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Reactogenicity of trivalent inactivated influenza vaccine in young children: Pronounced reactions by previous successive vaccinations

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ABSTRACT

In order to assess factors associated with reactogenicity of trivalent inactivated influenza vaccine (IIV3) among young children, data on 1538 vaccinees aged 0–5 years in a previous vaccine effectiveness study were analyzed.

The most frequent reaction was redness (19%), followed by induration, swelling, itching, and pain (6–12%); there were no serious adverse events. For some local reactions, multivariate analyses indicated associations of younger age, preschool attendance, presence of siblings, and allergy with lower risk, and use of thinner needles with higher risk. Most notably, administration of one or more IIV3 vaccines during the previous 3 seasons was positively associated with each local reaction (adjusted odds ratios: 3.6–5.4). For subjects aged ≥3 years, prior successive annual vaccinations were associated with substantially increased local reactions, with clear dose-response relationships (*P* for trend: <0.001 for each); for example, an 9.8-fold greater risk of swelling following three successive annual vaccinations before the study season.

1. Introduction

Administration of the influenza vaccine is the most effective measure to prevent progression to severe complications and mortality from the influenza virus [1]. However, vaccination has caused adverse events in a higher proportion compared to placebo [2,3]; that is, reactogenicity is inevitable. It is important when promoting vaccination to explain the risk of reactogenicity to provide the opportunity of vaccination with improved expectations.

Previous studies regarding factors associated with reactogenicity after influenza vaccination are inconsistent. For example, it was reported that females manifested significantly more local reactions than males [4], but another study showed that sex was not significantly associated with systemic and local reactions [5]. Such evidence regarding young children is very limited, although some studies of other vaccines, such as diphtheria–tetanus–acellular pertussis vaccine or human papillomavirus vaccine, were reported [6,7]. Accordingly, it is necessary to accumulate more data regarding reactogenicity after influenza vaccination in young children.

In Japan, young children were reportedly the most frequently affected by both serious and non-serious local or systemic reactions after receiving influenza vaccine [8,9], although vaccination for this age group is recommended by the United States Center for Disease Control and Prevention since they have a relatively high rate of influenza-associated hospitalization [1]. Therefore, we assessed the reactogenicity of the influenza vaccine and associated factors in children, using the data that we had previously collected to evaluate its effectiveness [10].

2. Materials and methods

2.1. Study subjects and vaccination

The study subjects were 1569 Japanese children aged less than 6 years who received trivalent inactivated influenza vaccine (IIV3) on parental request during the 2002/03 season at one of 54 pediatric

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clinics in Japan. They were vaccinees in our previous cohort study to assess influenza vaccine effectiveness [10].

Vaccinations were performed by the pediatrician in charge at each clinic using commercial, non-adjuvanted, inactivated influenza vaccines that included the following strains: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Shandong/7/97. These vaccines contained 30 μg/mL of hemagglutinin (HA) from each strain. Subjects received two doses by subcutaneous injections into their arms of 0.1 mL for children aged less than 1 year, or 0.2 mL for those aged 1–5.9 years, in accordance with the guideline for vaccination in Japan at that time. All parents or guardians gave informed consent. The study protocol was approved by the ethics committee of the Osaka City University Faculty of Medicine.

2.2. Information collection

Data on baseline characteristics were obtained from responses to 2 structured questionnaires. One was answered by the parents or guardians and included questions regarding sex, age, history of IIV3 vaccination during the previous 3 seasons, preschool attendance, and number of family members and siblings. The other was completed by the physician and provided information concerning body weight, underlying diseases (heart disease, kidney disease, diabetes, anemia, bronchial asthma, tonsillitis, hives, atopy, and allergy), needle gauge size used, and the vaccine manufacturer.

The parents or guardians were asked to report prospectively, by indicating "no" or "yes" on a postal questionnaire, the occurrence of local and systemic adverse events within 48 h after vaccination. Local reactions included redness, swelling, induration, itching, and pain. Systemic reactions were fever (defined at 0.5 °C intervals) and rash. Information on medical office visits due to the adverse events was also solicited.

2.3. Statistical analysis

After excluding 31 children (4 for age ≥6 years; 22 for vaccine doses in violation of protocol; and 5 for no information on adverse events), data from 1538 vaccinees were analyzed. Although the parents or guardians of 171 children (11%) failed to answer one or more questionnaire items on adverse events, they were included in the analyses of each adverse event in order to utilize the maximum of available information.

The frequencies of adverse events were compared after dose 1 and dose 2 using McNemar's test. The odds ratios (ORs) for associations of baseline characteristics with adverse events and their 95% confidence intervals (CIs) were calculated using the logistic regression model. To select the explanatory variables for the multivariate model, we used a stepwise method involving variables that had a statistically significant association, by univariate analysis, with one of the adverse events. Seven selected variables at this step were age, preschool attendance, history of IIV3 vaccination during the previous 3 seasons, presence of siblings, allergy, needle gauge size used, and the vaccine manufacturer. The final model also included sex in addition to these 7 variables.

For comparison, subjects aged less than 2 years were combined into a single category because only a few subjects less than 1 year of age reported adverse events. The needle gauge size was divided by approximate tertiles (23-25G/26G/27-30G). In calculating ORs for age and manufacturer, referent categories were assigned to the levels in which the maximum numbers of subjects were distributed.

For univariate and multivariate analyses, we used the adverse events after dose 1 as outcome measures since they were generally more frequent as compared to those occurring after dose 2 (e.g., $P = 0.02$ for redness and rash). A P value <0.05 was considered statistically significant. All statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Table 1
Characteristics of the study population ($N = 1538$).

	n (%) or median (range)	
Boy	793	(52)
Age (years)		
<1.0	25	(2)
1.0–1.9	229	(15)
2.0–2.9	352	(23)
3.0–3.9	369	(24)
4.0–4.9	316	(21)
5.0–5.9	247	(16)
Current body weight (kg)[a]	14.4	(6.9–30.0)
Preschool attendance (yes)	932	(61)
Sibling (yes)[b]	1096	(71)
Number of siblings[b]	1	(0–4)
Number of family members[b]	4	(2–45)
Influenza vaccination during the previous 3 seasons (yes)	1080	(70)
Underlying disease (yes)		
Heart disease	15	(1)
Kidney disease	5	(0)
Diabetes	0	(0)
Anemia	9	(1)
Bronchial asthma	191	(12)
Tonsillitis	34	(2)
Hives	57	(4)
Atopy	102	(7)
Allergy	106	(7)

[a] Missing information for 2 subjects.
[b] Residing in the same household.

3. Results

Table 1 lists the distribution of characteristics. The 3.0–3.9 years age group had the largest number of subjects (24%), and 70% of the children had a history of IIV3 vaccination during the previous 3 seasons. The frequent underlying diseases were bronchial asthma (12%), allergy (7%), and atopy (7%).

The occurrence of adverse events is presented in Table 2. About 25% of subjects reported one or more local reactions (hereinafter referred to as 'any local reaction') after dose 1 and dose 2. The most frequent local reaction was redness, followed by induration, swelling, itching, and pain. Systemic reactions (fever ≥37.5 °C and rash) were seen in 3% or fewer of subjects. Only one subject manifested high fever of ≥39.5 °C, which occurred after each dose. There were very few medical office visits related to reactions (for 3% of subjects with any local reaction after dose 1 and 1% after dose 2).

In univariate analyses (Table 3), significantly lowered ORs for local reactions were seen for the following variables: younger age (for each of the local reactions), preschool attendance (for redness), presence of siblings (for redness), allergy (for swelling), and C and

Table 2
Adverse events within 48 h after vaccination.

	After dose 1		After dose 2	
	n/N	(%)	n/N	(%)
Local reactions				
Any local reactions	394/1533	(26)	366/1503	(24)
Redness	285/1532	(19)	249/1503	(17)
Swelling	173/1531	(11)	157/1501	(11)
Induration	182/1531	(12)	173/1501	(12)
Itching	126/1531	(8)	122/1501	(8)
Pain	97/1532	(6)	90/1502	(6)
Systemic reactions				
Fever (≥37.5 °C)	42/1525	(3)	48/1481	(3)
Rash	25/1468	(2)	11/1433	(1)

Table 3
Odds ratios (95% confidence intervals) of selected variables for adverse events after dose 1 (univariate analyses).

Variable, category	Local reactions						Systemic reactions	
	Any	Redness	Swelling	Induration	Itching	Pain	Fever (≥37.5 °C)	Rash
No. of subjects†	1533	1532	1531	1531	1531	1532	1525	1468
Sex								
Girl (vs. boy)	1.1 (0.9–1.4)	1.1 (0.8–1.4)	0.9 (0.6–1.2)	1.1 (0.8–1.5)	1.2 (0.9–1.8)	1.3 (0.9–2.0)	0.7 (0.4–1.3)	0.7 (0.3–1.6)
Age (years)								
<2.0	0.3 (0.2–0.5)*	0.3 (0.2–0.5)*	0.3 (0.2–0.6)*	0.4 (0.2–0.7)*	0.1 (0.0–0.3)*	0.1 (0.0–0.4)*	0.4 (0.2–1.1)	1.2 (0.4–3.2)
2.0–2.9	0.9 (0.6–1.2)	1.0 (0.7–1.4)	1.0 (0.6–1.5)	0.9 (0.6–1.4)	0.6 (0.4–0.9)*	0.6 (0.3–1.2)	0.7 (0.3–1.5)	0.7 (0.3–2.0)
3.0–3.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
4.0–4.9	0.9 (0.6–1.2)	0.7 (0.5–1.1)	0.9 (0.6–1.4)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.9 (0.5–1.6)	0.1 (0.0–0.6)*	0.1 (0.0–1.0)
5.0–5.9	1.1 (0.8–1.5)	0.7 (0.5–1.1)	1.0 (0.6–1.6)	1.0 (0.6–1.5)	0.9 (0.5–1.5)	1.4 (0.8–2.4)	0.6 (0.3–1.5)	0.3 (0.1–1.5)
Preschool attendance								
Yes (vs. no)	1.0 (0.8–1.3)	0.8 (0.6–0.9)*	1.0 (0.7–1.3)	1.1 (0.8–1.4)	1.2 (0.8–1.7)	1.7 (1.1–2.6)	1.2 (0.6–2.2)	0.5 (0.2–1.1)
Presence of siblings								
Yes (vs. none)	0.8 (0.6–1.0)	0.7 (0.5–0.9)*	0.8 (0.6–1.1)	0.9 (0.6–1.2)	1.2 (0.8–1.8)	1.2 (0.8–2.0)	0.8 (0.4–1.6)	0.6 (0.3–1.3)
Allergy								
Yes (vs. none)	1.0 (0.6–1.6)	0.8 (0.4–1.3)	0.3 (0.1–0.8)*	0.6 (0.3–1.2)	0.9 (0.4–1.9)	1.4 (0.7–2.9)	1.4 (0.5–4.1)	1.9 (0.6–6.5)
Vaccination during the previous 3 seasons								
Yes (vs.none)	5.4 (3.8–7.8)*	5.7 (3.7–8.9)*	6.0 (3.4–10)*	4.4 (2.7–7.2)*	6.9 (3.3–14)*	5.9 (2.7–13)*	1.4 (0.7–2.8)	0.8 (0.3–1.7)
Needle gauge size								
23–25G	1.0	1.0	1.0	1.00	1.0	1.0	1.0	1.0
26G	1.7 (1.3–2.3)*	2.2 (1.5–3.1)*	2.2 (1.4–3.5)*	1.9 (1.3–2.9)*	1.8 (1.1–2.9)*	1.0 (0.6–1.8)	0.8 (0.4–1.7)	2.8 (0.9–8.7)
27–30G	1.7 (1.2–2.2)*	2.0 (1.4–2.9)*	2.0 (1.3–3.1)*	1.7 (1.1–2.6)*	1.9 (1.2–3.2)*	1.1 (0.7–1.9)	0.9 (0.4–1.8)	1.6 (0.5–5.3)
Vaccine manufacturer								
A	0.9 (0.6–1.4)	1.0 (0.7–1.6)	1.1 (0.6–1.8)	0.9 (0.6–1.5)	0.7 (0.4–1.4)	1.4 (0.7–2.6)	0.4 (0.1–1.7)	1.6 (0.3–8.0)
B	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
C	0.5 (0.3–0.7)*	0.5 (0.3–0.8)*	0.6 (0.3–1.0)	0.4 (0.2–0.7)*	0.7 (0.4–1.1)	0.6 (0.3–1.2)	0.5 (0.2–1.4)	2.5 (0.7–8.2)
D	0.6 (0.5–0.8)*	0.6 (0.4–0.8)*	0.8 (0.5–1.2)	0.7 (0.5–1.0)	0.6 (0.4–0.9)*	1.0 (0.6–1.6)	0.9 (0.4–1.7)	3.2 (1.2–8.5)*

* Statistically significant.
† Effective for analyses.

D manufacturer (for any local reaction, redness, induration, and itching). On the other hand, elevated ORs with significance were shown for the following: IIV3 vaccination during the previous 3 seasons (for each of the local reactions) and use of the thinner 26G and 27–30G needles (for each of the local reactions except for pain). Regarding systemic reactions, significant ORs were indicated in the age 4.0–4.9 years group (for fever) and for the D manufacturer (for rash).

In multivariate analyses (Table 4), statistically significant ORs were observed for almost the same variables, but not for the same categories, as in univariate analyses. Notably, multivariate ORs of previous IIV3 vaccination for each local reaction still were the highest as compared to those of other variables (ORs = 3.6–5.4 for each of the local reactions). The use of thinner needles also had increased ORs (1.6–2.2) for any local reaction, redness, swelling, induration, and itching.

Based on the strong positive association between previous IIV3 vaccination and occurrence of local reactions, we further assessed the effect of successive annual vaccinations immediately before the present season (Table 5). Among those subjects aged ≥3 years with information on annual vaccination history during the previous 3 seasons (882 subjects), ORs for all local reactions elevated with increasing numbers of successive annual vaccinations: taking the example of "swelling", ORs of the preceding one, two, and three annual vaccinations, as compared to no vaccination history, were 4.8, 5.6, and 9.8, respectively, with clear dose-response relationships (*P* for trend: <0.001). Similar findings were also observed among those aged ≥2 years (1226 subjects).

Because our subjects for analyses were those who received the first dose, the selection bias may have been introduced if children who experienced an unpleasant event at the first dose were less likely to receive a second dose. In order to explore the possible influence of the bias, we repeated the multivariate analyses shown in Table 4 and Table 5 after excluding subjects who did not receive a second dose. The results were not meaningfully changed (data not shown).

4. Discussion

In this study population, aged less than 6 years, the most frequent local reaction was redness. Systemic reactions (fever and rash) were few. These findings are consistent with those of an earlier study in children aged 6–23 months, in which redness was frequent and fever was not common [11]. On the other hand, in some studies of influenza vaccine in children aged 6–35 months or 6–9 and 10–13 years, pain was the most common symptom [12,13]. These study subjects received the vaccine by intramuscular injection, which was different from our study (subcutaneous injection). Other subjects' characteristics including age and race might also explain the different findings. In the present study, it was also observed that most adverse events were not so severe as to require a medical office visit, and no serious events occurred. Thus, we consider that adverse events occurring in this study were well tolerated.

The relationship between sex and occurrence of any adverse event after influenza vaccination was not significant in this study. This result is consistent with those of a study of elderly people, which showed no significant relationship between sex and systemic or local reactions [5], although a meta-analysis of 14 studies found that female adults report more local reactions than do males [4]. To our knowledge, there has been no previous study that assessed the effect of sex on occurrence of adverse events to influenza vaccination in young children. With respect to other vaccines, a recent review article reports inconsistent results among children aged 4–6 years [6], as well as that adult females tended to report local reactions more frequently than do adult males [6,7]. One possible explanation is that sex hormone levels at the extremes of life may contribute to the different findings between adults and young children or elderly people.

A few previously reported studies of young children included analysis of the frequencies of adverse events with regard to various age levels, but the age categories used for comparison were too broad (e.g., 5–6 and 7–8 years, 6–9 and 10–13 years) [13,14]. When

Table 4
Odds ratios (95% confidence intervals) of selected factors for adverse events after dose 1 (multivariate analyses [a]).

Variable, category	Local reactions						Systemic reactions	
	Any	Redness	Swelling	Induration	Itching	Pain	Fever (≥37.5 °C)	Rash
No. of subjects[†]	1530	1529	1528	1528	1528	1529	1522	1465
Sex								
Girl (vs. boy)	1.1 (0.9–1.5)	1.1 (0.8–1.4)	0.9 (0.7–1.3)	1.1 (0.8–1.5)	1.3 (0.9–1.9)	1.4 (0.9–2.1)	0.7 (0.4–1.3)	0.7 (0.3–1.7)
Age (years)								
<2.0	0.6 (0.4–1.0)	0.6 (0.3–1.1)	0.7 (0.4–1.5)	0.8 (0.4–1.6)	0.2 (0.1–0.7)*	0.1 (0.0–0.7)*	0.6 (0.2–1.8)	0.9 (0.3–3.2)
2.0–2.9	0.8 (0.6–1.2)	0.9 (0.6–1.3)	0.9 (0.6–1.5)	1.0 (0.6–1.6)	0.6 (0.4–1.1)	0.7 (0.4–1.3)	0.7 (0.3–1.5)	0.6 (0.2–1.9)
3.0–3.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
4.0–4.9	0.9 (0.7–1.4)	0.8 (0.6–1.3)	1.0 (0.6–1.6)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.9 (0.5–1.7)	0.1 (0.0–0.5)*	0.2 (0.0–1.2)
5.0–5.9	1.2 (0.8–1.8)	0.9 (0.6–1.4)	1.1 (0.7–1.9)	1.0 (0.6–1.6)	0.9 (0.5–1.6)	1.4 (0.8–2.5)	0.5 (0.2–1.3)	0.4 (0.1–1.9)
Preschool attendance								
Yes (vs. no)	0.7 (0.5–0.9)*	0.6 (0.5–0.9)*	0.8 (0.5–1.2)	1.0 (0.7–1.5)	0.9 (0.6–1.4)	1.0 (0.6–1.7)	1.6 (0.8–3.2)	0.8 (0.3–1.9)
Presence of siblings								
Yes (vs. none)	0.7 (0.5–0.9)*	0.7 (0.5–0.9)*	0.7 (0.5–1.1)	0.8 (0.6–1.2)	1.1 (0.7–1.7)	1.1 (0.7–1.8)	0.8 (0.4–1.5)	0.6 (0.3–1.4)
Allergy								
Yes (vs. None)	1.0 (0.6–1.5)	0.8 (0.4–1.4)	0.3 (0.1–0.8)*	0.6 (0.3–1.2)	0.9 (0.4–1.8)	1.3 (0.6–2.7)	1.5 (0.5–4.3)	1.8 (0.5–6.3)
Vaccination during the previous 3 seasons								
Yes (vs. none)	4.7 (3.2–7.0)*	5.3 (3.3–8.5)*	5.4 (2.9–10)*	4.1 (2.4–7.1)*	4.5 (2.1–9.5)*	3.6 (1.6–8.0)*	1.4 (0.6–3.1)	1.2 (0.4–3.3)
Needle gauge size								
23–25G	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
26G	1.6 (1.2–2.3)*	2.2 (1.5–3.2)*	2.1 (1.3–3.4)*	1.8 (1.2–2.9)*	1.6 (0.9–2.7)	1.0 (0.6–1.8)	0.7 (0.3–1.5)	3.4 (0.9–13)
27–30G	1.6 (1.2–2.3)*	2.0 (1.4–2.9)*	2.0 (1.3–3.3)*	1.8 (1.1–2.7)*	1.8 (1.1–3.0)*	1.2 (0.7–2.1)	0.8 (0.4–1.8)	2.4 (0.6–9.7)
Vaccine manufacturer								
A	1.1 (0.7–1.7)	1.3 (0.8–2.1)	1.3 (0.8–2.3)	1.1 (0.6–1.9)	0.9 (0.4–1.7)	1.5 (0.8–3.0)	0.3 (0.1–1.4)	2.0 (0.4–11)
B	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
C	0.5 (0.3–0.7)*	0.5 (0.3–0.8)*	0.6 (0.3–1.0)	0.4 (0.2–0.7)*	0.7 (0.4–1.2)	0.6 (0.3–1.3)	0.5 (0.2–1.4)	2.3 (0.7–7.7)
D	0.7 (0.6–1.0)	0.7 (0.5–1.0)	1.0 (0.6–1.4)	0.8 (0.5–1.2)	0.7 (0.4–1.2)	1.2 (0.7–2.0)	0.8 (0.4–1.7)	2.8 (1.0–8.0)

* Statistically significant.
[†] Effective for analyses.
[a] All variables in the table were included in the model.

categorized by 1-year intervals in the present study, a significant negative association with itching, pain, and fever was seen in some of the groups. Future studies assessing the association between age and adverse events among young children may need to incorporate analysis of smaller age intervals.

This study indicates that preschool attendance and presence of siblings significantly decreased the ORs for any local reaction and redness. To the best of our knowledge, there has been no previous study with a similar result. This might be most appropriately interpreted as a tendency for guardians of children with such characteristics to be less likely to report adverse events. It is important to note that the ORs for 'any local reaction' and 'redness' tend to overestimate the real associations, since the incidence proportions of these outcomes were as large as 20%.

In the present study, use of thinner needles was significantly more likely to be associated with any local reaction, redness, swelling, induration, and itching than use of the thickest needle. A previous study on the diphtheria, pertussis, and tetanus (DPT) vaccine reported that use of longer needles caused fewer local reactions in comparison to shorter needles [15–17]. This finding was interpreted by equating shorter needles with thinner needles, and therefore it was suggested that the greater ensuing pressure enhances the local reaction [18]. Subsequent comparisons of use of needles with the same length but different thicknesses found no significant differences in resulting local reactions [19]. However, whether the effect was due to the needle length or thickness could not be ascertained in this study, since there were no data regarding the length of the needles. In addition, other factors including site or route (intramuscular or subcutaneous) of injection reportedly affect the reactogenicity [20,21].

We found that having one or more IIV3 vaccinations during the previous 3 seasons increased the risk for all local reactions. One

Table 5
Odds ratios (95% confidence intervals) of successive annual vaccinations for local reactions (multivariate analyses [a]).

History of successive annual vaccinations during the preceding seasons	Any	Redness	Swelling	Induration	Itching	Pain
Subjects aged ≥3 years (*n*)[†]	879	878	878	879	879	879
No history	1.0	1.0	1.0	1.0	1.0	1.0
With history in the preceding						
1 season	3.1 (1.7–5.8)	3.3 (1.5–7.2)	4.8 (1.6–14)	2.5 (1.1–5.7)	1.8 (0.7–4.8)	2.3 (0.8–6.8)
2 seasons	5.3 (2.9–9.6)	5.2 (2.5–11)	5.6 (2.0–16)	2.8 (1.3–6.2)	3.8 (1.6–9.2)	4.3 (1.6–11)
3 seasons	6.5 (3.5–12)	7.1 (3.3–15)	9.8 (3.4–29)	4.3 (1.9–9.8)	4.6 (1.8–11)	4.4 (1.6–12)
(*P* for trend)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Subjects aged ≥2 years (*n*)[†]	1222	1221	1220	1221	1221	1222
No history	1.0	1.0	1.0	1.0	1.0	1.0
With history in the preceding						
1 season	3.5 (2.2–5.7)	3.9 (2.2–7.0)	4,1 (1.9–9.0)	3.6 (1.8–7.0)	3.1 (1.2–7.6)	2.3 (1.0–5.6)
2 seasons	6.4 (4.0–10)	7.4 (4.1–13)	6.9 (3.2–15)	4.6 (2.4–9.0)	7.1 (3.0–17)	4.2 (1.9–9.7)
(*P* for trend)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[†] Effective for analyses.
[a] Adjusted for sex, age (categorical variable with 1-year interval), preschool attendance, presence of siblings, allergy, needle gauge size (23–25G/26G/27–30G) and vaccine manufacturers (4 companies).

previous report suggested that subjects with a history of IIV3 vaccination were more likely to report redness, although this result was not significant [22]. On the other hand, in previous studies among young children or elderly people, use of multivariate analysis failed to detect significant association between previous vaccination and systemic or local reactions [5,23]. In further exploring the effect of increasing numbers of successive annual vaccinations before the present season, we demonstrated an association with increased local reactions, with clear dose–response relationships. An earlier study of healthy adults in 1977, in which a similar hypothesis was tested, showed that increased numbers of previous vaccinations did not elevate the occurrence of adverse events [24].

The possible mechanism by which successive annual vaccinations increase the occurrence of local reactions has not been discussed extensively. A study of DPT vaccination revealed that local reactions were more frequent after the booster dose than after the primary vaccination, and that the serum level of pertussis toxin-specific immunoglobulin E antibodies was higher after the booster dose [25], which might provide some insight into the present findings.

Major strengths of this study include its prospective design and large cohort. In addition, precise analysis of factors associated with adverse events was possible, because a variety of information on characteristics of subjects had been collected.

This study has the following limitations. First, because we did not collect information regarding the severity of the reactions, it is difficult to compare our results with the results of other studies in which a specific grading scale for adverse events was used. Secondly, the findings obtained from the present study, using data collected when Japanese guidelines on vaccine doses for children had not been revised, cannot be directly compared with more current results in Western countries and in present-day Japan. Vaccines with high HA content have been reported to cause both systemic and local reactions more frequently compared to the lower HA-content vaccines used in the current study [11,26].

In conclusion, we found that adverse events after IIV3 vaccination among young children were mainly local reactions and not serious events. Several characteristics of subjects, including younger age, preschool attendance, presence of siblings, and allergy were associated with lower risk of local reaction, and IIV3 vaccinations during the previous 3 seasons were associated with higher risk. Use of a thinner needle was also significantly associated with a higher risk for some of the local reactions. Of note is that further research is needed to confirm our finding of positive trends for substantially increased local reactions in those with a history of prior successive annual vaccinations.

Appendix.

Other members of the Influenza Vaccine Epidemiology Study Group are: Drs. Tatsuru Yamanaka and Shuji Nakata in Hokkaido Prefecture; Drs. Yuhei Takasago, Mitsuo Kamihara, Yukiko Usui, Shuka Watanabe, Toshiko Yamaguchi, Shinji Yoshida, Asaka Nishijima, Tsuneji Kanno, Hiroyasu Wada, Eiji Ogawa and Kazuhiko Suzuki in Iwate Prefecture; Drs. Takamitsu Matsudaira, Shunsuke Numaguchi, Noriyuki Wada, Kinjiro Kodaira, Takayoshi Yamada and Akira Kamikawa in Tokyo Prefecture; Drs. Hitoshi Ochiai, Ritsue Nii, Naoki Yasuda, Takashi Kato, Masakazu Umemoto and Masahiro Watanabe in Mie Prefecture; Drs. Urara Kohdera, Katsuhiko Kidera, Fumiyoshi Yamaue, Masanobu Mantani, Michiaki Hayashida, Rentaro Abumi, Yuko Fukuda, Michiko Hatano, Kazuo Wada, Chikara Nakahama, Yoshiyuki Tanaka and Kyoko Takizawa in Osaka Prefecture; Drs. Takao Nagai, Takamichi Mukaida, Tetsushi Inoue, Junji Suzue, Fumihiko Hamada, Akira Takehiro, Atsuko Nishioka, Hitoshi Jinnai, Takuji Fujisawa and Kenkichi Sasaki in Shikoku region; Drs. Yoshio Takasaki, Shizuo Shindo, Naoki Tsumura and Yuji Yamashita in Fukuoka prefecture; and Drs. Yoshio Ohgimi and Yoshinobu Goya in Okinawa prefecture.

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