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Original article

Effect of the 23-valent pneumococcal polysaccharide vaccine on the incidence of hospitalization with pneumonia in adults aged ≥65 years: retrospective cohort study using a population-based database in Japan

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ABSTRACT

Objectives: The effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in preventing pneumonia in older adults remains controversial. Some studies have suggested differences in their effectiveness according to age or sex.

Methods: We conducted an observational study using a database of vaccine subsidization data and health insurance claims for a city in Japan. Participants were residents from 2014 to 2018 turning 65, 70, 75, 80, 85, 90, or 95 years during a given fiscal year, and PPV23 during the first year of observation were identified. We matched vaccinated and non-vaccinated individuals of the same age using propensity scores for vaccination. The incidence of hospitalization with pneumonia was compared using the Fine-Gray regression model. We summarized the results for each age using random-effects meta-analysis and conducted a subgroup analysis by sex.

Results: A total of 102 136 participants were included, of whom 35% received PPV23. Propensity score matching selected 32 510 pairs of vaccinated and non-vaccinated individuals. Overall, PPV23 administration was associated with a decreased incidence of hospitalization with pneumonia (17.2 vs. 20.4 per 1000 person-years, sub-distribution hazard ratio: 0.84, 95% CI: 0.77 to 0.91). Vaccine effectiveness was the highest among those aged 70 years and decreased with increasing age. No statistically significant effect was observed in those aged 90 or 95 years. Vaccine effectiveness was observed in both males and females.

Conclusions: PPV23 was associated with an overall decrease in hospitalization with pneumonia in older adults. However, vaccine effectiveness was significant in those aged 65 to 85 years but not in the older population. **Hayato Yamana, Clin Microbiol Infect 2023;29:904**

Introduction

Streptococcus pneumoniae causes pneumonia and invasive pneumococcal disease (IPD) and is a major cause of morbidity and mortality in older adults [1,2]. The 23-valent pneumococcal polysaccharide vaccine (PPV23) has been recommended for the prevention of pneumococcal disease in many countries [3], and multiple meta-analyses have confirmed the efficacy of PPV23 against IPD [4–7]. However, less evidence is available regarding the effect of this vaccine in preventing pneumonia; meta-analyses of randomized controlled trials have shown inconsistent results depending on the inclusion criteria for trials, such as study setting and risk of bias [5–9].

Several population-based cohort studies have provided real-world evidence, informing vaccination policies [10–14]. However,

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their results on the effectiveness of PPV23 against pneumonia have also been inconclusive. Moreover, recent studies have reported differences in vaccine effectiveness by age and sex [14–18].

In Japan, a publicly funded routine vaccination with PPV23 for older adults was implemented nationally in October 2014 [19,20]. Individuals turning 65, 70, 75, 80, 85, 90, 95, or 100 years of age during a fiscal year can be vaccinated during that year. Hence, we conducted a retrospective cohort study using a vaccine registry linked to administrative claims data in a city in Japan to evaluate the effectiveness of PPV23 in preventing pneumonia in older adults.

Methods

Data source

We conducted a retrospective cohort study using a database of vaccine subsidization data and health insurance claim data for a city in Japan. The city is located in the Greater Tokyo area and has a population of approximately 600 000. The vaccine database contains all records of vaccinations whose costs were subsidized by the city. Health insurance claims data were obtained from the National Health Insurance and Late Elders' Health Insurance [21]. An indicator of suspected diagnosis and the date of treatment initiation for the diagnosis, as reported by the attending physicians, were recorded in the database. Using unique identification numbers, vaccine records were linked to health insurance claims data in the city office. All personal information was excluded and de-identified data was sent to the researchers for secondary use.

The study was approved by the Research Ethics Committee of the Graduate School of Medicine and the Faculty of Medicine, University of Tokyo. As the analyses involved a secondary use of anonymized data that were routinely collected by the local government, the requirement for individual informed consent was waived.

Participants

Please see Supplementary Material for the details of pneumococcal vaccines administered in Japan; an overview of vaccine eligibility and study participants is shown in Fig. S1. Using the linked database, we created cohorts of residents eligible for routine vaccination in each fiscal year from 2014 to 2018. For each fiscal year, we identified all residents (as of April) who would turn 65, 70, 75, 80, 85, 90, or 95 years of age by the next March and included those with at least 1 year of residency. The observation period for each cohort started in April, except for the 2014 cohort, for which the observation period commenced in October 2014 because routine vaccination with PPV23 was not implemented until that time. Although residents aged $\geq$100 years were also eligible for receiving PPV23, we excluded them from the present study because of the small sample size of this subgroup. From the cohort of city residents, we included those who were enrolled in National Health Insurance or the Late Elders' Health Insurance. We also included individuals who switched from the former to the latter insurance carrier but excluded those with an unobserved/discontinuous period between enrollments in these insurance plans. Residents who were not enrolled in either of the insurance carriers, such as those enrolled in health insurance for employees and those on public assistance, were not analyzed. We excluded those with a record of receiving PPV23 before cohort entry, those who received PPV23 more than once, and those with a missing lot number for PPV23.

Variables and outcomes

We identified the following comorbidities using confirmed diagnostic records during the six months before cohort entry: congestive heart failure, cerebrovascular disease, chronic pulmonary disease, diabetes, malignancy, liver disease, renal disease, and dementia. The International Classification of Diseases, 10th revision (ICD-10) codes for defining these medical conditions in the present study were based on the algorithm by Quan et al. [22]. Influenza vaccination in the preceding year, pneumonia or IPD (ICD-10: A40.3, G00.1, J10.0, J11.0, J12–J18) in the past 6 months, hospitalization for any cause in the past 6 months, and total medical costs during the past 6 months were identified as well. Medical costs were categorized into 0, 1–99 999, 100 000–199 999, and $\geq$200 000 yen based on the data distribution.

The main outcome was hospitalization with pneumonia, defined as inpatient claims data with confirmed ICD-10 codes of J10.0, J11.0, or J12–J18. Death due to other causes was considered a competing event. Follow-up ended when an individual withdrew from the insurance, moved out of the city, received the PPV23 after the scheduled year of routine vaccination, became eligible for routine vaccination again after 5 years, or in September 2020, whichever occurred first. A month was the relevant unit of time considered in this study, and individuals whose observations ended in the month of cohort entry were excluded from the analysis.

Statistical analysis

We conducted a separate propensity score-matched survival time analysis for each group of residents with the same age (overall range: 65–95 years), and the results were summarized via meta-analysis. First, propensity scores were estimated separately in each group of the same age using a logistic regression model with vaccination status during the first year as the dependent variable and the following baseline independent variables: cohort year, sex, the eight abovementioned comorbidities, influenza vaccination, history of pneumonia or IPD, previous hospitalization, and medical cost. Using the estimated propensity scores, we performed nearest-neighbor, one-to-one matching without replacement. The calliper of matching was set to 0.2 times the standard deviation of the estimated propensity scores. A Fine-Gray regression model was used to obtain the sub-distribution hazard ratio (SHR) and its 95% CI under the competing risk of death from other causes. Vaccination status was considered a time-varying variable; pre-vaccination periods of the vaccinated individuals were analyzed as non-vaccinated periods. Finally, the results from each age were summarized using random-effects meta-analysis. We also performed a subgroup analysis according to sex.

We conducted sensitivity analyses to confirm the robustness of the study findings and analysis of a falsification outcome (admissions other than those for pneumonia or IPD) [23] to confirm the specific effect of PPV23. Furthermore, we performed an additional cohort analysis starting in 2014 to assess the possibility of residual confounding in the main analysis. We compared non-vaccinated individuals in the 2014 cohort with those who were 1 year younger or older, all of whom were yet to be eligible for vaccination. Please see the Supplementary Material for the details of these analyses. Statistical analyses were performed using Stata/SE statistical software (v.17.0; StataCorp, College Station, TX). Statistical significance was set at $\alpha = 0.05$.

Results

Among the 158 508 residents, 102 980 participants were included in the cohort (Fig. 1). Vaccination status according to age and cohort year is presented in Table S1. After excluding 844 individuals whose observation period ended during the month of cohort entry, there were 102 136 eligible participants, including 35 317 (35%) vaccinated and 66 819 (65%) non-vaccinated

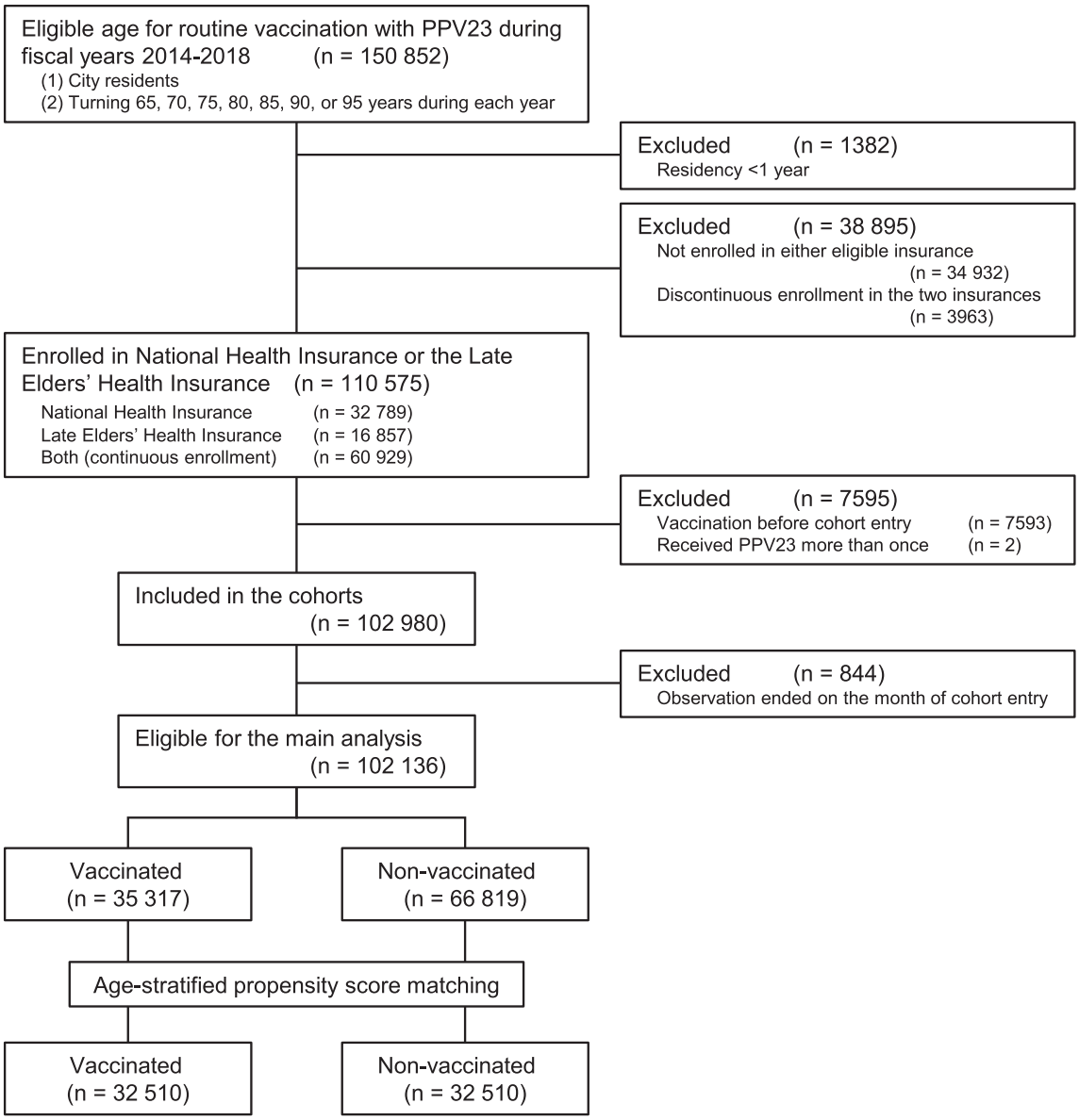

Fig. 1. Participant selection from the linked database of the vaccine registry and administrative claims data in a city in Japan.
Abbreviations: IPD, invasive pneumococcal disease; PPV23, 23-valent pneumococcal polysaccharide vaccine.

participants. Characteristics of the individuals excluded by different criteria are presented in Tables S2 and S3, and the analyzed population is compared with the 2015 Census in Fig. S2. The study population resembled the population of Japan, except for the relative absence of those aged 65 years.

The unadjusted incidence rates for pneumonia admission in the vaccinated and non-vaccinated periods were 16.2 per 1000 person-years (1879 cases in 115 652 person-years) and 25.9 per 1000 person-years (6119 cases in 236 086 person-years), respectively, with an incidence rate ratio of 0.63. Age-stratified propensity score matching selected 32 510 pairs of vaccinated and non-vaccinated individuals. Participants' medical and demographic characteristics were balanced after matching (Table 1).

In the matched cohort, the incidence rates of hospitalization with pneumonia in the vaccinated and non-vaccinated periods were 17.2 per 1000 person-years (1827 cases in 106 488 person-years) and 20.4 per 1000 person-years (2522 cases in 123 880 person-years), respectively, with an incidence rate ratio of 0.84. The results of the Fine-Gray regression are shown in Fig. 2. Overall, PPV23 was associated with a decreased hazard of hospitalization with pneumonia, with an SHR of 0.84 (95% CI: 0.77–0.91). This association was attenuated with increasing age, and vaccination was not associated with hospitalization with pneumonia in those aged 90 or 95 years. The results of the subgroup analysis by sex are presented in Table 2. The overall SHR was 0.79 (95% CI: 0.72– 0.85) in males and 0.88 (95% CI: 0.80–0.96) in females.

The results of additional analyses are summarized in Table 3, Table S4, and Figs. S3 and S4. Adding outpatient cases increased the incidence of the evaluated outcome and overall SHR. There was no statistically significant association between vaccine status and the falsification outcome. The non-vaccinated individuals in the 2014 cohort showed a higher unadjusted incidence of pneumonia admissions than those who were 1 year younger or older. However, the difference disappeared after matching.

Table 1
Characteristics of eligible vaccinated and non-vaccinated participants

Characteristics	Before propensity score matching			After propensity score matching		
	Vaccinated *n* (%) (*N* = 35 317)	Non-vaccinated *n* (%) (*N* = 66 819)	Standardized difference	Vaccinated *n* (%) (*N* = 32 510)	Non-vaccinated *n* (%) (*N* = 32 510)	Standardized difference
Age (y)						
65	6840 (19)	11 222 (17)	6.7	6744 (21)	6744 (21)	0
70	9783 (28)	14 269 (21)	14.8	7912 (24)	7912 (24)	0
75	8550 (24)	15 128 (23)	3.7	7736 (24)	7736 (24)	0
80	5925 (17)	13 044 (20)	-7.1	5900 (18)	5900 (18)	0
85	2898 (8)	8155 (12)	-13.2	2898 (9)	2898 (9)	0
90	1039 (3)	3686 (6)	-12.8	1039 (3)	1039 (3)	0
95	282 (1)	1315 (2)	-10.0	281 (1)	281 (1)	0
Sex						
Male	14 951 (42)	30 589 (46)	-6.9	14 301 (44)	13 809 (42)	3.1
Cohort year						
2014	7258 (21)	12 641 (19)	4.1	6939 (21)	6945 (21)	0.0
2015	6127 (17)	13 064 (20)	-5.7	6125 (19)	6006 (18)	0.9
2016	7256 (21)	12 802 (19)	3.5	6345 (20)	6428 (20)	-0.6
2017	7806 (22)	13 894 (21)	3.2	6568 (20)	6755 (21)	-1.4
2018	6870 (19)	14 418 (22)	-5.3	6533 (20)	6376 (20)	1.2
Comorbidities						
Congestive heart failure	4105 (12)	9110 (14)	-6.1	4052 (12)	3790 (12)	2.5
Cerebrovascular disease	5668 (16)	10 920 (16)	-0.8	5440 (17)	5273 (16)	1.4
Chronic pulmonary disease	5965 (17)	10 149 (15)	4.6	5427 (17)	5443 (17)	-0.1
Diabetes	2922 (8)	5755 (9)	-1.2	2879 (9)	2633 (8)	2.7
Malignancy	3802 (11)	6868 (10)	1.6	3505 (11)	3387 (10)	1.2
Liver disease	5693 (16)	9378 (14)	5.8	5137 (16)	5031 (15)	0.9
Renal disease	947 (3)	2417 (4)	-5.4	946 (3)	859 (3)	1.6
Dementia	1460 (4)	4220 (6)	-9.8	1459 (4)	1437 (4)	0.3
Influenza vaccination (past year)	16 084 (46)	17 728 (27)	40.4	13 367 (41)	13 348 (41)	0.1
Pneumonia or invasive pneumococcal disease (6 mo)	539 (2)	1350 (2)	-3.7	518 (2)	449 (1)	1.8
Hospitalization (6 mo)	2629 (7)	6306 (9)	-7.2	2629 (8)	2474 (8)	1.8
Medical cost in 6 mo (yen)						
0	2343 (7)	10 826 (16)	-30.4	2343 (7)	2308 (7)	0.4
1–99 999	13 474 (38)	22 286 (33)	10.0	12 640 (39)	12 288 (38)	2.2
100 000–199 999	9879 (28)	14 966 (22)	12.9	8249 (25)	8774 (27)	-3.7
≥200 000	9621 (27)	18 741 (28)	-1.8	9278 (29)	9140 (28)	0.9

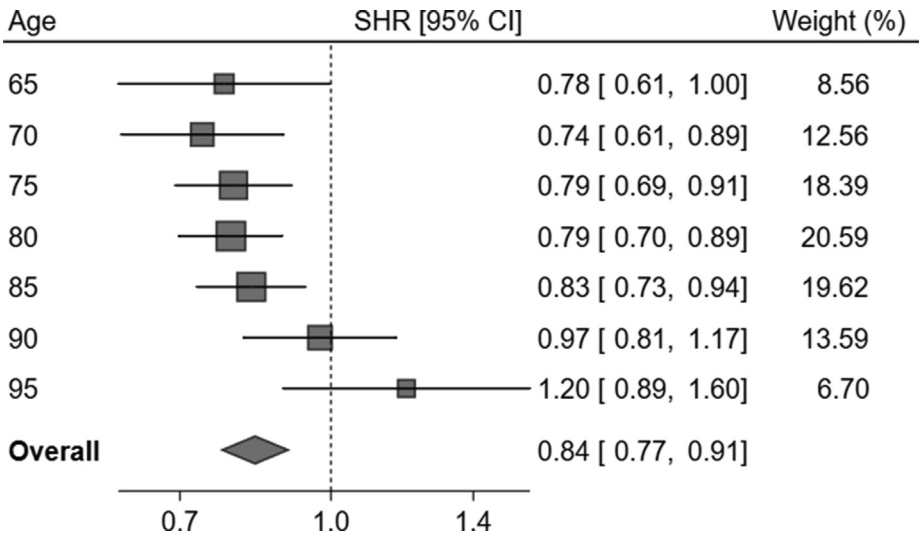

Fig. 2. Age-specific and overall comparison of pneumonia admissions between non-vaccinated individuals and individuals vaccinated with the 23-valent pneumococcal polysaccharide vaccine (reference: non-vaccinated individuals).
Abbreviation: SHR, sub-distribution hazard ratio.

Table 2
Results of Fine-Gray regression model evaluating pneumonia admission in males and females after propensity score matching

Age (y)	Males		Females	
	Number of matched pairs	SHR (95% CI)	Number of matched pairs	SHR (95% CI)
65	2767	0.75 (0.54, 1.03)	3893	0.85 (0.57, 1.28)
70	3561	0.64 (0.51, 0.82)	4334	0.88 (0.64, 1.21)
75	3464	0.83 (0.70, 0.99)	4285	0.75 (0.60, 0.94)
80	2545	0.76 (0.65, 0.89)	3335	0.83 (0.69, 1.00)
85	1169	0.86 (0.71, 1.03)	1717	0.88 (0.73, 1.05)
90	346	0.79 (0.60, 1.05)	684	1.01 (0.80, 1.27)
95	67	1.08 (0.62, 1.87)	214	1.14 (0.81, 1.61)
All	13 919	0.79 (0.72, 0.85)	18 462	0.88 (0.80, 0.96)

Abbreviation: SHR, sub-distribution hazard ratio.

Table 3
Summary of the sensitivity analyses

Analysis	Type of analysis	Vaccinated		Non-vaccinated		Unadjusted IRR	SHR (95% CI)
		N	Incidence rate/ 1000 person-years	N	Incidence rate/ 1000 person-years		
A	Outcome: pneumonia cases (inpatient and outpatient)	32 392	27.4	32 392	30.8	0.89	0.89 (0.83, 0.95)
B	Outcome: hospitalization for pneumonia or invasive pneumococcal disease	32 508	17.2	32 508	20.3	0.85	0.85 (0.77, 0.93)
C	Analysis: 3-months baseline period	32 515	17.2	32 515	20.2	0.85	0.84 (0.77, 0.92)
D	Participants: at least 6 months of insurance enrolment before cohort entry	31 892	17.3	31 892	20.5	0.84	0.83 (0.76, 0.91)
E	Analysis: not time-dependent	31 795	16.9	30 440	21.3	0.79	0.79 (0.74, 0.85)
F	Analysis: multivariable time-dependent regression without matching	35 317	16.2	66 819	25.9	0.63	0.80 (0.73, 0.86)

Abbreviations: IRR, incidence rate ratio; SHR, sub-distribution hazard ratio.

Discussion

Using a population-based database in Japan, we evaluated the effectiveness of PPV23 in preventing hospitalization with pneumonia in adults aged ≥65 years. In propensity score-matched pairs, PPV23 was associated with a decreased hospitalization rate. Vaccine effectiveness was found to decrease with age.

We report an overall SHR of 0.84 (95% CI: 0.77–0.91), indicating a statistically significant effect of PPV23 in preventing hospitalizations with pneumonia. Our sensitivity analysis which included outpatient cases yielded a slightly higher SHR (0.89), suggesting a possibility of a smaller vaccine effect in preventing mild cases of pneumonia. Our results should be cautiously compared with those of previous studies, as the proportion of healthcare-associated pneumonia could not be determined in the current study. However, our results suggest slightly greater vaccine effectiveness compared with those of previous studies. This difference may be due to the decreasing effectiveness of PPV23 over time after vaccination, as reported in some previous studies [13,16]. Because all participants who had received vaccines in the present study received PPV23 during the first year of observation, the effect may have been larger than that in studies enrolling subjects for whom vaccines were administered before cohort entry [11,13,14].

Several test-negative or case-control studies have suggested an age-dependent decrease in vaccine effectiveness against pneumonia [16–18]. A vaccine effect was also absent in adults aged ≥80 years according to a previous cohort study [14]. Here, we conducted a stratified analysis to clarify the effectiveness of vaccination within each age group. Effectiveness was the highest among those aged 70 years and was found to decrease with increasing age; no statistically significant effect was observed in those aged 90 or 95 years. A surveillance study from Japan reported a decrease in the proportion of pneumonia by *S. pneumoniae* among the oldest-aged patients [24]. Pneumonia by other or unknown pathogens could be more important in this population; thus, an aetiology-specific approach by PPV23 may not be sufficient. We also evaluated differences in vaccine effectiveness between males and females and found a slightly larger effect of PPV23 vaccination among males. Because some studies report a more pronounced effect in females [14–16], additional research within different populations may be necessary to clarify this question.

The major strength of this study lies in the rigorous analysis performed within a large, population-based database. Moreover, the 1-year limitation in eligibility enabled us to construct a relatively homogenous population of vaccinees who received PPV23 at nearly the same time. Finally, an analysis of very-aged individuals would be highly relevant to many countries in the near future. Although years have passed since the introduction of PPV23, its effect in preventing pneumonia remains controversial. Previous trials have targeted selected groups of individuals and demonstrated conflicting results [5–9]. Together with similar studies from different populations [10–14], this study contributes to accumulating real-world evidence of PPV23.

The clinical and policy implications of this study primarily relate to whether pneumococcal vaccines should be administered to very-aged adults. Our findings support primary vaccination by approximately 85 years of age, but not thereafter. Currently, few countries place an upper age limit for vaccination [3]. The initial Japanese policy for routine vaccination was intended to include adults aged 65 years. However, the transitional measure of vaccinating older individuals has continued to date. Several additional factors may influence vaccination policies, including vaccine type, duration of immunity after vaccination, and the effectiveness of re-vaccination. The efficacy of preventing IPD should also be considered because a similar age-dependent decrease in the effectiveness of PPV23 has been reported for IPD [18,25,26]. An additional cost-effectiveness analysis considering these issues should be conducted to identify the optimal vaccination policy for pneumococcal diseases.

We acknowledge several limitations of this research. First, this was a retrospective study that was conducted within an administrative database. Because of the lack of detailed clinical and microbiological data, we could not confirm community-acquired pneumonia or pneumococcal pneumonia diagnoses or the serotype of *S. pneumoniae*. Therefore, we analysed all pneumonia admissions and conducted sensitivity analyses for different outcome definitions. Second, information on vaccines that were not subsidized by the city could not be obtained within the present study. However, we consider the likely effect of this potential limitation to be small for the following reasons. First, the recommendations issued by the joint committee of the Japanese Respiratory Society and the Japanese Association for Infectious Diseases in 2015 and 2017 recommended against the use of PCV13 (either alone or in series with PPV23). This was owing to insufficient evidence because the vaccine-covered serotypes in adults decreased after the introduction of childhood immunization [27–30]. It was not until a recommendation issued in 2019 that PCV13 followed by PPV23 was listed as an option within the relevant medical guidelines, and the combination of PCV13 and PPV23 was therefore rare in our cohort. In addition, some individuals who received PPV23 privately outside of the routine vaccination schedule may have been included in the non-vaccinated cohort. Because this potential misclassification would bias the results toward the null, this limitation may have led to a small underestimation of vaccine effectiveness. The third noted limitation is that some individuals were excluded because they were aged <75 years and were not enrolled in the National Health Insurance or had discontinuous enrolment between the two insurance schemes. The relative lack of population representativeness may limit the generalizability of this population. Finally, as in any observational study, there may be residual confounding due to unmeasured factors.

In conclusion, PPV23 was associated with an overall decrease in hospitalization with pneumonia in adults aged ≥65 years. The age-dependent decrease in effectiveness warrants further evaluation of vaccination policies for pneumococcal disease in older adults, with a focus on determining the age group eligible for vaccination.

Author contributions

Conceptualization: H. Yamana, T.J., and H. Yasunaga. Methodology: H. Yamana, S.O., N.M., and K.U. Software: H. Yamana and N.M. Validation: S.O. Formal analysis: H. Yamana, S.O., N.M., K.U., T.J., and H. Yasunaga. Investigation: H. Yamana, S.O., and N.M. Resources: H. Yasunaga. Data curation: S.O. and N.M. Writing—original draft: H. Yamana. Writing—review and editing: S.O., N.M., K.U., T.J., and H. Yasunaga. Visualization: H. Yamana. Supervision, project administration, and funding acquisition: H. Yasunaga.

Transparency declaration

Conflict of interest

N.M. and T.J. have academic affiliations with the Department of Health Services Research, which is a cooperative programme between the University of Tokyo and Tsumura & Company. S.O. has an academic affiliation with the Department of Eat-loss Medicine, which is a cooperative programme between the University of Tokyo and ITO EN Ltd. H. Yamana, S.O., N.M., and H. Yasunaga received grants from the Ministry of Education, Culture, Sports, Science and Technology, Japan, outside the submitted work. S.O. and H. Yasunaga received grants from the Ministry of Health, Labour and Welfare, Japan outside the submitted work. K.U. received grants from the Japan Science and Technology Agency outside the submitted work. T.J. received honoraria for lectures from AstraZeneca, Nippon Boehringer Ingelheim, Sanofi, and Tsumura.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.04.006.

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