Community-Acquired Pneumonia in the Asia-Pacific Region

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Abstract

Community-acquired pneumonia (CAP) is an important cause of mortality and morbidity worldwide. Aging population, dense urbanization, and poor access to health care make the Asia-Pacific region vulnerable to CAP. The high incidence of CAP poses a significant health and economic burden in this region. Common etiologic agents in other global regions including *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydophila pneumoniae*, *Staphylococcus aureus*, and respiratory viruses are also the most prevalent pathogens in the Asia-Pacific region. But the higher incidence of *Klebsiella pneumoniae* and the presence of *Burkholderia pseudomallei* are unique to the region. The high prevalence of antimicrobial resistance in *S. pneumoniae* and *M. pneumoniae* has been raising the need for more prudent use of antibiotics. Emergence and spread of community-acquired methicillin-resistant *S. aureus* deserve attention, while the risk has not reached significant level yet in cases of CAP. Given a clinical and socioeconomic importance of CAP, further effort to better understand the epidemiology and impact of CAP is warranted in the Asia-Pacific region.

Keywords
- community-acquired pneumonia
- Asia-Pacific
- epidemiology
- antimicrobial resistance
- socioeconomic impact

The Asia-Pacific region in this article includes East Asia, Southeast Asia, South Asia, and Oceania. Asia-Pacific is home to more than 4.4 billion people, which is "nearly 60 percent of the world's population."[1] While collectively categorized as Asia-Pacific, considerable diversity exists. Seven of the world's 10 most populous countries are located in this region, as well as some of the world's smallest countries. Some have leading economies of the world, while some are struggling to meet the most basic needs of their people. Despite its large heterogeneity, the region shares some distinct characteristics. Population growth rate is declining (0.9% per year), infant mortality rate is still high (124 deaths per 100,000 live births), proportion of older adults are growing (12.1% of population are aged 60 and above), a large population is living in urban areas (48%), and some of the world's largest megacities are located in Asia-Pacific.[1] These characteristics are associated with the high burden of community-acquired pneumonia (CAP) in this region, probably taking considerable toll on its population, economy, and societies.[2] Information on the epidemiology of CAP in this region is limited by multiple hurdles: poor accessibility to health care,[3,4] lower utilization of microbiologic diagnosis,[5] lack of surveillance systems, and considerable heterogeneity among different geographic areas. Aging population, high population density, and high use of antibiotics are likely to result in increased incidence of CAP, in particular by less susceptible pathogens. In this review, we will describe the epidemiology, etiology, antimicrobial resistance, preventive measures, and outcomes of CAP in the Asia-Pacific region.

Epidemiology of CAP in the Asia-Pacific Region

Lack of surveillance in many countries and discrepancies in the surveillance methods make the accurate estimation of the burden of CAP in the region very difficult (►**Table 1**).[6–26]

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Table 1 Incidence of community-acquired pneumonia in the Asia-Pacific region (per 100,000 population unless noted otherwise)

Country	Year	Reference	Population	Incidence	Hospitalization	Mortality	Notes
Australia	1988–1993	Williams et al[6]	All		17 (nonaboriginal urban young adults) and 4,035 (aboriginal rural old adults)		
China	1991–2000	He et al[7]	All			43.9	Mortality surveillance
Indonesia	1998–1999	Sutanto et al[8]	Children (<2 y)	21,000	5,300	3,300	Rural areas showed higher incidence and mortality
Japan	2011–2013	Morimoto et al[9]	Adult (≥15 y)	1,690	530	70	
Japan	2008–2010	Takaki et al[10]	Adult (≥15 y)	960, 4,290 (≥ 75 y)			
New Zealand	2000–2002	Scott et al[11]	Adult (≥15 y)	859			
New Zealand	1999–2000	Chambers et al[12]	Adult (≥18 y)		92		
New Zealand	1993–1996	Grant et al[13]	Children (<15 y)		500		Pacific Islanders (1,400) and Maori (670) have higher incidence compared with Europeans/other (270)
Pakistan	2002–2003	Nizami et al[14]	Children (<5 y)	8,210			
Philippines	2011–2012	Kosai et al[15]	Children (<5 y)	10,500	6,100	90	
South Korea	2002–2005	Kim et al[16]	All		520 (all), 2,030 (≥75 y)		Influenza included
South Korea	2012	Lim et al[17]	All			20.8	
Southeast Asia and Western Pacific	Estimate	Rudan et al[18]	Children (<5 y)	30,000			
Taiwan	1994 (estimate)	Leung et al[19]	All			3.71–6.39%	
Taiwan	1997–2004	Wu et al[20]	Children (<18 y)		1,240	6.7 (<5 y)	
Thailand	2010	Reechaipichitkul et al[21]	Adult (≥15 y)			9.63%	
Thailand	2004–2006	Prapasiri et al[22]	All		199–256	6.9	Radiologically confirmed pneumonia
Thailand	2003–2009	Aungkulanon et al[23]	All			20–25	
Thailand	2002–2003	Olsen et al[24]	All		177–580		
Thailand	1999–2001	Kanlayanaphotporn et al[25]	All	211			
Thailand	2010	Teeratakulpisarn et al[26]	Children (<5 y)			11.29	

Overall incidences of pneumonia and pneumonia-attributed mortality rates were recently estimated from a multicenter prospective surveillance in Japan from 2011 to 2013.[9] The estimated annual incidence rates of adult community-onset pneumonia, hospitalization, and inhospital deaths were 1,690, 530, and 70 per 100,000 person-years, respectively. The overall estimated annual number of adult CAP cases in the entire Japanese population was 1,880,000; importantly, 69.4% were ≥65 years old. A prospective study in one Japanese city (Kochi) from May 2008 to April 2010 cited an incidence of 960 per 100,000 person years; 73.3% of cases were ≥65 years old.[10] More attention was given to the geriatric population in the latter study, in which annual incidence of CAP in older adults (≥75 years) was estimated to be 4,290 per 100,000. An Asian country that showed similar socioeconomic and ethnic characteristics to Japan would be South Korea. Although the exact nationwide overall incidence of CAP in Korea has not been reported, hospitalization rate was reported to be similar (520 per 100,000).[16] This study confirmed the significantly larger burden of CAP in the elderly population by estimating that hospitalization rate in people ≥ 75 years of age was 2,030 per 100,000 population. Several reports have been published on the disease burden of CAP in Thailand, including both urban and rural areas. The hospitalization rate due to CAP was reported to be 177 to 580 per 100,000 people in Thailand, which was lower than those of Japan and South Korea.[22,24] Because these studies were limited by low utilization of chest X-rays and variable access to health care, the estimates might not reflect the whole picture of CAP in Thailand.[24] Reports on the Pacific Island countries are scarce, but two studies from New Zealand reported the overall incidence in adults and hospitalization rate. Estimated incidences of CAP in all adults and those ≥65 years of age in New Zealand were 859 and 1,882 per 100,000, respectively.[11] Another study estimated that pneumonia hospitalization rate was 92 per 100,000.[12] Several studies on the burden of CAP among children in Southeast Asia have also been published. A surveillance in rural villages on Lombok Island, Indonesia, in 1998 to 1999 reported the incidence, hospitalization rate, and mortality among young children (≤2 year) as 21,000, 5,300, and 3,300 per 100,000 child-years, respectively.[8] Another interview survey in the Philippines revealed similar incidence rates: 10,500 cases of pneumonia, 6,100 admissions, and 90 deaths per 100,000 children each year.[15] The burden of CAP was much smaller in Taiwan (1,240 pneumonia cases per 100,000)[20] and New Zealand (500 hospitalizations per 100,000).[13] Rudan et al conducted an estimation of the global incidence of childhood pneumonia, in which the annual incidences in Southeast Asia and Western Pacific regions were estimated to be 36,000 and 22,000 per 100,000 children, respectively.[18] When specific demographic groups were studied for CAP, a larger burden was almost always observed in older adults,[6,7,10,16,22] those residing in rural areas,[6–8,15] and minority ethnicity.[6,13] Most studies on the epidemiology of CAP in the Asia-Pacific region are from either nationwide mortality statistics or surveillance in geographically limited areas. Differences in case definitions and potential underreporting due to limited accessibility to health care undermine the effort to measure the burden of CAP. Further studies on the epidemiology of CAP are warranted in the Asia-Pacific region based on more coordinated plans and resources.

Etiologic Pathogens of CAP in the Asia-Pacific Region

Distribution of etiologic agents of CAP is the most important information for the selection of appropriate antibiotics. It has been known that major identifiable pathogens of CAP include *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp.[27–29] The last three have been referred to as "atypical pathogens," the importance of which has been the subject of considerable debate.[29] Despite the importance of this subject, the majority of the data on the etiology of CAP have been reported from the U.S. and European countries. But, the number of studies from the Asia-Pacific region is recently increasing; they are summarized in ►**Table 2**. The most comprehensive data were reported by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) in 2007.[27] In this study, a total of 955 cases with CAP were collected from seven countries (South Korea, China and Hong Kong SAR, India, Singapore, Vietnam, Taiwan, and the Philippines). *Streptococcus pneumoniae* was the most common isolate, which comprised 29.2% of identified pathogens. Pneumococcus was followed by *Klebsiella pneumoniae* (15.4%), *H. influenzae* (15.1%), *C. pneumoniae* (13.4%), and *M. pneumoniae* (11.0%). The overall distribution of etiologic pathogens from this study was comparable to those from western countries.[30–33] *Streptococcus pneumoniae* was the most frequent pathogen identified in other studies from Japan,[34–38] South Korea,[39,40] Taiwan,[41,42] Australia,[43] and New Zealand.[44] However, the proportion of pneumococcus showed considerable variability, from 10%[37,40,43–45] to 25%.[46] The broad range seen in these studies could be attributed to variable detection rate in addition to the actual difference in the pathogen distribution. With regard to atypical pathogens, some reports from China,[47–49] Taiwan,[42,45] and Thailand[50] reported a relatively more important role of these pathogens in CAP.

Some pathogens are worth attention due to their unique importance in the Asia-Pacific region. *Klebsiella pneumoniae*, which is relatively uncommon in other regions, contributes to larger cases of CAP in Southeast Asia. This is especially evident in studies from Taiwan,[27,45,51] Malaysia,[52,53] Thailand,[54] India,[55] and the Philippines[27] (all >10% of total CAP cases), which showed a stark contrast to East Asian countries (usually ≤5%). Another important pathogen in this region is *Burkholderia pseudomallei*, which is endemic in Southeast Asia and often results in severe infections. It was detected in 13% of hospitalized CAP patients in Malaysia[52] and in 11% of patients with severe CAP in Thailand.[56] In another study from Singapore, which also focused on the patients who required intensive care unit admission, *B. pseudomallei* was isolated from 10% of the cases.[57]

There have been only small number of surveillance studies in which the burden of viral infections in CAP were reported. We could find 16 studies for our review, which are

Table 2 Etiology of CAP in the Asia-Pacific region. Note: Detection rates of pathogens are shown as percentage (%).

Country	Year	Reference	Age	No.[a]	Methods	Virus[b]	Sp	Hi	Kp	Mp	Cp	Mc	Sa	Lp	Bp	Pa	Ab	Flu A	Flu B	RSV	PIV	HRV	AdV	BoV	MPV
Asia[c]	2001–2002	Ngeow et al[5]	All (≥2)	1,374	PCR and serology	No				12.2	4.7			6.6											
Australia	2004–2006	Charles et al[43]	Adult (>18)	885	Culture, PCR, serology	Yes	13.9	5.1		8.8	1.7	0.8	1.2	3.4		1.6		7.7		1.9		5.2			
Australia	2005–2007	Rémond et al[111]	Adult (≥18)	293	Culture	No	13	18.2	3.1			4.2	2.6			1	1								
Cambodia	2007–2009	Vong et al[127]	All (>5)	959	Culture and PCR	Yes	2.2	5.4	2.9				0.5		2.6	2		1.7		2.4		9.1			0.7
China	2001–2003	Huang et al[47]	All (≥2)	389	Culture, PCR, serology	No	3.1	20.6	3.9	10.8	4.4	0.3	1.5	0.5											
China	2002–2004	Song et al[27]	Adult (≥15)	225	Culture and serology	No	9		5																
China	2003–2004	Liu et al[48]	Adult (≥18)	610	Culture and serology	Yes (n = 184)	6.1	5.4	3.8	13.4	4.8	0.8	2.8	2.8		0.8			3.3	1.1			1.6		
China	2004–2005	Liu et al[88]	Adult (≥18)	1,193	Culture and serology	No	8.5	5.2		6.5	4.6			0.1											
China	2006	Zhang et al[49]	All	610	N/A	No	6.1	5.4	3.8	13.4	4.8		2.8	2.8											
China	2009–2013	Wei et al[157]	Children (≤16)	3181	Culture and PCR	Yes	14.4	4.3	3.7									14.9		35	24.9			12.3	
China[d]	2010–2012	Liu et al[158]	Children (≤15)	39,756	IFA	Yes				19.1	0.1			0.4				0.2	4.7	2	1.4		4.8		
China	2010–2012	Wu et al[159]	Children (≤16)	10,435	Serology	Yes				56.9	0.2			1.6				2	35.4	18.9	7.5		4.9		
China	2011–2013	Chen et al[160]	Children (4–14)	1,204	Serology	Yes				40.8	0.3			0.9				0.08	7.06	3.32	4.82		1.08		
India	2002–2004	Song et al[27]	Adult (≥15)	104	Culture and serology	No	10	2	8																
India	2013	Acharya et al[55]	Adult (14–70)	100	Culture	No	31	5	13			8	8			15									
Indonesia	2007–2009	Farida et al[58]	Adult (>13)	148	Culture, PCR, serology	Yes	3		3		1	3	1	3				8	3	1	3	4	1		1
Japan	1994–1997	Ishida et al[34]	Adult (>15)	326	Culture and serology	Yes	23	7.4	4.3	4.9		1.8	2.1	0.6		2.5	0.3	0.9	0.3		0.6				
Japan	1998–2000	Kawai et al[87]	Adult (≥15)	231	Culture and serology	No	9.1	11.6	5	6.6	1.7	1.7	10.4			3.3									
Japan	1998–2003	Miyashita et al[35]	Adult	506	Culture, IFA, serology	No	23.3	11.3	1.6	13.0	7.7	3.2	2.8	1.2		1.6									
Japan	1998–2003	Miyashita et al[36]	Adult (>18)	200	Culture and serology	No	20.5	11	2.5	9.5	7.5	3	5	1		2									
Japan	1999–2000	Saito et al[46]	Adult (17–99)	232	Culture, PCR, serology	Yes	24.6	18.5	1.3	5.2	6.5	2.2	3.4	3.9		0.4		13.4		0.4	0.9		1.2		
Japan	2000–2002	Motomura et al[37]	Adult	124	Culture and serology	No	12.1	8.0		2.4		3.2				2.4									
Japan	2001–2004	Ishida et al[38]	Adult (>15)	349	Culture and serology	No	23.8	6	1.4	11.2	3.4	1.7	1.4	1.4		1.1									
Japan	2011–2013	Morimoto et al[9]	Adult (≥15)	1,772	Culture and PCR	Yes	9	10				6	8					5		4		9			2
Malaysia	1997–1999	Liam et al[113]	Mixed (≥12)	127	Culture and serology	No	5.5	5.5	10.2	3.9			1.6		1.6	3.9									
Malaysia	2002–2003	Loh et al[112]	Mixed (≥12)	80	Culture	No			17.8							2.7	4.1								
Malaysia	2006?	Liam et al[53]	Mixed (≥12)	346	Culture and serology	No	4	3.5	10.7	9	4		4	5.8	0.6	2.9	0.9								
Malaysia	2009–2010	Mustafa et al[52]	Adult (≥15)	46	Culture and PCR	No	21.7	2.1	17.3	6.5	4.3			2.1	13	6.5	2.1								
New Zealand	1999–2000	Laing et al[44]	Adult (>18)	474	Culture and serology	Yes	14	10		3	1	1	2	4		1		7	2	3	2		2		
Philippines	2002–2004	Song et al[27]	Adult (≥15)	55	Culture and serology	No	11	20	11																
Singapore	2002–2004	Song et al[27]	Adult (≥15)	96	Culture and serology	No	6	3																	
Singapore	2006?	Chiang et al[161]	Children (≤16)	1,702	Culture, PCR, serology	Yes	6.6	2.4		20.6		0.2	0.4			0.3		1.5 (A and B)		5.8	1.5	0.7	1.5		
South Korea	2001–2002	Sohn et al[39]	Adult (>15)	126	Culture, PCR, serology	No	13.5	0.8	3.2	6.3	7.1		0.8	2.4		3.2	3.2								
South Korea	2002–2004	Song et al[27]	Adult (≥15)	338	Culture and serology	No	14	1	3																
South Korea	2007–2008	Jeon et al[40]	Elderly (>60)	63	Culture and serology	No	12.0	4.0	7.4	1.1			5.1			2.3									
Taiwan	2001–2002	Lauderdale et al[41]	Adult (>16)	168	Culture and serology	Yes	23.8	4.8	4.8	14.3	7.1		1.8	1.2				6.5		1.2	1.2		1.2		
Taiwan	2001–2002	Yen et al[42]	Adult (≥18)	100	Culture and serology	No	26	9	5	20	13	2	1	3											
Taiwan	2002–2004	Song et al[27]	Adult (≥15)	65	Culture and serology	No	14	2	14																
Taiwan	2007	Wu et al[51]	All	933	Culture	No	5.9	7	24.7				9.7			10.2	5.2								

Table 2 (*Continued*)

Country	Year	Reference	Age	No.[a]	Methods	Virus[b]	Sp	Hi	Kp	Mp	Cp	Mc	Sa	Lp	Bp	Pa	Ab	Flu A	Flu B	RSV	PIV	HRV	AdV	BoV	MPV
Taiwan	2007–2008	Lee et al[45]	Adult (≥15)	156	Culture and serology	No	11.2		11.2	13.1	11.9					6									
Thailand	1998–2001	Wattanathum et al[50]	Adult (>15)	245	Culture and serology	No	18.8	2.0	5.7	15.9	24.5	0.0	2.0	6.5	0.8	0.4	0.8								
Thailand	2001–2002	Reechaipichitkul et al[54]	Adult (≥15)	254	Culture and serology	No	11.4	4.3	10.2	3.9	8.7	0.8	3.5		11	2.4									
Thailand	2001–2002	Prapphal et al[89]	All (≥2)	292	PCR and serology	No				14	3.4			0.4											
Thailand	2005–2010	Hasan et al[162]	Children (<5)	28,543	Culture, PCR, serology	Yes												6.2	2	19.5	9.1	18.7	3.5	12.8	
Vietnam	2002–2004	Song et al[27]	Adult (≥15)	72	Culture and serology	No	11	11	3																
Vietnam	2009–2010	Takahashi et al[59]	Adult (≥15)	154	Culture and PCR	Yes	23	27	2			2	4			3		6	3	1		5	2		

Abbreviations: Ab, *Acinetobacter baumannii*; AdV, adenovirus; BoV, bocavirus; Bp, *Burkholderia pseudomallei*; CAP, community-acquired pneumonia; Cp, *Chlamydophila pneumoniae*; Hi, *Haemophilus influenzae*; HRV, human rhinovirus; IFA, immunofluorescence assay; Kp, *Klebsiella pneumoniae*; Lp, *Legionella pneumophila*; Mc, *Moraxella catarrhalis*; Mp, *Mycoplasma pneumoniae*; MPV, metapneumovirus; N/A, not available; Pa, *Pseudomonas aeruginosa*; PCR, polymerase chain reaction; PIV, parainfluenza virus; RSV, respiratory syncytial virus; Sa, *Staphylococcus aureus*; Sp, *Streptococcus pneumoniae*.

[a]Number of patients included. [b]Inclusion of testing for respiratory virus. [c]Multicenter study including China, South Korea, Taiwan, Thailand, Indonesia, Malaysia, and Singapore. Only atypical pathogens were tested for. [d]Test for *S. pneumoniae* was not performed.

summarized in ►**Table 2**. The prevalence of respiratory virus varied from 1.8 to 21%. Most of the studies used polymerase chain reaction (PCR) for the detection of virus, but serologic tests were applied in some reports. Methods used for the detection seems to result in variable results, as different studies from same countries often showed vastly different detection rates. Proportion of viral pathogens among CAP was only 1.8% in an earlier report from Japan that used serologic test,[34] but virus was identified in 20% among 1,772 patients in a recent study from Japan using PCR.[9] In adult population, influenza A and B viruses seem to predominate, comprising 5 to 15% of pathogens detected including bacteria.[9,41,43,44,46,58,59] Rhinovirus, which is increasingly identified as etiologic agents of CAP in adults, was the second most commonly detected virus (4–9%).[60]

Multiple limitations hinder the effort to elucidate the etiologic agents of CAP, including suboptimal quality of respiratory specimens, difficulty to culture certain species of bacteria, interpretation of commensal bacteria detected in patients with CAP, ambiguous results of serologic tests, and methods for detection of virus. PCR, often performed in multiplex, enabled sensitive and accurate detection of respiratory pathogens, and recent studies using this technique are broadening our understanding of the pathogens causing CAP.[31]

Specific Pathogens of Community-Acquired Pneumonia

There are a couple of specific pathogens of CAP that are unique or notable in the Asia-Pacific region with regard to the incidence, antimicrobial resistance, clinical features, or clinical outcomes.

Streptococcus pneumoniae

The importance of *S. pneumoniae* as a major pathogen causing CAP remains unchallenged in the Asia-Pacific region, as discussed previously. Furthermore, the high prevalence rate of antimicrobial resistance in pneumococci in this region is a very serious threat to public health. Important data on the antimicrobial resistance of *S. pneumoniae* in the Asia-Pacific are summarized in ►**Table 3**. The most prominent resistance issue is macrolide resistance.[61] Two surveillance studies on pneumococcus conducted by ANSORP in the early 2000s revealed that about half of the isolates were resistant to erythromycin.[27,62] Considerable variability does exist between different countries, and resistance rates in China, Korea, Taiwan, and Vietnam exceed 70% with MIC_{90} (minimal inhibitory concentration, MIC, for 90% of the isolates) of >128 mg/L.[62] High resistance rates in East Asian countries were confirmed by Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) study.[63] In this international surveillance study in 40 countries, macrolide-resistant *S. pneumoniae* was most prevalent in Far East countries (China, Japan, South Korea, and Taiwan) with resistance rates ≥ 80%. While Southeast Asian countries were not included in this study, the resistance rate in Australia was comparable to countries in Northern Europe and America at <30%. Some Asian countries are showing the

Table 3 Antimicrobial resistance or nonsusceptibility rates (%) of *Streptococcus pneumoniae* in the Asia-Pacific region

Country	Year	Reference	MIC breakpoint for penicillin (mg/L)	Antibiotic class				
				Penicillin	Amox/clav[a]	Ceftriaxone	Erythromycin	Levofloxacin
ANSORP[b]	2002–2004	Song et al[27]	2	35.1	3.5	7	56.1	0
ANSORP[b]	2008–2009	Kim et al[72]	8/4	0.7/4.6		3.7		
China	1980–2008	Chen et al[163]	2	15.6	3.3	5	81.7	
China[b]	2000–2001	Song et al[62]	2	23.4	7.3	1.8	73.9	
China	2001–2003	Huang et al[47]	2	0			50	0
China	2003–2004	Liu et al[48]	2	3.2	1.6		79.4	0
China[b]	2008–2009	Kim et al[72]	8/4	2.2/13.2		8		
Hong Kong[b]	2000–2001	Song et al[62]	2	43.2	3.6	0	76.8	
Hong Kong[b]	2008–2009	Kim et al[72]	8/4	0/1.5		6.6		
India	1993–2008	Thomas et al[164]	4	2.7			< 20	
India[b]	2000–2001	Song et al[62]	2	0	0	0	1.3	
India[b]	2008–2009	Kim et al[72]	8/4	0/0		0		
Japan	1999–2004	Inoue et al[73]	2	30.9–44.5	0		77.2–81.9	1.0–1.3
Japan	2001–2003	Qin et al[74]	2	22.8		0	80.7	1.8
Japan	2003–2004	Ishida et al[75]	8/4	0/0	0	0.7	83.7	3.5
Japan	2003–2005	Ishiwada et al[165]	2	21.7				
Japan[b]	2008–2009	Kim et al[72]	8/4	0/0		0		
South Korea[b]	2000–2001	Song et al[62]	2	54.8	9.7	3.2	80.6	
South Korea[b]	2008–2009	Kim et al[72]	8/4	0.3/2.2		1.9		
Malaysia	1999–2007	Le et al[166]	2	21.2				
Malaysia[b]	2000–2001	Song et al[62]	2	29.5	0	2.3	34.1	
Malaysia[b]	2008–2009	Kim et al[72]	8/4	0/0		0.7		
Philippines	1994–2000	Sombrero et al[167]	2	0			0.2	
Philippines[b]	2000–2001	Song et al[62]	2	0	0	0	18.2	
Philippines[b]	2008–2009	Kim et al[72]	8/4	0/0		0.9		
Saudi Arabia[b]	2000–2001	Song et al[62]	2	10.3	0	0	10.3	
Singapore[b]	2000–2001	Song et al[62]	2	17.1	0	0	40	
Sri Lanka[b]	2000–2001	Song et al[62]	2	14.3	0	0	16.7	

Table 3 (*Continued*)

Country	Year	Reference	MIC breakpoint for penicillin (mg/L)	Antibiotic class				
				Penicillin	Amox/clav[a]	Ceftriaxone	Erythromycin	Levofloxacin
Sri Lanka[b]	2008–2009	Kim et al[72]	8/4	0/0		0		
Taiwan[b]	2000–2001	Song et al[62]	2	38.6	1.8	0	86	
Taiwan	2000–2001	Lee et al[168]	2	41.9–45.5				
Taiwan	2001–2006	Hsieh et al[76]						1.2–2.5
Taiwan	2004–2006	Hsieh et al[169]	8/4	1.7/10.2	7.8		4.7	
Taiwan	2007	Hsieh et al[76]						4.2
Taiwan[b]	2008–2009	Kim et al[72]	8/4	0/0.4		1.3		
Taiwan	2009–2012	Lee et al[77]	2	39.4		13.8	90.8	1
Thailand	1998–2001	Sangthawan et al[170]	2	4.3		4.3	34.8	
Thailand[b]	2000–2001	Song et al[62]	2	26.9	0	0	36.5	
Thailand[b]	2008–2009	Kim et al[72]	8/4	0/0.5		0		
Vietnam[b]	2000–2001	Song et al[62]	2	71.4	22.2	3.2	92.1	
Vietnam	2007	Hoa et al[171]	8/4	4/36	4/36		70	
Vietnam[b]	2008–2009	Kim et al[72]	8/4	0/0.9		1.8		

Abbreviations: ANSORP, Asian Network for Surveillance of Resistant Pathogens; MIC, minimal inhibitory concentration.
[a]Amoxicillin/clavulanic acid. [b]Multinational surveillance study conducted by ANSORP, including South Korea, China, Taiwan, India, Singapore, Vietnam, and the Philippines.

increasing resistance trend over time. A report from Sri Lanka, in which the resistance rate had been reported to be 16.7% in ANSORP studies in the early 2000s, showed that the resistance rate increased to 60.9% in the late 2000s.[64] Notable exceptions are India and the Philippines, where only <20% of the organisms were reported to be resistant to macrolides in ANSORP studies, although current status should be investigated. Since the macrolide MIC level in pneumococci from some Asian countries is too high to be achieved by increased dose of macrolides, single empiric therapy with macrolides for the treatment of CAP is generally not recommended.[65,66]

High resistance rates of pneumococcus to penicillin had raised concerns in the Asia-Pacific region.[62,67] But after subsequent reports showing comparable clinical outcomes in infections caused by *S. pneumoniae* with MIC ≤ 0.06 mg/L and those with 0.06 to 2 mg/L,[68–70] the penicillin MIC breakpoint for resistance in pneumococcus was revised from 2 to 8 mg/L in nonmeningeal isolates by the Clinical and Laboratory Standards Institute in 2008.[71] Since the MIC breakpoints used for the determination of penicillin resistance varied by studies, we selected the data using penicillin MIC breakpoint of 2 mg/L as resistance in ►**Table 3** to compare the temporal trend of penicillin resistance. Aforementioned ANSORP studies reported that 30 to 35% of the pneumococcus isolates in this region were resistant to penicillin.[27,62] Like macrolide resistance, higher penicillin-resistance rates were observed in East Asian countries, while those in Southeast and South Asian countries were considerably lower. The most comprehensive multinational surveillance study based on revised criteria had been conducted by ANSORP in 2008 to 2009, which revealed that the resistance rate according to the revised MIC breakpoint (8 mg/L) was only 0.7%.[72] It indicates that the resistance of pneumococci to penicillin is not a serious threat, at least in nonmeningeal infections treated with intravenous antibiotics. Fluoroquinolone resistance has been reported to be <5% in most countries.[27,47,48,73–77] The PROTEKT international surveillance study also showed the low resistance rates (<3%) in all countries except Hong Kong (14.3%),[78] which was likely to due to the dissemination of fluoroquinolone-resistant variant of the Spain23F-1 clone.[79] Spread of unrelated resistant clone was also reported from Taiwan.[76]

Widespread vaccination against pneumococci has significantly affected the incidence of pneumococcal diseases, serotype distribution, and antimicrobial resistance. Introduction of the 7- and 13-valent pneumococcal conjugate vaccine (PCV-7 and PCV-13) led to dramatic reduction of pneumococcal infections in the United States. As serotypes included in PCV-7 are often associated with penicillin and multidrug resistance, the incidence of antibiotic-resistant invasive pneumococcal infections has also declined.[80] However, there have been reports of the emergence of pneumococcal infections by nonvaccine types, especially 19A, which is often multidrug-resistant.[81–83] Two recent studies on adults from Japan during 2010 to 2013 reported that PCV-7 serotypes, especially 6B, decreased from 43.3 to 23.8%.[84,85] Some nonvaccine serotypes emerged, but genotypic penicillin resistance rate declined.[84] Nonetheless, the notable emergence of invasive pneumococcal infections caused by 19A was reported in Taiwan, which was associated with reduced susceptibility to β-lactams.[77] Serotype 19A was also the most prominent non-PCV-7 serotype in the latest ANSORP study, comprising 8.2% of isolates, while 52.5% showed PCV-7 serotypes. The majority of serotype 19A isolates were erythromycin-resistant (86.0%) and multidrug-resistant (79.8%).[72] Most prevalent clone among serotype 19A was ST320 (51.1%), which was found in Hong Kong, India, South Korea, Malaysia, Saudi Arabia, and Taiwan.[86] High prevalence of serotype 19A with multidrug resistance, even in countries with low vaccination rate, needs to be carefully evaluated.

Atypical Pathogens: *Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella* species

The most comprehensive study on the role of atypical pathogens in the Asia-Pacific region was reported by Ngeow et al in a multicenter surveillance study on the prevalence of atypical pneumonia in the early 2000s.[5] They used serology and PCR to detect *M. pneumoniae, C. pneumoniae*, and *L. pneumophila* from 1,374 patients in 8 countries (Malaysia, Thailand, China, the Philippines, Taiwan, South Korea, Singapore, and Indonesia). These three atypical pathogens were associated with 23.5% of CAP cases in this study, with *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* detected in 12.2, 4.7, and 6.6% of patients, respectively. The ANSORP study also showed that atypical pathogens account for 25.5% of the cases in which serologic tests were performed.[27] But *C. pneumoniae* (13.4%) and *M. pneumoniae* (11.0%) were detected in the comparable proportion of CAP patients in this study. Studies from individual countries reveal considerable differences in the burden of atypical pathogens within the region. In general, studies from Japan[34,36,37,46,87] and South Korea[39] have reported lower proportion of atypical pathogens in CAP, accounting for less than 10% in CAP cases (►**Table 2**). However, studies from China,[47–49] Taiwan,[42,45] and Thailand[50] showed the larger role of atypical pathogens. In a multicenter prospective study conducted at 12 centers in seven Chinese cities, atypical pathogens accounted for 31.3% of the cases with CAP when fourfold increase in titers of antibodies were defined as serologic evidence of the infection: *M. pneumoniae* (13.4%) was the single most prevalent pathogen, followed by *S. pneumoniae* (6.1%), *H. influenzae* (5.4%), and *C. pneumoniae* (4.8%).[48] *Legionella pneumophila* was detected in only 2.8% of the patients, which is in accordance with other studies in Asia.[5,27] Other studies from China, including one which used PCR, have reported the similar proportion of atypical pathogens (*M. pneumoniae*: 10%; *C. pneumoniae*: 4–5%).[27,49] Another report from Hong Kong on 1,193 adult patients with CAP requiring hospitalization showed 6.5% for *M. pneumoniae*, but still two atypical pathogens accounted for 28% of the patients in whom the etiologic agents were identified.[88] Two studies from Taiwan, which included adult CAP patients who were hospitalized, reported that the serologic evidence of *M. pneumoniae* and *C. pneumoniae* infection was found in 13.1 to 14.3% and in 7.1 to 11.9%, respectively.[41,45] Similar distribution and higher prevalence in mild CAP was also shown in a multicenter, prospective

study from Thailand in 1998 to 2001.[50] A more recent study at seven centers in Bangkok (2001–2002) using both PCR and serology reported comparable results.[89] Despite the existence of many studies on atypical pneumonia in this region, our understanding of the exact role of these pathogens is still inadequate. The diagnosis of CAP caused by atypical pathogens still mostly relies on the serologic tests, which requires serial testing and often yields equivocal results.[49] Further studies using molecular techniques can improve the correct understanding about the epidemiology of atypical pathogens.[90]

The most notable issue concerning *M. pnuemoniae* is the emergence of resistance to macrolides. As *M. pnuemoniae* harbors intrinsic resistance to β-lactams, most guidelines for the treatment of CAP recommend the inclusion of macrolides as empirical treatment regimen when the coverage for atypical pathogens are required.[28,65,66,91,92] But increased use of macrolides resulted in the emergence of erythromycin-resistant *M. pneumoniae* in the Asia-Pacific region. After the first report of macrolide-resistant *M. pneumoniae* in Japan from patients in 2000,[93] Matsuoka et al reported the isolation of 13 erythromycin-resistant strains (17%) among 76 *M. pneumoniae* strains isolated in Japan during 2000 to 2003.[94] All but one isolate harbored a point mutation (A2063G/C) in domain V of 23S rRNA gene, a binding site for macrolides. Another surveillance in Japan during 1976 to 2006 revealed that there were no resistant strains prior to 2000, yet the resistance rates were 14.6 and 21.6% in years 2000 to 2004 and 2005 to 2006, respectively.[95] The resistance rate in Japan increased further to approximately 45% in 2007 to 2008.[96] Macrolide-resistance strains were subsequently reported in China,[97–99] South Korea,[100] and Taiwan.[101] Reports from Beijing[98] and Shanghai[97] revealed remarkable resistance rates of 92% (46/50) and 83% (44/53), respectively. In the latter study, all strains isolated in 2007 and 2008 were resistant to macrolides. A Korean study with 378 isolates during 2000 to 2011 showed a similar picture; there were no resistant strains in 2000, but the resistance rate surged from 2.9% in 2003 to 62.9% in 2011.[100] A recent survey from Hong Kong reported the resistance rate of 47.1% (24/51) in 2014 and showed that the macrolide resistance was associated with increasing resistance in multilocus variable-number tandem-repeat analysis type 4-5-7-2.[102] A report from northern Taiwan showed that 12.3% of *M. pneumoniae* isolates were resistant to macrolides.[101] In contrast, only one strain was resistant among 30 specimens from Sydney, Australia.[103] Previous reports on the macrolide-resistant *M. pneumoniae* have been concentrated in three East Asian countries: Japan, China, and South Korea. The vast majority of macrolide-resistant *M. pneumoniae* strains found in Asia harbor point mutations on A2063 or A2064 in 23S rRNA gene. Mutations on A2063 or A2064 result in a high level of resistance to various macrolides, but do not affect the susceptibility to doxycycline or fluoroquinolones.[96] Information on the current status in other countries within the Asia-Pacific region is not available. Furthermore, the presence of a considerable regional difference in resistance rates within a single country has been reported.[104] Additional studies and enhanced surveillance are urgently warranted to clarify this issue. The clinical course of macrolide-resistant *M. pneumoniae* was reported to be prolonged; the duration of fever was 2 to 2.5 days longer and cough persisted for more than 4 days longer compared to patients with macrolide-susceptible *M. pneumoniae* infection.[101,105–107] Efficacy of macrolide was reduced to 22.7% in cases with resistant strains compared with 91.5% in cases caused by susceptible strains.[106] Treatment with broad-spectrum tetracyclines (minocycline and doxycycline) or fluoroquinolones has been suggested, and two small-scale studies reported that minocycline or doxycycline was superior to fluoroquinolone in terms of the duration of fever after the initiation of treatment.[108,109] Both classes of antibiotics have safety concerns in children (tooth discoloration and joint/cartilage toxicity, respectively), however, in whom *M. pneumoniae* infections are most prevalent. Use of fluoroquinolones is further complicated by its tendency to accelerate the emergence of antimicrobial resistance and the relatively high prevalence of tuberculosis in the region. As *M. pneumoniae* infections are often mild and self-limited, the conservative use of alternative agents other than macrolides only in severe or persistent cases was suggested.[110]

Klebsiella pneumoniae

Klebsiella pneumoniae accounts for approximately 6% of CAP cases in the ANSORP study,[27] while it is infrequently found in the Europe and Americas.[30–33] Even within the Asian-Pacific regions, Australia, Vietnam, and East Asian countries report smaller incidence at $\leq$3%,[35,36,38,39,46–49,59,111] while a recent report from South Korea showed a higher frequency of *K. pneumoniae* in elderly patients.[40] High burden of CAP caused by *K. pneumoniae* has been mostly seen in Taiwan (14–25%),[45,51] Thailand (10.2%),[54] India (13%),[55] the Philippines (11%),[27] and Malaysia (10.2–17.8%).[52,53,112,113] In a worldwide study on *K. pneumoniae* bacteremia, only 6% of community-acquired *K. pneumoniae* bacteremia were caused by CAP in the Europe and Americas.[114] In contrast, CAP was responsible for 29% of *K. pneumoniae* bacteremia in Taiwan, which made CAP the leading cause of bloodstream infection by this pathogen. According to a clinical study from Taiwan,[115] evaluating clinical outcome of bacteremic CAP caused by *K. pneumoniae* (49 patients) and *S. pneumoniae* (44 patients), mortality rate was significantly higher in patients with *K. pneumoniae* pneumonia (55.1 vs. 27.3%). High mortality rate was also reported in another study from Cambodia (37.5%).[116] Among 36 strains of *K. pneumoniae* tested for antimicrobial susceptibility in the 2008 ANSORP study, all but one were susceptible to ceftriaxone.[27] More recent data from Taiwan and Japan also suggest low resistance rate of community-acquired *K. pneumoniae* in this region, but further surveillance is warranted.[115,117]

Burkholderia pseudomallei

Melioidosis, which is caused by *B. pseudomallei*, is an endemic infectious disease in Southeast Asia, Northern Australia, Southern China, and India.[118] Humans are infected by exposure to contaminated soil or surface water.[119] Incubation

period is usually 3 to 14 days, but latency for decades has been reported.[120] Clinical manifestations have a broad spectrum, from asymptomatic infections to fulminant illness leading to death.[121] Approximately half of the patients with melioidosis present with pneumonia, which makes pulmonary infection the most common clinical presentation.[119] Among aforementioned studies, six reported the incidence of pneumonia caused by *B. pseudomallei* (►**Table 2**). Malaysian study that used multiplex PCR for pathogen detection from 46 adult patients reported that *B. pseudomallei* accounted for 13% of CAP.[52] In this study, 83% were positive by PCR alone and only 17% were culture positive. Among 145 patients with CAP from Northern Thailand, *B. pseudomallei* was identified in 11%, which is slightly less frequent than *S. pneumoniae* (11.4%) but more frequent than *K. pneumoniae* (10.3%).[54] The annual incidence of bacteremic melioidosis was reported to be 4.6 and 14.4 cases per 100,000 persons in two Thailand provinces.[122] A study on the etiology of severe CAP in Singapore between 1989 and 1993 revealed that *B. pseudomallei* was identified in 10 cases among 48 patients.[57] The presence of endemic melioidosis has been also reported from Northern Australia,[123–126] Cambodia,[127,128] Hong Kong,[129] India,[130] Taiwan,[131] and Southern China.[132] Melioidosis has been associated with poor outcomes in multiple studies. A retrospective review from Royal Darwin Hospital in Australia reported that its mortality rate in 1989 to 1997 was 92%, although it was reduced to 26% in 1998 to 2013.[133] Mortality rate of 20% was reported from the aforementioned Northern Thailand hospital between 1996 and 2002.[134] Also, in a case series of 11 patients with imported melioidosis from South Korea, overall mortality rate was 36.4%.[135] Ceftazidime, sometimes in combination with cotrimoxazole, has been the treatment of choice during the initial intensive phase.[119] *Burkholderia pseudomallei* is highly susceptible to carbapenems in vitro, and imipenem or meropenem showed comparative outcomes to ceftazidime.[136,137] After 2 to 4 weeks of initial intensive therapy, subsequent antimicrobial therapy for eradication of the bacteria should be followed using the combination of cotrimoxazole, doxycycline, and chloramphenicol for longer than 3 months.[138]

Staphylococcus aureus

Staphylococcus aureus is not a common etiologic agent of CAP, as it accounts for less than 5% of cases.[30,32,33] In the Asia-Pacific region, *S. aureus* has also been found in similar proportion, although there was a report of higher incidence of *S. aureus* in 10.4% of CAP cases in Japan (►**Table 2**).[87] One of the remarkable issues regarding *S. aureus* is the emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) with varying clinical syndromes and different strains during the last decade.[139] Most common presentation of CA-MRSA infections is skin and soft-tissue infection, but CA-MRSA can also cause severe CAP presenting as necrotizing pneumonia.[140–142] Since the emergence of CA-MRSA in Western Australia in the early 1990s,[143] numerous reports on small number of cases have been published from countries

Table 4 Mortality rates of adult patients with CAP in the Asia-Pacific region

Country	Year	Reference	No. of cases	Mortality rate (%)
ANSORP	2002–2004	Song et al[27]	955	7.3
Australia	2004–2006	Charles et al[43]	885	5.6
Australia	2005–2007	Rémond et al[111]	293	1.1
Indonesia	2007–2009	Farida et al[58]	148	30
Japan	1999–2002	Fujiki et al[154]	227	11.3
Japan	2012	Morimoto et al[9]	1,772	8
Malaysia	2002–2003	Loh et al[112]	108	12
New Zealand	1999–2000	Chambers et al[12]	474	6.1
South Korea	2007–2008	Jeon et al[40]	175	5.7
South Korea	2008–2010	Lee et al[153]	693	4.4 (age $\geq$ 65); 0.5 (age 50–65)
South Korea	2009–2011	Kim et al[172]	883	4.5
Taiwan	2001–2002	Lauderdale et al[41]	168	8.3
Taiwan	2007–2008	Lee et al[45]	208	13.9
Thailand	1998–2001	Wattanathum et al[50]	245	17.5
Thailand	2001–2002	Reechaipichitkul et al[54]	254	5.9
Thailand	2002–2003	Olsen et al[24]	777	9
Thailand	2004–2006	Prapasiri et al[22]	4,993	3
Vietnam	2009–2010	Takahashi et al[59]	174	9.8

Abbreviations: ANSORP, Asian Network for Surveillance of Resistant Pathogens; CAP, community-acquired pneumonia.

in the Asia-Pacific region.[144–148] But data on the prevalence of CA-MRSA causing CAP are lacking. A retrospective study from South Korea reported that *S. aureus* was isolated from 11.1% of cases with pathogens identified, and among them, two-thirds (6/9) were MRSA.[40] MRSA accounted for 4.3% of the cases with CAP in a Taiwanese multicenter study.[51] However, both studies did not examine the genotypic and phenotypic characteristics of MRSA isolates. In a report from South Korea that studied the community-onset sequence type 72 MRSA-SCC*mec* type IV infection, the predominant CA-MRSA clone in the country, showed that pneumonia was the focus of infection in 19% of the cases.[149] A multinational study conducted by ANSORP in 2004 to 2006 provided the most comprehensive information on the epidemiology of CA-MRSA in the Asia-Pacific region.[150] This multinational study collected 1,463 *S. aureus* isolates from various community-acquired infections, of which 373 (25.5%) were MRSA. Respiratory infection was the second most common type of infection (8.3%), following skin and soft-tissue infection (66.7%). Albeit more susceptible than hospital-acquired MRSA (HA-MRSA), CA-MRSA isolates from Asian countries also showed considerable resistance to gentamicin (61.2%), ciprofloxacin (52.5%), clindamycin (91.6%), tetracycline (69.3%), and trimethoprim/sulfamethoxazole (31.3%). There have been insufficient data on the exact incidence of CAP caused by CA-MRSA in this region. CA-MRSA pneumonia is often associated with poor clinical outcome, which emphasizes the importance of early appropriate treatment.[151] Therefore, further study on the epidemiology of CA-MRSA pneumonia in the Asia-Pacific region is of critical importance.

Clinical Outcomes and Socioeconomic Burden of CAP in the Asia-Pacific Region

Studies published since 2000 on the mortality caused by CAP in the Asia-Pacific region are summarized in ►**Table 4**. Reported mortality rates varied between 1.1 and 30%, depending on the country, study population, and hospitalization. But with some exceptions, mortality rates were between 5 and 15%, while a recent study showed moderately improved outcomes compared with a previous review.[61] Although it is difficult to draw a conclusion from these limited data, countries with more advanced economy seem to show better outcomes with regard to pneumonia-specific mortality. Older age,[152–154] comorbidities,[27,154] nursing home residence,[27] and poor performance status[152,154] were associated with worse outcome, as in other regions of the world.

A relatively small number of studies on the economic burden of CAP have been performed in the Asia-Pacific region. A multicenter study from Korea over a decade estimated that the mean direct medical cost was US$7,452 per case, with no difference among age and risk groups.[152] In New Zealand, the direct medical cost was estimated at US$636 per episode, which would translate into the national cost of US$16.8 million.[11] The total annual cost, which includes direct and indirect medical cost and loss of productivity, was US$36.6 million. Chen et al conducted a study to evaluate the cost benefits of pneumococcal vaccination and, in the process, estimated the national cost of CAP in the elderly to be US$30 million each year.[155] Another study on the cost of CAP in China reported the median cost for hospitalization to be US $556.50.[156] Because direct and indirect costs caused by the medical condition are determined by multiple socioeconomic factors, direct comparison of the cost between countries is not appropriate. But the published data invariably revealed that the economic burden of CAP is quite significant, especially in countries with limited resources.

Summary

The Asia-Pacific region shows its own landscape of CAP with regard to the incidence, etiologic pathogens, antimicrobial resistance, clinical outcomes, and socioeconomic burden of the disease, reflecting the diversity of the region. Since data on major issues of CAP need to be further collected in many countries in the region, appropriate and continuous surveillance of CAP is strongly warranted given the clinical and socioeconomic importance of the disease.

Conflict of Interest
All authors have nothing to declare.

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