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Direct effectiveness of pneumococcal polysaccharide vaccine against invasive pneumococcal disease and non-bacteremic pneumococcal pneumonia in elderly population in the era of pneumococcal conjugate vaccine: A case-control study

Jong Hun Kim [a,1], Byung Chul Chun [b,1], Joon Young Song [c], Hyo Youl Kim [d], In-Gyu Bae [e], Dong-Min Kim [f], Young Hwa Choi [g], Yoon Hee Jun [h], Won Suk Choi [i], Seong Hee Kang [j], Hyun Hee Kwon [k], Hye Won Jeong [l], Sae Yoon Kee [m], Jian Hur [n], Jin Won Chung [o], Young Kyung Yoon [a], Jang Wook Sohn [a], Kyung Sook Yang [p], Min Ja Kim [a,q,*]

[a] Division of Infectious Diseases, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[b] Department of Preventive Medicine, Korea University College of Medicine, Seoul, Republic of Korea
[c] Division of Infectious Diseases, Department of Internal Medicine, Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[d] Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[e] Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Republic of Korea
[f] Department of Internal Medicine, College of Medicine, Chosun University, Gwangju, Republic of Korea
[g] Department of Infectious Diseases, Internal Medicine, Ajou University Hospital, Suwon, Republic of Korea
[h] Department of Internal Medicine, Cheju Halla General Hospital, Jeju-si, Republic of Korea
[i] Division of Infectious Diseases, Department of Internal Medicine, Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea
[j] Department of Internal Medicine, Konyang University College of Medicine, Daejeon, Republic of Korea
[k] Department of Internal Medicine, Daegu Catholic University, Daegu, Republic of Korea
[l] Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, Chungbuk National University, Cheongju, Republic of Korea
[m] Division of Infectious Diseases, Department of Internal Medicine, Sahmyook Medical Center, Seoul, Republic of Korea
[n] Department of Internal Medicine, Yeungnam University Medical Center, Daegu, Republic of Korea
[o] Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea
[p] Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea
[q] The Research Institute of Emerging Infectious Diseases, Korea University, Seoul, Republic of Korea

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ABSTRACT

Background: While herd effects and serotype replacement by childhood pneumococcal protein conjugated vaccines (PCVs) continues to accumulate worldwide, direct effectiveness of 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal diseases in the elderly has been challenged. We estimated the direct effectiveness of PPV23 in the elderly population.

Methods: For a hospital-based case-control study, cases of invasive pneumococcal disease (IPD) and non-bacteremic pneumococcal pneumonia (NBPP) (adults ≥ 65 years) were identified in 14 hospitals participated in the pneumococcal surveillance program from March 2013 to October 2015, following implementation of PPV23 national immunization program (NIP) for the elderly in the Republic of Korea. Controls matched by age, sex, and hospital were selected at ratios of 1:2 (IPD) or 1:1 (NBPP). Clinical data and vaccination records were collected. Vaccine effectiveness was calculated as (1-adjusted odds ratio) × 100.

Results: We enrolled 148 IPD and 557 NBPP cases, and 295 IPD and 557 NBPP controls for analyses. Overall effectiveness of PPV23 against IPD was 28.5% [95% confidence interval (CI) −5.8%–51.6%] and against NBPP was 10.2% (-15.1-30.6) in all patients ≥ 65 years. However, in subgroup analysis of patients aged 65–74 years, PPV23 was protective against IPD [effectiveness 57.4% (19.4–77.5)] and against NBPP [effectiveness 35.0% (2.3–56.7)]. Furthermore, serotype-specific effectiveness of PPV23 against IPD was 90.6% (27.6–98.8) for PPV23-unique serotypes and 81.3% (38.6–94.3) for PPV23 serotypes excluding serotype 3.

* Corresponding author at: Division of Division of Infectious Diseases, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Inchon-ro 73, Seongbuk-gu, Seoul, 02841, Republic of Korea.
E-mail address: macropha@korea.ac.kr (M.J. Kim).
[1] These authors (JHK and BCC) contributed equally to this work.

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Conclusions: This study indicates that PPV23 with broad serotype coverage might be beneficial in preventing IPD and NBPP due to non-PCV13 serotypes in the young-elderly, with potentially increasing effectiveness in the setting of childhood PCV NIP.

1. Introduction

Streptococcus pneumoniae causes various types of infections including invasive pneumococcal disease (IPD) and non-bacteremic pneumococcal pneumonia (NBPP) [1,2]. Children < 2 years and the elderly population aged ≥ 65 years, especially with underlying medical conditions, are at higher risk of acquiring pneumococcal diseases [3]. The 23-valent pneumococcal polysaccharide vaccine (PPV23) and 13-valent pneumococcal conjugate vaccine (PCV13) are currently available for use in adults.

Recent studies of meta-analyses on previous trials and observational studies with PPV23 showed trends toward reduction of pneumococcal pneumonia in adults with significant reduction of IPD [4,5]. However, PPV23 has been found to be less effective in the elderly due to immunosenescence [6]. Furthermore, the immunosenescence-related effects may have a greater impact on the very elderly as the PPV23 effectiveness against IPD caused by PPV23 serotypes has been shown to be further decreased in the very elderly with ≥ 80 years (PPV23 effectiveness 25.5%) than in the young elderly with 60–69 years (PPV23 effectiveness 54.2%) [7]. In the meantime, the CAPITA trial showed effectiveness of PCV13 among adults ≥ 65 years against both bacteremic pneumonia and NBPP [8]. While PPV23 has broader serotype coverage containing all PCV13 serotypes except for serotype 6A, a significant decrease of PCV serotypes in older population has been reported in several countries due to indirect protection following introduction of PCVs into the childhood national immunization program (NIP) [9]. Currently, there is controversy regarding the right pneumococcal vaccine for the elderly population to be recommended not only for routine use but also for the NIP in terms of better efficacy and cost-effectiveness.

In the Republic of Korea (ROK), the proportion of the elderly population ≥65 years has increased rapidly from 9.8% in 2007 to 12.2% in 2013, and pneumonia has been placed as the fourth leading cause of death in 2013 [10]. In a retrospective study using the nationwide Health Insurance Review Assessment database from 2009 to 2013, the estimated annual incidence of hospitalized community acquired pneumonia was 631 per 100,000 persons, with particularly high incidence among those aged 65–74 years (1,664 per 100,000 persons) and ≥75 years (4,326 per 100,000 persons) [11]. However, the uptake of PPV23 in the elderly population was estimated as 15.4% in 2012, since the official recommendation was issued in 2005 [12]. On the other hand, optional use of childhood PCV7 vaccine was introduced in November 2003. The 4-dose childhood PCV vaccination coverage among children aged 3 years was 74.8% in 2013 [13]. There have been earlier reports on a significant decrease in the proportion of PCV7-specific serotypes of nasopharyngeal and IPD pneumococcal isolates among Korean children between 2006 and 2010, following optional use of PCV7 vaccine [14,15]. Expecting the potential herd effect of childhood PCVs on adult pneumococcal diseases and considering the broader serotype coverage of PPV23, the Korean government has launched the PPV23 NIP for the elderly aged ≥65 years in May 2013, and then achieved the cumulative uptake rate of approximately 58.4% for the targeted population by October 2015 [12]. In the meantime, the PCVs (PCV10 or PCV13) childhood NIP has been implemented since May 2014, achieving coverage rate of 97% by 2015 [16].

The purpose of this study was to assess the direct effectiveness of PPV23 in preventing IPD and NBPP among patients aged ≥65 years following implementation of the PPV23 NIP in the ROK where herd immunity continues to accumulate with introduction of PCV10 or PCV13 into the childhood NIP.

2. Methods

2.1. Study design, setting and population

A hospital-based, matched case-control study was conducted at the Korea University Anam Hospital, Seoul, ROK. The NIP for the elderly population (≥65 years) providing one dose of PPV23 free of charge has been implemented since May 2013. A multi-center pneumococcal diseases surveillance program consisting of 20 participating hospitals nationwide was established to monitor pneumococcal serotypes among adult IPD (≥18 years) and elderly NBPP(≥65 years), and maintained under the governmental funding from March 2013 to October 2015. All eligible IPD and NBPP cases were identified and enrolled from the surveillance database by area and involved hospitals. Inclusion criteria for IPD case were comprised of as an episode of illness in a hospitalized adult (≥65 years) with identification of *S. pneumoniae* from normally sterile sites (e.g. cerebrospinal fluid, blood, bone, pleural fluid, joint fluid, ascites). A case of NBPP was defined as clinical diagnosis of pneumococcal pneumonia in a hospitalized adult (≥65 years) who met all the following inclusion criteria: (1) at least one of clinical signs of infection (fever > 38 °C or hypothermia < 35.5 °C, leukocytosis > 10,000 cells/mm^3 or leukopenia < 4500 cells/mm^3; (2) at least two of respiratory symptoms and signs (cough, productive sputum, abnormal findings on lung auscultation, tachypnea or hypoxemia with SpO_2 < 90%); (3) radiographic findings consistent with pneumonia from either chest x-ray or chest computed tomography; and, (4) microbiological evidence of pneumococcal pneumonia (positive sputum culture for *S. pneumoniae* or positive conventional urinary pneumococcal antigen test) without bacteremia or empyema. Cases of IPD and NBPP were verified for their eligibility by infectious disease physicians after review of the medical records at each hospital by the infectious disease physicians. Separately, a control patient was identified and selected after screening of randomly chosen medical records of the identical hospital where the IPD or NBPP case was identified, matched with the respective case by sex, age group (65–74 years or ≥ 75 years), and a date of admission (±2 calendar months). Exclusion criteria included the following conditions; (1) hospitalized patients < 65 - years, (2) a patient who received PCV vaccination prior to the present study, (3) a patient who had any evidence of *S. pneumoniae* infection or colonization in their clinical specimens.

2.2. Data collection

Demographic and clinical data were collected using the standardized case report form at each hospital, including underlying medical conditions, immunocompromised conditions, microbiological data, and outcomes of 30-day in-hospital mortality. The definition of underlying medical conditions was adapted from a previous study [17]. Vaccination histories for PPV23, PCV7, PCV10, PCV13, and influenza vaccine were collected from the

national immunization registry and each hospital's records. Previous immunization was categorized as 'vaccinated' if a patient had received vaccine(s) as follows: PPV23 (4 weeks to 5 years), PCVs (≥4 weeks), and recent seasonal influenza vaccine (2 weeks to 6 months) before diagnosis of IPD or NBPP for case patients and the hospital admission for control patients.

Serotyping of pneumococcal isolates with positive pneumococcal culture from clinical specimens from cases of IPD and NBPP was performed at the study coordinating center, Korea University Anam Hospital, Seoul, ROK, using the automated multiplexed serotyping assay for *S. pneumoniae* in collaboration with the World Health Organization pneumococcal serology reference laboratory at the University of Alabama at Birmingham, as described previously [18].

2.3. Statistical analysis

Sample size estimation for our case-control study was based on the assumption that PPSV23 effectiveness would be 57% against IPD with PPV23 coverage rate among cases (30%) and controls (50%) [19]. With $\alpha = 0.05$ and a power of 80%, it was estimated that we would need to enroll at least 73 case patients and 146 control subjects for the total of IPD. Similarly, the sample size was calculated with the assumption that PPV23 effectiveness was 30% against NBPP with PPV23 coverage rate among cases (30%) and controls (50%) [4]. With $\alpha = 0.05$ and a power of 80%, we estimated that we would need at least 501 case patients and 501 control subjects for the total of NBPP.

The effectiveness of PPV23 including serotype-specific effectiveness was analyzed using generalized estimating equations (GEE). An independence correlation structure with the best fitting model was selected by quasi-likelihood under the independence model criterion. In multivariate analysis of GEE, the effectiveness of PPV23 was calculated after adjusting for risk factors such as sex, age group, underlying medical conditions, and recent seasonal influenza vaccination. The significant risk factors for multivariate analysis of GEE were selected based on backward elimination at a significance level of 0.10. The homogeneity of serotypes between PPV23 vaccinated and non-vaccinated groups of case patients was tested using the Chi-square or the Fisher's exact test. The multiple logistic regression model with Firth's penalized likelihood was used for the serotypes with p value < 0.1 to adjust the effects of significant variables between the vaccine and non-vaccine groups. Given the potential impact of age on the effectiveness of PPV23 due to immunosenescence, we performed stratified analyses by age group (65–74 years or ≥ 75 years). SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. A p value < 0.05 was considered to be statistically significant.

3. Results

From March 2013 through October 2015, 148 eligible patients with IPD and 564 eligible patients with NBPP cases were identified from 14 and 4 hospitals participated in the surveillance program, respectively. Controls were selected 1:2 ratio for IPD and 1:1 ratio for NBPP. However, one control patient for IPD and 7 case patients for NBPP were excluded because they had received the pneumococcal conjugate vaccine. Therefore, a total of 443 patients for IPD (148 case patients and 295 control patients) and 1114 patients for NBPP (557 case patients and 557 control patients) was enrolled in the analyses (Fig. 1).

3.1. Invasive pneumococcal disease

Among 148 IPD case patients, the majority (104; 70.3%) had bacteremic pneumonia, followed by primary bacteremia (18; 12.2%), deep-seated infections (15; 10.1%), and meningitis (11; 7.4%). The median age of the case patients was 75 years. The majority of the case and control patients had one or more underlying medical condition(s). Furthermore, immunocompromised conditions were noted in both case and control patients. The median time interval between PPV23 vaccination and date of admission due to IPD was 14 months (interquartile range [IQR] 7–20 months) for cases and 14 months (IQR 8–20 months) for controls (Table 1). The occurrence of IPD cases during influenza season (November–April) was noted in 82 cases (55.4%). There was no difference in receipt of recent influenza vaccination between case and control patients.

The unadjusted and adjusted overall effectiveness of PPV23 against IPD for all patients ≥ 65 years were not protective (Table 2). Since there was a borderline interaction effect between age and PPV23 vaccination (p = 0.05), we performed age-subgroup analyses. In the age-stratified analysis, the unadjusted and adjusted effectiveness of PPV23 in the age group 65–74 years were 55.4% (95% confidence interval (CI) 17.5–75.9) and 57.4% (95% CI 19.4–77.5), respectively, which were protective. For the age group ≥ 75 - years, the unadjusted and adjusted effectiveness of PPV23 were not protective.

Pneumococcal serotyping data were available for 93 cases (62.8%) of the IPD case patients, including 64 vaccine serotypes and 29 non-vaccine serotypes (Supplementary Table 1). Serotype 3 was the most common serotype among IPD isolates, accounting for 16.1% (15/93). The difference in distribution of vaccine serotypes was compared between vaccinated and unvaccinated IPD case patients by age groups. In the age group 65–74 years, there were significantly less IPDs due to PPV23 unique serotypes (PPV23 serotypes not included in PCV13) in vaccinated patients, compared to unvaccinated patients (12.5% vs. 39.3%, p = 0.010). Considering the low vaccine effectiveness for serotype 3, there were fewer IPDs due to PPV23 serotypes excluding serotype 3 (22 serotypes of PPV23 vaccine, excluding serotype 3) in vaccinated patients, compared to unvaccinated patients (37.5% vs. 73.5%, p = 0.090) (Supplementary Table 2).

The adjusted serotype-specific effectiveness of PPV23 against IPD after controlling for confounders is presented by age group (Table 3). In the age group ≥ 65 years, the adjusted vaccine effectiveness against IPDs due to PPV23 serotypes excluding serotype 3 and due to PPV23-unique serotypes was 57.6% (95% CI 17.1–78.3) and 78·0% (95% CI 34.6–92.6), respectively. In age group 65–74 years, the adjusted vaccine effectiveness against IPDs due to all PPV23 serotypes, PPV23 serotypes excluding serotype 3, and PPV23 unique serotypes were 69.9% (95% CI 24.8–88.0), 81.3% (95% CI 38.6–94.3), and 90·6% (95% CI 27.6–98.8), respectively. On the other hand, the adjusted vaccine effectiveness against IPDs due to PCV13 serotypes was not protective. In the age group ≥ 75 years, the adjusted vaccine effectiveness against IPDs due to all PPV23 serotypes, PPV23 serotypes excluding serotype 3, PCV13 serotypes or PPV23 unique serotypes was not protective.

3.2. Non-bacteremic pneumococcal pneumonia

The median age of 557 NBPP case patients was 76 years. The majority of the case and control patients had one or more underlying medical condition(s) (Table 1). Immunocompromised conditions were also noted in both case and control patients. The median time interval between PPV23 vaccination and date of admission due to NBPP was 15 months (IQR 9–22 months) for

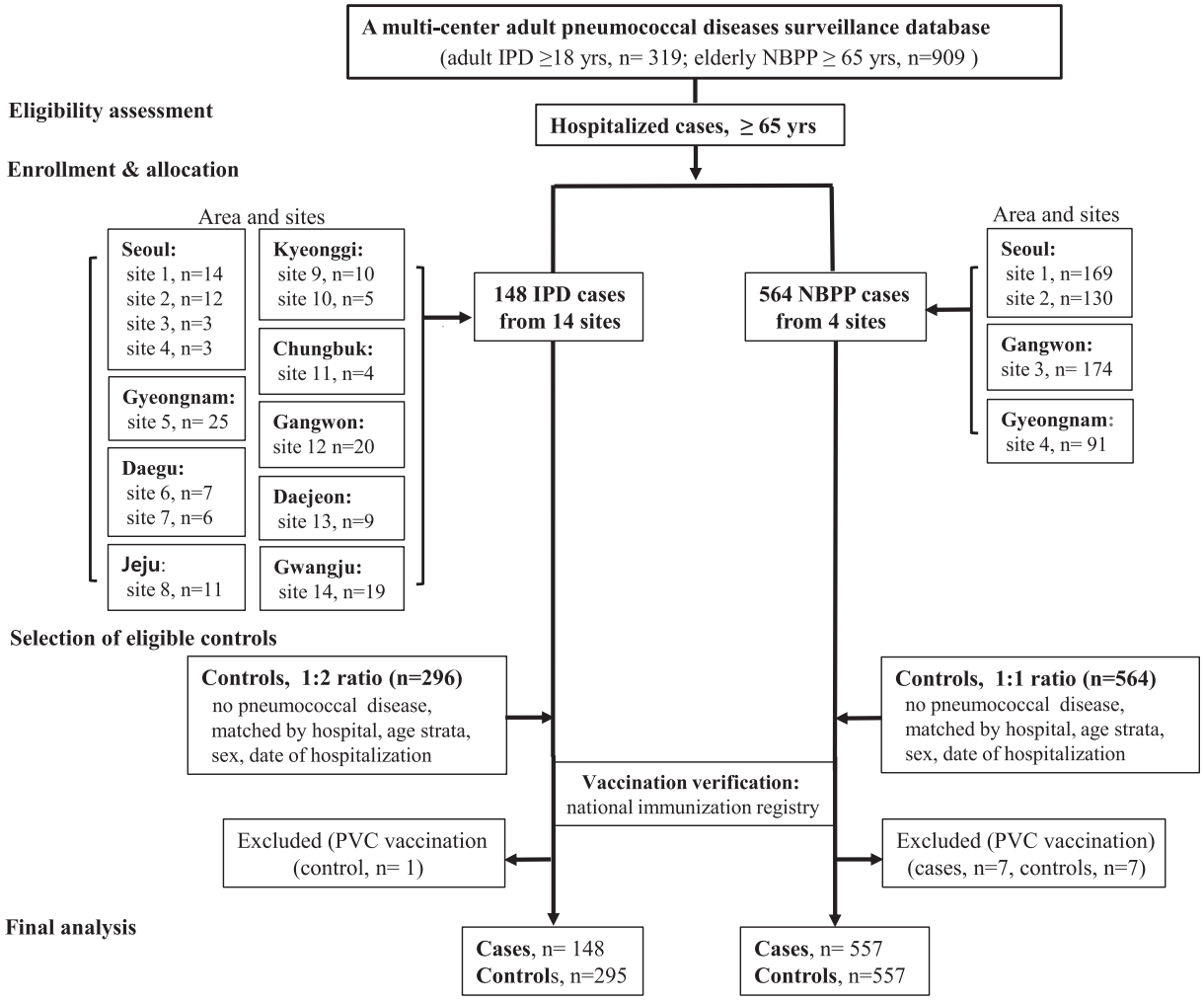

Fig. 1. Flowchart of IPD and NBPP patients enrolled in the study.

cases and 15 months (IQR 8–21 months) for controls. (Table 1). The occurrence of NBPP cases during influenza season (November–April) was noted in 319 cases (57.3%). There was no difference in receipt of recent influenza vaccination between case and control patients.

The unadjusted and adjusted overall effectiveness of PPV23 against NBPP for all patients ≥ 65 years were not protective. Based on a borderline interaction effect between age and PPV23 vaccination (P = 0.08), age-subgroup analyses were performed. In the age group 65–74 years, the adjusted effectiveness of PPSV23 was 35.0% (95% CI 2.3 – 56.7) after controlling for center effect, chronic heart disease, chronic pulmonary disease, chronic alcohol use, chronic smoking, and long-term care facility residency. For the age group ≥ 75 years, the unadjusted and adjusted effectiveness of PPSV23 were not protective (Table 2).

Pneumococcal serotyping data was available for 436 cases (78.3%) of the NBPP case patients, including 254 vaccine serotypes and 182 non-vaccine serotypes (Supplementary Table 3). The most common serotype was serotype 3 (59 cases; 13.5%), followed by serotype 11A (49 cases; 11.2%) and non-vaccine serotype 34 (40 cases; 9.2%) in decreasing frequency. There was no significant difference in the distribution of PPV23 serotypes, PPV23 serotypes excluding serotype 3, PCV13 serotypes, PCV13 excluding serotype 3, and PPV23-unique serotypes between PPV23 vaccinated and unvaccinated case patients in stratified age groups (Supplementary Table 4).

The adjusted serotype-specific effectiveness of PPV23 against NBPP after controlling for confounders is presented by age groups (Table 4). The adjusted serotype-specific effectiveness against NBPP due to PPV23 serotypes, PPV23 serotypes excluding serotype 3, PCV13 serotypes or PPV23-unique serotypes was not protective for the three age groups. However, there was a non-significant of increase in PPV23 effectiveness against PPV23 serotype excluding serotype 3 in patients aged 65–74 years.

4. Discussion

In the present case-control study, we assessed overall and serotype-specific effectiveness of PPV23 against IPD and NBPP among elderly hospitalized patients following the implementation of NIP. Two important observations from our results were made: (1) Our study was the first to demonstrate significant effectiveness of PPV23 for young elderly patients aged 65–74 years against IPD and NBPP when given as NIP in the setting of ongoing herd effects from pediatric PCV NIP in the ROK; (2) PPV23 had higher effectiveness against IPD due to PPV23 serotypes and PPV23-unique serotypes; however, it was non-effective against IPD due to PCV13 serotypes, implying direct effectiveness of PPV23 in prevention of IPD.

Variable PPV23 effectiveness estimates against IPD and pneumococcal pneumonia were reported in previous studies, depending

Table 1
Baseline characteristics of cases and controls for invasive pneumococcal disease and non-bacteremic pneumococcal pneumonia.

	All ≥ 65 years			65–74 years			≥75 years		
	Cases	Controls	*P*-value	Cases	Controls	*P*-value	Cases	Controls	*P*-value
Invasive pneumococcal disease									
Number of patients	148	295		73	145		75	150	
Age, median (IQR), years	75(71–80)	75(71–90)	0.508	71(69–73)	70(68–72)	0.794	80(78–84)	79(77–83)	0.095
Sex			0.316			0.908			1.000
Male	105 (70.9)	209 (70.8)		54 (74.0)	107 (73.8)		51 (68.0)	102 (68.0)	
Female	43 (29.1)	86 (29.2)		19 (26.0)	38 (26.2)		24 (32.0)	48 (32.0)	
Medical condition(s)									
IC condition	42 (28.4)	63 (21.4)	0.081	28 (38.4)	39 (26.9)	0·054	14 (18.7)	24 (16.0)	0.633
Chronic heart disease	23 (15.5)	50 (16.9)	0.711	11 (15.1)	21 (14.5)	0·908	12 (16.0)	29 (19.3)	0.550
Chronic pulmonary disease	30 (20.3)	69 (23.5)	0.409	10 (13.7)	28 (19.4)	0·272	20 (26.7)	41 (27.3)	0.908
Chronic liver disease	9 (6.1)	10 (3.4)	0.225	7 (9.6)	8 (5.5)	0·313	2 (2.7)	2 (1.3)	0.489
Chronic kidney disease	5 (3.4)	26 (8.8)	0.041	3 (4.1)	9 (6.2)	0·533	2 (2.7)	17 (11.3)	0.037
Chronic CNS disease	21 (14.2)	52 (17.6)	0.352	10 (13.7)	23 (15.9)	0·686	11 (14.7)	29 (19.3)	0.351
Diabetes mellitus	33 (22.3)	92 (31.3)	0.042	20 (27.4)	52 (35.9)	0·191	13 (17.3)	40 (26.8)	0.115
Chronic alcoholics	3 (2.0)	12 (4.1)	0.278	2 (2.7)	7 (4.8)	0·478	1 (1.3)	5 (3.3)	0.401
Chronic smoking	4 (2.7)	60 (20.4)	<0.001	3 (4.1)	33 (22.9)	0.003	1 (1.3)	27 (18.0)	0.006
Long-term care facility residence	31 (20.9)	41 (13.9)	0.067	9 (12.3)	18 (12.4)	0.986	22 (29.3)	23 (15.3)	0.010
A receipt of PPV23	54 (36.5)	130 (44.1)	0.086	16 (21.9)	56 (38.6)	0.010	38 (50.7)	74 (49.3)	0.836
Time since PPV23, month[a] (IQR)	14 (7–20)	14 (8–20)	0.956	8 (6–16)	14 (7–18)	0.258	16 (10–23)	15 (8–22)	0.722
A receipt of recent influenza vaccine	46 (31.1)	85 (28.8)	0.553	21 (28.8)	46 (31.7)	0.638	25 (33.3)	39 (26.0)	0.108
Non-bacteremic pneumococcal pneumonia									
Number of patients	557	557		233	233		324	324	
Age, median (IQR), years	76(71–80)	76(72–81)	0.645	70(68–73)	71(68–73)	0.360	80(77–84)	80(77–84)	0.629
Sex			1.000			1.000			1.000
Male, n (%)	424 (76.1)	424 (76.1)		190 (81.5)	190 (81.5)		234 (72.2)	234 (72.2)	
Female, n (%)	133 (23.9)	133 (23.9)		43 (18.5)	43 (18.5)		90 (27.8)	90 (27.8)	
Medical condition(s)									
IC condition, n (%)	144 (25.9)	207 (37.2)	<0.001	80 (34.3)	90 (38.6)	0.327	64 (19.8)	117 (36.1)	<0.001
Chronic heart disease, n (%)	95 (17.1)	129 (23.2)	0.012	31 (13.3)	49 (21.0)	0.029	64 (19.8)	80 (24.7)	0.137
Chronic pulmonary disease	206 (37.0)	130 (23.3)	<0.001	86 (36.9)	48 (20.6)	<0.001	120 (37.0)	82 (25.3)	0.002
Chronic liver disease	18 (3.2)	21 (3.8)	0.622	10 (4.3)	12 (5.2)	0.655	8 (2.5)	9 (2.8)	0.809
Chronic kidney disease	47 (8.4)	40 (7.2)	0.413	15 (6.4)	15 (6.4)	1.000	32 (9.9)	25 (7.7)	0.318
Chronic CNS disease	155 (27.8)	110 (19.7)	0.001	41 (17.6)	34 (14.6)	0.370	114 (35.2)	76 (23.5)	0.001
Ventriculoperitoneal shunt	0 (0.0)	1 (0.2)	0.317	0 (0.0)	0 (0.0)	NA[6]	0 (0.0)	1 (0.3)	0.317
Diabetes mellitus	132 (23.7)	167 (30.0)	0.020	61 (26.2)	78 (33.5)	0.094	71 (21.9)	89 (27.5)	0.106
Chronic alcoholics	2 (0.4)	52 (9.3)	<0.001	2 (0.9)	31 (13.3)	<0.001	0 (0.0)	21 (6.5)	<0.001
Chronic smoking	49 (8.8)	173 (31.1)	<0.001	24 (10.3)	86 (36.9)	<0.001	25 (7.7)	87 (26.9)	<0.001
Long-term care facility residence	99 (17.8)	34 (6.1)	<0.001	29 (12.4)	6 (2.6)	<0.001	70 (21.6)	28 (8.6)	<0.001
A receipt of PPV23	231 (41.5)	247 (44.3)	0.285	76 (32.6)	94 (40.3)	0.060	155 (47.8)	153 (47.2)	0.862
Time since PPV23, month (IQR)[a]	15 (9–22)	15 (8–21)	0.192	14 (8–19)	13 (7–17)	0.289	16 (9–23)	16 (8–23)	0.550
A receipt of recent influenza vaccine	176 (31.6)	178 (32.0)	0.871	77 (33.0)	77 (33.0)	1.000	99 (30.6)	101 (31.2)	0.831

Data are expressed as the number of persons (percentage of the working population) unless otherwise stated.
Abbreviations: IC, immunocompromised; CNS, central nervous system; PPV23, 23-valent pneumococcal polysaccharide vaccine; NBPP, non-bacteremic pneumococcal pneumonia; NA, not available; IQR, interquartile range
[a] Time interval between a date of vaccination and date of hospitalization due to pneumococcal disease

on study population characteristics, prevalent serotypes, coverage of pediatric pneumococcal vaccination, the time interval to assessment after vaccination, and case definition [4,5,20–22]. These factors should be cautiously reviewed in comparing the protective PPV23 effectiveness among studies. In this study, a subgroup of older patients (≥75 years) demonstrated decreased, non-significant overall PPV23 effectiveness against both IPD and NBPP, contrary to significant effectiveness in young elderly subgroup (65–74 years). The majority of the case and control patients of IPD and NBPP aged ≥ 75 years had one or more underlying medical condition(s) and the moderate number of the case and control patients were noted to have immunocompromised conditions. Functional antibody activity against *S. pneumoniae* following PPV23 vaccination has been shown to be reduced in relation to the advanced aging in the elderly [23]. Moreover, decreased PPV23 effectiveness has been reported in patients with underlying medical condition(s), particularly IC [19]. These factors might have contributed to lower PPV23 effectiveness in our subgroup of elderly patients ≥ 75 years. A Taiwan study conducted in 2008 using the National Health Insurance Research Database reported that PPV vaccination in the previous year among elderly people ≥ 75 years was associated with a 60% reduction in pneumonia hospitalization, a 76% reduction in IPD, and a > 90% reduction in death from pneumonia [24]. Unlike that our study included all hospitalized elderly patients as cases and controls, the Taiwan study may have different population characteristics such as inclusion of healthy older adults, which might lead to a difference in estimation of PPV23 effectiveness.

In this study, PPV23, PCV13, and non-vaccine serotypes accounted for 68.8%, 38.7%, and 31.2% of all detected serotypes from IPD cases, and 55.7%, 38.8%, and 41.7% of all detected serotypes from NBPP cases, respectively. Our study provided evidence of differential effectiveness of PPV23 by serotypes, in particular, significant effectiveness against IPD caused by PPV23-unique serotypes observed in 65–74-year-old patients indicates direct effectiveness of PPV23 by excluding the potential herd effects by PCV13 serotypes. On the other hand, serotype 3 was the most common serotype among our IPD and NBPP isolates. Low or lack of vaccine effectiveness of serotype 3 has been reported in previous studies [25–27], possibly due to abundant polysaccharide capsules of serotype 3 and reduced antibody response following vaccination [26]. Accordingly, we estimated the effectiveness of PPV23 against IPD due to PPV23 serotypes, excepting serotype 3 to limit its negative influence of serotype 3, resulting in increased effectiveness to

Table 2
Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease and non-bacteremic pneumococcal pneumonia in a matched case-control study by age group.

	Cases no. (%) of vaccinated	Controls no. (%) of vaccinated	Unadjusted effectiveness % (95% CI), *P*-value	Adjusted effectiveness % (95% CI), *P*-value
Invasive pneumococcal disease				
Number of patients	148	295		
All ≥ 65 years	54/148 (36.5)	130/295 (44.1)	27.1 (–4.6 to 49.1), 0.086	28·5 (-5.8 to 51.6), 0.094[a]
65–74 years	16/73 (21.9)	56/145 (38.6)	55·4 (17.5 to 75.9), 0.010	57·4 (19.4 to 77.5), 0.009[b]
≥75 years	38/75 (50.7)	74/150 (49.3)	−5·5 (–74.6 to 36.3), 0.836	6·7 (–73.9 to 49.9), 0.827[c]
Non-bacteremic pneumococcal pneumonia				
Number of patients	557	557		
All ≥ 65 years	231/557 (41.5)	247/557 (44.3)	11·1 (–10.3 to 28.3), 0.285	10·2 (–15.1 to 30.0), 0.394[d]
65–74 years	76/233 (32.6)	94/233 (40.3)	28·4 (–1.4 to 49.5), 0.060	35·0 (2.3 to 56.7), 0.038[e]
≥75 years	155/324 (47.8)	153/324 (47.2)	−2·5 (–35.5 to 22.4), 0.862	−13·1 (–56.1 to 18.1), 0.456[f]

[a] Adjusted for immunocompromised condition, chronic kidney disease, diabetes mellitus, chronic smoking, and long-term care facility residence.
[b] Adjusted for immunocompromised condition and chronic smoking.
[c] Adjusted for chronic kidney disease, chronic central nervous system disease, chronic smoking, diabetes mellitus, long-term care facility residence, and influenza vaccination.
[d] Adjusted for hospital centers, immunocompromised condition, chronic heart disease, chronic pulmonary disease, chronic alcohol consumption, chronic smoking, and long-term care facility residence.
[e] Adjusted for hospital centers, chronic heart disease, chronic pulmonary disease, chronic alcohol consumption, chronic smoking, and long-term care facility residence.
[f] Adjusted for hospital centers, immunocompromised condition, chronic heart disease, chronic pulmonary disease, chronic alcohol consumption, and long-term care facility residence.

Table 3
Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in a matched case-control study by age group.

	All ≥ 65 years			65–74 years			≥75 years		
	Cases	Controls (n = 295)	Adjusted effectiveness (95%CI), *P*-value	Cases	Controls (n = 145)	Adjusted effectiveness (95%CI), *P*-value	Cases	Controls (n = 150)	Adjusted effectiveness (95%CI), *P*-value
PPV23 serotypes	(n = 64)			(n = 37)			(n = 27)		
Vaccinated (%)	21 (32.8)	130 (44.1)	41.9%[a](-1.5 to 66.8), 0.056	6 (16.2)	56 (38.6)	69.9%[e](24.8 to 88.0), 0.010	15 (55.6)	74 (49.3)	−19.7%[f](−183.9 to 49.6), 0.684
PPV23 serotypes, excluding serotype 3	(n = 49)			(n = 28)			(n = 21)		
Vaccinated (%)	12 (24.5)	130 (44.1)	57.6%[b](17.1 to 78.3), 0.012	3 (10.7)	56 (38.6)	81.3%[e](38.6 to 94.3), 0.006	9 (42.9)	74 (49.3)	25.9%[g](−79.0 to 69.3), 0.506
PCV13 serotypes	(n = 36)			(n = 18)			(n = 18)		
Vaccinated (%)	17 (47.2)	130 (44.1)	−14.6%[c](−121.5 to 40.8), 0.686	5 (27.8)	56 (38.6)	38.5%(−75.2 to 78.4), 0.363	12 (66.7)	74 (49.3)	−96.4%[c](−466.8 to 32.0), 0.212
PPV23 unique typesVaccinated (%)	(n = 28) 4 (14.3)	130 (44.1)	78.0%[d](34.6 to 92.6), 0.007	(n = 19) 1 (5.3)	56 (38.6)	90.6%[d](27.6 to 98.8), 0.023	(n = 9)3 (33.3)	74 (49.3)	59.8%[h](−48.7 to 89.1), 0.172

Abbreviations: PPV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.
[a] Adjusted for chronic kidney disease, diabetes mellitus, smoking, and recent influenza vaccine exposure.
[b] Adjusted for immunocompromised status, chronic kidney disease, and smoking.
[c] Adjusted for diabetes mellitus and smoking.
[d] Adjusted for immunocompromised status and smoking
[e] Adjusted for smoking.
[f] Adjusted for diabetes mellitus, smoking, and recent influenza vaccine exposure.
[g] Adjusted for smoking and recent influenza vaccine exposure.
[h] Adjusted for recent influenza vaccine exposure

57.6% (95% CI 17.1–78.3) and 81·3% (95% CI 38.6–94.3) in the age groups ≥ 65 years and 65–74 years, respectively.

Our study demonstrated that overall effectiveness of PPV23 against NBPP was 35.0% (95% CI 2.3–56.7) in the young elderly group (65–74 years); however, it failed to show serotype-specific effectiveness of PPV23 against NBPP. The small number of available serotypes for analysis might have contributed to a lack of statistical power to detect such difference. On the other hand, a recent Japanese study reported not only low, overall effectiveness of PPV23 against pneumococcal pneumonia comprising 97% of NBPP (27.4%, 95% CI 3.2–45.6), but also moderate serotype-specific effectiveness against PPV23 serotypes (33.5%, 95% CI 5.6–53.1) in people aged ≥ 65 years [25]. The discrepancy between the two studies might be due to the difference in study design and partly serotype distribution. There are proportional differences in serotype distribution between our NBPP patients and patients in the Japanese study (PPV23 serotype: 55.7% vs 79.1%; PCV13 serotype: 38.8% vs 58.7%; PPV23-unique serotype: 19.·5% vs 20.3%; non-PPV23 serotype: 41.7% vs 20.9%). Besides, PCR-based serotyping applied to pneumococcal-positive sputum samples was used in the Japanese study, which detected multiple serotypes in 48% of the patients.

Time of assessment since PPV23 vaccination may influence the magnitude of the effectiveness against pneumococcal diseases [25,27,28]. The time interval between PPV vaccination and diagnosis of pneumococcal diseases or hospital admission was<36 months

Table 4
Serotype-specific effectiveness of the 23-valent pneumococcal polysaccharide vaccine against non-bacteremic pneumococcal pneumonia in a matched case-control study by age group.

	All ≥ 65 years			65–74 years			≥75 years		
	Cases	Controls (n = 557)	Adjusted effectiveness (95% CI), *P*-value	Cases	Controls (n = 233)	Adjusted effectiveness (95% CI), *P*-value	Cases	Controls (n = 324)	Adjusted effectiveness (95% CI), *P*-value
PPV23 serotypes	(n = 243)			(n = 105)			(n = 138)		
Vaccinated (%)	106 (43.6)	247 (44.3)	−2.0%[a](−39.9 to 25.6), 0.901	40 (38.1)	94 (40.3)	21.0%[d](−31.3 to 52.4), 0.364	66 (47.8)	153 (47.2)	−35.0%[h](−106.9 to 12.0), 0.169
PPV23 serotypes, excluding serotype 3	(n = 184)			(n = 81)			(n = 103)		
Vaccinated (%)	78 (42.4)	247 (44.3)	−5.6%[b](−49.3 to 25.3), 0.757	28 (34.6)	94 (40.3)	30.7%[e](−21.2 to 60.4), 0.198	50 (48.5)	153 (47.2)	−44.8%[h](−134.5 to 10.6), 0.132
PCV13 serotypes	(n = 169)			(n = 76)			(n = 93)		
Vaccinated (%)	77 (45.6)	247 (44.3)	−2.8%[a](−39.9 to 25.6), 0.901	29 (38.2)	94 (40.3)	14.9%[f](−49.7 to 51.7), 0.575	48 (51.6)	153 (47.2)	−16.9%[i](−85.0 to 26.2), 0.506
PPV23 unique types	(n = 85)			(n = 34)			(n = 51)		
Vaccinated (%)	35 (41.2)	247 (44.3)	−10.9%[c](−83.6 to 33.0), 0.687	12 (35.3)	94 (40.3)	20.5%[g](−77.4 to 64.4), 0.576	23 (45.1)	153 (47.2)	−65.8%[c](−230.1 to 16.7), 0.150

Abbreviations: PPV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.
[a] Adjusted for immunocompromised status, chronic heart disease, chronic pulmonary disease, chronic alcohol consumption, smoking, long-term care facility residence, and hospital center.
[b] Adjusted for chronic heart disease, chronic pulmonary disease, chronic central nervous system disease, smoking, long-term care facility residence, and hospital center.
[c] Adjusted for chronic pulmonary disease, chronic central nervous system disease, smoking, long-term care facility residence, and hospital center.
[d] Adjusted for chronic pulmonary disease, chronic alcohol consumption, smoking, long-term care facility residence, and hospital center.
[e] Adjusted for chronic pulmonary disease, smoking, long-term care facility residence, and hospital center.
[f] Adjusted for chronic pulmonary disease, chronic alcohol consumption, smoking, long-term care facility residence.
[g] Adjusted for chronic pulmonary disease, smoking, and long-term care facility residence.
[h] Adjusted for immunocompromised status, chronic heart disease, chronic pulmonary disease, chronic central nervous system disease, diabetes mellitus, smoking, long-term care facility residence, and hospital center.
[i] Adjusted for immunocompromised status, chronic pulmonary disease, smoking, and hospital center.

in the majority of vaccinated case and control patients in our study. Thus, relatively short time interval since PPV23 vaccination might have contributed to higher serotype-specific effectiveness estimates against IPD that might decrease over time in our cohort.

A recent study reported that there was a rapid increase of non-PCV13 serotype IPD since the introduction of PCV13, particularly among elderly adults, in England and Wales [29]. The vaccination rate of PCV13 among children has increased in the ROK (67% in 2011, 76% in 2012, and 83% in 2013) [13]. PCV vaccination coverage (third dose) among one-year-olds was 97% in 2015 and 98% by the end of 2016 [16]. Thus, the proportion of IPD and NBPP caused by non-PCV13 serotypes in elderly adults may increase in the ROK in the near future. Furthermore, our results of significantly fewer IPDs due to PPV23-unique serotypes among the PPV23 vaccinated case patients support the use of PPV23 among elderly adults as PPV23 vaccination would provide broader protection against non-PCV13 serotypes.

The strength of our study compared to other observational studies is the minimization of misclassification bias using rigorous exclusion criteria for any microbiological evidence of *S. pneumoniae* in the selection of control patients, and accessibility to past PPV23 vaccination records from the national immunization registry. Furthermore, this study has the advantage that IPD and NBPP cases were identified by infectious disease specialists who participated in the surveillance program. Despite this, our study has limitations. Sampling and selection bias by a small number of patients and confounding effects from unmeasured variables such as previous episodes of pneumonia and disease severity may have affected our analyses. However, we used a multivariate GEE analysis to control for potential confounding effects.

5. Conclusions

This study demonstrated that PPSV23 NIP for the elderly may be effective in preventing not only IPD but also NBPP among young elderly people aged 65–74 years in ROK in the setting of ongoing herd immunity from pediatric PCV NIP. Therefore, this study provides the first supporting evidence of the pneumococcal NIP strategy differentially using PPV23 for the elderly and PCV13 for the children, especially for countries which have insufficient coverage of pneumococcal vaccination and are considering pneumococcal NIP in the pediatric and elderly populations.

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Authors' contributions

JHK, BCC, and MJK were involved in the conception and the design of the study project. All authors contributed to the acquisition and interpretation of data for the work. JHK, BCC, and MJK were involved in the analyses of the study data. JHK drafted the manuscript. MJK revised the manuscript.

Conflict of interest statement

All authors declare no competing interests.

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Ethics approval

This study was approved by the institutional review board at the Korea University Anam Hospital (IRB Number 2016AN0249).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.017.

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