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Effects of sequential vs single pneumococcal vaccination on cardiovascular diseases among older adults: a population-based cohort study

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Abstract

Background: Recommendations around the use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13) seldom focus on potential benefits of vaccine on comorbidities. We aimed to investigate whether sequential vaccination with PCV13 and PPSV23 among older adults would provide protection against cardiovascular diseases (CVD) compared with using a single pneumococcal vaccine.

Methods: We conducted a Hong Kong-wide retrospective cohort study between 2012 and 2020. Adults aged ≥65 years were identified as receiving either a single or sequential dual vaccination and followed up until the earliest CVD occurrence, death or study end. To minimize confounding, we matched each person receiving a single vaccination to a person receiving sequential vaccination according to their propensity scores. We estimated the hazard ratio (HR) of CVD risk using Cox regression and applied structural equation modelling to test whether the effect of sequential dual vaccination on CVD was mediated via the reduction in pneumonia.

Results: After matching, 69 390 people remained in each group and the median (interquartile range) follow-up time was 1.89 (1.55) years. Compared with those receiving a single vaccine, those receiving sequential dual vaccination had a lower risk of CVD [HR (95% CI): 0.75 (0.71, 0.80), $P < 0.001$]. Post-hoc mediation analysis showed strong evidence that the decreased CVD risk was mediated by the reduction in all-cause pneumonia.

Conclusions: Sequential dual pneumococcal vaccination was associated with lower risk of CVD compared with single-dose PCV13 or PPSV23 in older adults. Such additional CVD benefits should be considered when making decisions about pneumococcal vaccination.

Keywords: Pneumococcal vaccine, PCV13, PPSV23, cardiovascular diseases, older adults

Key Messages

- Current evidence regarding pneumococcal vaccine effects on cardiovascular diseases (CVD) mainly covers short-term safety issues, with limited studies on long-term effects from the perspective of comorbidity prevention.
- Compared with those receiving a single pneumococcal vaccine, there was a lower risk of CVD associated with sequential dual vaccination. Post-hoc mediation analysis showed evidence that the decreased CVD risk was mediated by the reduction in all-cause pneumonia.
- In considering CVD risk alone, all older adults should receive sequential dual pneumococcal vaccination.
- This CVD risk reduction should be considered together with multiple other factors such as the risk–benefit, acceptability and preferences, and cost-effectiveness in future decisions about recommending single or sequential dual pneumococcal vaccination.

Background

Respiratory infection is a well-recognized risk factor associated with atherosclerosis that is capable of triggering cardiovascular diseases (CVD) with long-term comorbidities due to oxidative stress.[1,2] Pneumonia is a major acute respiratory infectious disease with severity ranging from mild to

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life-threatening for people of all ages. It is associated with CVD both in the short term (during the acute phase of respiratory infection) and long term (from several weeks up to 10 years after the pneumonia episode).[1,3] *Streptococcus pneumoniae* is a major causative pathogen for pneumonia and invasive diseases,[4] but pneumococcal vaccination is effective in preventing pneumococcal pneumonia caused by *S. pneumoniae*.[5]

Older adults are at high risk of both pneumonia and CVD.[3,6] Preventing these two life-threatening diseases would help alleviate two major sources of adult disease burden. Vaccines targeted at respiratory pathogens can reduce the risk of CVD by decreasing systemic inflammatory cytokines caused by respiratory infection.[7,8] Epidemiological studies have shown that influenza vaccination protects against both acute myocardial infarction and mortality from cardiovascular disease and stroke.[8,9] Currently, the two main vaccines used for preventing infection caused by different serotypes of *S. pneumoniae* are the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23). Recommendations on the use of PCV13 and PPSV23 among older adults still differ between countries. The main question is whether immunocompetent older adults should receive sequential doses of PCV13 and PPSV23 or a single dose of either.[10–13] Evidence supporting either recommendation mainly focuses on vaccine effectiveness against invasive pneumococcal diseases and vaccine-type community acquired pneumonia without consideration of other benefits of preventing infection-related comorbidities.[14,15]

A combination of both vaccines may induce a higher immune response than a single vaccine,[7] thereby decreasing the risk of infection and adverse health consequences. In this population-based cohort study using electronic medical records (EMRs) in Hong Kong, we aimed to investigate whether sequential dual pneumococcal vaccination for older adults would provide additional protection against CVD compared with using a single vaccine, in order to inform evidence-based vaccine policy.

Methods

Data source

We used the Hong Kong territory-wide EMR database—Clinical Data Analysis and Reporting System. The database covers all citizens who used public health services with 11 million cumulative patient records.[16] Anonymized records of demographics, dates and registered causes of death, immunizations, diagnoses and prescriptions from outpatient, inpatient and emergency settings are included in the database for research and audit purposes. Detailed descriptions and analyses of record accuracy are available in other publications.[9,17,18]

Study design and participants

This study used a retrospective cohort study design (Figure 1). We reported this study in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline. PCV13 was recommended for older adults starting from year 2014 in Hong Kong[19] and was added to the local Vaccination Subsidy Scheme for eligible adults in 2017. Hence PCV13 uptake was low prior to 2017.[20] We recruited all eligible ≥65-year-old adults who received at least one dose of pneumococcal vaccination between 1 January 2017 and 31 December 2020. Since an interval of ≥5 years is needed between two doses of PPSV23 and no repeated PCV13 dose is recommended in this age group,[10–13] we traced the vaccination records of recruited older adults for ≤5 years. We excluded participants (0.05%) with multiple doses of the same type of pneumococcal vaccine and divided the remaining cohort into a single-dose group (PPSV23 or PCV13 only) and a sequential dual vaccination group (both PCV13 and PPSV23), based on their vaccination records within 5 years before recruitment until 31 December 2020. The index date was the date of the first recorded vaccine received for the single-dose group and the date of the second recorded vaccine dose received for the sequential group. Consequently, those in the sequential group could have received a prior vaccine before the age of 65 years whereas all individuals would be ≥65 years old when they were included in the cohort. As we focused on immunocompetent older adults, we excluded participants with the immunocompromised conditions listed in Supplementary Table S1 (available as Supplementary data at *IJE* online). The remaining participants were followed up from the index date to the first occurrence of any CVD outcome of interest, death or study end date (31 December 2020), whichever came earliest.

Study outcomes

The main outcome was hospitalization for CVD, including atrial fibrillation, acute coronary syndrome, congestive heart failure, stroke or CVD-related death. The secondary outcomes were individual CVD events. The CVD outcomes, excluded conditions, comorbidities and all-cause pneumonia, were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and death records were identified using International Classification of Diseases, 10th Revision (ICD-10) codes (Supplementary Table S1, available as Supplementary data at *IJE* online). Subgroup analyses were conducted by age group (65–74, 75–84 and ≥85 years) and by the presence of chronic disease (any chronic heart, liver and lung disease or diabetes, Supplementary Table S1, available as Supplementary data at *IJE* online).

Statistical analysis

We used 1:1 propensity score (PS) matching with a caliper width equal to 0.2 times the standard deviation of the propensity score to minimize confounding and balance the baseline characteristics.[21] The propensity scores were derived using logistic regression with variables including age, sex and medical history from 1993 until time of recruitment. Variables with a between-group standardized mean difference of <0.1 were considered well balanced.[22] We report the descriptive statistics of baseline characteristics before and after propensity score matching. We used means (SD) or medians [interquartile ranges (IQRs)] to report continuous variables and used number (percentage) to report dichotomous variables. We estimated hazard ratios (HRs) using Cox regression with the proportional hazard assumption checked using Schoenfeld residuals with the R '*survival*' package. The likelihood ratio test between the crude regression model and the adjusted model was used to test the significance of variables.

We further conducted several sensitivity analyses to assess the robustness of the main results:

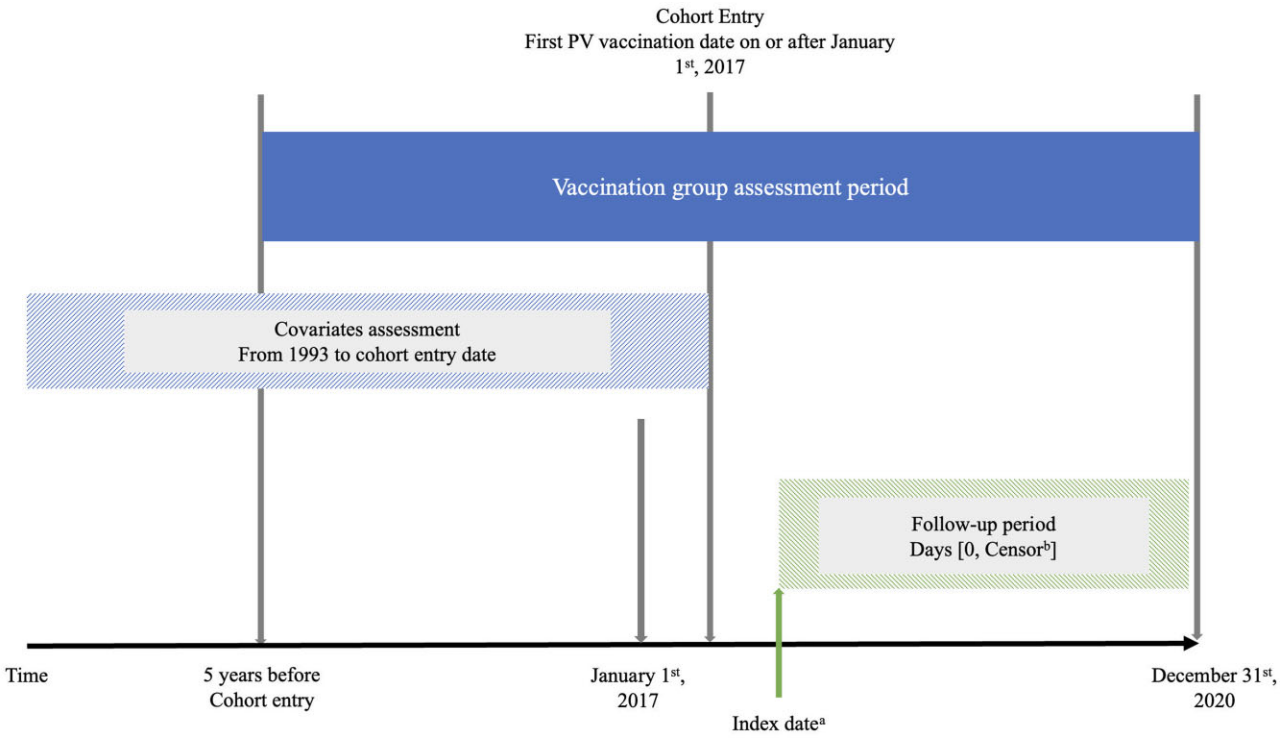


Figure 1. Schema of study design. (a) Single pneumococcal vaccine (PV) group—date of cohort entry. Sequential PV Group 1, who received the first PV before cohort entry—date of cohort entry. Sequential PV Group 2, who received the second PV after cohort entry—date of the second PV vaccination. (b) Cardiovascular diseases of interest (atrial fibrillation, acute coronary syndrome, congestive heart failure, stroke or CVD-related death), death or study end

i) We assumed sequential dual vaccination would reduce the risk of CVD by reducing the respiratory infection risk. To test this assumption, we analysed the effect of sequential vaccination on all-cause pneumonia using the same study design as the main analysis.
ii) We analysed unplanned CVD hospitalization to evaluate the effect of the vaccines on severe CVD events.
iii) We trimmed two-sided 5% propensity scores to ascertain the cohort matching.
iv) We excluded patients who had a history of CVD to test the effects of the vaccines on incident CVD only.
v) We excluded events that occurred within 30 days of the index date to decrease the effect of the acute safety outcome caused by the pneumococcal vaccine.
vi) We excluded patients with an index date later than 1 January 2020 to remove the impact of the COVID-19 pandemic on exposure and outcome recording.
vii) We further adjusted the year and seasonality of the index date during propensity score matching to account for the bias related to seasonality or time trends of vaccination and the occurrence of CVD.
viii) We conducted two other sensitivity analyses to ensure better comparability of the cohort entry and test the robustness of the primary analysis findings.
ix) Time-dependent propensity score matching with consideration of the potential 'late-entry' effect from the sequential vaccination group.[23] In this analysis, we calculated the time intervals between the second vaccination and the cohort entry for patients in the sequential group by month and sorted the time intervals in ascending order. We then matched the patients in the single-vaccination group based on the propensity score at the corresponding index date of patients in the sequential group without replacement. Matched patients in the single-vaccination group were added with the corresponding time interval as the new index date. Finally, a Cox regression with the new index date for patients in the single-vaccination group was used.
x) An analysis considering the time-varying exposure by following patients since their first vaccination.

We chose hospitalization for dehydration as the negative outcome control to assess the impact of residual confounding.

Post-hoc mediation analysis

We further tested whether the effect of sequential pneumococcal vaccination on the risk of CVD was mediated via the reduction in all-cause pneumonia using structural equation modelling based on binary probit link with the R '*lavaan*' package. Individuals were considered to have new-onset all--cause pneumonia if they had relevant diagnoses from the index date to death, incidence of CVD or end of study (censoring), whichever came first, and if they had no pneumonia-related diagnoses during the 1-year washout period before the index date.[24] Model goodness-of-fit was assessed using the root-mean-square error of approximation, comparative fit index and Tucker–Lewis index.

Data analysis and visualization were conducted using the R program (Version 4.1.2) and cross-checked individually by X.T., L.G. and V.C.

Results

Participant selection and baseline characteristics

We identified 262 421 older adults in total from the database who received PPSV23 or/and PCV13 during the study period. After participant selection, we included 230 119 people

(single dose: 157 244; sequential vaccination: 72 875). A flowchart of participant recruitment is shown in Supplementary Figure S1 (available as Supplementary data at *IJE* online). The baseline characteristics of all recruited participants before and after matching are listed in Table 1. Before matching, participants in the sequential dual vaccination group had a higher proportion of males (54.5%) and were younger (mean ± SD: 72.12 ± 5.84) than those in the single-dual-vaccine group (48.5%; mean ± SD: 76.09 ± 7.57). Generally, participants in the sequential group had more comorbidities than those in the single group with a higher Charlson Comorbidity Index score (mean ± SD: 0.62 ± 0.83 vs 0.53 ± 0.87). After 1:1 propensity score matching, 69 390 patients remained in each group with baseline variables all well balanced.

Incidence of interested CVD

Tables 2 and 3 show the results of the main and subgroup analyses. The median (IQR) follow-up times for participants were 1.96 (1.62) years in the single group and 1.83 (1.37) years in the sequential group. The crude incidence rates (95% CI) of CVDs were 30.91 (29.94, 31.91) and 21.45 (20.61, 22.31) per 1000 person-years in the single and sequential vaccination groups, respectively. The incidences of individual CVD in descending order were atrial fibrillation [single group: 7.97 (7.49, 8.48); sequential group: 5.06 (4.67, 5.49)], congestive heart failure [single group: 7.80 (7.32, 8.30); sequential group: 5.16 (4.76, 5.58)], acute coronary syndrome [7.23 (6.77, 7.71); 4.91 (4.51, 5.32)], stroke [5.87 (5.46, 6.31); 4.43 (4.06, 4.82)] and CVD-related deaths [2.12 (1.88, 2.39); 1.24 (1.05, 1.45)].

Effects of sequential vaccination on cardiovascular disease

Compared with those receiving a single dose, participants receiving sequential vaccination of PPSV23 and PCV13 had a significantly lower risk of adverse CVD outcomes [HR (95% CI): 0.75 (0.71, 0.80), $P < 0.001$]. The analysis by individual diseases and a series of subgroup analyses all showed a lower risk of CVD associated with sequential pneumococcal vaccination (HR ranged from 0.65 to 0.85; Tables 2 and 3). The cardio-protective effect had a higher effect size for CVD-related death [HR (95% CI): 0.65 (0.51, 0.82), $P < 0.001$] followed by atrial fibrillation [HR (95% CI): 0.70 (0.62, 0.79.), $P < 0.001$], congestive heart failure [HR (95% CI): 0.72 (0.64, 0.81), $P < 0.001$], acute coronary syndrome [HR (95% CI): 0.75 (0.67, 0.85), $P < 0.001$] and stroke [HR (95% CI): 0.79 (0.69, 0.90), $P < 0.001$]. In addition, similar effect sizes (*P*-value for interaction, 0.39) were found among older people with chronic comorbidities [HR (95% CI): 0.75 (0.68, 0.82), $P < 0.001$] and those without chronic comorbidities [HR (95% CI): 0.73 (0.67, 0.79, $P < 0.001$)]. The effect sizes of protective effect from sequential vaccination decreased with age (trend of *P*-value <0.001) in older participants [65–74 years old HR (95% CI): 0.75 (0.70, 0.82), $P < 0.001$; 75–84 years old: 0.84 (0.75, 0.94), $P = 0.003$; ≥85 years old: 0.85 (0.73, 0.98), $P = 0.031$]. Sensitivity analyses (Supplementary Table S2, available as Supplementary data at *IJE* online) showed consistent protective effects of

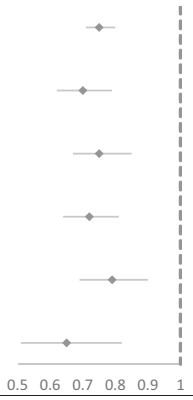
Table 1. Baseline characteristics before and after propensity score matching

Characteristic	Before matching			After matching		
	Sequential vaccination	Single vaccination	SMD	Sequential vaccination	Single vaccination	SMD
N	72 875	157 244		69 390	69 390	
Sex, male (%)	39 714 (54.5)	76 252 (48.5)	0.12	39 205 (56.5)	37 630 (54.2)	0.046
Age, years, mean (SD)	72.12 (5.84)	76.09 (7.57)	0.586	72.29 (6.19)	72.32 (5.91)	0.005
CCI, mean (SD)	0.62 (0.83)	0.53 (0.87)	0.104	0.57 (0.85)	0.62 (0.84)	0.058
Comorbidities (trace back to 1993 since EMR available)						
Cerebral- and cardio-related diseases						
Atrial fibrillation	1560 (2.1)	6218 (4.0)	0.106	1760 (2.5)	1558 (2.2)	0.019
Acute coronary syndrome	5296 (7.3)	10 781 (6.9)	0.016	4966 (7.2)	5191 (7.5)	0.012
Congestive heart failure	1559 (2.1)	5704 (3.6)	0.089	1509 (2.2)	1551 (2.2)	0.004
Myocardial infarction	2306 (3.2)	4810 (3.1)	0.006	2165 (3.1)	2270 (3.3)	0.009
Cerebrovascular disease	7290 (10.0)	15 587 (9.9)	0.003	6912 (10.0)	7140 (10.3)	0.011
Stroke	4305 (5.9)	9640 (6.1)	0.009	4183 (6.0)	4212 (6.1)	0.002
Hypertension	30 445 (41.8)	48 975 (31.1)	0.222	25 281 (36.4)	27 063 (39.0)	0.053
Cardiac surgery	2312 (3.2)	3499 (2.2)	0.058	2049 (3.0)	2245 (3.2)	0.016
Other comorbidities						
Chronic obstructive pulmonary disease	6244 (8.6)	12 076 (7.7)	0.033	5724 (8.2)	5865 (8.5)	0.007
Chronic renal failure	203 (0.3)	475 (0.3)	0.004	162 (0.2)	201 (0.3)	0.011
Dementia	363 (0.5)	1576 (1.0)	0.058	369 (0.5)	363 (0.5)	0.001
Diabetes without chronic complication	14 781 (20.3)	18 865 (12.0)	0.227	12 740 (18.4)	15 199 (21.9)	0.088
Diabetes with chronic complication	4509 (6.2)	8835 (5.6)	0.024	2123 (3.1)	2150 (3.1)	0.002
Lipid disorder	19 800 (27.2)	23 516 (15.0)	0.303	15 312 (22.1)	16 660 (24.0)	0.046
Mild liver disease	281 (0.4)	447 (0.3)	0.018	228 (0.3)	268 (0.4)	0.010
Moderate–severe liver disease	118 (0.2)	216 (0.1)	0.006	97 (0.1)	118 (0.2)	0.008
Peripheral vascular disease	566 (0.8)	1303 (0.8)	0.006	531 (0.8)	562 (0.8)	0.005
Paralysis	944 (1.3)	2130 (1.4)	0.005	910 (1.3)	938 (1.4)	0.004
Rheumatoid arthritis and other inflammatory polyarthropathies	824 (1.1)	1216 (0.8)	0.037	710 (1.0)	814 (1.2)	0.014
Gastric ulcers	3153 (4.3)	6950 (4.4)	0.005	3026 (4.4)	3074 (4.4)	0.003

CCI, Charlson Comorbidity Index; EMR, electronic medical records; SMD, standard mean difference.

Table 2. Hazard ratios of cardiovascular diseases among Hong Kong elderly people with sequential pneumococcal vaccines compared with those with single pneumococcal vaccine

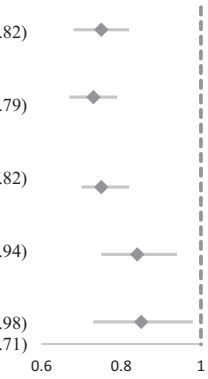
Main analysis	Cases/*N*	Follow-up median years (IQR)	Crude incidence rate per 1000 person-years (95% CI)	Hazard ratio	*P*
Total CVD					
Single vaccination	3776/69 390	1.96 (1.62)	30.91 (29.94, 31.91)	Ref	
Sequential vaccination	2450/69 390	1.83 (1.37)	21.45 (20.61, 22.31)	0.75 (0.71, 0.80)	<0.001
Atrial fibrillation					
Single vaccination	997/69 390	2.00 (1.62)	7.97 (7.49, 8.48)	Ref	
Sequential vaccination	587/69 390	1.86 (1.41)	5.06 (4.67, 5.49)	0.70 (0.62, 0.79)	<0.001
Acute coronary syndrome					
Single vaccination	905/69 390	2.01 (1.61)	7.23 (6.77, 7.71)	Ref	
Sequential vaccination	569/69 390	1.86 (1.41)	4.91 (4.51, 5.32)	0.75 (0.67, 0.85)	<0.001
Congestive heart failure					
Single vaccination	976/69 390	2.00 (1.62)	7.80 (7.32, 8.30)	Ref	
Sequential vaccination	598/69 390	1.86 (1.41)	5.16 (4.76, 5.58)	0.72 (0.64, 0.81)	<0.001
Stroke					
Single vaccination	736/69 390	2.01 (1.61)	5.87 (5.46, 6.31)	Ref	
Sequential vaccination	514/69 390	1.87 (1.41)	4.43 (4.06, 4.82)	0.79 (0.69, 0.90)	<0.001
CVD-related death					
Single vaccination	265/69 390	2.01 (1.62)	2.12 (1.88, 2.39)	Ref	
Sequential vaccination	143/69 390	1.86 (1.42)	1.24 (1.05, 1.45)	0.65 (0.51, 0.82)	<0.001



CI, confidence interval; CVD, cardiovascular disease; IQR, interquartile range.

Table 3. Hazard ratios of cardiovascular diseases among Hong Kong elderly people with sequential pneumococcal vaccines compared with those with single pneumococcal vaccine—subgroup analyses

Subgroup analysis	Cases/*N*	Follow-up median years (IQR)	Crude incidence rate per 1000 person-years (95% CI)	Hazard ratio	*P*
Participants with chronic disease					
Single vaccination	1826/21 779	2.08 (1.52)	43.45 (41.49, 45.47)	Ref	
Sequential vaccination	1091/21 779	1.16 (1.25)	36.01 (33.92, 38.19)	0.75 (0.68, 0.82)	<0.001
Participants without chronic disease					
Single vaccination	1962/46 462	1.94 (1.67)	24.58 (23.51, 25.68)	Ref	
Sequential vaccination	1362/46 462	1.96 (1.42)	16.62 (15.76, 17.53)	0.73 (0.67, 0.79)	<0.001
Participants aged 65–74 years					
Single vaccination	2126/49 035	1.94 (1.62)	24.62 (23.59, 25.68)	Ref	
Sequential vaccination	1379/49 035	1.88 (1.42)	16.69 (15.82, 17.58)	0.75 (0.70, 0.82)	<0.001
Participants aged 75–84 years					
Single vaccination	972/12 857	2.13 (1.51)	45.64 (43.36, 48.02)	Ref	
Sequential vaccination	654/12 857	1.77 (1.30)	38.39 (36.10, 40.78)	0.84 (0.75, 0.94)	0.003
Participants aged ≥85 years					
Single vaccination	537/4048	2.06 (1.53)	72.51 (66.57, 78.84)	Ref	
Sequential vaccination	381/4048	1.59 (1.17)	60.89 (55.00, 67.23)	0.85 (0.73, 0.98)	0.031
Trend of age group[1]				2.11 (1.64, 2.71)	<0.001



CI, confidence interval; CVD, cardiovascular disease; IQR, interquartile range.
[1] We classified participants in three age groups: 65–74 years old, 75–84 years old, and ≥85 years old. In analysis of age group trend, we treated age groups as continuous variables.

sequential vaccination compared with a single dose (HRs ranged from 0.74 to 0.77). The protective effect size of sequential pneumococcal vaccination was lower among participants without a history of CVD [HR (95% CI): 0.76 (0.68, 0.84), $P < 0.001$] compared with our main analysis. Lower risk of all-cause pneumonia was observed among sequential vaccination recipients compared with those who received a single dose [HR (95% CI): 0.76 (0.70, 0.82), $P < 0.001$]. Sensitivity analysis of hospitalization for dehydration showed no protective effect of sequential vaccination on dehydration [HR (95% CI): 1.08 (0.79, 1.49), $P = 0.624$], which supports that large residual confounding would not result in significant selection bias using the PS-matching-based study design. Sensitivity analyses on the potential bias from late entry (Supplementary Table S3, available as Supplementary data at *IJE* online) showed that when considering the comparability of two groups of cohort entry through the use of time-dependent propensity score matching, the protective effect size of sequential pneumococcal vaccination is 0.14 [HR (95% CI): 0.86 (0.80, 0.91)]. In the time-varying exposure analysis, we found that, compared with single pneumococcal vaccination, sequential vaccination would help to decrease CVD risk by 12% [HR (95% CI): 0.88 (0.81, 0.96)]. These analyses, although still demonstrating a beneficial effect, were lower than the effect size found in the other sensitivity analyses.

Mediating role of all-cause pneumonia

Figure 2 illustrates the total effect and direct effect of sequential vaccination on the risk of CVD, and the mediated effect acting through new-onset all-cause pneumonia, compared with single-dose vaccination. The structural equation model achieved fair goodness-of-fit and confirmed the strong evidence of the total protective effect of sequential vaccination

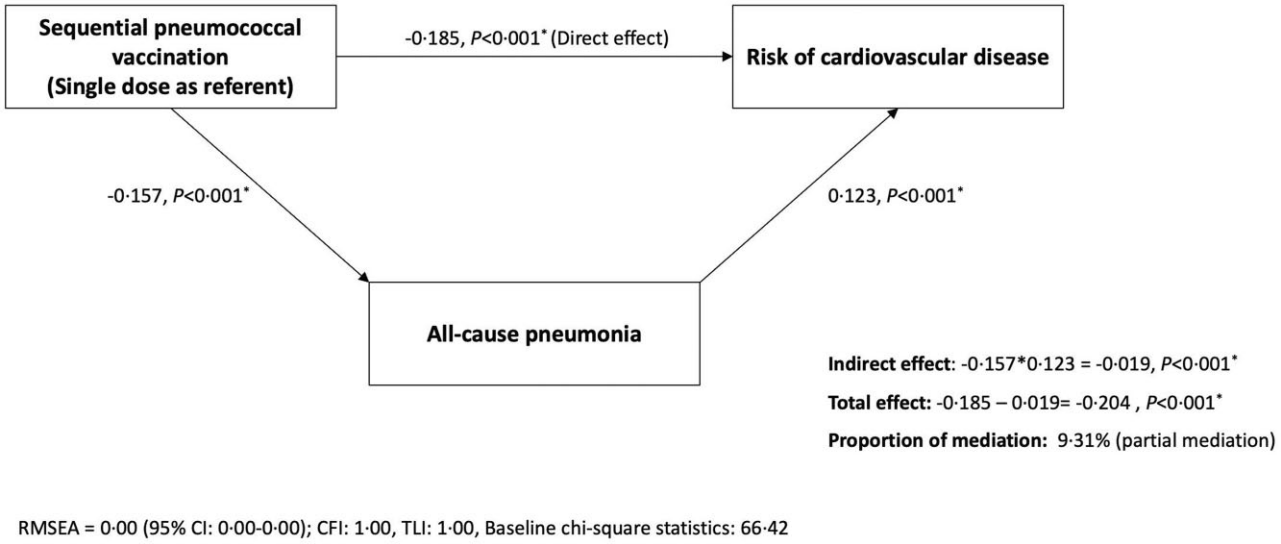


Figure 2. Mediating effect of sequential pneumococcal vaccination with PPSV23 and PCV13 on the risk of CVD from all-cause pneumonia. The values are binary probit estimates of the total effect of sequential pneumococcal vaccination on the risk of CVD, the direct effects of sequential pneumococcal vaccination on the risk of CVD, sequential pneumococcal vaccination on all-cause pneumonia and all-cause pneumonia on the risk of CVD, and the indirect effect of sequential pneumococcal vaccination on the risk of CVD via all-cause pneumonia. CFI, comparative fit index; CVD, cardiovascular disease; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; RMSEA, root-mean-square error of approximation; TLI, Tucker–Lewis index

on the risk of CVD ($P < 0.001$) in the main analysis. The reduction in CVD risk associated with sequential vaccination was mediated by a reduction in new-onset all-cause pneumonia ($P < 0.001$), which accounted for 9.31% (proportion of total effect attributable to indirect effect) of the total effect.

Discussion

Heart diseases are the leading cause of death globally and represent one-third of all global deaths, which renders CVD prevention meaningful in consideration of different risk factors.[25] To the best of our knowledge, this is the first study to investigate the cardiovascular benefits from sequential dual pneumococcal vaccination with PCV13 and PPSV23 compared with a single dose of either among older adults—a high-risk group for both pneumonia and CVD.[3] Our study found sequential pneumococcal vaccination using different vaccine types would provide protection against CVD in older adults and there was evidence that the beneficial effect was mediated through the reduction in all-cause pneumonia—a proxy for pneumococcal pneumonia in our study. A randomized clinical trial and its 4-year extension suggested that sequential vaccination with PCV13 and PPSV23 improved immunity responses to more serotypes compared with PCV13 or PPSV23 alone after a 3- to 4-year interval.[26,27] Our sensitivity analysis on all-cause pneumonia and mediation analysis support the hypothesized protective mechanism of sequential vaccination on the reduced risk of CVD via effective prevention of pneumonia. Although these are indirect findings, a sequential combination of PCV13 and PPSV23 would have better prevention effects on pneumonia, potentially leading to a decrease in systemic inflammation caused by infection and therefore a reduction in the occurrence of CVD.

Currently, PCV13 and PPSV23 guidelines are inconsistent because the focus is on the effectiveness of pneumonia prevention but they rarely consider the effect of vaccination on alleviating comorbidities. Guidelines around pneumococcal vaccination of older adults in Canada and the UK both recommended a single dose of PPSV23, regardless of any chronic diseases.[11,28] Meanwhile, Hong Kong and Australia recommend sequential pneumococcal vaccination among those who have chronic diseases.[10,19] In fact, most adults >65 years old are not immunocompromised but have chronic comorbidities.[29] Therefore, it would be meaningful to provide evidence in current guidelines for immunocompetent older adults from the perspective of comorbidity benefits. Previous epidemiological evidence on the effect of single pneumococcal vaccination on CVD risk showed that individuals at high risk of CVD (with chronic disease conditions or a history of CVD) have a lower risk of CVD, CVD-related deaths or all-cause mortality if they receive at least one dose of PPSV23 or PCV13 compared with those without any type of pneumococcal vaccination.[30,31] Our study supports that, compared with receiving only one dose of PCV13 or PPSV23, sequential vaccination with both provides protection by reducing CVD risk, although we did not observe a significant difference between older adults with and without chronic diseases (*P*-value for interaction analysis: 0.39). Additionally, we observed that the protective effects of sequential vaccination decreased with age. One reason could be that vaccination is insufficient to overcome other risks factors of CVD, such as very advanced age, impaired immunity and inferior health conditions. Nevertheless, our findings support that elderly patients would benefit from sequential pneumococcal vaccination in view of cardiovascular disease alleviation. Notably, the decision and recommendation for single or sequential vaccination should consider multiple factors such as the risk–benefit, acceptability and preferences, and cost-effectiveness.

Our 9-year retrospective cohort study that covered 230 119 eligible participants suggests a protective effect from sequential PPSV23 and PCV13 vaccination on CVD compared with receiving one dose of PPSV23 or PCV13 only. This study could provide evidence to inform pneumococcal vaccination recommendations among immunocompetent older adults, although a few limitations exist. First, we used EMRs to identify patients' immunization status, so the accuracy of immunization information cannot be validated. Misclassification for the single-vaccination group may exist and we may have underestimated

the effect size from the sequential vaccination group. Second, our study lacks data about participants' demographic variables such as dietary, smoking status, alcohol consumption and healthcare-seeking behaviour (e.g. individual social economic level, accessibility to healthcare resources), which may have given rise to residual confounding. We used propensity scores to minimize the health differences between groups and some included covariates could reflect the effects of lifestyle factors that were not adjusted for. The negative outcome control analysis also supports a small residual confounding without a significant impact on the study conclusion. Third, we did not adjust for the seasonal influenza vaccine as it was not usually recorded in routinely collected EMRs. We assumed the uptake of the influenza vaccine would be similar between two groups since the influenza vaccine is usually given at the same time as the pneumococcal vaccine in Hong Kong. Fourth, the generalizability of our finding that sequential pneumococcal vaccination has long-term beneficial effects on CVD should be interpreted with caution. As PCV13 was supplied in the local Vaccination Subsidy Scheme for eligible adults in 2017, receiving sequential vaccination was prevalent after year 2017. In consequence, our follow-up period was only ~2 years, which may not have been long enough for cardiovascular disease that results from a chronic inflammatory cascade to develop. Future studies with longer study periods are recommended to test our findings. In addition, our study was not designed to examine which vaccine should be taken first in the sequential group for better CVD prevention. Instead, we aimed to test the hypothesis that sequential vaccination will provide a stronger immune response and broader serotype coverage that would further prevent the infection-triggered CVD and be more effective than a single pneumococcal vaccination alone. It would also be meaningful to further investigate whether the sequential order of PPSV23 and PCV13 would influence the beneficial effects on CVD. Fifth, individuals in the sequential group were followed up since the later vaccination date, which would have induced the potential for 'late-entry bias' as they had to survive until the second vaccination. This situation may have meant that people in the sequential group were in better health than those in the single group, so we may have overestimated the protective effects of the sequential vaccination. Our sensitivity analysis (Supplementary Table S3, available as Supplementary data at *IJE* online) accounted for this late-entry bias. It supports the assumption that this bias had a diminishing effect on the observed effect size compared with our main analysis. Despite this potential bias, we still observed significant protective effects on CVD risk resulting from the implementation of sequential pneumococcal vaccination. Lastly, due to the limitation of our database, the majority of records of patients diagnosed with pneumonia do not include laboratory records about causative pathogens; we were therefore unable to ascertain whether the recorded pneumonia was pneumococcal-related. We used all-cause pneumonia as a proxy outcome for pneumococcal pneumonia, which may have led to an underestimation of the effect size and proportion of mediation in the overall relationship.

Conclusion

Sequential pneumococcal vaccination with PCV13 and PPSV23 is associated with a reduced risk of acute coronary syndrome, congestive heart failure, stroke and CVD-related deaths compared with a single vaccination with either PCV13 or PPSV23. The effect is partially mediated by the prevention of all-cause pneumonia.

Ethics approval

This study obtained ethics approval from the Institutional Review Board via The University of Hong Kong/Hospital Authority Hong Kong Western Cluster (UW 21–271).

Data availability

We are unable to directly share the patient-level data since the data custodian, the Hong Kong Hospital Authority, which manages the Clinical Data Analysis and Reporting System, has not given permission. However, researchers can apply to access the data via the Hospital Authority Data Sharing Portal (https://www3.ha.org.hk/data) for research purposes. The statistical procedures and R codes used in this study are available upon request.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

Study concept: X.L. Study design: X.L., X.T., L.G., V.C., M. J. Data extractions, analysis and cross-check: X.T., L.G., V. C. Drafting of the manuscript: X.T., V.C., X.L. Data interpretation: all authors. Clinical inputs: M.J., J.Y., K.Y., I.H. Critical revision of the manuscript: all authors. Resource and funding acquisition: X.L., I.C.K.W. Study supervision: X.L.

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Conflict of interest

X.L. received research grants from Hong Kong Health and Medical Research Fund (HMRF, HMRF Fellowship Scheme, HKSAR), Research Grants Council Early Career Scheme (RGC/ECS, HKSAR), Research Grants Council Research Impact Fund (RGC/RIF, HKSAR), Janssen and Pfizer; internal funding from the University of Hong Kong; consultancy fee from Merck Sharp & Dohme; she is also an non-executive director of Advanced Data Analytics for Medical Science (ADAMS) Limited Hong Kong, all are unrelated to this work. I.C.K.W. reports research funding outside the

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