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Disease Burden and Etiologic Distribution of Community-Acquired Pneumonia in Adults: Evolving Epidemiology in the Era of Pneumococcal Conjugate Vaccines

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ABSTRACT

Pneumonia is the leading cause of morbidity and mortality, particularly in old adults. The incidence and etiologic distribution of community-acquired pneumonia is variable both geographically and temporally, and epidemiology might evolve with the change of population characteristics and vaccine uptake rates. With the increasing prevalence of chronic medical conditions, a wide spectrum of healthcare-associated pneumonia could also affect the epidemiology of community-acquired pneumonia. Here, we provide an overview of the epidemiological changes associated with community-acquired pneumonia over the decades since pneumococcal conjugate vaccine introduction.

Keywords: Pneumonia; Incidence; Mortality; Epidemiology; Pneumococcal conjugate vaccine

INTRODUCTION

Pneumonia is the leading infectious disease and is ranked the fourth most common cause of death in South Korea as of 2017 [1]. Globally, three million people die annually due to pneumonia, exceeding all other infectious causes including tuberculosis, malaria, and human immunodeficiency virus (HIV) infection [2]. With the increase in elderly population with chronic disease, long-term care facilities (LTCF) have expanded in South Korea in the recent decade, and this increase in elderly people living in LTCF could be contributing to the rise in pneumonia-related morbidity and mortality.

Prior to 2005, pneumonia was classified as either community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP). Since 2005, healthcare-associated pneumonia (HCAP) was first incorporated into the HAP guidelines of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA), considering that HCAP patients might be at high risk for multi-drug resistant (MDR) pathogens through repeated contact with the healthcare system [3]. However, HCAP was removed from the revised HAP guidelines again in 2016, and was supposed to be included in the upcoming CAP guidelines [4]. Similar to

patients with CAP, most HCAP cases present from the community followed by frequent emergency room visits during acute disease phase. Furthermore, increasing evidence shows that the causative pathogens of HCAP cases are more closely related to pathogens associated with CAP than HAP [5-9].

In the beginning of the new millennium, pneumococcal conjugate vaccine (PCV) was developed and is now in widespread use. In children, PCV7 was first licensed in 2000, and extended to PCV10/PCV13 later in 2010 [10]. In turn, PCV13 was additionally licensed for adults in 2012 as the first conjugate vaccine for adults. PCV13 showed 45% efficacy against vaccine-type non-invasive pneumococcal pneumonia in the community-acquired pneumonia immunization trial in adults (CAPiTA), and 70% real world effectiveness [11, 12]. Vaccine efficacy could be variable depending on pneumonia types because of different vaccine uptake rates and host factors; therefore, PCVs might affect the epidemiology of pneumonia differentially for CAP and HCAP. This review focuses on the change of epidemiology and etiologic distribution of pneumonia over time after the introduction of PCVs.

INCIDENCE AND CASE-FATALITY RATE OF COMMUNITY-ACQUIRED PNEUMONIA

The incidence of CAP in adults varies worldwide by country, age, gender, and study period; however, reliable data on the incidence of CAP over a prolonged time period exists only for a few countries in North America and Europe, including the United States (107–370 cases per 100,000 persons aged 18–64 years, 630–5, 697 cases per 100,000 persons aged ≥65 years), the United Kingdom (52–106 cases per 100,000 persons aged 16–64 years, 275–1,006 cases per 100,000 persons aged ≥65 years), and Spain (68–320 cases per 100,000 persons aged 18–64 years, 237–1,400 cases per 100,000 persons aged ≥65 years) (**Table 1**) [13-25]. A wide variation of CAP incidence, even within the same country, results from distinctions in several factors such as inclusion of HCAP or outpatient pneumonia, and data sources of pneumonia assessment. Among these factors, CAP burden revealed a sharp divergence based on whether the study definition included HCAP. As for retrospective studies, it is difficult to differentiate HCAP from CAP cases by diagnostic codes alone. Thus, the burden in defining CAP using the International Classification of Diseases (ICD) code, which inevitably includes HCAP cases, is generally higher than those defined using clinical and radiological criteria. For example, Jain et al. reported that an annual incidence of CAP in the United States excluding patients with HCAP was 248 cases per 100,000 persons [17]. This result was substantially lower than 649 cases per 100,000 persons in another study by Ramirez et al., which included patients with HCAP [23]. Similarly, two Korean studies showed a large difference in the annual incidence of CAP regarding the inclusion of HCAP: 626 cases per 100,000 persons in one study defined by ICD codes *vs.* 308 cases per 100,000 persons in another study defined by physician assessment [1, 2]. Both studies included HCAP cases. However, the former study might include most HCAP cases, while the latter study excluded LTCF-associated HCAP cases. Although there was a substantial gap in the burden of CAP based on study method, the incidence of CAP increased consistently with age and is higher in men than in women in all studies. The CAP incidence for persons aged 65 years and older was at least three-fold higher compared to those under the age of 65.

Given the importance of pneumococcal pneumonia in the burden of CAP, both direct and indirect herd effect of PCVs should be considered in predicting the change of CAP incidence

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Table 1. Incidence and case fatality rate of community-acquired pneumonia in adults

Period	Authors [reference]	Study years	Country	Incidence[a]	Case-fatality rate	HCAP inclusion	Outpatient inclusion	Pneumonia assessment	Study type
Pre-PCV7 period	Kaplan et al. [18]	1997	US	≥65 years: 1,830	10.6	Inclusion	Exclusion	ICD code	Retrospective
	Jackson et al. [16]	1998–2001	US	≥65 years: 2,840	3.6	Inclusion	Inclusion	ICD code	Retrospective
	Griffin et al. [14]	1997–1999	US	18–64 years: 107–336 ≥65 years: 1,293–5,697	NA	Inclusion	Exclusion	ICD code	Retrospective
	Lovering et al. [19]	1994–1996	UK	16–59 years: 52–106 ≥60 years: 275–720	18.9	Inclusion	Inclusion	Physician assessment	Prospective
	Millett at al. [20]	1997–2005	UK	≥65 years: 630–793	NA	Inclusion	Inclusion	ICD code	Retrospective
	Monge et al. [21]	1995–1996	Spain	<65 years: 93 ≥65 years: 523	<65 years: 2.7 ≥65 years: 11.6	Inclusion	Exclusion	ICD code	Retrospective
	Gutierrez et al. [15]	1999–2001	Spain	15–64 years: 68–108 ≥65 years: 237–526	NA	Inclusion	Inclusion	Physician assessment	Prospective
Post-PCV7 period	Takaki et al. [32]	2008–2010	Japan	15–64 years: 340 65–74 years: 1,070 ≥75 years: 4,290	NA	Exclusion	Inclusion	Physician assessment	Prospective
	Griffin et al. [14]	2001–2009	US	18–64 years: 89–370 ≥65 years: 1,208–5,209	NA	Inclusion	Exclusion	ICD code	Retrospective
	Simonsen et al. [31]	2007–2009	US	18–64 years: 86.4–267.7 ≥65 years: 1,438.4	NA	Inclusion	Exclusion	ICD code	Retrospective
	Millett et al. [20]	2006–2010	UK	≥65 years: 1,375.2	NA	Inclusion	Inclusion	ICD code	Retrospective
	Schnoor et al. [30]	2003–2004	German	≥18 years: 370–1,010	3.6	Inclusion	Inclusion	Physician assessment	Prospective
	Vila-Corcoles et al. [33]	2002–2005	Spain	≥65 years: 1,050	15.0	Inclusion	Exclusion	Physician assessment	Prospective
	Sicras et al. [24]	2008–2009	Spain	18–64 years: 180–320 ≥65 years: 510–810	2.5	Inclusion	Inclusion	ICD code	Retrospective
	Ochoa et al. [22]	2002–2005	Spain	≥65 years: 1,400	13.0	Inclusion	Inclusion	ICD, physician assessment	Prospective
	Gil-Prieto et al. [13]	2003–2007	Spain	≥50 years: 627 ≥65 years: 1,029	17.0	Inclusion	Exclusion	ICD code	Retrospective
Post-PCV13 period	Choi et al. [1]	2009–2013	South Korea	50–64 years: 477–600 65–74 years: 1,557–1,801 ≥75 years: 3,679–4,935	NA	Inclusion	Exclusion	ICD code	Retrospective
	Heo et al. [2]	2011–2014	South Korea	50–69 years: 369 70–79 years: 1,679 ≥80 years: 4,865	6.2	Inclusion	Exclusion	Physician assessment	Retrospective
	Morimoto et al. [29]	2011–2013	Japan	55–64 years: 650 65–74 years: 1,690 75–84 years: 4,340	8.0	Inclusion	Exclusion	Physician assessment	Prospective
	Simonsen et al. [25]	2011–2012	US	18–64 years: 80.1–258.2 ≥65 years: 1,375.2	NA	Inclusion	Exclusion	ICD code	Retrospective
	Jain et al. [17]	2010–2012	US	50–64 years: 263 65–79 years: 630 ≥80 years: 1,643	NA	Exclusion	Exclusion	Physician assessment	Prospective
	Ramirez et al. [23]	2014–2016	US	18–64 years: 327 ≥65 years: 2,093	6.5	Inclusion	Exclusion	Physician assessment	Prospective
	Lopardo et al. [28]	2012–2015	Argentina	18–64 years: 228–1,100 ≥65 years: 2,949	12.1	Inclusion	Inclusion	Physician assessment	Prospective
			Uruguay	18–64 years: 270–612 ≥65 years: 1,981					
			Paraguay	18–64 years: 48–293 ≥65 years: 1,090					

HCAP, healthcare-associated pneumonia; PCV7, 7-valent pneumococcal conjugate vaccine; ICD, International Classification of Diseases; NA, not available; PCV13, 13-valent pneumococcal conjugate vaccine

[a]Cases/100,000 person-year.

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among adults. Since the introduction of pediatric PCV vaccination in national immunization programs (NIPs) in several countries, the incidence of invasive pneumococcal disease (IPD) was substantially decreased in both children and adults [26, 27]. However, although lots of studies were conducted to evaluate the incidence of CAP since the introduction of PCVs, indirect effects on adult CAP have not been conclusively determined [1, 2, 13, 14, 17, 20, 22-25, 28-33]. Previous reports in the United States have suggested that the incidence of hospitalized CAP among older adults showed a significant reduction in the last decade [14, 25, 31]. On the other hand, other studies have not shown any significant decrease in CAP rate in adults [20, 34]. These inconsistent results might be related to the diverse degree of indirect herd effect on older adults with respect to PCV coverage rates and time interval following PCV NIP implementation.

The case-fatality rate (CFR) of CAP has been published much more than those presented in **table 1**. Overall CFR ranged from 2.5% to 20%, reaching up to 50% in patients admitted to intensive care unit [35, 36]. CFR is influenced by several factors including age, sex, treatment regimen, vaccination status, and underlying comorbidities [37]. Although varied by country, approximately 10% of patients required intensive care, and 14% (median) died among hospitalized patients with CAP [38].

ETIOLOGIC DISTRIBUTION OF CAUSATIVE PATHOGENS IN COMMUNITY-ACQUIRED PNEUMONIA

Because the causative pathogen of CAP is unknown on initial presentation, it is important to know the distribution of CAP etiologic agents for the selection of appropriate empirical antibiotics. *Streptococcus pneumoniae* has been recognized as the most common identifiable pathogen of CAP, followed by *Staphylococcus aureus, Haemophilus influenzae, Klebsiella pneumoniae, Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* in varying order (**Table 2**). Traditionally, causative agents of CAP were identified using conventional culture methods, so microorganisms were identified in less than 30% of CAP cases during the pre-PCV7 period [39-43]. With advances in serological and molecular diagnostic tests, the diagnostic yield has improved by up to 40-50%, yet around 50% of CAP pathogens are still unidentified (**Table 2**) [7, 44-47]. Prior antibiotic use is one of the important reasons for test-negative results. It is unclear to what degree viral pathogens and oral streptococci contribute to the development of pneumonia, and these are points to be further clarified in the future.

Among CAP cases caused by identified bacterial pathogens, *S. pneumoniae* is the most important causative species, accounting for 26.9–69.4% of pneumonia cases in South Korea (**Table 2**) [48], and the proportion of pneumococcal pneumonia was higher in studies confined to older adults [7, 49]. However, in a study of severe CAP cases admitted to intensive care units (ICUs), *S. aureus* infection was more common compared to *S. pneumoniae* (37.8% *vs.* 13.5%) [46]. Etiologic distribution might be affected by disease severity, age, and underlying medical conditions.

Although IPDs were already reported as markedly decreased in both children and adults in the PCV13 era, data on pneumococcal CAP is still insufficient [50, 51]. The introduction of PCVs was expected to affect the etiologic distribution of CAP; however, significant change was not observed after the introduction of the pediatric PCV7 conjugate vaccine [5, 49, 52-56]. Even in the early period of PCV13 use, *S. pneumoniae* still remained as the predominant

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Table 2. Etiological distribution of community-acquired pneumonia in South Korea

Period	Authors [reference]	Study years (population age)	No. of cases	No. of cases with identified bacteria (%)	Gram-positive (%)[a]	Gram-negative (%)[a]	Atypical organisms (%)[a]
Pre-PCV7 period	Yu et al. [43]	1994–1997 (≥16 years)	214	81 (37.9)	*Streptococcus pneumoniae* (33.3) *Staphylococcus aureus* (16.0)	*Klebsiella pneumoniae* (14.8) *Pseudomonas aeruginosa* (6.2) *Haemophilus influenzae* (13.6)	*Mycoplasma pneumoniae* (6.2)
	Chung et al. [39]	1995–1996 (≥15 years)	246	54 (22.0)	*Streptococcus pneumoniae* (35.2) *Streptococcus* spp. (7.5) *Staphylococcus aureus* (9.3)	*Klebsiella pneumoniae* (14.8) *Pseudomonas aeruginosa* (1.9) *Haemophilus influenzae* (22.2)	*Mycoplasma pneumoniae* (2.0)
	Woo et al. [42]	1997–2000 (≥16 years)	585	219 (37.4)	*Streptococcus pneumoniae* (26.9) *Streptococcus* spp. (6.0) *Staphylococcus aureus* (11.4)	*Klebsiella pneumoniae* (20.0) *Pseudomonas aeruginosa* (12.8) *Haemophilus influenzae* (5.0)	-
	Sohn et al. [40]	2001–2002 (≥16 years)	202	39 (19.3)	*Streptococcus pneumoniae* (43.6) *Streptococcus* spp. (10.3) *Staphylococcus aureus* (2.6)	*Klebsiella pneumoniae* (10.3) *Pseudomonas aeruginosa* (10.3) *Haemophilus influenzae* (2.6)	*Mycoplasma pneumoniae* (7.4) *Chlamydia pneumoniae* (8.3) *Legionella pneumophila* (2.8)
	Song et al. [41]	2002–2004 (≥18 years)	955	108 (11.3)	*Streptococcus pneumoniae* (35.2) *Streptococcus* spp. (8.3) *Staphylococcus aureus* (11.1)	*Klebsiella pneumoniae* (11.1) *Pseudomonas aeruginosa* (6.5) *Haemophilus influenzae* (2.8)	*Mycoplasma pneumoniae* (11.0) *Chlamydia pneumoniae* (13.4) *Legionella pneumophila* (1.1)
Post-PCV7 period	Jeon et al. [54]	2007–2008 (≥60 years)	175	63 (36.0)	*Streptococcus pneumoniae* (33.3) *Staphylococcus aureus* (14.3)	*Klebsiella pneumoniae* (20.6) *Pseudomonas aeruginosa* (6.3) *Haemophilus influenzae* (11.1)	*Mycoplasma pneumoniae* (3.2)
	Choi et al. [52]	2007–2013 (≥18 years)	2,221	568 (25.6)	*Streptococcus pneumoniae* (48.6) *Streptococcus* spp. (1.6) *Staphylococcus aureus* (19.2)	*Klebsiella pneumoniae* (18.5) *Pseudomonas aeruginosa* (14.6) *Haemophilus influenzae* (18.5)	*Mycoplasma pneumoniae* (0.9)
	Jeong et al. [5]	2008–2010 (≥50 years)	519	122 (23.5)	*Streptococcus pneumoniae* (48.4) *Streptococcus* spp. (6.6) *Staphylococcus aureus* (10.7)	*Klebsiella pneumoniae* (11.5) *Pseudomonas aeruginosa* (9.0) *Haemophilus influenzae* (5.7)	-
	Yoo et al. [56]	2008–2010 (≥50 years)	693	220 (31.7)	*Streptococcus pneumoniae* (23.2) *Streptococcus* spp. (2.3) *Staphylococcus aureus* (9.5)	*Klebsiella pneumoniae* (7.7) *Pseudomonas aeruginosa* (10.0) *Haemophilus influenzae* (4.5)	*Mycoplasma pneumoniae* (25.5) *Chlamydia pneumoniae* (1.4) *Legionella pneumophila* (1.4)
	Chong et al. [53]	2009–2010 (≥18 years)	619	131 (21.2)	*Streptococcus pneumoniae* (39.7) *Streptococcus* spp. (0.8) *Staphylococcus aureus* (6.1)	*Klebsiella pneumoniae* (19.8) *Pseudomonas aeruginosa* (8.4) *Haemophilus influenzae* (0.8)	*Mycoplasma pneumoniae* (31.3)
	Seong et al. [55]	2010–2011 (≥18 years)	275	105 (38.2)	*Streptococcus pneumoniae* (41.9) *Streptococcus* spp. (4.8) *Staphylococcus aureus* (9.5)	*Klebsiella pneumoniae* (5.7) *Pseudomonas aeruginosa* (9.5) *Haemophilus influenzae* (1.0)	*Mycoplasma pneumoniae* (6.7)
	Kang et al. [49]	2008–2014 (≥65 years)	212	62 (29.2)	*Streptococcus pneumoniae* (69.4) *Staphylococcus aureus* (12.9)	*Klebsiella pneumoniae* (4.8) *Pseudomonas aeruginosa* (3.2) *Haemophilus influenzae* (11.3)	
Post-PCV13 period	Lee et al. [46][b]	2011–2013 (≥18 years)	75	37 (49.3)	*Streptococcus pneumoniae* (13.5) *Streptococcus* spp. (8.1) *Staphylococcus aureus* (37.8)	*Klebsiella pneumoniae* (23.3) *Pseudomonas aeruginosa* (10.8) *Haemophilus influenzae* (0)	
	Seo et al. [47]	2011–2016 (≥18 years)	1,665	832 (50.0)	*Streptococcus pneumoniae* (21.4) *Streptococcus* spp. (3.6) *Staphylococcus aureus* (4.8)	*Klebsiella pneumoniae* (13.6) *Pseudomonas aeruginosa* (2.9) *Haemophilus influenzae* (1.2)	*Mycoplasma pneumoniae* (19.8) *Chlamydia pneumoniae* (26.9) *Legionella pneumophila* (1.1)
	Koh et al. [7]	2012–2013 (≥65 years)	151	62 (41.1)	*Streptococcus pneumoniae* (46.8) *Staphylococcus aureus* (14.5)	*Klebsiella pneumoniae* (14.5) *Pseudomonas aeruginosa* (6.5) *Haemophilus influenzae* (3.2)	*Mycoplasma pneumoniae* (8.1)
	Ahn et al. [44]	2012–2014 (≥18 years)	647	177 (27.4)	*Streptococcus pneumoniae* (32.8) *Streptococcus* spp. (0.6) *Staphylococcus aureus* (5.7)	*Klebsiella pneumoniae* (19.8) *Pseudomonas aeruginosa* (14.5)	*Mycoplasma pneumoniae* (14.7)
	Kim et al. [45]	2016 (≥18 years)	101	47 (46.5)	*Streptococcus pneumoniae* (38.3) *Staphylococcus aureus* (23.4)	*Klebsiella pneumoniae* (21.3) *Pseudomonas aeruginosa* (8.5) *Haemophilus influenzae* (2.1)	*Mycoplasma pneumoniae* (4.3)

PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.
[a]Proportion among cases with identified bacteria.
[b]Cases requiring intensive care unit (ICU) care.

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agent causing CAP in South Korea, at 26.9–43.6% in the pre-PCV7 period, 23.2–69.4% in the post-PCV7 period, and 13.5–46.8% in the post-PCV13 period (**Table 2**) [7, 44-47]. Similarly, in the etiology of pneumonia in the community study conducted in the United States during the early PCV13 period (2011-2012), *S. pneumoniae* was the most common causative pathogen of community-acquired bacterial pneumonia (30.1%, 115 cases), followed by *S. aureus* (9.7%, 37 cases) among the total 382 bacterial pneumonia cases [17]. Considering that about 65% of pediatric PCV13 immunization is required to expect a herd effect in adults and a seven year time period may be required to get the maximal herd effect from childhood immunization, subsequent studies are required to see the PCV13 herd effect [57, 58]; however, there are several unpredictable uncertainties. First, it is not clear whether pediatric herd effect is enough to decrease non-invasive pneumococcal pneumonia in adults, not confined to IPDs. Second, depending on the degree of serotype replacement, the disease burden of pneumococcal pneumonia would be either persistent or decreased.

COMPARISON OF ETIOLOGIC DISTRIBUTION BETWEEN COMMUNITY-ACQUIRED PNEUMONIA *VS.* HEALTHCARE-ASSOCIATED PNEUMONIA

During the early 2000s, several studies in the United States reported a high prevalence of MDR pathogens including methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa* in HCAP cases, who had recent contact with healthcare systems through nursing homes, hemodialysis, chronic wound care, or recent hospitalization as examples [59, 60]. Based on this evidence, the 2005 ATS/IDSA guidelines for nosocomial pneumonia included recommendations for HCAP treatment, suggesting empirical coverage of MDR pathogens [3]. Since then, subsequent studies were conducted in South Korea, Japan, and Spain, but most studies showed that *S. pneumoniae* is the most common causative agent of HCAP, similar to CAP (**Table 3**) [5-9, 44-46, 49, 54, 55, 61-65]. In addition, although the proportion of MDR pathogens is higher in HCAP, some studies revealed indistinguishable etiologic distribution of causative agents between HCAP and CAP [5-9]. Prior meta-analysis suggested that higher mortality of HCAP might not be associated with higher frequency of resistant pathogens [66]. Moreover, empirical antibiotic therapy based on HAP guidelines did not show better clinical outcomes compared to CAP regimen, and resulted in higher mortality with inadequate coverage for atypical pathogens in some studies [67-69]. Accordingly, HCAP treatment will be covered in the next revised ATS/IDSA CAP guidelines. Given that the HCAP population is heterogeneous and overlaps with that of CAP and HAP, HCAP needs to be further sub-classified, and empirical antibiotic therapy for HCAP should be stratified based on the risk of MDR infection in each subgroup.

Since the introduction of PCV13, community-acquired pneumococcal pneumonia was expected to gradually decrease. In comparison, the disease burden of pneumococcal pneumonia might be persistent among at-risk HCAP populations particularly residing in LTCF with missed opportunity of vaccination [70], as pneumococcal pneumonia outbreaks have been reported among unvaccinated nursing home residents [71, 72]. In some studies conducted in Japan, the proportion of pneumococcal pneumonia in HCAP was similar or rather higher compared to that of CAP (**Table 3**) [6, 8, 9]. The concerning point is that MDR *S. pneumoniae* might be transmitted among LTCF residents with repeated antibiotic exposure. Actually, levofloxacin and ceftriaxone-resistant pneumococcal HCAP cases were recently

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Table 3. Etiologic distribution of pneumonia: community-acquired pneumonia *vs*. healthcare-associated pneumonia

Country	Authors [reference]	Study periods/age	CAP[a]	HCAP[a]
US	Kollef et al. [59]	2002–2003 year/≥18 years	*Streptococcus pneumoniae* (16.6)	*Streptococcus pneumoniae* (5.5)
			Staphylococcus aureus (25.5)	*Staphylococcus aureus* (46.7)
			MSSA (12.0)	MSSA (20.2)
			MRSA (6.2)	MRSA (26.5)
			Haemophilus influenzae (16.6)	*Haemophilus influenzae* (5.8)
			Klebsiella spp. (9.5)	*Klebsiella* spp. (7.6)
			Pseudomonas aeruginosa (17.1)	*Pseudomonas aeruginosa* (25.3)
			Escherichia coli (4.8)	*Escherichia coli* (5.2)
	Micek et al. [60]	2003–2005 year/≥18 years	*Streptococcus pneumoniae* (40.9)	*Streptococcus pneumoniae* (10.4)
			Staphylococcus aureus (25.5)	*Staphylococcus aureus* (46.7)
			MSSA (16.6)	MSSA (14.3)
			MRSA (8.9)	MRSA (18.3)
			Haemophilus influenzae (17.3)	*Haemophilus influenzae* (4.2)
			Klebsiella spp. (3.4)	*Klebsiella* spp. (6.5)
			Pseudomonas aeruginosa (4.8)	*Pseudomonas aeruginosa* (25.5)
			Escherichia coli (5.8)	*Escherichia coli* (4.2)
			Atypical pathogens (3.4)	Atypical pathogens (0.2)
South Korea	Jeon et al. [54]	2007–2008 year/≥60 years	*Streptococcus pneumoniae* (33.3)	*Streptococcus pneumoniae* (6.7)
			Staphylococcus aureus (11.1)	*Staphylococcus aureus* (40.0)
			MSSA (4.8)	MSSA (10.0)
			MRSA (6.3)	MRSA (30.0)
			Haemophilus influenzae (11.1)	*Haemophilus influenzae* (3.3)
			Klebsiella pneumoniae (20.6)	*Klebsiella pneumoniae* (26.7)
			Pseudomonas aeruginosa (6.3)	*Pseudomonas aeruginosa* (26.7)
			Mycoplasma pneumoniae (3.2)	*Mycoplasma pneumoniae* (0.0)
	Jeong et al. [5]	2008–2010 year/≥18 years	*Streptococcus pneumoniae* (48.4)	*Streptococcus pneumoniae* (30.8)
			Staphylococcus aureus (10.7)	*Staphylococcus aureus* (19.2)
			MSSA (9.0)	MSSA (9.2)
			MRSA (1.6)	MRSA (10.0)
			Haemophilus influenzae (5.7)	*Haemophilus influenzae* (6.9)
			Klebsiella pneumoniae (11.5)	*Klebsiella pneumoniae* (16.9)
			Pseudomonas aeruginosa (9.0)	*Pseudomonas aeruginosa* (15.4)
			Escherichia coli (0.8)	*Escherichia coli* (3.8)
	Kang et al. [49]	2008–2014 year/≥65 years	*Streptococcus pneumoniae* (69.4)	*Streptococcus pneumoniae* (35.2)
			Staphylococcus aureus (12.9)	*Staphylococcus aureus* (24.1)
			MSSA (11.3)	MSSA (3.7)
			MRSA (1.6)	MRSA (20.4)
			Haemophilus influenzae (11.3)	*Haemophilus influenzae* (0.0)
			Klebsiella spp. (4.8)	*Klebsiella* spp. (14.8)
			ESBL-producer (0.0)	ESBL-producer (7.4)
			Pseudomonas spp. (3.2)	*Pseudomonas* spp. (13.0)
			Escherichia coli (0.0)	*Escherichia coli* (9.3)
			ESBL-producer (0.0)	ESBL-producer (1.9)
	Seong et al. [55]	2010–2011 year/≥18 years	*Streptococcus pneumoniae* (41.9)	*Streptococcus pneumoniae* (33.3)
			Staphylococcus aureus (9.5)	*Staphylococcus aureus* (31.4)
			MSSA (6.7)	MSSA (15.7)
			MRSA (2.9)	MRSA (15.7)
			Haemophilus influenzae (1.0)	*Haemophilus influenzae* (0.0)
			Klebsiella spp. (5.7)	*Klebsiella* spp. (3.9)
			ESBL-producer (1.0)	ESBL-producer (2.0)
			Pseudomonas spp. (9.5)	*Pseudomonas* spp. (18.6)
			Mycoplasma pneumoniae (6.7)	*Mycoplasma pneumoniae* (0.0)
	Lee et al. [46][b]	2011–2013 year/≥18 years	*Streptococcus pneumoniae* (13.5)	*Streptococcus pneumoniae* (6.5)
			Staphylococcus aureus (37.8)	*Staphylococcus aureus* (26.1)
			MSSA (29.7)	MSSA (8.7)
			MRSA (8.1)	MRSA (19.6)
			Haemophilus influenzae (0.0)	*Haemophilus influenzae* (0.0)
			Klebsiella pneumoniae (23.3)	*Klebsiella pneumoniae* (45.6)
			Pseudomonas aeruginosa (10.8)	*Pseudomonas aeruginosa* (10.9)
			Escherichia coli (5.4)	*Escherichia coli* (15.3)

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Table 3. (Continued) Etiologic distribution of pneumonia: community-acquired pneumonia *vs.* healthcare-associated pneumonia

Country	Authors [reference]	Study periods/age	CAP[a]	HCAP[a]
	Koh et al. [7][c]	2012–2013 year/≥65 years	*Streptococcus pneumoniae* (46.8)	*Streptococcus pneumoniae* (46.7)
			Staphylococcus aureus (14.5)	*Staphylococcus aureus* (23.3)
			MSSA (3.2)	MSSA (3.3)
			MRSA (11.3)	MRSA (20.0)
			Haemophilus influenzae (3.2)	*Haemophilus influenzae* (0.0)
			Klebsiella pneumoniae (14.5)	*Klebsiella pneumoniae* (16.7)
			Pseudomonas aeruginosa (6.5)	*Pseudomonas aeruginosa* (16.7)
			Mycoplasma pneumoniae (8.1)	*Mycoplasma pneumoniae* (20.0)
	Ahn et al. [44]	2012–2014 year/≥18 years	*Streptococcus pneumoniae* (32.8)	*Streptococcus pneumoniae* (17.0)
			Staphylococcus aureus (5.7)	*Staphylococcus aureus* (18.9)
			MSSA (1.7)	MSSA (2.6)
			MRSA (4.0)	MRSA (16.3)
			Klebsiella pneumoniae (19.8)	*Klebsiella pneumoniae* (21.6)
			Pseudomonas aeruginosa (14.5)	*Pseudomonas aeruginosa* (19.6)
			ESBL-producing *Enterobacteriaceae* (2.3)	ESBL-producing *Enterobacteriaceae* (17.6)
			Mycoplasma pneumoniae (14.7)	*Mycoplasma pneumoniae* (6.5)
	Kim et al. [45]	2016 year/≥18 years	*Streptococcus pneumoniae* (38.3)	*Streptococcus pneumoniae* (21.8)
			Staphylococcus aureus (23.4)	*Staphylococcus aureus* (25.7)
			MSSA (17.0)	MSSA (7.9)
			MRSA (6.4)	MRSA (17.8)
			Haemophilus influenzae (2.1)	*Haemophilus influenzae* (6.9)
			Klebsiella pneumoniae (21.3)	*Klebsiella pneumoniae* (21.8)
			Pseudomonas aeruginosa (8.5)	*Pseudomonas aeruginosa* (19.8)
			Escherichia coli (4.3)	*Escherichia coli* (9.9)
			Mycoplasma pneumoniae (4.3)	*Mycoplasma pneumoniae* (0.0)
Japan	Ishida et al. [62]	2008–2010 year/≥18 years	*Streptococcus pneumoniae* (58.2)	*Streptococcus pneumoniae* (31.8)
			Staphylococcus aureus (0.0)	*Staphylococcus aureus* (19.1)
			MSSA (0.0)	MSSA (11.0)
			MRSA (0.0)	MRSA (8.1)
			Haemophilus influenzae (14.9)	*Haemophilus influenzae* (9.2)
			Klebsiella pneumoniae (5.0)	*Klebsiella pneumoniae* (11.6)
			Pseudomonas aeruginosa (3.0)	*Pseudomonas aeruginosa* (13.3)
			Escherichia coli (1.0)	*Escherichia coli* (7.5)
			Mycoplasma pneumoniae (3.5)	*Mycoplasma pneumoniae* (0.6)
	Maruyama et al. [9]	2009–2011 year/≥18 years	*Streptococcus pneumoniae* (58.5)	*Streptococcus pneumoniae* (54.4)
			Staphylococcus aureus (1.9)	*Staphylococcus aureus* (19.0)
			MSSA (1.9)	MSSA (7.7)
			MRSA (0.0)	MRSA (11.3)
			Haemophilus influenzae (15.1)	*Haemophilus influenzae* (5.6)
			Klebsiella pneumoniae (3.8)	*Klebsiella pneumoniae* (6.2)
			Pseudomonas aeruginosa (1.9)	*Pseudomonas aeruginosa* (11.3)
			Escherichia coli (1.9)	*Escherichia coli* (3.6)
			Mycoplasma pneumoniae (20.8)	*Mycoplasma pneumoniae* (6.7)
	Kosai et al. [8]	2009–2012 year/≥18 years	*Streptococcus pneumoniae* (54.4)	*Streptococcus pneumoniae* (45.7)
			Staphylococcus aureus (15.8)	*Staphylococcus aureus* (28.6)
			MSSA (8.8)	MSSA (5.7)
			MRSA (7.0)	MRSA (14.0)
			Haemophilus influenzae (19.3)	*Haemophilus influenzae* (8.6)
			Klebsiella pneumoniae (3.5)	*Klebsiella pneumoniae* (17.1)
			Pseudomonas aeruginosa (3.5)	*Pseudomonas aeruginosa* (8.6)
			Escherichia coli (1.8)	*Escherichia coli* (5.7)
			Mycoplasma pneumoniae (33.3)	*Mycoplasma pneumoniae* (28.6)
	Fukuyama et al. [61]	2010–2012 year/≥18 years	*Streptococcus pneumoniae* (36.9)	*Streptococcus pneumoniae* (29.9)
			Staphylococcus aureus (1.0)	*Staphylococcus aureus* (4.3)
			Haemophilus influenzae (29.6)	*Haemophilus influenzae* (28.9)
			Klebsiella pneumoniae (5.3)	*Klebsiella pneumoniae* (15.2)
			Pseudomonas aeruginosa (5.8)	*Pseudomonas aeruginosa* (8.1)
			Mycoplasma pneumoniae (4.4)	*Mycoplasma pneumoniae* (0.5)

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Table 3. (Continued) Etiologic distribution of pneumonia: community-acquired pneumonia *vs.* healthcare-associated pneumonia

Country	Authors [reference]	Study periods/age	CAP[a]	HCAP[a]
	Kamata et al. [6]	2010–2013 year/≥18 years	*Streptococcus pneumoniae* (40.6)	*Streptococcus pneumoniae* (59.2)
			Staphylococcus aureus (7.5)	*Staphylococcus aureus* (26.2)
			MSSA (7.5)	MSSA (14.6)
			MRSA (0.0)	MRSA (11.6)
			Haemophilus influenzae (7.5)	*Haemophilus influenzae* (10.7)
			Klebsiella pneumoniae (1.0)	*Klebsiella pneumoniae* (16.5)
			Pseudomonas aeruginosa (2.8)	*Pseudomonas aeruginosa* (20.4)
			Mycoplasma pneumoniae (15.1)	*Mycoplasma pneumoniae* (6.8)
	Parrott et al. [63]	2011–2013 year/≥18 years	*Streptococcus pneumoniae* (35.2)	*Streptococcus pneumoniae* (29.5)
			Staphylococcus aureus (9.3)	*Staphylococcus aureus* (11.4)
			MSSA (7.4)	MSSA (6.8)
			MRSA (1.9)	MRSA (4.5)
			Haemophilus influenzae (25.9)	*Haemophilus influenzae* (18.2)
			Klebsiella pneumoniae (3.7)	*Klebsiella pneumoniae* (15.9)
			Pseudomonas aeruginosa (3.7)	*Pseudomonas aeruginosa* (15.9)
			Escherichia coli (0.0)	*Escherichia coli* (9.1)
			ESBL-producer (0.0)	ESBL-producer (4.5)
			Mycoplasma pneumoniae (3.7)	*Mycoplasma pneumoniae* (0.0)
Spain	Polverino et al. [64]	2008–2010 year/≥18 years	*Streptococcus pneumoniae* (70.8)	*Streptococcus pneumoniae* (62.7)
			Staphylococcus aureus (2.8)	*Staphylococcus aureus* (2.4)
			Haemophilus influenzae (1.4)	*Haemophilus influenzae* (1.2)
			Pseudomonas aeruginosa (1.4)	*Pseudomonas aeruginosa* (4.8)
			Gram-negative bacilli (5.6)	Gram-negative bacilli (7.2)
			Atypical pathogens (4.2)	Atypical pathogens (2.4)
	Valles et al. [65]	2011–2012 year/≥18 years	*Streptococcus pneumoniae* (63.6)	*Streptococcus pneumoniae* (44.8)
			Staphylococcus aureus (4.1)	*Staphylococcus aureus* (10.3)
			MSSA (3.7)	MSSA (5.2)
			MRSA (0.4)	MRSA (5.2)
			Haemophilus influenzae (3.3)	*Haemophilus influenzae* (8.6)
			Pseudomonas aeruginosa (2.9)	*Pseudomonas aeruginosa* (6.9)
			Enterobacteriaceae (7.0)	*Enterobacteriaceae* (10.3)
			Atypical pathogens (2.5)	Atypical pathogens (3.4)

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum beta-lactamases.
[a]Proportion (%) among cases with identified bacteria.
[b]Cases requiring intensive care unit (ICU) care.
[c]Comparison between community-acquired pneumonia *vs.* nursing home-acquired pneumonia.

reported in South Korea [73-75] and these MDR pneumococcal pneumonia cases were related to underlying neurological diseases and LTCF residence[73-75]. Pneumococcal disease burden among these high-risk populations should be monitored, and targeted vaccination strategy could be considered.

CONCLUSIONS

In this review, we summarized the incidence, CFR, and etiologic distribution of CAP since the introduction of PCV use. The incidence and etiologic distribution of this disease might be variable based on study population characteristics (density and age distribution), vaccine uptake rate, and case definitions as whether to include HCAP in the analysis. In the future, pneumonia-related morbidity and mortality could increase with our increasing aged population, and the proportion of HCAP might be higher with the rising prevalence of coexisting medical conditions. The current HCAP definition should be better clarified and further categorized to avoid overtreatment or undertreatment for MDR pathogens. Considering recent reports of MDR pneumococcal HCAP cases in South Korea,

pneumococcal vaccination strategy should be tailored to minimize the missed vaccination opportunity in patients with chronic medical conditions [73-75].

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