Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine 36 (2018) 2960–2967

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

Motoi Suzuki [a,b,*], Naoko Katsurada [b,c,d], Minh Nhat Le [e], Norihiro Kaneko [b,c], Makito Yaegashi [b,f], Naoto Hosokawa [b,g], Yoshihito Otsuka [b,h], Masahiro Aoshima [b,c], Lay Myint Yoshida [b,e] Konosuke Morimoto [a,b]

[a] Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
[b] Adult Pneumonia Study Group-Japan, Japan
[c] Department of Pulmonology, Kameda Medical Center, Kamogawa, Japan
[d] Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[e] Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
[f] Department of General Internal Medicine, Kameda Medical Center, Kamogawa, Japan
[g] Department of Infectious Diseases, Kameda Medical Center, Kamogawa, Japan
[h] Department of Laboratory Medicine, Kameda Medical Center, Kamogawa, Japan

ARTICLE INFO

Article history:
Received 9 February 2018
Received in revised form 19 March 2018
Accepted 16 April 2018

Keywords:
Inactivated influenza vaccine
Vaccine effectiveness
Influenza pneumonia
Test-negative case-control design

ABSTRACT

Background: The effectiveness of inactivated influenza vaccine (IIV) against laboratory-confirmed influenza pneumonia in older adults remains to be established.
Methods: Pneumonia patients aged ≥65 years who visited a study hospital in Chiba, Japan, were prospectively enrolled from February 2012 to January 2014. Sputum samples were collected from participants and tested for influenza virus by polymerase chain reaction assays. Influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza pneumonia was estimated by a test-negative design.
Results: Among a total of 814 pneumonia patients, 42 (5.2%) tested positive for influenza: 40 were positive for influenza A virus, and two were positive for influenza B virus. The IVE against laboratory-confirmed influenza pneumonia was 58.3% (95% confidence interval, 28.8–75.6%). The IVE against influenza pneumonia hospital admission, severe pneumonia, and death was 60.2% (95% CI, 22.8–79.4%), 65.5% (95% CI, 44.3–78.7%), and 71% (95% CI, −62.9% to 94.8%), respectively. In the subgroup analyses, the IVE against influenza pneumonia was higher for patients with immunosuppressive conditions (85.9%; 95% CI, 67.4–93.9%) than for those without (48.7%; 95% CI, 2.7–73%) but did not differ by patients' statin use status.
Conclusion: IIV effectively reduces the risk of laboratory-confirmed influenza pneumonia in older adults.

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

* Corresponding author at: Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan.
E-mail address: mosuzuki@nagasaki-u.ac.jp (M. Suzuki).

https://doi.org/10.1016/j.vaccine.2018.04.037
0264-410X/

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 (eg, 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 IIVs 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/m^2) 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%)

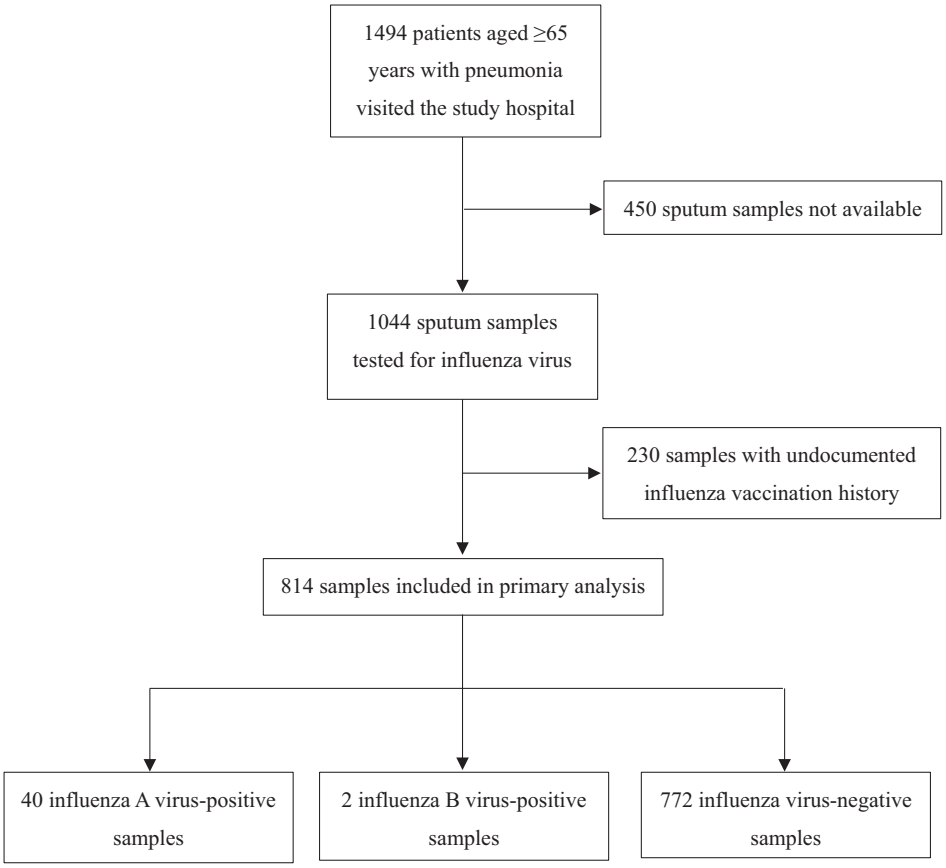

Fig. 1. Study flow diagram.

Table 1
Demographic characteristics of study participants by influenza infection and vaccination status.

	By case status, n (%)			By vaccination status, n (%)		
	Non-influenza pneumonia (n = 772)	Influenza pneumonia (n = 42)	P value[a]	Unvaccinated (n = 289)	Vaccinated (n = 525)	P value[a]
Age group, years						
65–74	199 (25.8)	8 (19.1)	0.619	78 (27.0)	129 (24.6)	0.732
75–84	333 (43.1)	20 (47.6)		124 (42.9)	229 (43.6)	
85+	240 (31.1)	14 (33.3)		87 (30.1)	167 (31.8)	
Female sex	306 (39.6)	21 (50.0)	0.182	106 (36.7)	221 (42.1)	0.131
No. of children aged <5 y at home						
0	673 (87.2)	36 (85.7)	0.636[b]	253 (87.5)	456 (86.9)	0.959
1+	49 (6.4)	4 (9.5)		18 (6.2)	35 (6.7)	
Unknown	50 (6.5)	2 (4.8)		18 (6.2)	34 (6.5)	
Long-term care needed	191 (24.7)	11 (26.2)	0.832	67 (23.2)	135 (25.7)	0.424
Period of hospital visit						
Feb 2012-Apr 2012	62 (8.0)	11 (26.2)	<0.001[b]	23 (8.0)	50 (9.5)	0.668
May 2012-Oct 2013	157 (20.3)	3 (7.1)		61 (21.1)	99 (18.9)	
Nov 2012-Apr 2013	233 (30.2)	25 (59.5)		97 (33.6)	161 (30.7)	
May 2013-Oct 2013	202 (26.2)	2 (4.8)		66 (22.8)	138 (26.3)	
Nov 2013-Jan 2014	118 (15.3)	1 (2.4)		42 (14.5)	77 (14.7)	

[a] Chi-square tests were performed unless otherwise indicated.
[b] Fisher's exact test.

Table 2
Clinical characteristics of study participants by influenza infection and vaccination status.

	By case status, n (%)			By vaccination status, n (%)		
	Non-influenza pneumonia (n = 772)	Influenza pneumonia (n = 42)	P value[a]	Unvaccinated (n = 289)	Vaccinated (n = 525)	P value[a]
Home oxygen therapy used	71 (9.2)	3 (7.1)	1[b]	12 (4.2)	62 (11.8)	<0.001
BMI categories						
Underweight	205 (26.6)	12 (28.6)	0.87[b]	84 (29.1)	133 (25.3)	0.251
Normal	372 (48.2)	21 (50.0)		126 (43.6)	267 (50.9)	
Overweight	91 (11.8)	3 (7.1)		35 (12.1)	59 (11.2)	
Unknown	104 (13.5)	6 (14.3)		44 (15.2)	66 (12.6)	
Current/ex-smoker						
Yes	427 (55.3)	20 (47.6)	0.482[b]	154 (53.3)	293 (55.8)	0.285
No	329 (42.6)	21 (50.0)		126 (43.6)	224 (42.7)	
Unknown	16 (2.1)	1 (2.4)		9 (3.1)	8 (1.52)	
Comorbidities						
Bronchial asthma	56 (7.3)	6 (14.3)	0.094	21 (7.3)	41 (7.8)	0.78
Chronic obstructive pulmonary disease	201 (26.1)	12 (28.6)	0.716	56 (19.4)	157 (30.0)	0.001
Coronary artery disease	74 (9.6)	4 (9.5)	1[b]	33 (11.4)	45 (8.6)	0.187
Heart failure	118 (15.3)	10 (23.8)	0.139	38 (13.1)	90 (17.1)	0.134
Diabetes mellitus	194 (25.1)	7 (16.7)	0.215	74 (25.6)	127 (24.2)	0.654
Chronic renal disease	70 (9.1)	5 (11.9)	0.536[b]	23 (8.0)	52 (9.9)	0.358
Chronic liver disease	26 (3.4)	2 (4.8)	0.651[b]	14 (4.8)	14 (2.7)	0.103
Cancer	159 (20.6)	5 (11.9)	0.171[b]	57 (19.7)	107 (20.4)	0.823
Cerebrovascular disease	153 (19.8)	8 (19.0)	0.903	58 (20.1)	103 (19.6)	0.877
Dementia	109 (14.2)	7 (16.7)	0.646	36 (12.5)	80 (15.2)	0.277
Medication						
Oral steroids	86 (11.1)	6 (14.3)	0.531	29 (10.0)	63 (12.0)	0.397
Immunosuppressants	16 (2.1)	1 (2.4)	0.597[b]	7 (2.4)	10 (1.9)	0.621
Statins	129 (16.7)	7 (16.7)	0.994	51 (17.7)	85 (16.2)	0.594
Time from disease onset to hospital visit ≥4 days	287 (37.2)	17 (40.5)	0.667	111 (38.4)	193 (36.8)	0.642
Influenza vaccinated ≤12 months prior to the hospital visit	506 (65.5)	19 (45.2)	0.007			
Time from influenza vaccination to hospital visit, months, median (IQR)	5 (6)	3 (2)	0.003[c]		5 (6)	

[a] Chi-square tests were performed unless otherwise indicated.
[b] Fisher's exact test.
[c] Wilcoxon rank sum test.

(Table 3). 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

Table 3
Influenza vaccine effectiveness and sensitivity analyses.

	Cases who were vaccinated, No./Total No.	Controls who were vaccinated, No./Total No.	Crude vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness (95% CI)[a]
Primary outcome				
Influenza pneumonia	19/42	506/772	56.6 (25.8–74.6)	58.3 (28.8–75.6)
Sensitivity analysis				
Restricted to influenza season (Nov-Apr)	17/37	271/413	55.5 (19.1–75.5)	57.1 (20.1–77)
Excluded patients vaccinated <1 month prior to hospital visit	19/42	485/751	54.7 (22.1–73.6)	55.8 (23–74.6)
Excluded patients vaccinated >6 months prior to hospital visit	19/42	313/579	29.8 (−20.6 to 59.1)	48 (8.4–70.5)
Controls positive for non-influenza viruses	19/42	118/172	62.2 (32.2–78.9)	68.9 (46.4–81.9)
Controls negative for all viruses	19/42	388/600	54.9 (22.5–73.7)	57.8 (26.9–75.7)
Propensity score-adjusted analysis[b]	19/42	506/772	56.6 (25.8–74.6)	60.1 (35.1–75.5)
Included patients with unknown vaccination status[c]	Imputed/49	Imputed/995	55.4 (27.2–72.6)	59.2 (31.5–75.7)
Secondary outcomes				
Primary influenza pneumonia (without bacterial infection)	6/16	506/772	68.5 (20.8–87.4)	70.1 (19.8–88.9)
Influenza-associated bacterial pneumonia	13/26	506/772	47.4 (13.1–68.2)	49.1 (17.1–68.7)
Influenza pneumonia admission	12/30	345/550	60.4 (25.3–79)	60.2 (22.8–79.4)
Influenza severe pneumonia	6/17	151/241	67.5 (46.8–80.1)	65.5 (44.3–78.7)
Influenza pneumonia death	2/7	27/47	70.4 (−40.7 to 93.8)	71 (−62.9 to 94.8)

CI = confidence interval.
[a] Adjusted for sex, age, smoking status, chronic conditions, immunosuppressive conditions, duration of symptoms, and period of hospital visit.
[b] Propensity scores were created using 34 variables including those for demographic characteristics and 15 comorbidities.
[c] Two hundred thirty pneumonia patients whose influenza vaccination histories were not documented were included in the analysis. The vaccination histories of these patients were considered missing data, and multiple imputations were performed.

against influenza-associated bacterial pneumonia (49.1%; 95% CI, 17.1–68.7%). The IVE against influenza pneumonia-related hospital admission (60.2%; 95% CI, 22.8–79.4%) and severe influenza pneumonia (65.5%; 95% CI, 44.3–78.7%) was comparable to that against influenza pneumonia. The point estimate of IVE against influenza pneumonia death was also high (71%; 95% CI, −62.9% to 94.8%), but its CI was wide because of the limited sample size.

Stratified analyses are shown in Table 4. The IVE against influenza pneumonia was higher in patients with immunosuppressive conditions (85.9%; 95% CI, 67.4–93.9%) than in those without these conditions (48.7%; 95% CI, 2.7–73%; test for interaction, p = 0.001). IVE did not differ by sex. The point estimate of IVE decreased with increased age, but the difference 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

IIV 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, 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 (48.4%; 95% CI, −33.3% to 80%). Therefore, the authors concluded that additional studies were needed to establish the IVE against pneumonia in older adults. Our study targeted this age group and demonstrated that the vaccine effectively reduces the risk of laboratory-confirmed influenza pneumonia by 58.3% (95% CI, 28.8–75.6%).

Our IVE estimates against influenza pneumonia in older adults may be higher than generally expected values. IVE is commonly lower for severe outcomes than for medically attended influenza and is lower in older adults than in children [3,9]. In addition, IVE is usually lower for the H3N2 stain than for the H1N1pdm09 strain [4]. However, our estimates are not dissimilar to those of previous reports: in the study by Grijalva et al, the IVE against influenza pneumonia related to the H3N2 strain in all age groups was 45.1% (95% CI, −9.3% to 72.4%) [10], and in another study conducted during the 2011–12 influenza season when H3N2 was the dominant circulating strain, the IVE against influenza hospitaliza-

Table 4
Stratified analysis of the influenza vaccine effectiveness against influenza pneumonia.

	Cases who were vaccinated, No./Total No.	Controls who were vaccinated, No./Total No.	Adjusted vaccine effectiveness[a] (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[b]				
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[c]				
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.

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-

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 NH YO MA KM. Analyzed the data: MS NAK MNL LMY KM. Wrote the paper: MS NAK KM.

Acknowledgments

We are grateful to all the Adult Pneumonia Study Group-Japan contributors. We would like to thank Professor Koya Ariyoshi, Dr. Eiichiro Sando, and Dr. Tomoko Ishifuji for their contribution to the study. We also thank Rina Shiramizu, Kyoko Uchibori for performing the PCR and Yumi Araki for administrative work.

Funding sources

This study was supported by Nagasaki University and Pfizer Japan, Inc.

Appendix A. Supplementary material

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

References

[1] Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. Bmj 2013;347:f5061.
[2] Morimoto K, Suzuki M, Ishifuji T, Yaegashi M, Asoh N, Hamashige N, et al. The burden and etiology of community-onset pneumonia in the aging Japanese population: a multicenter prospective study. PloS One 2015;10:e0122247.
[3] Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:36–44.
[4] Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis 2016;16:942–51.
[5] WHO. WHO vaccine-preventable diseases: monitoring system; 2017.
[6] Plowden J, Renshaw-Hoelscher M, Engleman C, Katz J, Sambhara S. Innate immunity in aging: impact on macrophage function. Aging Cell 2004;3:161–7.
[7] Lord JM. The effect of ageing of the immune system on vaccination responses. Hum Vaccines Immunotherap 2013;9:1364–7.
[8] Darvishian M, van den Heuvel ER, Bissielo A, Castilla J, Cohen C, Englund H, et al. Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies. Lancet Resp Med 2017;5:200–11.
[9] Rondy M, El Omeiri N, Thompson MG, Leveque A, Moren A, Sullivan SG. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. J Infect 2017;75:381–94.
[10] Grijalva CG, Zhu Y, Williams DJ, Self WH, Ampofo K, Pavia AT, et al. Association between hospitalization with community-acquired laboratory-confirmed influenza pneumonia and prior receipt of influenza vaccination. Jama 2015;314:1488–97.
[11] Ishifuji T, Sando E, Kaneko N, Suzuki M, Kilgore PE, Ariyoshi K, et al. Recurrent pneumonia among Japanese adults: disease burden and risk factors. BMC Pulmonary Med 2017;17:12.
[12] Suzuki M, Dhoubhadel BG, Ishifuji T, Yasunami M, Yaegashi M, Asoh N, et al. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. Lancet Infect Dis 2017;17:313–21.
[13] Katsurada N, Suzuki M, Aoshima M, Yaegashi M, Ishifuji T, Asoh N, et al. The impact of virus infections on pneumonia mortality is complex in adults: a prospective multicentre observational study. BMC Infect Dis 2017;17:755.
[14] Yoshida LM, Suzuki M, Yamamoto T, Nguyen HA, Nguyen CD, Nguyen AT, et al. Viral pathogens associated with acute respiratory infections in central vietnamese children. Pediatric Infect Dis J 2010;29:75–7.
[15] Suzuki M, Minh le N, Yoshimine H, Inoue K, Yoshida LM, Morimoto K, et al. Vaccine effectiveness against medically attended laboratory-confirmed influenza in Japan, 2011–2012 Season. PloS One 2014;9:e88813.
[16] Le MN, Yoshida LM, Suzuki M, Nguyen HA, Le HT, Moriuchi H, et al. Impact of 2009 pandemic influenza among Vietnamese children based on a population-based prospective surveillance from 2007 to 2011. Influenza Other Resp Viruses 2014;8:389–96.
[17] Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. Int J Epidemiol 2007;36:623–31.
[18] De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Euro surveillance: bulletin Europeen sur les maladies transmissibles = Eur Communicable Dis Bull 2013;18.
[19] Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical basis of the test-negative study design for assessment of influenza vaccine effectiveness. Am J Epidemiol 2016;184:345–53.
[20] Saito N, Komori K, Suzuki M, Morimoto K, Kishikawa T, Yasaka T, et al. Negative impact of prior influenza vaccination on current influenza vaccination among people infected and not infected in prior season: a test-negative case-control study in Japan. Vaccine 2017;35:687–93.
[21] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
[22] Suzuki M, Camacho A, Ariyoshi K. Potential effect of virus interference on influenza vaccine effectiveness estimates in test-negative designs. Epidemiol Infect 2014;142:2642–6.
[23] Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2010. CD004876.
[24] Bauer JM, De Castro A, Bosco N, Romagny C, Diekmann R, Benyacoub J, et al. Influenza vaccine response in community-dwelling German prefrail and frail individuals. Immun Ageing: I & A 2017;14:17.
[25] Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine 2006;24:1159–69.
[26] Foster DA, Talsma A, Furumoto-Dawson A, Ohmit SE, Margulies JR, Arden NH, et al. Influenza vaccine effectiveness in preventing hospitalization for pneumonia in the elderly. Am J Epidemiol 1992;136:296–307.
[27] Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. Am J Epidemiol 2001;154:155–60.
[28] Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. New Engl J Med 2007;357:1373–81.
[29] Andrew MK, Shinde V, Ye L, Hatchette T, Haguinet F, Dos Santos G, et al. The importance of frailty in the assessment of influenza vaccine effectiveness against influenza-related hospitalization in elderly people. J Infect Dis 2017;216:405–14.
[30] Falsey AR, Formica MA, Walsh EE. Yield of sputum for viral detection by reverse transcriptase PCR in adults hospitalized with respiratory illness. J Clin Microbiol 2012;50:21–4.
[31] Jeong JH, Kim KH, Jeong SH, Park JW, Lee SM, Seo YH. Comparison of sputum and nasopharyngeal swabs for detection of respiratory viruses. J Med Virol 2014;86:2122–7.
[32] Jia L, Xie J, Zhao J, Cao D, Liang Y, Hou X, et al. Mechanisms of severe mortality-associated bacterial co-infections following influenza virus infection. Front Cell Infect Microbiol 2017;7:338.
[33] Lopez A, Mariette X, Bachelez H, Belot A, Bonnotte B, Hachulla E, et al. Vaccination recommendations for the adult immunosuppressed patient: a systematic review and comprehensive field synopsis. J Autoimmun 2017;80:10–27.
[34] Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev 2013. CD008983.
[35] Black S, Nicolay U, Del Giudice G, Rappuoli R. Influence of statins on influenza vaccine response in elderly individuals. J Infect Dis 2016;213:1224–8.

[36] Omer SB, Phadke VK, Bednarczyk RA, Chamberlain AT, Brosseau JL, Orenstein WA. Impact of statins on influenza vaccine effectiveness against medically attended acute respiratory illness. J Infect Dis 2016;213:1216–23.
[37] McLean HQ, Chow BD, VanWormer JJ, King JP, Belongia EA. Effect of statin use on influenza vaccine effectiveness. J Infect Dis 2016;214:1150–8.
[38] Mascitelli L, Goldstein MR. How regulatory T-cell induction by statins may impair influenza vaccine immunogenicity and effectiveness. J Infect Dis 2016;213:1857.
[39] Janda S, Young A, Fitzgerald JM, Etminan M, Swiston J. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. J Crit Care 2010;25(656):e7–e22.
[40] Chopra V, Rogers MA, Buist M, Govindan S, Lindenauer PK, Saint S, et al. Is statin use associated with reduced mortality after pneumonia? A systematic review and meta-analysis. Am J Med 2012;125:1111–23.
[41] Havers F, Bramley AM, Finelli L, Reed C, Self WH, Trabue C, et al. Statin use and hospital length of stay among adults hospitalized with community-acquired pneumonia. Clin Infect Dis: Off Publ Infect Dis Soc Am 2016;62:1471–8.
[42] Nobuhara H, Watanabe Y, Miura Y. Estimated influenza vaccination rates in Japan. [Nihon koshu eisei zasshi]. Jpn J Publ Health 2014;61:354–9.
[43] Shay DK, Chillarige Y, Kelman J, Forshee RA, Foppa IM, Wernecke M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. J Infect Dis 2017;215:510–7.
[44] Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Resp Med 2017;5:738–46.
[45] Ferdinands JM, Gargiullo P, Haber M, Moore M, Belongia EA, Shay DK. Inactivated influenza vaccines for prevention of community-acquired pneumonia: the limits of using nonspecific outcomes in vaccine effectiveness studies. Epidemiology 2013;24:530–7.