

Penicillin-Resistant trend of *Streptococcus pneumoniae* in Asia: A systematic review

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ABSTRACT

The high prevalence of resistance to penicillin by *Streptococcus pneumoniae* is considered as a great concern, particularly in Asian countries. The aim of this study was to investigate the changing trend of penicillin-resistant *S. pneumoniae* (PRSP) in Asia over a 20 years period.

A review of the literature was conducted using the PubMed database, Google Scholar, Scopus, two Persian scientific search engines "Scientific Information Database" (www.sid.ir), and "Mag Iran" (www.magiran.com) through 1993 to 2013. Our study provides a unique chance to investigate the changing trend in PSSP in Asia over a 20 years period. Susceptibility rates among different centers in each country varied widely. In Malaysia, the PSSP rate decreased from 97.2% in 1995-1996 to 69% in 2000. In Singapore, PSSP levels decreased from 72.6% in 1997 to 30.5% in 2007-2008. In Iran, PSSP ranged from 0% to 100%. In Taiwan, the rate of PSSP was 60.3% in 1995 and <50% in other years. In Lebanon, the rate of PSSP was less than 50% (ranging from 30.1% to 50%) in all published data. In Hong Kong, the level of penicillin susceptibility decreased from 71.1% during 1993-1995 to less 42% in 2007.

Continuous surveillance of resistance data from clinical isolates as well as implementation of strict infection control policies is recommended. More studies are needed for better evaluation PSSP rate in some Asian countries such as Vietnam, Singapore, Philippines, Pakistan, Nepal, Kuwait, Korea and Indonesia.

Keywords: *S. pneumoniae*, penicillin resistant, Asia

INTRODUCTION

Streptococcus pneumoniae is considered as one of the most important pathogen that causes variety of serious infections such as meningitis, acute otitis media, sinusitis, sepsis, bronchitis, pneumonia and bacteremia (1, 2). The life-threatening morbidity and

mortality due to these infections commonly occur in children less than 2 years old, adults older than 65 years as well as immunocompromised individuals (3). According to the previous studies, more than 860,000 death occur annually due to *S. pneumoniae* infections in children worldwide (4-7). World Health Organization (WHO) has reported mortality rate of 700,000 to 1 million cases in children less than 5 years old due to *S. pneumoniae* infection (6, 8). In recent years pneumococcal infections has been increased due to rapid development of antimicrobial resistance such as penicillin resistance (8). The first Penicillin Resistance *S. pneumoniae* (PRSP) was reported in Australia in 1967 (9, 10). During the past three decades, several studies have been reported different resistance pattern of *S. pneumoniae* to

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penicillin particularly in developing countries. The aim of this study was to evaluate PRSP trend of *S. pneumoniae* in Asian countries.

MATERIALS AND METHODS

Literature search. A review of the literature was conducted using the PubMed database, Google Scholar, Scopus, two Persian scientific search engines “Scientific Information Database” (www.sid.ir), and “Mag Iran” (www.magiran.com) (1993 through 2013). Search strategy was a combination of the following keywords, subjects and title words: *Streptococcus pneumoniae* (pneumococcus), Penicillin-resistant *S. pneumoniae* (PRSP), Penicillin-susceptible *S. pneumoniae* (PSSP), Asia and each country independently. Articles published between January 1993 and December 2013 were included. Articles and abstracts were limited to studies written in English only.

Inclusion criteria. Studies that fulfilled the following criteria were included in the review article:

1. Conducted in Asia (we searched each country independently)
2. Conducted after 1993

Relevant abstracts were reviewed, and studies with any potential to meet inclusion criteria were chosen for full-text review.

Exclusion criteria.

1. All kind of review articles were excluded.
2. Articles including only abstract without full-text were excluded.
3. Interventional studies that showed antimicrobial resistance patterns after vaccination or antibiotic therapy.
4. Studies that described antimicrobial resistance patterns based on the serotypes were excluded.
5. Because the number of PCR method was low, this method was excluded.

Data Extraction. The frequency and percentage of PSSP were determined and reported for each study (Table 1).

Analytical strategy and statistical analysis. Studies were classified / extracted by country, year of sample collection, sources, method of antimicrobial susceptibility testing, and the percent of PSSP.

The demographic characteristics of PSSP including detailed age of the study subjects, methods, and source of specimens were extracted from Asian countries during 1993-2013. In all studies intermediate resistance was considered as resistant.

RESULTS

The prevalence of PSSP in the Asian regions according to different countries, time period and the using method is shown in Table 1.

A total of 21 countries including Bangladesh (n=7), China (n=15), Hong Kong (n=9), India (n=16), Indonesia (n=2), Iran (n=20), Israel (n=2), Japan (n=17), Korea (n=3), Kuwait (n=3), Lebanon (n=3), Malaysia (n=5), Nepal (n=3), Pakistan (n=1), Philippine (n=1), Saudi Arabia(n=5), Singapore (n=2), Taiwan (n=6), Thailand (n=5), Turkey (n=14) and Vietnam (n=3) were included in the study.

Based on our data, *S. pneumoniae* isolates were isolated from different clinical specimens such as blood, cerebrospinal fluid (CSF) culture, pus, nasopharyngeal swab, nasal swab, bronchoalveolar lavage, ear exudates, eye swabs, endo-tracheal tube, respiratory tract, sputum, pleural fluid, throat, and non-sterile areas.

The most methods applying in Asian region were disk diffusion and broth microdilution. Other methods such as E-test and agar dilution were less frequently used.

The following countries had the most published data on PSSP in Asia, while the others had been reported a few published data on this issue.

Bangladesh. According to Table 1, the least rate of penicillin susceptibility was seen during 1993-1997 in children < 5 years of age (87.3%), while in the other studies the rate of PSSP was more than 90%. However, the subject of all studies in this country was children (4, 11-16).

China. The least and the most rate of penicillin susceptibility was seen during 2009-2012 in children < 14 years (the rate of penicillin-susceptibility was 0%) and 2005-2011 in pediatric and adult patients (100%), respectively. In general, the frequency of PSSP has been changed according to different methods in China. The different antimicrobial susceptibility methods in this country was agar dilution (n=21, 58.3%), E-test (n=7, 19.4%), E-test

Table1. The prevalence of PSSP in 22 countries during 1993-2013

Country	Periods analyzed		Methods			
	1993-2003	2003-2013	Disk Diffusion	E-test	Broth micro dilution	Agar dilution
	% (References)	% (References)				
Bangladesh	87.3(11), 97.0 ⁴ (12), 93.0 ⁷ (12)			+		
	100.0(13)					+
	91.2(14)	90.0(15), 97.1(16), 100.0(4)	+	+		
China	88.1(21), 60.1(19)	99.2 ³ (22), 23.4 ⁴ (22), 41.9 (23), 96.1 ³ (24), 0 ⁴ (24)		+		
	75.0(25)	36.9 ¹ (30), 79.5 ² (30)			+	
		80.9(27), 35.7 ⁵ (20), 44.8 ⁶ (20), 59.3(31), 89.3 ³ (29), 39.3 ⁴ (29), 96.2 ^{3,11} (29), 48.5 ^{4,11} (29), 58.6 ³ (29), 39.7 ⁴ (29), 63.9 ³ (29), 49.2 ⁴ (29), 72.7 ³ (29), 58.3 ⁴ (29), 61.5 ³ (29), 53.8 ⁴ (29), 66.7 ³ (29), 47.6 ⁴ (29), 100 ³ (29), 66.7 ⁴ (29), 61.9(32)				+
	42.1 (26)		+	+		
	86.1 ^{5,8} (17), 85.7 ^{8,9} (17)	10.4 ¹ (28), 70.6 ² (28)		+		+
Hong Kong	62.6(38), 58.0 (36)	58.0(36)12.5 ⁶ (33), 17.2 ⁹ (33), 42.0(37)		+		
	71.1 ¹² (39), 60.0 ¹ (39), 76.1 ² (39), 44.4(125)	44.4(125), 35.1(35)			+	
	51.0(34)		+	+		
	62.0(126)		+			+
India	100.0(41), 81.7 ⁵ (40), 84.0 ⁹ (40), 96.7 (49), 100.0 (42), 100.0(43)	100.0(41), 100.0(44), 100.0(45), 33.3(47), 67.0(52), 100(46)	+			
	75.0(42)			+		
		95.0(52)			+	
		95.5(54)				+
	93.6(48)	84.6(50)	+	+		
		25.0(55)	+		+	
		86.0(51)	+			+
Indonesia		100.0(127)	+			
	97.8(128)		+	+		
Iran:	Tehran: 0(56), 44.0(59), 43.3(65), 75.7(129), 34.0(60) Urmia: 68.2(72) Yazd: 50.0(67)	Tehran: 0(56), 43.3(65), 34.0(60) Ahvaz: 25.0 ¹⁰ (69) Tehran: 100.0(58) Shahrekord: 71.1(61) Tehran: 40.0(62), 90.8(63) Shiraz: 40.0(71)	+			
		Tehran: 65.0(58) Tehran: 92.0(66) Isfahan: 30.0(68)		+		
	Tehran: 71.0 (129)	Shahrekord: 0 (57) Shiraz: 66.1(70) Zahedan: 68.5(1) Tehran: 82.0(73)			+	
	Tehran: 70.0(64)	Tehran: 70.0(64)				+

PENICILLIN-RESISTANT TREND OF *STREPTOCOCCUS PNEUMONIAE*

Country	Periods analyzed		Methods			
	1993-2003	2003-2013	Disk Diffusion	E-test	Broth micro dilution	Agar dilution
	% (References)	% (References)				
Pakistan	65.0(130), 65.2 ¹² (131), 63.3 ¹ (131), 73.5 ² (131)		+	+		
Japan	60.0(89)			+		
	52.8 (87), 54.6 (87), 49.6 (77), 60.5 (88), 51.5(82), 35.7 (85), 49.3 (87), 45.2 (85), 5.7(83), 36.1 (85), 39.3 (84), 42.0 (132), 49.0 (87), 38.0 (86), 81.0 (86)	34.9(82), 48.5(82), 42.0 (132), 81.0 (86), 38.0 (86), 53.9(80), 30.0 (86), 35.7 (78), 100.0 (79)			+	
	27.4(81)					+
	39.4(75)		+		+	
	53.2 (76)				+	+
		36.0 [*] (74)				
	Korea	25.0(133)	32.0(134), 79.1(135)	+		
Kuwait	46.2(136)		+			
	60.0(137)	59.0(138)	+	+		
Lebanon		47.9(139)		+		
	50.0(140), 44.4(140), 45.5(140), 38.9(140)	40.6 (140)			+	
			+	+		
		30.1(141)	+		+	
Malaysia	97.2(93)	99.4(91)	+			
	89.1(142), 69.0(90)			+		
	93.0(92)		+	+		
Nepal	96.0(143)	12.3(144)	+			
		100.0 (145)		+		
Pakistan		83.0 ¹³ (146), 77.0 ¹⁴ (146)	+			
Philippines	97.9(147)		+	+		
Saudi Arabia		93.0 (95)	+			
	46.0(96)	46.0(96)		+		
		49.0 (97)				+
		63.4 (98)	+		+	
	40.9 [*] (94)					
Singapore	36.7(148)			+		
	72.6(3)	30.5(3)	+	+		
Taiwan	60.3(149), 46.3(149)		+			
	4.5 ¹ (99), 45.2 ² (99)	91.8 ³ (100), 16.8 ⁴ (100)			+	
	43.6 (150)	26.3 (103)				+
	23.8 [*] (102)					
Thailand	54.2(105), 54.4(105), 53.3 (105)	57.2(105), 57.6(105), 52.3 (105)	+			
	24.5 (104)			+		
	58.0 (108)				+	
	97.5 (105)	97.5 (105)	+	+		
	82.9 (107)		+			+
		48.0 [*] (109)				

Country	Periods analyzed		Methods			
	1993-2003	2003-2013	Disk Diffusion	E-test	Broth micro dilution	Agar dilution
	% (References)	% (References)				
Turkey	97.0 (111)	72.0(115), 68.7 (116)	+			
	70.3(151), 77.0(152), 94.0 ¹² (117), 73.7 ^{1,4} (117), 88.5 ^{2,4} (117), 60.6 (119)	94.0(117), 73.7(117), 88.5(117), 67.8(118)		+		
	54.0 (120)	89.8 (116)			+	
	0(110), , 64.6 ⁹ (112), 58.5 ^{9,13} (112), 73.4 ^{9,15} (112)	9.1 (114)				+
		89.5 [*] (113)				
Vietnam	48.0 (153)					+
	26.4 [*] (154)	54.0 [*] (155)				

* The method is not determined

¹ In children

² In adults

³ Among non-meningitis isolates

⁴ Among meningitis isolates

⁵ In clinical isolates

⁶ In invasive isolates

⁷ In carriage isolates

⁸ The agreement between the MICs obtained by E-test and agar dilution for penicillin was >97.5%

⁹ In nasopharyngeal carriage isolates

¹⁰ In hospitalized and non-hospitalized cancer patients

¹¹ In total strains

¹² In older children and adults

¹³ In the group of sick children

¹⁴ In the control group

and agar dilution (n=4, 11.1%), broth micro dilution (n=3, 8.3%) and finally disk diffusion and E-test (n=1, 2.8%). The subject of most studies in this country was children (17-26); while only one study evaluated adults (27) and in three surveys (28-30) study subjects included both groups. However, in two studies, study subjects were not known (31, 32).

Hong Kong. The least and the most rate of penicillin susceptibility was reported in 2004 (33) in children <6 years (12.5%) and between 1993 and 1995 in adult patients (76.1%). The rate of PSSP was varied by different methods in Hong Kong. Several studies worked on children and adolescents (33-37). However, there are studies which evaluated both groups (38, 39).

India. The least and the most rate of penicillin susceptibility was seen during 1999-2002 (40) (6.7%) and in the period of 1996-2009 (41-46) from children and adults (100%), respectively. In general, the rate of PSSP was varied in India. In the most studies, study

subjects were children (43-45, 47-50). However, there are some studies which worked on children and adults (41, 42, 46, 51-54) and even unknown subjects (40, 55).

Iran. The least and the most level of penicillin susceptibility were seen in Tehran during 1995-2005 (56), Shahrekord in 2005 (57) (0%) and between 2004-2006 (58) in children (100%). Totally, the frequency of PSSP has been changed in Iran (rate of PSSP with different rates was seen during 1995-2008; then increased up to 2009; and finally decrease until 2012). The most prevalent used method in this country was disk diffusion (n= 13, 59.1%); followed by broth micro dilution (n=5, 22.7%), E-test (n=3, 13.6%) and agar dilution (n=1, 4.5%). The subjects of most studies were children and adolescents (1, 56, 58-68); while there are some reports which was evaluated both age groups (69-72). Moreover, in two studies, the study subjects were unknown (57, 73).

Japan. Rate of PSSP varied in Japan in the period

of 1993-2006. In Japan, the most prevalent methods which was used for antimicrobial susceptibility was broth micro dilution (n=22, 81.5%) followed by E-test, agar dilution, disk diffusion and broth micro dilution. The subject of most studies was children (74-79); however, there are some reports that evaluated adults (80, 81), both groups (82-86) and indeterminate subjects (87-89).

Malaysia. Rate of penicillin susceptibility was the least and the most in 1999-2000 (90) (69%) and between 2009-2010 (91)(99.4%), respectively. Totally, the frequency of PSSP decreased during 1995-2000; then increased up to 2010. Among studies, two surveys evaluated children (92, 93). However, one report worked on all age groups (91).

Saudi Arabia. The least and the most rate of penicillin susceptibility was seen in 2000 (94) in children < 10 years old (40.9%) and during 2004-2005 (95) in infants and patients >50 years old (93%). The penicillin susceptibility rate in this country decreased from 2000-2005; then, increased up to 2006. The most studies worked on children (94, 96); however, two research evaluated all age groups (95, 97) and in one study, study subjects were unknown (98)

Taiwan. The least and the most rate of penicillin susceptibility was seen in the period of 2000-2001 (99) in children (4.5%) and between 2003-2006 (100) (91.8%), respectively. Rate of PSSP decreased in the period of 1995-2004; and different rates was seen until 2006. However, based on reports from 1996 to 2001, isolates from this country indicated high prevalence of penicillin susceptibility (101). Different methods which was used in this country was broth micro dilution (n=4, 44.4%) and disk diffusion and agar dilution (n=2, 22.2%), respectively. In different survey, study subjects selected from children and adolescents (102), however, some studies worked on both groups (99) and in determinate subjects (100, 103).

Thailand. The least and the most rate of penicillin susceptibility was seen during 2001-2002 (104) (24.5%) and in 2000-2005 (105) in isolates aged range <6 and >60 years old (97.5%), respectively. Surveillance researches in 11 Asian countries during 2000 to 2001 (106), estimated that the penicillin susceptibility rate was almost low in this region. The most common used methods in this country were

disk diffusion (n=7, 58.3%), followed by E-test, broth micro dilution, disk diffusion and E-test and finally disk diffusion and agar dilution (n=1, 8.3%). One study worked on children (107); but three studies evaluated the both groups (105, 108, 109) and one research evaluated indeterminate subjects (104).

Turkey. The least and the most rate of penicillin susceptibility was seen between 1997 and 2001 (110) (0%) and during 1997-1998 (111) among adults (97%). In general, the frequency of PSSP changed by different methods in this region. In this country, rate of PSSP evaluate by using E-test (n=7, 36.8%), agar dilution (n=5, 26.3%), disk diffusion (n=3, 15.8%), broth micro dilution (n=2, 10.5%), disk diffusion altogether E-test (n=1, 5.3%), respectively. The most studies worked on children (112-116); one report worked on adults (111); but two survey applied the both groups (117, 118). However, in two studies, study subjects were not known (119, 120).

DISCUSSION

This study describes the changing trends in antimicrobial resistance of pneumococcal isolates collected from Asian countries during 1993 to 2013. Our review confirms that PRSP is a significant health problem among children in the most Asian countries. Although comparisons among countries are difficult due to differences in study design and methods, we evaluated 155 studies in Asia.

Our study provides a unique chance to investigate the changing trend in PSSP in Asia over a period of 20 years. Susceptibility rates among different centers in each country varied widely. Regards to current research, in children, prevalence of PSSP was as low as 0% in China (24) and Iran (56) while the highest susceptibility rate was seen in Bangladesh (4), India (43, 45), Iran (58) and Japan (79)(100%). As documented in previous report, children younger than age 5 years are more frequently infected with penicillin resistant strains (106).

In large countries, it is more likely that the resistance rates differ between one region and another. Therefore, due to great variation in resistance rates by hospital and patient type within countries good laboratory facilities and qualified personnel are needed for each region.

In Malaysia, the PSSP rate decreased from 97.2% in 1995-1996 to 69% in 2000. In Singapore, PSSP levels

decreased from 72.6% in 1997 to 30.5% in 2007-2008. In Thailand, the rate of PSSP was stably low, ranging from 24.5% to 58%, except one study during 2000-2005 (97.5%) and 1993-1994 (82.9%). In Taiwan, the rate of PSSP was 60.3% in 1995 to <50% in other years, ranging from 46.3% to 4.5% during 1996 to 2006. In Lebanon, the rate of PSSP was less than 50% (ranging from 30.1% to 50%) in all published data. In Hong Kong, the level of penicillin susceptibility decreased from 71.1% in 1993-1995 to less 42% until 2007. In Iran, PSSP ranged from 0% to 100%. Penicillin susceptibility among *S. pneumoniae* isolates from Nepal was only 96% in 2000-2001, but decreased to 2.3% in 2009-2010.

More studies are needed for better evaluation of PSSP rate in countries such as Vietnam, Singapore, Philippines, Pakistan, Nepal, Kuwait, Korea and Indonesia. In addition, the leading factors associated with low susceptibility rate of penicillin in countries such as Hong Kong, Iran, Japan, Lebanon, Taiwan, and Vietnam should be evaluated in the future.

There were different rates of penicillin susceptibility in some countries such as Japan, Iran, China, Hong Kong, India, Saudi Arabia and Thailand based on the age groups, types of isolates, used methods and periods analyzed. It has been reported that the spread of PRSP strains in Saudi Arabia and Kuwait might be derived by the selective pressure created by excessive use, misuse of antimicrobial agents or even easy availability of these agents (121).

Song *et al.* reported that the rates of PSSP in Asia are decreasing in 11 countries in Asia and the Middle East during 2000-2001 (106). Recent data collected by the Asian Network for Surveillance of Resistant Pathogen (ANSORP) with respect to pneumococcal isolates from clinical specimens, reported a low prevalence of penicillin and multidrug susceptibility in some Asian countries such as Korea, Japan and Vietnam (106). Totally, the prevalence of susceptibility to commonly used antimicrobial agents in *S. pneumoniae* isolates in far East countries is less than in European and North/South American countries (122).

The high prevalence of resistance to penicillin, particularly in Asian countries, is of great concern. Developing countries face substantial problems of antimicrobial resistance due to several factors including self-medication, absence of diagnostic tools, over-the-counter use, inadequate storage or even use of expired drugs (123).

Prior antibiotic use is considered as the leading risk factor associated with drug-resistant *S. pneumoniae* (124). Therefore, it should be another possible factor in frequency of penicillin resistance in some countries with low rate of PRSP.

According to this study, some countries had the most published data on PSSP, while some other Asian countries have been reporting a few published data on this issue. With regard to microbiological methods, few studies mentioned application of quality assurance in identification and susceptibility testing. In addition, quantitative susceptibility data (e.g. MICs or inhibition diameters) were only rarely available.

In conclusion, the current study has provided updated information and changing trends in penicillin resistance of *S. pneumoniae* in Asian countries. Continuous surveillance of resistance data from clinical isolates as well as implementation of strict infection control policies, evaluation of the new generation of conjugate vaccines and enhanced public health efforts to reduce transmission are required to diminish the progression of antimicrobial resistance.

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