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Effectiveness of inactivated influenza vaccine against laboratory-confirmed influenza pneumonia among adults aged ≥65 years in Japan

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1. Introduction

Influenza is a major public health concern for older adults. Influenza infections generally cause self-limited illnesses but can result in severe disease such as pneumonia in older adults with and without underlying conditions. Older age is associated with a higher risk of pneumonia and mortality in influenza patients [1]. Based on our recent estimates, the incidence of influenza pneumonia and its related mortality among people aged ≥65 years in Japan were 210 and 24 per 100,000 persons/year, respectively [2].

Cumulative evidence has suggested that influenza vaccines are effective at reducing the risk of medically attended influenza in children and adults [3,4]. Currently, seasonal influenza vaccination is recommended for older adults in more than 90 countries [5]. However, its clinical benefit has long been discussed because vaccine responses are reduced by an age-related decline in adaptive immunity [6,7]. Positive results have been reported from recent meta-analyses: influenza vaccines reduce medically attended influenza by 20–44% [8] and influenza-associated hospitalization by 37% in older adults [9]. However, evidence is lacking for the protective effect of influenza vaccination on influenza pneumonia, including primary influenza pneumonia and secondary bacterial pneumonia. In a study by Grijalva et al., influenza vaccination reduced the risk of hospitalization from laboratory-confirmed influenza pneumonia in older adults.© 2018 Elsevier Ltd. All rights reserved.
influenza pneumonia by 56.7%, although the majority of their patients were people aged <65 years [10]. Therefore, the influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza pneumonia in older adults remains to be established.

We conducted this study to investigate the effectiveness of the trivalent inactivated influenza vaccine (IIV) against laboratory-confirmed influenza pneumonia and its related outcomes in adults aged ≥65 years. We also conducted subgroup analyses to explore differences in IVE by patient characteristics, particularly those related to immunosuppressive status.

2. Methods

2.1. Study setting and patients

This single-center prospective study was conducted at Kameda Medical Center (KMC), Kamogawa, Chiba, Japan, as part of the Adult Pneumonia Study Group-Japan (APSG-J) Study [2,11–13]. The APSG-J Study was a multicenter prospective study of adult pneumonia conducted at four community-based hospitals in Japan from September 2011 to August 2014. To investigate IVE, influenza vaccination history was systematically collected at KMC. In this study, pneumonia patients aged ≥65 years who visited KMC from February 2012 to January 2014 were included. The diagnosis of pneumonia was made by staff physicians according to clinical signs, symptoms, and radiological findings. Demographic and clinical information was collected from patients and medical charts. Sputum samples were collected from patients at the time of enrollment. If the patient was unable to cough up sputum, sputum was induced with the inhalation of hypertonic saline solution. Details of study settings and designs have been described previously [2,13].

2.2. Laboratory confirmation of influenza and other viruses

Gram staining and sputum culture were performed on site. Sputum samples were transferred to the Institute of Tropical Medicine, Nagasaki University, and tested by in-house multiplex polymerase chain reaction (PCR) assays to identify the influenza virus (A and B) and 11 other viral pathogens (respiratory syncytial virus [RSV], human metapneumovirus, human parainfluenza virus types 1–4, human rhinovirus [HRV], human coronavirus 229E/OC43, human adenovirus, and human bocavirus) [14]. The detection limits of the multiplex PCR assays were 10–100 copies per reaction as reported previously [14]. Influenza virus subtyping was performed for influenza A-positive samples via RT-PCR of the influenza HA genes using previously published methods [15,16].

Patients were defined as having laboratory-confirmed influenza pneumonia if their sputum sample tested positive for influenza A or B virus by PCR. Influenza pneumonia patients were classified as having influenza-associated bacterial pneumonia if their sputum samples were microscopically purulent (i.e., Geckler’s classification groups 4 and 5) and tested positive for bacterial pathogens by culture or PCR; otherwise, they were classified as having primary influenza pneumonia.

2.3. Cases and controls

A test-negative design (TND) case-control study was applied to estimate IVE [17]. Unlike the conventional case-control design, the TND does not require non-disease controls; instead, in this study design, researchers collect clinical samples from patients with a specific condition (e.g., influenza like illnesses) and classify the patients into cases (i.e., influenza tested positive patients) and controls (i.e., influenza tested negative patients) according to the influenza test results. The TND is less susceptible to bias due to differences in health care-seeking behavior among cases and controls and provides reliable IVE estimates [18,19]. Recently, TND studies have been widely used to estimate IVE against medically attended influenza and influenza-associated hospitalization [8,9].

In the current study, our primary outcome was laboratory-confirmed influenza pneumonia. Cases were pneumonia patients who tested positive for influenza A or B, and controls were pneumonia patients who tested negative for both influenza A and B. The odds of vaccination were compared between cases and controls, and IVE was expressed as (1-odds ratio) × 100%. Our secondary outcomes were (1) primary influenza pneumonia, (2) influenza-associated bacterial pneumonia, (3) influenza pneumonia-related hospital admission, (4) severe influenza pneumonia, and (5) influenza pneumonia death.

2.4. Influenza vaccination status

In Japan, all adults aged ≥65 years are recommended by the Ministry of Health, Labor and Welfare to receive one dose of the seasonal influenza vaccine [20]. The trivalent IIV vaccine was used during the study period (2011–12, 2012–13, and 2013–14 seasons); the quadrivalent IIV vaccine was introduced in the 2015–16 season. High-dose or adjuvanted IVVs have not been licensed in Japan. The compositions of the trivalent IIV vaccines used during the study seasons and their antigenic match status are summarized in Supplementary Table 1.

Influenza vaccination histories were collected from medical records and confirmed by patients and/or their guardians. Patients were considered vaccinated for influenza if they had received at least one dose of influenza vaccine in the 12 months before the hospital visit. Because the duration from influenza vaccination to the hospital visit was recorded as a monthly data, all patients who had been vaccinated within a month were considered vaccinated in our primary analysis. Patients were considered as having unknown influenza vaccination statuses if their influenza vaccination histories were not recorded in medical charts and could not be confirmed by the patients or their guardians; this group was excluded from our primary analysis.

2.5. Procedures

Patients were categorized into three age groups: 65–74 years, 75–84 years, and 85 years or older. Patient disability status was evaluated using the Eastern Cooperative Oncology Group Performance Status score [21]. Body mass index (BMI, kg/m²) was classified as underweight (<18.5), normal (18.5–24.9), or overweight (≥25.0). Chronic conditions included diabetes mellitus, heart failure, ischemic heart disease, cerebrovascular disease, liver disease, renal disease, neurological disease, cancer, chronic obstructive pulmonary disease, bronchial asthma, and previous tuberculosis disease. Immunosuppressive status included cancer, oral steroid use, and immunosuppressive drug use. Patients were considered to have severe pneumonia if they required oxygen therapy, mechanical ventilation, or a vasopressor after admission. The period from November to April was considered the influenza season.

2.6. Statistical analysis

The characteristics of patients were compared according to influenza infection status (i.e., influenza pneumonia vs. non-influenza pneumonia) and influenza vaccination status (i.e., vaccinated vs. unvaccinated) using chi-square tests and Fisher’s exact tests for categorical variables and Wilcoxon rank sum tests for numerical variables. IVE was estimated using logistic regression models. Pre-specified confounding factors were sex, age, the pres-
ence of chronic conditions, the presence of immunosuppression, smoking status, the duration from onset to hospital visit, and the period of the study, and all these variables were included in the final multivariable logistic regression models. We also considered the performance status score and BMI category as potential confounders and examined if IVE estimates changed after adjusting for these variables. Confidence intervals (CIs) were adjusted for the residential area level clustering of patients using robust standard errors.

We conducted sensitivity analyses as follows: (1) restricting the analysis to patients who visited during influenza seasons; (2) excluding patients vaccinated <1 month prior to hospital visit; (3) excluding patients vaccinated >6 months prior to hospital visit; (4) using patients who were negative for influenza virus but positive for non-influenza respiratory viruses as controls; (5) using patients who were negative for all viruses as controls [22]; (6) using propensity scores for adjustment; and (7) including patients with unknown vaccination status using multiple imputation.

Stratified analyses were conducted to investigate the potential effect modifications by patient characteristics (i.e., sex, age group, underlying condition, immunosuppressive status, and statin use status). Stratum-specific IVE estimates were compared using a likelihood ratio test (test for interaction).

2.7. Ethics

This study was approved by the institutional review board (IRB) of the Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan and the IRB of Kameda Medical Center, Chiba, Japan. Anonymized data were used in this study.

3. Results

During the study period, a total of 1494 pneumonia patients aged ≥65 years were enrolled in the study. Among them, sputum samples were obtained from 1044 patients (70%). After excluding 230 patients whose influenza vaccination history were unavailable (22% of patients with sputum samples), a total of 814 patients were eligible for our analyses (Fig. 1). Among them, 42 (5%) tested positive for influenza virus by PCR: 40 were positive for the influenza A virus, and the other two were positive for the influenza B virus. Among the 26 influenza A-positive samples that were subtyped (65% of all influenza A-positive samples), all were positive for the H3N2 strain. Non-influenza viruses were detected in 178 patients: HRV was the leading virus detected (n = 77, 9%), followed by RSV (n = 36, 4%). Non-influenza viruses were co-detected in 6 of the 42 influenza-positive patients (14%) and detected in 172 of the 772 influenza-negative patients (22%). Bacterial pathogens were co-detected in 26 of the 42 influenza-positive patients (62%).

Demographic and clinical characteristics were compared between influenza pneumonia patients (i.e., cases) and non-influenza pneumonia patients (i.e., controls) (Tables 1 and 2). Cases were more frequently found in winter seasons than controls, but other characteristics were similar between cases and controls.

Among 814 patients, 525 (65%) had been vaccinated for influenza. Vaccinated patients more frequently had received home oxygen therapy and had been diagnosed with chronic respiratory obstructive disease than unvaccinated patients, while other characteristics were similar between two groups (Tables 1 and 2).

After adjusting for confounders, the IVE against laboratory-confirmed influenza pneumonia was 58.3% (95% CI, 28.8–75.6%).

Fig. 1. Study flow diagram.
The change in IVE estimates was marginal after additional adjustment for performance status (58.9%; 95% CI, 30.6–75.7%) or BMI category (58.0%; 27.6–75.6%); therefore, these variables were not included in the final models. The sensitivity analyses showed similar results. IVE was relatively higher (68.9%; 95% CI, 46.4–81.9%) when we used patients who were negative for influenza but positive for non-influenza viruses as controls, but the value was almost identical to the primary analysis when we used patients who were negative for all viruses (57.8%; 95% CI, 26.9–75.7%).

For the secondary outcomes, the IVE against primary influenza pneumonia (70.1%; 95% CI, 19.8–88.9%) was higher than that
older adults. According to a systematic review by Belongia et al., the benefit of seasonal influenza vaccination against medically attended influenza in older adults is debated [3,23]. In this age group, the age-related decline in adaptive immunity results in reduced responses to influenza vaccination [6,7]; moreover, multiple chronic conditions and frailty may also contribute to weak immune responses [24]. However, despite an observed lower antibody response compared with that of younger adults [25], recent evidence supports the protective effect of influenza vaccination against medically attended influenza in older adults. According to a systematic review by Belongia et al., the pooled IVE was 24% (95% CI, –6% to 45%) for the H3N2 strain, 63% (95% CI, 33–79%) for type B, and 62% (95% CI, 36–78%) for the H1N1pdm09 strain among adults aged >60 years [4]. Darvishian et al conducted an individual participant data meta-analysis of TND studies and demonstrated that influenza vaccination is moderately effective against laboratory-confirmed influenza in this age group during epidemic seasons but not during non-epidemic seasons [8].

On the other hand, evidence is still limited for the beneficial effect of influenza vaccination against influenza-related severe outcomes such as pneumonia. Previous studies have estimated the IVE against all-cause pneumonia or influenza-related hospitalization in older adults [9,26–28]; however, these studies used less specific outcomes and may have underestimated the true IVE [17]. The TND study by Grijalva et al demonstrated that the overall estimate of IVE against hospitalization with laboratory-confirmed influenza pneumonia was 56.7% (95% CI, 31.9–72.5%) [10]. However, their study included all age groups, and only 16% of their patients were aged >65 years. In their analysis restricted to patients aged >65 years, IVE showed a positive effect but did not reach a statistically significant level (test for interaction, p = 0.17). Patients’ chronic conditions and statin use status did not modify IVE.

4. Discussion

IVE effectively reduced the risk of laboratory-confirmed influenza pneumonia in adults aged ≥65 years. IVE was higher among patients with immunosuppressive conditions, while statins did not modify IVE. To our knowledge, this is the first study that confirmed the beneficial effect of seasonal influenza vaccination against laboratory-confirmed influenza pneumonia in older adults.

4.1. Influenza vaccine effectiveness in older adults

The benefit of seasonal influenza vaccination in older adults is still debated [3,23]. In this age group, the age-related decline in adaptive immunity results in reduced responses to influenza vaccination [6,7]; moreover, multiple chronic conditions and frailty may also contribute to weak immune responses [24]. However, despite an observed lower antibody response compared with that of younger adults [25], recent evidence supports the protective effect of influenza vaccination against medically attended influenza in older adults. According to a systematic review by Belongia et al,
tion in adults aged >65 years was 58.0% (95% CI, 34.2–73.2%) [29]. The use of sputum samples in our study may also explain our high IVE estimate. Identification of influenza from sputum samples may be more sensitive and specific than that from upper respiratory tract samples in diagnosing influenza pneumonia and may provide less biased IVE estimates [17,30,31]. Consistent findings in our sensitivity analyses also support the robustness of our IVE estimates.

### 4.2. Primary influenza pneumonia and secondary bacterial pneumonia

Although a higher IVE estimate was observed for primary influenza pneumonia, IIV was also effective at preventing influenza-associated bacterial pneumonia (49.1%; 95% CI, 17.1–68.7%). This finding is important because influenza-bacterial co-infection increases the risk of severe outcomes [32]. Our finding also suggests that IIV may be effective at preventing influenza pneumonia death; however, the association did not reach a statistically significant level because of the limited sample size.

### 4.3. Immunosuppressive conditions and statins

It was unexpected that the IVE was significantly higher among people with immunosuppressive conditions (85.9%; 95% CI, 67.4–93.9%) than among those without (48.7%; 95% CI, 2.7–73%). The opposite finding was observed in the study by Grijalva et al, which included children and adults (−21.9% vs. 73.4%) [10]. This difference might be, at least partially, explained by a lower HIV prevalence in our patients. Although seasonal influenza vaccinations have been recommended for adults with immunosuppressive conditions [33], only a few studies have evaluated the IVE against clinical outcomes among this population [34]. Our finding provides supporting evidence for the current recommendations but needs to be confirmed in future studies.

Recent studies have suggested that statins may reduce the IVE against medically attended influenza among older adults by their immunomodulatory effects [35–38]. However, such an effect has not been observed in our study. Although the degree of its effect remains controversial, statins are also known to modify the risk of pneumonia and pneumonia-related outcomes [39–41]. The impact of statin use on the IVE may be different according to influenza outcomes.

### 4.4. Implications and future studies

Influenza infection is a threat to older adults because of its potential to cause pneumonia and secondary bacterial infections [13]. The burden of pneumonia is rapidly increasing in high-income countries such as Japan because of the aging population [2]. Therefore, the prevention of influenza pneumonia is an important public health measure in controlling pneumonia. The moderate effectiveness observed in our study supports the current seasonal influenza vaccination policy. In Japan, the proportion of people vaccinated against influenza among adults aged >65 years has been increasing but still remains approximately 60% [42]. In addition to improving vaccination coverage, an introduction of newer vaccines such as the more immunogenic high-dose influenza vaccine must be considered [43,44]. On the other hand, it must be noted that only 5% of pneumonia cases have influenza pneumonia, and thus, the impact of influenza vaccination on all-cause pneumonia is limited [45]. Newer multidimensional approaches are needed to reduce the pneumonia burden in the aging population.

### 5. Limitations

Our study has limitations. Influenza vaccination history was not documented for 22% of our patients. However, our sensitivity analysis using multiple imputations showed very robust estimates. We believe that the exclusion of this patient group did not affect our IVE estimates. Although all potential confounders were considered, unmeasured confounders may have remained. Recently, Andrew et al argued that frailty must be considered in estimating IVE for older adults [29]. We have not measured the frailty of our patients but measured their performance status and BMI. We confirmed that the inclusion of performance status or BMI category in the final model did not change the IVE estimates. Our observation is based on the analyses of older patients aged ≥65 years and there-

| Stratified by | Cases who were vaccinated, No./Total No. | Controls who were vaccinated, No./Total No. | Adjusted vaccine effectiveness (95% CI) | P value (test for interaction) |
|-------------|----------------------------------------|------------------------------------------|--------------------------------------|-------------------------------|
| Overall estimate | 19/42 | 506/772 | 58.3 (28.8–75.6) | |
| Stratified by sex | | | | |
| Male | 9/21 | 295/466 | 62.3 (12.7–83.7) | 0.802 |
| Female | 10/21 | 211/306 | 56.6 (13.7–78.2) | |
| Stratified by age group, years | | | | |
| 65–74 | 3/8 | 126/199 | 80.2 (61.8–89.7) | 0.17 |
| 75–84 | 9/20 | 220/333 | 64.3 (4.8–86.6) | |
| 85+ | 7/14 | 160/240 | 38.3 (27.4 to 70.1) | |
| Stratified by chronic conditions | | | | |
| With chronic conditions | 16/35 | 418/632 | 57.2 (27–74.9) | 0.986 |
| Without chronic conditions | 3/7 | 88/140 | 70.2 (−51.5 to 94.1) | |
| Stratified by immunosuppressive conditions | | | | |
| With immunosuppressive conditions | 3/10 | 158/234 | 85.9 (67.4–93.9) | 0.001 |
| Without immunosuppressive conditions | 16/32 | 348/538 | 48.7 (2.7–73) | |
| Stratified by statin use status | | | | |
| Statin use | 2/7 | 83/129 | 74.2 (−39.9 to 95.3) | 0.617 |
| No statin use | 17/35 | 423/643 | 57.1 (24–75.8) | |

CI = confidence interval.

a Adjusted for sex, age, smoking status, chronic conditions, immunosuppressive conditions, duration of symptoms, and period of hospital visit.

b Chronic conditions included diabetes mellitus, heart failure, ischemic heart disease, cerebrovascular disease, liver disease, renal disease, neurological disease, cancer, chronic obstructive pulmonary disease, bronchial asthma, and previous tuberculosis disease.

c Immunosuppressive status included cancer, oral steroid use, and immunosuppressive drug use.
fore may not be generalizable to younger adults. Finally, our sample size was too small to estimate subtype-specific IVE.

6. Conclusion
Seasonal influenza vaccination is moderately effective against laboratory-confirmed influenza pneumonia in adults aged >65 years. Considering the increasing burden of pneumonia in an aging population, we must improve influenza vaccination coverage and establish newer approaches.

Conflicts of interest
Konosuke Morimoto reports speaker fees from Taisho Toyama Pharmaceutical, Pfizer, and Asahi Kasei Pharma. All other authors declare no competing interests.

Author contributions
Conceived and designed the experiments: MS KM. Data collection: NAK NOK MY NY MA KM. Analyzed the data: MS NAK MNL LMY KM. Wrote the paper: MS NAK KM.

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Appendix A. Supplementary material
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2018.04.037.

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