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Effectiveness of 23-valent pneumococcal polysaccharide vaccine on diabetic elderly

Chia-Sheng Kuo (MD, MPH)[a,b], Chia-Wen Lu (MD, MSc)[c], Yu-Kang Chang (PhD)[d], Kuen-Cheh Yang (MD, MSc)[e], Shou-Hung Hung (MD)[a], Ming-Ching Yang (DrPH)[b], Hao-Hsiang Chang (MD, MSc)[c], Chi-Ting Huang (MS)[d], Chih-Cheng Hsu (MD PhD)[d,f,g,*], Kuo-Chin Huang (MD, PhD)[c,e,*]

Abstract

Diabetes mellitus is associated with increased risk of pneumonia, and 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for prevention of pneumonia. However, the effectiveness of PPV23 remains unclear in the older diabetic patients who usually have compromised immune function.

We used data extracted from the Taiwanese National Health Insurance Research Database (NHIRD) from 2000 to 2009 to conduct a population-based retrospective cohort study, comparing the incidence of pneumococcal diseases among PPV23-vaccinated and propensity-score matched PPV23-unvaccinated groups in diabetic elderly. The primary outcome was invasive pneumococcal diseases (IPDs), and the secondary outcomes were medical utilization.

PPV23-vaccinated group had reduced risks of IPD (adjusted OR: 0.86, 95% CI: 0.78–0.94), respiratory failure (0.84, 0.77–0.93), and shorter length of hospitalization (-1.27 ± 0.19 days, *P* value: 0.0012). In flu-vaccinated group, subjects who received PPV23 had reduced risks of IPD, hospitalization, and respiratory failure; had shorter lengths of hospitalization; and less medical costs, than those without receiving PPV23. In not flu-vaccinated group, PPV23 vaccination was associated with reduced risks of IPD and respiratory failure. Receiving both vaccines could bring better protection in IPD, hospitalization, visits of emergency department, and respiratory failure.

PPV23 vaccination was effective in prevention of pneumococcal diseases and reduction of medical utilization in diabetic elderly aged 75 and more. Receiving both vaccines resulted in better outcomes than PPV vaccination alone.

Abbreviations: IPD = invasive pneumococcal disease, MPR = medication possession ratio, NHIRD = National Health Insurance Research Database, P4P = pay for performance, PPV23 = 23-valent pneumococcal polysaccharide vaccine, VE = vaccine effectiveness.

Keywords: diabetes, elderly, pneumococcal disease, polysaccharide pneumococcal vaccine

1. Introduction

Immunization is one of the most effective methods to induce host immunity against specific organisms for infection prevention. The effectiveness of 23-valent pneumococcal polysaccharide vaccine (PPV23) in general population and the elderly (either community-dwelling or institutionalized) was described previously.[1–4] According to the recommendations of US and Taiwan Advisory Committee on Immunization Practices (ACIP) in 2016, the elderly are recommended to receive PPV23.[5] Also, PPV23 was recommended for diabetic adults by ACIP and American Diabetes Association (ADA) guidelines.[6]

Diabetes mellitus, a common chronic disease in the elderly, has caused a global burden in perspectives of clinical medicine and public health. Diabetes mellitus is not only associated with many comorbidities, including hypertension, dyslipidemia, and cardiovascular diseases, but also brings the concerns about the vulnerability to infections.[7] Previous studies have demonstrated that diabetes and hyperglycemia are related to many common infections and poorer outcomes, such as pneumococcal diseases,[8] latent tuberculosis infection,[9] infections after peripheral vascular surgery,[10] postoperative bacterial infections,[11] and mortality of infective endocarditis.[12] Focusing on pneumonia, previous investigations also showed the relationship between diabetes mellitus and higher risks of pneumococcal pneumonia,[8] invasive pneumococcal disease (IPD),[13] all-cause pneumonia,[14] and higher mortality rates due to pneumonia-related illnesses.[15–17]

Based on these evidences and recommendations, clinicians ought to suggest diabetic patients, especially the elderly, to be vaccinated with PPV23 for prevention. However, diabetes mellitus has been found to be associated with immune

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C-CH and K-CH equally contributed to this work

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[a] Department of Community and Family Medicine, National Taiwan University Hospital YunLin Branch, [b] College of Public Health, National Taiwan University, [c] Department of Family Medicine, National Taiwan University Hospital, [d] Institute of Population Health Sciences, National Health Research Institutes, Zhunan, [e] Department of Community and Family Medicine, National Taiwan University Hospital Bei-Hu Branch, [f] Department of Health Services Administration, China Medical University, Taichung, [g] Min-Sheng General Hospital, Taoyuan, Taiwan.

[*] Correspondence: Kuo-Chin Huang, Department of Family Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan (e-mail: bretthuang@ntu.edu.tw); Chih-Cheng Hsu, Institute of Population Health Sciences, National Health Research Institutes, 35 Keyan Road, Zhunan Town, Miaoli County 350, Taiwan (e-mail: cch@nhri.org.tw).

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dysfunction,[17–19] which may, in turn, influence the effectiveness of PPV23. Impaired immunogenicity in diabetic patients has been reported previously[20] and the immune function can also further deteriorate in the elderly.[21] It remains to be clarified whether the effectiveness of PPV23 in diabetic elderly is compatible with in general elderly. Therefore, we designed this population-based retrospective cohort study to compare the outcomes between PPV23-vaccinated and unvaccinated diabetic elderly.

2. Material and methods

2.1. Data source

The source of database was based on the Taiwanese National Health Insurance Research Database (NHIRD), which included the healthcare utilization information of nearly 99% of entire Taiwanese population enrolled in the universal National Health Insurance Program.[22] The investigated comorbid diseases were identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The study protocol was approved by the institutional review boards of National Health Research Institutes.

2.2. Design and study subjects

We used a population-based retrospective cohort study design to compare outcomes of the PPV23-vaccinated and PPV23-unvaccinated diabetic elderly. The diabetic patients were defined as those who had diabetes diagnosis (ICD-9-CM 250) for at least 2 times within 1 year. The diabetic patients aged 75 years or older between 2007 and 2009 were then divided into 2 groups based on their PPV23-vaccination record in 2007 to 2009. The date of 1st PPV23 received was defined as the index date for the PPV23-vaccinated subjects (n = 33,395). We used 1:1 propensity score method,[23] on age, gender, and Charlson comorbidity index (CCI), to match and select PPV23-unvaccinated subjects (n = 33,395). The propensity score was estimated using a logistic regression model including covariates generally considered important factors associated with diabetic patients' outcomes, including age, gender, status of joining pay for performance (P4P) program, medication compliance, and the comorbidities listed in the CCI[24] such as myocardial infarction, congestive heart failure, peripherial vascular disease, dementia, cerebrovascular disease, connective tissue disease, liver disease, hemiplegia, chronic renal disease, and cancer. The comorbid status was identified using the NHIRD record 1 year prior to the index date. The nearest-neighbor algorithm was applied to construct matched pairs, assuming that the proportion of 0.95 to 1.0 is perfect.[25] The index date of the PPV23-unvaccinated subjects was assigned as the 1st day (January 1) of the year corresponding to their matched vaccinated pairs.

2.3. Definition of primary and secondary outcomes

The primary outcomes of this study included IPDs (ICD9 038.0, 038.2, 038.9, 790.7, 320.1) happening within 1 year after the index date. The secondary outcomes of this study were respiratory failure (ICD9 518.81, 518.84 and NHI procedure code 57001B) and medical utilization happening within 1 year after the index date. We calculated hospitalization rates, emergency department (ED) visits, length of hospitalizations, and total medical costs to estimate differences of medical utilization between vaccinated and unvaccinated subjects.

2.4. Statistical analysis

The differences of baseline characteristics between PPV23-vaccinated and unvaccinated subjects were presented as the frequencies with percentages for categorical variables and means with standard deviation for continuous variables. We used logistic regression models to estimate the odds ratio (OR) and 95% confidence interval (CI) for the risk of primary and secondary outcomes. Possible confounding factors, which might clinically interfere with the relationship between PPV23 vaccination status and primary/secondary outcomes, were adjusted in multivariate analyses. In the subgroup analyses, we repeated our linear and logistic regression analyses in both flu vaccinated and unvaccinated groups. Within each group, we compared outcomes between PPV23 vaccinated and unvaccinated group, and demonstrated results by using PPV23 unvaccinated group as reference. Those who received influenza vaccine within 1 year prior to or after the index date were categorized as flu-vaccinated group, otherwise as not flu-vaccinated group. In subsequent analyses, we used logistic regression models to estimate the odds ratios of primary and secondary outcomes for those who received PPV23-vaccine only, and those who received both vaccines, compared to those who had not received any (double negative). All P values were 2-sided, with the P value < 0.05 was considered as a significance level. All analyses were conducted using the SAS version 9.3 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 66,790 elderly were enrolled in our study, including 33,395 subjects in each group. The baseline characteristics and comorbidities were shown in Table 1. There was no significant difference between PPV23-vaccinated and unvaccinated cohort in age group, gender, and CCI. In general, the PPV23-vaccinated group had more comorbidities. The duration of diabetes mellitus was significantly longer in PPV23-vaccinated group, and PPV23-vaccinated group had significantly higher rates of influenza vaccination (91.3% vs 46.5%), joining P4P program (8.1% vs 7.1%), and good medication compliance (34.8% vs 32.2%).

3.2. Vaccine effectiveness: primary outcomes

Compared to the unvaccinated group, PPV23-vaccinated group had lower risks of IPD (OR = 0.80, 95% confidence interval: 0.74–0.87). After adjustment for age, gender, chronic obstructive pulmonary disease (COPD), flu vaccination, CCI, duration of diabetes, P4P, and medication possession ratio (MPR) in the model 4, PPV23-vaccinated group was associated with lower risks of IPD (0.86, 0.78–0.94). The results of primary outcomes are summarized in Table 2.

3.3. Vaccine effectiveness: secondary outcomes

As shown in Table 2, the PPV23-vaccinated group had lower risks of hospitalization (0.94, 0.91–0.98), respiratory failure (0.73, 0.67–0.80), shorter length of hospitalizations (-1.72 ± 0.21 days, P value: ≤ 0.0001) and less medical costs (-166.92 ± 42.68 US dollars, P value: ≤ 0.0001). The exchange rate between US dollars and New Taiwan dollars in 2009 was about 32. After adjustment for age, gender, COPD, flu vaccination, CCI, duration of diabetes, P4P, and MPR in the model 4, PPV23-vaccinated group had decreased risks of respiratory failure (0.84,

Table 1

Characteristics, comorbidities, and medications among 23-valent pneumococcal polysaccharide vaccine vaccinated and unvaccinated group.

	Unvaccinated		Vaccinated		
	n	(%)	n	(%)	*P*-value
N	33,395		33,395		
Age in years (mean ± SD)	80.6	(5.4)	80.5	(4.7)	<0.005
Age group					1.00
75–79	18,382	(55.0)	18,382	(55.0)	
80–84	9940	(29.8)	9940	(29.8)	
85–89	3722	(11.1)	3722	(11.1)	
≧90	1351	(4.1)	1351	(4.1)	
Male (%)	17,403	(52.1)	17,403	(52.1)	1.00
Duration of diabetes (mean ± year)	4.4	(2.3)	4.9	(2.5)	<0.0001
0–1	6741	(20.2)	5940	(17.8)	<0.0001
2–4	11,878	(35.6)	10,402	(31.1)	
5–6	9753	(29.2)	8407	(25.2)	
≧7	5023	(15.0)	8646	(25.9)	
Comorbidities (%)					
Hypertension	22,088	(66.1)	23,560	(70.6)	<0.0001
Ischemic heart disease	7549	(22.6)	8174	(24.5)	<0.0001
Myocardial infarction	516	(1.6)	482	(1.4)	0.28
Congestive heart failure	2707	(8.1)	2491	(7.5)	<0.005
Atrial fibrillation	1211	(3.6)	1179	(3.5)	0.51
Hyperlipidemia	7627	(22. 8)	8446	(25.3)	<0.0001
Cerebrovascular disease	6760	(20.2)	6632	(19.9)	0.22
Stroke	3889	(11.7)	3823	(11.5)	0.42
Peripheral vascular disease	615	(1.8)	630	(1.9)	0.67
Retinopathy	475	(1.4)	535	(1.6)	0.06
Neuropathy	1606	(4.8)	1564	(4.7)	0.44
Depression	1227	(3.7)	1500	(4.5)	<0.0001
Chronic kidney disease	1271	(3.8)	1369	(4.1)	0.05
Chronic obstructive pulmonary disease	3169	(9.5)	3472	(10.4)	<0.0001
Chronic liver disease	2511	(7.5)	2461	(7.4)	0.46
Malignancy	3588	(10.7)	3704	(11.1)	0.15
Charlson index (mean ± SD)	2.4	(1.7)	2.4	(1.7)	0.57
Flu vaccination	15,533	(46.5)	30,499	(91.3)	<0.0001
P4P	2365	(7.1)	2693	(8.1)	<0.0001
MPR	10,740	(32.2)	11,628	(34.8)	<0.0001

The above comorbidities were defined by the ICD-9-CM for at least 1 hospitalization or 2 ambulatory visits within 1 year prior to index date. The ICD9 codes were as follows: hypertension (401–405), ischemic heart disease (410–414), myocardial infarction (410, 412), congestive heart failure (428), atrial fibrillation (427.31), hyperlipidemia (272.0–272.4), cerebrovascular disease (430–438), stroke (430–434, 436), peripheral vascular disease (440.2, 440.4, 443.81, 443.9), retinopathy (362.0–362.2), diabetic neuropathy (250.6, 357.2), depression (296.2, 296.3, 298.0, 300.4, 309.0, 309.1, 293.83, 296.90, 309.28, 296.82, 311), chronic kidney disease (403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585,V45.1, V56.0, V56.8), chronic obstructive pulmonary disease (490, 492, 496), chronic liver disease (070.2×, 070.3×, V02.61, 070.41, 070.44, 070.51, 070.54, V02.62, 571.0, 571.1, 571.2, 571.3, 571.4, 571.5, 571.6), and malignancy (140–239). MPR = medication possession ratio, P4P = pay for performance (P1401C, P1402C, P1403C, P1404B, P1404C, P1406B, P1406C, P1407C, P1408C, P1409C, P1410C, P1411C), SD = standard deviation.

0.77–0.93) and had shorter length of hospitalizations (−1.27 ± 0.19 days, *P* value: 0.0012), but there was no significant difference in terms of medical costs.

3.4. Subgroup analysis

In the flu-vaccinated group, PPV23 vaccination was associated with lower risks of IPD (0.88, 0.79–0.97). In the flu-unvaccinated group, there was no significant difference of IPD risk between PPV23-vaccinated and unvaccinated group. After adjustment for age, gender, COPD, CCI, duration of diabetes, P4P, and MPR, PPV23 vaccination in flu-vaccinated group was related to significantly lower risks of IPD (0.87, 0.79–0.97) than those without PPV23 vaccination. In flu-unvaccinated group, PPV23 vaccination was associated with lower risks of IPD (0.78, 0.63–0.95) compared to those without PPV23 vaccination.

With regard to secondary outcomes in the flu-vaccinated group, PPV23 vaccination was associated with lower risks of hospitalization (0.95, 0.91–0.99), respiratory failure (0.85, 0.76–0.95), shorter length of hospitalization (−0.58 ± 0.22 days, *P* value: 0.0072), and less medical costs (−64.39 ± 47.63 USD, *P* value: 0.0343) compared to those without PPV23 vaccination. In the flu-unvaccinated group, PPV23 vaccination was associated with higher ED visits (1.11, 1.03–1.21) and higher medical costs (234.33 ± 127.94 USD, *P* value: 0.0106) than those without PPV23 vaccination. In the adjusted models, those who received both flu and PPV23 vaccines were related to lower risks of IPD (0.87, 0.79–0.97), hospitalization (0.96, 0.92–0.99), respiratory failure (0.85, 0.76–0.95), and shorter length of hospitalizations (−0.56 ± 0.23 days, *P* value: 0.0010), compared to those who received flu but no PPV23 vaccination. As for the flu-unvaccinated group, PPV23 vaccination was associated with lower risks of IPD (0.78, 0.63–0.95), respiratory failure (0.79, 0.65–0.97). The results are shown in Table 3.

Compared to the PPV23-vaccinated group, the group receiving both PPV23 and flu vaccine had significantly lower risks of IPD, hospitalization, ED visits, and respiratory failure. The results of the 3-group comparison are shown in Fig. 1.

Table 2

Comparisons of primary outcomes and secondary outcomes between 23-valent pneumococcal polysaccharide vaccine vaccinated and unvaccinated group.

	Nonvaccination N = 33,395		Vaccination N = 33,395		Crude OR	Adjusted OR	Adjusted OR	Adjusted OR	Adjusted OR
	n	(%)	n	(%)	(95% CI)	(95% CI) model 1	(95% CI) model 2	(95% CI) model 3	(95% CI) model 4
Primary outcomes									
Invasive pneumococcal disease	1416	(4.2)	1147	(3.4)	0.80 (0.74–0.87)**	0.80 (0.73–0.86)**	0.85 (0.77–0.93)**	0.85 (0.77–0.93)**	0.86 (0.78–0.94)**
Secondary outcomes									
Hospitalization	10,211	30.6	9810	29.4	0.94 (0.91–0.98)**	0.94 (0.90–0.97)**	0.96 (0.92–0.99)*	0.96 (0.92–0.99)*	0.97 (0.93–1.01)
ED visits	11,674	35.0	11,562	34.6	0.99 (0.95–1.02)	0.98 (0.95–1.01)	1.02 (0.98–1.06)	1.02 (0.98–1.06)	1.02 (0.98–1.06)
Respiratory failure	1294	3.9	958	2.9	0.73 (0.67–0.80)**	0.72 (0.66–0.78)**	0.83 (0.75–0.92)**	0.83 (0.75–0.92)**	0.84 (0.77–0.93)**

	Mean	SD	Mean	SD	Crude estimate (SE)	Model 1 estimate (SE)	Model 2 estimate (SE)	Model 3 estimate (SE)	Model 4 estimate (SE)
Length of hospitalization (days)	8.33	29.05	6.61	23.46	−1.72 (0.21)**	−1.69 (0.20)**	−0.64 (0.20)**	−0.61 (0.20)**	−1.27 (0.19)*
Medical costs (USD)	2940.16	5745.55	2773.24	4958.60	−166.92 (42.68)**	−160.75 (40.69)**	−31.06 (40.66)	−30.12 (40.87)	−18.66 (40.19)

Primary outcome: invasive pneumococcal disease; secondary outcomes: hospitalization, emergency department visits, respiratory failure, length of hospitalization and medical costs.
Reference (OR = 1.00): unvaccinated group of 23-valent pneumococcal polysaccharide vaccine. Model 1: adjusted for age, gender, and COPD; Model 2: adjusted for age, gender, COPD, and flu vaccination; Model 3: adjusted for age, gender, COPD, flu vaccination, and Charlson index; Model 4: adjusted for age, gender, COPD, flu vaccination, Charlson index, duration of diabetes, P4P, and MPR. *P-value < 0.05; **P-value < 0.01. CI = confidence interval, COPD = chronic obstructive pulmonary disease, ED = emergency department, MPR = medication possession ratio, OR = odds ratio, P4P = pay for performance, SE = standard error.

4. Discussion and conclusions

To our knowledge, there was very limited research focusing on the effectiveness of PPV23 on the diabetic elderly. Our study found that PPV23 vaccination in diabetic elderly was related to better primary and secondary outcomes. Receiving both vaccines could bring significantly additive protection in hospitalization, ED visits, and severe complications.

Several investigations explored the effectiveness of PPV. One meta-analysis enrolling 22 trials found that PPV could decrease the risks of presumptive pneumococcal pneumonia and all-cause pneumonia.[26] Another case–control study focusing on geriatric patients revealed that PPV reduced the risk of all-cause pneumonia.[14] Besides, the Cochrane review concluded that PPV decreased the risks of IPD, but not mortality in adult.[27] Also, some previous studies described the effectiveness of PPV23 in adults, general elderly, and institutionalized elderly.[1–4,28] In a double blind, randomized controlled trial, PPV23 was found to decrease the risks and mortality of pneumococcal pneumonia in nursing home residents.[2] In a retrospective case–control study, PPV23 was also found to be associated with decreased IPD risk in the elderly.[3] Another ecological study conducted in England and Wales concluded that PPV23 could decrease the incidence of IPD.[28] In a population-based cohort study, PPV23 was found to be associated with reduced risks of bacteremic pneumococcal, nonbacteremic pneumococcal, overall pneumococcal, and all-cause community acquired pneumonia.[4] Similarly, a study using the Taiwan NHIRD demonstrated that PPV23 could decrease the risks of IPD, death from IPD, pneumonia hospitalization, death from pneumonia, and all-cause mortality in the elderly.[1]

Among our study and others, the most comparable outcome measurement was the amount of IPD risk reduction. In our study, the vaccine effectiveness (VE) of PPV23 in diabetic elderly was 14%. One review article comparing the meta-analyses concluded that the VE of PPV23 in general elderly was 65%.[29] In a retrospective case–control study enrolling general elderly in USA,

Table 3

Comparisons of primary and secondary outcomes in flu-vaccinated and flu-unvaccinated group.

	Flu-vaccinated group		Flu-unvaccinated group	
	(95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
PPV23-vaccinated				
IPD	0.88 (0.79–0.97)*	0.87 (0.79–0.97)*	0.83 (0.68–1.02)	0.78 (0.63–0.95)*
Hospitalization	0.95 (0.91–0.99)*	0.96 (0.92–0.99)*	1.06 (0.97–1.15)	0.99 (0.91–1.08)
ED visits	1.01 (0.97–1.05)	1.01 (0.97–1.05)	1.11 (1.03–1.21)*	1.06 (0.98–1.15)
Respiratory failure	0.85 (0.76–0.95)*	0.85 (0.76–0.95)*	0.88 (0.72–1.08)	0.79 (0.65–0.97)*
	Crude estimate (SE)	Adjusted estimate (SE)	Crude estimate (SE)	Adjusted estimate (SE)
Length of hospitalization (days)	−0.58 (0.22)*	−0.56 (0.23)*	0.15 (0.68)	−0.45 (0.71)
Medical costs (USD)	−64.39 (47.63)*	−52.92 (51.28)	234.33 (127.94)*	103.64 (131.18)

Primary outcome: invasive pneumococcal disease; secondary outcomes: hospitalization, emergency department visits, respiratory failure, length of hospitalization and medical costs. Reference (OR = 1.00): unvaccinated group of 23-valent pneumococcal polysaccharide vaccine. Adjusted for age, gender, COPD, Charlson index, duration of diabetes, P4P, and MPR. *P-value < 0.05; **P-value < 0.01. CI = confidence interval, COPD = chronic obstructive pulmonary disease, ED = emergency department, MPR = medication possession ratio, OR = odds ratio, P4P = pay for performance, SE = standard error.

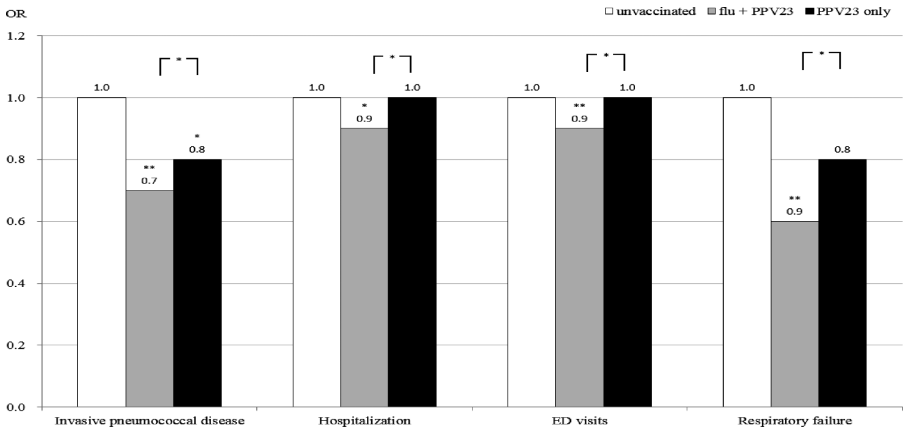

Figure 1. Comparison of odds ratios of primary outcomes and secondary outcomes between unvaccinated, PPV23-vaccinated only, and both PPV23 and flu vaccination, after adjustment for age, gender, COPD, Charlson index, duration of diabetes, P4P, and MPR. Reference (OR = 1.00): unvaccinated group of 23-valent pneumococcal polysaccharide vaccine and flu vaccine. $^{*}P$-value < 0.05, $^{**}P$-value < 0.01. COPD = chronic obstructive pulmonary disease, MPR = medication possession ratio, OR = odds ratio, P4P = pay for performance, PPV23 = 23-valent pneumococcal polysaccharide vaccine.

the VE was 42%.[3] Another study enrolling the general elderly in Taiwan revealed that the VE was 72%.[1] One ecological study in England and Wales concluded that the VE was 48% within 2 years after vaccination and 15% after 5 years.[28] Another population-based case–control study reported that the VE was 68% in adults aged 60 to 79 and was 71% in the elderly aged 80 and older.[30] The VE of our study was lower than other studies, and we proposed some hypotheses to explain the findings. First, diabetes mellitus was associated with immune dysfunction, which may further impair the effectiveness of PPV23. In diabetic patients, low complement factor 4, decreases cytokine response after stimulation in humoral innate immunity, decreased functions of chemotaxis, phagocytosis, killing of diabetic polymorphonuclear cells, and diabetic monocytes/macrophages was described previously.[19] Hyperglycemia was found to have influences on all major components of innate immunity and impair the ability against infections including decreased neutrophil activity, increased concentration of the early proinflammatory cytokines, decreased endothelial nitric oxide formation, and impaired complement function.[18] Diabetes mellitus was also found to be associated with considerable immunological abnormalities, along with chronic and low-grade inflammation.[17] Besides, impaired immunogenecity in diabetic patients was reported previously.[20] Second, our study participants were aged 75 and older, which were older than most of other studies. Age was found to be an important factor associated with clinical outcomes of pneumococcal diseases; therefore, the age distribution in our study might be another causes for the differences.[16] Although 1 population-based case–control study reported better VE in the elderly aged 80 and older than in adults aged 60 to 79, limited case number of the group aged 80 and older made the results of adjusted analysis questionable.[30]

Another important finding in our study was the additive effects of flu and PPV23 vaccination. PPV23 vaccination was associated with better primary and secondary outcomes, especially in flu-vaccinated group. One study using health administrative databases in Ontario reported that flu vaccine could reduce the composite endpoint of hospitalization for pneumonia, influenza, and all-cause mortality.[31] Regarding the relationships between flu vaccine and secondary outcomes of our study, 1 systematic review and meta-analysis concluded that flu vaccine in diabetic elderly could reduce all-cause hospitalization and hospitalization due to influenza or pneumonia.[32] Another study in USA also described the positive effects of flu vaccine on reduction of hospitalization.[33] The findings of these studies and ours implied the additive effects of PPV23 and flu vaccine on outcomes about medical utilization in diabetic elderly.

Although the amount of IPD risk reduction in diabetic elderly was different from in general elderly,[1,3] we considered PPV23 immunization in diabetic elderly to be necessary. Regarding the primary outcomes, PPV23 was effective in reducing the risks of IPD. In secondary outcomes, we also found that PPV23 was associated with decreased risks of hospitalization, respiratory failure, and shorter length of hospitalizations in the flu-vaccinated group, and decreased risks of respiratory failure in the flu-unvaccinated group. These effects might, in turn, bring benefits for public health in perspectives of cost-effectiveness. The price of PPV23 was about 26.59 to 28.11 USD in United States.[34] In our study, the reduction of medical cost was 166.92 $\pm$42.68 USD without adjustment and 18.66 $\pm$ 40.19 USD after adjustment, both of which were higher than the price of PPV23. Some studies also supported the use of PPV23 in the view of cost-effectiveness, although limited data focusing on diabetic elderly.[35,36]

Finally, our study revealed receiving both vaccines could bring significantly better outcomes of IPD, hospitalization, ED visits, and respiratory failure, compared with PPV23-vaccination alone. A prospective cohort study reported that the outcomes of survival and hospitalization for pneumonia were better in the group receiving both vaccines, compared with PPV23 or influenza vaccination alone.[37] Another population-based comparative study also described better outcomes of receiving both vaccines, comparing with flu vaccination alone.[38] Some studies investigated the relationship between pneumococcus and influenza infection and found that there were more colonization and infection of pneumococcus followed by influenza infection,[39,40] and resulting in higher mortality.[41]

Comparing with the previous study using Taiwan NHIRD,[1] our study had some strengths and limitations. First, we included IPD, hospitalization, ED visits, respiratory failure, length of hospitalizations, and medical costs as our primary and secondary outcomes, which provided more information to estimate both

effectiveness and cost-effectiveness. Second, our study analyzed the effectiveness of PPV23 on diabetic elderly, while the previous NHIRD study did not perform formal adjustment for diabetes mellitus, duration of diabetes, or other comorbidities. These possible confounder might interfere with the effectiveness of PPV23 on clinical outcomes. Third, our study was a retrospective cohort study enrolling diabetic elderly receiving PPV23 between 2007 and 2009, while the previous NHIRD study enrolled the elderly receiving PPV23 only during October to December 2008, which might bring more concerns about selection bias. Finally, our study did not include mortality as our outcomes because the Taiwan NHIRD itself did not provide detailed information about deaths. In diabetic elderly, the effects of PPV23 on mortality remained to be clarified in the future.

There were some limitations in our study. First, although we have used propensity score to match the comparison cohort, there were some demographic differences between PPV23-vaccinated and unvaccinated cohort. As shown in Table 1, the PPV23-vaccinated cohort had younger age, longer duration of diabetes mellitus, higher percentage of comorbidities, influenza vaccination, joining P4P program, and good medication compliance. Although we have performed multiple regression analysis to adjust possible confounders, there were some unobserved confounding factors which we could not address. These unobserved confounding factors could possibly interfere with the effects of PPV23 on clinical outcomes. Second, the Taiwan NHIRD did not provide sufficient information about medical services in detail, including the severity of diabetes, the HbA1C levels, renal function, and previous out-of-pocket vaccination history. In 2007, the health insurance-covered PPV23 started to be given for the elderly aged 75 and older. We believed that most of the elderly received health insurance-covered PPV23 instead of out-of-pocket. In addition, the variables in our study were all measured according to the ICD-9 code, and there might be some bias between coding status and clinical conditions. However, the bias shall be limited because the healthcare providers applied all reimbursements from the Taiwan National Health Insurance Administration, and coding mistakes were not allowed. IPD has been a statuary disease in Taiwan, so coding mistake was not permitted, too. Third, the PPV23-vaccinated cohort enrolled in our study was those receiving health insurance-covered PPV23 during 2007 to 2009. Therefore, patients receiving out-of-pocket PPV23 were not recognized as PPV23-vaccinated in our study, which might cause underestimation of the effectiveness of PPV23. Furthermore, all the study participants in our study were diabetic patients aged 75 and older; therefore, the findings in our study might not be applicable for nondiabetic populations or younger diabetic patients.

In conclusion, PPV23 vaccination was effective in prevention of pneumococcal disease and reduction of medical utilization among diabetic elderly aged 75 and older. Receiving both vaccines resulted in additive effects. Further cost-effectiveness study was warranted.

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