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Effectiveness of inactivated influenza vaccine in children by vaccine dose, 2013–18

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ABSTRACT

Objectives: We assessed the vaccine effectiveness (VE) of inactivated influenza vaccine (IIV) by vaccine dose in children aged 6 months to 12 years for whom two doses are recommended in Japan to ascertain the appropriate vaccine doses.
Methods: VE was assessed according to a test-negative case-control design based on rapid influenza diagnostic test (RIDT) results. Children aged 6 months to 12 years with a fever ≥38 °C who had received an RIDT in outpatient clinics of 24 hospitals were enrolled for all five seasons since 2013/14. VE by vaccine dose (none vs. once or twice, and once vs. twice) was analyzed.
Results: In the dose analysis, 20,033 children were enrolled. Both one- and two-dose regimens significantly reduced cases in preventing any influenza, influenza A, and influenza B, but there was no significant difference in adjusted VE between one- and two-dose regimens overall (adjusted OR, 0.560 [95% CI, 0.505–0.621], 0.550 [95% CI, 0.516–0.586]), 0.549 [95% CI, 0.517–0.583], and 1.014 [95% CI, 0.907–1.135], for none vs. once, none vs. twice, none vs. once or twice, and once vs. twice for any influenza, respectively). Both one- and two-dose regimens significantly reduced cases with any influenza and influenza A every season. Also, both regimens significantly reduced cases of any influenza, influenza A, and

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influenza B among children aged 1–12 years, especially among those aged 1–5 years. In the 2013/14, 2015/16, and 2016/17 seasons, however, only the two-dose regimen was significantly effective in preventing influenza B. Both one- and two-dose regimens significantly reduced cases involving hospitalization due to any influenza and influenza A.

Conclusions: Both one- and two-doses regimens of IIV were effective in preventing influenza for children aged 6 months to 12 years. The two-dose regimen was more effective against influenza B in some seasons.

1. Introduction

Immunization with influenza vaccine is the most effective way to prevent infection and severe complications caused by influenza A and B viruses. Influenza vaccine is especially effective for children aged 1–5 years [1–4]. Routine annual influenza vaccination is recommended for all persons aged 6 months and older without contraindications [5,6]. Only inactivated influenza vaccine (IIV) is licensed in Japan.

We have calculated vaccine effectiveness (VE) using similar methods every season in order to compare VE over time [1–4]. To investigate VE of influenza vaccine, a test-negative case-control (TNCC) design has become the standard design in recent years [7–11], replacing prospective design [12,13]. Children with fever during an influenza epidemic in Japan can conveniently receive a rapid influenza diagnostic test (RIDT), which is covered by the Japanese universal insurance system, and we have used the results of these RIDTs in our studies since 2013/14 [1–4]. From these studies, adjusted VE rates against influenza A during A (H1N1)pdm09 seasons, against influenza A during A(H3N2) seasons, and against influenza B in trivalent and quadrivalent eras were approximately 60%, 35%, 25% and 35%, respectively.

According to the recommendations of the Advisory Committee on Immunization Practices (ACIP) [5], children aged 6 months through 8 years require two doses of influenza vaccine administered at least 4 weeks apart during their first season of vaccination for optimal protection. Children aged 6 months through 8 years who have previously received more than two total doses at least 4 weeks apart before July 1 require only one dose for the upcoming season. Children in this age group who have previously received no or only one dose of trivalent or quadrivalent influenza vaccine before July 1 require two doses at least 4 weeks apart for the upcoming season. The American Academy of Pediatrics also supports this recommendation [6]. These recommendations were based on data from the 2003/04 or 2004/05 influenza seasons for children aged 6–21 months old [14], 6–59 months old [15], 6 months to 8 years [16] and 5–8 years old [17].

In Japan, only one 0.5 ml dose is recommended for children aged 13 years and over according to the Japanese interview forms, but a two-dose regimen is still recommended for all children aged 6 months to 12 years, regardless of whether they have received vaccination previously [18]. Two 0.25 ml doses and two 0.5 ml doses are recommended for children aged 6 months to 2 years and 3–12 years, respectively. However, not all vaccinated children aged 6 months to 12 years receive two doses [19].

The purpose of this study was to compare VE in children aged 6 months to 12 years by vaccine dose over the last five seasons (2013/14–2017/18) to ascertain the appropriate vaccine doses.

2. Methods

To assess VE in each of the last five seasons, we used similar methods including enrollment and location, influenza diagnostic methods, case and control patient identification, and TNCC design for VE [1–4,20,21]. These methods are briefly summarized here.

2.1. Influenza vaccine strains

Only trivalent IIV was licensed in the 2013/14 and 2014/15 seasons, and only quadrivalent IIV was licensed in the 2015/16–2017/18 seasons. Vaccine strains are shown in Table 1.

2.2. Diagnosis of influenza

Nasopharyngeal swabs were obtained from all enrollees. Several different RIDT kits capable of differentiating between influenza A and influenza B were used in the hospitals. RIDT is used in daily practice and covered by the Japanese universal insurance system. Different institutions chose to use different RIDT kits, but doctors and nurses followed the manufacturers' instructions for all kits. The same kits were used this year as in the 2016/17 season: ImmunoAce FLU (http://www.info.pmda.go.jp/tgo/pack/22000AMX01876000_A_01_10/) (Tauns Laboratories, Inc., Shizuoka, Japan), Quick Chaser Flu A, B (http://www.info.pmda.go.jp/tgo/-pack/22300AMX00568000_A_01_10/22300AMX00568000_A_01_10) (Mizuho Medy Co., Ltd., Saga, Japan), QuickNavi Flu (http://www.info.pmda.go.jp/tgo/pack/22000AMX01645000_A_01_11/) (Denka Seiken Co., Ltd., Tokyo, Japan), Espline Influenza A&B-N (http://www.info.pmda.go.jp/tgo/pack/21500AMZ00511000_A_01_08/) (Fujirebio Inc., Tokyo, Japan), Spotchem FLORA FluAB (http://www.info.pmda.go.jp/tgo/pack/22800EZX00045000_A_01_03/) (Arkray, Inc., Kyoto, Japan), and BD Veritor System (http://www.info.pmda.go.jp/tgo/pack/22400AMX00064000_A_01_04/) (Nippon Becton Dickinson Company, Ltd., Tokyo, Japan) [3]. According to the manuals, all of these have high sensitivity (approximately 90–95%) and specificity (up to 100%) [3].

2.3. Case and control patient identification

The RIDT-positive patients were enrolled as cases, and the RIDT-negative patients as controls. Information regarding symptoms, influenza vaccination, the number of vaccine doses (one or two), influenza complications, sex, age, comorbidities, and treatment with anti-influenza viral drugs was collected and recorded. The source of vaccination information, including doses, was medical records or self-reports made by parents. One study found that decreased exposure specificity (poorer identification of non-vaccinees) had the greatest impact on influenza VE estimation [22]. In our study, however, the Maternal and Child Health Handbooks provided by local governments were used, in which all vaccinations are recorded by the physicians in charge. Those who had already taken anti-influenza viral drugs prior to the visit were excluded.

2.4. VE by vaccine dose

In similar studies on VE in previous seasons (2013/14–2016/17), we used the databases of 24 hospitals [1–4]. In these studies, we recorded numbers of vaccine doses per patient (none, once or twice) and compared the odds ratios for developing influenza. The odds ratios were calculated between all three

Table 1
Influenza epidemics in Japan (2013/14 to 2017/18).

Seasons	Subtypes or lineages	Vaccine strains	Epidemic strains in Japan*	Antigenical difference to vaccine strains*	Epidemic peak months according to weekly reports*
2013/14	A(H1N1)pdm09	A/California/7/2009	43%	Not reported	January
	A(H3N2)	A/Texas/50/2012	21%	Not reported	January
	B/Yamagata	B/Massachusetts/2/2012	24%	Not reported	February to March
	B/Victoria	None	9%	Not reported	January to March
2014/15	A(H1N1)pdm09	A/California/7/2009	1%	Similar	
	A(H3N2)	A/New York/39/2012	85%	Distant**	January
	B/Yamagata	B/Massachusetts/2/2012	12%	Similar	February to March
	B/Victoria	None	1%	Similar	
2015/16	A(H1N1)pdm09	A/California/7/2009	48%	Similar	February
	A(H3N2)	A/Switzerland/9715293/2013	8%	50% similar**	January
	B/Yamagata	B/Phuket/3073/2013	24%	Similar	February to March
	B/Victoria	B/Texas/2/2013	18%	Similar	January to March
2016/17	A(H1N1)pdm09	A/California/7/2009	4%	Similar	
	A(H3N2)	A/Hong Kong/4801/2014	78%	50% similar**	January
	B/Yamagata	B/Phuket/3073/2013	8%	Similar	March
	B/Victoria	B/Texas/2/2013	9%	Similar	March
2017/18	A(H1N1)pdm09	A/Singapore/GP1908/2015	24%	Similar	December
	A(H3N2)	A/Hong Kong/4801/2014	30%	50% similar**	January
	B/Yamagata	B/Phuket/3073/2013	44%	Similar	January
	B/Victoria	B/Texas/2/2013	1%	Similar	

Underlines present the major circulating virus strain in each season.
* Reported by the National Institute of Infectious Diseases [23].
** In addition, influenza A(H3N2) viruses are more likely to result in antigenic changes when they are grown in eggs.

groups (“none,” “once”, and “twice”) using three or four combinations (1. none vs. once, 2. none vs. twice, 3. none vs. once or twice, and/or 4. once vs. twice). Children aged 13 years and over were excluded from this analysis because the two-dose regimen is not recommended for them. A TNCC design was used to estimate odds ratios based on RIDT results. We also calculated the adjusted odds ratio. VE at preventing hospitalization due to influenza by vaccine dose for this age group was estimated by a TNCC method similar to that described above.

2.5. Statistics and ethics

Statistical analysis was performed using SPSS 24.0 software (IBM, U.S.A.) and the Ekuseru-Toukei 2015 for Windows software program (Social Survey Research Information Co., Ltd., Tokyo, Japan). To reduce the chance of type-1 errors, p values were Bonferroni corrected for the dose analysis (p value < 0.05/4 = 0.0125 is significant for the combinations described above). This study was approved by the Keio University Ethics Committee (Approval Number 20130216, first version approved in 2013 and revised version in 2018).

3. Results

3.1. Vaccine strains and epidemic strains in Japan

Antigenic differences between vaccine strains and epidemic strains, along with peak months of epidemics in each season (2013/14–2017/18) are summarized in Table 1 [23].

3.2. Characteristics of the enrollees for the vaccine dose analysis over five seasons

A total of 21,715 children aged 6 months to 12 years were enrolled during the five seasons from 2013/14 to 2017/18, but 1682 of them were excluded for reasons described in Fig. 1. Among 20,033 matched enrollees, 9215 were RIDT-positive (5539 with influenza A and 3676 with influenza B) and 10,818 were RIDT-negative.

The characteristics of the enrollees are shown in Table 2. The epidemic peak months of influenza A and influenza B were January and February, respectively. Of the RIDT-positive children, 94% (8053/8620) had been brought to the hospital within 48 h of onset. The overall vaccine coverage rates were 36% (2015/5539), 40% (1459/3676), and 52% (5662/10,818) for influenza A-positive patients, influenza B-positive patients, and control patients (RIDT-negative), respectively (Table 2). Of the influenza A-positive patients, 64%, 8% and 28% had received zero, one and two doses; for the influenza B-positive patients, these figures were 60%, 9% and 31%, and for the influenza-negative patients, 48%, 11% and 41%.

The number of patients by vaccine dose for each season and for each age group are shown in Table 3a.

3.3. Vaccine effectiveness by vaccine dose for five seasons (6 months to 12 years old)

In general, both one- and two-dose regimens significantly reduced cases with any influenza, influenza A and B (Table 3b, top, “none vs. once”, “none vs. twice” and “none vs. once or twice”), and there was no significant difference in adjusted VE between one- and two-dose regimens (Table 3b, “once vs. twice”). Only the two-dose regimen was effective (Bonferroni-corrected α P value < 0.05/4) in preventing influenza B in 2013/14 (Adjusted OR, 0.731 [95% CI, 0.62–0.862]), 2015/16 (Adjusted OR, 0.627 [95% CI, 0.522–0.753]), and 2016/17 (Adjusted OR, 0.545 [95% CI, 0.392–0.759]) (Table 3b, middle). No VE difference was observed between one- and two-dose regimens in the analysis by age group except in “6 months to 2 years” for influenza B (Table 3b, bottom). The VE in preventing influenza B in the 2015/16–2017/18 seasons (both lineages of type B antigen was included in the vaccine) was superior to the VE in the 2013/14 and 2014/15 seasons (only a lineage of type B antigen was included in the vaccine) (The odds ratios, 0.56 and 0.68; N = 8928 and 5566, respectively; Breslow-Day test, p = 0.0182).

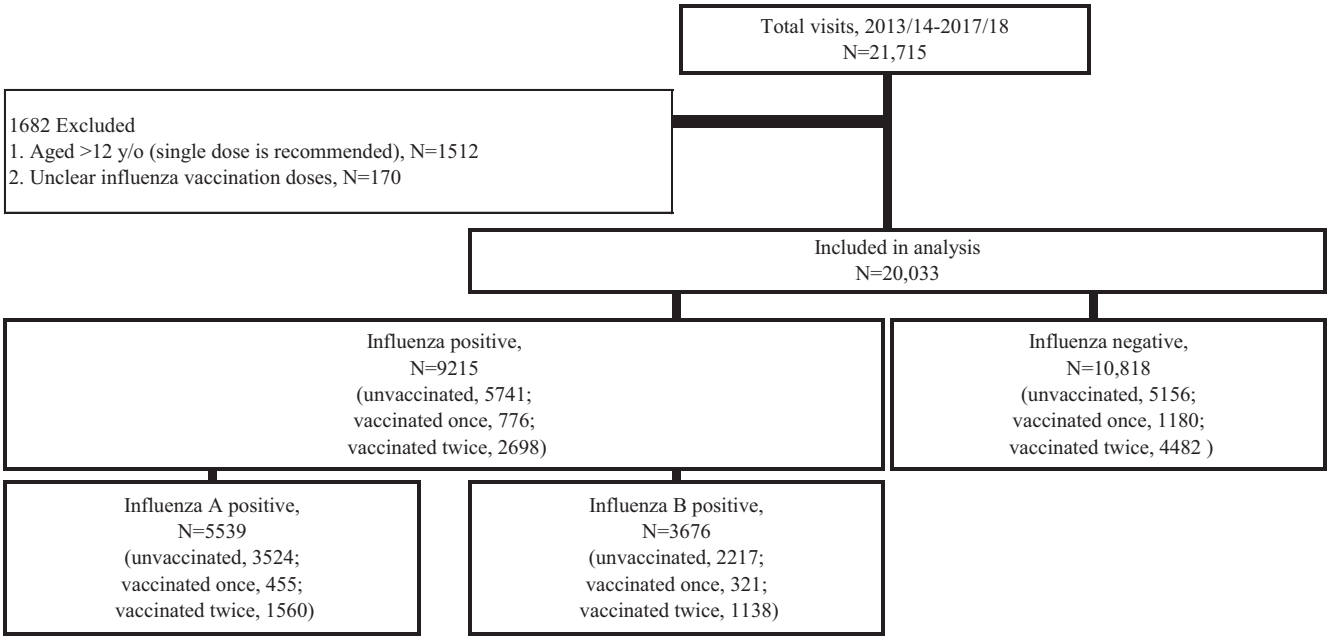

Fig. 1. Flow diagram of enrollees for vaccine effectiveness by vaccine doses for influenza in children aged 6 months to 12 years (2013/14–2017/18).

VE at preventing hospitalization was significant for any influenza and influenza A (Table 4a, "none vs. once", "none vs. twice" and "none vs. once or twice"). The adjusted VE against any influenza was 59% (95% CI, 37–73) for "none vs. once" and 41% (95% CI, 26–53) for "none vs. twice". There was no significant difference in adjusted VE between the regimens. The adjusted VE against any influenza, influenza A and influenza B among non-hospitalized patients was significant for "none vs. once", "none vs. twice" and "none vs. once or twice" (Table 4b). There was no significant difference between the regimens.

4. Discussion

This is our fifth study on VE against pediatric influenza in a metropolitan area in Japan since the 2013/14 season. 3000–5000 children have been enrolled every season. In the portion of this study assessing VE by vaccine dose over five years, more than 20,000 children aged 6 months through 12 years were enrolled.

We have previously reported VE by vaccine dose for single seasons only and with unadjusted data [1,3,4]. Here we show adjusted VE by vaccine dose for five consecutive seasons, as well as VE for each single season and for each age group (Table 3). Both one- and two-dose regimens were effective at preventing influenza A and B in our five-year combined analysis. Both one- and two-dose regimens significantly reduced cases of any influenza and influenza A every season. Children aged 1–12 years, especially those aged 1–5 years, were effectively protected against influenza.

Only the two-dose regimen was effective against influenza B in three seasons: 2013/14, 2015/16 and 2016/17. One of the explanations for this may involve the delayed epidemic months of influenza B (Table 1). In general, the epidemic months of influenza B are February and March every year [2–4]. In 2017/18, when, unusually, the one- and two-dose regimens were equally effective against influenza B, the epidemic peak was earlier, in January. This correlation may have occurred because the vaccine immunity induced by only one dose (usually administered in October or November) may not persist until March in some patients. It has been reported that the immunogenicity of one highly-purified inactivated, egg-based trivalent influenza vaccine made in China met immunological standards after one month and geometric mean titers peak could persist at least into the third month [24]. Similarly, according to the Japanese interview form for IIV, VE persists for three months but may be shorter in non-priming patients [18]. In a 24-year study during 1984–2007 in a single elementary school, there was a significant inverse correlation between the vaccine coverage rates and both the number of class cancellation days and absentee rates [25]. Classes were cancelled in 13 of the 24 influenza seasons, and the main circulating virus was influenza B virus (6 out of the 13 seasons). As influenza B virus plays a major role in school outbreaks, it warrants more attention. Moreover, we also showed superior immunogenicity for the additional lineage of influenza B of the quadrivalent vaccine as previously reported [26,27]. Further studies regarding VE against influenza B by vaccine dose as well as the timing of the second shot are needed.

Adjusted VE at preventing hospitalization due to influenza A in the five-season analysis for children 6 months to 12 years was significant. The VE values at preventing hospitalization for any influenza, influenza A and influenza B were 46% (95% CI, 33–56), 50% (95% CI, 36–60) and 31% (95% CI, 4–51), respectively, and were similar to the adjusted VE among non-hospitalized patients (Table 4). The effectiveness of neuraminidase inhibitors was not included in our study because all enrolled hospitalized children were hospitalized just after the diagnosis of influenza and before treatment. The VE at preventing influenza B hospitalization by vaccine dose should be interpreted carefully because few patients receiving the one-dose regimen were hospitalized for influenza B throughout the study period (Table 4a). In the present analysis, the two-dose regimen offers no significant benefit against influenza B hospitalization.

The reliability of RIDT has been questioned. A recent published systematic review and meta-analysis incorporating 130 studies reported that, compared with real-time reverse-transcriptase polymerase chain reaction (RT-PCR), pooled sensitivities for detecting influenza A and B were 54.4% (48.9–59.8) and 53.2% (41.7–64.4), respectively, although pooled specificity was high (>98%) [28]. For two reasons, however, we believe that our RIDT results are more reliable than theirs were. First, the timing of clinical sampling in the compiled studies was not recorded in the review, though

Table 2
Characteristics of the children aged 6 months to 12 years enrolled in influenza vaccine effectiveness analysis by dose (N = 20,033) (2013/14–2017/18).

	Any influenza		Type A		Type B		Influenza negative		Difference between any influenza and influenza negative p-value, Cramer's V
	N = 9215	(%)	5539	(%)	3676	(%)	10,818	(%)	
Sex									
Female	4246	(46)	2524	(46)	1722	(47)	4903	(45)	p = 0.290
Male	4967	(54)	3014	(54)	1953	(53)	5911	(55)	0.007
Not reported	2	(0)	1	(0)	1	(0)	4	(0)	
Total	9215		5539		3676		10,818		
Age									
6–11 m/o	252	(3)	194	(4)	58	(2)	692	(6)	
1–2 y/o	1450	(16)	1072	(19)	378	(10)	3786	(35)	p < 0.001
3–5 y/o	2512	(27)	1624	(29)	888	(24)	3216	(30)	0.287
6–12 y/o	5001	(54)	2649	(48)	2352	(64)	3124	(29)	
Total	9215		5539		3676		10,818		
Comorbidity									
No	7517	(83)	4546	(84)	2971	(82)	8706	(83)	p = 0.688
Yes	1522	(17)	882	(16)	640	(18)	1790	(17)	0.003
Total	9039		5428		3611		10,496		
Province									
North	930	(10)	568	(10)	362	(10)	1129	(10)	
Central	4358	(47)	2685	(48)	1673	(46)	5216	(48)	p = 0.186
South	3927	(43)	2286	(41)	1641	(45)	4473	(41)	0.013
Total	9215		5539		3676		10,818		
Month of onset									
November	71	(1)	67	(1)	4	(0)	432	(4)	
December	1170	(13)	1003	(18)	167	(5)	2264	(21)	p < 0.001
January	3389	(37)	2424	(44)	965	(26)	2963	(27)	0.189
February	3288	(36)	1701	(31)	1587	(43)	3055	(28)	
March	1297	(14)	344	(6)	953	(26)	2104	(19)	
Total	9215		5539		3676		10,818		
Clinic visit timing (hours after onset)									
<12 h	2727	(32)	1754	(33)	973	(29)	3033	(30)	
12–48 h	5326	(62)	3262	(62)	2064	(61)	5828	(58)	p < 0.001
>48 h	567	(7)	243	(5)	324	(10)	1104	(11)	0.079
Total	8620		5259		3361		9965		
>12 h	5893	(68)	3505	(67)	2388	(71)	6932	(70)	
Received vaccine in same season as clinic visit									
No	5741	(62)	3524	(64)	2217	(60)	5156	(48)	p < 0.001
Yes	3474	(38)	2015	(36)	1459	(40)	5662	(52)	0.146
Total	9215		5539		3676		10,818		
Vaccine dose in same season as clinic visit									
None	5741	(62)	3524	(64)	2217	(60)	5156	(48)	
Once	776	(8)	455	(8)	321	(9)	1180	(11)	p < 0.001
Twice	2698	(29)	1560	(28)	1138	(31)	4482	(41)	0.147
Total	9215		5539		3676		10,818		
Treatment with neuraminidase inhibitors									
No	291	(4)	171	(4)	120	(5)	6687	(98)	p < 0.001
Any	6351	(96)	3919	(96)	2432	(95)	168	(2)	0.932
Total	6642		4090		2552		6855		
After diagnosis									
Hospitalized, total	839		610		229		761		
Unvaccinated	565	(67)	426	(70)	139	(61)	398	(52)	
Vaccinated, once	46	(5)	36	(6)	10	(4)	75	(10)	
Vaccinated, twice	228	(27)	148	(24)	80	(35)	288	(38)	
Non-hospitalized, total	7794		4567		3227		8182		
Unvaccinated	4826	(62)	2885	(63)	1941	(60)	3907	(48)	
Vaccinated, once	666	(9)	387	(8)	279	(9)	900	(11)	
Vaccinated, twice	2302	(30)	1295	(28)	1007	(31)	3375	(41)	
Unknown, total	582		362		220		1875		
Unvaccinated	350	(60)	213	(59)	137	(62)	851	(45)	
Vaccinated, once	64	(11)	32	(9)	32	(15)	205	(11)	
Vaccinated, twice	168	(29)	117	(32)	51	(23)	819	(44)	
Total	9215		5539		3676		10,818		

samples are usually taken within 48 h after onset of illness. In the present study, by contrast, 94% of patients were diagnosed within 48 h of onset (Table 2), which is the period when viral shedding is high. We believe that this is the most important reason why the sensitivity of RIDT kits used in Japan is reportedly higher. WHO has confirmed this, reporting that the RIDTs that are used widely in Japan seem to be more reliable than those in other countries, possibly because most patients are tested within 48 h of the onset of illness, when influenza viral load in the upper respiratory tract is high [29]. Although the analytical detection sensitivity of the tests

Table 3
Vaccine effectiveness against influenza by vaccine dose in children aged 6 months to 12 years (2013/14–2017/18).

(a) Number of enrollees

		Any influenza				Type A				Type B				Negative			
	Vaccine doses	0	1	2	Total	0	1	2	Total	0	1	2	Total	0	1	2	Total
Seasons	Total	5741	776	2698	9215	3524	455	1560	5539	2217	321	1138	3676	5156	1180	4482	10,818
	2013/14	1274	172	646	2092	587	62	191	840	687	110	455	1252	1076	235	1004	2315
	2014/15	845	167	462	1474	823	164	451	1438	22	3	11	36	869	294	800	1963
	2015/16	1272	137	584	1993	725	63	286	1074	547	74	298	919	984	199	911	2094
	2016/17	949	127	527	1603	810	103	452	1365	139	24	75	238	901	175	860	1936
	2017/18	1401	173	479	2053	579	63	180	822	822	110	299	1231	1326	277	907	2510
Age groups	Total	5741	776	2698	9215	3524	455	1560	5539	2217	321	1138	3676	5156	1180	4482	10,818
	6–11 m/o	209	10	33	252	159	8	27	194	50	2	6	58	543	26	123	692
	1–2 y/o	926	88	436	1450	696	65	311	1072	230	23	125	378	1612	378	1796	3786
	3–5 y/o	1546	202	764	2512	1029	123	472	1624	517	79	292	888	1359	407	1450	3216
	6–12 y/o	3060	476	1465	5001	1640	259	750	2649	1420	217	715	2352	1642	369	1113	3124
	6 m/o-2 y/o (for 0.25 ml/dose)	1135	98	469	1702	855	73	338	1266	280	25	131	436	2155	404	1919	4478

(b) Vaccine effectiveness by vaccine dose

			Any influenza		Type A		Type B	
			OR	95%CI	OR	95%CI	OR	95%CI
Total (a)		None vs once	**0.560**	**(0.505–0.621)***	**0.505**	**(0.448–0.571)***	**0.682**	**(0.589–0.789)***
		None vs twice	**0.550**	**(0.516–0.586)***	**0.536**	**(0.498–0.578)***	**0.611**	**(0.559–0.669)***
		None vs once or twice	**0.549**	**(0.517–0.583)***	**0.527**	**(0.492–0.565)***	**0.623**	**(0.573–0.678)***
		Once vs twice	1.014	(0.907–1.135)	1.103	(0.967–1.257)	0.924	(0.79–1.081)
By season (b)	2013/14 **	None vs once	**0.54**	**(0.429–0.678)***	**0.384**	**(0.28–0.526)***	0.707	(0.536–0.933)
Main types/subtypes	A/H1, B	None vs twice	**0.519**	**(0.452–0.596)***	**0.347**	**(0.286–0.421)***	**0.731**	**(0.62–0.862)***
		Once vs twice	0.958	(0.751–1.223)	0.881	(0.625–1.241)	1.058	(0.793–1.412)
	2014/15	None vs once	**0.517**	**(0.411–0.65)***	**0.518**	**(0.412–0.653)***	0.509	(0.147–1.764)
	A/H3	None vs twice	**0.671**	**(0.571–0.788)***	**0.681**	**(0.579–0.802)***	0.479	(0.225–1.02)
		Once vs twice	1.347	(1.05–1.727)	1.362	(1.06–1.75)	1.043	(0.27–4.031)
	2015/16 **	None vs once	**0.494**	**(0.386–0.632)***	**0.375**	**(0.275–0.511)***	0.734	(0.535–1.009)
	A/H1, B	None vs twice	**0.49**	**(0.426–0.564)***	**0.421**	**(0.355–0.499)***	**0.627**	**(0.522–0.753)***
		Once vs twice	0.987	(0.758–1.284)	1.132	(0.812–1.577)	0.845	(0.606–1.179)
	2016/17 **	None vs once	**0.628**	**(0.484–0.815)***	**0.589**	**(0.448–0.774)***	0.958	(0.567–1.616)
	A/H3	None vs twice	**0.609**	**(0.525–0.706)***	**0.63**	**(0.54–0.735)***	**0.545**	**(0.392–0.759)***
		Once vs twice	0.977	(0.744–1.282)	1.065	(0.8–1.417)	0.611	(0.351–1.065)
	2017/18	None vs once	**0.596**	**(0.482–0.736)***	**0.523**	**(0.39–0.702)***	**0.675**	**(0.524–0.868)***
	B, A/H3, H1	None vs twice	**0.525**	**(0.456–0.603)***	**0.478**	**(0.395–0.578)***	**0.585**	**(0.495–0.692)***
		Once vs twice	0.922	(0.727–1.169)	0.92	(0.662–1.28)	0.921	(0.696–1.219)
By age group (c)	6-11m/o	None vs once	1.13	(0.523–2.44)	1.043	(0.451–2.411)	1.277	(0.274–5.945)
		None vs twice	0.677	(0.445–1.03)	0.712	(0.451–1.123)	0.596	(0.245–1.451)
		Once vs twice	0.554	(0.234–1.316)	0.612	(0.237–1.576)	0.486	(0.085–2.78)
	1–2 y/o	None vs once	**0.42**	**(0.326–0.54)***	**0.381**	**(0.286–0.507)***	**0.536**	**(0.341–0.844)***
		None vs twice	**0.413**	**(0.361–0.473)***	**0.4**	**(0.343–0.466)***	**0.461**	**(0.365–0.583)***
		Once vs twice	1.011	(0.775–1.317)	1.085	(0.801–1.47)	0.873	(0.545–1.399)
	3–5 y/o	None vs once	**0.444**	**(0.368–0.536)***	**0.382**	**(0.306–0.478)***	**0.578**	**(0.44–0.76)***
		None vs twice	**0.456**	**(0.406–0.512)***	**0.441**	**(0.386–0.505)***	**0.492**	**(0.416–0.582)***
		Once vs twice	1.015	(0.834–1.234)	1.148	(0.908–1.452)	0.849	(0.639–1.127)
	6–12 y/o	None vs once	**0.674**	**(0.579–0.785)***	**0.646**	**(0.541–0.771)***	**0.708**	**(0.584–0.859)***
		None vs twice	**0.679**	**(0.614–0.751)***	**0.694**	**(0.616–0.781)***	**0.677**	**(0.598–0.766)***
		Once vs twice	1	(0.852–1.174)	1.062	(0.878–1.283)	0.95	(0.775–1.164)
	6 m/o-2 y/o	None vs once	**0.475**	**(0.374–0.603)***	**0.432**	**(0.33–0.566)***	0.603	(0.391–0.931)
	(for 0.25 ml/dose)	None vs twice	**0.455**	**(0.401–0.516)***	**0.442**	**(0.384–0.51)***	**0.503**	**(0.403–0.628)***
		Once vs twice	0.961	(0.747–1.238)	1.03	(0.773–1.373)	0.554	(0.234–1.316)

[a]Adjusted for comorbidity (yes or no), area (northern, central, southern Kanto region), month of onset, age, and influenza season (2013/14–2017/18).
[b]Adjusted for comorbidity (yes or no), area (northern, central, southern Kanto region), month of onset, and age.
[c]Adjusted for comorbidity (yes or no), area (northern, central, southern Kanto region), month of onset, and influenza season (2013/14–2017/18).
* Bonferroni-corrected α P value < 0.05/4 = 0.0125.
** Only two-dose regimen was effective against influenza B in the 2013/14, 2015/16 and 2016/17 seasons.

is 10^3 to 10^4 median tissue culture infective dose (TCID50)/100 μL [30,31]), greatly reduced sensitivity would be expected later in the course of illness [29]. The second reason why we believe that our RIDT results are reliable is that our study used only nasopharyngeal swabs, and the doctors followed the manufacturers' instructions [3], such as "rubbing several times around the nasopharyngeal membrane using swabs through the nasal cavity", as written in the accompanying pamphlets. In contrast, 50% (65/130) of the studies incorporated into the review used nasal aspirates, swabs or washes and throat swabs as specimens rather than the more reliable nasopharyngeal aspirates [28].

The strengths of the present study are as follows: large numbers of subjects were enrolled for dose analysis (≈20,000). As the methods for sample collection were almost identical throughout our five seasons, we can combine the data with only minor adjustment [1–4]. As in our previous report [3], controls had a similar vaccine coverage rate to that of the Japanese population. The vaccine coverage rate, which is reported every year by the National Institute of

Table 4
Effectiveness of influenza vaccine for preventing influenza hospitalization among children aged 6 months to 12 years who were hospitalized after diagnosis, by vaccine doses (2013/14–2017/18, 6mo-12 y/o).

a. Among those who were hospitalized after the rapid influenza diagnosis test

			Any influenza		Type A		Type B	
			VE% (95% CI)	(vaccinated once, twice, and unvaccinated cases) [vaccinated once, twice, and unvaccinated controls]	VE% (95% CI)	(vaccinated once, twice, and unvaccinated cases) [vaccinated once, twice, and unvaccinated controls]	VE% (95% CI)	(vaccinated once, twice, and unvaccinated cases) [vaccinated once, twice, and unvaccinated controls]
6 m/o–12 y/o	None vs once	Crude	57 (36–71)*	(46, 228, 565)	55 (32–71)*	(36, 148, 426)	62 (24–81)*	(10, 80, 139)
		Adjusted [a]	59 (37–73)*	[75, 288, 398]	59 (36–74)*	[75, 288, 398]	53 (0–78)	[75, 288, 398]
	None vs twice	Crude	44 (31–55)*		52 (39–62)*		21 (−9–42)	
		Adjusted [a]	41 (26–53)*		45 (29–57)*		26 (−4–48)	
	none vs once or twice	Crude	47 (35–57)*		53 (41–62)*		29(4–48)	
		Adjusted [a]	46 (33–56)*		50 (36–60)*		31 (4–51)	
	Once vs twice	Crude	−29 (−94–14)		−7 (−67–31)		−108 (−322–−3)	
		Adjusted [a]	−47 (−129–6)		−44 (−136–12)		−67 (−262–23)	

b. Among those who were not hospitalized after the rapid influenza diagnosis test

			Any influenza		Type A		Type B	
			VE% (95% CI)	(vaccinated once, twice, and unvaccinated cases) [vaccinated once, twice, and unvaccinated controls]	VE% (95% CI)	(vaccinated once, twice, and unvaccinated cases) [vaccinated once, twice, and unvaccinated controls]	VE% (95% CI)	(vaccinated once, twice, and unvaccinated cases) [vaccinated once, twice, and unvaccinated controls]
6 m/o–12 y/o	None vs once	Crude	40 (33–46)*	(666, 2302, 4826)	42 (34–49)*	(387, 1295, 2885)	38 (28–46)*	(279, 1007, 1941)
		Adjusted [a]	44 (37–50)*	[900, 3375, 3907]	49 (42–55)*	[900, 3375, 3907]	34 (22–43)*	[900, 3375, 3907]
	None vs twice	Crude	45 (41–48)*		48 (44–52)*		40 (34–45)*	
		Adjusted [a]	44 (40–48)*		46 (41–50)*		39 (32–44)*	
	None vs once or twice	Crude	44 (40–47)*		47 (43–51)*		39 (34–44)*	
		Adjusted [a]	45 (41–48)*		47 (43–51)*		38 (32–43)*	
	Once vs twice	Crude	8 (−3–18)		11 (−2–22)		4 (−12–17)	
		Adjusted [a]	−4 (−18–8)		−11 (−28–4)		2 (−16–18)	

[a] Adjusted for comorbidity (yes or no), area (northern, central, southern Kanto region), month of onset, age and season (2013/14, 14/15, 15/16, 16/17 and 17/18).
* $p < 0.05$.

Infectious Diseases in Japan, was 55.1% (3757/6815) for children 6 months to 12 years old during our first four seasons (2013/14–2016/17) [19]. The vaccine coverage rate of our control group for this age group was 53.9% (4478/8303) for the first four seasons (2013/14–2016/17) and 52.3% (5662/10818) for all five (2013/14–2017/18) (Table 2). Another strength is that, thanks to Japan's recommendation that children under 12 years receive two vaccine doses, the number of patients who received two doses was large.

There were several limitations inherent to the study design. First, because this is an observational study, one- and two-dose regimens were not randomly allocated. We did not know why some children had received only one dose. However, the data shown were adjusted. Second, we used RIDT for diagnosis. We are unable to discriminate between the two subtypes of influenza A and between the two lineages of influenza B. Yet we do know the dominant strain in each season from surveillance data [32]. Because we used RIDT kits for clinical testing, VE would have been underestimated. One report pointed out that the use of clinical testing using rapid tests compared to systematic testing using molecular assays resulted in underestimation of VE [33]. They reported that adjusted VE estimates were 5–33% lower in clinical testing vs. an active surveillance group. Although, as discussed, we used RIDT kits with high sensitivity, this possibility could not be ruled out. Recently, appropriate controls for test-negative study have been discussed—other respiratory virus positive controls, all respiratory virus negative controls, or mixed controls [34,35]. We could not identify "other respiratory virus positive controls," as no other rapid diagnostic test results were reported. Third, in the present analysis of VE by dose, we did not consider previous vaccination status. Further combined analysis will be needed.

In conclusion, annual immunization with influenza vaccine was effective in preventing influenza illness and influenza hospitalization for children, especially those aged 1–5 years, in the five seasons since 2013/14. Both one- and two-dose regimens of IIV were effective in preventing influenza in children. The two-dose regimen was more effective against influenza B in some seasons.

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Declaration of Competing Interest

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