CAP Treatment Options; Are Quinolones the Same ?

Tunis, Hammamat Yasmine 23 -26 July 2011

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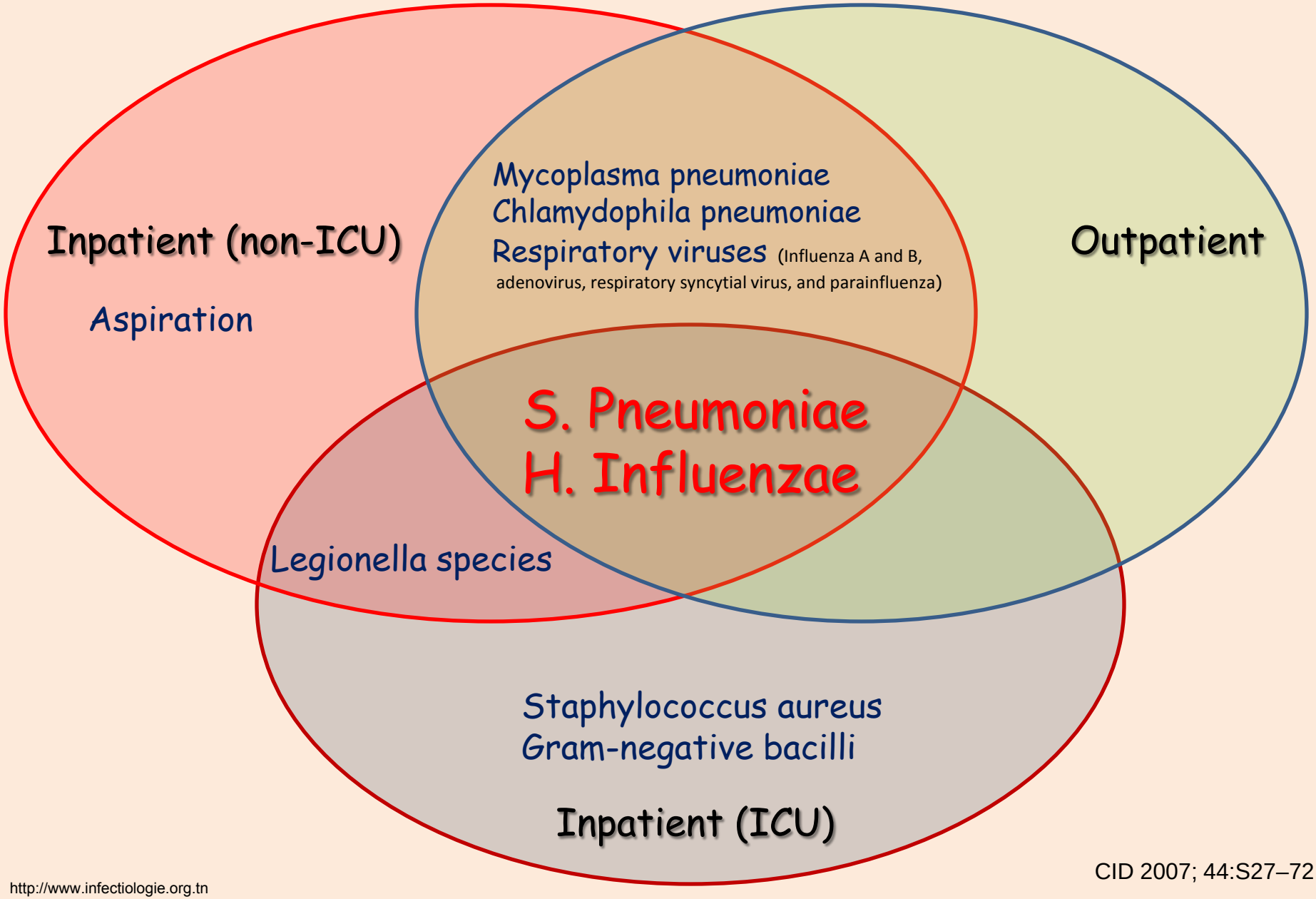
Schema

- CAP Epidemiology
- CAP diagnosis; Sputum is still useful!
- Quinolones Quorum sensing; comparative antibiogram susceptibility testing
- Comparative quinolones MICs
- Induction of resistance among respiratory pathogens: are quinolones the same ?
- PK/PD, Quinolones
- Quinolones Clinical Trials in CAP

LRTI: Most Common Etiological Pathogens of CAP



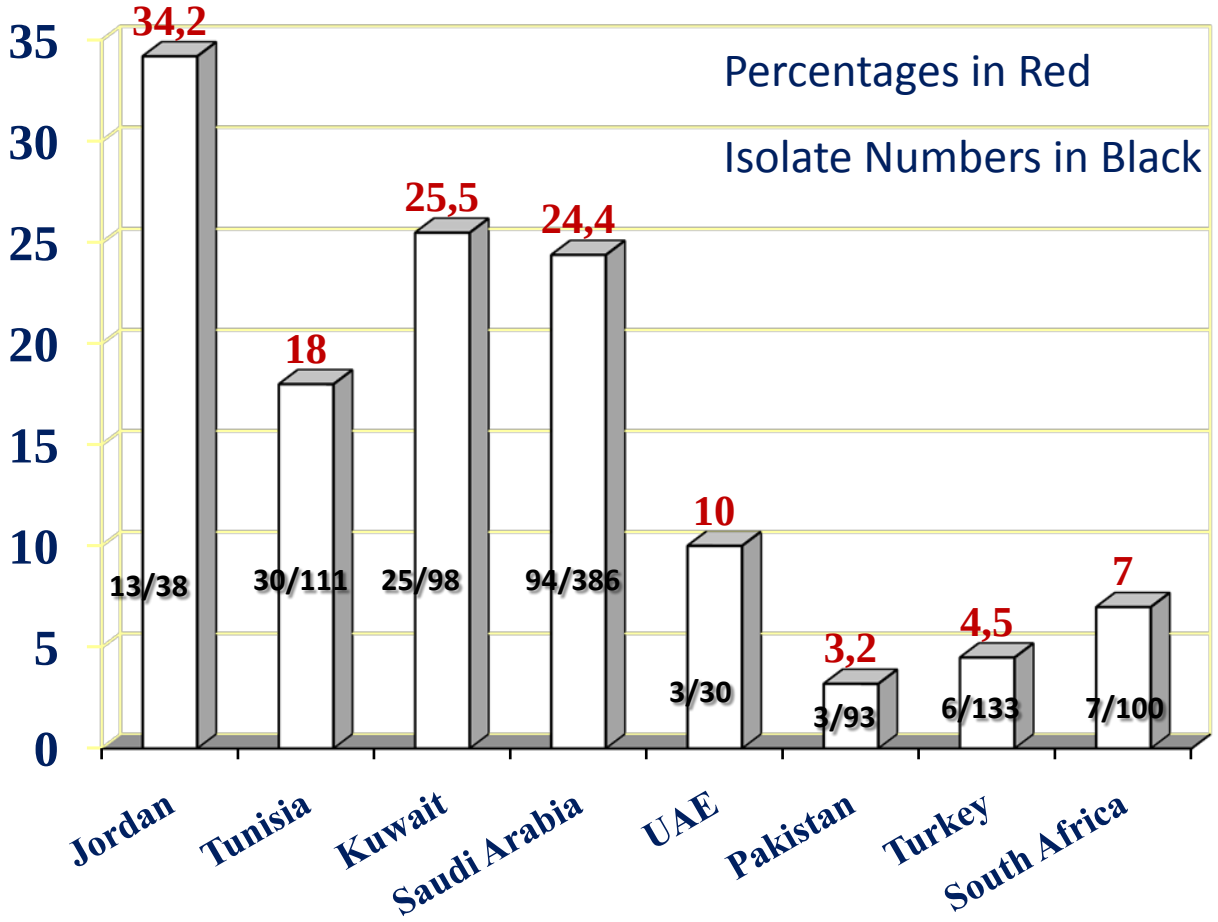
CID 2007; 44:S27–72

Haemophilus influenzae and β-lactamases (started after 1972)

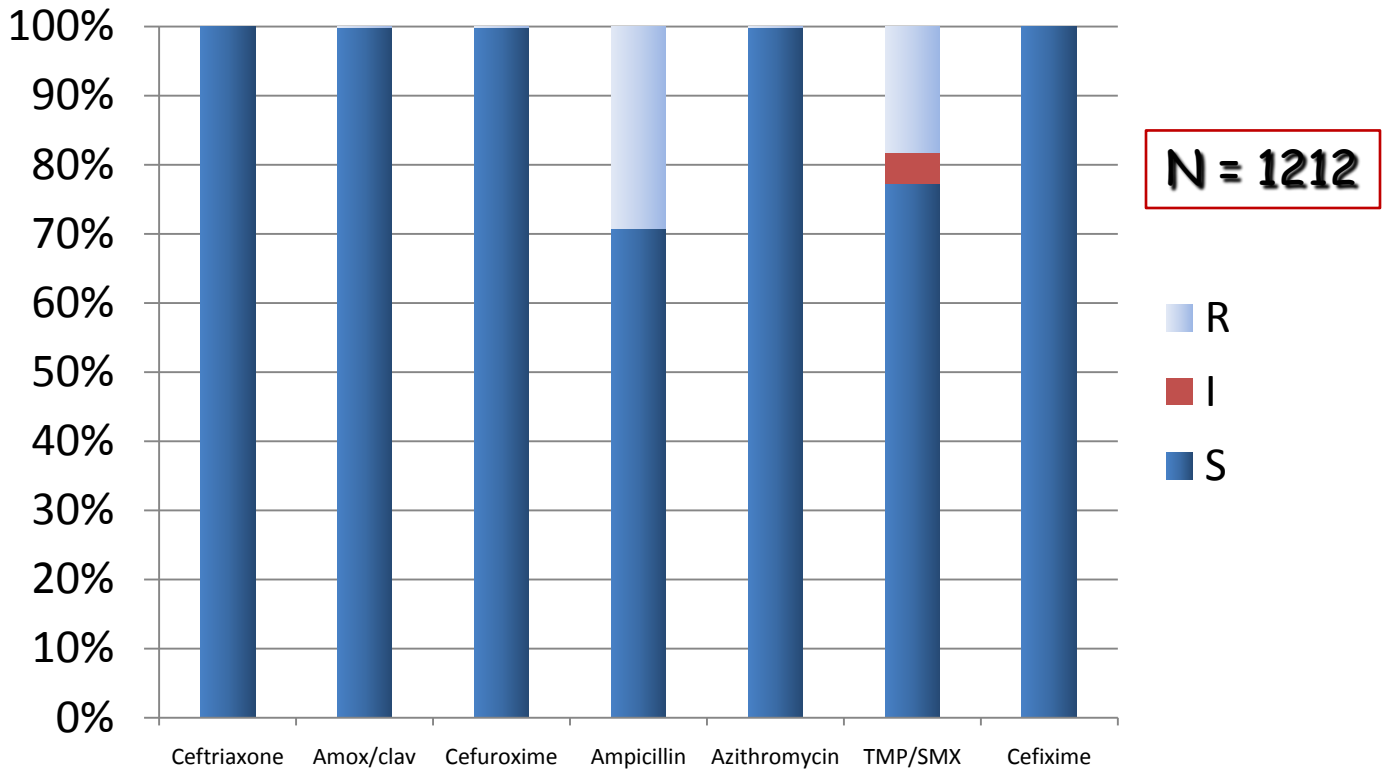
- Before 1972, Penicillin and Ampicillin MICs of 0.25-0.5 mg/l.
- MIC_{90} changed from 1mg/dl to 32 mg/dl in β -lactamases positive ones.
- In a decade:
  - Amoxicillin susceptibility dropped from 84% to 53.5%
  - Cefuroxime susceptibility has dropped from 94 to 76%
  - Cefixime susceptibility remains 100%, MIC_{90} of 0.1mg/dl

Jan Verhoef, International Journal of Antimicrobial agents 21 (2003) 501-509

Prevalence of β-Lactamase Positive Haemophilus influenzae



H. influenzae Resistance TRUST 7 (2003)



NICs : Ceftriaxone ≤0.015: Amox/clav 2: Cefuroxime 2: Ampicillin >8: Azithromycin 2: TMP-SMX >4: Cefixime 0.01.

TRUST = Tracking Resistance in the United States Today

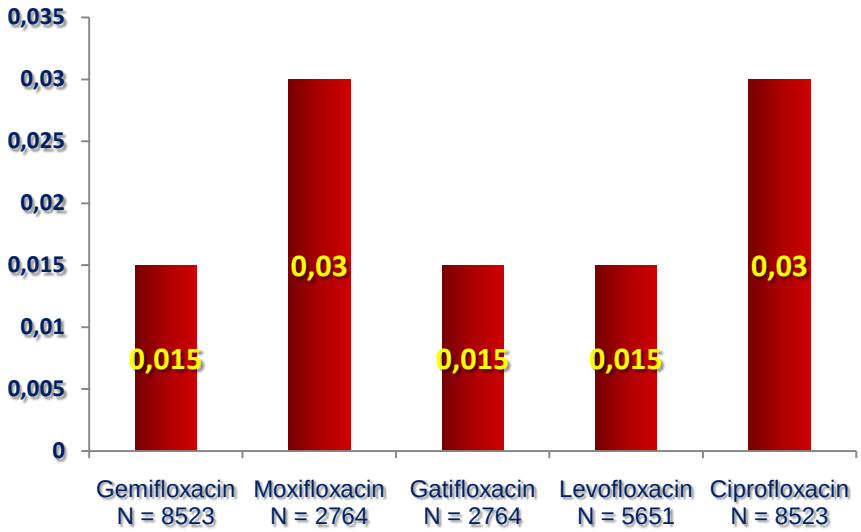
MIC_{90} = minimum inhibitory concentration required to inhibit 90% of isolates; S = susceptible; I = intermediate; R = resistant

Daniel F. Sahm PhD Clinical Cornerstone Volume 2003 Suppl 3 • 2003

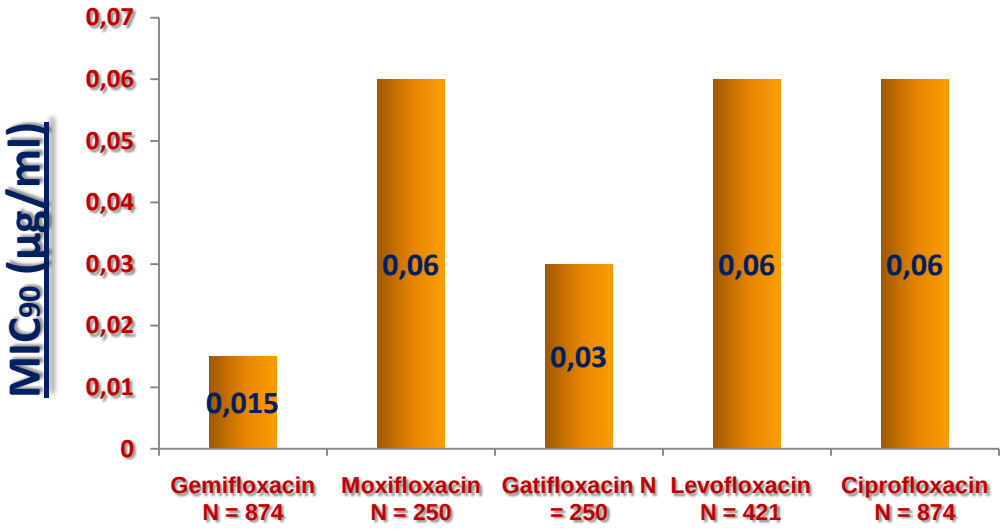
Blondeau, Missaghi; Expert Opinion on Pharmacotherapy, May 2004, Vol. 5, No. 5, 1117-1152.

•*Jan Verhoef, International Journal of Antimicrobial agents 21 (2003) 501-509

Selected Quinolones MIC_{90} Against Isolates of



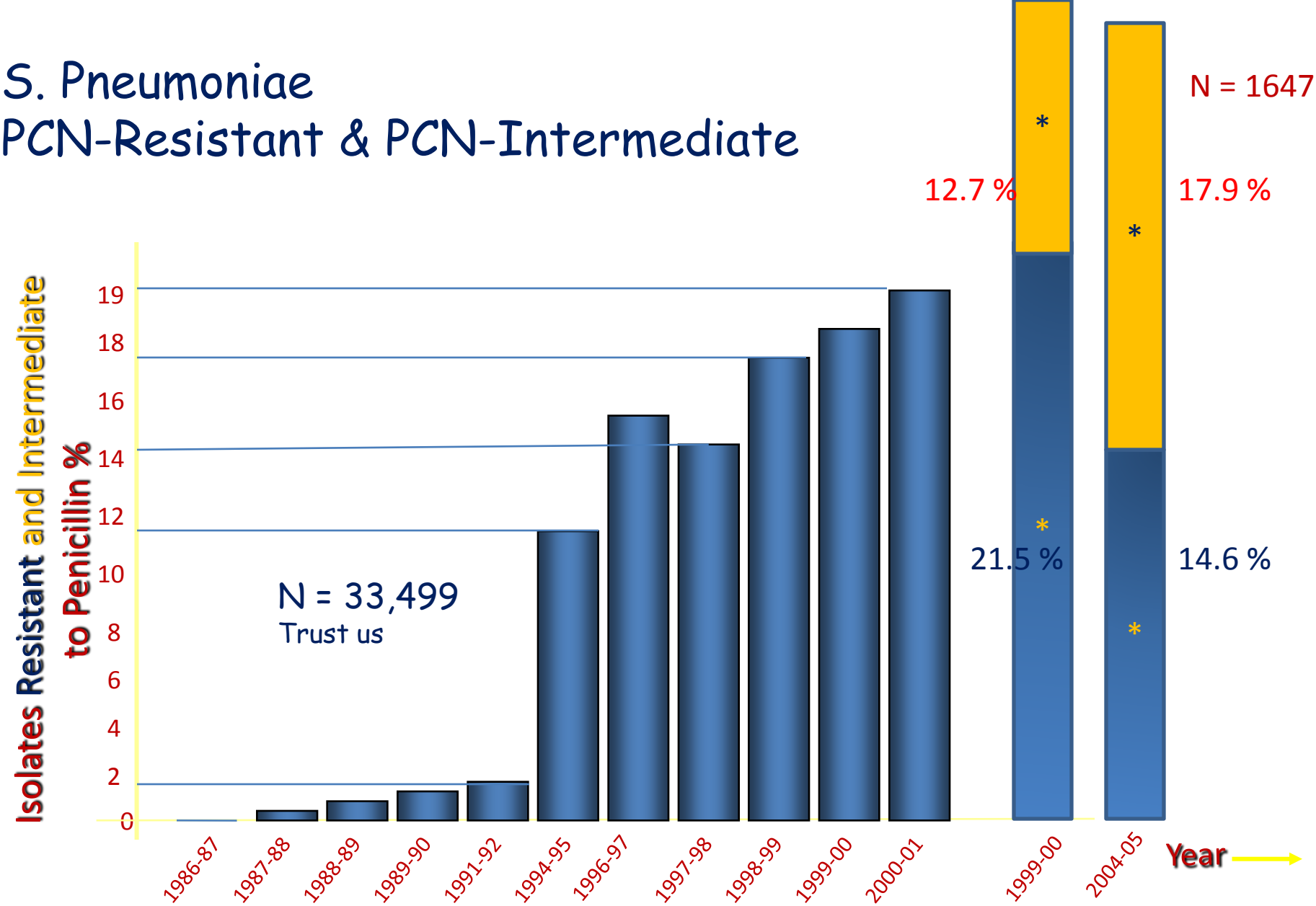
H. influenzae



M. catarrhalis

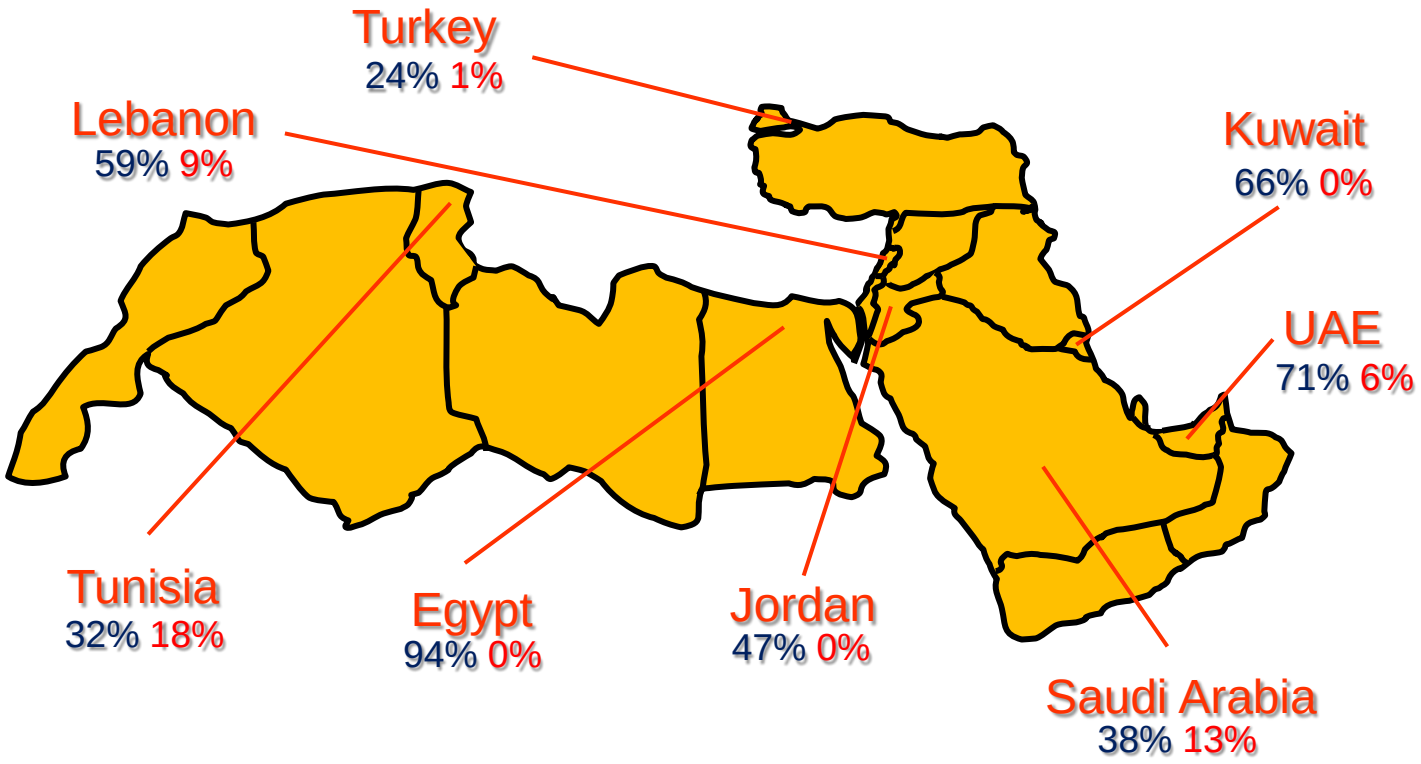
Alexander Project 1998-2000

S. Pneumoniae
PCN-Resistant & PCN-Intermediate



*Clinical Infectious Diseases 2009; 48. e 23 – e33
Clinical Infectious Diseases 2004; 39:S142–50

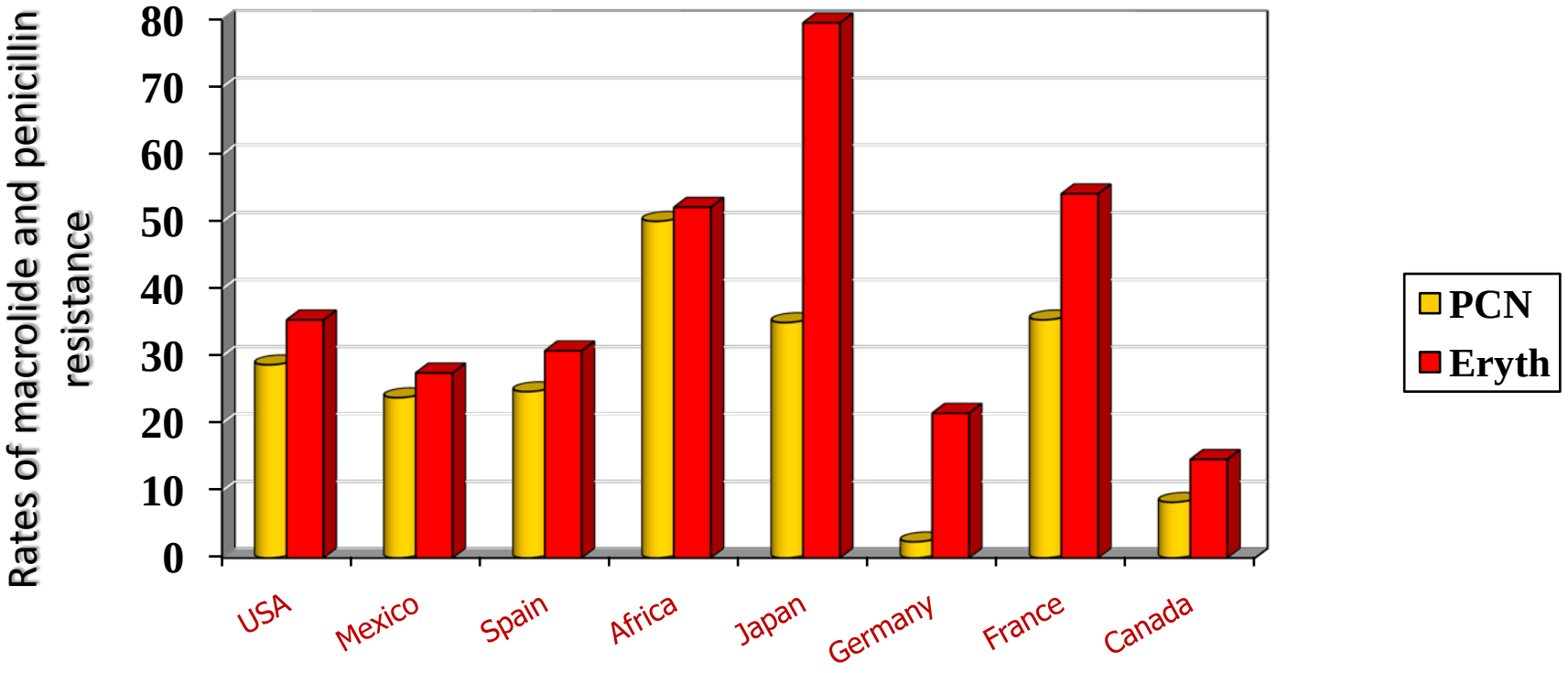
S. pneumoniae: Prevalence of PCN-Resistant Strains



Penicillin-intermediate (MIC 0.12 – 1 µg/ml)
Penicillin-resistant (MIC ≥2 µg/ml)

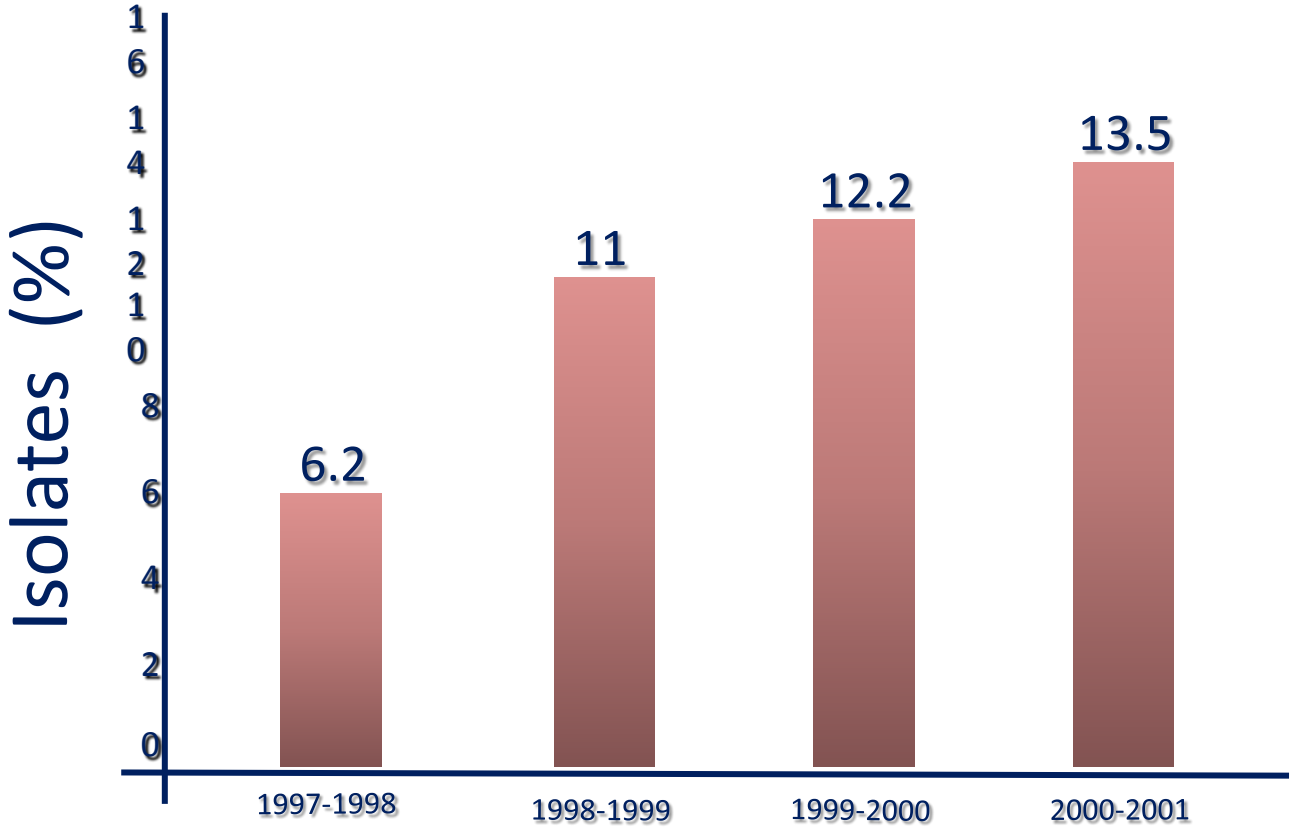
Clin Microbiol Infect. 2004;10 Suppl 3:111, Abs No P507.

Worldwide Rates of macrolide and penicillin resistance in *Streptococcus pneumoniae* from



Penicillin resistance (Pen R) is defined as MIC ≥2 mg/L
Erythromycin resistance (Ery R) is defined as MIC ≥ 1mg/L
PROTEKT US: Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin, for 2002–2003.

TRUST US, MDR-Streptococcus pneumoniae



Resistant to 3 antimicrobial classes, (most commonly penicillin, trimethoprim-sulfamethoxazole, and macrolides)

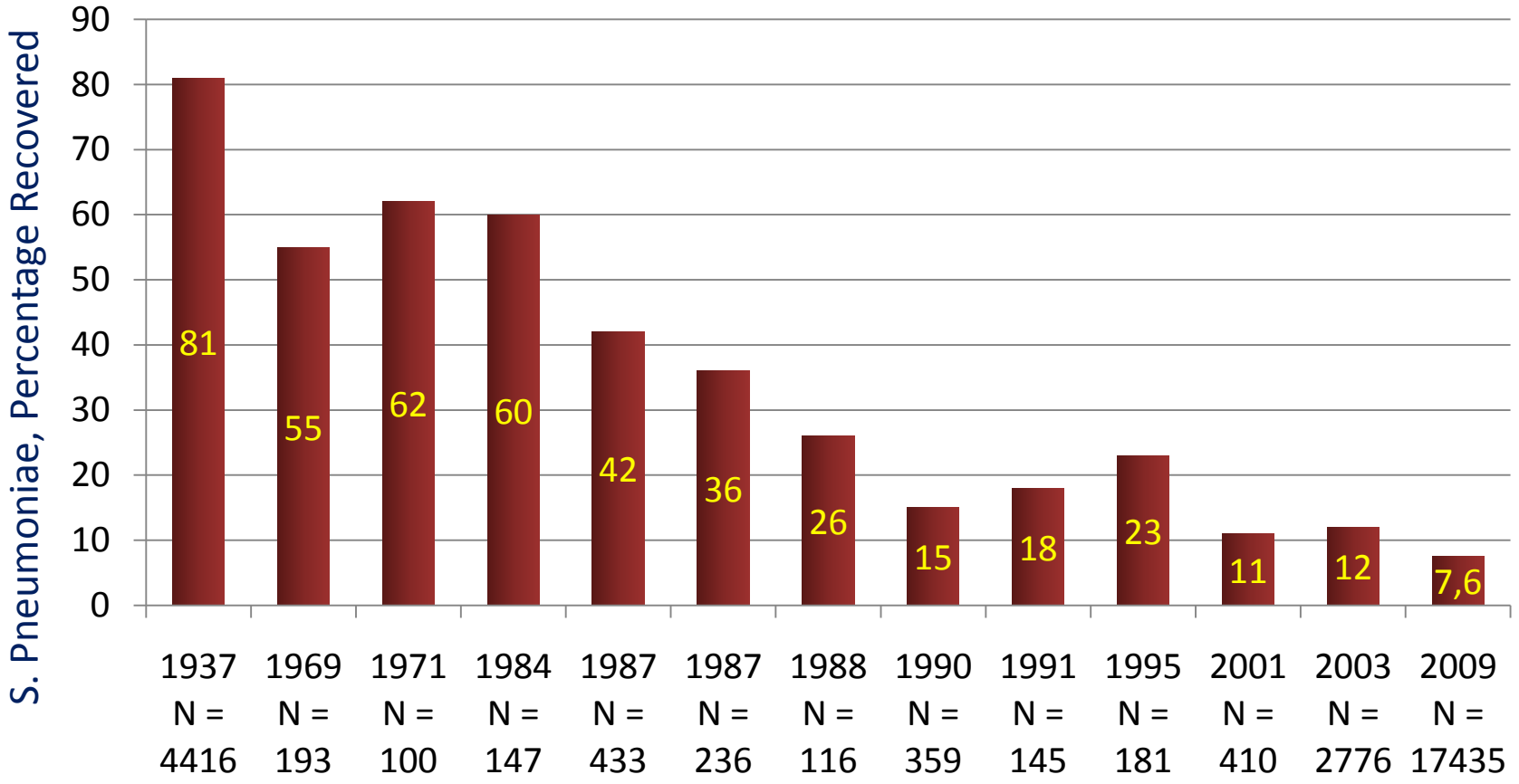
Dr. Adolf W. Karchmer, Clinical Infectious Diseases 2004; 39:S142–50

Clinical indications for more diagnostic testing

Indication	Blood culture	Sputum culture	*Legionella* UAT	Pneumococcal UAT	Other
Intensive care unit admission	X	X	X	X	X[a]
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X[b]
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia (anatomic or functional)	X			X	
Recent travel (within past 2 weeks)			X		X[c]
Positive *Legionella* UAT result		X[d]	NA		
Positive pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X[e]

Clinical Infectious Diseases 2007; 44:S27–72

Recovery of S. pneumoniae in Sputum Adults with CAP



John G. Bartlet. CID 2011;52(S4):S296–S304

Diagnostic Tests for Agents of CAP

Expectorated Sputum

- CAP approved sputum samples for analysis is 32-76%

- Upper airways; colonized 10^9– 10^{10} CFU/mL
  - Sputum washing in tea strainer, careful fleck picking, and cytological screening
  - SEC < 25/LPF, PMN > 25/LPF, dominant microorganisms
  - Plate within 2 hours, or store at $4C^O$

- Sputum is good for:
  - S. pneumoniae, S. aureus, S. pyogenes, H. influenzae, Enterobacteriaceae, M. catarrhalis, N. meningitidis, and pseudomonads

John G. Bartlet. CID 2011;52(S4):S296-S304

Diagnostic Tests for Agents of CAP

Transtracheal aspiration

- Originally described in 1959
- Disfavored in the 1980s;
  - patient non acceptance
  - questionable complications
  - sentiment that the procedure was unnecessary?
- Not good in chronic lung disease

Transthoracic needle

- Was introduced in 1883
- This procedure is now rarely performed; patient safety, patient acceptance, and need.
- False negative by not hitting the diseased area

John G. Bartlet. Clinical Infectious Diseases 2011;52(S4):S296–S304

Diagnostic Tests for Agents of CAP

Bronchoscopy

- Initially viewed as an excellent method
- Clear evidence of contamination by oral flora
- Largely restricted to NAP and VAP; rarely for CAP
- Alternative methods subsequently gained favor with threshold for:
  - BAL samples is 10^4CFU/mL (since 1978)
  - PSB specimens is 10^3CFU/mL (since 1979)

John G. Bartlet. Clinical Infectious Diseases 2011;52(S4):S296–S304

Diagnostic Tests for Agents of CAP

Urinary Antigens Detection and other tests

Advantages

- Better yield even after antibiotic treatment.
- One prospective, controlled trial positive results:
  - 88 (82%, N =107) adults with bacteremic pneumococcal pneumonia
  - false positive in just 3 (3%, N = 106) with septicemia due to other microbes.
  - Sensitivity of 82% and a specificity of 97%
- Good for Legionnaires disease, (accounts for 2%–6% of CAP)

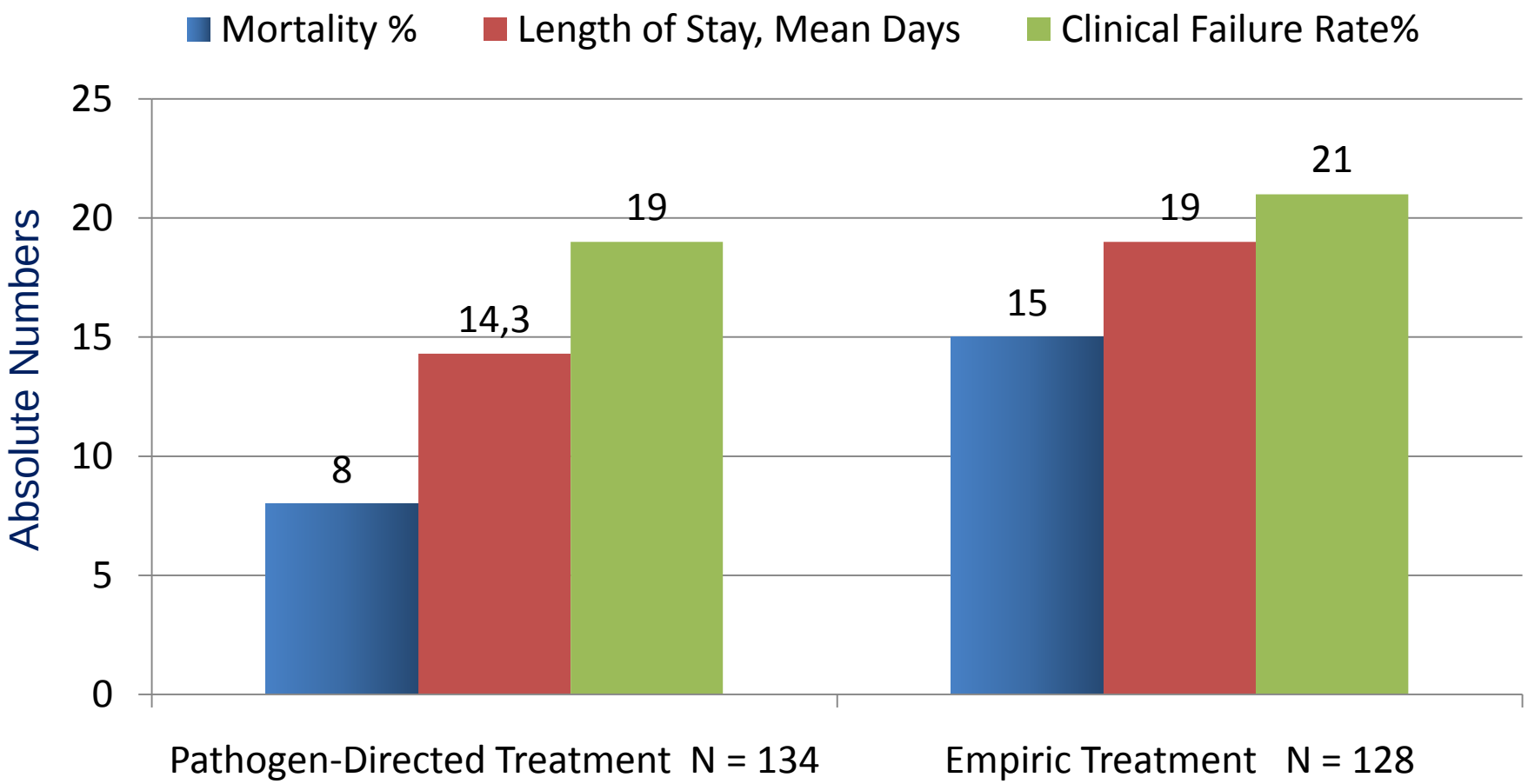
Disadvantages and other tests

- Sensitivity and specificity are less in non bacteremic Pneumonia
- For C. pneumoniae and M. pneumoniae, there is no test that has been cleared by the FDA
- PCR assay that has been cleared by the FDA for detection of 12 respiratory tract viruses

John G. Bartlet. Clinical Infectious Diseases 2011;52(S4):S296–S304

Why we need a microbiological Diagnosis?

Pathogen-Directed Antibiotic Treatment Compared with Empiric Antibiotic Treatment for CAP



John G. Bartlet. Clinical Infectious Diseases 2011;52(S4):S296–S304
van der Eerden. Thorax 2005; 60:672–8

Classification of quinolone antimicrobials

First generation

- Nalidixic acid
- Cinoxacin

Second generation

- Norfloxacin
- Ciprofloxacin (a)
- Lomefloxacin
- Ofloxacin
- Levofloxacin

Third generation (b)

- Sparfloxacin
- Gatifloxacin
- Grepafloxacin

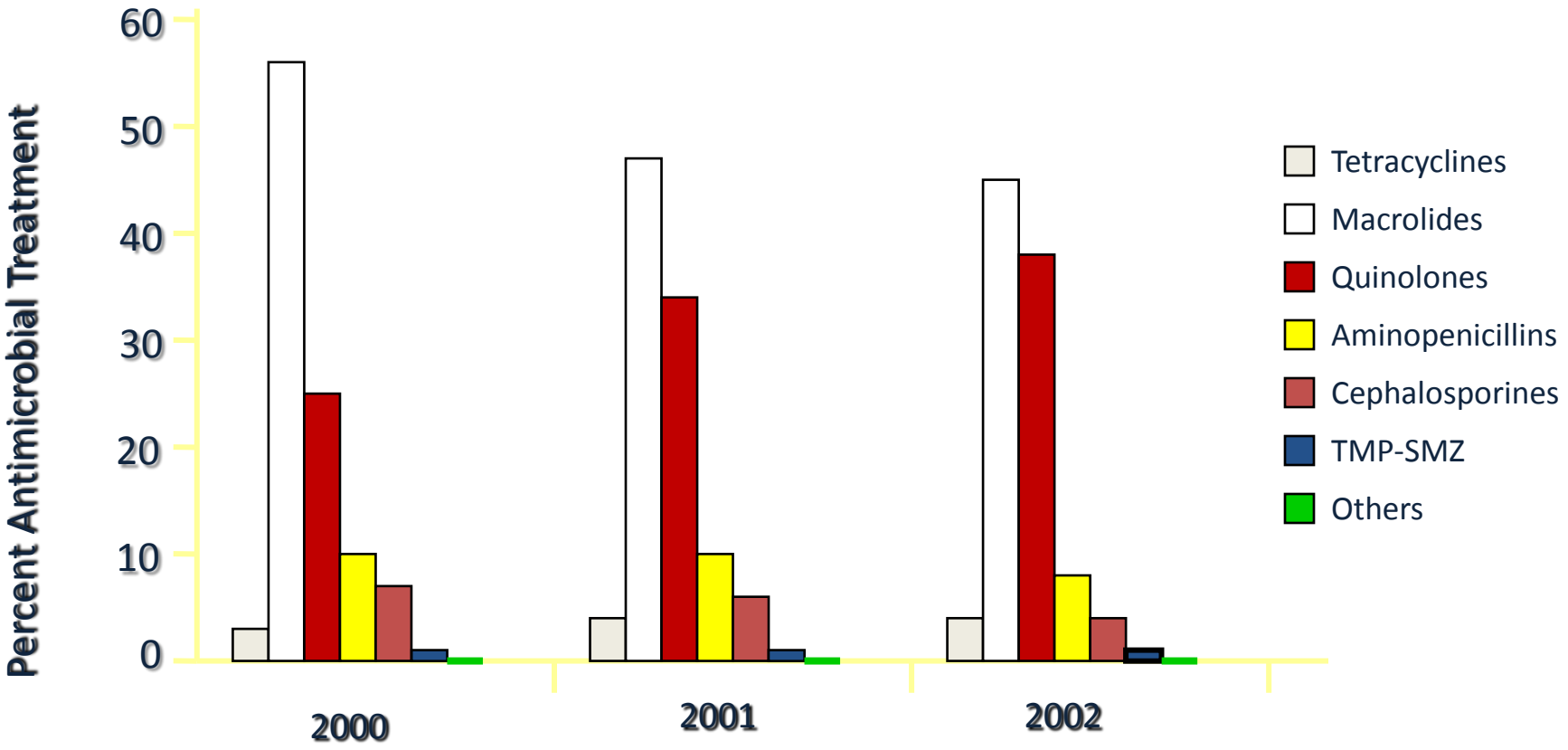
Fourth generation (c)

- Trovafloxacin
- Moxifloxacin
- Gemifloxacin

a Most potent agent against *Pseudomonas aeruginosa.*
b More potent against *Streptococcus pneumoniae* and anaerobes, compared with earlier agents.
c Most potent against *S. pneumoniae and* anaerobes.

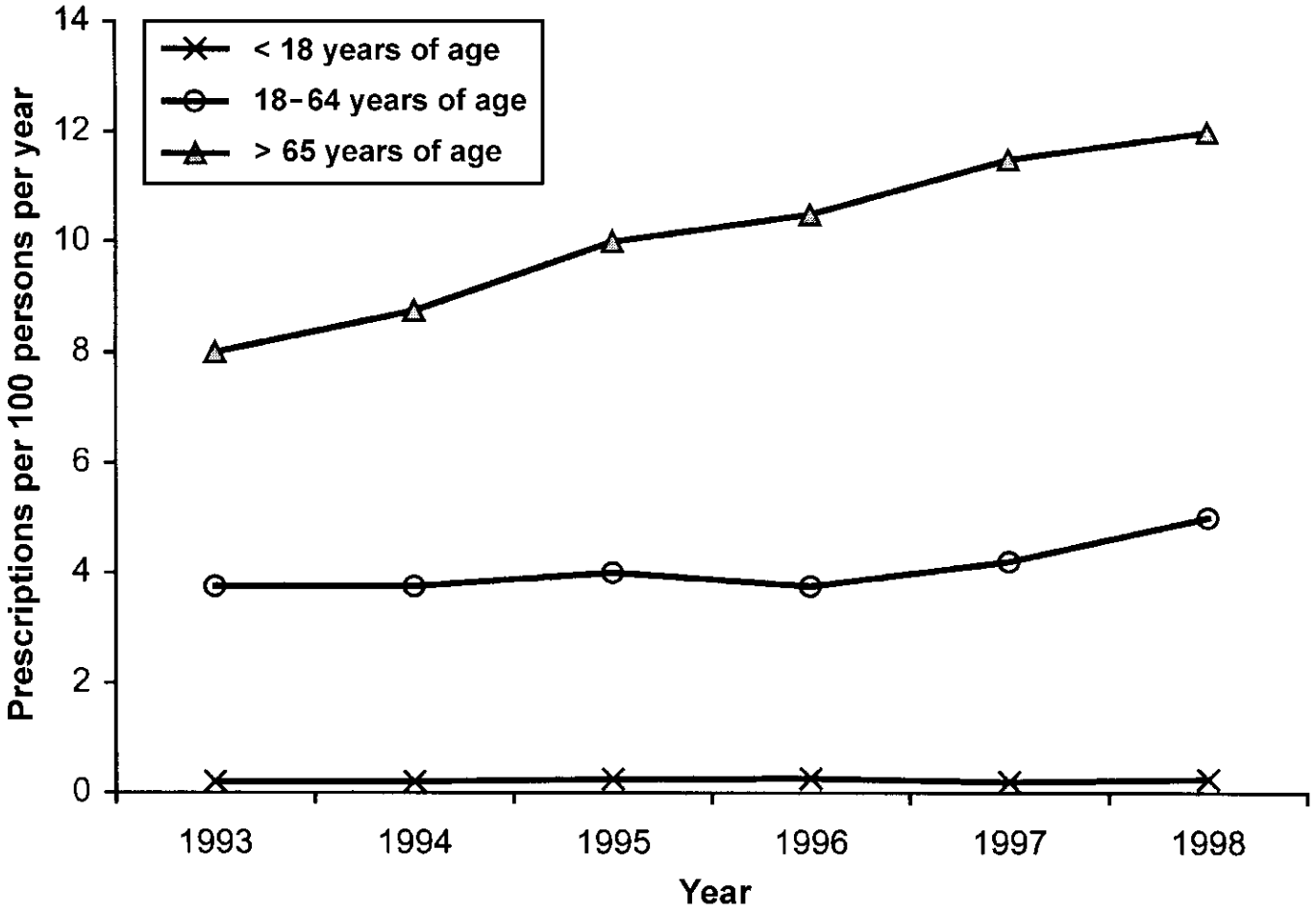
Vincent Andriole CID 2005:41, S114 (Suppl 2)

Trends of outpatient CAP Antimicrobial drug treatment by Year & percentage, across all age groups.



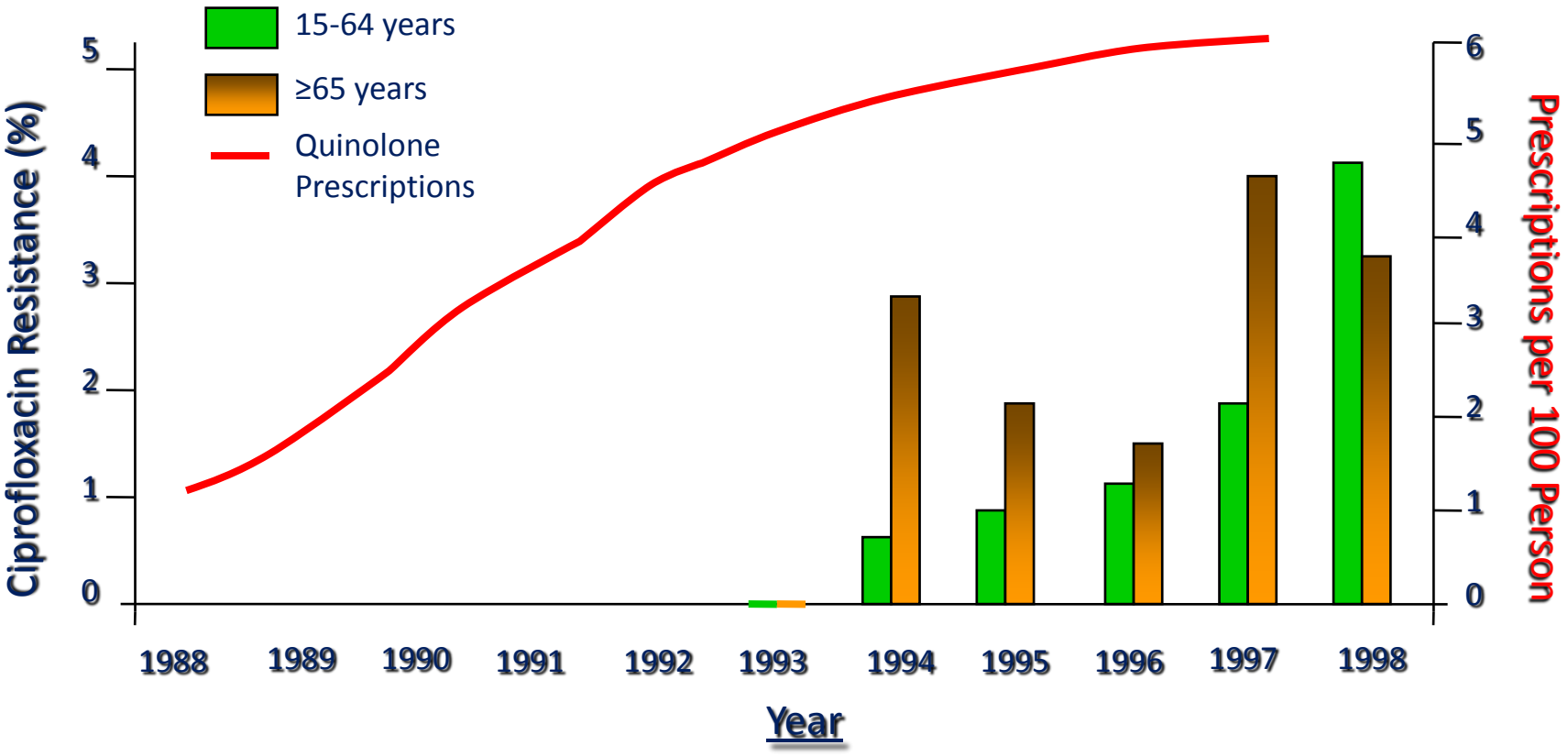
Emerging Infectious Diseases, 2005 CDC

Fluoroquinolone prescriptions, by age group, in the United States, 1993–1998



Ellie J. C. Goldstein and Susan M. Garabedian-Ruffalo. Clinical Infectious Diseases 2002; 35:1505–11

Ciprofloxacin Use and Pneumococcal Resistance in Canada 1988-1998



Dr. Donald E. Low, CID 2004; 38(Suppl 4):S357–62a

IDSA Guidelines in CAP Treatment

Outpati

- **A macr**
  (azithr
  erythr
- **A: A R**
  (moxif
  levoflo
- **B:** A ß-
- **Preferr**
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Inpatient

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Inpatient, ICU

•A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin (level II evidence) or **a fluoroquinolone** (level I evidence) (strong recommendation)

•For PCN-allergic patients, a respiratory **fluoroquinolone** and aztreonam are recommended.

•For Pseudomonas infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either **ciprofloxacin or levofloxacin (750-mg dose)**

or

•the above β-lactam plus an aminoglycoside and azithromycin

or

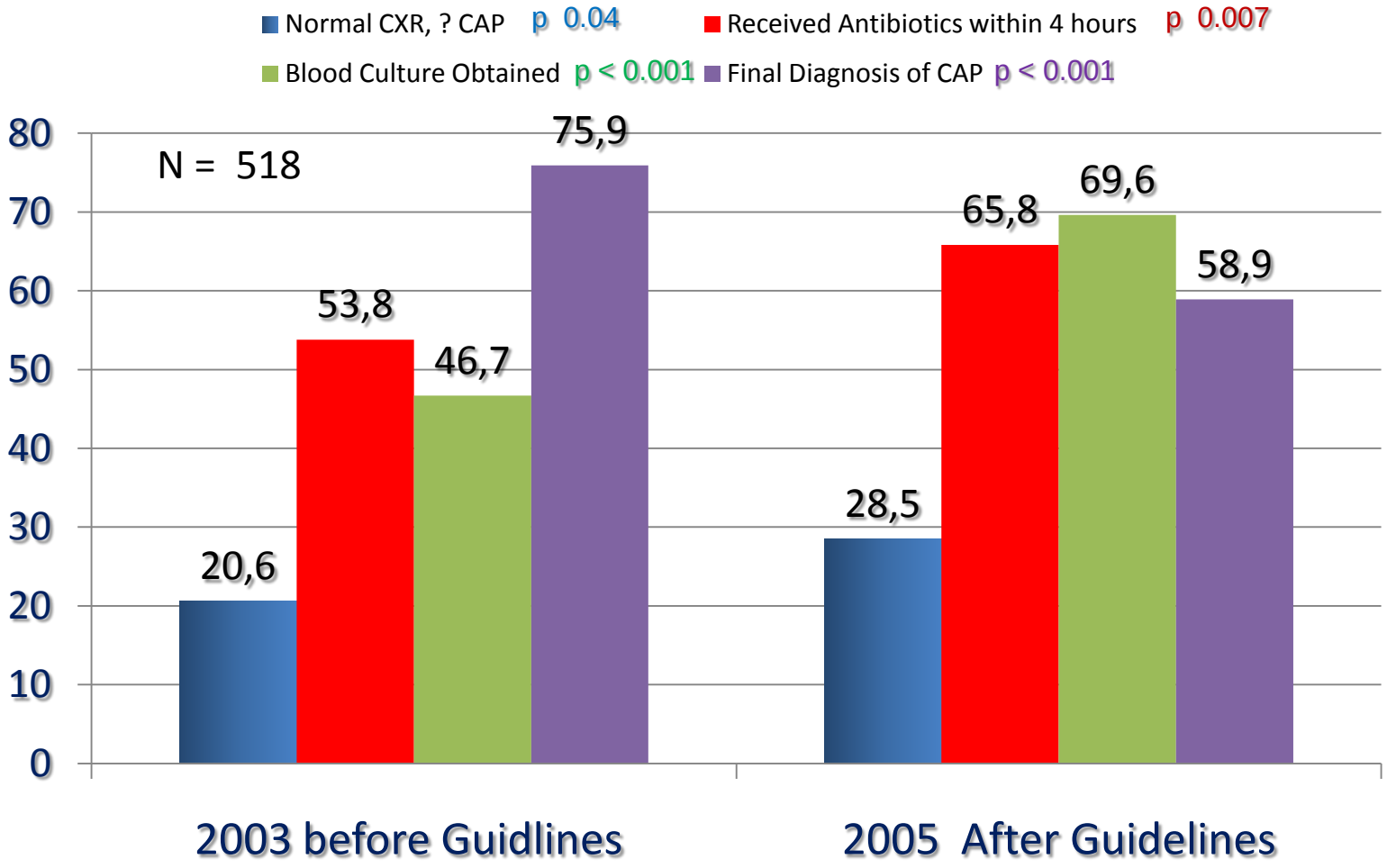
•the above β-lactam plus an aminoglycoside and an antipneumococcal **fluoroquinolone** (for PCN-allergic patients, substitute aztreonam for the above β-lactam). (Moderate recommendation; level III evidence.)

•For CA-MRSA infection, add vancomycin or linezolid.
•(Moderate recommendation; level III evidence.)

Clinical Infectious Diseases 2007;44:S27-S72

Do following guidelines lead to better results ?

Detroit, Michigan for the years 2003 – 2005 for the Recommendation of Administering Antibiotics Within 4 hours



Their was significant increase in antibiotic utilization for 2005 compared with 2003 ($p < 0.001$).

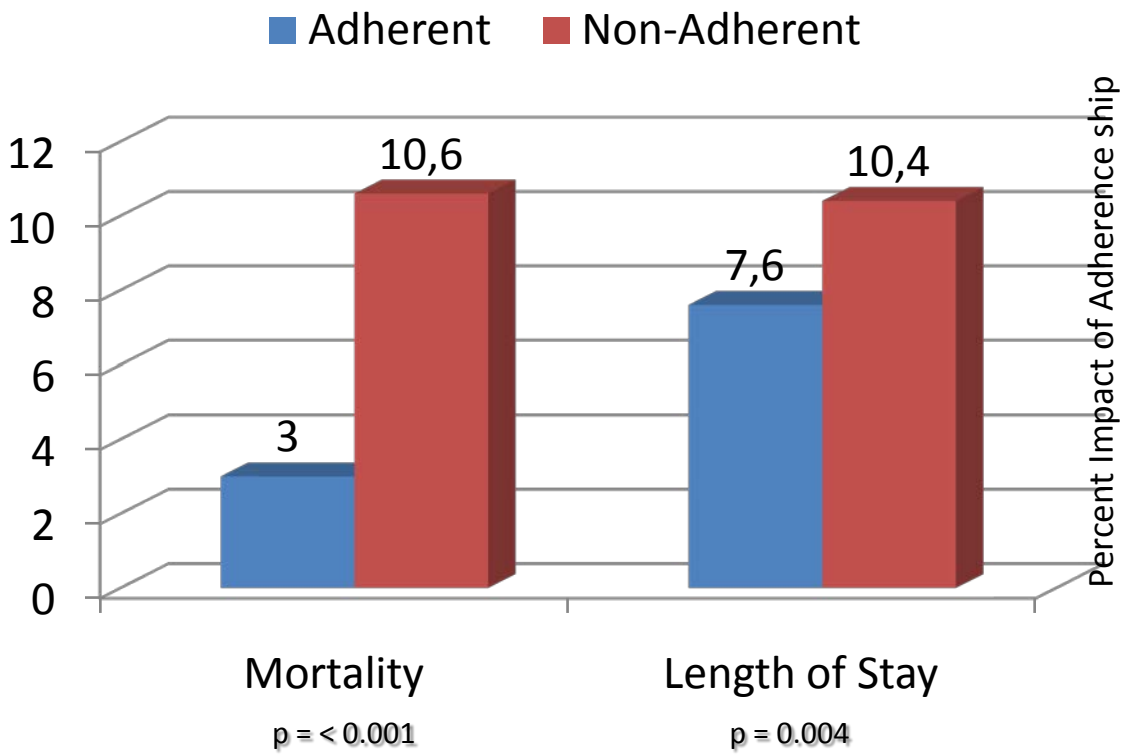
There were no significant differences in PSI or CURB-65 scores

The 4 hour period was changed to 6 -8 hours in 2007 IDSA Guidlines

Clinical Infectious Diseases 2007; 44:S27–72
Mohamad G. Fakih. CHEST 2007; 131:1865–1869)

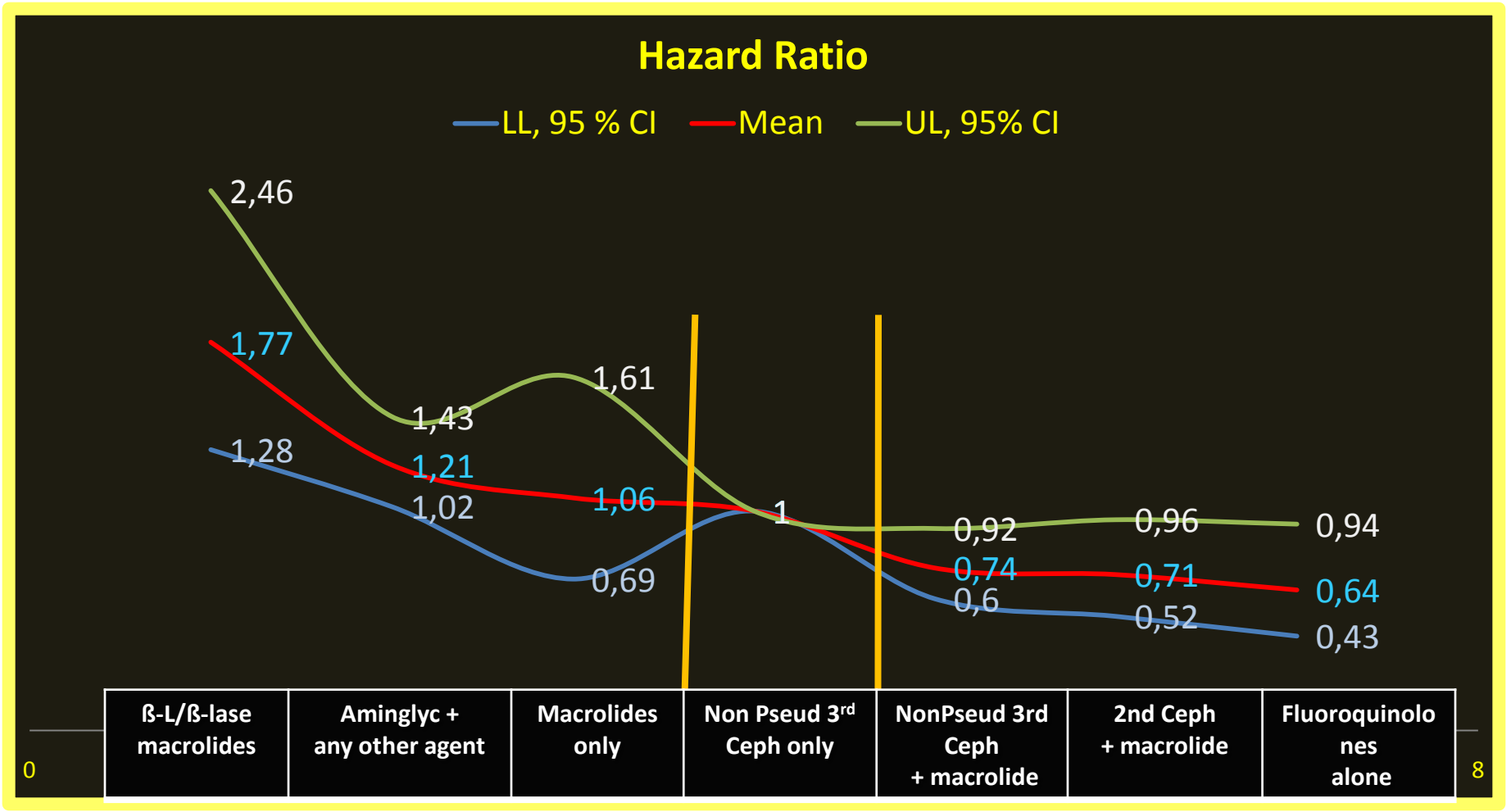
Adherence to ATS guidelines' empirical antibiotic recommendations for 2001 and CAP outcome

- 780 CAP pt., in Barcelona
- Multivariate analysis.
- Overall adherence 84%
- ICU adherence (52%)
- Adherence to the 2001 ATS guidelines was high except in CAP patients admitted to an intensive care unit



Eur Respir J 2008; 32: 892–901
DOI: 10.1183/09031936.00163407

Independent Associations Between Initial Antimicrobial Therapy & 30-day Mortality

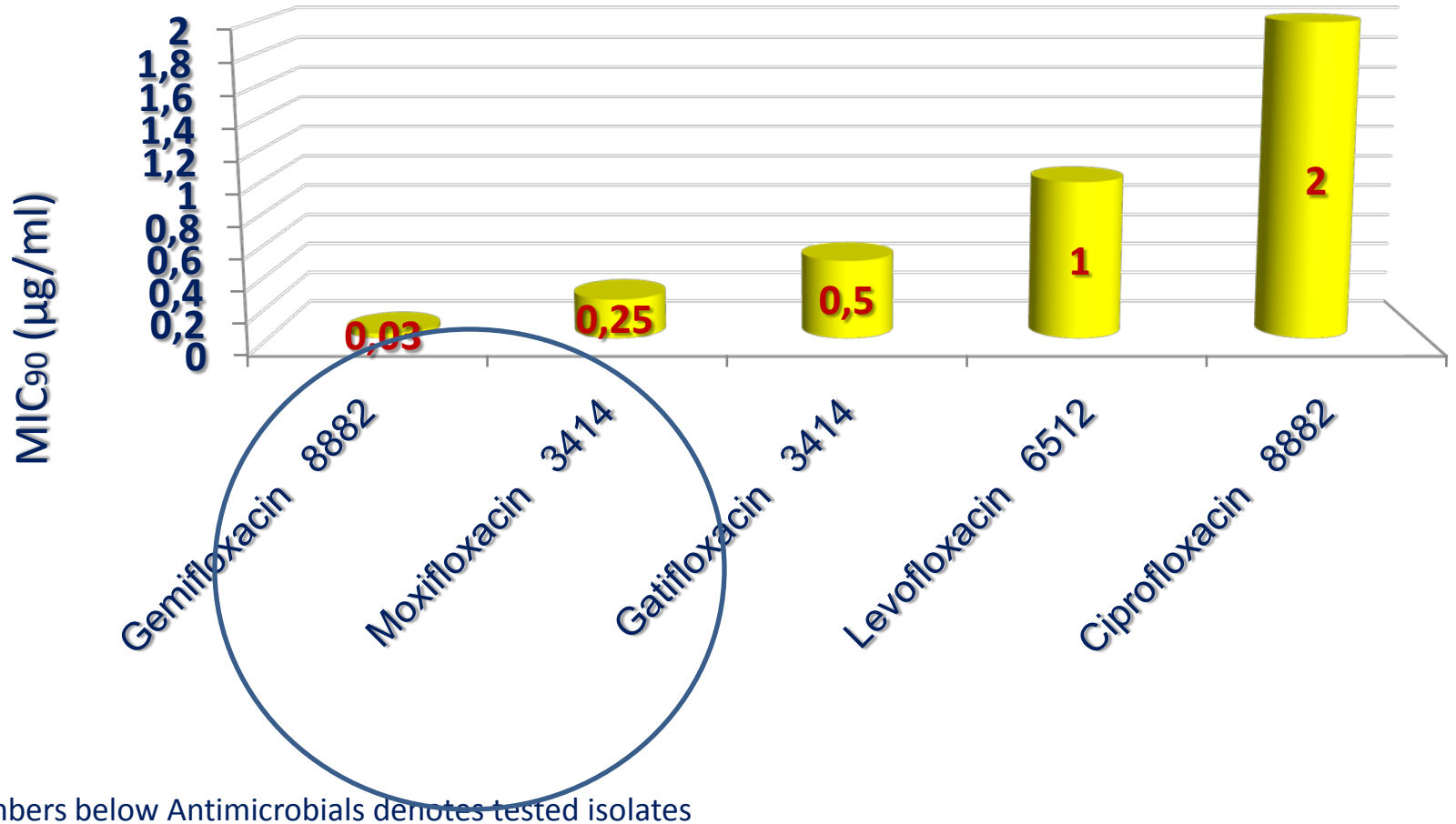


Drugs, 71(6), 16 April 2011 , pp. 757-770(14)

ß -Lactam–Resistant S. pneumoniae • CID 2002:34 (Suppl 1) • S23

Quinolones; MICs, resistance and Evolution of resistance (genotype/phenotype)

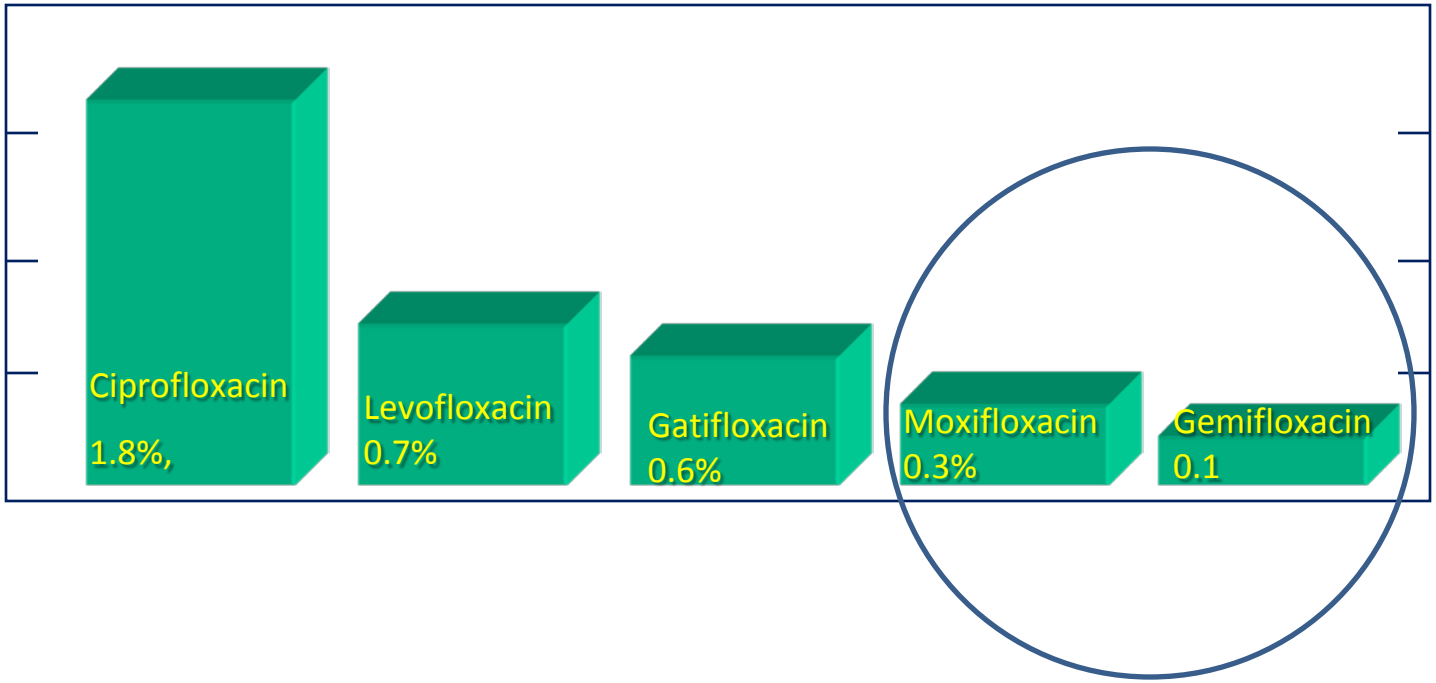
Selected Quinolones MIC_{90} Against Isolates of Streptococcus pneumoniae



Numbers below Antimicrobials denotes tested isolates

Alexander Project 1998-2000

Fluoroquinolone Resistance Among Canadian isolates of S. pneumoniae



TRUST, and PROTEKT US Surveillance Data

Karchmer, CID 2004; 39:S142–50
Jacobs et al, JAC; 2003, 52, 229-246

Activity of Various Antibiotics Against Ciprofloxacin-Susceptible Pneumococcal strains with Different Susceptibility Patterns to Penicillin

Antibiotic MIC_{90} (µg/ml)	Penicillin-susceptible (n=64)	Penicillin-intermediate (n=68)	Penicillin-resistant (n=75)
Gemifloxacin	0.03	0.06	0.06
Ciprofloxacin	2	2	4
Levofloxacin	2	2	2
Clarithromycin	0.03/0.06	0.03/32.0	2.0/>128.0
Amoxicillin	0.06	1	4
Cefuroxime	0.25	2	16
Azithromycin	0.5	>128	>128

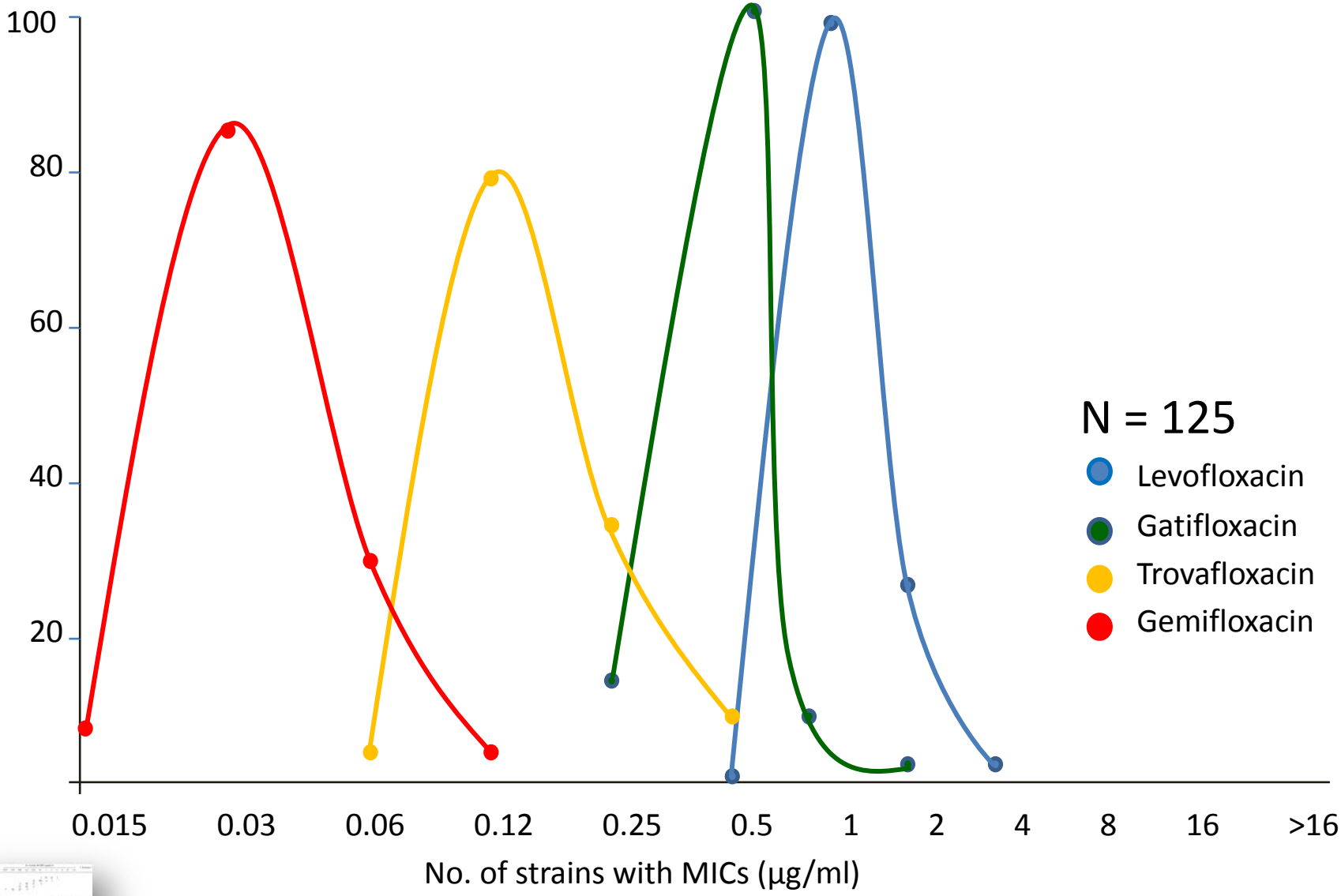
Adopted from Todd A. Davies et al, Antimicrobial Agents and Chemotherapy, February 2000, p. 304-310, Vol. 44, No. 2

Activity of Various Quinolones Against 28 Ciprofloxacin-Resistant Pneumococcal Strains

Fluoroquinolone	Range of MIC (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Ciprofloxacin	8-32	16	>32
Gemifloxacin	0.03-1	0.25	0.5
Levofloxacin	4 ->32	16	>32
Sparfloxacin	0.25-32	8	16
Grepafolxacin	0.5-16	4	8
Trovafloxacin	0.25	1	4

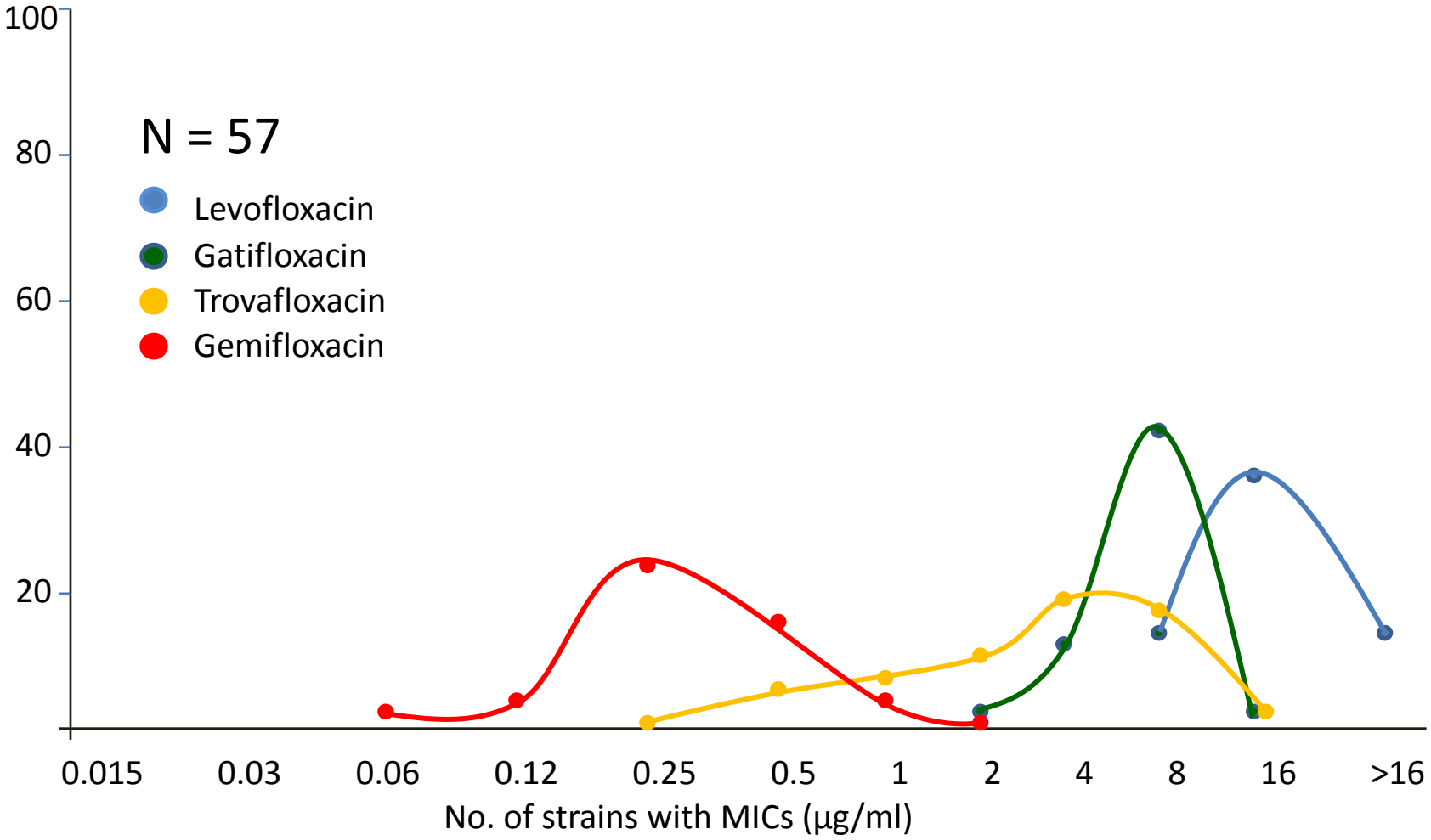
Davies et al. AAC. 2000;44:304-310

Comparative activities of fluoroquinolones against levofloxacin-susceptible S. pneumoniae clinical isolates



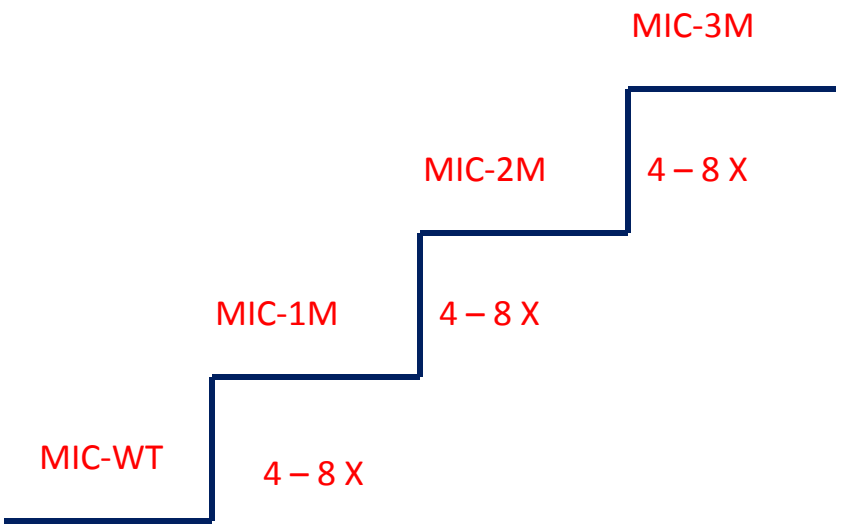
Adopted from Jorgrnsen et al. AAC, Nov. 2000, p. 2962–2968

Comparative activities of fluoroquinolones against levofloxacin-resistant S. pneumoniae clinical isolates



Adopted from Jorgrnsen et al. AAC, Nov. 2000, p. 2962–2968

The Evolution of Resistance to Quinolones

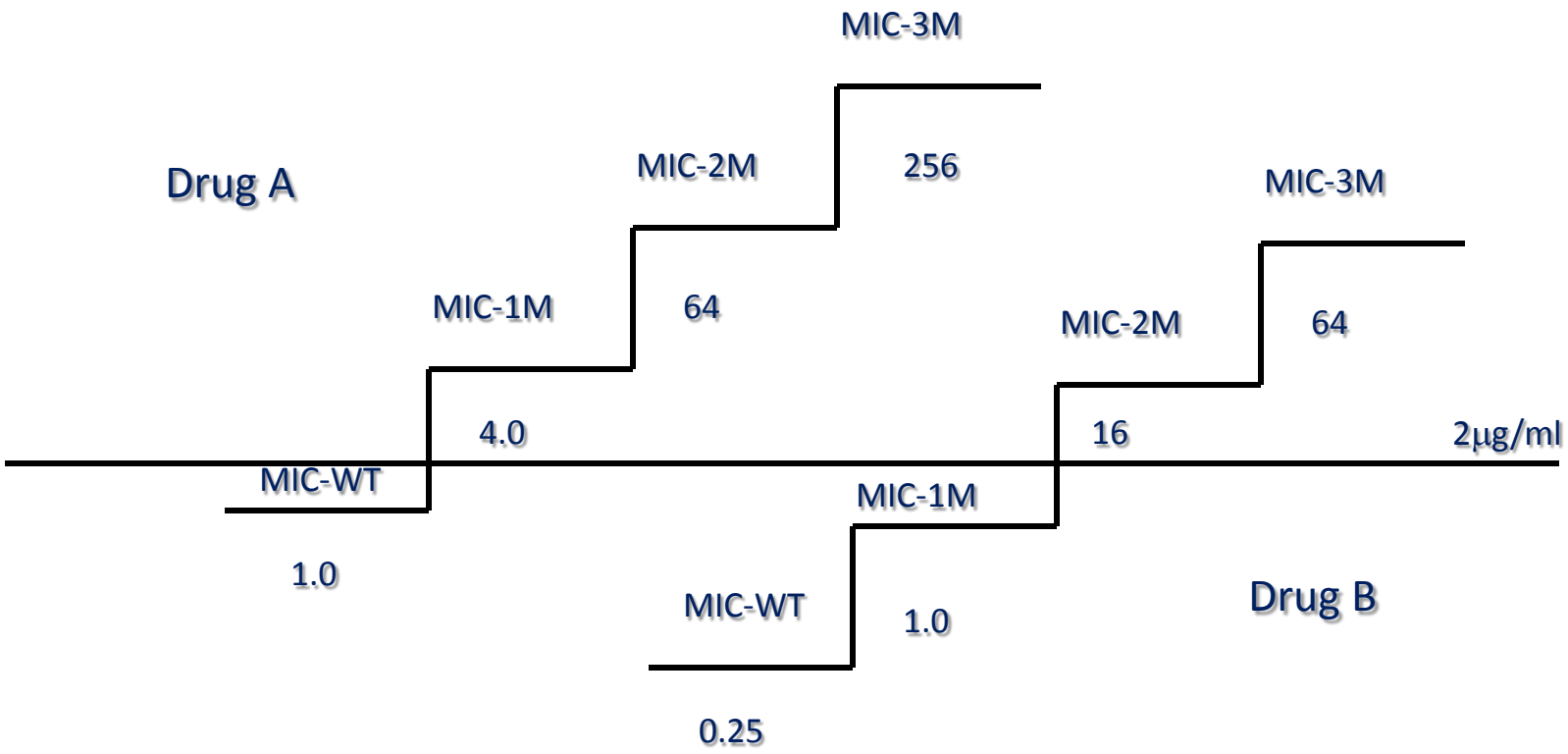


Each step in the evolution represents a spontaneous mutation that diminishes quinolone susceptibility 4-8 fold. Thus the MIC of the quinolone used to select mutants from the wild type (WT) is 4-8 fold diminished for successive first-step (1M), second-step (2M), and third-step (3M) mutants.

Resistance among the Quinolones x CID 2001:32 (Suppl 1)

The Evolution of Resistance to Quinolones

Cross-resistance Among the Quinolones

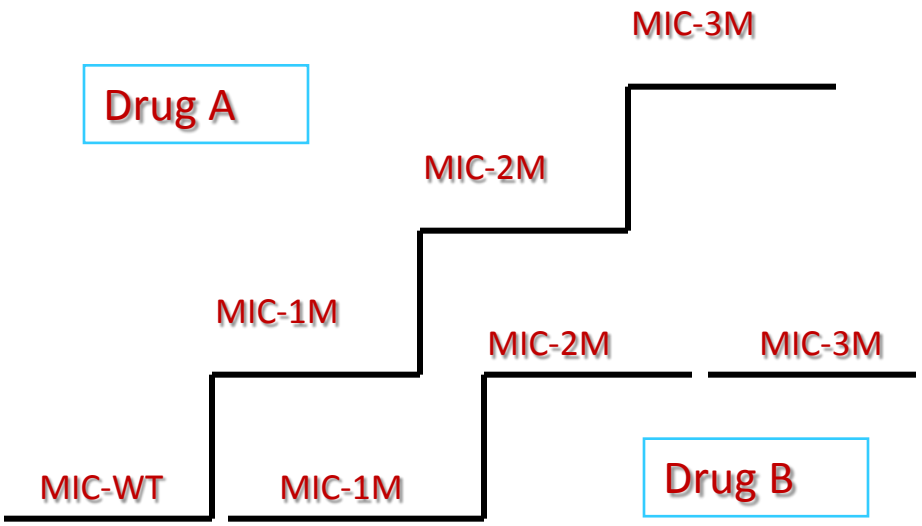


If both quinolones achieve a concentration of 2 µg/mL at the site of infection, the 8-fold rule would predict that quinolone B would provide the most effective therapy and be less likely to select for resistance because achievable concentrations exceed the MIC for the wild-type and first-step mutants.

Resistance among the Quinolones x CID 2001:32 (Suppl 1)

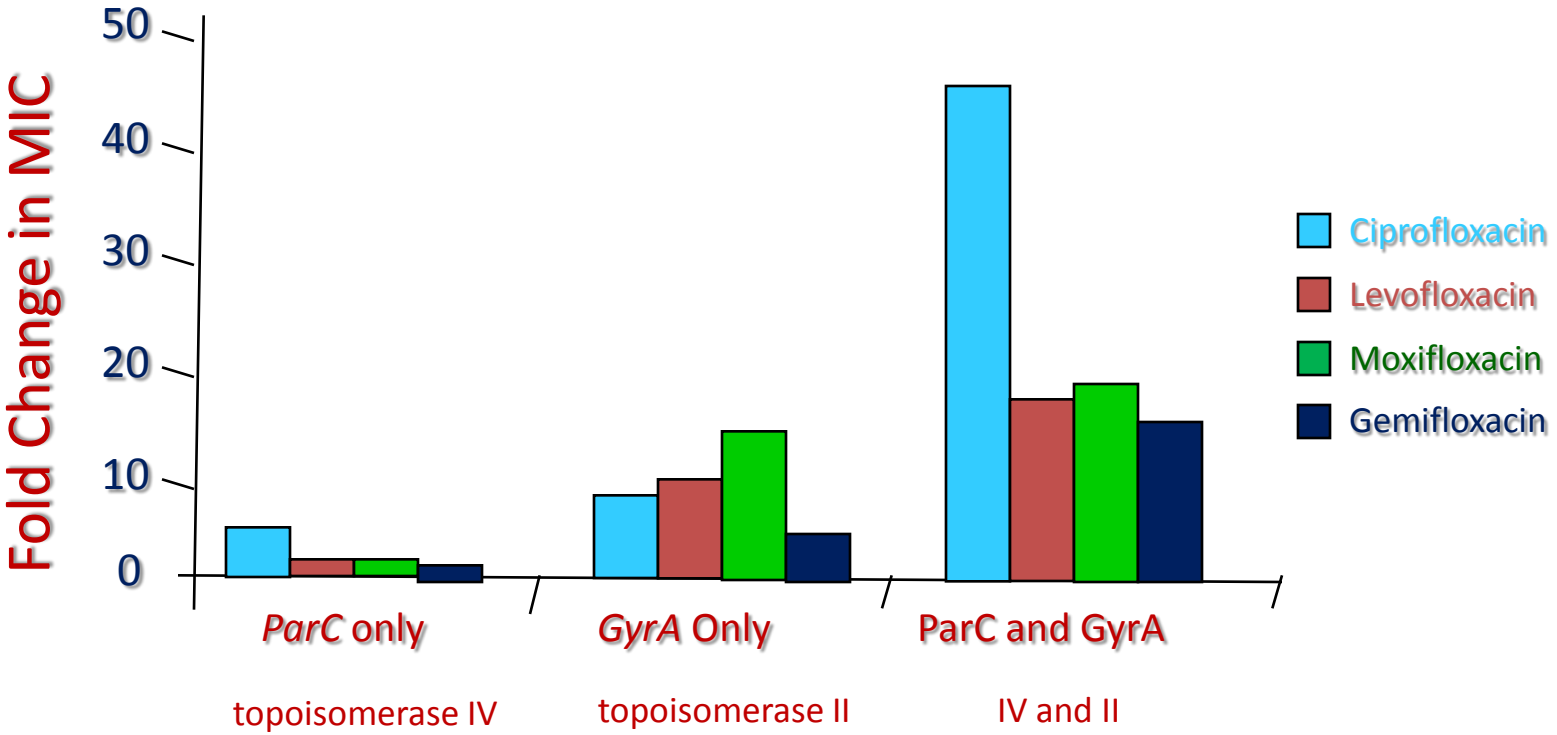
The Evolution of Resistance to Quinolones

Dichotomous resistance among the quinolones



A as selected by quinolone A is shown (left), with each successive mutation causing diminished susceptibility to quinolone A. Because the mechanisms responsible for the mutations in the first-step (1M) and third-step (3M) mutants do not affect susceptibility to quinolone B, a pattern of dichotomous resistance emerges. Only the mutation in the second-step (2M) mutant reduces susceptibility to quinolone B.

Effect of ParC and GyrA mutations on the in vitro MICs of 4 Quinolones against S. pneumoniae



George M. Eliopoulos, Clinical Infectious Diseases 2004; 38(Suppl 4):S350–6

Stephen H. Gillespie et al. Microbial Drug Resistance. June 2002, 8(2): 79-84.

L. MARK FISHER .AAC. Nov. 2000, p. 3112–3117

Mutant Prevention Concentration

- Initially described in *M. bovis* and *S. aureus*
- It is the difference between wild bacteria inhibited at MIC and other colonies inhibited at a higher concentration (i.e. first step mutant), the higher concentration was coined MPC.
- Other definition; The MIC of most first step mutant in a heterogeneous population using standard inoculum of 10^5 CFU/ml as recommended by CLSI.

Yuzhi Dong, et al. AAC, July 1999, p. 1756–1758
Blondeau & Missaghi. Expert Opin. Pharmacother. 2004, 5 (5): 1117-1152
AAC, Feb. 2001, p. 433–438

Mutant Prevention Concentration

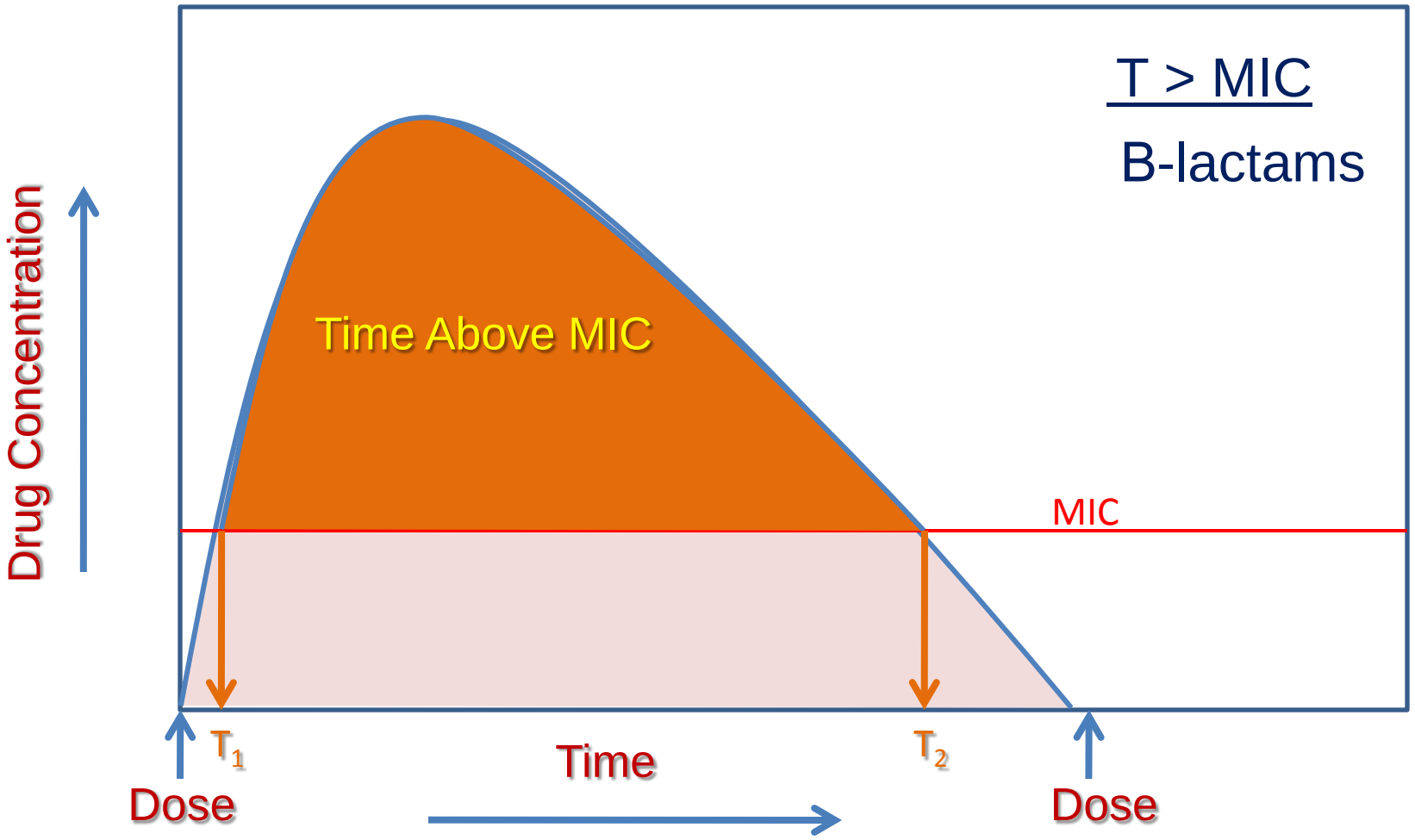
- Dual targeting fluoroquinolone e.g. Gemifloxacin and moxifloxacin have less potential to select out mutants

- Based on their potential for restricting the selection of resistant mutants, the five fluoroquinolones, in descending order, were found to be *Gemifloxacin* > moxifloxacin > trovafloxacin > gatifloxacin > grepafloxacin > levofloxacin

Yuzhi Dong, et al. AAC, July 1999, p. 1756–1758
AAC, Feb. 2001, p. 433–438
Blondeau & Missaghi. Expert Opin. Pharmacother. 2004, 5 (5): 1117-1152
AAC, Apr. 2007, p. 1315–1320

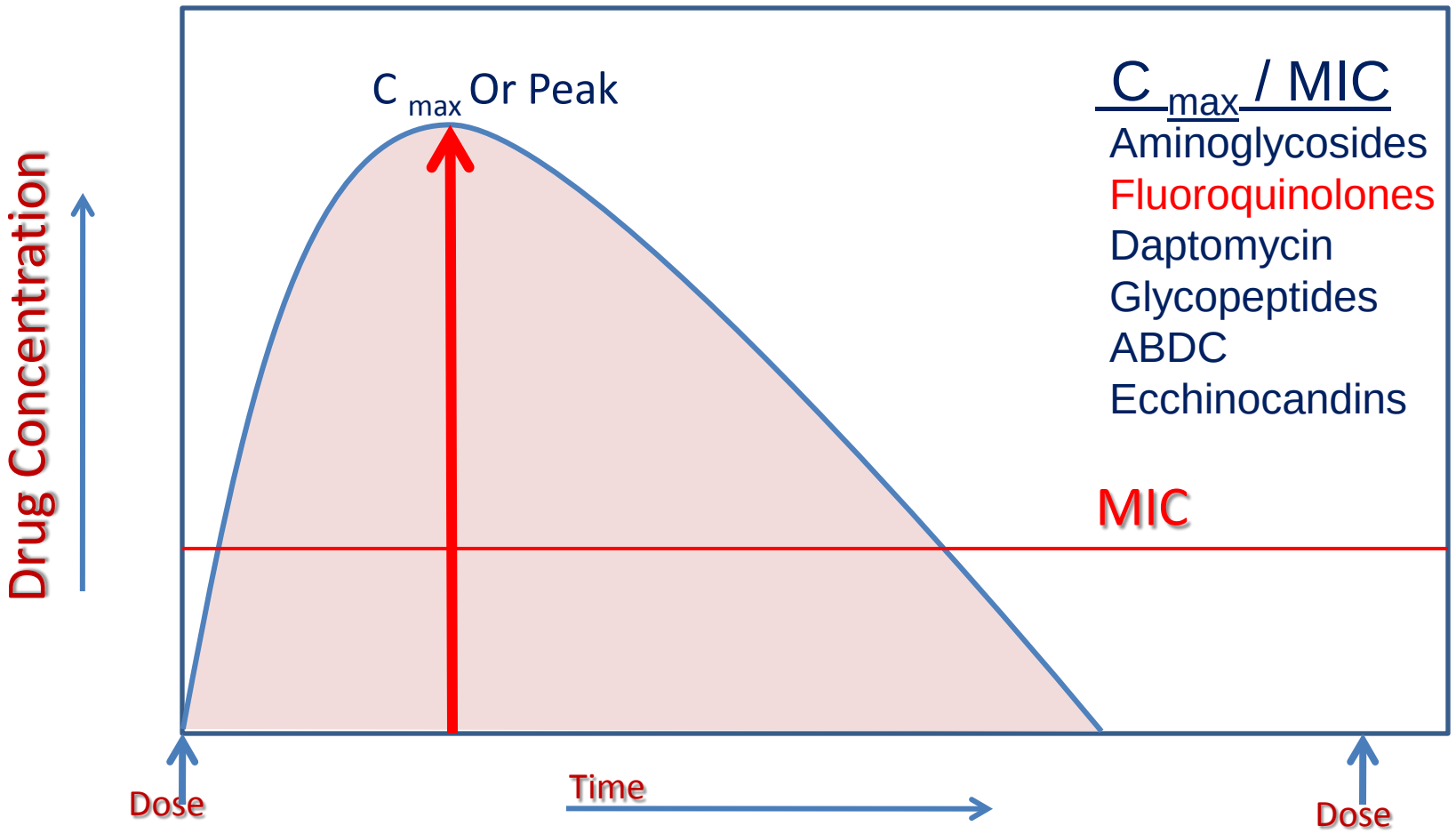
Quinolones and Pharmacodynamics/Pharmacokinetics

PK/PD: Time Dependent Killing



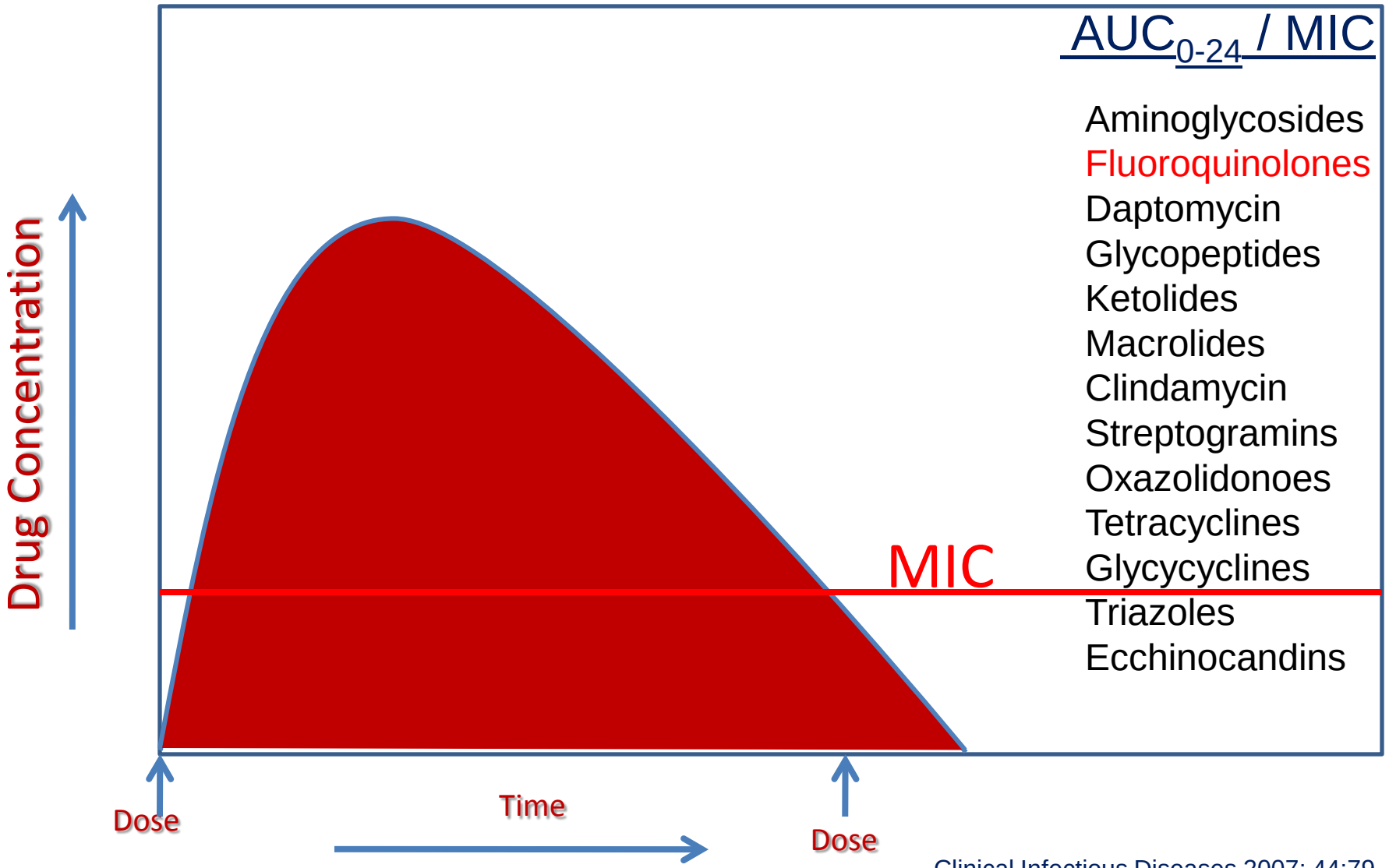
Clinical Infectious Diseases 2007; 44:79–86

PK/PD: Concentration Dependent Killing



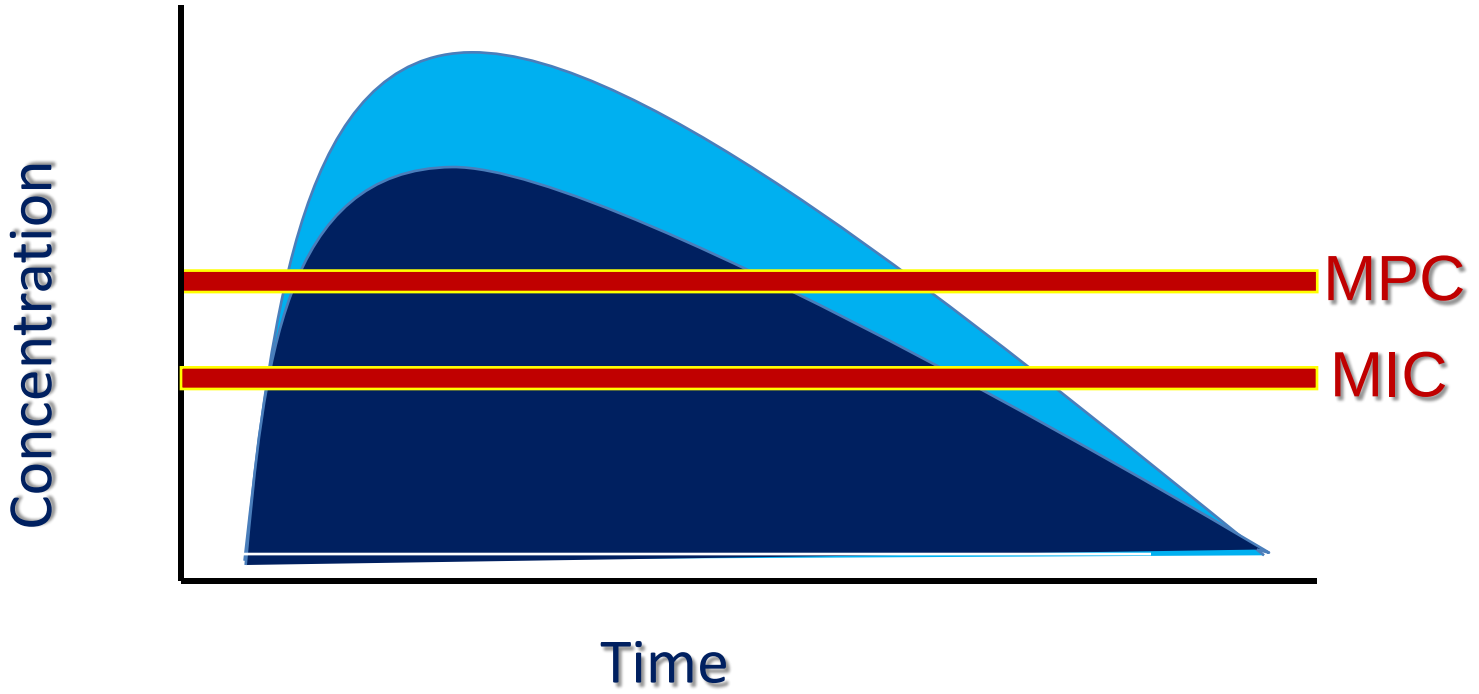
Clinical Infectious Diseases 2007; 44:79–86

PK/PD: Exposure Dependent Killing



Clinical Infectious Diseases 2007; 44:79–86

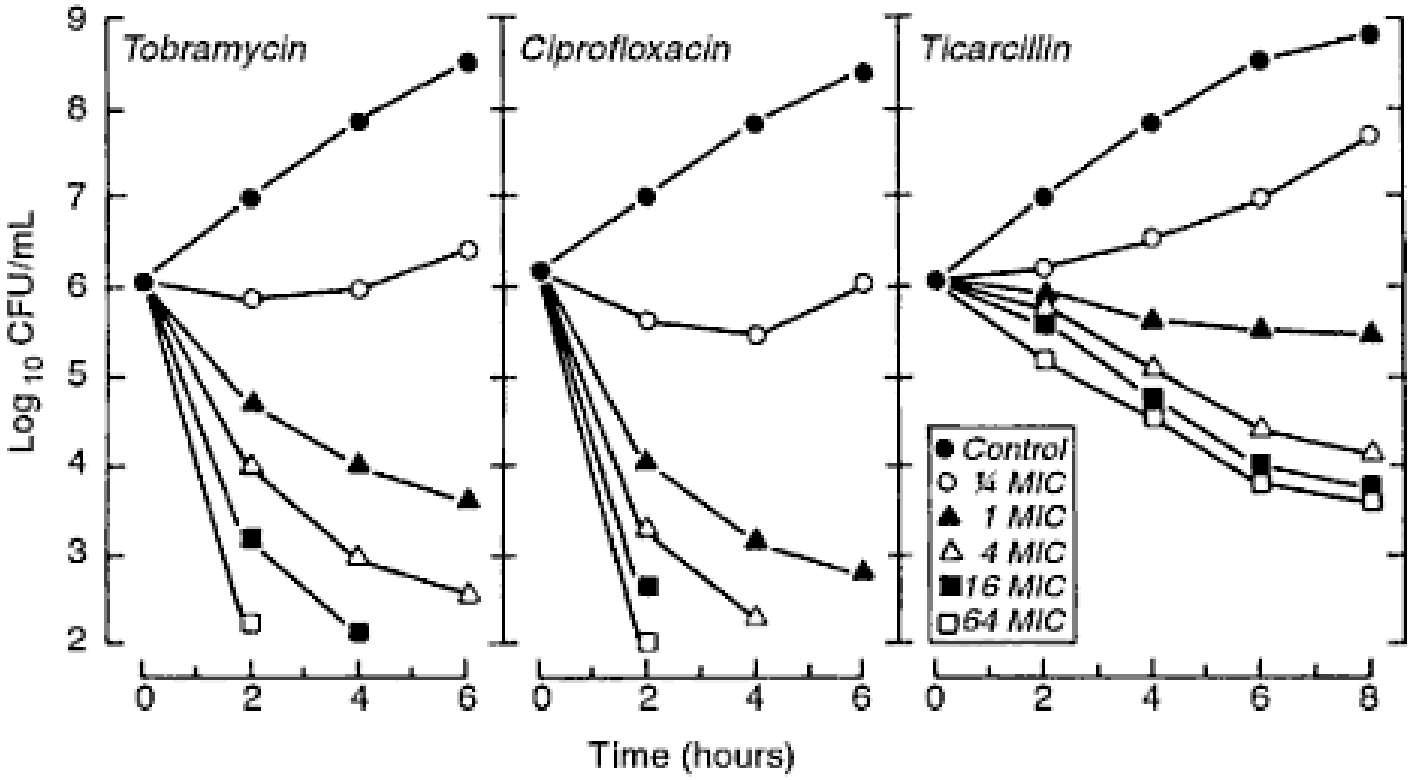
Desired AUC_{24}/MIC and $fAUC_{24}$/MIC ratios for major pathogens are:



- Pneumococcal 30 to 50
- Gram-negative organisms 125-250
- In immunocompromised patients on intravenous therapy, a ratio of at least 100 is required

Adopted: Peter C. Appelbaum. AAC, 2010 Feb: 673–677

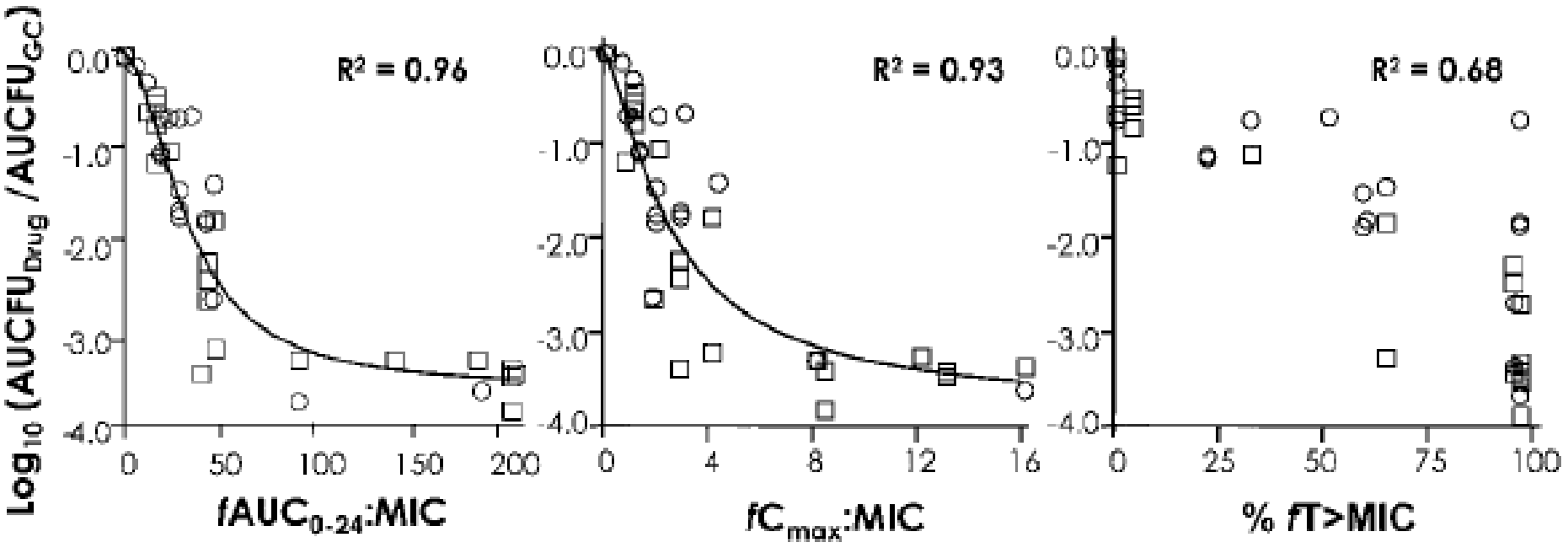
Time-kill curves of *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one-fourth to 64 times the MIC. *Abbreviations*: CFU; colony-forming units; MIC, minimum inhibitory concentration.



B-Lactam, poor killing with increased concentrations

Clinical Infectious Diseases 2007; 44:79–86
Clinical Infectious Diseases 2001; 33(Suppl 3):S233–7
W. Craig Clinical Infectious Diseases 1998;26:1–12

Different Relationships for gatifloxacin between above Parameters for 2 strains of Salmonella enterica serotype Typhi with differing MIC values and changes in bacterial density

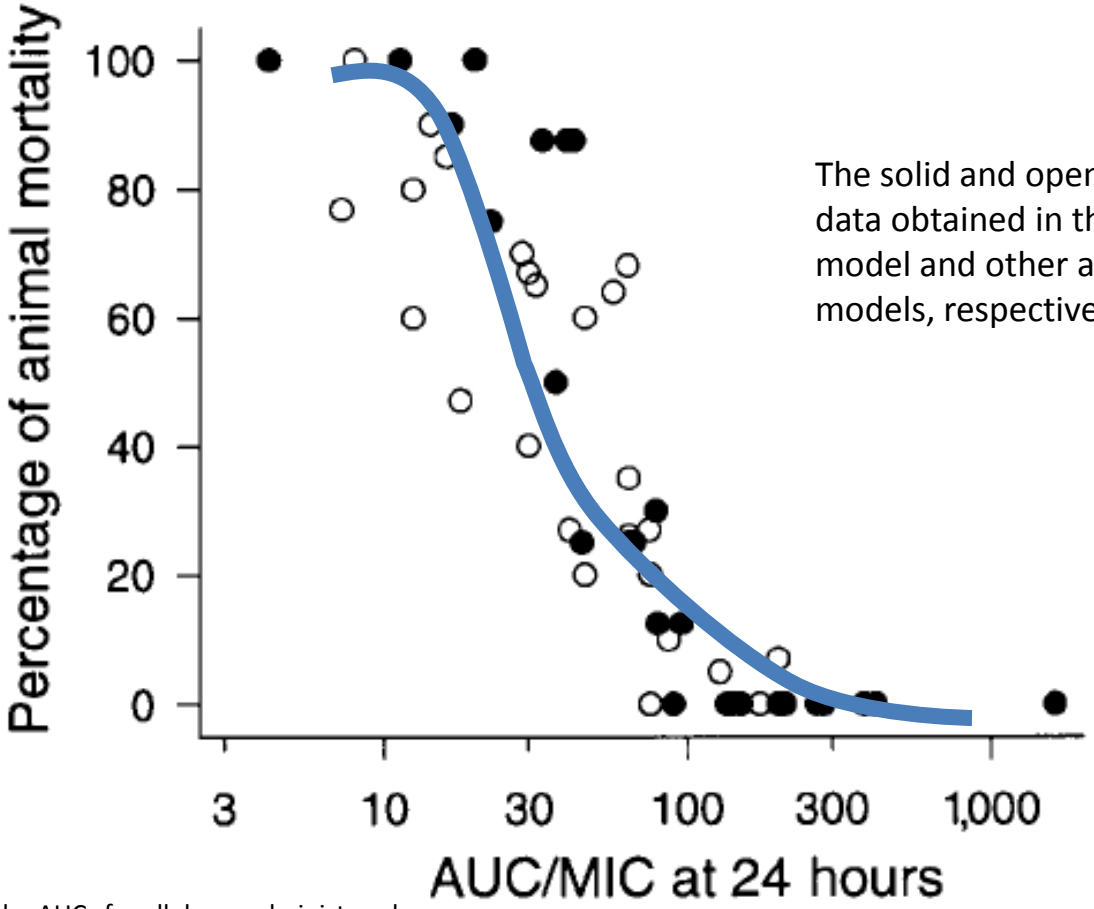


- a susceptible strain with a GyrA mutation (Asp87rAsn) and a gatifloxacin MIC of 0.5 mg/mL
- a resistant strain with GyrA (Ser83rTry; Asp87rGly) and ParC (Thr57rSer; Ser80rIle) mutations and a gatifloxacin MIC of 4 mg/mL.

GC, growth control. AUCFU, area under the colony-forming unit time curve

Clinical Infectious Diseases 2007; 44:79–86

Relationship between the 24-hour AUC/MIC ratio and survival among animal models infected with a variety of gram-positive and gram-negative pathogens

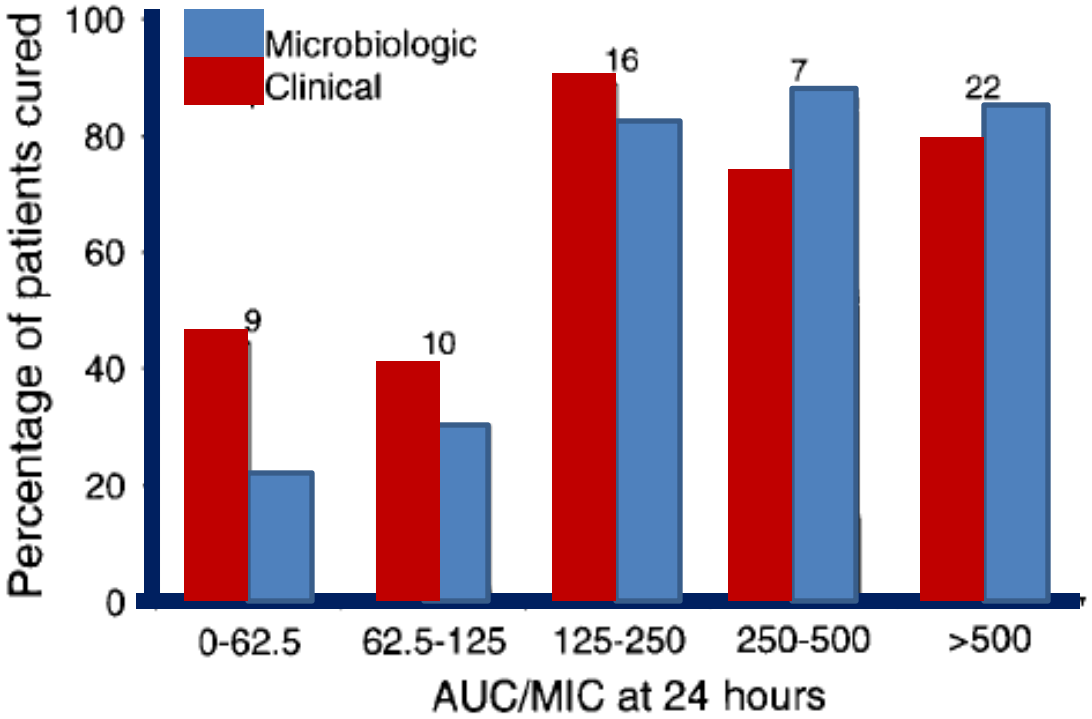


The solid and open circles represent data obtained in the thigh-infection model and other animal models, respectively

The 24-hour AUC/MIC is the sum of the AUCs for all doses administered every 24 hours divided by the MIC

W. Craig Clinical Infectious Diseases 1998;26:1–12

Relationship between the 24-hour AUC/MIC ratio and the ME and CE of Ciprofloxacin in 64 patients with serious bacterial infections.

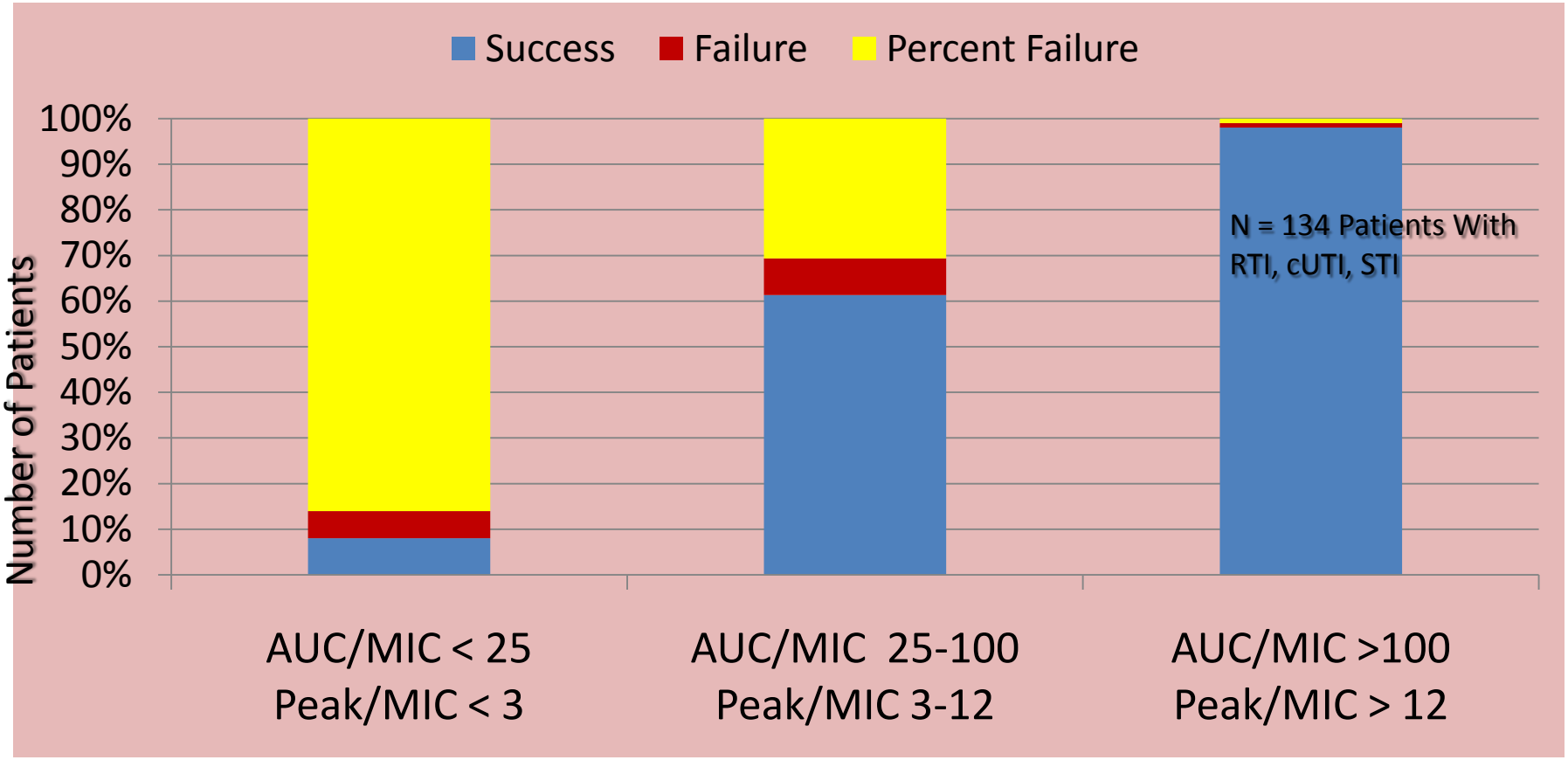


Number on column tops are total of 64 patients

The 24-hour AUC/MIC is the sum of the AUCs for all doses administered every 24 hours divided by the MIC

W. Craig Clinical Infectious Diseases 1998;26:1–12

Correlation of PK/PD parameters in patients treated with 500 mg of levofloxacin for 5-14 Days

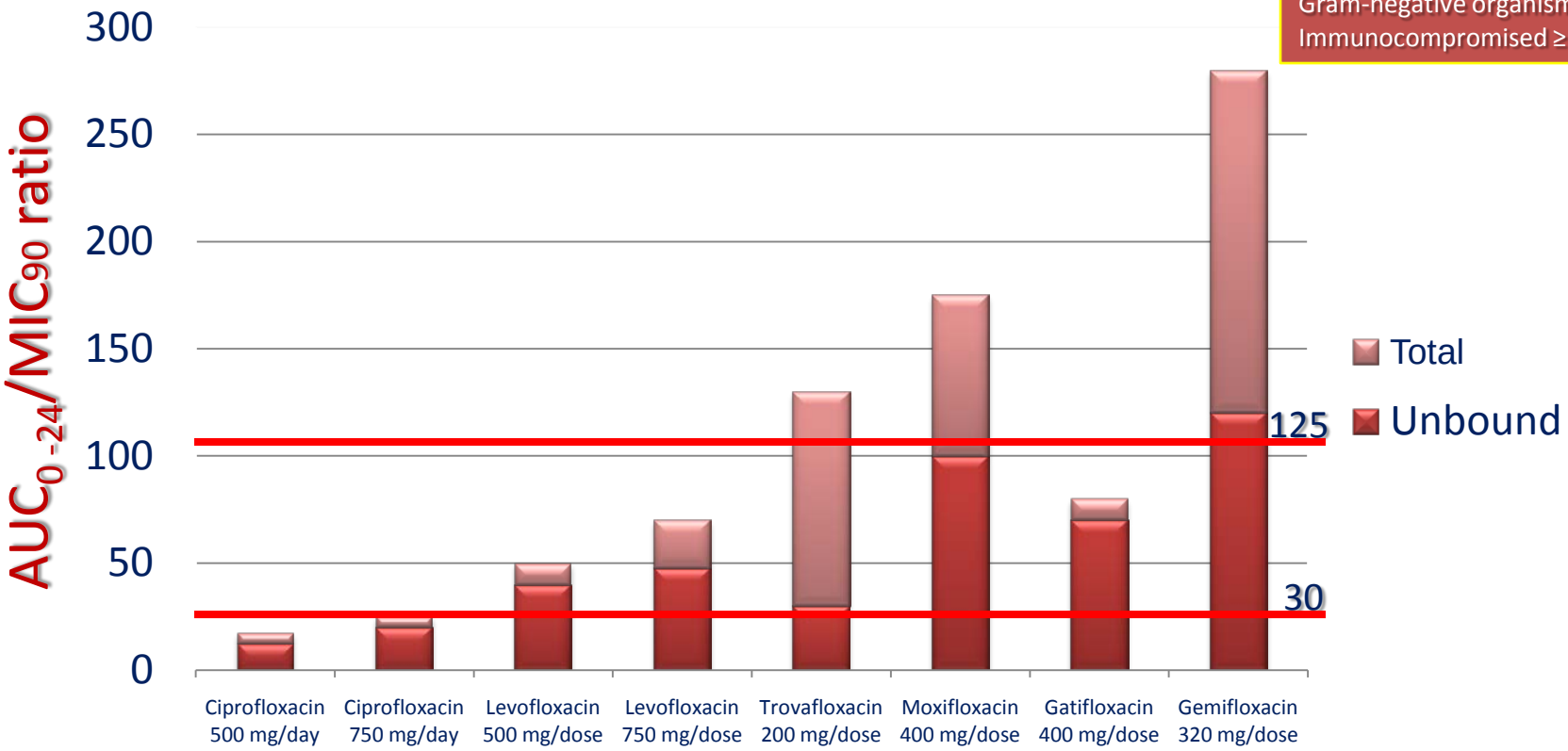


Jacobs MR. Clin Micobiol infec . 2001 November: l7(11)

MPC, AUC/MIC$_{90}$ Concept of *S. pneumoniae*

The exact role of protein binding in calculation
of the above number is also a matter of discussion

Pneumococcal 30 - 50
Gram-negative organisms 125-250
Immunocompromised ≥ 100



AAC, Feb. 2010, p. 673–677
Christopher R. Frei, et al. Pharmacotherapy. 2005;25(9):1161-1167:
Jacobs MR. Clin Micobiol infec . Vol 7, Num 11, November 2001

Potential for Resistance Evolution

RFQ Resistance in S. pneumoniae: AUIC (AUC /MIC) Ratio and Resistance Development with Gatifloxacin, Gemifloxacin, Levofloxacin, and Moxifloxacin

- Simulation model, $10^{8.5}$ to 10^{9} log10 CFU/ml
- S. pneumonia ATCC 49619, and BSP2443
- Strains have no mutations in the (QRDRs) of parC, parE, gyrA, and gyrB and no efflux
- Antimicrobial were infused to simulate target f AUC/MIC
- Protein binding (manufacturer guidelines); 20% for gatifloxacin, 60% for gemifloxacin, 30% for levofloxacin and 40% for moxifloxacin
- Objective: Head-to-head comparison of resistance development potentials between the four respiratory fluoroquinolone

QRDR: quinolone resistance-determining regions

Michael J, Ryback .AAC, 2007 Apr: 1315–1320

Time-kill assessment and resistance development at fAUC/MIC of Selected quinolones versus WT S. pneumoniae (BSP2443 and ATCC 49619). Each graph represents in vitro model results at the highest simulated fAUC/MIC for each organism where resistance development occurred

Michael J, Ryback .AAC. Apr. 2007, p. 1315–1320

Conclusion (*f AUC/MIC*)

- Clinical doses of gatifloxacin, gemifloxacin, and moxifloxacin exceed the *f AUC/MIC* resistance breakpoint against wild-type *S. neumoniae*
- With regard to the prevention of resistance, moxifloxacin = gemifloxacin > levofloxacin.
- These differences possibly related to structural variations within the cslass.
- Using a fluoroquinolone regimen that exceeds the PK/PD breakpoint for resistance development may decrease the emergence of resistance in patients with *S. pneumoniae infections.*

Michael J, Ryback .AAC. Apr. 2007, p. 1315–1320

In vitro susceptibilities of S. pneumoniae strains to Some Quinolones and mutations identified in the QRDRs (parC, gyrA, and gyrB)

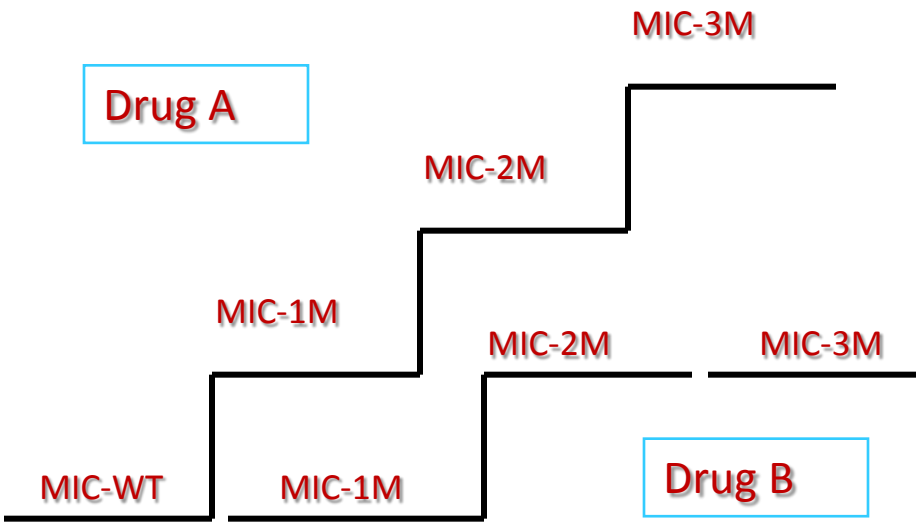
	Strain	Concn (mg liter^{-1})				
		MIC			MPC	
		CIP	LVX	MFX	LVX	MFX
None	16089	0.5	0.5	0.125	0.5	0.125
Efflux	MS1A	2	1	0.25	2	0.25
Par C	MS2A	8	1.75	0.25	28	4
Par C	MR3B4	10	2	0.25	32	4
Par C	M16	64	8	0.5	32	2
Gyr A	Gyr-1207	6	8	1.5	16	3
Par C + Gyr A	MQ3A	>64	16	4	64	4

CIP: Ciprofloxacin
LVX: Levofloxacin
MFX: Moxifloxacin
QRDR: Quinolone resistance determining region

AAC, May 2004, p. 1699–1707

The Evolution of Resistance to Quinolones

Dichotomous resistance among the quinolones



A as selected by quinolone A is shown (left), with each successive mutation causing diminished susceptibility to quinolone A. Because the mechanisms responsible for the mutations in the first-step (1M) and third-step (3M) mutants do not affect susceptibility to quinolone B, a pattern of dichotomous resistance emerges. Only the mutation in the second-step (2M) mutant reduces susceptibility to quinolone B.

Clinical Studies

Severe pneumococcal pneumonia: impact of new quinolones on prognosis

- Guidelines propose β-lactam + a quinolone **or** a macrolide for severe CAP

- To evaluate new versus old RFQ combined with β-lactam

- Retrospective, consecutive patients admitted in ICU
- January 1996 - January 2009

- Severe CAP (PSI ≥ 4)
- All were PCN-S pneumococci, treated with a β-lactam + RFQ

- Doses and Antiinfectives: Amoxicillin > 50 mg/kg/d: Cefotaxime > 50 mg/kg/d: Ceftriaxone > 20 mg/kg/d: Piperacillin > 200 mg/kg/d: Ofloxacin = 200 mg/12 h: Ciprofloxacin = 400 mg/12 h; Levofloxacin = 500 mg/12 h

Olive et al. BMC Infectious Diseases 2011, 11:66

Severe pneumococcal pneumonia: impact of new quinolones on prognosis

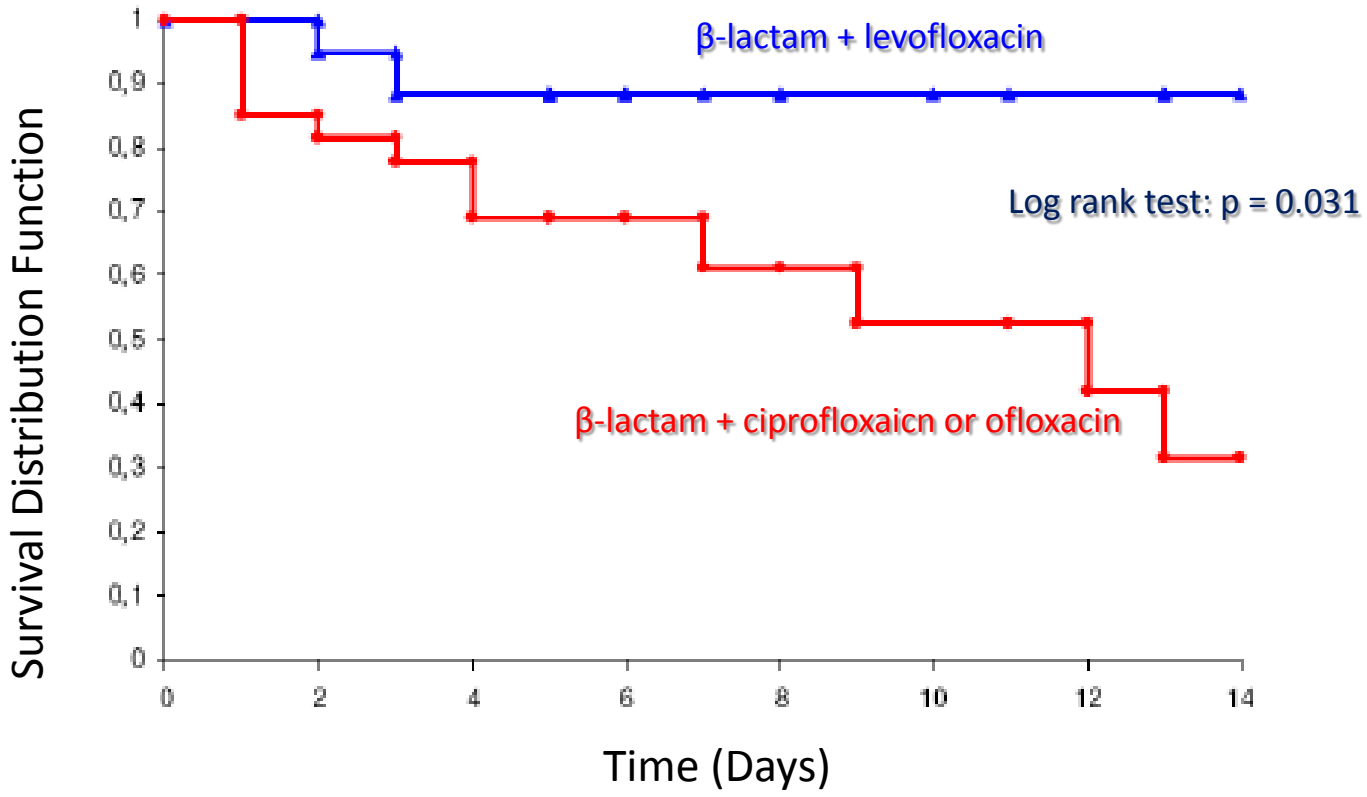
- N = 70
  - n = 38 β-lactam combined with ofloxacin or ciprofloxacin
  - n = 32 β-lactam combined with levofloxacin

- 26 (37.1%) patients died in the ICU

- Independent factors associated with mortality in ICU were:
  - septic shock on ICU admission (AOR = 10.6; 95% CI 2.87-39.3; p = 0.0004)
  - age > 70 yrs. (AOR = 4.88; 95% CI 1.41-16.9; p = 0.01)
  - initial treatment with a β-lactam with ofloxacin or ciprofloxacin (AOR = 4.1; 95% CI 1.13-15.13; p = 0.03)

Olive et al. BMC Infectious Diseases 2011, 11:66

15-day survival curves in patients treated with β-lactam combined with levofloxacin versus β-lactam combined with ofloxacin or ciprofloxacin



Adopted: Olive et al. BMC Infectious Diseases 2011, 11:66

ofloxacin or ciprofloxacin

levofloxacin

Table 2 Therapeutics data and evolution during ICU stay of patients with severe pneumococcal pneumonia*

Characteristics	Overall population n = 70	Group A n = 38	Group B n = 32	P
Cephalosporin in initial treatment	46 (65.7%)	20 (52.6%)	26 (81.3%)	0.01
Use of drotrecogin alpha	4 (5.7%)	0	4 (12.5%)	0.02
Intensive insulin therapy	30 (42.8%)	4 (10.5%)	26 (81.2%)	<0.0001
Use of hydrocortisone	24 (34.3%)	6 (15.7%)	18 (56.3%)	0.0004
Haemo				
Body t				
SOFA				
Improv				
Body t				
SOFA				
Body t				
SOFA				
Sepsis-				
HA-LRT superinfections				
ICU-related complications	12 (17.1%)	8 (21.0%)	4 (12.5%)	0.34
Duration of MV (days)	11.3 ± 14.3	11.2 ± 15.6	11.5 ± 12.9	0.93
Duration of vasopressor use (days)	3.5 ± 4.8	3.6 ± 5.6	3.3 ± 3.9	0.80
LOS in ICU (days)	14.6 ± 16.3	14.5 ± 19.0	14.6 ± 12.6	0.97
Mortality on D-15	14 (20%)	12 (31.6%)	2 (6.3%)	0.02
Mortality in ICU	26 (37.1%)	17 (44.8%)	9 (28.1%)	0.15

*Data are presented as No. (%) or mean ± SD.

MV: mechanical ventilation; SAPS: simplified acute physiology score; LOD score: logistic organ dysfunction score: SOFA: Sepsis-related Organ Failure Assessment score; PSI: Pneumonia Severity Index; HA-LRT superinfections: hospital-acquired lower respiratory tract superinfections; LOS = length of stay.

Conclusion: Results suggest that, when combined to a β-lactam, Levofloxacin is associated with lower mortality than Ofloxacin or Ciprofloxacin in severe pneumococcal CAP

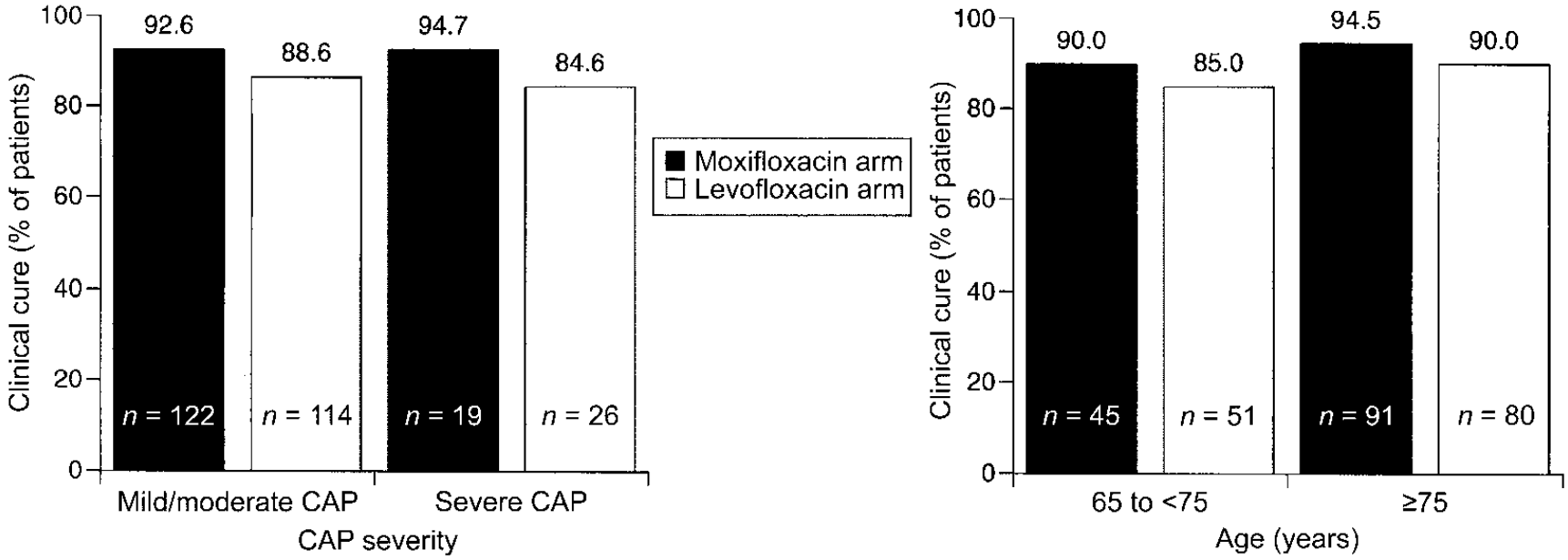
Olive et al. BMC Infectious Diseases 2011, 11:66

CAP Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus That of Levofloxacin Therapy

- Age, 65 years or older hospitalized patients with CAP
- Efficacy and safety of moxifloxacin vs. levofloxacin for the treatment of CAP
- Intravenous/oral moxifloxacin (400 mg daily) or intravenous/oral levofloxacin (500 mg daily) for 7–14 days
- PPP; 141 in the moxifloxacin, and 140 in the levofloxacin group
- test-of-cure; the primary efficacy end point was between days 5 - 21 after completion of therapy

Clinical Infectious Diseases 2006; 42:73–81

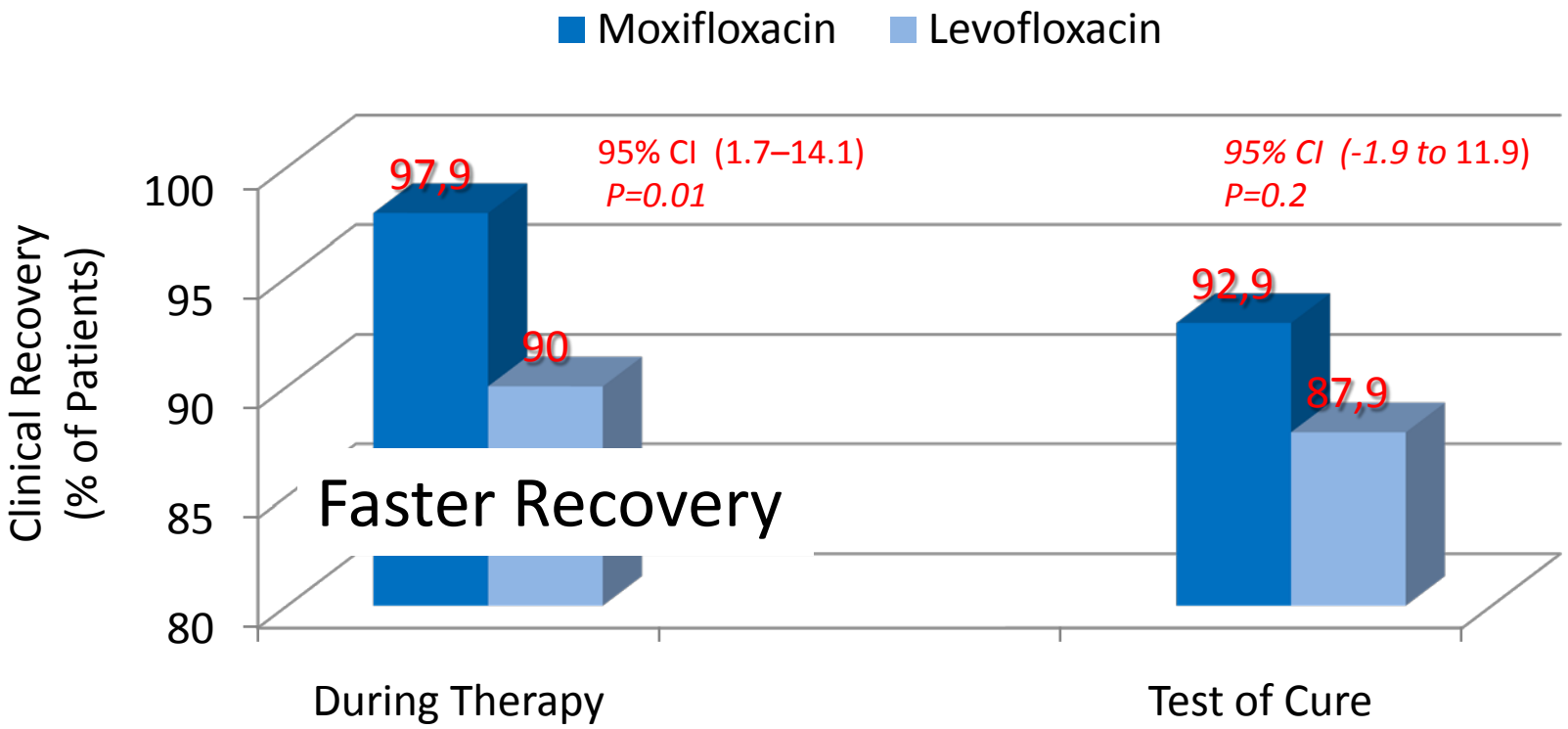
Clinical cure rates at the test-of-cure visit for the clinically valid population, stratified by CAP severity and age



No Statistical significant Difference in Both Sides, tested by P value and C.I.

Clinical Infectious Diseases 2006; 42:73–81

Clinical outcomes for the clinically valid population



Clinical recovery during therapy (between days 3 and 5 after the start of treatment)

Clinical cure at the test-of-cure visit i.e., primary efficacy outcome)

Clinical Infectious Diseases 2006; 42:73–81

Efficacy of short-course antibiotic regimens for CAP: a meta-analysis

PURPOSE:

There is little consensus on the appropriate duration of antibiotic treatment for CAP.

METHODS:

Searched in MEDLINE, Embase, and CENTRAL
1980 - 2006
Studies included RCT that compared
short-course **(≤ 7)** versus extended-course **(>7 days)**
antibiotic **monotherapy** for CAP in adults

The primary outcome measure was failure to achieve clinical improvement.

Li JZ, Winston LG, Moore DH, Bent S. Am J Med. 2007 Sep;120(9):783-90.

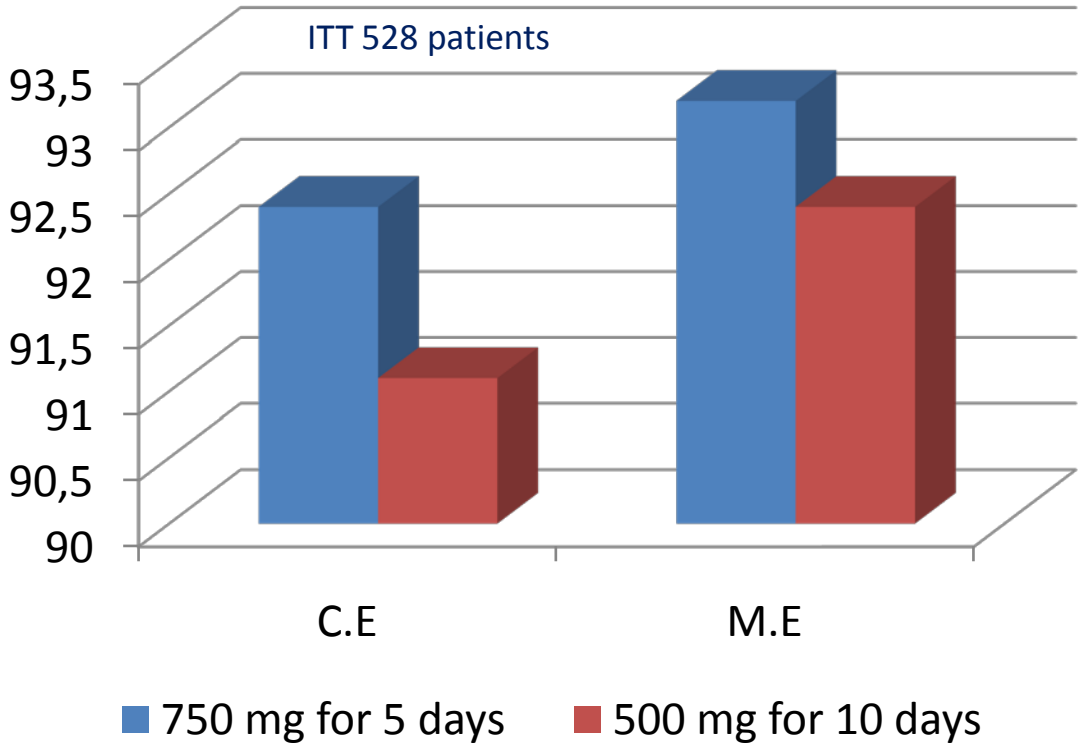
Efficacy of short-course antibiotic regimens for CAP: a meta-analysis

RESULTS	15 RCT , N = 2796 patients
≤ 7 >7	azithromycin (n=10), ß-lactams (n=2), fluoroquinolones (n=2), ketolides (n=1), 3 studies utilized the same antibiotic whereas 9 involved an antibiotic of the same class.
Clinical failure Risk of mortality Bacteriologic eradication	No difference (0.89, 95% CI, 0.78-1.02) No differences (0.81, 95% CI, 0.46-1.43) No difference (1.11, 95% CI, 0.76-1.62)
Subgroup analyses: a trend toward favorable clinical efficacy for the short-course regimens in all antibiotic classes (range of relative risk, 0.88-0.94)	
Conclusion	Adults with mild to moderate CAP can be safely and effectively treated with an antibiotic regimen of ≤7 days Less antimicrobial exposure May be less resistance Less cost Better patinets' adherence and tolerability.

Li JZ, Winston LG, Moore DH, Bent S. Am J Med. 2007 Sep;120(9):783-90.

High-Dose, Short-Course Levofloxacin for the treatment of mild to severe CAP

A multicenter, randomized, double-blind investigation



These data demonstrate that 750 mg of levofloxacin per day for 5 days is at least as effective as 500 mg per day for 10 days for treatment of mild-to-severe CAP.

Clinical Infectious Diseases 2003; 37:752–60

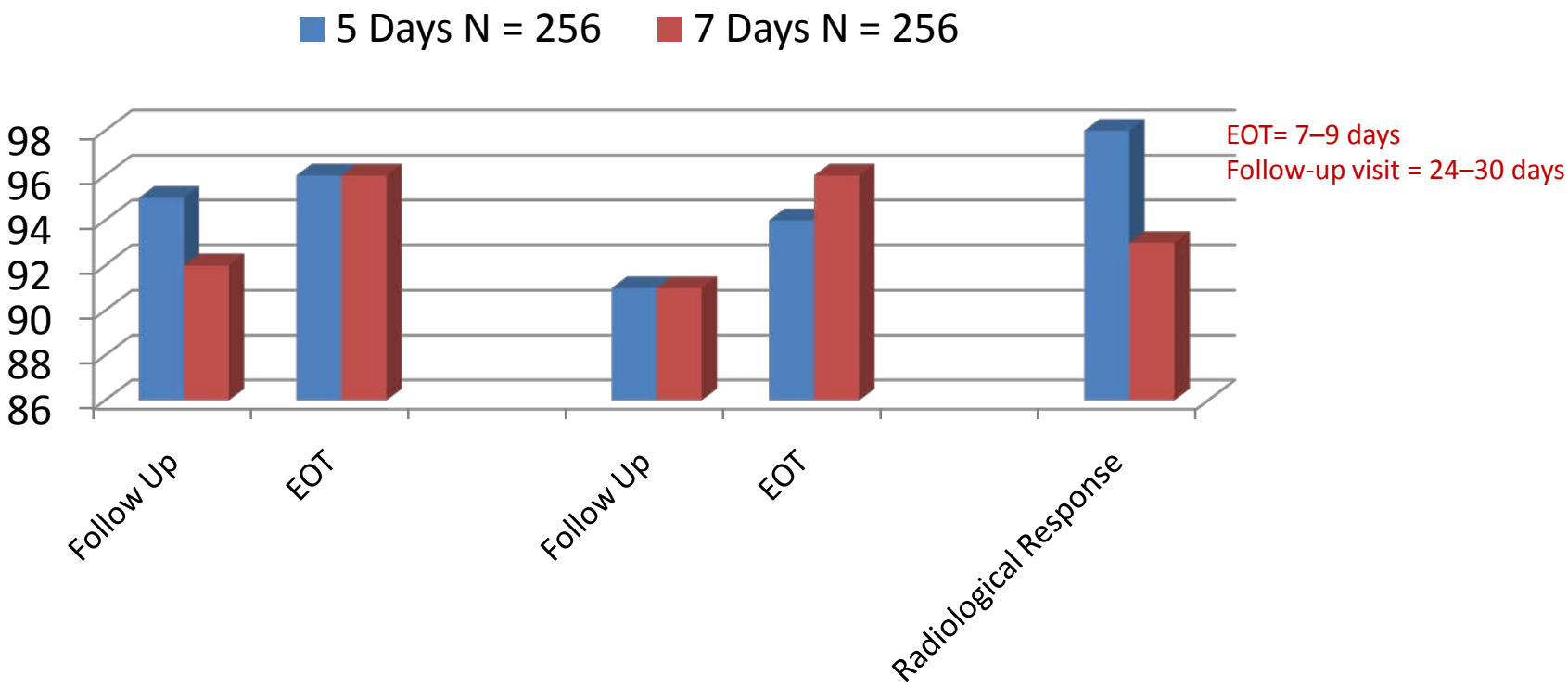
Gemifloxacin QD for 5 days versus 7 days for the treatment of CAP: a randomized, multicentre, double-blind study

- Objectives: Short-course therapy has been advocated for the treatment of CAP
- The efficacy and safety of 5 and 7 day courses of gemifloxacin for outpatient treatment of mild–moderate CAP were compared.

- Patients and methods:
  - A multicentre, double-blind, parallel group RCT
  - 320 mg of oral gemifloxacin once daily for 5 or 7 days.
  - Over 95% of all patients in each cohort had a Fine score of III
  - The primary efficacy endpoint was **clinical cure** at follow-up (days 24–30)
  - Secondary outcomes were **clinical and bacteriological responses** at the EOT (days 7–9) and bacteriological and **radiological responses** at follow-up
  - Adverse events (AEs) were also monitored.

Thomas M. File, Jr, Lionel A. Mandell, et al. JAC (March, 2007) 60, 1-9

Gemifloxacin once daily for 5 days versus 7 days for the treatment of CAP: PPS



Clinical Responses

Bacteriological Responses

	5 days	7 days
Discontinuation rates	1.2%	2%
Rash (P = 0.04).	0.4%	2.8%

Conclusions: Gemifloxacin once daily for 5 days is not inferior to 7 days in the PPP with respect to clinical, bacteriological and radiological efficacy

Thomas M. File, Jr, Lionel A. Mandell, et al. JAC (March, 2007) 60, 1–9

Gemifloxacin for the treatment of CAP and AECB: a meta-analysis of RCT

- To evaluate the comparative effectiveness and safety of gemifloxacin for the treatment of patients with CAP
- A meta-analysis of RCTs comparing gemifloxacin with other approved antibiotics
- PubMed, EMBASE, Chinese Biomedical Literature Database and the Cochrane Central Register of Controlled Trials were searched, with no language restrictions.
- Primary outcome measures:
  (1) all-cause mortality
  (2) treatment success in ITT and CE populations
- N_{RCT} = 10 comparing gemifloxacin with other quinolones (in 5 RCTs) and β-lactams and/or macrolides (in 5 RCTs), $N_{patients}$ = 3940 patients

LIU You-ning, Falagas E. Matthew, et al. Chinese Medical Journal 2012;125(4):687-695

Main characteristics of randomized controlled trials in the meta-analysis and outcome

Studies	Publication year	Study design	Population	Regimen 1	Regimen 2	Additional antibiotics	Enrolled patients (*n*)	ITT patients (*n*)	Jadad score	Clinical success (*n*/*N* (%))	
										ITT at TOCV	CE at TOCV
Yao[50]	2008	DB, RCT	Patients (22–67 years) with AECB	Oral gemifloxacin 320 mg q.d. for 14 days	Oral levofloxacin 200 mg b.i.d. for 14 days	Not allowed	31 vs. 31	31 vs. 31	3	29/31 (93.5) vs. 26/31 (83.9)	NA
Shi et al[47]	2007	SB, RCT	Patients (18–65 years) with CAP and patients (18–70 years) with AECB	Oral gemifloxacin 320 mg q.d. 7–14 days for CAP and 5 days for AECB	Oral levofloxacin 200 mg b.i.d. 7–14 days for CAP and 7 days for AECB	Not allowed	17 vs. 16	17 vs. 16	3	17/17 (100) vs. 15/16 (93.8)	17/17 (100) vs 15/15 (100)
Sethi et al[46]	2004	MC, DB, RCT	Patients (>40 years) with AECB	Oral gemifloxacin 320 mg q.d. for 5 days	Oral levofloxacin 500 mg q.d. for 7 days	Not allowed	400	182 vs. 178	4	155/182 (85.2) vs. 139/178 (78.1)	134/152 (88.2) vs 126/148 (85.1)
File et al[43]	2001	MC, DB, RCT	Adult patients with CAP	Oral gemifloxacin 320 mg q.d. for 7 days	Oral trovafloxacin 200 mg q.d. for 7 days	Not allowed	573	290 vs. 281	3	254/290 (87.6) vs. 228/281 (81.1)	203/216 (94.0) vs. 186/207 (89.9)
Ball et al[41]	2001	MC, DB, RCT	Patients (≥40 years) with AECB	Oral gemifloxacin 320 mg q.d. for 5 days	Oral trovafloxacin 200 mg q.d. for 5 days	Not allowed	303 vs. 314	302 vs. 314	3	270/302 (89.4) vs. 261/314 (83.1)	249/272 (91.5) vs. 241/275 (87.6)

TOCV: test-of-cure visit. CE: clinical efficacy. ITT: intent to treat. NA: not available. RCT: randomized controlled trial MC: multicenter. DB: double blind. SB: single blinded

Adopted: LIU You-ning, Falagas E. Matthew, et al. Chinese Medical Journal 2012;125(4):687-695

Clinical success in ITT patients

A

Study or subgroup	Gemifloxacin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI	Year
1.1.1 other quinolones							
File 2001	254	290	228	281	15.8%	1.64 [1.04, 2.60]	2001
Ball 2001	270	302	261	314	14.9%	1.71 [1.07, 2.74]	2001
Sethi 2004	155	182	139	178	11.5%	1.61 [0.94, 2.77]	2004
Shi 2007	17	17	15	16	0.2%	3.39 [0.13, 89.37]	2007
Yao 2008	29	31	26	31	0.9%	2.79 [0.50, 15.62]	2008
Subtotal (95% CI)		**822**		**820**	**43.4%**	**1.69 [1.28, 2.23]**	
Total events	725		669				

Heterogeneity: Chi² = 0.55, df = 4 (P = 0.97); I^2 = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)

Odds ratio M-H, Fixed, 95% CI

Analysis in subgroup of different antibiotics: gemifloxacin compared with other quinolones

Study or subgroup	Gemifloxacin Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI
1.3.1 CAP						
File 2001	254	290	228	281	15.8%	1.64 [1.04, 2.60]
Leophonte 2004	129	167	121	153	15.8%	0.90 [0.53, 1.53]
Sethi 2004	155	182	139	178	11.5%	1.61 [0.94, 2.77]
Shi 2007	7	7	6	7	0.2%	3.46 [0.12, 100.51]
Subtotal (95% CI)		**646**		**619**	**43.4%**	**1.37 [1.03, 1.83]**
Total events	545		494			

Heterogeneity: Chi² = 3.65, df = 3 (P = 0.30); I^2 = 18%
Test for overall effect: Z = 2.14 (P = 0.03)

Odds ratio M-H, Fixed, 95% CI

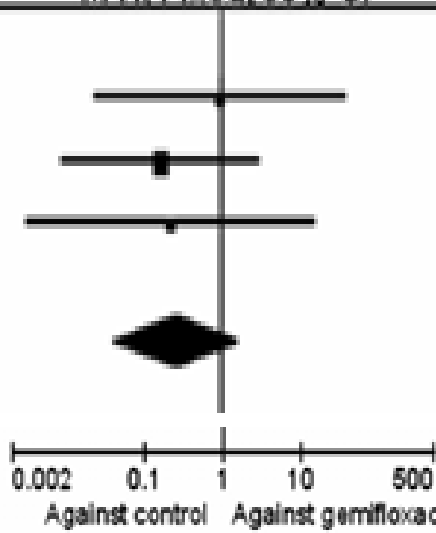
0.1 0.2 0.5 1 2 5 10
Favours control Favours gemifloxacin

Analysis in subgroup of different diseases: CAP

LIU You-ning, Falagas E. Matthew, et al. Chinese Medical Journal 2012;125(4):687-695

All-cause mortality

Study or subgroup	Gemifloxacin Events	Total	control Events	Total	Weight	Odds ratio M-H, Fixed, 95% *CI*	Year	Odds ratio M-H, Fixed, 95% *CI*
3.7.1 other quinolones								
File 2001	1	290	1	281	5.7%	0.97 [0.06, 15.57]	2001	
Ball 2001	1	302	4	314	22.0%	0.26 [0.03, 2.32]	2001	
Sethi 2004	0	182	1	178	8.5%	0.32 [0.01, 8.01]	2004	
Shi 2007	0	17	0	16		Not estimable	2007	
Subtotal (95% *CI*)		**791**		**789**	**36.1%**	**0.39 [0.09, 1.67]**		



Adopted: LIU You-ning, Falagas E. Matthew, et al. Chinese Medical Journal 2012;125(4):687-695

Gemifloxacin for the treatment of CAP and AECB: a meta-analysis of RCT

Conclusions

- Overall, the treatment success was higher for gemifloxacin when compared with other antibiotics
  - ITT- OR 1.39, 95% C.I 1.15–1.68
  - CE-OR 1.33 , 95% C.I 1.02–1.73
- No significant difference in microbiological success
- No significant difference in all-cause mortality
- The total drug related AE were:
  - similar for gemifloxacin when compared with other quinolones (0.89, 0.56–1.41)
  - lower when compared with β-lactams and/or macrolides (0.71, 0.57–0.89)
  - gemifloxacin was associated with less cases of diarrhoea (0.66, 0.48–0.91)
  - more rashes compared with other antibiotics (2.36, 1.18–4.74)
- The available evidence suggests that gemifloxacin 320 mg oral daily is equivalent or superior to other approved antibiotics in effectiveness and safety for CAP

LIU You-ning, Falagas E. Matthew, et al. Chinese Medical Journal 2012;125(4):687-695

Hospital visits and costs following outpatient treatment of CAP with levofloxacin or moxifloxacin

Outpatient

- To differentiate between outpatient treatment with levofloxacin and moxifloxacin.
- Retrospective 2004 – 2007
- Treatment with levofloxacin or moxifloxacin
- Subsequent 30-day risk of pneumonia-related hospital visits and 30-day health care costs
- Results:
- N(15,472 levofloxacin and 6474 moxifloxacin)
- N = 6352 matched pairs
- levofloxacin treatment was associated with a:
  - 35% reduction in the odds of pneumonia-related hospital visits (odds ratio = 0.65, $P = 0.004$)
  - lower per-patient costs for pneumonia-related hospital visits ($102 vs. $210, $P = 0.001$)
  - lower pneumonia-related total costs ($363 vs. $491, $P < 0.001$)
  - lower total costs ($1308 vs. $1446, $P < 0.001$) vs. moxifloxacin over the 30-day observation period.

James E. Signorovitch et al. Current Medical Research and Opinion, 2010 February: 26(2); 355-363

A comparison of levofloxacin and moxifloxacin use in CAP patients in the US: focus on length of stay

Hospitalized patients:

- A retrospective study. Cohorts were matched 1:1
- N = levofloxacin = 797 750 mg I.V QD Initially treated for the first 3 days
  moxifloxacin = 797 400 mg I.V. QD
- Outcome measure: Complications and relationship of LOS and comorbidities were examined.

Results:

- patients treated with **levofloxacin had a significantly shorter mean hospital** compared with moxifloxacin (5.8 vs. 6.4 days; least squares mean difference = 0.54 days; p = 0.020)
- Hospitalization **costs were also lower for the levofloxacin** patients (least squares mean difference = US$129; p = 0.753)
- Complications; similar

Jeff Schein et al. Current Medical Research and Opinion 2008: 24(3); 895-906

Comparative Analysis of Length of Stay, Total Costs, and Treatment Success between Intravenous Moxifloxacin 400 mg and Levofloxacin 750 mg among

- Hospitalized Patients with CAP (US)
- Retrospective, Adults patients identified in the Premier Perspective comparative database

- I.V. moxifloxacin 400 mg or I.V. levofloxacin 750 mg for ≥3 days were

- Primary outcomes were LOS and costs

- Secondary outcomes included treatment consistency, which was defined as:
  1) no additional IV moxifloxacin or levofloxacin after ≥1 day off study drug
  2) no switch to another IV antibiotic
  3) no addition of another IV antibiotic

Howard Friedman, Science Direct 2009 November–December:12(8); 1135–1143
http://dx.doi.org/10.1111/j.1524-4733.2009.00576.x,

Comparative Analysis of Length of Stay, Total Costs, and Treatment Success between Intravenous Moxifloxacin 400 mg and Levofloxacin 750 mg among Hospitalized Patients with CAP

N = 7720 patients

6040 receiving moxifloxacin

= 1680 receiving levofloxacin

mean LOS (5.87 vs. 5.46 days; $P = 0.0004$) and
total costs/patient ($7302 vs. $6362; $P < 0.0001$)
(significantly greater with moxifl

costs ($6624 vs. $6473; $P = 0.476$)

Conclusions

In-hospital treatment of CAP with IV moxifloxacin 400 mg or IV levofloxacin 750 mg was associated with similar hospital LOS and costs in propensity-matched cohorts.

Treatment consistency
Moxi (propesity) = before 81.0% s
= After 82.8%

$P = 0.048$

$P = 0.002$

Treatment consistency
Levo (propensity)= before 78.9% s
= After 78%

Howard Friedman, Science Direct 2009 November–December:12(8); 1135–1143
http://dx.doi.org/10.1111/j.1524-4733.2009.00576.x,

To Wrap Up

- Penicillin- and cipro-resistant *S. pneumoniae* do not preclude using other generations RFQ
- Based on several surveillance studies RFQ resistance is low and steady so far (lowest for the 4th generation e.g. Gemifloxacin, moxifloxacin)
- *In this context, all quinolones are not equal and should not be used interchangeably

*Vincent Andriole CID 2005:41, S114 (Suppl 2)

To Wrap Up

- *Key observations have demonstrated that, not only is the level of resistance different among various quinolones, but it also is different among the various species of bacteria.
- Speed of Recovery Occurs faster with Fourth Generation Quinolones Compared with Second generation.
- Using Mortality as an end point, RFQ were the same.
- 4th generation RFQ treatment is more consistant
- Cost saving may be associated with some quinolones

Drugs, 71(6), 16 April 2011 , pp. 757-770(14
*Vincent Andriole CID 2005:41, S114 (Suppl 2)

Thank You

Discussion ?

Comments !

Questions ?

CAP Treatment Options; Are quinolones the Same ?

Tunis, Yasmine Hammat 22 -26 May 2012

Jamal Wadi Al Ramahi M.D.