Antimicrobial susceptibility

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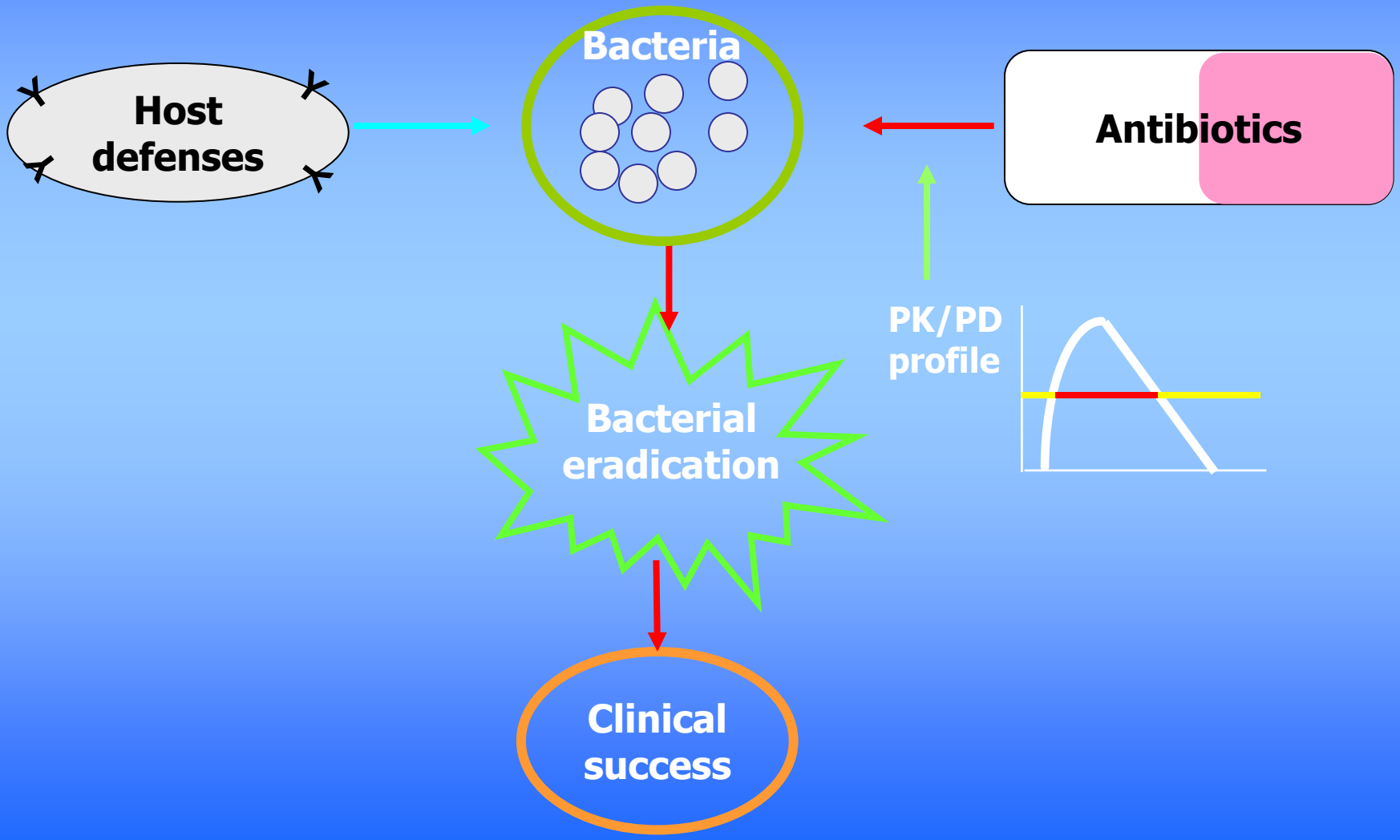
Determinants of clinical success



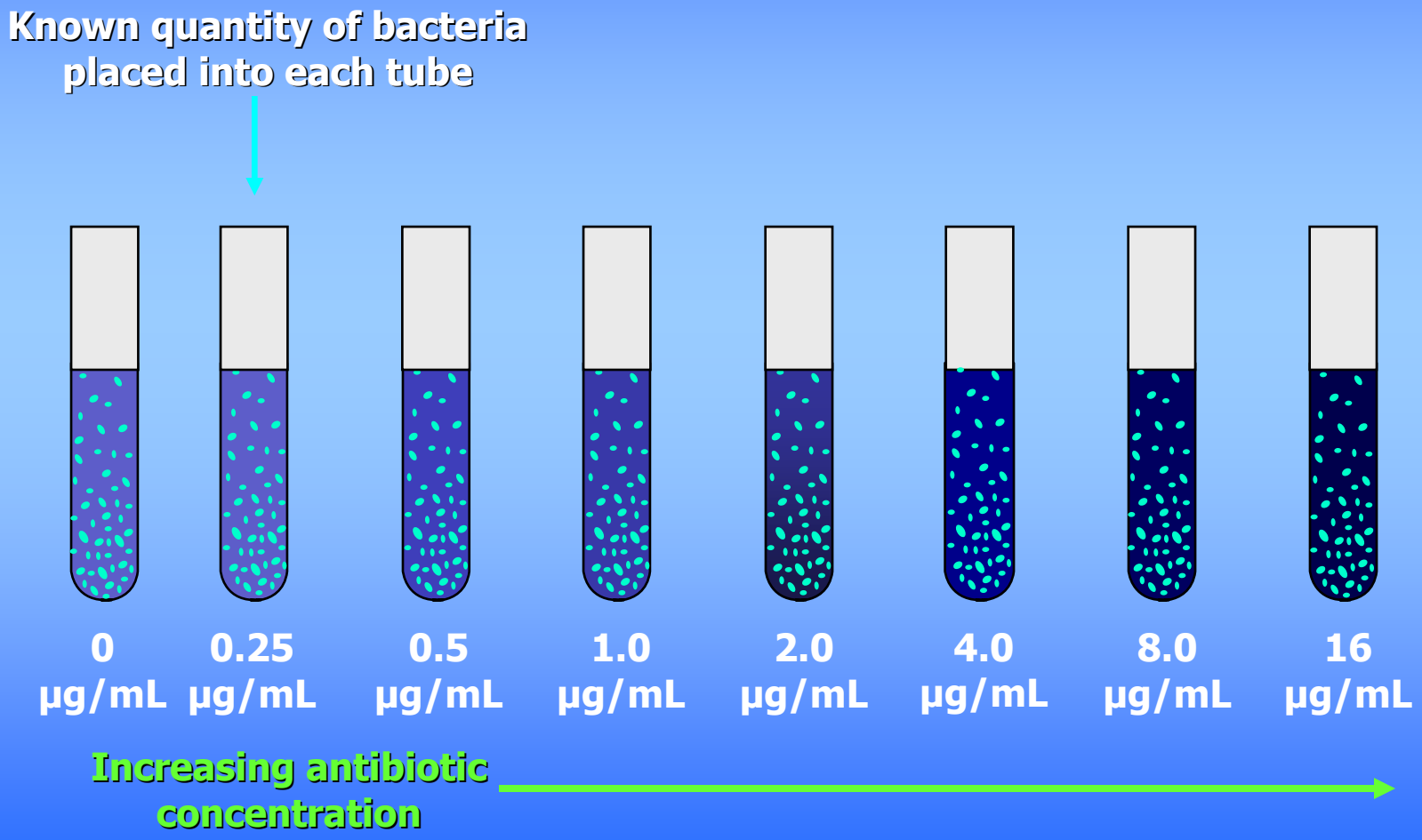
Determining "potency" of antimicrobial agents

- Minimal inhibitory concentration (MIC) determination
- Minimal bactericidal concentration (MBC) determination
- Subinhibitory and post-antibiotic effects (SME and PAE)
- Interpreting MICs
  - MIC_{50} and MIC_{90} values
  - MIC distributions
  - Interpretative breakpoints

Minimal inhibitory concentration (MIC): measure of "potency"

- **MICs** are the most common measures used for the evaluation of antimicrobial activity
- **MICs** are *in vitro* measurements:
  - **the antibiotic concentration required to completely inhibit visible growth in a test tube**
  - **Bacterial inoculum, medium and incubation time are standardized**
  - **Antibiotic concentration is constant**

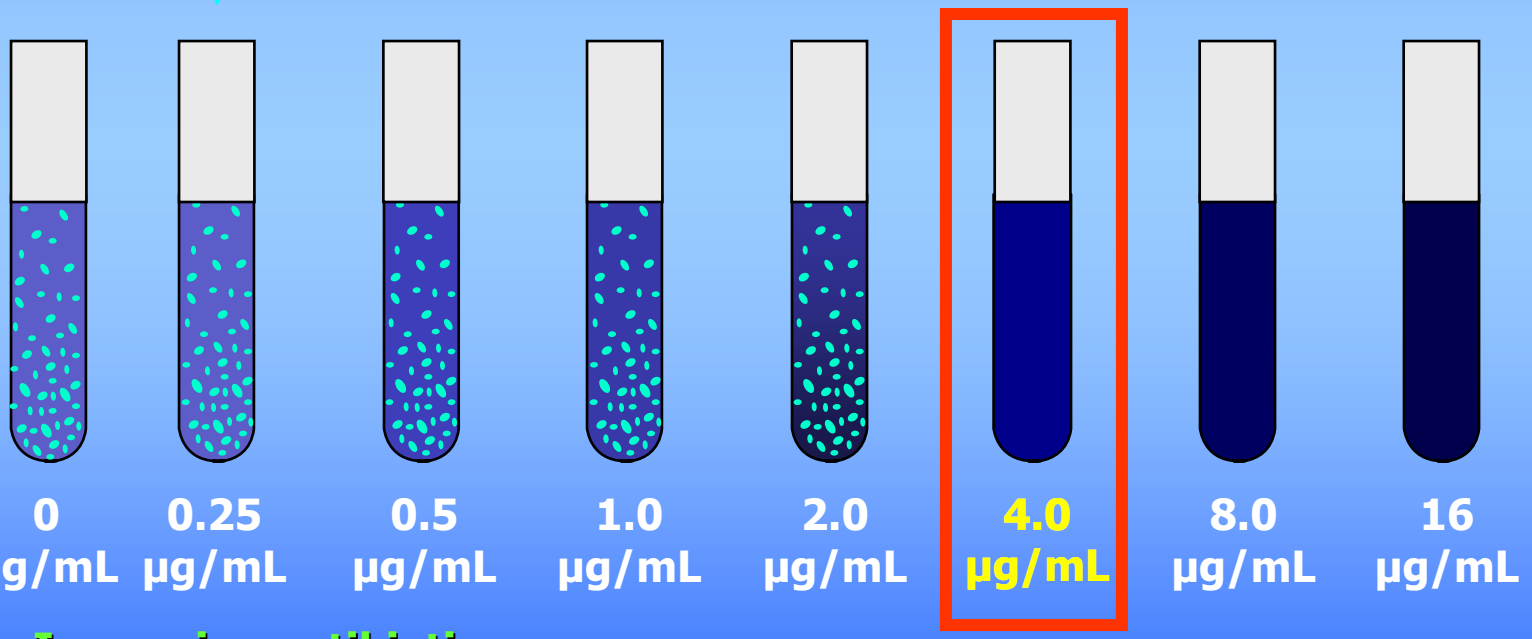
Minimal inhibitory concentration



Minimal inhibitory concentration

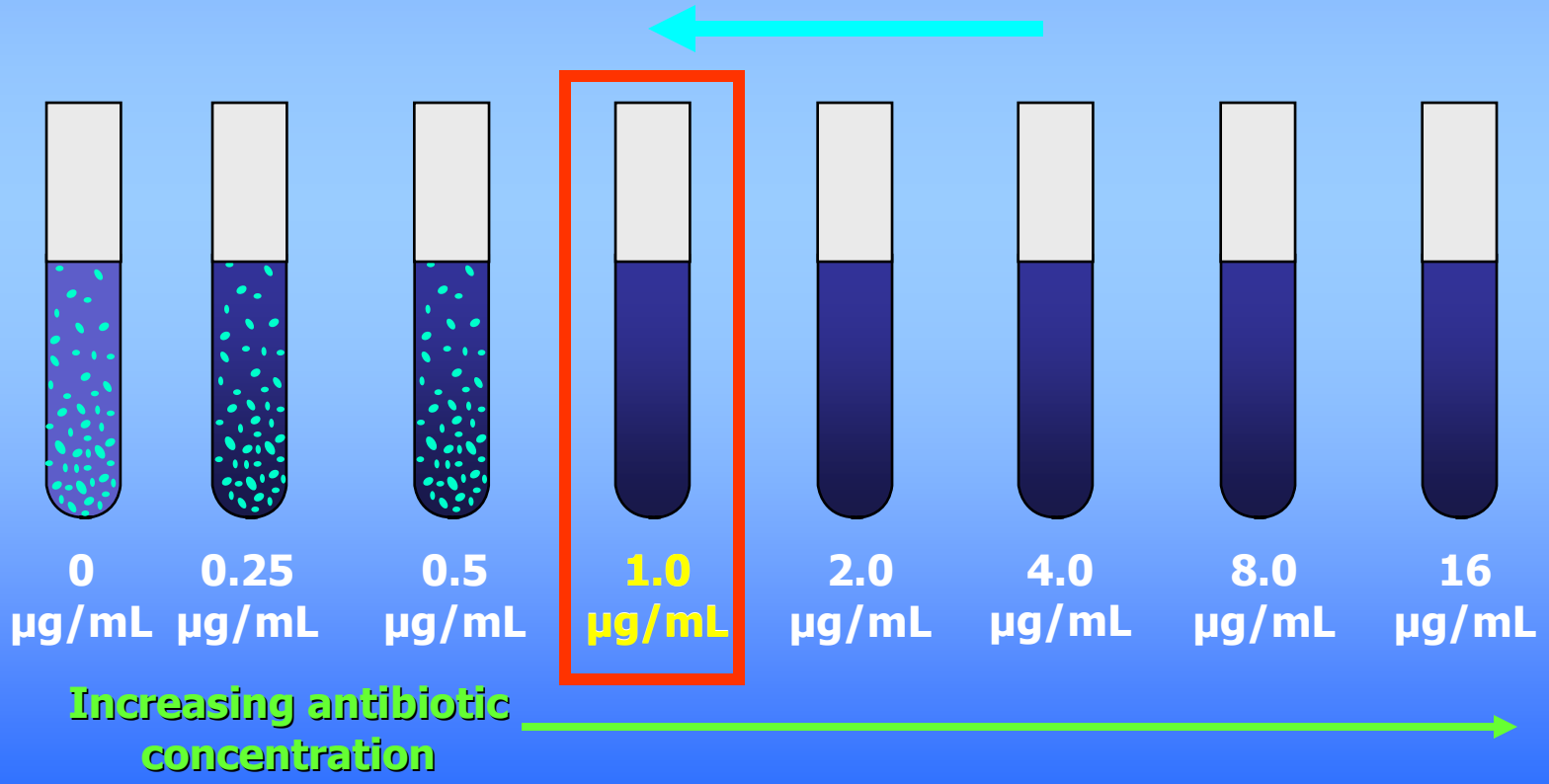
Known quantity of bacteria placed into each tube

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism

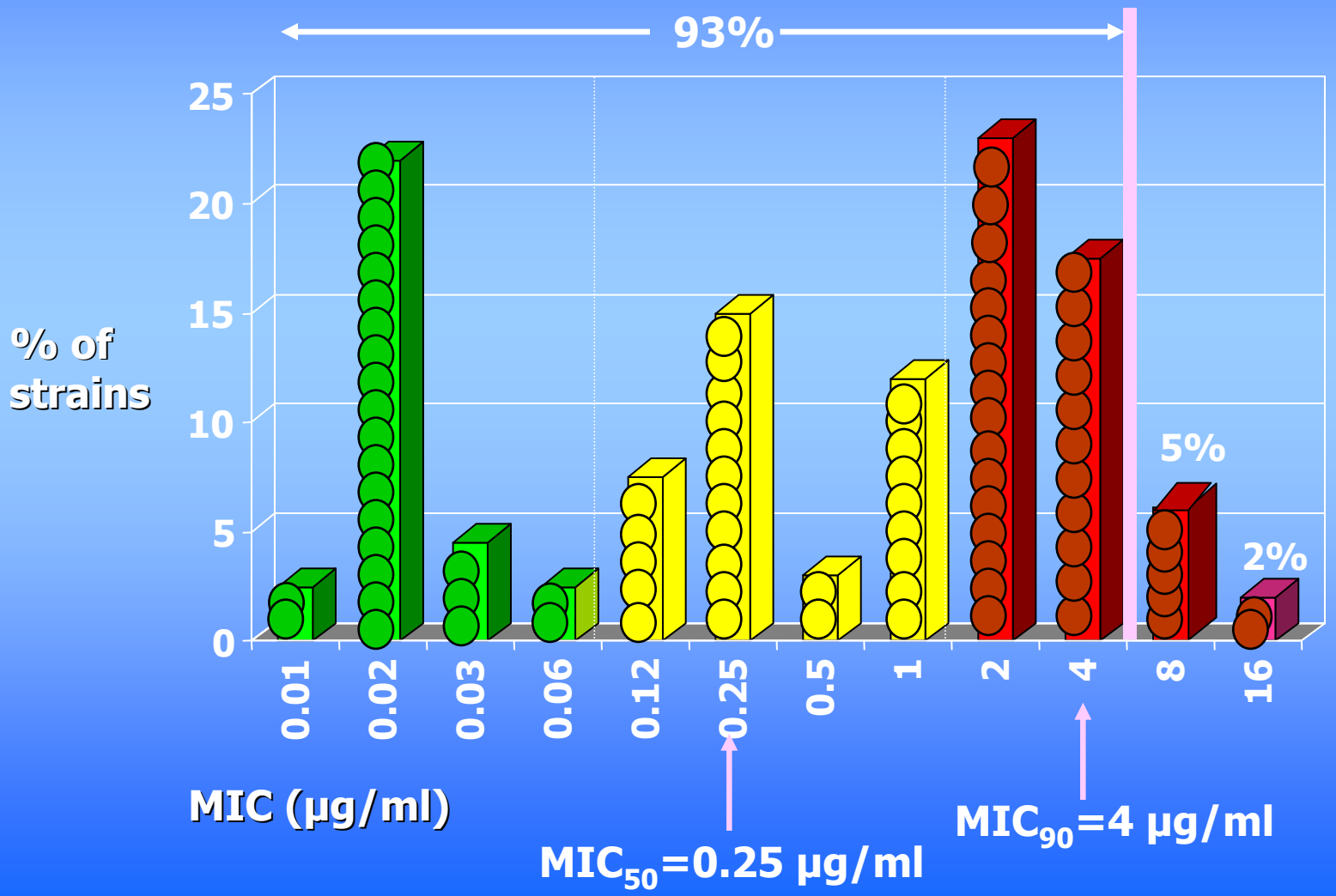


Minimal inhibitory concentration

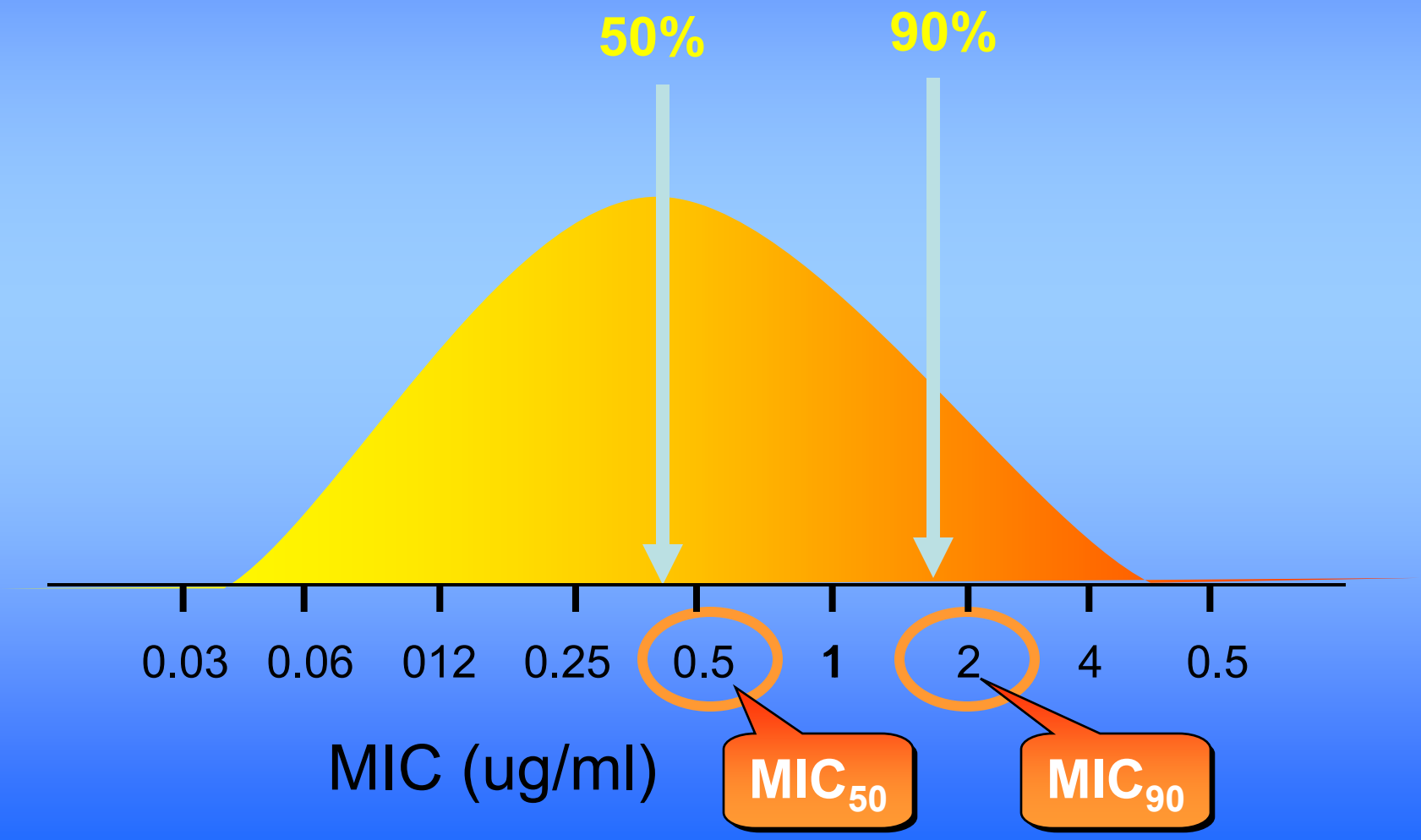
The more "potent" the antibiotic, the less is needed to kill the bacteria, and the MIC is LOWER



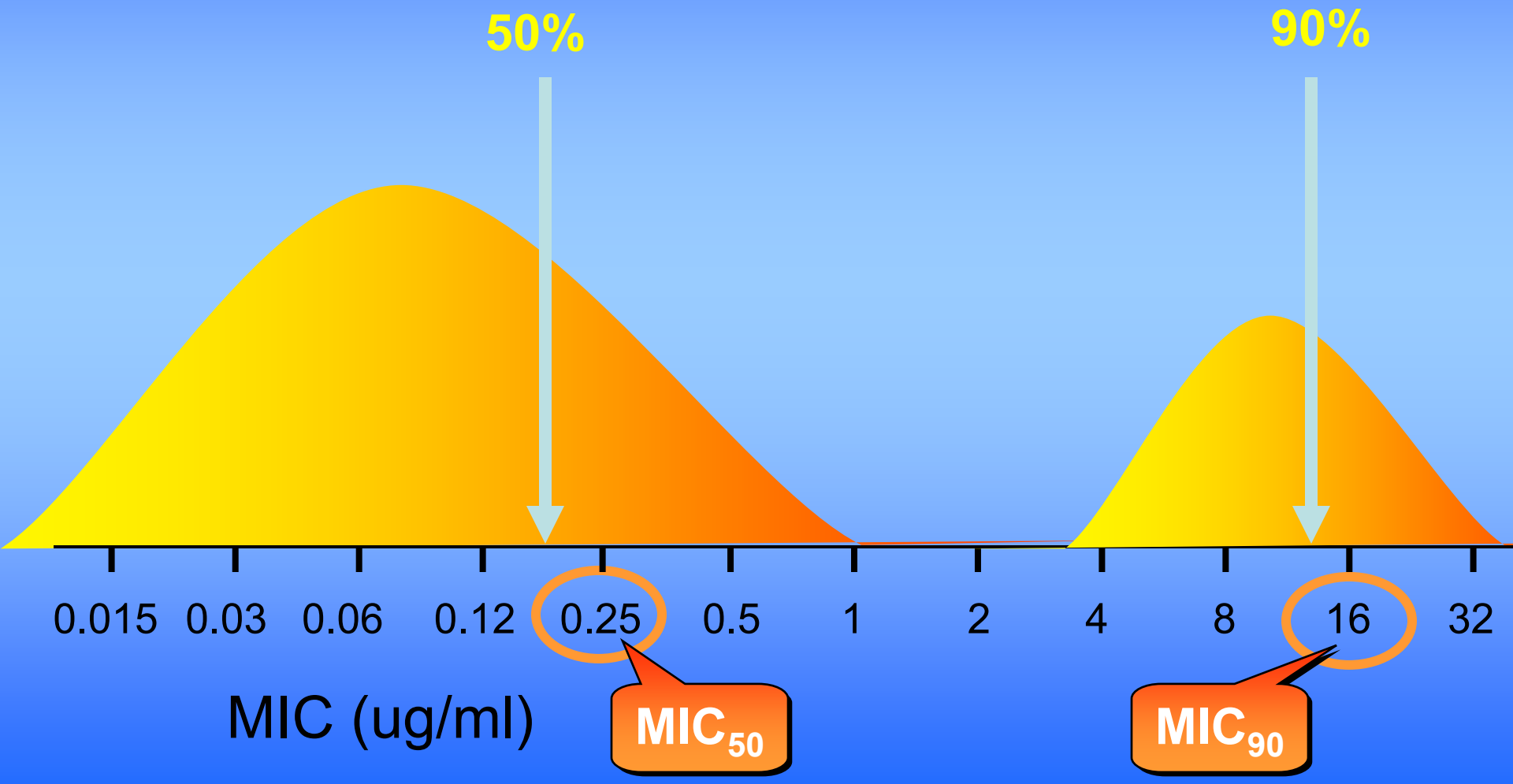
MIC_{90}: the lowest concentration that includes at least 90% of the strains tested



MIC_{50} and MIC_{90} unimodal population

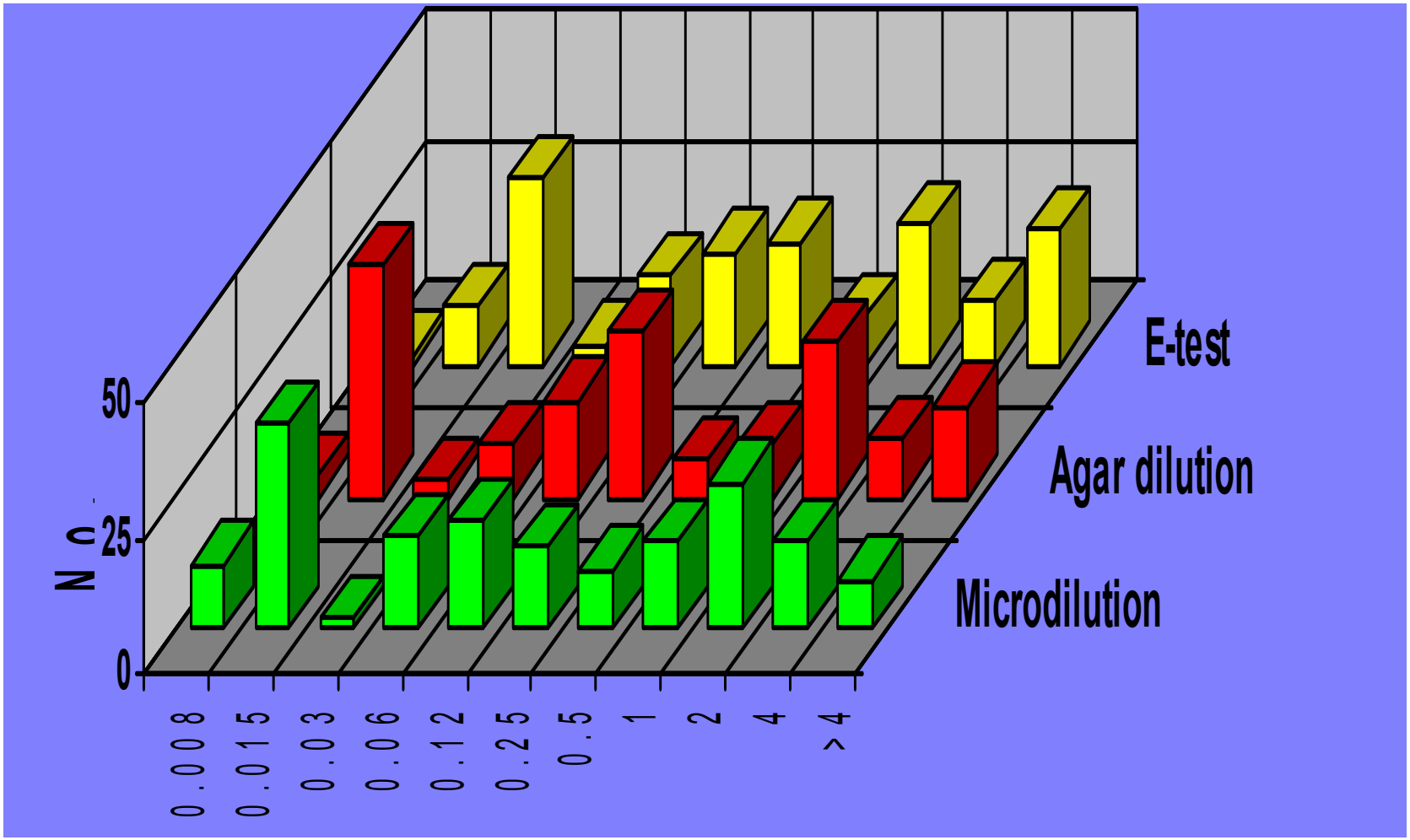


MIC_{50} and MIC_{90} bimodal population



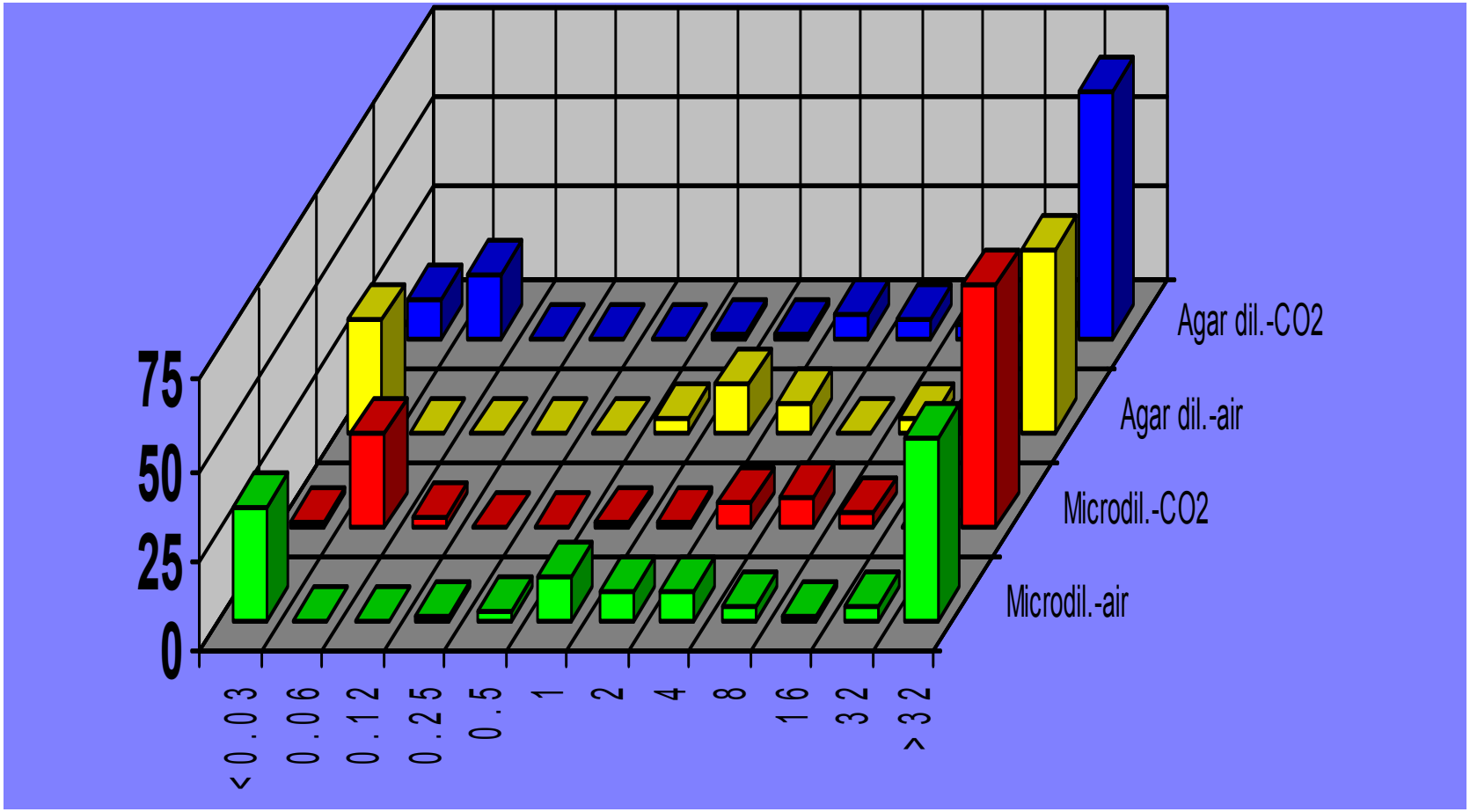
Streptococcus pneumoniae

Penicillin MIC variation by method



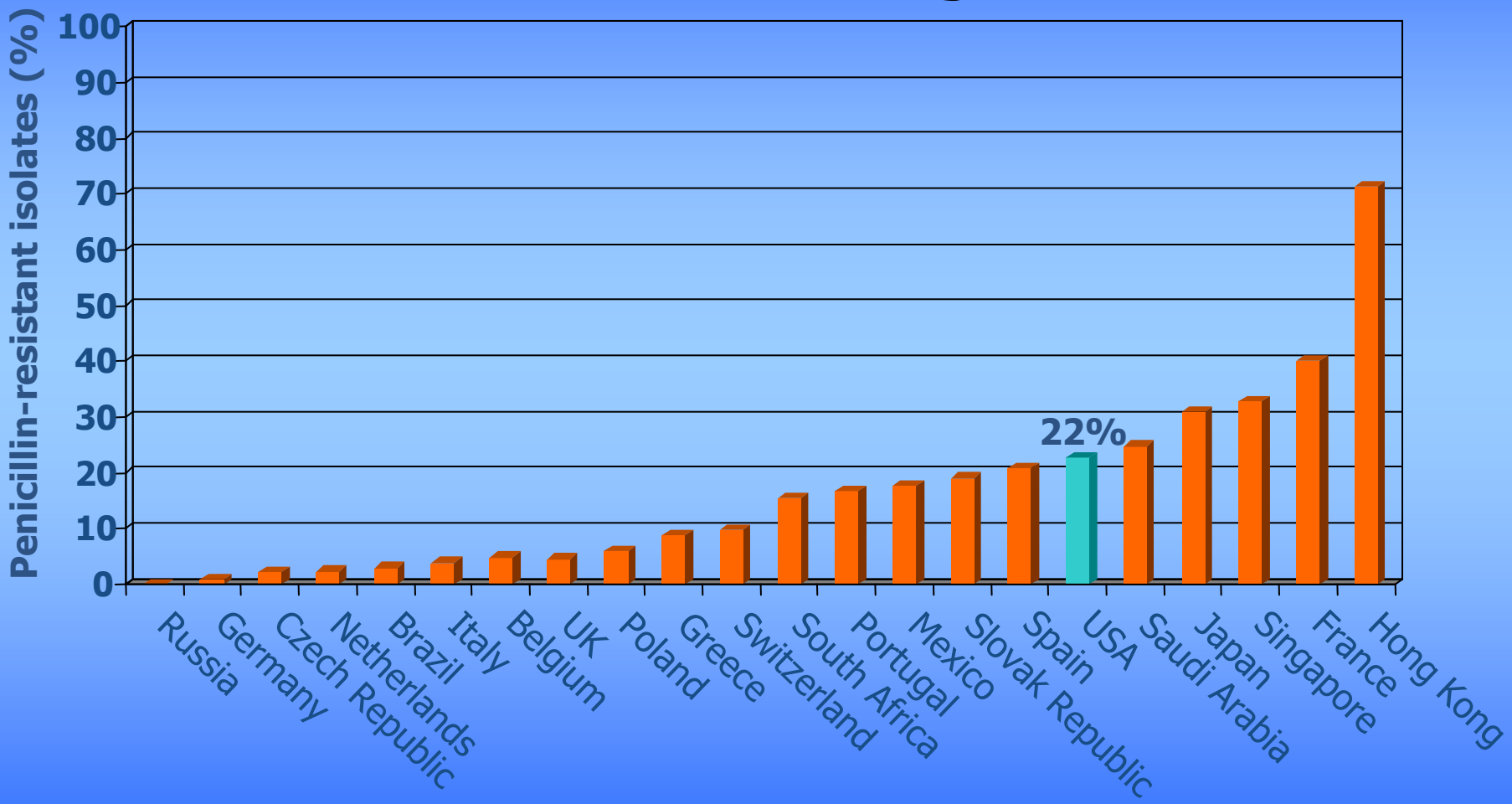
From Jacobs et al., J. Clin. Micro. 1998, 36:179

Streptococcus pneumoniae
Erythromycin MIC variation by method



From Fasola et al., Antimicr. Agents Chemother. 1997, 41:129-134

S. pneumoniae Pen-R: The Alexander Project 2000



Penicillin-resistant defined as penicillin MIC ≥2 µg/mL

Alexander Project data 2000 – GlaxoSmithKline, data on file.

Subinhibitory effects of antibiotics

Postantibiotic effect; PAE in vitro

Definition:

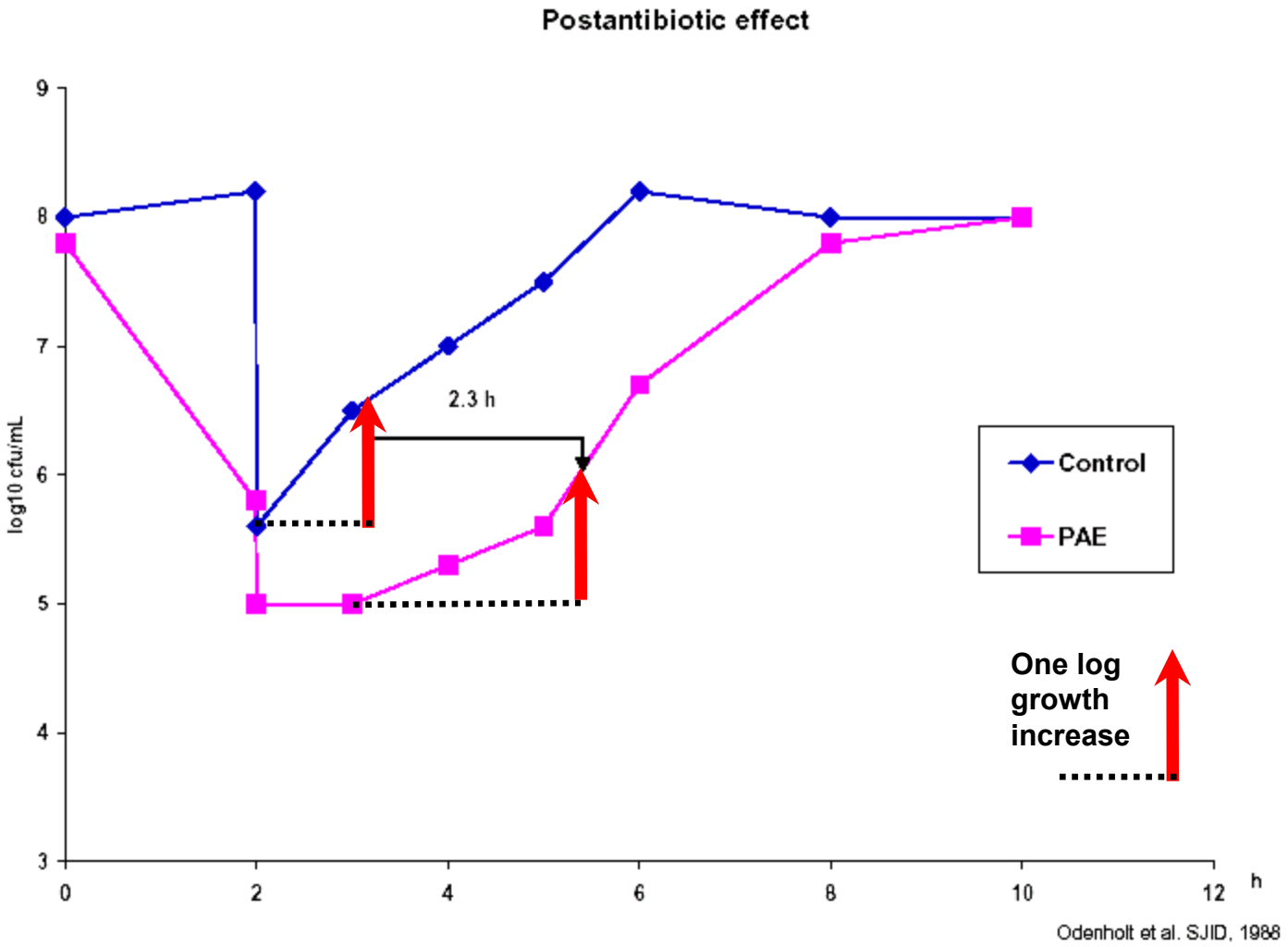
- Suppression of bacterial growth after short exposure of organisms to antibiotics

  PAE=T-C

  T= The time required for the exposed culture to increase one $\log_{10}$ above the count observed immediately after drug removal

  C= The corresponding time for the unexposed control

Odenhalt 2001



Odenhalt 2001

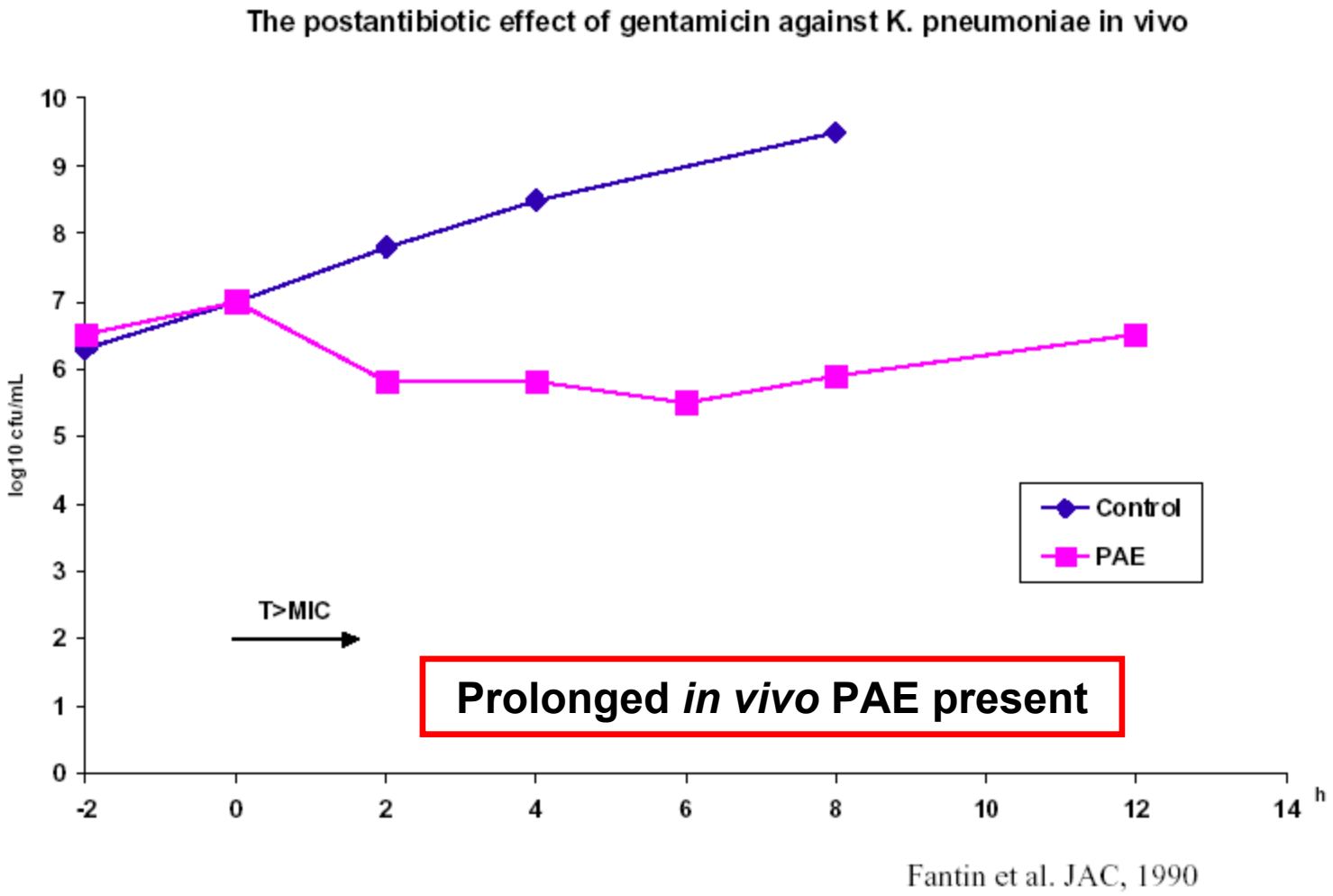
Postantibiotic effect in vivo

Definition

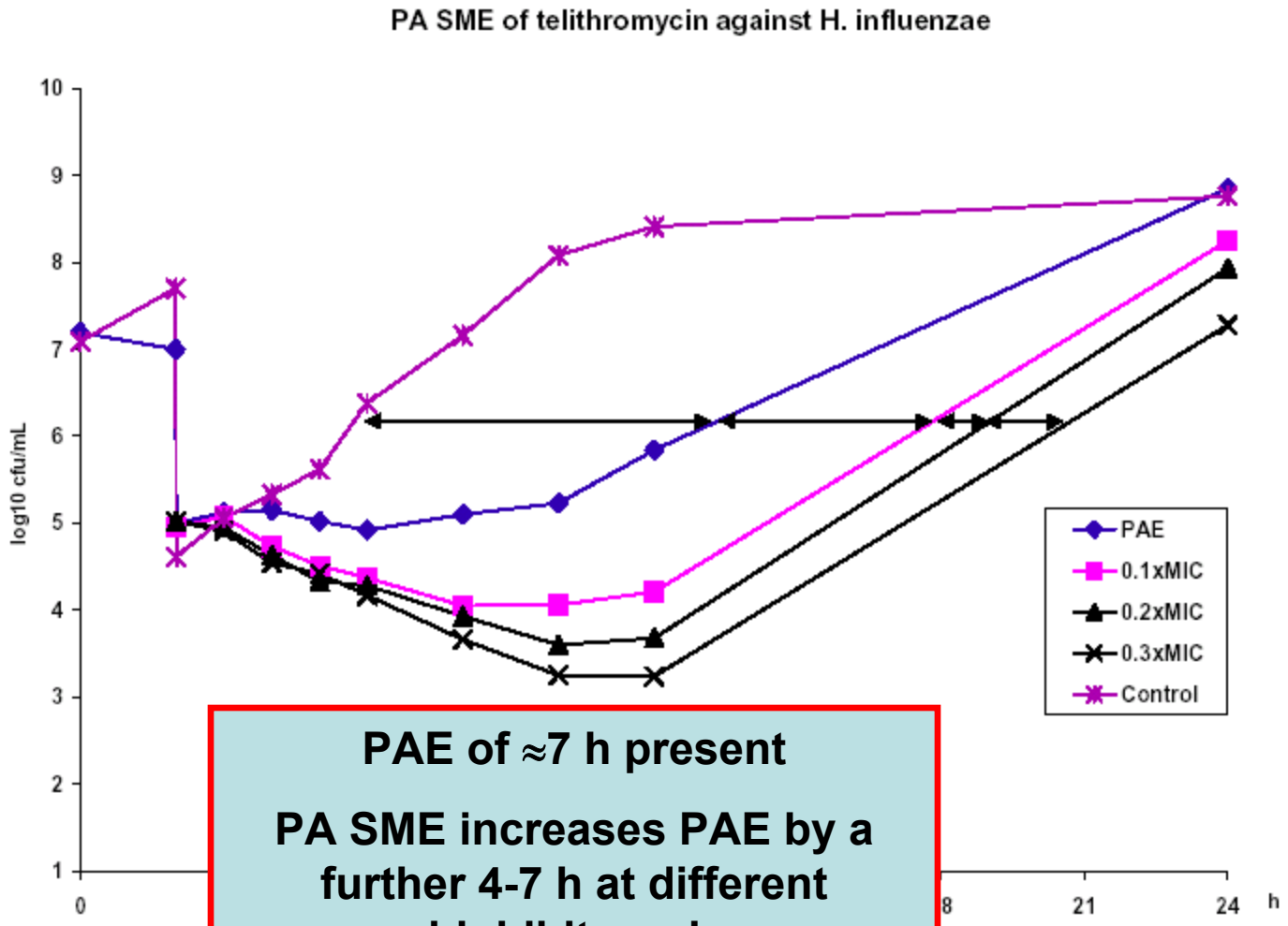
PAE= T-C-M

- T= the time required for the counts of cfu in thighs of treated mice to increase one $\log_{10}$ above the count closest to but not less than the time M
- C= the time required for the counts of cfu in thighs of untreated mice to increase one $\log_{10}$ above the count at time zero
- M= the time serum concentration exceeds the MIC

Odenhalt 2001



Odenhalt 2001



PAE of ≈7 h present

PA SME increases PAE by a further 4-7 h at different subinhibitory drug concentrations

Odenhalt 2001

Subinhibitory effects of antibiotics

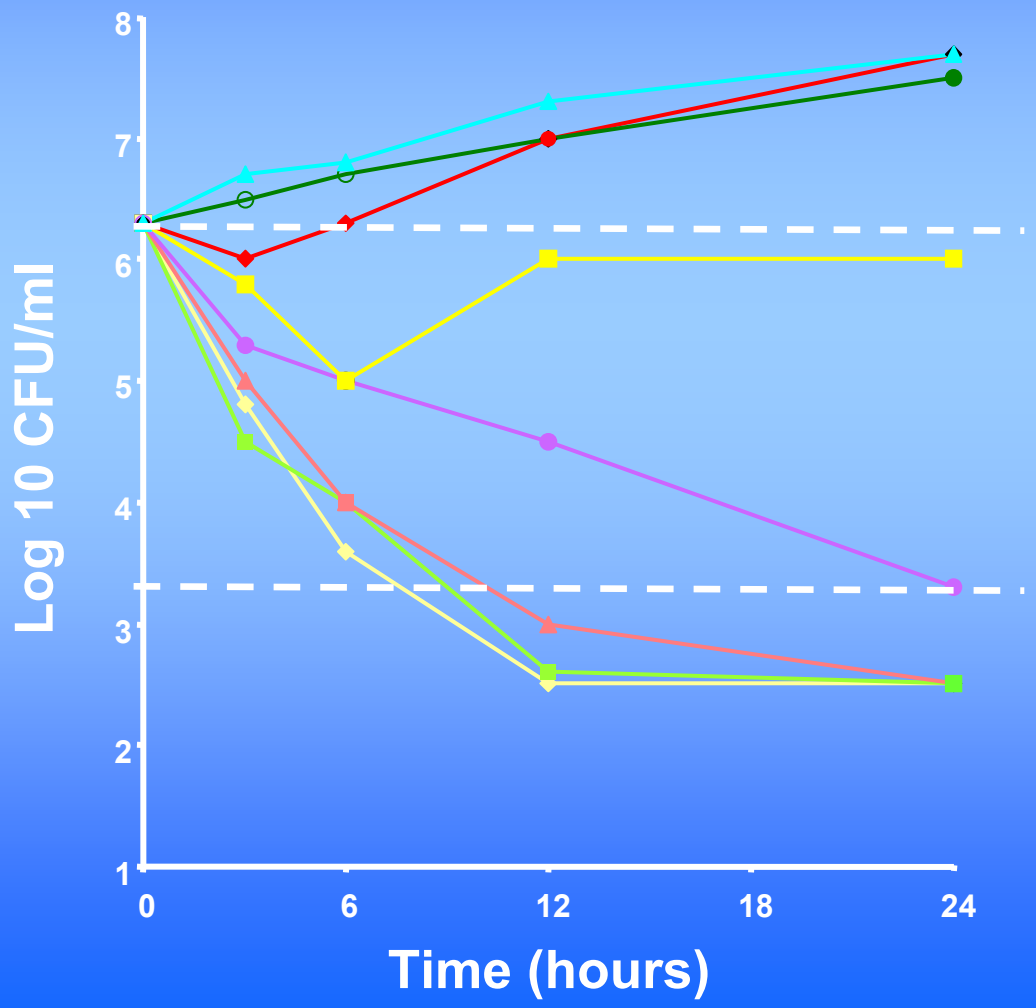
Subinhibitory effects such as PAE and PAE-SME can often be demonstrated and may account in part for concentration-dependent PK/PD interactions in vivo

Bactericidal activity

Bactericidal activity: Time-kill determination

- MICs do not provide data on whether the isolate has only been inhibited or has been "killed"
- MBCs provide data on bacterial killing (defined as a 3 $\log_{10}$ kill in 24 h)
- Time-kill curves provide more detailed data on extent and time course of killing

Gemifloxacin time kill of a penicillin resistant strain of S.*pneumoniae* (gemifloxacin MIC 0.016 ug/ml)

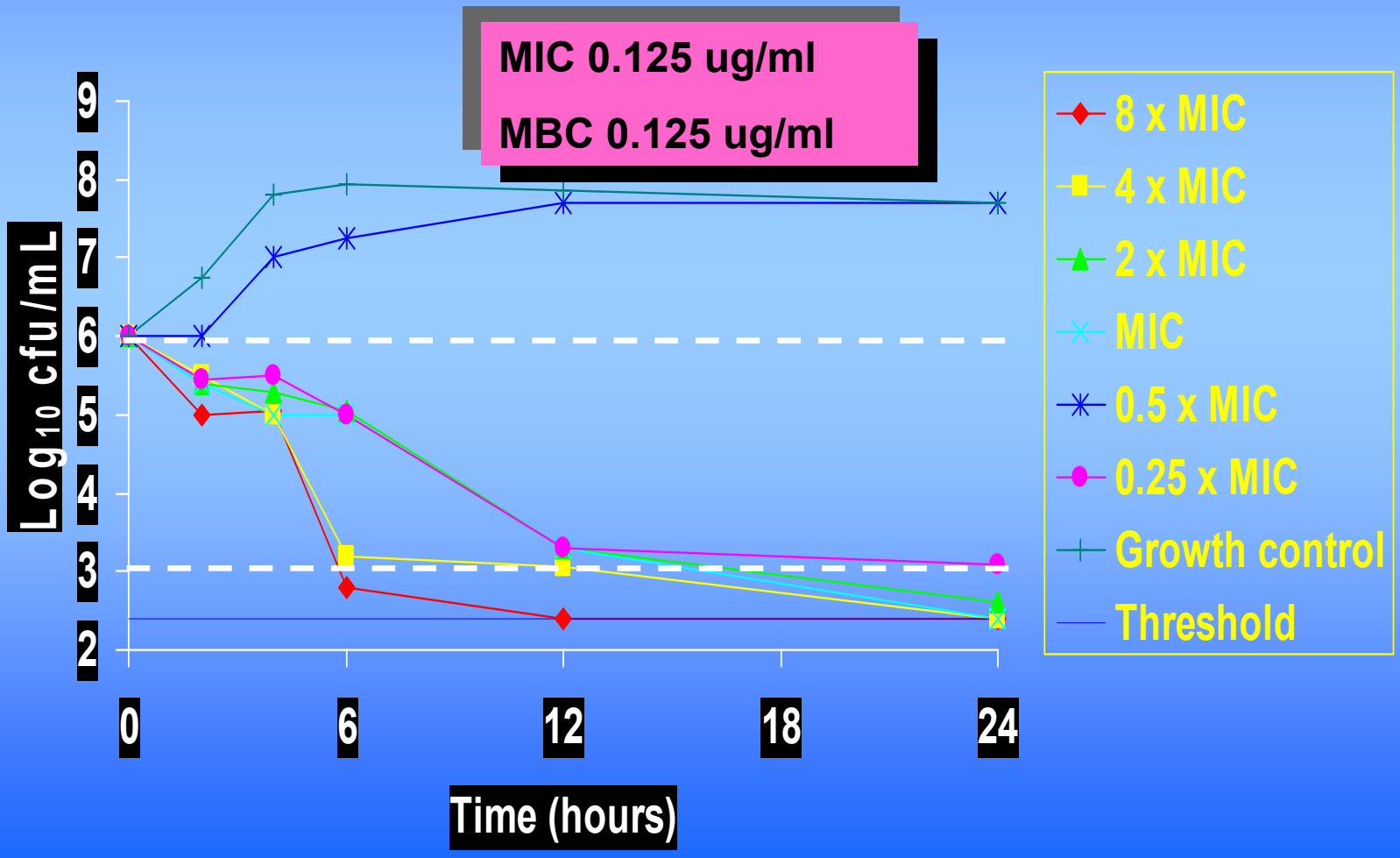


MIC 0.008 ug/ml

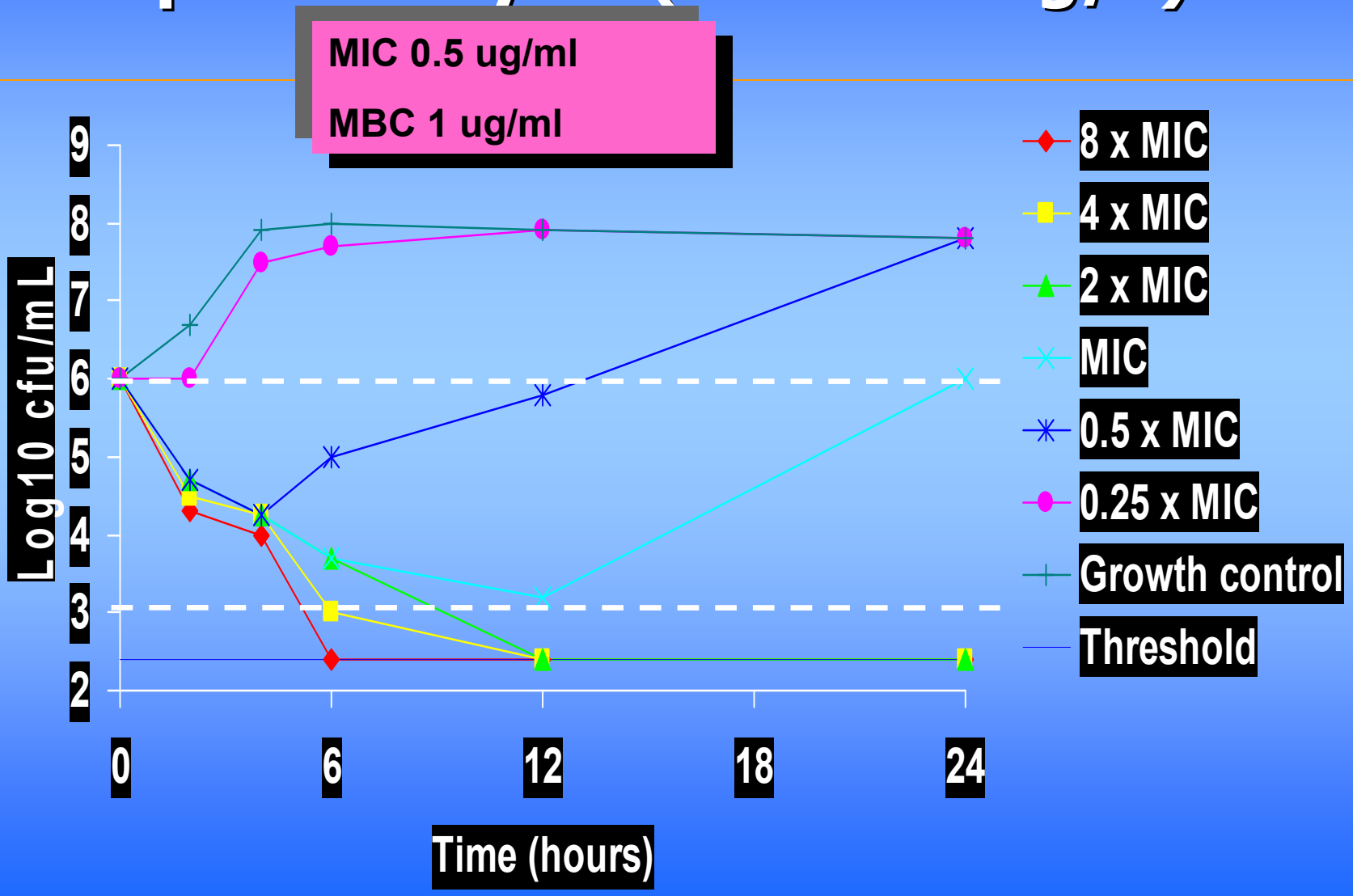
MBC 0.015 ug/ml

- 8 X MIC
- 4 X MIC
- 2 X MIC
- 1 X MIC
- 0.5 X MIC
- 0.25 X MIC
- 0.125 X MIC
- Growth control

Time Kill of S. pneumoniae for telithromycin (MIC 0.125 mg/L)



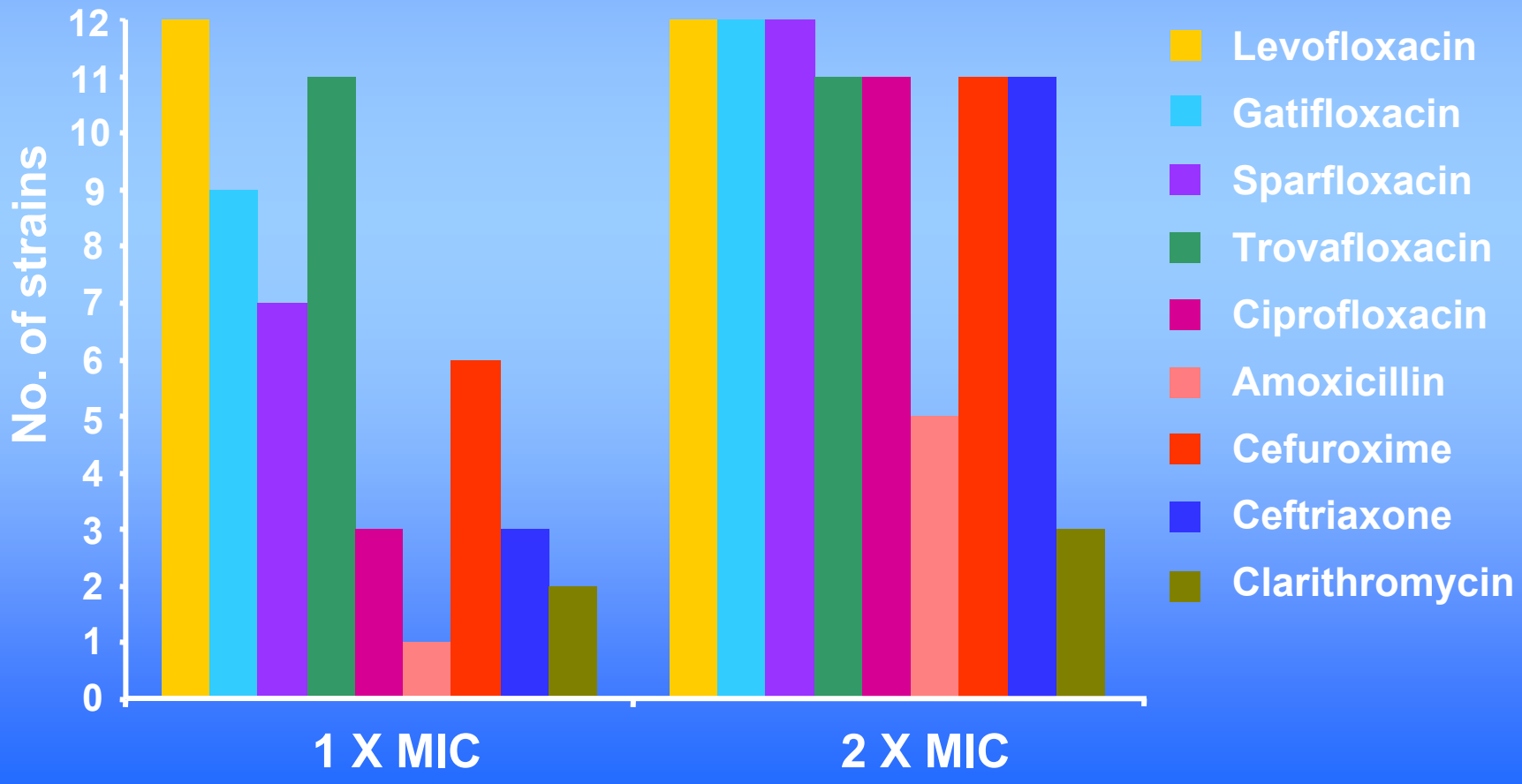
Time Kill of S. pneumoniae for pristinomycin (MIC 0.5 mg/L)



Time kill of *S.pneumoniae*

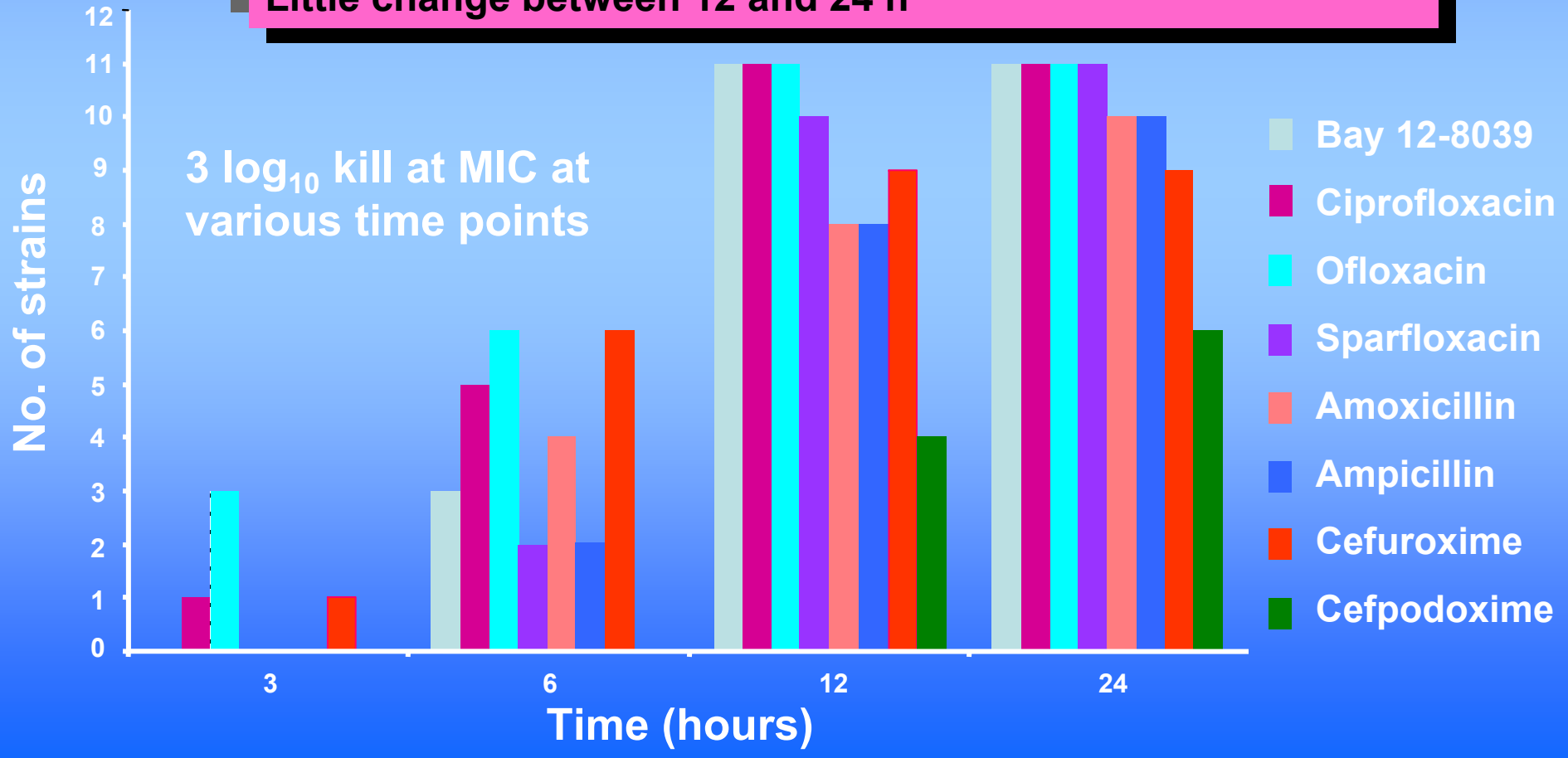
Bactericidal activity against most strains at MICs for quinolones compared to at 2X MICs for beta-lactams

3 $\log_{10}$ kill in 24 hours



Time kill of *S.pneumoniae*

- Little bactericidal activity at MIC at 3 h
- Bactericidal activity against up to half of the strains at 6 h
- Bactericidal activity against most strains at 12 h, with faster killing by quinolones that by beta-lactams
- Little change between 12 and 24 h



MIC distributions of RTI pathogens

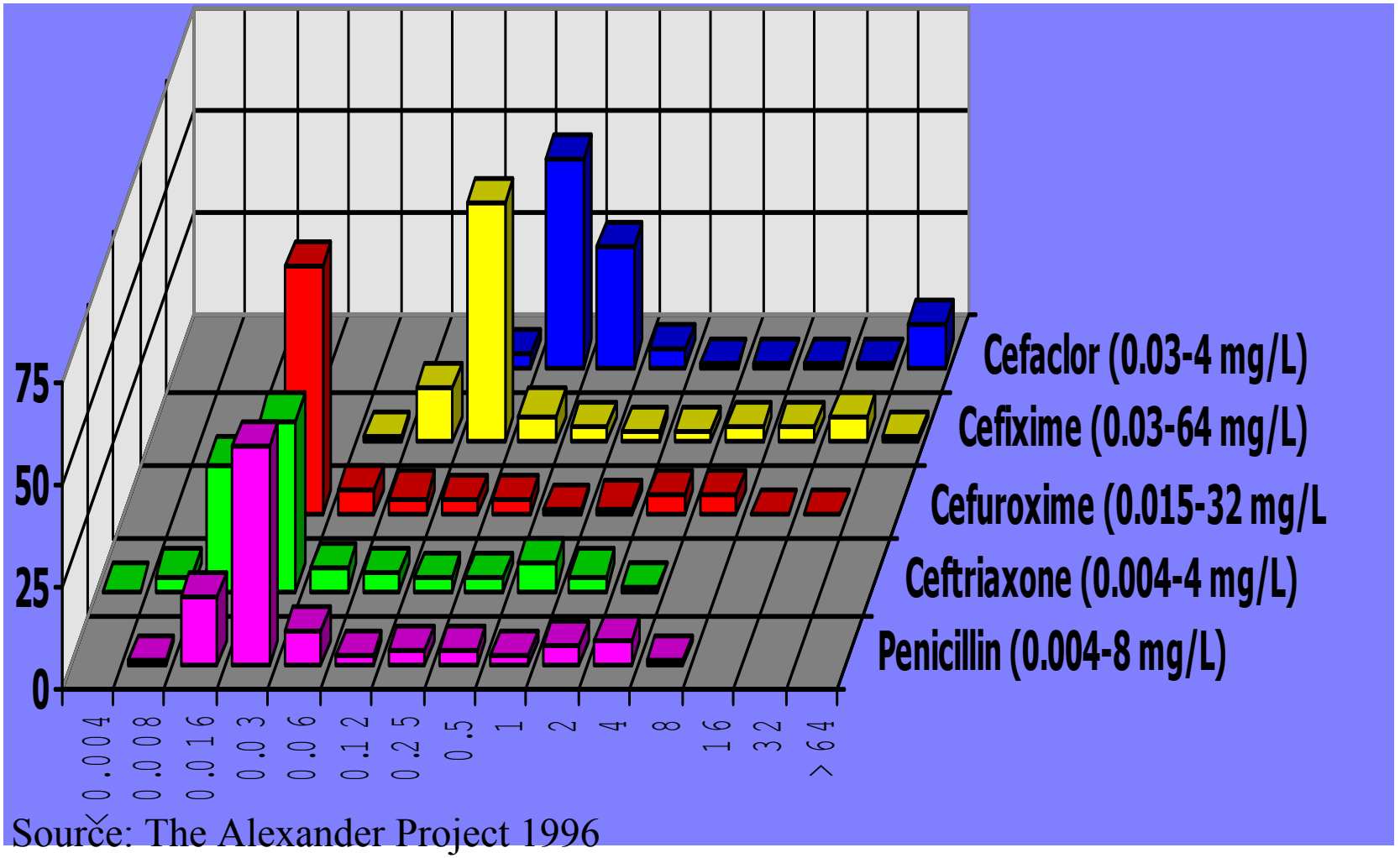
MIC distributions of RTI pathogens

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

MIC distributions

Streptococcus pneumoniae

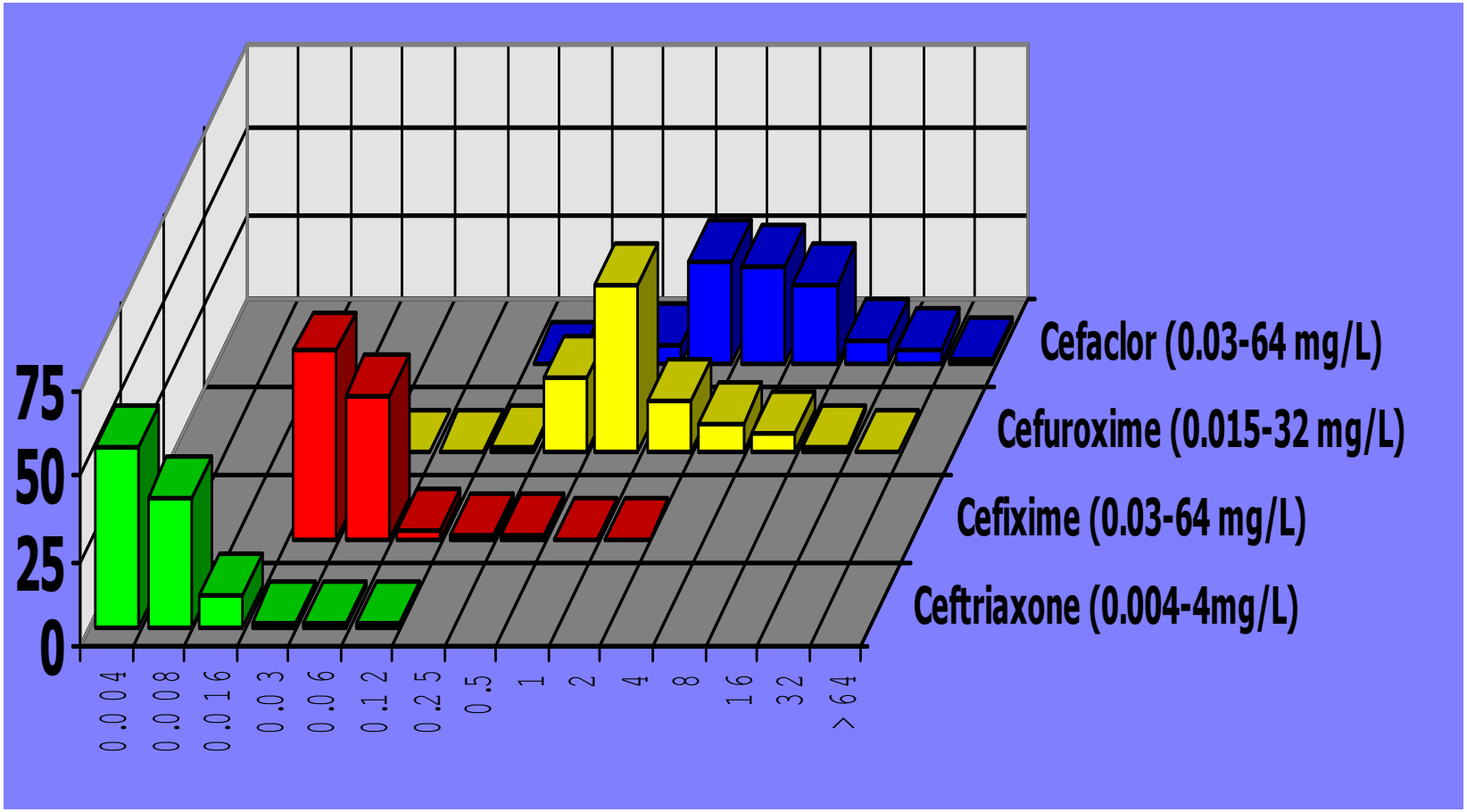
MIC distributions of penicillin and selected cephalosporins



Source: The Alexander Project 1996

Haemophilus influenzae

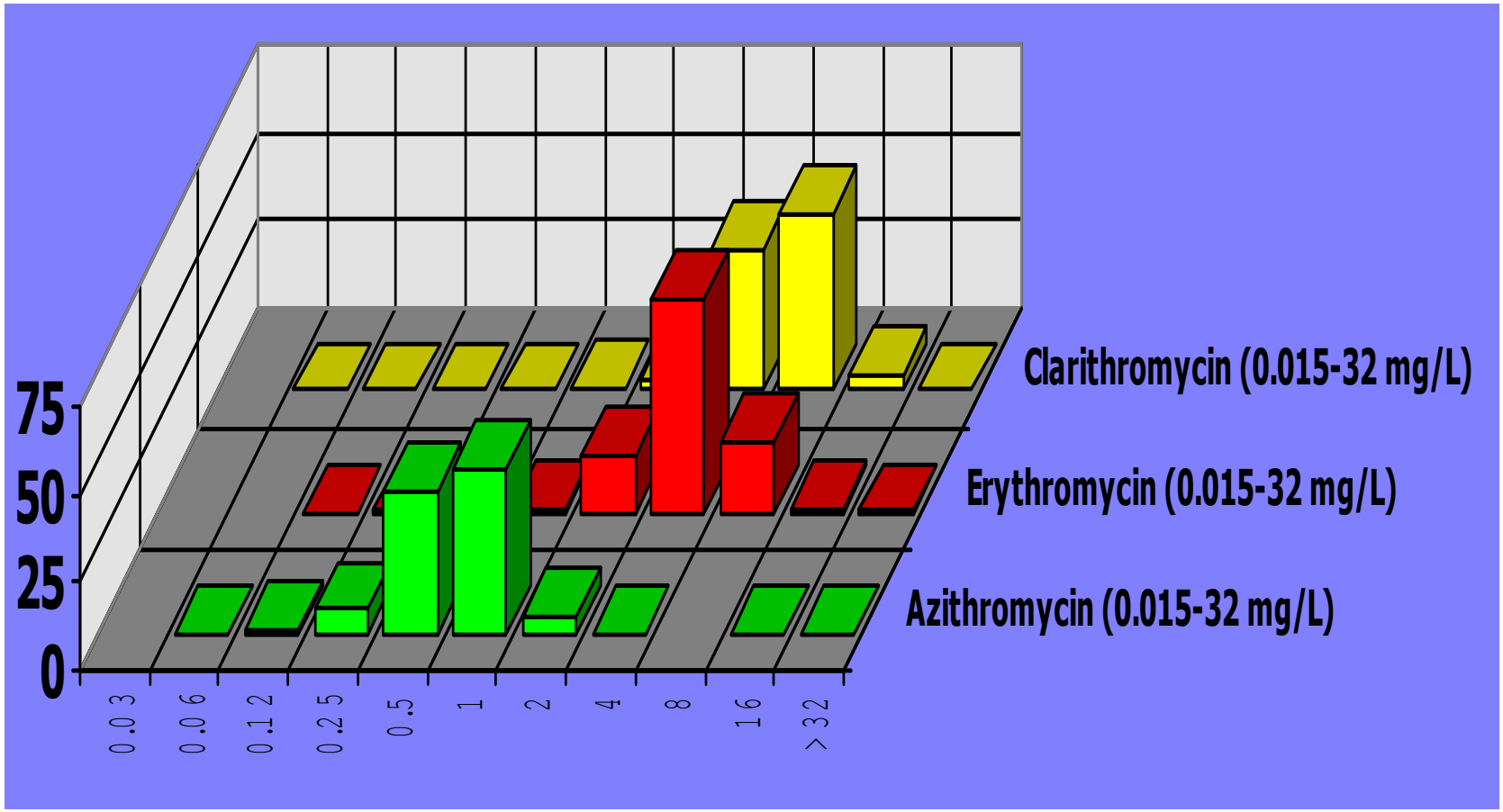
MIC distributions of cephalosporins



Source: The Alexander Project 1996

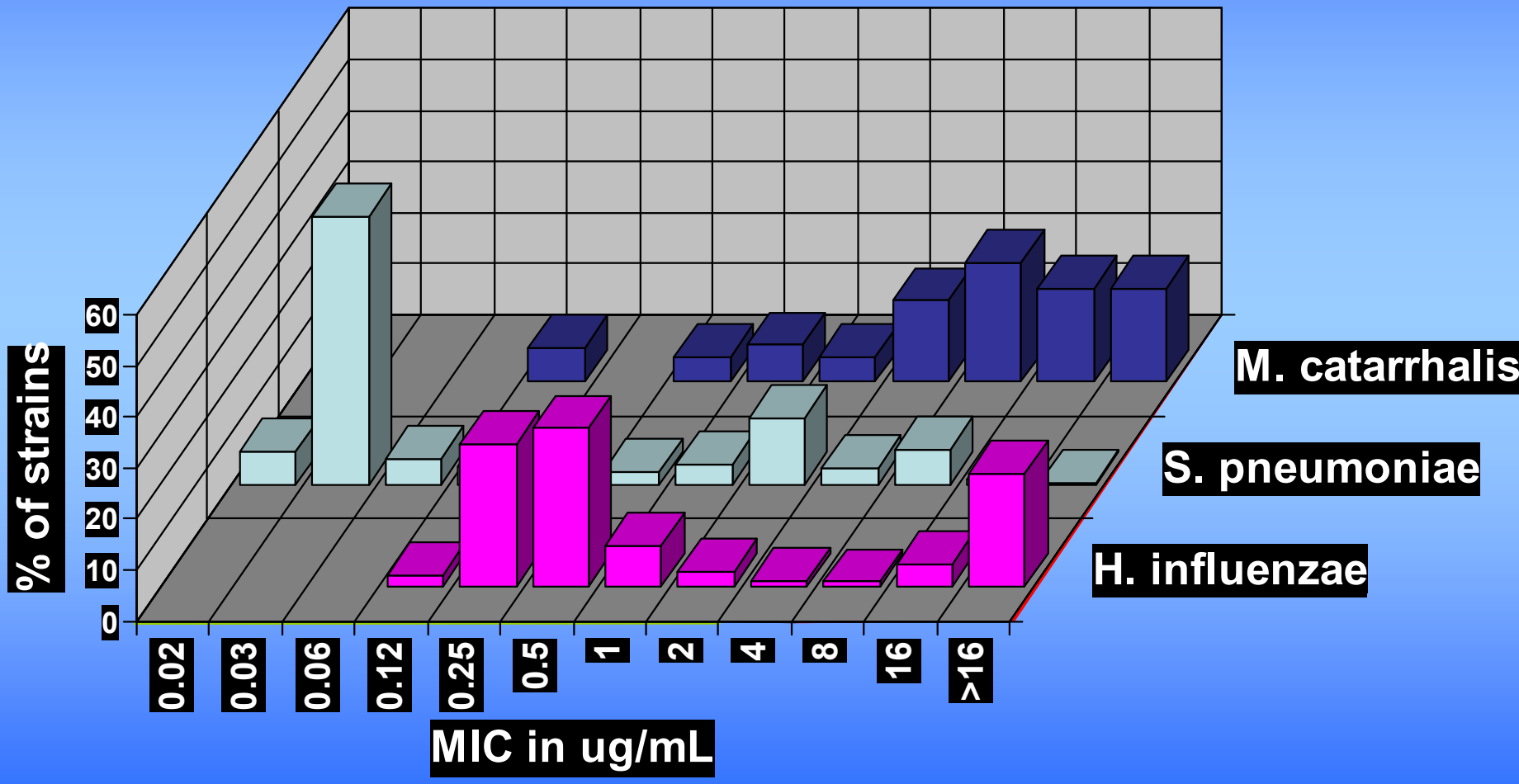
Haemophilus Influenzae

MIC distributions of macrolides



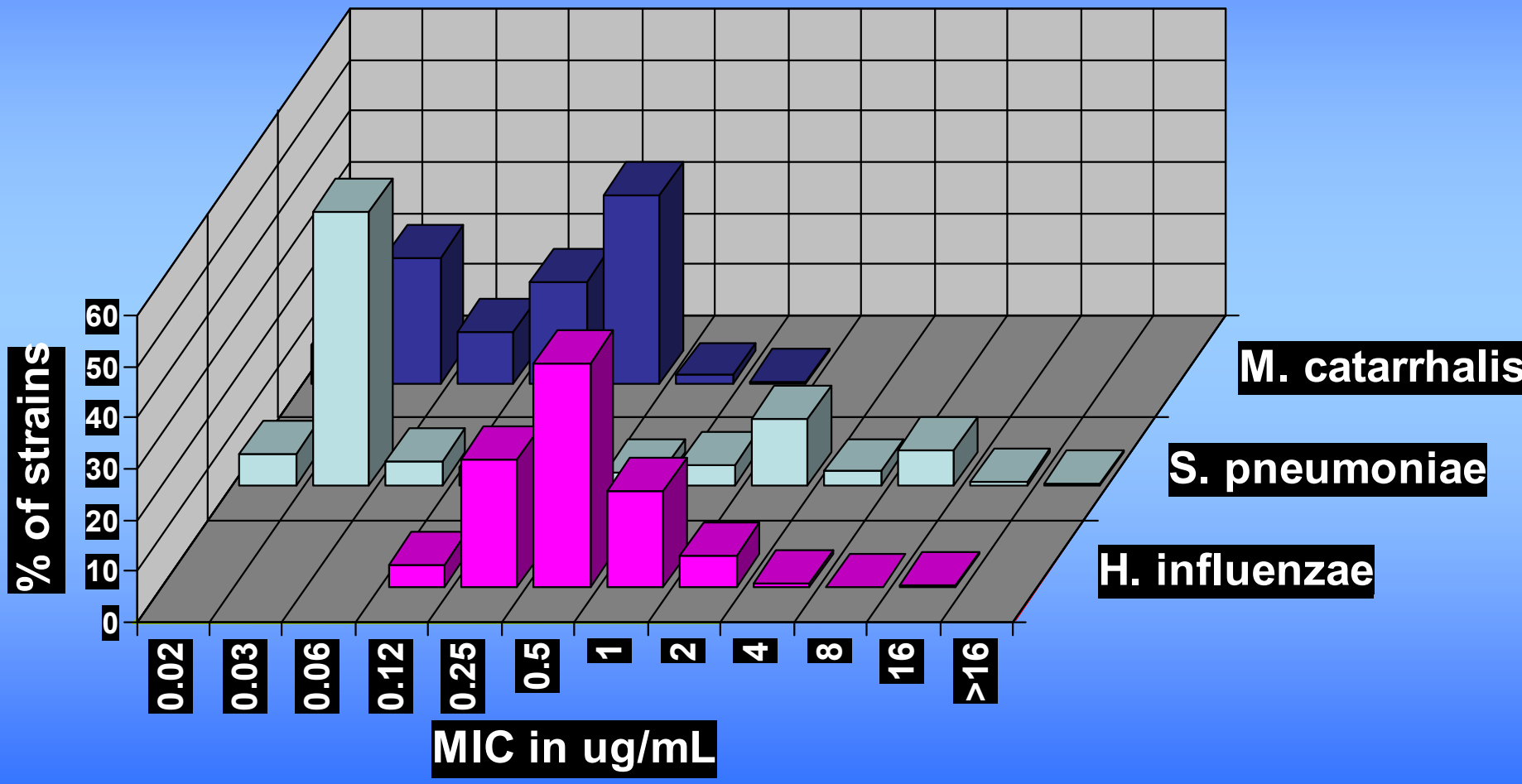
Source: The Alexander Project 1996

Amoxicillin



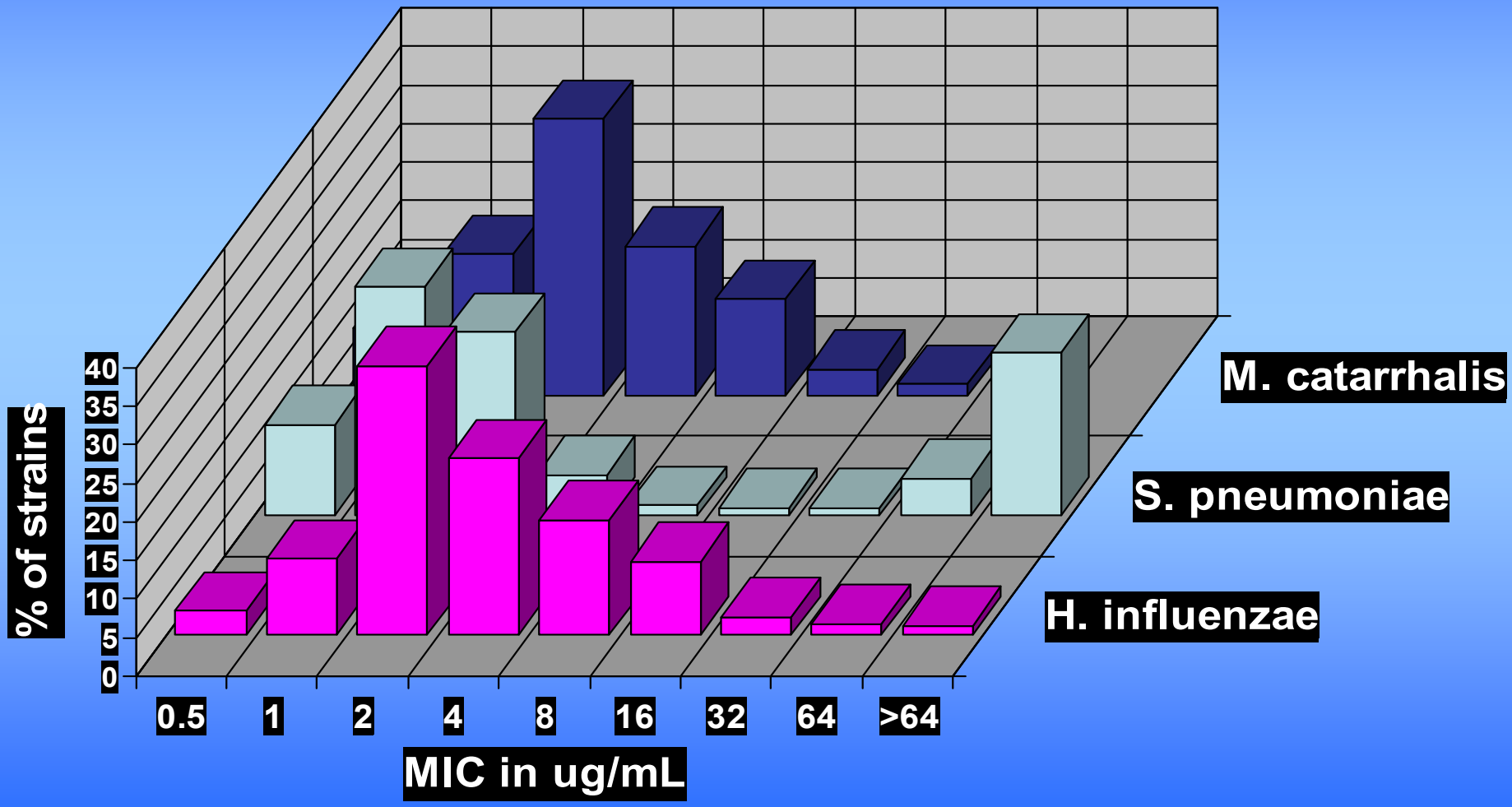
Alexander Project USA 2000: *S. pneumoniae* (n=1362), *H. influenzae* (n=634), *M. catarrhalis* 2000 (n=206)

Amoxicillin-clavulanate



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

Cefaclor



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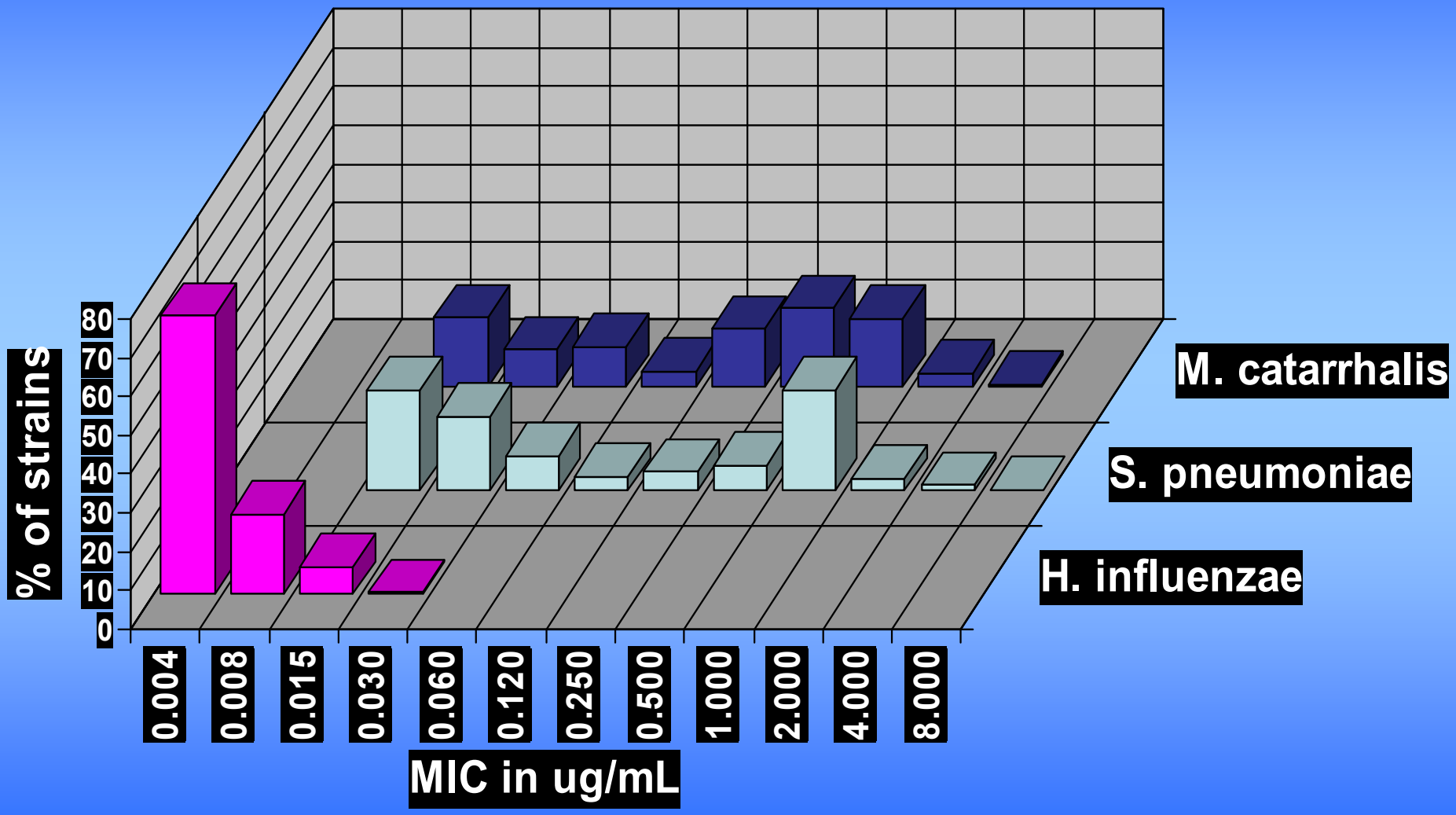
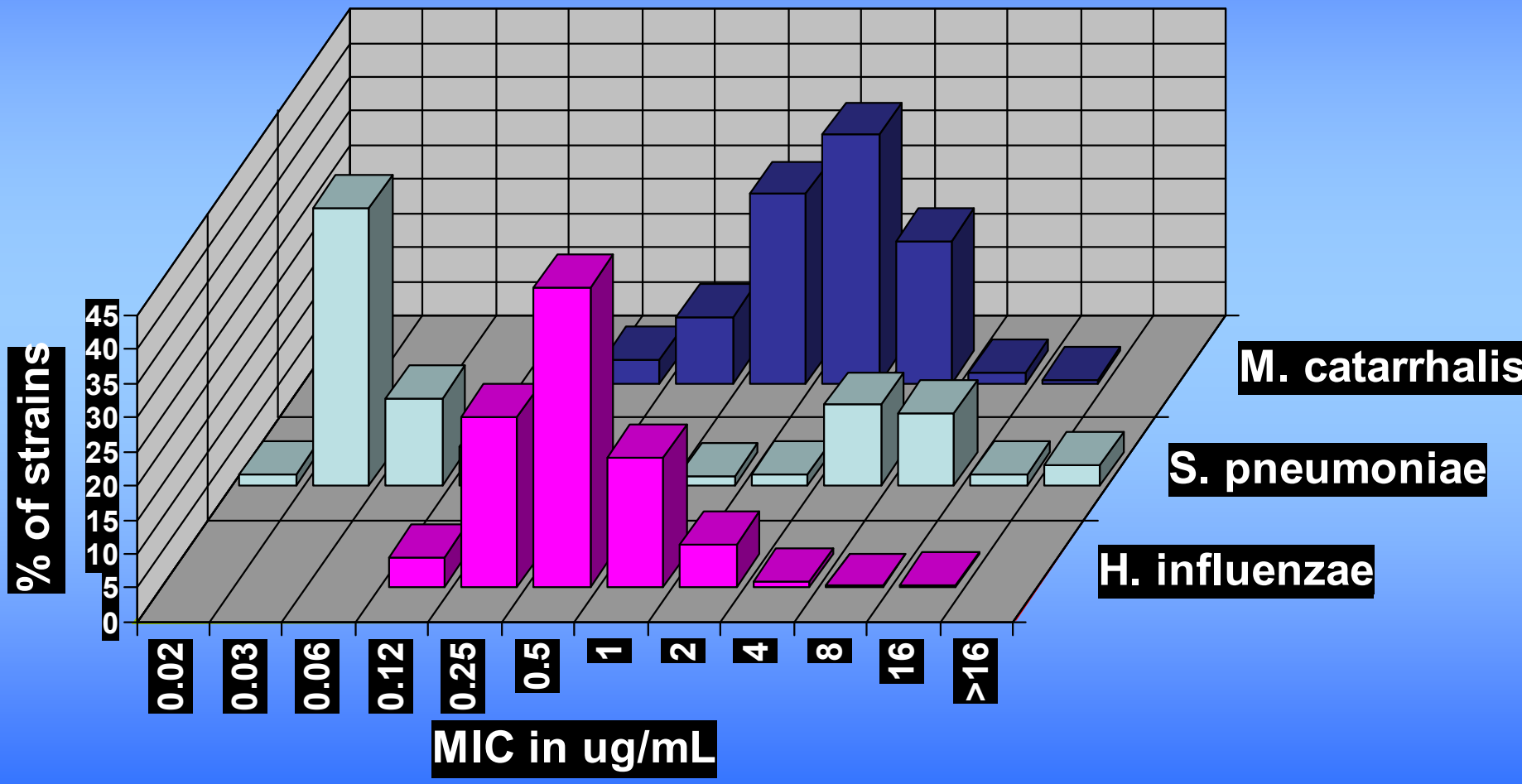
Ceftriaxone



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

Cefuroxime



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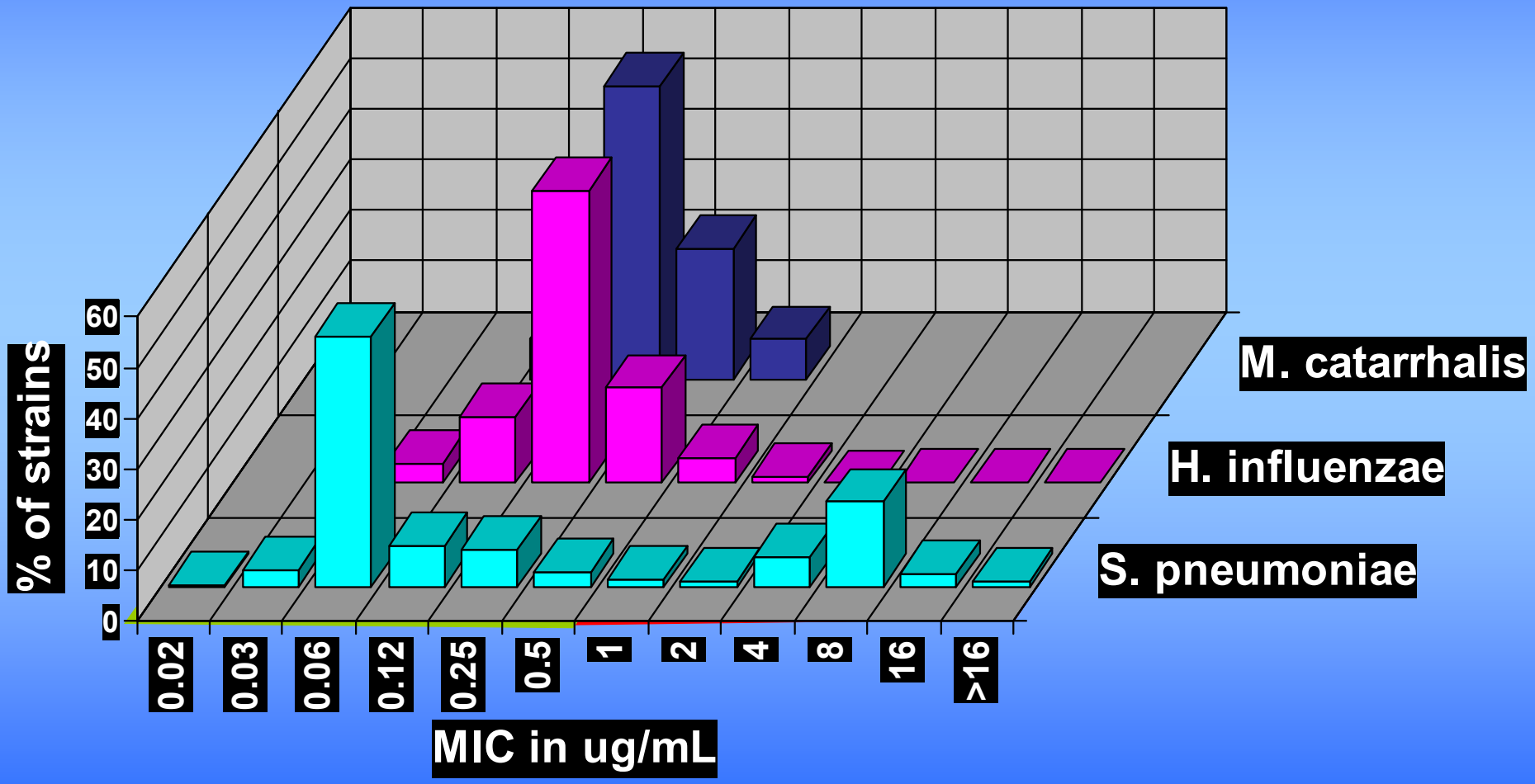
Cefdinir



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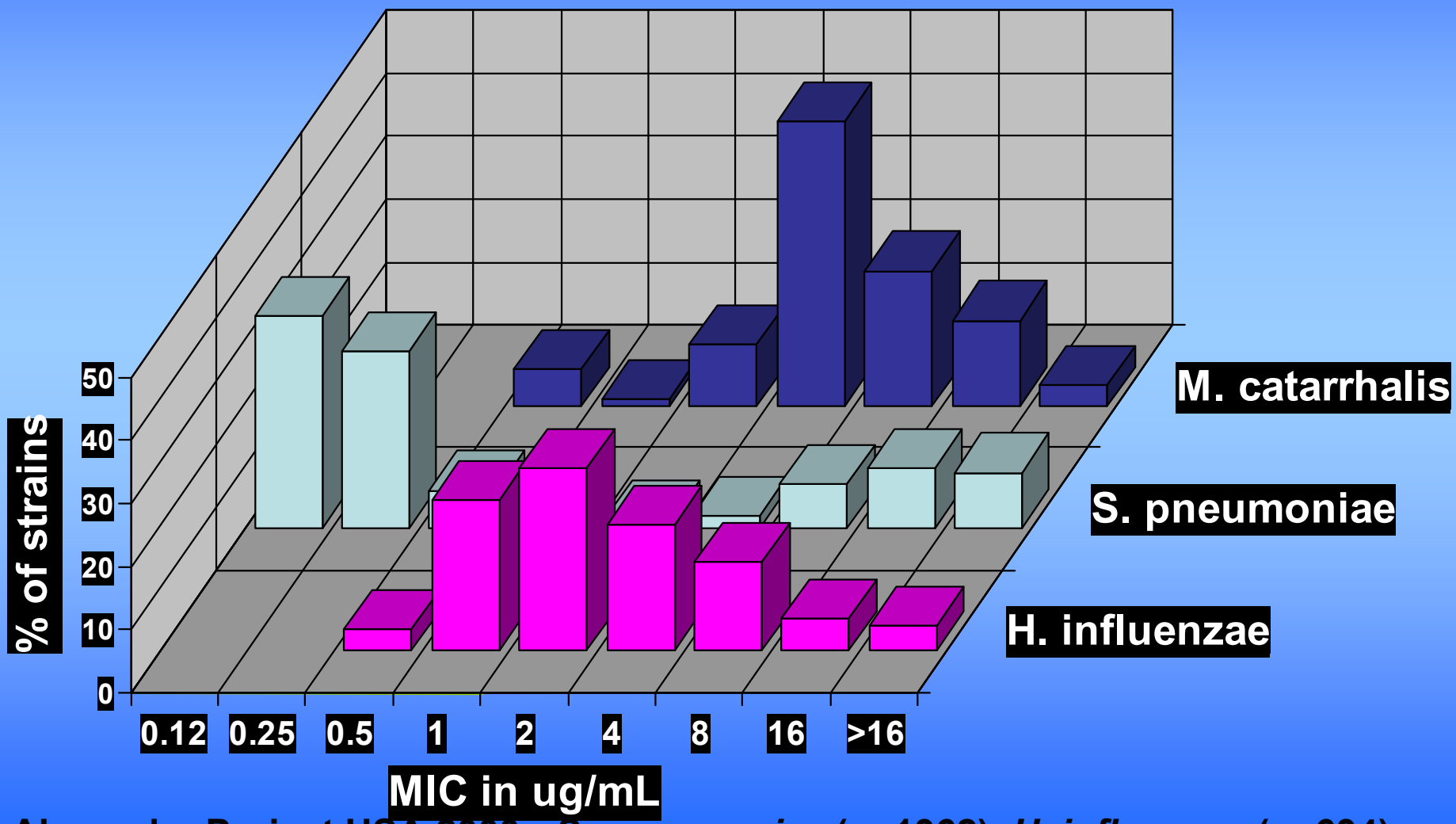
Cefprozil



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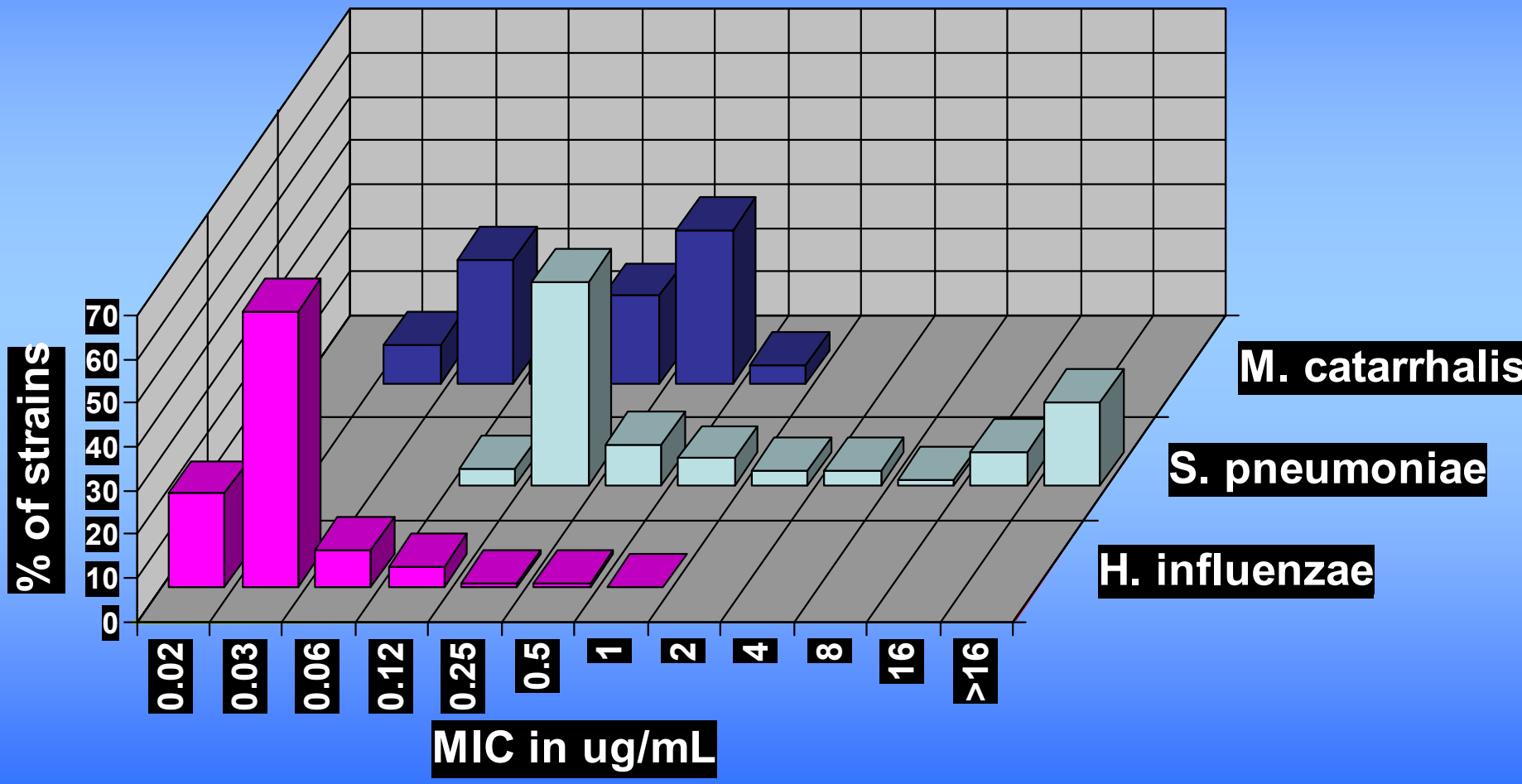
Cefixime



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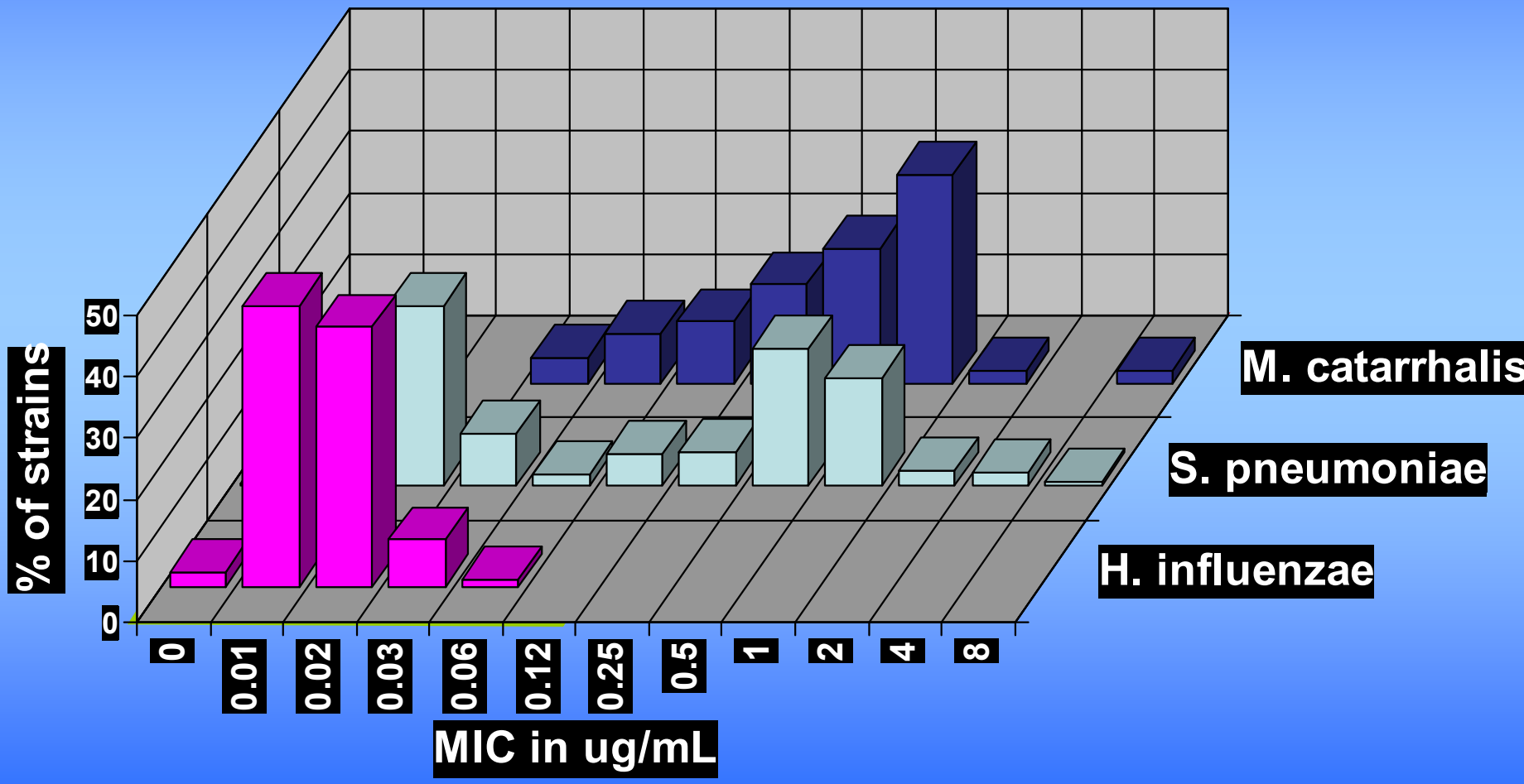
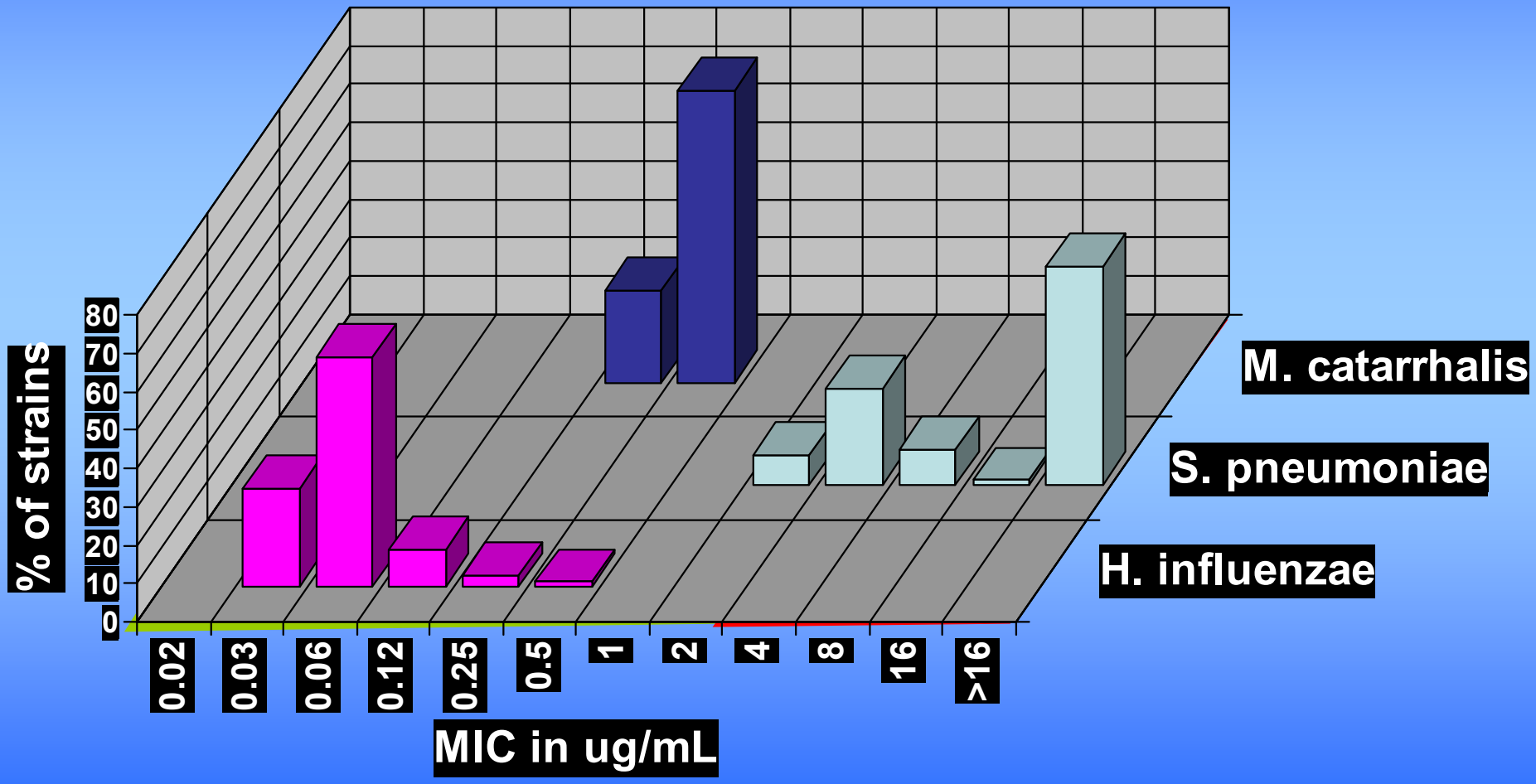
Cefditoren



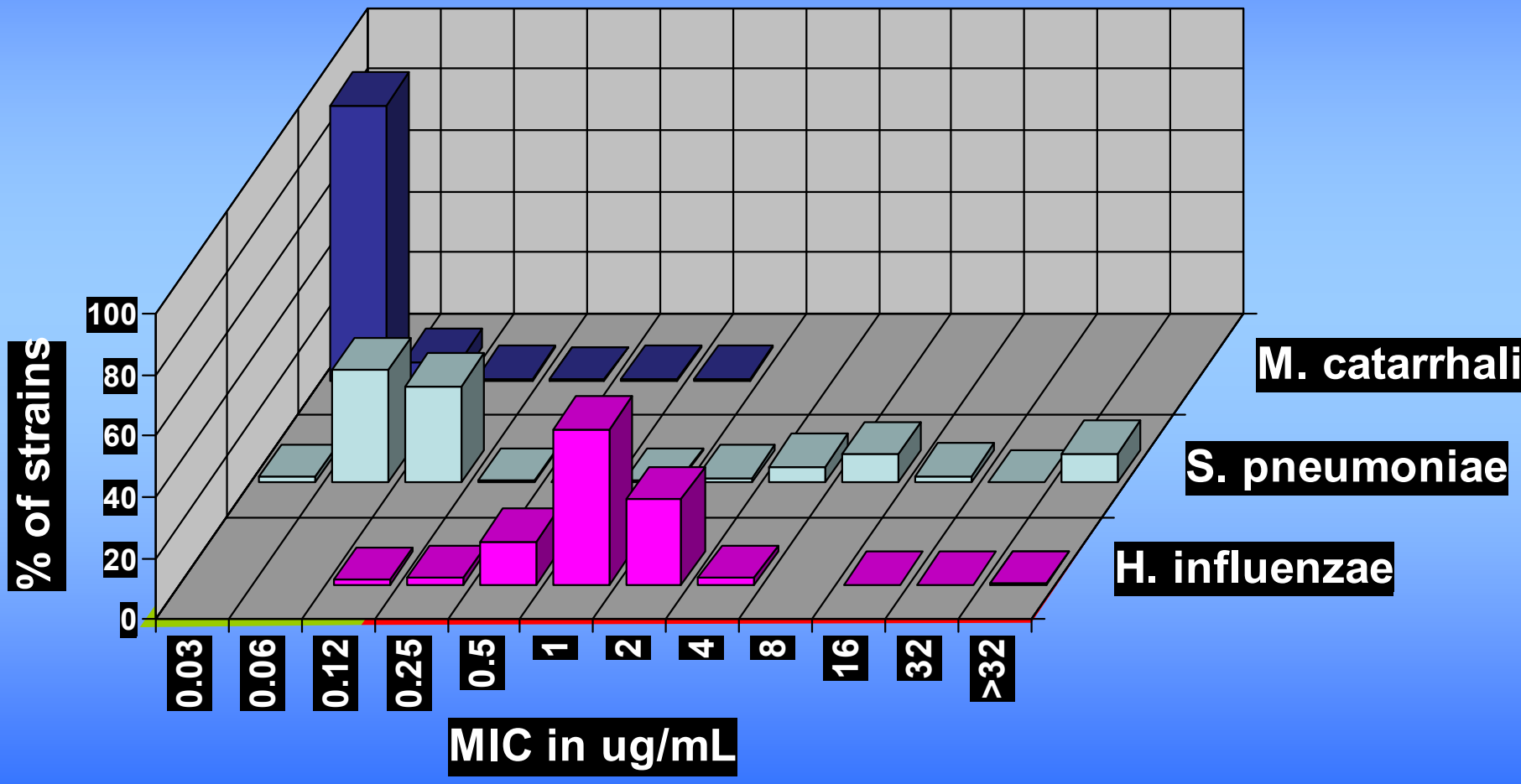
Adapted from Jacobs ICAAC 1997 abstr E103, Kelly ICAAC 1999 abstr 2323, and Spectracef Prescribing Information 2002

Ceftibuten



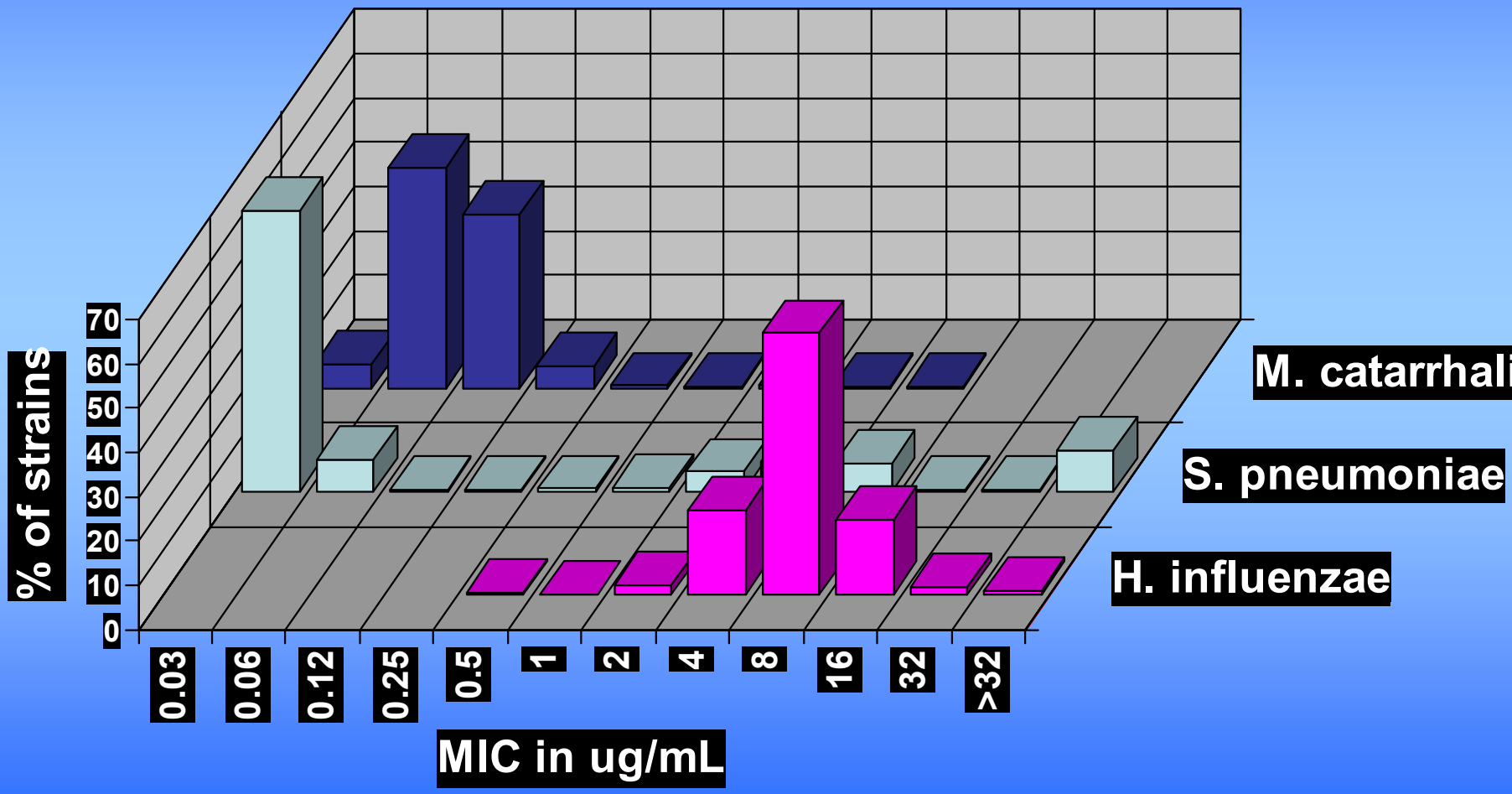
Adapted from Jacobs ICAAC 1997 abstr E103,
and Cedax Prescribing Information 2002

Azithromycin



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

Clarithromycin



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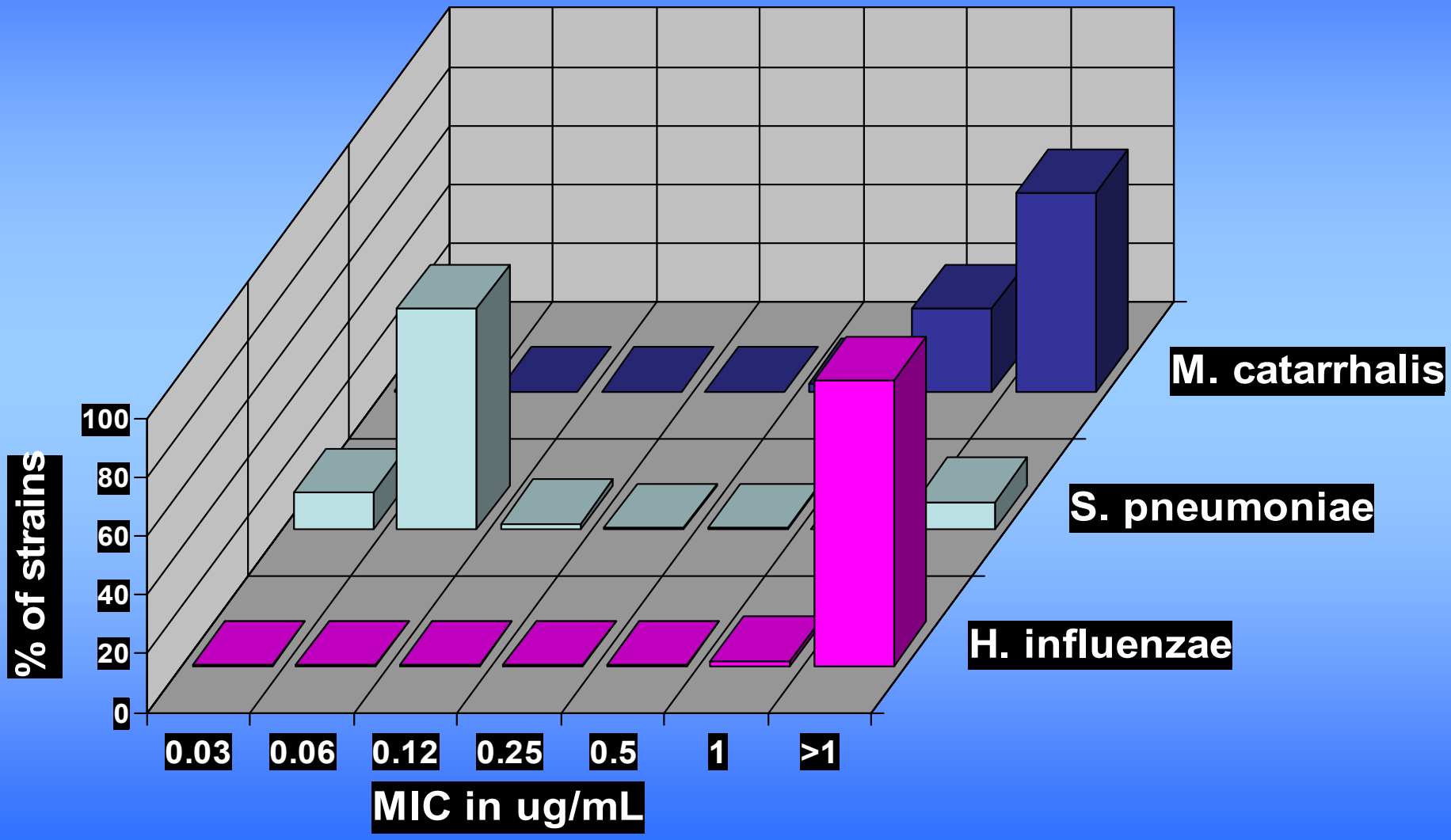
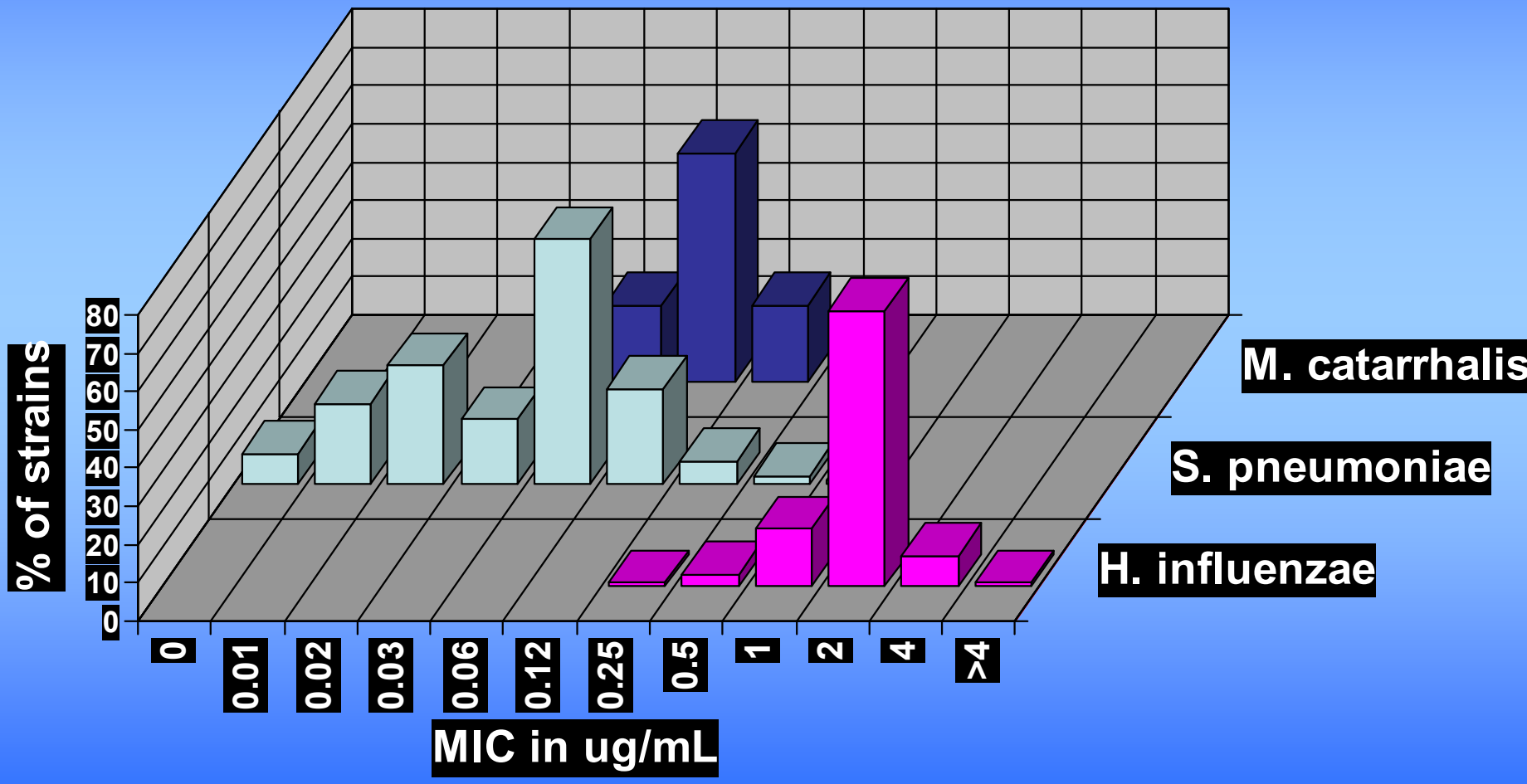
Clindamycin



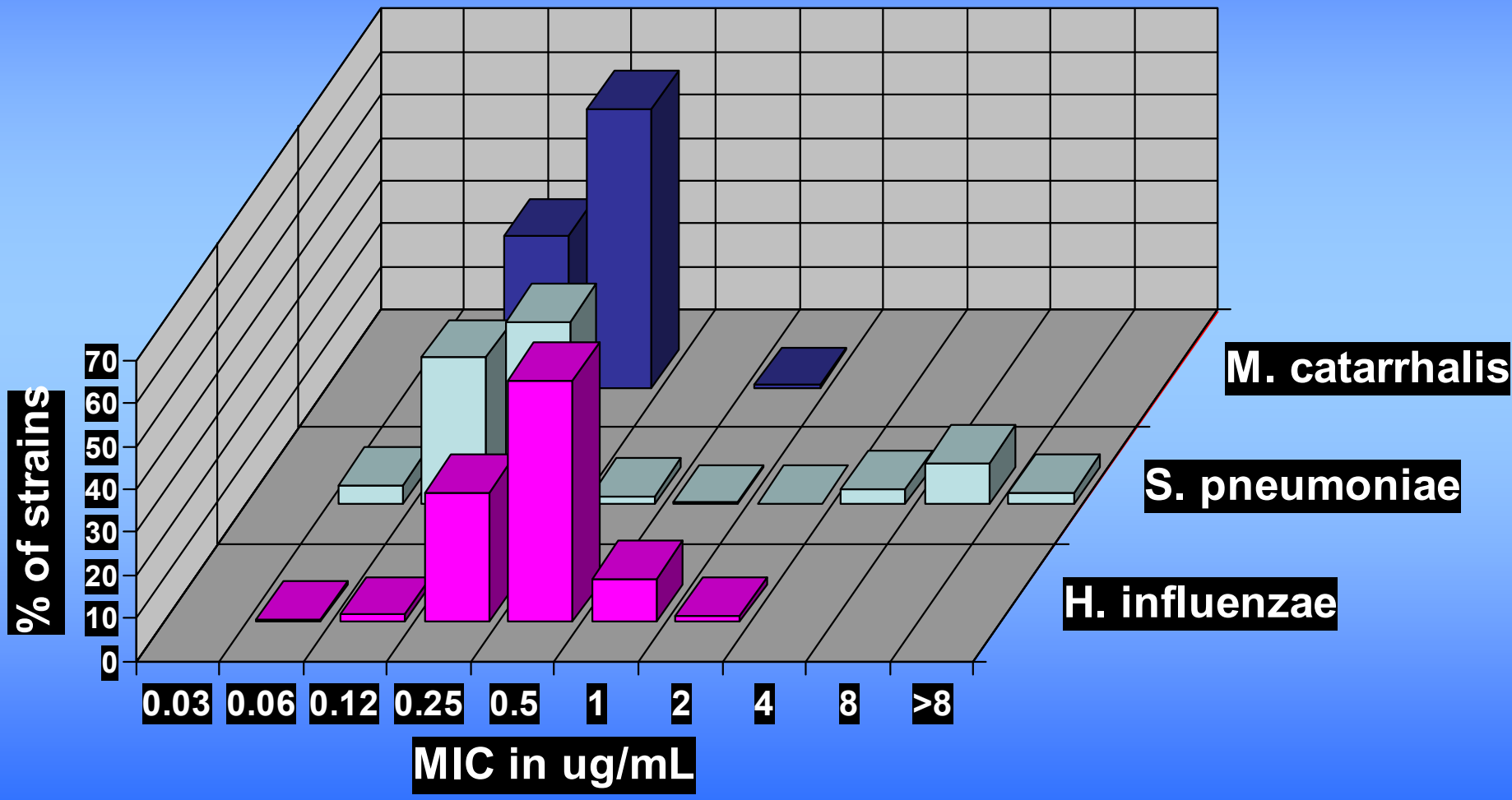
Alexander Project USA 2000: *S. pneumoniae* (n=1362)
AugSR H. influenzae (n=3793) *M. catarrhalis* 2000 (n=970)

Telithromycin



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

Doxycycline



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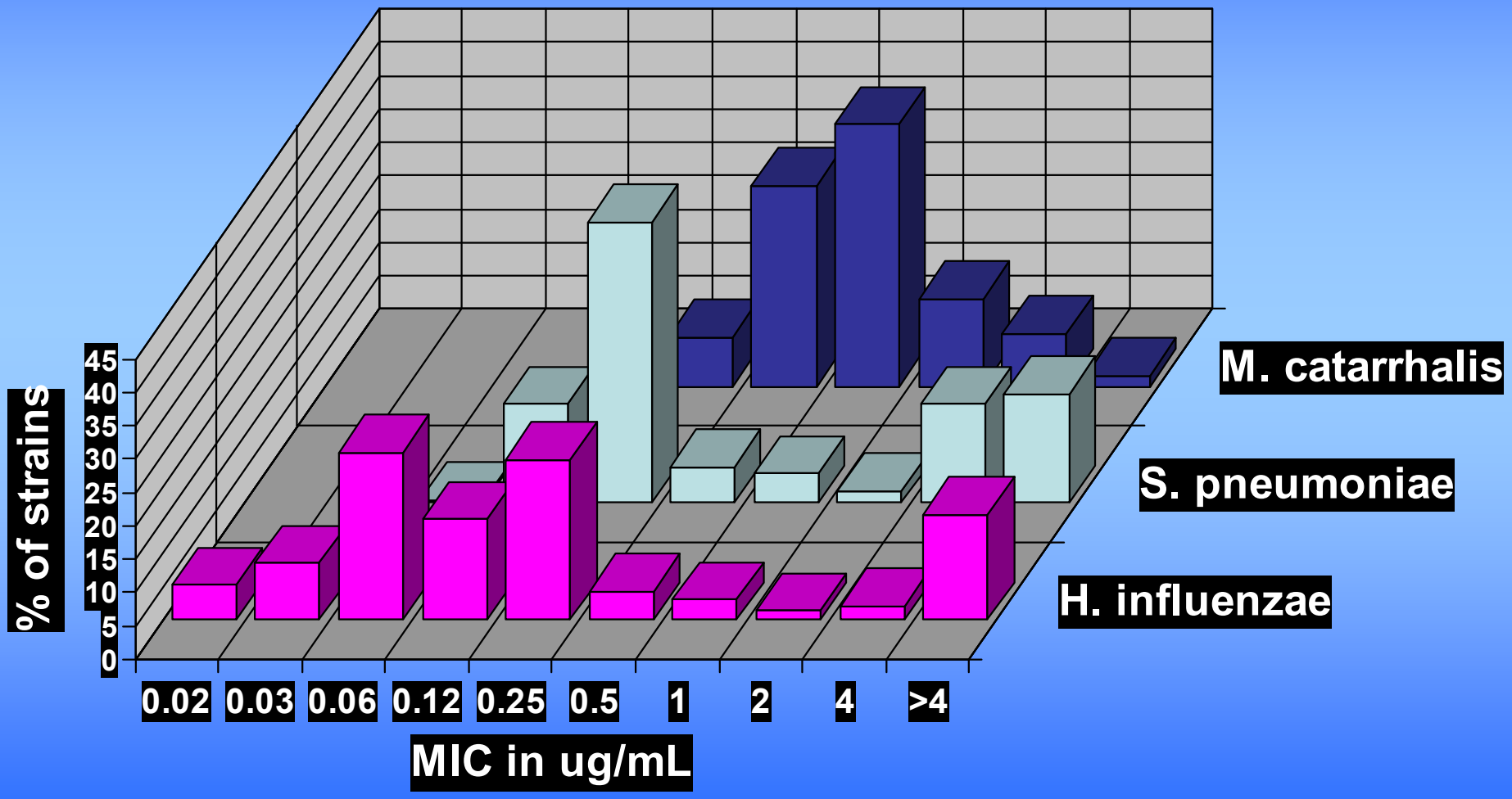
Trimethoprim-sulfamethoxazole



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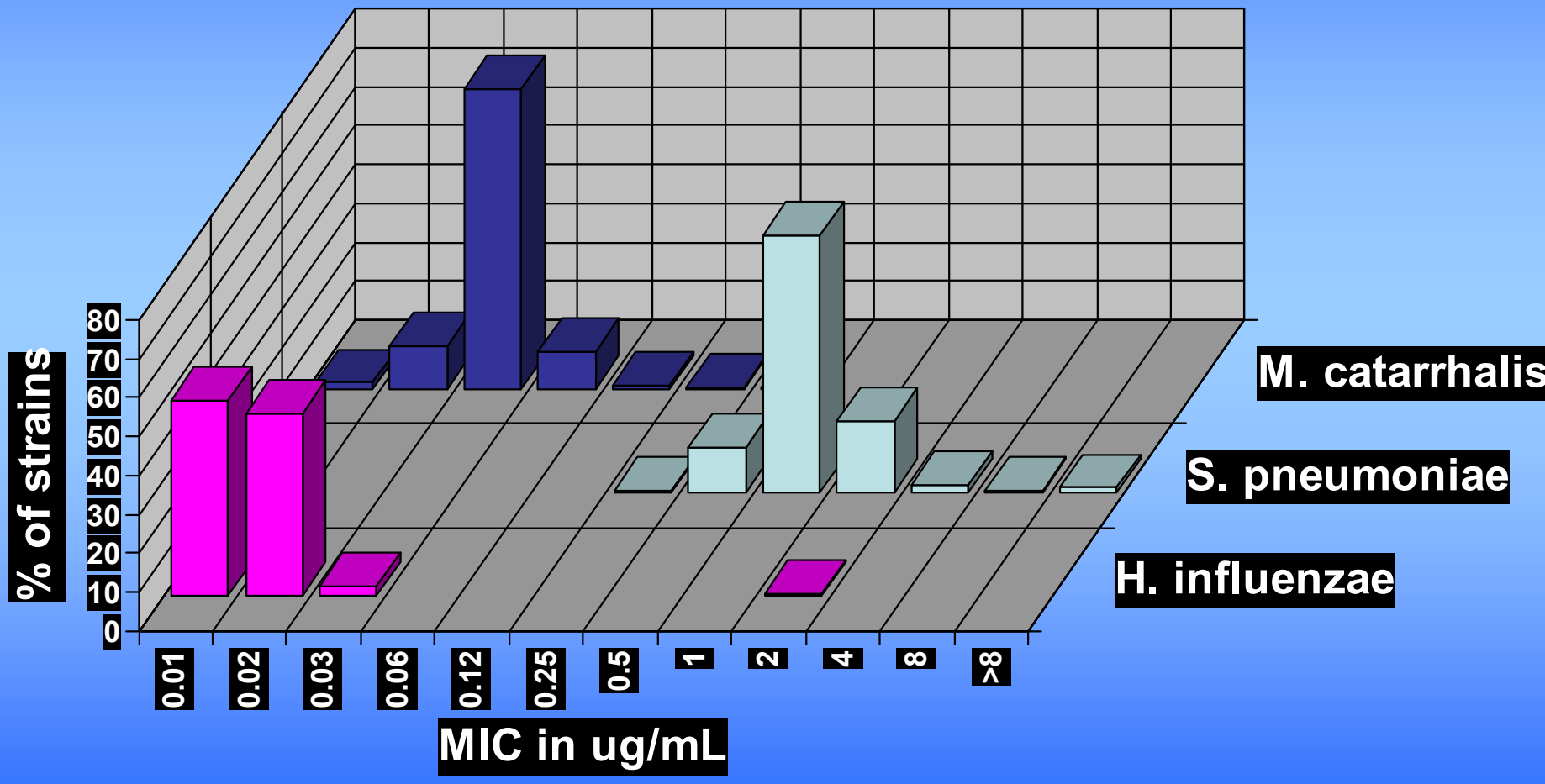
Ciprofloxacin



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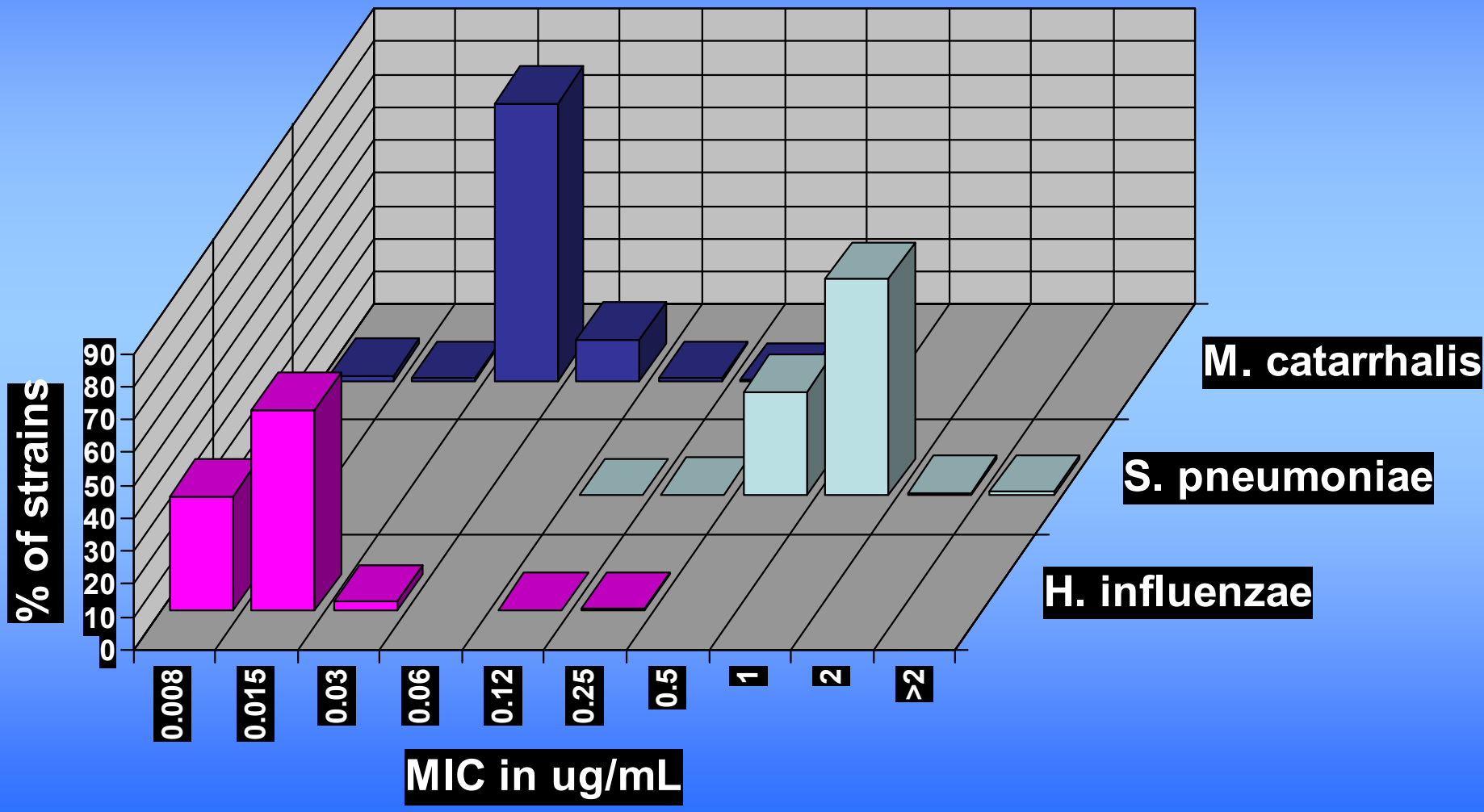
Levofloxacin



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