Efficacy of Trivalent Seasonal Influenza Vaccination in Reducing Mortality and Hospitalization in Chinese Nursing Home Older Adults

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Abstract

Objective: To examine the clinical efficacy of the trivalent seasonal influenza vaccination among Chinese older adults residing in a nursing home.

Design: A 12-month prospective cohort study. Participants were divided into 2 groups based on their own choice on vaccination of trivalent seasonal influenza vaccine: vaccinated group and unvaccinated group.

Setting: Fifty-eight nursing homes in Hong Kong.

Participants: A total of 1859 older adults residing in a nursing home.

Measurements: All-cause mortality, pneumonia-related mortality, all-cause hospitalization, and pneumonia-related hospitalization.

Results: A total of 1859 older adults residing in a nursing home were included: 1214 (65.3%) in the vaccinated group and 645 (34.7%) in the unvaccinated group. At 12 months of study, for all-cause mortality, 14.6% (177 of 1214) of the vaccinated group and 20.2% (130 of 645) of the unvaccinated group died (P < .001). Multivariate analysis showed the hazard ratio for the vaccinated group was 0.72 (95% confidence interval [CI]: 0.54–0.95; P < .01). For pneumonia-related mortality, 9.4% (114 of 1214) of the vaccinated group and 12.7% (82 of 645) of the unvaccinated group died (P = .033). Multivariate analysis showed the hazard ratio for the vaccinated group was 0.80 (CI: 0.62–0.98; P < .05). The median number of all-cause hospitalizations per 1000 person-months was 55 (0–111) for the vaccinated group and 55 (0–167) for the unvaccinated group (P < .01). The median number of pneumonia-related hospitalizations per 1000 person-months was 0 (0–55) for the vaccinated group and 0 (0–111) for the unvaccinated group (P < .01).

Conclusions: Vaccination of trivalent seasonal influenza vaccine in Chinese nursing home older adults significantly reduced all-cause and pneumonia-related mortality and hospitalization.

Keywords: Efficacy influenza vaccination nursing home mortality hospitalization Chinese
a prospective cohort study to examine the clinical efficacy of the trivalent influenza vaccine 2010 in older Chinese adults who reside in a nursing home, with comprehensive measurement of comorbidity and functional status.

Methods

This was a prospective cohort study performed from 2010 to 2011 in the Hong Kong West Cluster (HKWC), 1 of the 7 major health districts in Hong Kong. In 2010, the population of HKWC was more than 530,000 and there were 70 nursing homes. Fourteen of the nursing homes were run by nongovernmental charitable organizations and 56 were privately run. The nursing homes took care of more than 6000 older adults. Because many older adults who reside in a nursing home have impaired mobility that limits their ability to attend an outpatient clinic, the Community Geriatric Assessment Team (CGAT) of HKWC, including geriatricians and community nurses, provide comprehensive outreach services for those older adults. HKWC CGAT covers 58 of the 70 nursing homes in this cluster. The HKWC CGAT has a complete record of patient medical and functional status, which allows a prospective cohort to be established.

Apart from HKWC CGAT, which provides management for medical illnesses, the Department of Health of Hong Kong provides an annual vaccination program for older adults living in nursing homes. In 2010, the seasonal influenza vaccination program was carried out beginning in October. The trivalent influenza vaccine 2010 contains an A/California/7/2009 (H1N1)pdm09-like virus, an A/Perth/16/2009 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. All participants gave informed consent for vaccination of trivalent influenza vaccine 2010 in October 2010. For those who were mentally incompetent to provide informed consent, the consent was made by a guardian.

Inclusion criteria were adults aged 65 or older living in the nursing home and followed-up by HKWC CGAT. Exclusion criteria were older adults who reside in a nursing home who were admitted to a hospital during the vaccination program and those who were diagnosed with advanced malignancy before the vaccination program began. Participants were divided into 2 groups according to their vaccination status: older adults who received the vaccination (vaccinated) and older adults who did not receive the vaccination (unvaccinated).

Sample Size Calculation

Sample size was calculated with reference to the study “Efficacy and effectiveness of influenza vaccine in elderly,” which is a systematic review of the efficacy of influenza vaccine among nursing home older adults. In this study, the survival rate at 3 months was 96.2% in the unvaccinated group and 97.4% in the vaccinated group. The difference in proportion was 0.012 over 3 months in this study. Power Analysis and Sample Size 2008 (Windows version 2008; NCSS, Kaysville, UT) was used in sample size calculation. It showed that a group sample size of 1004 and 502 in treatment and control groups, respectively, with a 2:1 ratio, would be able to achieve 80% power to detect a difference in proportion of 0.048 over 1 year between the null hypothesis and the alternative hypothesis using a 2-sided chi-square test with continuity correction and with a significance level of .05.

Data Collection

Vaccination status was collected from patient records of nursing homes, which have documentation of vaccination status of each resident even if the resident was vaccinated in the private sector. If a resident dies, the nursing home keeps a hard copy of the patient’s records for 3 years.

Baseline data were collected by reviewing the Computer Management System (CMS) and patient medical records. The CMS is a computerized patient medical record system that is connected to the nursing homes via remote Internet access. Patient comorbidities were coded in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The CMS also contains records of hospitalizations, medications (number and type), investigation results, and death for all patients. Number and type of comorbidity on the basis of ICD-9-CM from CMS was collected and quantified using the Charlson Comorbidity Index, which is valid and reliable to measure comorbidity. Functional status of patients was assessed by the Barthel Index, which is a validated functional scale for basic activities of daily living. It is also a major predictor of mortality and influenza vaccine efficacy. Registered nurses of HKWC CGAT performed the Barthel Index for all patients every year and filed assessment results in the patient consultation record. The number of nonscheduled hospitalizations is an independent predictor for mortality, and all hospitalizations documented in CMS between November 2009 and October 2010 were recorded and regarded as “admission in the preceding year.” Because anemia and chronic renal disease are common and important prognosticators for older adults who reside in a nursing home, serum hemoglobin level and glomerular filtrate rate (GFR) (estimated by Modified Diet for Renal Disease equation adjusted for Chinese population) were also recorded. Nutritional status was assessed using serum albumin level.

Outcome Measures

The clinical data of each patient were reviewed from November 2010 to October 2011. All deaths and hospitalizations were reviewed. Mortality was divided into all-cause and pneumonia-related (based on ICD-9 coding). Hospitalizations due to scheduled clinical admission were excluded from analysis and the rates of all-cause hospitalization and pneumonia-related hospitalization were expressed as the number of hospitalizations per 1000 person-months. The research was formally approved by the institutional review boards at the University of Hong Kong and Hospital Authority HKWC.

Statistical Analysis

Statistical Package for Social Sciences (Windows version 18; SPSS Inc, Chicago, IL) was used in the statistical analysis. Continuous variables were expressed as either mean ± SD of the mean (mean ± SD) or median with interquartile range, as appropriate. Independent t test and Mann-Whitney U test were used to compare the change of continuous variables for 2 different groups as appropriate. Chi-square test and Fisher’s exact test were used to compare categorical variables. Kaplan-Meier curves were constructed to illustrate the cumulative rate of mortality between groups during the 12-month follow-up and the differences were compared with log-rank test. For mortality due to pneumonia, patient death due to causes other than pneumonia was regarded as censored in Kaplan-Meier curves. The effectiveness of the vaccine in the prevention of mortality was estimated using multivariable Cox proportional hazard models adjusted for covariables. Statistical significance was inferred by a 2-tailed P value of .05.

Results

A total of 1859 older adults who reside in a nursing home were included in the study; 1214 (65.3%) of them received the vaccine
(vaccinated) and 645 (34.7%) refused the vaccine (unvaccinated). There was no significant difference between the 2 groups regarding age, gender, Charlson Comorbidity Index, Barthel Index, glomerular filtration rate, albumin level, hemoglobin level, and hospitalization in the preceding year (Table 1). Over 12 months, there was no loss to follow-up or missing data.

At 12 months of study, for all-cause mortality, 14.6% (177 of 1214) of the vaccinated group and 20.2% (130 of 645) of the unvaccinated group died ($P < .001$) (Figure 1). Multivariate analysis for all-cause mortality was performed using Cox proportional hazard models by entering covariate. It showed the hazard ratio for the vaccinated group was 0.72 (95% confidence interval [CI]: 0.54–0.95; $P < .01$).

For mortality due to pneumonia, 9.4% (114 of 1214) of the vaccinated group and 12.7% (82 of 645) of the unvaccinated group died ($P = .033$) (Figure 2). Multivariate analysis for mortality due to pneumonia showed the hazard ratio for the vaccinated group was 0.80 (CI: 0.62–0.98; $P < .05$).

Over 12 months, there were a total of 1762 hospitalizations (vaccinated group: 1171 hospitalizations; unvaccinated group: 591 hospitalizations). The median number of all-cause hospitalizations per 1000 person-months was 55 (0–111) for the vaccinated group and 55 (0–167) for the unvaccinated group ($P < .01$) (Figure 3). The median number of hospitalizations due to pneumonia per 1000 person-months was 0 (0–55) for the vaccinated group and 0 (0–111) for the unvaccinated group ($P < .01$) (Figure 4).

Discussion

Influenza can cause significant morbidity and mortality. For all influenza-related deaths, up to 90% occur among people aged 65 years or older.1–3 However, the vaccination rate for this trivalent influenza vaccine 2010 was very low.4 Fewer than 5% of the general population in Hong Kong received the vaccination. The vaccination rate was also low in nursing homes. Compared with an approximate 80% vaccination rate in nursing homes before 2009, only 65% of older adults who reside in a nursing home in this study received vaccination. Fear of side effects and inadequate publicity about the efficacy of the influenza vaccine may be the major reasons for the low vaccination rate.10–11 The inclusion of influenza A(H1N1)pdm in the trivalent influenza vaccine 2010 and the occurrence of suspected cases of major adverse events from the monovalent influenza A(H1N1)pdm vaccine may have increased the perceived risk of influenza vaccine 2010 among the lay public. However, influenza A(H1N1)pdm was the major isolated strain in 2011. In the laboratory surveillance results of the Center of Health Protection from January to March 2011, more than 80% of the isolated strains of influenza was H1N1 2009 and it was isolated in most months of 2011.4 The efficacy of influenza vaccine was well demonstrated by its efficacy in reducing all-cause mortality, pneumonia-related mortality, all-cause hospitalization rate, and rate of pneumonia-related hospitalizations in the vaccinated group. Multivariate analysis showed that vaccination of trivalent influenza vaccine 2010 in older adults who reside in a nursing home significantly reduced all-cause mortality and pneumonia-related mortality by 28% and 20%, respectively. The high clinical efficacy of the vaccine 2010 on mortality and hospitalization in our study could be explained by the good match of the vaccine strain with the strain of high viral circulation during this period. Findings of this study could be important from a public health perspective. The health authority should make every effort to inform the lay public of these results that show high efficacy of the vaccine. A reassuring result on the efficacy of the influenza vaccine may not only increase the confidence of the vaccine in older adults who reside in a nursing home, their relatives, and the general public, it may also increase the vaccination rate in subsequent years.

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<th>Table 1 Baseline Characteristics of Participants*</th>
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<td>Age (years)</td>
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<td>Hospitalizations in the preceding year</td>
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CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVA, cerebrovascular accident; DM, diabetes melitus; GFR, glomerular filtration rate estimated by Chinese version of Modified Diet for Renal Disease; IHD, ischemic heart disease; PVD, peripheral vascular disease.

†Data are mean ± SD if values are normally distributed or median (interquartile range) if the distribution of values is skewed.

‡Percentage (n).
The efficacy of influenza vaccines in older adults who reside in a nursing home on reducing mortality and hospitalization is controversial.12 A previous systematic review by Jefferson et al13 suggested that, in older adults who reside in a nursing home, with good vaccine match and high viral circulation, vaccination could significantly reduce mortality and hospitalization.13 But the efficacy was criticized by subsequent reviews because of healthy vaccine bias and frailty selection bias.15,33 Healthy vaccine bias means healthy individuals who are least likely to succumb to infection are those who are most likely to seek and receive vaccinations. Frailty selection bias means a subset of under-vaccinated and frail elderly people have contributed a substantial proportion of all deaths studied. Functional status and comorbidities, which are both important prognosticators for older adults, are not measured in many cohorts.14 Those factors may contribute to overestimation of vaccine efficacy. Another criticism is the use of nonspecific outcome, such as all-cause mortality, in some cohorts because influenza-related mortality may constitute only a small proportion of all deaths.34 Compared with all-cause mortality, pneumonia and hospital admissions both have high specificity.

There were several strengths in this study. This study involved functional assessment, comorbidity assessment, and frailty assessment by using the Barthel Index, hospitalization in the preceding year, and the Charlson Comorbidity Index. We also included important predictors for mortality, including glomerular filtration rate, nutritional status, and presence of anemia. Including those important covariates reduced the chance of overestimation of the vaccine’s efficacy. Apart from measuring all-cause mortality, we also reviewed every mortality and hospitalization to measure mortality and hospitalization due to pneumonia. We also performed sample size calculation using results from a systematic review to ensure the sample size of our study is adequate to detect a significant difference between groups.

There were several limitations in this study. First, we did not include data collection for laboratory-confirmed influenza. A monitoring of mortality and hospitalization can only indirectly assess the efficacy of influenza vaccine; however, we reviewed each individual mortality and hospitalization and included mortality and hospitalization due to pneumonia to increase the specificity of our outcome. Second, the participants were not randomized. An observational study has all the inherent biases and limitations thereof; however, our study included a sufficient number of older adults who reside in a nursing home based on sample size calculation. We also performed measurement of parameters known to affect mortality and hospitalization, and we mitigated much of the usual risks of such an analysis. Third, we focused our study on older adults who reside in a nursing home who were followed-up by HKWC CGAT. Their functional statuses are worse and such shortcomings might limit the generalizability of our results. Fourth, the Geriatric Index of Comorbidity (GIC) might be more suitable than the Charlson Comorbidity Index for older adults who reside in a nursing home.35,36 However, as much of the data were retrieved from the CMS and progress notes, there might be inaccurate information regarding severity of disease and hence renders it difficult to generate the GIC score properly. Fifth, although we quantified nutritional status using serum albumin level, which is a well-known marker for protein energy malnutrition, its use for quantifying

![Fig. 2. Kaplan-Meier curve of 12-month mortality due to pneumonia for participants in different vaccination groups.](image)

- **Influenza Vaccine 2010**
  - **Vaccinated**
    - Death at 12 months, n (%) 114 (9.4)
    - Survival at 12 months, n (%) 1100 (90.6)
  - **Not Vaccinated**
    - Death at 12 months, n (%) 82 (12.7)
    - Survival at 12 months, n (%) 563 (87.3)

  Total, n (%) 1214 (100.0) 645 (100.0)

Comparison by log-rank test: *P* = .033.

![Fig. 3. Box plot diagram for number of hospitalizations per 1000 person-months of different vaccination status.](image)

- **Influenza Vaccine 2010**
  - **Not Vaccinated**
    - Value* 56 (0–167)
  - **Vaccinated**
    - Value* 56 (0–111)

*Comparison by Mann-Whitney *U* test.*

*Median (interquartile range).*
• Nutritional status is questionable in frail older adults. Other measures, such as body mass index and skin fold thickness, should be included to provide more comprehensive information on nutritional status. Sixth, the use of ICD-9 coding may wrongly estimate the importance of diagnoses.38,39 There may be misclassification of diagnoses included to provide more comprehensive information on nutritional status. The Health Authority should make further effort to a nursing home signiﬁcance on nutritional status. The Health Authority should make further effort to a nursing home, their relatives, and the general lay public.

Fig. 4. Box plot diagram for number of hospitalizations due to pneumonia per 1000 person-months of different vaccination status.

 Acknowledgments

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References