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Current Trend in Pneumococcal Serotype Distribution in Asia

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Abstract

Asia is one of the continents in the world heavily impacted by pneumococcal diseases but yet the information on disease burden and serotype distribution remained largely unclear. The data is essentially needed to inform the burden of pneumococcal diseases as a priority public health concern among the Asian countries. The formulations of pneumococcal conjugate vaccines (PCV) included a number of prevailing serotypes in the Western world but geographical and temporal variations of vaccination effectiveness could be expected in Asia. This review focuses specifically on the most recent five years trend in serotype distributions from both invasive and non-invasive pneumococcal diseases in Asia. Other important features such as antimicrobial resistance and associated clones were also noted. All latest studies reported that complied with the scopes of this review were included and the serotyping data were extracted for comparison analysis between countries, regions, and to represent Asia as the whole. The most common serotypes detected in highest to lowest frequencies order are 19F, 14, 23F, 6B, 19A, 3, and 6A, accounted for approximate two third of the incidences. Heptavalent PCV (PCV7) is expected to cover half of the incidences with significant increment in efficacy with PCV13. East Asia, Southeast Asia, and West Asia have relatively similar serotype distributions though slight variations were observed. The more unique pattern is noted in South Asia region. Initiation of surveillance study in countries with no reporting data is needed. Continued surveillance involving nationwide or multinational collaborative networks need to be set up to enhance and standardize the reporting incidences.

Keywords: *Streptococcus pneumonia*; Asia; Serotype distribution; Pneumococcal conjugate vaccine; Pneumococcal disease; Clonal complex; Antimicrobial resistance

Abbreviations: PCV7: Heptavalent Pneumococcal Conjugate Vaccine; PCV10: Decavalent Pneumococcal Conjugate Vaccine; PCV13: Triskaivalent Pneumococcal Conjugate Vaccine; AOM: Acute Otitis Media; VT: Vaccine Serotype; NVT: Non-Vaccine Serotype; MDR: Multidrug Resistant; NIP: National Immunization Program

Introduction

Streptococcus pneumoniae is one of major human pathogens causing various major infections such as pneumonia, bacteremia, meningitis, and acute otitis media (AOM) worldwide [1-4]. In year 2005, the World Health Organization (WHO) estimated that out of the 1.6 million total deaths due to pneumococcal disease every year, 0.7 – 1 million were children <5 years of age [5]. To date, 93 distinct pneumococcal serotypes have been identified so far. Serotype 6C [6], 6D [7], and 11E [8] are the latest known serotypes and more are yet to be characterized. Nevertheless, only a limited set of serotypes are capable of causing infections [9-11]. Some serotype also display increase tendency in certain diseases. For instance, the most common serotypes detected in AOM were serotypes 19F, 23F, 19A, 6A, 6B, and 14 [12,13] while serotype 1, 5, and 7F were unusual in AOM.

The 23-valent pneumococcal polysaccharide vaccine (PPV23, Pneumovax) covers 23 pneumococcal serotypes and is able to induce protective immune responses in adults [14-17] though conflicting data has been reported [18]. However, the immune response is particularly poor in younger children <2 years of age and individual with underlying immunosuppressive conditions [19]. The maximal efficacy of PPV23 was estimated to be only 70% and revaccination might be needed in certain people as the antibody level begins to falls the following year after vaccination [20]. In February 2000, the heptavalent pneumococcal conjugate vaccine, PCV7 (PCV7, Prevnar) formulated with serotypes 4, 6B, 9V, 14, 18C, 19F, 23F was licensed in the United States and was later incorporated under the childhood vaccination programme in mid 2000 for all infants and children <2 years of age [21,22]. Those 24 – 59 months old who are at particular risks of pneumococcal invasive infections such as immunocompromised conditions (chronic heart diseases, chornic lung diseases), diabetes mellitus, sickle cell diseases, and human Immunodeficiency virus (HIV) infections were also recommended [21,22]. Each of the individual strain antigens (capsular polysaccharide) is conjugated to the nontoxic diphtheria proteins, CRM_{197} eliciting strong T-cell dependent immune responses and protective PCV7-specific antibodies level (>1 µg/ml specific antibody in 51 – 90% immunized children after 3 doses) in the children [21,23-26] and stimulation of T-cell memory [26]. No major safety issue is associated with PCV7 use though mild local reaction at the injection site and fever were noted [27-28]. Later, European countries such as Netherlands [29], Norway [30], and the United Kingdom [31,32] have also made PCV7 into routine immunization. This vaccine comprises seven of most common serotypes causing invasive pneumococcal disease (IPD) among young children in US and European countries, representing approximately 60 – 80% of the serotypes [5,28,33]. PCV10 and PCV13 were reported with mean increase in coverage of 7% and 16% respectively among the Europeans [34]. Up to May 2009, PCV7 was introduced in over 90 countries and incorporated under the National Immunization Program (NIP) of 36 countries in the world.

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Following the widespread use of PCV7, dramatic reductions in the incidences of pneumococcal diseases caused by vaccine serotypes (VT) have been documented in many countries such as US [35-38], Germany [39], Norway [40], France [41,42], Canada [43], Australia [44], and other countries. On top of this, the use of PCV has led to the reduction in antibiotics-resistant strains of pneumococci and the rate of antibiotics prescribed [45-49]. PCV7 also has comparable effects in reducing the carriage rate of VT among the population [50,51]. PCV7 also resulted in reduction of most causes of pneumonia hospitalization in children less than 2 years of age in the US [35]. In AOM patients, a shift into and also the nontypeable *Haemophilus influenzae* as the emerging strains have been observed [52-54]. The herd immunity effect conferred by PCV7 appears to have indirectly benefited the non-vaccinated children and adults [43,44,55,56]. This is probably due to the indirect protective effects of PCV7 as a result of decreased VTs transmissions from the primary PCV age group [57,58] However, the degree of effectiveness of PCV7-VT differs from 100% efficacy in serotype 9V (100%) and 23F (98%) to the lowest in 19F (87%) [51]. The efficacy of PCV7 also depends on several factors, including number of doses received, age of vaccination, proportion of vaccinated population, and geographical variations of serotypes [10,51,59].

The effect of PCV7 in reducing the VT was gradually dissolved by the concomitant increase in IPD due to non-vaccine serotypes (NVT). Findings from the post vaccination studies elsewhere underlined in particular the "serotype replacement" phenomenon [60,62] whereby significant rise in proportion of NVT were detected mainly with serotype 19A and others such as serotypes 3, 15, 22F, and 33F [36,63-69]. Of real concern is the documentation of increasing antibiotic resistance pneumococci, particularly the multidrug resistant (MDR) NVT strains as a result of selective pressures from the conjugate vaccine in parallel with the common antimicrobial agents used [36,38,64]. This indicates that the selected strains have not only escaped/avoided the immunity developed towards PCV7 but have also become more resistant.

Changes in the pneumococcal serotypes population can occur naturally due to the background fluctuation of pneumococcal serotypes [70]. In addition, the circulating genotypes may also change from time to time or due to the selective pressures from vaccines or antibiotic use. Isolates expressing the same serotype are usually, but not necessarily, have the same genotypes [71-73]. Molecular genotyping technique such as Multilocus sequence typing (MLST) has been increasingly used to investigate the sequence type (ST) of pneumococci based on the allelic variation of the seven housekeeping genes [73]. The collection of closely related strains with defined ST variances form the clonal complex (CC), which can be used to evaluate the relationship between the local clonal lineages to the international clones to deduce the pattern of global dissemination of the clones [73]. For instance, the global widespread of the Spain^{23F}-1 and France^{9V}-3 international clones have been documented in Europe and Asia [74-76]. Serotype that is associated with clone of higher antibiotic resistance tendency would in turn confer higher resistance to the associated serotype. For example, penicillin resistant or MDR clones of serotypes 14, 23F, 6B, and 9V have been reported in Spain since 1980s [77-79]. Prior to the introduction of PCV7 in the UK, significant reduction in ST306 which was associated with serotype 1 and a concomitant reduction in ST124 which was associated with serotype 14 have been reported [80]. In the postvaccination era, significant expansion of serotype 19A was mainly attributed to the clones CC199 and CC320 in the US [68,81-83]. CC199 represents the major clonal lineage even before PCV7 introduction but the multidrug resistant clone CC320 mainly emerged after the introduction of PCV7 [68,81-83]. In Europe, the increase in MDR serotype 19A was mainly associated with ST276 and ST320 [84].

In the developing world data on the pneumococcal disease burden have been very limited. The serotype epidemiology corresponding to the respective country is largely unavailable as well. The same situation is happening in many of the countries in Asia that represents the major barrier in estimating the pneumococcal disease burden in Asia. Its use is still mainly restricted to the private market on an individual basis to those who can afford the vaccination and this comprises a small percentage of the population. Hence, the actual effect could not be translated to benefit the whole community. This is largely due to the lack of information on disease burden and serotype distribution as well as the cost-effectiveness estimation with the widespread use of PCVs [85,86]. Various efforts in introducing PCV7 to the developing world are currently underway but prior evaluations on the potential effectiveness of the vaccine must be collected [87-89]. A recent review by Lin et al. [90] focusing on pneumococcal disease burden among children in the Asia-Pacific region from 1999 - 2010, highest incidences of 100 - 200 cases per 100 000 children <1 or 2 years old and the preventable disease reach as high as 6 - 200 cases per 100 000 children. It was reported that the coverage of PCV7 is relatively low (45%) among the Asian countries [91,92]. Since PCV7 was initially designed to contain largely the IPD serotypes in the western countries and serotype distribution exhibit substantial geographical and temporal variations [59,93], the outcome might not be the same in Asia. For all the reasons mentioned above, there is an urgent need to revise into the most recent situation in serotypes distributions in Asia, which outlined the main objective for review article. Here we look extensively into the current five years trend of serotype epidemiology implicated in both invasive and noninvasive pneumococcal diseases in Asia. The associated ST and antibiotic susceptibility were also noted.

Methods

The MEDLINE (National Library of Medicine, National Institute of Health) database was used to identify relevant studies published between January 2006 and September 2011 on patients of any age group with invasive or noninvasive pneumococcal diseases. Isolates were collected from any site appropriate to the respective methodology. Several criteria were applied: (1) If the data involved consecutive sampling period from date prior to and the date defined above (e.g. year 2001 through 2008) and where the data is cumulative and not divisible by years, all data were included; If divisible, only data from the defined date is extracted for analysis (2) Not carriage isolates (3) Isolates were not subset of a particular pneumococci characteristics, such as serotypes of only levofloxacin-resistant pneumococcal isolates. The search was carried out in English and is limited to studies published in English. General search terms included: *Streptococcus pneumoniae,* serotype, and pneumococcal diseases, separated by binary operators "OR" or "AND" in combination with the name of country/territory as specific search term: "Afghanistan", "Armenia", "Azerbaijan", "Bahrain", "Bangladesh", "Bhutan", "Brunei", "Burma/Myanmar", "Cambodia", "China", "Cyprus", "East Timor", "Georgia", "Hong Kong", "India", "Indonesia", "Iran", "Iraq", "Israel", "Japan", "Jordan", "Kazakhstan", "North Korea", "South Korea", "Kuwait", "Kyrgyzstan", "Laos", "Lebanon", "Macau", "Malaysia", "Maldives", "Mongolia", "Nepal", "Oman", "Pakistan", "Papua New Guinea", "Philippines", "Qatar", "Saudi Arabia", "Singapore", "Sri Lanka", "Syria", "Taiwan", "Tajikistan", "Thailand", "Turkey", "Turkmenistan", "United Arab Emirates", "Uzbekistan", "Vietnam", and "Yemen". Relevant studies were also identified by hand searching of the reference list of the primary papers. In addition, occasional search of published articles and government/network surveillance databases were performed using Google search engine. Of all the countries listed only 17 had data

Country/ Territory	Study	Sampling period[a]	no. of isolates[b]	Sample type[c]	Age (years)
East Asia					
China	Liu et al. 2008 [94]	1/2005 – 12/2006	451	both	1d – 4y
	Chen et al. 2010 [95]	2007	31	non-invasive	<3
	Xue et al. 2010 [96]	2006 – 2008	171	invasive	<14
	Yao et al. 2011 [97]	2/2006 – 2/2008	338	non-invasive (only one from invasive)	≤5
	Zhang et al. 2011 [98]	3/2009 – 3/2010	91	Both	all
	Zhou et al. 2011 [99]	2010	140	non-invasive	children
Hong Kong	Ip et al. 2007 [100]	3/2005 – 3/2006	519	non-invasive	1m – 15y
	Ho et al. 2011 [101]	7/2005 – 12/2009	563	invasive	all
	Hon et al. 2010 [102]	1/2007 – 12/2009	12	both	children
	Center for Health Protection Hong Kong, 2011 [103]	9/2010 – 6/2011	160	invasive	all
Taiwan	Hsieh et al. 2008 [104]	2003 – 12/2006	364	invasive	all
Japan	Suzuki et al. 2010 [105]	2006 - 2007	323	both	all
	Hotomi et al. 2008 [106]	2/2006 – 6/2007	175	non-invasive	1m – 127m
	Chiba et al. 2010 [107]	8/2006 – 7/2007	492	invasive	all
	Sakai et al. 2011 [108]	1/2007 – 12/2009	115	invasive	≤15
	Oishi et al. 2011 [109]	10/2007 – 12/2009	79	both	children
South Korea	Choi et al. 2008 [110]	1991 - 2006	444	both	children
	Song et al. 2009 [111]	2007	94	both	all
	Baek et al. 2011 [112]	2008 - 2009	329	both	all
Southeast Asia					
Singapore	Hsu et al. 2009 [113]	1/2000 – 12/2007	192	invasive	14 - 96
	Jefferies et al. 2011 [114]	2001 - 2006	86	invasive	≤16
Malaysia	Le et al. 2011 [115]	3/1999 – 2/2007 (except 2001 and 2004)	151	both	all
	Yasin et al.2011 [116]	1/2008 – 12/2009	433	both	all
Thailand	Srifeungfung et al. 2010 [117]	1/2006 – 2/2009	214	invasive	all
	Baggett et al. 2009 [118]	5/2005 – 6/2007	74	invasive	all
Laos	Moore et al. 2010 [119]	1/2003 – 4/2009	33	invasive	all
South Asia					
Bangladesh	Brooks et al. 2007 [120]	4/2004 – 3/2006	34	invasive	<5
	Saha et al. 2009 [121]	5/2004 – 5/2007	137	invasive	<5
	Arifeen et al. 2009 [122]	7/2004 – 6/2007	26	invasive	<5
Sri Lanka	Ministry of Health Sri Lanka, 2008 [123]	2006 - 2008	36	invasive	<5
Nepal	Williams et al. 2009 [124]	4/2005 – 12/2006	17	invasive	2m – 59m
	Kelly et al. 2011 [125]	4/2005 – 12/2006	34	invasive	≤12
	Shah et al. 2009 [126]	11/2004 – 3/2007	28	invasive	2m – 5y
	Rijal et al. 2010 [127]	11/2004 – 12/2008	47	invasive	2m – 60m
Pakistan[d]	Zaidi et al. 2009 [128]	5/2005 – 4/2006	3	invasive	<5
West Asia					
Oman	Al-Yaqoubi et al. 2011 [129]	9/2002 – 12/2007	85	both	all
Turkey	Percin et al. 2010 [130]	1/1998 – 7/2007	332	invasive	all
	Ceyhan et al. 2010 [131]	2005 – 2007	27	invasive	children
	Ceyhan et al. 2011 [132]	7/2008 – 2/2010	202	invasive	≤18
Palestine	Kattan et al. 2011 [133]	1/2001 – 4/2010	120	invasive	1d – 11y
Israel	Somech et al. [134]	1/1999 – 12/2008	5236	non-invasive	<5

[a]Specific period of the sampled isolates included in the current analysis, might be only part of the original study conducted
[b]Actual number of serotyped isolates included in the current analysis
[c]Invasive or noninvasive isolates
[d]Pakistan is excluded from any of the analysis due to extremely low sample size (n=3)

Table 1: Studies included in this review reporting pneumococcal serotypes data from Asian countries.

available for analysis in English and hence as such only these will be presented in this review. Table 1 summarizes the details of all the studies included in this review. The term National Immunization Program (NIP) was used to refer to the childhood or routine immunization program or equivalent throughout this review.

The combined percentage was calculated by summation of the number of isolates for the particular serotype from each study (as numerator) and divided by total number of isolates from each study (as denominator), adjusted to percentage (%). For regional and overall Asian estimations, respective data for countries/territories and regions were used directly and calculated using the same method. The serotype coverage of three licensed PCVs (PCV7, PCV10, and PCV13) was estimated via summation of the combined values (PCV7: 4, 6B, 9V, 14, 19F, 23F, 18C; PCV10: PCV7 + 1, 5, 7F; PCV13: PCV10 + 3, 6A, 19A) and includes the seven most common serotypes by country/territory, regions, and Asia in total. The serotypes distribution and predicted PCVs efficacy based on our analysis are listed under Table 2.

Country/ Territory	Predominant Serotypes (%)[a]							PCV coverage (%)		
								7-	10-	13-
East Asia	**19F (19.9)**	**14 (11.1)**	**6B (10.7)**	**23F (10.4)**	***19A (6.9)***	***3 (6.4)***	***6A (3.8)***	56.9	58.3	75.4
China[b]	**19F (39.1)**	***19A (12.6)***	**14 (8.4)**	**23F (7.7)**	**6B (6.8)**	15 (2.7)	***6A (1.7)***	63.4	64.8	79.8
Hong Kong[c]	**14 (17.4)**	**6B (13.1)**	***3 (11.7)***	**19F (11.3)**	**23F (10.1)**	**4 (3.4)**	***19A (2.6)***	56.9	59.3	75.8
Taiwan	**19F (20.1)**	**23F (20.1)**	**6B (18.4)**	**14 (16.8)**	***3 (6.3)***	15 (3.3)	23A (2.7)	79.9	79.9	89.8
Japan	**6B (11.2)**	***3 (8.8)***	**19F (8.6)**	**14 (8.5)**	**23F (7.8)**	12F/A (4.4)	***6A (4.3)***	42.8	44.0	60.6
South Korea	**19F (20.3)**	**23F (14.1)**	***19A (12.0)***	***6A (9.0)***	**6B (8.7)**	**14 (6.9)**	**9V (5.0)**	57.3	58.2	83.0
Southeast Asia	**19F (14.4)**	**6B (11.7)**	**14 (11.2)**	**23F (7.6)**	*19A (6.0)*	***1 (4.4)***	***3 (3.9)***	49.9	56.5	69.7
Singapore	**14 (25.2)**	**6B (13.7)**	***3 (8.3)***	**19F (7.2)**	8 (4.7)	**23F (4.3)**	***19A (4.3)***	54.0	58.6	74.1
Malaysia	**19F (20.7)**	**6B (9.4)**	***19A (6.5)***	**23F (6.3)**	**14 (5.8)**	***1 (5.3)***	***6A (3.8)***	46.9	54.5	66.4
Thailand	**6B (16.0)**	**23F (13.2)**	**19F (10.1)**	**14 (9.0)**	***19A (6.9)***	***3 (4.5)***	***6A (3.5)***	54.2	57.6	72.6
Laos	***1 (18.2)***	***5 (12.1)***	**14 (9.1)**	**23F (9.1)**	6 (9.1)	**4 (6.1)**		30.3	63.6	66.7
South Asia	***1 (16.2)***	2 (8.6)	***5 (8.1)***	**14 (6.7)**	12F/A (6.7)	**23F (4.2)**	**19F (3.9)**	24.8	52.4	57.1
Bangladesh	2 (12.2)	***1 (11.7)***	**14 (8.6)**	***5 (7.1)***	12F/A (7.1)	45 (6.1)	**18C (4.6)**	24.4	47.2	53.8
Sri Lanka	**19F (22.2)**	**23F (16.7)**	**6B (13.9)**	**14 (11.1)**	15B (8.3)	***3 (5.6)***	38 (5.6)	63.9	63.9	69.4
Nepal	***1 (27.8)***	***5 (11.9)***	12F/A (7.9)	2 (5.6)	***7F (3.2)***	**4 (3.2)**	19B/C, 16/36/47 (3.2)	14.3	57.1	58.7
Pakistan[d]	**19F (66.7%)**	***1 (33.3%)***						Not evaluated		
West Asia	**19F (14.3)**	**14 (13.4)**	**23F (9.2)**	***19A (9.0)***	**6B (7.2)**	***6A (5.3)***	***3 (4.0)***	50.8	58.5	76.8
Oman	**6B (11.8)**	**19F (11.8)**	**23F (11.8)**	**14 (7.1)**	9A/L (7.1)	***1 (5.9)***	11A/D (4.7)	45.9	57.6	65.9
Turkey	***1 (18.9)***	19 (11.1)	**19F (7.8)**	***3 (6.2)***	**14 (5.3)**	**4 (4.5)**	18 (4.1)	24.4	46.7	56.2
Palestine	**6A/B (14.2)**	**14 (13.3)**	***1 (11.7)***	**9V (9.2)**	***5 (7.5)***	**19F (6.7)**	**4 (5.0)**	55.0	77.5	85.0
Israel	**19F (15.2)**	**14 (14.4)**	**23F (10.1)**	***19A (10.0)***	**6B (7.4)**	***6A (5.9)***	***3 (3.8)***	53.6	59.3	79.0
Asia	**19F (16.2)**	**14 (12.1)**	**23F (9.4)**	**6B (8.9)**	***19A (7.7)***	***3 (4.8)***	***6A (4.4)***	52.4	58.1	75.0

[a]Serotypes in bold-face only denotes PCV7-VT; bold-face and italic denotes PCV10-specific VT in addition to PCV7; bold-face, italic, and underline denotes PCV13-specific VT in addition to PCV10

[b]Refer to mainland China only

[c]Hong Kong is one of the Special Administrative Territories of China and is analyzed separately

[d]Pakistan is excluded from any of the analysis due to extremely low sample size (n=3)

Table 2: Current trend in predicted effectiveness of PCVs and prevailing serotypes in Asia.

As the way in which the respective authors reporting serotypes/serogroups varied greatly among each other due to the serotyping method adopted, we have reorganized them into appropriate groupings to ease the analysis process and to standardize among all studies (e.g. serotype 9A and 9L become 9A/L). Hence the serotype reported here might differ slightly from the original paper but yet is accurately defined. Individual study with minor serotypes/groups categorized together as "other" was noted. Although these serotypes/groups might differ between the respective studies, these are mainly minor PCV-VT and the effect on the serotypes and PCVs calculations should be negligible.

East Asia

China

Many studies concerning pneumococcal surveillance have been reported throughout the years from China. The PCV7 was introduced in China in September 2008. Six studies [94-99] were included to describe the current situation of *S. pneumoniae*. Strikingly, serotype 19F alone accounted for approximately 40% of all isolates. Such pattern of major dominance by serotype 19F or any other single serotype was not observed anywhere in Asia and elsewhere in the world. The next most prevalent serotype is serotype 19A which differs vastly from serotype 19F by approximate three-fold in percentage. As a result, the predicted efficacy for PCV7 and PCV13 are relatively high (63.4% and 79.8% respectively), mainly due to the abundance of serotype 19F and serotype 19A. The coverage by PCV10 does not differ very much from PCV7. Such dominance would be valuable from the public health perspective as more than half of the incidences among the Chinese can be prevented by just targeting two serotypes. Despite this, other common serotypes including 14, 23F, 6B, 15, and 6A also play important role in disease incidences as together, they accounted for about 80% of all cases in China. In terms of ranking order, this distribution is rather different (except 19F) from two previous studies describing serotypes detected from pediatric patients with respiratory infections [135,136]. Hence, the use of PCV13 is expected to produce the optimal coverage for the Chinese population in general. The remaining 20% is stratified fairly equally into more than 30 minor serotype/groups including nontypable strains. No major difference in serotype distribution and the PCV7 coverage was noted between children <2 and those 2 – 4 years old [94,96]. The serotypes 19F, 19A, 6B, and 23F have been reported by Zhang et al. [98] to be associated with the global predominant clones of ST271, ST320, ST90, and ST81 respectively. These clones were responsible for the highly-resistant isolates within the individual serotypes.

In addition, significant difference in serotype distributions due to geographical variations between different districts has been reported. Eastern and Southern Central China were reported to have more serotypes of PCV7 and thus PCV7 vaccination would be effective, but the coverage in Northern region was noted to be lower presumably due to lower presence of the vaccine types [97]. In another study, serotype 19A was commonly detected from northern regions but not southern and eastern regions [96]. Of note, the prevalence of serotype 19A in China had occurred even before the introduction of PCV7 [96].

As prescription is not compulsory, widespread use of antibiotics is common in China. Because of this, the rate of PNSP remained considerably high in China [97,98]. Although varied slightly between studies, the rate of PNSP is generally 58% - 88% [94,95,97,98] and these strains are likely to exhibit tolerability to other classes of antibiotics as well [98]. The high antibiotic selective pressure could have contributed to the selection of serotypes associated with resistance such as serotype 19A [94,97]. Serotype 19A has also been reported with high resistance against cefuroxime [97]. In addition, serotype 19A and serotype 5 were more invasive [94]. In contrast, serotype 19F was closely associated with PNSP (87.3%) but was rather noninvasive [94]. Of note, both the serotype 19F and 19A also exhibited higher (>50%) resistance against amoxicillin-clavulanic acid and ceftriaxone, and have greater tendency to become MDR strains [94] In China, the rate of MDR could reach up to as high as 90% and have been frequently reported [94-96].

Hong Kong

Since Hong Kong is considered one of two Special Administrative Territories (SAPs) of China, the serotype distribution will be evaluated separately. Of note, the prevalence of serotype 14, 6B, 3, 19F, and 23F, range from 17.4% to 10.1% and covers 63.6% of all isolates. PCV7 was introduced in Hong Kong in October 2005 and was incorporated under the NIP starting September 2009 [137]. PCV10 was made available in August 2009 and PCV13 in May 2010. The efficacy of PCV7 and PCV10 is predicted to be substantial (56.9% and 59.3% respectively) while for PCV13, 75.8% of the isolates were covered, mainly due to the inclusion of serotype 3. Of note, serotype 5 though only present in minority was reported to be highly resistant to erythromycin [101].

To evaluate the change in serotype epidemiology with the introduction but prior to routine immunization of PCV7, Ho et al. [101] conducted a multicenter study involving patients of all ages and covering >90% of isolates from the districts involved. Several important findings were noted where significant reduction was detected for three of the PCV7-VT 9V, 23F, and 14. The drop was greatest among children <5 years old (89.5% to 65.7%) while moderately in older adults ≥65 years old. Also, serotype distribution differed among age groups at which serotype 6B was the commonest among the children while serotype 3 was prevalent in adults. In addition, serotype 19A as well as 6A, 6B, 14, 19F, and 23F were frequently linked to dual resistance against penicillin and erythromycin. The rate of dual resistance had increase from 44.1% to 64.2% in children <5 years of age in the postvaccination era. Serotype 14 was the only serotype equally common across age groups. In contrast, the prevalence of PCV7-NVT 7F and 19A have seen significant increased but no change was noted with the PCV13-NVT over time. For this reason and also to provide additional protection against pneumococcal infections, a switch to the PCV13 to replace PCV7 is being considered [138].

Gradual increase in penicillin resistance strains since 1990s in Hong Kong was linked to the MDR clones, Spain23F-1 and Spain6B-2 [139,140]. In the mid 2000s, the incidence of PNSP was reported to be between 46 – 66% [141]. In recent years, the percentages of PNSP was still high (50% - 65%) and the nonsusceptibility to erythromycin and tetracycline were even higher (76% and 62% respectively) [100,102]. On the contrary, resistance to cefotaxime was lower (17% - 38%) while all strains were fully susceptible to vancomycin and fluoroquinolones (except ciprofloxacin at 2.3%). Expansion of the Spain ST320 clone had contributed to the rises of serotype 19A [101].

Taiwan

Since the data reported by Hsieh et al. [142] represent part of their earlier work in 2008 (64/68, except 4 new isolates), we evaluate the serotype distribution based solely on the initial study [104] to avoid redundancy. The four predominant serotypes in Taiwan, serotype 19F (20.1%), 23F (20.1%), 6B (18.4%), and 14 (16.8%) accounted for three quarters (75.3%) of the cases. Because of this, the efficacy of PCV7 is

exceptionally high (80%) among the Taiwanese population. PCV7 was licensed in Taiwan in October 2005. No additional protection is conferred by PCV10 due to the absence of PCV10-specific VT in Taiwan while PCV13 gave an additional 10% in coverage. Thus, great majority of the pneumococcal disease incidences among the Taiwanese population could have been prevented by the use of PCVs. Moreover, the efficacies of all three PCVs are highest in Taiwan as compared to other Asian countries.

Serotype 14, 23F, and 6B were reported to be associated with pneumonia, bacteremia, and meningitis, respectively [142]. A number of serotypes which were linked to the internationally-disseminated clones, namely England serotype 14 ST9, Spain 23F ST81, Spain 6B ST95, Colombia 23F ST33, Taiwan 19F ST236, and Taiwan 23F ST242 were widespread in Taiwan and responsible for approximate half of all invasive isolates [142]. The prevalence of resistant serotype 19F in Taiwanese children was attributed to the expansion of Taiwan 19F ST236 [142]. Beside the international clones, the penicillin-resistance clones ST876, ST46, ST76, and ST2889 were recently identified in Taiwan and believe to be the main invasive clones prevailing among the children [142]. Higher invasive tendency of certain serotypes have also been reported [143]. In particular, serotype 14 was well recognized for its invasiveness and IPD causing ability [144-147].

The problems of penicillin- and macrolide-resistant *S. pneumoniae* have long been recognized in Taiwan [144,145,148]. High resistance to erythromycin and penicillin were constantly reported [104] and cephalosporin resistance has also been reported since 2005 [149]. This pattern of resistance was related to geographical distribution of the isolates as well [104]. On the contrary, susceptibility to coamoxiclav, vancomycin, and fluoroquinolones (lovofloxacin, moxifloxacin, gemifloxacin) were high.

Japan

Japan has very well-established coordinated surveillance network. This is seen with a number of recent studies involving multicenter, single prefecture [105], large multicenter-multiprefecture [108], as well as two nationwide surveillances [106,107]. Of course, separate single-centered study that also provided valuable finding [109]. The overall predominant serotypes based on these five recent studies are as follow: serotype 6B, 3, 19F, 14, 23F, 12F/A, and 6A. The predicted PCV7 effectiveness among the Japanese would be 42.8%, 55.2%, and 71.7%. If serogroups 6 and 19 which were nondifferentiated by Suzuki et al. [105] were included, further 11.2% additional coverage is expected for each PCV. In February 2010, PCV7 was available in Japan and has become the routine immunization recently in 2011. We do not observe serotype 19A in Japan to be as common as in other East Asian countries. However, two individual studies [107,109] had pointed out the relatively high incidence of serotype 19A (approximate 6% - 13%) and this rate was higher than the Western countries during the prevaccination era [43,55,56,150]. Hence, this warrants the continued monitoring of the serotype epidemiology in Japan.

Sepsis was the more common cause of IPD among the Japanese (46.2%), followed by pneumonia (31.5%) and meningitis (17.5%) [107]. Serotypes 19F, 14, and 6A were the predominant serotypes in pediatric community-acquired pneumonia [151]. Remarkably, great majority (92%) of pediatric IPD cases were children aged ≤4 years of age [107]. Meningitis was most frequent during infancy period (≤12 months) and it has been predicted that PCV7 and PCV13 shall protect 70.6% and 82.4% of the cases [108]. In addition, the four most predominant serotypes from our analysis above (except serotype 3) also represent the common serotypes responsible for pediatric meningitis as reported by Sakai et al. [108]. On the other hand, two third of strains isolated from children with AOM aged ≤2 years were PNSP.

The higher penicillin tolerability in serotype 19F and 23F might be the factor contributed to the higher penicillin resistance among AOM isolates obtained from the younger children [106]. Similar finding was reported in Niigata prefecture at which the PNPS rates in serotype 19F and 23F were as high as 92.9% and 84.6% respectively [109]. Other important PNSP serotypes noted were 6B (73.3%) and 14 (100%, n=4 only), respectively [109]. Among the PNSP, serotype 19F has the largest proportion of PRSP (61.5%) as compared to 23F (18.2%) and 6B (9.1%). In contrast, the prevailing PSSP serotypes were 19A (n=6/10) and 33F (n=2/2, low sample size) [109]. This suggests the clear difference in serotype distribution between PSSP and PRSP serotypes. However, this does depends on the study methodology adopted as Suzuki et al. [105] had observed no significant association between PNSP with specific serogroups. Hence, the relationship between these two determinants remained elusive.

Interestingly, although penicillin-resistance has observed gradual increase since 1998 in Tohoku, the incidences then fell slightly recently following the peak in 2004 [105]. The underlying PNSP serogroups 19 and 23 persist steadily over years, but serogroups 6 and 14 becoming less common since 2002. Close association among serotypes and STs were observed [108]. The high heterogeneity of STs (especially among the dominant serotypes/groups) as well as the proportion of novel STs in Japan were also reported by Jefferies et al. in Singapore [114], High homogeneity in DNA restriction patterns were noted among strains of same resistance genotype, thus strongly indicates that the widespread were originated from a few parent strains to distant areas [107].

South Korea

Similar to China, serotype 19F is the most common (20.3%) in South Korea while. serotype 23F ranked second with 6% lower in percentage. Other serotypes include 19A, 6A, 6B, 14 and 9V and these are the seven most common serotypes which cover 76% of the isolates. PCV7 and PCV10 are expected to provide coverage to more than half (57% - 58%) of the isolates. On the other hand, PCV13 confers significant enhancement by 25% in addition to PCV7 and PCV10 which is largely due to the inclusion of serotype 19A and 6A.

Most of the children from urban areas have received PCV7 vaccination since the introduction of PCV7 in November 2003 [111]. Significant reduction in PCV7-VT such as serotype 19F and 23F and an increase in PCV7-NVT have been well-documented in South Korea [110-112]. However, no reduction in prevalence of serotype 14 was observed and this serotype was mainly related to the presence of the CC554 clonal complex [112]. Although the actual reasons were not clearly stated, the lower effectiveness of PCV7 against serotype 14 led to the postulation of the possible existence of undiscovered serotype 14 subtypes [112]. This is similar to the recent discovery of serotype 6 subtypes (6C and 6D) that responded differently to the PCV7 due to cross-reactivity from VT 6B.

Serotype 19F showed diverse genotypic heterogeneity whereby as high as 18 STs were found to associate with this serotype and ST271 represented the dominant clone [110,111]. In contrast, increasing prevalence of the PCV7-NVT serotype 19A postintroduction was essentially due to the underlying single clonal expansion of ST320 [110,111]. In fact, all recent serotype 19A isolates were ST320 based on a study performed by Song et al. [111]. Furthermore, prevaccination

expansion of serotype 19A due to ST320 has been reported [110]. Interestingly, ST320 has also been detected in serotype 19F and the author hypothesized that ST320 might have been originated from the serotype 19F dominant clones ST271 or ST236 [110]. These clones are already in existence in South Korea for the past two decades ago [152]. Unlike serotype 19F, genotypes of serotype 19A were much less diverse [110]. In addition, the inherent MDR property of ST320 probably had conferred additional survival advantage to serotype 19A against antibiotic selective pressure rendering the continued expansion of this serotype even with widespread antibiotics usage in South Korea [110]. This has also contributed to the domination by ST320 over other serotype 19A genotypes such as ST1374 which were less resistant to beta-lactam antibiotics [110].

On the other hand, the increase in serotype 6A has also been noted and was related to ST81 genotype or its single or double locus variants [112]. Interestingly, this serotype 6A-ST81 association was only reported in and widely distributed in South Korea [111,112]. The same was observed with serotype 6B-ST282 and this genotype has become the dominant clone of serotype 6B [112]. Unlike serotypes 19F and 19A, no common ST was found between 6B and 6A.

Southeast Asia

Singapore

PCV7 was introduced in Singapore in October 2005 and later be incorporated under the NIP in November 2009 [153] thus the data represent the baseline serotype distribution prior to large scale vaccination in NIP, and the five most common serotypes in Singapore are serotypes 14, 6B, 3, 19F, 8, 23F, and 19A, which account for 67.7% of IPD cases. The proportion of the most dominant serotype 14 is about two-fold higher than the second serotype 6B. The serotypes distributions observed in these studies [113,114] were comparable to previous study by Chong et al. [154]. No significant fluctuation with regard to the serotypes associated with PCV7 and PPV23 was observed throughout the years [113], partially due to the fact that PCV7 has not been incorporated under the Singapore NIP.

Recently, Jefferies et al. [114] reported data on clonal relationship among the IPD isolates using MLST. The predominant STs in decreasing order were: ST9 (12.8%), ST156 (7.0%), ST236 and ST90 (5.8% each). Two of the predominant serotypes, 14 and 6B displayed widest genotypic heterogeneity with 15 and 14 STs respectively. In addition, studies conducted earlier by the same group in UK [80,155] also showed high number of serotype 14 as well as the high heterogeneity (12 STs) of this serotype. Such occurrence can be attributed to, in part, the genomic dynamicity which facilitates the adaption of the strain against drug selective pressure [156]. High percentage (32%) of the reported genotypes were indeed novel STs, suggesting potential undiscovered STs in Singapore as well as the SEA region [114].

Malaysia

In Malaysia, serotype 19F predominated the population at the rate of 20.7%, followed by serotype 6B (9.4%), 19A (6.5%), 23F (6.3%), 14 (5.8%), 1 (5.3%), and 6A (3.8%, not differentiated 6B/A in our previous study [115]). These serotypes accounted for 57.9% of the circulating serotypes in Malaysia. Moderate proportions of these common serotypes are covered by PCVs, giving the rate of PCV7, PCV10, and PCV13 to 46.9%, 54.5%, and 66.4% respectively. This is probably due to the large overall non typable and agglutinated isolates that constitute about 14.7% of all the isolates analyzed. This is of concern as it indicates the presence of a number of NVT as well as those uncommon/ undiscovered serotypes not usually identified and not contained in the PCVs. Hence, the overall effectiveness of PCVs among the local population could be affected considerably.

The changes in the prevailing serotypes have been observed among the Malaysian population. As mentioned by Yasin et al. [116], remarkable increment of serotypes 6A, 19F, and 19A have been observed since 1995/96 based on data from a multicenter surveillance study done by the same group [157]. The concomitant reduction in serotype 1 was noted as well. The rate of PNSP stains in Malaysia range from 33% - 50% [115,116]. Serotype 19F was the commonest serotype detected from PNSP strains [115,116] and this serotype had been found to be significantly associated with strains of higher resistance against penicillin [115]. In term of invasive serotypes, Yasin et al. [116] reported that the common invasive strains were serotypes 6B, 19F, and 1, while our previous study [115] reported differing serotypes which were 19F, 19A, and 23F. Despite this, it was noted that majority of serotype 19A strains were invasive [115,116] while serotype 19F was frequently detected from noninvasive site [115]. As high as 81% of isolates obtained from children <5 years of age were noninvasive [115]. Besides that, those at the extreme age (<5 and ≥60 years old) were commonly infected with pneumococcal disease [115,116]. Among these age group, serotype 19F was the predominant serotype [115].

Thailand

Two recent studies have reported serotype distributions in Thailand: one covering the heavily-populated urban area in central Bangkok (Bangkok, Nakorn Pratom, and Nonthaburi) [117] and another covering two rural areas (Nakhon Phanom and Sa Kaeo bordering Laos and Cambodia, respectively) [118]. The most common serotypes based on data from these two studies are 6B (16.0%), 23F (13.2%), 19F (10.1%), 14 (9.0%), and 19A (6.9%), 3 (4.5%), and 6A (3.5%), responsible for 63.2% of all. Overall, the coverage for PCV7 and PCV10 are around 56% while PCV13 has better coverage at 72.6%. It was reported PCV7 covered 70.3% of the invasive isolates from Thai children <5 years of age [117], with serotype 6B and 23F highest at 21.9% each, 14 (17.1%), 19F (6.2%), 4 and 9V (1.6% each). Serotype 19A (7.2%) was the highest non-VT strains, followed by 6A (3.6%).

The distribution of VT remained fairly stable although with the introduction of PCV7 since June 2006, probably due to the low vaccination rate among the population. The low coverage rate of PCV7 especially among the low- and middle-income families is mainly attributed to the high cost of PCV7 vaccination (~122 USD/ dose) [5] and competing interest from other vaccines under the NIP [118]. The newer generations of PCV (PCV10 and PCV13) are predicted to confer greater coverage (84% and 95% respectively).

The penicillin- and ciprofloxacin-susceptibility were high in Thailand, but at the same time the resistance to cotrimoxazole (55%) was also high in Thailand [117,118]. Prevalence of PNSP has been steadily increasing over the years from 63% in 1997-1998 [158] to 69% seven years later [159]. The rate climbed further to as high as 73.8% among non-invasive isolates in young children recently [117]. Fortunately, most antibiotic-nonsusceptible strains belonged to the PCV7-VT [118] and approximately 83% and 100% of PNSP and cefotaxime-nonsusceptible strains were covered under the PCV7 formulations [117]. From the same study, the author also expressed the concern on the detection of cefotaxime-nonsusceptible strains because cefotaxime has been the main treatment choice for pneumococcal meningitis in Thailand.

Laos

Study on pneumococcal disease burden in Laos is extremely limited. The first study was only reported in year 2006 by Phetsouvanh et al. [160] and recently by Moore et al. [119] in year 2010, both based in Ventiane, the capital city of Laos. Only data from the latter study was discussed in this review as the sampling period of the former one was during year 2000 – 2004. The most prevalent circulating serotypes in Laos are 1 (18.2%), 5 (12.1%), 14, 23F and 6 (9.1% each), and 4 (6.1%). All other detectable serotypes/groups had only one isolate (3.0%). Although serotype 1 is generally recognized as the "outbreak" serotype [161-163], the author found no linkage between serotype 1 and any disease outbreak among the patients examined [119]. Interestingly, serotype 19F that is highly prevalent in other Asian countries especially Malaysia, Singapore, and Thailand, as mentioned earlier in this review was not a frequent serotype in Laos. The predicted PCV7 coverage (assuming 6A/B/C to be PCV7-VT) is 39.4%. However it is predicted that the coverage rate increase dramatically to 63.6% if PCV10 is used and a further 3% if PCV13 is used. Based on these data, PCV10 instead of PCV7 might be the potential vaccine candidate to be considered. However, due to the low sample size (n=33), continued monitoring of serotype distribution in Laos is urgently needed to provide comprehensive data. Apart from this, the isolates exhibit full susceptibility to ceftriaxone and ofloxacin while 61% of the isolates were resistant to cotrimoxazole.

South Asia

Bangladesh

Three recent studies [120-122] have conducted extensive population-based studies on pneumococcal serotype distribution involving countrywide coordinated surveillance of both urban and suburban areas in Bangladesh. We noted that the above mentioned surveillances have in common investigated the IPD burden among young children <5 years of age. Since seeking healthcare services in the course of infections is rather uncommon, thus active population-based surveillance is important and would better reflect accurately the pneumococcal disease burden in Bangladesh [122]. The estimated overall incidences of IPD is 86 cases per 100 000 child-years of observation [122]. Among those <5 years of age, respiratory tract infections is the main manifestation and more than 90% of total pneumococcal isolates were obtained from children ≤24 months old [121]. Of note, since all three studies reviewed here had not involve any older age groups (≥5 years old), thus the data is skewed towards the young children.

The current prevailing serotypes (in decreasing order) are as follows: serotype 2 (12.2%), 1 (11.7%), 14 (8.6%), 5 and 12 F/A (7.1% each), 45 (6.1%), and 18C (4.6%). All other minor serotypes/groups were sparsely distributed at <4.1%. From our analyzed data, we express a concern over the efficacy of PCV among the Bangladesh populations; As all recent studies examined specifically the young children, which are also the PCV-targeted group, only two (serotype 14 and 18C) of the PCV7-VT are found among the seven most prevalent serotypes but merely at the rate of 13.2% in total. Thus, the low efficacy of PCV7 among Bangladeshi children (24.4%) is expected. Compared to all other Asian countries, the coverage of PCV7 is more than two-fold than in Bangladesh (except Nepal, Laos, and Turkey). Even with PCV13, additional of 29.4% to 53.8% coverage rate is still comparatively low.

The more striking finding from the analysis is that a number of uncommon and non-VT is remarkably abundant here. For example, serotypes 2, 45, and 38 are responsible for 20.8% of the cases. The highly abundant serotype 2 as well as 45 is rather unique to Bangladesh as reports of these serotypes from other Asia countries is extremely rare which usually present as minor strains (not more than 5% rate). Serotype 2 has almost never been detected from the developed countries [92]. In addition, this serotype has undergone stable expansion in Bangladesh since 1992 until now [121,164,165]. Importantly, it should be noted that this expansion of serotype 2 is not due to "serotype replacement" as PCV usage is still low in Bangladesh [122]. Although it has been predicted that widespread use of PCVs can prevent >1 million pediatric pneumonia cases in Bangladesh [120], the low coverage rate of PCVs shall mean that pneumococcal infections might not be efficiently controlled by PCVs among the Bangladesh population. In comparison, the coverage for pneumonia and bacteremia by PCV10 and PCV13 is better than meningitis serotypes [121]. The serotype distribution in Bangladesh has observed noticeable changes over time. Serotypes 1, 2, and 5 are emerging while 12F and 15B are becoming less common [121].

In contrast to China, South Korea, and Taiwan, and others, in Bangladesh, susceptibility of *S. pneumoniae* to penicillin is high (>84%), as well as to chloramphenicol (>85%), and ciprofloxacin (>96%, except for the 76% rate reported by Brooks et al. [120]) [120-122]. No significant change in penicillin and chloramphenicol susceptibility was observed over the past decade [164,166,167] In contrast, susceptibility to cotrimoxazole is low (<28%) which was demonstrated by a previous study [164]. This was reasoned to be due to widespread use of cotrimoxazole by community healthcare workers [121]. Nevertheless, use of cotrimoxazole as the main therapeutic agent is still in practice even though amoxicillin has been proposed to be the better drug with superior efficacy [166,168]. This is partly due to the arguable *in vitro* susceptibility profile and the treatment outcomes [169].

Sri Lanka

Sri Lanka is one of the members of the South Asian Pneumococcal Surveillance (SAPNA) network and the pneumococcal surveillance project in Sri Lanka is managed by the Epidemiology Unit of Ministry of Health Care and Nutrition of Sri Lanka [123]. Encouraging efforts to control significant morbidity and mortality was undertaken by the Sri Lankan policymakers. Although PCV7 is available, low vaccine coverage rate among the population is expected considering the high cost of the dose. Focus is now on pneumococcal vaccination but we need to note that the NIP (termed Expanded Programme of Immunization, EPI) in Sri Lanka is self-funded, thus ample data on pneumococcal disease burden and vaccine coverage must first be collected so as to provide adequate assistance towards policy and decision-making processes. Hence, joining the SAPNA in 2004 greatly reflected the desire of the Sri Lankan government to take a step further to improve the healthcare of the population.

The serotype prevalence was estimated based on the latest report (with additional isolates) by the Epidemiological Bulletin of Sri Lanka in 2008 [123] as data published by Batuwanthudawe et al. [170] constituted part of the work. Important findings underlined in both reports are discussed. Four of the most prevalent serotypes are all included under the PCV7, giving the predicted efficacy among the children <5 years old (subject population of the study) to be 63.9%. The distributions order are: serotype 19F (22.2%), 23F (16.7%), 6B (13.9%), and 14 (11.1%). Thus, the PCV7 and newer PCVs would be highly effective for Sri Lanka. Together with serotype 15B (8.3%), 3 and 38 (5.6% each), these seven serotypes accounted for the great majority (83.3%) of the isolates detected. However, the sample size

(n=36) is still small and continue surveillance is needed. Similar to Bangladesh, the pneumococcal isolates exhibited high tolerance to cotrimoxazole (69.7%) and high susceptibility to chloramphenicol (72.7%), but differ significantly with regard to the rates of penicillin (90.9%) and erythromycin (66.7%) nonsusceptibility. The overly high resistance to penicillin is of concern and the situation is closely similar to countries from the East Asia. Serotypes 19F and 23F were closely associated with penicillin-resistance which has contributed to the high PNSP rate observed [170]. However, the antimicrobial susceptibility of the isolates has not been analyzed for correlation with regard to the serotypes.

Nepal

Nepal is one of several countries in the world with a high poverty rate. It was estimated that one over three of the population are living below the poverty line [171]. Nepal is among 72 countries qualified for financial support from the Global Alliance for Vaccines and Immunization (GAVI) alliance. The data was analyzed based on surveillance studies by four research groups, two based in Kanti hospital [126,127] and two based in Patan hospital [124,125]. Both hospitals are situated within Kathmandu of Nepal and are the only two hospitals providing pediatric health care services. The most common serotypes are serotypes 1 (27.8%), 5 (11.9%), 12F/A (7.9%), 2 (5.6%), 7F, 4, 19B/C and 16/36/47 (3.2% each). None of the PCV7-VT appears as single dominant group, which gives a low (14.3%) predicted efficacy for PCV7 and also the lowest among all other Asian countries. This coverage is much lower than Bangladesh. Since both countries resided within the same region, it could possibly be due to geographical or demographical relationships between them leading to such observation. Despite this, a drastic increase in 42.8% coverage of PCV10 which is higher than Bangladesh is estimated with the inclusion of serotype 1, 5, and 7F. PCV13 has only minimal (1.6%) additional coverage due to serotype 19A alone. In this case, at least PCV10 or PCV13 should be the vaccine to be considered by the Nepal local policymaker since PCV7 is not expected to give sufficient protection to the population. Of note, pre-hospital antibiotic use could affect the isolation of pneumococci from the specimens which resulted in underestimation of actual pneumococcal incidences in Nepal [124-127]. In addition, the authors have noted the high incidences of pneumococcal diseases among young children in Nepal [172].

All except one [125] study documented the antimicrobial susceptibility of *S. pneumoniae* in Nepal. The only antibiotic that showed considerable resistance is cotrimoxazole, which exhibit >48% reduced susceptibility. This overwhelming resistance was also reported in Bangladesh and Sri Lanka, largely due to the low cost, easy availability, and frequent prescription of cotrimoxazole by the attending doctor in this region [124,126,127]. Hence cotrimoxazole exhibited significantly higher resistance as compared to other class of antibiotics. Other antibiotics including penicillin, chloramphenicol, erythromycin, and cefotaxime remained highly effective against the strains tested, with susceptibility of more than 95%, 89%, 92%, and 96% respectively [124,126,127] due to infrequent use of these drugs in Nepal [126]. Low incidence of penicillin-resistance has also been reported in central Europe [173,174].

Pakistan

Due to the extremely low pneumococcal sample (3/15 available for serotyping) in the only Pakistani study by Zaidi et al. [128], the data could not accurately represent the IPD serotypes circulating in the population and thus was not included in our analysis to avoid extreme bias. Nevertheless, several important findings outlined were noted. The detection of two serotype 19F and one serotype 1 out of the three isolates might indicates that these serotypes are more frequently detected among the population. Pneumonia is responsible for the more serious public health problem as compared to meningitis in Pakistan. More than 1 million cases and approximate 135 600 deaths in Pakistan were attributed to pneumonia annually. These two serotypes are included under the PCV7 (19F) and PCV10 (19F and 1) formulations. Similar to Nepal, Pakistan is one of the countries eligible for GAVI financial support. Although the current data is insufficient to evaluate the PCV efficacy, the author estimated that assuming PCV7 is incorporated under NIP with 50% protection efficacy against VT detected from the meningitis cases, the use of PCV7 will not only save the young children life but at the same time provide financial burden reliefs to the individual and the government as a whole.

West Asia

Oman

The coverage of PCV7 among the Arabian Peninsula and Egypt was estimated to be 49% - 83% [175]. Data based on the only available study by Al-Yaqoubi et al. [129] showed that about 46% of the diseases isolates in Oman was covered by PCV7. The impact of PCV13 is of little additional effect (3.1%) as compared to PCV7. However, high coverage (62.6%) of PNSP by PCV7 represents an additional benefit for reducing the incidence of penicillin-resistance in Oman. A total of 60.0% of the pneumococci obtained from various specimens of patients of all ages were serotype 6B (11.8%), 19F (11.8%), 23F (11.8), 14 (7.1%), 9A/L (7.1%), 1 (5.9%), and 11A/D (4.7%).

Turkey

S. pneumoniae was recognized as the predominant bacterial pathogen implicated in community-acquired sepsis in central region of Turkey where the mortality rate in adults could reach up to 50% [176]. About one third of bacterial meningitis in Turkish children was attributed to pneumococci [177]. High percentage of Turkish invasive strains were obtained from CSF specimen and these meningitis isolates were significantly associated with penicillin resistance in children but not adults ($p < 0.05$) [130]. No other relationship between serotypes and invasive sites was found. However such studies were few and need further substantiation.

The PCV7 was introduced into the Turkish NIP in November 2008. Of the three studies included [130-132], one involved data reported during and after the routine immunization [132]. The estimation based on specific serotypes showed that PCV7, PCV10, and PCV13 coverage are relatively low among Turkish with 24.4%, 46.7%, and 56.2% respectively. However, if we included the percentages of the serogroups 19, 18, 23, 6, and 7 reported by Percin et al. [130] and one serogroup 6 isolate by Ceyhan et al. [132] into the estimations, the coverage will be enhanced by more than 20% to 45.5%, 70.6%, and 80.0% respectively. The superior coverage by PCV10 and PCV13 over PCV7 are clearly evident despite the slightly overrepresented values due to the non differentiated serogroups. The comparatively high coverage by PCV10 and PCV13 are mainly attributed to the high prevalence of serotype 1 (18.9%), which is also the predominated serotype in Turkey. Other common serotypes detected are serotypes/groups 19 (11.1%), serotype 19F (7.8%), 3 (6.2%), 14 (5.3%), 4 (4.5%), and 18 (4.1%). Compared to a previous study by Firat et al. [178] which detected a large proportion of serotypes/groups 23, 19, and 14, serogroup 14 had become less common while serogroup 23 was not even a common serogroup.

However, the study focused only on pneumococcal meningitis isolates hence the differences might also be due to the type of isolates sourced from patients. The NVT serogroups 15 and 20 are responsible for 10% of invasive diseases among children <3 years old [130].

Ceyhan et al. [131] estimated that PCVs are predicted to be highly effective among children <2 years old, covering all cases (100%) with the use PCV13 but the effect was lower among the older aged children. Serotypes/groups 6, 14, 19, and 23 were also found to be associated with PNSP strains [176,178-180]. Of these serogroup 19 was frequently detected from children ≤2 years old but the proportion gradually reduced with increasing ages up to ≤18 years old with the majority (66.2%) of PNSP being detected in younger children [132]. It was surprising that the rate of penicillin resistance remained fairly low (6% – 13%) despite the easy availability even without prescription in Turkey [130,181]. The rising incidence of PNSP in Turkey had been reported previously [182]. In a separate study by Telli et al. [181], serogroup 19 was the largest group detected among macrolide-resistant *S. pneumoniae*. In addition, a significant proportion (35.3%) of the MDR strains showing resistance to penicillin and/or cotrimoxazole belonged to serogroup 19 [130]. Based on the experience in US and Europe, decrease of PNSP as well as other antibiotic-resistant strains in Turkey is expected with the routine immunization [49,183]. Whilst resistance to cefotaxime, chloramphenicol, vancomycin, tetracycline, and fluoroquinolones (levofloxacin) were low (<5%), macrolide (azithromycin, erythromycin) and cotrimoxazole resistances are high (>35%) [130,181]. A number of studies had similarly found ermB to be the dominant macrolide-resistant genotype [181,184,185] but no clonal dissemination of the macrolide-resistance strains were detected [181].

Palestine

Serotypes 6A/B (14.2%, not differentiated), 14 (13.3%), 1 (11.7%), 9V (9.2%), 5 (7.5%), 19F (6.7%), and 4 (5.0%) are among the common serotypes, accounting for 67.5% of all isolates reported in Palestine. Fortunately, five of these dominant serotypes are covered by PCV7 (assuming 6A/B as VT) and all seven are covered by PCV10. Hence, this reflects the potential high efficacy of PCVs among the Palestinians. PCV7 coverage is estimated to be 55.0% (including serogroup 18) while PCV10 and PCV13 cover 77.5% and 85.0% of the isolates, respectively. The prevalence was predicted based on patients <11 years old suspected with sepsis or endocarditis, but no meningitis or pneumonia cases were included due to the rare occurrence of these infections in Palestine [133]. Overall, all were susceptible to vancomycin and almost all (98.3%) of the isolates were susceptible to penicillin and ofloxacin [133]. In contrast, susceptibility to erythromycin and cotrimoxazole were lower at 68.3% and 38.3% respectively and serotype 14 was indeed responsible for majority (75%) of the less susceptible isolates from these two classes of antibiotics. This is further supported by the fact that 53.3% of serotype 14 isolates were resistant to two or more antibiotics [133].

Israel

A study performed by Somech et al. [134] investigated into the serotypes causing pediatric AOM in Southern Israel. Although the isolates under studied were from noninvasive middle ear fluid and does not represent the more invasive serotypes, the data was used to reflect partly the current overall serotype distribution in Israel. Based on the data, the most common serotypes, serotype 19F (15.2%), 14 (14.4%), 23F (10.1%), 19A (10.0%), 6B (7.4%), 6A (5.9%), and 3 (3.8) accounted for two thirds of the isolates. Apart from the PCV7-VT, the PCV13 specific serotypes were also listed among the major serotypes. PCV7 has been incorporated under NIP since July 2009. The predicted PCV7 and PCV10 effectiveness among the Israelis are 53.6% and 59.3% respectively and the proportion is further enhanced by approximately 20% with PCV13, mainly due to the inclusion of three prevailing PCV13-VT. Children under 2 years of age accounted for the great majority (90%) of AOM patients among all children aged 5 and less [134]. The author noted the ethnic-dependent differences in serotype distribution, where serotype 14 was common among the Jewish children but serotype 19F was the dominant one among Bedouin children [134]. Thus, the predicted PCVs coverage also differed between them with Bedouin children having 10% lower protection than the Jewish children. On the other hand, reduction in cotrimoxazole nonsusceptibility over years was accompanied with the concurrent increase in macrolide-resistance as well as the proportions of MDR strains [134]. This is speculated to be due, in part, to the decreased usage of cotromoxazole in southern Israel. Similar findings have been reported by previous studies [186-188], however, no significant changes over the years have been observed with penicillin nonsusceptibility. Despite this, the considerably high proportion of macrolide-resistance and MDR strains covered by PCV13 represent a strong supporting factor for the potential shift to PVC13 in the future.

Discussion

All the data reviewed here showed the latest five year trend of the prevailing serotypes causing various invasive and noninvasive pneumococcal diseases in Asia. Unlike the US and many European countries, most of the countries in Asia being reviewed here, have PCV7 introduced but not yet into the NIP. Hence the data are likely to reflect the baseline serotype distribution with minimal changes due to the vaccine's selective pressure on serotypes.

Although PCV7 is introduced in Asia, only a small number of countries have officially incorporated the vaccine into the NIP (based on data available only for 17 countries). The overall PCV7, PCV10, and PCV13 coverage predicted are 52.4%, 58.1%, and 75.0%, respectively. If we include the nondifferentiated serogroups, the coverage increases slightly to 54.8%, 60.6%, and 77.5% respectively. The addition of serotypes 3, 19A, and 6A into the PCV13 formulation are expected to confer higher protection with the number of serotypes included, but this specific formulation is proven to be of exceptional performance at which as much as 17% increase in coverage as compared to PCV10 has been observed. On the other hand, PCV10 has comparatively little advantages effect over PCV7 with only a 5.7% increase in coverage. In Asia, about half (54.2%) of the disease burden is said to be due to serotypes 19F, 14, 23F, 6B, and 19A. This is followed by serotypes 3 and 6A which further covers 9.2% of the incidences. Fortunately, all these prevailing serotypes are formulated in the currently available PCVs, mainly in the PCV7 and PCV13. Although large numbers of diverse serotypes/groups were detected, only three serotypes predominate in Asia. Serotype 19F represents the dominant serotype in majority (7 out of 16) of countries/territories which included China, Taiwan, South Korea, Malaysia, Sri Lanka, Pakistan, and Israel. On the other hand, serotype 1 is the most prevalent in three countries, Laos, Nepal, and Turkey. This serotype is commonly found in developing countries [10,92] and together with serotype 5, they are widely recognized as "developing country serotypes". The special features with serotype 1 are that it is invasive and is frequently associated with outbreaks [161-163]. However, there is no evidence of outbreak reported in any of the studies reviewed here and this therefore needs further substantiation with its relatedness to outbreaks. It is possible that serotype 1 has

become a persistent serotype in the populations like other serotypes but this requires further supporting studies. Apart from this, serotype 6B is more prevalent in Japan and Thailand (serotype 6A/B in Palestine) while serotype 14 is more prevalent in Singapore and Hong Kong. Notably, Bangladesh is the only country with high prevalence of serotype 2.

Since the serotype distributions displayed remarkable difference by geographical location [96,97], it is important to examine this from the perspective of regions where the particular country is located in. In the East Asia and SEA regions, it is interestingly to note that both have almost same serotypes prevalence order for serotype 19F, 14, and 6B, 23F, and 19A, differing only with the ranking order of serotype 14. Moreover, a similar pattern is observed in West Asia ranking of serotypes 23F, 19A, and 6B. In contrast, the serotype distribution is quite different in the South Asia region. As observed apart from serotype 1, other prevalent serotypes such as 2, 5, and 12F/A are rare in SEA, East Asia (only serotype 12F/A at 4.4% in Japan), and West Asia (only serotype 5 at 7.5% in Palestine). For serotype 1 which is the most prevalent serotype in South Asia, it is less frequently detected elsewhere in West Asia and SEA but not in East Asia. However some exceptions have been observed as that in the single study reported by Moore et al. [119], where the serotype distribution in Laos appeared to resemble that of South Asia. A similar situation is also observed with the pattern of serotype distribution in Sri Lanka which differed greatly among other South Asian countries, and the four most prevalent serotypes (19F, 23F, 6B, 14) closely resembling those from all other three regions. The overall effectiveness of the three PCVs by regions in highest to lowest order are East Asia > West Asia > SEA > South Asia.

We also noted the presence of some NVT belonged to the common serotypes in the respective regions. Serotype 15 has been reported in China and Taiwan. Despite being defined as VRT, serotype 23A is rather common in Taiwan as well. Together, Taiwan has a greater number of NVT than any other countries from the same region. In addition, serotype 12F/A has been reported in Japan as well. Towards the south, countries in SEA have similar serotype distribution. Singapore is the only country in SEA commonly reporting NVT, specifically serotype 8. Also in West Asia, serotype 9A/L and 11A/D (as 9A and 11A in study conducted by Mubarak et al.) is only identified in Oman as one of the common serotypes, but none elsewhere in Asia. On the other hand, serotype 5 is unique to Palestine. In South Asia, a number of NVT are found to be common with serotype 2 being reported in Nepal and Bangladesh. Most strikingly, this serotype represent the dominant serotype in Bangladesh as well as serotypes 12F/A and 45. Altogether, these three NVT occupy a quarter of all incidences in Bangladesh. Because of this, the estimated PCVs coverage among the Bangladeshi population became substantially low. Poor PCV7 coverage has been reported in Malawi [189]. In Asia the lowest coverage of PCV7 is seen in Nepal. One of the reasons is because Nepal is predominated by NVT, namely 12F/A, 2, 19B/C, and 16/36/47 which is responsible for about 20% of pneumococcal infections in the Nepalese population. Another reason is due to the low number of serotypes covered under PCV7 as observed in the individual studies included for analysis. The proportions of these PCV7-VT are low as well (<4%). The better PCV choice would be PCV10 and PCV13 which is estimated to increase the coverage four-fold.

The GAVI of the Pneumococcal Accelerated Development and Implementation (PneumoADIP) plays a major role to support the financial demand especially for the developing countries towards making the pneumococcal vaccines available to the eligible countries [190]. Asian countries which are GAVI-eligible include Indonesia, Vietnam, Mongolia, North Korea, Nepal, India, Pakistan, and Sri Lanka. Apart from this, useful and effective collaborative networks are especially important to gather essential information of circulating pneumococcal serotypes in the member countries. Several of these networks have been set up, such as SAPNA, a network in India, Nepal, and Sri Lanka for the purpose of conducting standardized IPD surveillance and to investigate the serotype epidemiology and antimicrobial susceptibly profiles of strains circulating in the region and this network is funded by the GAVI; Asian Network for Surveillance of Resistant Pathogens (ANSORP), one of the largest multicountry collaborative network in the world for region-wide surveillance of antimicrobial resistance in Asia [191,192].

The main limitation of this review is the lack of relevant data from quite a number of Asian countries especially in Central Asia, West Asia, and SEA. Overall, only 17 out of the 51 countries in Asia were presented in this review. Although some studies have been reported in these countries (e.g. Indonesia, Vietnam, Philippines, Iran, Yemen, etc) but were then excluded from this review due to incompatibility with our review parameters. Of these, majority are due to isolates used sampled from a prior time frame set (January 2006), carriage isolates, and data corresponding to subset of antibiotic-resistant strains. This will probably underestimate the actual prevalence and serotype distribution in Asia. However, this is to ensure the data reported here reflect the current situation in circulating pneumococcal serotypes involved in pneumococcal diseases. Beside this, the small sample size in a number of studies might result in relatively weak convincing power of the findings stated. In this aspect, several countries have satisfactory sample size, this includes Thailand, Singapore, Malaysia, Bangladesh, Nepal, Turkey, and Taiwan with approximate 200 and more isolates while China, Hong Kong, Korea, Japan, Israel have >800 isolates. Overall, the total isolates included in this review is 12435 (additional three isolates from Pakistan were not included in the analysis) and about half (5236 isolates) were from Israel.

Many of the studies were single-center based or studies examining a certain area of the country/territory. Also, studies which investigated into selected patients group (e.g. meningitis patients or pediatric patients only) may as well misrepresent the serotypes distributions in general. Another problem as similarly pointed out by various authors of the studies included is the low detection of pneumococcal isolates from specimens obtained from the patients, particular those with prior antibiotic used before they have their specimen obtained. This will definitely underestimate the actual number of serotypes and their prevalence. Hence, there is a need for the respective laboratories to better adapt to newer molecular technique such as multiplex PCR [193] which do not always rely on cultured isolates, in contrast to the culture-based Quellung reaction which is currently the gold standard.

Conclusions

In conclusion, the coverage of PCV shows considerable but otherwise related geographical and temporal variations. Surveillance study is still absent in many Asian countries. For countries with previous reported studies but of which recent data is not available, continued surveillance is important to track the possible fluctuations in local serotype epidemiology. In addition, the data is valuable to assist policymakers when considering the potential effectiveness pneumococcal vaccination might have on the population. To evaluate accurately the trend in serotype distribution of a country, establishment of nation-wide surveillance as well as inter-nations collaborative

network are essentially needed. If the vaccine manufacturers are taking their next step to formulate newer vaccine, specifically to the Asian population, serotypes/groups 15, 12F/A, 8, 23A, 11A/D, 2, 10A could be the next potential candidates on the list.

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