**Abstract**

**Introduction:** Influenza infection is common among institutionalized older adults. Many nonrandomized observational studies on influenza vaccination suggested that it could reduce influenza-related hospitalizations and mortality in institutionalized older adults. Criticism regarding the effectiveness of influenza vaccine estimated by nonrandomized observational studies include the frailty selection bias and use of nonspecific outcome, such as all-cause mortality.

**Methods:** We conducted a systematic review of studies of influenza vaccination in institutionalized older adults to determine the effects on clinical outcomes. We searched for studies from 3 databases from 1946 to June 2013 assessing effectiveness against influenza infection. We selected studies with good comparability between vaccine group and control group. We expressed vaccine effectiveness (VE) as a proportion, using the formula VE = 1−relative risk or 1−odds ratio. We focused on the following outcomes: influenza-like illness (ILI), laboratory confirmed influenza, hospitalizations due to ILI, or pneumonia and death due to influenza or pneumonia. We did not include all-cause mortality.

**Results:** Eleven studies that satisfied the inclusion criteria were identified, representing 11,262 institutionalized older adults. After meta-analysis, we found a significant reduction in pneumonia (VE: 37%, 95% confidence interval [CI]: 18%–53%, P = .01) and death due to pneumonia or influenza (VE: 34%, CI: 10% –53%, P = .01). There was no significant heterogeneity between studies. There was no significant publication bias.

**Conclusion:** Influenza vaccination in institutionalized older adults could reduce pneumonia and death due to pneumonia or influenza. Influenza vaccination is recommended for institutionalized older adults.

Influenza is a leading cause of infection death among older adults.¹ The main strategy for prevention and control of seasonal and pandemic influenza for the past 50 years has been vaccination. The yearly influenza vaccination of at-risk individuals is a common practice, and adults 65 years and older (≥60 years in some countries) are suggested to have the vaccination.²,³ However, despite the widespread availability of influenza vaccination programs, vaccine coverage rates are generally unsatisfactory.⁴,⁵ This largely explains why influenza infections are still a major public health concern across the world.

Institutionalized older adults have high infection-related hospitalization and mortality rates.⁶–⁹ High vaccine coverage in this population is very important. Most studies on influenza vaccination among older adults were nonrandomized observational studies. Previous systematic reviews on influenza vaccination suggested that influenza vaccination could reduce influenza-related hospitalizations and mortality in institutionalized older adults.¹⁰,¹¹ However, the effectiveness of the influenza vaccine estimated by nonrandomized observational studies is frequently criticized for 2 major reasons: the frailty selection bias and use of nonspecific outcomes.¹²–¹⁴ Some physicians may feel that vaccine is futile in very frail older adults. A subset of undervaccinated frail elderly people could contribute a substantial proportion of adverse outcomes. If undervaccination were a direct consequence of the poor health status of those who are elderly, it would be the major source of bias. Many studies used nonspecific outcomes, especially all-cause mortality, that may contribute...
to overestimation of vaccine efficacy. Therefore, we performed a systematic review and meta-analysis for effectiveness of influenza vaccination in institutionalized older adults with measures to minimize these confounding factors.

Methodology

We carried out a literature search using the following electronic databases: Medline 1946 to June 2013, Embase 1974 to June 2013, and the Cochrane Controlled Trials Register (The Cochrane Library 2013, Issue 4). We used the medical subject headings “influenza vaccine,” “influenza immunization,” “nursing home,” “institution,” “long-term care,” “elderly,” and “older adults.” Citations of relevant articles were reviewed. The Science Citation Index was used to trace any articles quoting a previous meta-analysis. Trial identification was based on PRISMA statement 2009. Studies with the following criteria were included:

1. Participants who were institutionalized adults aged 60 years or older.
2. Study design was a randomized controlled trial or observational study.
3. The outcome measures were all clinically relevant: clinically defined influenza-like illness (ILI), laboratory-confirmed influenza infection, pneumonia, hospitalization due to pneumonia or ILI, or death due to influenza or pneumonia. ILI was defined as fever together with respiratory and systemic signs and symptoms. Laboratory-confirmed influenza infection was defined as viral isolation with or without serological supporting evidence. Pneumonia was defined by clinical and radiological changes suggestive of pneumonia. We did not include all-cause mortality.
4. Data on outcomes of interest had to be reported in numerical format, including numerator and denominator data.

Two observers independently extracted data and methodological details from the unmasked published reports. The following data were extracted: (1) description of the interventions, including the strain of the vaccine; (2) total number of subjects, and their age and sex; (3) follow-up duration; (4) study outcome definition and the number of outcome events corresponding to the requested definition in each group; (5) whether there was an outbreak in the nursing home during the study; and (6) whether the vaccine strain matched the circulating influenza strain. Discrepancies were documented and resolved by the consensus of both observers. For each included study, if there were 2 or more nursing homes involved and outcomes of the 2 nursing homes were individually presented, data of each nursing home were individually analyzed during the meta-analysis (eg, Saito 2002a and Saito 2002b). Because in Saito 2002, there were 2 nursing homes in this cohort study. And the data of each individual nursing home was presented, hence the data of each nursing home was analyzed individually.

Calculations were done with comprehensive meta-analysis software 2.0 (Biostat, Englewood, CA). The Mantel-Haenszel fixed effects model odds ratio (OR) was used to quantify the protective effect of the influenza vaccine. The heterogeneity between studies was assessed using the Cochrane Q statistical method, and a P value less than .10 was considered significant. When significant heterogeneity was found, a method based on a random effects model was used. Analyses were performed for different clinical outcomes. Within each clinical outcome, subgroup analyses were performed according to outbreak status in the nursing home and matching between vaccine strains and circulating influenza strain. There were 4 possible subgroup analyses for each clinical outcome: A, There was an outbreak, vaccine strain matched circulating influenza strain; B, There was an outbreak, vaccine strain unmatched with circulating influenza strain or unknown; C, There was no outbreak, vaccine strain matched circulating influenza strain; and D, There was no outbreak, vaccine strain unmatched with circulating influenza strain or unknown. Publication bias was assessed using funnel plot. We expressed vaccine effectiveness (VE) as a proportion, using the formula $VE = 1 - \text{relative risk or } 1 - OR$.

![Fig. 1. Flow diagram of study identification, based on the PRISMA statement.](image-url)
<table>
<thead>
<tr>
<th>Study [Reference No.]</th>
<th>Design</th>
<th>Sample Size</th>
<th>Outcome Measurement</th>
<th>Vaccine Matching</th>
<th>Quality Assessment Scales*</th>
<th>Comparison Between Groups (Apart From Age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan 2013 [18]</td>
<td>Prospective cohort (1 y)</td>
<td>1859 residents (1214 vaccinated and 645 controls) from 58 nursing homes</td>
<td>-Death due to pneumonia</td>
<td>Matched</td>
<td>**** ** ***</td>
<td>Comorbidity using comorbidity index; functional status using Barthel Index</td>
</tr>
<tr>
<td>Currier 1988 [19]</td>
<td>Retrospective case-control for outbreak (6 mo)</td>
<td>121 residents (87 vaccinated and 34 controls) from a nursing home</td>
<td>-Clinically defined ILI</td>
<td>Not matched</td>
<td>*** ** ***</td>
<td>Comorbidity including cardiac and pulmonary disease; cognitive status</td>
</tr>
<tr>
<td>Gross 1988 [20]</td>
<td>Prospective cohort study of outbreak (6 mo)</td>
<td>305 residents (181 vaccinated and 124 controls) from a nursing home</td>
<td>-Laboratory-confirmed influenza</td>
<td>Matched</td>
<td>*** ** ***</td>
<td>Comorbidity, including cardiac, pulmonary, stroke, and so forth; medication</td>
</tr>
<tr>
<td>Horman 1986 [21]</td>
<td>Retrospective case control for outbreak (3 mo)</td>
<td>159 residents (100 vaccinated and 59 controls) from a nursing home</td>
<td>-Clinically defined ILI</td>
<td>Matched</td>
<td>**** ** ***</td>
<td>Comorbidity, including cardiac, pulmonary, DM, stroke and so forth; cognitive status; functional status using level of nursing care</td>
</tr>
<tr>
<td>Leung 2007 [22]</td>
<td>Retrospective case control (1 y)</td>
<td>3177 residents (2943 vaccinated and 234 controls) from 46 nursing homes</td>
<td>-Clinically defined ILI</td>
<td>Unknown</td>
<td>**** ** ***</td>
<td>Comorbidity, including cardiac, pulmonary disease, DM, malignancy, and so forth; functional status using level of mobility</td>
</tr>
<tr>
<td>Monto 2001 [23]</td>
<td>Prospective cohort study (6 mo)</td>
<td>2351 residents (1728 vaccinated and 623 controls) from 26 nursing homes</td>
<td>-Clinically defined ILI</td>
<td>Matched</td>
<td>**** ** ***</td>
<td>Comorbidity, including mainly cardiac and pulmonary disease</td>
</tr>
<tr>
<td>Murayama 1999 [24]</td>
<td>Retrospective case control for outbreak (6 mo)</td>
<td>128 residents (60 vaccinated and 68 controls) from a nursing home</td>
<td>-Clinically defined ILI</td>
<td>Matched</td>
<td>**** ** ***</td>
<td>Comorbidity, including mainly cardiac and pulmonary disease</td>
</tr>
<tr>
<td>Saah 1986 [25]</td>
<td>Prospective cohort study (6 mo)</td>
<td>1352 residents (678 vaccinated and 674 controls) from 20 nursing homes</td>
<td>-Clinically defined pneumonia</td>
<td>Matched in 1 y, other unmatched</td>
<td>**** ** ***</td>
<td>Comorbidity, including cardiac, pulmonary, stroke, DM, and so forth</td>
</tr>
<tr>
<td>Saito 2002 [26]</td>
<td>Prospective cohort study (1 y)</td>
<td>1629 residents (1074 vaccinated and 555 controls) from 20 nursing homes</td>
<td>-Clinically defined ILI</td>
<td>Matched</td>
<td>**** ** ***</td>
<td>Comorbidity, including cardiac, pulmonary disease and stroke</td>
</tr>
<tr>
<td>Strassburg 1986 [27]</td>
<td>Retrospective case control study for outbreak (6 mo)</td>
<td>84 residents (65 vaccinated and 19 controls) from a nursing home</td>
<td>-Clinically defined ILI</td>
<td>Matched</td>
<td>**** ** ***</td>
<td>Comorbidity, including mainly cardiac and pulmonary disease</td>
</tr>
<tr>
<td>Taylor 1992 [28]</td>
<td>Retrospective case control study for outbreak (6 mo)</td>
<td>97 residents (45 vaccinated and 52 controls) from a nursing home</td>
<td>-Clinically defined ILI</td>
<td>Matched</td>
<td>**** ** ***</td>
<td>Functional status using level of mobility</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; ILI, influenza-like illness.

*In Newcastle-Ottawa quality assessment scale, any study is graded according to 3 categories: selection, comparability, and outcome. There are 4 items in selection, 1 item in comparability, and 3 items in outcome. A study can be awarded a maximum of 1 star (asterisk in this table) for each number item within the selection and outcome categories. A maximum of 2 stars can be given for comparability. In this review, 1 star would be given for comparability if age were compared between groups. Another star would be given if comorbidity and/or functional status were compared between groups in the study. The maximum possible score was 9 points. We took studies scoring <8 to be of low methodological quality and only studies scoring 2 in the comparability category are included in the review.
Results

Figure 1 shows the trial identification process. Table 1 summarizes the characteristics and outcome data of the studies included.\textsuperscript{10–28} Eleven studies that satisfied the inclusion criteria were identified, representing 11,262 institutionalized older adults.

Meta-analysis was performed for ILI, pneumonia, and death due to influenza or pneumonia. Meta-analysis was not performed for laboratory-confirmed influenza or hospitalization due to ILI or pneumonia because number of included studies was less than 3 in those clinical outcomes.

Keyword “Pneumonia”

After meta-analysis (Figure 2), we found a significant reduction in pneumonia (VE: 37%, 95% confidence interval [CI]: 18%–53%, \( P = .001 \)). In subgroup analysis, the reduction was also significant if there was an outbreak with vaccine matched (VE: 42%, CI: 18%–59%, \( P = .002 \)) (subgroup D) and there was no outbreak and vaccine unmatched or matching status unknown (VE: 44%, CI: 2%–58%, \( P = .042 \)) (subgroup A). There was no significant heterogeneity between studies (\( \chi^2: 3.55, I^2: 0\% ; P = .895 \)). There was no significant publication bias in funnel plot.

Keywords “Death Due to Pneumonia or Influenza”

After meta-analysis (Figure 3), we found a significant reduction in death due to pneumonia or influenza (VE: 34%, CI: 10%–53%, \( P = .01 \)). There was no significant heterogeneity between studies (\( \chi^2: 6.00, I^2: 0\% ; P = .647 \)). There was no significant publication bias in funnel plot.

Keyword “Influenza-like Illness”

After meta-analysis (Figure 4), we found a trend of reduction in ILI (OR: 0.79, CI: 0.61–1.03; \( P = .086 \)); however, there was significant heterogeneity between studies (\( \chi^2: 17.95, I^2: 49.99\% ; P < .036 \)). There was no significant publication bias in funnel plot.

Discussion

This meta-analysis and review suggested that influenza vaccination could reduce pneumonia and death due to influenza or pneumonia. There was also a trend to reduce ILI. In all 3 clinical outcomes, the protection was most significant during an outbreak and vaccine strain matched the circulating influenza strains. The findings concurred with the findings from a systematic review by Jefferson et al,\textsuperscript{10} which suggested that, with good vaccine match and high viral circulation, influenza vaccination could reduce pneumonia, hospitalization from influenza or pneumonia, death from influenza or pneumonia, and all-cause mortality. The major differences between this review and the review by Jefferson et al\textsuperscript{10} were the different selection criteria for studies in the meta-analysis, exclusion of nonspecific outcome, such as all-cause mortality, and inclusion of more recent studies. We ensured all subjects in those involved studies were age 60 or older. Because the age variation of some studies was large and the age of subjects may be as low as 18, it minimized the effect of age difference on vaccine effectiveness. We further ensured that those studies had taken further steps to compare other characteristics (apart from age), including co-morbidity and functional status between vaccine group and control group. We included only studies that had made comparison of co-morbidity and/or functional status between the vaccinated group and control group by detailed review of methodology of each study to minimize the effect of difference in other baseline characteristics on vaccine effectiveness. Our attempts might be effective because there was no significant residual between-studies heterogeneity in meta-analysis for pneumonia and death due to pneumonia or influenza. Our attempts could possibly minimize frailty selection bias. Moreover, we did not include all-cause mortality as an outcome because it was frequently criticized to be nonspecific and could contribute to overestimation of vaccine efficacy.\textsuperscript{14} Compared with all-cause mortality, pneumonia, influenza, and death from pneumonia or influenza have higher specificity.

The benefit of influenza vaccination in older adults is an ongoing controversy.\textsuperscript{14} Many previous reviews found inconsistent conclusions about the effectiveness of influenza vaccination in community-dwelling older adults but a protective effect could be found in

A: There was outbreak, vaccine strain matched circulating influenza strain
B: There was outbreak, vaccine strain unmatched with circulating influenza strain or unknown
C: There was no outbreak, vaccine strain matched circulating influenza strain
D: There was no outbreak, vaccine strain unmatched with circulating influenza strain or unknown

<table>
<thead>
<tr>
<th>Group by</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Events / Total</th>
<th>MH odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vaccine</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MH odds ratio</td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p-Value</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Gross 1988</td>
<td>0.497</td>
<td>0.168</td>
<td>1.470</td>
</tr>
<tr>
<td>A</td>
<td>Hurley 1996</td>
<td>0.689</td>
<td>0.201</td>
<td>2.366</td>
</tr>
<tr>
<td>A</td>
<td>Monte 2001</td>
<td>0.655</td>
<td>0.371</td>
<td>0.829</td>
</tr>
<tr>
<td>A</td>
<td>Taylor 1992</td>
<td>0.733</td>
<td>0.690</td>
<td>1.007</td>
</tr>
<tr>
<td>A</td>
<td>Currier 1988</td>
<td>0.807</td>
<td>0.400</td>
<td>0.821</td>
</tr>
<tr>
<td>B</td>
<td>Leung 2007</td>
<td>1.502</td>
<td>0.337</td>
<td>6.705</td>
</tr>
<tr>
<td>B</td>
<td>Smit 1992</td>
<td>0.855</td>
<td>0.412</td>
<td>2.210</td>
</tr>
<tr>
<td>C</td>
<td>Smit 1992</td>
<td>0.855</td>
<td>0.412</td>
<td>2.210</td>
</tr>
<tr>
<td>D</td>
<td>Smit 1992</td>
<td>0.855</td>
<td>0.412</td>
<td>2.210</td>
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<tr>
<td>D</td>
<td>Smit 1992</td>
<td>0.855</td>
<td>0.412</td>
<td>2.210</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.855</td>
<td>0.412</td>
<td>2.210</td>
</tr>
</tbody>
</table>

Heterogeneity: Test\( \chi^2 = 0.01, I^2 = 0.0\% ; P = .895 \).
institutionalized older adults. The main reason for the difference may be the homogeneity of institutionalized older adults, who are a homogeneous subgroup of the geriatric population with different personal and environmental characteristics. Many have malnutrition, multiple comorbidities, and functional impairment. They are hence frail, functionally dependent, immunocompromised, and more vulnerable to complications from influenza infection and infection-related mortality, as well as hospitalization. The biological activity of the vaccine depends on the probability of exposure to the relevant pathogen. The crowded living environment, shared physical therapy activities, shared bathing equipment, and group dining facilities have the potential to foster person-to-person transmission of infectious agents and to predispose to spreading and outbreak of influenza infection. Hence, influenza vaccination in this population could be effective.

There were several limitations in this review. First, although co-morbidity and/or functional status were compared between groups in most studies, the measurement of comorbidity and functional status were not standardized. Some studies used a validated comorbidity index, whereas some studies measured common cardiac and pulmonary diseases only. For functional assessment, some studies used validated functional index but some studies used only level of mobility. It indicated that the selection criteria in this review could possibly reduce frailty selection bias but we reckoned that this bias could not be eliminated by our measures. Second, among the 11 studies involved, 6 were retrospectively conducted, which affected the data accuracy of the baseline characteristics. Third, the follow-up time for included studies was different. Three had follow-up time of up to 1 year, which affected the specificity of the study. It may be a stretch to include events that occur months after the last

Fig. 3. Meta-analysis for death due to pneumonia or influenza.

Fig. 4. Meta-analysis for ILI.
laboratory-confirmed case in the community. Last, although we used more specific outcomes, only 2 of the selected studies used laboratory-confirmed influenza, which is the most specific outcome.

Randomized double-blind controlled trials would be the best design to assess influenza vaccine efficacy, but it is ethically not feasible given the background of global recommendation of influenza vaccination. The nonrandomized observational study is the main study design that could be chosen; however, data collection should be improved with inclusion of more baseline characteristics (especially frailty status or functional status) and use of more specific outcomes (especially laboratory-confirmed influenza). Moreover, comorbidity and functional status should be measured using a validated scale to facilitate comparison between studies. Follow-up time should be appropriate to increase specificity of the study.

In conclusion, this review suggested that influenza vaccination in institutionalized older adults could reduce pneumonia and death due to pneumonia or influenza. Influenza vaccination is recommended for institutionalized older adults.

References

22. Leung JKC. Effectiveness of influenza vaccination among elderly home residents in Hong Kong: A retrospective cohort study. Hong Kong Practitioner 2007;29:123–133.