The post-infection outcomes of influenza and acute respiratory infection in patients above 50 years of age in Japan: an observational study

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Objectives Influenza can be a serious illness, especially for older people, and reducing the impact of influenza in elderly is important. The objective of this study was to estimate the prevalence and postinfection outcomes of influenza among the over-50 population in Japan.

Design An observational study was designed to ascertain the proportion of influenza cases in a population aged $\geq$ 50 years with acute respiratory infection (ARI) and to determine the postinfection outcomes of their illness during the 2008–09 influenza season in Japan. Respiratory specimens obtained from a total of 401 patients were tested by PCR for influenza viruses, respiratory syncytial virus (RSV) and human metapneumovirus (hMPV). The effectiveness of the seasonal trivalent influenza vaccine was estimated by a test-negative case control analysis.

Setting Seventeen outpatient clinics located in four separate areas of Japan.

Sample Respiratory swab specimens from the ARI patients aged $\geq$ 50 years.

Main outcome measures Laboratory confirmed influenza in patients presenting with ARI.

Results In all, 89 (22.2%) of the patients were positive for one of the tested viruses; 70 (78.7%) with influenza, 17 (19.1%) with RSV, and 2 (2.2%) with hMPV. Cough (95.7% vs 73.4%), loss of appetite (67.1% vs 35.5%), absence from work (50.0% vs 23.0%), impact on daily activity (90.0% vs 62.5%), and caregiver absence from work (5.7% vs 0.6%) were observed higher in influenza patients. The duration of feeling weakness (6.3 ± 5.4 vs 3.6 ± 1.9 days) and average days of reduced activity (5.2 vs 3.6 days) were longer for influenza patients. Vaccine effectiveness was estimated to be 32.1% (95% CI: −14.9, 59.9%).

Conclusions Influenza was the dominant ARI-causing virus and the clinical and socio-economic outcomes imposed on patients over 50 years of age was high for influenza.

Keywords Acute respiratory infection, human metapneumovirus, influenza, influenza-like illness, post-infection outcomes, respiratory syncytial virus, test-negative case–control, vaccine effectiveness.

Introduction

Seasonal influenza is an important cause of morbidity and mortality. Influenza viruses have the potential to cause not only epidemics but also occasional pandemics. While influenza viruses remain of high scientific interest, studies based on clinical features without laboratory confirmation of diagnoses may lack reliability because of the similarity and overlap of influenza symptoms with those of other etiological agents that can give rise to acute respiratory infections (ARI).

Older people are at greater risk from complications arising from influenza than younger adults. In the United States, the elderly account for a significant number of influenza-associated hospitalizations. In Japan, a study of excess mortality associated with influenza epidemics across all ages during the period 1987–2005 estimated that 85–90% occurred among persons aged 65 and above. With declining birth and death rates, Japan already has one of the highest rates of aging globally, and it is projected that by 2050 over 30% of the Japanese population aged 60 or older will be 80 or above. Recently, treatment
for influenza with neuraminidase inhibitors has become popular in Japan, and they are prescribed very often even for mild cases of influenza. However, there have been no studies addressing the post-infection outcomes of laboratory-confirmed seasonal influenza on those aged 50 and above under such special circumstance. We therefore conducted an observational study using a population of patients with ARI in this age group from a primary care setting. The primary objective was to determine the proportion of ARI cases that were affected by influenza among the study population during the 2008–2009 influenza season. Secondary objectives were to ascertain both the clinical and socioeconomic post-infection outcomes imposed on the subjects during their influenza episode. We also carried out a test-negative case–control analysis to assess the effectiveness of the trivalent influenza vaccine (TIV) in preventing influenza in this age group.

**Methods**

The observational study was conducted in compliance with Good Clinical Practice (GCP) guidelines and the Japanese Ministry of Health, Labor and Welfare’s (MHLW) ethical guidelines for epidemiological research. A central Institutional Review Board (IRB) provided ethics review and approval. Seventeen outpatient clinics located in four separate areas of Japan, Fukuoka, Ishikawa, Gifu and Tokushima prefectures participated in the study. The recruitment period was from November 2008 to May 2009. Patients aged 50 years or over presenting with ARI were enrolled following informed consent. The inclusion criteria were a temperature of 37°C or more and/or feverishness at least one of the following respiratory symptoms: coryza and/or nasal congestion, cough, and sore throat (criteria adapted from the ARI subsection of ‘influenza’ case definitions’ specified by the European Centre for Disease Prevention and Control).

Medical histories were collected to obtain baseline data on demographics, underlying medical conditions (pneumonia, chronic obstructive lung disease, asthma, immunocompromised, diabetes, dialysis, arteriosclerosis, coronary artery disease, cardiac failure, cerebrovascular disease, regular smoking), and whether the patient had received a TIV vaccination prior to the 2008–2009 influenza season. Clinical symptoms and medical histories were recorded by the physician in clinical interview and through the subjects’ medical record. Participants were requested to keep a daily record of body temperature, clinical symptoms, medication taken and information on the socioeconomic outcomes of their ARI episode, such as reduced activity and workdays lost by themselves or their care givers. Follow-up contact was made by telephone 12–21 days after the initial visit, when participants were asked to complete a questionnaire while referring to their diary as a memory aid. Interviewers were blinded to the laboratory test results of the subjects. All subjects participating in the study were accounted for and followed up.

Two respiratory swab specimens were taken, one for rapid testing as part of the clinical diagnosis and the other for subsequent laboratory testing. Specimens for laboratory testing were collected and sent to the central laboratory at Hara-Doi Hospital by designated courier. All clinical specimens were labeled, handled, analyzed, and stored in accordance with GCP and JNIPH guidelines and standard operating procedures (SOPs). Agreement between rapid diagnosis kit and laboratory confirmation was analyzed to assess an any misclassification of disease.

Clinical samples were tested for influenza, respiratory syncytial virus (RSV), and human metapneumovirus (hMPV) by reverse transcription polymerase chain reaction (RT-PCR). The PCR mixture comprised 7.5 μl nuclease-free water, 62 μl GoTaq® Green Master Mix, 2X (Promega KK, Promega Corp., Madison, WI, USA), 0.15 μl forward primer, 0.15 μl reverse primer, and 1.0 μl template. Detection and subtyping of influenza type A (H1N1 and H3N2) and type B viruses were carried out as described by Stockton et al. Amplification conditions consisted of initial denaturation at 94°C for 10 seconds followed by 94°C for 5 seconds, 53°C for 20 seconds, and 72°C for 20 seconds applied for 32 cycles in the first round and 28 cycles in the second round, and final extension at 72°C for 10 seconds.

Infections by RSV were detected as described by Falsye et al. Amplification conditions consisted of initial denaturation at 95°C for 10 seconds followed by 95°C for 5 seconds, 42°C for 20 seconds, and 72°C for 20 seconds applied for 32 cycles in the first round and 28 cycles in the second round, and final extension at 72°C for 10 seconds. Infections by hMPV were detected as described by Peret et al. Amplification conditions consisted of initial denaturation at 94°C for 10 seconds followed by 94°C for 5 seconds, 55°C for 20 seconds, and 72°C for 20 seconds applied for 40 cycles in the first round and 40 cycles in the second round, and final extension at 72°C for 10 seconds.

The statistical software used were sas 8.2 (or later versions) and STATA/SE 10. Standard parametric techniques employed for statistical analysis (including comparison of baseline characteristics) were χ², Fisher’s exact and Student’s t-tests. With the power of the study set at 80% and significance level at 5%, the minimum sample size was estimated to be 500.

To evaluate crude estimates of the effectiveness of the seasonal vaccine in preventing influenza, we conducted a test-negative case–control analysis using the data obtained for the study population of patients with ARI who were infected with one of the three influenza viruses contained in the seasonal TIV (A/H1N1, A/H3N2, and B). The...
controls were patients with ARI who tested influenza negative. Participants were considered vaccinated if they had received the TIV at least 14 days before presenting with ARI.

**Results**

A total of 401 patients were enrolled into the study, 233 (58.1%) women and 168 (41.9%) men. A comparison of detailed baseline characteristics of the study population grouped by influenza diagnosis revealed that baseline characteristics of the influenza and non-influenza groups were similar in terms of age, gender, and vaccination status (Table 1). The two groups were also similar with respect to the presence of an underlying medical condition (45.7% and 43.2%, respectively). The medical conditions did not differ significantly between the two groups (data not shown).

In all, 89 (22.2%) of the 401 study participants were found to be infected with one of the tested viruses: 70 (78.7%) with influenza, 17 (19.1%) with RSV, and 2 (2.2%) with hMPV. According to the assessment of possible misclassification of disease between the rapid diagnosis kit and laboratory confirmation, specificity, sensitivity, positive predictive value, and negative predictive value were 93.0%, 78.6%, 70.5%, and 95.3%, respectively. Only laboratory-confirmed influenza was categorized as influenza positive for further analyses. Among the 70 patients positive for influenza, H1N1, H3N2, and B were detected in 33 (47.1%), 33 (47.1%), and 4 (5.7%) cases, respectively. Influenza was diagnosed in 70 (17.5%) of the 401 participants, of whom 28 (40.0%) had received the seasonal vaccination, while 42 (60.0%) had not. Among the 70 patients positive for influenza, neuraminidase inhibitors were prescribed at the initial visit to 50 (71.4%), of whom 23 (46.0%) had been vaccinated, but 27 (54.0%) had not. Among the 331 influenza-negative patients, 164 (49.5%) had been vaccinated and 167 (50.5%) had not (Table 1).

Significant differences were observed between influenza and non-influenza cases with regard to both clinical symptoms and socioeconomic post-infection outcomes (Table 2). The prevalence of cough, headache, loss of appetite, and both the feeling and duration of weakness were significantly higher among influenza-positive patients: Cough was observed in 95.7% and 73.4% (P < 0.01), headache in 64.3% and 49.5% (P = 0.03), loss of appetite in 67.1% and 35.5% (P < 0.01), feeling of weakness in 32.9% and 20.5% (P = 0.03), of influenza positive and negative, respectively. The duration of feeling weakness was 6.3 ± 5.4 days for positive and 3.6 ± 1.9 days (P < 0.01) for negative participants. Although there was no significant difference, it is particularly worth noting that the total duration of illness was more than 2 weeks in influenza-positive patients probably due to the vulnerability of the study population of this age. In terms of the socioeconomic outcomes of their ARI episode, absence from work, impact on daily activity, and caregiver absence from work were all reported to be significantly higher for those with influenza: Absence from work were observed in 50.0% and 23.0% (P < 0.01), impact on daily activity in 90.0% and 62.5% (P < 0.01), caregiver absence from work in 57.7% and 0.6% (P = 0.010) of influenza positive and negative, respectively (Table 2). Average days of absence was 3.1 days and 2.2 days (P = 0.026), and days of reduced activity was 5.2 days and 3.6 days (P < 0.001) for influenza-positive and influenza-negative participants. When the clinical symptoms and socioeconomic outcomes of only the influenza-positive cases were compared between those vaccinated or unvaccinated in the 2008–2009 season, there were no significant differences for any of the clinical or socioeconomic parameters (Table 3).

The test-negative case–control analysis of vaccine effectiveness indicated that the 2008–2009 seasonal influenza vaccination was 32.1% (−14.9, 59.9%) effective in preventing influenza in the study population overall. We were unable to determine age-specific vaccine effectiveness because of the small number of influenza cases in each age group.

**Discussion**

This is the first study in Japan to quantify the post-infection outcomes of seasonal influenza confirmed by labora-

| Characteristics                  | Influenza (+)* (n = 70) | Influenza (–)** (n = 331) | Difference (P-value) |
|----------------------------------|--------------------------|---------------------------|----------------------|
| Age                              | 63.1                     | 65.0                      | 0.330                |
| Gender                           | 50–84 (61.4%)            | 171 (107.2%)              |                     |
| Average                          | 65–74 years (25.7%)      | 107 (32.3%)               |                     |
| ≥75 years                        | 9 (12.9%)                | 53 (16.0%)                |                     |
| Male                             | 29 (41.4%)               | 139 (42.0%)               | 0.931                |
| Female                           | 41 (58.6%)               | 192 (58.0%)               |                     |
| Underlying medical condition     |                          |                           |                      |
| Yes                              | 32 (45.7%)               | 143 (43.2%)               | 0.700                |
| No                               | 38 (54.3%)               | 188 (56.8%)               |                     |
| Vaccinated influenza 2008–2009   |                          |                           |                      |
| Season                           | 28 (40.0%)               | 164 (49.5%)               | 0.146                |
| Unvaccinated                     | 42 (60.0%)               | 167 (50.5%)               |                      |

ARI, acute respiratory infection.
*Influenza positive.
**Influenza negative.
Respiratory viral pathogens are frequent ARI-causing viral pathogens. Influenza is the predominant ARI-causing viral pathogen among patients with ARI aged 50 and above. Because the symptoms of influenza are similar to those arising from other viral respiratory pathogens, diagnostic respiratory samples obtained from each patient were laboratory-confirmed using RT-PCR, which is highly sensitive and specific for detecting influenza viruses and those with no pathogen detected. In particular, the prevalence of cough, headache, loss of appetite, feeling of weakness, and duration of weakness was all significantly greater for those with laboratory-confirmed influenza, even though anti-influenza drug was prescribed to 50 of the 70 influenza-positive cases (71%). Our study demonstrated that influenza-positive patients suffered from more severe outcomes in terms of clinical symptoms than patients with ARI who were influenza negative including those who may have been infected with other viruses and those with no pathogen detected. In particular, the prevalence of cough, headache, loss of appetite, feeling of weakness, and duration of weakness was all significantly greater for those with laboratory-confirmed influenza, even though anti-influenza drug was prescribed to 50 of the 70 influenza-positive cases (71%).

The results showed that in the study population of 401 patients with ARI, 70 (17%) were influenza positive. Among the respiratory viruses tested for and identified, influenza was dominant (almost 80%), which agrees with previous reports relating to the elderly.8,9 The latter two commonly cocirculate with influenza in winter months and give rise to similar symptoms, which can be severe in the elderly.8,9 The symptoms of influenza are similar to those arising from other viral respiratory pathogens. Diagnostic respiratory samples obtained from each patient were laboratory-confirmed using RT-PCR, which is highly sensitive and specific for detecting influenza viruses and those with no pathogen detected. In particular, the prevalence of cough, headache, loss of appetite, feeling of weakness, and duration of weakness was all significantly greater for those with laboratory-confirmed influenza, even though anti-influenza drug was prescribed to 50 of the 70 influenza-positive cases (71%). Previous studies have also reported that elderly influenza patients suffered from longer-lasting coughs14 and that weakness was a common symptom of influenza.15 The socioeconomic outcomes on influenza-positive patients was also significantly greater than for the non-influenza patients with ARI in terms of impact on daily activity and the absence from work by both the patient and caregiver. It is particularly noteworthy that half of the influenza patients reported being absent from work (with a median duration of 3 days), whereas less than a quarter of the non-influenza ARI patients reported work days lost (median duration 2 days). In Japan, the majority of elderly people continue to do some form of work. Sometimes full-time worker, but part-time jobs and volunteering are regarded as work. The number of days of absenteeism of other persons who provided patient care during the follow-up period was analyzed because it is quite common for people around patients to care for the patient because of the limited availability of home nursing service in Japan. Patient absenteeism and the need for care-

### Table 2. Clinical symptoms and socioeconomic outcomes in 401 patients with ARI in Japan 2008–2009 by laboratory confirmation

| Clinical symptoms | Influenza (+) (n = 70)* | Influenza (-) (n = 331)** | OR (95%CI) | P-value |
|-------------------|-------------------------|---------------------------|------------|---------|
| Coryza and/or nasal congestion | 53 (75.7%) | 235 (71.0%) | 1.27 (0.70–2.31) | 0.43 |
| Cough | 67 (95.7%) | 243 (73.4%) | 8.09 (2.48–26.37) | <0.01 |
| Headache | 45 (64.3%) | 164 (49.5%) | 1.83 (1.07–3.13) | 0.03 |
| Loss of appetite | 47 (67.1%) | 117 (35.5%) | 3.74 (2.16–6.46) | <0.01 |
| Myalgia | 42 (60.0%) | 160 (48.3%) | 1.60 (0.95–2.71) | 0.08 |
| Sore throat | 50 (32.9%) | 256 (77.3%) | 0.73 (0.41–1.31) | 0.29 |
| Feeling of weakness | 23 (32.9%) | 68 (20.5%) | 1.89 (1.08–3.33) | 0.03 |
| Duration of feeling of weakness (days) | 6.3 ± 5.4 | 3.6 ± 1.9 | 2.09 (1.14–3.83) | <0.01 |
| Total duration of illness (days) | 19.0 ± 3.4 | 18.4 ± 5.7 | 1.41 (0.64–3.12) | 0.39 |

**Socioeconomic outcomes**

| Absence from work | 35 (50.0%) | 76 (23.0%) | 3.36 (1.97–5.72) | <0.01 |
| Days absent (average) | 3.1 | 2.2 | 1.62 (1.04–2.54) | 0.026 |
| Impact on daily activity | 63 (90.0%) | 207 (62.5%) | 5.93 (2.39–12.14) | <0.01 |
| Days of reduced activity | 4 | 3 | – | – |
| Days of reduced activity | 5.2 | 3.6 | 1.51 (1.18–1.93) | 0.001 |
| Caregiver absence from work | 4 (5.7%) | 2 (0.6%) | 9.97 (1.79–55.55) | 0.010 |
| Days absent (average) | 3.5 | 2 | 3.15 (0.16–63.12) | 0.492 |

**Daily symptoms**

ARI, acute respiratory infection.

*Influenza positive.

**Influenza negative.
givers to also take time off work appears to have also been substantially higher in the influenza-positive group. The burden of reduced daily activity would be reflected in diminished performance – with its consequent economic impact and loss of productivity, as well as intruding on the quality of life of both patients and their care givers.

Comparison of the clinical symptoms and socioeconomic criteria between vaccinated and unvaccinated influenza-positive participants revealed no significant differences. In addition, the proportion of vaccinated and unvaccinated patients was similar among those who had antiviral prescriptions (23/50 versus 27/50, respectively). Among this group of above 50 years of age, the seasonal vaccine appeared to have only a limited mitigating effect regarding clinical symptoms and reducing the socioeconomic outcomes of influenza.

To assess the effectiveness of the 2008–2009 TIV seasonal vaccine, we employed a test-negative case–control analysis in which the control group consisted of all the ARI participants who tested negative for influenza. Such a design is relatively easy to implement, controls better for bias related to healthcare service utilization than the traditional case–control method and has been shown to provide accurate estimates of vaccine effectiveness.16 The findings on the effectiveness of TIV in preventing influenza in this age group were inconclusive [32.1% (–14.9, 59.9%)]. However, this study was not primarily designed to study vaccine effectiveness, and these results should be interpreted with caution given the limited power and potential bias including lack of control for confounding. Nevertheless, the degree of effectiveness is broadly comparable with the results of large-scale cohort studies carried out annually by the Japan Physicians Association, which indicate that classical influenza vaccination of the over 65s has generally provided only moderate benefit to this age group.19 In the United States, the Centers for Disease Control estimates that vaccination of the elderly can be 30–70% effective.18 Although this refers to the prevention of hospitalization rather than the disease itself, our figure of 32.1% lies at the lower end of this range. Vaccine effectiveness in any given year is influenced by how well the strains used in the seasonal vaccine antigenically match those circulating in the community.19 In 2008–2009, the vaccine and circulating A/H1N1 subtype matched (A/Brisbane/59/2007); the A/H3N2 subtype matched in the first part of the season (A/Uruguay/716/2007), but there was a mismatch from March when A/Perth/16/2009 began circulating. In the case of type B, there was also a mismatch between the vaccine strain and the dominant circulating strain.20

Seasonal influenza vaccination is recommended for the elderly in Japan21 and is available at a subsidized cost,22 and the benefits are mostly seen in factors such as reduced hospitalization, fewer complications, and lower mortality.2,23,24 However, the evidence for seasonal vaccination in reducing the incidence of influenza in this age group remains weak,25 indicating a need for improved vaccines.

The study had some limitations. First, although the participants were living in the community, they were recruited solely from among clinic attendees and may therefore not be representative of the Japanese over-50

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### Table 3. Clinical symptoms and socioeconomic outcomes of influenza-positive vaccinated and unvaccinated patients in Japan 2008–2009

| Clinical symptoms | Vaccinated (n = 28) | Unvaccinated (n = 42) | OR (95% CI) | P-value |
|-------------------|--------------------|-----------------------|-------------|---------|
| Coryza and/or nasal congestion | 23 (82.1%) | 30 (71.4%) | 1.84 (0.57–5.96) | 0.31 |
| Cough | 26 (92.9%) | 41 (97.6%) | 0.32 (0.03–3.68) | 0.56 |
| Headache | 17 (60.7%) | 28 (66.7%) | 0.77 (0.29–2.09) | 0.61 |
| Loss of appetite | 19 (67.9%) | 28 (66.7%) | 1.06 (0.38–3.93) | 0.92 |
| Myalgia | 15 (53.6%) | 27 (64.3%) | 0.64 (0.24–1.70) | 0.37 |
| Sore throat | 18 (64.3%) | 32 (76.2%) | 0.56 (0.20–1.61) | 0.28 |
| Feeling of weakness | 10 (35.7%) | 13 (31.0%) | 1.24 (0.45–3.41) | 0.68 |
| Duration of feeling of weakness (days) | 8.1 ± 6.7 | 5.2 ± 4.4 | 1.62 (0.69–3.82) | 0.27 |
| Total duration of illness (days) | 18.6 ± 3.2 | 19.3 ± 3.6 | 0.32 (0.02–4.60) | 0.41 |

| Socioeconomic outcomes | Vaccinated (n = 28) | Unvaccinated (n = 42) | OR (95% CI) | P-value |
|------------------------|---------------------|-----------------------|-------------|---------|
| Absence from work | 14 (50.0%) | 21 (50.0%) | 1.00 (0.38–2.60) | 1.000 |
| Days absent (average) | 3.3 | 2.9 | 1.49 (0.45–4.94) | 0.52 |
| Impact on daily activity | 24 (85.7%) | 39 (92.9%) | 0.46 (0.09–2.24) | 0.43 |
| Days of reduced activity (average) | 5.5 | 4.9 | 1.15 (0.69–1.94) | 0.59 |
| Caregiver absence from work | 2 (7.1%) | 2 (4.8%) | 1.54 (0.20–11.61) | 1.00 |
| Days absent (average) | 1.5 | 5.5 | – | 0.13 |
population as a whole in terms of their general health. In fact, baseline data showed that nearly half of the subjects (43.6%) had an underlying medical condition, even though more than half were aged under 65. Second, our estimate of TIV effectiveness based on a test-negative case–control analysis needs to be treated with some caution because of possible overestimation\(^2\) and lack of adjustment for confounders and limited sample size. Nevertheless, baseline comparison of the influenza-positive and influenza-negative groups showed that overall the two groups were very similar. Furthermore, information/recall bias was minimized by ensuring that participants were able to keep track of the study variables by means of the prospective diary they were provided.

In summary, these results indicate that influenza is an important cause of ARI leading to higher socioeconomic outcomes and more severe symptoms than other viral ARI. Although clinical effectiveness of neuraminidase inhibitors has been reported, burden of influenza is significant. Current TIV vaccines may not offer an effective prevention against influenza in the elderly population. Continuing research and development toward improving influenza vaccines may play a vital part in reducing the clinical and socioeconomic outcomes of the influenza illness for a growing older population.

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Conflicts of interest

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