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Effectiveness of the 2019-2020 Influenza Vaccine and the Effect of Prior Influenza Infection and Vaccination in Children during the First Influenza Season Overlapping with the COVID-19 Epidemic

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Background: Behavioral changes among Japanese, along with the coronavirus disease 2019 (COVID-19) epidemic, may affect the seasonal influenza epidemic in Japan and change influenza vaccine effectiveness (VE).

Methods: This single-center, test-negative case-control (TNCC) study estimated influenza VE in children for the first influenza season (2019/20) to overlap the COVID-19 epidemic in. Effects of prior influenza infection and vaccination in children were assessed for the 2019-2020 season.

Results: Among 386 children, adjusted VE was significant for influenza A/H1N1 (45.5%; 95% confidence interval [CI]: 2.0-69.7) and influenza B (66.7%; 95% CI: 35.9-82.7). Among patients aged 0-6 years, adjusted VE was significant for influenza A (total: A/H1N1+A/H3N2) (65.0%; 95% CI: 22.2-84.3), influenza A/H1N1 (64.8%; 95% CI: 16.9-85.1) and influenza B (87.4%; 95% CI: 50.5-96.8). No VE was observed in patients aged 7-15 years. Administration of two vaccine doses tended to decrease incidences of influenza A (total) and influenza A/H1N1 in patients aged 0-6 years. The adjusted odds ratios (ORs) of influenza B infection in patients, who had influenza during the previous season, were significantly lower among all participants (0.29; 95% CI: 0.11-0.78) and patients aged 7-15 years (0.34; 95% CI: 0.12-0.94). The adjusted ORs of influenza infections were not significant in patients vaccinated during the previous season.

Conclusions: TNCC-based estimates of influenza VE were consistent despite the overlapping COVID-19 epidemic. (J Nippon Med Sch 2021; 88: 524–532)

Key words: influenza vaccine effectiveness, single-center study, test-negative case-control study

Introduction

The test-negative case-control (TNCC) study design is a validated approach for evaluating vaccine effectiveness (VE) against influenza[1–3]. Multiple studies published in Japan used a TNCC design to estimate the efficacy of quadrivalent influenza vaccines[4–8]. During the 2019-2020 influenza season, the outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in Wuhan, China, in December 2019[9]. In Japan, the first case was reported on January 16, 2020, followed by the gradual spread of the COVID-19 epidemic throughout the country[10]. The Japanese government recommended that people should exercise self-restraint as a social distancing measure, which led to a clear decline in trips outside the home and person-to-person contact. Moreover, people were regularly reminded to wear a mask and wash their hands frequently.

The behavioral changes among Japanese individuals, along with the COVID-19 epidemic, may affect the seasonal influenza epidemic in Japan and change influenza vaccine effectiveness (VE). Furthermore, although the effect of prior infection and vaccinations on seasonal influenza VE has been examined recently[11–13], it has not been assessed in the context of the specific circumstances of the 2019-2020 influenza season. Here, I designed a TNCC study to estimate the effectiveness of the quadrivalent influenza vaccine formulation in children during the 2019-

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https://doi.org/10.1272/jnms.JNMS.2022_89-102
Journal Website (https://www.nms.ac.jp/sh/jnms/)

2020 season and examine the potential effect of prior infection and vaccination on the influenza VE in the current season.

Materials and Methods

Patients and Data Collection

The participants were children who underwent rapid influenza diagnostic testing (RIDT) in the Ando Clinic (Narashino City, Chiba, Japan) because of suspected influenza infection during the 2019-2020 season. The children, their parents, or both were informed of the study concept. Patients who fulfilled the criteria of influenza-like illness (ILI) were included. The ILI diagnosis was based on the definition issued by the World Health Organization (WHO): "Patients in whom influenza infection was suspected, evidenced by symptoms including acute onset, nasal discharge, sore throat, cough, arthralgia, and myalgia"[14]. The interval from the time of administration of quadrivalent inactivated influenza vaccination to diagnosis of ILI was ≥14 days and <5 months[15]. Patients were excluded if they had already experienced the same type of influenza infection during the 2019-2020 season or had already received a neuraminidase inhibitor because of a negative RIDT result.

Patient age was classified as 0-6 and 7-15 years. The following clinical information was collected: sex, age, period of influenza infection onset, vaccination status for the quadrivalent influenza vaccine, comorbidities, influenza infection status during the previous season, and vaccination status from the previous season at presentation. Comorbidities were defined as conditions that could affect immune status, namely, chronic pulmonary, cardiovascular (excluding hypertension), renal, hepatic, hematologic, and neurological disorders; diabetes; autoimmune disorders; congenital anomalies; and cancer.

Influenza Diagnosis

Nasopharyngeal swabs were obtained and tested using ImunoAce Flu and Linjudge FluA/pdm (TAUNS Laboratories, Inc., Shizuoka, Japan). As previously reported, influenza A (H1N1) pdm09 was diagnosed based on both ImunoAce Flu, which detected positivity for influenza A, and Linjudge FluA/pdm, which also detected positivity[8]. Influenza A (H3N2) was diagnosed when the ImunoAce Flu test was positive for influenza A and the Linjudge FluA/pdm test was negative[8].

Vaccine

The quadrivalent influenza vaccine contained influenza A/Brisbane/02/2018(IVR-190) (H1N1) pdm09 strain, A/Kansas/14/2017 (X-327) (H3N2) strain, B/Phuket/3073/2013 strain (Yamagata lineage), and influenza B/Maryland/15/2016 (NYMC BX-69A) strain (Victoria lineage). At 2-4-week intervals, two 0.25 mL and 0.5 mL doses of vaccine were administered to children aged 6 months to 2 years and 3-12 years, respectively. A single 0.5 mL vaccine dose was generally administered to children aged ≥13 years.

VE and TNCC Study

As previously reported, VE was estimated using a TNCC study design. VE was defined as {1-odds ratio (OR)} × 100, and the OR was calculated as (number of influenza-positive among vaccinated patients × influenza-negative among unvaccinated patients)/(number of influenza-negative among vaccinated patients × influenza-positive among unvaccinated patients)[4–8]. ORs were assessed using the Wald test. First, crude VE was calculated and adjusted for sex, age group (0-6 *vs.* 7-15 years), period of influenza infection onset (December 2019-January 2020 *vs.* February-March 2020), and comorbidity. When the VE assessment was based on the number of vaccine doses in children, a multivariate logistic regression analysis was performed using age, body temperature, time from onset, and number of vaccine doses as covariables[7,8].

Effect of Influenza Infection and Vaccination Status for the Previous Season

Using data from a previous report[15], I compared the OR of influenza infection of the current season for patients, irrespective of whether they had an influenza infection or influenza vaccination during the previous season. Patients with unknown influenza infection status or vaccination status were excluded. In addition, patients younger than 1 year (*i.e.*, patients not born in the previous year) were excluded. Crude ORs were calculated according to the TNCC study design. Thereafter, ORs were adjusted for sex, age group (0-6 *vs.* 7-15 years), period of influenza infection onset (December 2019-January 2020 *vs.* February-March 2020), and influenza vaccination in all patients during the current season. In each age group, ORs were adjusted for sex, period of influenza infection onset (December 2019-January 2020 *vs.* February-March 2020), and influenza vaccination during the current season.

Statistical Analysis

The Mann-Whitney U test was used to compare continuous variables (*i.e.*, age, body temperature, and time from onset) between RIDT-positive (case) and RIDT-negative (control) subjects. Fischer's exact tests were used to compare nominal variables (*i.e.*, sex, age group, onset

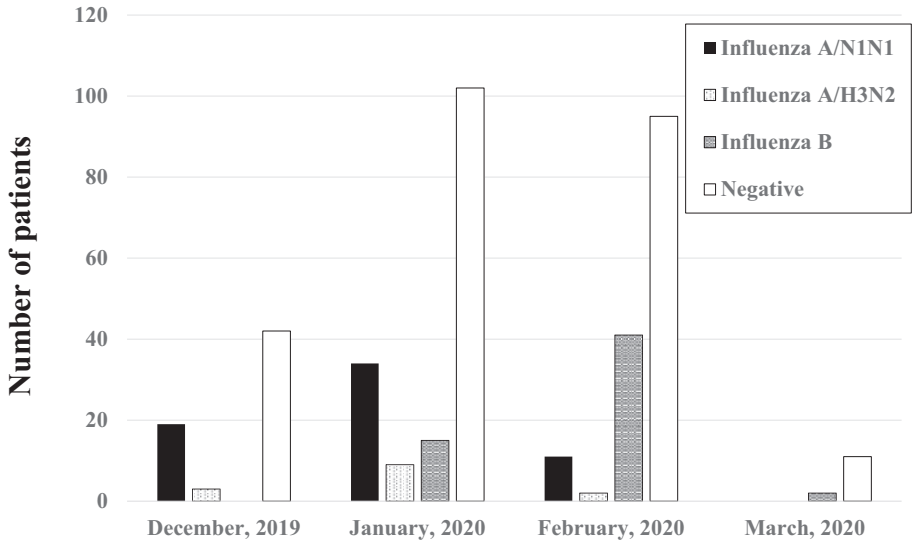

Fig. 1 Proportion of infections caused by influenza A/H1N1, influenza A/H3N2, and influenza B among children during the 2019–2020 influenza season.

period, and comorbidities). VE was adjusted for sex, age group, period of influenza infection onset, and presence/absence of comorbidities[4-8]. A two-sided *P* value of <0.05 was considered significant. Statistical analyses were performed using JMP 15.2 (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA).

Ethics

This study was conducted in accordance with The Code of Ethics of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patients, their parents, or both. Participants were recruited prospectively. The study design was approved by the Joint Institutional Review Board (approval number: 14000050.20191220-4830).

Results

Enrollment and Trend in Influenza Infection during the 2019-2020 Season

From December 21, 2019 to March 31, 2020, 386 patients were enrolled. In total, 386 patients and 386 episodes were analyzed (no patient had an episode of influenza A and B). The trend in influenza A infection started in December 2019 and peaked in January 2020 (**Fig. 1**). The influenza A epidemic then declined and disappeared by March 2020. Among all influenza A infections, the proportion of influenza A/H1N1 was substantially higher than that of influenza A/H3N2. The influenza B epidemic started in January 2020 and peaked and overtook the influenza A epidemic in February 2020 (**Fig. 1**). The influenza B epidemic declined in March 2020.

Patient Characteristics

Patient characteristics are summarized in **Table 1**. In total, 136 episodes were RIDT-positive (cases) and 250 were RIDT-negative (controls). RIDT-positive patients were significantly older than RIDT-negative patients (mean age ± standard error: 8.2 ± 0.3 *vs.* 6.4 ± 0.2; $P < 0.0001$). The proportion of cases without influenza vaccination during the previous season was significantly smaller among the RIDT-positive cases than among the RIDT-negative cases (presence:absence of influenza vaccination during the previous season: 57:76 *vs.* 134:103, respectively; $P = 0.0128$). The body temperature of RIDT-positive patients was significantly higher than that of RIDT-negative patients (mean body temperature [°C] ± standard error: 39.2 ± 0.1 *vs.* 38.8 ± 0.0, respectively; $P < 0.0001$). The time from influenza infection onset was significantly longer for RIDT-positive patients than for RIDT-negative patients (mean time from onset [h] ± standard error: 22.7 ± 1.3 *vs.* 17.7 ± 1.0, respectively; $P = 0.0002$). Regarding comorbidities, 21 patients had bronchial asthma, 1 had epilepsy, 1 had Kawasaki disease, and 1 had hereditary spherocytosis.

VE Assessment

Table 2 presents the results of VE analysis. Among all patients, the adjusted VE was significant for influenza A/H1N1 (45.5%; 95% confidence interval [CI]: 2.0-69.7) and influenza B (66.7%; 95% CI: 35.9-82.7). In the age group 0-6 years, the adjusted VE was significant for influenza A (total), A/H1N1+A/H3N2 (65.0%; 95% CI: 22.2-84.3), influenza A/H1N1 (64.8%; 95% CI: 16.9-85.1), and influenza B (87.4%; 95% CI: 50.5-96.8). There was no

Table 1 Patient characteristics

Characteristic	Total	Rapid influenza diagnostic test		P-value
		Test-positive (case) [a]	Test-negative (control)	
Number (*n*)	386	136	250	-
Age (mean age)	7.0 ± 0.2	8.2 ± 0.3	6.4 ± 0.2	<0.0001 *
Sex (male:female)	211:175	78:58	133:117	0.4551
Onset period (first half:second half) [b]	224:162	80:56	144:106	0.8299
Vaccination (yes:no)	213:173	58:78	155:95	0.0004 *
Comorbidity [c] (yes:no)	24:362	13:123	11:239	0.0500
Influenza infection during previous season (yes:no) [d]	70:301	18:115	52:186	0.0535
Influenza vaccination during previous season (yes:no) [e]	191:179	57:76	134:103	0.0128 *
Body Temperature (°C)	38.9 ± 0.0	39.2 ± 0.1	38.8 ± 0.0	<0.0001 *
Time from onset [e] (hours)	19.4 ± 0.8	22.7 ± 1.3	17.7 ± 1.0	0.0002 *

Age, body temperature, time from onset: mean ± standard error

* statistically significant

[a] Types of influenza were as follows: 64, influenza A/H1N1; 14, influenza A/H3N2; 58, influenza B.

[b] First half: December 2019–January 2020; second half: February–March 2020

[c] Comorbidities included the following: 21, bronchial asthma; 1, epilepsy; 1, Kawasaki disease; 1, hereditary spherocytosis.

[d] Fifteen patients were excluded (13: Not born in the previous season; 2: Unknown influenza infection status in the previous season).

[e] Sixteen patients were excluded (13: Not born in the previous season; 3: Unknown influenza vaccination status in the previous season).

Table 2 Vaccine effectiveness during the 2019–2020 season

	Test-positive (vaccinated/ not vaccinated)	Test-negative (vaccinated/ not vaccinated)	Crude VE (95% CI)	Adjusted VE [c] (95% CI)
Overall				
Influenza A (total) [a]	78 (36/42)	250 (155/95)	47.5% (12.2 to 68.6) *	38.5% (–5.6 to 64.2)
Influenza A/H1N1	64 (28/36)	250 (155/95)	52.3% (16.9 to 72.7) *	45.5% (2.0 to 69.7) *
Influenza A/H3N2	14 (8/6)	250 (155/95)	18.3% (–142.8 to 72.5)	–8.0% (–230.8 to 64.7)
Influenza B	58 (22/36)	250 (155/95)	62.5% (32.5 to 79.2) *	66.7% (35.9 to 82.7) *
Age 0–6 years [b]				
Influenza A (total) [a]	34 (13/21)	148 (99/49)	69.4% (33.7 to 85.8) *	65.0% (22.2 to 84.3) *
Influenza A/H1N1	28 (11/17)	148 (99/49)	68.0% (26.4 to 86.1) *	64.8% (16.9 to 85.1) *
Influenza A/H3N2	6 (2/4)	148 (99/49)	75.3% (–39.8 to 95.6)	75.6% (–38.9 to 95.7)
Influenza B	13 (3/10)	148 (99/49)	85.2% (43.6 to 96.1) *	87.4% (50.5 to 96.8) *
Age 7–15 years				
Influenza A (total) [a]	44 (23/21)	102 (56/46)	10.0% (–82.8 to 55.7)	–5.3% (–124.3 to 50.6)
Influenza A/H1N1	36 (17/19)	102 (56/46)	26.5% (–57.4 to 65.7)	17.8% (–86.6 to 63.8)
Influenza A/H3N2	8 (6/2)	102 (56/46)	–146.4% (–1,179.5 to 52.5)	–216.9% (–1,620.8 to 41.6)
Influenza B	45 (19/26)	102 (56/46)	40.0% (–21.9 to 70.4)	53.3% (–2.1 to 78.6)

VE: vaccine effectiveness, CI: confidence interval

* statistically significant

[a] Influenza A (total) includes influenza A/H1N1 and A/H3N2.

[b] Eleven patients aged 6–11 months were included.

[c] VE adjusted for age group (0–6 *vs*. 7–15 years), sex, period of influenza infection onset, and comorbidities among all children. VE adjusted for sex, period of influenza infection onset, and comorbidities in each age group. In the analysis of influenza A/H3N2, comorbidities were excluded from variables. In the analysis of influenza A/H3N2 by age group 0–6 years, comorbidities and period of influenza infection onset were excluded from variables.

Table 3 Vaccine effectiveness according to number of vaccine doses

	Adjusted odds ratio[a] (95% CI)			*P*-value
Vaccine Dose	None	Once	Twice	
Total child [b]				
Influenza A (total) [c]	1.0	0.80 (0.58–1.10)	0.63 (0.33–1.20)	0.1635
Influenza A/H1N1	1.0	0.78 (0.55–1.10)	0.60 (0.30–1.21)	0.1537
Influenza A/H3N2	1.0	0.97 (0.50–1.87)	0.94 (0.25–3.50)	0.9290
Influenza B	1.0	0.75 (0.52–1.09)	0.56 (0.27–1.18)	0.1280
Age 0–6 years [b]				
Influenza A (total) [c]	1.0	0.58 (0.37–0.88)	0.33 (0.14–0.78)	0.0116 *
Influenza A/H1N1	1.0	0.58 (0.37–0.93)	0.34 (0.14–0.86)	0.0231 *
Influenza A/H3N2	1.0	0.55 (0.21–1.41)	0.30 (0.04–1.98)	0.2111
Influenza B	1.0	0.57 (0.25–1.26)	0.32 (0.06–1.59)	0.1644
Age 7-15 years				
Influenza A (total) [c]	1.0	1.27 (0.74–2.17)	1.61 (0.55–4.70)	0.3824
Influenza A/H1N1	1.0	1.22 (0.67–2.19)	1.48 (0.46–4.79)	0.5157
Influenza A/H3N2	1.0	1.74 (0.65–4.66)	3.03 (0.42–21.69)	0.2703
Influenza B	1.0	0.78 (0.50–1.22)	0.61 (0.25–1.49)	0.2780

CI: confidence interval

* statistically significant

[a] Adjusted for age (years), body temperature (°C), and time from onset (h).

[b] Eleven patients aged 6–11 months were included.

[c] Influenza A (total) includes influenza A/H1N1 and A/H3N2.

significant VE in the age group 7-15 years.

Vaccine Doses

The correlation between number of vaccine doses and the adjusted ORs of influenza incidence is shown in **Table 3**. In the age group 0-6 years, two vaccine doses tended to decrease the incidence of influenza A (total) and influenza A/H1N1, as compared with the incidence among those without vaccination or receiving only one dose. Specifically, in the age group 0-6 years, the adjusted OR was significant for influenza A (total): 0.58 (95% CI: 0.37-0.88) in cases with one dose, and 0.33 (95% CI: 0.14-0.78) with two doses (P = 0.0116). In the same age group, the adjusted ORs against influenza A/H1N1 were 0.58 (95% CI: 0.37-0.93) in cases with one dose and 0.34 (95% CI: 0.14-0.86) with two doses (P = 0.0231). A dose-dependent response relationship was suggested for VE in the age group 0-6 years. However, regardless of dosing regimen, adjusted VE was not significant in the age group 7-15 years (**Table 3**).

Effect of Influenza Infection during the Previous Season

The ORs of influenza infection for the current season in relation to influenza infection during the previous season are shown in **Table 4**. Among all participants, the adjusted OR was significant for influenza B (0.29; 95% CI: 0.11-0.78; P = 0.0140). The age group 0-6 years had no significant ORs associated with influenza A (total) and influenza A/H1N1, and ORs could not be calculated for influenza A/H3N2 and influenza B. In the age group 7-15 years, the adjusted OR was significant for influenza B (0.34; 95% CI: 0.12-0.94; P = 0.0368). Furthermore, the adjusted OR tended to be lower for influenza A (total) (0.43; 95% CI: 0.16-1.14; P = 0.0890) and influenza A/H1 N1 (0.39; 95% CI: 0.13-1.15; P = 0.0878) in the age group 7-15 years, but none of the adjusted ORs was significant (**Table 4**).

Effect of Influenza Vaccination Status during the Previous Season

The ORs of influenza infection for the current season in relation to influenza vaccination during the previous season are shown in **Table 5**. Neither the influenza types nor the two age groups were associated with a significant OR (**Table 5**).

Discussion

The 2019-2020 influenza season was unusual because of the COVID-19 epidemic. Most Japanese were forced to refrain from going out and having person-to-person contacts, and they were regularly reminded to wear a mask and wash their hands frequently. Japanese initiatives for public health differed substantially from previous influenza seasons. The COVID-19 epidemic, along with the

Table 4 Odds ratio of influenza infection during the 2019–2020 season in relation to the presence or absence of influenza infection during the previous season

Influenza infection during previous season	Test-positive (Yes/No)	Test-negative (Yes/No)	Crude odds ratio (95% CI)	Adjusted odds ratio [d] (95% CI)	*P*-value [e]
Overall					
Influenza A (total) [a]	75 (12/63)	238 (52/186)	0.68 (0.34–1.36)	0.60 (0.29–1.24)	0.1653
Influenza A/H1N1	61 (10/51)	238 (52/186)	0.70 (0.33–1.48)	0.64 (0.29–1.39)	0.2588
Influenza A/H3N2	14 (2/12)	238 (52/186)	0.60 (0.13–2.75)	0.48 (0.10–2.28)	0.3540
Influenza B	58 (6/52)	238 (52/186)	0.41 (0.17–1.01)	0.29 (0.11–0.78) *	0.0140 *
Age 0–6 years [b]					
Influenza A (total) [a]	31 (5/26)	137 (23/114)	0.95 (0.33–2.74)	1.00 (0.33–3.05)	0.9990
Influenza A/H1N1	25 (5/20)	137 (23/114)	1.24 (0.42–3.64)	1.28 (0.41–3.98)	0.6673
Influenza A/H3N2	6 (0/6)	137 (23/114)	Not available	Not available	Not available
Influenza B	13 (0/13)	137 (23/114)	Not available	Not available	Not available
Age 7–15 years [c]					
Influenza A (total) [a]	44 (7/37)	101 (29/72)	0.47 (0.19–1.17)	0.43 (0.16–1.14)	0.0890
Influenza A/H1N1	36 (5/31)	101 (29/72)	0.40 (0.14–1.13)	0.39 (0.13–1.15)	0.0878
Influenza A/H3N2	8 (2/6)	101 (29/72)	0.83 (0.16–4.34)	0.72 (0.13–3.95)	0.7006
Influenza B	45 (6/39)	101 (29/72)	0.38 (0.15–1.00)	0.34 (0.12–0.94)	0.0368 *

CI: confidence interval

* statistically significant

[a] Influenza A (total) includes influenza A/H1N1 and A/H3N2.

[b] Fourteen patients were excluded (13: Not born before previous season, 1: Unknown status of influenza infection during previous season).

[c] One patient was excluded (1: Unknown status of influenza infection during previous season).

[d] Odds ratios among all participants were adjusted for sex, age group (0–6 *vs*. 7–15 years), period of influenza infection onset (December 2019–January 2020 *vs*. February–March 2020), and influenza vaccination during the current season. Odds ratios in each age group were adjusted for sex, period of influenza infection onset (December 2019–January 2020 *vs*. February–March 2020), and influenza vaccination during the current season.

[e] *P* value is value of adjusted odds ratio.

changes in the behavior of Japanese individuals, might have affected the seasonal influenza epidemic and influenza VE. In fact, in the author's clinic approximately twice as many patients were enrolled during the previous season than during the current season[7,8]. The COVID-19 epidemic spread more widely abroad than in Japan[16]. In Europe, the interim VE estimate against influenza A/H1N1 was not significant among children in primary care settings[17]. In the United States, the interim VE estimate against influenza A/H1N1 was significant in older adults (age ≥50 years) but was not significant against influenza A/H1N1 in younger adults (age 19-49 years)[18]. These results differed slightly from those for the prior season[19,20]. However, the present results are comparable with those of previous studies[7,8]. This can be attributed to the following reasons. First, the TNCC study design is robust despite the small number of patients. Second, the influenza epidemics ended before the COVID-19 epidemic seriously influenced the influenza epidemics. In the present analysis of all participants, VE was significant for influenza A/H1N1 (45.5%) and influenza B (66.7%) in children. This result was comparable or slightly inferior to those reported in the United States (influenza A/H1N 1: 51%; 95% CI: 22-69; influenza B: 56%; 95% CI: 42-67)[18] and Canada (influenza A/H1N1: 63%; 95% CI: 25-81; influenza B: 77%; 95% CI: 59-87)[21]. Furthermore, trends in the present age groups were similar to those observed in my previous studies[7,8]. Although the quadrivalent influenza vaccine showed significant VE against influenza A (total), influenza A/H1N1, and influenza B among children aged 0-6 years, there was no substantial VE among children aged 7-15 years. The VE of the quadrivalent influenza vaccine against influenza A (total) and influenza A/H1N1 appeared to be dose-dependent among children aged 0-6 years. The reason for this substantial difference in VE between younger and older children remains unclear. Sugaya et al. speculated that low VE in older children (age 13-15 years) was attributable to the immunological effects of repeated vaccination, as opportunities for influenza vaccination and/or influenza infection in-

Table 5 Odds ratio of influenza infection during the 2019–2020 season in relation to the presence or absence of influenza vaccination during the previous season

Influenza vaccination during previous season	Test-positive (Yes/No)	Test-negative (Yes/No)	Crude Odds ratio (95% CI)	Adjusted Odds ratio [c] (95% CI)	*P*-value [d]
Overall					
Influenza A (total) [a]	75 (33/42)	237 (134/103)	0.60 (0.36–1.02)	0.84 (0.40–1.76)	0.6406
Influenza A/H1N1	61 (25/36)	237 (134/103)	0.53 (0.30–0.95) *	0.75 (0.34–1.64)	0.4710
Influenza A/H3N2	14 (8/6)	237 (134/103)	1.02 (0.34–3.05)	1.35 (0.33–5.63)	0.6759
Influenza B	58 (24/34)	237 (134/103)	0.54 (0.30–0.97) *	1.38 (0.53–3.61)	0.5058
Age 0–6 years [b]					
Influenza A (total) [a]	31 (14/17)	135 (83/52)	0.52 (0.23–1.13)	1.12 (0.33–3.79)	0.8542
Influenza A/H1N1	25 (12/13)	135 (83/52)	0.58 (0.25–1.36)	1.24 (0.34–4.51)	0.7491
Influenza A/H3N2	6 (2/4)	135 (83/52)	0.31 (0.06–1.77)	0.86 (0.06–13.55)	0.9175
Influenza B	13 (4/9)	135 (83/52)	0.28 (0.08–0.95) *	3.19 (0.38–27.04)	0.2864
Age 7–15 years					
Influenza A (total) [a]	44 (19/25)	102 (51/51)	0.76 (0.37–1.55)	0.81 (0.31–2.12)	0.6702
Influenza A/H1N1	36 (13/23)	102 (51/51)	0.57 (0.26–1.24)	0.62 (0.22–1.73)	0.3661
Influenza A/H3N2	8 (6/2)	102 (51/51)	3.00 (0.58–15.57)	2.97 (0.43–20.73)	0.2718
Influenza B	45 (20/25)	102 (51/51)	0.80 (0.40–1.62)	1.18 (0.40–3.45)	0.7677

CI: confidence interval

* statistically significant

[a] Influenza A (total) includes influenza A/H1N1 and A/H3N2.

[b] Sixteen patients were excluded (13: Not born before previous season, 3: Unknown status of influenza vaccination during previous season).

[c] Odds ratios among all participants were adjusted for sex, age group (0–6 *vs*. 7–15 years), period of influenza infection onset (December 2019–January 2020 *vs*. February–March 2020), and influenza vaccination during the current season. Odds ratios in each age group were adjusted for sex, period of influenza infection onset (December 2019–January 2020 *vs*. February–March 2020), and influenza vaccination during the current season. In analysis of influenza H3N2 among patients aged 0–6 years, onset of influenza infection was excluded from the variables because there were no patients with influenza infection during the February–March 2020 period.

[d] *P* value is value of adjusted odds ratio.

crease with age[5]. In contrast, younger children are immunologically naïve. However, the present adjusted OR of the current influenza B epidemic was significantly lower among patients aged 7-15 years with influenza infections during the previous season (0.34; 95% CI: 0.12-0.94; $P = 0.0368$). Furthermore, although the adjusted OR was not significant, it was lower for influenza A (total) (0.43; 95% CI: 0.16-1.14; $P = 0.0890$) and influenza A/H1N1 (0.39; 95% CI: 0.13-1.15; $P = 0.0878$) among patients aged 7-15 years with influenza infections during the previous season. However, influenza infection status during the previous season had no effect on patients aged 0-6 years during the current season. Thus, several factors from the previous season, other than vaccination, may affect influenza VE in older children, which is not the case for younger children. Moreover, there were no significant ORs of influenza infection in the current season in relation to the influenza vaccination during the previous season in any age group. This result was similar to those of previous studies and indicates the importance of the current vaccination[11–13].

This study had some limitations. First, bias due to the small sample size may have affected the results of this TNCC study. However, the present study lays a solid foundation for future studies enrolling a larger number of patients. Furthermore, the present results were very similar to those of my studies in previous influenza seasons, as well as to studies in the United States and Europe during the 2019-2020 season[7,8,18,21]. Second, sampling bias was unavoidable because this study was conducted in a single clinic. However, because patients were treated by the same physician, medical practice was consistent across all cases. Third, as 2.9% of the positive cases detected by Linjudge FluA/pdm yielded a weak positive reaction for influenza A/H3N2 (information provided on package insert), the diagnosis of influenza A/H1N1 pdm09 may not always be accurate. However, a diagnosis of influenza A/H1N1 pdm09 was only made

when Linjudge FluA/pdm showed a clear positive reaction, as described in my previous study[8]. Fourth, the VE against influenza A/H3N2 pdm09 could not be confirmed because this study had a relatively small number of influenza A/H3N2 cases. However, a paucity of such cases was a trend this season in Japan. Fifth, because of the small number of participants, I was unable to subdivide the patient population into multiple groups, as was done in an earlier study of ORs of seasonal influenza cases in relation to prior influenza infection and vaccination[13]. However, the present results were comparable with those of previous studies[11–13]. Finally, RIDT is not completely accurate, and the influenza virus was not precisely identified by techniques such as virus isolation and RT-PCR. A previous study reported no significant differences between RT-PCR data and results estimated by RIDT using a brand different from that used in the present study[22]. Furthermore, the RIDT of this study had a comparable or higher concordance rate with viral isolation cultures, as compared with previously reported studies[8,22]. Thus, although a confirmation study should still be conducted, the present results might be equivalent to a study using RT-PCR.

In conclusion, this is the first study to assess the VE of the inactivated quadrivalent influenza vaccine in children during the 2019-2020 influenza season, which was the first influenza season to overlap the COVID-19 epidemic in Japan. In patients aged 0-6 years, the VE was significant against influenza A (total), influenza A/H1N1, and influenza B. VE this season was comparable with those of previous years, and it appears that the TNCC study generated robust results during the 2019-2020 season. Although no significant VE was observed in the age group 7-15 years, there was a significantly lower OR for influenza B with influenza infection during the previous season. In addition to prior influenza vaccination, multiple factors from previous influenza seasons may affect the 2019-2020 influenza VE in older children. Interestingly, influenza vaccination during the current season, but not during the previous season, appeared to have a beneficial effect, which highlights the importance of having children vaccinated annually. Because there was a significant influenza VE in younger children aged 0-6 years, annual vaccination of this age group is recommended for the 2020-2021 season. Moreover, annual vaccination of older children without influenza infection during the 2019-2020 season is recommended.

Acknowledgements: I would like to thank Editage (www.editage.com) for the English language editing.

Conflict of Interest: None declared.

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(Received, November 19, 2020)
(Accepted, January 6, 2021)
(J-STAGE Advance Publication, March 9, 2021)