Effectiveness of influenza vaccination on in-hospital death in older adults with respiratory diseases

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ABSTRACT

Influenza vaccination is associated with lower risk of hospitalization outcomes among older adults with respiratory diseases, but there is limited evidence by disease subtypes and patients’ characteristics. This study included patients aged ≥60 years hospitalized for respiratory diseases from the Beijing Urban Employee Basic Medical Insurance database during 6 influenza seasons. Vaccination status was assessed by linking with the Beijing Elderly Influenza Vaccination database. Multi-variable logistic regression was performed to calculate effect estimates. After adjusting for measured and unmeasured confounders, influenza vaccination was associated with a lower risk of in-hospital death among older adults hospitalized for respiratory diseases (odds ratio [95% confidence interval], 0.70 [0.62–0.80]). The protective association was observed among patients with chronic obstructive pulmonary disease (0.67 [0.47–0.98]) as well as those with pneumonia or influenza (0.77 [0.64–0.93]). The protective association was stronger in younger patients (0.59 [0.43–0.81] for <75 and 0.72 [0.63–0.83] for ≥75) and those with fewer comorbidities (0.49 [0.16–1.62] for 0, 0.65 [0.50–0.86] for 1–2, and 0.72 [0.63–0.83] for ≥3 comorbidities). Influenza vaccination was associated with lower risk of in-hospital death among older patients hospitalized for respiratory diseases, with stronger associations in patients with younger age and fewer comorbidities.

PLAIN LANGUAGE SUMMARY

We found that influenza vaccination was associated with lower risk of in-hospital death among older adults hospitalized for respiratory diseases. The associations were stronger in patients with younger age and fewer comorbidities. The study suggested that, in addition to prevent influenza itself, influenza vaccination may also prevent in-hospital death among patients with respiratory diseases.

Influenza is a major cause of morbidity and mortality worldwide, especially among older adults.1,2 According to the Global Burden of Disease study, influenza accounted for 145,000 deaths in 2017, with half occurring among those aged ≥70 years.3 The World Health Organization (WHO) recommends annual influenza vaccination for people aged six months or older.4,5 People aged ≥60 are included among the high-priority groups targeted for annual vaccination, particularly during the recent COVID-19 pandemic.6 Pneumococcal vaccination is also recommended for older adults.7 Beijing’s municipal government launched free influenza vaccination for adults ≥60 years old since 2007 and free 23-valent pneumococcal polysaccharide vaccine for adults ≥65 years old since 2018.

Observational studies conducted in the general older population showed that influenza vaccines were associated with lower risk of hospitalization and death.7,8 Our previous studies showed that influenza vaccination was associated with lower risk of in-hospital death among older patients with respiratory disease.9,10 However, we did not examine the effectiveness by disease subtypes and by comorbidity patterns because of the relatively small sample size. Other studies in western counties showed that influenza vaccination was associated with lower risk of all-cause mortality in patients with chronic obstructive pulmonary disease (COPD).11 However, there is limited evidence in the Chinese population. With regard to joint vaccination, a retrospective cohort study12 showed that influenza and pneumococcal vaccination was associated with lower risk of hospitalization among COPD patients, but this study was restricted to COPD instead of respiratory diseases.

In this study, we examined the association of influenza vaccination with in-hospital death among older patients with respiratory diseases during six influenza seasons (2013–2014 through 2018–2019) and assessed whether the association differed by subtypes of respiratory diseases and comorbidities. We also assessed the joint association of influenza and pneumococcal vaccinations on in-hospital death among older adults with respiratory diseases.

A retrospective cohort study was designed by combining two databases, namely the Beijing Urban Employee Basic Medical Insurance (UEBMI) and the Beijing Elderly
Influenza Vaccination (EIV), and included patients aged ≥60 hospitalized for respiratory diseases (ICD-10, codes J00-J99) from January 2013 to December 2019. We defined the influenza season as 1 October to 31 March and summer months as 1 June to 31 August (Figure 1).

Within each influenza season, participants were considered vaccinated if they received the vaccine ≥14 days before hospitalization. In-hospital death was defined as death from any cause during the hospitalization extracted from the UEBMI database. Alcohol-related diagnoses and obesity-related diagnoses were used as markers of lifestyle factors because lifestyle factors were not collected in medical records (Supplementary Methods).

Univariate analyses of baseline characteristics were performed using Chi-square and Student-t tests. The effectiveness of vaccination on in-hospital death was assessed by multi-variable logistic regression and adjusted for age, age squared, sex, number of inpatient visits in the past 12 months, Charleston Comorbidity Index (CCI), operation status, hospital size, quintiles of propensity score, obesity-related diagnosis, and alcohol-related diagnosis (adjusted model, Supplementary Methods). In order to address unmeasured confounding (Supplementary Methods), The generalized estimating equations techniques were used in logistic regression models to estimate the influence of within-person dependency with the independence correlation structure.

We calculated the effect estimate during influenza seasons adjusted for that during summer months according to the formula below:

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\text{OR}_{\text{adjusted}} = \frac{\text{OR}_{\text{influenza season}}}{\text{OR}_{\text{summer}}} = \exp\left(\beta_{\text{influenza season}} - \beta_{\text{summer}}\right)
\]

We sampled 1000 times using bootstrap techniques to estimate a 95% confidence interval (CI) of OR_{adjusted} (ratio of ORs). Analyses were performed using R, version 4.1.2.

The total number of periods of observation (i.e. records of hospitalization) was 399,632 across all study years. 14,523 patients with respiratory diseases died during the influenza seasons and 6,663 patients died during the summer seasons. The overall vaccination rate was 12.4%. Vaccinated participants were younger, more likely to be male, and had fewer inpatient visits and lower CCI (Table 1).

Influenza vaccination was associated with a 59% lower risk of in-hospital death among older adults with respiratory diseases during influenza seasons (OR [95% CI] 0.41 [0.38, 0.45], adjusted model). After accounting for unmeasured confounders, influenza vaccination was associated with a 30% lower risk of in-hospital death (ratio of OR 0.70 [0.62, 0.80], adjusted model). For disease subtypes, influenza vaccination was associated with 33% and 23% lower risk of in-hospital death among those hospitalized for COPD and pneumonia/influenza, respectively (ratio of

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**Figure 1.** Flow diagram. Flowchart showing the selection of study participants and linkage to the Beijing Elderly Influenza Vaccination (EIV) database. Abbreviation: EIV, the Beijing Elderly Influenza Vaccination; UEBMI, Beijing Urban Employee Basic Medical Insurance.
Table 1. Patient characteristics by vaccination status.

|                                | Total          | Vaccinated     | Not vaccinated |
|--------------------------------|----------------|----------------|---------------|
| Periods of observation         | 399632         | 49733          | 349899        |
| Age, mean (SD)                 | 76.9 (9.0)     | 76.8 (7.7)     | 77.0 (9.1)    |
| Female sex                     | 44.8           | 40.6           | 45.4          |
| Inpatient visits, mean (SD)    | 1.9 (3.5)      | 1.0 (1.6)      | 2.0 (3.6)     |
| CCI, mean (SD)                 | 2.5 (1.6)      | 2.2 (1.5)      | 2.5 (1.6)     |
| Surgical operation             | 9.2            | 7.8            | 9.4           |
| Alcohol-related diagnosis      | 0.02           | 0.01           | 0.03          |
| Obesity-related diagnosis      | 52.2           | 51.8           | 52.2          |
| COPD diagnosis                  | 102057 (25.5)  | 15560 (31.3)   | 86497 (24.7)  |
| Pneumonia/influenza diagnosis  | 110952 (27.8)  | 11954 (24.0)   | 98998 (28.3)  |
| Asthma diagnosis               | 11866 (3.0)    | 1698 (3.4)     | 10168 (2.9)   |
| Death                          | 27784 (7.0)    | 1609 (3.2)     | 26175 (7.5)   |

Values are mean (SD) for continuous variables or proportions for categorical variables.

Abbreviation: CCI, Charleston Comorbidity Index.
All p-values <.001.

OR, 0.67 [0.47, 0.98] and 0.77 [0.64, 0.92], adjusted model. The number of events for asthma patients was too small to provide reliable estimates (Table 2).

The protective effects of influenza vaccination on inhospital death were stronger among respiratory disease patients with fewer comorbidities and those with younger age (Figure 2). The effect estimates for ratio of ORs were 0.49 [0.16, 1.62], 0.65 [0.50, 0.86], and 0.72 [0.63, 0.83] among patients with 0, 1–2, and ≥3 comorbidities (P-value for trend: <.001), the corresponding effect estimates were 0.59 [0.43, 0.81] and 0.72 [0.63, 0.83] among those aged 60–75 and ≥75 years old (P-value for heterogeneity: .04).

During the 2018–2019 influenza season, the vaccination rate was 10.3% for influenza vaccination only, 0.8% for pneumococcal

Table 2. Associations of influenza vaccination with in-hospital death among patients with respiratory disease by subtypes.

| Disease subtypes               | Effect size (95% CI) | Ratio of ORs |
|--------------------------------|----------------------|-------------|
|                                | Influenza seasons    | Summer months |          |
| Respiratory disease Basic model| 0.35 (0.32, 0.38)    | 0.52 (0.48, 0.57) | 0.67 (0.59, 0.76) |
| Adjusted model                 | 0.41 (0.36, 0.45)    | 0.59 (0.54, 0.65) | 0.70 (0.62, 0.80) |
| COPD Basic model               | 0.35 (0.28, 0.43)    | 0.50 (0.38, 0.65) | 0.70 (0.51, 0.98) |
| Adjusted model                 | 0.39 (0.32, 0.49)    | 0.58 (0.44, 0.77) | 0.67 (0.47, 0.98) |
| Pneumonia/influenza Basic model| 0.38 (0.34, 0.43)    | 0.56 (0.49, 0.64) | 0.68 (0.57, 0.83) |
| Adjusted model                 | 0.39 (0.32, 0.49)    | 0.62 (0.54, 0.71) | 0.77 (0.64, 0.93) |
| Asthma Basic model             | 0.20 (0.03, 1.52)    | 0.53 (0.06, 4.84) | 0.38          |
| Adjusted model                 | 0.22 (0.03, 1.50)    | 0.74 (0.09, 6.24) | 0.29          |

Abbreviation: OR, odds ratio.

a. The reference group was those not vaccinated in the current seasons. The basic model was adjusted for age, age square, and sex. The adjusted model was adjusted for age, age squared, sex, number of inpatient visits in the past 12 months, Charleston Comorbidity Index, operation status, hospital size, quintiles of propensity score, obesity-related diagnosis, and alcohol-related diagnosis.

b. For asthma, 6% of the ratio of ORs were not reported because of the small number of events included.

Figure 2. Associations of influenza vaccination with in-hospital death among patients with respiratory disease by subgroups. Boxes represent odds ratios (ORs) of in-hospital death among older patients with respiratory disease during influenza seasons and summer seasons. The model was adjusted for age, age squared, sex, number of inpatient visits in the past 12 months, Charleston Comorbidity Index, operation status, hospital size, quintiles of propensity score, obesity-related diagnosis, and alcohol-related diagnosis. Ratio of ORs were estimates adjusted for measured and unmeasured confounders. Details of subgroup analyses are shown in the supplementary methods.
vaccination only, and 1.3% for both. The effectiveness of influenza vaccination was similar to that of joint vaccinations (ratio of ORs: influenza vaccination 0.69 [0.52, 0.93], joint vaccinations 0.68 [0.23, 1.62]), but the effectiveness of pneumococcal vaccination only was limited because of the small number of vaccinated patients.

Among older adults with respiratory diseases, influenza vaccination was associated with lower risk of in-hospital death across six influenza seasons. The protective effect was observed among patients with different disease subtypes, including COPD and pneumonia/influenza. The protective effect was stronger in patients with fewer comorbidities and those with younger age.

Previous studies using linkages to hospital records have reported that influenza vaccination is associated with lower risks of influenza infection and death among patients with respiratory diseases.\textsuperscript{11,18,19} However, previous studies had limited power because of the small sample size and may suffer from unmeasured confounding.\textsuperscript{19} Our findings among older patients with respiratory diseases are in line with a retrospective cohort study in UK which showed a 41% lower risk of death among COPD patients associated with influenza vaccination.\textsuperscript{11}

We showed that the protective association of influenza vaccination was stronger among respiratory patients with fewer comorbidities. This finding was in line with a case-control study which reported that the effectiveness of influenza vaccine against influenza-related mortality decreased with more comorbidities.\textsuperscript{12} Previous studies have shown lower vaccine effectiveness in patients with immunosuppressive conditions, including cancers and HIV infection. Although such mechanisms are irrelevant to noncommunicable diseases, it might be possible that higher level of local or systemic inflammation can reduce the protective effect of influenza vaccination among patients with comorbid chronic conditions.

The strengths of the current study included the large population-based cohort, availability of vaccination history of influenza and pneumococcal vaccines, and statistical methods to adjust for measured and unmeasured confounders. However, our sample size was inadequate to perform analyses for asthma and for single pneumococcal vaccination. In addition, influenza season was defined in accordance with influenza surveillance results from Beijing Center for Disease Control and Prevention and may not be comparable with studies conducted in other countries.

In conclusion, influenza vaccination was associated with lower risk of in-hospital death among older patients hospitalized for respiratory diseases, with stronger associations in patients with fewer comorbidities and those with younger age. These findings provide preliminary evidence for the "free influenza vaccine" policies among older adults in Beijing, which serve as a reference for other cities in China and other developing countries.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Author’s contributions

MY and YH had full access to the data. RZ, SW, and YH conducted data analysis and are responsible for accuracy of the results and the decision to submit for publication. All authors were involved in study design, conduct, long-term follow-up, review and coding of disease events, interpretation of the results, or writing the report.

References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736–1788. doi:10.1016/S0140-6736(18)32203-7.

2. GBD 2017 Influenza Collaborators. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2019;7(1):69–89. doi:10.1016/S2213-2600(18)30496-X.

3. World Health Organization. Vaccines, 2019 [accessed 2019 Jun 1]. https://www.who.int/influenza/vaccines/en/.

4. Vaccines against influenza WHO position paper—November 2012. World Health Organization; 2012 [accessed 2020 Sept 17]. https://www.who.int/wer/2012/wer8747.pdf?ua=1.

5. WHO SAGE Seasonal Influenza Vaccine Recommendations during the COVID-19 Pandemic. Published 2020 Sept 21 [accessed 2022 Apr 2]. https://www.who.int/news/item/21-09-2020-who-sage-seasonal-influenza-vaccination-recommendations-during-the-covid-19-pandemic.

6. US Centers for Disease Control and Prevention. Pneumococcal vaccination: summary of who and when to vaccinate [accessed 2022 Apr 2]. https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html.

7. Groenwold RH, Hoes AW, Hak E. Impact of influenza vaccination on mortality risk among the elderly. Eur Respir J. 2009;34 (1):56–62. doi:10.1183/09031936.00190008.

8. Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med. 2007;357(14):1373–1381. doi:10.1056/NEJMoa070844.
9. Pang Y, Wang Q, Lv M, Yu M, Lu M, Huang Y, Wu J, Xie Z. Influenza vaccination and hospitalization outcomes among older patients with cardiovascular or respiratory diseases. J Infect Dis. 2021;223(7):1196–1204. doi:10.1093/infdis/jiaa493.
10. Pang Y, Yu M, Lv M, Lu M, Wu J, Xie Z, Huang Y. Repeated influenza vaccination and hospitalization outcomes among older patients with cardiovascular or respiratory diseases. Hum Vaccin Immunother. 2021;17(12):5522–5528. doi:10.1080/21645515.2021.2007012.
11. Schembri S, Morant S, Winter JH, MacDonald TM. Influenza but not pneumococcal vaccination protects against all-cause mortality in patients with COPD. Thorax. 2009;64(7):567–572. doi:10.1136/thx.2008.106286.
12. Nation ML, Moss R, Spittal MJ, Kotsimbos T, Kelly PM, Cheng AC. Influenza vaccine effectiveness against influenza-related mortality in Australian hospitalized patients: a propensity score analysis. Clin Infect Dis. 2021;72(1):99–107. doi:10.1093/cid/ciz1238.
13. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Expert Rev Vaccines. 2014;13(12):1571–1591. doi:10.1586/14760584.2014.966695.
14. Ortvist A, Granath F, Askling J, Hedlund J. Influenza vaccination and mortality: prospective cohort study of the elderly in a large geographical area. Eur Respir J. 2007;30(3):414–422. doi:10.1183/09031936.00135306.
15. Mangtani P, Cumberland P, Hodgson CR, Roberts J, Cutts F, Hall A. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. J Infect Dis. 2004;190(1):1–10. doi:10.1086/421274.
16. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc. 1984;79:516–524. doi:10.2307/2288398.
17. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med. 1997;127(8 Pt 2):757–763. doi:10.7326/0003-4819-127-8_part_2-199710151-00064.
18. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018;2(2):CD004876. doi:10.1002/14651858.CD004876.pub4.
19. Darvishian M, van den Heuvel ER, Bisieleo A, Castilla J, Cohen C, Englund H, Gefenaite G, Huang W-T, la Bastide-van Gemert S, Martinez-Baz I, et al. Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies. Lancet Respir Med. 2017;5(3):200–211. doi:10.1016/S2213-2600(17)30043-7.