Antimicrobial Use for Respiratory Tract Infections: Needs and Consequences

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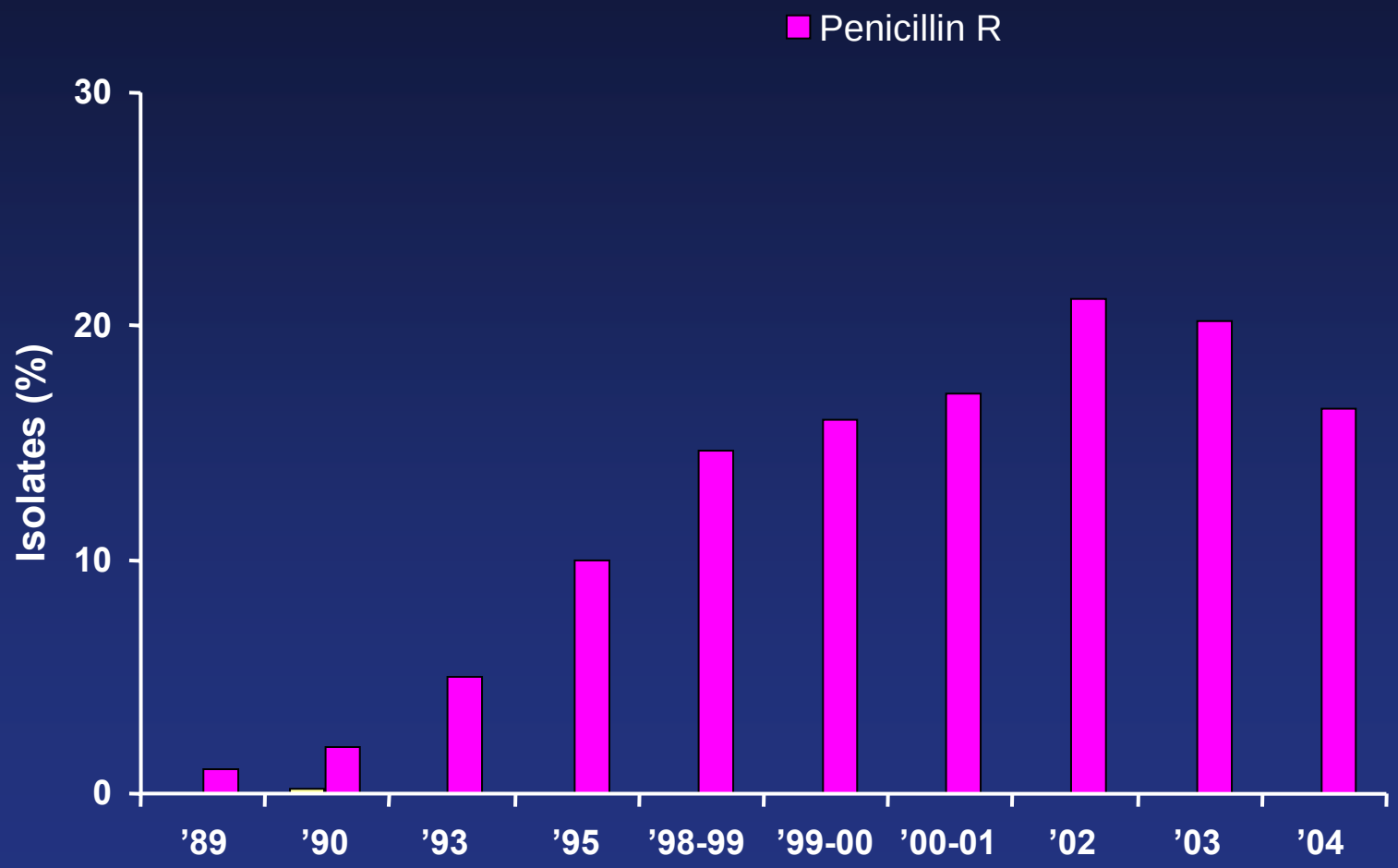
Respiratory tract infections with *S. pneumoniae*

- *S. pneumoniae*
  - most common bacterial cause of acute maxillary sinusitis and community acquired pneumonia (CAP)
  - 2nd most common bacterial cause of acute exacerbations of chronic bronchitis
- When an organism is identified in CAP:
  - 2/3s of bacteremic cases are pneumococcus
  - 2/3s of fatal CAP are caused pneumococcus

1. File TM Jr. Lancet 2003; 2. Bartlett JG, Mundy LM. NEJM 1995; 3. Guthrie R. Chest 2001; 4. Sinus and Allergy Health Partnership. Otolaryngol Head Neck Surg 2004; Bartlett et al. CID, 2000; Fine et al. JAMA, 1996.)

Penicillin and Macrolide-Resistant *S. pneumoniae* Emerged Rapidly in U.S.



1. Alexander Project 1992–2000. www.alexandernetwork.com; 2. Data on file (PROTEKT US Study Report 2001–2004). Aventis Pharmaceuticals. Bridgewater, NJ, USA

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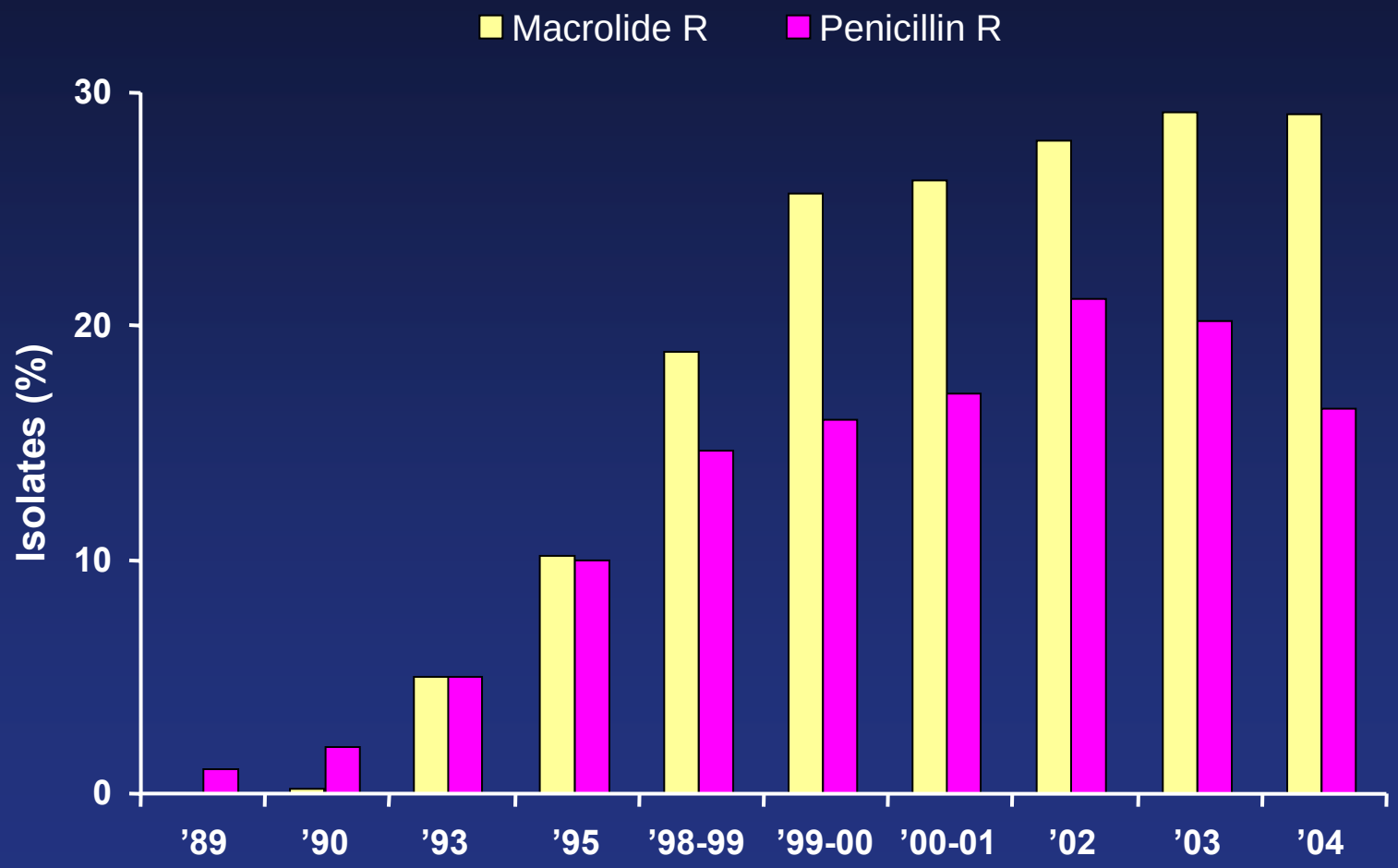

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Growing Need for Antimicrobials for the Empirical Treatment of Possible Multi-Drug Resistant Pneumococci

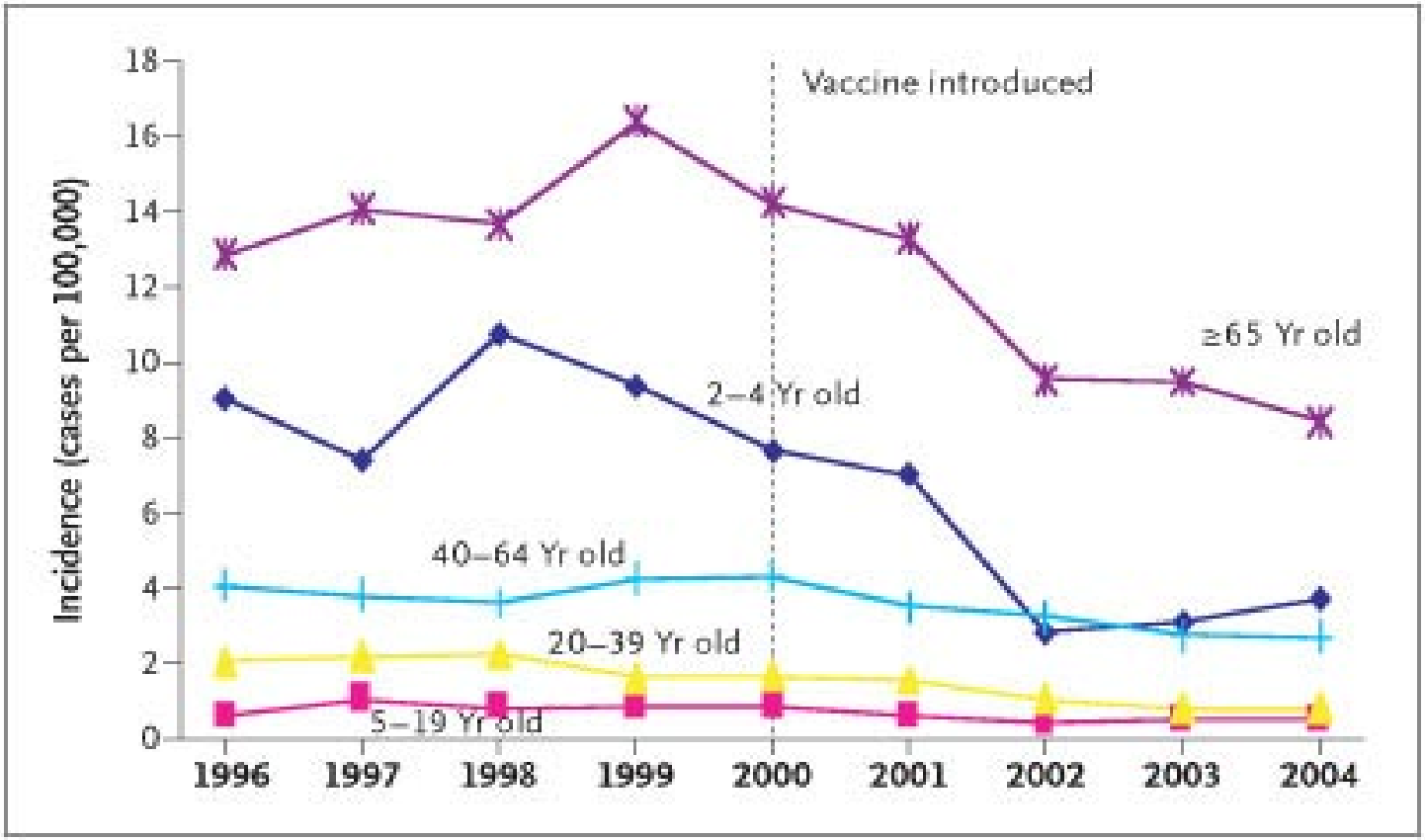
n=1,817 Isolates; 44 U.S. Medical Centers, Winter 2002-2003

Antimicrobial	Percent Resistant
Macrolides	32.9
Clindamycin	8.6
Tetracyclines	8.4
Telithromycin	0
Levofloxacin	0.7
MDRSP	**25.2**

Doern et al, *Clin Infect Dis*, 2005

Effect of the Pneumococcal Conjugate Vaccine on Drug-Resistant *S. pneumoniae*

Active Bacterial Core surveillance (CDC)



Kyaw et al. *NEJM* April 2006

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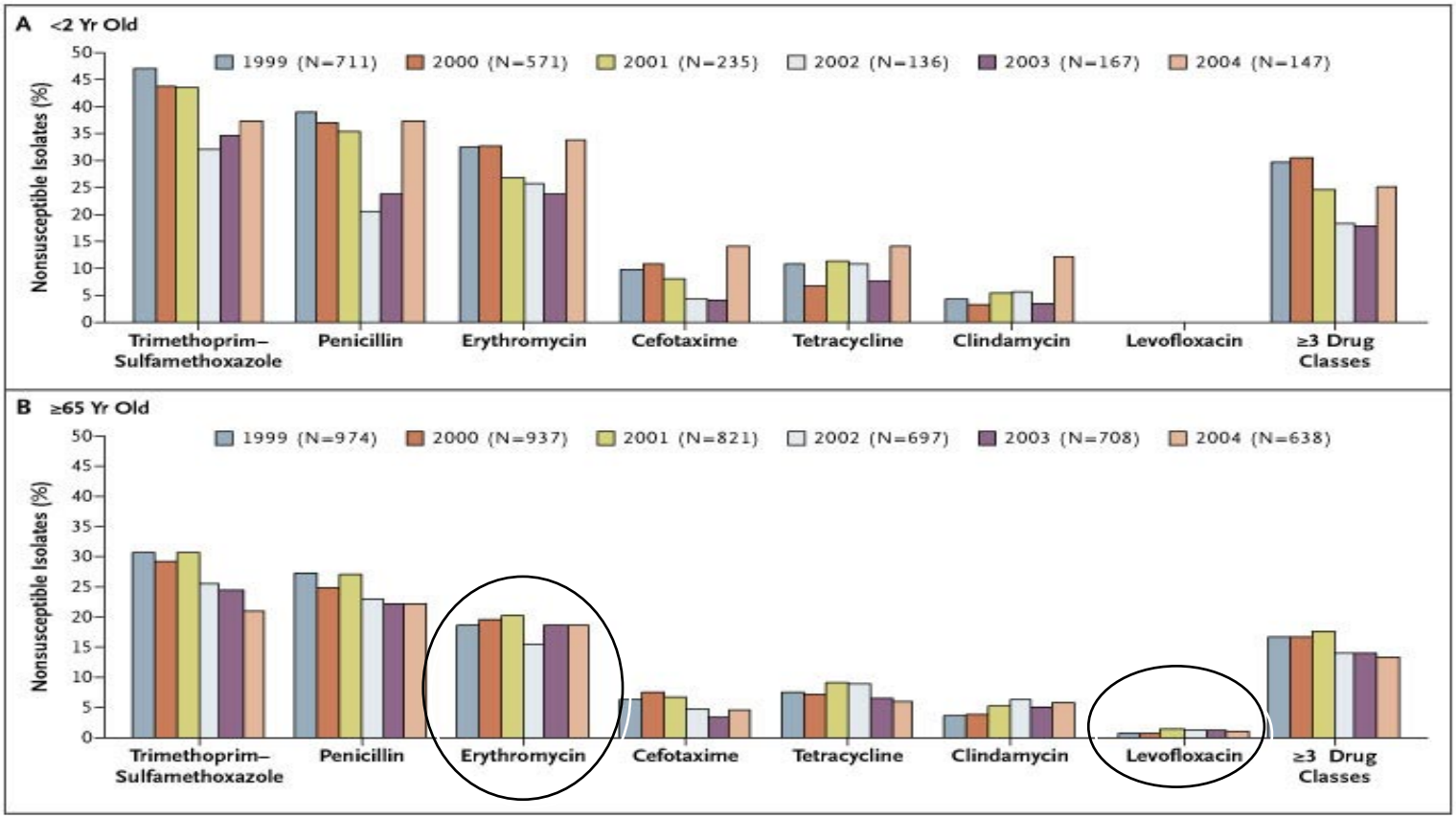

Kyaw et al. NEJM April 2006

Warning about emerging pneumococcal resistance: the emergence of multi-drug resistant of 19A

- The rate of disease caused by nonsusceptible 19A, a vaccine-related serotype, increased markedly from 2.0 to 8.3 per 100,000
- 19A
  - Macrolide resistant (*mef* and *erm*)
  - Non-susceptible to amoxicillin (MIC $\geq$ 4 µg/ml)
  - Non-susceptible to third generation cephalosporins (MIC $\geq$ 2 µg/ml)
  - Resistant to trimethoprim-sulphamethoxazole and tetracycline
  - Causes invasive disease

Antimicrobial Resistance

Haemophilus influenzae

- 25% amoxicillin resistant
- 25-30% TMP-SMX resistant

Moraxella catarrhalis

- 98% amoxicillin resistant
- 30-40% TMP-SMX resistant

What is the evidence that resistance matters?

Why this belief by some of a "resistance paradox"?

1. Outcome studies are difficult to carry out
2. Measuring the impact of discordant therapy is difficult:
   - In the community empiric therapy
   - In the hospitalized patient multidrug therapy
   - Mortality is an insensitive measure of the impact of drug resistance
3. In vitro MICs do not necessarily reflect true drug levels in vivo
   - Thus, substantial numbers of clinical infections are mislabeled

Klugman KP, et al. *IJAA.* 2004. Metlay JP, et al. *CID.* 2000. Peterson LR, et al. *CID.* 2006

Discordant β-lactam therapy in CAP

- Although there is anecdotal evidence suggesting that resistance to β-lactam causes failure in the treatment of respiratory tract infection due to *S. pneumoniae,* documentation of penicillin treatment failure, particularly with aminopenicillins administered at adequate dosages (e.g., parenterally), remains virtually nonexistent.

Peterson LR *Clin Infect Dis* 2006;42:224-233

Discordant β-lactam therapy in CAP

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However, *S. pneumoniae* strains with penicillin MICs >2 µg/ml were rare.

With the exception of some older cephalosporins, the PK/PD properties of most β-lactams ensure activity against the vast majority of β-lactam-susceptible, -intermediate and -resistant strains

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Discordant Macrolide therapy in CAP

- Fogarty C et al. *Clin Infect Dis* 2000;31:613-5
- Kelley MA et al. *Clin Infect Dis* 2000;31:1008-11
- Lonks J et al. *Clin Infect Dis* 2002;35:556-64
- Kerkhoven DV et al. *J of Antimicrob Chem* 2003;51:691

Daneman N, et al. *Clin Infect Dis.* 2006;43:432-8.

Macrolide Resistance in Bacteremic Pneumococcal Disease: Implications for Patient Management

- Prospective population-based surveillance of pneumococcal bacteremia in Toronto between 2000 and 2004
- Macrolide failures: bacteremia occurring during treatment with outpatient macrolide antibiotics or within 2 days following treatment
- 1,696 episodes of pneumococcal bacteremia of which 60 (3.5%) were failures of outpatient macrolide therapy

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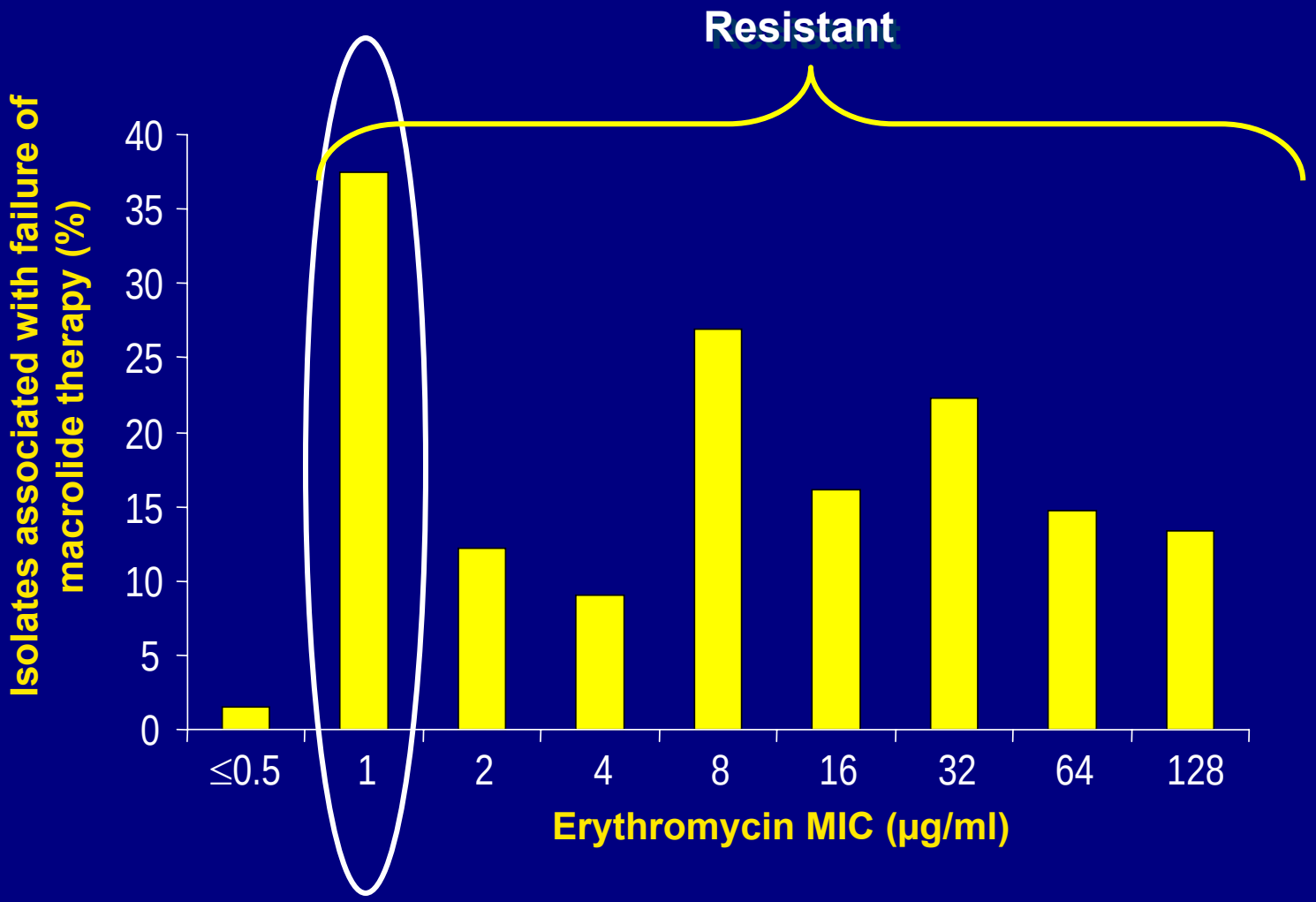
Pneumococcal Blood Culture Isolates Associated with Failure of Outpatient Therapy with Erythromycin



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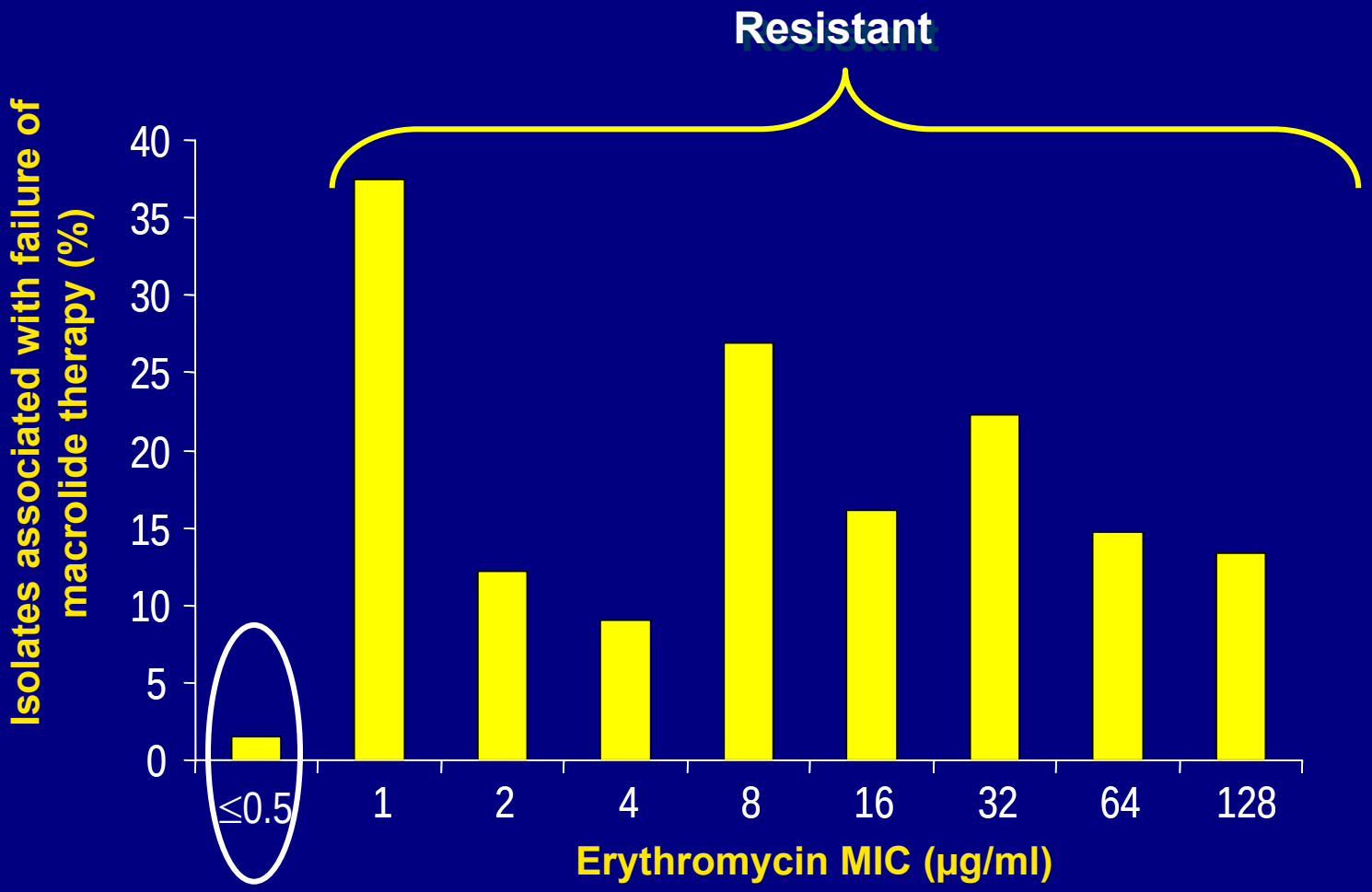

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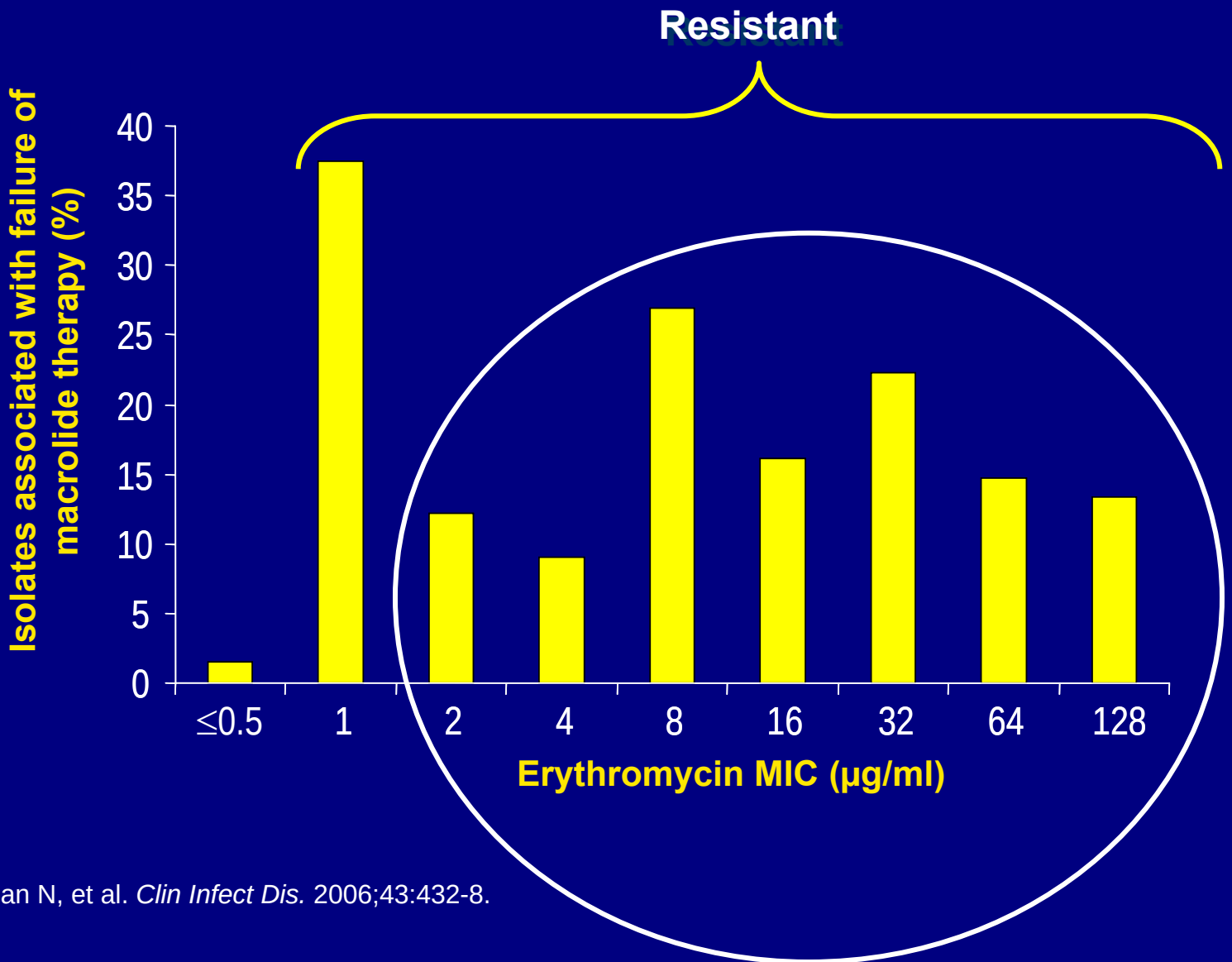

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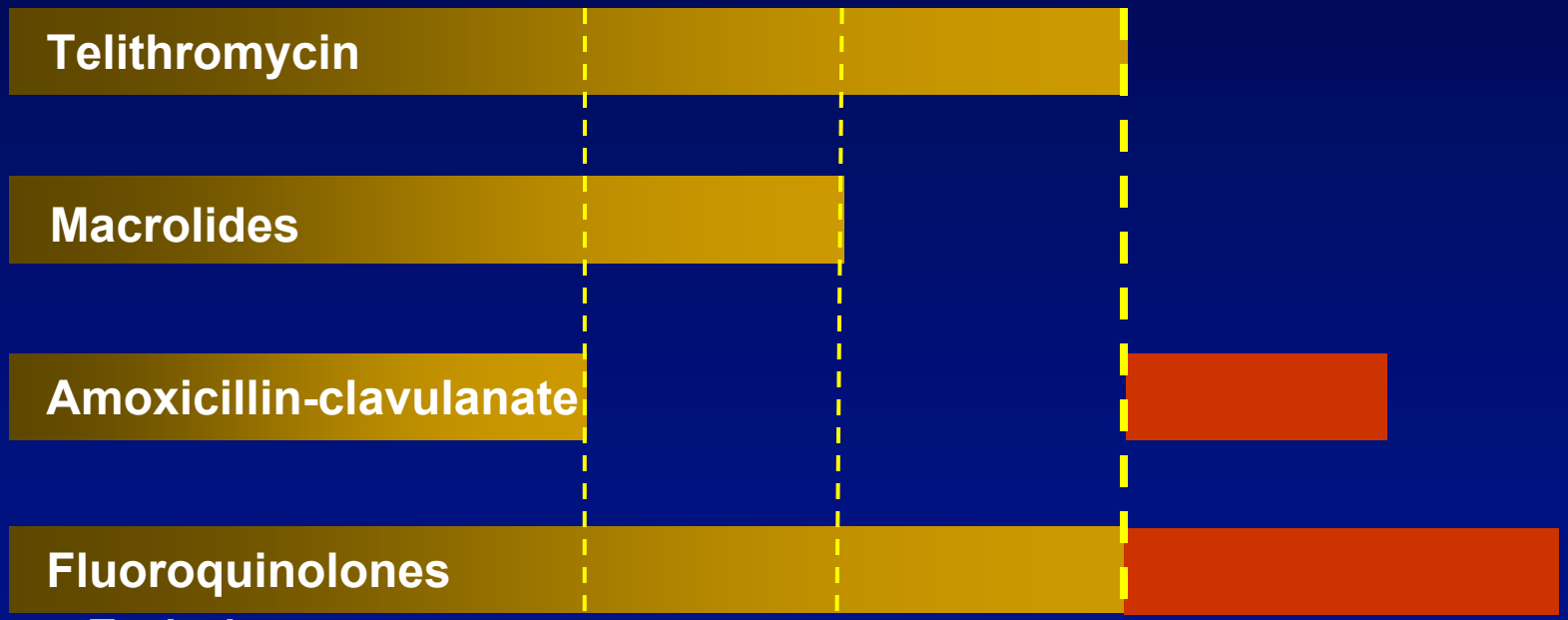
Macrolide Resistance in Breakthrough Pneumococcal Bacteremia

- Identified cases from Active Bacterial Core surveillance (CDC) sites
- Treatment failure was defined as development of bacteremia while taking a macrolide
- Of those patients that failed therapy isolates were more often resistant as compared to those that didn't fail
- They also found that failures often occur at macrolide MICs <16 µg/ml.

Grant et al. ICAAC 2006

Consequences of broad spectrum therapy



MDRSP = Multidrug-resistant *Streptococcus pneumoniae.*

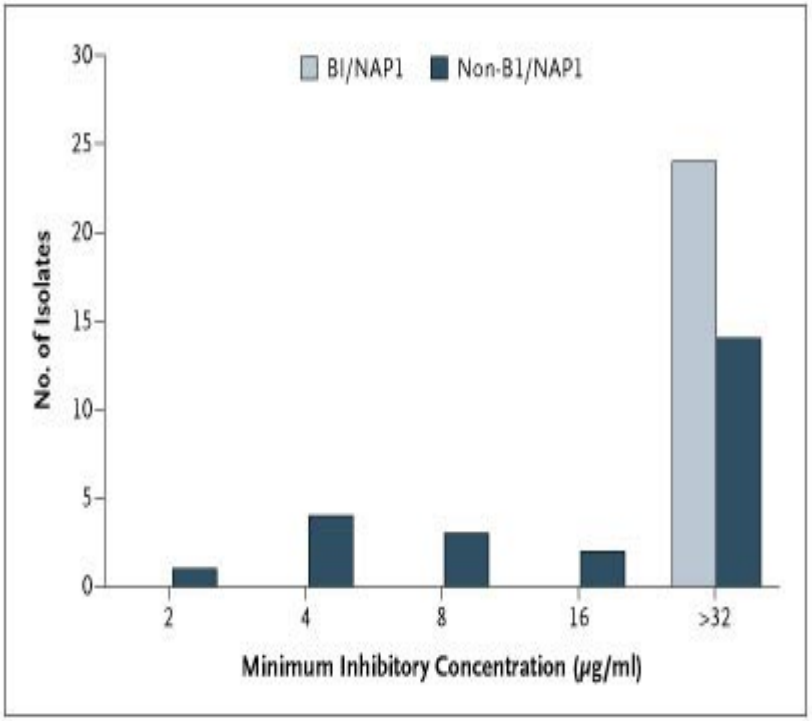
Fluoroquinolone-Resistant Urinary Isolates of *E. coli* from Outpatients Are Frequently Multidrug Resistant: Results from the North American UTI Study

- Outpatient urine specimens at North American clinical laboratories
  - 10.8% of isolates were resistant to ciprofloxacin alone[1]
  - Fluoroquinolone-resistant isolates of *E. coli* from urine were frequently multidrug resistant[1]
  - Resistance to ampicillin: 79.8%[1]
  - Resistance to amoxicillin/clavulanic acid 12.5%[2]
  - Resistance to trimethoprim-sulfamethoxazole: 66.5%[1]

[1]Karlowsky et al. AAC, 2006. [2]Gaspari et al. Intern J Antimicrob Agents 2005

An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

- A total of 187 *C. difficile* isolates were collected from 8 health care facilities in 6 states in which outbreaks of *C. difficile*–associated disease had occurred between 2000 and 2003
- **Epidemic strain (BI/NAP1) positive for binary toxin, was resistant to fluoroquinolones**
- Produced 16 to 23 times more toxins A and B in vitro than did other strains



Fluoroquinolone MICs

MacDonald et al. NEJM Dec, 2005

Conclusions

- RTIs are a frequent cause of disease in the community
- *S. pneumoniae* is the most common bacterial pathogen and the one associated with the greatest morbidity and mortality
- Relevance of resistance is now better established for some classes of antimicrobials including the macrolides
- The use of broad-spectrum agents for the treatment of community-acquired RTIs may not only result in resistance in by-stander organisms but may also be related to the increase of antibiotic-associated colitis
- There is a need for antibiotics with efficacy against resistant pathogens and targeted anti-bacterial spectrum