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Changing Trends in Antimicrobial Resistance and Serotypes of *Streptococcus pneumoniae* Isolates in Asian Countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study

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Antimicrobial resistance in *Streptococcus pneumoniae* remains a serious concern worldwide, particularly in Asian countries, despite the introduction of heptavalent pneumococcal conjugate vaccine (PCV7). The Asian Network for Surveillance of Resistant Pathogens (ANSORP) performed a prospective surveillance study of 2,184 *S. pneumoniae* isolates collected from patients with pneumococcal infections from 60 hospitals in 11 Asian countries from 2008 to 2009. Among nonmeningeal isolates, the prevalence rate of penicillin-nonsusceptible pneumococci (MIC, ≥4 μg/ml) was 4.6% and penicillin resistance (MIC, ≥8 μg/ml) was extremely rare (0.7%). Resistance to erythromycin was very prevalent in the region (72.7%); the highest rates were in China (96.4%), Taiwan (84.9%), and Vietnam (80.7%). Multidrug resistance (MDR) was observed in 59.3% of isolates from Asian countries. Major serotypes were 19F (23.5%), 23F (10.0%), 19A (8.2%), 14 (7.3%), and 6B (7.3%). Overall, 52.5% of isolates showed PCV7 serotypes, ranging from 16.1% in Philippines to 75.1% in Vietnam. Serotypes 19A (8.2%), 3 (6.2%), and 6A (4.2%) were the most prominent non-PCV7 serotypes in the Asian region. Among isolates with serotype 19A, 86.0% and 79.8% showed erythromycin resistance and MDR, respectively. The most remarkable findings about the epidemiology of *S. pneumoniae* in Asian countries after the introduction of PCV7 were the high prevalence of macrolide resistance and MDR and distinctive increases in serotype 19A.

Streptococcus pneumoniae is one of the most important pathogens causing various types of mucosal and invasive infections with significant mortality worldwide. The disease burden of pneumococcal infections has increased due to widespread emergence of antimicrobial resistance in many countries during the past few decades (17). Previous reports documented very high prevalence rates of beta-lactam and macrolide resistance in *S. pneumoniae* in Asian countries (6, 7, 11). Particularly, erythromycin resistance has remarkably increased in many Asian countries, where >70% of clinical isolates were fully resistant (17, 23, 24). A previous surveillance study by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) showed that 53.1% of pneumococcal isolates from Asian countries, up to 92% in Vietnam, were resistant to erythromycin (23). In addition, multidrug resistance (MDR) was also very prevalent in Asian countries: 71.4% in Vietnam, 45.9% in South Korea, and 44.9% in Hong Kong (18, 23), rates which were much higher than those in other parts of the world (17, 18, 23).

After the introduction of heptavalent pneumococcal conjugate vaccine (PCV7), the epidemiology of *S. pneumoniae* has been changing in many countries (1, 8). One of the most prominent changes is the emergence of nonvaccine serotypes such as serotype 19A worldwide (20). According to recent data from the United States in 2007, 93.2% of penicillin-nonsusceptible isolates which caused invasive diseases showed non-PCV7 serotypes, and serotype 19A accounted for 53.2% of these penicillin-nonsusceptible isolates (5). However, since the introduction of PCV7 to Asian countries, the epidemiology of *S. pneumoniae* in Asian countries has not been well investigated (21, 26). Therefore, the ANSORP Study Group performed a prospective, multinational, hospital-based surveillance study in patients with pneumococcal infections in 11 Asian countries during 2008 to 2009 to investigate the current status of antimicrobial resistance and serotype distribution in *S. pneumoniae* after the introduction of PCV7.

MATERIALS AND METHODS

Pneumococcal isolates. *S. pneumoniae* isolates were prospectively collected from patients with community-acquired pneumococcal infections at 60 hospitals in 11 Asian countries from March 2008 to December 2009. Pneumococcal isolates were collected from clinical specimens represen-

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tative of normally sterile body sites, such as blood, cerebrospinal fluid (CSF), pleural fluid, ascites, joint fluid, sinus aspirates, and middle ear aspirates. Isolates from lower respiratory tract specimens were also included only if they were cultured from adequate respiratory specimens from patients with clinical and radiographic findings of pneumonia. Pneumococcal isolates from throat swab, nasal swab, or nasopharyngeal aspirate specimens were excluded from this study. Isolates obtained from a patient later than 72 h after admission of the patient to the hospital were not included in this study.

Pneumococcal isolates from participating hospitals, except those in China, were transported to the central laboratory (Samsung Medical Center, Seoul, South Korea) in transport tubes containing Ames transport medium (Copan, Brescia, Italy) and stored at −70°C until use. Isolates from Chinese hospitals were transported to the regional laboratories in Beijing, China (Beijing Union Medical College Hospital and Beijing Children's Hospital), and stored until the test using the same methods performed in the central laboratory in South Korea.

***In vitro* antimicrobial susceptibility test.** *In vitro* antimicrobial susceptibility tests of pneumococcal isolates were performed by the broth microdilution method according to guidelines of the Clinical and Laboratory Standards Institute (CLSI) (3) against 14 antimicrobial agents: penicillin, amoxicillin, amoxicillin-clavulanic acid, ceftriaxone, cefuroxime, erythromycin, azithromycin, clarithromycin, levofloxacin, moxifloxacin, gatifloxacin, ciprofloxacin, clindamycin, and co-trimoxazole. Interpretive criteria for susceptibility were those indicated in a CLSI document (4). We used two separate interpretive breakpoints for meningeal and nonmeningeal isolates to define penicillin and ceftriaxone resistance: MICs of ≥0.12 and ≥8 μg/ml for parenteral penicillin and ≥2 and ≥4 μg/ml for ceftriaxone for meningeal and nonmeningeal isolates, respectively. The breakpoint for ciprofloxacin resistance was 4 μg/ml (23). *S. pneumoniae* ATCC 49619 was used as a control strain. MDR was defined as resistance to more than any three antimicrobial agents of different classes tested in this study.

Detection of *erm*(B) and *mef*(A) genes. Erythromycin-resistant *S. pneumoniae* isolates were subjected to PCR analysis to detect *erm*(B) and *mef*(A) genes as described elsewhere (13, 25).

Serotyping. Serotypes of *S. pneumoniae* isolates were determined by the capsular quellung method with commercial antisera (Statens Serum Institut, Copenhagen, Denmark), as recommended by the manufacturer. Serotypes 6c and 6d were confirmed by PCR (9).

Statistical analysis. Statistical analysis was performed by using SPSS for Windows (version 11.5 software package; SPSS, Chicago, IL). Fisher's exact *t* test or χ^2 test was used to determine the significant differences in resistance and serotype proportion, as appropriate.

RESULTS

Collection of pneumococcal isolates. A total of 2,184 nonduplicate *S. pneumoniae* isolates were prospectively collected from patients with pneumococcal infections. Among 2,184 strains, specimen sources and the age of the patient were available in 2,021 cases. Of these, the most prevalent specimen source was sputum (69.5%), followed by blood (13.4%), sinus aspirate (4.8%), pleural fluid (2.4%), middle ear fluid (2.3%), and CSF (2.0%). Among the 2,021 isolates, 781 (38.6%) were isolated from children <5 years of age and 541 (26.8%) from elderly patients (≥65 years old). The mean (±standard deviation) patient age was 34.4 (±31.8) years. A total of 2,100 patients, whose clinical data were available, were included in the analysis of demographic and clinical characteristics of patients with pneumococcal infections (Table 1). Of these patients, 1,344 (64.0%) were male and 756 (36.0%) were female. The most common type of infection was pneumonia (80.0%), and 13.5% of patients with pneumonia had concomitant bacteremia. The most common comorbid condition among patients with pneumococcal diseases was smoking (25.3%). In this study, the prevalence of smoking in patients with pneumococcal diseases was highest in Hong Kong (61.2%) followed by China (41.6%) and Taiwan (32.3%).

TABLE 1 Demographic and clinical characteristics of patients with pneumococcal infection

Characteristic	No. of patients/total no. (%) (n = 2,100)
Type of infection	
Pneumonia	1,680 (80.0)
Acute sinusitis	108 (5.1)
Meningitis	102 (4.9)
Primary bacteremia	67 (3.2)
Acute otitis media	54 (2.6)
Empyema	17 (0.8)
Abscess	17 (0.8)
Peritonitis	10 (0.5)
Other	45 (2.1)
Concomitant bacteremia	284 (13.5)
Underlying disease	
Pulmonary disease	337/1,656 (20.4)
Cerebrovascular disease	134/1,631 (8.2)
Solid tumor	146/1,643 (8.9)
Hematologic malignancy	30/1,630 (1.8)
Chronic renal disease	79/1,637 (4.8)
Chronic liver disease	70/1,653 (4.2)
Cardiovascular disease	108/1,633 (6.6)
Diabetes mellitus	225/1,649 (13.6)
Comorbid condition	
Smoking	389/1,540 (25.3)
Corticosteroid use	49/1,603 (3.1)
Immunosuppressant use	12/1,599 (0.8)
Neutropenia	23/1,599 (1.4)

Antimicrobial resistance in *S. pneumoniae*. According to the revised CLSI breakpoints for parenteral penicillin (resistant [R], ≥8 μg/ml for nonmeningeal isolates and ≥0.12 μg/ml for meningeal isolates), prevalence rates of penicillin resistance were 0.7% and 57.5% in nonmeningeal and meningeal isolates, respectively (Table 2). Compared with previous ANSORP studies in Asian countries in 1996 to 1997 (996 clinical isolates), 1998 to 1999 (1,105 nasopharyngeal isolates), and 2000 to 2001 (685 clinical isolates) (14, 22, 23), current data show a persistently high prevalence of penicillin nonsusceptibility in Asian countries if we apply the previous penicillin susceptibility breakpoints (intermediate [I], 0.12 to 1 μg/ml, and R, ≥ 2 μg/ml) (Table 3). However, according to the revised CLSI breakpoints, the prevalence rate of penicillin-nonsusceptible pneumococci (PNSP) in nonmeningeal isolates was only 4.6% and fully resistant isolates were found only in China (2.2%) and South Korea (0.3%).

Ceftriaxone resistance was 3.7% and 0.1% in nonmeningeal and meningeal isolates, respectively (Table 2). Cefuroxime resistance was 53.9% (from 4.4% in Philippines to 70.0% in Vietnam; MIC_{90}, 8 μg/ml), which was higher than previous data from the ANSORP study in 2000 to 2001 (32.4%) (23). In particular, very high rates of resistance to cefuroxime were found in Vietnam (70.0%), South Korea (68.5%), Sri Lanka (68.4%), and China (62.3%).

Resistance to macrolides in pneumococcal isolates was 72.7%,

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TABLE 2 Susceptibilities to antimicrobial agents of *Streptococcus pneumoniae* isolates from patients with pneumococcal infections in 11 Asian countries[c]

Country	No. of cities (no. of hospitals)	No. of isolates (invasive[a]/ meningeal isolates)	Resistance to: Penicillin: Nonmeningeal isolates MIC_{50} (μg/ml)	Penicillin: Nonmeningeal isolates MIC_{90} (μg/ml)	Penicillin: Nonmeningeal isolates % I	Penicillin: Nonmeningeal isolates % R	Penicillin: Meningeal isolates MIC_{50} (μg/ml)	Penicillin: Meningeal isolates MIC_{90} (μg/ml)	Penicillin: Meningeal isolates % R	Ceftriaxone: Nonmeningeal isolates MIC_{50} (μg/ml)	Ceftriaxone: Nonmeningeal isolates MIC_{90} (μg/ml)	Ceftriaxone: Nonmeningeal isolates % I	Ceftriaxone: Nonmeningeal isolates % R	Ceftriaxone: Meningeal isolates MIC_{50} (μg/ml)	Ceftriaxone: Meningeal isolates MIC_{90} (μg/ml)	Ceftriaxone: Meningeal isolates % I	Ceftriaxone: Meningeal isolates % R
China	8 (14)	642 (33/5)	1	4	11.0	2.2	0.12	2	60.0	0.5	2	11.5	8.0	0.06	2	20.0	20.0
Hong Kong	1 (2)	196 (8/0)	0.25	2	1.5	0	NA[b]	NA	NA	0.5	1	3.1	6.6	NA	NA	NA	NA
India	2 (3)	23 (NA/NA)	<0.03	1	0	0	NA	NA	NA	<0.03	0.5	4.4	0	NA	NA	NA	NA
Japan	1 (1)	18 (0/0)	0.5	1	0	0	NA	NA	NA	0.5	1	0	0	NA	NA	NA	NA
South Korea	8 (13)	327 (70/12)	1	2	1.9	0.3	1	2	83.3	0.5	1	1.3	1.9	0.5	1	41.7	0
Malaysia	7 (9)	165 (118/13)	<0.03	0.5	0	0	<0.03	1	23.1	<0.03	0.5	0	0.7	<0.03	0.5	7.7	0
Philippines	5 (5)	118 (49/3)	<0.03	0.06	0	0	<0.03	<0.03	0	<0.03	0.12	0	0.9	<0.03	<0.03	0	0
Sri Lanka	1 (1)	19 (9/0)	1	2	0	0	NA	NA	NA	1	2	21.1	0	NA	NA	NA	NA
Taiwan	3 (3)	231 (30/0)	1	2	0.4	0	NA	NA	NA	0.5	1	3.5	1.3	NA	NA	NA	NA
Thailand	1 (2)	212 (24/1)	0.25	2	0.5	0	NA	NA	100	0.12	1	1.4	0	NA	NA	0	0
Vietnam	3 (7)	233 (24/6)	1	2	0.9	0	2	2	100	0.5	1	2.6	1.8	1	1	83.3	0
Total	40 (60)	2,184 (365/40)	0.5	2	3.9	0.7	0.5	2	57.5	0.5	1	4.9	3.7	0.25	1	30.0	0.1

[a] Invasive strains were isolated from sterile sites such as blood, CSF, pleural fluid, ascites, and joint fluid in patients with pneumococcal infections.
[b] NA, not available.
[c] The MIC breakpoints for pneumococcal isolates were determined according to the CLSI guidelines (4). For ciprofloxacin, isolates with MICs of ≥4 μg/ml were determined as resistant (23).

69.7%, and 68.9% for erythromycin, azithromycin, and clarithromycin, respectively, and resistance rates were highest in China (96.4%), Taiwan (84.9%), and Vietnam (80.7%) (Table 2). Erythromycin resistance was more frequently found in children (<5 years old; 44.8%) than in adults (≥65 years old; 25.1%) (odds ratio [OR], 2.9; 95% confidence interval [CI], 2.2 to 3.8; $P < 0.0001$). Compared with the previous data from Asian countries found by ANSORP, erythromycin resistance has markedly increased ($P < 0.0001$) in Asian countries, particularly in China and Sri Lanka, and was persistently high in Hong Kong, South Korea, Taiwan, and Vietnam (Table 3).

The resistance to fluoroquinolones was 1.7%, 0.4%, 1.5%, and 13.4% for levofloxacin, moxifloxacin, gatifloxacin, and ciprofloxacin, respectively, in the region (Table 2). Isolates from Taiwan (6.5%) and South Korea (4.6%) showed the highest rates of levofloxacin resistance.

The overall rate of MDR in pneumococcal isolates was 59.3% (59.4% and 57.5% in nonmeningeal and meningeal isolates, respectively), with the highest MDR rate being 83.3% in China, followed by Vietnam (75.5%), South Korea (63.9%), Hong Kong (62.2%), and Taiwan (59.7%). The most common pattern of MDR was resistance to cefuroxime, erythromycin, clindamycin, and co-trimoxazole (20.2%), followed by resistance to erythromycin, clindamycin, and co-trimoxazole (7.1%). All strains with MDR were resistant to at least one of the macrolides tested.

Distribution of *erm*(B) and *mef*(A) genes. Of 1,588 erythromycin-resistant isolates, *erm*(B) and *mef*(A) genes were identified in 969 isolates excluding 619 isolates from China. Of these isolates, 477 (49.2%) carried only *erm*(B) (MIC_{90}, 128 μg/ml) and 190 (19.6%) carried only *mef*(A) (MIC_{90}, 16 μg/ml), whereas 287 (29.6%) contained both *erm*(B) and *mef*(A) (Table 4). Of the 287 erythromycin-resistant *S. pneumoniae* isolates with both *erm*(B) and *mef*(A), 70.7% displayed the typical macrolide-lincosamide-streptogramin B (MLS_B) phenotype, characterized by high-level resistance to macrolides (MIC, ≥64 μg/ml). The most common serotypes among pneumococcal isolates carrying both the *erm*(B) and *mef*(A) genes were 19F (61.3%), 19A (16.4%), and 6A (9.8%), while the majority of isolates of serotype 19A (78.3%), 19F (73.0%), or 6A (54.9%) carried both *erm*(B) and *mef*(A).

Serotype distribution. Of 2,184 isolates of *S. pneumoniae*, 2,166 isolates were serotyped except 18 isolates from China. Major serotypes of *S. pneumoniae* in the Asian region were 19F (23.5%), 23F (10.0%), 19A (8.2%), 14 (7.3%), 6B (7.3%), and 3 (6.2%) (Table 5), which together accounted for 62.5% of all isolates. The frequencies of serotypes included in PCV7, PCV10, and PCV13 were 52.5%, 55.9%, and 74.5% in all isolates, respectively, while those in invasive isolates were 46.3%, 58.1%, and 78.6%, respectively. The rates of serotypes covered by PCV7 were relatively high in Vietnam (75.1% of all isolates and 70.8% of invasive isolates) and Sri Lanka (73.7% and 88.9%, respectively), while the rates were very low in Philippines (16.1% and 8.2%, respectively). Major serotypes of invasive pneumococcal isolates were 19F (13.7%) and 14 (12.1%), followed by 19A (8.8%), 3 (8.2%), 6B (7.7%), and 23F (6.9%), accounting for 57.3% of all invasive isolates. The prevalences of serotypes covered by PCV7, PCV10, and PCV13 in *S. pneumoniae* isolates from children (<5 years old) and adults (≥65 years old) were 62.4% and 46.2%, 63.7% and 47.3%, and 83.8% and 68.8%, respectively. Major serotypes of *S. pneumoniae* isolated from children (<5 years old) were 19F (33.7%), followed by 19A (13.5%), 14 (10.0%), 23F (9.6%), 6B (7.0%), and 6A (5.8%), which together accounted for 79.5% of isolates. In particular, a high frequency of serotype 19A strains in children (<5 years old) was observed in Taiwan (6/27, 33.3%), China (76/447, 17.0%), and South Korea (10/67, 14.9%). Of the pneumococcal isolates from adults (≥65 years old), 19F (17.0%), 3 (12.4%), 23F (9.8%), 6B (7.9%), 14 (5.5%), and 19A (5.0%) accounted for 57.7% of isolates.

Among non-PCV7 serotypes, serotype 3 was more prevalent in adults, particularly in elderly adults aged ≥65 years (54.9%), than in children <5 years old (4.9%), while serotype 19A was more prevalent in children <5 years of age (62.7%) than in adults ≥65 years of age (16.3%).

Compared with the data from a previous ANSORP study in 2000 to 2001 (23), the PCV7 coverage rate has significantly de-

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TABLE 2 (Continued)

Resistance to:																				
Erythromycin				Levofloxacin			Moxifloxacin			Gatifloxacin			Ciprofloxacin			Clindamycin			Co-trimoxazole		
MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	% I	% R	MIC_{90} (μg/ml)	% I	% R	MIC_{90} (μg/ml)	% I	% R	MIC_{90} (μg/ml)	% I	% R	MIC_{90} (μg/ml)	% I	% R	MIC_{90} (μg/ml)	% I	% R	MIC_{90} (μg/ml)	% I	% R
>128	>128	0	96.4	1	0.3	0.2	0.25	0.3	0	0.5	0.3	0	4	NA	26.5	>32	0.5	92.4	>32/60	12.7	73.4
32	128	0	75.5	2	0	2.6	0.12	2.0	0	1	0	2.6	2	NA	7.1	>32	1.5	49.5	16/304	7.7	63.3
<0.12	8	0	17.4	1	0	0	0.25	0	0	1	0	0	2	NA	0	0.25	0	4.4	16/304	8.7	91.3
2	128	5.6	61.1	2	0	0	0.12	0	0	0.25	0	0	2	NA	0	>32	0	38.9	8/152	55.6	22.2
32	128	4.0	77.7	2	0.6	4.6	0.12	1.5	0.9	1	0.6	4.3	2	NA	9.5	>32	0.6	68.2	32/608	13.5	55.4
<0.12	64	0.6	32.7	1	0	0	0.12	0	0	0.5	0.6	0	2	NA	7.3	1	0	15.2	8/152	18.2	21.8
<0.12	0.25	0.9	4.4	1	0	0.9	0.12	0	0.9	0.5	0	0.9	2	NA	7.9	0.12	0.9	3.5	2/38	27.0	6.1
32	>128	0	79.0	1	0	0	0.12	0	0	1	0	0	4	NA	10.5	>32	5.3	42.1	32/608	26.3	63.2
32	128	2.2	84.9	2	2.6	6.5	0.12	2.2	1.7	1	0.9	5.2	4	NA	12.6	>32	2.6	55.0	16/304	16.9	61.9
0.5	64	7.1	44.3	2	2.8	0.5	0.12	0	0.5	0.5	0	0.5	2	NA	9.9	>32	1.9	20.3	8/152	25.5	46.7
64	128	2.2	80.7	1	0	0	0.12	0	0	0.5	0.9	0	2	NA	2.2	>32	1.7	60.1	32/608	6.9	84.6
32	>128	1.9	72.7	2	0.7	1.7	0.25	0.7	0.4	0.5	0.4	1.5	4	NA	13.4	>32	1.1	58.1	32/608	15.0	59.3

creased in Asian countries (60.5% in 2000 to 2001 to 52.4% in 2008 to 2009; $P = 0.002$), while the prevalence of serotype 19A isolates has markedly increased (3% in 2000 to 2001 to 8.2% in 2008 to 2009; $P < 0.0001$) (Fig. 1).

Antimicrobial resistance and serotypes. Among the 1,138 isolates with PCV7 serotypes, 5.5% of isolates (China, 45; Hong Kong, 3; South Korea, 5; Taiwan, 1; Thailand, 2; Vietnam, 7) were PNSP with the revised breakpoints. However, 19.1% of serotype 19A isolates were not susceptible to penicillin, which accounted for 28.1% of PNSP. Among non-PCV7 serotypes, a high prevalence of erythromycin resistance was observed in isolates with serotypes 19A and 6A (86.0% and 85.7%, respectively). Serotype 19A isolates also showed a high prevalence of MDR (79.8%), while non-19A isolates showed a lower prevalence of MDR (58.0%). In particular, a high prevalence of MDR in serotype 19A pneumococci was observed in Hong Kong (100%), China (94.7%), Taiwan (90.9%), and South Korea (90.6%).

DISCUSSION

This study describes the changing trends in antimicrobial resistance and serotype distribution of pneumococcal isolates collected from Asian countries during 2008 to 2009. With regard to the changing trends in antimicrobial resistance in the Asian region, the first remarkable finding was a distinctive and persistent increase in macrolide resistance, which was consistent with other reports (10, 18). Previous ANSORP studies with clinical isolates and nasopharyngeal isolates have already revealed that many Asian countries showed a much higher prevalence of macrolide resistance in pneumococci than did Western countries (14, 22, 23). More seriously, the level of macrolide resistance has remarkably increased with very high MIC_{90}s (64 to $\geq$128 μg/ml) in China, Hong Kong, Japan, South Korea, Malaysia, Sri Lanka, Taiwan, Thailand, and Vietnam. With regard to the mechanism of macrolide resistance, *erm*(B)-mediated high-level resistance is the major mechanism in most Asian countries and Europe and is also increasing in the United States recently (10), while the *mef*(A) gene is still predominant in Canada (16). Compared with our previous study (24), the frequency of macrolide-resistant isolates with *erm*(B) has increased in Asian countries. An interesting finding was the persistently high prevalence of pneumococci carrying both *erm*(B) and *mef*(A) in South Korea (43.3%) and Vietnam (41.0%) and the increased prevalence of those isolates in Hong Kong (8.9% in 1998 to 2001 to 26.4%), Taiwan (0% in 1998 to 2001 to 21.4%), and Thailand (0% in 1998 to 2001 to 11.7%) (24). Major reasons for the high prevalence of macrolide resistance in Asian countries would be widespread use of macrolides in clinical practice and clonal spread of macrolide-resistant strains. Given the current epidemiology of macrolide resistance, an empirical use of macrolides alone for the treatment of community-acquired pneumonia or presumed pneumococcal pneumonia may not be an appropriate choice in many Asian countries, where it may cause the clinical failure of antimicrobial therapy.

The second important finding of pneumococcal resistance in the Asian region was the increasing prevalence of MDR. We found a high prevalence of MDR pneumococci in Asian countries, particularly in China, Vietnam, South Korea, Hong Kong, and Taiwan. The prevalence of MDR pneumococci in Asian countries (59.3%) shown in this study was significantly higher than those reported from other parts of the world such as 9 to 24% in North America and 0 to 43% in Europe (17, 18, 23).

Third, we found a dramatic decrease in the prevalence of penicillin resistance in nonmeningeal isolates according to the revised CLSI breakpoints for resistance to parenteral penicillin, although penicillin MICs have increased in some countries such as China and India compared with our previous studies. Most of the nonmeningeal isolates from Asian countries were susceptible to parenteral penicillin, a finding consistent with other studies worldwide (0 to 7%) (17). However, we found 15 nonmeningeal isolates with a very high level of resistance to penicillin (MIC, $\geq$8 μg/ml), suggesting that a continued monitoring of PNSP in the region is important.

The overall rates of resistance to fluoroquinolones in pneumococci remained low in most Asian countries, while levofloxacin and gatifloxacin resistance was more frequent in South Korea and Taiwan. We found 10 isolates from South Korea and Taiwan which showed high-level fluoroquinolone resistance with MICs of $\geq$16 μg/ml for levofloxacin, gatifloxacin, and ciprofloxacin, simultaneously. Therefore, given the popular use of respiratory fluoroquinolones in clinical practice, the emergence of these

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TABLE 3 Changing trends in penicillin and erythromycin resistance among *Streptococcus pneumoniae* isolates from patients with pneumococcal infections in Asian countries

Country	MIC_{90} of penicillin (μg/ml) by yr and isolate type (*n*)				% penicillin-nonsusceptible strains (I/R) by yr and isolate type (*n*)				MIC_{90} of erythromycin (μg/ml) by yr and isolate type (*n*)		% erythromycin-resistant strains by yr and isolate type (*n*)			
	1996–1997,[a] clinical (996)	1998–1999,[b] carriage (1,105)	2000–2001,[c] clinical (685)	2008–2009, clinical (2,184)	1996–1997,[a] clinical (996)[d]	1998–1999,[b] carriage (1,105)[d]	2000–2001,[c] clinical (685)[d]	2008–2009, clinical: Previous breakpoint (2,184)[d]	2008–2009, clinical: Revised breakpoint (2,144)[e]	2000–2001,[c] clinical (685)	1996–1997,[a] clinical (996)	1998–1999,[b] carriage (1,105)	2000–2001,[c] clinical (685)	2008–2009, clinical (2,184)
China	0.06	0.06	2	4	9.8/0	13.4/0	19.8/23.4	40.0/31.6	11.2/2.2	>32	35.2	71.0	73.9	96.4
Hong Kong	NA[f]	NA	4	2	NA/NA	NA/NA	24.1/43.8	36.2/20.4	1.5/0	>32	NA	NA	76.8	75.5
India	0.06	0.06	0.03	1	3.8/0	12.8/0	7.8/0	30.4/0	0/0	0.12	0	0	1.3	17.4
Japan	4	NA	NA	1	38.4/26.9	NA/NA	NA/NA	77.8/0	0/0	NA	67.9	NA	NA	61.1
South Korea	8	2	4	2	24.3/55.4	54.5/31.3	9.7/54.8	58.1/19.0	1.9/0.3	>32	74.6	77.8	80.6	77.7
Malaysia	0.06	0.06	2	0.5	6.0/3.0	8.4/4.9	9.1/29.5	24.2/2.4	0/0	>32	3.0	11.4	34.1	32.7
Philippines	NA	0.02	0.25	0.06	NA/NA	2.1/0	27.3/0	6.8/0.9	0/0	16	0.25	0	18.2	4.4
Sri Lanka	0.5	0.9	2	2	41.2/0	70.6/5.9	71.4/14.3	89.5/10.5	0/0	8	>128	10.2	16.7	79.0
Taiwan	8	1	4	2	9.3/29.4	43.5/47.8	24.6/38.6	58.9/14.7	0.4/0	>32	128	NA	86.0	84.9
Thailand	1	0.75	2	2	35.7/22.2	41.8/3.8	26.9/26.9	46.2/10.9	0.5/0	16	64	32.8	36.5	44.3
Vietnam	NA	1.5	4	2	28.2/32.6	58.2/12.2	20.6/71.4	61.4/17.6	0.9/0	>32	128	87.5	92.1	80.7
Total	NA	NA	4	2	19.5/23.1	47.0/8.8	22.7/31.3	44.9/18.8	3.9/0.7	>16	>128	46.1	53.1	72.7

[a] Data are from the work of Song et al. (22). The MIC_{90} of erythromycin for pneumococcal isolates from this study was not available.
[b] Data are from the work of Lee et al. (14). The MIC_{90} of erythromycin for pneumococcal isolates from this study was not available.
[c] Data are from the work of Song et al. (23).
[d] The MIC was determined according to the previous susceptibility breakpoints for penicillin (I, 0.12 to 1 μg/ml, and R, ≥2 μg/ml).
[e] The MIC was determined according to the revised susceptibility breakpoints for penicillin (I, 4 μg/ml, and R, ≥8 μg/ml in nonmeningeal isolates) in the CLSI guidelines. Data for meningeal isolates ($n = 40$) from this study were not included in this column.
[f] NA, not available.

TABLE 4 Distribution of macrolide resistance determinants among *Streptococcus pneumoniae* isolates from patients with pneumococcal infections in Asian countries[a]

Country	No. of erythromycin-resistant isolates	% of isolates with macrolide resistance determinants			
		erm(B)	*mef*(A)	*erm*(B) + *mef*(A)	None
Hong Kong	148	45.9	27.7	26.4	0
India	4	25.0	75.0	0	0
Japan	11	63.6	27.3	9.1	0
South Korea	254	43.3	13.0	43.3	0.4
Malaysia	54	35.2	42.6	9.3	13.0
Philippines	5	20.0	40.0	0	40.0
Sri Lanka	15	73.3	13.3	13.3	0
Taiwan	196	55.1	22.5	21.4	1.0
Thailand	94	47.9	37.2	11.7	3.2
Vietnam	188	56.9	2.1	41.0	0
Total	969	49.2	19.6	29.6	1.6

[a] Among 1,588 erythromycin-resistant isolates, 619 isolates from China were excluded because genotyping of those isolates was not performed.

strains highly resistant to fluoroquinolones could be a concern in the future in the treatment of pneumococcal pneumonia.

With regard to the serotype distribution, this study revealed significant changes in the distribution of serotypes in Asian countries after the introduction of PCV7 vaccination. In the Asian region, the frequency of serotypes covered by PCV7 (52.5%) in this study was lower than 74% and 61% in 1996 to 1997 and 2000 to 2001, respectively (22, 23). PCV7 was recently licensed and introduced into the Asian countries of South Korea (2003); Malaysia, Philippines, and Taiwan (2005); China (2008); and Japan (2009) (19). However, it was included in the National Immunization Program in only a very few Asian countries and areas, including Hong Kong (from 2009), Macau (from 2009), and Singapore (from 2009) (15). Although the PCV7 vaccination rate in most Asian countries has not been investigated, it seems to be very low in most Asian countries due to lack of awareness among both the general public and physicians and due to vaccination cost, while the vaccination rate in children under 5 years of age is relatively high in South Korea (over 60% in urban areas) (12). Vietnam, where PCV7 was not available at the time of the study, showed the highest coverage rate of PCV7 serotypes in this study, while the coverage rates have decreased in most other Asian countries compared with our previous studies. The PCV7 coverage rate in Asian countries was much lower, particularly in Philippines (16.1%), than that in Western countries (80 to 90% in North America and 70 to 75% in Europe) (6). However, the PCV13 coverage rate was 74.5% in overall isolates and 83.8% in isolates from children <5 years of age from Asian countries, which was due to the coverage of non-PCV7 serotypes 19A, 3, and 6A by PCV13.

Emergence of nonvaccine serotypes was associated with increasing prevalence of antimicrobial resistance (8). In the Asian region, serotype 19A was the most prevalent nonvaccine serotype. Compared with our previous ANSORP study in 2000 to 2001 (23), serotype 19A has significantly increased in Asian countries, particularly in China, India, and South Korea. Serotype 19A showed a high rate of penicillin nonsusceptibility, erythromycin resistance, and MDR. The prominent increase in serotype 19A and other non-PCV7 serotypes would be one of the major reasons for a high

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TABLE 5 Serotype distribution of *Streptococcus pneumoniae* isolates from patients with pneumococcal infections in 11 Asian countries

Serotype	No. (%) of isolates from country:											Total no. (%) of isolates (n = 2,166)
	China (n = 624)	Hong Kong (n = 196)	India (n = 23)	Japan (n = 18)	South Korea (n = 327)	Malaysia (n = 165)	Philippines (n = 118)	Sri Lanka (n = 19)	Taiwan (n = 231)	Thailand (n = 212)	Vietnam (n = 233)	
PCV7	329 (52.7)	114 (58.2)	13 (56.5)	8 (44.4)	125 (38.2)	86 (52.1)	19 (16.1)	14 (73.7)	134 (58.0)	121 (57.1)	175 (75.1)	1,138 (52.5)
19F	202(32.4)	41 (20.9)	10 (43.5)	—[b]	54 (16.5)	15 (9.1)	7 (5.9)	5 (26.3)	56 (24.2)	41 (19.3)	79 (33.9)	510 (23.5)
23F	45 (7.2)	30 (15.3)	1 (4.3)	2 (11.1)	16 (4.9)	10 (6.1)	2 (1.7)	1 (5.3)	26 (11.3)	37 (17.5)	46 (19.7)	216 (10.0)
14	47 (7.5)	14 (7.1)	—	—	14 (4.3)	26 (15.8)	1 (0.8)	5 (26.3)	20 (8.7)	9 (4.2)	23 (9.9)	159 (7.3)
6B	25 (4.0)	23 (11.7)	2 (8.7)	6 (33.3)	14 (4.3)	21 (12.7)	3 (2.5)	3 (15.8)	23 (10.0)	24 (11.3)	14 (6.0)	158 (7.3)
9V	3 (0.5)	—	—	—	17 (5.2)	2 (1.2)	2 (1.7)	—	6 (2.6)	2 (0.9)	9 (3.9)	41 (1.9)
18C	6 (1.0)	5 (2.6)	—	—	2 (0.6)	10 (6.1)	1 (0.8)	—	3 (1.3)	5 (2.4)	2 (0.9)	34 (1.6)
4	1 (0.2)	1 (0.5)	—	—	8 (2.4)	2 (1.2)	3 (2.5)	—	—	3 (1.4)	2 (0.9)	20 (0.9)
PCV10	338 (54.2)	116 (59.2)	19 (82.6)	8 (44.4)	130 (39.8)	99 (60.0)	51 (43.2)	14 (73.7)	134 (58.0)	124 (58.5)	177 (76.0)	1,210 (55.9)
1	3 (0.5)	—	1 (4.3)	—	2 (0.6)	8 (4.8)	16 (13.6)	—	—	1 (0.5)	2 (0.9)	33 (1.5)
5	3 (0.5)	—	3 (13.0)	—	1 (0.3)	5 (3.0)	13 (11.0)	—	—	—	—	25 (1.2)
7F	3 (0.5)	2 (1.0)	2 (8.7)	—	2 (0.6)	—	3 (2.5)	—	—	2 (0.9)	—	14 (0.6)
PCV13	485 (77.7)	151 (77.0)	22 (95.7)	14 (77.8)	220 (67.3)	132 (80.0)	67 (56.8)	15 (78.9)	173 (74.9)	159 (70.8)	184 (79.0)	1,613 (74.5)
19A	94 (15.1)	6 (3.1)	3 (13.0)	2 (11.1)	32 (9.8)	15 (9.1)	2 (1.7)	1 (5.3)	11 (4.8)	11 (5.2)	1 (0.4)	178 (8.2)
3	26 (4.2)	24 (12.2)	—	—	30 (9.2)	9 (5.5)	13 (11.0)	—	22 (9.5)	10 (4.7)	—	134 (6.2)
6A	27 (4.3)	5 (2.6)	—	4 (22.2)	28 (8.6)	9 (5.5)	1 (0.8)	—	6 (2.6)	5 (2.4)	6 (2.6)	91 (4.2)
Other	139 (22.3)	45 (23.0)	1 (4.3)	4 (22.2)	107 (32.7)	343 (20.0)	51 (43.2)	4 (21.1)	58 (25.1)	62 (29.2)	49 (21.0)	553 (25.5)
15	30 (4.8)	6 (3.1)	1 (4.3)	—	21 (6.4)	6 (3.6)	3 (2.5)	1 (5.3)	6 (2.6)	4 (1.9)	4 (1.7)	82 (3.8)
11	8 (1.3)	7 (3.6)	—	—	18 (5.5)	2 (1.2)	2 (1.7)	2 (10.5)	6 (2.6)	6 (2.8)	15 (6.4)	66 (3.0)
13/28	12 (1.9)	2 (1.0)	—	2 (11.1)	11 (3.4)	3 (1.8)	3 (2.5)	—	4 (1.7)	4 (1.9)	2 (0.9)	43 (2.0)
23A	3 (0.5)	—	—	—	5 (1.5)	2 (1.2)	1 (0.8)	—	15 (6.5)	7 (3.3)	3 (1.3)	36 (1.7)
20	3 (0.5)	5 (2.6)	—	—	2 (0.6)	1 (0.6)	6 (5.1)	—	—	—	4 (1.7)	21 (1.0)
35	—	7 (3.6)	—	1 (5.6)	4 (1.2)	1 (0.6)	—	—	5 (2.2)	1 (0.5)	—	19 (0.9)
16/36/37	2 (0.3)	1 (0.5)	—	—	4 (1.2)	3 (1.8)	3 (2.5)	—	—	4 (1.9)	2 (0.9)	19 (0.9)
10	6 (1.0)	—	—	—	1 (0.3)	1 (0.6)	—	—	3 (1.3)	4 (1.9)	2 (0.9)	17 (0.8)
17	5 (0.8)	5 (2.6)	—	—	—	1 (0.6)	2 (1.7)	—	—	1 (0.5)	1 (0.4)	15 (0.7)
6C	—	—	—	—	3 (0.9)	3 (1.8)	—	—	4 (1.7)	3 (1.4)	1 (0.4)	14 (0.6)
33	8 (1.3)	—	—	—	2 (0.6)	—	1 (0.8)	—	—	2 (0.9)	—	13 (0.6)
27/32/41	2 (0.3)	2 (1.0)	—	—	3 (0.9)	—	—	—	4 (1.7)	2 (0.9)	—	13 (0.6)
24/31/40	4 (0.6)	—	—	—	2 (0.6)	—	1 (0.8)	—	—	4 (1.9)	—	11 (0.5)
6D	—	—	—	—	9 (2.8)	—	—	—	1 (0.4)	—	—	10 (0.5)
7C	—	1 (0.5)	—	—	1 (0.3)	2 (1.2)	1 (0.8)	—	2 (0.9)	1 (0.5)	2 (0.9)	10 (0.5)
NT[c]	49 (7.9)	7 (3.6)	—	—	17 (5.2)	3 (1.8)	10 (8.5)	1 (5.3)	5 (2.2)	15 (7.1)	11 (4.7)	118 (5.4)
Others[a]	7 (1.1)	2 (1.0)	—	1 (5.6)	4 (1.2)	5 (3.0)	18 (15.3)	—	3 (1.3)	4 (1.9)	2 (0.9)	46 (2.1)

[a] Others include serotypes 2, 7B, 8, 9N, 12, 18A, 18B, 18F, 19C, 21/39, 22, and 23B.
[b] —, no isolates.
[c] NT, nontypeable.

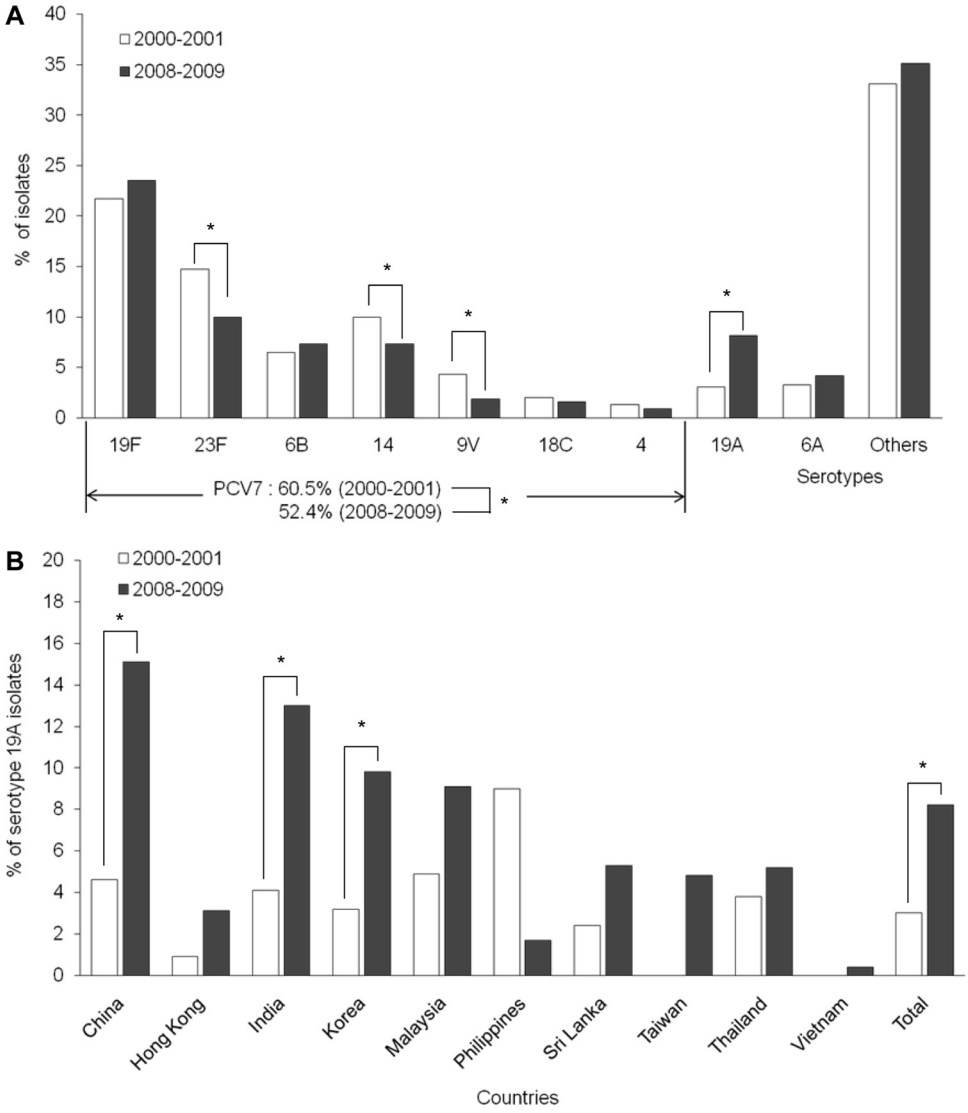

FIG 1 (A) Serotype distribution of *Streptococcus pneumoniae* isolates from Asian countries. (B) Distribution of serotype 19A pneumococcal isolates from Asian countries. Data from 2000 to 2001 are from the work of Song et al. (23). Data from Japan in this study were excluded because *S. pneumoniae* isolates were not collected from Japan in the previous study (2000 to 2001). Asterisks represent significant differences ($P < 0.05$).

prevalence of macrolide resistance and MDR in Asian countries. This increase in serotype 19A in Asian countries might be due to the selection of nonvaccine serotypes after PCV7 vaccination, clonal spread of serotype 19A strains (2), or injudicious use of antibiotics in clinical practice.

Since a limited number of isolates were collected from a few hospitals which are mostly located in urban areas, data from this study may not reflect the national status of antimicrobial resistance and serotype distribution. Therefore, nationwide surveillance of pneumococcal resistance and serotypes is strongly warranted.

The current study has provided updated information and changing trends in antimicrobial resistance and serotype distribution of *S. pneumoniae* in Asian countries. Data showed an extremely high prevalence of macrolide resistance and an increasing prevalence of MDR in many Asian countries. After the introduction of PCV7 vaccination into Asian countries, a distinctive emergence of serotype 19A was observed which was also associated with the increasing prevalence of antimicrobial resistance in *S. pneumoniae* in the region. Given the high prevalence of resistance and its clinical impact, continuous surveillance of pneumococcal epidemiology and active application of pneumococcal vaccination that can cover non-PCV7 serotypes are strongly warranted in Asian countries.

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