

Gemifloxacin Comparative In Vitro Surveillance Study of Penicillin- and Macrolide-resistant Pneumococci and other Respiratory Pathogens in Asian and Pacific Rim Countries

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Abstract

Background: Macrolide- and penicillin-resistant *Streptococcus pneumoniae* (>60% and >30%, respectively) and evolving antimicrobial-resistant *Haemophilus influenzae* and *Moraxella catarrhalis* strains are prevalent in Asian and Pacific Rim countries. The introduction of respiratory quinolones has provided alternatives to less dependable agents in the treatment of respiratory infections. Gemifloxacin, an enhanced-affinity quinolone, and other agents were tested against *S. pneumoniae* (670), *H. influenzae* (308) and *M. catarrhalis* (107) isolates from 11 countries in Asia and the Pacific Rim, collected as part of a larger study representing 9233 organisms. **Methods:** Isolates were collected in 1999–2000 from centers throughout Asia and the Pacific Rim and sent to one central testing center. MIC determinations were performed following NCCLS recommended procedures using broth microdilution panels and ancillary products from Dade MicroScan. **Results:** MIC₉₀ expressed as µg/ml and percent non-susceptible (%):

Agent	PSSP (n = 268)	PRSP (n = 177)	MSSP (n = 284)	MRSP (n = 369)	<i>H. influenzae</i> (n = 308)	<i>M. catarrhalis</i> (n = 107)
Gemifloxacin	0.06 (NA) ^a	0.06 (NA)	0.06 (NA)	0.06 (NA)	0.015 (NA)	0.03 (NA)
Levofloxacin	1 (0.4)	1 (0)	1 (0.3)	1 (0)	0.03 (0.3)	0.06 (NA)
Ofloxacin	2 (0.8)	2 (3)	2 (0)	2 (2)	<0.06 (0.6)	0.12 (NA)
Ciprofloxacin	2 (NA)	2 (NA)	2 (NA)	2 (NA)	<0.015 (1.0)	0.06 (NA)
Trovafoxacin	0.12 (0)	0.12 (0)	0.12 (0)	0.12 (0)	<0.015 (0.3)	0.03 (NA)
Azithromycin	>64 (16)	>64 (96)	0.5 (0)	>64 (100)	4 (3)	0.12 (NA)
Clarithromycin	>16 (16)	>16 (96)	0.06 (0)	>16 (100)	>16 (38.0)	0.25 (NA)
Penicillin	0.06 (0)	2 (100)	0.5 (22)	2 (89)	>16 (NA)	>16 (NA)
Ampicillin	<0.06 (NA)	4 (NA)	0.5 (NA)	4 (NA)	>64 (40.0)	>64 (NA)

PSSP, penicillin-susceptible *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*; MSSP, macrolide-susceptible *S. pneumoniae*; MRSP, macrolide-resistant *S. pneumoniae*
^aNA, breakpoints have not been established by NCCLS

Conclusions: *S. pneumoniae* demonstrated high prevalences of resistance to macrolides and penicillin. The MIC₉₀ for gemifloxacin was the lowest against *S. pneumoniae*, including penicillin- and macrolide-resistant strains, among all antimicrobials tested.

Introduction

Gemifloxacin, an enhanced-affinity fluoroquinolone, has demonstrated *in vitro* activity that includes Gram positive bacteria, including streptococci and staphylococci, as well as Gram negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae* and *Haemophilus influenzae*. However, the therapeutic utility of new and currently marketed antimicrobials may vary greatly from region to region of the world.

Gemifloxacin and comparative agents were tested against 9233 organisms isolated from 11 countries in Asia and the South Pacific during 1999 and 2000. The *in vitro* activities of gemifloxacin and other agents against respiratory pathogens, such as *Streptococcus pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*, were determined for isolates collected in this region.

Materials and Methods

Isolates

- Isolates were collected between January 1999 and April 2000. Most sites in 11 countries contributed up to 50 isolates each of aerobic Gram positive and Gram negative pathogens, including up to 100 isolates each of *E. coli* and *K. pneumoniae*. Only one isolate per patient was accepted.
- Each isolate was identified and deemed to be a significant pathogen using local laboratory criteria.
- Isolate collection, processing, transport and antimicrobial susceptibility testing methods, as well as the construction of a centralized database to record worldwide antimicrobial susceptibility testing results, were coordinated by Laboratories International for Microbiology Studies, International Health Management Associates (IHMA) (Rolling Meadows, IL, USA).
- Available demographic information included patient age, specimen source and inpatient versus outpatient information.

MIC Determination

MICs were determined by the NCCLS recommended broth microdilution testing method.¹ The microdilution panels used in this study were purchased from MicroScan® (Dade Behring Inc, Sacramento, CA). Gemifloxacin was supplied by SmithKline Beecham (Collegeville, PA) and comparative antimicrobials by their respective manufacturers or the panel manufacturer. Appropriate broth media were also provided directly by the panel manufacturer.¹

All antimicrobial susceptibility testing was performed at one central laboratory. The antimicrobial breakpoints used for data analysis were those recommended by the NCCLS for broth dilution susceptibility testing.² Each designated testing laboratory performed quality controls each day of testing using *E. coli* ATCC 35218 and 25922, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49766 and 49247 and *Staphylococcus aureus* ATCC 29213. Test isolate results were accepted into the final analysis only if the quality control isolate MICs were within the acceptable range defined by NCCLS guidelines (M100-S10, 2000).

Participating Study Centers

The number of isolates from each participating country is shown in Table 1.

Table 1. Number of Isolates Per Country

Country	n	<i>S. pneumoniae</i>	<i>H. influenzae</i>	<i>M. catarrhalis</i>
China	109	51	58	0
Indonesia	52	52	0	0
Japan	109	46	27	36
Korea	191	170	11	10
Malaysia	49	49	0	0
Philippines	93	48	40	5
Singapore	132	49	36	47
Sri Lanka	32	32	0	0
Taiwan	36	36	0	0
Thailand	133	88	36	9
Vietnam	149	49	100	0

Results

Results are shown in Tables 2–6.

Conclusions

- The highest prevalences of penicillin resistance to *S. pneumoniae* were found in Taiwan, Korea, Vietnam, Japan, Thailand and Singapore at 61.1%, 52.4%, 38.7%, 30.5%, 21.6% and 18.4%, respectively.
- Macrolide susceptibility to *S. pneumoniae* varied greatly from 100% in Indonesia and the Philippines to 2.8%, 10.2% and 13% in Taiwan, Vietnam and Japan, respectively.
- MIC₉₀s for gemifloxacin against *S. pneumoniae* were the lowest of all agents tested regardless of country of origin of each isolate.
- The *in vitro* activity of gemifloxacin, levofloxacin, ofloxacin, grepafloxacin, ciprofloxacin and trovafoxacin did not appear to be related to penicillin-intermediate, penicillin-resistant and macrolide-resistant isolates of *S. pneumoniae*.
- Gemifloxacin, ciprofloxacin, grepafloxacin and trovafoxacin were the most active quinolones against *H. influenzae*.
- Gemifloxacin, grepafloxacin and trovafoxacin were more active against *M. catarrhalis* than all other agents tested.
- The MIC₉₀ for gemifloxacin was the lowest against *S. pneumoniae*, including penicillin- and macrolide-resistant strains, among all antimicrobials tested.
- The activity of newer quinolones, such as gemifloxacin, against penicillin- and macrolide-resistant isolates of *S. pneumoniae* promises a new therapeutic alternative to currently available agents.

Table 2. In Vitro Activity (MIC µg/ml) of Gemifloxacin and Four Comparative Agents Against 670 Isolates of *S. pneumoniae* from Countries in Asia and the South Pacific

Country	Antimicrobial	MIC ₅₀	MIC ₉₀	% S ^a	% I ^b	% R ^c
China (n = 51)	Gemifloxacin	0.03	0.06	NA ^a	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	64	>64	39.2	0	60.8
	Clarithromycin	>16	>16	39.2	0	60.8
	Penicillin	0.06	0.12	82.3	17.7	0
Indonesia (n = 52)	Gemifloxacin	0.03	0.03	NA	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	<0.06	0.12	100	0	0
	Clarithromycin	0.03	0.06	100	0	0
	Penicillin	0.06	0.06	94.2	5.8	0
Japan (n = 46)	Gemifloxacin	0.03	0.12	NA	NA	NA
	Levofloxacin	1	2	100	0	0
	Azithromycin	8	>64	13	0	87
	Clarithromycin	4	>16	13	0	87
	Penicillin	0.5	2	6.5	63	30.5
Korea (n = 170)	Gemifloxacin	0.03	0.06	NA	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	>64	>64	20	1.8	78.2
	Clarithromycin	>16	>16	20.8	1.2	78.2
	Penicillin	2	2	18.8	28.8	52.4
Malaysia (n = 49)	Gemifloxacin	0.03	0.06	NA	NA	NA
	Levofloxacin	1	1	98	2	0
	Azithromycin	<0.06	4	87.8	0	12.2
	Clarithromycin	0.03	1	89.8	0	10.2
	Penicillin	0.03	1	83.6	8.2	8.2
Philippines (n = 48)	Gemifloxacin	0.03	0.12	NA	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	0.12	0.12	100	0	0
	Clarithromycin	0.03	0.06	100	0	0
	Penicillin	0.06	0.06	93.8	6.2	0
Singapore (n = 49)	Gemifloxacin	0.03	0.06	NA	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	4	>64	36.7	8.2	55.1
	Clarithromycin	1	>16	36.7	8.2	55.1
	Penicillin	0.5	2	36.7	44.9	18.4
Sri Lanka (n = 32)	Gemifloxacin	0.03	0.03	NA	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	0.12	>64	75	0	25
	Clarithromycin	0.03	>16	75	0	25
	Penicillin	0.5	1.0	25	71.9	3.1
Taiwan (n = 36)	Gemifloxacin	0.03	0.06	NA	NA	NA
	Levofloxacin	0.5	1	100	0	0
	Azithromycin	>64	>64	2.8	0	97.2
	Clarithromycin	>16	>16	2.8	0	97.2
	Penicillin	2	4	2.8	36.1	61.1
Thailand (n = 88)	Gemifloxacin	0.03	0.06	NA	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	8	>64	39.8	1.1	59.1
	Clarithromycin	2	>16	43.2	1.1	55.7
	Penicillin	1	2	28.4	50	21.6
Vietnam (n = 49)	Gemifloxacin	0.03	0.12	NA	NA	NA
	Levofloxacin	1	1	100	0	0
	Azithromycin	>64	>64	10.2	0	89.8
	Clarithromycin	>16	>16	10.2	0	89.8
	Penicillin	1	2	8.2	53.1	38.7

^aNCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories
^bNA, breakpoints have not been established by NCCLS

Table 3. In Vitro Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobial Agents Against 670 Isolates of *S. pneumoniae* from Asia and the South Pacific Susceptible, Intermediate and Resistant to Penicillin

Phenotype (n)	Antimicrobial	MIC ₅₀	MIC ₉₀	Range	% S ^a	% I ^b	% R ^c
PSSP ^a (n = 268)	Gemifloxacin	0.03	0.06	0.002–0.12	NA ^a	NA	NA
	Levofloxacin	1	1	0.12–4	99.6	0.4	0
	Ofloxacin	2	2	0.5–8	99.2	0.4	0.4
	Grepafoxacin	0.12	0.25	<0.015–1	98.9	1.1	0
	Ciprofloxacin	1	2	0.25–8	NA	NA	NA
	Trovafoxacin	0.06	0.12	0.03–0.25	100	0	0
	Azithromycin	0.12	>64	<0.06–>64	83.6	0.4	16.0
	Clarithromycin	0.03	>16	<0.015–>16	84.3	0.4	15.3
	Penicillin	0.06	0.06	<0.015–0.06	100	0	0
	PISP ^b (n = 225)	Gemifloxacin	0.03	0.06	0.008–0.12	NA	NA
Levofloxacin		1	1	0.12–2	100	0	0
Ofloxacin		1	2	0.5–8	99.6	0	0.4
Grepafoxacin		0.12	0.25	<0.015–1	99.6	0.4	0
Ciprofloxacin		1	2	0.03–8	NA	NA	NA
Trovafoxacin		0.06	0.12	<0.015–0.5	100	0	0
Azithromycin		32	>64	<0.06–>64	24.4	2.2	73.4
Clarithromycin		8	>16	<0.015–>16	25.3	1.8	72.9
Penicillin		0.5	1	0.12–1	0	100	0
PRSP ^c (n = 177)		Gemifloxacin	0.03	0.06	0.015–0.25	NA	NA
	Levofloxacin	1	1	0.25–2	100	0	0
	Ofloxacin	2	2	1–4	96.6	3.4	0
	Grepafoxacin	0.12	0.5	<0.015–1	99.4	0.6	0
	Ciprofloxacin	1	2	0.25–8	NA	NA	NA
	Trovafoxacin	0.06	0.12	0.03–0.25	100	0	0
	Azithromycin	>64	>64	<0.06–>64	4.0	1.1	94.9
Clarithromycin	>16	>16	0.03–16	4.5	1.1	94.4	
Penicillin	2	2	>=16	0	0	100	

^aNCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories
^bPenicillin susceptible (PSSP) = <0.06 µg/ml; penicillin intermediate = 0.12–1.0 µg/ml; penicillin resistant = ≥2.0 µg/ml
^cNA, breakpoints have not been established by NCCLS

Table 4. In Vitro Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobial Agents Against 653 Isolates of *S. pneumoniae* from Asia and the South Pacific Susceptible, Intermediate and Resistant to Macrolides

Phenotype (n)	Antimicrobial	MIC ₅₀	MIC ₉₀	Range	% S ^a	% I ^b	% R ^c
MSSP ^a (n = 284)	Gemifloxacin	0.03	0.06	0.002–0.12	NA ^a	NA	NA
	Levofloxacin	1	1	0.12–4	99.7	0.3	0
	Ofloxacin	2	2	0.5–2	100	0	0
	Grepafoxacin	0.12	0.25	<0.015–0.5	99.2	0.8	0
	Ciprofloxacin	1	2	0.03–8	NA	NA	NA
	Trovafoxacin	0.06	0.12	<0.015–0.5	100	0	0
	Azithromycin	0.12	0.5	<0.06–0.5	100	0	0
	Clarithromycin	0.03	0.06	<0.015–0.25	100	0	0
	Penicillin	0.06	0.5	<0.015–>16	78.5	19.0	2.5
	MRSP ^b (n = 369)	Gemifloxacin	0.03	0.06	0.008–0.25	NA	NA
Levofloxacin		1	1	0.12–2	100	0	0
Ofloxacin		2	2	0.5–8	97.6	1.9	0.5
Grepafoxacin		0.12	0.5	<0.015–1	98.6	1.4	0
Ciprofloxacin		1	2	0.25–8	NA	NA	NA
Trovafoxacin		0.06	0.12	<0.015–0.5	100	0	0
Azithromycin		>64	>64	2–>64	0	0	100
Clarithromycin		>16	>16	1–16	0	0	100
Penicillin		1	2	0.03–>16	10.8	44.2	45.0

^aNCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories
^bMacrolide susceptible (MSSP) = azithromycin breakpoint ≤0.5 µg/ml and clarithromycin breakpoint ≤0.25 µg/ml
^cMacrolide resistant (MRSP) = azithromycin breakpoint ≥2.0 µg/ml and clarithromycin breakpoint ≥1.0 µg/ml
^d