Effect of Influenza Vaccination of Nursing Home Staff on Mortality of Residents: A Cluster-Randomized Trial

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OBJECTIVES: To evaluate the effect of staff influenza vaccination on all-cause mortality in nursing home residents.

DESIGN: Pair-matched cluster-randomized trial.

SETTING: Forty nursing homes matched for size, staff vaccination coverage during the previous season, and resident disability index.

PARTICIPANTS: All persons aged 60 and older residing in the nursing homes.

INTERVENTION: Influenza vaccine was administered to volunteer staff after a face-to-face interview. No intervention took place in control nursing homes.

MEASUREMENTS: The primary endpoint was total mortality rate in residents from 2 weeks before to 2 weeks after the influenza epidemic in the community. Secondary endpoints were rates of hospitalization and influenza-like illness (ILI) in residents and sick leave from work in staff.

RESULTS: Staff influenza vaccination rates were 69.9% in the vaccination arm versus 31.8% in the control arm. Primary unadjusted analysis did not show significantly lower mortality in residents in the vaccination arm (odds ratio = 0.86, $P = .08$), although multivariate-adjusted analysis showed 20% lower mortality ($P = .02$), and a strong correlation was observed between staff vaccination coverage and all-cause mortality in residents (correlation coefficient = -0.42, $P = .007$). In the vaccination arm, significantly lower resident hospitalization rates were not observed, but ILI in residents was 31% lower ($P = .007$), and sick leave from work in staff was 42% lower ($P = .03$).

CONCLUSION: These results support influenza vaccination of staff caring for institutionalized elderly people. **J Am Geriatr Soc 57:1580–1586, 2009.**

Key words: elderly; nursing homes; residents; staff influenza vaccination

Influenza is a leading cause of death in older adults.[1] In developed temperate countries, influenza accounts for an average excess all-cause mortality of approximately 5% during winter in the elderly population.[2] Influenza vaccination is an effective means of preventing cases of influenza in children aged 2 and older and healthy adults,[3–5] but in elderly people, influenza vaccination is less effective against influenza or influenza-like illness (ILI), although well-matched vaccines still prevent serious events from pneumonia and influenza and reduce all-cause mortality by 40% to 60%.[6] However, despite high levels of immunization, there have been reports of influenza outbreaks in homes for elderly individuals.[7–11] Vaccination of persons caring for elderly people has therefore been recommended to limit transmission, yet nearly 50% of French nursing homes have a staff influenza vaccine coverage rate less than 40%.[12]

Two randomized controlled trials have suggested that staff influenza vaccination can reduce mortality in elderly residents of long-term care facilities.[13,14] These findings must be interpreted with caution given the presence of selection and performance bias.[15] More recently, a group-randomization trial conducted in nursing homes showed 27% lower all-cause mortality and 50% lower ILI rates in

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the vaccination arm than the control arm during the first year of the study but no benefit the following year.[16]

The current study examined the effect of staff influenza vaccination on all-cause mortality in institutionalized elderly people and on morbidity in residents and staff.

MATERIAL AND METHODS

Study Design

A cluster-randomized controlled trial was conducted in which 40 nursing homes matched in pairs were randomly allocated to a vaccination (intervention) arm or a no-intervention control arm. The Saint-Germain-en-Laye hospital ethics committee (June 16, 2006; 06046) and the French Data Protection Authority (907162) approved the study.

This study focused on nursing homes housing between 50 and 200 seniors, corresponding to 376 of the 1,105 nursing homes listed in the Paris area at the time of the study. Each of these 376 nursing homes was sent a written invitation to participate, and 88 responded positively. Of these, 40 nursing homes in which the staff influenza vaccination coverage rate was less than 40% during the 2005/06 winter season were selected. Each institution was then pair-matched for the following characteristics: size, staff vaccination coverage rate in 2005/06 (0–20% or 20–40%), and Group Iso Resources (GIR) weighted-average score. The GIR score is used in France as a disability index for institutionalized elderly people and takes into account degrees of physical and mental autonomy. The score is based on the Table of Geriatric Autonomy GIR and is measured in all institutionalized elderly people twice a year.[17] The scores range from 1 (severe disability) to 6 (total autonomy). Only residents aged 60 and older who were in the nursing home at the beginning of the study or who were admitted during the overall study period were included. The study started on December 4, 2006, and ended on April 1, 2007.

Methods

Randomization was centralized and based on a simple computerized random number generator. In the intervention arm, a promotional campaign based on posters, leaflets, and an information meeting with the study team between September 15 and October 31, 2006, first sensitized staff to the benefits of influenza vaccination. The campaign described the potential benefits of influenza vaccination for one's own protection and that of the residents. Influenza vaccination was further recommended during face-to-face interviews with each member of staff present in the nursing homes between November 6 and December 15, 2006. The study team individually met all administrative staff, technicians, and caregivers to invite them to participate, and volunteers were vaccinated at the end of the interview. During the interview, prior vaccination status and, if appropriate, the reason for nonvaccination were also collected. The vaccine was an inactivated preparation (Influvac, Solvay Pharma Laboratory, Suresnes, France) containing 15 μg each of strains A/Wisconsin/67/2005-like (H3N2), A/New Caledonia/20/99 (H1N1), and B/Malaysia/2506/2004.

In the control arm, only routine information on influenza vaccination was provided. No particular instruction was given regarding hygiene and infection control practices (e.g., use of masks, handwashing, isolation, or use of antivirals for treatment or prophylaxis) in either arm. The numbers of residents leaving the nursing homes permanently or temporarily were recorded. Investigating physicians entered data online using an electronic form designed specifically for the study.

The extent of vaccination coverage in the control arm and information regarding sick leave for staff in both arms were determined with a questionnaire sent to all staff at the end of the study.

Rapid diagnostic tests (Quick View Influenza Test; Quidel Corp., San Diego, CA) were distributed to each nursing home for use when clusters of ILI occurred in residents. When suspected clusters occurred, a team of monitors was sent to the nursing home to document signs and symptoms in all residents and staff and to record the results of the rapid diagnostic tests and neuraminidase inhibitor prescriptions given to residents.

Analysis

The influenza epidemic period was defined as a weekly ILI incidence of more than 127 cases per 100,000 inhabitants, as reported by the Sentinelles General Practitioners Network.[18] A moderate influenza epidemic was reported in the general French community between January 15, 2007, and March 4, 2007, predominantly due to A/Wisconsin/67/2005-like (H3N2) strains.[19] For the purposes of this study, the primary study period was defined as the period starting 2 weeks before and ending 2 weeks after the observed epidemic (January 1, 2007 to March 18, 2007). The primary endpoint was total mortality rate during the primary study period.

Secondary endpoints were the incidence rates of hospitalization and ILI in residents during the primary study period. ILI was defined as a fever of 37.8°C or more and onset of respiratory symptoms or worsening of chronic respiratory conditions. Another secondary endpoint was the proportion of staff who reported at least 1 day of sick leave.

Sample Size

An influenza epidemic period lasting 2 months, an expected mortality rate of 8% in the control arm,[20] a 40% reduction in all-cause mortality rate in residents after staff vaccination (expected mortality rate in the intervention arm of 4.8%), and two-sided hypothesis testing were assumed.[15] The intrapair coefficient of variation of all-cause mortality was set at 0.3,[21] and the median size of the nursing homes was set at 100 residents (range 50–200). Twenty pairs of nursing homes were necessary to obtain a power of 80% with 2,000 residents in each group. The effect size of this design was 1.9.

Statistical Methods

The analyses included all residents who were present on at least 1 day in a participating nursing home between the beginning and end of the primary study period. All analyses were done on an intention-to-treat basis. To compare study outcomes between arms, a cluster-specific method was used, because nursing homes rather than residents were randomized. The analysis was performed considering that outcomes were measured at the individual resident level. Odds ratios were calculated using alternating logistic regression, with one-nested log odds ratios to model the association between responses of the same pair and the same nursing home within the pair.[22,23] The primary analysis, as specified in the protocol, was a univariate estimate of the effectiveness of the intervention on mortality. In secondary analyses, multivariate estimates were adjusted for the residents' age, vaccination status, GIR disability score, and Charlson comorbidity index. The GIR disability score was used instead of the Barthel disability score, because French physicians had greater experience with it, the Barthel score was missing for all residents in one nursing home, and introducing the Barthel score in the multivariate analysis did not change the results (not shown). Missing vaccination status and Charlson comorbidity index values were imputed using a Bayesian multiple imputation procedure with 10 replicates. Correlation between staff vaccination coverage and all-cause mortality was tested using the Spearman correlation coefficient. Statistical tests were two tailed, with a type I one error of 5%. Statistical analyses were performed with SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

The total number of residents present in the participating nursing homes during the overall study was 3,483: 1,751 in the vaccination arm and 1,732 in the control arm. There were 3,400 residents during the primary study period: 1,722 in the vaccination arm and 1,678 in the control arm (Figure 1). The average staff influenza vaccination rate was 69.9% in the vaccination arm (range 48.4–89.5%). Five hundred sixty-six (55.8%) vaccination questionnaires were collected in the control arm and 448 (45.3%) in the vaccination arm. The average staff influenza vaccination rate was 31.8% in the control arm (range 0–69.0%). No serious adverse events were attributed to vaccination. Stated reasons for not being vaccinated were distributed similarly in the two arms, as follows: fear of vaccine adverse effects (53.4%), belief that vaccination is not effective (31.3%), preference for other modes of influenza prevention (12.3%), and contraindications (3.0%).

The characteristics of the residents in the two arms were similar, with a mean age of 86, a majority of women (77.4%), an average GIR disability score of 2.92, an average Barthel disability score[24] of 43.4, an average Charlson comorbidity index[25] of 2.34, and a vaccination coverage rate of 91.8% for the 2006/07 winter season in residents whose vaccination status was known (Table 1). The only significant difference was a higher proportion of residents vaccinated against pneumococci during winter 2005/06 in the control arm owing to 100% vaccine coverage in two control nursing homes. After removing the two pairs including these homes, the difference was no longer significant.

The primary analysis—an unadjusted analysis restricted to the primary study period—showed no significant difference in mortality in the vaccination arm than in the control arm (Table 2, odds ratio (OR) = 0.86, 95% confidence interval (CI) = 0.72–1.02). Likewise, there was no difference in mortality from respiratory causes, although mortality from cardiovascular causes was lower in the vaccination arm. The incidence of hospital admissions did not differ between the arms. In contrast, the incidence of ILI was significantly lower in the vaccination arm.

In the vaccination arm, 8.7% of staff reported at least 1 day of sick leave during the primary study period, versus

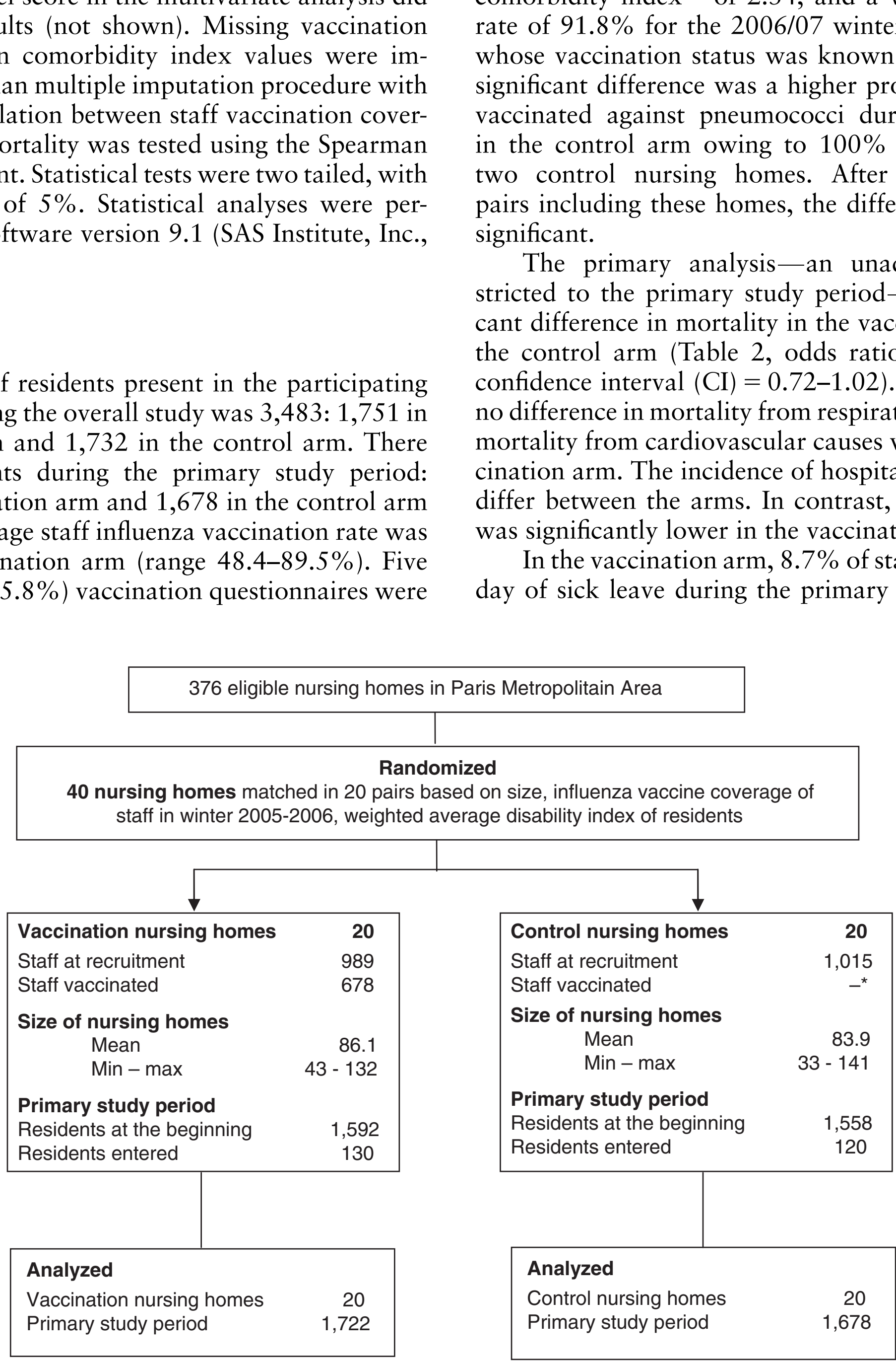

Figure 1. Flow chart.
*Immunization coverage was estimated at the end of the overall study period.

Table 1. Characteristics of the Nursing Home Residents

Characteristic	Vaccination Arm (n = 1,722)	Control Arm (n = 1,678)
Age, mean ± SD	86.1 ± 8.4	86.0 ± 8.7
Female, n (%)	1,334 (77.5)	1,282 (76.4)
Group Iso Resources disability score, mean ± SD	2.95 ± 1.44	2.90 ± 1.45
Barthel disability score, mean ± SD*	42.8 ± 34.8	44.6 ± 34.6
Charlson Comorbidity Index, mean ± SD†	2.35 ± 1.95	2.33 ± 1.75
Influenza vaccination, winter 2006/07, n (%)		
Yes	1,452 (84.3)	1,385 (82.5)
No	150 (8.7)	103 (6.1)
Unknown‡	120 (7.0)	190 (11.3)
Influenza vaccination, winter 2005/06, n (%)		
Yes	961 (57.3)	985 (57.2)
No	96 (5.7)	143. (8.3)
Unknown‡	621 (37.0)	594 (34.5)
Documented pneumococcal vaccination, 2005, n (%)	59 (3.4)	222 (13.2)§

* Pair 19 not considered, data not available.
† Pairs 19, 12, and 14 not considered, data not available in three nursing homes.
‡ No written information on vaccination status in the medical files.
§ Two nursing homes with 100% vaccination in the control arm.
SD = standard deviation.

13.3% in the control arm (OR = 0.58, 95% CI = 0.36–0.96, P = .03), although in the control arm, vaccinated staff were more likely than unvaccinated staff to take sick leave (36/175 (20.6%) vs 39/388 (10.0%), P < .001).

Multivariate-adjusted analysis identified a significant difference in all-cause mortality between the arms during the primary study period (Table 3, OR = 0.80, 95% CI = 0.66–0.96). Other predictors of mortality were sex, age, Charlson Comorbidity Index, and GIR disability score. Influenza vaccination of residents did not appear to prevent death (P = .40). A correlation was observed between staff vaccination coverage and all-cause mortality in residents during the primary study period (Figure 2).

Detailed examination of weekly rates of health outcomes showed that the largest difference in all-cause mortality and ILI between the two arms occurred between December 4, 2006, and January 8, 2007, corresponding to the period from 9 to 4 weeks before the peak of influenza in the community (Supporting Information, Figure S1).

Four ILI clusters were reported in four nursing homes between February 8 and March 13, 2007: three in the control arm and one in the vaccination arm. In two of these outbreaks, the index case was a staff member. The staff vaccination rates in these nursing homes were 7.1%, 33.3%, and 40.9% in the control arm and 55.0% in the vaccination arm. The ILI attack rates in residents were 9.9%, 32.3%, 12.8%, and 12.2%, respectively; 56 residents developed an ILI, of whom 47 had been vaccinated against influenza. Twelve of 25 residents tested for influenza virus were positive. Forty-two residents (75.0%) were treated with oseltamivir, nine were hospitalized (all were treated), and seven died (all were treated).

DISCUSSION

Despite a high staff influenza vaccine coverage rate in the vaccination arm of this study (69.9%), analysis showed no significant effect on all-cause mortality in residents during the primary study period. This may have been due to a lack of power, owing to multiple factors. First, the hypothesis of a 40% lower all-cause mortality may seem “optimistic,” compared with the average estimate of 5% of winter deaths that has been found to be attributed to influenza in elderly people.[2] However, this hypothesis was extracted from a recent systematic review on the effectiveness of influenza vaccination for healthcare workers[15] and was consistent with findings of another clustered randomized trial published after the start of the current study.[16] Nevertheless, the 5% all-cause mortality attributable to influenza in a general population aged 65 and older cannot be applied to the institutionalized population of the current study aged 86 years old on average with multiple comorbidities. Conse-

Table 2. Outcomes in the Vaccination and Control Arms During the Primary Study Period (January 1 to March 18, 2007)

	n (%)			
Outcome	Vaccination Arm (n = 1,722)	Control Arm (n = 1,678)	Odds Ratio* (95% Confidence Interval) Reference = Control	*P*-Value
Death	89 (5.2)	100 (6.0)	0.86 (0.72–1.02)	.08
Respiratory	19 (1.1)	12 (0.7)	1.55 (0.59–4.10)	.38
Cardiovascular	26 (1.5)	39 (2.3)	0.66 (0.44–0.99)	.045
Other causes	44 (2.6)	49 (3.0)	0.87 (0.84–1.35)	.46
Admission to hospital	150 (8.7)	143 (8.5)	1.03 (0.76–1.40)	.85
Respiratory	29 (1.7)	28 (1.7)	1.01 (0.43–2.34)	.98
Cardiovascular	22 (1.3)	30 (1.8)	0.72 (0.45–1.13)	.15
Other causes	99 (5.7)	85 (5.0)	0.88 (0.78–1.68)	.49
Influenza-like illness	116 (8.7)	163 (11.8)	0.69 (0.52–0.91)	.007

* Alternating logistic regression estimate.
[Correction added after online publication August 4, 2009: the alignment of “Influenza-like illness” has been changed in the Outcome column]

Table 3. Predictors of All-Cause Mortality in Nursing Homes Residents, Winter 2006/07

Variable	Odds Ratio (95% Confidence Interval)	*P*-Value
Sex (male vs female)	1.66 (1.15–2.41)	.008
Arm (vaccination vs control)	0.80 (0.67–0.97)	.02
Age (per 1-year increase)	1.04 (1.02–1.05)	<.001
Charlson Comorbidity Index (per 1-point increment)	1.10 (1.02–1.18)	.01
Group Iso Resources disability score (per 1-point increment)	0.73 (0.64–0.83)	<.001
Influenza vaccination of residents (yes vs no)	0.87 (0.63–1.20)	.40

Alternating logistic regression estimate.

quently, excess optimism did not a priori underpower the initial hypothesis.

However, fewer subjects were included during the primary study period than expected (3,400 vs 4,000), and in the control arm, the mortality rate (6%) was lower than expected (8%), possibly owing to a high vaccine coverage rate in residents (>80%) or to a high staff vaccine coverage rate in the control arm (31.8% instead of an anticipated value of 10–15%). By comparison with other trials,[13,16] the vaccine coverage rate in the control arm was 6 to 10 times as high in the current study, possibly owing partly to coincidental passage of a bill requiring mandatory influenza vaccination for healthcare workers through the French Senate.[26] Another likely explanation for the lack of power is the moderate nature of the influenza epidemic, and the low accompanying mortality rate, in France and Europe during the 2006/07 winter season.[18,19,27] The French national influenza mortality surveillance system reported only 44 deaths from influenza, of which 16 occurred in nursing homes and seven in long-term care facilities.[28] By comparison, 228 deaths were reported during winter 2004/05.[29] Finally, it has been shown that death attributable to pneumonia and influenza can occur as late as 1 year after the primary episode of pneumonia,[30] and the possibility cannot be excluded that the primary study period was too short to encompass the full mortality burden related to influenza. All these factors may have contributed to undermining the statistical power of the trial.

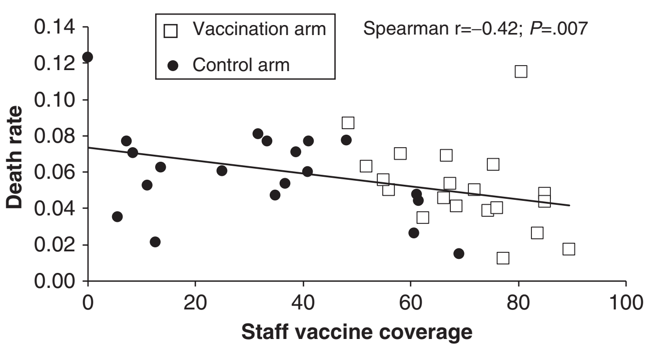

Figure 2. All-cause mortality according to staff vaccine coverage rates during the primary study period (January 1 to March 15, 2007).

In contrast, multivariate analysis showed that belonging to the vaccination arm was a significant independent predictor of mortality in the elderly residents when adjusted for other prognostic factors. Although the intervention and control arms were well balanced with regard to prognostic factors, there were differences in these factors between intervention and control nursing homes belonging to the same pair, possibly accounting for the results of multivariate analysis. Among other potential confounders, the residents' nutritional status—an independent predictor of mortality in elderly people[31]—was not measured in this study. Also, the Charlson Comorbidity Index may not have fully captured the severity of the underlying chronic conditions; other scales (e.g., the Cumulative Illness Rating Scale[32]) might have been more appropriate. It is unclear whether an imbalance between the arms in terms of nutritional status or underlying disease severity would have altered the strength of the observed association between influenza vaccination and mortality in elderly subjects. Nonetheless, this study is the first to show a significant beneficial effect of staff vaccination on mortality in elderly residents of nursing homes after adjustment for other major prognostic factors.

Nevertheless, it was surprising to find that weekly all-cause mortality and ILI incidence rates were clearly lower in the vaccination arm than in the control arm between 9 and 4 weeks before the peak of the influenza epidemic observed in the general community. In the control arm and, to a lesser degree, in the vaccination arm, the total mortality and ILI incidence rates peaked between December 25 and January 7, which coincided closely with the peak circulation of respiratory syncytial virus (RSV) in France. It is therefore likely that some of these deaths and cases of ILI were related to RSV, a virus associated with substantial mortality and morbidity in elderly people,[33,34] although this does not explain why staff influenza vaccination appeared to limit the burden of RSV in nursing homes. In particular, post hoc analyses showed that a few influential pairs of nursing homes did not cause this result (not shown). Among other possibilities, confounding due to lack of blinding may have occurred. The influenza vaccination intervention may have made vaccinated staff more aware of the risks of influenza, leading them to be less exposed to respiratory viruses (including RSV) in the community or to adopt nonspecific preventive measures and thus to be less contagious. Influenza virus may also have circulated in the nursing homes before the national epidemic, but this is unlikely, because the four clusters of cases were all observed during the influenza epidemic period.

Finally, although vaccination of residents did not appear to reduce influenza mortality in this study, the vaccine coverage rate was high, and an imbalance in underlying disease severity might have influenced the results.

This study found that influenza vaccination of staff reduced the incidence of ILI in nursing home residents and sick leave in staff. Multivariate-adjusted analysis identified 20% lower all-cause mortality in the intervention arm, and a significant correlation was observed between staff vaccination coverage and all-cause mortality in residents. The relatively moderate nature of the 2006/07 influenza epidemic and the higher-than-anticipated vaccine coverage rate in the control arm must be taken into account when interpreting the lack of significantly lower all-cause mortality in residents. Together, these results support influenza vaccination of staff caring for institutionalized elderly people and encourage further evaluation of this practice.

REGISTERING CLINICAL TRIALS

This study was registered with ClinicalTrials.gov, number NCT: 00359554.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Figure S1. Weekly rates of all-cause mortality, hospitalization and influenza-like illness among residents in the two arms. The gray areas indicate the primary study period, which was used for all primary analyses. The black arrows indicate the peaks of respiratory syncytial virus and influenza virus isolation in the community.

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