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# Quinolone resistance in *Streptococcus pneumoniae* evaluated in three Asian countries during 2003-2004

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## REVISED ABSTRACT

**Background:** *Streptococcus pneumoniae* (SP) resistant to levofloxacin has been reported in Asian countries. The extent of these findings has not been clearly defined to date. This study follows the activity of 12 antimicrobials against strains of SP from outpatients in Hong Kong (HK), Taiwan (TI) and Japan (JP). All strains were isolated from patients with respiratory tract infections or isolated from blood. **Materials and Methods:** 1,408 SP isolates were collected (HK n=636; TI n=411; JP n=361) and identified using the collecting laboratories' normal procedure. Isolates were stored in TSB with glycerol vials at 20 degrees C or lower and shipped to a central laboratory in the United States. Susceptibility testing was performed using broth microdilution with panels produced by Trek Diagnostics. All testing was performed according to NCCLS guidelines. **Results:** SP non-susceptible to levofloxacin (LV), moxifloxacin (MX) and gatifloxacin (GX) were determined from isolates in HK are 14.1%, 11.2% and 10.8%, respectively. JP exhibited the next highest level of quinolone non-susceptibility with 3.8%, 3.0% and 3.6% to LV, MX and GX, respectively. TI showed the least amount of non-susceptibility among the three countries with 1.6%, 1.3% and 0.6% to LV, GX and MX, respectively. Macrolide/penicillin resistance still remains high at 78.6/63.2, 70.2/40.6 and 73.4/37.6 in HK, TI and JP, respectively.

**Conclusion:** Penicillin and macrolide resistance levels are high in these countries. Fluoroquinolone resistance is documented in Hong Kong and Japan at levels that suggest a close monitoring of these trends to ensure these agents are viable in the future.

## INTRODUCTION

Recently, evidence of problematic levels of fluoroquinolone resistance in *S. pneumoniae* has emerged from the Asian cities and countries, particularly Hong Kong [1, 2]. This is particularly notable since *Streptococcus pneumoniae* remains a critical bacterial pathogen in upper and lower respiratory tract infections worldwide. During the 1990s numerous in vitro surveillance studies monitored the rapid emergence of penicillin, macrolide and multi-drug resistance among isolates of *S. pneumoniae*. Concerns over these observations and increased clinical failures during the 1990's have resulted in new recommendations for the treatment of community-acquired pneumonias [3]. Newer fluoroquinolones entered the marketplace with great promise of treating resistant strains of *S. pneumoniae* particularly those resistant to  $\beta$ -lactam antibiotics, and quinolone resistance in *S. pneumoniae* has increased along with usage. Various presentations have reported increased *S. pneumoniae* resistance to all fluoroquinolones at varying rates in different areas of the world [4, 5]. This study focuses on measuring the incidence of fluoroquinolones resistance in three countries in Asia – Hong Kong, Japan and Taiwan. Community sites in these countries were asked to collect a total of 700 *S. pneumoniae* from each country for testing and shipping back to a central laboratory for analysis.

## MATERIALS & METHODS

### *S. Pneumoniae* Isolates

- Between September 2003 and September 2004, 9 study sites in 3 countries prospectively collected isolates, with most sites contributing approximately 150 isolates of *S. pneumoniae* for study. Isolates were selected to include those from male and female, and adults and children.

- Each isolate was identified as *S. pneumoniae* and deemed to be a significant pathogen.

- The *S. pneumoniae* isolates described here are from community-acquired infections and may include isolates from: sinus, ear, blood, lung, bronchioles, sputum and other sites from both upper and lower respiratory tract infections.

- Isolate collection, processing, transport, antimicrobial susceptibility testing methods and the construction of a centralised database to record worldwide antimicrobial susceptibility testing results was co-ordinated by Laboratories International for Microbiology Studies, International Health Management Associates (IHMA, Schaumburg, IL, USA).

- Available demographic information included patient gender, patient age and specimen source.

### Participating Study Centres

Country	Sites (n)	<i>S. pneumoniae</i> (n)
Hong Kong	4	636
Japan	2	361
Taiwan	3	411

### ANTIMICROBIAL SUSCEPTIBILITY TESTING

- MICs were determined by the NCCLS recommended broth microdilution testing method [6]. The microdilution panels used in this study were purchased from Sensititre (Trek Diagnostics Inc, Westlake, OH). Appropriate broth media was also provided directly by the panel manufacturer.

- The antimicrobial breakpoints for *S. pneumoniae* used for data analysis were those recommended by the NCCLS for broth dilution susceptibility testing [7].

- Laboratories International performed all antimicrobial testing for Microbiology Studies (LIMS) in Schaumburg, Illinois USA.

- LIMS performed daily quality control testing using *S. pneumoniae* ATCC 49619. Test isolate results were accepted into the final analysis only if the quality control isolate MIC was within the acceptable range defined by NCCLS guidelines [7].

## RESULTS

- Resistance to penicillin was highest in Hong Kong, followed by Taiwan, then Japan at 63.2%, 40.6% and 37.6%, respectively (Tables 1-3).
- Erythromycin resistance was high in all three countries at rates of 78.6%, 73.4% and 70.2% in Hong Kong, Japan and Taiwan, respectively (Tables 1-3).
- Non-susceptible strains of *S. pneumoniae* for levofloxacin were highest in Hong Kong, then Japan and Taiwan at 14.1%, 3.1% and 1.6%, respectively (Tables 1-3). All strains of *S. pneumoniae* were inhibited by levofloxacin at >16 mcg/mL in each of the 3 countries (Tables 4-6).
- Moxifloxacin non-susceptible strains of *S. pneumoniae* were highest in Hong Kong, followed by Japan, then Taiwan at 11.2%, 3.0% and 0.6%, respectively (Tables 1-3). All strains of *S. pneumoniae* were inhibited by moxifloxacin at >8 mcg/mL, 2 mcg/mL and 2 mcg/mL in Hong Kong, Japan and Taiwan, respectively (Tables 4-6).
- Gatifloxacin non-susceptible strains of *S. pneumoniae* were highest in Hong Kong, followed by Japan, then Taiwan at 10.8%, 3.6% and 1.3%, respectively (Tables 1-3). All strains of *S. pneumoniae* were inhibited by gatifloxacin at >8 mcg/mL in each of the 3 countries (Tables 4-6).
- Non-susceptible strains of *S. pneumoniae* to ceftriaxone varied from country to country. Hong Kong exhibited the highest percent, followed by Taiwan, then Japan at 30.7%, 6.6% and 3.8%, respectively (Tables 1-3). All other cephalosporins tested exhibited high rates of resistance in all countries (Tables 1-3).
- Amoxicillin/clavulanic acid non-susceptible strains of *S. pneumoniae* were highest in Taiwan, followed by Hong Kong, then Japan at 24.4%, 14.3% and 2.4%, respectively.
- Resistant rates to clindamycin, trimethoprim/sulfamethoxazole and tetracycline varied from country to country and can be found in Tables 1-3.

Table 1. In Vitro Activities of Twelve (12) Antimicrobial Agents Against 636 Isolates of *S. pneumoniae* Collected from Hong Kong

Antimicrobial	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)	Range (mg/L)	%-S <sup>a</sup>	%-I <sup>b</sup>	%-R <sup>c</sup>
Penicillin	2	4	≤0.015->8	29.1	7.7	63.2
Amox/clav	2	4	≤0.015->16	85.7	13.4	0.9
Erythromycin	>0.5	>0.5	≤0.06->0.5	21.1	0.3	78.6
Clindamycin	0.6	>0.5	≤0.015->0.5	74.4	-	25.6
TMP/SMX <sup>b</sup>	>1	>1	0.12->1	24.6	9.6	65.8
Moxifloxacin	0.12	2	≤0.03->8	88.8	10.5	0.7
Gatifloxacin	0.5	2	0.25->16	89.2	9.6	1.2
Levofloxacin	1	4	0.25->16	85.9	9.9	4.2
Cefprozil	8	16	≤0.12->32	35.1	.8	64.1
Cefdinir	8	8	≤0.015->8	34.2	-	65.8
Ceftriaxone	1	2	≤0.03->4	69.3	27.1	3.6
Tetracycline	4	>4	≤0.06->4	45.6	6.9	47.5

<sup>a</sup>NCCLS recommended breakpoints (mg/L) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories.  
<sup>b</sup>TMP/SMX = trimethoprim/sulfamethoxazole, ratio tested was 1:19

Table 2. In Vitro Activities of Twelve (12) Antimicrobial Agents Against 361 Isolates of *S. pneumoniae* Collected from Japan

Antimicrobial	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)	Range (mg/L)	%-S <sup>a</sup>	%-I <sup>b</sup>	%-R <sup>c</sup>
Penicillin	1	4	≤0.015->8	39.8	22.6	37.6
Amox/clav	0.25	2	≤0.015->16	97.6	1.6	0.8
Erythromycin	>0.5	>0.5	≤0.06->0.5	26.4	0.2	73.4
Clindamycin	0.6	>0.5	≤0.015->0.5	55.0	-	45.0
TMP/SMX <sup>b</sup>	1	>1	0.12->1	67.4	25.2	7.6
Moxifloxacin	0.12	.25	≤0.03->2	97.0	3.0	0.0
Gatifloxacin	0.25	0.5	0.25->16	96.4	3.0	0.6
Levofloxacin	1	2	0.25->16	97.1	2.3	0.8
Cefprozil	2	16	≤0.12->32	53.6	9.8	36.6
Cefdinir	1	>8	≤0.015->8	54.8	0.4	44.8
Ceftriaxone	0.25	0.5	≤0.03->4	96.2	2.2	1.6
Tetracycline	2	>4	≤0.06->4	62.2	1.0	36.8

<sup>a</sup>NCCLS recommended breakpoints (mg/L) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories.  
<sup>b</sup>TMP/SMX = trimethoprim/sulfamethoxazole, ratio tested was 1:19

Table 3. In Vitro Activities of Twelve (12) Antimicrobial Agents Against 411 Isolates of *S. pneumoniae* Collected from Taiwan

Antimicrobial	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)	Range (mg/L)	%-S <sup>a</sup>	%-I <sup>b</sup>	%-R <sup>c</sup>
Penicillin	4	4	≤0.015->8	22.8	36.6	40.6
Amox/clav	.5	4	≤0.015-16	75.6	15.6	8.8
Erythromycin	>0.5	>0.5	≤0.06->0.5	29.2	0.6	70.2
Clindamycin	0.6	>0.5	≤0.015->0.5	86.2	-	13.8
TMP/SMX <sup>b</sup>	>1	>1	0.12->1	32.6	26.4	41
Moxifloxacin	0.12	0.25	≤0.03->2	99.4	0.6	0
Gatifloxacin	0.25	0.5	0.25->16	98.6	0.5	0.8
Levofloxacin	1	2	0.25->16	98.4	0.6	1.0
Cefprozil	2	16	≤0.12->32	60.8	0.4	38.8
Cefdinir	2	8	≤0.015->8	58.2	0.8	41
Ceftriaxone	0.25	0.5	≤0.03->4	93.4	6.0	0.6
Tetracycline	2	>4	≤0.06->4	56.8	0.8	42.2

<sup>a</sup>NCCLS recommended breakpoints (mg/L) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories.  
<sup>b</sup>TMP/SMX = trimethoprim/sulfamethoxazole, ratio tested was 1:19

Table 4. In Vitro Activity of Fluoroquinolones Against 636 Isolates of *S. pneumoniae* from Hong Kong. The Number of Isolates Inhibited (and Cumulative % Inhibited) are Given for Each Fluoroquinolone Tested

	MIC (mg/L)														
Fluoroquinolone	0.008	0.015	≤0.03	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	16	>16
Levofloxacin	-	-	-	-	-	-	17 (2.7)	35 (5.5)	302 (47.5)	192 (30.0)	63 (9.9)	4 (0.6)	-	-	-
Moxifloxacin	-	-	92 (14.5)	-	134 (21.0)	185 (29.2)	33 (5.2)	86 (13.5)	47 (7.4)	3 (0.5)	1 (0.2)	-	-	-	-
Gatifloxacin	-	-	-	-	51 (8.0)	78 (12.3)	260 (41.0)	77 (12.1)	102 (16.1)	61 (9.6)	4 (0.6)	1 (0.2)	-	-	-

<sup>a</sup>Established intermediate interpretative standards for susceptibility as defined by the NCCLS

Table 5. In Vitro Activity of Fluoroquinolones Against 361 Isolates of *S. pneumoniae* from Japan. The Number of Isolates Inhibited (and Cumulative % Inhibited) are Given for Each Fluoroquinolone Tested

	MIC (mg/L)														
Fluoroquinolone	0.008	0.015	≤0.03	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	16	>16
Levofloxacin	-	-	-	-	-	-	61 (17)	10 (2.8)	29 (8.1)	194 (54.0)	111 (30.9)	4 (1.1)	-	-	-
Moxifloxacin	-	-	14 (3.9)	-	89 (24.4)	172 (47.6)	61 (16.9)	6 (1.7)	8 (2.2)	1 (0.3)	-	-	-	-	-
Gatifloxacin	-	-	-	-	10 (2.8)	29 (8.1)	149 (41.3)	142 (39.4)	10 (2.8)	1 (0.3)	-	-	-	-	-

<sup>a</sup>Established intermediate interpretative standards for susceptibility as defined by the NCCLS

Table 6. In Vitro Activity of Fluoroquinolones Against 411 Isolates of *S. pneumoniae* from Taiwan. The Number of Isolates Inhibited (and Cumulative % Inhibited) are Given for Each Fluoroquinolone Tested

	MIC (mg/L)														
Fluoroquinolone	0.008	0.015	≤0.03	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	16	>16
Levofloxacin	-	-	-	-	-	-	9 (2.2)	21 (5.1)	37 (9.0)	252 (61.3)	135 (32.8)	3 (0.7)	-	-	-
Moxifloxacin	-	-	34 (8.3)	-	81 (20.0)	175 (42.6)	50 (12.2)	10 (2.4)	3 (0.7)	-	-	-	-	-	-
Gatifloxacin	-	-	-	-	2 (0.5)	41 (10.0)	193 (47.0)	152 (37.0)	3 (0.7)	1 (0.2)	-	-	-	-	-

<sup>a</sup>Established intermediate interpretative standards for susceptibility as defined by the NCCLS

## CONCLUSIONS

- Rates of non-susceptible strains of *S. pneumoniae* to respiratory fluoroquinolones were highest in Hong Kong (14.1%, 11.2% and 10.8%) for levofloxacin, moxifloxacin and gatifloxacin, respectively.
- Rates of non-susceptible strains of *S. pneumoniae* were lower for all three antimicrobials in Japan and Taiwan.
- Resistance to penicillin by strains of *S. pneumoniae* were high in all three countries with Hong Kong rates approximately 30% to 50% higher than Japan and Taiwan.
- Erythromycin rates of resistance to all isolates of *S. pneumoniae* were greater than 70% in all three countries making the use of macrolides to treat pneumococcal infections problematic.
- While fluoroquinolones remain a viable treatment regimen for *S. pneumoniae*, this study suggests a need to continue surveillance of these agents in countries throughout the world.

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