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Trends in effectiveness of inactivated influenza vaccine in children by age groups in seven seasons immediately before the COVID-19 era



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ABSTRACT

Background: We have reported the vaccine effectiveness of inactivated influenza vaccine in children aged 6 months to 15 years between the 2013/14 and 2018/19 seasons. Younger (6–11 months) and older (6–15 years old) children tended to have lower vaccine effectiveness. The purpose of this study is to investigate whether the recent vaccine can be recommended to all age groups.

Methods: The overall adjusted vaccine effectiveness was assessed from the 2013/14 until the 2020/21 season using a test-negative case-control design based on rapid influenza diagnostic test results. Vaccine effectiveness was calculated by influenza type and by age group (6–11 months, 1–2, 3–5, 6–12, and 13–15 years old) with adjustments including influenza seasons.

Results: A total of 29,400 children (9347, 4435, and 15,618 for influenza A and B, and test-negatives, respectively) were enrolled. The overall vaccine effectiveness against influenza A, A(H1N1)pdm09, and B was significant (44% [95% confidence interval (CI), 41–47], 63% [95% CI, 51–72], and 37% [95% CI, 32–42], respectively). The vaccine was significantly effective against influenza A and B, except among children 6 to 11 months against influenza B. The age group with the highest vaccine effectiveness was 1 to 2 years old with both influenza A and B (60% [95% CI, 55–65] and 52% [95% CI, 41–61], respectively).

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Analysis for the 2020/21 season was not performed because no cases were reported.

Conclusions: This is the first report showing influenza vaccine effectiveness by age group in children for several seasons, including immediately before the coronavirus disease (COVID-19) era. The fact that significant vaccine effectiveness was observed in nearly every age group and every season shows that the recent vaccine can still be recommended to children for the upcoming influenza seasons, during and after the COVID-19 era.

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1. Introduction

Immunizing children with the influenza vaccine is effective for both direct protection (reducing an individual's chance of infection) and indirect protection (decreasing transmission to others) [1–4]. Thus, the influenza vaccine is recommended widely, and routine annual influenza vaccination has been recommended for children aged ≥ 6 months without contraindications by the Center for Disease Control's Advisory Committee on Immunization Practices [5].

In Japan, immunization with influenza vaccine is not included in routine immunizations, and is a voluntary immunization. Thus, children have no duty to receive this vaccination. The overall vaccine coverage rate in Japan remained low at approximately 30%, 60%, and 40% for children aged 1, 2–12, and 13–15 years, respectively [6]. A two-dose regimen is recommended for all children aged 6 months to 12 years old regardless of recent immunization histories, and a single dose is recommended only for children 13 years and older in Japan [7]. In the United States, children who previously received ≥ 2 total doses of influenza vaccine ≥ 4 weeks apart before July 1 of the season require only one dose for the season, and others require two [8]. Dose volumes of 0.25 ml and 0.5 ml are recommended for children 6 months to 2 years old and for children 3 years old and over, respectively, similar to the United States.

Although children aged 6–11 months are included in the recommended group, the vaccine effectiveness (VE) for this specific age group has not been proved recently. Our series of VE studies since the 2013/14 season [7,9–13] demonstrated that vaccines in younger (6–11 months) and older (6–15 years old) children tended to be less effective. We showed significant VE against influenza A in the 2018/19 season for children aged 6–11 months (63% [95% confidence interval (CI), 15–84]) [7], but the VE for this age was not statistically significant against either influenza A and B in other seasons (95% CI of the odds ratio included 1.0). In one of our studies in the five-season analysis (2013/14–2017/18) [13], all age groups (1–2, 3–5, 6–12 years old) except 6–11 months showed significant VE for both influenza A and B. The small sample size in this age group in the dose analysis (none, once, or twice) may be one of the reasons for this result.

The purpose of this study was to measure the VE for preventing influenza by age group to investigate whether the recent vaccine can be recommended to all age groups of children, including 6–11 months and 6–15 years old, using the data on several seasons immediately before and during the COVID-19 era, including unreleased analysis for the 2019/20 season and dose (once or twice) analysis for 6 months to 12 years old.

2. Methods

As previously reported, we used a test-negative case-control design based on rapid influenza diagnostic test (RIDT) results to assess the VE. We enrolled children who were 6 months to 15 years old with a fever of ≥ 38 °C who were suspected of having influenza and had received an RIDT at one of our outpatient clinics at 20 hos-

pitals in the north (Gunma, Tochigi), middle (Saitama, Tokyo, Chiba), and south (Kanagawa, and Shizuoka) Kanto region in Japan between the 2013/14 and 2020/21 seasons (November 1–March 31). The data were obtained from the database that we used in our recent VE studies, including the risk analysis study [7,9–14].

2.1. Influenza vaccine strains and vaccine dose

Only trivalent (A(H1N1)pdm09, A(H3N2), and either of the Yamagata and Victoria lineages for type B) inactivated influenza vaccine (IIV) was licensed in the 2013/14 and 2014/15 seasons, and only quadrivalent (A(H1N1)pdm09, A(H3N2), and both of the Yamagata and Victoria lineages for type B) IIV has been licensed since the 2015/16 season in Japan. The vaccine strains in the 2013/14 to 2020/21 seasons are shown in [Supplementary Table 1](#) [15]. A two-dose regimen is recommended for all children aged 6 months to 12 years old in Japan [7].

2.2. Influenza diagnosis

Similar to our recent reports [7,9–14], nasopharyngeal swabs were obtained from patients. RIDT kits that were capable of differentiating between influenza A and influenza B were used. All of these kits have high sensitivity (approximately 85–95% and 83–93% for influenza A and B, respectively) and specificity (up to 100% for both influenza A and B) [7,16–18] compared to reverse transcription polymerase chain reaction (RT-PCR). A limited number of hospitals introduced Linjudge FluA/pdm (TAUNS Laboratories, Inc., Shizuoka, Japan), which is designed to detect A(H1N1)pdm09 with high sensitivity (97.6%) [18].

2.3. Case and control patient identification

Cases and controls were defined as RIDT-positive and RIDT-negative patients, respectively. Medical interviews and/or medical records from the Maternal and Child Health Handbooks provided by local governments were the source of vaccine information. Patients who had already been prescribed any anti-influenza viral drugs prior to the visit were excluded. All patients were enrolled during the period of influenza each season (December–March). Total number of lifetime doses of the vaccine was not investigated.

To analyze the VE for preventing hospitalization, cases and controls were defined as RIDT-positive and RIDT-negative hospitalized patients, respectively. The method for calculation is similar to that used in previous studies [12,13,19,20].

2.4. Evaluation of VE

VE was defined as “1- odds ratio (OR),” and OR was calculated as follows:

$$\text{VE} = 1 - \frac{(\text{Number of influenza-positives among vaccinated patients} \times \text{number of influenza-negatives among unvaccinated patients})}{(\text{number of influenza-negatives among vaccinated patients} \times \text{number of influenza-positives among unvaccinated patients})}$$

Adjustments to the VE are explained in “Statistical anal-

Table 1
Influenza A and B in children in the 2013/14–2019/20 seasons.

Clinical characteristics		Influenza A (%)	Influenza B (%)	Test-negatives (%)	Total
Season	Total	9347	4435	15,618	29,400
	2013/14	872 (9)	1403 (32)	2430 (16)	4705 (16)
	2014/15	1594 (17)	41 (1)	2016 (13)	3651 (12)
	2015/16	1146 (12)	1030 (23)	2215 (14)	4391 (15)
	2016/17	1562 (17)	261 (6)	2046 (13)	3869 (13)
	2017/18	878 (9)	1421 (32)	2659 (17)	4958 (17)
	2018/19	2135 (23)	10 (0)	2098 (13)	4243 (14)
	2019/20	1160 (12)	269 (6)	2154 (14)	3583 (12)
	Total	9347 (100)	4435 (100)	15,618 (100)	29,400 (100)
Months	November	166 (2)	4 (0)	806 (5)	976 (3)
	December	1963 (21)	192 (4)	3449 (22)	5604 (19)
	January	4498 (48)	1180 (27)	4508 (29)	10,186 (35)
	February	2301 (25)	1951 (44)	4328 (28)	8580 (29)
	March	419 (4)	1108 (25)	2527 (16)	4054 (14)
	Total	9347 (100)	4435 (100)	15,618 (100)	29,400 (100)
	Age groups	6–11 m/o	301 (3)	61 (1)	947 (6)
1–2 y/o		1589 (17)	400 (9)	5202 (33)	7191 (24)
3–5 y/o		2466 (26)	947 (21)	4411 (28)	7824 (27)
6–12 y/o		4172 (45)	2565 (58)	4298 (28)	11,035 (38)
13–15 y/o		819 (9)	462 (10)	760 (5)	2041 (7)
Total		9347 (100)	4435 (100)	15,618 (100)	29,400 (100)
Sex		female	4268 (46)	2042 (46)	7054 (45)
	male	5075 (54)	2392 (54)	8558 (55)	16,025 (55)
	Total	9343 (100)	4434 (100)	15,612 (100)	29,389 (100)
Underlying diseases	No	7784 (85)	3591 (82)	12,571 (83)	23,946 (83)
	Yes	1410 (15)	770 (18)	2664 (17)	4844 (17)
	Total	9194 (100)	4361 (100)	15,235 (100)	28,790 (100)
Visiting time after onset	less than 12 h	2901 (33)	1144 (28)	4448 (31)	8493 (31)
	12–48 h	5609 (63)	2530 (62)	8308 (58)	16,447 (60)
	48 h–	362 (4)	384 (9)	1550 (11)	2296 (8)
	Total	8872 (100)	4058 (100)	14,306 (100)	27,236 (100)
Treatment by neuraminidase inhibitors or baloxavir	No	270 (4)	135 (4)	10,516 (98)	10,921 (51)
	Yes	7101 (96)	2926 (96)	268 (2)	10,295 (49)
	Total	7371 (100)	3061 (100)	10,784 (100)	21,216 (100)
Vaccination	No	6016 (64)	2713 (61)	7541 (48)	16,270 (55)
	Yes	3331 (36)	1722 (39)	8077 (52)	13,130 (45)
	Total	9347 (100)	4435 (100)	15,618 (100)	29,400 (100)
Hospitalization	No	8470 (96)	4065 (97)	12,529 (94)	25,064 (95)
	Yes	391 (4)	114 (3)	752 (6)	1257 (5)
	Total	8861 (100)	4179 (100)	13,281 (100)	26,321 (100)

yses” below. The VE for preventing influenza A(H1N1)pdm09 was also analyzed in three hospitals where ImunoAce Flu and Linjudge FluA/pdm were utilized.

We recorded the number of vaccine doses per patient (none, one, or two) and compared the VE among them. Because a single dose is recommended only for children ≥ 13 years old, as explained above, this analysis was performed only among children aged 6 months to 12 years old including the sub-analysis for 6 months to 2 years old (for 0.25 ml/dose), and 6 months to 5 years (for young children).

2.5. Statistical analyses

Statistical analyses were performed using the SPSS 26.0 or 27.0 software program (IBM, Chicago, USA) and the BellCurve for Excel for Windows software program (Social Survey Research Information Co., Ltd., Tokyo, Japan). *p* less than 0.05 was considered statistically significant.

Binary logistic regression methods were used to analyze the VE. Confounding factors, such as sex, age (0–15 years old), comorbidity (yes or no), colder or warmer area (northern, middle, or southern area), month of onset, and season were entered in the analysis by the forced entry method. For the analysis by age group, we calculated the VE for 6–11 months, 1–2, combined 6 months–2 years (0.25 ml per dose), 3–5, 6–12 (elementary school age), and 13–15 years (junior high school age) separately. For some analyses,

the patients were limited to those who visited 12–48 h after onset as overall sensitivity analysis, as we have done in our previous studies [7,9–13], because the sensitivity in this period appeared more stable [9,18]. All but sex as confounding factors for adjustment have remained the same since our 2013/14 study [7,9–13].

2.6. Ethics

This study was approved by the Keio University Ethics Committee (Approval Number 20130216, recently revised in 2020) [7,9–14]. Eligible patients and their guardians were informed about the study objectives and methods verbally, via posters in outpatient clinics, or on our Japanese website.

3. Results

3.1. Characteristics of the vaccine dose analysis enrollees over seven seasons

The analysis was performed for the seven seasons (2013/14–2019/20) immediately before the COVID-19 era, as no cases were reported in the 2020/21 season. In the 2019/20 season, in the early phase of the COVID-19 era, a total of 3583 children aged 6 months to 15 years (1160, 269, and 2154 for influenza A and B, and test-negatives, respectively) were enrolled (Table 1). During the seven seasons from 2013/14 to 2019/20, a total of 29,400 children aged

6 months to 15 years (9347, 4435, and 15,618 for influenza A and B, and test-negatives, respectively) were enrolled. A total of 3500 to 5000 children were enrolled every year. The peak month of influenza A and B was January and February, respectively (Table 1).

The majority age group was 6–12 years for both influenza A and B and total participants. There were more boys (55%) than girls (45%). The percentage of children with any underlying disease was similar (15–18%) among influenza A and B, and test-negatives. Approximately 55% of patients with underlying disease had respiratory diseases (59%; 836/1410, 58%; 450/770, and 52%; 1395/2664 in influenza A and B, and test-negatives, respectively). More than 90% of children with influenza visited hospitals within 48 h. Also, 96% (7101/7371) and 96% (2926/3061) of the children with influenza A and B were treated with an anti-influenza agent (neuraminidase inhibitors or baloxavir), respectively, whereas only 2.5% (268/10784) were for test-negatives. Only 36% (3331/9347) and 39% (1722/4435) of the children with influenza A and B were vaccinated, respectively, whereas 52% (8077/15618) were for test-negatives. Approximately 5% of patients were hospitalized after diagnosis (Table 1).

3.2. Vaccine effectiveness for preventing influenza a illness and hospitalization, by age group

In the 2019/20 season, the adjusted VE for preventing influenza A illness was 44% (95 %CI, 35%–52%, n = 3290) (Table 2). The overall adjusted VE for seven seasons for preventing influenza A illness was 44% (95 %CI, 41%–47%, n = 24,419) and 48% (95 %CI, 44%–51%, n = 13,806) for all participants and those who visited 12–48 h after onset only, respectively.

Significant adjusted VE for preventing influenza A illness was shown for all age groups. The highest adjusted VE was 60% (95% CI, 55%–65%, n = 6611) for children aged 1–2 years old. Significant adjusted VE was also shown among the children aged 6–11 months (36% [95% CI, 10–55], n = 1210). Adjusted VE was 55% (95% CI, 42%–66%, n = 1136) and 44% (95% CI, 41%–47%, n = 20,851) for inpatients and outpatients, respectively. The former, which indicated the adjusted VE for preventing hospitalization, was higher but was not statistically significant (Breslow-Day test, *p* = 0.3972). Significant adjusted VE for preventing influenza A hospitalization was shown for all age groups between 1 and 12 years old (Table 2).

Table 2
Vaccine effectiveness (VE) against influenza A by age groups.

Characteristics	Influenza A						VE	95 %CI
	Total ^a		Cases ^a		Controls ^a			
			Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		
All children		24,965	3331	6016	8077	7541	48	(46–51)
All children ^b		24,419	3266	5924	7869	7360	44	(41–47)
All children ^c		13,806	1900	3676	4271	3959	48	(44–51)
All children, by age ^d								
	6–11 m	1210	50	245	216	699	36	(10–55)
	1–2 y	6611	555	1005	2935	2116	60	(55–65)
	6 m–2 y	7821	605	1250	3151	2815	57	(52–61)
	3–5 y	6707	893	1523	2463	1828	55	(51–60)
	6–12 y	8333	1561	2546	1996	2230	29	(22–35)
	13–15 y	1558	207	605	259	487	29	(11–43)
Inpatients, by age (hospitalization)	Any age ^b	1136	132	256	391	357	55	(42–66)
	6–11 m ^d	90	3	17	8	62	NA	NA
	1–2 y ^d	453	43	85	193	132	67	(48–78)
	6 m–2 y ^d	543	46	102	201	194	57	(35–71)
	3–5 y ^d	276	37	61	98	80	56	(22–75)
	6–12 y ^d	284	44	81	80	79	47	(10–68)
	13–15 y ^d	33	5	12	12	4	NA	NA
Outpatients ^b	Any age	20,851	2969	5435	6336	6111	44	(41–47)
All children, by season ^e	2013/14	3104	246	588	1204	1066	63	(56–69)
	2014/15	3497	622	934	1041	900	35	(25–44)
	2015/16	3260	377	741	1141	1001	56	(49–62)
	2016/17	3586	598	953	1080	955	38	(29–46)
	2017/18	3514	252	623	1218	1421	51	(42–58)
	2018/19	4168	754	1348	1019	1047	39	(30–46)
	2019/20	3290	417	737	1166	970	44	(35–52)
All children, by underlying diseases ^f	Without	20,347	2665	5116	6352	6214	45	(42–48)
	With	4072	601	808	1517	1146	39	(30–46)
Once compared with none ^b	6 m–2 y	4708	100	1250	543	2815	62	(53–70)
	6 m–5 y	8743	286	2773	1041	4643	58	(52–64)
	6 m–12 y	14,398	676	5319	1530	6873	46	(40–51)
Twice compared with none ^b	6 m–2 y	7137	496	1250	2576	2815	59	(54–64)
	6 m–5 y	13,090	1179	2773	4495	4643	57	(53–60)
	6 m–12 y	20,484	2324	5319	5968	6873	45	(42–49)
Twice compared with once ^b	6 m–2 y	3715	496	100	2576	543	–7	(–36–16)
	6 m–5 y	7001	1179	286	4495	1041	–4	(–21–10)
	6 m–12 y	10,498	2324	676	5968	1530	–7	(–20–4)

Patient number for adjusted analysis.

^b Adjusted for sex, age, comorbidity (yes or no), area (north, central, or south Kanto region), month of onset, and season.

^c The children who visited 12 to 48 h after onset only, and adjusted for sex, age, comorbidity (yes or no), area (north, central, or south Kanto region), month of onset, and season.

^d Adjusted for sex, comorbidity (yes or no), area (north, central, or south Kanto region), month of onset, and season.

^e Adjusted for sex, age, comorbidity (yes or no), area (north, central, or south Kanto region), and month of onset.

^f Adjusted for sex, age, area (north, central, or south area of the Kanto region), month of onset, and season.

NA, Not analyzed because of limited cases.

The influenza vaccine was significantly effective in all seven seasons. Among them, relatively higher adjusted VE (more than 50%) was observed in 2013/14, 2015/16, and 2017/18 seasons. There was no significant difference in the VE between participants with and without underlying diseases (Breslow-Day test, $p = 0.180$), and between one and two doses (see “Twice compared with once” at the bottom of Table 2).

3.3. Vaccine effectiveness against influenza A(H1N1)pdm09

Only three hospitals used Linjudge FluA/pdm to detect A(H1N1)pdm09 [18] (Table 3). The overall adjusted VE for seven seasons for preventing influenza A(H1N1)pdm09 illness was 63% (95% CI, 51%–72%, $n = 1603$) and 60% (95% CI, 38%–74%, $n = 589$) for all participants and those who visited 12–48 h after onset only, respectively (Table 3).

Significant adjusted VE for preventing influenza A(H1N1)pdm09 illness was shown for all age groups except 6–11 months and 13–15 years, in which the number of enrollees was insuffi-

cient. The highest adjusted VE was 79% (95% CI, 63%–88%, $n = 567$) for children aged 1–2 years old.

The influenza vaccine was significantly effective for all seven seasons except for the 2014/15 season in which no children were enrolled as unvaccinated cases. Among them, the relatively lower adjusted VE (less than 50%) was observed in the 2019/20 season. Similar to the VE against overall influenza A, there was no significant difference in the VE between participants with and without underlying diseases (Breslow-Day test, $p = 0.598$), and between one and two doses for children aged less than 13 (Table 3). In addition, the VE was not different between A/California/7/2009 (64%) and A/Singapore/GP1908/2015 (73%) as the vaccine strains of the seasons (Breslow-Day test, $p = 0.335$).

3.4. Vaccine effectiveness for preventing influenza B illness and hospitalization, by age group

In the 2019/20 season, the adjusted VE for preventing influenza B illness was 29% (95% CI, 5%–46%, $n = 2405$) (Table 4). The overall

Table 3
Vaccine effectiveness (VE) against influenza A(H1N1)pdm09 by age groups.

Characteristics	Influenza A(H1N1)pdm09						VE	95 %CI
	Total ^a		Cases ^a		Controls ^a			
			Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		
All children		1681	108	174	867	532	62	(50–71)
All children ^b		1603	106	171	828	498	63	(51–72)
All children ^c		589	54	75	290	170	60	(38–74)
All children, by age ^d								
	6–11 m	93	1	8	23	61	NA	NA
	1–2 y	567	21	48	336	162	79	(63–88)
	6 m–2 y	660	22	56	359	223	75	(58–85)
	3–5 y	444	25	39	236	144	59	(27–77)
	6–12 y	446	51	66	219	110	60	(38–74)
	13–15 y	53	8	10	14	21	NA	NA
Inpatients, by age (hospitalization)	Any age ^b	73	13	30	23	7	75	(–73–96)
	6–11 m ^d	NA	NA	NA	NA	NA	NA	NA
	1–2 y ^d	NA	NA	NA	NA	NA	NA	NA
	6 m–2 y ^d	NA	NA	NA	NA	NA	NA	NA
	3–5 y ^d	NA	NA	NA	NA	NA	NA	NA
	6–12 y ^d	NA	NA	NA	NA	NA	NA	NA
	13–15 y ^d	NA	NA	NA	NA	NA	NA	NA
Outpatients ^b	Any age	659	88	132	254	185	63	(44–76)
All children, by season ^e	2013/14	341	15	42	184	100	80	(61–89)
	2014/15	116	1	0	71	44	NA	NA
	2015/16	356	40	49	158	109	53	(20–72)
	2016/17	154	2	8	92	52	84	(20–97)
	2017/18	239	7	18	125	89	72	(27–89)
	2018/19	167	10	26	84	47	74	(39–89)
	2019/20	230	31	28	114	57	45	(–8–72)
All children, by underlying diseases ^f	without	1054	67	120	530	337	66	(53–76)
	with	549	39	51	298	161	56	(30–73)
Once compared with none ^b	6 m–2 y	332	3	56	50	223	79	(29–94)
	6 m–5 y	569	12	95	95	367	55	(13–76)
	6 m–12 y	813	25	161	150	477	59	(34–75)
Twice compared with none ^b	6 m–2 y	603	19	56	305	223	77	(60–87)
	6 m–5 y	992	35	95	495	367	73	(59–82)
	6 m–12 y	1369	73	161	658	477	67	(56–76)
Twice compared with once ^b	6 m–2 y	377	19	3	305	50	1	(–259–72)
	6 m–5 y	637	35	12	495	95	35	(–34–68)
	6 m–12 y	906	73	25	658	150	10	(–51–46)
All children ^{b, g}	2013/14–16/17	967	58	99	505	305	64	(49–75)
	2017/18–18/19	406	17	44	209	136	73	(50–86)

^a Patient number for adjusted analysis (limited number of hospitals introduced Linjudge FluA/pdm).

^b Adjusted for sex, age, comorbidity (yes or no), area (north, central, or south Kanto region), month of onset, and season.

^c The children who visited 12 to 48 h after onset only, and adjusted for sex, age, comorbidity (yes or no), area (north, central, or south Kanto region), month of onset, and season.

^d Adjusted for sex, comorbidity (yes or no), area (north, central, or south Kanto region), month of onset, and season.

^e Adjusted for sex, age, comorbidity (yes or no), area (north, central, or south Kanto region), and month of onset.

^f Adjusted for sex, age, area (north, central, or south area of the Kanto region), month of onset, and season.

^g 2013/14–16/17 and 2017/18–18/19 seasons for the vaccine strains A/California/7/2009 and A/Singapore/GP1908/2015, respectively

NA, Not analyzed because of limited cases.

NA, Not analyzed because of limited cases.

Table 4
Vaccine effectiveness (VE) against influenza B by age groups.

Characteristics	Influenza B						VE	95 %CI
	Total ^a	Cases ^a		Controls ^a				
		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated			
All children	20,053	1722	2713	8077	7541	41	(37–45)	
All children ^b	19,589	1691	2669	7869	7360	37	(32–42)	
All children ^c	10,742	954	1558	4271	3959	39	(33–45)	
All children, by age ^d								
6–11 m	973	8	50	216	699	39	(–34–72)	
1–2 y	5445	158	236	2935	2116	52	(41–61)	
6 m–2 y	6418	166	286	3151	2815	48	(36–57)	
3–5 y	5224	397	536	2463	1828	50	(42–57)	
6–12 y	6746	1007	1513	1996	2230	33	(26–40)	
13–15 y	1201	121	334	259	487	40	(21–54)	
Inpatients, by age (hospitalization)								
Any age ^b	856	51	57	391	357	33	(–5–57)	
6–11 m ^d	72	1	1	8	62	NA	NA	
1–2 y ^d	348	12	11	193	132	27	(–80–70)	
6 m–2 y ^d	420	13	12	201	194	–7	(–149–54)	
3–5 y ^d	201	9	14	98	80	59	(–7–84)	
6–12 y ^d	215	28	28	80	79	0	(–106–52)	
13–15 y ^d	20	1	3	12	4	NA	NA	
Outpatients ^b	16,480	1557	2476	6336	6111	37	(32–42)	
All children, by season ^e								
2013/14	3633	597	766	1204	1066	25	(14–36)	
2014/15	1982	15	26	1041	900	50	(2–74)	
2015/16	3146	410	594	1141	1001	34	(22–44)	
2016/17	2296	105	156	1080	955	39	(19–55)	
2017/18	4052	452	961	1218	1421	37	(28–46)	
2018/19	2075	3	6	1019	1047	NA	NA	
2019/20	2405	109	160	1166	970	29	(5–46)	
All children, by underlying diseases ^f								
without	16,156	1353	2237	6352	6214	36	(30–41)	
with	3433	338	432	1517	1146	43	(33–53)	
Once compared with none ^b								
6 m–2 y	3673	29	286	543	2815	41	(12–61)	
6 m–5 y	6614	108	822	1041	4643	42	(28–54)	
6 m–12 y	11,076	338	2335	1530	6873	30	(20–39)	
Twice compared with none ^b								
6 m–2 y	5811	134	286	2576	2815	57	(46–65)	
6 m–5 y	10,403	443	822	4495	4643	53	(46–59)	
6 m–12 y	16,375	1199	2335	5968	6873	40	(35–45)	
Twice compared with once ^b								
6 m–2 y	3282	134	29	2576	543	26	(–14–51)	
6 m–5 y	6087	443	108	4495	1041	17	(–5–34)	
6 m–12 y	9035	1199	338	5968	1530	12	(–3–24)	

^a Patients number for adjusted analysis.

^b Adjusted for sex, age, comorbidity (yes or no), area (north, central, or south area of the Kanto region), month of onset, and season.

^c The children who visited 12–48 h after the onset only, and adjusted for sex, age, comorbidity (yes or no), area (north, central, or south area of the Kanto region), month of onset, and season.

^d Adjusted for sex, comorbidity (yes or no), area (north, central, or south area of the Kanto region), month of onset, and season.

^e Adjusted for sex, age, comorbidity (yes or no), area (north, central, or south area of the Kanto region), and month of onset.

^f Adjusted for sex, age, area (north, central, or south area of the Kanto region), month of onset, and season.

NA, Not analyzed because of limited cases.

adjusted VE for seven seasons for preventing influenza B illness was 37% (95% CI, 32%–42%, n = 19,598) and 39% (95% CI, 33%–45%, n = 10,742) for all participants and those who visited 12–48 h after onset only, respectively (Table 4).

Significant adjusted VE for preventing influenza B illness was shown for all age groups except for 6–11 months old. The highest adjusted VE was 52% (95% CI, 41%–61%, n = 5445) for children aged 1–2 years old. Adjusted VE for preventing hospitalization was not significant (33% [95% CI, –5%–57%, n = 856]).

The influenza vaccine was significantly effective for all seven seasons except for the 2018/19 season in which only 9 children developed influenza B. The VE in the trivalent 2013/14 to 2014/15 seasons of 32% (n = 5615) was significantly lower than the VE in the quadrivalent 2015/16 to 2017/18 and 2019/20 seasons of 45% (n = 13,974) (Breslow-Day test, p = 0.007). There was no significant difference in the VE between participants with and without underlying diseases (Breslow-Day test, p = 0.991, and between one and two doses for children aged less than 13 (Table 4).

4. Discussion

The vaccine was significantly effective against influenza A and B in all age groups, except among children 6–11 months against influenza B. Compared to our recent reports [7,9–13], we have newly shown 1) overall adjusted analysis of the seven most recent consecutive seasons, 2) sex-adjusted data, 3) significant adjusted VE for children aged 6–11 months (influenza A) and 13–15 years, and 4) decreased VE against A(H1N1)pdm in the 2019/20 season.

In most of our previous data, the VE for children 6–11 months has not been investigated statistically [7,9–13]. Although the VE is not high, the children in this age group were also protected by IIV in the present study. This suggests that recent IIV should be recommended for all children, including infants aged 6–11 months.

Interestingly, the adjusted VE was the highest in the 1–2-year-old groups against all influenza subtypes (influenza A, A(H1N1)pdm09, and B for 60%, 79%, and 52%, respectively). One of the explanations is immaturity of the immune system in the children aged 6–11 months. Also, both vaccinated and unvaccinated older

children tended to have a similar level of immunity at baseline, because of the possible prior history of immunization or influenza itself [9]. In other words, both vaccinated and unvaccinated older children tended to have a similar antibody titer at baseline. In fact, the pre-seasonal titers of serum hemagglutination inhibition (HAI) antibodies increased with age during childhood against almost all influenza types every season according to the national surveillance data [6].

Similar to our report, the VE among children aged 1–2 years was higher (63%) than the VE among children aged 2–5 years (45%–57%) in a prospective, non-randomized, observational study [21]. In contrast, according to a recent report in Australia, the adjusted VE analyzed by a matched case-control study increased with age among children 6 months to 4 years [22]. However, it is difficult to compare the VE with the previously published data because we could not exclude the effect of infection history or previous immunization, maternal immunization during pregnancy, dose-effect (once or twice), and difference in analyzed season and methodology.

The adjusted VE for preventing hospitalization was significant in influenza A as seen in adults [19,20]. Similar to overall VE against influenza A, the VE in younger children (1–2 years) was the highest (67% [95% CI, 48–77]). The adjusted VE for influenza B was statistically insignificant, probably because older children (less effective) tended to be hospitalized more often in influenza B than in influenza A. (Table 2 and 4). Influenza B still causes mortality and has an impact on children, although it is reported to be less severe than influenza A [23,24]. Actually, in the present study, the hospitalization rate was not low in influenza B (4% and 3% among influenza A and B, respectively, Table 1).

There is no data to explain why not all children aged 6 months to 12 years old receive two doses. We suppose that some children do not receive the vaccine twice because the cost (approximately \$30–40 per dose) is not covered by national health insurance or the national government, because parents/guardians do not have time to take their children to the clinic, or because parents/guardians forget to arrange the second vaccination. Vaccine dose (once or twice) may influence the VE among young children [22,25,26]. However, no significant difference was observed in the present overall age-adjusted analysis when once or twice vaccine doses were compared (Table 2–4). We reported previously that only the two-dose regimen was effective in preventing influenza B in some seasons (2013/14, 2015/16, and 2016/17) or in some age groups (6 months–2 years old) [13], and that only the two-dose regimen is effective in children aged 6 months to 12 years in one of our related hospitals [27]. In a systematic review, the VE was higher for fully vaccinated children than for partially vaccinated children, especially those aged 6 to 23 months [25]. Similarly, another report showed that the adjusted VE against any influenza was 51% (95% CI 44–57) and 41% (95% CI 25–54) among fully and partially vaccinated children aged 6 months to 8 years, respectively [26]. We speculate that the VE related to vaccine dose depends on many factors, including history of immunization and influenza infection [22], seasons, and vaccine mismatch. Thus, the two-dose regimen can be recommended, especially for younger children.

The adjusted VE against influenza A varied with the season. The most reliable explanation was that the VE was higher in the seasons when A(H1N1)pdm was dominant or comparable to A(H3N2), as the ratios of A(H1N1)pdm09 to A(H3N2) in Japan ((Supplementary Table 1) [15]. The present data on the adjusted VE against influenza A(H1N1)pdm in three institutes (Table 3) also supported this explanation. However, the adjusted VE in the 2019/20 season was relatively low when most of the influenza A was A(H1N1)pdm09 [15]. The lower or non-significant effectiveness against A(H1N1)pdm09 in the 2019/20 season in children

was also reported [28,29]. The recent accumulation of several substitutions of antigenic sites, including N156K of HA protein, led to immune selection pressure [30]. This N156K escape mutant increased up to 7% and 9% of isolated A(H1N1)pdm09 viruses in Japan [31] and in one of the study areas, Yokohama City [32], respectively, in the 2019/20 season. In contrast, the adjusted VE against influenza B remained constant in both trivalent and quadrivalent seasons, except for the 2014/15 and 2018/19 seasons when only a small number of children developed influenza B. The VE in the trivalent seasons was significantly lower than the VE in the quadrivalent seasons. Quadrivalent vaccine, which includes two lineages of influenza B, is more recommended than trivalent vaccine, which includes only one of the two lineages.

The reasons why we recommend effective influenza vaccine for children in this COVID-19 era are as follows: first, the timing and intensity of the upcoming influenza seasons cannot be predicted during the COVID-19 era. Regardless of vaccine status or pre-seasonal titers of serum HAI antibodies against the vaccine strains [6], the estimated influenza incidence in Japan was extremely low, as only five virus strains (0.07%) were isolated in the Japanese 2020/21 surveillance compared with 7518 strains (the average number) in the 2016/17–2019/20 surveillance [33]. A similar phenomenon was observed worldwide, including both northern and southern hemispheres, in 2020 [34,35]. However, the number of isolated influenza viruses in 2021 is increasing compared to 2020 in both the Southeast Asia region [36] and the southern hemisphere [37]. This may be a sign of major influenza activity in the near future. Second, theoretically, immunity to influenza viruses likely waned due to the low influenza activity in 2020, especially among young children who have not been previously immunized or who have had no natural exposure. A delayed or unseasonable influenza epidemic may arise, as seen in the respiratory syncytial virus epidemic [38,39]. Third, recent reports have revealed that immunization with influenza vaccine is associated with reduced symptoms and mortality among patients with COVID-19, including children [40–43], possibly through the mechanism such as virus interference induced by the vaccine.

The strength of our study was the large number of participants and adjustments with many confounding factors. A key limitation of our series was that our diagnostic tools were RIDTs, not RT-PCR. The sensitivity of RIDTs in children was reported to be low (61.2% for influenza A and 65.7% for influenza B in children), but the specificity was high (99.2% for influenza A and 99.6% for influenza B) [44]. In this report [44], the timing of the sample collection was not mentioned, and nasal and throat specimens were included. The World Health Organization Agenda for Public Health [45] states that the reliability of RIDTs in Japan appears to be higher than that in other countries, as most patients are tested within 48 h of illness onset, as seen in our report. In addition, the bias in test-negative design is influenced by the low specificity of RIDTs rather than low sensitivity [46]. Although the use of RIDT kits for clinical testing may lead to underestimation of the VE [47,48], we have shown the significant VE even using the RIDT kits. Also, we have repeatedly discussed this problem in our previous studies and the kits that we used have good sensitivities, including ImunoAce Flu [7,9–13,18]. Another disadvantage of the RIDTs was that they were unable to discriminate between the two subtypes of influenza A (A(H1N1)pdm09 and A(H3N2)) and between the two lineages (Yamagata and Victoria) of influenza B. Because we enrolled many children, the estimated epidemiological distribution of the two subtypes of influenza A and the two lineages of influenza B is similar to the local and national data. Because the influenza virus is usually detected by RIDT [16,17] 48 h after the onset of influenza, when antivirals should be started [49], we believe that RIDT is useful in the diagnosis of clinical influenza. In addition, the PCR method is not routinely available in outpatient

clinics. A second limitation is the possible fluctuation of the estimation of the VE in case-control design in clinical settings [50,51]. Another limitation is that we combined the seasonal data. However, we always adjusted the data by season. We believe that this combined but adjusted data may lead to an answer to the question, “Is IIV effective overall?”.

5. Conclusions

In conclusion, during the recent seven seasons immediately before the COVID-19 era, IIV was effective against both influenza A and B in all age groups of children, except for influenza B in infants aged 6–11 months. The highest VE was observed among 1–2 year olds in both influenza A and B. Also, the vaccine is effective in preventing hospitalization with influenza A for children aged 1–12. As approximately half of children are not immunized every year in Japan [6], IIV should be recommended to children of all age groups to reduce both influenza illness and influenza hospitalization.

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Declaration of Competing Interest

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Appendix A. Supplementary data

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