

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*, *Chlamydomphila 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 in-hospital 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*, *Chlamydia 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 Thailand⁵⁰ 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 Philippines²⁷ (all $>10\%$ of total CAP cases), which showed a stark contrast to East Asian countries (usually $\leq 5\%$). 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 Malaysia⁵² 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 ¹¹	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					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	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				15										
Indonesia	2007-2009	Farida et al ⁵⁸	Adult (>13)	148	Culture, PCR, serology	Yes	3	7.4	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						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	Monimoto et al ⁹	Adult (≥15)	1,772	Culture and PCR	Yes	9	10				6	8					5		4					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 ¹²	Mixed (≥12)	80	Culture	No			17.8																	
Malaysia	20067	Liam et al ⁵³	Mixed (≥12)	346	Culture and serology	No	4	3.5	10.7	9	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	20067	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						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	1.8	1.2				6.5		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	Watanatham 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	Reechapichitkul 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 ⁸⁹	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, *Chlamydia 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*.
^aNumber of patients included. ^bInclusion of testing for respiratory virus. ^cMulticenter study including China, South Korea, Taiwan, Thailand, Indonesia, Malaysia, and Singapore. Only atypical pathogens were tested for. ^dTest 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 MIC₉₀ (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.

^aAmoxicillin/clavulanic acid. ^bMultinational 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 \leq 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 be 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*, *Chlamydia 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 Korea³⁹ 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 Thailand⁵⁰ 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. pneumoniae* is the emergence of resistance to macrolides. As *M. pneumoniae* 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 Beijing⁹⁸ and Shanghai⁹⁷ 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 sur-

veillance 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 ≥ 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-SCCmec 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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References

- 2015 Population Data Sheet. United Nations Economic and Social Commission for Asia and the Pacific (UNESCAP). 2015. Available at <http://www.unescap.org/publications/2015-escap-population-data-sheet>. Accessed May 1, 2016
- The global burden of disease: 2004 update. World Health Organization. 2008. Available at http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/. Accessed April 1, 2016
- Jordan HT, Prapasiri P, Areerat P, et al. A comparison of population-based pneumonia surveillance and health-seeking behavior in two provinces in rural Thailand. *Int J Infect Dis* 2009;13(3): 355–361
- Shimouchi A, Huong ND, Hiep H, Co NV. A household survey on morbidity and treatment of acute respiratory infections in communities in Vietnam. *Environ Health Prev Med* 2002;7(4):151–155
- Ngeow YF, Suwanjutha S, Chantarajanariri T, et al. An Asian study on the prevalence of atypical respiratory pathogens in community-acquired pneumonia. *Int J Infect Dis* 2005;9(3): 144–153
- Williams P, Gracey M, Smith P. Hospitalization of aboriginal and non-aboriginal patients for respiratory tract diseases in Western Australia, 1988–1993. *Int J Epidemiol* 1997;26(4):797–805

- 7 He J, Gu D, Wu X, et al. Major causes of death among men and women in China. *N Engl J Med* 2005;353(11):1124–1134
- 8 Sutanto A, Gessner BD, Djilantik I, et al. Acute respiratory illness incidence and death among children under two years of age on Lombok Island, Indonesia. *Am J Trop Med Hyg* 2002;66(2):175–179
- 9 Morimoto K, Suzuki M, Ishifuji T, et al; Adult Pneumonia Study Group-Japan (APSG-J). The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. *PLoS ONE* 2015;10(3):e0122247
- 10 Takaki M, Nakama T, Ishida M, et al. High incidence of community-acquired pneumonia among rapidly aging population in Japan: a prospective hospital-based surveillance. *Jpn J Infect Dis* 2014;67(4):269–275
- 11 Scott G, Scott H, Turley M, Baker M. Economic cost of community-acquired pneumonia in New Zealand adults. *N Z Med J* 2004;117(1196):U933
- 12 Chambers S, Laing R, Murdoch D, et al. Māori have a much higher incidence of community-acquired pneumonia and pneumococcal pneumonia than non-Māori: findings from two New Zealand hospitals. *N Z Med J* 2006;119(1234):U1978
- 13 Grant CC, Scragg R, Tan D, Pati A, Aickin R, Yee RL. Hospitalization for pneumonia in children in Auckland, New Zealand. *J Paediatr Child Health* 1998;34(4):355–359
- 14 Nizami SQ, Bhutta ZA, Hasan R. Incidence of acute respiratory infections in children 2 months to 5 years of age in periurban communities in Karachi, Pakistan. *J Pak Med Assoc* 2006;56(4):163–167
- 15 Kosai H, Tamaki R, Saito M, et al. Incidence and risk factors of childhood pneumonia-like episodes in Biliran Island, Philippines—a community-based study. *PLoS ONE* 2015;10(5):e0125009
- 16 Kim SA, Kilgore PE, Lee SY, Nyambat B, Ki M. Trends in pneumonia and influenza-associated hospitalizations in South Korea, 2002–2005. *J Health Popul Nutr* 2011;29(6):574–582
- 17 Lim D, Ha M, Song I. Trends in the leading causes of death in Korea, 1983–2012. *J Korean Med Sci* 2014;29(12):1597–1603
- 18 Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ* 2008;86(5):408–416
- 19 Leung KK, Tang LY, Chie WC, Lue BH, Lee LT. Mortality trends of elderly people in Taiwan from 1974 to 1994. *Age Ageing* 1999;28(2):199–203
- 20 Wu PS, Chang IS, Tsai FY, et al. Epidemiology and impacts of children hospitalized with pneumonia from 1997 to 2004 in Taiwan. *Pediatr Pulmonol* 2009;44(2):162–166
- 21 Reechaipichitkul W, Thavornpitak Y, Sutra S. Burden of adult pneumonia in Thailand: a nationwide hospital admission data 2010. *J Med Assoc Thai* 2014;97(3):283–292
- 22 Prapasiri P, Jareinpituk S, Keawpan A, et al. Epidemiology of radiographically-confirmed and bacteremic pneumonia in rural Thailand. *Southeast Asian J Trop Med Public Health* 2008;39(4):706–718
- 23 Aungkulanon S, McCarron M, Lertiendumrong J, Olsen SJ, Bundhamcharoen K. Infectious disease mortality rates, Thailand, 1958–2009. *Emerg Infect Dis* 2012;18(11):1794–1801
- 24 Olsen SJ, Laosiritaworn Y, Siasiriwattana S, Chunsuttiwat S, Dowell SF. The incidence of pneumonia in rural Thailand. *Int J Infect Dis* 2006;10(6):439–445
- 25 Kanlayanaphotporn J, Brady MA, Chantate P, et al. Pneumonia surveillance in Thailand: current practice and future needs. *Southeast Asian J Trop Med Public Health* 2004;35(3):711–716
- 26 Teeratakulpisarn J, Uppala R, Thepsuthammarat K, Sutra S. Burden of acute lower respiratory infection in children in Thailand in 2010: have we achieved the national target in under-five morbidity and mortality? *J Med Assoc Thai* 2012;95(Suppl 7):S87–S96
- 27 Song JH, Oh WS, Kang CI, et al; Asian Network for Surveillance of Resistant Pathogens Study Group. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. *Int J Antimicrob Agents* 2008;31(2):107–114
- 28 Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44(Suppl 2):S27–S72
- 29 File TM. Community-acquired pneumonia. *Lancet* 2003;362(9400):1991–2001
- 30 Jain S, Self WH, Wunderink RG, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373(5):415–427
- 31 Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. *Clin Infect Dis* 2016;62(7):817–823
- 32 Cillóniz C, Ewig S, Polverino E, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax* 2011;66(4):340–346
- 33 Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis* 2010;50(2):202–209
- 34 Ishida T, Hashimoto T, Arita M, Ito I, Osawa M. Etiology of community-acquired pneumonia in hospitalized patients: a 3-year prospective study in Japan. *Chest* 1998;114(6):1588–1593
- 35 Miyashita N, Fukano H, Mouri K, et al. Community-acquired pneumonia in Japan: a prospective ambulatory and hospitalized patient study. *J Med Microbiol* 2005;54(Pt 4):395–400
- 36 Miyashita N, Fukano H, Niki Y, Matsushima T, Okimoto N. Etiology of community-acquired pneumonia requiring hospitalization in Japan. *Chest* 2001;119(4):1295–1296
- 37 Motomura K, Masaki H, Terada M, et al. Usefulness of the Japanese Respiratory Society guidelines for community pneumonia: a retrospective analysis of community-acquired pneumonia between 2000 and 2002 in a general hospital. *Respirology* 2005;10(2):208–214
- 38 Ishida T, Hashimoto T, Arita M, Tojo Y, Tachibana H, Jinnai M. A 3-year prospective study of a urinary antigen-detection test for *Streptococcus pneumoniae* in community-acquired pneumonia: utility and clinical impact on the reported etiology. *J Infect Chemother* 2004;10(6):359–363
- 39 Sohn JW, Park SC, Choi YH, et al. Atypical pathogens as etiologic agents in hospitalized patients with community-acquired pneumonia in Korea: a prospective multi-center study. *J Korean Med Sci* 2006;21(4):602–607
- 40 Jeon EJ, Cho SG, Shin JW, et al. The difference in clinical presentations between healthcare-associated and community-acquired pneumonia in university-affiliated hospital in Korea. *Yonsei Med J* 2011;52(2):282–287
- 41 Lauderdale TL, Chang FY, Ben RJ, et al. Etiology of community acquired pneumonia among adult patients requiring hospitalization in Taiwan. *Respir Med* 2005;99(9):1079–1086
- 42 Yen MY, Hu BS, Chen YS, et al. A prospective etiologic study of community-acquired pneumonia in Taiwan. *J Formos Med Assoc* 2005;104(10):724–730
- 43 Charles PG, Whitby M, Fuller AJ, et al; Australian CAP Study Collaboration. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. *Clin Infect Dis* 2008;46(10):1513–1521
- 44 Laing R, Slater W, Coles C, et al. Community-acquired pneumonia in Christchurch and Waikato 1999–2000: microbiology and epidemiology. *N Z Med J* 2001;114(1143):488–492
- 45 Lee YT, Chen SC, Chan KC, Wu TC, Tsao SM, Chan CH. Impact of infectious etiology on the outcome of Taiwanese patients hospitalized with community acquired pneumonia. *J Infect Dev Ctries* 2013;7(2):116–124

- 46 Saito A, Kohno S, Matsushima T, et al; Study Group. Prospective multicenter study of the causative organisms of community-acquired pneumonia in adults in Japan. *J Infect Chemother* 2006; 12(2):63–69
- 47 Huang HH, Zhang YY, Xiu QY, et al. Community-acquired pneumonia in Shanghai, China: microbial etiology and implications for empirical therapy in a prospective study of 389 patients. *Eur J Clin Microbiol Infect Dis* 2006;25(6):369–374
- 48 Liu Y, Chen M, Zhao T, et al. Causative agent distribution and antibiotic therapy assessment among adult patients with community acquired pneumonia in Chinese urban population. *BMC Infect Dis* 2009;9:31
- 49 Zhang X, Wang R, Di X, Liu B, Liu Y. Different microbiological and clinical aspects of lower respiratory tract infections between China and European/American countries. *J Thorac Dis* 2014;6(2): 134–142
- 50 Wattanathum A, Chaoprasong C, Nunthapisud P, et al. Community-acquired pneumonia in Southeast Asia: the microbial differences between ambulatory and hospitalized patients. *Chest* 2003;123(5):1512–1519
- 51 Wu CL, Ku SC, Yang KY, et al. Antimicrobial drug-resistant microbes associated with hospitalized community-acquired and healthcare-associated pneumonia: a multi-center study in Taiwan. *J Formos Med Assoc* 2013;112(1):31–40
- 52 Mustafa MI, Al-Marzooq F, How SH, Kuan YC, Ng TH. The use of multiplex real-time PCR improves the detection of the bacterial etiology of community acquired pneumonia. *Trop Biomed* 2011; 28(3):531–544
- 53 Liam CK, Pang YK, Poosparajah S. Pulmonary tuberculosis presenting as community-acquired pneumonia. *Respirology* 2006; 11(6):786–792
- 54 Reechaipichitkul W, Lulitanond V, Tantiwong P, Saelee R, Pisprasert V. Etiologies and treatment outcomes in patients hospitalized with community-acquired pneumonia (CAP) at Srinagarind Hospital, Khon Kaen, Thailand. *Southeast Asian J Trop Med Public Health* 2005;36(1):156–161
- 55 Acharya VK, Padyana M, B. U, R. A, Acharya PR, Juneja DJ. Microbiological profile and drug sensitivity pattern among community acquired pneumonia patients in tertiary care centre in Mangalore, Coastal Karnataka, India. *J Clin Diagn Res* 2014;8(6): MC04–MC06
- 56 Reechaipichitkul W, Tantiwong P. Clinical features of community-acquired pneumonia treated at Srinagarind Hospital, Khon Kaen, Thailand. *Southeast Asian J Trop Med Public Health* 2002;33(2): 355–361
- 57 Tan YK, Khoo KL, Chin SP, Ong YY. Aetiology and outcome of severe community-acquired pneumonia in Singapore. *Eur Respir J* 1998;12(1):113–115
- 58 Farida H, Gasem MH, Suryanto A, et al. Viruses and Gram-negative bacilli dominate the etiology of community-acquired pneumonia in Indonesia, a cohort study. *Int J Infect Dis* 2015; 38:101–107
- 59 Takahashi K, Suzuki M, Minh N, et al. The incidence and aetiology of hospitalised community-acquired pneumonia among Vietnamese adults: a prospective surveillance in Central Vietnam. *BMC Infect Dis* 2013;13:296
- 60 Self WH, Williams DJ, Zhu Y, et al. Respiratory viral detection in children and adults: comparing asymptomatic controls and patients with community-acquired pneumonia. *J Infect Dis* 2016;213(4):584–591
- 61 Song JH, Thamlikitkul V, Hsueh PR. Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. *Int J Antimicrob Agents* 2011;38(2):108–117
- 62 Song JH, Jung SI, Ko KS, et al. High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP study). *Antimicrob Agents Chemother* 2004; 48(6):2101–2107
- 63 Felmingham D, Cantón R, Jenkins SG. Regional trends in beta-lactam, macrolide, fluoroquinolone and telithromycin resistance among *Streptococcus pneumoniae* isolates 2001–2004. *J Infect* 2007;55(2):111–118
- 64 Batuwanthudawe R, Karunaratne K, Dassanayake M, et al. Surveillance of invasive pneumococcal disease in Colombo, Sri Lanka. *Clin Infect Dis* 2009;48(Suppl 2):S136–S140
- 65 Song J-H, Jung K-S. Treatment guidelines for community-acquired pneumonia in Korea: an evidence-based approach to appropriate antimicrobial therapy. *J Korean Med Assoc* 2010;53:20–42
- 66 Miyashita N, Matsushima T, Oka M; Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. *Intern Med* 2006;45(7):419–428
- 67 Kim SN, Kim SW, Choi IH, Pyo SN, Rhee DK. High incidence of multidrug-resistant *Streptococcus pneumoniae* in South Korea. *Microb Drug Resist* 1996;2(4):401–406
- 68 Song JH, Jung SI, Ki HK, et al; Asian Network for Surveillance of Resistant Pathogens Study Group. Clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries: a study by the Asian Network for Surveillance of Resistant Pathogens. *Clin Infect Dis* 2004;38(11):1570–1578
- 69 Yanagihara K, Otsu Y, Ohno H, et al. Clinical characteristics of pneumonia caused by penicillin resistant and sensitive *Streptococcus pneumoniae* in Japan. *Intern Med* 2004;43(11):1029–1033
- 70 Reechaipichitkul W, Assawasanti K, Chaimanee P. Risk factors and clinical outcomes of penicillin resistant *S. pneumoniae* community-acquired pneumonia in Khon Kaen, Thailand. *Southeast Asian J Trop Med Public Health* 2006;37(2):320–326
- 71 Centers for Disease Control and Prevention (CDC). Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*—United States, 2006–2007. *MMWR Morb Mortal Wkly Rep* 2008;57(50):1353–1355
- 72 Kim SH, Song JH, Chung DR, et al; ANSORP Study Group. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob Agents Chemother* 2012;56(3):1418–1426
- 73 Inoue M, Farrell DJ, Kaneko K, et al. Antimicrobial susceptibility of respiratory tract pathogens in Japan during PROTEKT years 1–5 (1999–2004). *Microb Drug Resist* 2008;14(2):109–117
- 74 Qin L, Watanabe H, Yoshimine H, et al. Antimicrobial susceptibility and serotype distribution of *Streptococcus pneumoniae* isolated from patients with community-acquired pneumonia and molecular analysis of multidrug-resistant serotype 19F and 23F strains in Japan. *Epidemiol Infect* 2006;134(6):1188–1194
- 75 Ishida T, Maniwa K, Kagioka H, et al. Antimicrobial susceptibilities of *Streptococcus pneumoniae* isolated from adult patients with community-acquired pneumonia in Japan. *Respirology* 2008; 13(2):240–246
- 76 Hsieh YC, Chang LY, Huang YC, Lin HC, Huang LM, Hsueh PR. Circulation of international clones of levofloxacin non-susceptible *Streptococcus pneumoniae* in Taiwan. *Clin Microbiol Infect* 2010;16(7):973–978
- 77 Lee MR, Chen CM, Chuang TY, Huang YT, Hsueh PR. Capsular serotypes and antimicrobial susceptibilities of *Streptococcus pneumoniae* causing invasive pneumococcal disease from 2009–2012 with an emphasis on serotype 19A in bacteraemic pneumonia and empyema and β -lactam resistance. *Int J Antimicrob Agents* 2013;42(5):395–402
- 78 Canton R, Morosini M, Enright MC, Morrissey I. Worldwide incidence, molecular epidemiology and mutations implicated in fluoroquinolone-resistant *Streptococcus pneumoniae*: data from the global PROTEKT surveillance programme. *J Antimicrob Chemother* 2003;52(6):944–952
- 79 Ho PL, Yung RW, Tsang DN, et al. Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: results of a

- Hong Kong multicentre study in 2000. *J Antimicrob Chemother* 2001;48(5):659–665
- 80 Kyaw MH, Lynfield R, Schaffner W, et al; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med* 2006;354(14):1455–1463
 - 81 Jacobs MR, Good CE, Bajaksouzian S, Windau AR. Emergence of *Streptococcus pneumoniae* serotypes 19A, 6C, and 22F and serogroup 15 in Cleveland, Ohio, in relation to introduction of the protein-conjugated pneumococcal vaccine. *Clin Infect Dis* 2008;47(11):1388–1395
 - 82 Pelton SI, Huot H, Finkelstein JA, et al. Emergence of 19A as virulent and multidrug resistant pneumococcus in Massachusetts following universal immunization of infants with pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2007;26(6):468–472
 - 83 Gertz RE Jr, Li Z, Pimenta FC, et al; Active Bacterial Core Surveillance Team. Increased penicillin nonsusceptibility of nonvaccine-serotype invasive pneumococci other than serotypes 19A and 6A in post-7-valent conjugate vaccine era. *J Infect Dis* 2010;201(5):770–775
 - 84 Ubukata K, Chiba N, Hanada S, et al; Invasive Pneumococcal Diseases Surveillance Study Group. Serotype changes and drug resistance in invasive pneumococcal diseases in adults after vaccinations in children, Japan, 2010–2013. *Emerg Infect Dis* 2015;21(11):1956–1965
 - 85 Akata K, Chang B, Yatera K, et al. Distribution and annual changes in *Streptococcus pneumoniae* serotypes in adult Japanese patients with pneumonia. *J Infect Chemother* 2015;21(10):723–728
 - 86 Shin J, Baek JY, Kim SH, Song JH, Ko KS. Predominance of ST320 among *Streptococcus pneumoniae* serotype 19A isolates from 10 Asian countries. *J Antimicrob Chemother* 2011;66(5):1001–1004
 - 87 Kawai S, Ochi M, Nakagawa T, Goto H. Antimicrobial therapy in community-acquired pneumonia among emergency patients in a university hospital in Japan. *J Infect Chemother* 2004;10(6):352–358
 - 88 Lui G, Ip M, Lee N, et al. Role of 'atypical pathogens' among adult hospitalized patients with community-acquired pneumonia. *Respirology* 2009;14(8):1098–1105
 - 89 Prapphal N, Suwanjutha S, Durongkaveroj P, et al. Prevalence and clinical presentations of atypical pathogens infection in community acquired pneumonia in Thailand. *J Med Assoc Thai* 2006;89(9):1412–1419
 - 90 Thurman KA, Walter ND, Schwartz SB, et al. Comparison of laboratory diagnostic procedures for detection of *Mycoplasma pneumoniae* in community outbreaks. *Clin Infect Dis* 2009;48(9):1244–1249
 - 91 Lim WS, Baudouin SV, George RC, et al; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009;64(Suppl 3):iii1–iii55
 - 92 Infectious Diseases Society of Taiwan; Taiwan Society of Pulmonary and Critical Medicine; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines. Guidelines on antimicrobial therapy of pneumonia in adults in Taiwan, revised 2006. *J Microbiol Immunol Infect* 2007;40(3):279–283
 - 93 Okazaki N, Narita M, Yamada S, et al. Characteristics of macrolide-resistant *Mycoplasma pneumoniae* strains isolated from patients and induced with erythromycin in vitro. *Microbiol Immunol* 2001;45(8):617–620
 - 94 Matsuoka M, Narita M, Okazaki N, et al. Characterization and molecular analysis of macrolide-resistant *Mycoplasma pneumoniae* clinical isolates obtained in Japan. *Antimicrob Agents Chemother* 2004;48(12):4624–4630
 - 95 Okazaki N, Ohya H, Sasaki T. *Mycoplasma pneumoniae* isolated from patients with respiratory infection in Kanagawa Prefecture in 1976–2006: emergence of macrolide-resistant strains. *Jpn J Infect Dis* 2007;60(5):325–326
 - 96 Morozumi M, Takahashi T, Ubukata K. Macrolide-resistant *Mycoplasma pneumoniae*: characteristics of isolates and clinical aspects of community-acquired pneumonia. *J Infect Chemother* 2010;16(2):78–86
 - 97 Liu Y, Ye X, Zhang H, et al. Antimicrobial susceptibility of *Mycoplasma pneumoniae* isolates and molecular analysis of macrolide-resistant strains from Shanghai, China. *Antimicrob Agents Chemother* 2009;53(5):2160–2162
 - 98 Xin D, Mi Z, Han X, et al. Molecular mechanisms of macrolide resistance in clinical isolates of *Mycoplasma pneumoniae* from China. *Antimicrob Agents Chemother* 2009;53(5):2158–2159
 - 99 Cao B, Zhao CJ, Yin YD, et al. High prevalence of macrolide resistance in *Mycoplasma pneumoniae* isolates from adult and adolescent patients with respiratory tract infection in China. *Clin Infect Dis* 2010;51(2):189–194
 - 100 Hong KB, Choi EH, Lee HJ, et al. Macrolide resistance of *Mycoplasma pneumoniae*, South Korea, 2000–2011. *Emerg Infect Dis* 2013;19(8):1281–1284
 - 101 Wu HM, Wong KS, Huang YC, et al. Macrolide-resistant *Mycoplasma pneumoniae* in children in Taiwan. *J Infect Chemother* 2013;19(4):782–786
 - 102 Ho PL, Law PY, Chan BW, et al. Emergence of macrolide-resistant *Mycoplasma pneumoniae* in Hong Kong is linked to increasing macrolide resistance in multilocus variable-number tandem-repeat analysis type 4-5-7-2. *J Clin Microbiol* 2015;53(11):3560–3564
 - 103 Xue G, Wang Q, Yan C, et al. Molecular characterizations of PCR-positive *Mycoplasma pneumoniae* specimens collected from Australia and China. *J Clin Microbiol* 2014;52(5):1478–1482
 - 104 Ishiguro N, Koseki N, Kaiho M, et al. Regional Differences in Prevalence of Macrolide Resistance among Pediatric *Mycoplasma pneumoniae* Infections in Hokkaido, Japan. *Jpn J Infect Dis* 2015;69(3):186–190
 - 105 Suzuki S, Yamazaki T, Narita M, et al. Clinical evaluation of macrolide-resistant *Mycoplasma pneumoniae*. *Antimicrob Agents Chemother* 2006;50(2):709–712
 - 106 Matsubara K, Morozumi M, Okada T, et al. A comparative clinical study of macrolide-sensitive and macrolide-resistant *Mycoplasma pneumoniae* infections in pediatric patients. *J Infect Chemother* 2009;15(6):380–383
 - 107 Ma Z, Zheng Y, Deng J, Ma X, Liu H. Characterization of macrolide resistance of *Mycoplasma pneumoniae* in children in Shenzhen, China. *Pediatr Pulmonol* 2014;49(7):695–700
 - 108 Okada T, Morozumi M, Tajima T, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children. *Clin Infect Dis* 2012;55(12):1642–1649
 - 109 Kawai Y, Miyashita N, Kubo M, et al. Therapeutic efficacy of macrolides, minocycline, and tosufloxacin against macrolide-resistant *Mycoplasma pneumoniae* pneumonia in pediatric patients. *Antimicrob Agents Chemother* 2013;57(5):2252–2258
 - 110 Principi N, Esposito S. Macrolide-resistant *Mycoplasma pneumoniae*: its role in respiratory infection. *J Antimicrob Chemother* 2013;68(3):506–511
 - 111 Rémond MG, Ralph AP, Brady SJ, Martin J, Tikoff E, Maguire GP. Community-acquired pneumonia in the central desert and north-western tropics of Australia. *Intern Med J* 2010;40(1):37–44
 - 112 Loh LC, Khoo SK, Quah SY, et al. Adult community-acquired pneumonia in Malaysia: prediction of mortality from severity assessment on admission. *Respirology* 2004;9(3):379–386
 - 113 Liam CK, Lim KH, Wong CM. Community-acquired pneumonia in patients requiring hospitalization. *Respirology* 2001;6(3):259–264
 - 114 Ko WC, Paterson DL, Sagnimeni AJ, et al. Community-acquired *Klebsiella pneumoniae* bacteremia: global differences in clinical patterns. *Emerg Infect Dis* 2002;8(2):160–166

- 115 Lin YT, Jeng YY, Chen TL, Fung CP. Bacteremic community-acquired pneumonia due to *Klebsiella pneumoniae*: clinical and microbiological characteristics in Taiwan, 2001–2008. *BMC Infect Dis* 2010;10:307
- 116 Ramaert B, Goyet S, Beauté J, et al. *Klebsiella pneumoniae* related community-acquired acute lower respiratory infections in Cambodia: clinical characteristics and treatment. *BMC Infect Dis* 2012;12:3
- 117 Ito R, Shindo Y, Kobayashi D, et al. Molecular epidemiological characteristics of *Klebsiella pneumoniae* associated with bacteremia among patients with pneumonia. *J Clin Microbiol* 2015; 53(3):879–886
- 118 Tsang KW, File TM Jr. Respiratory infections unique to Asia. *Respirology* 2008;13(7):937–949
- 119 Currie BJ. Melioidosis: an important cause of pneumonia in residents of and travellers returned from endemic regions. *Eur Respir J* 2003;22(3):542–550
- 120 Currie BJ, Ward L, Cheng AC. The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20 year Darwin prospective study. *PLoS Negl Trop Dis* 2010;4(11):e900
- 121 Gibney KB, Cheng AC, Currie BJ. Cutaneous melioidosis in the tropical top end of Australia: a prospective study and review of the literature. *Clin Infect Dis* 2008;47(5):603–609
- 122 Bhengsi S, Lertiendumrong J, Baggett HC, et al. Economic burden of bacteremic melioidosis in eastern and northeastern, Thailand. *Am J Trop Med Hyg* 2013;89(2):369–373
- 123 Currie B, Howard D, Nguyen VT, Withnall K, Merianos A. The 1990–1991 outbreak of melioidosis in the Northern Territory of Australia: clinical aspects. *Southeast Asian J Trop Med Public Health* 1993;24(3):436–443
- 124 Scott IA, Bell AM, Staines DR. Fatal human melioidosis in south-eastern Queensland. *Med J Aust* 1997;166(4):197–199
- 125 Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical northern Australia: a 10-year prospective study and review of the literature. *Clin Infect Dis* 2000;31(4):981–986
- 126 Currie BJ, Fisher DA, Howard DM, et al. The epidemiology of melioidosis in Australia and Papua New Guinea. *Acta Trop* 2000; 74(2–3):121–127
- 127 Vong S, Guillard B, Borand L, et al. Acute lower respiratory infections in ≥ 5 year-old hospitalized patients in Cambodia, a low-income tropical country: clinical characteristics and pathogenic etiology. *BMC Infect Dis* 2013;13:97
- 128 Ramaert B, Beauté J, Borand L, et al. Pulmonary melioidosis in Cambodia: a prospective study. *BMC Infect Dis* 2011;11:126
- 129 So SY, Chau PY, Leung YK, Lam WK. First report of septicaemic melioidosis in Hong Kong. *Trans R Soc Trop Med Hyg* 1984;78(4): 456–459
- 130 Vidyalakshmi K, Lipika S, Vishal S, Damodar S, Chakrapani M. Emerging clinico-epidemiological trends in melioidosis: analysis of 95 cases from western coastal India. *Int J Infect Dis* 2012;16(7): e491–e497
- 131 Chou DW, Chung KM, Chen CH, Cheung BM. Bacteremic melioidosis in southern Taiwan: clinical characteristics and outcome. *J Formos Med Assoc* 2007;106(12):1013–1022
- 132 Fang Y, Chen H, Li YL, Li Q, Ye ZJ, Mao XH. Melioidosis in Hainan, China: a retrospective study. *Trans R Soc Trop Med Hyg* 2015; 109(10):636–642
- 133 Stephens DP, Thomas JH, Ward LM, Currie BJ. Melioidosis causing critical illness: a review of 24 years of experience from the Royal Darwin Hospital ICU. *Crit Care Med* 2016; 44(8):1500–1505
- 134 Reechaipichitkul W. Clinical manifestation of pulmonary melioidosis in adults. *Southeast Asian J Trop Med Public Health* 2004; 35(3):664–669
- 135 Kim SW, Kwon GY, Kim B, Kwon D, Shin J, Bae GR. Imported melioidosis in South Korea: a case series with a literature review. *Osong Public Health Res Perspect* 2015;6(6):363–368
- 136 Simpson AJ, Suputtamongkol Y, Smith MD, et al. Comparison of imipenem and ceftazidime as therapy for severe melioidosis. *Clin Infect Dis* 1999;29(2):381–387
- 137 Cheng AC, Fisher DA, Anstey NM, Stephens DP, Jacups SP, Currie BJ. Outcomes of patients with melioidosis treated with meropenem. *Antimicrob Agents Chemother* 2004;48(5):1763–1765
- 138 Samuel M, Ti TY. Interventions for treating melioidosis. *Cochrane Database Syst Rev* 2002;(4):CD001263
- 139 Chuang YY, Huang YC. Molecular epidemiology of community-associated methicillin-resistant *Staphylococcus aureus* in Asia. *Lancet Infect Dis* 2013;13(8):698–708
- 140 Francis JS, Doherty MC, Lopatin U, et al. Severe community-onset pneumonia in healthy adults caused by methicillin-resistant *Staphylococcus aureus* carrying the Panton-Valentine leukocidin genes. *Clin Infect Dis* 2005;40(1):100–107
- 141 Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet* 2002;359(9308):753–759
- 142 Rubinstein E, Kollef MH, Nathwani D. Pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2008;46(Suppl 5):S378–S385
- 143 Riley TV, Rouse IL. Methicillin-resistant *Staphylococcus aureus* in Western Australia, 1983–1992. *J Hosp Infect* 1995;29(3):177–188
- 144 Chua AP, Lee KH. Fatal bacteraemic pneumonia due to community-acquired methicillin-resistant *Staphylococcus aureus*. *Singapore Med J* 2006;47(6):546–548
- 145 Chen CJ, Su LH, Chiu CH, et al. Clinical features and molecular characteristics of invasive community-acquired methicillin-resistant *Staphylococcus aureus* infections in Taiwanese children. *Diagn Microbiol Infect Dis* 2007;59(3):287–293
- 146 Ito T, Iijima M, Fukushima T, et al. Pediatric pneumonia death caused by community-acquired methicillin-resistant *Staphylococcus aureus*, Japan. *Emerg Infect Dis* 2008;14(8):1312–1314
- 147 Geng W, Yang Y, Wu D, et al. Community-acquired, methicillin-resistant *Staphylococcus aureus* isolated from children with community-onset pneumonia in China. *Pediatr Pulmonol* 2010; 45(4):387–394
- 148 Sohn KM, Chung DR, Baek JY, et al. Post-influenza pneumonia caused by the USA300 community-associated methicillin-resistant *Staphylococcus aureus* in Korea. *J Korean Med Sci* 2012;27(3): 313–316
- 149 Joo EJ, Chung DR, Ha YE, et al. Clinical predictors of community-genotype ST72-methicillin-resistant *Staphylococcus aureus*-SCCmec type IV in patients with community-onset *S. aureus* infection. *J Antimicrob Chemother* 2012;67(7):1755–1759
- 150 Song JH, Hsueh PR, Chung DR, et al; ANSORP Study Group. Spread of methicillin-resistant *Staphylococcus aureus* between the community and the hospitals in Asian countries: an ANSORP study. *J Antimicrob Chemother* 2011;66(5):1061–1069
- 151 Boussaud V, Parrot A, Mayaud C, et al. Life-threatening hemoptysis in adults with community-acquired pneumonia due to Panton-Valentine leukocidin-secreting *Staphylococcus aureus*. *Intensive Care Med* 2003;29(10):1840–1843
- 152 Song JY, Choi JY, Lee JS, et al. Clinical and economic burden of invasive pneumococcal disease in adults: a multicenter hospital-based study. *BMC Infect Dis* 2013;13:202
- 153 Lee JY, Yoo CG, Kim HJ, Jung KS, Yoo KH. Disease burden of pneumonia in Korean adults aged over 50 years stratified by age and underlying diseases. *Korean J Intern Med* 2014;29(6): 764–773
- 154 Fujiki R, Kawayama T, Ueyama T, Ichiki M, Aizawa H. The risk factors for mortality of community-acquired pneumonia in Japan. *J Infect Chemother* 2007;13(3):157–165
- 155 Chen YH, Yang GY, Loh CH, et al. Cost benefits of targeting the pneumococcal vaccination program to the elderly population in Taiwan. *Am J Infect Control* 2006;34(9):597–599

- 156 Zhou QT, He B, Zhu H. Potential for cost-savings in the care of hospitalized low-risk community-acquired pneumonia patients in China. *Value Health* 2009;12(1):40–46
- 157 Wei L, Liu W, Zhang XA, et al. Detection of viral and bacterial pathogens in hospitalized children with acute respiratory illnesses, Chongqing, 2009–2013. *Medicine (Baltimore)* 2015; 94(16):e742
- 158 Liu J, Ai H, Xiong Y, et al. Prevalence and correlation of infectious agents in hospitalized children with acute respiratory tract infections in Central China. *PLoS ONE* 2015;10(3):e0119170
- 159 Wu Z, Li Y, Gu J, Zheng H, Tong Y, Wu Q. Detection of viruses and atypical bacteria associated with acute respiratory infection of children in Hubei, China. *Respirology* 2014;19(2):218–224
- 160 Chen K, Jia R, Li L, Yang C, Shi Y. The aetiology of community associated pneumonia in children in Nanjing, China and aetiological patterns associated with age and season. *BMC Public Health* 2015;15:113
- 161 Chiang WC, Teoh OH, Chong CY, Goh A, Tang JP, Chay OM. Epidemiology, clinical characteristics and antimicrobial resistance patterns of community-acquired pneumonia in 1702 hospitalized children in Singapore. *Respirology* 2007;12(2):254–261
- 162 Hasan R, Rhodes J, Thamthitawat S, et al. Incidence and etiology of acute lower respiratory tract infections in hospitalized children younger than 5 years in rural Thailand. *Pediatr Infect Dis J* 2014; 33(2):e45–e52
- 163 Chen Y, Deng W, Wang SM, et al. Burden of pneumonia and meningitis caused by *Streptococcus pneumoniae* in China among children under 5 years of age: a systematic literature review. *PLoS ONE* 2011;6(11):e27333
- 164 Thomas K, Mukkai Kesavan L, Veeraraghavan B, et al; IBIS Study Group IndiaCLEN Network. Invasive pneumococcal disease associated with high case fatality in India. *J Clin Epidemiol* 2013; 66(1):36–43
- 165 Ishiwada N, Kurosaki T, Terashima I, Kohno Y. The incidence of pediatric invasive pneumococcal disease in Chiba prefecture, Japan (2003–2005). *J Infect* 2008;57(6):455–458
- 166 Le CF, Palanisamy NK, Mohd Yusof MY, Sekaran SD. Capsular serotype and antibiotic resistance of *Streptococcus pneumoniae* isolates in Malaysia. *PLoS ONE* 2011;6(5):e19547
- 167 Sombrero L, Nissinen A, Esparar G, Lindgren M, Siira L, Viro-lainen A; ARIVAC consortium. Low incidence of antibiotic resistance among invasive and nasopharyngeal isolates of *Streptococcus pneumoniae* from children in rural Philippines between 1994 and 2000. *Eur J Clin Microbiol Infect Dis* 2008; 27(10):929–935
- 168 Lee CY, Chiu CH, Huang YC, et al. Invasive pneumococcal infections: a clinical and microbiological analysis of 53 patients in Taiwan. *Clin Microbiol Infect* 2003;9(7):614–618
- 169 Hsieh YC, Huang YC, Lin HC, et al. Characterization of invasive isolates of *Streptococcus pneumoniae* among Taiwanese children. *Clin Microbiol Infect* 2009;15(11):991–996
- 170 Sangthawan P, Chantaratchada S, Chanthadisai N, Wattanatham A. Prevalence and clinical significance of community-acquired penicillin-resistant pneumococcal pneumonia in Thailand. *Respirology* 2003;8(2):208–212
- 171 Hoa NQ, Trung NV, Larsson M, et al. Decreased *Streptococcus pneumoniae* susceptibility to oral antibiotics among children in rural Vietnam: a community study. *BMC Infect Dis* 2010;10:85
- 172 Kim HI, Kim SW, Chang HH, et al. Mortality of community-acquired pneumonia in Korea: assessed with the pneumonia severity index and the CURB-65 score. *J Korean Med Sci* 2013; 28(9):1276–1282