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Effectiveness of influenza vaccination in the elderly: a population-based case-crossover study

Chun-Yu Liang ,[1] Shinn-Jang Hwang,[2,3] Kuan-Chia Lin,[4] Chung-Yi Li ,[5,6] Ching-Hui Loh,[7,8] James Yi-Hsin Chan,[9] Kwua-Yun Wang[9,10,11]

ABSTRACT

Background There is limited information regarding the effectiveness of influenza vaccines for older adults. Particularly, controlling for healthy senior bias is challenging in observational studies. We aimed to assess the efficacy of influenza vaccination in the elderly while addressing potential healthy senior bias and whether it was related to virus-vaccine strains matching.

Method To control between-individual confounder, we used a case-crossover study design using Taiwan's National Health Insurance Research Dataset to analyse the association between influenza vaccination in older adults and the risk of hospitalisation for community-acquired pneumonia (CAP). Individuals were a 'case' in vaccinated years and a 'control' in unvaccinated years. The study periods were 2006/2007 and 2007/2008 seasons because virus-vaccine strains were matching in 2006/2007 season and unmatching in 2007/2008 season. Older adults were categorised into two groups: admitted for CAP during the pre-vaccination period (Admitted, n=311) and not hospital admitted for CAP (Non-admitted, n=572 432). The outcome was hospitalisation for CAP during the influenza period. Conditional logistic regression assessed influenza vaccine efficacy in reducing CAP.

Results Influenza vaccination had no protective effects in Admitted group. However, because of the tiny numbers in Admitted group, we could draw very limited conclusions. Receiving an influenza vaccine significantly prevented CAP in Non-admitted group only during the vaccine-circulating strain-matched year (OR, 0.72; 95% CI, 0.64 to 0.83). In addition, there was no protective effect against CAP hospitalisation among individuals with a Charlson Comorbidity Index score over 2.

Conclusion Influenza vaccine efficacy was associated with vaccine-circulating strain-matched. When vaccine-circulating strains were all matching, receiving a shot reduced the probability of CAP hospitalisation by 28% in Non-admitted group. However, high comorbidity may reduce the vaccine efficacy. Therefore, it is necessary to educate older adults to receive annual influenza vaccination and in combination with non-pharmaceutical interventions to reduce the risk of CAP.

Strengths and limitations of this study

► We performed a case-crossover study design while addressing between-person confounders such as potential healthy senior bias, using a nationalised database.
► This study also controlled the within-person confounder, individual's health status before receiving a shot, in estimating the effect of influenza vaccination.
► We used medical records to identify influenza vaccination status to avoid recall bias and misclassification.
► The population selected in this study were individuals who get vaccinated intermittently may be different from those who get vaccinated annually, which may affect the generalisation of the results.
► There was a tiny sample size in Admitted group, with very limited conclusions that we could draw.

population aged 65 years and over are significantly increased during influenza seasons.[1] As recommended by the WHO, influenza vaccination is the major strategy to control influenza in high-risk populations.[2] The vaccines are licensed based on the results of randomised controlled trials that demonstrate safety and efficacy. The effectiveness of influenza vaccination in older individuals in the real world is a worldwide concern.[3]

The benefits of influenza vaccination in the elderly are inconsistent and controversial. Several observational studies found that the influenza vaccine effectively reduced hospitalisation for pneumonia or influenza by 27%–33% and reduced the mortality rate by 48%–50% in community-dwelling elderly persons.[4 5] Another observational study noted that influenza vaccination was not associated with a reduced risk of community-acquired pneumonia (CAP).[6] Several studies revealed that the protective effects of the influenza vaccine depended on the match between the vaccine and circulating virus strains.[3] However, some studies indicated that

BACKGROUND

The risks of hospitalisation, physician visits and emergency department visits for influenza and pneumonia in the elderly

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mismatched influenza vaccines still provided protective effects.[4 7 8] The limited evidence on the effectiveness of influenza vaccination in older adults, and more research is needed.[3 9]

Case–control methodology is frequently used to evaluate the protection afforded by vaccines in a real-world context.[10] Evidence from meta-analyses and review articles is mostly based on case–control and observational studies, which are likely influenced by the presence of bias due to difficulty in identifying and adjusting for confounders.[3 4 11–13] The limited evidence of observational studies was also attributed to healthy senior bias in influenza vaccination.[14–18] The individual's vaccination history and immune status affect the protective response after influenza vaccination, which were not easy to adjust in a case–control study.[19] Some studies noted that morbidity and mortality were relatively low in vaccinees even before the start of the influenza season, which is related to bias.[20 21] Although cohort studies are generally adjusted for comorbidities, and case–control studies are matched for age and gender, these studies have not completely controlled for bias.[14 21 22] Therefore, we used a case-crossover study design for self-matching and determine the effectiveness of influenza vaccine. We aim to realise whether the protective effects of influenza vaccination depended on the virus-vaccine strains matching in the elderly while addressing potential healthy senior bias.

METHOD
Influenza vaccine and circulating virus strains
To evaluate the effectiveness in preventing hospitalisation due to pneumonia by the level of viral circulation and vaccine matching in two consecutive years. We chose 2006/2007 season and 2007/2008 season as the study periods because virus-vaccine strains were all matching in 2006/2007 season and all unmatching in 2007/2008 season. The influenza vaccine strains were A/ New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2) and B/Malaysia/2506/2004 (type B) in 2006/2007 season. The epidemic influenza viral strains for 2006/2007 season were A/Wisconsin/67/2005-like (H3N2) and B/Malaysia/2506/2004-like (type B). The influenza vaccine strains in 2007/2008

season were A/Solomon Islands/3/2006 (H1N1), A/ Wisconsin/67/2005 (H3N2) and B/Malaysia/2506/2004 (type B).[23 24] The epidemic influenza viral strains for 2007/2008 season were A/Brisbane/59/2007-like virus (H1N1), A/Brisbane/10/2007-like virus (H3N2) and B/ Florida/4/2006-like virus (type B).

Source of data
This study used anonymised data of 30% of Taiwan's total older population (>65 years) from 2005 to 2009. The study sample was randomly selected from all elderly insurers in Taiwan's National Health Insurance Research Dataset (NHIRD). The decision to choose 30% of the total older population for analysis was made by the Review Committee of the National Health Research Insurance (NHRI) that manages the NHIRD with the reason of personal data protection. The NHI programme, which was instituted in March 1995, has contracts with almost every clinic and hospital in Taiwan. The NHI programme coverage rate has reached almost 99% in 1997 and has remained at that level ever since.[25]

Definition of pre-vaccination, vaccination and influenza periods
As shown in figure 1, the vaccination period was 1 October through 31 December, which coincided with the influenza vaccination programme governed by the Centers for Disease Control in Taiwan. We defined the influenza period as 1 January, after the close of the influenza vaccination period, through 30 April of the next year because influenza-like illness first peaked around early February, and the second peak occurred in March in Taiwan.[26] The pre-vaccination period was defined as the period from 1 May to 30 September, which was before the start of the influenza vaccination.

Study cohort
A case-crossover study design was used to analyse associations between influenza vaccination in the elderly and their risk of hospitalisation for CAP in 2006–2007 and 2007–2008. Every individual was a 'case' during the influenza vaccinated years and a 'control' in unvaccinated years (figure 1). As shown in figure 2, the study cohort was established in the following steps. First, we included

Time	May 1 2006	Oct. 1	Jan. 1 2007	May 1	Oct. 1	Jan. 1 2008	May 1
Period	*Pre-vaccination period*	*2006 vaccination period*	*2006-2007 Influenza period*	*Pre-vaccination period*	*2007 vaccination period*	*2007-2008 Influenza period*	
Admitted Group							
2006-vaccinated	Admitted for CAP	Vaccinated		Admitted for CAP	Unvaccinated		
2007-vaccinated	Admitted for CAP	Unvaccinated		Admitted for CAP	Vaccinated		
Non-admitted Group							
2006-vaccinated	Non-admitted for CAP	Vaccinated		Non-admitted for CAP	Unvaccinated		
2007-vaccinated	Non-admitted for CAP	Unvaccinated		Non-admitted for CAP	Vaccinated		

Figure 1 The case-crossover study design. CAP, community-acquired pneumonia.
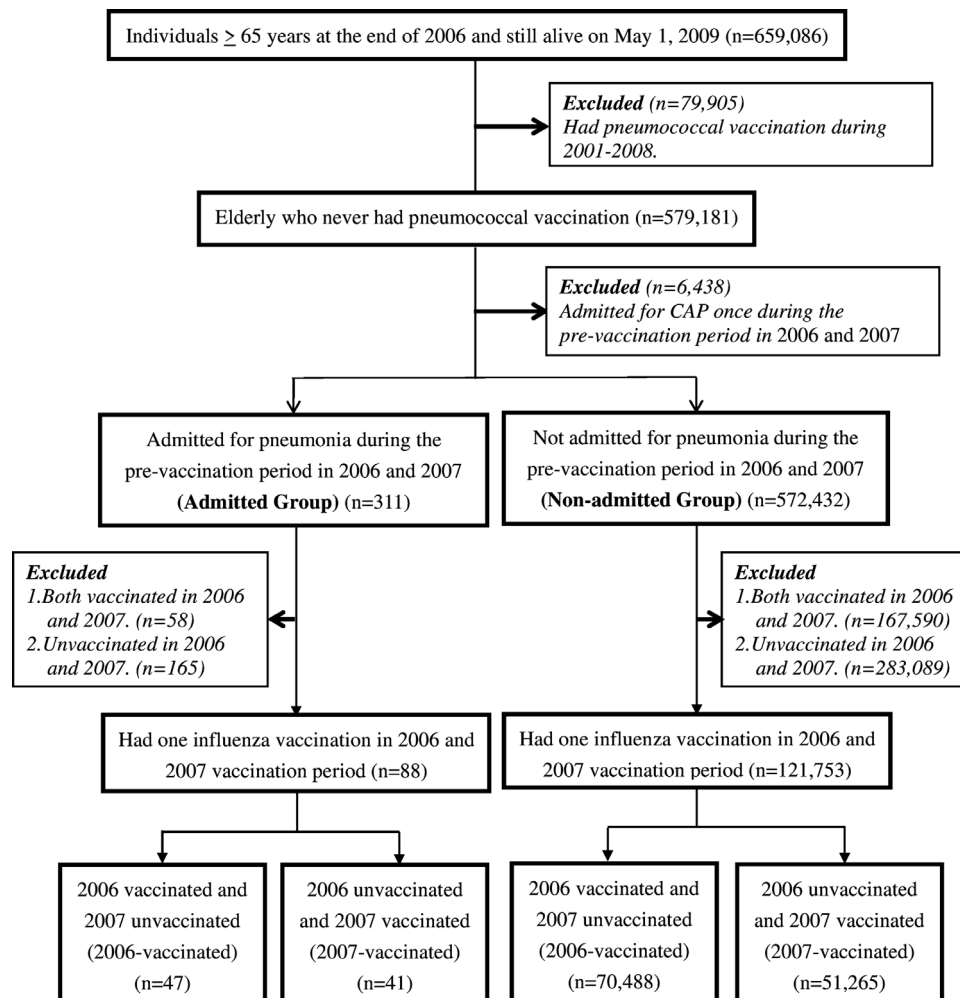
Figure 2 Sample flowchart of the study cohort. CAP, community-acquired pneumonia.

elderly people who were over 65 years as of 31 December 2006 and who were still alive on 1 May 2009. Second, we excluded the elderly who received pneumococcal vaccination from 2001 to 2008 to avoid data contamination from pneumococcal vaccination effects. Third, individuals hospitalised only once for CAP in the 2006 and 2007 pre-vaccination periods were excluded to ensure that these people had similar health conditions before receiving the influenza vaccine for reducing within-person confounder. Fourth, we categorised the elderly into the following groups: those who were never hospital admitted for CAP during the pre-vaccination period in two consecutive years (abbreviated Non-admitted) and those who were hospital admitted for CAP (abbreviated Admitted). Fifth, we identified individuals receiving only one influenza vaccination in calendar years 2006 and 2007 vaccination periods which meant that everyone could be a case in the vaccinated year and be a control in the unvaccinated year. Sixth, based on vaccination status, we divided these individuals into two groups. One group was the 2006 vaccinated and 2007 unvaccinated group (abbreviated 2006-vaccinated), and the other group was the 2006 unvaccinated and 2007 vaccinated (abbreviated 2007-vaccinated).

Definition of outcomes and other variables

The outcome was identified as hospitalisation for CAP during the influenza periods. An episode of CAP was defined as hospitalisation with a discharge diagnosis of pneumonia or influenza (ICD-9-CM codes 480.XX-487. XX). NHI claim records present each individual's age, gender and comorbidity. Comorbidity was assigned a Charlson Comorbidity Index (CCI)[27] score based on admission and ambulatory care diagnosis codes (ICD-9-CM codes) between October 2005 and September 2006. A higher score indicates more severe comorbidity.

Patient and public involvement

It was a population-based study using the NHIRD for analysis. No patient was involved in the design, conduct, reporting or dissemination of this study.

STATISTICAL ANALYSIS

A case-crossover study design was proposed to evaluate the effect of transient changes on the risk of acute-onset disease. As in a matched case–control study, inference is based on a comparison of exposure distribution rather than on the risk of disease.[28] In this study, each study

individual had a 'control window', with the same risk of CAP hospitalisation before the vaccination period, and a 'case window', the period of different vaccination status in two consecutive years. Conditional logistic regression with each individual's ID considered a stratum variable was applied to compare the risk of CAP hospitalisation during the influenza periods of vaccinated and unvaccinated years and to estimate the effectiveness of influenza vaccination. After adjustment for years, ORs and 95% CIs were derived from the regression coefficients and SEs of conditional logistic regression models. For all analyses, a 5% significance level was used. All statistical analyses were carried out using SAS (V.9.2).

RESULTS

As shown in figure 1, 579 181 elderly did not receive pneumococcal vaccination from 2001 to 2008. The number of elderly in the Admitted group was 311, and the number of elderly in the Non-admitted group was 572 432. The Admitted group consisted of 47 cases who received influenza vaccination in 2006 but not in 2007 (2006-vaccinated) and 41 cases who received influenza vaccination in 2007 but not in 2006 (2007-vaccinated). In contrast, the Non-admitted group consisted of 70 488 cases who were vaccinated in 2006 but not in 2007 (2006-vaccinated) and 51 265 cases who were vaccinated in 2007 but not in 2006 (2007-vaccinated).

Among the Admitted and Non-admitted groups, the demographic characteristics of the 2006-vaccinated individuals were similar to the 2007-vaccinated individuals (table 1). Nearly 66% of individuals in the Admitted group were aged ≥75 years old, the proportion of men was slightly higher than that of women and 21.6% had a CCI score ≥3. For individuals in the Non-admitted group, 35.6% were aged ≥75 years old, the number of men was approximately equal to women and only 3.8% had a CCI score ≥3. This result showed that the individuals in Non-admitted group were younger and healthier than the Admitted group.

The observed CAP hospitalisation rates of the Admitted group during the influenza periods for the 2006-vaccinated individuals in the vaccinated and unvaccinated years were 38.3% and 31.7%, respectively, and 26.8% and 27.7% in vaccinated and unvaccinated years, respectively, for the 2007-vaccinated individuals. The CAP hospitalisation rates of the Non-admitted group in vaccinated and unvaccinated years were 0.6% and 0.8%, respectively, for the 2006-vaccinated individuals and 0.8% and 0.7%, respectively, for the 2007-vaccinated individuals during the influenza period (table 2).

Table 3 that shows the ORs for the risk of CAP hospitalisation for the Admitted group were non-significant in the 2006-vaccinated individuals (OR, 1.79; 95% CI, 0.60 to 5.26) and 2007-vaccinated individuals (OR, 0.67; 95% CI, 0.19 to 2.38). However, the sample size was tiny; we could not draw accurate conclusions. Influenza vaccination in the Non-admitted group was associated with a significantly reduced risk of CAP hospitalisation during the influenza period in the 2006-vaccination individuals (OR, 0.72; 95% CI, 0.64 to 0.83) but not in the 2007-vaccination

Table 1 Characteristics of the study cohorts according to admission status during the pre-vaccination period

	Admitted group*		Non-admitted group†	
	2006-vaccinated (n=47) N (%)	2007-vaccinated (n=41) N (%)	2006-vaccinated (n=70 488) N (%)	2007-vaccinated (n=51 265) N (%)
Age (years), range Mean age (SD)	66–92 77.7 (6.5)	65–96 77.9 (7.7)	65–103 73.4 (6.1)	65–102 72.8 (6.0)
Age group (years)				
65–74	15 (31.9)	15 (36.6)	44 300 (62.8)	34 129 (66.6)
75–84	24 (51.1)	17 (41.5)	22 192 (31.5)	14 634 (28.5)
≥85	8 (17.0)	9 (21.9)	3996 (5.7)	2502 (4.9)
Gender				
Male	27 (57.5)	26 (63.4)	32 720 (46.4)	24 233 (47.3)
Female	20 (42.5)	15 (36.6)	37 768 (53.6)	27 032 (52.7)
CCI score‡				
0	1 (2.1)	1 (2.4)	28 787 (40.8)	21 448 (41.8)
1	19 (40.4)	15 (36.6)	30 635 (43.5)	21 759 (42.4)
2	14 (29.8)	18 (46.3)	8386 (11.9)	6054 (11.8)
≥3	13 (27.7)	6 (14.7)	2680 (3.8)	2004 (3.9)

*In each of the two consecutive years, the elderly who were hospital admitted with pneumonia during the pre-vaccination period.
†In two consecutive years, the elderly who were not hospital admitted with pneumonia during the pre-vaccination period.
‡CCI, Charlson Comorbidity Index.

Table 2 Community-acquired pneumonia (CAP) hospitalisation rates of older adults during the influenza period

Year	Admitted group*				Non-admitted group†			
	2006-vaccinated (n=47)		2007-vaccinated (n=41)		2006-vaccinated (n=70 488)		2007-vaccinated (n=51 265)	
	Vaccinated (2006–2007) n (%)	Unvaccinated (2007–2008) n (%)	Vaccinated (2007–2008) n (%)	Unvaccinated (2006–2007) n (%)	Vaccinated n (%)	Unvaccinated n (%)	Vaccinated n (%)	Unvaccinated n (%)
Hospitalised for CAP‡	18 (38.3)	13 (31.7)	11 (26.8)	13 (27.7)	413 (0.6)	569 (0.8)	403 (0.8)	376 (0.7)

*In each of two consecutive years, the elderly who were hospital admitted with pneumonia during the pre-vaccination period.
†In two consecutive years, the elderly who were not hospital admitted with pneumonia during the pre-vaccination period.
‡Hospitalised for CAP during the influenza period.

individuals (OR, 1.06; 95% CI, 0.92 to 1.23). Influenza vaccination did not offer protection for the risk of CAP hospitalisation in the elderly who had a CCI score ≥3 during the influenza period in the 2006-vaccination individuals (table 4).

DISCUSSION

We provide evidence of the effects of the influenza vaccine in older adults in the real world using a population-based nationwide database. We estimated the effectiveness of the influenza vaccination in protecting people aged 65 years or older from CAP hospitalisation using a case-crossover study design. The case-crossover study design allows the case to serve as his/her own control to completely control for between-person confounders, such as the healthy senior bias that is generally mentioned in case–control studies. It is used to investigate transient effects of accurately recorded preventive agents, and it is better than cohort designs for vaccines.[28 29] The case-crossover comparisons of vaccine effectiveness reduce confounders that are stable over time in a person, including health behaviours and the tendency to seek professional care.[29] For a case-crossover study, there should be a 'washout' period to avoid carry-over effects.[30] In our study, the 2006-vaccinated group had a 12-month washout period from the end of the first vaccination period to the second outcome period. The prior vaccination in the previous year does not influence the seroprotection rates 12 months post-influenza vaccination,[19] which means there

were no carry-over effects in the 2006-vaccined group. Because the case-crossover design compares the same person at different times, any time variation should be a concern.[31] Therefore, we stratified the individuals into a 2006-vaccinated group and a 2007-vaccinated group for analysis because the vaccine strains, circulating viruses and magnitude of influenza epidemics changed year by year. We provide evidence that the case-crossover study design is suitable for evaluations of vaccine effects, and it may be used in future research. In addition, we used medical records to identify influenza vaccination status, which is more reliable than recall, to avoid the misclassification that may bias the effectiveness estimate towards or away from the null hypothesis.[32] We used several ways in study design to increase the reliability of the influenza vaccine effects.

An individual's health status before an influenza shot is a main within-person confounder in evaluations of vaccine effects.[6 9] We controlled for the confounder, the individual's health status before receiving the vaccine, by dividing individuals into Admitted and Non-admitted groups. We showed that these two groups had different responses to the effects of the influenza vaccine. Compared with Non-admitted group, the individuals in Admitted group were older and had higher CCI scores that might be the reason for the different protection effects. However, our sample numbers in the Admitted group were insufficient to show good power and make a firm conclusion. Further study with a larger sample size is needed. For the Non-admitted

Table 3 ORs and 95% CIs for the risk of community-acquired pneumonia hospitalisation during the influenza period

	Admitted group*				Non-admitted group†			
	2006-vaccinated (n=47)		2007-vaccinated (n=41)		2006-vaccinated (n=70 488)		2007-vaccinated (n=51 265)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Influenza vaccination (Yes/No)	1.79 (0.60 to 5.26)	0.292	0.67 (0.19 to 2.38)	0.529	0.72 (0.64 to 0.83)	<0.001	1.06 (0.92 to 1.23)	0.391

Adjusted by year using conditional logistic regression.
*In each of the two consecutive years, the elderly who were hospital admitted with pneumonia during the pre-vaccination period.
†In two consecutive years, the elderly who were not hospital admitted with pneumonia during the pre-vaccination periods.

Table 4 ORs for the risk of community-acquired pneumonia hospitalisation in Non-admitted individuals during the influenza period using stratified analysis

| | Non-admitted group* | | | |
| | 2006-vaccinated | | 2007-vaccinated | |
	OR (95% CI)	P value	OR (95% CI)	P value
Age group (years)				
65–74	0.74 (0.60 to 0.91)	0.003	0.97 (0.78 to 1.22)	0.820
75–84	0.74 (0.61 to 0.89)	0.001	1.08 (0.86 to 1.33)	0.536
≥85	0.61 (0.42 to 0.89)	0.012	1.41 (0.93 to 2.08)	0.104
Gender				
Male	0.69 (0.58 to 0.83)	<0.001	1.16 (0.96 to 1.41)	0.128
Female	0.77 (0.63 to 0.93)	0.009	0.94 (0.76 to 1.19)	0.648
CCI score†				
0	0.73 (0.54 to 0.90)	0.041	1.08 (0.79 to 1.49)	0.629
1	0.76 (0.64 to 0.92)	0.043	1.07 (0.88 to 1.32)	0.492
2	0.62 (0.47 to 0.82)	0.001	1.16 (0.85 to 1.59)	0.346
3	0.75 (0.49 to 1.15)	0.192	0.70 (0.39 to 1.27)	0.241

*In the two consecutive years, the elderly who were not hospital admitted with pneumonia during the pre-vaccination period.
†CCI, Charlson Comorbidity Index.

group, influenza vaccination had a protective effect in 2006/2007 season but not in 2007/2008 season. This finding may be attributed to difference in the virus-vaccine match, which was excellent for 2006/2007 season but poor for 2007/2008 season.[23] This result is similar to the results of previous meta-analyses that indicates vaccine protection against CAP admission varies according to vaccine-circulating strain-matched or not.[3 5] In addition, because of the possible immune memory and heterotypic cross-protection by influenza vaccination.[33] Annual influenza vaccination is still a cost-effective strategy to prevent CAP.

We assessed factors that affected the effectiveness of influenza vaccination in the prevention of CAP admissions during influenza periods in the Non-admitted group in vaccine-circulating strain-matched years. Previous studies mentioned that comorbidity, frailty and age were confounding factors for the assessment of influenza vaccine effects.[3 34] Our study showed that vaccine effectiveness against CAP was affected by comorbidity but not by age. The progressive decline in systemic immunity may be one reason for comorbidities in the elderly and their possible influence on the reduction in vaccine response.[35] Vaccination had a smaller effect on reducing the risk of CAP hospitalisation in older individuals who had a higher comorbidity in the present study, even in vaccine-circulating strain-matched seasons.

Influenza viruses primarily spread via contact, droplets and airborne transmission when people with the influenza cough, sneeze or talk, which is similar to COVID-19.[36 37] The policy of yearly influenza vaccination is highly recommended in protecting against influenza viruses.[38] Because some older adults do not feel necessary for influenza

vaccination, multiple prompts from family, particularly from healthcare providers, were important triggers for receiving immunisation.[39] However, we demonstrated that vaccination only had protective effects when vaccine-circulating strain-matched. The reduced vaccine effects even in the vaccine-circulating strain-match seasons may be attributed to complex health problems in older adults. To protect against influenza, non-pharmaceutical interventions, including hand washing, social-distancing, covering your mouth and nose with a mask when around others, and increasing ventilation may be recommend, especially for older adults with high comorbidity.[38 40] Healthy habits and lifestyle, including plenty of sleep, physical activity, stress management, drinking plenty of fluids and eating nutritious food, are also helpful to prevent influenza.[41]

The following limitations were identified in this study. First, the population selected in this study were individuals with intermittent vaccination (ie, one vaccine in two consecutive years). The percentage of intermittent vaccination sample was 28% among Admitted Group, and 21% among Non-admitted group of the population. It is unclear how that crossover subgroup differs from the overall cohort, and whether the relationship observed for that subgroup would generalise to the overall cohort and the larger community of older adults. Second, the specific outcome for the evaluation of the effects of influenza vaccine needs to be confirmed by clinical laboratory data. Because there was no laboratory data in NHIRD, we used CAP as a common, but less specific, outcome in this study. Third, tiny numbers in Admitted group affected the results' accuracy and only limited conclusions that we could draw.

CONCLUSIONS

The present study provides evidence that the effects of influenza vaccination against CAP in older adults depends on the vaccine-circulating strain-matched. The policy of providing a free influenza vaccine to older adults is highly supported. An individual's comorbidity may reduce the influenza vaccine effects. Therefore, healthcare providers should use vaccination in combination with non-pharmaceutical interventions to keep older adults away from influenza.

Author affiliations
[1]School of Nursing, National Defense Medical Center, Taipei, Taiwan
[2]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[3]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[4]Institute of Hospital and Health Care Administration, National Yang Ming Chiao Tung University, Taipei, Taiwan
[5]Department of Public Health, College of Medicine, National Cheng-Kung University, Tainan, Taiwan
[6]Department of Public Health, China Medical University, Taichung, Taiwan
[7]Center for Aging and Health, Hualien Tzu Chi Hospital, Hualien, Taiwan
[8]School of Medicine, Tzu Chi University, Hualien, Taiwan
[9]Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan
[10]School of Nursing, National Defense Medical Centre, Taipei, Taiwan
[11]Department of Nursing, Taipei Veterans General Hospital, Taipei, Taiwan

Contributors C-Y L and K-Y W designed the model and the computational framework. C-YL analysed the data with support from C-Y L and K-C L. C-Y L wrote the manuscript with support from S-J H and K-Y W. K-Y W made critical revisions to the paper for important intellectual content. JY-H C and C-H L contributed to the interpretation of the results. K-Y W responsible for the overall content as the guarantor. All authors discussed the results and commented on the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The Review Committee of NHRI and Institutional Review Board of the Taipei Veterans General Hospital approved the study protocol (No. 2011-03-006IC).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data in this study was provided by the Bureau of National Health Insurance. The data was used under license for the current study and not publicly available.

ORCID iDs
Chun-Yu Liang http://orcid.org/0000-0002-2007-9583
Chung-Yi Li http://orcid.org/0000-0002-0321-8908

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