Overview of the Disease Burden of Invasive Pneumococcal Disease in Asia

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ABSTRACT

This paper represents a collaborative effort by the Asian Strategic Alliance for Pneumococcal Disease Prevention (ASAP) Working Group to collate data on the disease burden due to invasive pneumococcal disease (IPD) in participating Asian countries and territories; namely, Brunei, Hong Kong, India, Indonesia, Korea, Macau, Malaysia, Pakistan, the Philippines, Singapore, Sri Lanka, Taiwan and Thailand. A review of both published and unpublished data revealed that the incidence of IPD in some countries is well documented by way of large, long-duration studies, while in other countries, much of the available data have been extrapolated from international studies or have come from small population studies of limited geographical coverage. This paper confirms that data regarding the incidence of IPD in Asia are grossly lacking and reinforces the need for urgent and more substantial studies.

Running title: Pneumococcal disease in Asia

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Introduction

Pneumococcal disease can be regarded as a serious global problem based on the number of deaths attributed to it. The World Health Organization (WHO) estimates that 1.6 million die every year from the disease, 0.7 to 1 million of which are children aged < 5 years [1]; while community-based studies of invasive pneumococcal disease (IPD) and vaccine efficacy trials reveal that approximately 814,000 pneumococcal deaths occur each year in children aged < 5 years in developing countries, most of them in Asia and Africa [2].

The Asian region is unique in that, while it consists of developed and newly emerging markets, it is still home to 600 million children living in absolute poverty and large numbers of children < 5 years old dying from malnutrition, diarrhea and acute respiratory infections (ARIs)—
mostly pneumonia, malaria and vaccine-preventable diseases [3]. Reducing healthcare inequalities remains a challenge for the region, and substantial differences in health coverage may exist between the poorest and wealthiest groups within a single country; for example, in India and the Philippines, the wealthiest people are three times more likely to receive care than the poorest [4].

Health authorities in the region have yet to act on the need to protect all young children, regardless of social background, against the life-threatening pneumococcal disease. Although pharmacological interventions such as antibiotics and vaccines are available for treatment and prevention, policymakers cite the lack of data on pneumococcal disease as reason for indecision [5,6]. While the United Nations Children’s Fund (UNICEF) and WHO report provides epidemiological evidence on the burden of pneumonia in children (Table 1) [7], information on pathogen-specific etiology is lacking. The number of published data from the region to confirm the impact of IPD and specific clinical presentations is also limited.

For this reason, many Asian countries still have not included pneumococcal vaccination in their national immunization programs even though the rationale for vaccination has long been supported by studies. In light of the additional benefits of herd immunity and with the threat of widespread antibiotic resistance, the inclusion of this vaccine can become a cost-effective intervention with long-term benefits [8,9].

1. **Collation of available data on pneumococcal disease in Asia**

   The Asian Strategic Alliance for Pneumococcal Disease Prevention (ASAP) was organized in 2007 to raise awareness of the morbidity and mortality caused by pneumococcal disease and of the importance of preventing the disease through surveillance and advocacy. It is composed of healthcare professionals from 13 Asian countries and territories; namely, Brunei, Hong Kong,
India, Indonesia, Korea, Macau, Malaysia, Pakistan, the Philippines, Singapore, Sri Lanka, Taiwan and Thailand.

This paper represents the collaborative effort of ASAP members to gather local-level data on pneumococcal disease, both published and unpublished, taking into account the incidences of pneumococcal disease and its clinical manifestations (meningitis, pneumonia, otitis media and septicemia) stratified according to age, mortality and case fatality rates, serotype distribution and antibiotic resistance. With this collection of data, ASAP will then be able to determine the importance of pneumococcal disease in the region and generate a regional consensus on essential issues. This information will also provide an impetus for health officials and policymakers to create strategies to manage anticipated cases and, more importantly, to prevent disease. Summaries of data gathered by ASAP members are presented in this paper and individual study objectives are outlined in Table 2.

2. Summaries of data from ASAP countries and territories

3.1. Brunei

The WHO reports that the mortality rate for < 5-year-olds in Brunei is 9/1000 live births. Pneumonia and related meningitis, sepsis/septicemia and other infections are the highest causes of neonatal deaths, contributing 7% to total deaths [10]. Records from Raja Isteri Pengiran Anak Saleha (RIPAS) hospital, the main referral hospital in Brunei, indicate that most pneumococcal-positive samples in children < 12 years old came from those with respiratory tract infections (268 out of the total 316 samples; RIPAS hospital, unpublished data, 2007).

3.2. Hong Kong

3.2.1. Epidemiology

A retrospective, population-based study, which included records dated between 1995 and 2004, showed that the annual incidence of IPD requiring hospitalization in children aged
The incidence rate was 15.6/100,000 in children aged ≤ 5 years old. More recent data from 2000 to 2005 showed that the hospitalization rate with IPD for children ≤ 2 years old was 23.7/100,000 person-years [12] and 16.1/100,000 person-years in children ≤ 5 years old. Based on laboratory results from the Hospital Authority in Hong Kong, the average annual incidences among children aged < 2 years and adults aged > 65 years old were both 7.7/100,000 (95% CI 2–13/100,000) from 2000 to 2004 [13].

2.2.2. **Serotype distribution**

A study conducted by Ho et al. in 79 daycare centers and kindergartens in Hong Kong (December 1999–June 2000) determined the serotype distribution of *Streptococcus pneumoniae* from both nasopharyngeal and invasive isolates in children aged < 6 years [14]. The most common carriage serotypes found were similar to the invasive isolates—that is, 6B, 14, 19F and 23F. Furthermore, the serotypes in the 7-valent pneumococcal conjugate vaccine (PCV7) accounted for 89.7% and 66.1% of the carriage and invasive isolates, respectively. The serotypes in PCV7—4, 6B, 9V, 14, 18C, 19F and 23F—accounted for 89.8% of all serotypes found in invasive isolates taken from children (age ≤ 5 years) in five Hong Kong hospitals between 1995 and 2001 [14,15].

3.2.3. **Antibiotic resistance**

As of 2000, the overall prevalence rate of penicillin resistance among pneumococci was 49% in Hong Kong [14]. Retrospective data gathered from patients aged ≤ 2 and ≥ 65 years admitted to five Hong Kong hospitals with pneumococcal bacteremia between 1995 and 2001 determined that 37.4% of *S. pneumoniae* isolates were nonsusceptible to penicillin and 63.4% were resistant to clarithromycin [15]. In the same study, 3.8% of *S. pneumoniae* isolates were resistant to levofloxacin.

Of 383 nasopharyngeal isolates from the 79 centers in the Ho et al. study, 42.0% were penicillin sensitive, 32.1% were intermediate and 26.1% were resistant [14]. The isolates had
high rates of resistance to cefotaxime and erythromycin at 42.8% and 77.0%, respectively. The same study included 88 pneumococci isolated from children with IPD who were hospitalized in five Hong Kong hospitals [14]. Isolates were obtained from the blood, cerebrospinal fluid or brain tissue of children 0–6 years old. Among this group of isolates, 52.3% were penicillin sensitive, 31.8% were intermediate and 15.9% were resistant. The rates of resistance to cefotaxime and erythromycin were 33.0% and 85.2%, respectively.

More recent data from 519 *S. pneumoniae* isolates from nasopharyngeal aspirates of 3157 children (age < 16 years old) in Hong Kong in 2005 and 2006 were included in a surveillance study [16]. Results showed that 64.9% and 37.2% of the isolates were not susceptible to penicillin and cefotaxime, respectively.

3.3. *India*

3.3.1. *Epidemiology*

The Invasive Bacterial Infection Surveillance (IBIS) group and the International Clinical Epidemiology Network (INCLEN) conducted a prospective multicenter hospital-based surveillance study in India and reported that, of the 314 patients identified as having IPD, 32.8% of cases occurred in children aged ≤ 5 years, including 22.6% in children ≤ 2 years and 10.2% in 2–5-year-olds [17]. Of the 304 IPD patients whose clinical outcome was known, the case fatality rate (CFR) was 22% in children aged < 2 years, 10% in 2–12-year-olds, 26% in 13–50-year-olds and 28% in adults > 50 years. Meningitis was found to cause approximately one-third (34%) of the fatalities, while septicemia caused 21% and pneumonia 19%.

The IBIS group extended to other South Asian countries and established surveillance systems in Nepal and Sri Lanka through the South Asian Pneumococcal Alliance (SAPNA) project [18]. A semi-annual technical report from SAPNA revealed that there were 1273 enrollees to the study from October 2006 to March 2007. *S. pneumoniae* has been identified as pathogen in 28 of the participants, and 11 of them are from India [19].
3.3.2 Serotype distribution

A prospective observational study by Jebaraj et al. found 6, 19, 15, 14 and 23 to be the most common serotypes isolated from the nasopharynges of 100 infants attending a well baby clinic in Vellore. These serotypes comprise 55% of the pneumococcal isolates found by the study [20]. While the IBIS–INCLEN study identified more than 25 serotypes in the total population, the most common serotypes in children aged < 5 years were 6, 1, 19, 14 and 4 [17]. The more recent study by the SAPNA group reported the most prevalent serotypes to be 6B, 20, 16 and 1 [19].

3.3.3 Antibiotic resistance

The IBIS–INCLEN group also performed antimicrobial susceptibility testing on 307 S. pneumoniae isolates, finding that intermediate resistance to penicillin was noted in only 1.3% of the isolates tested, but that resistance to cotrimoxazole and chloramphenicol was seen 56% and 17% of the isolates, respectively [17]. The Asian Network for Surveillance of Resistant Pathogens (ANSORP), a multicountry collaborative group for antimicrobial research, has observed that India still has the lowest pneumococcal resistance to penicillin and erythromycin in the region [21,22].

3.4 Indonesia

3.4.1 Epidemiology

Records obtained from six hospitals in Jakarta, Surabaya, Bandung, Bali, Padang, and Makassar from January to December 2006 revealed that of the 1796 children aged < 5 years admitted due to IPD, 1425 (79.3%) had pneumonia, 283 (15.8%) had sepsis (bacteremia) and 88 (4.9%) had meningitis. The CFR was 29.2% and 21.0% in infants aged 1–11 months and 12–23 months, respectively, while the overall CFR attributable to IPD was 23.5% (Hadinegoro, in press),[23,24].
A hospital-based study involving pediatric patients with acute purulent meningitis showed that in 155 cases confirmed by cerebrospinal fluid (CSF) culture, the most common etiological agents were *Salmonella sp.* (12.9%), *Acinetobacter sp.* (7.1%), *S. pneumoniae* (5.8%) and *Hemophilus influenzae* (5.2%) [25], whereas a more recent study showed that of the 177 positive nasopharyngeal specimens from 698 patients between 2 and 5 years of age with nonsevere pneumonia, 120 (67.8%) had *S. pneumoniae*, 21 (11.9%) had *Staphylococcus epidermidis* and another 21 (11.9%) had alpha-streptococcus [26].

A pneumococcal nasopharyngeal carriage study in neonates showed that 38.9% of the 108 assessed had positive isolates: 0.9% in newborns; 2.8% at 2, 4, 6 and 8 weeks; 9.3% at 10 weeks; 12.0% at 13 weeks; and 13.9% at 15 weeks. The most common sources of transmission were siblings (57.1%) and mothers (11.9%) [27].

Records of Sanglah Hospital in Bali identified 25 cases of meningitis between 2000 and 2005; three of these patients died. Hydrocephalus, hemiplegia, monoparesis, deafness and epilepsy were found to be the most common sequelae [28].

### 3.4.2. Serotype distribution and antibiotic resistance

A pneumococcal carriage study conducted in Lombok involving 484 healthy children aged 0–25 months found pneumococcal isolates in 221 (48%) children. The most common serogroups were 6, 23, 15, 33 and 12. Sixty-one percent of the isolates found are covered by the current PCV7. Susceptibility testing revealed that 2.2% of the 221 specimens were nonsusceptible to penicillin and 0% were nonsusceptible to cefotaxime [29].

### 3.5. Republic of Korea

#### 3.5.1. Epidemiology

While there are no published data on the incidence rate of pneumococcal disease in Korea, a survey of 13 hospitals found that *S. pneumoniae* (30%) is the most common invasive pathogen among Korean children, especially among the immunocompromised and patients aged
3 months to 5 years (Lee HJ, unpublished data, 2007). In the same survey, the most common clinical features of IPD in immunocompetent children were meningitis (39%) and bacteremic pneumonia at 35%, whereas, in immunocompromised children, the most common clinical features were bacteremia without focus (48%) and meningitis (18%).

Among the immunocompetent children, IPD was most common in children aged <2 years, with incidence declining as age increased. In the immunocompromised children, however, IPD episodes did not decrease with increasing age (Fig. 1). The CFR for children with IPD was 12% (27/222): 13% (19/144) for immunocompetent children and 10% (8/78) for immunocompromised children (Lee HJ, unpublished data, 2007).

3.5.2. Serotype distribution

A study evaluating serotype distribution among isolates from various clinical specimens at Seoul National University Children’s Hospital from 1991 to 2006 showed that the most common serotypes were 19F (21.0%), 23F (17.8%), 19A (10.8%), 6B (9.3%), 6A (8.0%), 14 (7.4%) and 9V (4.5%) [30]. Between 1991 and 2003, it was observed that the proportion of 19A isolates increased from 0 to 26% while 19F decreased during the same period. From 2001 to 2003, just prior to the introduction of the pneumococcal vaccine, serotypes covered by the vaccine accounted for 57% of isolates while vaccine-related serotypes accounted for another 24%. Although the serotype distribution of isolates changed after the introduction of pneumococcal vaccine in 2004, similar trends were observed, i.e. the proportion of serotypes covered by the vaccine were decreasing and the increase of 19A became more evident from 2004 to 2006 [30].

3.5.3. Antibiotic resistance

3.6. Macau

Macau is a small city south of China and Hong Kong with only two hospitals and no serotyping facility. A review of records dated 2001–2007 from the public acute care hospital Centro Hospitalar Conde São Januário found only one IPD case—a pneumococcal meningitis case (Kin-Man Lui, personal communication, 2007). PCVs are provided free by the government for high-risk groups: premature infants and those with complex heart diseases.

3.7. Malaysia

3.7.1. Epidemiology

Published studies on pneumococcal infection in Malaysia have shown pneumonia to be its most common clinical presentation, with morbidity and mortality being highest in children aged < 2 years [31,32]. A more recent hospital-based study confirmed this finding by showing that majority of the cases occurred in patients aged < 2 years and that definite pneumonia, probable pneumonia, meningitis, bacteremia without focus and septic arthritis were the most common types of IPD in Malaysian patients. Those with meningitis had the highest rate of long-term complications [33]. Earlier studies on childhood meningitis in Malaysia showed that most cases occurred in those < 5 years of age and that H. influenzae and S. pneumoniae were the most common causative organisms [34,35,36]. As the H. influenzae type b (Hib) vaccine was incorporated in the country’s national immunization program in 2002, it is presumed that S. pneumoniae is now the leading cause of meningitis in Malaysia.

However, there are no published data to date on the incidence of invasive pneumococcal infection post-Hib vaccination except for a paper by Suhaimi, which reported on a single-center retrospective study conducted at Queen Elizabeth Hospital in Kota Kinabalu evaluating the incidence of childhood meningitis both before the introduction of Hib vaccine (January 1999–December 2001) and afterwards (January 2004–December 2006). This study showed that the incidence of pneumococcal meningitis increased following the introduction of
Hib vaccination (3.7 vs. 8.6/100,000 per year in children aged < 5 years) [37]. Larger studies involving more centers in Malaysia are needed to confirm this finding.

3.7.2. Serotype distribution

Several studies have documented the serotype distribution in Malaysia with differing results. Rohani et al. reported that the most common serotypes that cause IPD in children aged < 2 years were 1, 5, 23B, 2, 8, 14, 20, 6A, 12A, 19B and 23B [32]. Cheong et al. looked at pneumococcal serotypes isolated from children aged < 5 years presenting with ARI in three centers in Malaysia and the most common serotypes isolated were 19F, 6A and 23F [38]. A 4-year prospective study was also undertaken by Jamal and colleagues in Kuala Lumpur and, out of 43 isolates in children aged < 12 years with pneumococcal disease, the most common serotypes were 6A (25.6%), 6B (16.3%) 14 (18.6%) and 19A (18.6%) [31]. Currently, a prospective multicenter study is underway to evaluate IPD incidence and serotype prevalence in hospitalized children (N.K. Nik Yusoff, personal communication, 2008).

3.7.3. Antibiotic resistance

The ANSORP study showed that pneumococcal disease serotypes prevalent in Malaysia have a considerable degree of resistance to penicillin (29.5%) and erythromycin (34.1%) [21].

3.8. Pakistan

3.8.1. Epidemiology

A previous systematic review of all national published studies by Bhutta revealed that pneumonia and meningitis account for over 85,000 childhood deaths and cases of disability in infancy in Pakistan and that 33% of these are attributable to infections caused by S. pneumoniae and H. influenzae [39]. These results have recently been updated and indicate that the proportion of meningitis cases attributable to S. pneumoniae and H. influenzae may be higher in recent studies (Bhutta et al. unpublished observations, 2008). The 2007 Pakistan Demographic
and Health Survey indicates that 25.7% and 9.1% of all postneonatal child deaths in Pakistan were related to pneumonia and meningitis, respectively [40]. These figures are remarkably similar to the estimates obtained earlier by Bhutta [39].

A number of community- and hospital-based studies provide an overview of the etiology of ARIs among children <5 years old in Pakistan. In a census conducted in four periurban communities, Nizami et al. isolated S. pneumoniae in 3.7% of a total of 791 oropharyngeal swab cultures and calculated the S. pneumoniae burden in these communities to be 3.0/1000 children [41]. Using the same technique, Rehman and colleagues identified 139 positive cultures from 500 pediatric patients at Bahawal Victoria Hospital in Bahawalpur; 36 of the 139 (25.9%) were S. pneumoniae positive [42]. Ghafoor et al. meanwhile reported that, of the 1331 blood specimens included in their study, H. influenzae was the leading bacterial isolate (11% of the cases) followed by S. pneumoniae (10%) [43].

3.8.2. Serotype distribution and antibiotic resistance

Serotypes 6, 9, 15, 16, 19 and 31 comprised 60% of the S. pneumoniae isolates found in the study by Ghafoor et al. [43]. This finding was confirmed by Mastro and colleagues who reported a year later that the most common serotypes detected were 19F, 31, 16, 19A, 9V, 15C and 6A. They also tested 87 strains of S. pneumoniae isolates for antimicrobial susceptibility and found that 97% had decreased susceptibility to at least one antimicrobial agent: 31% were fully resistant to cotrimoxazole, 39% were resistant to chloramphenicol and 9% were moderately resistant to penicillin [44]. Recent data on antimicrobial sensitivity patterns of respiratory isolates of S. pneumoniae and H. influenzae also confirm increasing resistance to cotrimoxazole and penicillin.

3.9. Philippines

3.9.1. Epidemiology
Statistics from the Philippines’ Department of Health (DOH) in 2000 attributed child mortality rates of 37.8/100,000 to pneumonia, 4.7/100,000 to meningitis and 4.5/100,000 to septicemia, although the statistics do not describe pathogen-specific causality [45].

A few hospital- and community-based studies have examined the etiology of infections in children aged < 5 years with pneumonia, bacteremia and meningitis. In a study by Lupisan et al., *S. pneumoniae* was found to be the leading isolate among blood cultures (1.3% of the total from an overall culture positivity of 8.9%) [46]; while Capeding et al. documented *S. pneumoniae* in 3.7% of acute lower respiratory tract infections and in 35.0% of patients with confirmed bacteremia [47].

Data on the frequency distribution of bacterial meningitis from three tertiary hospitals in Metro Manila have shown that *S. pneumoniae* and Hib are the most prevalent etiological agents (Philippine General Hospital; Philippine Children’s Medical Center; University of Santo Tomas Hospital, unpublished data, 2002–2006). The mortality rate in patients positive for *S. pneumoniae* was 23.5% compared to 5.0% for patients with Hib.

### 3.9.2. Serotype coverage and antibiotic resistance

A study of nasopharyngeal samples from Filipino children with ARI showed serotypes 6, 14, 19 and 23 to be the most common [48], while in a recent study among children with IPD, the most common serotypes were 6, 18, 14 and 5 [49]. Pneumococcal antibiotic resistance is low in the Philippines at 1% for penicillin, 5% for chloramphenicol and 18% for cotrimoxazole [50].

### 3.10. Singapore

#### 3.10.1. Epidemiology

A retrospective review of more than 4000 hospital records from 1995 to 2004 in Singapore indicated that children aged < 5 years and adults aged ≥ 65 years were most susceptible to pneumococcal disease, with hospitalization rates of 38.4/100,000 and 56.4/100,000, respectively [51]. Pneumococcal pneumonia was the most common disease
manifestation (97.9%), followed by septicemia (1.1%) and meningitis (0.7%). The CFR for all age groups in this study was 3.2%. Cause of death was primarily attributable to pneumococcal meningitis, followed by septicemia and pneumococcal peritonitis, and pneumococcal pneumonia.

A retrospective survey among all pneumococcal-positive patients (n=146; aged 3 months to 19.5 years) admitted to Kandang Kerbau Women’s and Children’s Hospital from 1997 to 2004 showed that 46.9% of these patients were between the ages of 2 and 5 years, with a mean age of 45 months. Pneumonia (63.3%) was also the most common form of IPD, followed by bacteremia (17%) and meningitis (15.6%). The morbidity rate was found to be 25.2% and the mortality rate 6.1%. Using the country’s 2005 population estimates, IPD incidence was found to be 13.6/100,000 in children < 5 years and 16.9/100,000 in children < 2 years [52].

3.10.2. **Serotype coverage and antibiotic resistance**

The four most common serotypes in the pediatric population were found to be 14 (21.8%), 6B (10.2%), 23F (10.1%), 19F (5.4%) and 6A (3.4%). Overall penicillin resistance was at 44.4%, most of which were observed in serotypes 14 and 19F, whereas resistance to ceftriaxone was 15.0% [52].

3.11. **Sri Lanka**

3.11.1. **Epidemiology**

One of the largest Sri Lankan children’s hospitals, the Lady Ridgeway Hospital for Children (LRH) in Colombo, reported 794 pneumonia cases and 295 meningitis cases in 2003, of which 32 and 9 died, respectively (LRH, Annual Health Bulletin, 2003 unpublished), while SAPNA reported in 2005 that of 228 patients from LRH, 75% had pneumonia, 8% had meningitis and 4% had septicemia. Nine of these patients were found to have IPD [53]. In SAPNA’s semi-annual technical report, 10 of the 28 participants identified with *S. pneumoniae* as pathogen were from Sri Lanka [19]
Being one of the hardest hit countries by the December 2004 tsunami, Sri Lanka has data available on the prevalence and transmission of ARIs caused by \textit{S. pneumoniae} and \textit{H. influenzae} in the evacuation camps. Nasopharyngeal swabs were collected from 324 displaced people staying in three different camps and 21 \textit{H. influenzae} isolates from 20 people and 25 \textit{S. pneumoniae} isolates from 22 were identified. It is suggested that some of these infections may have been transmitted from person to person while staying in the camps [54].

3.11.2. Serotype distribution and antibiotic resistance

The most prevalent serotypes in Sri Lanka are 23F, 19F and 14 [53, 21]. Isolates have shown markedly increased penicillin resistance (1996–1997: 0.0%; 1998–1999: 5.9%; 2000–2001: 14.3%) in the course of the ANSORP studies [21]. Ciprofloxacin resistance is also high at 11.8%. The SAPNA study also revealed high penicillin resistance at 22% and cotrimoxazole resistance at 67%.

3.12. Taiwan

3.12.1 Epidemiology

In 2006, data from the Bureau of National Health Insurance suggested that the overall incidence of IPD in Taiwan was 216/100,000. Adults aged >65 years old had the highest incidence (1147/100,000), followed by children aged <5 years (422/100,000). The incidence of pneumonia showed a reversed trend, being highest among children aged <5 years at 45,956/100,000 [55]. This differs substantially from UNICEF–WHO report where the incidence of pneumonia among children aged <5 years in East Asia and the Pacific was estimated to be 23,000/100,000 [7]. The incidences of septicemia and meningitis in children aged <5 years were 1095/100,000 and 185/100,000, respectively. The IPD mortality rate was highest in the elderly (>65 years), mainly due to pneumonia (30,806/10,000) [55].
In a study conducted by Siu et al. from July 1998 to June 1999, the CFR for IPD was highest among the elderly (≥ 65 years; 42.5%) and children ≤ 5 years (7.2%) [56]. A similar trend, but reduced CFR, was observed in an island-wide IPD surveillance study conducted from January to November 2007—two years after PCV7 was introduced in Taiwan. The CFRs were 21.7% in the elderly (≥ 70 years) and 2.5% in children aged ≤ 5 years (Fig. 2) (Taiwan Center for Disease Control and Prevention [CDC], unpublished data, 2007).

3.12.2. *Serotype coverage and antibiotic resistance*

Serotype 14 predominated in children aged ≤ 5 years with IPD, followed by 19F, 23F, 6B and 19A. Penicillin susceptibility testing showed *S. pneumoniae* to be 65–70% resistant, while resistance to ceftriaxone was 38% (Taiwan CDC, unpublished data, 2007).

3.13. *Thailand*

3.13.1. *Epidemiology*

Two studies have reported on the etiology of ARI in young Thai children. Sunakorn et al. performed a study between 1988 and 1989 among children admitted to the Queen Sirikit National Institute of Child Health (formerly known as the Children’s Hospital Bangkok) and found that the most severe ARI cases were in children aged < 2 years. Most cases were caused by Hib and few cases by *S. pneumoniae* [57]. In the second study, Ekalaksanananan et al. reported that pneumonia presented most frequently in children aged < 1 year, with *S. pneumoniae* and *H. influenzae* contributing equally to the number of cases. Viral and bacterial co-infection was also detected [58].

The Bureau of Epidemiology of the country’s Ministry of Public Health (MOPH) reported that, from 1999 to 2005, the incidence rate of pneumonia among children aged < 5 years was about 1500–2000/100,000 (Bureau of Epidemiology, MOPH, unpublished data, 2006).
A population-based survey in the provinces of Sa Kaeo and Nakhon Phanom, conducted by the MOPH and the surveillance network of the International Emerging Infections Program (IEIP) detected a minimum IPD incidence of 4/100,000 by blood culture. The highest IPD incidence occurred in children aged <5 years (8.8–12.3/100,000) and in the elderly ≥75 years (26/100,000); this was compounded by substantial antibiotic resistance, with vaccine serotypes found to be especially resistant (IEIP, unpublished data, 2007). Childhood meningitis was studied by Chotpitayasunondh who found that Hib (42.3%) and *S. pneumoniae* (22.2%) were the leading causative organisms [59].

### 3.13.2. Serotype coverage and antibiotic resistance

In a recent study, Phongsamart et al. found that the most common *S. pneumoniae* serotypes were 6B (27.8%), 23F (20.0%), 14 (10.4%) and 19F (9.6%). Seventy-four percent of these serotypes are covered by PCV7 and 88% are covered by the 13-valent PCV (PCV13). Seventy percent were found to be penicillin resistant [60]. In another study, Levine et al. showed that, among rural children aged <5 years, nasopharyngeal colonization was 60%, with 6B, 19F and 23F being the most common serotypes isolated. About 55% of the serotypes found were covered by PCV7 and 68% were penicillin nonsusceptible strains [61].

### 3. Discussion

The collection of data from the ASAP members confirms that pneumococcal disease is an important cause of morbidity and mortality in the Asian region. Overall CFRs resulting from IPD, as reported by studies from India, Indonesia, Singapore and Taiwan, are illustrated in Figure 3. In many of the studies, pneumonia was identified as the most common clinical manifestation. Interestingly, four ASAP member countries, namely, India (with 44 million pneumonia cases), Pakistan (7 million), Indonesia (6 million) and the Philippines (3 million) were among the 15 countries identified by both UNICEF–WHO and Rudan et al. as accounting for
three-quarters of the total childhood pneumonia cases worldwide. Both reports identified *S. pneumoniae* as the leading pathogen [7,62].

The high antimicrobial resistance of *S. pneumoniae* in Asia contributes to both the treatment and economic burden caused by IPD [21,22,63]. In the ANSORP studies, Korea, Taiwan and Thailand have consistently shown high rates of penicillin resistance [21]. The judicious use of antibiotics and promotion of vaccination have been suggested as methods to control these resistant infections [8]. However, pneumococcal vaccination is currently not part of the national immunization programs of any of the ASAP member countries and territories, despite it being projected to prevent around 260,000 deaths annually as well as having the potential to mitigate widespread antibiotic resistance [64].

Rinaldi and Chong confirmed that vaccination of infants with PCV7 would lead to a substantial reduction in the incidence of IPD, not only among children but also in adults due to herd protection conferred by immunization [65]. Using a decision-analytic model previously used in the United Kingdom, Lee et al. evaluated the clinical and economic benefits of routine infant immunization with PCV7 in Hong Kong and found that 524 cases of IPD and over 2580 cases of otitis media were potentially prevented over a 10-year period, leading to a reduction of at least HK$35 million (US$4.5 million) in direct medical costs. The study also took into account the additional cost savings from the indirect prevention of 919 adult cases of IPD during the same period. Universal PCV7 vaccination was estimated to have an incremental cost per life-year gain of HK$44,644 (US$5718) [66].

IPD incidences in Hong Kong, Singapore and Taiwan have been documented by way of long-duration national studies, with the objective of understanding the epidemiology of invasive *S. pneumoniae*. However, the primary objectives of the studies from other ASAP member countries were to determine the bacterial etiology of ARI, pneumonia, or meningitis; to assess antimicrobial sensitivity; to describe the dynamics of nasopharyngeal colonization; or to determine serotype distribution of *S. pneumoniae*. Data from some countries were also obtained
from very small studies with limited geographic coverage or were extrapolated from results of international studies. In addition, it is likely that the IPD incidence in some of the studies was underestimated given the inherent limitation of blood cultures. Moreover, not all meningitis cases were confirmed by CSF cultures and outpatient pediatric bacteremia cases were not reported. These differences in study objectives, methodologies and reporting criteria, as well as the limited coverage prevent comparative analysis and the estimation of regionwide burden of disease.

IPD is currently not a notifiable disease in any of the ASAP member countries and territories—with the exception of Taiwan—and no comprehensive and standardized laboratory surveillance system for IPD has been established. A surveillance system is needed to provide valuable data on serotype distribution, antibiotic resistance and the impact of vaccination. This also has to be supported by statistical models and clinical trial results to be able to accurately estimate disease burden [67,68]. Currently, several surveillance projects and clinical studies are being conducted in Asia that will be able to provide a more accurate estimate of the epidemiology and impact of IPD in the region [67].

4. Conclusion

This review of available data confirms the substantial burden of IPD and prevalence of antibiotic resistance of pneumococci in the Asian region. High incidence is observed in both children aged < 2 years and adults aged > 65 years. Incidence rates vary between countries. More substantial and specific studies and continued surveillance are therefore needed to better assess the incidence of IPD throughout Asia and be able to develop strategies for prevention and management. The collection of studies also highlights the need to strengthen ARI management programs. Lastly, the overview of disease burden due to IPD emphasizes the need to deliver effective interventions, such as early recognition and treatment, prevention through vaccination and methods to address increasing antimicrobial resistance.
Acknowledgements

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The authors thank Tina V. Garcia of In Vivo Communications Ltd for medical writing assistance.
<table>
<thead>
<tr>
<th></th>
<th>Brunei</th>
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<th>Malaysia</th>
<th>Pakistan</th>
<th>Philippines</th>
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<th>Sri Lanka</th>
<th>Thailand</th>
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<tbody>
<tr>
<td>Total number of children &lt; 5 years (000s)</td>
<td>40</td>
<td>120,155</td>
<td>21,477</td>
<td>2521</td>
<td>2738</td>
<td>20,922</td>
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<tr>
<td>Total number of deaths among children &lt; 5 years (000s)</td>
<td>0</td>
<td>2210</td>
<td>171</td>
<td>3</td>
<td>7</td>
<td>478</td>
<td>69</td>
<td>0</td>
<td>5</td>
<td>21</td>
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<tr>
<td>Mortality rate among children &lt; 5 years (per 1000 live births)</td>
<td>9</td>
<td>85</td>
<td>38</td>
<td>6</td>
<td>12</td>
<td>101</td>
<td>34</td>
<td>3</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Total number of pneumonia cases</td>
<td>0</td>
<td>410</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>92</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Deaths among children aged &lt; 5 years (000s)</td>
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</tr>
<tr>
<td>Case fatality rate in children aged &lt; 5 years</td>
<td>1%</td>
<td>19%</td>
<td>14%</td>
<td>2%</td>
<td>4%</td>
<td>19%</td>
<td>13%</td>
<td>9%</td>
<td>9%</td>
<td>11%</td>
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*Hong Kong SAR ceased to be a WHO member state in 1997 and thus was excluded from the world health reports. Taiwan and Macau are represented in the WHO system by China.*
<table>
<thead>
<tr>
<th>Table 2. Summary of sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>Brunei</td>
</tr>
<tr>
<td><strong>Raja Isteri Pengiran Anak Saleha (RIPAS) hospital. Unpublished hospital data. 2007</strong></td>
</tr>
<tr>
<td><strong>WHO. Mortality country fact sheet 2006. Brunei Darussalam</strong></td>
</tr>
<tr>
<td>Hong Kong</td>
</tr>
<tr>
<td><strong>Ho PL, Que TL, et al. 2004 [15]</strong></td>
</tr>
<tr>
<td><strong>Ho PL, Lam KF, et al. 2004 [14]</strong></td>
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<tr>
<td><strong>Ho PL et al. 2006 [11]</strong></td>
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<tr>
<td><strong>Ho PL et al. 2007 [12]</strong></td>
</tr>
<tr>
<td><strong>Ip M et al. 2007 [16]</strong></td>
</tr>
<tr>
<td><strong>Scientific Committee on Vaccine Preventable Diseases. 2007 [13]</strong></td>
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<td><strong>India</strong></td>
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### Objectives

<table>
<thead>
<tr>
<th>Invasive Bacterial Infections Surveillance (IBIS) group; International Clinical Epidemiology Network (INCLEN). 1999 [17]</th>
<th>To determine pattern of diseases due to <em>S. pneumoniae</em>, distribution of invasive serotypes and antimicrobial susceptibility in India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jebaraj R et al. 1999 [20]</td>
<td>To describe the dynamics of nasopharyngeal colonization by <em>pneumococci</em> and to determine the prevalence of different serotypes and their antimicrobial susceptibility</td>
</tr>
</tbody>
</table>

### Indonesia

| Kartasasmita CB et al. 2001 [26] | To determine nasopharyngeal bacterial carriage and antimicrobial resistance in children aged < 5 years with community-acquired pneumonia |
| Soewignjo S. et al. 2001 [29] | To determine *S. pneumoniae* nasopharyngeal carriage prevalence, serotype distribution and antibiotic resistance among children aged 0–25 months |
| Kari K et al. 2006 [28] | To study the bacterial meningitis profile of patients in Sanglah hospital in Denpasar, Indonesia. |
| Kartasasmita CB et al. 2006 [27] | To determine prevalence of pneumococcal nasopharyngeal carriage in neonates and possible sources of acquisition |
| Hadinegoro SR et al. 2008 (in press) | To provide an overview of pneumococcal disease in Indonesian children |
### Objectives

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Details</th>
</tr>
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<tbody>
<tr>
<td>Lee HJ. Unpublished hospital data. 2007</td>
<td>To identify major pathogens of invasive diseases in Korean children</td>
</tr>
<tr>
<td>Choi EM et al. 2008 [30]</td>
<td>To describe <em>S. pneumoniae</em> serotype distribution changes, with an emphasis on serogroup 19</td>
</tr>
<tr>
<td>Jamal F et al. 1987 [31]</td>
<td>To describe the clinical features and outcomes of systemic pneumococcal infection</td>
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<tr>
<td>Cheong YM et al. 1988 [38]</td>
<td>To describe the antibiotic susceptibility pattern and serotypes of the pneumococcal strains</td>
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<tr>
<td>Choo KE et al. 1990 [34]</td>
<td>To study retrospectively pyogenic meningitis in hospitalized children in Kelantan, Malaysia, with regard to etiology, clinical features, investigation, treatment and outcome</td>
</tr>
<tr>
<td>Tee AC. 1993 [35]</td>
<td>To determine the relationship of presenting features and outcome in primary childhood meningitis among patients admitted to the pediatric department of University Hospital Kuala Lumpur from 1980 to 1989</td>
</tr>
<tr>
<td>Hussain IHM et al. 1998 [36]</td>
<td>To determine the pattern of post neonatal childhood meningitis in</td>
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<td>Objectives</td>
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<tr>
<td>Rohani MY et al. 1999 [32]</td>
<td>To determine the distribution of serotypes that cause various types of infections in hospitalized patients and to study antibiotic susceptibility patterns</td>
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<tr>
<td>Lim LH et al. 2007 [33]</td>
<td>To identify the clinical syndromes of IPD in Malaysia</td>
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<tr>
<td>Suhaimi M et al. 2007 [37]</td>
<td>To study the effect of Hib vaccines on pneumococcal meningitis at Queen Elizabeth Hospital, Kota Kinabalu, Sabah</td>
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<tr>
<th>Pakistan</th>
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<td>Ghafoor A et al. 1990 [43]</td>
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<td>Mastro TD et al. 1991 [44]</td>
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<td>Rehman A et al. 1996 [42]</td>
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<tr>
<td>Bhutta ZA. 2001 [39]</td>
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<tr>
<td>Nizami SQ et al. 2006 [41]</td>
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<td>Bhutta ZA et al. 2007 [40]</td>
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| Philippines |
### Objectives

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<td>Capeding MRZ et al. 1994 [47]</td>
<td>To determine the etiology of acute lower respiratory infection in children under 5 years old</td>
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<td>Lankinen KS et al. 1994 [48]</td>
<td>To compare the sensitivity of pneumococcal culture with that of antigen detection methods</td>
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<tr>
<td>Lupisan S. 2000 [46]</td>
<td>To investigate the etiology of serious infections in children aged &lt; 5 years admitted to a tertiary care government hospital in Bohol province</td>
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<td>Philippine General Hospital; University of Santo Tomas Hospital; Philippine Children’s Medical Center.</td>
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<td>To determine the etiology of bacterial meningitis</td>
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<td></td>
<td><strong>Survey of bacterial meningitis.</strong></td>
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<tr>
<td>Capeding 2007 [49]</td>
<td>To describe the pneumococcal serotypes seen among Filipino children admitted in a tertiary care center in the Philippines due to infectious diseases</td>
</tr>
<tr>
<td>Carlos C. 2007 [50]</td>
<td>To determine the antimicrobial resistance patterns of common pathogens in 2007</td>
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</table>

### Singapore

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Low S et al. 2007 [51]</td>
<td>To describe the epidemiology of pneumococcal disease based on hospitalization rates for all age groups for the evaluation of prevention and control strategies</td>
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<tr>
<td>Chong CY et al. 2008 [52]</td>
<td>To assess the adequacy of PCV7 and future expanded vaccine</td>
</tr>
</tbody>
</table>
Objectives

formulations in relation to the predominant IPD serotypes; to determine the epidemiology of IPD, antibiotic susceptibility patterns and the morbidity and mortality of children with community-acquired IPD

Sri Lanka


SAPNA. Newsletter. Jan–March 2005 To provide updates on the SAPNA project

[53]


Watanabe H et al. 2007 [54] To determine the status of ARIs caused by S. pneumoniae and H. influenzae in tsunami evacuation camps in Sri Lanka

Taiwan

Siu LK et al. 2002 [56] To understand the epidemiology of invasive S. pneumoniae in Taiwan

Department of Health Statistics; Department of Health, Executive Yuan, Republic of China. 2006 [55] To collect essential information on several areas such as population, economy, education, labor and healthcare among others.

Taiwan Centers for Disease Control and Prevention (CDC). Unpublished data. 2007. To collect information necessary for the notification and control of disease outbreaks, syndromes and communicable diseases
## Objectives

### Thailand

<table>
<thead>
<tr>
<th>Reference</th>
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<tr>
<td>Sunakorn P et al. 1990 [57]</td>
<td>To detect the etiology of severe ARIs in children aged &lt; 5 years and to correlate this with clinical findings</td>
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<tr>
<td>Chotpitayasunondh T. 1994 [59]</td>
<td>To conduct a retrospective study on the etiology and clinical features of bacterial meningitis in children</td>
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<tr>
<td>Ekalaksananan T et al. 2001 [58]</td>
<td>To determine the etiology of ARIs in children &lt; 5 years admitted to Srinagarind Hospital</td>
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<tr>
<td>Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health. Unpublished data. 2006</td>
<td>To collect information on the incidence and distribution of diseases in Thailand</td>
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<tr>
<td>Levine S et al. 2006 [61]</td>
<td>To determine <em>S. pneumoniae</em> carriage prevalence, serotype distribution and antimicrobial resistance patterns among patients with respiratory illness; to summarize national data on invasive pneumococcal isolates</td>
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<tr>
<td>Phongsamart W et al. 2007 [60]</td>
<td>To determine the serotype coverage of PCV7, PCV9, PCV11 and PCV13 among isolates causing IPD in Thai children &lt; 5 years to guide decisions on the use of PCV</td>
</tr>
<tr>
<td>International Emerging Infections Program (IEIP) surveillance network. Unpublished data. 2007</td>
<td>To collect useful information on the burden of vaccine-preventable pneumococcal disease</td>
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</table>

ARI, acute respiratory infection; IPD, invasive pneumococcal disease; PCV7, pneumococcal conjugate vaccine.
Figure 1. Age distribution of IPD in immunocompetent and immunocompromised children in Korea (Lee HJ, unpublished data, 2007).

Figure 2. Case fatality rates in two IPD surveillance studies in Taiwan before and after the introduction of the 7-valent pneumococcal conjugated vaccine (Taiwan CDC 2007), [56].
Figure 3. Overall case fatality rates due to IPD as reported by studies from different ASAP member countries (Hadinegoro, in press), [18, 23, 24, 52].
References


[35] Tee AC. Childhood meningitis at University Hospital, Kuala Lumpur, 1980–89. Dissertation for Master’s Degree in Medicine (Paediatrics), University Malaya, 1993.


[67] GAVI’s PneumoADIP comprehensive report with data. February 2007. Available at: