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Review

Regional epidemiology of invasive pneumococcal disease in Asian adults: epidemiology, disease burden, serotype distribution, and antimicrobial resistance patterns and prevention

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SUMMARY

Objectives: To summarize published data on the clinical and economic burden, epidemiology, antimicrobial resistance levels, serotype prevalence, and prevention strategies for pneumococcal disease among adults in Asia.
Methods: We performed a systematic search of the PubMed database for relevant, peer-reviewed articles published between January 1995 and December 2011, covering China, Hong Kong, India, Indonesia, Japan, Malaysia, Pakistan, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam.
Results: Taiwan and Thailand had the most comprehensive epidemiological data on adult pneumococcal disease. Very little relevant data were found for Indonesia, Pakistan, the Philippines, and Vietnam; surveillance is urgently needed in these countries. The emergence and spread of resistance emphasize the importance of vaccination to prevent infection in adults at increased risk for serious pneumococcal disease. Vaccination policies and opinions on the efficacy of vaccination vary widely in Asian countries, although a new option in the form of a pneumococcal conjugate vaccine is now available.
Conclusions: Increased awareness of the public health and economic benefits of pneumococcal vaccination is critically needed to help both the public and policymakers in making changes to vaccination policies in the region. Maximizing access to pneumococcal vaccines will decrease the number of hospitalizations, complications, and deaths associated with pneumococcal disease.
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1. Introduction

Streptococcus pneumoniae (pneumococcus) is the most common cause of community-acquired pneumonia, meningitis, and bacteremia in children and adults, including the elderly, and is responsible for high rates of morbidity and mortality worldwide. The vast majority of disease-burden data and epidemiological studies on pneumococcal disease have been reported in child populations; however, limited data are available regarding the burden and epidemiology of pneumococcal disease in adults, particularly in Asia. Importantly, the population of Asia is the fastest growing population in the world, and identifying key strategies for combating pneumococcal disease has the greatest potential public health impact worldwide.

The incidence of invasive pneumococcal disease (IPD) is expected to rise secondary to the increase in the elderly populations. Groups most at risk of pneumococcal infection include those of extreme age, immunocompetent persons with underlying medical conditions (chronic cardiovascular, pulmonary, liver and neurological diseases, and diabetes mellitus), and individuals with defects of immune defenses or decreased immune responses (functional or anatomic asplenia, immunosuppressive conditions, post organ or bone marrow transplantation, or on therapy with alkylating agents, anti-metabolites, or systemic corticosteroids).[1] Other risk factors include male sex, alcohol abuse, cigarette smoking, asthma, cerebral spinal fluid leakage, cochlear implant, recent influenza infection, institutionalization, and certain ethnic groups.[1]

Adult mortality rates for bacteremic pneumococcal pneumonia range from 10% to 30%, and for meningitis from 16% to 37%.[1] Mortality rates are substantially higher in the elderly and in patients with comorbidities.[1] Factors that are associated with worsened outcomes in some studies include >65 years of age,

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multilobar involvement, shock, need for mechanical ventilation or intensive care, alcohol abuse, chronic cardiac or pulmonary disease, renal failure, immunosuppressive therapy, and serious underlying disease.[1] Importantly, mortality rates are much higher in young children in developing countries (10–40%), likely due to poorer access to health care and comorbidities, particularly HIV infection and malnutrition. A recent study of >18 000 IPD cases in Denmark confirmed that age and comorbidities influence survival.[2] In this cohort, mortality rates were <3% for children younger than 5 years of age, 14% for individuals aged 5–65 years, and 24% for adults ≥65 years of age. These findings underscore the public health impact of pneumococcal disease in adult populations.

Pneumococcal vaccines can prevent the development of antibiotic-resistant infections by reducing the carriage of antibiotic-resistant serotypes, limit the spread of pneumococcal disease, and may decrease the incidence of drug resistance through reducing the use of antibiotics.[3] Licensed pneumococcal vaccines are currently available for use in adults and children. The 23-valent pneumococcal polysaccharide vaccine (PPV23), a non-conjugated polysaccharide vaccine, was first licensed in 1983 and is used almost exclusively in adults.[4,5] Three pneumococcal conjugate vaccines (PCV) are licensed for use in children. The heptavalent PCV (PCV7) was first licensed in the USA in 2000 and is now available in more than 100 countries worldwide.[5] PCV7 contains poly- or oligosaccharides from seven *S. pneumoniae* serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), each conjugated to genetically detoxified diphtheria toxin CRM197. A 10-valent PCV (PCV10) using recombinant non-typeable *Haemophilus influenzae* protein D as the conjugate, was first licensed in Canada, Europe, and Australia in 2009; this vaccine includes serotypes 1, 5, and 7F in addition to those included in PCV7. In 2009, the 13-valent PCV (PCV13) was first licensed; it includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

PCVs are approved for use in children all over the world, are immunogenic in adults, and very recently a PCV13 was approved for use in many countries including the USA and the countries of the European Union.[6–8] The impact of dual vaccination against *S. pneumoniae* and influenza is also being studied.[9,10] To aid policymakers and health authorities in understanding the clinical need for adult PCV vaccination and its potential impact, the clinical and economic burden, epidemiology, antimicrobial resistance levels, and serotype prevalence of pneumococcal disease among adults must be known for each individual country or region.

The aim of this review is to provide a summary of all available English-language data published from January 1995 to December 2011 on pneumococcal disease in adults, including the clinical and economic burden of disease, available epidemiological data, current data regarding antimicrobial resistance levels, data regarding serotype prevalence of pneumococcal isolates, and current vaccination policies. This review will discuss these parameters of pneumococcal disease in 13 Asian countries, including China, Hong Kong, India, Indonesia, Japan, Malaysia, Pakistan, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam. Further, this review will provide suggestions for improving country surveillance in adults and discuss the impact of antibiotic and vaccine administration in these countries.

2. Methods

2.1. Search strategy

This is a systematic literature review of published data on the burden, epidemiology, antimicrobial resistance levels, and serotype prevalence of pneumococcal disease among adults in Asia. The data included in this review were published between January 1995 and December 2011, and relate to the following 13 countries: China, Hong Kong, India, Indonesia, Japan, Malaysia, Pakistan, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam.

EndNote version XI (Thomson Reuters) was used to search the PubMed database for relevant, peer-reviewed articles published between January 1995 and October 2010. We used three search strings of differing stringency, repeated for each country, combining the search terms: country name, pneumonia, Streptococcus, pneumococcal, incidence, and adults, as well as terms aimed to exclude studies limited to children, animal studies, vaccine development, and studies primarily related to other organisms causing pneumonia (Klebsiella and Pneumocystis). A manual search of PubMed with the same search strings was used to identify references published between November 2010 and December 2011, inclusive. We also searched for relevant reports on the World Health Organization website and on government/ministry of health websites of individual countries for any reported available in English. Figure 1 shows a flow diagram of the study selection process.

2.2. Exclusion criteria

The titles and abstracts of all articles identified on PubMed by these searches were scanned for relevance and duplicates were removed. The full texts of potentially relevant papers were obtained, critically appraised once more, and the remaining unsuitable articles were then eliminated. The following types of article were excluded: case studies; studies in Asian populations residing outside Asia; pneumococcal vaccine efficacy, immunogenicity, and safety studies; antibiotic efficacy studies; molecular characterization of bacterial strains; studies involving only children or infants; studies involving only nosocomial or hospital-acquired infections; studies on diagnostic, sampling, or

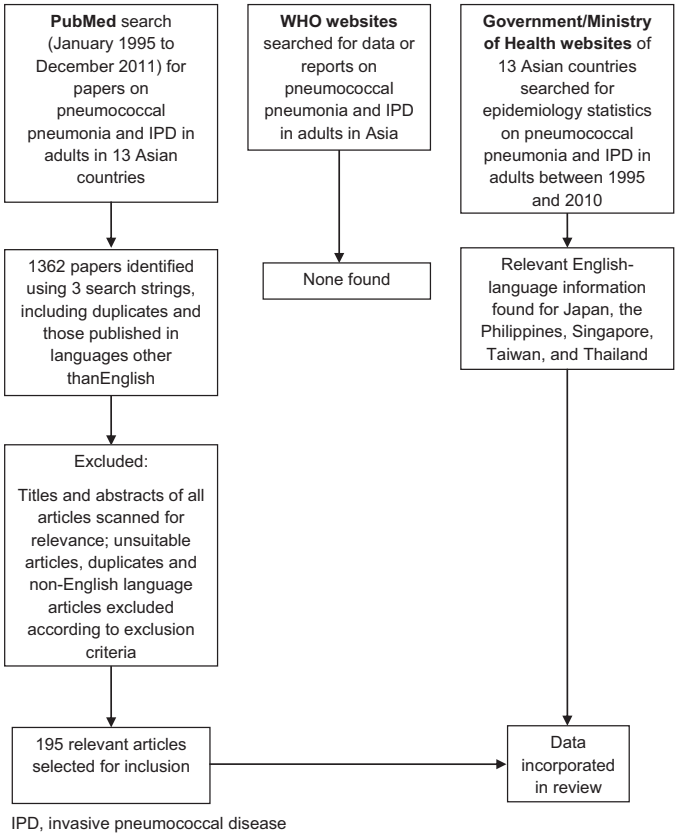

Figure 1. Process of study selection for the systematic review.

serotyping methods; animal studies; review articles; studies that that did not mention *S. pneumoniae*, but described only other organisms that cause pneumonia (e.g., *Klebsiella pneumoniae*, *Mycoplasma pneumoniae, Pneumocystis jiroveci*, *Pseudomonas aeruginosa*, and *Pneumocystis carinii*); and non-English language articles.

3. Results and discussion

3.1. Incidence and mortality of pneumococcal disease

Studies identified reporting the incidence and mortality of pneumococcal disease varied greatly in quality and design, with differing population demographics. Many study populations were small (<50–200), in particular for mortality data, were drawn from a small number (one or two) of urban centers, were published more than a decade ago, or were published before PCVs became widely used. The data reviewed here may therefore not be representative of the current situation in the countries described.

Incidence data for pneumococcal disease were variable in the type of statistics published, and are available for only five of the 13 countries surveyed (Hong Kong, Malaysia, Singapore, Taiwan, and Thailand); a summary of the largest and most recent studies identified from PubMed is presented in Table 1. There were no English-language articles published on incidence data for pneumococcal disease in adults in China, India, Indonesia, Japan, Pakistan, the Philippines, South Korea, and Vietnam.

The most comprehensive incidence data came from Singapore, Taiwan, and two provinces of Thailand. Many of the studies involved hospital-based surveillance and were therefore likely to underestimate true incidence figures, as they did not capture patients not admitted to hospital. In Singapore, a study of 4275 cases of pneumococcal disease (97.9% were pneumococcal pneumonia) from all Singapore hospitals over 10 years found an overall incidence of 10.9 per 100 000 population, with 56.4 per 100 000 in those aged >65 years.[14] In Taiwan, an 8-year analysis of 4275 nationwide hospital admissions for community-acquired pneumonia (CAP) found an annual incidence of 36.5 admissions per 10 000 in 2004.[15] According to the Taiwan Department of Health, the incidence of IPD was 216 per 100 000 in the overall population, and was 1147 per 100 000 in adults aged >65 years.[11] In Malaysia, the estimated incidence of all-cause pneumonia was 20.406 hospitalizations per 1000 population in adults aged >65 years.[13]

The rural provinces of Nakhon Phanom and Sa Kaeo account for approximately 2% of the total population of Thailand.[17] In these provinces, one study reported the incidence of all-cause radiographically confirmed pneumonia as 34.7 per 100 000 aged ≥50 years.[17] In a second study confined to the Nakhon Phanom province from a similar period, however, the annual incidence of radiographically confirmed pneumonia in the overall population ranged from 199 to 256 per 100 000 and from 717 to 877 per 100 000 in adults aged >65 years.[18] A population-based survey reported the incidence of IPD as 26 per 100 000 aged ≥75 years,[11] while the incidence of hospitalized pneumococcal bacteremia was 3.7 and 7.6 per 100 000 in Sa Kaeo and Nakhon Phanom, respectively.[19]

Mortality data were available for the above five countries, and also for India, Japan, and South Korea, but data published in English were lacking for China, Indonesia, Pakistan, the Philippines, and Vietnam. The Asian Network for Surveillance of Resistant Pathogens (ANSORP) has published several studies. In their most recently published study of CAP in 955 adults from eight countries, the overall mortality was 7.3%.[20] In another study of 255 Asian adults with antibiotic-resistant pneumococcal pneumonia,

Table 1
Summary of the incidence of pneumonia and invasive pneumococcal disease in adults, by country[a] and by study

Country	Study period	Study population	Incidence
Hong Kong	2000–2004[11]	Adults aged >65 years with laboratory data collated by the Hospital Authority in Hong Kong	IPD annual incidence: 7.7/100 000
Malaysia	1994–1995[12]	Patients with clinical infections (mainly CAP) from six hospitals in five geographic regions; 59% aged >10 years	Overall incidence of invasive and non-invasive *Streptococcus pneumoniae* infections: 75.4/100 000
	2006–2007[13]	Patients with pneumococcal disease from six hospitals	In adults aged ≥20 years, annual incidence per 1 000 population: pneumococcal pneumonia: 7.784; pneumococcal bacteremia: 3.278; pneumococcal meningitis: 0.108 Hospitalization rate in adults aged >65 years: 20.406 per 1000 population
Singapore	1995–2004[14]	4275 hospitalization records of patients aged <1 to ≥75 years (64% >15 years) from all Singapore hospitals	Mean annual hospitalization rate with pneumococcal infection: (i) overall: 10.9/100 000; (ii) in adults aged ≥65 years: 56.4/100 000
Taiwan	1998–2005[15]	All adults aged ≥18 years hospitalized with pneumonia (N=477 541); data from the National Health Insurance Research Database	Mean monthly admission rate for CAP during whole study period: 3.27/10 000 Annual incidence of admissions with CAP: 36.5/10 000 in 2004
	2006[11]	Data from the Bureau of National Health Insurance	IPD incidence: (i) overall: 216/100 000; (ii) in adults aged >65 years: 1147/100 000
	2000–2008[16]	328 patients hospitalized in the National Taiwan University Hospital	IPD incidence among those hospitalized: (i) from 2000 to 2005: 6.2/10 000; (ii) from 2006 to 2008: 3.8/10 000
Thailand	2003–2005[17]	3910 patients (all ages) enrolled from the Nakhon Phanom and Sa Kaeo provinces	Adjusted (for enrolment) annual incidence of radiographically confirmed pneumonia: (i) 5–49 years: 3.1/100 000; (ii) ≥50 years: 34.7/100 000
	2004–2006[18]	4993 patients aged <5 to >65 years with pneumonia requiring hospitalization from the Nakhon Phanom province	Annual incidence of radiographically confirmed pneumonia: (i) overall: 199–256/100 000; (ii) in adults aged >65 years: 717–877/100 000
	Cited as unpublished data from 2007[11]	Population-based survey in the provinces of Nakhon Phanom and Sa Kaeo by the Ministry of Public Health and International Emerging Infections Program	IPD incidence in adults aged ≥75 years: 26/100 000
	2005–2007[19]	23 853 hospitalized patients from the Nakhon Phanom and Sa Kaeo provinces with indications for blood culture (31% aged <5 years)	Annual incidence of hospitalized pneumococcal bacteremia: (i) Nakhon Phanom: 7.6/100 000; (ii) Sa Kaeo: 3.7/100 000

CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease.
[a] There were no incidence data published in English for China, India, Indonesia, Japan, Pakistan, the Philippines, South Korea, and Vietnam.

Table 2
Summary of the mortality from pneumonia and invasive pneumococcal disease in adults, by country[a] and by study

Country	Study period	Study population	Mortality
Hong Kong	1995–2001[22]	$N=214$; mean age 40 ± 33.7 years; pneumococcal bacteremia	27.3% overall; 50.6% for adults aged >65 years
India	1999–2001[23]	$N=2222$; randomly selected death records	All-cause pneumonia overall mortality: 3.7%
	2000–2001[24]	$N=70$; 17–93 years; CAP	11%
	1998–2000[25]	$N=100$; 15–80 years; CAP	14%
	1993–2003[26]	$N=564$; median age 45 years; IPD	30%
Japan	1947–2009[27]	General population in Japan	Deaths from all-cause pneumonia in 2010: 94.1/100 000
	2003–2005[28]	$N=156$; adult; CAP	5.1%
	2001–2003[29]	$N=156$; adult; CAP	1.9%
	2000–2002[30]	$N=124$; adult; CAP	5.6%
	1998–2000[31]	$N=231$; ≥15 years; CAP	8.7%
	1994–1997[32]	$N=318$; >15 years; CAP	6.1%
	2006–2007[33]	$N=496$; 61% adults; IPD	Mortality in adults: 22.1%
	1997–2001[34]	$N=306$; median age 65.5 years; pneumococcal pneumonia	1.3%
Malaysia	1997–1999[35]	$N=127$; >12 years (mean 55.5 years); CAP	Overall mortality: 10.2%; 2/13 (15.4%) patients who died had pneumococcal bacteremia
	1999–2009[13]		Overall mortality: 10.4%
Singapore	1995–2004[14]	$N=4275$; <1 to ≥75 years (64% >15 years); pneumococcal disease	Overall: 3.2%; in adults aged ≥75 years: 8.4%
	2000–2007[8]	$N=192$; 14–96 years (median 64 years); *Streptococcus pneumoniae* isolates causing invasive disease	Mortality from pneumococcal septicemia: 21.4%
	2000–2001[36]	$N=38$; 14–90 years (median 57 years); *Streptococcus pneumoniae* bacteremia	13.1%
South Korea	2008[37]	$N=345$; HCAP and CAP	HCAP mortality: 19.2%; CAP mortality: 7.4%
	1997–2000[38]	$N=562$; mean age 59.9 years; CAP	7.1%
	2002–2007[39]	$N=168$; IPD	18.6%
	1997–2006[40]	$N=59$; >16 years; pneumococcal bacteremia in patients with liver cirrhosis	30-day mortality: 16.9%
	1996–2001[41]	$N=149$; adults; pneumococcal bacteremia	23.8%
Taiwan	NR[42]	Taiwan population	Mortality rate for pneumonia: 23.6/100 000
	NR[43]	$N=348$ younger adults; $N=438$ elderly patients; $N=201$ very old patients (age ≥85 years)	30-day mortality rate was 5.2% in younger adults, 7.1% in elderly patients, and 9.5% in very old patients
	2004–2008[44]	$N=134$; all ages; non-bacteremic CAP	Overall 6%, but all deaths occurred in patients aged ≥65 years (i.e., mortality rate 27.6% in this age group)
	2000–2008[45]	$N=87$; bacteremic CAP	30-day mortality: 14.9%
	2004–2008[45]	$N=87$ non-bacteremic CAP; $N=134$ bacteremic CAP (same population as above)	The overall mortality rates at 7, 14, and 30 days were significantly higher in bacteremic than non-bacteremic patients (12.6% vs. 2.2%, 14.9% vs. 3.7%, 19.5% vs. 5.1%, all $p<0.01$)
	2001–2002[46]	$N=168$; mean age 56.1 years; CAP	8.3%
	2000–2008[16]	$N=328$; IPD	Overall mortality 2000–2005: 24.4% Overall mortality 2006–2008: 21.8%
	2000–2001[47]	$N=53$; 58.5% adults; IPD	Mortality in adults: 35.5%
	2000–2008[48]	$N=265$; community-acquired IPD	30-day mortality: 40.5%
	1986–2001[49]	$N=269$ with bacterial meningitis of whom $N=22$ (all adult) with *Streptococcus pneumoniae*	Pneumococcal meningitis: 50%
	1986–1989[50]	$N=38$; 17–75 years; streptococcal meningitis	Pneumococcal meningitis: 52.6%
Thailand	1985–2004[51]	Total elderly Thai population (aged >60 years)	Mortality due to pneumonia in 2003: 107.4/100 000
	2004–2006[18]	$N=4993$; <5 to >65 years; pneumonia requiring hospitalization	Overall mortality: 6.9/100 000; in-patients >65 years: 44/100 000

IPD, invasive pneumococcal disease; CAP, community-acquired pneumonia; HCAP, healthcare-associated CAP; NR, not reported.
[a] There were no mortality data published in English for China, Indonesia, Pakistan, the Philippines, and Vietnam.

mortality was 13.3%, rising to 31.9% of those who had bacteremic pneumonia.[21] The most common comorbidities in both studies were bronchopulmonary disease, cardiovascular disease, malignancy, and diabetes mellitus; adult patients with these illnesses may be at higher risk of contracting pneumonia and IPD.

The principle studies reporting mortality data by country are summarized in Table 2. In general, mortality from CAP was <10%, but appeared slightly higher (11–14%) in India,[24,25] as well as in patients with bacteremic CAP (14.9%)[45] and in elderly patients (27.6%).[44] Mortality from IPD ranged from approximately 18% in a South Korean study[39] to 40% for community-acquired IPD in Taiwan;[48] IPD-related mortality in a relatively large, recent, Japanese study was 22%,[33] and in a similarly large Indian study was 30%.[26] In 2009, pneumonia was the fourth leading cause of death in Ministry of Health hospitals in Malaysia, with 10.4% of hospital mortality.[13] Mortality from pneumococcal meningitis was approximately 50% in two Taiwanese studies.[49,50]

3.2. Clinical characteristics and outcomes of S. pneumoniae as the etiological agent

In the published studies identified, the etiology of the pneumonia was often either not determined at all, or if determined, the proportion of cases for which any etiological agent could be found was low. The study populations were typically small (<50–200). The findings often varied widely within countries, reflecting differences in study population demographics and in the efficiency or methodology of detecting causative pathogens. We found only a single published study that included the etiology of IPD.

The incidence of *S. pneumoniae* detected as the causative agent of CAP, IPD, and bacterial meningitis, as well as that associated with other conditions, is summarized in Table 3. In India, South Korea, Taiwan, Thailand, and Japan, as well as in a pan-Asian study, *S. pneumoniae* was the most common pathogen associated with

Table 3
Summary of the incidence of *Streptococcus pneumoniae* as etiological agent by clinical condition and country

Clinical condition	Country	Incidence of *Streptococcus pneumoniae* as etiological agent (%)
CAP	Pan-Asian[20]	29.2
	China[52–54]	3.0–8.5
	India[24,25,55]	3.4–35.8
	Japan[30–32,56–59]	9.1–65.0
	Malaysia[35,60]	3.1–5.5
	Singapore[61,62]	5.0–12.5
	South Korea[37,38,63]	13.5–60.8
	Taiwan[46]	23.8
	Thailand[19,64–66]	4.4–23.1
IPD	India[67]	5.4
Bacterial meningitis	India[68]	61.8
	Japan[33]	18.8
	Singapore[69]	27.0
	Taiwan[49,50]	8.2–50.0[a]
Chemotherapy-associated pneumonia	South Korea[70]	31.1
Otitis media	Taiwan[15]	44.0
Stroke-associated pneumonia	Pakistan[71]	3.9

CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease.
[a] Patients in this study were diagnosed with streptococcal meningitis.

CAP. In a recent study in Taiwan, bacteremia caused by *S. pneumoniae* increased the risk of mortality and extrapulmonary involvement in patients with pneumococcal CAP.[45] In another study in Taiwan, elderly patients were more likely to have atypical clinical manifestations and worse outcomes. In this study, the 30-day mortality rate was 5.2% in younger adults, 7.1% in elderly patients, and 9.5% in very old patients (≥85 years).[43] In Japan and Singapore, *S. pneumoniae* was the most common causative agent of CAP in some but not all studies, while in China and Malaysia, *S. pneumoniae* was not the most frequently-associated etiological agent. Studies from India, Japan, Singapore, and Taiwan have reported that *S. pneumoniae* accounted for 69%, 19%, 27%, and 8%, respectively, of bacterial meningitis cases.[33,49,50,67–69] In a recent study in Japan, CAP was associated with better outcomes and a lower 30-day mortality rate compared to the nursing home-acquired pneumonia group.[72]

3.3. Serotype prevalence

Pneumococcal serotype prevalence varied widely between and within countries. For countries such as Indonesia and Vietnam, the only published data on serotype prevalence have come from multinational studies conducted a decade ago involving very small numbers of isolates from single centers within each country. These data may therefore not reflect the current serotype prevalence in these countries. No serotype prevalence data could be found for Pakistan. In China, the prevalent serotypes were 19F, 19A, 6B, 23F, 14, and 6A in isolates taken from 2009 to 2010.[73] In a recent report from Thailand, out of 172 isolates taken between 2006 and 2009, the most common serotypes were 6B, 23F, 14, 19F, and 19A in patients <5 years old, and 6B, 19A, 23F, 4, and 9 V in patients >65 years old.[74] Another study from Thailand found that, at the Phramongkutklao Hospital in Bangkok, the most common serotype in patients from 2004 to 2008 was 6B.[75]

In Hong Kong, the most common serotypes identified in the studies reviewed here were 23F, 19F, 14, 6A, and 6B (in approximate order of decreasing prevalence); note that these studies were carried out between 1995 and 2001.[76] Several studies on serotype prevalence in India consistently showed serotype 1 to be the most prevalent amongst adults, with other common serotypes being 5, 6, 7, and 19.[26,77–79] In Japan, serotypes 19F, 23F, 3, 6A, and 6B were consistently predominant in older studies.[80–84] The most recent Japanese study, carried out from 2006 to 2007, showed that 12F, 3, 6B, and 14 were the most prevalent serotypes.[39] The most common serotypes identified in Malaysia were 19F, 19A, 23F, 6A, and 6B in studies between 1999 and 2008.[12,85–88] Serotypes 1, 6B, 19B, and 19F were predominant in an older study dating from 1994 to 1995.[12]

Serotype prevalence among *S. pneumoniae* isolates in Singapore varied in the most recently published studies. A study of invasive isolates collected between 2000 and 2007 showed that serotypes 14, 3, 6B, 8, and 19F were the most common, comprising 51.1% of the total number of isolates.[8] In a 2009 study, serotypes 7F, 3, and 19A were most frequent among adults, accounting for 45.3% of adult IPD cases.[89] Multi-country studies predating 2001 found that 23, 19, 6, and 14 were the most prevalent serogroups in Singapore.[86,87,90,91]

Serotypes 19F and 23F were consistently the most commonly identified in all South Korean studies,[91–94] although a 2009 study shows that their combined prevalence decreased from approximately 50% in 2000 to 15% in 2007.[94] In Taiwan, the most common serotypes consistently identified in adults over the past decade include 23F, 19F, 14, 6B, and 3,[44,86,87,95–100] which together generally account for over 80% of *S. pneumoniae* isolates.

3.4. Antibiotic resistance

In global multi-country studies of antimicrobial susceptibility in *S. pneumoniae*, regional rates of antibiotic resistance were consistently the highest in Asia.[101–103] In the two most recently published studies of antibiotic resistance by ANSORP, which include individual country data from multiple Asian countries, isolates from China, Hong Kong, South Korea, Taiwan, Thailand, and Vietnam generally had the highest antibiotic resistance rates, although it should be noted that these studies were carried out a decade ago.[86,87] More detailed results from these studies are discussed by country below. Recent (within the last decade), reliable antibiotic resistance data were not found for *S. pneumoniae* isolates from adults in Indonesia or Pakistan. It is important to note that the Clinical and Laboratory Standards Institute (CLSI) published a set of new *S. pneumoniae* breakpoints for penicillin in 2008.[104] Therefore, only studies on penicillin resistance published after 2008 were reviewed.

In China, erythromycin resistance rates for *S. pneumoniae* increased from 35–53% in 1996–1999, to over 75% by 2001.[86,87,105,106] Among isolates collected during 1999–2000, levofloxacin resistance was 3.3%, and this increased to 6.8% by 2002.[105,107] In a recent report, approximately 10%, 30%, 70%, 25%, and 40% were resistant to the beta-lactam antibiotics penicillin, amoxicillin, cefuroxime, ceftriaxone, and meropenem, respectively, and 96% were resistant to erythromycin and clindamycin. The majority of isolates were also resistant to tetracycline (84%) and to co-trimoxazole (74%).[73]

Hong Kong has some of the highest antibiotic resistance rates for *S. pneumoniae* in the world. Erythromycin resistance rates increased above 70% in separate surveillance studies conducted between 1998 and 2001.[86,87] Levofloxacin resistance peaked around 1999–2000 at rates of up to 14.3%, then decreased to 5.1% in 2007.[22,102,107,108] With the new penicillin breakpoint, a recent study showed that 66.9% and 97.8% of the isolates from adults were penicillin-sensitive at the meningitis and non-meningitis breakpoints, respectively.[109]

Antibiotic resistance levels reported in the Indian studies were lower than in many other Asian countries. An Indian multicentre surveillance study published in 1999 reported resistance rates of

4.2% to erythromycin, 56% to co-trimoxazole, and 17% to chloramphenicol.[3] In Japan, penicillin-resistant *S. pneumoniae* was isolated in 12.5% of non-hospital-acquired pneumonia cases in a recent retrospective study.[110] Erythromycin resistance rates were reported to be around 80% in the more recently published studies, which are among the highest in the world.[28,111–114]

A recent study in Malaysia showed that serotype 19F had increased antibiotic resistance and was highly invasive.[88] This study also found that out of 151 clinical isolates, 21.2% were penicillin-resistant *S. pneumoniae* strains, 29.1% penicillin-intermediate, and 49.7% penicillin-susceptible,[88] whereas another study published in 2011 estimated the penicillin resistance rate to be higher, at 31.78%.[115] Besides, erythromycin resistance rates also appeared to be increasing from 3% (1996–1997) to 36.8% (1998–2001).[86,87,116] The most recent data on antibiotic resistance in Singapore were published between 1995 and 2001. In multicountry studies that included small numbers of isolates from Singapore, the highest levels of antibiotic resistance were reported against erythromycin (52.9%) and cefuroxime (28.6%).[86,87]

A number of studies showed that resistance rates to erythromycin in South Korea remained high over the period 1996–2001 (75–85%).[86,87] Interestingly, a recent report analysis from South Korea found that antibiotic non-susceptibility did not have an effect on mortality in adult patients with pneumococcal bacteremia.[117] Despite the Taiwanese government issuing a directive to reduce antibiotic usage in 2001, which resulted in a 45% decrease in macrolide consumption between 1999 and 2001,[96] erythromycin resistance remained high at 94%.[118] Non-susceptibility to levofloxacin increased from 1.2% in 2001 to 4.2% in 2007.[98]

In a recent study in Thailand, 92% of the sterile site isolates were penicillin-susceptible.[64] In contrast, high resistance rates to co-trimoxazole (>50%) and erythromycin (>40%) were reported.[19,119–121] A recent study provided the first data on the mechanisms of fluoroquinolone resistance in *S. pneumoniae* in Thailand and the resistance rate remained low at 6.5%.[122] In two multinational antimicrobial susceptibility studies carried out between 2000 and 2004, Vietnam's isolates had one of the highest resistance rates against cefuroxime, clindamycin, and erythromycin out of 11 Asian countries.[87,123,124]

3.5. Current pneumococcal disease prevention strategies

The first vaccine available for immunization of adults was the plain PPV23. Plain polysaccharide vaccines, such as PPV23, appear to have a limited duration of efficacy against invasive pneumococcal disease,[125] and there is inconsistent evidence that PPV23 is effective against non-bacteremic CAP.[126–128] Furthermore, PPV23 does not decrease nasopharyngeal carriage, a substantial source of transmission of pneumococci, and thus may fail to generate herd immunity.[129] Such an effect remains to be reported. In addition, revaccination with PPV23 appears to result in a lower functional immune response compared with the responses after initial immunization.[130,131] This could be explained by the down-regulation of memory B-cells, particularly the B1b cell subset, leading to B-cell depletion of the PPV23. This phenomenon is partially reversible by the PCV.[132] PPV23 is almost exclusively administered to adults, although its efficacy remains controversial.[133–136]

The immunological limitations of polysaccharide vaccines can be overcome with pneumococcal conjugate vaccines.[132] PCVs have been shown in infants and children to induce long-term protection, immunological memory, and herd immunity.[137–139]

Of the two existing pneumococcal conjugate vaccines, PCV10 and PCV13 (Prevnar 13®), only PCV13 has recently been approved by the United States Food and Drug Administration, the European Union, and many other countries for use in adults aged ≥50 years. The clinical program for PCV13 has demonstrated that when administered as the first pneumococcal vaccine to adults aged ≥50 years, or when administered to those previously immunized with PPV23, PCV13 provides the immunologic advantages associated with conjugate vaccines, and thus has the potential for improved efficacy against pneumococcal disease compared to the PPV23 vaccine.[140,141]

Since the introduction of conjugate vaccines in the USA, rates of pneumococcal disease have decreased among persons of all ages, including those aged ≥65 years.[7] Further, rates of pneumococcal meningitis have decreased in children <5 years of age (reduction from 97 cases per 100 000 population during 1998–1999 to 24 cases per 100 000 in 2005; disease caused by vaccine-type strains fell from 80 cases per 100 000 population to 4.6)[142] and also in adults since PCV7 was introduced in the USA.[143] The reduction in pneumococcal disease in the adult population >65 years old reported in the USA appears to be the result of an increase in herd immunity.[144]

Information regarding the benefits of current pneumococcal vaccination strategies was found for Malaysia, Taiwan, Singapore, China, Japan, Thailand, South Korea, and Hong Kong. In Malaysia, a recent Pfizer-sponsored study determined that at current vaccine prices, PCV7 vaccination of 90% of a hypothetical 550 000 birth cohort would incur costs of 439.6 million RM ($128 million USD).[13] The study concluded that vaccination would reduce episodes of pneumococcal hospitalization by 9585 cases (taking into account both the pediatric population and the impact of herd protection in the adult population) to 73 845 hospitalizations, with cost savings of 37.5 million RM ($10.9 million USD) to the health system, and with 11 422.5 life-years saved (in pediatric and adult populations together), at a cost-effectiveness ratio of 35 196 RM ($10 261 USD) per life-year gained.[13] In Taiwan, a hospital-based surveillance of IPD in a medical center was conducted from 2000 to 2008 to evaluate the epidemiologic changes after pneumococcal vaccination with PPV23 and PCV7. The cumulative coverage rate of PPV23 among persons aged ≥75 years increased from 12% in 2007 to 41% in 2008, and that of PCV7 among children <5 years old was 0.7% in 2005 and 25.2% in 2008. The annual incidence of IPD decreased from 6.2 cases per 10 000 hospitalizations in 2000–2005 to 3.8 cases in 2006–2008 (38.5% reduction, $p < 0.001$), but the fatality rate did not change significantly (24.4% and 21.8%, $p = 0.74$).[16]

In a recent cost-effectiveness estimate of pneumococcal vaccination in Singapore, PCV13 prevented 834 cases and seven deaths due to pneumonia, meningitis, and bacteremia in the vaccinated population, and 952 cases and 191 deaths in the unvaccinated population (due to herd effects) over the 5-year time period.[145] The calculated cost-effectiveness ratio for PCV13 was $37 644 USD ($51 854 SGD) per quality-adjusted life-year (QALY). The PCV7 cost per QALY was $43 275 USD ($59 610 SGD).[145] These estimates demonstrate that pneumococcal vaccination in Singapore is cost-effective, especially when considering the impact of herd immunity. Similar results were demonstrated in a Markov state-transition model conducted in the USA.[146]

A study in China at a single hospital during 2009–2011 showed that the majority of pneumococcal isolates (76%) were of serotypes included in the PCV13.[73] A recent report from Japan showed that PPV23 vaccination in adults significantly reduced medical costs for all study subjects during the first year ($p = 0.027$). This study also demonstrated that PPV23 was effective for all-cause pneumonia for study subjects >75 years of age, although the effect was not significant for all study subjects >65 years of age.[147] Another recent Japanese study found that PPV23 vaccination of nursing home residents significantly reduced the incidence of pneumococcal pneumonia and all-cause pneumonia when compared with placebo ($p \leq 0.001$), as well as the death rate from pneumococcal

pneumonia ($p < 0.01$), although deaths from all-cause pneumonia did not differ between the two groups.[136]

In Thailand, PCV7 covered 70.3%, 43.6%, and 43.5% of patients aged <5, 5–64, and ≥65 years, respectively, while PCV13 covered 81.2%, 59.7%, and 60.9%, respectively.[124] In South Korea, the pneumococcal carriage rate was 18% in subjects who were vaccinated with PCV7 vs. 31.5% in unvaccinated subjects.[148] Multidrug resistance was also lower in vaccinated subjects compared with unvaccinated subjects. Another study showed that since PCV7 introduction to Korea, PCV7 serotypes decreased significantly from 66.8% in 1996–2001 to 41.3% in 2008–2009.[149] However, non-PCV7 serotypes have been increasing, and some clones are becoming antibiotic-resistant. A multi-country study found that among 19A isolates from 10 Asian countries, the prevalent clone was multidrug-resistant ST320.[150] Changing serotypes due to the introduction of vaccines is important to consider for future vaccination strategies in these regions.

Dual vaccination of PPV23 and trivalent inactivated influenza vaccine (TIV) is recommended by the World Health Organization for elderly, chronically ill populations; however, in many Asian countries vaccination rates are low due to doubts regarding the effectiveness of dual vaccination. The cost-effectiveness of dual vaccine administration has already been demonstrated in the USA.[9] A recent study from Hong Kong demonstrated the effectiveness and clinical impact of dual vaccination in elderly patients.[10] Dual vaccinations resulted in fewer coronary (hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.44–0.79; $p < 0.001$) and intensive care admissions (HR 0.45, 95% CI 0.22–0.94; $p = 0.03$), compared with unvaccinated subjects. Dual vaccination with PPV23 and TIV was shown to be effective in reducing the development of complications from respiratory, cardiovascular, and cerebrovascular diseases in elderly patients with chronic illnesses.[10] Currently, there is free coverage with the PPV23 vaccination for high-risk groups in Hong Kong.[151] Dual vaccination is important to consider in elderly, chronically ill patients to reduce hospitalization, coronary or intensive care admissions, and death.

4. Conclusions

Determining the true incidence and mortality of pneumococcal disease amongst adults in many Asian countries is constrained by the wide variation in study quality and design, and variations in the sizes and demographics of the study population. Often, study populations were small (<50–200), studies were carried out in only one or two centers, or they were carried out a decade ago or before PCVs became widely used. Hence these data may not be representative of the current situation over the entire country in many cases. Furthermore, it is possible that further epidemiological data are available for China, Japan, and South Korea, but have not been published in English.

The countries with the most comprehensive epidemiological data on adult pneumococcal disease are Taiwan and Thailand. The ongoing surveillance program by the International Emerging Infections Program in Thailand appears to be unique in Asia in providing long-term information on the incidence, mortality, and seasonality of pneumococcal disease in large populations, although the data are limited to two large rural provinces where surveillance is carried out. Very little relevant data on pneumococcal disease of any kind could be found for Indonesia, Pakistan, the Philippines, and Vietnam, and surveillance is urgently needed in these countries. When setting up surveillance studies, the methods used in Thailand and Taiwan are likely to be of use in countries that lack comprehensive data on the burden and epidemiology of pneumococcal disease in adults.

The antibiotic resistance status in countries was constrained by a limited number of referral centers, and relatively few isolates were involved in the studies and may not be an accurate reflection of the true antibiotic resistance status of the country. The majority of data on serotype prevalence and antimicrobial susceptibility in *S. pneumoniae* in Asian adults were published by scientists from Hong Kong, Taiwan, South Korea, and Japan, although studies were also found from China, Thailand, Malaysia, Singapore, Vietnam, and India. The most common studies often carried out detailed molecular analyses to determine the mechanisms of antibiotic resistance and the reasons behind its spread. Importantly, these data highlight increased penicillin and multidrug resistance among pneumococci as a serious problem in many countries in the region and globally.

Overall, data were lacking on the economic burden of pneumococcal disease in Asia. However, several recent studies have shown decreases in economic burden of pneumococcal disease after the introduction of vaccinations. The emergence and spread of resistance emphasize the importance of vaccination to prevent infection in adults at increased risk of serious pneumococcal disease. While vaccination with PCV7, PCV13 in children, PPV23 in adults, and dual PPV23/TIV vaccinations in elderly, chronically ill individuals decreases the spread of pneumococcal disease, leading to better clinical and economic outcomes, the vaccination policies vary widely in Asia. There is a critical need for increased awareness of the public health and economic benefits of pneumococcal vaccination, which will aid both the public and policymakers in making changes to vaccination policies in the region.

Observational studies have demonstrated that PPV reduces the risk of IPD in immunocompetent elderly individuals, but neither observational studies nor clinical trials have demonstrated consistent evidence for a reduction in the incidence of pneumonia in vaccinated older adults.

Conjugate vaccines may offer an advantage over polysaccharide vaccines. Possible advantages of PCVs in elderly adults include higher levels of protection against the vaccine serotypes after vaccination and the ability to prolong the duration of protection by use of repeated vaccinations over time. The effectiveness of PCVs against pneumonia in children also raises the possibility that PCVs may protect against non-bacteremic pneumococcal pneumonia in adults. A limitation of PCVs, however, is that fewer serotypes are included in those vaccines than in PPV.

Providing as many individuals as possible access to pneumococcal vaccines will decrease the overall number of hospitalizations, complications, and deaths associated with pneumococcal disease.

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