Review Article

http://dx.doi.org/10.3947/ic.2013.45.2.145
Infect Chemother 2013;45(2):145-158
pISSN 2093-2340 · eISSN 2092-6448

Infection & Chemotherapy

The Changing Epidemiology of Childhood Pneumococcal Disease in Korea

Young June Choe[1], Eun Hwa Choi[1,2], and Hoan Jong Lee[1,2]

[1]Department of Pediatrics, Seoul National University Children's Hospital; [2]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea

The wide use of antimicrobial agents and 7-valent pneumococcal conjugate vaccine (PCV7) has led to major changes in the epidemiology of childhood pneumococcal diseases. In Korea, data on the population-based incidence of childhood invasive pneumococcal diseases (IPD) are not available; however, institution-based surveillance data suggest a substantial burden of childhood IPD. Following the introduction of the PCV7 in Korea in 2003, the proportion of IPD caused by vaccine-type pneumococci has decreased, while non-PCV7 serotypes, especially serotypes 19A and 6A, whose proportions had been increasing before the introduction of the vaccine, became predominant among childhood IPD isolates. This article reviews the overall impact of PCV7 utilization and summarizes the results obtained so far. Continuous monitoring and gathering of scientific evidence for the epidemiological transition of pneumococcal carriage and IPD will be important for the management of pneumococcal infections in Korea.

Key Words: *Streptococcus pneumoniae*, Epidemiology, Antimicrobial resistance, Serotype

Background

Streptococcus pneumoniae is a gram-positive diplococcus that has high levels of antigenic diversity between serotypes that are identified on the basis of unique polysaccharide capsules. Of the 92 different pneumococcal serotypes, those belonging to around 10 serogroups are responsible for most of pneumococcal infections. The magnitude of the diseases caused by each of those serotypes varies over time and population demographics.

The clinical spectrum of pneumococcal infection varies from mild, noninvasive infections to severe, invasive infections. Invasive pneumococcal diseases (IPD) include bacteremia, meningitis, and complicated pneumonia, and are major causes of childhood morbidity and mortality worldwide. In the past, the highest risk was noted among children aged < 2 years. Between 1995 and 1998, the incidence of invasive pneumococcal infection in children < 2 years of age in the United States was estimated at 166.9 cases in 100,000 population as compared to 35.2 cases in children aged 2–4 years and 3.9 cases in children aged 5–17 years [1].

The pneumococcal polysaccharide vaccine introduced in

Received: May 13, 2013
Corresponding Author : Hoan Jong Lee, MD, PhD
Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-769, Korea
Tel: +82-2-2072-3633, Fax: +82-2-745-4703
E-mail: hoanlee@snu.ac.kr

1977 was not effective in inducing protective immunity in children aged <2 years, who were at the highest risk for IPDs. Indeed, the introduction of 7-valent pneumococcal conjugate vaccine (PCV7, Prevenar®, Wyeth Pharmaceuticals, Philadelphia, USA) in the early 2000s has led to changes in the epidemiology of diseases caused by pneumococcus. In countries where the PCV7 has been widely used, the vaccine has reduced the incidence of IPDs in the target age group and has led to the reduction of disease transmission to the populations outside the PCV7 target group.

Although the PCV7 has exerted a noteworthy effect on the overall burden of IPD, pneumococcus remains one of the leading causes of childhood morbidity and mortality in countries that have limited resources. In the last decade, pneumococcus caused approximately 14.5 million serious infections per year globally, and was responsible for 11% of deaths in children aged <5 years [2]. Reports from Asian countries where the PCV7 has not been included in national immunization programs suggest that the burden of pneumococcus is high, and is comparable to the burden of disease prior to the introduction of the PCV7 in regions where the vaccine has been included in national immunization programs [3].

The PCV7 was introduced in November 2003 in Korea; it has been used as an optional vaccine primarily for children aged <24 months and was later recommended as a catch-up immunization in children aged 24–59 months. Indeed, the magnitude of IPD in Korea has not been defined fully, and the impact of the PCV7 on IPD among Korean children remains to be determined. The objective of this review is to describe the change in the epidemiology of childhood IPD in Korea in the era of pneumococcal conjugate vaccines and to discuss future perspectives regarding the control and prevention of pneumococcal infection in Korea.

Epidemiology of childhood invasive pneumococcal diseases

An IPD is defined as an acute illness associated with the isolation of *S. pneumoniae* from normally sterile body fluids such as blood, cerebrospinal fluid, pleural fluid, joint fluid, etc. Children aged <5 years, especially those <2 years old, are vulnerable to such diseases. During 1992–1995 in Southern California, the United States, the incidence of IPD was highest in children aged <2 years, numbering 145 cases per 100,000 persons, compared to the 72 and 32 cases in children aged <5 years and the elderly aged >65 years, respectively [4]. For pneumococcal meningitis, the incidence calculated from 8 surveillance sites in the United States in 1998–1999 was 10.16 cases per 100,000 persons in children aged <2 years, whereas the incidence ranged between 0.27 and 1.90 in older age groups [5]. The reason for the increased susceptibility in children aged <2 years is partly due to the immaturity of their immune systems and the high burden of pneumococci colonization of the nasopharynx.

1. Overall invasive pneumococcal diseases

Following the introduction of the PCV7 in the United States, surveillance program that involved 8 children's hospitals demonstrated that the incidence of IPD requiring hospitalization in children ≤24 months of age declined by 58% in 2001 and by 66% in 2002 as compared with the mean of the years between 1994 and 2000 [6]. The analysis from Active Bacterial Core (ABC) surveillance conducted between 1998 and 2003 in the United States revealed that after the PCV7 was introduced, the incidence of vaccine-type (VT) IPD among children aged <5 years decreased from 80.0 cases per 100,000 persons to 4.6 cases per 100,000 persons (94% reduction, 95% confidence interval 92–96%) [7]. The reduction of disease incidence was also demonstrated in populations outside the PCV7 target population: there was a 62% reduction in IPD incidence attributable to VT pneumococcal isolates among children aged ≥5 years and a 29% reduction in the total incidence of IPD among the elderly aged ≥65 years. In 2007, the incidence of total and VT IPD in the United States remained low at 13.5 cases (45% reduction from 1998–1999) and 1.0 case (94% reduction from 1998–1999) per 100,000 persons, respectively [8]. The overall incidence of pneumococcal meningitis in the United States has declined from 1.13 to 0.79 cases per 100,000 populations between 1998–1999 and 2004–2005 [5].

The reduction in IPD incidence has been reproduced in other countries as well. After the PCV7 was introduced in the United Kingdom, the overall IPD incidence in infants has decreased by 83% [9]. In Israel, the inclusion of the PCV7 into the national immunization program has resulted in a 43–81% reduction in IPD incidence [10]. In Taiwan, the annual incidence of IPD has decreased from 6.2 (2000–2005) to 3.8 (2006–2008) cases per 10,000 hospitalizations following the introduction of the pneumococcal polysaccharide vaccine for adults and the PCV7 for children [11].

In Korea, population-based incidence data of pneumococcal infection are not available. IPD has not been deemed a nationally notifiable disease; therefore, measuring of the effect of the PCV7 is challenging, and data on the quantification of its

effects in terms of effectiveness are limited. However, the importance of IPD in children can be partly estimated by measuring the relative proportion of pneumococci among all childhood invasive bacterial infections.

In the late 1990s, the first attempt to describe the burden of childhood IPD in Korea was carried out at a single institution [12]. The investigators retrospectively reviewed the medical records of invasive bacterial infection in apparently immunocompetent children diagnosed between 1986 and 1995. Among 115 invasive bacterial infections that occurred in children ≥2 months of age, pneumococci were detected in 28 patients (24%). Of the 28 IPD cases, nearly half (46.4%) were infants aged between 2 and 12 months; 28.6% involved children aged between 1 and 4 years. Thereafter, a retrospective multicenter study was conducted to describe the invasive bacterial infections in immunocompetent children caused by 8 major pathogens: *S. pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Listeria monocytogenes*, and *Salmonella* species from 1996 to 2005 (Table 1) [13]. Among 766 infections that occurred in children aged <15 years, 179 (23.4%) were caused by pneumococci. When infants and children aged 3 months to <5 years were investigated, it was found that 140 (45.3%) of 309 infections were caused by pneumococci. Among the 179 IPD patients, 11 (6.1%) were <3 months of age, 140 (78.2%) were between 3 months and 4 years old, and 28 (15.6%) were ≥5 years of age.

Notably, the proportion of IPD cases among childhood invasive bacterial infections can be affected by the vaccines that prevent major bacterial pathogens: *H. influenzae* type b (Hib) vaccine and the PCV7. In Korea, the Hib vaccine has been used since the mid-1990s, and PCV7 has been used since the end of 2003. The proportion of *H. influenzae* among childhood invasive infections caused by the 8 pathogens listed above decreased from 20.1% in 1996–2000 to 4.5% in 2001–2005 [13]. A recent multi-center study that surveyed childhood invasive bacterial infections between 2006 and 2010 indicated that the proportion of *H. influenzae* was 2.4% [14]. During the same study periods, the proportion of pneumococcus among invasive bacterial infections was 21.9% in 1996–2000, 24.1% in 2001–2005, and 23.2% in 2006–2010.

2. Pneumococcal meningitis

The childhood bacterial meningitis studies in Korea suggest that pneumococcus is one of the most important causes of childhood bacterial meningitis. A multi-center study that included 13 university-affiliated hospitals analyzed the cause of childhood bacterial meningitis on the basis of the data collected from 1986 through 1995 [15]. The authors identified 140 cases of bacterial meningitis; pneumococci, *H. influenzae*, and *N. meningitidis* accounted for 35%, 34.3%, and 6.4% of the cases, respectively. Notably, more than 80% of the cases involved patients aged ≤5 years. The 1996–2005 follow-up study that reviewed 402 bacterial meningitis cases from 18 university-affiliated hospitals reported that among children aged ≥3 months, *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* composed 44.4%, 28.3%, and 8.1% of the cases, respectively, suggesting that pneumococcus was one of the leading causes of bacterial meningitis in Korean children [16].

Although the incidence of overall IPD has not been estimated in the Korean population before, a community-based surveillance program attempted to calculate the approximate in-

Table 1. Causative organisms among 766 invasive infections diagnosed in immunocompetent Korean children aged <15 years from 1996 to 2005[a]

Causative organisms	Age group, N (%)					
	<3 mon	3 mon - 4 yr			≥5 yr	Total
		3-23 mon	2-4 yr	Subtotal		
Staphylococcus aureus	106 (37.2)	24 (12.1)	20 (18.2)	44 (14.2)	87 (50.6)	237 (30.9)
Streptococcus pneumoniae	11 (3.9)	90 (45.2)	50 (45.5)	140 (45.3)	28 (16.3)	179 (23.4)
Streptococcus agalactiae	137 (48.1)	6 (3.0)	0 (0.0)	6 (1.9)	1 (0.6)	144 (18.8)
Salmonella spp.	5 (1.8)	25 (12.6)	19 (17.3)	44 (14.2)	29 (16.9)	78 (10.2)
Haemophilus influenzae	11 (3.9)	49 (24.6)	14 (12.7)	63 (20.4)	4 (2.3)	78 (10.2)
Streptococcus pyogenes	10 (3.5)	4 (2.0)	5 (4.5)	9 (2.9)	10 (5.8)	29 (3.8)
Neisseria meningitidis	2 (0.7)	0 (0.0)	1 (0.9)	1 (0.3)	13 (7.6)	16 (2.1)
Listeria monocytogenes	3 (1.1)	1 (0.5)	1 (0.9)	2 (0.6)	0 (0.0)	5 (0.7)
Total	285	199	110	309	172	766

[a]Adapted from [13].

cidence of pneumococcal meningitis in Korean children. Using a prospective, population-based survey, the study aimed to estimate the incidence of childhood bacterial meningitis in Jeonbuk Province from 1999 through 2011, which involved 124,502 children aged <5 years [17]. According to the investigators, the annual incidence of pneumococcal meningitis in children aged <5 years was estimated to be 2.1 per 100,000 persons, which was the second highest pathogen-specific incidence following *H. influenzae* (6.0 per 100,000 persons). As the study involved a population from a region with low Hib vaccine immunization coverage (16%), the apparent burden of Hib meningitis was observed, yet pneumococcus remained one of the major pathogens causing childhood bacterial meningitis in the country.

3. Pneumococcal pneumonia

Pneumococcus is a major causative organism of childhood bacterial pneumonia in both developed and developing countries. Yet, diagnosis is particularly difficult in children because obtaining an adequate respiratory specimen is a practical challenge. Therefore, accurate etiological diagnosis of bacterial pneumonia in children is often limited to cases of bacteremic pneumonia and pneumonia with empyema.

Although data are scarce in Korea, it was reported that pneumococcus accounted for 26.9% of all childhood bacterial pneumonia with empyema in the 1960s, whereas *S. aureus* and *Streptococcus* other than pneumococcus accounted for 65.4% and 7.7% of cases, respectively [18]. In the 1970s, it was reported that the most frequent causative organism of childhood empyema was *S. aureus* (76.0–86.4%), whereas pneumococci accounted for 4.5–16.0% of cases [19, 20]. However, a higher proportion of pneumococci was noted recently. In a multi-center study comprising 32 institutions in Korea between 1999 and 2004, of 80 bacterial isolates from 122 childhood empyema cases, 45 (36.9%) were identified as pneumococci [21]. In the 1996–2005 multi-center study, the proportion of pneumococci among childhood bacteremic pneumonia or pneumonia with empyema among children aged 3–23 and 24–59 months was 85.7% and 81.8%, respectively [13]. In the 2006–2010 multi-center study, 73 (84.9%) of 86 cases of bacteremic pneumonia or pneumonia with empyema in children aged 3–59 months were caused by *S. pneumoniae* [14].

When compared to IPD such as meningitis and bacteremia, the burden of pneumococcus among childhood bacterial pneumonia is potentially being underestimated, for several reasons. First, unlike adult patients, obtaining an adequate respiratory specimen from children is challenging. Second, pneumococcus is part of the normal flora in the nasopharynx of children; therefore, its isolation from the respiratory tract of a child is often not considered a causative pathogen and is discarded. Third, although the conventional bacterial culture from normally sterile body fluid (i.e., blood, cerebrospinal fluid, pleural fluid, etc.) is the gold standard for the diagnosis of IPD, its low sensitivity may often result in negative results in patients with pneumococcal pneumonia with empyema, which may be partly associated with antimicrobial therapy being administered before the specimens are obtained. As routine conventional culture of pleural fluid is frequently negative following prior antibiotic administration and confirmatory results often require time, new techniques have been tested for better clinical applicability in Korea. The pneumococcal immunochromatographic test (ICT) was applied in 2 university-affiliated hospitals in Korea to 62 exudative parapneumonic effusion specimens collected from childhood pneumococcal pneumonia cases in 2003–2010 [22]. Compared to the conventional culture and polymerase chain reaction sequencing confirmation, the sensitivity of ICT was 76.9%, which was 3.3 times higher than that of conventional culture techniques ($P=0.015$). The data suggested that ICT was sensitive for detecting cases of childhood pneumococcal pneumonia with empyema that were initially overlooked.

It is likely that the burden of pneumococcal pneumonia among childhood bacterial pneumonia has been largely underestimated; therefore, expanding the scope to determine the general picture, including all-cause pneumonia and lower respiratory diseases, in Korean children should be discussed in the near future.

Antimicrobial susceptibility

Since the first clinical isolate of penicillin-resistant *S. pneumoniae* (PRSP) was discovered in 1967, PRSP has been transmitted worldwide [23]. Although there is considerable geographical variation, PRSP isolates have become relatively common in Asian countries [24]. The emergence of PRSP in Korea was also remarkable, where antibiotic usage was not tightly regulated until the institution of the national health system reform.

1. Antibiotic susceptibility pattern of pneumococcus in Korea

Earlier reports on the antimicrobial susceptibility of clinical isolates of pneumococcus in Korea are limited. In 1985, no *S.*

pneumoniae isolates among 50 clinical isolates from 1974 to 1983 in a single institution were resistant to penicillin [25]. The emergence of PRSP among clinical isolates in Korea was noted in the early 1980s, when a hospital-based survey reported that the penicillin resistance rate increased from 0% to 10% between 1981 and 1983 [26]. The increase in the rate of penicillin nonsusceptibility of pneumococci in Korea was also reported in the mid-1990s, when the non-susceptibility rate among all pneumococcal isolates increased from 29% in 1988 to 47% in 1990 and to 77% in 1993 [27]. A hospital-based survey between 1991 and 1993 revealed that among 131 clinical isolates of *S. pneumoniae*, 37% and 33% were strains with intermediate and high-level resistance to penicillin, respectively [28]. In the same institution, among 161 isolates from IPD cases diagnosed during 1985–1996, PRSP was first detected in 20% of cases in 1989, and the rate of penicillin nonsusceptibility increased to 89% in 1995 [29]. Upon further analysis, the study determined that among nonmeningeal IPD, a favorable outcome and death were recorded for 83% and 2.5% of cases involving penicillin-susceptible strains, respectively, as compared with 86% and 7.1% of cases involving intermediate strains and 61% and 11% of PRSP-infected cases, respectively. A study in the mid-1990s reported that among 105 clinical isolates from patients with bacteremia, meningitis, pneumonia, and otitis media, 78% were nonsusceptible to penicillin [30]. Overall, studies reported in the early 1990s in Korea showed that the rate of nonsusceptibility ranged between 40% and 60%; that in the late 1990s ranged between 60% and 80% [31-34]. When compared to other Asian countries during this period, Korea was noted as having the highest proportion of penicillin-nonsusceptible strains of pneumococcus at 79.7% of cases, followed by Japan (65.3%) and Vietnam (60.8%) [34]. More recent data suggest that the nonsusceptibility rate among all pneumococci in Korea ranged between 64.6% and 71.1% since the 2000s [24, 35]. Levels of antimicrobial resistance tend to plateau, the height of which is mainly determined by antibiotic pressure. Antibiotic usage in Korea since the 2000s may have been partly controlled by the national health system reform: separation of pharmaceutical prescription and dispensation was implemented in 2000 and quality assessment of antibiotic prescription in healthcare facilities has been carried out since 2001 [36].

2. Impact of vaccines on antimicrobial susceptibility

It has been reported that the introduction of the PCV7 resulted in the decrease of overall incidence of IPD caused by PRSP. Among childhood IPD cases in Utah, U.S., the proportion of IPD cases caused by penicillin-resistant serogroups decreased from 34% in 1997–2000 to 22% in 2001–2003 [37]. An active laboratory surveillance program that spanned 8 states in the United States reported that following the introduction of the PCV7, the rates of IPD due to PCV7 serotypes that were nonsusceptible to penicllin, cefotaxime, or erythromycin has decreased by 75% from 2.30 per 100,000 live births (1997-2000) to 0.57 per 100,000 live birthes (2000-2004) [38]. Multiple studies to date have demonstrated the general decrease in the proportion of antibiotic-nonsusceptible pneumococcal isolates following the introduction of the PCV7. Before the vaccine was introduced, a hospital-based survey in the United States determined that penicillin-nonsusceptible pneumococci accounted for 44% of all IPD cases in 2000; however, after the PCV7 was introduced, the proportion of nonsusceptible pneumococci decreased to 33% in 2002 [6]. In Northern California, U.S., a population-based study suggested that the high level of penicillin resistance decreased from 15% in 2000 to 5% in the first half of 2003 [39]. In Tennessee, U.S., the proportion of penicillin-nonsusceptible pneumococci decreased from 59.8% in 1999 to 30.4% in 2002 among children aged < 2 years [40].

As demonstrated in the reported evidence, the PCV7 may have reduced the level of antibiotic resistance in pneumococci by decreasing the carriage of antibiotic-resistant serotypes in children. Generally, the selective pressure generated by the PCV7 has induced a decline in the proportion of antibiotic-resistant isolates. However, the replacement with remaining serotypes not included in the vaccine but with a high level of antibiotic resistance has led to an unexpected increase in the level of resistance among the remaining pneumococci in the post-vaccine era [41].

In Korea, the change in serotype distribution following the introduction of the PCV7 has resulted in an increase in penicillin-nonsusceptible strains of pneumococci. The overall nonsusceptibility rate of pneumococci isolated from the nasopharyngeal aspirates of children aged 1–5 years in 1997–1999 (n = 72) and children aged < 5 years (n = 67) in 2001–2002 was 83.5% (pre-vaccine); it increased to 95.4% in isolates from the nasopharynx of children aged < 5 years in 2009–2010 (n = 151) (by meningitis criteria for epidemiological comparison) [42]. The rate of penicillin nonsusceptibility has increased in both PCV7 (from 83.7% to 100%, $P = 0.010$) and non-PCV7 serotypes (from 83.0% to 93.9%, $P = 0.044$). PCV7 serotypes 19F (21.6%), 23F (17.3%), and 14 (12.2%) were the most common penicillin-nonsusceptible serotypes in the pre-PCV7 period. In the post-PCV7 period, the proportion of PCV7 serotypes

decreased. Serotypes 19A and 6A were the most common penicillin-nonsusceptible serotypes in the post-PCV7 period. In particular, serotype 19A was 100% nonsusceptible to penicillin in both the pre-PCV7 and post-PCV7 periods. The nonsusceptibility rate of serotypes 6A/6C has increased from 78.6% in the pre-PCV7 period to 100% in the post-PCV7 period ($P=0.037$). The proportionally-increased serotypes (34, 35B, and serogroup 15) in the post-PCV7 period also exhibited higher rates of nonsusceptibility. In the pre-PCV7 period, PCV7 serotypes accounted for 62.1% (72/116) of the total penicillin-nonsusceptible isolates. However, in the post-PCV7 period, PCV7 serotypes accounted for only 25.0% (36/144) of total penicillin-nonsusceptible isolates, indicating a significant decrease in PCV7 serotypes among the penicillin-nonsusceptible pneumococci ($P<0.001$). Among the non-PCV7 serotypes, the proportion of serotypes 6A/6C has increased from 9.5% to 18.1% ($P=0.052$), and that of serotype 19A has increased from 9.5% to 16.7% ($P=0.102$), even though the difference is statistically insignificant.

In some countries where PCV7 is included in the national immunization program, serotype 19A was notably the most affected by the wide use of the vaccine [43]. In the U.S., the percentage of serotype 19A that were nonsusceptible to penicillin (including isolates with intermediate susceptibility or resistance to penicillin) among childreb aged < 5 years increased slightly between prevaccine years (63%) and 2004 (74%) from [44]. However, amon children, a marked increase in the percentage of serotype 19A isolates that were resistant to penicillin was observed during same period (from 10% during prevaccine years to 31% in 2004; $P=0.002$). Moreover, a population-based estimate determined that the rate of IPD due to penicillin-nonsusceptible serotype 19A pneumococci had increased from 2.0 to 8.3 cases per 100,000 children aged <2 years and from 1.3 to 2.2 cases per 100,000 in elderly adults aged ≥65 years [45]. The following section discusses materials on the emergence of non-vaccine serotypes; however, the greatest impact on the rate of antimicrobial resistance was likely the change in the breakpoints for susceptibility, which were revised by the clinical and laboratory standards institute (CLSI) in 2008.

3. Revision of CLSI breakpoints and considerations

Traditionally, penicillin resistance was defined by the minimal inhibitory concentration (MIC) of *S. pneumoniae*: MIC ≤0.06 μg/mL was considered susceptible; 0.12–1 μg/mL, intermediate; and ≥2 μg/mL, resistant. However, there were doubts because the traditional definitions of penicillin susceptibility in pneumococci had little clinical predictive value in nonmeningeal pneumococcal diseases [46]. Similar findings were also reported from investigations in Asian countries, including Korea [29, 47]. One study investigated adult pneumococcal pneumonia cases in 9 Asian countries in 2000–2001, and suggested that the clinical severity was not significantly different between antibiotic-resistant and antibiotic-susceptible groups [47].

The prognosis of serious bacterial infection depends on not only the antimicrobial susceptibility of the infecting organism; but in conjunction with the immune status of the patient, underlying illness, type of infection, and the spectrum and pharmacodynamics of the administered antibiotics. Following the accumulation of evidence, the CLSI reported revised breakpoints for susceptibility when testing penicillin against pneumococcal infections in 2008 [48]. The revised definition differentiates between meningeal and nonmeningeal infections. The revised breakpoints for meningitis are now: susceptible, ≤0.06 μg/mL; resistant, ≥0.12μg/mL. For nonmeningeal infections, the breakpoints are now: susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; and resistant, ≥8 μg/mL. The 2008 change in breakpoints has resulted in an increase in the proportion of susceptible *S. pneumoniae* isolates among nonmeningeal pneumococcal strains [49]. Following the revised CLSI breakpoints, it was estimated that under the new MIC breakpoints, 92.6% of pneumococcus in nonmeningeal pneumococcal infections in the U.S. are now susceptible to penicillin, followed by 7.1% with intermediate susceptibility, and 0.3% that are resistant [49]. The Asian Network for Surveillance of Resistant Pathogens reported that 0.7% of nonmeningeal pneumococcal isolates are now resistant to penicillin; whereas 57.7% of meningeal isolates are still resistant to penicillin [50]. The study suggested that in Korea in particular, 83% of meningeal isolates remained resistant to penicillin. A recent Korean study reported that when the pre-revision breakpoint was applied to 156 pneumococci isolates, the rates of susceptibility, intermediate susceptibility, and resistance were 42.3%, 42.3%, and 15.4%, respectively; however, when the revised breakpoint was applied, 87.8%, 9.6%, and 2.6% of nonmeningeal isolates were susceptible, intermediate, and resistant to penicillin, respectively [51].

Serotype changes

The polysaccharide component of the pneumococcal capsule plays a major role in vaccine development and is impor-

tant in understanding the serotype replacement phenomenon following the introduction of the PCV7. Currently, more than 92 serotypes of *S. pneumoniae* have been identified on the basis of the antigenicity of their capsular polysaccharides, but a relatively limited number of serotypes cause IPD, which vary geographically and over time [52]. From 1975 to the years before the PCV7 was introduced in the U.S., Canada, Oceania, Africa, and Europe, serotypes belonging to serogroups 4, 6, 9, 14, 18, 19, and 23 caused 70–88% of childhood IPD while accounting for less than 65% of childhood IPD in Latin American and Asian countries [53]. Shortly before the PCV7 was introduced in the U.S., active population-based laboratory surveillance of IPD among Navajo Indians aged 0–23 months between 1989 and 1996 revealed that the most common serotypes were 14, 4, 18C, 9V, and 19F [54]. In 2000, the PCV7 was first licensed in the U.S. and was recommended for use in children aged 2–23 months, and later for catch-up immunization in unvaccinated children aged 24–59 months. The PCV7 includes the following serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F.

The increase in the uptake of the PCV7 resulted in altered serotype distribution among IPD isolates and carriage isolates. Although the vaccine reduced the overall incidence and mortality of pneumococcal infections, the residual diseases caused by serotypes outside the coverage of the PCV7 were substantial. A need for alternative vaccines with broader coverage emerged. In 2009, the European Medicines Agency (EMEA) licensed the use of the 10-valent pneumococcal conjugate vaccine (PCV10; Synflorix®, GlaxoSmithKline) for children aged between 6 weeks and 2 years (and further to 5 years). The PCV10 covers 10 serotypes: the 7 serotypes covered in the PCV7 and an additional 3 serotypes (1, 5, and 7F). In 2010, the U.S. Food and Drug Administration and the EMEA licensed the 13-valent pneumococcal conjugate vaccine (PCV13; Prevenar 13®, Pfizer) and recommended it for routine use in children aged 2–59 months. The PCV13 covers 13 serotypes: the 7 serotypes included in the PCV7 and an additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A). In July 2010, the PCV10 and PCV13 were both introduced in Korea, replacing the PCV7 by the end of 2010. Currently, it is important to identify the serotype distribution of isolates from carriers (nasopharynx) and IPD cases to use the appropriate pneumococcal vaccine.

1. Serotype changes in carriage isolates

It is important to identify the serotypes among pneumococci carried in the nasopharynx of healthy children because of the association with risk of childhood IPD and the risk of transmission to population that are not target of PCV. After the PCV7 was introduced in the early 2000s, it was postulated that the vaccine might facilitate the reduction of the pneumococcal carriage rate in children; therefore, the introduced vaccine would subsequently result in the decrease of overall disease incidence in the general population, as demonstrated by the Hib vaccine [55]. Moreover, reports have suggested the indirect effect of the PCV7 on the carriage rate among those who were not the initial target of the vaccination program. Between 1998–2000 and 2004 in Alaska, U.S., the proportion of adult carriers with VT pneumococci decreased from 28% to 4.5% [56]. Among Southwestern American Indian communities, adults and unvaccinated children aged < 5 years living with those who were vaccinated with the PCV7 were less likely to be colonized with VT pneumococci, with odds ratios of 0.57 (adults, 95% CI: 0.33 to 0.99) and 0.57 (children, 95% CI: 0.26 to 0.98) as compared to those living in households with those who were vaccinated with meningococcal vaccine [57].

However, the introduction of the PCV7 may not have resulted in remarkable change in the overall carriage rate. A clinical trial involving pneumococcal conjugate and polysaccharide vaccines identified a significant reduction in the carriage of VT pneumococci (from 25% to 7%) after PCV7 immunization; however, an increase was seen in the carriage rate of non-VT (NVT) pneumococci [58]. After the introduction of the PCV7 in the U.S. among children aged < 2 years, the carriage rate of VT pneumococci between 12- and 18-month visits decreased significantly from 18% to 9%; however, the carriage of NVT strains remained relatively high at 18% after the booster dose of PCV7 at the 15–18-month visit [59]. The investigators in that study suggested that the replacement of VT pneumococcal isolates by NVT organisms after the booster immunization indicates the possibility that PCV7 utilization may result in the replacement of pneumococci mainly by antimicrobial-susceptible NVT strains. In Massachusetts, U.S., during 2000–2001, 2003–2004, and 2006–2007, the overall carriage rates for children carrying *S. pneumoniae* were 27%, 23%, and 30%, respectively; the carriage rates of NVT pneumococci increased from 15% to 19% and to 29% in 2000–2001, 2003–2004, with that of VT decreasing to 3% in 2006–2007 [60]. Although the carriage of vaccine serotypes had virtually disappeared by 2007, their rapid replacement by penicillin-nonsusceptible non-vaccine serotypes became alarming.

Several publications available after the 2000s investigated the carriage rate and serotypes of pneumococci in the Korean population. An earlier study measured the relative proportion of serogroups among pneumococci isolated from the naso-

pharynx of 500 healthy Korean children in 2001 [61]. The overall carriage rate of pneumococci was 19.8% (n = 99); among 62 isolates tested; the most frequently isolated serogroups were 23 (n = 16), 19 (n = 14), 6 (n = 13), and 14 (n = 9). Other studies aimed to identify the serotypes among pneumococci isolated from the nasopharynx of symptomatic or asymptomatic children. Among isolates identified in 1997–1998 from the nasopharynx of children aged 1–5 years with respiratory symptoms (n = 72) and isolates identified in 2000–2001 from children aged < 5 years who visited pediatric clinics with respiratory symptoms (n = 67), the most common serotypes were 19F (21.6%), 23F (17.3%), 14 (12.2%), 6A/6C (10.1%), and 19A (7.9%); the overall PCV7 and PCV13 serotypes accounted for 61.9% and ≤ 80.6%, respectively (Table 2) [42]. After the PCV7 was introduced, a study conducted in 2008 examined the nasopharyngeal swab isolates obtained from 400 children aged 18–59 months attending daycare centers [62]. Pneumococcal carriage rates for the vaccinated and control group were18.0% (36/200) and 31.5% (63/200), respectively; the carriage rates for the PCV7 serotypes were 11.1% among vaccinated children and 52.4% among unvaccinated children, while that for the PCV13 serotypes were 36.1% and 58.7%, respectively. In the study conducted during 2009–2010 on 1,243 children < 18 years of age who visited outpatient clinics or emergency departments with respiratory symptoms, the overall detection rate of pneumococci was 16.5% (205/1,243) [42]. The detection rate for each age group was 16.3% (93/571) for children aged < 2 years, 24.9% (77/309) for children aged 2–4 years, and

Table 2. Distribution of *Streptococcus pneumoniae* according to serotypes isolated from the nasopharynx of children in Korea (1997-2010)

Authors	Study period	Isolates	Common serotype (%)	Vaccine-type serotype coverage (%)		
				PCV7	PCV10	PCV13
Cho et al. [42][a]	1997-1998; 2001-2002	Nasopharyngeal isolates from healthy children aged 1-5 yr ('97-'98, n = 72); from children aged <5yr who visited pediatric clinics ('01-'02, n = 67)	19F (21.6); 23F (17.3); 14 (12.2); 6A/6C (10.1); 19A (7.9)	61.9	62.6	≤ 80.6[b]
	2009-2010	Nasopharynx of children < 5 yr with respiratory symptoms (n = 151)	19A (15.9); 6A (15.2); 19F (11.3); 15C and 35B (6.0, each)	23.8	23.8	55.0
Kim et al. [62][a]	2008	Nasopharynx of vaccinated (4 doses of PCV7) children aged 18-59 mo attending daycare centers (n = 36)	6C (16.7); 6A (13.9); 19A (11.1); 23F and 10A (5.6, each); NT (30.6)	11.1	11.1	36.1
		Nasopharynx of children with no vaccination history aged 18-59 mo attending daycare centers (n = 63)	14 (14.3); 6B and 23F (12.7, each); 19F (11.1); 6C, 15B, and 19A (4.8, each); NT (22.2)	52.4	52.4	58.7
Ahn et al. [63][a]	2009-2010	Nasopharynx of hospitalized children aged < 5 yr with lower respiratory tract infection (n = 163)	19A (23.4), 6A/6B (16.2), 19F (11.4), 15A (5.4), 15B/C (4.8), NT (25.7)	30.5	30.5	≤ 53.9[b]
Lee et al. [64][a]	2010	Nasopharynx of healthy children with vaccination record (PCV7) aged < 5 yr who visited pediatric clinics or who attended kindergartens (n = 79)	19F (13.9); 34 (11.4); 19A, 6D, and 23F (6.3, each); NT (20.3)	≤ 26.6[b]	≤ 26.6[b]	≤ 38.0[b]
		Nasopharynxes of healthy children without vaccination record aged < 5 yr (n = 58)	6A (15.5); 6D (12.1); 23F (10.3); 19F and 35B (6.9, each); NT (22.4)	≤ 20.7[b]	≤ 20.7[b]	≤ 43.1[b]

PCV7, serotypes included in 7-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); PCV10, serotypes included in 10-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F); PCV13, serotypes included in 13-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A); NT, nontypable pneumococci.

[a]Nontypable pneumococci were excluded from analysis in Cho et al. [42], while Kim et al. [62], Ahn et al.[63], and Lee et al. [64] included the nontypable pneumococci.

[b]In the Cho et al.1997-1998 and 2001-2002 study periods [42], differentiation of serotypes 6C/6D from 6A/6B was not carried out; in Ahn et al. [63], differentiation between serotypes 6A and 6B was not carried out; in Lee et al. [64], differentiation between serotypes 9A and 9V was not carried out; therefore only the estimated vaccine types are described.

9.6% (35/363) for children aged ≥5 years. The detection rate was significantly higher among children aged 2–4 years ($P<0.001$). Among the 151 isolates obtained from children aged <5 years, the most common serotypes were 19A (15.9%), 6A (15.2%), and 19F (11.3%). PCV7 and PCV13 serotypes accounted for 23.8% and 55.0% of the isolates, respectively. In one hospital, among 842 hospitalized children with lower respiratory infections tested between 2009 and 2010, the pneumococci serotypes were determined using multiplex polymerase chain reaction tests, which reported among 167 specimens from which pneumococcal DNA was detected a predominance of serotypes 19A (23.4%), 6A/B (16.2%), 19F (11.4%), and 15A (5.4%) [63]. A hospital-based study reported that among pneumococci isolated from the nasopharynx of healthy children, 19F (13.9%) and 34 (11.4%) were the major serotypes among children with vaccination records, while 6A (15.5%) and 6D (12.1%) were the main serotypes identified among children with no vaccination records [64].

2. Serotype changes among IPD isolates

The introduction of the PCV7 clearly led to the overall decrease in IPD incidence caused by PCV7-serotype pneumococci. Between 1998–1999 and 2005, the incidence of IPD caused by PCV7-serotype pneumococci in 8 states in the U.S. decreased from 144.0 cases per 100,000 population to 2.7 cases per 100,000 population aged <5 years, being a 98% (ranging -99 to -96) reduction [65]. In 2008, after 7 years of PCV7 use in the U.S., ABC surveillance data indicated that PCV7 serotypes caused only <2% of IPD in children aged <5 years [66]. Another dataset from the United Kingdom suggested that after the PCV7 was universally recommended in 2006, the proportion of PCV7-serotype pneumococci among IPD in children aged ≤5 years decreased from 76.6% in 2000–2006 to 8.2% in 2008–2010 [67].

Clearly, PCV7 was a triumph and was well accepted in many other regions of the world during the past decade; however, as seen in the cases of noninvasive pneumococcal diseases or in carriage isolates, use of the PCV7 has raised some concerns in regard to the replacement with non-vaccine serotypes among IPD cases. Between 2000–2001 and 2003–2004 in the U.S., the rates of non-PCV7 serotypes among IPD increased significantly, by 1.61-fold and 1.28-fold in children and adults, respectively [68]. Laboratory-based surveillance from the U.S. reported that the rates of IPD caused by nonsusceptible strains peaked in 1999 (6.3/100,000) and decreased by 2004 (2.7/100,000); however, an increase was observed in IPD cases caused by serotype 19A (from 2.0 to 8.3 per 100,000), which is not included in the PCV7 [45]. Among 1,182 isolates from IPD cases collected from 1998 to 2007 in Canada, the total number of IPD cases decreased by 32–77%, however, the incidence of IPD due to non-PCV7 serotypes increased by 183% [69]. Among the predominant non-PCV7 serotypes, including serotypes 15, 19A, and 33F, the increasing antibiotic resistance of serotype 19A was particularly worrying [43, 70]. The levels of penicillin-nonsusceptibility of serotype 19A isolates in European countries increased from 0–50% in 1996–1997 to 21% (Belgium), 48% (Spain), and 86% (France) in 2005–2006 among IPD cases in children aged <5 years [70]. It has been postulated that this phenomenon of serotype replacement may be attributable to the higher invasiveness of this particular serotype and the antibiotic pressure generated by the overuse of antimicrobial agents.

In Korea, the PCV7 was introduced in November 2003 for optional use as an out-of-pocket expense borne by the person vaccinated. In hospital-wide surveillance data from 1991–2006 that included 158 pneumococci isolates from IPD cases just before the PCV7 was introduced, the overall proportion of PCV7 serotypes and PCV7-related serotypes in 2001–2003 was 54% and 10% (excluding 19A), respectively (Fig. 1) [71]. Serotype 19A first emerged in 1995–1997, comprising 5% of total IPD cases and increasing to 18% in 2001–2003, just before the introduction of the PCV7 in Korea. Therefore, the data from that study suggested that serotype 19A had emerged as a common serotype before the introduction of the PCV7 in the

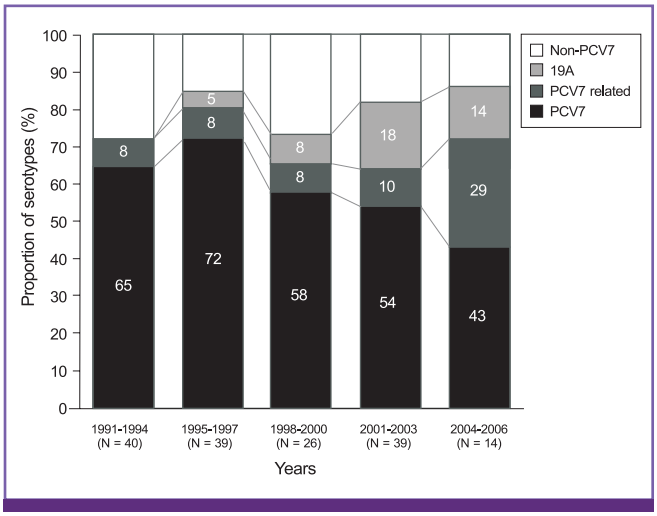

Figure 1. Distribution of serotypes with regard to 7-valent pneumococcal conjugate vaccine (PCV7) among invasive pneumococcal isolates from 1991 to 2006, Korea.

Adapted from [71].

PCV7, serotypes included in 7-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); PCV7-related, serotypes not directly targeted by PCV7 but of the same serogroups (6A, 9A, 9N, 18B, 18F, 23A); serotype 19A was analyzed separately because of its distinct epidemiology).

Table 3. Distribution of *Streptococcus pneumoniae* according to serotype among invasive pneumococcal diseases in children in Korea (1991-2010)

Authors	Study period	Study site and isolates	Common serotypes (%)	Vaccine-type serotype coverage (%)		
				PCV7	PCV10	PCV13
Choi et al. [71]	1991-2006	Single institution, childhood IPD < 18 yr (n = 158)	23F (16.5), 14 (13.9), 19F and 6B (11.4, each), 19A (8.2)	60.8	62.7	80.4
KCDC [72]	1996-2008	Multiple institutions, childhood IPD < 5 yr (n = 74)	23F (16.2), 14 (13.5), 19A (12.2), 6A, 6B, 19F (10.8, each)	59.5	62.2	86.6
Cho et al. [73]	2006-2010	Multiple institution, childhood IPD < 18 yr for common serotypes (n = 140)	19A (22.9), 19F (12.1), 6B (8.6), 23F (7.9), 14 (7.1), 9V (5.7)	45.0	47.9	77.2

PCV7, serotypes included in 7-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F); PCV10, serotypes included 10-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F); PCV13, serotypes included in 13-valent pneumococcal conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A); KCDC, Korea Centers for Disease Control and Prevention; IPD, invasive pneumococcal disease.

country. It was assumed that the increase in the proportion of serotype 19A before the introduction of the PCV7 in Korea was associated with the emergence of a highly resistant clone, ST320, in conjunction with the pressure generated by antibiotic overuse [71]. With the increase of serotypes 19A, 6A, and 23A, the proportion of serotypes directly prevented by the PCV7 declined from 65% during 1991–1994 to 54% during 2001–2003. The consequent decrease in the proportion of PCV7 serotypes among IPD was even more remarkable in children aged < 2 years. Overall, between 1991 and 2006 in the authors' institution, the most frequent serotypes identified among IPD cases in children aged < 18 years (n = 1,158) were 23F (16.5%), 14 (13.9%), 19F and 6B (11.4%, each), and 19A (8.2%) (Table 3) [71]. During this period, PCV7 serotypes accounted for 60.8% of IPD cases, while PCV13 serotypes accounted for 80.4%. According to a report from a multi-center study that collected isolates from IPD cases from 1996 through 2008, serotypes 23F (16.2%), 14 (13.5%), 19A (12.2%), 6A, 6B, and 19F (10.8%, each) were the 6 major serotypes identified from 74 isolates from children aged < 5 years, and PCV7 and PCV13 serotypes were responsible for 59.5% and 86.6% of IPD cases, respectively [72].

Data on the serotype distribution of pneumococci isolated from invasive infections in children after the introduction of the PCV7 in Korea are limited. A recent multi-center surveillance study indicated a gradual decrease in serotypes included in the PCV7 from 2006 to 2010 [73]. Among 140 IPD isolates from children aged < 18 years collected between 2006 and 2010, the most common serotypes were 19A (22.9%), 19F (12.1%), and 6B (8.6%), while the proportion of serotypes covered by the PCV7 decreased from 62.5% in 2006 to 51.7% in 2008, and to 21.4% in 2010. The proportion of the 3 additional serotypes in the PCV10 was relatively small, ranging from 0% to 7.1% each year. Meanwhile, the proportion of the 3 PCV13-specific serotypes increased from 18.8% in 2006 to 34.5% in 2008, and to 42.9% in 2010. Among the PCV13-specific serotypes, a remarkable increase was noted for serotype 19A (from 15.6% to 24.1% and 35.7%, in 2006, 2008, and 2010, respectively).

Although a decrease in the proportion of PCV7-serotype pneumococcal isolates from IPD cases has been noted in Korea, it is less dramatic compared with that of other countries where PCV7 has been included in the national immunization program. The difference may be associated with the fact that the PCV7 has been used as an optional vaccine in Korea and is not included in the national immunization program; therefore, the increase in uptake rate has been slow and the impact of the vaccine may be smaller than that of other regions. In a recent nationwide immunization survey, the estimated PCV7 coverage rate among children aged 7–83 months was 44.8% (primary series) and 31.3% (booster series) in 2006, increasing to 73.8% (primary series) and 50.8% (booster series) in 2010. It was obvious that PCV7 coverage had increased since its introduction in 2003; however, coverage was significantly lower than that of the vaccines included in the national immunization program [74].

Perspectives

Overall, on the basis of the available evidence reported prior to the introduction of the PCV7, it is apparent that pneumococcus is a major pathogen of childhood IPD in Korea; nevertheless, it is widely acknowledged that the true burden of IPD has potentially been underestimated. Further changes in the epidemiology of pneumococcal infection and IPD due to the pressure generated by antibiotics and vaccines are to be ex-

pected in the future. The introduction and utilization of pneumococcal conjugate vaccines has been implemented in Korea for nearly 10 years; however, timely immunization and the vaccine coverage among certain vulnerable populations may remain suboptimal. As the presence of susceptible populations may result in the future increase of IPD cases and in further spread of infection to the population, vaccine coverage should be expanded to maximize the direct and herd protection effect. Furthermore, continual data collection and analysis of *S. pneumoniae* serotypes from routine surveillance should be carried out to evaluate the impact of newly introduced vaccines on the prevalence of IPD and carriage in the population. In addition, efforts to develop a novel pneumococcal conjugate vaccine with a broader range must be continued.

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