〈Original Article〉

Effectiveness of current and repeated vaccination with quadrivalent influenza vaccine during the 2017/18 season in Japan

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The effectiveness of repeated vaccination of the quadrivalent influenza vaccine is currently unknown. This study aims to estimate current and repeated vaccination effectiveness (VE) of the quadrivalent influenza vaccine. A test-negative case-control study was performed during the 2017–2018 season. The participants were Japanese children divided into four groups (6–11 months and ages 1–5, 6–12, and 13–15 years). Current VE: Overall, the adjusted VE was significant for influenza B (36.4; 95% confidence interval [CI]: 9.8–55.2); the adjusted VE was significant for any influenza (A＋B; 47.3%; 95% CI: 12.2–68.3) and influenza B (56.2%; 95% CI: 17.9–76.6) only in the 1–5 year age group. In other groups, VE was not observed. Vaccine doses: Two vaccine doses significantly decreased the incidence of any influenza and influenza B compared to no vaccination or only one dose in only the 1–5 year old group. Repeated VE: The adjusted VE was significant for any influenza (72.6%; 95% CI: 27.1–89.7) and influenza B (69.7%; 95% CI: 4.5–90.4) in only the 1–5-year age group without vaccination in the previous season. It was also significant for influenza B (68.6%; 95% CI: 1.3–90.0) in the 6–12-year age group with two vaccination doses in the previous season. In other groups, repeated VE was not observed for any influenza types. The reason for that repeated VE may depend on age, repeated vaccination with two doses may be valuable in the 6–12 year age group, although current VE was not observed.

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Introduction

The effect of previous vaccination on current season influenza vaccine effectiveness (VE) varies, and a conclusion has not yet been reached[1,2]. In response to the recommendation of the World Health Organization (WHO), quadrivalent influenza vaccines replaced trivalent vaccines in the 2015–2016 season in Japan[3]. The test-negative case-control study has been validated by evaluating vaccine effectiveness (VE) against influenza[4~6]. In Japan, several reports have described the efficacy of quadrivalent influenza vaccines, using the test-negative case-control design[7~10]. However, information on the effect of previous vaccinations on current season influenza VE of quadrivalent influenza vaccines has not yet been published.

This study aimed ① to estimate the effectiveness of quadrivalent influenza vaccines in children during the 2017–2018 season based on a test-negative case-control design and ② to confirm whether previous vaccinations affected the current season's influenza VE, particularly that of influenza B.

Patients and Methods

Patients

The examinees in this research were children who underwent the rapid influenza diagnostic test (RIDT) in the Ando Clinic (Narashino City, Chiba, Japan) due to possible infections of influenza in the 2017–2018 season. Those patients ① were informed of the concept of this study, ② fulfilled the criteria of influenza-like illness (ILI) and ③ divided into four age groups (6–11 months and 1–5, 6–12, and 13–15 years) in order to analyze age effects. In the course of this study, following clinical information was collected: sex, age, vaccination status for quadrivalent influenza vaccine (current and previous season), comorbidities, and month of influenza infection onset. In this research comorbidities were defined as: chronic pulmonary, cardiovascular (excluding hypertension), renal, liver, hematologic, and neurological disorders, diabetes mellitus, autoimmune disorders, and cancer.

Eligibility criteria

1) Patients who underwent RIDT due to an ILI, in the 2017–2018 season. ILI was defined based on the WHO's definition[11] as follows:
   a) Patients with a fever (body temperature (BT) ≥38.0℃),
   b) Patients in whom influenza infection was suspected, evidenced by symptoms including acute onset, nasal discharge, sore throat, cough, arthralgia, and myalgia,
2) The interval from the time the quadrivalent inactivated influenza vaccination was administered was ≥14 days and <5 months[12].

3) If patients had multiple episodes:
   a) For patients with any influenza-negative episodes, the episode where the highest BT was observed was employed,
   b) For patients with both influenza-positive and negative episodes, the positive episode was employed,
   c) For patients with both influenza A and B-positive episodes, both episodes were employed.

Exclusion criteria

1) Already had an influenza infection during the 2017–2018 season.
2) Patients who had already been given the neuraminidase inhibitor due to negative results of RIDT.
3) The interval from the time of quadrivalent inactivated influenza vaccination was ＜14 days or ≥5 months.
4) Patients ≥16 years of age.

Diagnosis of influenza

Nasopharyngeal swabs were obtained from all patients and tested using Statmark™ FLU stick-N® (Statmark®) (Nichirei Bioscience Co., Tokyo, Japan) and Alsonic® Flu (Alsonic®) (Alfresa Pharma Co., Osaka, Japan). These RIDT kits can detect and differentiate between influenzas A and B, with high positive concordance (Statmark: Alsonic＝influenza A: 100%: 90.8%, influenza B: 93.3%: 88.8%) and negative concordance rates (Statmark: Alsonic＝influenza A: 99.1%: 98.1%, influenza B: 98.8%: 100%) with a viral isolation culture. Statmark® was used till January 27, 2018 covering the peak of the influenza epidemic. Alsonic® was used after January 27, 2018.

Vaccine

The quadrivalent influenza vaccine contained influenza A/Singapore/GP1908/2015 (IVR-180) (H1N1) pdm09, A/Hong Kong/4801/2014 (X-263) (H3N2), B/Phuket/3073/2013 (Yamagata lineage), and influenza B/Texas/2/2013 (Victoria lineage) viral strains.

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.

Test-negative case-control study

VE was estimated by a test-negative case-control design: patients who were ILI- and RIDT-positive for influenza infection were considered as cases, and patients who were ILI and RIDT-negative for influenza infection were considered as controls. VE was defined as {1-odds ratio

(OR)}×100 (%); 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)[7~10,13]. OR was calculated using the Wald test. First, the crude VE was calculated and adjusted for sex, month of onset of influenza infection, comorbidity, and rapid-influenza diagnostic test to obtain the adjusted VE. Secondly, to ensure statistical reliability, the VE was adjusted for sex, month of onset of influenza infection, and rapid-influenza diagnostic test for ages 13–15 years (only one patient had a comorbidity). Cases in which the statistical analyses results did not overlap among the month of onset of influenza infection, VE was adjusted for sex, comorbidity and rapid-influenza diagnostic test (sex and rapid-influenza diagnostic test in those aged 13–15 years) since RIDT (Statmark® was used by January 27, 2018 covering the peak of the influenza epidemic. Alsonic® was used after January 27, 2018) could be substituted for month of onset of influenza infection to a certain degree.

Effect of previous vaccination on current season influenza VE

To estimate the effect of previous vaccinations on current season influenza VE, participants were divided into subgroups (the number of previous vaccinations/none, once and twice). Twenty-one patients ages 6–11 months were excluded. In each subgroup, VE was similarly estimated by a test-negative case-control design.

Statistical analysis

Student's *t*-test was used to compare continuous variables (i.e., time from onset, age) between participants with and without influenza infection. χ^2 tests were used to compare nominal variables (i.e., sex, comorbidities, and month of onset). The VE was adjusted for sex, age group, presence/absence of comorbidities, and month of onset of influenza infection[6,8~10,13]. When considering the effect of age, the stratified analysis was performed. Treating both vaccine doses and age groups as continuous variables, the rates of incidence of influenza infection are shown both using the unit OR (i.e., the OR for an increase of 1; unit＝1 vaccine dose). The adjusted OR was calculated, and the unit OR was adjusted for other continuous variables (age, body temperature, time from onset, and vaccine doses). Two-sided P values <0.05 were considered significant. Statistical analyses were performed using JMP® 13.2 (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA).

Ethics

This study was conducted according to the Declaration of Helsinki. 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: 14000050.20171215-4550).

Results

Enrollment

From December 20, 2017 to April 2018, 1,807 episodes were enrolled; 988 episodes were those of patients aged 6 months to 15 years: 229 were excluded (819: patients ≥16 years old, 155: BT <38.0℃, 71: overlapped episodes, 1: uncertain vaccination, 1: the neuraminidase inhibitor had already been given before presentation, and 1: interval from the time of vaccination was ≥5 months). In total, 752 patients and 759 episodes were analyzed (7 patients had episodes of influenza both A and B).

Patients characteristics

Patient characteristics are summarized in Table 1. In total, 402 episodes were RIDT-positive (case) and 357 were RIDT-negative (control). Comorbidities included bronchial asthma (n=46), febrile convulsions (undergoing treatment) (n=3), epilepsy (n=3), milk allergy (undergoing treatment) (n=2), and congenital anomalies such as Down syndrome (n=2) (overlapping: yes). Overall, Statmark® had more significant positivity associated with RIDT than Alsonic® for both influenzas. This may be because Statmark® was used till January 27, 2018 including the peak of influenza epidemics. The distribution of influenza infection is shown in Figure 1. Both influenza A and B epidemics peaked from January 2018 and both peaked out in February. The influenza B epidemic also peaked in January 2018. Both influenza epidemics then sharply declined in March.

Vaccine effectiveness

Current vaccine effectiveness (in the 2017–2018 season) is shown in Table 2. The adjusted VE was only significant against influenza B: 36.4% (95% CI: 9.8–55.2). When participants were divided into three age groups (patients aged 6–11 months were excluded following analyses because of their small number), VE was only significant in the group of those aged 1–5 years; it was 47.3% effective (95% CI: 12.2–68.3) against any influenza, 24.1% (95% CI: −52.9–62.4) against influenza A, and 56.2% (95% CI: 17.9–76.6) against influenza B. The adjusted VE was not significant in the older age group (Table 2).

Vaccine doses

The relation between vaccine doses and the adjusted ORs of incidences of influenza is shown in Table 3. Vaccine doses also affected the incidence of influenza. Two doses significantly decreased the rates of RIDT-positive cases, compared to no vaccination or only one dose in the younger age group (those 1–5 years old). Vaccination doses were correlated with decreasing the rates of incidence of any influenza and influenza B in this age group. The adjusted VE was significant against any influenza: 0.68 (95% CI: 0.51–0.91) in cases with one dose, and 0.47 (95% CI:

Table 1. Patient characteristics

	Rapid influenza diagnostic test			
Characteristics	Total	Test-positive (case)	Test-negative (control)	*P*-value
n	759	402	357	
Type of influenza				
Influenza A (%)		130 (32.3)		Not available
Influenza B (%)		272 (67.7)		Not available
Age (mean age)	6.7			
Any influenza		7.6	5.6	<0.0001*
Influenza A		6.9		0.0014*
Influenza B		7.9		<0.0001*
Sex (Male : Female)	389 : 370			
Any influenza		208 : 194	181 : 176	0.8273
Influenza A		70 : 60		0.6084
Influenza B		138 : 134		1.0000
Comorbidity[a] (yes/no)	53/706			
Any influenza		30/372	23/334	0.6691
Influenza A		11/119		0.4271
Influenza B		19/253		0.8722
Vaccination (yes/no)	308/451			
Any influenza		151/251	157/200	0.0759
Influenza A		58/72		0.9181
Influenza B		93/179		0.0137*
RIDT[b] (Statmark/Alsonic)	338 : 422			
Any influenza		205/197	127/230	<0.0001*
Influenza A		90/40		<0.0001*
Influenza B		115/157		0.0981
Body Temperature[c] (℃)	39.0±0.0			
Any influenza		39.0±0.0	38.9±0.0	0.0148*
Influenza A		39.2±0.1		<0.0001*
Influenza B		38.9±0.0		0.7921
Time from onset[d]	24.5±0.7			
Any influenza		24.7±1.0	24.3±1.0	0.7690
Influenza A		22.0±1.7		0.2329
Influenza B		26.1±1.2	24.3±1.1	0.2783

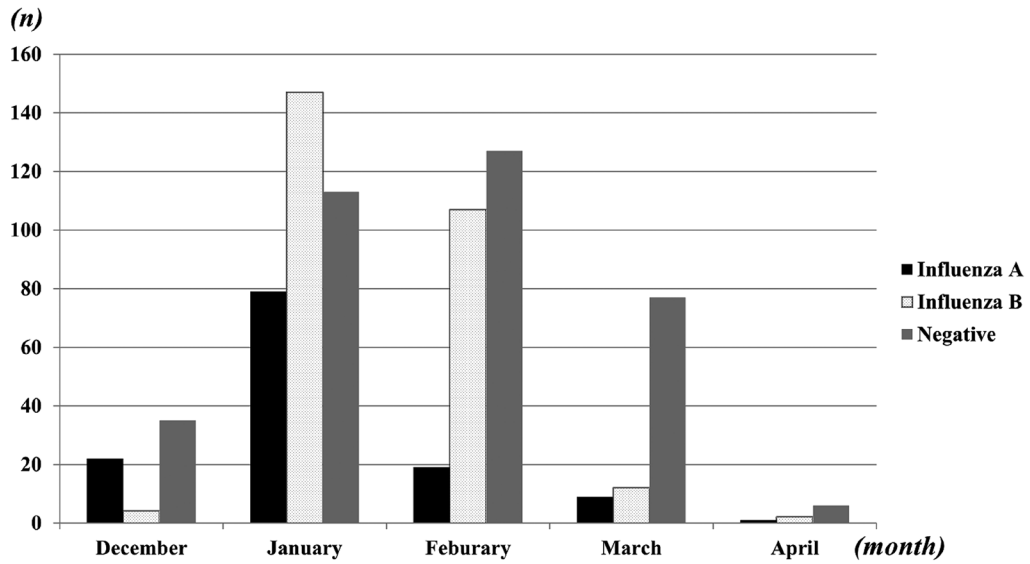
[a] Comorbidities included chronic disease of the lung (bronchial asthma), neurological disease (such as epilepsy), and others such as (Down syndrome).
[b] RIDT: Rapid-influenza diagnostic test
[c] Mean±standard error
[d] Hours±standard error

0.27–0.83) with two doses (trend *P*-value＝0.0090). The values were 0.57 (95% CI: 0.40–0.82) in cases with one dose, and 0.33 (95% CI: 0.16–0.67) with two doses, against influenza B (trend *P*-value＝0.0024). However, in those aged 6–12 and 13–15 years, the adjusted VE was not significant against any influenza, influenza A and influenza B (Table 3).

Repeated vaccine effectiveness

Current vaccine effectiveness (in the 2017–2018 season) correlated to the status of vaccinations in the previous season (in the 2016–2017 season) shown in Table 4. The age group with

Figure 1. Distribution of influenza infection in the 2017/18 season



						total
Influenza A	**22**	**79**	**19**	**9**	**1**	**130**
Influenza B	**4**	**147**	**107**	**12**	**2**	**272**
Negative	**35**	**113**	**127**	**77**	**6**	**358**

Table 2. Vaccine effectiveness in children in the 2017–2018 season

	n	Test-positive (vaccinated/ not vaccinated)	Test-negative (vaccinated/ not vaccinated)	Crude VE (95% CI)	Adjusted VE[b] (95% CI)
Total	759				
Any influenza		(151/251)	(157/200)	23.4% (−2.5 to 42.7)	23.2% (−4.4 to 43.5)
Influenza A		(58/72)	(157/200)	−2.6% (−53.7 to 31.5)	−23.6% (−90.7 to 19.9)
Influenza B		(93/179)	(157/200)	33.8% (8.3 to 52.2)*	36.4% (9.8 to 55.2)*
Age group[a]					
1–5 years	298				
Any influenza		(40/70)	(97/91)	46.4% (13.2 to 66.9)*	47.3% (12.2 to 68.3)*
Influenza A		(20/25)	(97/91)	24.9% (−44.3 to 61.0)	24.1% (−52.9 to 62.4)
Influenza B		(20/45)	(97/91)	58.3% (24.1 to 77.1)*	56.2% (17.9 to 76.6)*
6–12 years	372				
Any influenza		(95/148)	(52/77)	5.0% (−47.0 to 38.5)	1.6% (−53.9 to 37.1)[c]
Influenza A		(33/37)	(52/77)	−32.1% (−137.4 to 26.5)	−81.4% (−252.1 to 6.5)
Influenza B		(62/111)	(52/77)	17.3% (−32.3 to 48.3)	17.7% (−33.3 to 49.1)[c]
13–15 years	68				
Any influenza		(13/28)	(7/20)	−32.7% (−291.9 to 55.1)	−66.1% (−452.6 to 50.0)
Influenza A		(4/7)	(7/20)	−63.3% (−631.7 to 63.6)	−141.7% (−1228.5 to 56.0)[c]
Influenza B		(9/21)	(7/20)	−22.4% (−291.4 to 61.7)	−32.5% (−365.0 to 62.3)[c]

VE: Vaccine effectiveness, CI: confidence interval

* Statistically significant

[a] Twenty-one patients in age with 6–11 months were excluded.

[b] VE adjusted for sex, month of onset of influenza infection, comorbidity and rapid-influenza diagnostic test; VE adjusted for sex, month of onset of influenza infection and rapid-influenza diagnostic test in age with 13–15 years.

[c] VE adjusted for sex, comorbidity and rapid-influenza diagnostic test; VE adjusted for sex and rapid-influenza diagnostic test in age with 13–15 years.

Table 3. Vaccine effectiveness by vaccine doses

Vaccine dose	Adjusted odds ratio[a] (95% CI)			Trend *P*-value
	None	Once	Twice	
Total				
Any influenza	1.0	0.91 (0.77–1.09)	0.83 (0.59–1.18)	0.3017
Influenza A	1.0	1.11 (0.87–1.42)	1.24 (0.76–2.03)	0.3835
Influenza B	1.0	0.83 (0.68–1.01)	0.69 (0.46–1.03)	0.0688
Age group[b]				
1–5 years				
Any influenza	1.0	0.68 (0.51–0.91)	0.47 (0.27–0.83)	0.0090*
Influenza A	1.0	0.85 (0.57–1.25)	0.72 (0.33–1.56)	0.3993
Influenza B	1.0	0.57 (0.40–0.82)	0.33 (0.16–0.67)	0.0024*
6–12 years				
Any influenza	1.0	1.04 (0.80–1.34)	1.07 (0.64–1.80)	0.7943
Influenza A	1.0	1.33 (0.92–1.90)	1.76 (0.86–3.63)	0.1247
Influenza B	1.0	0.94 (0.71–1.24)	0.88 (0.50–1.54)	0.6565
13–15 years				
Any influenza	1.0	1.07 (0.39–2.91)	1.15 (0.15–8.48)	0.8940
Influenza A	1.0	1.39 (0.36–5.42)	1.93 (0.13–29.4)	0.6375
Influenza B	1.0	1.02 (0.35–2.96)	1.04 (0.12–8.75)	0.9716

VE: Vaccine effectiveness, CI: confidence interval
* Statistically significant
[a] VE adjusted for age, body temperature, time from onset and vaccine doses.
[b] Twenty-one patients in age with 6–11 months were excluded.

13–15 years was excluded because of their small numbers. In children aged 1–5 years, the current adjusted VE was significant: 72.6% (95% CI: 27.1–89.7) against any influenza and 69.7% (95% CI: 4.5–90.4) against influenza B in only in the cohort without receiving vaccination in the previous season. Conversely, in children aged 6–12 years, the current adjusted VE was significant: 68.6% (95% CI: 1.3–90.0) against influenza B in only those with two doses of vaccination in the previous season. However, in other age groups, the current adjusted VE that correlated to the status of vaccination in the previous season was not significant (Table 4).

Discussion

Here, the current significant VE was observed against any influenza (47.3%: 95% CI: 12.2–68.3) and influenza B (56.2%: 95% CI: 17.9–76.6). The dose-dependent VE of the quadrivalent influenza vaccine was seen in children aged 1–5 years. This was similar to my previous study which identified in the 2016–2017 season, significant VE and dose-dependence of the quadrivalent influenza vaccine, but only for children aged 6 months to 4 years[9]. However, this study failed to identify significant VE against influenza A in both total patients or any specific age group. The low VE in the season in which influenza A/H3N2 was dominant was possibly due to mutations in the egg-adapted A/H3N2 vaccine strain and mismatches due to the antigenic drift of

Table 4. Vaccine effectiveness in the 2017–2018 season correlating to vaccination in the 2016–2017 season

Age group[a]	Test-positive (vaccinated/ not vaccinated)	Test-negative (vaccinated/ not vaccinated)	Crude VE (95% CI)	Adjusted VE[b] (95% CI)
1–5 years				
a) Any influenza				
Vaccination in last season				
None	(6/59)	(29/80)	71.9% (28.1 to 89.1)*	72.6% (27.1 to 89.7)*
Once	(7/6)	(10/2)	76.7% (−51.3 to 96.4)	76.8% (−63.6 to 96.7)[c]
Twice	(27/5)	(57/9)	14.7% (−178.9 to 73.9)	5.9% (−390.7 to 81.9)
b) Influenza A				
Vaccination in last season				
None	(2/20)	(29/80)	72.4% (−25.4 to 93.9)	77.1% (−12.4 to 95.3)[c]
Once	(3/4)	(10/2)	85.0% (−26.5 to 98.2)	88.9% (−48.8 to 99.2)[c]
Twice	(15/1)	(57/9)	−136.8% (−1918.8 to 72.2)	−147.4% (−2157.0 to 72.9)[c]
c) Influenza B				
Vaccination in last season				
None	(4/39)	(29/80)	71.7% (13.9 to 90.7)*	69.7% (4.5 to 90.4)*
Once	(4/2)	(10/2)	60.0% (−290.0 to 95.9)	not available
Twice	(12/4)	(57/9)	52.6% (−79.5 to 87.5)	56.3% (−80.7 to 89.5)[c]
6–12 years				
a) Any influenza				
Vaccination in last season				
None	(8/110)	(2/63)	−129.1% (−1012.4 to 52.8)	−407.8% (−3224.0 to 22.4)
Once	(25/20)	(11/8)	9.1% (−168.8 to 69.3)	not available
Twice	(62/18)	(39/5)	55.8% (−28.6 to 84.8)	55.7% (−33.8 to 85.2)[c]
b) Influenza A				
Vaccination in last season				
None	(1/26)	(2/63)	21.2% (−1294.9 to 89.5)	−25.6% (−1455.6 to 89.9)[c]
Once	(6/7)	(11/8)	37.7% (−158.1 to 84.9)	6.0% (−355.1 to 80.6)[c]
Twice	(26/4)	(39/5)	16.7% (−239.7 to 79.6)	−56.6% (−720.6 to 70.1)
c) Influenza B				
Vaccination in last season				
None	(7/84)	(2/63)	−162.5% (−1206.8 to 47.3)	−206.9% (−1476.4 to 40.2)[c]
Once	(19/13)	(11/8)	−6.3% (−236.4 to 66.4)	not available
Twice	(36/14)	(39/5)	67.0% (−0.7 to 89.2)	68.6% (1.3 to 90.0)*[c]

VE: Vaccine effectiveness, CI: confidence interval
* Statistically significant
[a] Twenty-one patients in age with 6–11 months were excluded.
[b] VE adjusted for sex, month of onset of influenza infection, comorbidity and rapid-influenza diagnostic test.
[c] VE adjusted for sex, comorbidity and rapid-influenza diagnostic test.
The age group with 13–15 years was excluded because of their small numbers.

the virus[14]. Recently, the discrepancy between the vaccine strain and epidemic strain of A/H3N2 has been extended but not for other influenza types[15]. The lack of effectiveness against influenza A due to this discrepancy may become apparent in the 2017–2018 season.

VE and dose-dependent VE were not observed in children aged 6–12 years. This could be due to extreme pandemics in elementary schools and the decline of VE associated with increasing age[7]. No VE or dose-dependent VE in those aged 13–15 years, and no VE in adults may be due to the decline of VE with increasing age from a low rate of vaccinations[7,9].

The effectiveness of a repeated vaccine is controversial and several hypotheses support

this[16~19]. Among them, the antigenic distance hypothesis (ADH) suggests that influenza VE is determined by the antigenic distances (AD) between prior ($v1$) and current ($v2$) season's vaccine, and between $v1$ and current epidemic influenza strain (e)[16]. The prior vaccination effects represent a balance between a preexisting $v1$-induced antibody potentially interfering with a $v2$ antigen and $v2$ stimulation of rapid $v1$ memory responses potentially protective against e[16]. For example, when previous and current season's vaccine is nearly equal (i.e., $v1=v2$) and AD between $v1$ and e is small (i.e., $v1=e$), a higher VE is possible[16]. One study showed the effectiveness of serial vaccinations against influenza A/H3N2 based on this hypothesis[20]; however, in influenza A (A/H3N2), the AD becomes more variable by the antigenic drift and egg-adaptation[7]. Recent epidemic strains of A (H3N2) belong to the 3C.2a subclade. Although this subclade belongs to vaccine strain A/Hong Kong/4801/2014, within the 3C.2a subclade, there are several groups of subclades such as 3C.2a1, 3C.2a2, 3C.2a3, and 3C.2a4. Antigenic diversity has expanded, and a discrepancy is developing between the vaccine and epidemic strains[15]. However, in influenza B, the antigenic drift occurs more rarely. The prior and current season's vaccine was the same (B/Victoria: B/Texas/02/2013, B/Yamagata: B/Phuket/3073/2013) and additionally, the current epidemic influenza strain (B/Victoria: B/clade 1A, B/Yamagata: clade 3) was identical to the previous season's strain, which could be effective for the prior and current season's vaccine in the two latest seasons[17]. Also, quadrivalent vaccines cover both lineages of influenza B. Therefore, the 2017–2018 season showed the most effective with repeated vaccination against influenza B. This study showed that in children aged 1–5 years, the current adjusted VE was significant against any influenza: 72.6% (95% CI: 27.1–89.7) and against influenza B in the cohort without vaccination in the previous season 69.7% (95% CI: 4.5–90.4). The reason for this is uncertain. Among 152 patients who did not receive a vaccination in the previous season, 144 were not vaccinated in the two years before the last season. Although the precise number is unknown, most patients in this age group may be vaccine-naïve individuals. Since most hypotheses postulate that prior vaccination might interfere with current vaccinations, VE may be more clearly detected in vaccine-naïve individuals.

In children aged 6–12 years, the current adjusted VE was significant: 68.6% (95% CI: 1.3–90.0) effective against influenza B with only two doses of the vaccination administered during the previous season. This age group may represent ADH in certain cases. Though current VE was not observed in this age group, VE may be promising in patients who received two vaccine doses in the previous season. In other age groups, the current adjusted VE correlating to the status of vaccination in the previous season was not significant. This may be caused by the low rate of vaccination or the influence of more numerous prior vaccinations.

This study had several limitations. First, bias due to sample size may have affected the results, given the small size of this test-negative case-control study. Second, RIDT-negative cases may have had influenza infections. If RIDT is performed at shorter intervals from the time of

onset, it tends to provide negative results; such cases may be diagnosed as influenza infections later. However, in this study, the time between RIDT and the time of onset was not significantly different between RIDT-positive and negative cases. This was likely due to a minimal number of false-negative RIDT cases. Third, I did not perform the hemagglutination inhibition assay and calculate precise ADs. Fourth, since this study was conducted in a single hospital, sampling bias was unavoidable. Finally, RIDT is not 100% accurate. Precise identification of the influenza virus was not performed, such as by polymerase chain reaction (PCR); however, a previous study indicated no differences between the results estimated by RIDT and PCR data[21].

In conclusion, this study is the first to focus on the current and repeated VE and dose-dependent VE (in children) of the inactivated quadrivalent influenza vaccine through the 2016–2017 to 2017–2018 season in Japan. The quadrivalent influenza vaccine showed significant VE and dose-dependent VE against any influenza, as well as influenza B, in only children aged 1–5 years. As for the effectiveness of repeated vaccination in children aged 1–5 years, the current adjusted VE was significant against influenza B only, without vaccination in the previous season. In children aged 6–12 years, although the adjusted VE was not significant against influenza B in this season, the current adjusted VE was significant against influenza B only, when two vaccine doses were received during the previous season. VE and current VE with or without prior vaccination were not observed in other age groups. The effectiveness of repeated vaccine may vary with age.

Conflict of interest

The author has no potential conflict of interest to disclose.

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