Fluoroquinolones in 2007: the Angels, the Devils, and What Should the Clinician Do?

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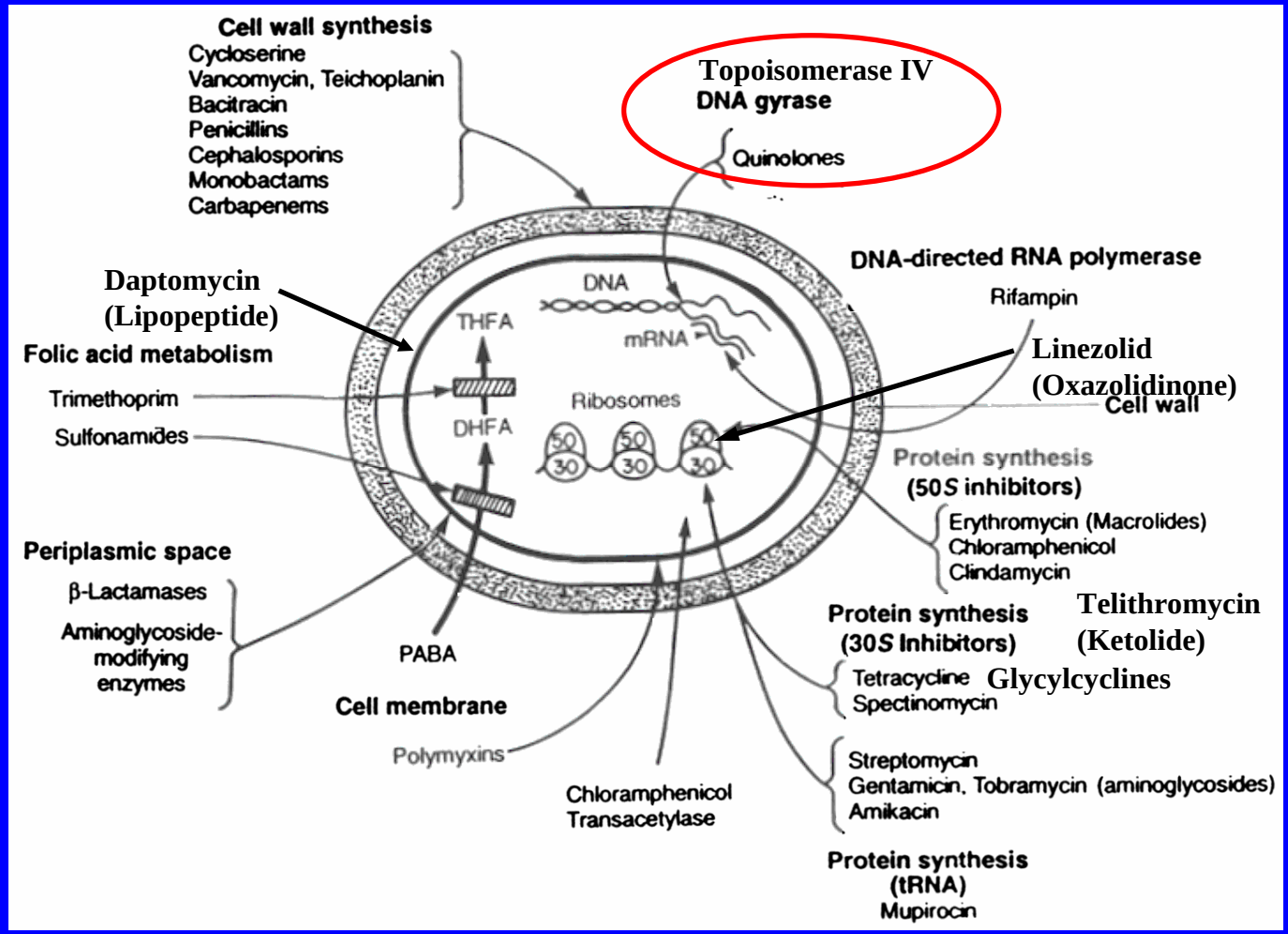
Sites of Action of Antimicrobial Agents in Clinical Use

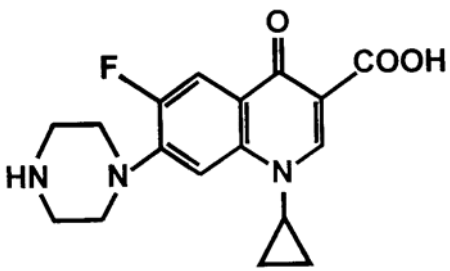


Neu HC. Science 1992; 257:1064-73

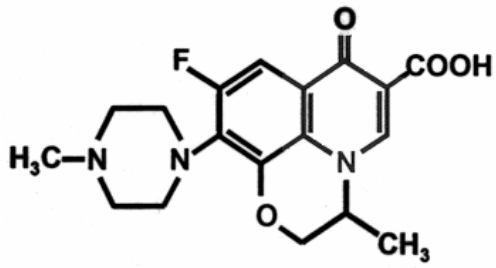
Fluoroquinolones Available in the United States

- Norfloxacin (Noroxin) 1986 (PO)
- Ciprofloxacin (Cipro) 1987 (PO), 1990 (IV)
- Ofloxacin (Floxin) 1990 (PO), 1992 (IV)
- Levofloxacin (Levaquin) 1996 (IV & PO)
- Gatifloxacin (Tequin) 1999 (IV & PO)
- Moxifloxacin (Avelox) 1999 (PO), 2001 (IV)
- Gemifloxacin (Factive) 2003 (PO)

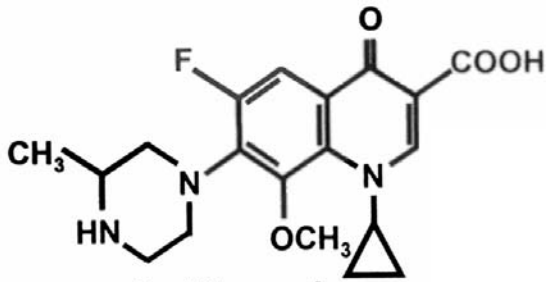
Fluoroquinolone Structures



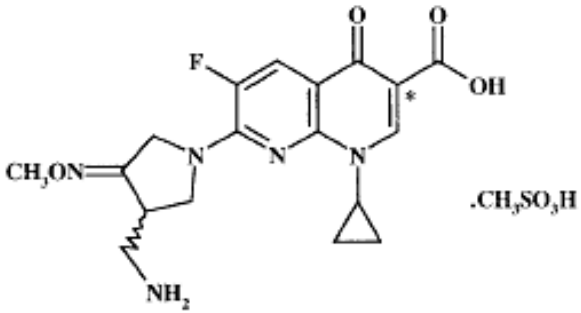
Ciprofloxacin



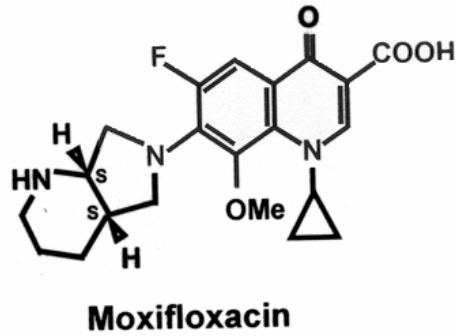
Levofloxacin



Gatifloxacin

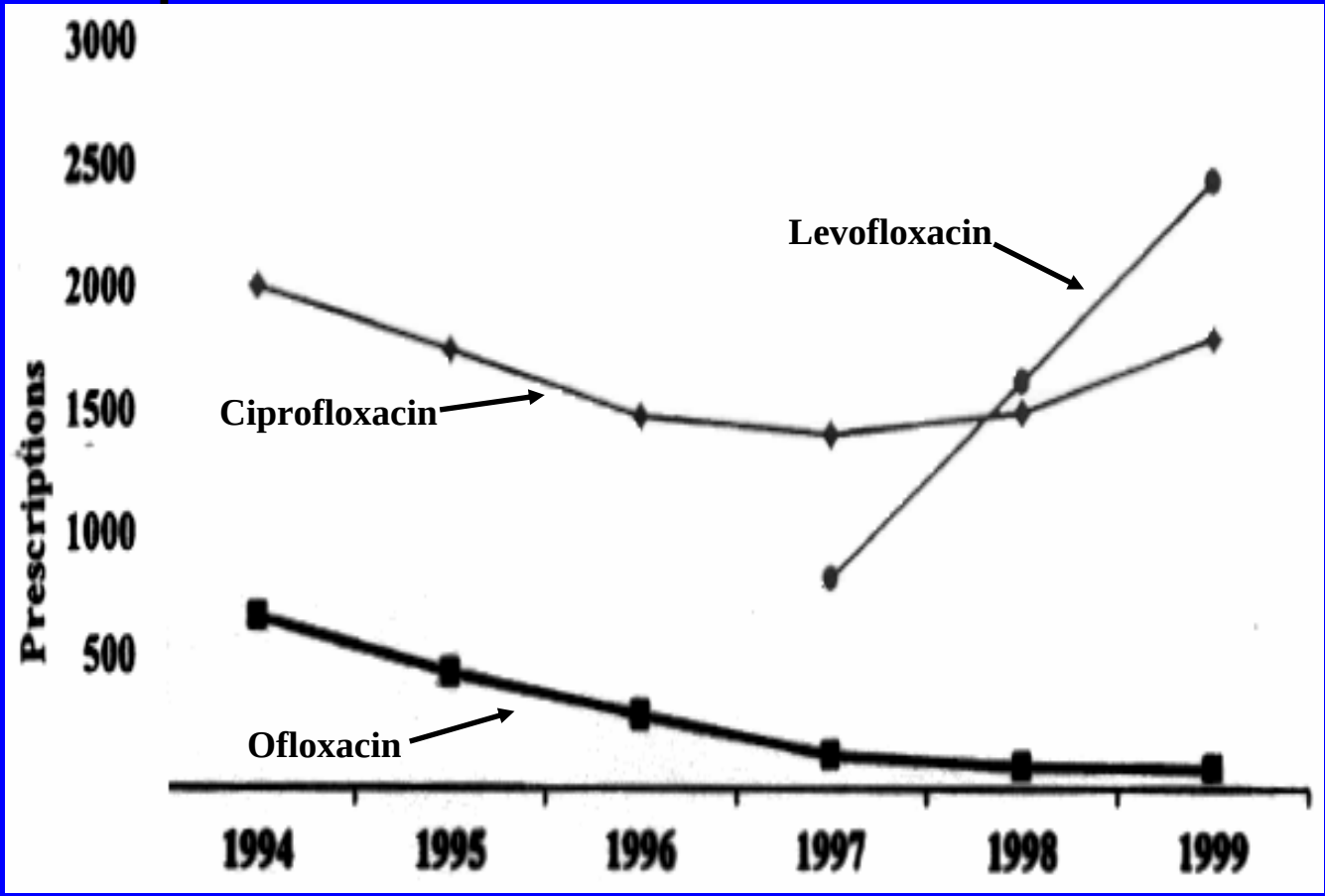


Gemifloxacin



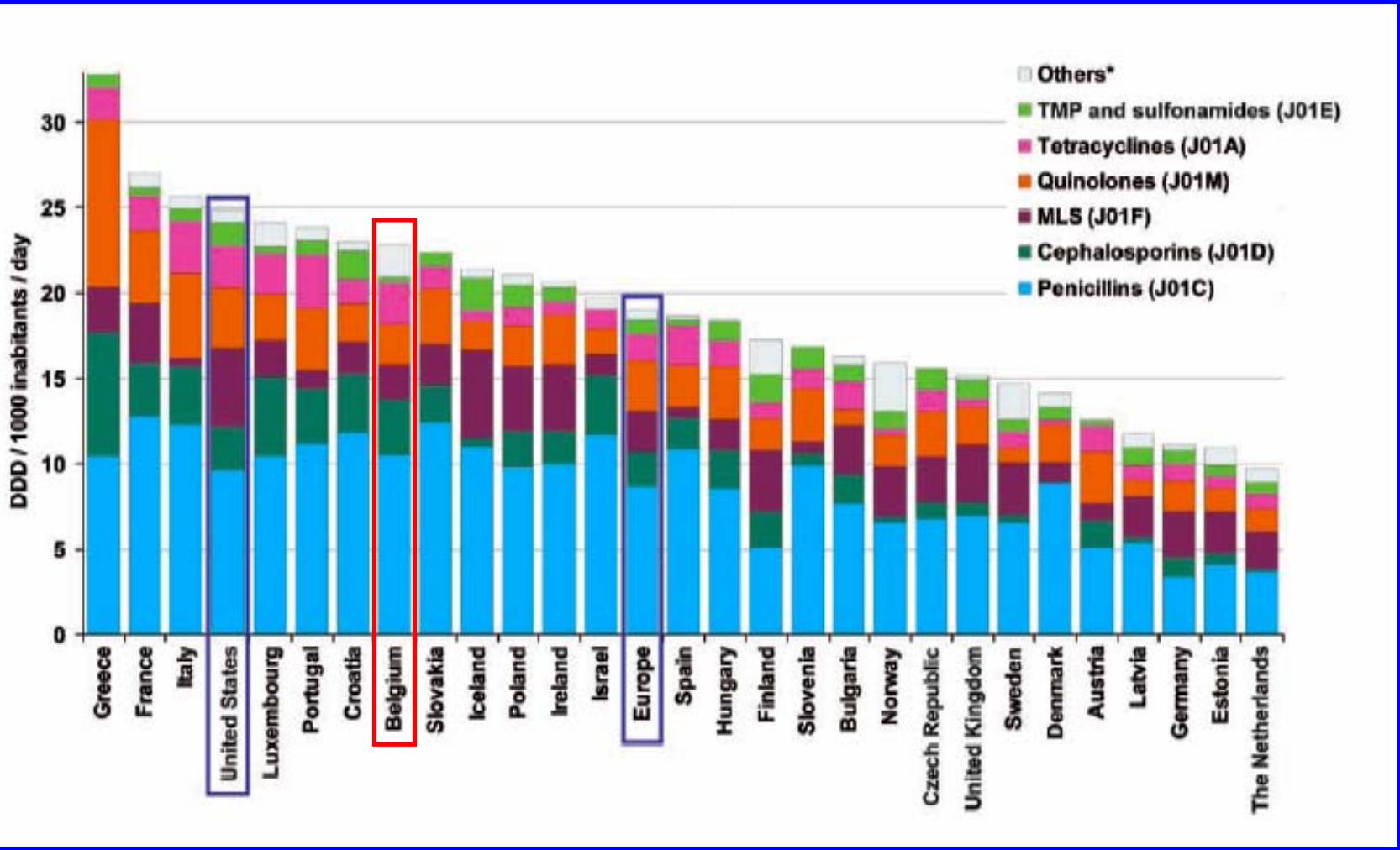
Moxifloxacin

Fluoroquinolone Use in Patients with Respiratory Tract Infections in the United States



Doern GV Clin Infect Dis. 2001;23(suppl 3):S187-92

Outpatient Systemic Antibacterial Use – Europe vs. United States



Goossens H et al. Clin Infect Dis. 2007; 44:1091

Quinolone Use – Europe vs. US

Table 1. Outpatient systemic use of major antibacterial classes in the United States and Europe in 2004.

ATC code	Corresponding antibacterial (sub)class	DID (%) United States	DID (%) Europe
J01A	Tetracyclines	4.63 (18.60)	2.37 (12.42)
J01C	Penicillins [9]	9.70 (38.93)	8.71 (45.73)
J01CE	Narrow-spectrum penicillins	0.68 (2.71)	0.75 (3.92)
J01CA	Broad-spectrum penicillins	5.68 (22.81)	4.49 (23.58)
J01CR	Combination of penicillins	3.29 (13.22)	3.20 (16.82)
J01CF	Penicillinase-resistant penicillins	0.05 (0.19)	0.27 (1.40)
J01D	Cephalosporins, monobactams, and carbapenems [10]	2.48 (9.94)	2.03 (10.65)
J01DB	First-generation cephalosporins	1.47 (5.90)	0.31 (1.62)
J01DC	Second-generation cephalosporins	0.61 (2.46)	1.12 (5.89)
J01DD	Third-generation cephalosporins	0.39 (1.57)	0.59 (3.11)
J01E	Sulfonamides and trimethoprim	1.34 (5.37)	0.77 (4.04)
J01F	Macrolides, lincosamides, and streptogramins [11]	3.52 (14.14)	2.98 (15.66)
	Short-acting macrolides	0.43 (1.73)	0.48 (2.54)
	Intermediate-acting macrolides	1.16 (4.66)	1.71 (8.96)
	Long-acting macrolides	1.68 (6.74)	0.53 (2.77)
J01FF	Lincosamides	0.25 (1.02)	0.16 (0.85)
J01FG	Streptogramins	<0.01 (0.00)	0.10 (0.55)
J01M	Quinolones [12]	2.47 (9.91)	1.58 (8.32)
	First-generation quinolones	0.01 (0.03)	0.41 (2.15)
	Second-generation quinolones	2.07 (8.30)	1.01 (5.31)
	Third-generation quinolones	0.39 (1.58)	0.16 (0.86)
J01B+G+R+X	Others	0.78 (3.11)	0.61 (3.18)
Total	…	24.92 (100.00)	19.04 (100.00)

NOTE. ATC, Anatomical Therapeutic Chemical; DID, defined daily doses per 1000 inhabitants per day.

Goossens H et al. Clin Infect Dis. 2007; 44:1091

Quinolone Use – Europe vs. US

Table 2. Outpatient systemic use of antibacterial substances in the United States and Europe in 2004.

	DID (%)		Range of use in Europe	
Antibacterial	United States	Europe	Highest DID (country)	Lowest DID (country)
Amoxicillin	5.59 (22.4)	4.26 (22.3)	12.83 (France)	3.76 (The Netherlands)
Co-amoxiclav	3.29 (13.2)	3.16 (16.6)	7.32 (Portugal)	<0.01 (Norway)
Doxycycline	2.98 (12)	1.73 (9.1)	5.17 (Iceland)	0.31 (Italy)
Azithromycin	1.68 (6.7)	0.52 (2.7)	1.34 (Croatia)	0.04 (Sweden)
Cephalexin	1.39 (5.6)	0.17 (0.9)	1.89 (Finland)	No use (Greece)
TMP-SMX	1.31 (5.2)	0.56 (2.9)	1.62 (Croatia)	<0.01 (Denmark)
Clarithromycin	1.10 (4.4)	1.23 (6.5)	7.16 (Greece)	0.06 (Sweden)
Minocycline	1.07 (4.3)	0.24 (1.3)	1.36 (Ireland)	No use (>1 country)
Levofloxacin	1.06 (4.3)	0.24 (1.3)	1.05 (Italy)	No use (>1 country)
Ciprofloxacin	0.97 (3.9)	0.59 (3.1)	1.81 (Portugal)	0.17 (Croatia)
Phenoxymethylpenicillin	0.68 (2.7)	0.64 (3.4)	5.23 (Denmark)	No use (>1 country)
Nitrofurantoin	0.63 (2.5)	0.27 (1.4)	0.8 (The Netherlands)	No use (>1 country)
Tetracycline	0.57 (2.3)	0.08 (0.4)	1.02 (Finland)	No use (>1 country)
Erythromycin	0.43 (1.7)	0.34 (1.8)	1.72 (United Kingdom)	0.01 (Bulgaria)
Cefuroxime	0.35 (1.4)	0.70 (3.7)	3.40 (Luxembourg)	No use (Norway)
Cefdinir	0.34 (1.4)	No use	No use	No use (>1 country)
Clindamycin	0.25 (1.0)	0.14 (0.8)	0.70 (Hungary)	<0.01 (Italy)
Moxifloxacin	0.25 (1.0)	0.16 (0.9)	0.56 (Belgium)	No use (>1 country)
Total	24.91 (100)	19.04 (100)	33.37 (Greece)	9.75 (The Netherlands)

NOTE. Data are for antibacterials with ≥1.0% of total use in the United States. DID, defined daily doses per 1000 inhabitants per day; TMP-SMX, trimethoprim-sulfamethoxazole.

Goossens H et al. Clin Infect Dis. 2007; 44:1091

Fluoroquinolones Spectrum of Activity

- *Enterobacteriaceae*
- *Haemophilus* spp. *Neisseria* spp.
- *Legionella, Mycoplasma, Chlamydia* [Levofloxacin, Gatifloxacin, Moxifloxacin]
- *Pseudomonas aeruginosa* [Ciprofloxacin, Levofloxacin]

Fluoroquinolones Spectrum of Activity

- Staphylococci (MSSA, MSSE) [Levofloxacin, Gatifloxacin, Moxifloxacin, Gemifloxacin]
- Streptococci (+/- enterococci) [Levofloxacin, Gatifloxacin, Moxifloxacin, Gemifloxacin]
- Anaerobes [Gatifloxacin, Moxifloxacin]
- Mycobacteria (*M. tuberculosis*, *M. kansasii*, *M. fortuitum*) [Ciprofloxacin, Levofloxacin, Gatifloxacin, Moxifloxacin]

General Clinical Uses of Fluoroquinolones

- Urinary Tract Infections
- Prostatitis
- Sexually Transmitted Diseases
- Gastroenteritis
- Intraabdominal Infections
- Respiratory Tract Infections
- Bone & Joint Infections
- Skin & Soft Tissue Infections
- Other Broad Uses in Hospitalized Patients

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Cross Resistance Among Penicillin-Resistant Strains of *Streptococcus pneumoniae*

Antimicrobial	% Resistant to Other Antimicrobial		
	Penicillin Susceptible (n=2636)	Penicillin Intermediate (n=356, 10%)	Penicillin Resistant (n=483, 14%)
Amoxicillin	0.0	1.8	82.2
Cefuroxime	0.1	34.8	100
Cefotaxime	0.0	2.8	42.4
Meropenem	0.0	0.8	52.0
Erythromycin	3.2	35.1	61.3
TMP-SMX	6.6	49.4	92.3
Tetracycline	1.3	19.1	25.5

Whitney CG et al. N. Engl. J. Med. 2000;343:1917-24

Cross Resistance Among Penicillin-Resistant Strains of *Streptococcus pneumoniae*

Antimicrobial	% Resistant to Other Antimicrobial		
	Penicillin Susceptible (n=2636)	Penicillin Intermediate (n=356)	Penicillin Resistant (n=483)
Chloramphenicol	0.4	6.7	14.7
Clindamycin	0.5	10.7	12.2
Rifampin	0.2	0.0	0.2
Levofloxacin	0.1	0.3	0.7
Quinupristin-dalfopristin	0.0	0.6	0.2

Whitney CG et al. N. Engl. J. Med. 2000;343:1917-24

Activity of Quinolones Against 75 Ciprofloxacin-Resistant Isolates of *Streptococcus pneumoniae*

Quinolone	Cumulative % Isolates at MIC (μg/ml)					
	≤0.06	0.12-0.25	0.5-1	2-4	8-16	32-64
Levofloxacin			16	67	95	100
Gatifloxacin		4	64	93	100	
Moxifloxacin		56	71	97	100	
Gemifloxacin	61	92	100			

Chen DK et al. 1999. N Engl J Med. 341:233-9

Pharmacokinetic Properties of Oral Fluoroquinolones

Drug	Dose (mg - frequency)	C_{max} (μg/ml)	$t_{½}$ (h)	Renal Clearance (% of total)
Ciprofloxacin	500 BID	2.2	3.3	50
Levofloxacin	500 QD	5.7	6-8	65
	750 QD	8.6		
Gatifloxacin	400 QD	4.1	7-8	80
Moxifloxacin	400 QD	4.5	13	22
Gemifloxacin	320 QD	1.8	7	30

Randomized Comparison of Levofloxacin with Ceftriaxone/Cefuroxime for Treatment of Community-Acquired Pneumonia

Pathogen	No. (%) of Patients Responding to:					
	Levofloxacin			Ceftriaxone/Cefuroxime		
	Cured	Improved	Failed	Cured	Improved	Failed
S. pneumoniae	23(77)	7(23)	0	24(73)	7(21)	2(6)
[bacteremic]	7(78)	2(22)	0	4(50)	4(50)	0
H. influenzae	24(80)	6(20)	0	17(71)	2(8)	5(21)
C. pneumoniae	34(72)	12(26)	1(2)	34(63)	16(30)	4(7)
M. pneumoniae	15(79)	4(21)	0	17(77)	5(22)	0
L. pneumophila	4(80)	1(20)	0	2(66)	0	1(33)

File TM *et al.* Antimicrob Agents Chemother. 41:1965 (1997)

Comparison of High-Dose Short-Course with Conventional-Course Levofloxacin for Community-Acquired Pneumonia

Clinical Responses by Severity

Patient category	*n/N* (%)[a] 750-mg group[b] (*n* = 198)	500-mg group[c] (*n* = 192)	95% CI[d]
Evaluable patients	183/198 (92.4)	175/192 (91.1)	−7.0 to 4.4
Stratum I[e]			
Total	69/76 (90.8)	73/86 (84.9)	−16.5 to 4.7
PSI class III[f]	44/49 (89.8)	44/51 (86.3)	−17.2 to 10.2
PSI class IV[g]	25/27 (92.6)	27/32 (84.4)	−26.1 to 9.6
PSI class V[h]	0/0 (0.0)	2/3 (66.7)	Not applicable
Stratum II[i]	114/122 (93.4)	102/106 (96.2)	−3.4 to 9.0

Dunbar LM et al. Clin Infect Dis 2003; 37: 752

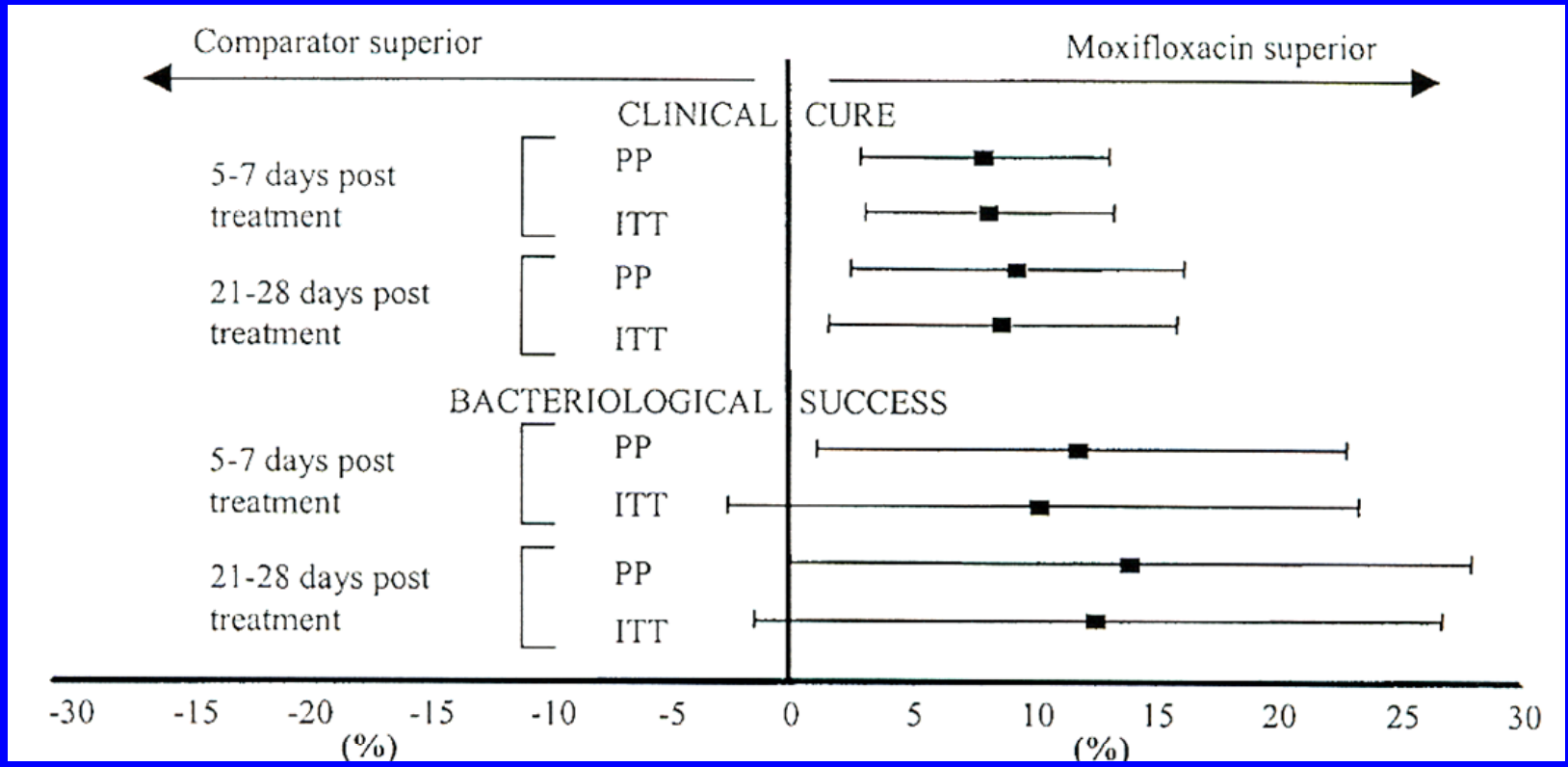
Comparison of High-Dose Short-Course with Conventional-Course Levofloxacin for Community-Acquired Pneumonia

Clinical Responses by Pathogen

Pathogen class, species	*n/N* (%)[a]	
	750-mg group[b]	500-mg group[c]
Typical pathogen[d]		
Haemophilus influenzae	12/13 (92.3)	13/14 (92.9)
Haemophilus parainfluenzae	12/12 (100.0)	9/10 (90.0)
Streptococcus pneumoniae	20/22 (90.9)	18/20 (90.0)
Atypical pathogen[e]		
Chlamydia pneumoniae	20/22 (90.9)	16/16 (100.0)
Legionella pneumophila	11/11 (100.0)	3/3 (100.0)
Mycoplasma pneumoniae	41/43 (95.3)	34/36 (94.4)

Dunbar LM et al. Clin Infect Dis 2003; 37: 752

Moxifloxacin vs Amoxicillin-Clavulanate in Community-Acquired Pneumonia



Moxifloxacin 400 mg QD IV → PO
Amox-clav 1.2g TID IV → 625 mg TID-QID PO (± clarithromycin)

Finch R et al. Antimicrob Agents Chemother. 2002; 46:1746-54

Moxifloxacin vs Amoxicillin-Clavulanate in Community-Acquired Pneumonia

Eradication	Moxifloxacin % (n/N)	Amox-Clav % (n/N)
Total	94 (60/64)	82 (58/71)
S. pneumoniae		
Sputum	100 (18/18)	77 (17/22)
Blood	100 (11/11)	90 (9/10)
H. influenzae	100 (12/12)	90 (9/10)
M. pneumoniae	100 (13/13)	95 (16/17)

Finch R et al. Antimicrob Agents Chemother. 2002; 46:1746-54

IDSA Guidelines for Initial Empiric Treatment of Patients with Community-Acquired Pneumonia

Outpatients

- Previously healthy without use of antimicrobials within 3 months (except in areas with >25% macrolide resistance)
  - a macrolide or doxycycline
- Patients with co-morbid illness or prior antimicrobials (chronic heart, lung, or liver disease, diabetes, malignancy, immunosuppression or antimicrobials within last 3 mo)
  - Respiratory fluoroquinolone[A] OR
  - β-Lactam plus a macrolide

[A][levofloxacin (750 mg), moxifloxacin (400 mg), or gemifloxacin (320mg)]

Mandell LA *et al*. Clin Infect Dis 2007; 44:S27

IDSA Guidelines for Initial Empiric Treatment of Patients with Community-Acquired Pneumonia

Hospitalized patients (non-ICU)

- Respiratory fluoroquinolone[A] OR
- β-Lactam plus a macrolide

Hospitalized patients (ICU)

- (Cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus (azithromycin or respiratory fluoroquinolone)

[A][levofloxacin (750 mg), moxifloxacin (400 mg), or gemifloxacin (320mg)]

Mandell LA *et al*. Clin Infect Dis 2007; 44:S27

IDSA Guidelines for Initial Empiric Treatment of Patients with Community-Acquired Pneumonia

Special considerations

- If *Pseudomonas aeruginosa*
  - (Piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus [ciprofloxacin or levofloxacin (750 mg)] OR
  - (Piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus aminoglycoside plus (azithromycin or respiratory fluoroquinolone[A])
- If community-acquired MRSA
  - Add vancomycin or linezolid

[A][levofloxacin (750 mg), moxifloxacin (400 mg), or gemifloxacin (320mg)]

Mandell LA *et al*. Clin Infect Dis 2007; 44:S27

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Quinolone Treatment of Hospital-Acquired Pneumonia

Reference	Included patients without NP	No. of patients with NP	Blinded	Agent (dose)	Comparator	Combination therapy permitted	Patients receiving combination therapy, %	Patients with VAP, %	APACHE II score, mean ± SD		Percentage of patients requiring vasopressors at enrollment	
									In quinolone arm	In comparator arm	Among patients receiving quinolones	Among patients receiving comparators
Fink et al. [17]	Yes	312	Yes	Cpfx (400 mg q8h)	Imipenem-cilistatin	Yes	45.1	58.9	17.7± 6.5	17.6 ± 6.4	NR	NR
Saginur et al. [18]	Yes	149	No	Cpfx (300 mg q8h)	Ceftazadime	Yes	52.3	51.7	NR	NR	NR	NR
Krumpe et al. [19]	Yes	138	No	Cpfx (400 mg q8h)	Not standardized; left to primary physician	Yes	22.5	NR	NR	NR	NR	NR
Torres et al. [20]	No	152	No	Cpfx (400 mg q8h)	Imipenem-cilistatin	No	NA	100	13.8 ± 7.5	13.9 ± 8.6	NR	NR
West et al. [21]	No	435	No	Lvfx (750 mg q.d.)	Imipenem-cilistatin	Yes	58.3	50.7	15.0 ± 5.8	14.8 ± 6.0	17.3	11.5

NOTE. Cpfx, ciprofloxacin; Lvfx, levofloxacin; NA, not applicable; NR, not reported in trial; VAP, ventilator-associated pneumonia.

Shorr AF et al. Clin Infect Dis 2005; 40:S115

Quinolone Treatment of Hospital-Acquired Pneumonia

Reference	Microbiologically evaluable population, no. of patients (% of entire cohort)	*Pseudomonas* species isolates, %	*Acinetobacter* species isolates, %	MRSA isolates, %
Fink et al. [17][a]	159 (51.0)	19.5	3.6	0.3
Saginur et al. [18]	119 (79.9)	3.4	0	0
Krumpe et al. [19][a]	109 (79.0)	15.6	1.9	NR
Torres et al. [20]	75 (49.3)	34.7	12.0	1.3
West et al. [21]	187 (43)	18.2	5.9	10.7

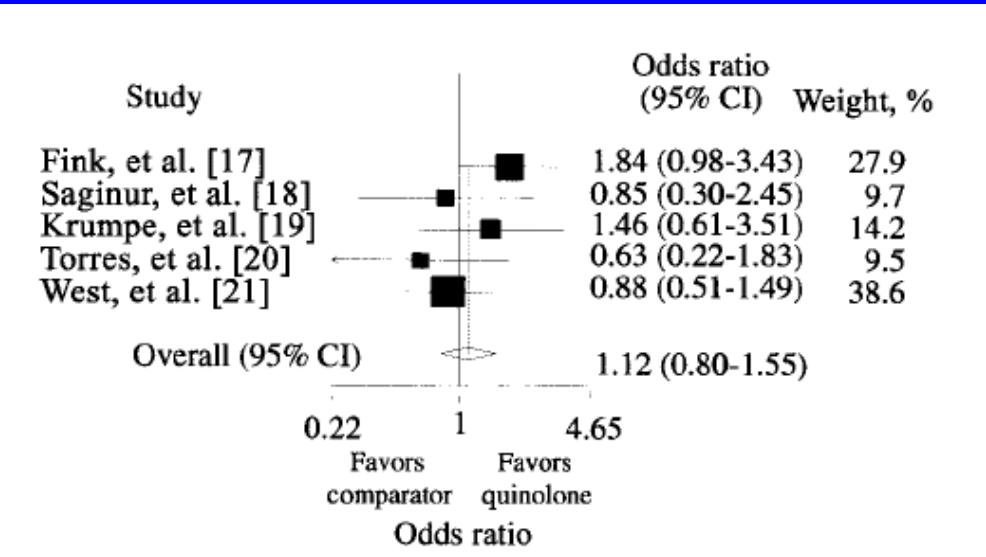
NOTE. MRSA, methicillin-resistant *Staphylococcus aureus;* NR, not reported.

[a] For the trials that included patients with infections other than NP, reported results represent findings based of the data available for the entire study cohort (i.e., patients with both NP and other infections).

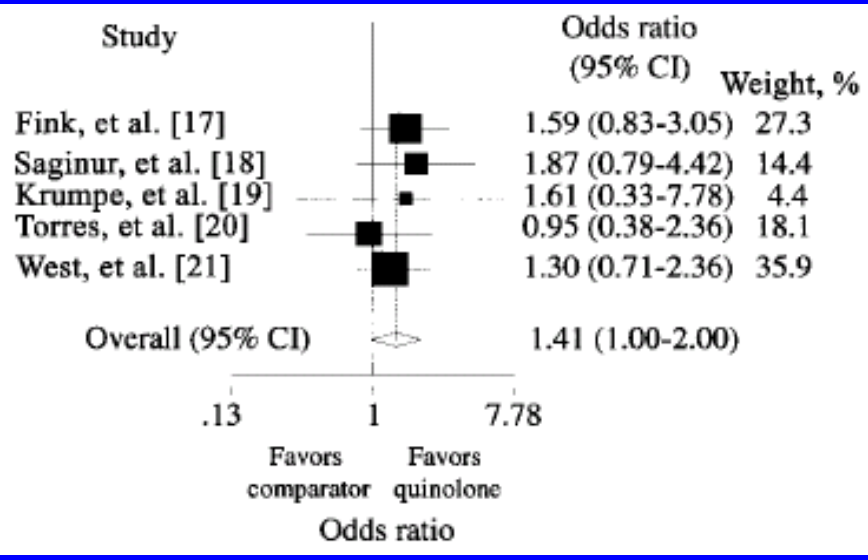
Shorr AF et al. Clin Infect Dis 2005; 40:S115

Outcomes of Quinolone Treatment of Hospital-Acquired Pneumonia

Clinical Outcomes

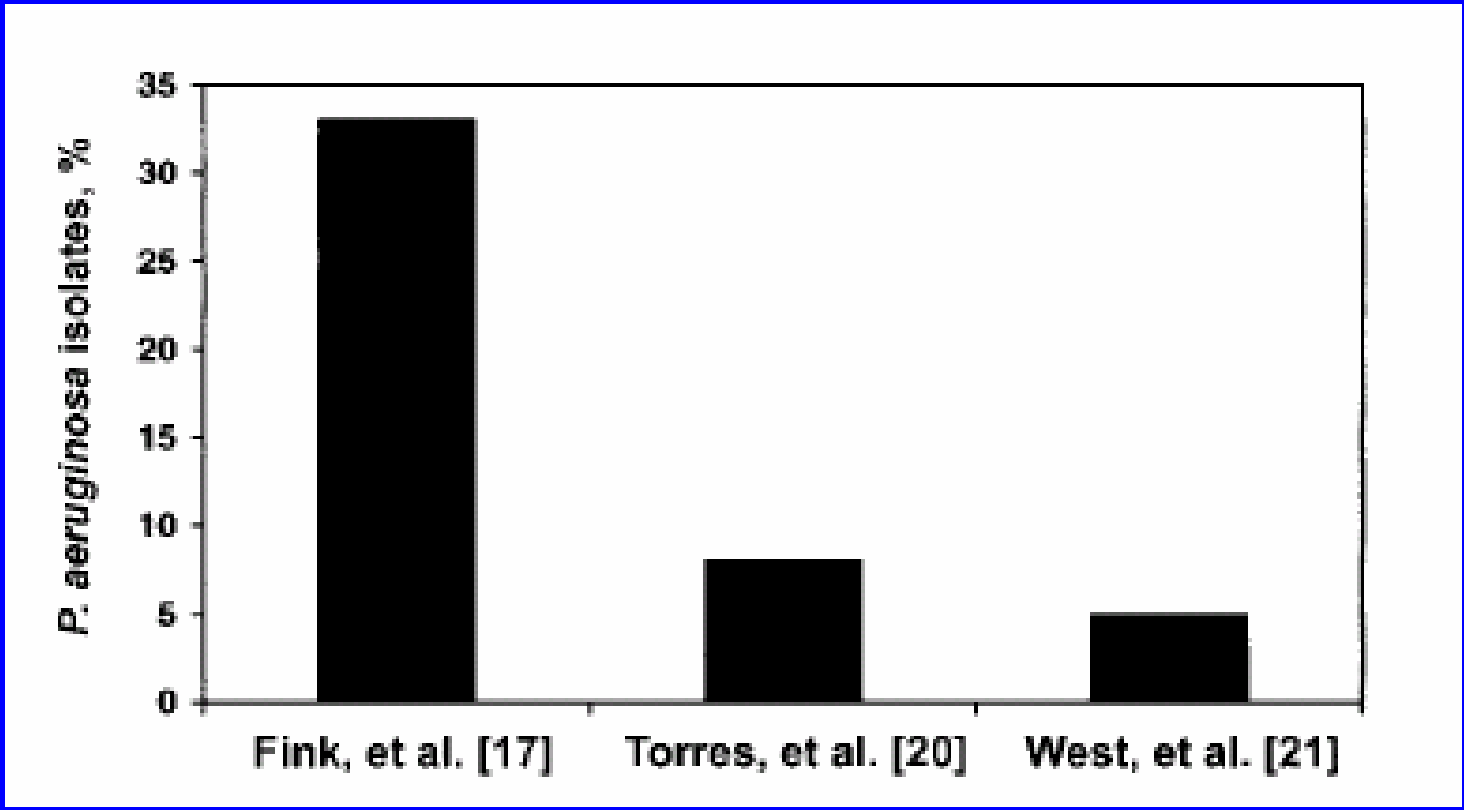


Microbiological Outcomes



Shorr AF et al. Clin Infect Dis 2005; 40:S115

Development of Quinolone Resistance Related to Therapy in Hospital-Acquired Pneumonia

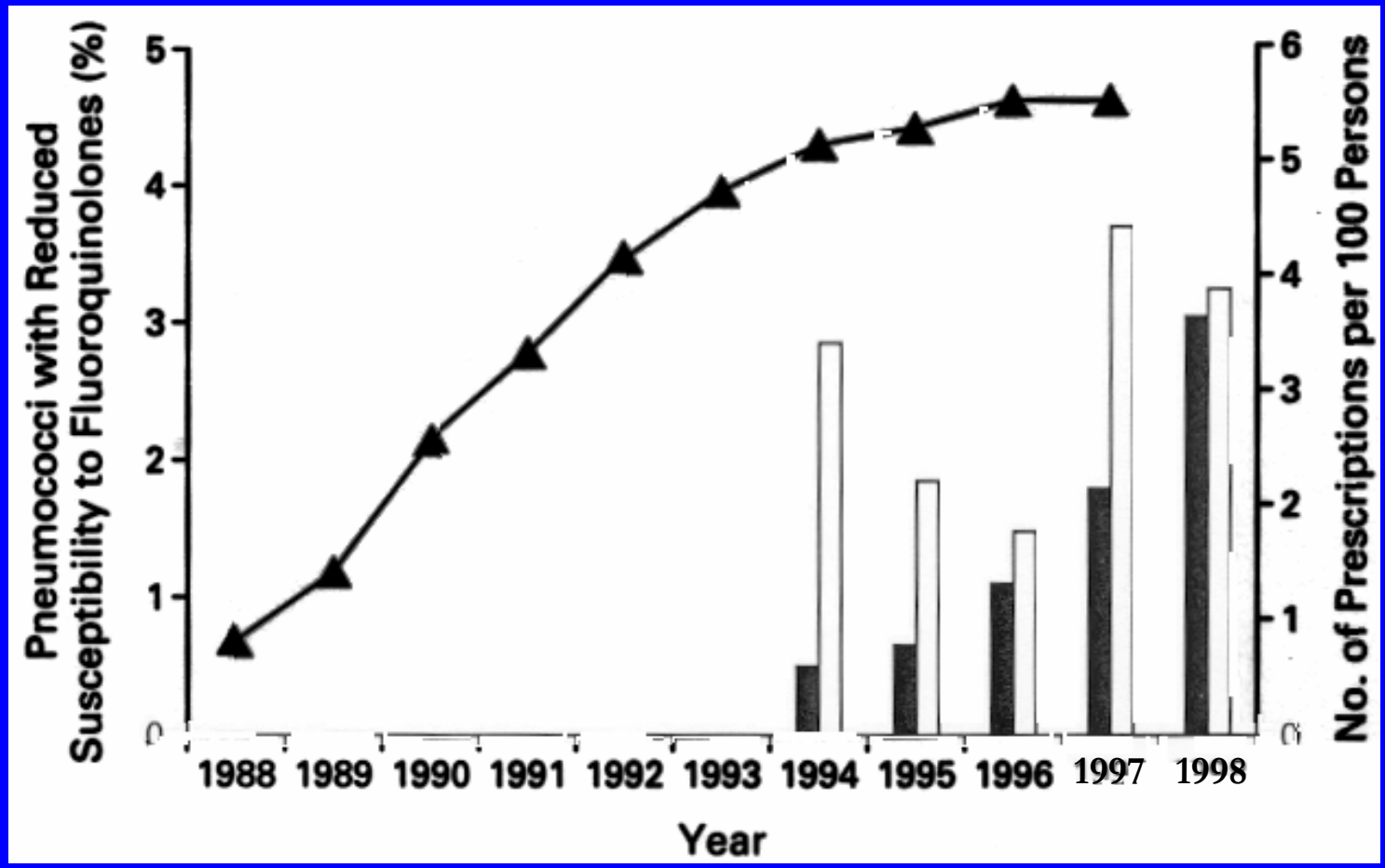


Shorr AF et al. Clin Infect Dis 2005; 40:S115

Fluoroquinolones Adverse Effects

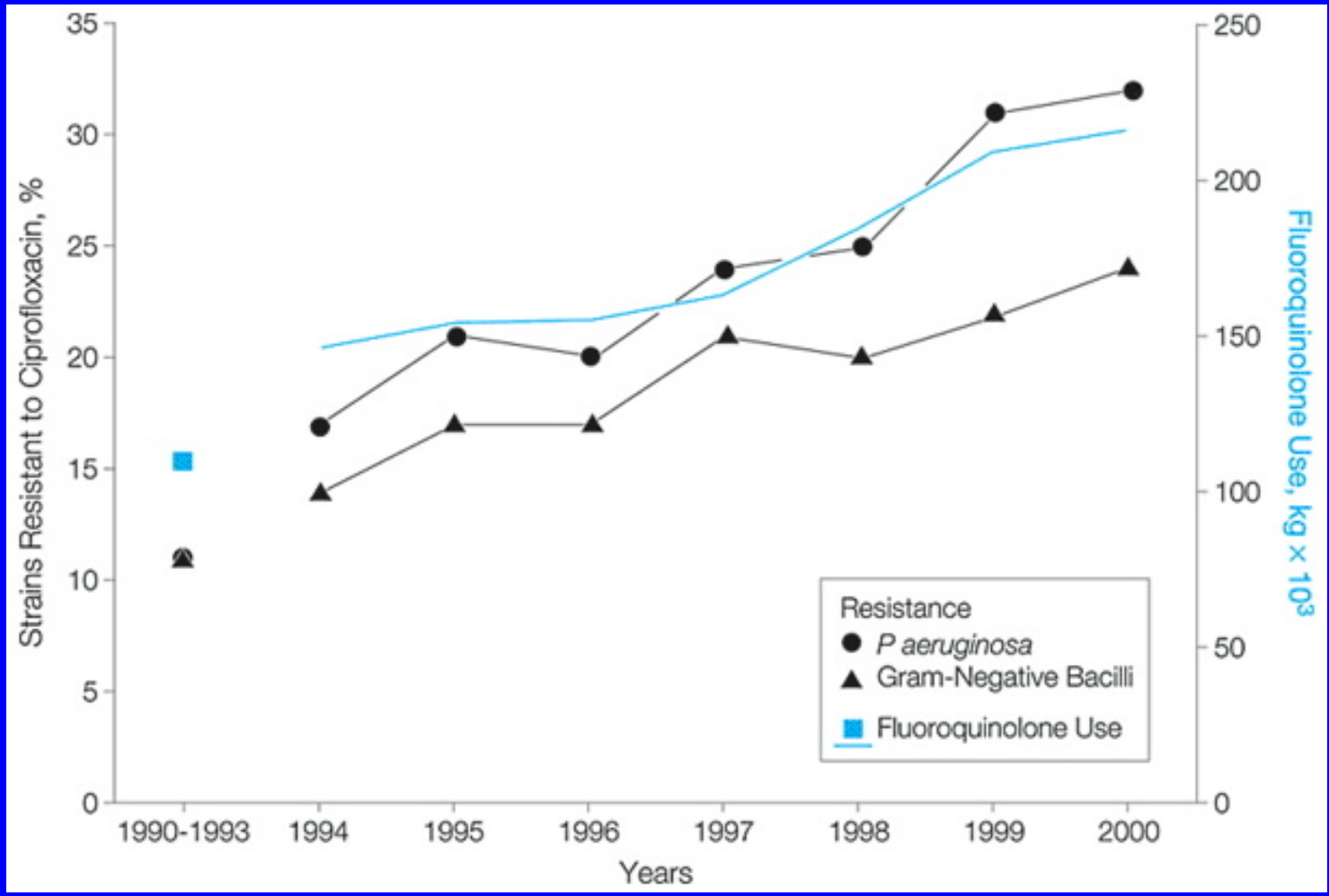
- Nausea, vomiting, diarrhea, taste perversion
- Insomnia, HA, dizziness (trovafloxacin), psychiatric, seizures [inhibit GABA binding to receptors]
- Rash, photosensitivity (lomefloxacin, sparfloxacin, gemifloxacin)
- Hepatotoxicity (trovafloxacin)
- Dysglycemia (gatifloxacin)
- QT prolongation (sparfloxacin > moxifloxacin)
- Cartilage erosions in juvenile animals
- Tendinitis

Temporal Trends in Quinolone Resistance in *S. pneumoniae*



Chen DK et al. 1999. N Engl J Med. 341:233-9

Increasing Quinolone Resistance Associated with Increasing Use



Neuhauser MM et al. JAMA 2003; 289:885-8

Ciprofloxacin Resistance in Gram-Negative Bacilli in ICUs in the United States - 1994-2000

Species	Resistant (%)	Change[A] (%)	Cross Resistance to: Gent (%, CipR/CipS)	Ceftaz (%, CipR/CipS)	Imip (%, CipR/CipS)
P. aeruginosa	24	+13	66/21	40/14	38/11
Enterobacter sp.	10	+6	49/4	82/32	4/1
K. pneumoniae	12	+7	67/7	65/6	3/0.5
E. coli	3	+2			
All isolates[B]	19	+10			

[A]Change relative to 1990-1993 [B]n=35,790

Neuhauser MM *et al*. JAMA 2003; 289:885-888

Prevalence of Bacterial Resistance to Fluoroquinolones

Staphylococci (MRSA, MRSE)	60-95%
Pseudomonas aeruginosa	24-44%
Klebsiella pneumoniae	12-20%
Enterobacter spp.	10-12%
Escherichia coli	3-50%
Campylobacter jejuni	3-70%

Epidemiology of Ciprofloxacin Resistance in *Klebsiella pneumoniae*

- 455 Bacteremias (440 patients) in 12 hospitals in 7 countries
- 25 (5.5%) with MIC of ciprofloxacin ≥ 4 μg/ml
  - 15/25 (60%) also ESBL-producing
- 83 (18%) ESBL-producing
  - 15/83 (18%) also ciprofloxacin-resistant

Paterson DL *et al*. Clin Infect Dis 30:473-8 (2000)

Epidemiology of Ciprofloxacin Resistance in *Klebsiella pneumoniae*

- Risk factors for resistance (multivariate)
  - Prior receipt of quinolone (p=0.0065)
  - ESBL-producing strain (p=0.012)
  - Hospitalization in Turkish center (p=0.011)
  - Not prior receipt of 3rd-gen cephalosporin (p=0.17)
  - Not indwelling urinary catheter (p=0.24)

Paterson DL *et al*. Clin Infect Dis 30:473-8 (2000)

Epidemiology of Ciprofloxacin Resistance in *Klebsiella pneumoniae*

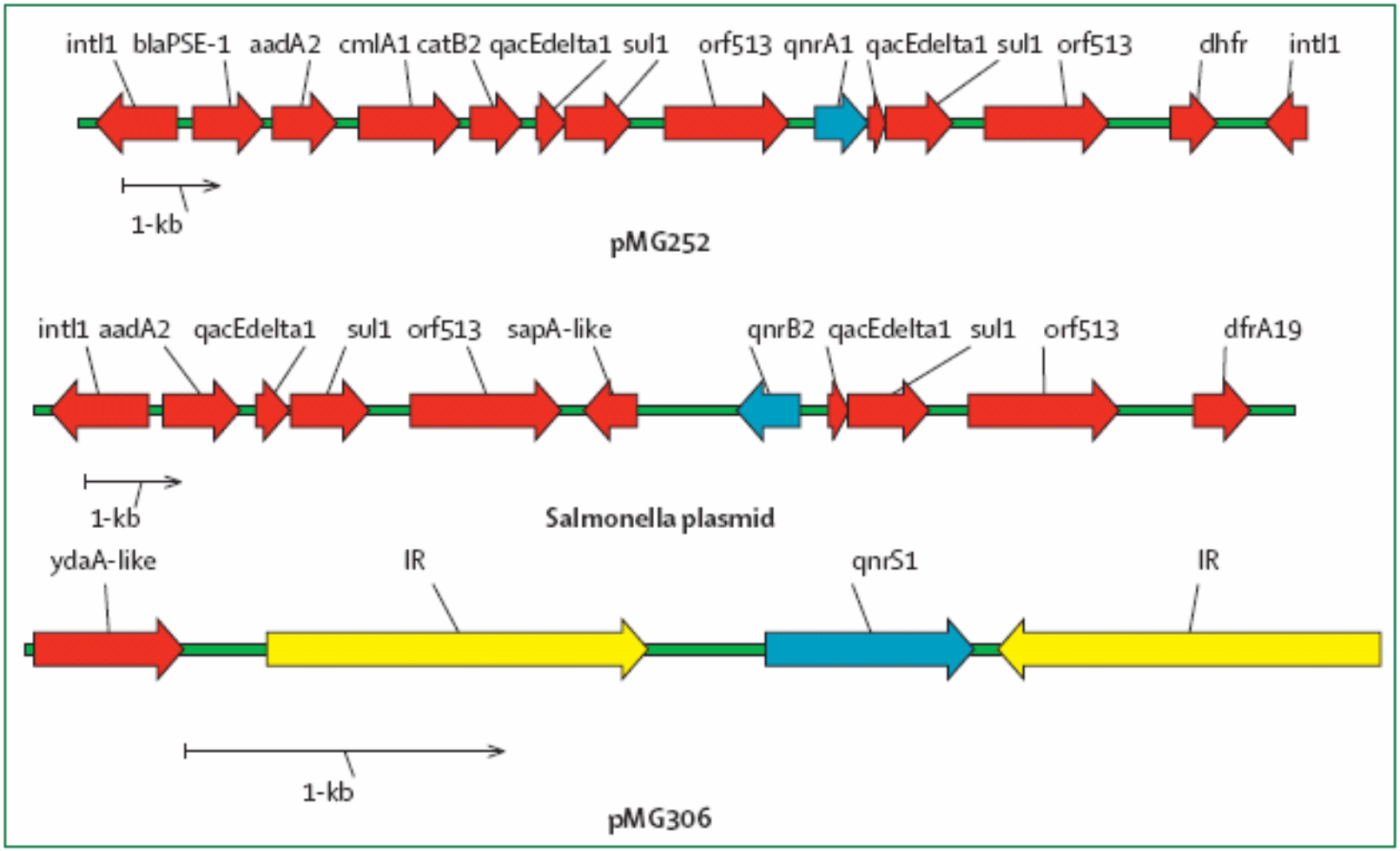
- Nosocomial acquisition
  - 72% of ciprofloxacin-resistant cases
  - 54% of ciprofloxacin-susceptible cases (p=0.08)
- Clustering based on PFGE genotype
  - 4 clusters of 2-4 cases each in 3 hospitals
  - In 2 clusters exposure to quinolone occurred in 1st case
- Mortality (14 days)
  - 4/25 (16%) Cip-R vs. 120/427 (28%) Cip-S (p=0.19)

Paterson DL *et al*. Clin Infect Dis 30:473-8 (2000)

Mechanisms of Resistance to Fluoroquinolones

- Chromosomal mutations
  - Alterations in DNA gyrase and/or topoisomerase IV
  - Active drug efflux (MDR pumps) +/- reduced porin diffusion channels
- Plasmid-mediated resistance
  - Enteric gram-negative bacteria; target protection mechanism by Qnr proteins
  - Drug modification

Plasmid-Encoded Quinolone Resistance: *qnr* Genes



Robicsek A et al. Lancet Infect Dis 2006; 6:629-40

Occurrence of Integron-Carrying Enteric Bacteria in ICUs

Variable	No. (%) of ICU Patients	
	Medical (n = 277)	Neurosurgical (n = 180)
Total colonized	19 (7)	12 (7)
Acquired colonization	14 (5)	9 (5)
Time to acquisition (d)	10 ± 10	12 ± 10
Acquisition rate (per 1000 patient-days)	10	8

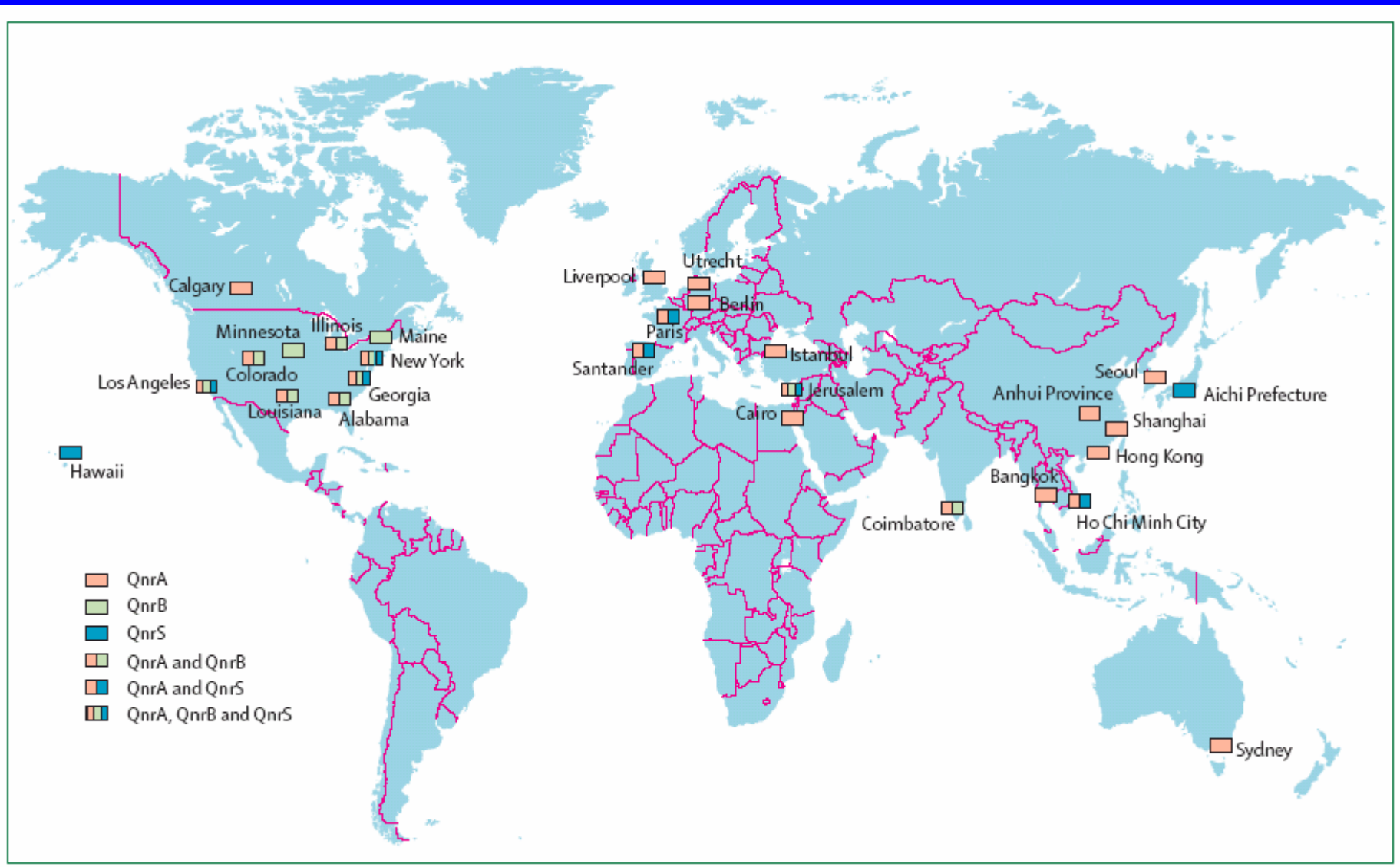
Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

Resistance Profiles of Integron-Carrying Enteric Bacteria

Antimicrobial	Percent Resistant	
	Integron (-) (n = 120)	Integron (+) (n = 54)
Piperacillin	24	94*
Ceftazidime	26	33
Cefotaxime	29	44*
Meropenem	0	0
Gentamicin	2	94*
Ciprofloxacin	3	33*

Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

Worldwide Distribution of *qnr* Quinolone Resistance Genes



Robicsek A et al. Lancet Infect Dis 2006; 6:629-40

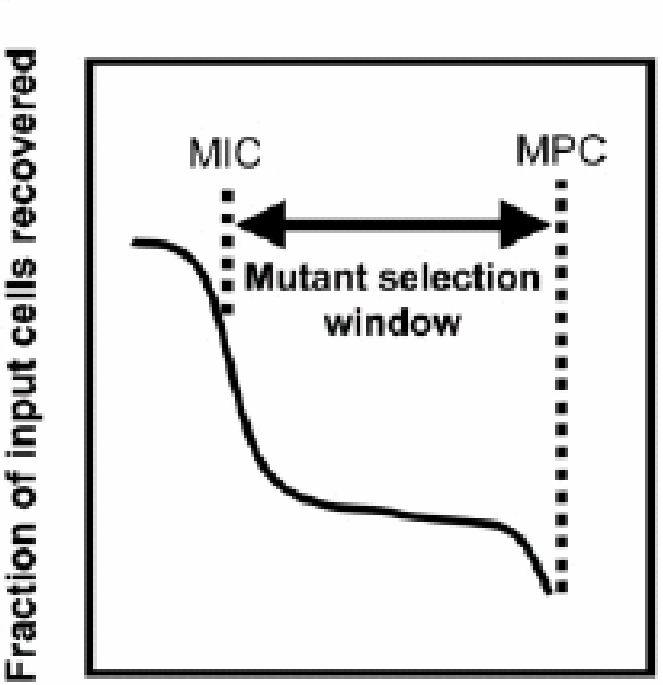
Limiting Bacterial Resistance to Fluoroquinolones

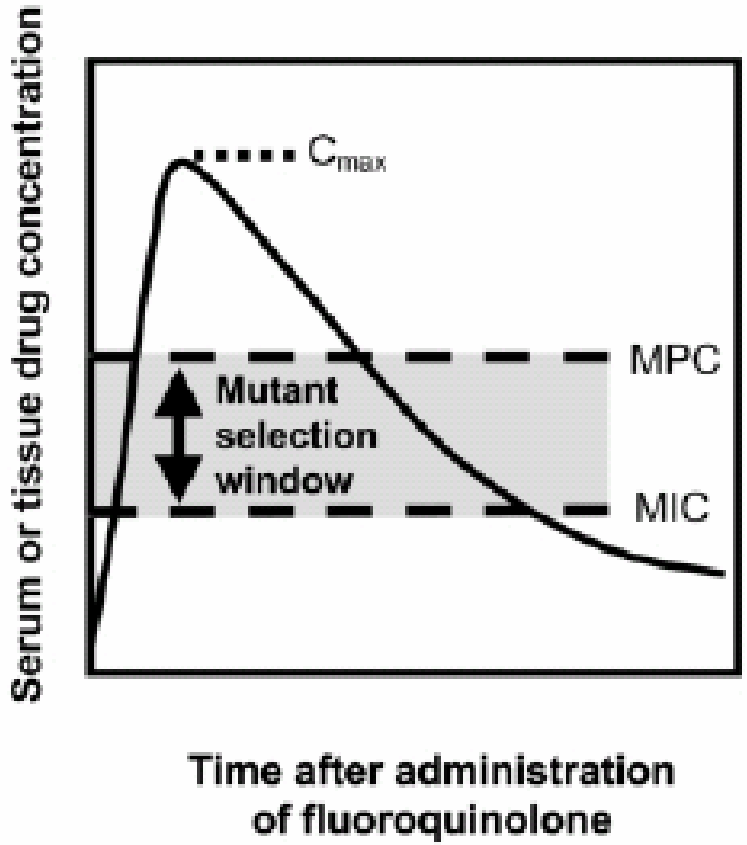
- Monitor Resistance
- Good Infection Control to Limit Spread
- Focused and Balanced Use to Limit Selective Pressures
- Adequate Dosing to Limit Mutant Selection

Pharmacodynamic Factors Affecting Risk of Selection of Quinolone Resistance

- Selecting Drug Concentration in Vitro
- C_{max}/MIC - Animal Models
- AUC/MIC - Human Use

Pharmacodynamics of Quinolone-Resistant Mutant Selection





Drlica K and Zhao X. Clin Infect Dis. 2007; 44:681

Limiting Bacterial Resistance to Fluoroquinolones

- Possible Use of Combination Regimens:
  - With Other Antibiotics
  - Specific Inhibitors of Resistance Mechanisms
- Development of New Quinolones
  - Similar Activity Against Both Enzyme Targets
  - Improved Therapeutic Index