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Effectiveness of influenza vaccination for children in Japan: Four-year observational study using a large-scale claims database

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ABSTRACT

Background: To date, few large-scale comparative effectiveness studies of influenza vaccination have been conducted in Japan, since marketing authorization for influenza vaccines in Japan has been granted based only on the results of seroconversion and safety in small-sized populations in clinical trial phases not on the vaccine effectiveness. We evaluated the clinical effectiveness of influenza vaccination for children aged 1–15 years in Japan throughout four influenza seasons from 2010 to 2014 in the real world setting.

Methods: We conducted a cohort study using a large-scale claims database for employee health care insurance plans covering more than 3 million people, including enrollees and their dependents. Vaccination status was identified using plan records for the influenza vaccination subsidies.

The effectiveness of influenza vaccination in preventing influenza and its complications was evaluated. To control confounding related to influenza vaccination, odds ratios (OR) were calculated by applying a doubly robust method using the propensity score for vaccination.

Results: Total study population throughout the four consecutive influenza seasons was over 116,000. Vaccination rate was higher in younger children and in the recent influenza seasons. Throughout the four seasons, the estimated ORs for influenza onset were statistically significant and ranged from 0.797 to 0.894 after doubly robust adjustment. On age stratification, significant ORs were observed in younger children. Additionally, ORs for influenza complication outcomes, such as pneumonia, hospitalization with influenza and respiratory tract diseases, were significantly reduced, except for hospitalization with influenza in the 2010/2011 and 2012/2013 seasons.

Conclusions: We confirmed the clinical effectiveness of influenza vaccination in children aged 1–15 years from the 2010/2011 to 2013/2014 influenza seasons. Influenza vaccine significantly prevented the onset of influenza and was effective in reducing its secondary complications.

1. Introduction

Because children are considered the primary infection center of influenza epidemics in the community, influenza vaccination, especially in the group aged less than 6 years, is recommended by WHO [1–4]. Influenza vaccination for children has been shown to effectively prevent the onset and spread of influenza by establishing herd immunity [5]. Currently, although influenza vaccination is highly recommended in Japan for school-aged children, it is available only through medical institutions on a voluntary basis at the vaccinees' own expense. Some employee health insurance plans subsidize influenza vaccination in children, especially in those aged under 16 years.

Although large-scale studies of the effectiveness of influenza vaccination have been conducted in many countries [6–9], evidence generated from large-scale studies using the vaccines available in Japan is lacking. Only inactivated, non-adjuvanted products are manufactured by a limited number of domestic suppliers, and supply is controlled under the Health Authority's vaccine policy [10]. Marketing authorization for influenza vaccines in Japan is normally granted based on the results of seroconversion

Abbreviations: DR, doubly robust method; OR, odds ratio; PS, propensity score; RTD, respiratory tract diseases.

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and safety in small-sized populations in clinical trial phases. These marketing authorization holders of influenza vaccines have long been reluctant to submit clinical evidence affirming the effectiveness of vaccination. From a public health perspective, it is therefore essential to evaluate the clinical effectiveness of vaccination in the post-marketing stage. Partly due to the absence of a nationwide vaccine registry, no large-scale effectiveness study of childhood influenza vaccination has yet been reported in Japan, although some hospital- or community-based studies have been reported [11,12].

Here, we evaluated the clinical effectiveness of influenza vaccination for children in Japan across four influenza seasons using a large-scale claims database.

2. Methods

2.1. Study design and population

We conducted a cohort study using a large-scale claims database which covered more than 3 million enrollees of employee health care insurance plans and their dependents, and contained enrollee claims records for ambulatory care, hospitalization and pharmacy benefits. The database was provided by JMDC (Japan Medical Data Center Co., Ltd., Tokyo, Japan) [13]. The present subjects were children aged 1–15 years who were the dependents of employees covered by the health plans and eligible for the insurers' vaccine subsidiary programs. Total study duration covered four consecutive influenza seasons, from October 2010 to May 2014. Influenza season for the analysis was determined to extend from October 1, the start date of influenza vaccination at medical institutes in Japan for each year according to the Health Ministry's policy, to the following May 31, when less than one influenza case per week per sentinel site on national average was reported after the peak, according to the weekly reports of infectious diseases published by the National Institute of Infectious Diseases [14,15].

Before data were retrieved from the health plan databases and transferred to the JMDC claims database, all identifiable personal data were anonymized and study subjects were coded with a unique identifier. Ethical approval for the study and waiver of informed consent by study subjects were obtained from the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (No. E-1822).

2.2. Outcome definition

The primary outcome was the effectiveness of influenza vaccination in preventing the onset of influenza. For this, a diagnosis of influenza was based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes (J101, J110, J111 and J118). To test the robustness of influenza diagnosis, sensitivity analyses were performed using three different outcome definitions for influenza occurrence: (1) combination of the above defined ICD-10 codes with records for the use of a rapid-testing kit; (2) combination of these ICD-10 codes with the prescription of antiviral drugs; or (3) combination of the J101 code "influenza due to identified seasonal influenza virus" with the use of a rapid-testing kit [16]. Antiviral drugs were determined using the Anatomical Therapeutic Chemical J05B4 classification of the European Pharmaceutical Marketing Research Association: laninamivir, oseltamivir, peramivir and zanamivir, and use of a rapid testing was identified by claim records for the influenza virus antigen (High-sensitive) test.

The secondary outcome was the effect of influenza vaccination on complications of influenza infection. Patients with diagnosis codes for pneumonia (J12-J18) and respiratory tract diseases (RTD: J00-J22, except for the above codes for influenza) were identified. Hospitalized cases met the following criteria: hospitalized within three days before or after the date of influenza diagnosis (hospitalization with influenza); and hospitalized within seven days after the diagnosis date of RTD (hospitalization with RTD).

2.3. Influenza vaccination

Seasonal trivalent inactivated, non-adjuvanted influenza vaccines were available for children aged 6 months or older during the study period in Japan. Influenza A(H1N1pdm09) was the most prevalent circulating strain in the 2010/2011 (52%) and 2013/2014 (43%) seasons, and A(H3N2) was the most prevalent circulating strain in the 2011/2012 (71%) and 2012/2013 (76%) seasons [15] (Table 1). Antigenic characteristics of vaccine strains are shown in Table 1. The dose of vaccine for children aged under 13 years was increased from the 2011/2012 season to be equivalent to the world standard dose (Appendix 1). Vaccination status and dates were identified from the records for influenza vaccination subsidies of the health plan. Subjects who were vaccinated after the onset of an outcome of concern were censored at the time of outcome diagnosis and classified as non-vaccinees.

2.4. Confounding factors

Covariates considered for adjustment of potential confounders were influenza vaccination status in the immediately preceding season, age group (low-age group, 1–5 years old; high-age group, 6–15 years old), sex, the presence of siblings aged 0–15 or over 15 years, preceding onset of influenza among siblings aged 1–15 years during each influenza season, a history of high-risk medical conditions, emergent hospitalization, and number of outpatient visits during or out of office hours in the preceding influenza off-season (June to September). High-risk medical conditions were defined in accordance with the definition of the US Center for Disease Control and Prevention [17]. Siblings were identified by having the same insurance number for dependents. "Preceding onset of influenza among siblings" was defined as the risk of second infection to which a subject was exposed when his/her siblings aged 1–15 years had had any influenza diagnosis code prior to his/her first influenza occurrence, or during the influenza season in the case of no occurrence; this was considered only in the analyses of the primary outcome and in the secondary outcome for hospitalization with influenza.

2.5. Statistical analysis

Subject characteristics during the four seasons were summarized with descriptive statistics. Comparison of continuous variables between vaccinees and non-vaccinees was tested with the Mann-Whitney test. The chi-square test was used for comparison of categorical variables.

The primary analysis was odds ratios (ORs) of outcome events for influenza vaccination, with a lower OR indicating better effectiveness. First, ORs for influenza vaccination and other covariates were calculated by conventional multivariate logistic regression for whole subjects and age groups. Next, a doubly robust method (DR) using inverse probability treatment weighting (IPTW) by propensity score (PS) was applied to calculate the OR_{DR}s to adjust confounding related to influenza vaccination [18,19]. Whether to be vaccinated is known to be strongly associated with health-seeking behaviors, and PS implementation has an advantage in adjusting the channeling bias that health-seeking behaviors involve [20,21]. However, it is known that PS adjustment methods yield biased estimates when the model used to specify the PS is misspecified, and the IPTW estimator

Table 1
Antigenic characteristics of vaccine strains and influenza viruses in the 2010 /2011 to 2013/2014 influenza seasons in Japan.

Influenza season and type or subtype	Vaccine component	Circulating strain
2010/2011		
H1N1pdm09 (52%)[a]	A/California/7/2009pdm	A/California/7/2009pdm-like
H3N2 (32%)	A/Victoria/210/2009	A/Victoria/210/2009-like or A/Perth/16/2009-like
B/Victoria (12%)	B/Brisbane/60/2008	B/Brisbane/60/2008-like or B/Wisconsin/1/2010-like
B/untyped (3%)		
2011/2012		
H1N1pdm09 (0.2%)	A/California/7/2009pdm09	A/California/7/2009pdm09-like
H3N2 (71%)[a]	A/Victoria/210/2009	A/Victoria/361/2011-like
B/Victoria (15%)	B/Brisbane/60/2008	B/Brisbane/60/2008-like
B/Yamagata (8%)		B/Wisconsin/1/2010-like
B/untyped (5%)		
2012/2013		
H1N1pdm09 (2%)	A/California/7/2009pdm09	A/California/7/2009-like
H3N2 (76%)[a]	A/Victoria/361/2011	A/Victoria/361/2011-like
B/Yamagata (13%)	B/Wisconsin/1/2010	B/Wisconsin/1/2010-like
B/Victoria (6%)		B/Brisbane/60/2008-like
B/untyped (4%)		
2013/2014		
H1N1pdm09 (43%)[a]	A/California/7/2009(X-179A)pdm09	A/California/7/2009-like
H3N2 (21%)	A/Texas/50/2012(X-223)	A/Texas/50/2012-like
B/Yamagata (24%)	B/Massachusetts/2/2012(BX-51B)	B/Massachusetts/2/2012-like B/Wisconsin/1/2010-like
B/Victoria (9%)		B/Brisbane/60/2008-like
B/untyped (4%)		

[a] Main subtype of circulating viruses in each year [38].

may then be biased. DR incorporates regression model of outcomes into IPTW, which can provide unbiased estimators if any one of these modellings fits [22,23]. The PSs were calculated for OR_{DR}s as the probability of being vaccinated in the current season. Covariates considered in calculating the PSs were the above-mentioned variables, except for preceding onset of influenza among siblings aged 1–15 years. C-statistics were calculated and the Hosmer-Lemeshow test was conducted for validity of PSs. Vaccinees with PS < 0.1 and non-vaccinees with PS > 0.9 were excluded from the primary analysis. Since their vaccination status was in fact contrary to that predicted by the estimated PSs, subjects with such extreme PSs would have been excessively weighted with the inverse of PSs and could have been highly influential in causing bias if they had been included in the IPTW analysis. Excessive weighting warranted the trimming of these subjects to eliminate bias [24].

Cox proportional hazard survival function with vaccination and preceding onset of influenza among siblings as a time-dependent covariate was applied to estimate the hazard ratios for influenza onset as a secondary analysis. A potential bias which induces greater apparent vaccine effectiveness has been reported for elderly mortality studies using electronic health record databases [27–29]. We examined this bias by applying a Cox-hazard model in a pre-epidemic period with minimum influenza circulation, defined as follows: the start date was October 1st, and the end date was the day before the beginning of the 1st week when more than one influenza case per sentinel site on national average was reported for each season [15].

Subjects who had a defined outcome within 13 days after vaccination were excluded from the primary and secondary analyses because of potentially incomplete vaccine-induced protection [9,25,26].

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY) and SAS version 9.1 (SAS Institute). All tests were 2-tailed with a significance level of 0.05.

3. Results

The total study population throughout the four seasons was over 116,000. For primary analysis, over 26,000 children were included in every season, after excluding a total of 529 children with extreme PSs or with the onset of an outcome within 13 days after their vaccination date. Vaccination rate differed by age and year of influenza season; it was higher in the low-age group and in the later years (Fig. 1). Annual vaccination rate gradually increased with statistical significance; 41.8% (2010/2011 season), 44.8% (2011/2012), 50.6% (2012/2013), and 51.3% (2013/2014) (chi-square test, $p < 0.001$). Characteristics were similar among the four seasons, whereas those between vaccinees and non-vaccinees were significantly different in every season (Table 2).

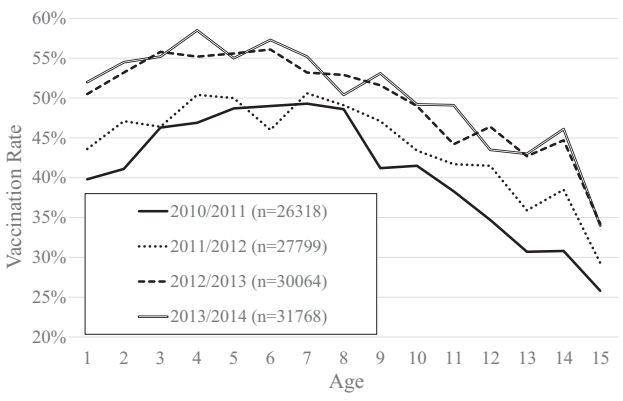

Fig. 1. Annual vaccination rates by age in Japanese children.

Table 2
Characteristics of Japanese children in the primary analysis, stratified by vaccination status in the current influenza season.

Influenza season	2010/2011			2011/2012		
	Vaccinee (n = 10,997)	Non-vaccinee (n = 15,321)		Vaccinee (n = 12,442)	Non-vaccinee (n = 15,357)	
Characteristic	No. (%)	No. (%)	*P* Value[a]	No. (%)	No. (%)	*P* Value[a]
Age (median [interquartile range])	6 [3,10]	7 [3, 11]	<0.001†	6 [3, 10]	7 [4, 11]	<0.001†
<5 yrs	3806 (34.6%)	4957 (32.4%)	<0.001*	4332 (34.8%)	4925 (32.1%)	<0.001*
Female	5357 (48.7%)	7401 (48.3%)	0.516*	6019 (48.4%)	7487 (48.8%)	0.538*
Have siblings						
Aged 0–15 yrs	9278 (84.4%)	11,594 (75.7%)	<0.001*	10,327 (83.0%)	11,645 (75.8%)	<0.001*
Aged 16 yrs or older	620 (5.6%)	1732 (11.3%)	<0.001*	755 (6.1%)	1794 (11.7%)	<0.001*
Vaccination in previous season	6789 (61.7%)	2209 (14.4%)	<0.001*	8137 (65.4%)	2571 (16.7%)	<0.001*
Before influenza season						
Number of outpatient visits						
During office hours (median [range])	6 [0–183]	2 [0–53]	<0.001†	6 [0–212]	2 [0–40]	<0.001†
Out-of-office hours (median [range])	0 [0–36]	0 [0–47]	<0.001†	0 [0–26]	0 [0–11]	<0.001†
Emergent hospitalization	6 (0.05%)	9 (0.06%)	1.000*	5 (0.04%)	10 (0.07%)	0.444*
High-risk condition	2998 (27.3%)	2940 (19.2%)	<0.001*	3253 (26.1%)	2998 (19.5%)	<0.001*
During influenza season						
Preceding onset of influenza among siblings	2140 (19.5%)	2541 (16.6%)	<0.001*	2267 (18.2%)	2508 (16.3%)	<0.001*

Influenza season	2012/2013			2013/2014		
	Vaccinee (n = 15,207)	Non-vaccinee (n = 14,857)		Vaccinee (n = 16,308)	Non-vaccinee (n = 15,460)	
Characteristic	No. (%)	No. (%)	*P* Value[a]	No. (%)	No. (%)	*P* Value[a]
Age (median [interquartile range])	6 [3, 10]	7 [4, 11]	<0.001†	6 [3, 10]	7 [4, 11]	<0.001†
<5 yrs	5356 (35.2%)	4639 (31.2%)	<0.001*	5732 (35.1%)	4696 (30.4%)	<0.001*
Female	7329 (48.2%)	7269 (48.9%)	0.208*	7881 (48.3%)	7535 (48.7%)	0.465*
Have siblings						
Aged 0–15 yrs	12,479 (82.1%)	11,351 (76.4%)	<0.001*	13,441 (82.4%)	11,677 (75.5%)	<0.001*
Aged 16 yrs or older	988 (6.5%)	1725 (11.6%)	<0.001*	1083 (6.6%)	1822 (11.8%)	<0.001*
Vaccination in previous season	10,054 (66.1%)	2065 (13.9%)	<0.001*	12,297 (75.4%)	2511 (16.2%)	<0.001*
Before influenza season						
Number of outpatient visits						
During office hours (median [range])	6 [0–116]	1 [0–41]	<0.001†	6 [0–148]	2 [0–53]	<0.001†
Out-of-office hours (median [range])	0 [0–54]	0 [0–20]	<0.001†	0 [0–32]	0 [0–53]	<0.001†
Emergent hospitalization	11 (0.07%)	11 (0.07%)	1.000*	7 (0.04%)	9 (0.06%)	0.622*
High-risk condition	3913 (25.7%)	2547 (17.1%)	<0.001*	4040 (24.8%)	2758 (17.8%)	<0.001*
During influenza season						
Preceding onset of influenza among siblings	2294 (15.1%)	2033 (13.7%)	0.001*	2441 (15.0%)	2313 (15.0%)	0.987*

[a] The χ^2 test was used for categorical variables (*) and the Mann-Whitney test for continuous variables (†) between vaccinees and non-vaccinees in each influenza season.

Table 3
Incidence of influenza onset and odds ratios (OR_{DR}) for influenza vaccination using multiple outcome definitions in Japanese children by season; doubly robust method.

Influenza season	2010/2011	2011/2012	2012/2013	2013/2014
Outcome definition	No. (%) OR_{DR} (95% CI)	No. (%) OR_{DR} (95% CI)	No. (%) OR_{DR} (95% CI)	No. (%) OR_{DR} (95% CI)
Influenza diagnosis codes only[a]	6788 (25.8) 0.894 (0.838–0.950)	6954 (25.0) 0.797 (0.748–0.847)	5844 (19.4) 0.841 (0.788–0.895)	6602 (20.8) 0.821 (0.769–0.873)
Influenza diagnosis codes + Prescription of antiviral drugs	6160 (23.4) 0.897 (0.839–0.955)	6339 (22.8) 0.793 (0.742–0.843)	5243 (17.4) 0.849 (0.793–0.905)	5940 (18.7) 0.808 (0.755–0.862)
Influenza diagnosis codes + Use of rapid testing	6108 (23.2) 0.911 (0.853–0.970)	6170 (22.2) 0.803 (0.752–0.855)	5214 (17.3) 0.858 (0.801–0.915)	5884 (18.5) 0.815 (0.761–0.869)
ICD10 J101 code + Use of rapid testing[b]	3814 (14.5) 0.889 (0.820–0.959)	4047 (14.5) 0.829 (0.766–0.892)	3533 (11.7) 0.832 (0.767–0.897)	4124 (13.0) 0.811 (0.749–0.873)

For each outcome, we excluded subjects who had the outcome within 13 days after vaccination. Therefore, the number of study subjects in one season differed by outcome definition. All confounders were adjusted using a doubly robust method.
[a] Defined by ICD-10 influenza diagnosis codes (J101, J110, J111, J118).
[b] Defined by combination of ICD-10 influenza diagnosis codes (J101: influenza due to identified seasonal influenza virus) with use of a rapid-testing as outcome.

3.1. Vaccine effectiveness for influenza onset

Current-year vaccination significantly reduced the risk of influenza onset throughout the four seasons after adjustment for covariates in logistic regression analysis (Appendix 2). ORs of influenza onset for current-year vaccination were 0.895 in 2010/2011 (p-value: 0.001), 0.804 in 2011/2012 (<0.001), 0.828 in 2012/2013 (<0.001), and 0.815 in 2013/2014 (<0.001), although ORs for previous year vaccination were significantly larger than one except for the 2013/2014 season. Having siblings aged over

Table 4
Incidence of influenza complications and odds ratios (OR_{DR}) for influenza vaccination in Japanese children by season; doubly robust method.

Influenza season	2010/2011	2011/2012	2012/2013	2013/2014
Outcome	No. (%) OR_{DR} (95% CI)	No. (%) OR_{DR} (95% CI)	No. (%) OR_{DR} (95% CI)	No. (%) OR_{DR} (95% CI)
Hospitalization with influenza[a]	42 (0.2) 0.636 (0.186–1.087)	22 (0.1) 0.388 (-0.027–0.803)	16 (0.1) 1.651 (-0.214–3.515)	27 (0.1) 0.290 (0.003–0.577)
Pneumonia[b]	411 (1.6) 0.626 (0.478–0.774)	1101 (4.0) 0.591 (0.507–0.674)	981 (3.3) 0.426 (0.361–0.491)	706 (2.2) 0.541 (0.445–0.636)
Respiratory tract diseases[c]	18,538 (73.3) 0.625 (0.587–0.664)	20,089 (74.8) 0.631 (0.593–0.669)	20,849 (72.0) 0.580 (0.548–0.612)	21,418 (70.2) 0.544 (0.515–0.573)
Hospitalization with respiratory tract diseases [d]	299 (1.1) 0.661 (0.475–0.848)	385 (1.4) 0.714 (0.547–0.881)	301 (1.0) 0.593 (0.435–0.750)	289 (0.9) 0.519 (0.376–0.661)

For each outcome, we excluded subjects who had the outcome within 13 days after vaccination. Therefore, the number of study subjects in one season differed by outcome. All confounders were adjusted using a doubly robust method. Preceding onset of influenza among siblings was included only for the analysis of "hospitalization with influenza" outcome.

[a] Hospitalization started within 3 days before or after the data of influenza diagnosis codes.
[b] Pneumonia including the ICD-10 codes: J12-J18.
[c] Respiratory tract disease including the ICD-10 codes: J00-J22 except for influenza diagnosis codes, J10 and J11.
[d] Hospitalization started within 7 days after diagnosis of respiratory tract diseases other than influenza.

15 years and female sex significantly reduced the risk; in contrast, some confounders such as high-age group significantly increased the risk of influenza (Appendix 2).

Given that influenza was defined only by ICD-10 codes, the OR_{DR}s ranged from 0.797 (2011/2012 season) to 0.894 (2010/2011 season) and were significantly reduced throughout all the seasons after doubly robust adjustment (Table 3). Sensitivity analysis using the combination of J101 with the use of a rapid-testing kit gave similar, statistically significant OR_{DR}s, ranging from 0.811 (2013/2014 season) to 0.889 (2010/2011 season). The C-statistics of the PSs were 0.791 or more and the Hosmer-Lemeshow test was statistically significant (p-value: <0.001).

Age-stratified ORs were lower in younger children (Appendix 3). However, in children over 8 years, except for those aged 12, there were no statistically significant ORs in any of the four influenza seasons.

Cox hazard regression also produced significantly reduced hazard ratios showing similar but slightly smaller vaccine effectiveness overall, compared with the ORs derived from logistic regression (Appendix 4). No significant, positive vaccine effectiveness was shown during the pre-epidemic periods throughout the four seasons (Appendix 5).

3.2. Vaccine effectiveness for influenza-related complications

Reduction in the OR_{DR}s for influenza complications, including hospitalization with influenza, pneumonia, RTD and hospitalization with RTD, were statistically significant, except for insignificant OR_{DR}s for hospitalization with influenza in the 2010/2011 and 2012/2013 seasons (Table 4).

4. Discussion

Our study confirmed that influenza vaccination was effective in preventing influenza onset and its complications such as pneumonia in a post-marketing real world setting, as previously reported [6,11,30,31]. Given the similar ORs yielded by sensitivity analysis of the primary outcome, these study results of influenza prevention appear to be robust. Although all the estimated ORs were significant, there were variations in the estimated ORs with outcomes; the reductions in ORs for influenza onset were modest while the reductions in ORs for influenza complications were substantial.

Of note, vaccine effectiveness estimated with the ORs for influenza onset was lower than our expectation. Modest effectiveness was also reported in other studies, especially in older children, albeit that these were higher than in our study [11,31]. Several plausible reasons include use of less specific outcome definitions employing claims records rather than laboratory-confirmed diagnosis and a lack of herd immunity at school. Use of PCR for over 26 thousand cases around Japan to identify laboratory-confirmed influenza is too costly and resource-consuming. Instead, we confirmed robustness of the risk estimates in the present study by differentiating the outcome definitions for influenza occurrence. Compared with the approximately 50% vaccination coverage necessary to establish herd immunity in schools [7], coverage was lower in many of our present age groups. Furthermore, the local communities to which our study subjects belonged and their vaccination status were not specified, since the study was not population-based. A lower vaccination rate would be expected in families not covered by a vaccine subsidiary program, possibly leading to even lower immunity in the community than that observed in this study.

The PS was calculated using several proxies of health-care seeking behavior including influenza vaccination status in the immediately preceding season. Given the high values of C-statistics, the estimated PSs were considered to be valid [32,33]. Owing to the very large sample size, however, all of the Hosmer-Lemeshow tests indicated statistical significance between the observed and model-predicted treatment allocation. Because PS directly considers the bias related to exposure, which regression models are only able to adjust indirectly, PS implementation was considered preferable for adjusting bias due to healthcare seeking behaviors [20,21]. The DR method adjusts for both direct and indirect confounders via vaccination status and therefore provides better estimates, but tends to result in larger variance [33]. Waning effectiveness of inactivated influenza vaccines indicated potential difficulty in applying Cox proportional hazard model which do not assume time-varying efficacy of vaccines, and therefore we used semi-parametric methods for the primary analysis [34].

Further, the use of a claims database for employee insurance with excellent traceability of enrollees also allows us to capture the enrollees without flu-related symptoms or diseases requiring medical encounters after vaccination. Inclusion of such subjects in the analysis would be advantageous in the interpretability of the results by practitioners as well as the public, including health-care payers, policy makers and insurance enrollees. The absence of

the bias reported in several elderly mortality studies was suggested by the lack of a significant positive estimate during the pre-epidemic periods in the present study, as reported in another database study [35].

Sensitivity analysis using different outcome definitions provides important insights into the validity of study results. Since the study database did not provide laboratory-confirmed influenza diagnoses, a less stringent criterion using the ICD10 codes only was applied. This is likely to capture the incidence of both influenza and influenza-like illness. In contrast, use of the J101 code in combination with a rapid-testing kit may provide the most conservative estimate of incidence, albeit that it may possibly also lead to an increase in the number of false-negative cases; this is because the sensitivity of available rapid-testing kits is approximately 60%, and testing in clinical settings is frequently negative in the early stage of influenza infection even in true-positive cases [36].

Effectiveness of vaccination varied in degree between the 2010/2011 and 2011/2012 seasons, probably reflecting the dose change. The dose of vaccine increased in the 2011/2012 season to an equivalent dosage to Western countries, with the total dose more than doubling in children aged 3–5 (0.4–1.0 ml; Appendix 1). Antigenic mismatch of vaccines with circulating strains occurred in the 2011/2012 season: the main circulating strain was H3N2 (A/Victoria/361/2011-like), which slightly differed from the vaccine component (A/Victoria/210/2009, Table 1) [37]. However, this seems to have not substantially affected vaccine effectiveness in the 2011/2012 season, as indicated by the significant ORs and HR for influenza onset and complications.

Significantly lower ORs for the onset of influenza were observed in younger children, particularly those aged 1–5 years (Appendix 3), in agreement with a previous study [11]. In contrast, insignificant ORs were frequently found in the higher aged children. A possible explanation might include the small sample size after age stratification.

Several risk factors for the onset of influenza were detected, including prior season vaccination during the three consecutive seasons and the presence of siblings aged 0–15 years. Potential negative effects of repeated vaccination have been reported in association with the antigenic subtype of epidemic strains and vaccine components [38,39]. Due to the lack of antigenic test results, it is impossible to relate observed increases in the OR for previous season vaccination with the viral strains and vaccine components; however, the largest OR for prior season vaccination was found in the 2012/2013 season, when the H3N2 strain was dominant. Having siblings itself seems to increase the chance of exposure to influenza virus by peer contact at home. In contrast, having siblings aged over 15 years significantly decreased the risk of influenza onset, although this might have been confounded by the age effect: that is, children with siblings aged over 15 years were older than those who did not have such older siblings. In fact, children aged 13–15 years accounted for more than 60% of children having siblings aged over 15 years, versus only around 15% of all subjects. Because older children had a lower incidence of influenza (data not shown), children with siblings aged over 15 years appears to have had a lower risk of influenza onset. Our study is the first to consider the risk of preceding onset of influenza among siblings. Although employee insurance numbers helped identify familial infection, it is impossible to exclude the possibility that children lived apart from their families, particularly for children of junior high school age.

Influenza vaccination significantly reduced the risks of several outcomes related to influenza complications, including pneumonia, underpinning the Japanese health authority's position statement on influenza vaccination [40].

There were several limitations inherent to the claims database used in this study. First, given the nature of observational studies, unmeasured confounders may have remained unadjusted. Previous studies have reported that observational studies using PS adjustment might yield larger effect sizes than randomized studies, and concluded that PS analysis could be relied on only if randomized studies were impossible, as in the present study including tens of thousands of children over four consecutive years [41,42].

Second, we used application for an influenza vaccination subsidy as the most reliable proxy for an actual vaccination records. A few vaccinating enrollees may have failed to apply for subsidization, and misclassification of truly vaccinated children as unvaccinated is unavoidable, leading to bias towards null. Further, the lack of data on the number of vaccinations which an individual received in the same season did not allow us to assess differences in vaccine effectiveness by the number, because subsidy records for influenza vaccination were submitted only once per season to most health plans and did not include the number of vaccinations.

Third, we excluded subjects who had an outcome within 13 days post-vaccination, potentially causing overestimation or underestimation of ORs. However, this exclusion was in accord with previous studies [9,25,26].

Fourth, the true reasons for hospitalization could not be specified, and misclassification of events requiring hospitalization was unavoidable. Since patients with influenza complications are sometimes not diagnosed with influenza, we used multiple definitions.

Finally, while familial or school infection may be responsible for the risk of secondary infection, such risk remains to be adjusted, because of the insufficiency and complexity of explanatory variables.

In conclusion, our analysis confirmed that influenza vaccination in a large population of children aged 1–15 years significantly prevented the onset of influenza, and may have been effective in reducing influenza complications such as pneumonia and influenza-related hospitalizations.

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Conflict of interest

Kimura. S is a representative director of Japan Medical Data Center Co., Ltd., which has provided data for this study. All other authors declare no potential conflicts of interest.

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.2018.03.082.

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