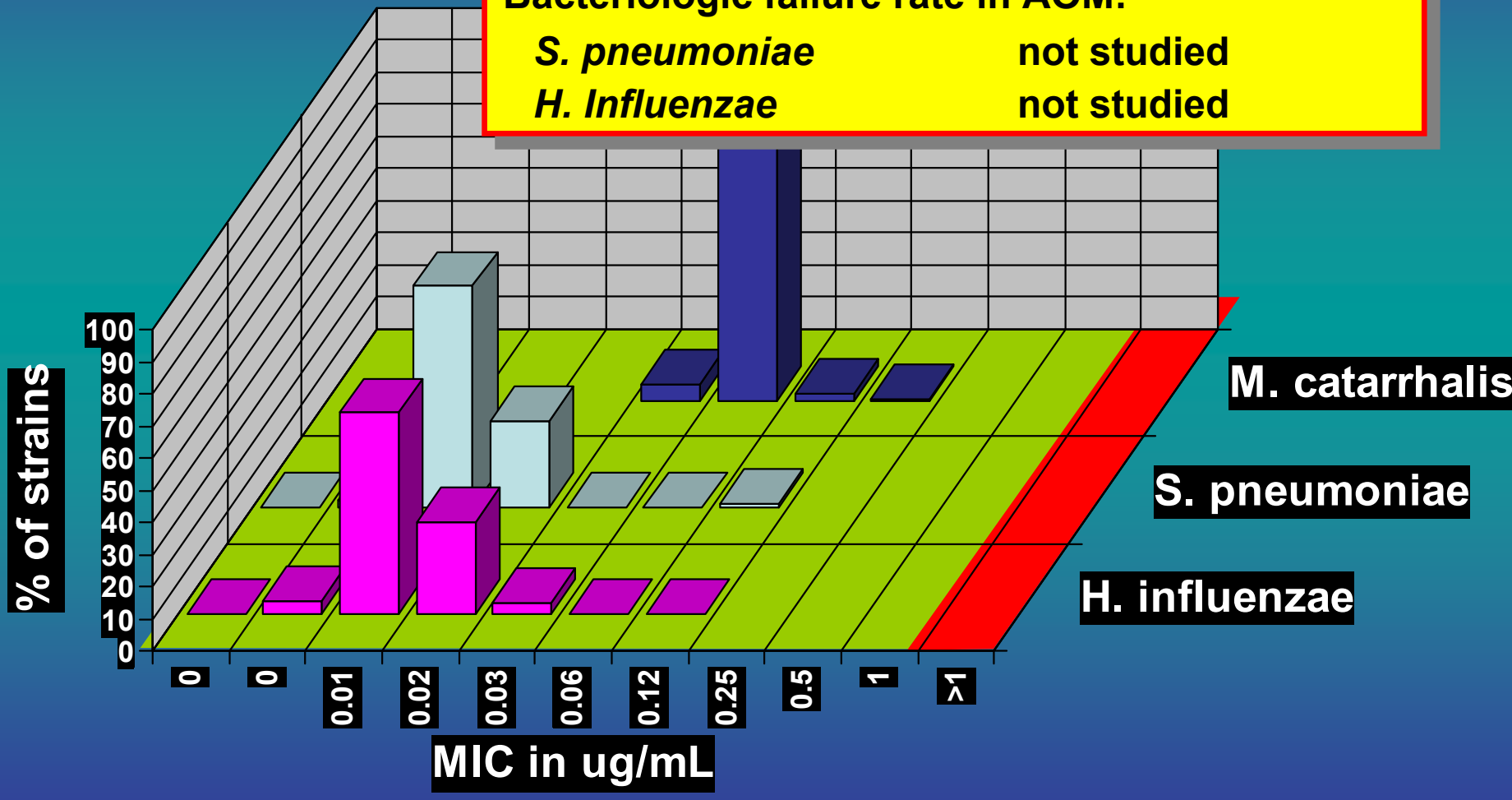
Augmentin XR surveillance data

*Dagan et al. ICAAC 2001, abstract G-1558a

Moxifloxacin

Bacteriologic failure rate in AOM:

S. pneumoniae	**not studied**
H. Influenzae	**not studied**



Augmentin XR surveillance data

Conclusions

In vitro **resistance does correlate with outcome in humans provided appropriate studies are performed (adequately sized clinical outcome studies, bacteriologic outcome studies, PK/PD studies) AND appropriate PK/PD-based susceptibility breakpoints are used**