Gemifloxacin; A Distinctive Quinolone or a By-passer

Jamal Wadi Al Ramahi M.D.

Schema

- Quinolones
- Epidemiology of Resistance
- Quinolones Differences in Resistant bugs
- Mechanism of Quinolones Resistance and the Difference among Them.
- PK/PD and MPC
- Quinolones and Gemifloxacin in Clinical Syndromes

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)

Bacterial Pathogens Involved in Respiratory Infections

Lower Respiratory:

Streptococcus pneumoniae

Haemophilus influenzae

Moraxella catarrhalis

Staphylococcus aureus

Major Bacterial Pathogens Associated With AECB

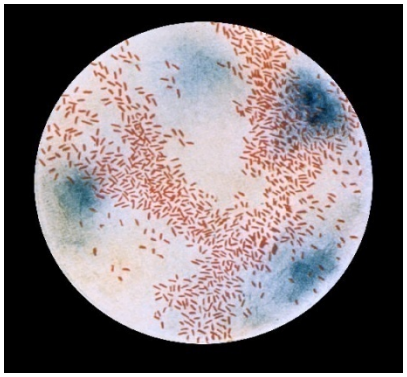
Haemophilus influenzae
Moraxella catarrhalis
Streptococcus pneumoniae --- *10-15 %*

Staphylococcus aureus
Pseudomonas aeruginosa
Haemophilus parainfluenzae
Enterobacteriaceae
} *20%*

Mycoplasma pneumoniae
Chlamydia pneumoniae
} *10%*

Adel Obaji and Sanjay Sethi. Drugs And Aging 2001;18

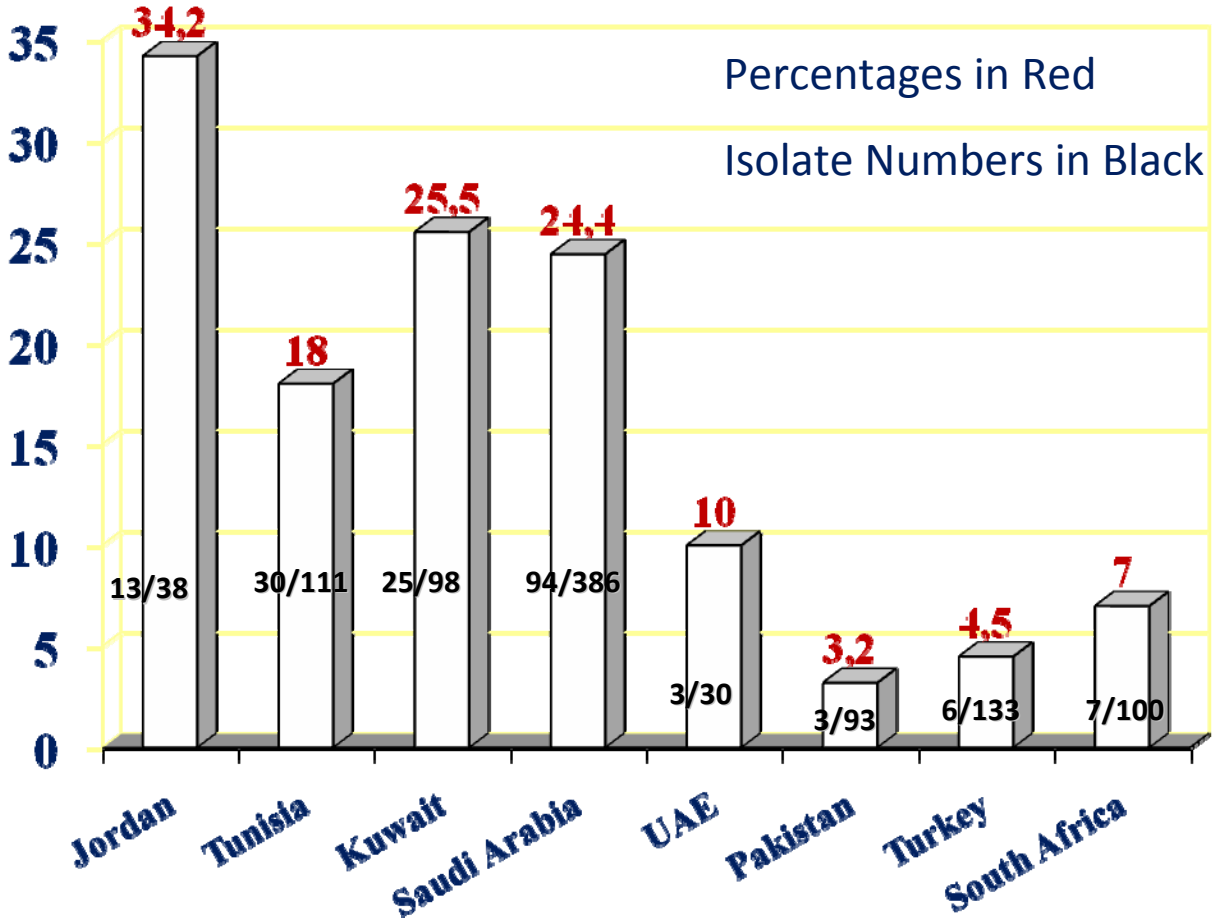
Haemophilus influenzae and β-lactamases (started after 1972)



- 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)

N = 1212

Agent	*MIC_{90} (µg/mL)*	*%S*	*%I*	*%R*
Ceftriaxone	≤0.015	100	–	–
Amox/clav	2	99.9	–	0.1
Cefuroxime	2	*76-99.8	0.1	0.1
Ampicillin	>8	*53.5-70.7	0.1	29.2
Azithromycin	2	99.8	–	–
TMP-SMX	>4	77.3	4.5	18.2
*Cefixime	0.01	100	0	0

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

Moraxella catarrhalis Resistance TRUST 7 (2003)

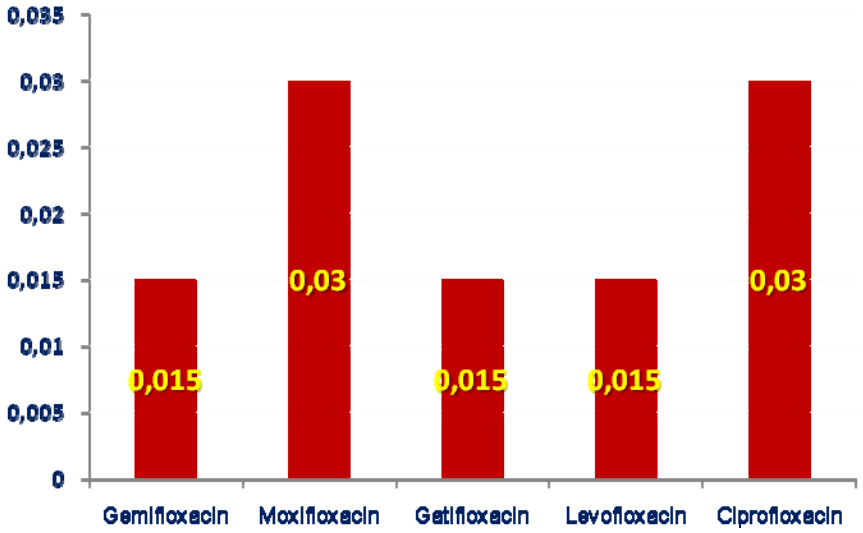
N = 817

Agent	*MIC_{90} (µg/mL)*
Ceftriaxone	1
Amoxicillin/clavulanate	0.25
Cefuroxime	2
Ampicillin	8
Azithromycin	0.03
TMP-SMX	0.25

TRUST = Tracking Resistance in the United States Today
MIC_{90} = minimum inhibitory concentration required to inhibit 90% of isolates

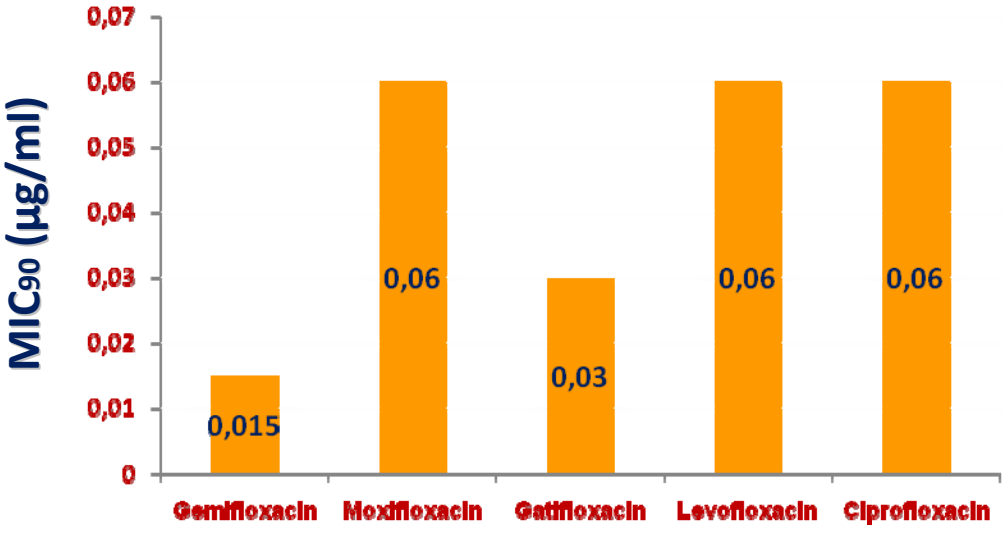
Daniel F. Sahm PhD Clinical Cornerstone Volume 2003 Suppl 3 • 2003
Blondeau, Missaghi: Expert Opinion on Pharmacotherapy, May 2004, Vol. 5, No. 5, 1117-1152

Selected Quinolones MIC_{90} Against Isolates of H. influenzae



Gemifloxacin (N=8523)
Ciprofloxacin (N= 8523)
Levofloxacin (N = 5651)
Gatifloxacin (N= 2764)
Moxifloxacin (N= 2764)

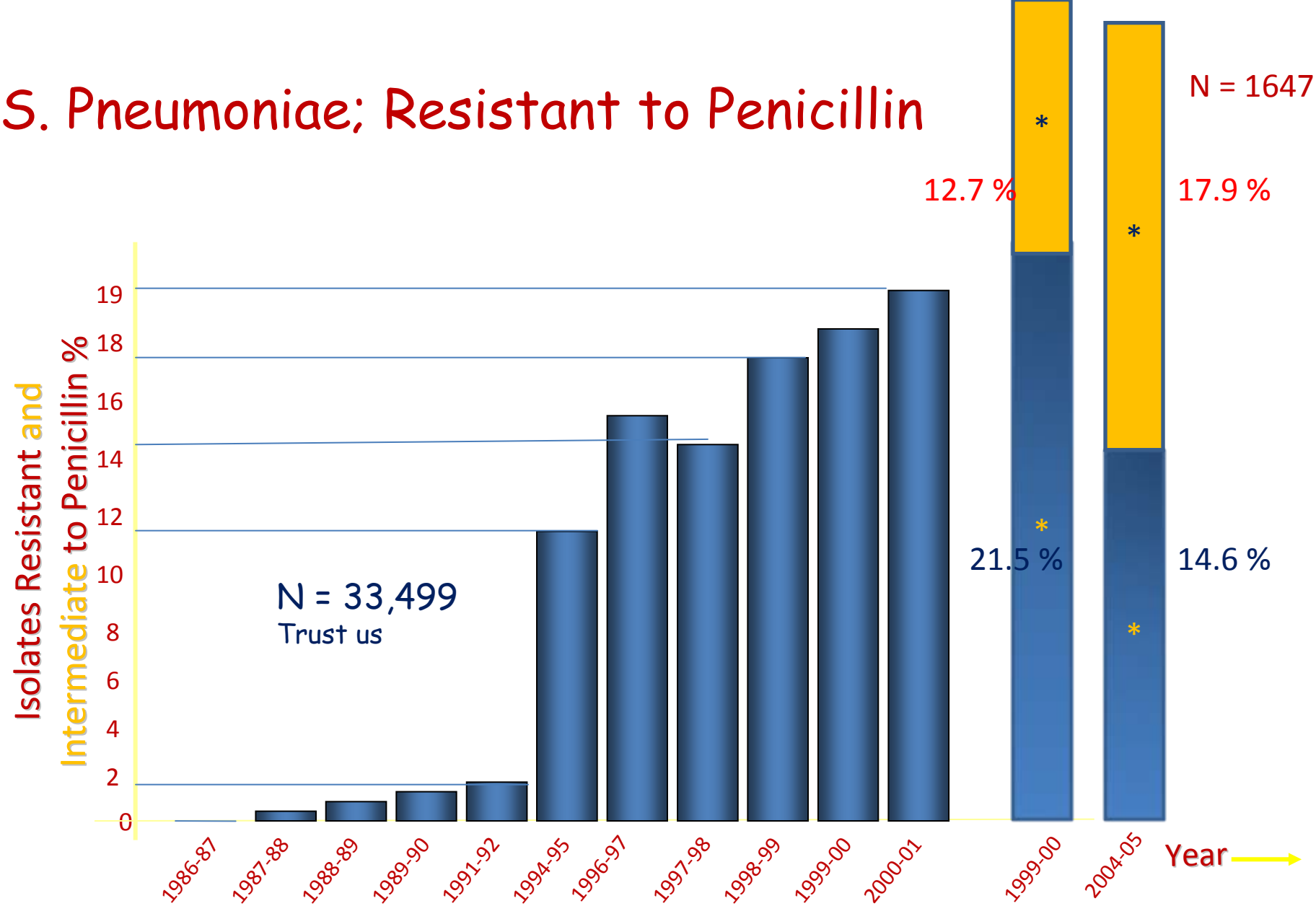
Selected Quinolones MIC_{90} Against Isolates of M. catarrhalis



Gemifloxacin (N=874)
Ciprofloxacin (N= 874)
Levofloxacin (N = 421)
Gatifloxacin (N= 250)
Moxifloxacin (N= 250)

Alexander Project 1998-2000

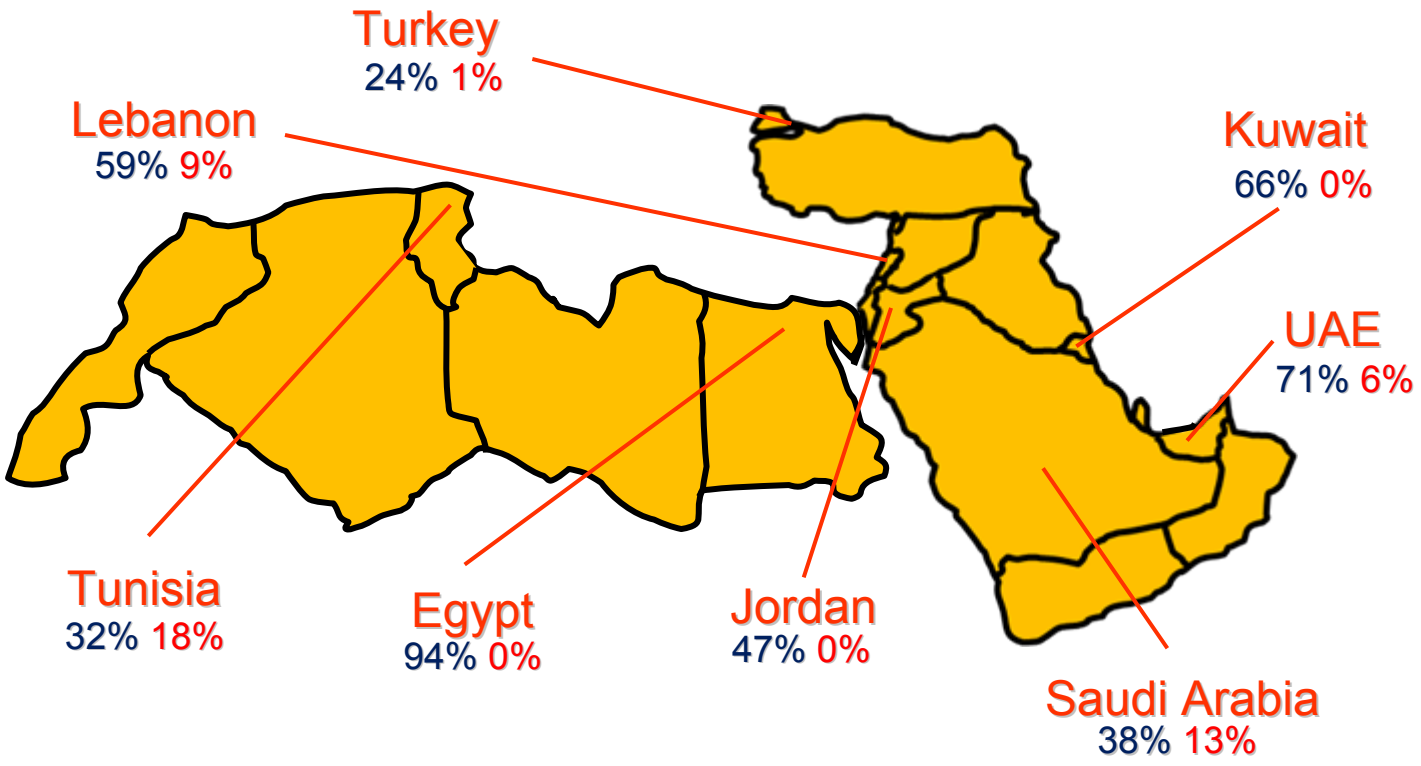
S. Pneumoniae; Resistant to Penicillin



Clinical Infectious Diseases 2004; 39:S142–50

*Clinical Infectious Diseases 2009; 48. e 23 – e33

S. pneumoniae: Prevalence of Penicillin-Resistant Strains

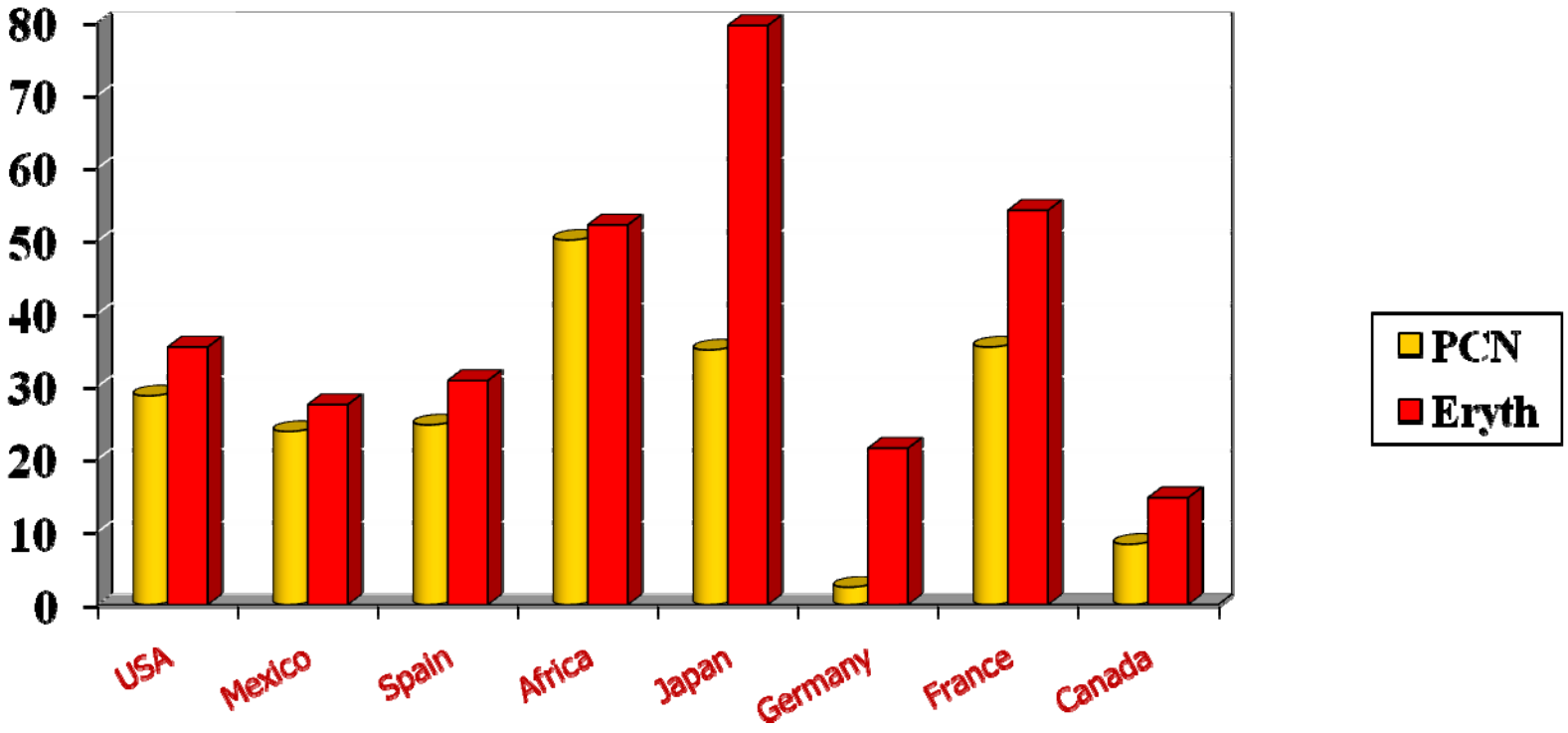


Penicillin-intermediate (MIC 0.12 – 1 µg/ml)

Penicillin-resistant (MIC ≥2 µg/ml)

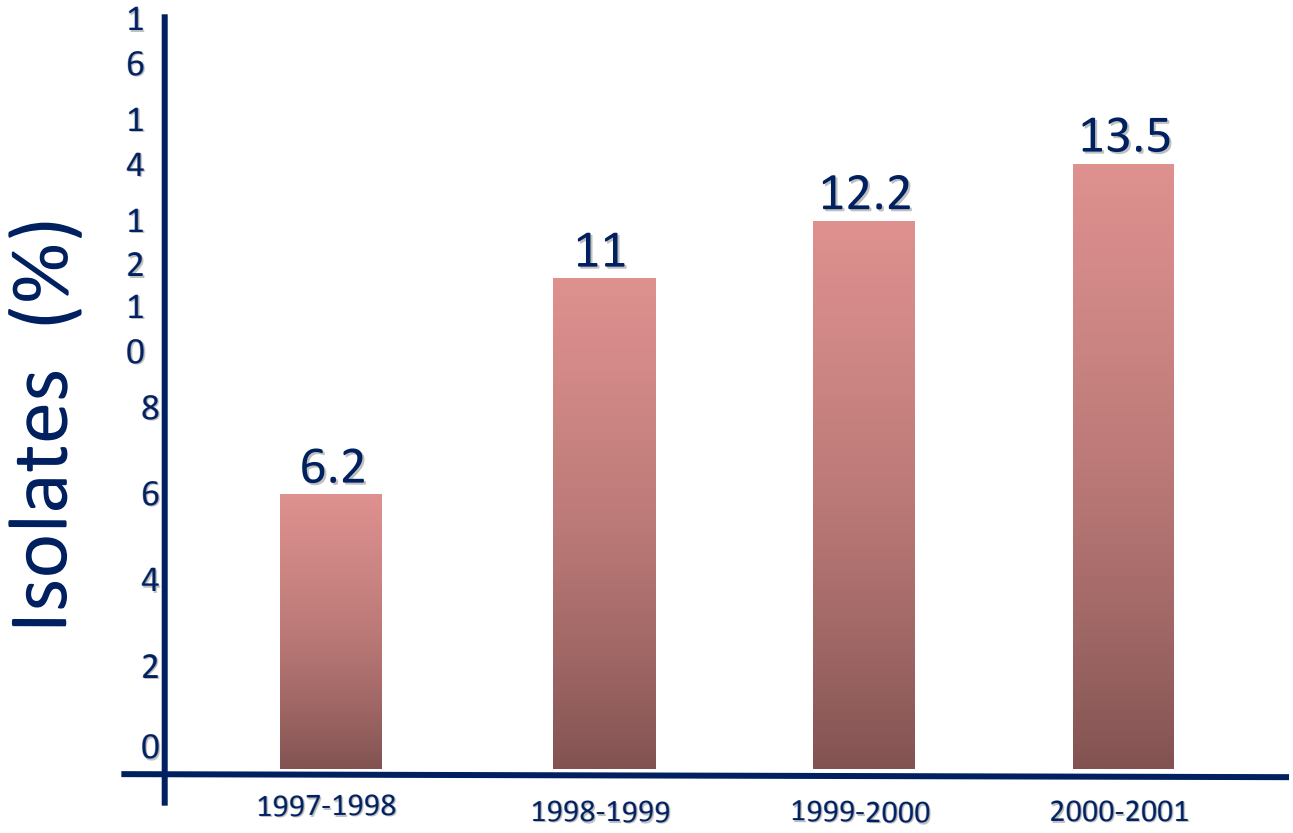
Clin Microbiol Infect. 2004;10 Suppl 3:111, Abs No P507.

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



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

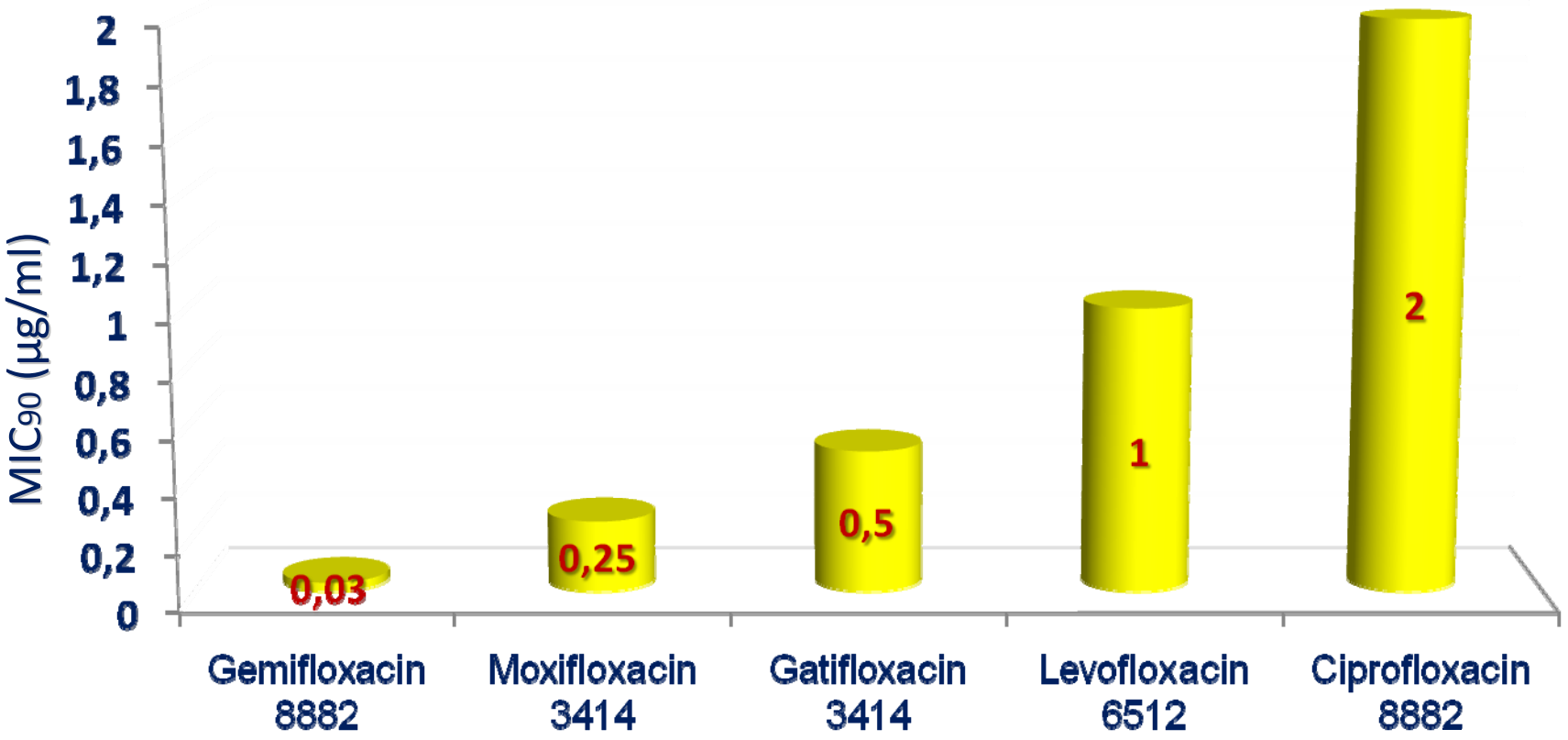
TRUST US MDR, Streptococcus pneumoniae



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

Dr. Adolf W. Karchmer, Harvard Medical School, Beth Israel Deaconess Medical Center
Clinical Infectious Diseases 2004; 39:S142–50; by the Infectious Diseases Society of America

Selected Quinolones MIC_{90} Against Isolates of Streptococcus pneumoniae



Numbers below Antimicrobials denotes tested isolates

Alexander Project 1998-2000

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)
Gemifloxacin	0.03-1	0.25	0.5
Ciprofloxacin	8-32	16	>32
Levofloxacin	4 ->32	16	>32
Sparfloxacin	0.25-32	8	16
Grepafolxacin	0.5-16	4	8
Trovafloxacin	0.25	1	4

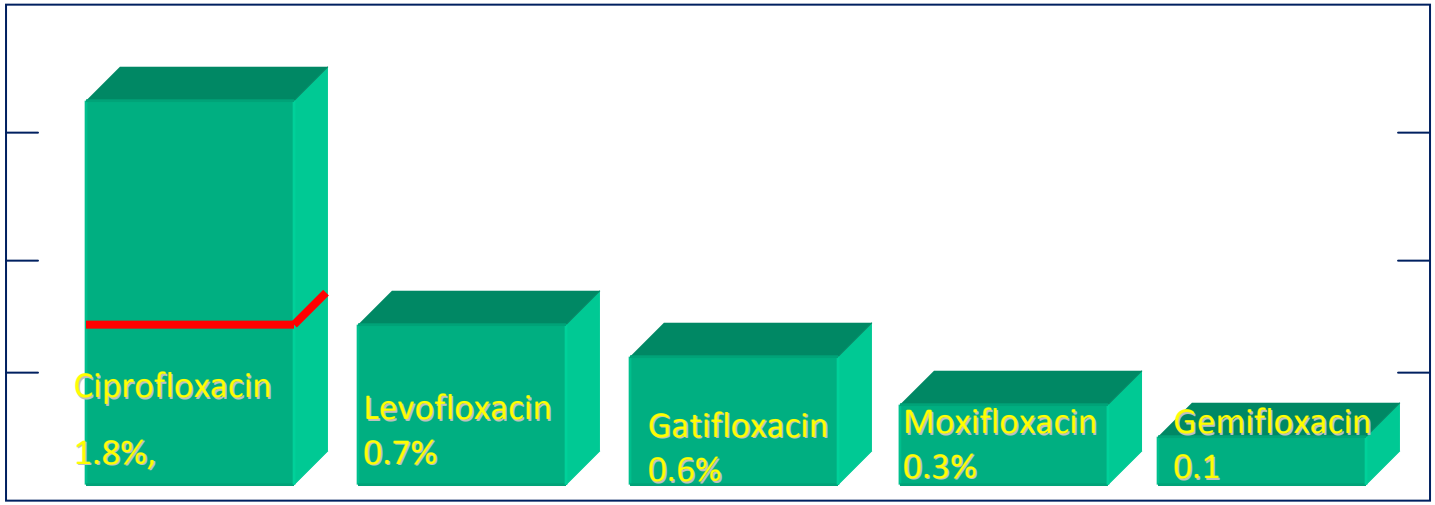
From; Davies et al. Antimicro Agents Chemother. 2000;44:304-310

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

Susceptibility group and fluoroquinolone	No. of strains with MICs (μg/ml) of:												% Resistance[a]
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	
Levofloxacin susceptible (n = 125)													
Levofloxacin						1	97	25	2				
Gatifloxacin					16	100	8	1					
Trovafloxacin			6	80	35	4							
Clinafloxacin			33	86	6								
Gemifloxacin	7	84	29	5									
Levofloxacin-resistant strains (n = 57)													
Levofloxacin										11	35	11	100
Gatifloxacin								2	9	43	3		96
Trovafloxacin					1	4	6	8	18	17	3		67
Clinafloxacin					1	32	22	1	1				
Gemifloxacin			3	5	25	16	7	1					

AAC, Nov. 2000, p. 2962–2968

Fluoroquinolone Resistance!
TRUST, and PROTEKT US Surveillance Data Among Canadian isolates of *S. pneumoniae*



Ciprofloxacin-R, Levofloxacin-S, *S. pneumoniae* may have first-step mutations reducing fluoroquinolone susceptibility.

Dr. Adolf W. Karchmer, Clinical Infectious Diseases 2004; 39:S142–50
M. R. Jacobs et al, Journal of Antimicrobial Chemotherapy; 2003, 52, 229-246

Patterns & Mechanisms of Resistance, Respiratory Anti-Infective Agents

- β-Lactamases like Penicillins and Cephalosporins in *Haemophilus influenzae* and *Moraxella catarrhalis*
- Protein Binding Proteins, (PBP) like in *Streptococcus pneumoniae*
- Efflux and Methylation like in $MKLS_B$ in *Streptococcus pneumoniae*

Patterns & Mechanisms of Resistance, Respiratory Anti-Infective Agents:

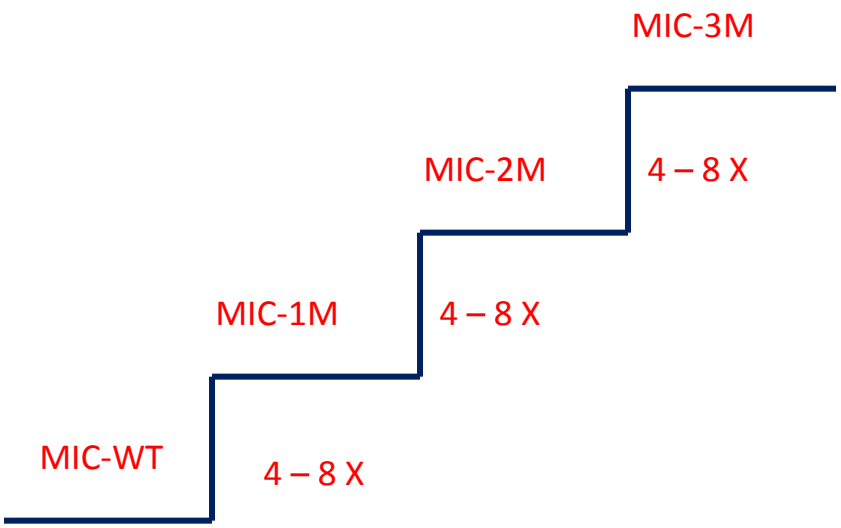
Quinolones Resistance in *S. pneumoniae*

- Enzyme Modification like in Quinolones, mutations in the genes encoding the target enzymes
  - *parC, par E,* encodes the A subunit of DNA topoisomerase IV.
  - *gyrA,* encodes the A subunit of DNA gyrase (topoisomerase II).
  - Combined *parC* and *gyrA*
- First-step mutations in *parC* occur fairly frequently(~ $1/10^7$)
- Once the *S. pneumoniae* has a first-step *parC* mutation, the acquisition of increased fluoroquinolone resistance is dependent on a second-step mutation in *gyrA.*

•Also mutations in *parE* and *gyrB* have been reported, but to a lesser extent.

•Resistance can also be mediated by active efflux, although its role in contributing to resistance to the newer FQ is unclear

The Evolution of Resistance to Quinolones

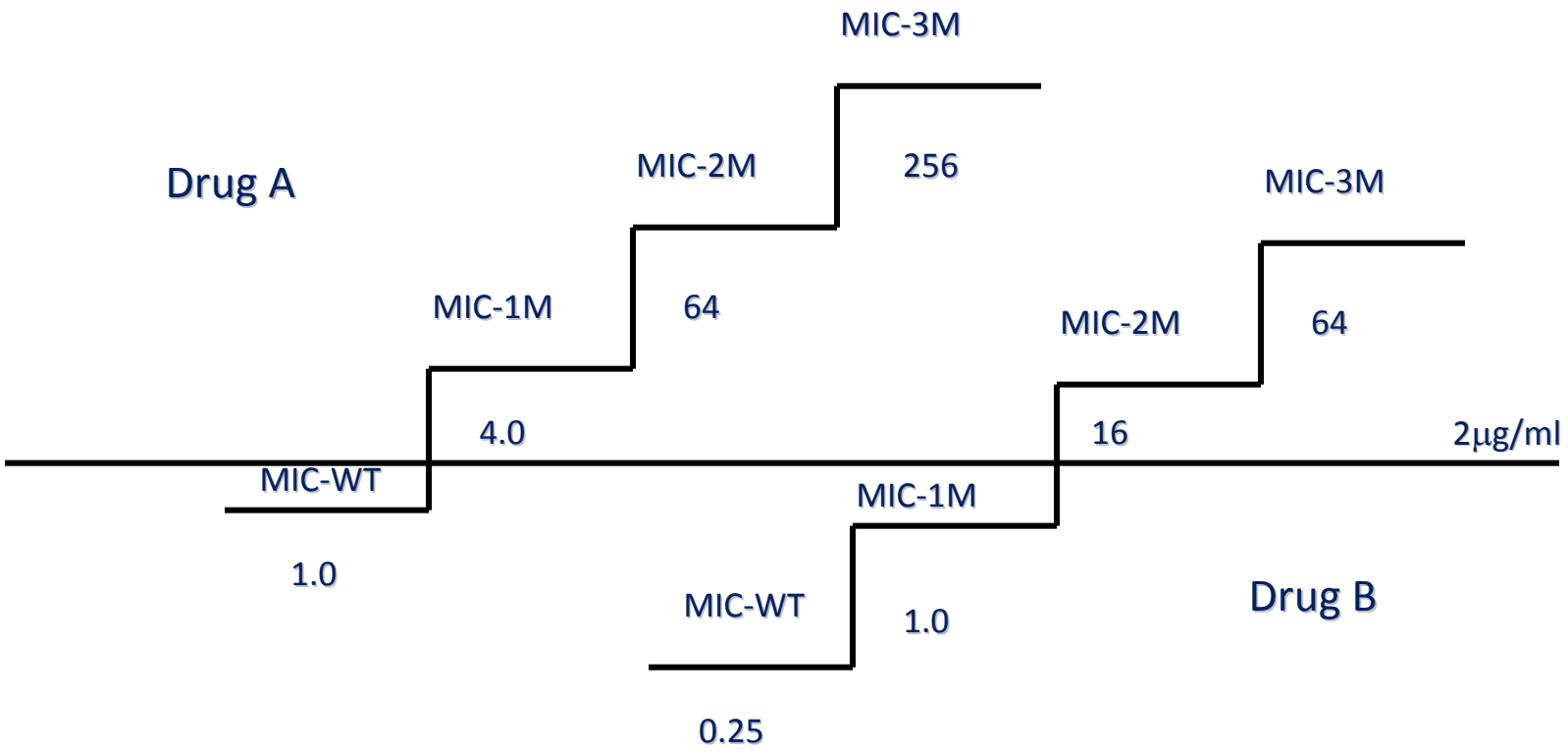


Each step in the evolution represents a spontaneous mutation that diminishes quinolone susceptibility 4-8 fold. Thus the MIC of the quinolone used to select mutants from the wild type (WT) is 4-8 fold diminished for successive first-step (1M), second-step (2M), and third-step (3M) mutants.

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

The Evolution of Resistance to Quinolones

Cross-resistance Among the Quinolones

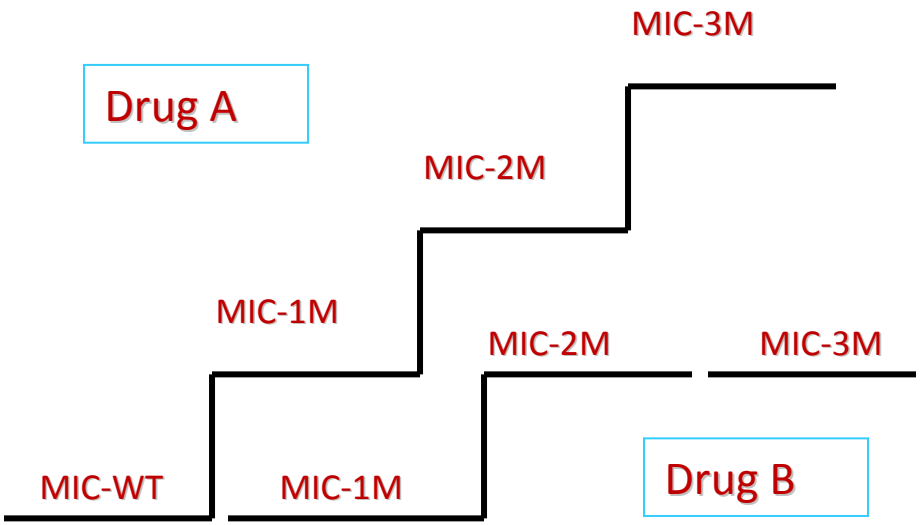


If both quinolones achieve a concentration of 2 µg/mL at the site of infection, the 8-fold rule would predict that quinolone B would provide the most effective therapy and be less likely to select for resistance because achievable concentrations exceed the MIC for the wild-type and first-step mutants.

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

The Evolution of Resistance to Quinolones

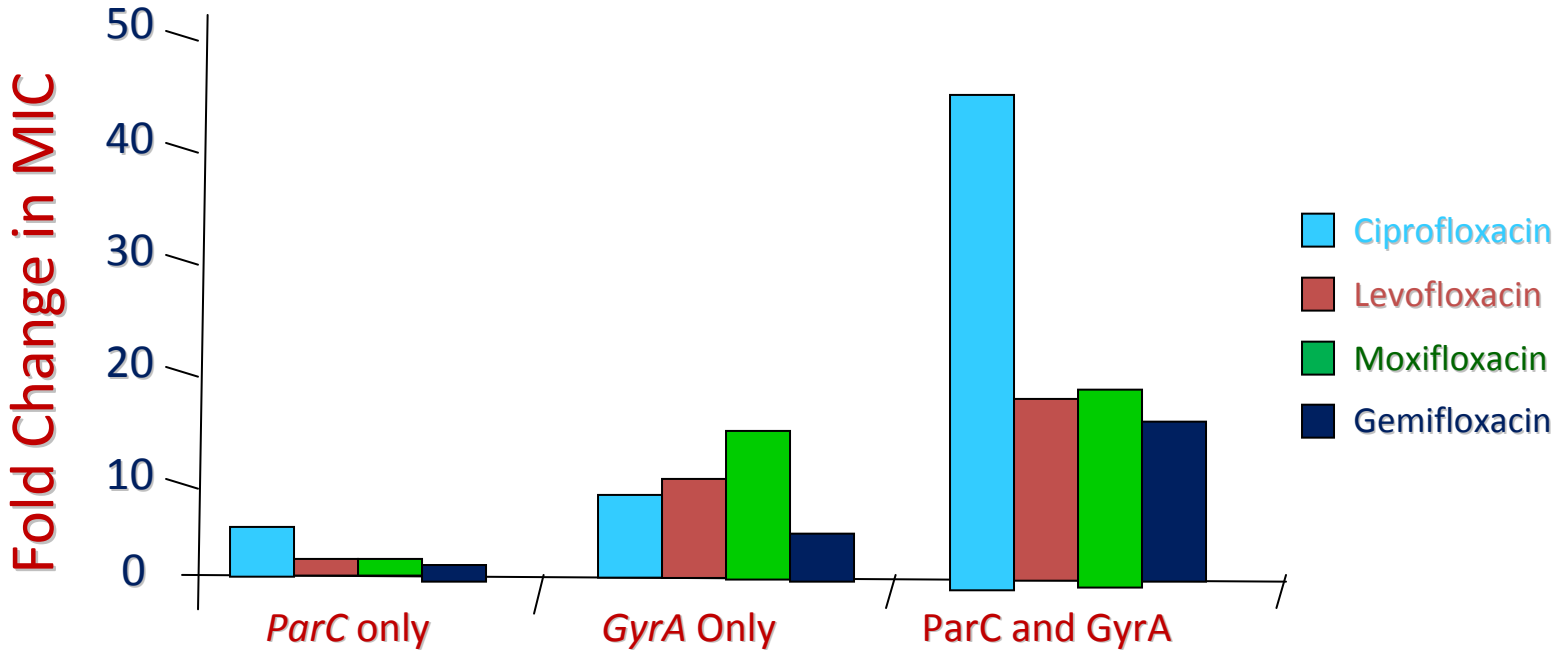
Dichotomous resistance among the quinolones



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.

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

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.

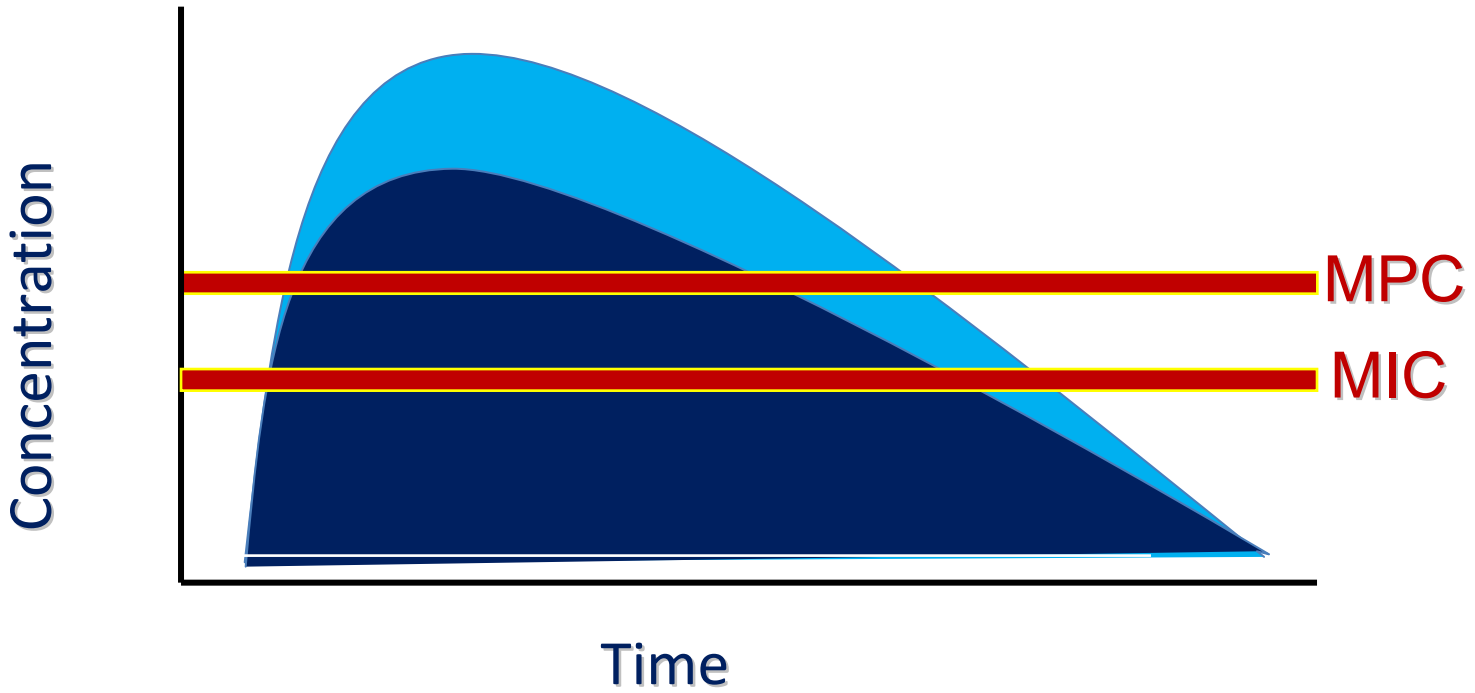
L. MARK FISHER .AAC. Nov. 2000, p. 3112–3117

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

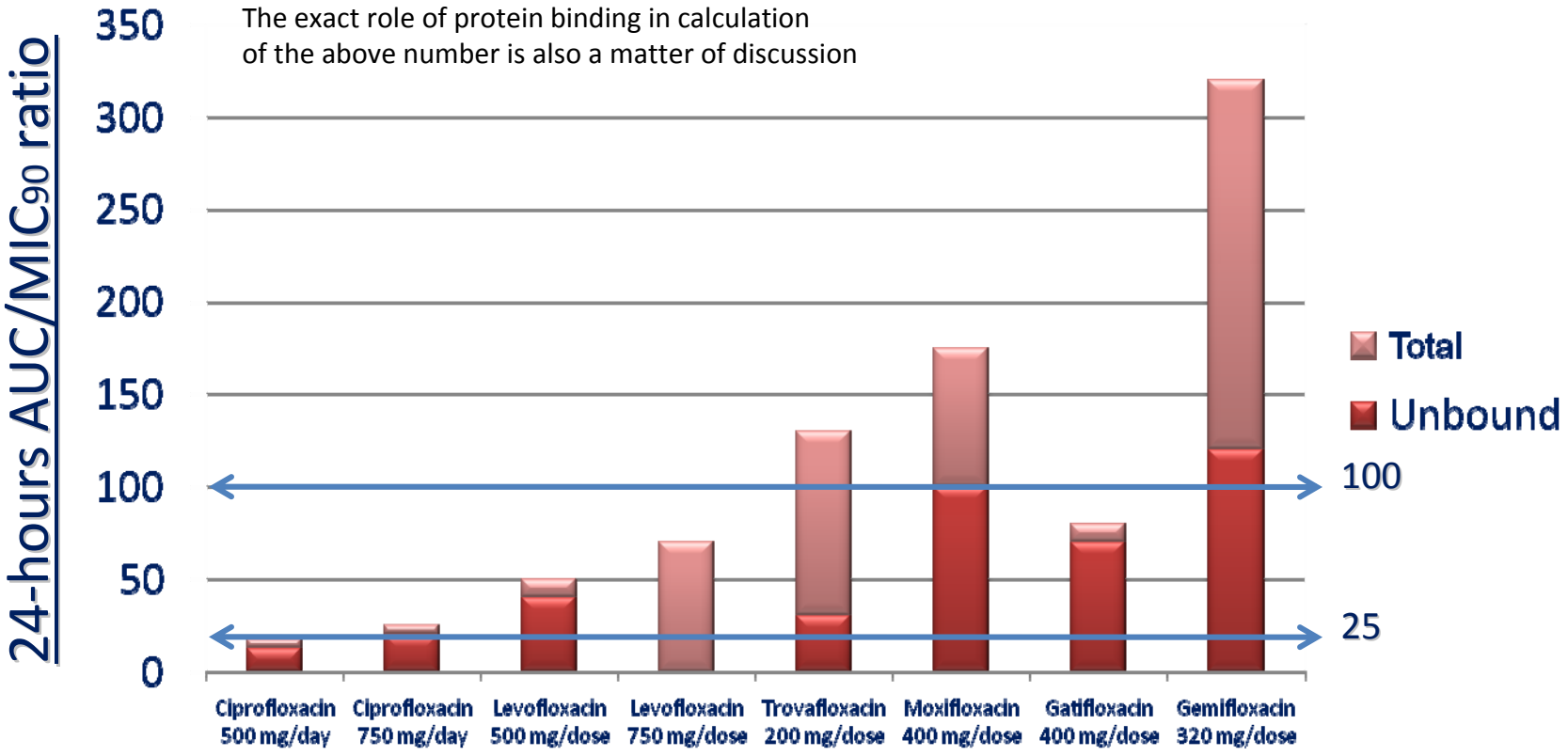
Desired AUC_{24}/MIC and $fAUC_{24}$/MIC ratios for major pathogens are:



- 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, Feb. 2010, p. 673–677

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



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

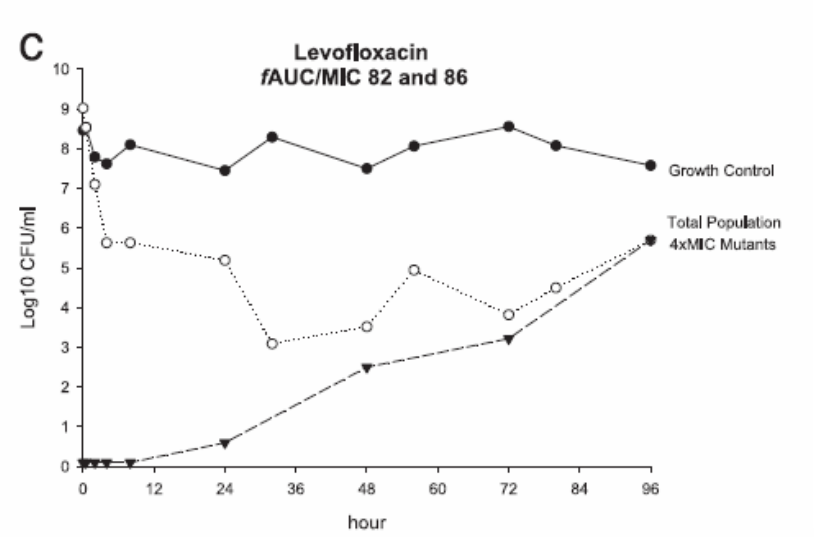
Fluoroquinolone Resistance in Streptococcus pneumoniae: AUIC (AUC concentration-Time Curve/MIC) Ratio and Resistance Development with Gatifloxacin, Gemifloxacin, Levofloxacin, and Moxifloxacin

- Simulation model, $10^{8.5}$ to 10^{9} log10 CFU/ml were used
- S. pneumonia ATCC 49619, and BSP2443 (susceptible but Erythromycin resistant)
- 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. Apr. 2007, p. 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 ? related to structural variations within the class.
- 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

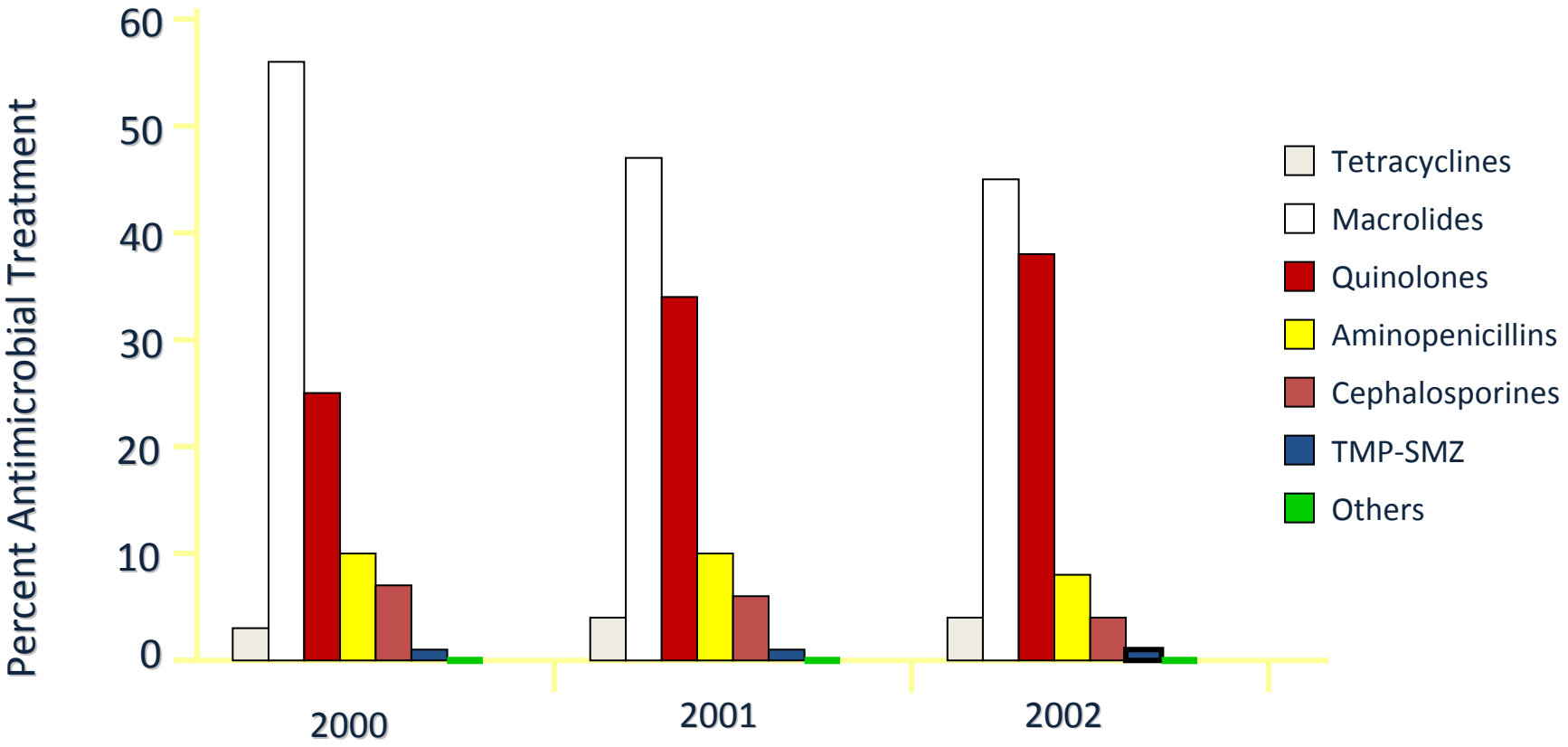
Mutant Prevention Concentration

- 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

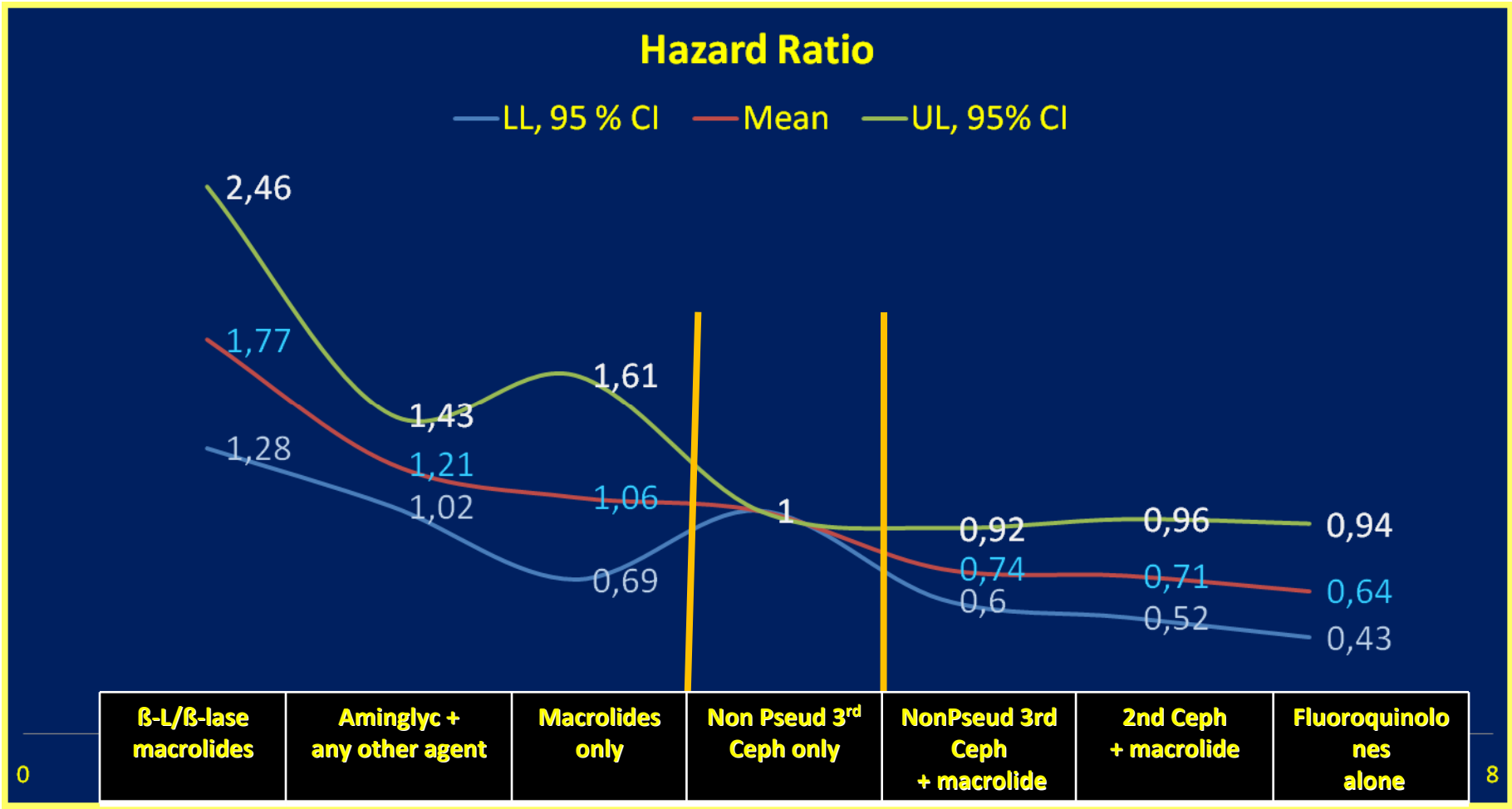
Yuzhi Dong, et al. AAC, July 1999, p. 1756–1758
AAC, Feb. 2001, p. 433–438
Blondeau & Missaghi. Expert Opin. Pharmacother. 2004, 5 (5): 1117-1152
AAC, Apr. 2007, p. 1315–1320

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



Emerging Infectious Diseases, 2005 CDC

Independent Associations Between Initial Antimicrobial Therapy & 30-day Mortality



Outpatient treatment

Adopted; IDSA/ATS Consensus Guidelines on the Management of CAP in Adults,

Previously healthy and no risk factors for DRSP infection	A macrolide (azithromycin, clarithromycin, or erythromycin)
Presence of comorbidities; such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:	**A:** A Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) **B:** A ß-lactam **plus** a macrolide **Preferred** (High-dose amoxicillin [e.g., 1 gm TID] or amoxicillin-clavulanate [2 gm BID] is **Alternatives** include ceftriaxone, cefpodoxime, and cefuroxime [500 mg BID]; doxycycline [level II evidence] is an alternative to the macrolide.)

In regions with a high rate (>25%) of infection with high-level (MIC, 16 g/mL) macrolide-resistant *S. pneumoniae,* consider the use of alternative agents listed above in recommendation 16 for any patient, including those without co morbidities.

Clinical Infectious Diseases 2007;44:S27-S72

Inpatient, non-ICU treatment

Adopted; IDSA/ATS Consensus Guidelines on the Management of CAP in Adults, Clinical

A respiratory fluoroquinolone (strong recommendation) e.g. Gemifloxacin, Moxifloxacin, Gatifloxacin

A ß-lactam **plus** a macrolide (strong recommendation)

Preferred -lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide

A respiratory fluoroquinolone should be used for penicillin-allergic patients

*Macrolide alone can be used only for the treatment of **carefully selected hospitalized** patients with **non severe disease** and **without risk factors for infection with drug-resistant pathogens**. However, such **monotherapy cannot be routinely recommended.**

*Due to increasing resistance rates

Clinical Infectious Diseases 2007;44:S27-S72

Gemifloxacin

- Gemifloxacin is “classified” as a fourth generation quinolone” because it has a potent activity against anaerobes and increased activity against pneumococci

- FDA approved since 2004 for AECB and mild to moderate CAP including pneumonia due to MDRSP

- In addition, gemifloxacin provides a potent activity against H. influenzae, M. catarrhalis, and S aureus, the agents that mostly contribute to the microbial pathogenesis in ABRS, but so far, not FDA approved for this indication

Vincent T. Andriole. Clinical Infectious Diseases 2005; 41:S113–9
M. R. Jacobs, et al. The Alexander Project 1998-2000: Journal of Antimicrobial Chemotherapy 2003; 52: 229–246
Jennifer Le, et al The American Journal of Managed Care 2004 November; 1972 (10): S3-8

Gemifloxacin in CAP

Drug	Patients evaluated	Dosage	Duration Days	Clinical Outcome	Bacteriological Outcome
Gemifloxacin	169	320 mg/day	7-14	92.2	90.6
Ceftraixone Cefuroxim ± Macrolide	172	2gm/day 500 mg bid	1-7 1-13	93.4	87.3
Gemifloxacin Trova	290	320 mg/day 200 mg/day	7 7	95.8% 93.6%	94% 94.4%
Gemifloxacin	280	320 mg/day	10	88.7	96.3
Amox/clav		1gm tid	10	87.6	91.8

Lode et al. *Clin Ther*. 2002;24:1915
File et al. *J Antimicrob Chemother*. 2001;48:67
Leophonte P, File JR. TM Feldman. Resp Med(In press)
Expert Opin. Pharmacother. (2004) 5(5) 1129 1130

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

PURPOSE:

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

Review randomized controlled trials comparing short-course and extended-course antibiotic regimens for CAP.

METHODS:

Searched in MEDLINE, Embase, and CENTRAL ,1980- June 2006

Studies included; randomized controlled trials that compared

short-course (7 days or less) 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

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

RESULTS	15 randomized controlled trials Comprising 2796 total subjects
Short-course regimens	azithromycin (n=10), ß-lactams (n=2), fluoroquinolones (n=2), ketolides (n=1),
Extended-course regimens	3 studies utilized the same antibiotic whereas 9 involved an antibiotic of the same class.
Clinical failure	No difference in the risk (0.89, 95% CI, 0.78-1.02)
Risk of mortality	No differences (0.81, 95% CI, 0.46-1.43)
Bacteriologic eradication	No difference (1.11, 95% CI, 0.76-1.62)

In subgroup analyses, there was a trend toward favorable clinical efficacy for the short-course regimens in all antibiotic classes (range of relative risk, 0.88-0.94)

Conclusion	The available studies suggest that adults with mild to moderate CAP can be safely and effectively treated with an antibiotic regimen of 7 days or less. Reduction in patient exposure to antibiotics may limit the increasing rates of antimicrobial drug resistance, decrease cost, and improve patient adherence and tolerability.

Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study

- Objectives: Short-course therapy has been advocated for the treatment of community-acquired pneumonia (CAP). We compared the efficacy and safety of 5 and 7 day courses of gemifloxacin for outpatient treatment of mild–moderate CAP.

- Patients and methods:
  - A multicentre, double-blind, parallel group study, patients were randomized to receive 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 end of therapy (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. Journal of Antimicrobial Chemotherapy (March, 2007) 60, 1-9

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

Thomas M. File, Jr, Lionel A. Mandell, et al. Journal of Antimicrobial Chemotherapy (March, 2007) 60, 1–9

Results: PPS		EOT= 7–9 days Follow-up visit = 24–30 days
Duration	5 day	7 day
N=469	256	256
Clinical resolution: -Follow up -EOT	95% 96%	92% 96%
Bacteriological response: - Follow up -EOT	91% 94%	91% 96%
Radiological Response at Follow up	98%	93%
AE	21%	21%
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

Gemifloxacin in AECB

Number	Drug	Dosage	Duration Days	Clinical Outcome	Bacteriological Outcome	Comments
#121 112	Gemifloxacin Ceftriaxone/ Cefuroxime	320 mg/day 1 gm/day 500 mg BID	5 3 7	86.8 81.3	81.3 82.4	Median Time to Discharge 9 Days Median Time to Discharge 11Days
*351 361	Gemifloxacin Clarithromycin	320 mg/day 500 mg BID	5 7	85.4 84.6	86.7 73.1	More patients in gemifloxacin remain free AECB recurrence. Gemifloxacin had shorter time to H. influenzae irradication
$304 269	Gemifloxacin Amox/clav	320 mg/day 500/125 TID	5 7	87.2 87.4	90.9 79.5	Gemifloxacin was found to be as effective as amox/clav in the treatment of AECB.

#Wilson R, Langan C, Ball P, et al: Respir Med 2003;97: 242–249.
*Wilson R, Schentag JJ, Ball P, Mandell L: *Clin Ther* 2002;24:639–652
$ File T, Schlemmer B, Garau J, et al. *J Chemother 2000;12: 314*–325

Cost-Effectiveness of Gemifloxacin: Results From the GLOBE Study

- The cost-effectiveness of treatment with oral gemifloxacin vs. oral clarithromycin for AECB was evaluated.
- Prospective double-blind, controlled, health outcomes study compared health, economic, and clinical outcomes
- Base case analysis was performed from the third-party payer's perspective and considered the costs of respiratory tract infection related medical care.
- Analysis from the societal perspective also included costs of lost productivity.
- Treatment effectiveness was measured as the proportion of patients without recurrence requiring antimicrobial treatment following resolution of the initial AECB.

Michael T. Halpern, Cynthia S. Palmer, Marc Zodet, and Jeff Kirsch Am J Health-Syst Pharm 59(14):1357-1365, 2002

Cost-Effectiveness of Gemifloxacin: Results From the GLOBE Study

	Gemifloxacin	Clarithromycin	Significance
Patients AECB free after 26 weeks (No Abx. Needed)	73.8%	63.8%	P=0.024
Hospitalization	5/214 (2%)	14/224 (6.2%)	P=0.059
Off Days	8.3	10.1	1.8 days
Cost of Treatment ($)	247	374	-127
Mean Total Cost $(direct plus indirect) per patient	1413	1742	-329

Gemifloxacin was more cost-effective, improving AECB outcomes and producing substantial cost offsets compared with clarithromycin

Michael T. Halpern, Cynthia S. Palmer, Marc Zodet, and Jeff Kirsch Am J Health-Syst Pharm 59(14):1357-1365, 2002

What About ACABS

Clinical Success for Gemifloxacin treated patients. Both study arms with and without comorbidities*.

Intent to Treat Population (ITT)			
Clinical Success	N =100 Five Days Treatment (%) 95% CI	N = 107 Seven Days treatment (%) 95% CI	P-value for the difference in responses between both study arms
Two weeks after the EOT			
With comorbidities	84% (76.8 - 91.2)	84.1% (77 - 91)	0.1% p = 1
Without comorbidities	90.3% (82.9 - 97.7)	88.2% (80.5 - 95.9)	2.1% p = 0.7
Four weeks after EOT			
With comorbidities	88% (81.6 - 94.4)	90.7% (85.2 - 96.2)	2.7% p = 0.5
Without comorbidities	90.3% (82.9 - 97.7)	94.1 (88.5 - 99.7)	3.8% p = 0.4

*Co-morbidities evaluated include; Allergic rhinitis, Bronchial asthma and COPD

Jamal Wadi et al. Hospital Infectoin and Epidemiology. 2011 (In review)

Clinical Success for Gemifloxacin treated patients. Both study arms with and without comorbidities*.

Per Protocol Population (PPP)

Response (Clinical Success)	N = 94, Five Days Treatment (%) 95% CI	N = 105 Seven Days treatment (%) 95% CI	95% CI and P-value for the difference in responses between both study arms
Two weeks after the EOT			
With comorbidities	89.4% (83.1 - 96)	85.7% (79.0 - 92.4)	3.7% (-5.4 - 12.8), p = 0.43
Without comorbidities	98.2% (95 - 102)	89.6%(82.3 - 97)	8.6% (5.0 - 16.7), p =.052
Four weeks after EOT			
With comorbidities	93.6% (89 - 99)	92.4% (87.3 - 97.5)	1.2%(-5.9 - 8.3), p = 0.74
Without comorbidities	98.2% (95 - 102)	95.5% (91 - 100.5)	2.7% (-3.3 - 8.7), p = 0.39

*Co-morbidities evaluated include; Allergic rhinitis, Bronchial asthma and COPD

Jamal Wadi et al. Hospital Infectoin and Epidemiology. 2011 (In review)

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JAC

Synergy between gemifloxacin and trimethoprim/sulfamethoxazole against community-associated methicillin-resistant *Staphylococcus aureus*

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Objectives: The rapid emergence of methicillin-resistant *Staphylococcus aureus* from the community (CA-MRSA) presents difficulties in making treatment choices. We evaluated whether combining another orally available agent commonly used to treat CA-MRSA with gemifloxacin would enhance gemifloxacin activity against CA-MRSA.

Methods: Fifty strains of SCC*mec* IV, *agr* group 1, Panton–Valentine leucocidin-positive CA-MRSA were evaluated for susceptibilities to gemifloxacin, trimethoprim/sulfamethoxazole, doxycycline, levofloxacin, rifampicin, clindamycin and erythromycin. Twenty of these strains were evaluated for the potential for synergy between gemifloxacin and trimethoprim/sulfamethoxazole, clindamycin and rifampicin by time–kill analysis. Two strains were further evaluated in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model.

Results: In time–kill analyses, gemifloxacin combined with trimethoprim/sulfamethoxazole produced additivity (6/20) or synergy (11/20) in 85% of the isolates tested. The addition of clindamycin to gemifloxacin showed additivity (3/20) or synergy (2/20) in 25% of the isolates. All isolates displayed indifference to the combination of gemifloxacin and rifampicin. In the PK/PD model, combining gemifloxacin and trimethoprim/sulfamethoxazole provided potent and sustained bactericidal activity to detection limits of 2 $\log_{10}$ cfu/mL by 48 h; gemifloxacin combined with clindamycin or with rifampicin killed to detection limits by 56 h or later. One isolate developed efflux-mediated resistance to gemifloxacin at 96 h with gemifloxacin monotherapy. All combinations prevented the emergence of this resistance.

Conclusions: Synergy or additivity was demonstrated by time–kill analysis between gemifloxacin and trimethoprim/sulfamethoxazole in most isolates tested. In the PK/PD model, the addition of trimethoprim/sulfamethoxazole, clindamycin and rifampicin enhanced the activity of gemifloxacin against CA-MRSA and suppressed the emergence of resistance to gemifloxacin.

A Question of Resistance,

Does This Warrant Reconsideration in Approaching Antimicrobial Treatment ?

- Resistance patterns escalate among respiratory pathogens for some commonly prescribed antibacterials
- The relatively recent increase in other pathogens like S. aureus
- Amoxicillin resistance is high in both Moraxella and Hemophilus (β-lactamase)
- Lately (USA), isolates form nasal passages have more resistance:
  - S. pneumoniae to penicillin
  - H. influenzae to macrolides
  - M. catarrhalis to erythromycin and penicillin
- Both amoxicillin and amoxicillin/clavulonate are recommended for ABRS treatment, however in higher than previously recommended dosages.

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A Question of Resistance,

Does This Warrant Reconsideration in Approaching Antimicrobial Treatment ?

- 166 isolate of S. pneumoniae in Saudi Arabia:
  - penicillin susceptible in 38.6%
  - intermediate 39.8%
  - resistant 21.7%

(Alexander project, 1998-2000)

To Wrap Up

- Resistance is increasing world wide
- Penicillin resistant *S. pneumoniae* do not preclude using relatively, recently introduced RFQ
- Based on several surveillance studies RFQ resistance is low and steady so far (lowest for Gemifloxacin)
- Resistant to old generation quinolones do not speak against using new RFQ e.g. ciprofloxacin vs. Gemifloxacin, moxifloxacin and levofloxacin
- *In this context, all quinolones are not equal and should not be used interchangeably
- *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.

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

Thank You

Discussion ?

Comments !

Questions ?

Gemifloxacin; A Distinctive Quinolone or a By-passer

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