Tohoku J. Exp. Med., 2022, **258**, 69-78

Effectiveness of Influenza Vaccination among Children in Satellite Cities of a Metropolitan Area in Tokyo, Japan during the 2014/2015-2018/2019 Season

Ayako Matsuda,[1] Kei Asayama,[2,3,4] Taku Obara,[5] Naoto Yagi[6] and Takayoshi Ohkubo[2,3]

[1]Center for Public Health Informatics, National Institute of Public Health, Wako, Saitama, Japan
[2]Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
[3]Tohoku Institute for Management of Blood Pressure, Sendai, Miyagi, Japan
[4]Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium
[5]Tohoku Medical Megabank Organization, Tohoku University, Sendai, Miyagi, Japan
[6]Warabi-Toda Medical Association, Toda, Saitama, Japan

Influenza vaccination is recommended for children. In particular, those aged 6 months to 12 years were recommended two vaccinations in Japan, whereas the recommended year range for the twice vaccination is 6 months to 8 years by the World Health Organization (WHO). This study assessed the effectiveness of influenza vaccination and whether the twice vaccinations enhanced preventive effects against influenza infection among children living in two satellite cities of a metropolitan area in Tokyo, Japan. During the influenza season of 2014-2018, parents of all preschool, elementary school, and junior high school children participated in an annual survey. Adjusted odds ratios (AOR) with 95% confidence intervals (CIs) were calculated via multivariate logistic regression analysis to evaluate influenza vaccination effectiveness and trends in the number of vaccinations. Among the 108,362 children who received the research questionnaire, 76,753 (70.8%) responded. After excluding responses without basic information, 64,586 children were included in the analysis. Vaccination was more effective in preschool and lower grade elementary school children given the increase in the number of vaccinations (test for trend: $P < 0.001$). The AOR of influenza for pre, grade 1 elementary, and grade 2 schoolchildren who received two vaccinations was 0.63 (95% CI, 0.59-0.69), 0.75 (0.67-0.83), and 0.81 (0.71-0.92), respectively, when compared to those without vaccination. However, no trend in vaccinations and their effectiveness was observed in the third and higher-grade school children. Our findings support the recommendation by the WHO, and could help guide influenza vaccination policies for children in Japan.

Keywords: children; influenza; Japan; satellite cities of metropolitan areas; vaccination
Tohoku J. Exp. Med., 2022 September, **258** (1), 69-78.
doi: 10.1620/tjem.2022.J057

Introduction

Evidence has shown that influenza vaccines can reduce cases of influenza among healthy children below 16 years of age (Jefferson et al. 2018). The World Health Organization (WHO) recommends influenza vaccination, especially for children aged between 6 months and 5 years considering that internationally available vaccines for the control of seasonal influenza can prevent significant annual morbidity and mortality (WHO 2012). In Japan, some epidemiological studies have confirmed the effectiveness of influenza vaccination for schoolchildren (age 1-15 years) (Shibata et al. 2018; Kuniyoshi et al. 2020), as well as infants and toddlers (age 1-3 years) (Yokomichi et al. 2021). However, only a few studies have been available on the effectiveness of influenza vaccination for each school grade in Japan.

The WHO (2012) and Advisory Committee on

Received March 16, 2022; revised and accepted June 29, 2022; J-STAGE Advance online publication July 14, 2022
Correspondence: Ayako Matsuda, Ph.D., National Institute of Public Health, Center for Public Health Informatics, 2-3-6 Minami, Wako, Saitama 351-0197, Japan.
e-mail: matsuda.a.yk@niph.go.jp

Immunization Practices (ACIP) [ARCHIVED Influenza Immunization Publications (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html)] further recommend that children aged 6 months to 8 years who have not received seasonal influenza vaccine during the previous influenza season should receive two vaccinations per year. In Japan, two influenza vaccinations are recommended for children aged 6 months to 12 years, whereas one vaccination is recommended for children aged ≥ 13 years (MHLW, Ministry of Health, Labour and Welfare 2010). Although vaccination conditions should differ according to country, to the best of our knowledge, there is no robust evidence to support this arranged vaccination condition among children in Japan.

The current study assessed the effectiveness of influenza vaccination and whether the twice vaccinations enhanced the preventive effect against influenza infection among preschool (kindergarten or nursery school, 0-6 years old), elementary school (7-12 years old), and junior high school (13-15 years old) children in a metropolitan area of Tokyo, Japan over five consecutive seasons from 2014 to 2018.

Materials and Methods

Study area

The study area comprised two cities, Toda and Warabi, located north of Tokyo, Japan. The study region was 23.3 km^2 (Toda: 18.2 km^2 and Warabi: 5.1 km^2) and had a population of 215,182 (Toda: 140,899 and Warabi: 74,283), including a young population of 28,029 14-year-olds (Toda: 20,134 and Warabi: 7,895) in the 2020 census [Portal Site of Official Statistic of Japan (https://www.e-stat.go.jp/en)].

Informed consent

Ethical approval for this study was obtained from the Institutional Review Board of Todachuo General Hospital (Number 0436). Informed consent was obtained from a parent and/or legal guardian regarding the anonymized scientific evaluation of their reported data, and unidentifiable information was used in the present study. All methods were conducted in accordance with relevant guidelines and regulations and were approved by the Institutional Review Board of Todachuo General Hospital.

Study design

Throughout five consecutive seasons, from 2014 to 2018 (ending March 2019), an annual survey of parents of children attending preschool (kindergarten or nursery school), elementary school, and junior high school in the Toda and Warabi regions was conducted. We collected the questionnaire every June, with the responses pertaining to the preceding season. The class schoolteacher collected the questionnaire that the parents administered to their children.

The questionnaire obtained the following parent's responses regarding their children's school grade: (1) preschool: infant younger than 3 years, 0-3 years old; the first year, 4 years old; the second year, 5 years old; the third year, 6 years old. (2) Elementary school: grade 1, 7 years old; grade 2, 8 years old; grade 3, 9 years old; grade 4, 10 years old; grade 5, 11 years old; and grade 6, 12 years old. (3) Junior high school: grade 1, 13 years old; grade 2, 14 years old; grade 3, 15 years old. Given that Japan does not have a system for staying in school during the compulsory education period and that the school year starts in April, the ages of the children at the end of each season were always the same in each grade. We further obtained the following information: sex, siblings, underlying diseases, frequency of the hand washing (none, somewhat, and frequently), frequency of wearing a mask (none, somewhat, and frequently), vaccination status with date (none, vaccinated once during the season, and vaccinated twice during the season), and date of influenza infection if experienced during the season.

We excluded respondents who did not provide basic information regarding school grade, sex, siblings, underlying diseases, date of vaccination, and date of influenza (n = 4,445) and received influenza vaccination before September 30 or suffered from influenza after April 1 of each season (n = 7,722) (El Guerche-Séblain et al. 2019; Kuniyoshi et al. 2020).

A total of 76,753 responses were collected using the survey conducted via post mail on 108,362 parents of children attending preschool, elementary school, or junior high school during the 2014 to 2018 seasons (questionnaire collection rate, 70.8%). The present analysis, therefore, consisted of 64,586 respondents (Fig. 1).

Statistical analysis

After analyzing pooled data, results for five consecutive seasons were presented (2014, 2015, 2016, 2017, and 2018). Additionally, three seasons were extracted and analyzed, excluding the 2014 and 2016 seasons for sensitivity analysis given that the Infectious Agents Surveillance Report from the National Institute of Infectious Diseases reported that influenza strains of the main epidemic in the 2014 and 2016 differed from candidate influenza vaccine strains for the 2014 (Sugaya et al. 2018) and 2016 season (National Institute of Infectious Diseases 2015) in Japan.

The characteristics of the children were compared according to vaccination status. Categorical variables were compared using the chi-squared test.

To determine the effects of the influenza vaccination, logistic regression analysis was used to determine the crude odds ratio (OR) with 95% confidence intervals (CIs) for preschool, elementary school, and junior high school children. Additionally, explanatory variables were adjusted for independent variables [vaccination status, school grade, siblings, underlying diseases, frequency of the hand washing, frequency of the mask wearing, and season (1: 2014, 2: 2015, 3: 2016, 4: 2017, 5: 2018)] using multivariate logistic regression analysis. For trend evaluation in influenza infection with increasing vaccination status (test for trend), vac-

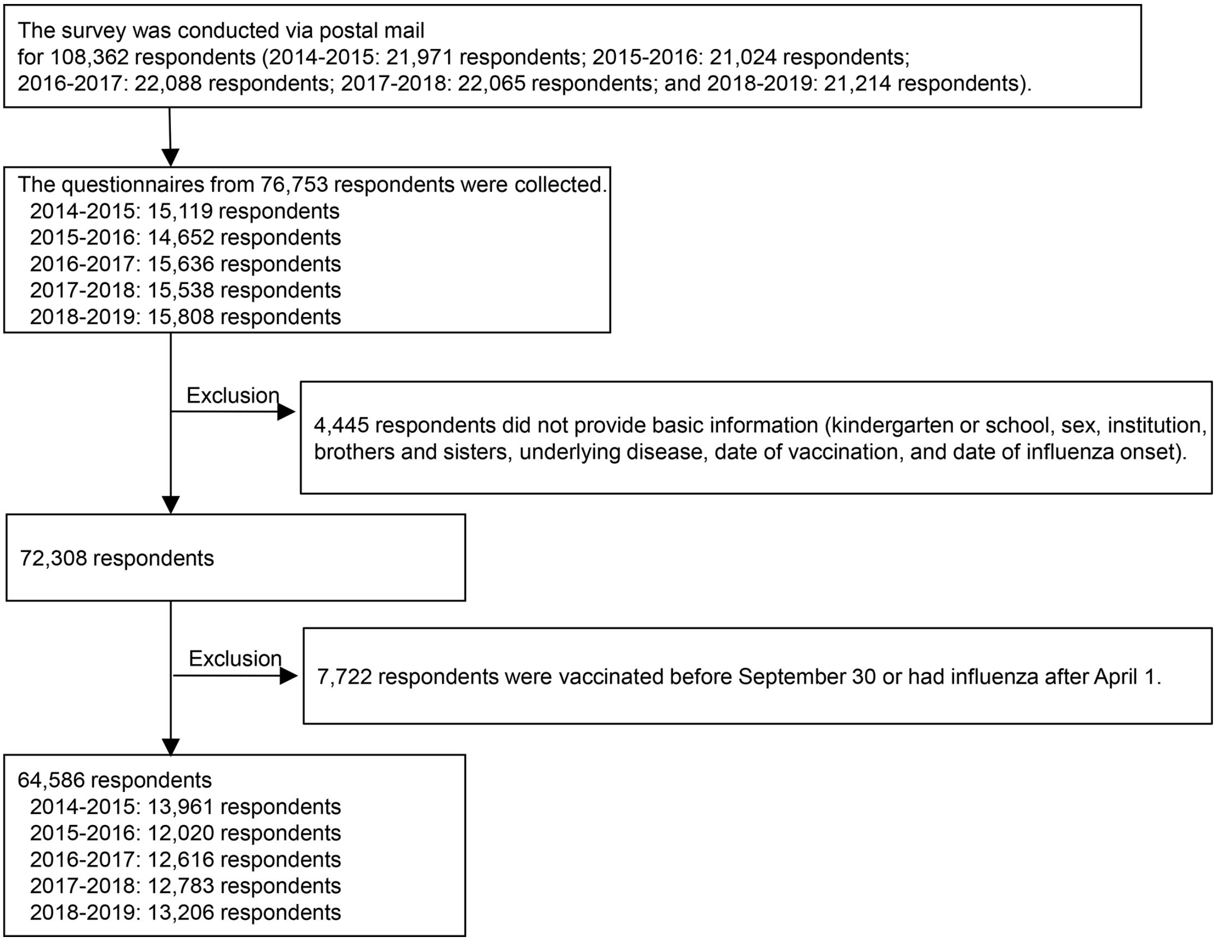

Fig. 1. Study population selection.

cination status was treated as a continuous variable in the multivariate logistic model.

The goodness of fit of the model ($P > 0.05$) was checked using the Hosmer–Lemeshow test. If the model was unfit ($P \leq 0.05$), the interaction between vaccination status and each factor was confirmed. Subgroup analysis was then performed using variables that showed significant interaction.

Statistical analyses were conducted using SAS (Statistical Analysis Software 9.4, SAS Institute Inc., Cary, NC, USA).

Results

The characteristics of the 64,586 children and those according to each school are displayed in Tables 1 and 2, respectively. With regard to influenza vaccination, 8.0% and 51.4% preschool children were given one and two influenza vaccinations, respectively. Moreover, 10.7% and 35.3% of the elementary school children received one and two shots, whereas 21.9% and 11.5% of those junior high school children received the same, respectively (Table 1). Among the included children, 50.4% were female, with most of the children having brothers and/or sisters and no underlying medical problems. Most of the children performed hand washing (Tables 1 and 2). Moreover, approximately 50% of the preschool children did not wear the mask, whereas most of the elementary or school junior high school children wore masks (Table 2). The number of children in each season according to each school is displayed in Table 3.

The association between vaccination status and influenza infection is shown in Table 3 (number of influenza infection and OR) and adjusted OR (AOR) is demonstrated in Fig. 2. With regard to the fit of the model, the multivariate logistic regression model showed a statistically good fit in the preschool (Hosmer–Lemeshow test, $P = 0.87$) and junior high school students (Hosmer–Lemeshow test, $P = 0.73$) and a poor fit in elementary school students (Hosmer–Lemeshow test, $P < 0.001$). Therefore, the multivariate logistic regression models were constructed according to each school grade considering the interaction between vaccination status and school grade as a subgroup analysis in elementary school children.

Among preschool and grade 1 and 2 elementary school children, a linear trend was observed between the AOR and number of vaccination (test for trend, $P < 0.001$). Compared to no vaccination, the AOR for one and two influenza vaccinations was 0.83 (95% CI, 0.72-0.96) and

Table 1. Characteristics of children.

Variables	Total (n = 64,586)	Number of vaccinations		
		No (n = 34,107)	Once (n = 7,845)	Twice (n = 22,634)
School category				
Preschool	17,260	7,009 (40.6)	1,385 (8.0)	8,866 (51.4)
≤ 3 y	6,211	2,780 (44.8)	384 (6.2)	3,047(49.0)
1st year (4 y)	4,103	1,546 (37.7)	326 (7.9)	2,231 (54.4)
2nd year (5 y)	4,161	1,597 (38.4)	376 (9.0)	2,188 (52.6)
3rd year (6 y)	2,785	1,086 (39.0)	299 (10.7)	1,400 (50.3)
Elementary school	34,966	18,869 (54.0)	3,750 (10.7)	12,347 (35.3)
Grade 1 (7 y)	8,186	3,772 (46.1)	853 (10.4)	3,561 (43.5)
Grade 2 (8 y)	5,803	3,038 (52.4)	617 (10.6)	2,148 (37.0)
Grade 3 (9 y)	5,807	3,153 (54.3)	626 (10.8)	2,028 (34.9)
Grade 4 (10 y)	6,311	3,506 (55.5)	675 (10.7)	2,130 (33.8)
Grade 5 (11 y)	5,344	3,188 (59.7)	577 (10.8)	1,579 (29.5)
Grade 6 (12 y)	3,515	2,212 (62.9)	402 (11.5)	901 (25.6)
Junior high school	12,360	8,229 (66.6)	2,710 (21.9)	1,421 (11.5)
Grade 1 (13 y)	5,768	3,690 (64.0)	933 (16.2)	1,145 (19.8)
Grade 2 (14 y)	4,301	2,897 (67.3)	1,186 (27.6)	218 (5.1)
Grade 3 (15 y)	2,291	1,642 (71.7)	591 (25.8)	58 (2.5)
Sex (male)	32,039	16,850 (49.4)	3,925 (50.0)	11,264 (49.8)
Siblings	50,756	27,550 (80.8)	6,348 (80.9)	16,858 (74.5)
Underlying medical problem	5,347	2,432 (7.1)	668 (8.5)	2,247 (9.9)
Hand washing				
No	3,645	2,779 (76.2)	247 (6.8)	619 (17.0)
Somewhat	15,166	9,756 (64.3)	1,714 (11.3)	3,696 (24.4)
Frequently	45,744	21,555 (47.1)	5,879 (12.9)	18,310 (40.0)
Mask wearing				
No	23,405	12,328 (52.7)	2,365 (10.1)	8,712 (37.2)
Somewhat	17,799	9,991 (56.1)	2,082 (11.7)	5,726 (32.2)
Frequently	23,282	11,724 (50.4)	3,387 (14.5)	8,171 (35.1)

The number (percentage for those according to the number of vaccination) of children who fulfilled each variable were shown. Data on hand washing and mask wearing were missing in 31 and 100 children, respectively. Categorical variables were compared using the chi-squared test. Significant differences ($P < 0.001$) were observed except sex ($P = 0.51$).

0.63 (95% CI, 0.59-0.69) for preschool children, 0.81 (95% CI, 0.68-0.96) and 0.75 (95% CI, 0.67-0.83) for grade 1 elementary school children, and 0.82 (95% CI, 0.67-1.00) and 0.81 (95% CI, 0.71-0.92) for grade 2 elementary school children.

For grade 3, 4, 5, and 6 elementary school and junior high school students, the linear trend test showed no significant association between AOR and number of vaccination (test for trend, $P = 0.27$, $P = 0.39$, $P = 0.085$, $P = 0.077$, and $P = 0.23$, respectively), and no enhanced effectiveness of the influenza vaccination was observed. Compared to no vaccination, AORs in the aforementioned elementary school grade children were 0.84 (95% CI, 0.68-1.03), 1.29 (95% CI, 1.05-1.57), 0.82 (95% CI, 0.65-1.03), and 0.95 (95% CI, 0.73-1.22) for one influenza vaccination and 0.93 (95% CI, 0.82-1.07), 1.05 (95% CI, 0.91-1.21), 0.88 (95% CI, 0.76-1.03), and 0.84 (95% CI, 0.69-1.02) for two influenza vaccinations, respectively. Moreover, the AOR for influenza was 0.97 (95% CI, 0.86-1.08) for one influenza vaccination and 0.91 (95% CI, 0.79-1.06) for two influenza vaccinations in junior high school students.

For sensitivity analysis, we analyzed for three seasons excluding the 2014 and 2016 seasons. Notably, the obtained results were similar to those of the analysis for the five consecutive seasons excluding those for grade 2 elementary school children, in whom no increasing trend in the number of vaccination (test for trend, $P = 0.093$) and effectiveness of two vaccinations (AOR, 0.88; 95% CI, 0.74-1.03) were observed over the three selected seasons. However, a similar trend was found in the results for the

Table 2. Characteristics of children according to school category.

Variables	Preschool			Elementary school			Junior high school		
	No (n = 7,009)	Once (n = 1,835)	Twice (n = 8,866)	No (n = 18,869)	Once (n = 3,750)	Twice (n = 12,347)	No (n = 8,229)	Once (n = 2,710)	Twice (n = 1,421)
Sex (male)	3,456 (49.3)	682 (49.2)	4,473 (50.5)	9,376 (49.7)	1,903 (50.8)	6,099 (49.4)	4,018 (48.8)	1,340 (49.5)	692 (48.7)
Siblings	4,946 (70.6)	989 (71.4)	6,085 (68.6)	15,670 (83.1)	3,101 (82.7)	9,621 (77.9)	6,934 (84.3)	2,258 (83.3)	1,152 (81.1)
Underlying medical problem	483 (6.9)	112 (8.1)	802 (9.1)	1,376 (7.3)	328 (8.8)	1,283 (10.4)	573 (7.0)	228 (8.4)	162 (11.4)
Hand washing									
No	656 (67.8)	39 (4.0)	273 (28.2)	1,247 (76.6)	98 (6.0)	284 (17.4)	876 (83.6)	110 (10.5)	62 (5.9)
Somewhat	1,728 (50.6)	276 (8.1)	1,414 (41.4)	5,263 (65.5)	793 (9.9)	1,973 (24.6)	2,765 (74.3)	645 (17.3)	309 (8.4)
Frequently	4,621 (35.9)	1,070 (8.3)	7,175 (55.8)	12,348 (48.8)	2,855 (11.3)	10,086 (39.9)	4,586 (60.5)	1,954 (25.7)	1,049 (13.8)
Mask wearing									
No	3,824 (41.2)	704 (7.6)	4,752 (51.2)	6,284 (57.4)	1,053 (9.6)	3,620 (33.0)	2,220 (70.1)	608 (19.2)	340 (10.7)
Somewhat	1,706 (43.2)	307 (7.8)	1,938 (49.1)	6,052 (57.0)	1,128 (10.6)	3,437 (32.4)	2,233 (69.1)	647 (20.0)	351 (10.9)
Frequently	1,461 (36.5)	374 (9.3)	2,166 (54.1)	6,499 (48.7)	1,564 (11.7)	5,275 (39.5)	3,764 (63.3)	1,449 (24.4)	730 (12.3)

The number (percentage) of children who fulfilled each variable according to the number of vaccinations (no, once, or twice) were shown. Data on hand washing and mask wearing were missing in 31 (8, 19, and 4 for preschool, elementary school, and junior high school) and 100 (28, 54, and 18 for preschool, elementary school, and junior high school) children, respectively.

Table 3. The number of children in each season according to the number of vaccinations (no, once, or twice).

Season	Total			School category: Preschool			Elementary school			Junior high school		
	No	Once	Twice	No	Once	Twice	No	Once	Twice	No	Once	Twice
2014	6,665 (47.7)	1,834 (13.1)	5,462 (39.1)	1,346 (35.3)	335 (8.8)	2,128 (55.9)	3,515 (48.4)	802 (11.0)	2,952 (40.6)	1,804 (62.6)	697 (24.2)	382 (13.2)
2015	6,316 (52.6)	1,323 (11.0)	4,381 (36.5)	1,398 (42.1)	210 (6.3)	1,713 (51.6)	3,446 (53.5)	615 (9.5)	2,384 (37.0)	1,472 (65.3)	498 (22.1)	284 (12.6)
2016	6,719 (53.3)	1,438 (11.4)	4,459 (35.3)	1,367 (40.8)	227 (6.8)	1,754 (52.4)	3,688 (54.3)	689 (10.1)	2,416 (35.6)	1,664 (67.2)	522 (21.1)	289 (11.7)
2017	7,272 (56.9)	1,577 (12.3)	3,934 (30.8)	1,536 (44.2)	321 (9.3)	1,615 (46.5)	3,968 (58.3)	758 (11.1)	2,081 (30.6)	1,768 (70.6)	498 (19.9)	238 (9.5)
2018	7,135 (54.0)	1,673 (12.7)	4,398 (33.3)	1,362 (41.2)	292 (8.8)	1,656 (50.0)	4,252 (55.6)	886 (11.6)	2,514 (32.9)	1,521 (67.8)	495 (22.1)	228 (10.1)

The number (percentage) of children according to the consecutive season and the number of vaccinations (no, once, or twice) among all children and each school category were shown. Preschool consists of kindergarten and nursery schools, and details of the school categories are described in the Study design section.

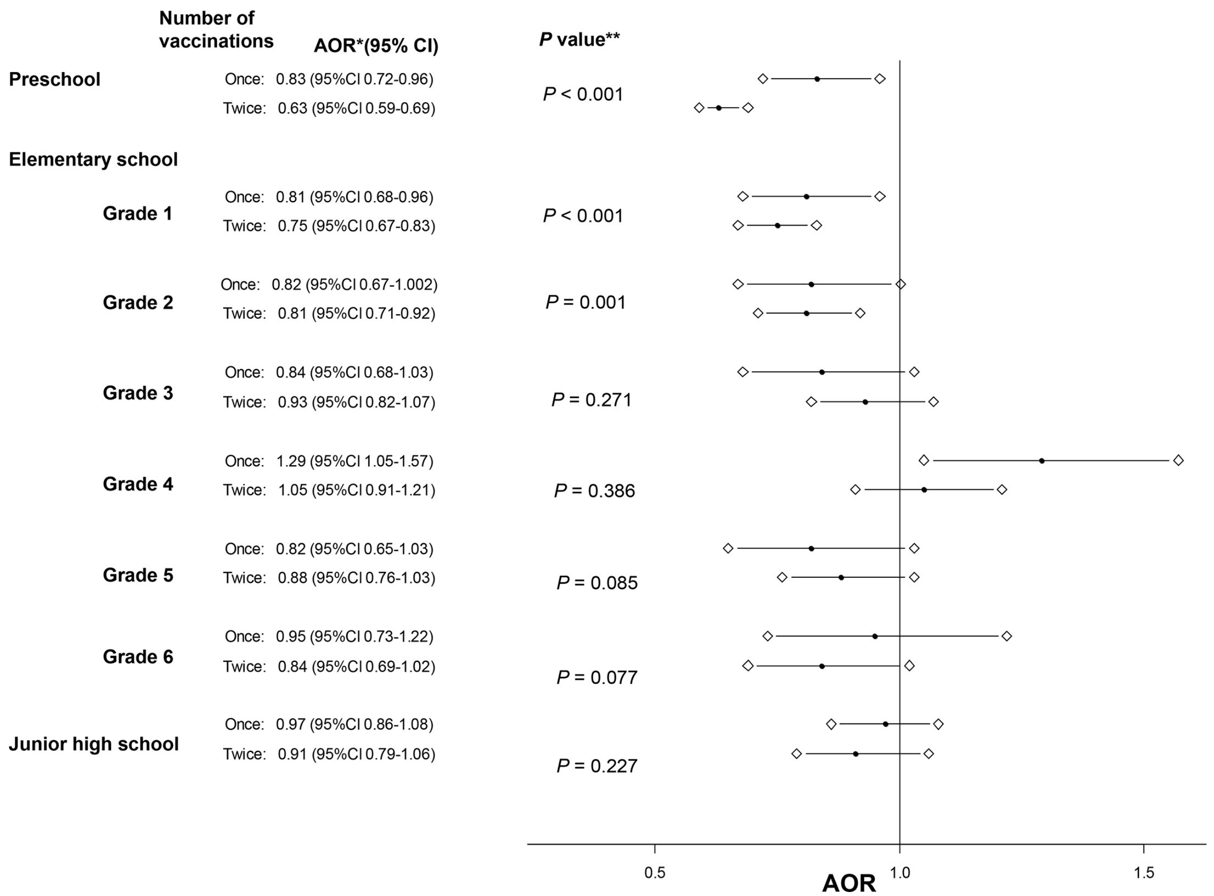

Fig. 2. Adjusted odds ratios for influenza infection in each school category.

The goodness of fit of the model was determined using the Hosmer–Lemeshow test in preschool ($P = 0.87$) and junior high school ($P = 0.73$) children. For elementary school children, the model demonstrates a poor fit (Hosmer–Lemeshow test, $P < 0.001$). The logistic regression model was created according to each grade because of the significant interaction between vaccine and grade ($P = 0.015$).

*Adjusted odds ratios (AORs) with 95% confidence interval (CI) were adjusted for school grade, sex, siblings, underlying diseases, frequency of the hand washing, frequency of the mask wearing, and seasons.

***P* values denote the trend evaluation of influenza infection with increasing vaccination status (test for trend).

five consecutive seasons (Fig. 3). Finally, AORs of the influenza infection according to the vaccination status when children with a single influenza vaccination were set as references are demonstrated in Fig. 4. Grossly, point estimates of the AOR were between those with no and two influenza vaccinations; however, statistically significant decreases in AOR among children with two vaccinations were not observed except for preschool children (AOR, 0.76; 95% CI, 0.66-0.88).

Discussion

After adjusting for confounding factors, the results of the current observational study demonstrated that the twice vaccinations enhanced preventive effects against influenza infection among preschool and lower grade (grade 1 and 2) elementary school children (Table 4 and Fig. 2) by the trend test. However, no trend in the number of vaccinations and its effectiveness was observed in the third and higher-grade elementary school and junior high school children (Table 4 and Fig. 2). Although the direct comparison provided no significant differences between one and two vaccinations among children of the first and higher-grade elementary school (Fig. 4), the recommendation by WHO and ACIP that children aged 6 months to 8 years should receive two doses would be reasonable based on the present study.

The current study found the trend of vaccinations for ≤ 2 grade of elementary school, and statistically significant decrease in AOR was observed for preschool children. Katayose et al. (2011) reported that two vaccination doses of trivalent inactivated influenza vaccine were effective at preventing influenza for children aged 6 months to 6 years. However, Lin et al. (2016) described that two-dose compliance remained low in children aged < 9 years, especially in older children (2-8 years) from the 2010-11 through the 2014-15 influenza vaccination season, which impacted full influenza vaccination coverage. Our findings can be considered as supportive evidence for parents and children about the recommendation of two influenza vaccinations among children ≤ 8 years old, though cannot be pushed too far.

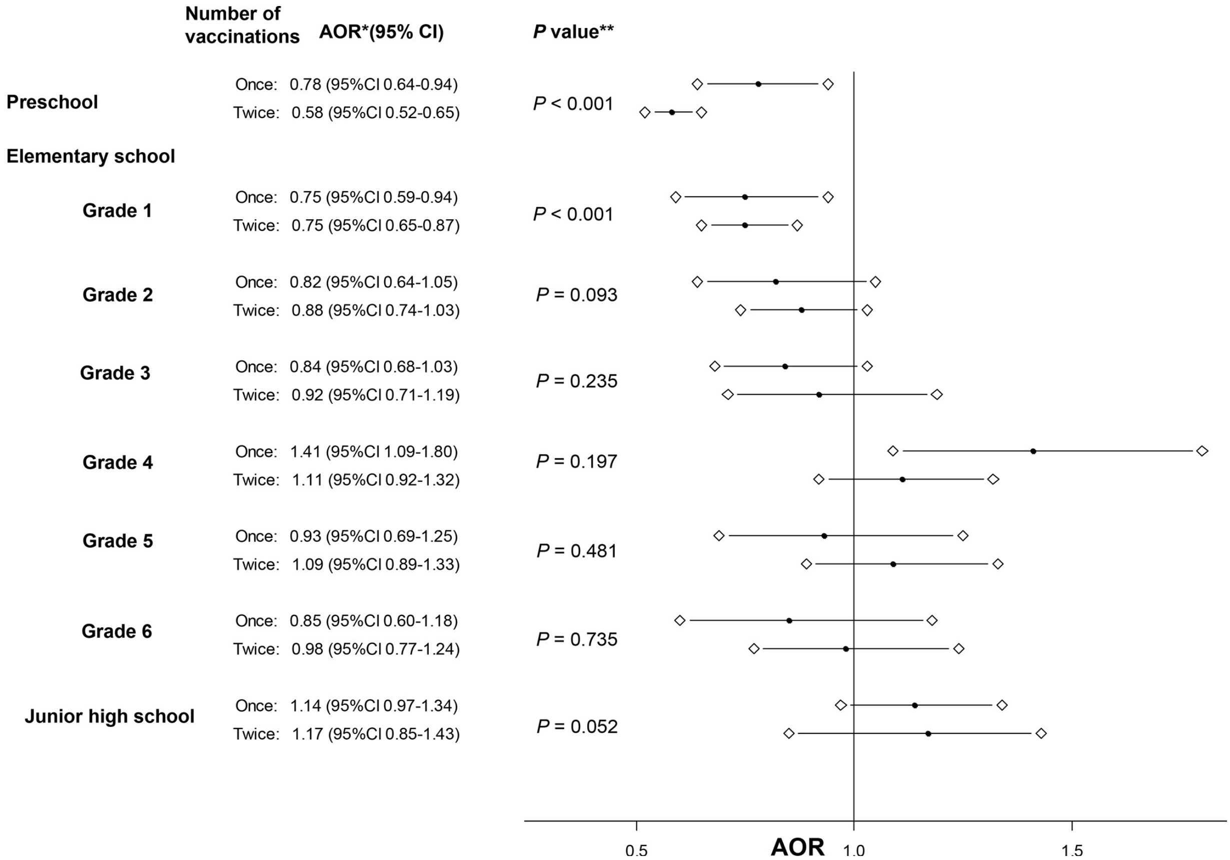

Fig. 3. Adjusted odds ratios for influenza infection in each school category (2015, 2017, and 2018 seasons).
The goodness of fit of the model was determined using the Hosmer–Lemeshow test in preschool ($P = 0.67$) and junior high school ($P = 0.10$) children. For elementary school children, the model showed a poor fit (Hosmer–Lemeshow test, $P < 0.001$). The logistic regression model was created according to each grade because of the significant interaction between vaccine and grade ($P = 0.006$).
*Adjusted odds ratios (AORs) with 95% confidence interval (CI) were adjusted for school grade, sex, sibling, underlying disease, frequency of the hand washing, frequency of mask wearing, and seasons.
***P* values denote the trend evaluation of influenza infection with increasing vaccination status (test for trend).

The current findings on the effectiveness of influenza vaccinations for preschool and lower grade elementary school children are similar to that of the summary of the 2013 to 2017 influenza season report from the MHLW-funded study group for children of preschool in Japan (National Institute of Infectious Diseases 2019). In contrast, a cohort study for nursery school children in China showed that influenza vaccine protection did not significantly differ between vaccinated and unvaccinated children but that influenza vaccination significantly reduced the incidence of developing influenza-like illness (Wang et al. 2018). Moreover, a previous study conducted according to test-negative case-control design showed that the AOR (none vs. twice) was 0.68 (95% CI, 0.61-0.75) for elementary school children aged 6-12 years during the 2013-2017 season (Shinjoh et al. 2019). In addition, an epidemiological study based on a self-reported questionnaire indicated that the effectiveness of vaccination was better in lower (grade 1-3) grade groups than higher grade (grade 4-6) groups in 2014 (Uchida et al. 2017). In line with this, our results showed that the vaccine was effective only for grade 1 and 2 elementary school children. For junior high school children, a previous study (National Institute of Infectious Diseases 2017) utilizing the test-negative case-control design reported low or nonsignificant influenza vaccine effectiveness for 13- to 15-year-old children during the 2015 season in Japan, which was similar to our results. The study design and setting of study population might account for the differences in the effectiveness of influenza vaccination. Another reason for these differences might be our analysis of five consecutive seasons (2014-2018) considering that influenza strains of the main epidemic in the 2014 and 2016 differed from that of the candidate influenza vaccine strains in Japan (National Institute of Infectious Diseases 2015; Sugaya et al. 2018). However, our sensitivity analysis for three seasons excluding the 2014 and 2016 seasons showed a trend similar to that observed for the five consecutive seasons (Fig. 3). A previous study described that among children under the age of 16 years, influenza vaccines likely reduced influenza infection rates and could potentially reduce influenza-like illness (ILI) over a single influenza season. Apart from the variable certainty of the

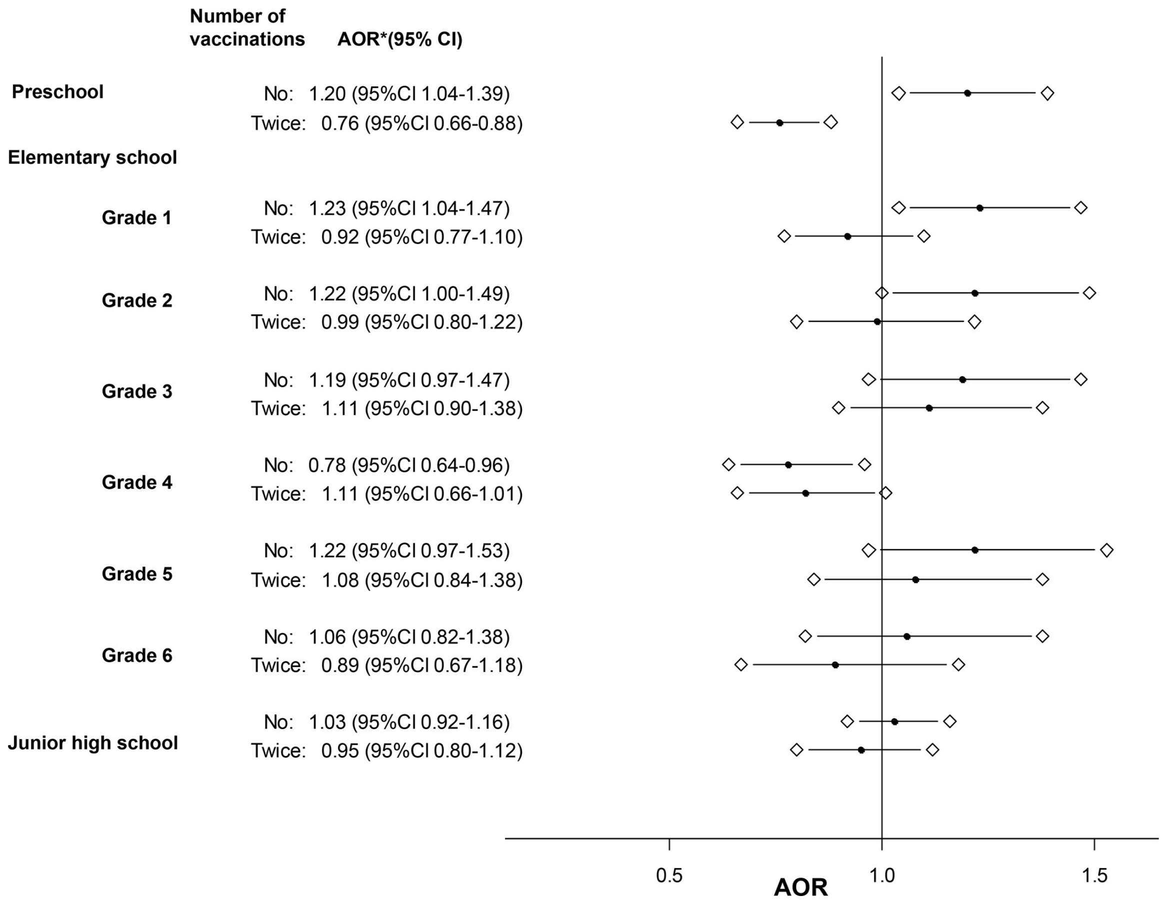

Fig. 4. Adjusted odds ratios for influenza infection in each school category when children with a single vaccination are set as the reference.
*Adjusted odds ratios (AORs) with 95% confidence interval (CI) were adjusted for school grade, sex, sibling, underlying disease, frequency of the hand washing, frequency of mask wearing, and seasons.

evidence, decision-makers should be aware of the wide variation in absolute effects for protection against influenza and ILI, in the context of local or national policy making (Jefferson et al. 2018).

With regard to public health implications, Lutz et al. (2020) suggested that overall efforts should be mostly directed toward improving awareness regarding the recommendations, safety, and effectiveness of influenza vaccination among younger adults. Similar efforts might be needed for children. In light of the WHO position paper, countries should consider reviewing or developing their seasonal influenza vaccination policies or recommendations to reduce morbidity and mortality associated with annual epidemics and as part of ongoing efforts for pandemic preparedness (Members of the Western Pacific Region Global Influenza Surveillance Response System et al. 2013). A global review of national influenza immunization policies suggested that knowledge of the factors influencing the development of influenza immunization policies would be of considerable significance for improving efforts aimed at increasing influenza vaccine use globally (Ortiz et al. 2016). Additionally, early knowledge regarding influenza vaccine effectiveness might contribute to the adoption of other countermeasures in scenarios wherein vaccine protective effects against seasonal epidemics are suboptimal (Jiménez-Jorge et al. 2015). The most appropriate vaccination policy should be established based on obtained data (Shinjoh et al. 2015). The results presented herein can be used as the reference to guide influenza vaccination policies for children in Japan.

Our study has several limitations worth noting. First, it was difficult to definitively conclude the effectiveness of influenza vaccination considering that this study was not a randomized controlled trial (RCT). However, RCTs do not provide generalizable results given the limited population. Our results showed high generalizability considering that the population was collected after extensive investigation and the obtained results were adjusted for main factors. Second, our surveillance was performed for only a few months after the corresponding season. Therefore, recall bias might have affected the results due to the method in which vaccination information and influenza cases had been determined, although exclusion criteria had been established to obtain accurate dates. Third, we used a questionnaire that did not request detailed medical information; therefore, the answers might not be accurate. However, we

Table 4. The number and crude odds ratio of influenza infection among children in each school category (2014-2018).

School category	No	Once		Twice	
	Influenza infection/ Population, n	Influenza infection/ Population, n	Odds ratio (95% CI)	Influenza infection/ Population, n	Odds ratio (95% CI)
Preschool	1,578/7,009	276/1,385	0.86 (0.74-0.99)	1,408/8,866	0.65 (0.60-0.70)
Elementary school					
Grade 1	1,068/3,772	209/853	0.82 (0.69-0.97)	838/3,561	0.78 (0.70-0.87)
Grade 2	872/3,038	155/617	0.83 (0.68-1.02)	540/2,148	0.83 (0.74-0.95)
Grade 3	786/3,153	138/626	0.85 (0.69-1.05)	489/2,028	0.96 (0.84-1.09)
Grade 4	649/3,506	152/675	1.28 (1.05-1.56)	395/2,130	1.00 (0.87-1.15)
Grade 5	689/3,188	107/577	0.83 (0.66-1.04)	313/1,579	0.90 (0.77-1.04)
Grade 6	508/2,212	90/402	0.97 (0.75-1.25)	188/901	0.88 (0.73-1.07)
Junior high school	1,553/8,229	493/2,710	0.96 (0.85-1.07)	260/1,421	0.96 (0.83-1.11)

The reference group was set to children with no vaccination.
CI, confidence interval.

emphasize that the influenza antigen rapid test is widely available in Japan, and, in most cases, patients with a fever who visit an outpatient clinic are routinely assessed using the test kit to detect the presence and type of influenza. We are thus confident regarding the diagnosis of influenza, despite having been based on the questionnaire. Fourth, despite our best efforts to adjust for independent variables using multivariate logistic regression analysis, it is likely that some inherent characteristics of the children, including recruitment heterogeneity, could not be accounted for due to pooling of the data across seasons. Furthermore, we could not exclude duplicated participants across seasons, given that the information did not enable the identification of a specific individual for each season. This is a significant limitation of this type of panel data survey, although similar studies have assessed the effect of influenza vaccination based on pooled data without personal identifiers of consecutive seasons (Sofia Arriola et al. 2019). Finally, our survey was completed in March 2019 and was not affected by the COVID-19 pandemic and related confounding circumstances. Whether the current estimates regarding the influenza epidemic will be applicable after the COVID-19 pandemic has subsided remains unknown. This issue remains true for the epidemiology of most infectious diseases. Additionally, although the restriction of activities before the COVID-19 pandemic might have affected our results, our analysis had been adjusted for the frequency of hand washing and mask wearing.

In conclusion, our study on the 2014-2018 influenza seasons for preschool, elementary school, and junior high school children in satellite cities of a metropolitan area of Tokyo in Japan demonstrated the effectiveness of the influenza vaccination, with the trend of vaccinations among preschool and lower grade elementary school children. These findings support the recommendation by WHO and ACIP that children aged 6 months to 8 years old, and could help guide influenza vaccination policies for children in Japan.

Acknowledgments

This work was supported by a Grant-in-Aid for Health Research from Warabi-Toda Medical Association, ACRO Incubation Grants of Teikyo University, from the Ministry of Education, Culture, Sports, Science and Technology, Japan, the Japan Foundation for Pediatric Research (13-009), and a Grant-in-Aid for Early-Career Scientists (15K20862) and Scientific Research (21H04984, 22H03358) from the Ministry of Education. We thank the anonymous school staff in Warabi-Toda area for their support in this study.

Author Contributions

A.M., K.A., and T.O. participated in the study design. A.M. performed statistical analysis and drafted the manuscript. All authors helped collect data and draft the manuscript. K.A. and T.O. advised the statistical analysis. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

El Guerche-Séblain, C., Caini, S., Paget, J., Vanhems, P. & Schellevis, F. (2019) Epidemiology and timing of seasonal influenza epidemics in the Asia-Pacific region, 2010-2017: implications for influenza vaccination programs. *BMC Public Health*, **19**, 331.

Jefferson, T., Rivetti, A., Di Pietrantonj, C. & Demicheli, V. (2018) Vaccines for preventing influenza in healthy children. *Cochrane Database Syst. Rev.*, **2**, CD004879.

Jiménez-Jorge, S., Pozo, F. & Larrauri, A.; cycEVA Study Team (2015) Interim influenza vaccine effectiveness: a good proxy for final estimates in Spain in the seasons 2010-2014. *Vaccine*, **33**, 3276-3280.

Katayose, M., Hosoya, M., Haneda, T., Yamaguchi, H., Kawasaki, Y., Sato, M. & Wright, P.F. (2011) The effectiveness of trivalent inactivated influenza vaccine in children over six consecutive influenza seasons. *Vaccine*, **29**, 1844-1849.

Kuniyoshi, Y., Obara, T., Ishikuro, M., Matsubara, H., Nagai, M., Murakami, K., Noda, A., Kikuya, M., Kure, S. & Kuriyama, S. (2020) Effectiveness of seasonal inactivated influenza vaccination in Japanese schoolchildren: an epidemiologic study at the community level. *Hum. Vaccin. Immunother.*, **16**, 295-300.

Lin, X., Fiebelkorn, A.P. & Pabst, L.J. (2016) Trends in compliance with two-dose influenza vaccine recommendations in children aged 6 months through 8 years, 2010-2015. *Vaccine*, **34**, 5623-5628.

Lutz, C.S., Fink, R.V., Cloud, A.J., Stevenson, J., Kim, D. & Fiebelkorn, A.P. (2020) Factors associated with perceptions of influenza vaccine safety and effectiveness among adults, United States, 2017-2018. *Vaccine*, **38**, 1393-1401.

Members of the Western Pacific Region Global Influenza Surveillance Response System; Dwyer, D., Barr, I., Hurt, A., Kelso, A., Reading, P., Sullivan, S., Buchy, P., Yu, H., Zheng, J., Shu, Y., Wang, D., Lam, Aguon, A., Oliva, R.Q., et al. (2013) Seasonal influenza vaccine policies, recommendations and use in the World Health Organization's Western Pacific Region. *Western Pac. Surveill. Response J.*, **4**, 51-59.

Ministry of Health, Labour and Welfare (MHLW) (2010) Annual report on health, labour and welfare.
https://www.mhlw.go.jp/wp/hakusyo/kousei/10/dl/02-01-05.pdf
[*Accessed*: October 1, 2021] (Japanese).

National Institute of Infectious Diseases (2015) Influenza 2014/15 season, Japan. IASR, **36**, 11.
https://www.niid.go.jp/niid/images/idsc/iasr/36/429e.pdf
[*Accessed:* October 1, 2021].

National Institute of Infectious Diseases (2017) Influenza 2016/17 season, Japan. IASR Vol. 38.
https://www.niid.go.jp/niid/images/idsc/iasr/38/453e.pdf
[*Accessed:* October 1, 2021].

National Institute of Infectious Diseases (2019) Influenza 2018/19 season, Japan. IASR Vol. 40.
https://www.niid.go.jp/niid/images/idsc/iasr/40/477e.pdf
[*Accessed:* October 1, 2021].

Ortiz, J.R., Perut, M., Dumolard, L., Wijesinghe, P.R., Jorgensen, P., Ropero, A.M., Danovaro-Holliday, M.C., Heffelfinger, J.D., Tevi-Benissan, C., Teleb, N.A., Lambach, P. & Hombach, J. (2016) A global review of national influenza immunization policies: analysis of the 2014 WHO/UNICEF Joint Reporting Form on immunization. *Vaccine*, **34**, 5400-5405.

Shibata, N., Kimura, S., Hoshino, T., Takeuchi, M. & Urushihara, H. (2018) Effectiveness of influenza vaccination for children in Japan: four-year observational study using a large-scale claims database. *Vaccine*, **36**, 2809-2815.

Shinjoh, M., Sugaya, N., Furuichi, M., Araki, E., Maeda, N., Isshiki, K., Ohnishi, T., Nakamura, S., Yamada, G., Narabayashi, A., Nishida, M., Taguchi, N., Nakata, Y., Yoshida, M., Tsunematsu, K., et al. (2019) Effectiveness of inactivated influenza vaccine in children by vaccine dose, 2013-18. *Vaccine*, **37**, 4047-4054.

Shinjoh, M., Sugaya, N., Yamaguchi, Y., Tomidokoro, Y., Sekiguchi, S., Mitamura, K., Fujino, M., Shiro, H., Komiyama, O., Taguchi, N., Nakata, Y., Yoshida, N., Narabayashi, A., Myokai, M., Sato, M., et al. (2015) Effectiveness of trivalent inactivated influenza vaccine in children estimated by a test-negative case-control design study based on influenza rapid diagnostic test results. *PLoS One*, **10**, e0136539.

Sofia Arriola, C., El Omeiri, N., Azziz-Baumgartner, E., Thompson, M.G., Sotomayor-Proschle, V., Fasce, R.A., Von Horoch, M., Enrique Carrizo Olalla, J., Aparecida Ferreira de Almeida, W., Palacios, J., Palekar, R., Couto, P., Descalzo, M. & Maria Ropero-Alvarez, A.; REVELAC-I network participants (2019) Influenza vaccine effectiveness against hospitalizations in children and older adults-data from South America, 2013-2017. A test negative design. *Vaccine X*, **3**, 100047.

Sugaya, N., Shinjoh, M., Nakata, Y., Tsunematsu, K., Yamaguchi, Y., Komiyama, O., Takahashi, H., Mitamura, K., Narabayashi, A. & Takahashi, T.; Keio Pediatric Influenza Research Group (2018) Three-season effectiveness of inactivated influenza vaccine in preventing influenza illness and hospitalization in children in Japan, 2013-2016. *Vaccine*, **36**, 1063-1071.

Uchida, M., Kaneko, M., Hidaka, Y., Yamamoto, H., Honda, T., Takeuchi, S., Saito, M. & Kawa, S. (2017) Effectiveness of vaccination and wearing masks on seasonal influenza in Matsumoto City, Japan, in the 2014/2015 season: an observational study among all elementary schoolchildren. *Prev. Med. Rep.*, **5**, 86-91.

Wang, Y., Chen, L., Yu, J., Pang, Y., Zhang, J., Zhang, T. & Zhao, G. (2018) The effectiveness of influenza vaccination among nursery school children in China during the 2016/17 influenza season. *Vaccine*, **36**, 2456-2461.

World Health Organization (WHO) (2012) Vaccines against influenza WHO position paper - November 2012. *Wkly. Epidemiol. Rec.*, **87**, 461-476.

Yokomichi, H., Kojima, R., Horiuchi, S., Ooka, T., Akiyama, Y., Miyake, K., Mochizuki, M., Otawa, S., Shinohara, R. & Yamagata, Z.; Japan Environment and Children's Study Group (2021) Effectiveness of influenza vaccination in infants and toddlers with and without prior infection history: The Japan Environment and Children's Study. *Vaccine*, **39**, 1800-1804.