

# Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: a population-based, nested case-control study

Michael L Jackson, Jennifer C Nelson, Noel S Weiss, Kathleen M Neuzil, William Barlow, Lisa A Jackson

## Summary

**Background** Pneumonia is a common complication of influenza infection in elderly individuals and could therefore potentially be prevented by influenza vaccination. In studies with data from administrative sources, vaccinated elderly people had a reduced risk of admission for pneumonia compared with unvaccinated seniors; however, these findings could have been biased by underlying differences in health between the groups. Furthermore, since most individuals with pneumonia are not treated in hospital, such studies should include both outpatient and inpatient events. We therefore assessed whether influenza vaccination is associated with a reduced risk of community-acquired pneumonia in immunocompetent elderly people after controlling for health status indicators.

**Methods** We did a population-based, nested case-control study in immunocompetent elderly people aged 65–94 years (cases and controls) enrolled in Group Health (a health maintenance organisation) during the 2000, 2001, and 2002 preinfluenza periods and influenza seasons. Cases were individuals with an episode of outpatient or inpatient community-acquired pneumonia (validated by review of medical records or chest radiograph reports). We randomly selected two age-matched and sex-matched controls for each case. The exposure of interest was influenza vaccination. We reviewed medical records to define potential confounders, including smoking history, presence and severity of lung and heart disease, and frailty indicators.

**Findings** 1173 cases and 2346 controls were included in the study. After we adjusted for the presence and severity of comorbidities, as defined by chart review, influenza vaccination was not associated with a reduced risk of community-acquired pneumonia (odds ratio 0·92, 95% CI 0·77–1·10) during the influenza season.

**Interpretation** The effect of influenza vaccination on the risk of pneumonia in elderly people during influenza seasons might be less than previously estimated.

**Funding** Group Health Center for Health Studies internal funds and Group Health Community Foundation fellowship grant.

## Introduction

Yearly influenza epidemics cause a substantial burden of illness and death, particularly in the elderly population.<sup>1,2</sup> A common and serious complication of influenza infection in these individuals is pneumonia, which results either from direct viral infection of the lung parenchyma or from secondary bacterial infection.<sup>3</sup> Influenza vaccination could reduce the risk of these complications. However, the possible benefit of vaccination in elderly individuals is controversial at the moment.<sup>4–6</sup>

Data from randomised trials suggest that vaccination reduces the risk of influenza infection in healthy elderly people 60 years of age and older.<sup>7</sup> The benefit of influenza vaccination in the general elderly population (65 years and older), many of whom have chronic health conditions, has not been adequately assessed in randomised trials. In a number of observational studies, elderly people who received influenza vaccine were much less likely to be admitted for pneumonia than were those who were not vaccinated.<sup>8–18</sup> However, these studies generally defined potential confounders with only International

Classification of Diseases (ICD-9) codes assigned to medical visits and so might not have adequately controlled for influential differences between vaccinated and unvaccinated individuals, such as functional impairments and illness severity.<sup>2,19,20</sup> Failure to account for healthy elderly people preferentially seeking vaccination would lead to an overestimation of vaccine effectiveness. Further, most of the previous studies have only assessed pneumonia events in the hospital. Since most cases of pneumonia in elderly people are treated on an outpatient basis,<sup>21</sup> assessments of the benefits of vaccination against influenza-related pneumonia should include both outpatients and inpatients with this illness.

We did a large population-based, nested case-control study to estimate the effectiveness of the influenza vaccine in preventing both outpatient and inpatient pneumonia in elderly people.

## Methods

### Study design and population

We did a population-based, nested case-control study with members of Group Health, a health maintenance

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Group Health Center for Health Studies, Seattle, WA, USA (M L Jackson PhD, J C Nelson PhD, Prof W Barlow PhD, Prof L A Jackson MD); Department of Biostatistics (J C Nelson, W Barlow), Department of Epidemiology (Prof N S Weiss MD, L A Jackson), and Department of Medicine, University of Washington, Seattle, WA, USA (K M Neuzil MD); Fred Hutchinson Cancer Research Center, Seattle, WA, USA (N S Weiss); and PATH, Seattle, WA, USA (K M Neuzil)

Correspondence to:

Dr Michael L Jackson, Group Health Center for Health Studies, 1730 Minor Ave Suite 1600, Seattle, WA 98101-1448, USA  
mj3@cornell.edu

	Preinfluenza period*	Influenza season*	Peak influenza season*	Influenza season†	Peak influenza season†
2000–01	Sept 21–Nov 12, 2000	Nov 13, 2000–April 2, 2001	Jan 1–Feb 5, 2001	Dec 24, 2000–March 3, 2001	Jan 14–Feb 3, 2001
2001–02	Sept 7–Nov 18, 2001	Nov 19, 2001–May 20, 2002	Jan 28–March 4, 2002	Dec 23, 2001–April 13, 2002	Jan 20–March 2, 2002
2002–03	Sept 27–Dec 1, 2002	Dec 2, 2002–April 28, 2003	Jan 13–Feb 17, 2003	Jan 26–April 19, 2003	March 9–April 5, 2003

\*Dates (defined with the methods presented in reference 19) based on national influenza surveillance data. †Dates (defined as presented in text) based on local influenza surveillance data.

**Table 1: Preinfluenza periods and influenza seasons**

organisation in the western Washington state, USA. In each of the study years—ie, 2000, 2001, and 2002—we identified a cohort of elderly people aged 65–94 years enrolled as of Sept 1. We then used administrative data from Group Health to select only community-dwelling immunocompetent elderly individuals who represented the source cohorts for our study. These individuals were not residents of a nursing home or other institution and were not receiving hospice care. Immunocompetence was defined as no history of serious cancer, chronic renal failure, or prescriptions for immunosuppressive medications during the 2 years before Sept 1, and no history of treatment for cancer during the 3 months before Sept 1. We excluded individuals if they had less than two visits to Group Health providers in the 2 years before this date. Within each cohort, participants were followed up until date of death, non-membership of Group Health, admission to a nursing home, or first episode of community-acquired pneumonia as defined below.

For this study, cases were all source cohort members with a validated episode of community-acquired pneumonia between the date the influenza vaccine first became available and the end of the influenza season in each year (table 1). An episode of community-acquired pneumonia was first presumptively identified on the basis of the ICD-9 codes 480–487·0 assigned to inpatient and outpatient visits. These episodes were then validated either by review of electronically available reports of chest radiographs obtained within 30 days before or after the visit or, for events in the hospital, by review of the hospital records. Presumptive events were considered to be true pneumonia episodes if a chest radiograph report suggested the presence of a parenchymal infiltrate not known to be chronic or if the hospital records showed that the attending physician concluded that pneumonia was the most likely diagnosis for the patient's illness. Reviewers were unaware of the influenza vaccination history.

We randomly selected two controls (matched for sex and age within 1 year of the case's birth date) for each case, based on a priori power calculations. Controls were members of the source cohorts who had not had an episode of community-acquired pneumonia before the pneumonia onset date of the matched case. Individuals could be sampled several times—ie, controls could be matched to more than one case, and cases could be sampled in more than 1 year.

To verify study eligibility and to account for potentially influential differences in baseline health status between individuals vaccinated and those not vaccinated, we reviewed all medical records during the 2 years before Sept 1. After review of medical records, we excluded cases who were living in a nursing home or other institution, or were immunocompromised. Ineligible controls were excluded and replaced with new randomly selected controls.

This study was approved by the Group Health institutional review board.

#### Influenza vaccination and other covariates

For each study year, the exposure of interest was vaccination with that year's trivalent inactivated influenza vaccine before the pneumonia onset date for the cases, or before the onset date of the matched case for the controls. Vaccinated individuals were identified from the Group Health immunisation database.

We defined the presence and severity of potentially confounding conditions, including asthma, chronic obstructive pulmonary disease, congestive heart failure, dementia, stroke, alcoholism, and diabetes mellitus based on medical record review (table 2). To further define severity of lung disease, for example, we assessed visits for asthma or chronic obstructive pulmonary disease exacerbation, prescriptions for oral corticosteroids for asthma or chronic obstructive pulmonary disease exacerbation, measures of forced expiratory volume in 1 s (FEV<sub>1</sub>), antibiotics prescribed for a lower-respiratory-tract condition, and prescriptions for medications for lung disease (mast cell stabilisers, anticholinergics, bronchodilators, corticosteroids, anti-tussives, or expectorants).

Additionally, since functional status limitations were proven to be important confounders in a study of influenza vaccination and all-cause mortality in elderly individuals,<sup>20</sup> we gathered data for the presence of functional status limitations, such as the need for assistance when bathing, eating, or walking. We obtained information about the use of health services such as routine optometry or ophthalmology visits. We reasoned that elderly people who make use of such services might be more mobile and less likely to be terminally ill than those who do not use these services, making health-service use a marker of fair or good overall health or improved functional ability. We

obtained information about smoking history, including dates of cigarette use and total pack-years of exposure when available.

We supplemented the chart review data with information about other medication prescriptions from the Group Health pharmacy database. These medications could further define disease presence or severity and so

help reduce confounding. Medications included dispensed prescriptions for lipid-lowering drugs (statins), oral or inhaled corticosteroids, sedatives or antidepressants (benzodiazepines, norepinephrine-reuptake inhibitors, monoamine oxidase inhibitors, and selective-serotonin-reuptake inhibitors), and antipsychotic drugs (phenothiazines and dibenzoxazepines) during the 2 years

	Cases N=1173	Controls N=2346	Association with community-acquired pneumonia	Controls		Association with vaccine
				Vaccinated N=1838	Not vaccinated N=508	
<b>Lung conditions</b>						
No asthma	964 (82%)	2158 (92%)	Ref	1684 (92%)	474 (93%)	Ref
Asthma, no exacerbation	95 (8%)	110 (5%)	1.9 (1.5-2.4)	89 (5%)	21 (4%)	1.2 (0.7-2.0)
Asthma, with visit(s) for exacerbation	114 (10%)	78 (3%)	3.3 (2.6-4.2)	65 (4%)	13 (3%)	1.4 (0.8-2.7)
<b>Smoking</b>						
Never known to have smoked	397 (34%)	1104 (47%)	Ref	855 (47%)	249 (49%)	..
Ever smoked, dose not recorded	462 (39%)	907 (39%)	1.5 (1.3-1.7)	729 (40%)	178 (35%)	1.2 (0.9-1.5)
Ever smoked, dose recorded in chart	314 (27%)	335 (14%)	2.5 (2.1-3.0)	254 (14%)	81 (16%)	0.9 (0.7-1.3)
Medication for lung disease	450 (38%)	382 (16%)	3.2 (2.8-3.6)	307 (17%)	75 (15%)	1.2 (0.9-1.5)
Antibiotics to treat lung infection	485 (41%)	433 (18%)	3.1 (2.7-3.5)	355 (19%)	78 (15%)	1.3 (1.0-1.7)
<b>FEV<sub>1</sub></b>						
Never measured	975 (83%)	2255 (96%)	Ref	1762 (96%)	493 (97%)	Ref
>80 L	32 (3%)	23 (1%)	3.0 (1.9-4.6)	20 (1%)	3 (1%)	2.0 (0.6-6.6)
50-80 L	75 (6%)	42 (2%)	3.9 (2.8-5.4)	36 (2%)	6 (1%)	1.7 (0.7-4.2)
<50 L	91 (8%)	26 (1%)	8.3 (5.5-12.5)	20 (1%)	6 (1%)	0.8 (0.3-2.0)
<b>Home oxygen</b>						
No COPD	103 (9%)	23 (1%)	9.7 (6.4-14.7)	20 (1%)	3 (1%)	1.7 (0.5-5.8)
COPD, no exacerbation	793 (68%)	2102 (90%)	Ref	1639 (89%)	463 (91%)	Ref
COPD, steroids for exacerbation	255 (22%)	199 (9%)	3.3 (2.8-3.9)	161 (9%)	38 (7%)	1.2 (0.8-1.7)
COPD, steroids for exacerbation	125 (11%)	45 (2%)	7.5 (5.3-10.6)	38 (2%)	7 (1%)	1.4 (0.6-3.3)
<b>Oxygen saturation tested during baseline</b>						
No CHF	246 (21%)	114 (5%)	5.1 (4.2-6.3)	98 (5%)	16 (3%)	1.6 (0.9-2.8)
CHF, no exacerbation	956 (82%)	2181 (93%)	Ref	1713 (93%)	468 (92%)	Ref
CHF, no exacerbation	120 (10%)	97 (4%)	3.0 (2.3-3.8)	75 (4%)	22 (4%)	0.9 (0.5-1.4)
CHF, with visit(s) for exacerbation	97 (8%)	68 (3%)	3.3 (2.5-4.3)	50 (3%)	18 (4%)	0.7 (0.4-1.3)
<b>Hypertension</b>						
Hypertension	539 (46%)	1104 (47%)	1.0 (0.9-1.1)	875 (48%)	229 (45%)	1.1 (0.9-1.4)
<b>History of myocardial infarction</b>						
History of myocardial infarction	142 (12%)	234 (10%)	1.2 (1.0-1.5)	188 (10%)	46 (9%)	1.0 (0.7-1.5)
<b>History of coronary revascularisation</b>						
History of coronary revascularisation	161 (14%)	268 (11%)	1.2 (1.0-1.5)	222 (12%)	46 (9%)	1.3 (0.9-1.8)
<b>Dementia</b>						
Dementia	54 (5%)	79 (3%)	1.4 (1.1-1.9)	57 (3%)	22 (4%)	0.7 (0.4-1.1)
<b>No diabetes</b>						
No diabetes	971 (83%)	1990 (85%)	Ref	1560 (85%)	430 (85%)	Ref
<b>Diabetes, without complications*</b>						
Diabetes, without complications*	91 (8%)	163 (7%)	1.2 (1.0-1.5)	126 (7%)	37 (7%)	1.0 (0.6-1.4)
<b>Diabetes, with complications*</b>						
Diabetes, with complications*	111 (9%)	193 (8%)	1.1 (0.9-1.4)	152 (8%)	41 (8%)	1.0 (0.7-1.5)
<b>History of stroke</b>						
History of stroke	99 (8%)	161 (7%)	1.3 (1.0-1.6)	125 (7%)	36 (7%)	0.9 (0.6-1.4)
<b>Parkinson's disease</b>						
Parkinson's disease	15 (1%)	23 (1%)	1.3 (0.8-2.2)	17 (1%)	6 (1%)	0.7 (0.3-1.8)
<b>Alcoholism</b>						
Alcoholism	19 (2%)	27 (1%)	1.4 (0.9-2.3)	15 (1%)	12 (2%)	0.3 (0.1-0.8)
<b>Functional status limitations</b>						
Needs assistance bathing	25 (2%)	15 (1%)	3.6 (2.1-6.3)	9 (<1%)	6 (1%)	0.4 (0.1-1.1)
Needs assistance dressing	15 (1%)	13 (1%)	2.4 (1.3-4.3)	9 (<1%)	4 (1%)	0.6 (0.2-2.0)
Needs assistance eating	8 (1%)	4 (<1%)	4.0 (1.5-10.4)	3 (<1%)	1 (<1%)	0.7 (0.1-6.3)
Needs assistance using toilet	14 (1%)	12 (1%)	2.4 (1.3-4.5)	11 (1%)	1 (<1%)	3.2 (0.4-24.8)
Need assistance with bed-to-chair transfer	11 (1%)	15 (1%)	1.5 (0.8-2.7)	9 (<1%)	6 (1%)	0.4 (0.1-1.1)
Needs assistance walking	209 (18%)	263 (11%)	1.8 (1.5-2.1)	192 (10%)	71 (14%)	0.7 (0.5-0.9)
Any optometry/ophthalmology visits	976 (83%)	1975 (84%)	0.9 (0.8-1.1)	1565 (85%)	410 (81%)	1.4 (1.0-1.8)

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	Cases N=1173	Controls N=2346	Association with community-acquired pneumonia	Controls		Association with vaccine
				Vaccinated N=1838	Not vaccinated N=508	
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Prescription and administrative data						
Number of outpatient visits in previous year	13.8 (10.1)	10.8 (8.6)	1.04 (1.03–1.04)	11.1 (8.8)	9.7 (7.7)	1.02 (1.01–1.04)
Oral corticosteroids	193 (16%)	115 (5%)	3.7 (3.0–4.5)	93 (5%)	22 (4%)	1.2 (0.7–2.0)
Inhaled corticosteroids	278 (24%)	187 (8%)	3.5 (3.0–4.1)	158 (9%)	29 (6%)	1.6 (1.0–2.4)
Bronchodilators	164 (14%)	62 (3%)	5.7 (4.4–7.4)	52 (3%)	10 (2%)	1.4 (0.7–2.8)
Statins	234 (20%)	450 (20%)	1.1 (0.9–1.2)	371 (20%)	79 (16%)	1.3 (1.0–1.8)
Antidepressants	160 (14%)	247 (11%)	1.4 (1.1–1.6)	188 (10%)	59 (12%)	0.9 (0.6–1.2)
Antipsychotics	19 (2%)	19 (1%)	2.0 (1.2–3.3)	15 (1%)	4 (1%)	1.2 (0.4–3.6)
Pneumonia in past year	191 (16%)	92 (4%)	4.6 (3.7–5.8)	76 (4%)	16 (3%)	1.3 (0.7–2.3)
Ever received PPV	1078 (92%)	2155 (92%)	1.0 (0.8–1.3)	1753 (95%)	402 (79%)	5.1 (3.7–7.1)
Influenza vaccination before case's index date	714 (61%)	1436 (61%)	..	..	..	..
Ever received influenza vaccine during follow-up	904 (77%)	1838 (78%)	..	..	..	..

Data are number (%), odds ratio (95% CI), or mean (SD). Ref=reference category for calculation of odds ratios. FEV<sub>1</sub>=forced expiratory volume in 1 s. COPD=chronic obstructive pulmonary disease. CHF=congestive heart failure. PPV=pneumococcal polysaccharide vaccine. \*Complications are neuropathy, nephropathy, or retinopathy, or both.

**Table 2: Baseline health status of participants from medical record data**

before the start of the follow-up. We identified any history of presumptive pneumonia events during this period and any record of ever receiving pneumococcal polysaccharide vaccine. The data were gathered for this study between February, 2006, and January, 2007.

### Definitions of influenza seasons and preinfluenza periods

We defined preinfluenza periods to be the time from when the influenza vaccine first became available until the start of the influenza season (table 1); the preinfluenza periods represent control times when a true benefit of influenza vaccine was not biologically plausible.<sup>19</sup> We defined influenza seasons with national influenza viral surveillance data,<sup>22–24</sup> as explained in detail previously.<sup>19</sup> Briefly, we defined the start of the influenza season as the beginning of the first week with at least 50 positive influenza isolates, and the end of influenza season as the end of the last week with at least 50 positive isolates. This definition is deliberately liberal, resulting in a long virus season, to ensure that influenza circulation is essentially absent during the preinfluenza control period. We defined the peak season to be 5 weeks with the week with the most positive influenza isolates in the middle (table 1).

### Statistical and sensitivity analyses

For cases, we used conditional logistic regression to estimate the association of each covariate with risk of validated community-acquired pneumonia. For controls, we used unconditional logistic regression, adjusted for age and sex, to estimate the association of

each covariate with the likelihood of vaccination by the end of the influenza season. We then used a two-step process to remove confounding and improve estimation of the association between influenza vaccination and risk of community-acquired pneumonia.

Generally, in the USA a lag exists between when influenza vaccine becomes available and the onset of the influenza season (table 1). Circulation of the virus is minimum if not completely absent during these preinfluenza periods, and so influenza infection does not meaningfully contribute to the burden of preinfluenza community-acquired pneumonia. Therefore, the vaccine cannot appreciably reduce the risk of preinfluenza pneumonia, and the observed odds ratio (OR) for the association between vaccine and community-acquired pneumonia during the preinfluenza period should be 1.0. Any difference from 1.0 represents uncontrolled confounding. Thus, our goal was to identify a combination of covariates that resulted in a preinfluenza OR of 1.0, indicating successful control for differences in underlying health between vaccinated and unvaccinated elderly people.

We used conditional logistic regression to estimate the age-adjusted and sex-adjusted OR for the association between influenza vaccination and risk of community-acquired pneumonia during the preinfluenza periods. We then added each covariate to this model individually to assess its potential to reduce this confounding. We included in a multivariable model those covariates that individually reduced the confounding to any degree (ie, moved the OR for the vaccine and community-acquired pneumonia association towards 1.0). This model was

simplified to only the smallest set of covariates that yield an OR of 1·0 for the association between influenza vaccination and pneumonia. To simplify the model we sequentially removed each covariate and re-estimated the association between influenza vaccination and community-acquired pneumonia and identified the variable whose removal caused the smallest change in that association. If the change was less than 1% we removed that variable and repeated the process. If not, we considered the existing covariates to be the minimum set for removal of confounding.

After identification of a set of covariates that successfully controlled for confounding in the preinfluenza periods, our next step was to apply this model to the influenza seasons. Specifically, we estimated the association between influenza vaccination and community-acquired pneumonia during the influenza season, adjusted for the covariates selected for the preinfluenza model. As secondary analyses, we estimated this association among all cases with onsets during the peak influenza seasons (table 1), and the association during influenza seasons restricted to inpatient cases of community-acquired pneumonia and their controls. We also estimated the association between influenza vaccination and risk of this pneumonia in each influenza season individually.

To evaluate whether our variable selection process produced a robust final model, we did a bootstrap analysis<sup>25</sup> of the adjusted association between influenza vaccination and the risk of community-acquired pneumonia during influenza seasons. We created 1000 bootstrap samples of the sets of cases and controls with index dates during the influenza seasons. In each sample we estimated the adjusted vaccination and pneumonia association. We calculated the mean OR from these bootstrap samples, and 95% CIs with the percentile method. To account for the possibility that confounding factors during influenza seasons might differ from those during the preinfluenza periods, we did a traditional analysis in which we identified factors associated with vaccination and with risk of pneumonia during influenza seasons and adjusted for these factors.

To assess whether our results were sensitive to the definition of the influenza season, we repeated the influenza season analysis with local surveillance data to define periods of influenza circulation. Data were all positive influenza isolates from sentinel providers in King County submitted to Public Health: Seattle and King County, and all positive influenza isolates identified by the University of Washington Clinical Virology Laboratory. For each study year we defined the local influenza season as the shortest set of weeks during which at least 90% of that year's positive influenza isolates were obtained, combining data from the University of Washington Clinical Virology Laboratory and Public Health: Seattle and King County.

We defined the local peak influenza season as the shortest set of weeks during which at least 50% of that year's positive isolates were obtained.

All analyses used robust methods of variance estimation to account for potential correlation caused by resampling of cases and controls. None of the variables as modelled had missing values (table 2). We used SAS (version 9.1) for the analyses.

#### Role of the funding source

The study sponsor had no role in the design of this study; collection, analysis, or interpretation of the data; writing of the report; or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Results

In 2000, 2001, and 2002, a total of 53 929 Group Health members were 65–94 years of age as of Sept 1. 46 824 (87%) met the eligibility criteria and were included in the source cohorts. The members in the source cohorts had 4006 first presumptive community-acquired episodes, of which 1481 (37%) were validated. Because 308 (21%) of these were ineligible, the case-control study included 1173 validated cases of community-acquired pneumonia and 2346 matched controls. 752 (64%) cases were outpatients, 447 (38%) were younger than 75 years of age, 531 (45%) were aged between 75 and 84 years, and 195 (17%) were at least 85 years old; 597 (51%) cases were men. Compared with controls, cases were more likely to have chronic diseases recorded in their medical records and, when recorded, these conditions tended to be more severe than in the controls (table 2). Cases were also more likely to have functional status impairments and have prescriptions for lung medications and antipsychotics than were controls (table 2). However, cases were equally likely to have received influenza vaccinations by the index date as were controls (table 2).

1838 (78%) controls had received influenza vaccination by the end of the influenza season. Vaccinated controls were more likely than were unvaccinated controls to have lung disease but were less likely to have functional status impairments and other comorbidities (table 2). In the control group, few variables were strongly associated with vaccination against influenza. These predictors included abnormal FEV<sub>1</sub> and previous vaccination with pneumococcal polysaccharide vaccine.

The age-adjusted and sex-adjusted OR for the association between influenza vaccination and risk of outpatient or inpatient community-acquired pneumonia during the preinfluenza periods was 0·60 (95% CI 0·38–0·95,  $p=0\cdot03$ ). This value shows the presence of confounding because vaccinated individuals had a 40% lower risk of pneumonia than did unvaccinated

elderly people at a time when the vaccine could not protect against community-acquired pneumonia. The fully adjusted model—ie, adjusted for age and sex; asthma or visit for asthma exacerbation; smoking history (ever *vs* never, and an indicator for whether pack-years was ever recorded in the chart); antibiotics prescribed for a lower respiratory condition; abnormal FEV<sub>1</sub>; use of home oxygen; previous pneumonia episode during the baseline period; use of inhaled corticosteroids, oral corticosteroids, bronchodilators, statins, or antipsychotic drugs; and any visit to an optometrist or ophthalmologist—yielded a preinfluenza OR of 1.01 (0.58–1.76, *p*=0.98), indicating control of confounding.

The age-adjusted and sex-adjusted OR for the association between influenza vaccination and risk of community-acquired pneumonia was 1.04 (95% CI 0.88–1.22, *p*=0.66) during the influenza seasons. After adjustment for the covariates identified in the preinfluenza periods, the influenza season OR was 0.92 (0.77–1.10, *p*=0.35). When we restricted the analysis to the 210 cases that occurred during the peak influenza seasons and their matched controls, the fully adjusted OR was 1.04 (0.70–1.55, *p*=0.84). The ORs for the association between influenza vaccination and the risk of community-acquired pneumonias for 2000–01, 2001–02, and 2002–03 seasons were 0.94 (0.67–1.31, *p*=0.70), 1.02 (0.75–1.37, *p*=0.91), and 0.79 (0.58–1.08, *p*=0.14), respectively.

When we restricted the analyses to the 421 cases who had been treated in hospital and their matched controls, the fully-adjusted OR during the preinfluenza periods was 0.99 (95% CI 0.30–3.26, *p*=0.99), suggesting control of confounding. The OR for patients treated in hospital was 0.85 (0.62–1.15, *p*=0.28) during the influenza seasons. For the 246 pneumonia cases admitted during the peak influenza seasons, the association between influenza vaccination and risk of pneumonia was 1.41 (0.35–3.02, *p*=0.39).

With the 1000 bootstrapped samples, the mean OR for the association between influenza vaccination and the risk of community-acquired pneumonia during the influenza seasons was 0.91 (percentile-based CI 0.74–1.13). Confounders selected on the basis of standard model-building procedures during the influenza seasons resulted in a similar set of variables as those selected during the preinfluenza periods. Adjustment for these variables gave an OR of 0.87 (95% CI 0.73–1.04, *p*=0.11). The adjusted OR for association between influenza vaccination and risk of pneumonia was 1.07 (0.83–1.38, *p*=0.59) during the influenza seasons defined by local viral surveillance. The OR was 1.06 (0.69–1.61, *p*=0.80) during the local peak influenza seasons. For pneumonia admissions, the adjusted OR during the locally defined influenza seasons was 1.23 (0.78–1.93, *p*=0.38) and during local peak seasons it was 1.24 (0.47–3.28, *p*=0.67).

## Discussion

In this large population-based, nested case-control study done across three influenza seasons, vaccination was not associated with a significant reduction in the risk of community-acquired pneumonia in elderly individuals.

Our study had several strengths. We used preinfluenza periods—as the control times—to assess and reduce confounding. To maximise our ability to detect a vaccine benefit, we studied three influenza seasons in which the vaccine was well matched to the circulating virus strains,<sup>22–24</sup> and we restricted our study population to immunocompetent elderly people for whom vaccination is most likely to elicit a protective immune response.

Unlike with previous assessments of influenza vaccine effectiveness in elderly individuals,<sup>8–18</sup> we systematically reviewed medical records to obtain detailed information about the health and functional status of the cases and controls. Previous studies had adjusted for factors such as any lung disease or any heart disease, and often defined these solely on the basis of ICD-9 codes assigned to medical visits. Such variables do not capture the important differences in health status between vaccinated and unvaccinated individuals,<sup>20</sup> and adjustment for these variables alone does not remove confounding.<sup>19</sup> We were able to control for confounding with detailed medical record information, as shown by the adjusted OR of 1.0 during the preinfluenza control period.

Unlike studies that defined pneumonia outcomes based only on ICD-9 codes,<sup>8–17</sup> we verified the presence of pneumonia by reviewing medical records or chest radiograph reports. By validation of the pneumonia outcomes we excluded admissions for conditions that could falsely be assigned a pneumonia code in the administrative data.<sup>26</sup> The true effect of influenza vaccination on these non-pneumonia events is probably negligible, but such events can easily be affected by confounding due to differences in underlying health of the individuals. We reduced the effect of confounding in our study by exclusion of these non-pneumonia events. This reduction can be seen in the age-adjusted and sex-adjusted associations of vaccination and risk of pneumonia during the influenza seasons. In our study, the association was close to 1.0 for both all-pneumonia episodes and pneumonia admissions. In a previous study of influenza vaccination of the elderly members of Group Health, which included the years assessed in the present study, the age-adjusted and sex-adjusted ORs for pneumonia admissions, defined only by ICD-9 codes, were of the order of 0.7, suggesting residual confounding in the assessment of the non-validated outcome.<sup>8–11,19</sup>

Although most previous studies of influenza vaccination and the risk of pneumonia focused on admissions for pneumonia, we studied both inpatient and outpatient pneumonia events. Inclusion of out-

patient pneumonia is important for two reasons. First, most cases of pneumonia in elderly people are treated on an outpatient basis,<sup>21</sup> so combination of inpatient and outpatient events is the most relevant outcome for assessment of the effect of vaccination on pneumonia risk. Second, the decision to admit a patient with pneumonia to the hospital is related not only to disease severity but also to the presence of comorbidities, so that individuals with comorbid disease are more likely to be admitted than are those without.<sup>27</sup> Admissions for pneumonia therefore represent a biased sample of the total population at risk of pneumonia, preferentially including sicker individuals, which can lead to biased estimates of vaccine effectiveness.

A limitation of this study is the possible misclassification of influenza vaccination status because some participants might have received influenza vaccination outside of the Group Health system without notifying their primary-care provider that they had been vaccinated. However, we noted that more than three-quarters of controls in our study received influenza vaccine. Between 1999 and 2003, influenza vaccination coverage of elderly people in Washington state ranged from 69% to 73%.<sup>28–30</sup> Because vaccine coverage in our study population was greater than these averages, misclassification of an important number of vaccinated individuals seems unlikely.

Estimates of the incidence of serious complications of influenza and of the effectiveness of vaccine against these complications are important for pandemic planning and for the optimum control strategies for non-pandemic influenza. In our study, influenza vaccination was not associated with a reduced risk of all-cause pneumonia in elderly individuals. These results could mean that influenza infection only causes a small proportion of pneumonias in these people, so that reduction of the risk of influenza infection does not lead to an important reduction in all-cause pneumonia. Alternatively, these results could mean that the vaccine is not very effective in reducing the risk of influenza infection in elderly people at risk of pneumonia. These two possibilities have quite different implications for vaccine development and vaccination recommendations; differentiation between them will need studies with laboratory-confirmed endpoints, such as pneumonia or serious respiratory outcomes after a confirmed influenza infection. Such studies could include randomised trials comparing different influenza vaccines, or observational studies of vaccinated and unvaccinated elderly people that include appropriate measures to remove confounding.

#### Contributors

MLJ had main responsibility for the conception and design of the study, data collection, data analysis, and writing the first draft of the report. LAJ, JCN, KMN, and NSW helped design the study and interpret the results. WB participated in the study design and provided statistical suggestions. All authors participated in reviewing and editing the entire report, and approved the final version to be published.

#### Conflict of interest statement

LAJ has been a paid consultant to Sanofi Pasteur and to Novartis, manufacturers of the influenza vaccine. The other authors declare that they have no conflict of interest.

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