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Original Article

Effectiveness of influenza vaccine in children in day-care centers of Sapporo

Mitsuru Mori,[1] Junko Hasegawa,[1] Satoko Showa,[1] Aiko Matsushima,[1] Hirofumi Ohnishi,[1] Yuko Yoto[2] and Hiroyuki Tsutsumi[2]
Departments of [1]Public Health, and [2]Pediatrics, Sapporo Medical University School of Medicine, Sapporo, Japan

Abstract ***Background***: We conducted a retrospective cohort study for evaluating the effectiveness of the trivalent inactivated influenza vaccine (TIV) among children aged 0–6 years in the 2011–2012 season in Sapporo City, Japan, because of scarce evidence.

Methods: From 10 day-care centers in Sapporo City, Japan, 629 parents participated in the study. Each parent of the subjects described whether a subject received TIV once or twice in the 2011–2012 season, as well as the exact dates of receiving TIV from records in a maternal and child health handbook marked by a pediatrician. The incidence of influenza was defined as being affected with influenza as diagnosed by a pediatrician. Cox's proportional model was used for calculating a hazard ratio (HR) and its 95% confidence interval (95%CI) of TIV on an influenza incidence.

Results: After adjusting potential confounding variables, such as the day-care center, presence of comorbidity, size of household, number of siblings, and number of smokers in the home in addition to the age and sex of the child, HR was significantly reduced in the subjects aged 1 year (HR = 0.22, 95%CI 0.09–0.54) as well as in the total subjects (HR = 0.72, 95%CI 0.52–0.99). Consequently, the effectiveness of TIV was calculated as 78% for the subjects aged 1 year and 28% for the total subjects.

Conclusion: Our study suggests that TIV is effective, especially in subjects aged 1 year. Further studies are necessary in different seasons, places, and populations to clarify the effectiveness of the influenza vaccine in children.

Key words children, effectiveness, influenza vaccine, retrospective cohort studies.

The influenza virus causes annual epidemics in the winter season in Japan, and it has been stated that vaccination against influenza in children should be promoted to prevent influenza-associated encephalitis-encephalopathy.[1] Increased awareness of the importance of influenza infection in children has led to an increase in the use of the influenza vaccine in Japan.[2] Trivalent inactivated vaccine (TIV) is now used every year for children in Japan.

According to the recent definition of vaccine efficacy and effectiveness,[3,4] efficacy is best measured by randomized controlled trials (RCT), and effectiveness is usually measured by observational studies. Efficacy or effectiveness of the live attenuated vaccine,[5–9] as well as the inactivated vaccine,[10–14] has been reported around the world. An RCT of the influenza vaccine in children aged 6–59 months showed superior efficacy of the live attenuated vaccine, as compared with the inactivated vaccine.[15] However, this trial also showed a higher rate of hospitalization for any cause among children aged 6–11 months in the live-attenuated-vaccine group than in the inactivated-vaccine group.[15] Other RCT of the influenza vaccine showed similar efficacy of the inactivated vaccine to the live attenuated vaccine in children aged 1–16 years[16] and in school children aged 9–12 years.[17]

Several RCT[10,11] or cohort studies[12–14] have shown significant efficacy or effectiveness of TIV to reduce the incidence of influenza in children. However, efficacy or effectiveness of TIV in children less than 3 years old is scarce in evidence and even controversial.[12,14] Accordingly, a retrospective cohort study was conducted for evaluating the effectiveness of TIV among children aged 0–6 years in the 2011–2012 season in Sapporo City, Japan.

Methods

Every large day-care center was identified from 10 districts in Sapporo. Then, 1570 parents of children attending these 10 day-care centers were invited to participate in the survey, and eventually, 629 parents (40.1%) gave written, informed consent to participate in this survey. Age distribution of the study subjects at the end of April 2012, was as follows: 43 were 0 years old, 122 were 1 year old, 127 were 2 years old, 119 were 3 years old, 106 were 4 years old, and 112 were 5 or 6 years old. A self-administered and structured questionnaire was distributed to their parents at the end of April 2012, and they returned a filled-out questionnaire in May by mail. Each parent described whether a subject received TIV once or twice in the 2011–2012 season, and if so, we noted the exact dates of receiving TIV according to records in a maternal and child health handbook marked by a

Correspondence: Mitsuru Mori, MD PhD, Department of Public Health, Sapporo Medical University School of Medicine, South 1, West 17, Chuo-ku, Sapporo 060-8556, Japan. Email: mitsurum@sapmed.ac.jp

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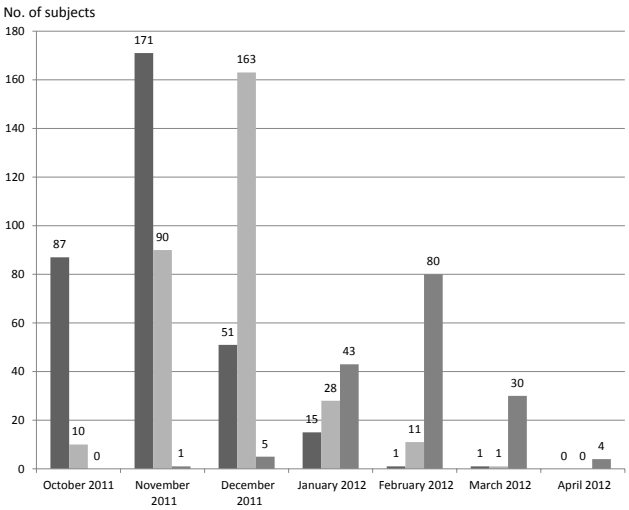

Fig 1. Distributions of the subjects in the first and second vaccinations of the trivalent inactivated vaccine and the incidence of influenza according to each month in the 2011–2012 season. ■, The first vaccination; ■, the second vaccination; ■, incidence of influenza.

pediatrician. TIV consisted of A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Prisbane in the 2011–2012 season.[18] In addition, the questionnaire included inquiries about age, sex, size of household, number of siblings, number of smokers in the home, and so on.

The incidence of influenza was defined as being affected with influenza as diagnosed by a pediatrician. The exact date of the visit to a pediatrician and the name of the medical institute where the pediatrician worked were also obtained with the questionnaire. Cox's proportional model was used for calculating a hazard ratio (HR) and its 95% confidence interval (95%CI) of TIV on the influenza incidence. The start and end of observations were set at 1 October 2011, and 30 April 2012, respectively. SAS version 9.2 (SAS Institute, Cary, NC, USA) was utilized for every analysis. The significance level was set at 5%. This study was approved by the Ethical Committee of Sapporo Medical University (Approval date, 28 March 2012; Approval number, 23-2-76).

Results

From October 2011 to March 2012, 324 subjects among 629 participants (51.5%) received TIV at least once, and they were classified into the Vaccine group. In the Vaccine group, 302 subjects (93.2%) were fully vaccinated with two doses. As shown in Figure 1, the distribution of the subjects for the first vaccination according to months in the 2011–2012 season was as follows: 87 in October, 171 in November, 51 in December, 15 in January, one in February, and one in March. Furthermore, the distribution of the subjects on the second vaccination according to each month in the 2011–2012 season was as follows: 10 in October, 90 in November, 163 in December, 28 in January, 11 in February, and one in March.

Table 1 shows baseline characteristics of the subjects according to the status of receiving TIV, namely, the Vaccine and No vaccine groups. A subject who was vaccinated after being affected with influenza was classified into the No vaccine group. Various kinds of comorbidity were reported from 123 study children, including otitis media in 37 children and atopy or allergy in 19 children as the two most common comorbidities. The average age, proportion of boys, and presence of comorbidity were not different between the Vaccine and No vaccine groups. However, the distribution of day-care centers, size of the household, number of siblings, and number of smokers in the home were all significantly different between the two groups.

In the 2010–2011 season, 163 subjects (25.9%) were diagnosed as being affected with influenza by a pediatrician. As shown in Figure 1, the distribution of the subjects at the diagnosis of influenza according to months in the 2011–2012 season was as follows: one in November, five in December, 43 in January, 80 in February, 30 in March, and four in April.

Table 2 shows the sex-adjusted HR of TIV on the influenza incidence stratified by age. HR was significantly reduced in the subjects aged 1 year (relative risk = 0.24, 95%CI 0.10–0.56). Furthermore, sex- and age-adjusted HR were significantly

Table 1 Baseline characteristics of the subjects according to status of trivalent inactive vaccine in 2011–2012 season

Items	Vaccine group (n = 324)		No vaccine group (n = 305)		P-value
Age in years (mean, SD)	2.72	1.43	2.78	1.74	0.629
Boys (n, %)	155	47.8	149	48.9	0.799
Day-care center 1 (n, %)	44	13.6	19	6.2	<0.001
Day-care center 2 (n, %)	34	10.5	14	4.6	
Day-care center 3 (n, %)	37	11.4	40	13.1	
Day-care center 4 (n, %)	28	8.6	22	7.2	
Day-care center 5 (n, %)	19	5.9	32	10.5	
Day-care center 6 (n, %)	28	8.6	34	11.2	
Day-care center 7 (n, %)	42	13.0	49	16.1	
Day-care center 8 (n, %)	35	10.8	18	5.9	
Day-care center 9 (n, %)	32	9.9	32	10.5	
Day-care center 10 (n, %)	25	7.7	45	14.8	
Presence of comorbidity (n, %)	69	21.3	54	17.7	0.256
Size of household (mean, SD)	3.68	0.85	3.91	1.04	0.002
Number of siblings (mean, SD)	1.66	0.71	1.94	0.82	<0.001
Number of smokers in home (mean, SD)	0.49	0.66	0.63	0.71	0.011

Table 2 Sex-adjusted HR and its 95%CI of trivalent inactive vaccine on influenza incidence in 2011–2012 season

Age	Vaccine group				No vaccine group						
	n	Person-days	Incidence	Incidence rate‡	*n*	Person-days	Incidence	Incidence rate‡	HR	95%CI	*P*-value
0 years	3	506	1	19.8	40	6 921	4	5.8	2.23	0.20, 24.60	0.513
1 year	75	12 973	8	6.2	47	7 194	17	23.6	0.24	0.10, 0.56	0.001
2 years	85	13 971	19	13.6	42	6 675	14	21.0	0.66	0.33, 1.33	0.246
3 years	61	9 847	17	17.3	58	8 443	26	30.8	0.56	0.31, 1.04	0.067
4 years	53	8 455	15	17.7	53	8 205	16	19.5	0.90	0.44, 1.83	0.760
5 or 6 years	47	7 519	12	16.0	65	10 791	14	13.0	1.23	0.57, 2.67	0.602
Total	324	53 271	72	13.5	305	48 229	91	18.9	0.71†	0.52, 0.97	0.032

Incidence was defined as being affected with influenza diagnosed by pediatrician. †Age- and sex-adjusted HR in the total subjects. ‡Incidence rate per 10 000 person-days. HR, hazard ratio.

decreased in the total subjects (HR = 0.71, 95%CI 0.52–0.97). As shown in Table 3, the HR of TIV on the influenza incidence were not meaningfully changed even after adjusting potential confounding variables, such as the day-care center, presence of comorbidity, size of household, number of siblings, and number of smokers in the home in addition to age and sex of the patient. Namely, HR was significantly reduced in the subjects aged 1 year (HR = 0.22, 95%CI 0.09–0.54) as well as in the total subjects (HR = 0.72, 95%CI 0.52–0.99). Consequently, effectiveness of TIV was calculated as 78% for the subjects aged 1 year, and 28% for the total subjects.

Discussion

It was found that the HR of TIV on influenza incidence was significantly reduced in the subjects aged 1 year and in the total subjects, but not in the subjects aged 0 years, or 2–6 years. Fujieda *et al*.[14] reported, from the results of a follow-up study at 54 pediatric clinics in eight areas of Japan in the 2002–2003 season, that risk was significantly reduced in the group, aged 2.0–3.9 years, receiving an inactivated vaccine, but not those aged under 1.9 years or over 4.0 years. Similar to this study, they found an insignificantly increased risk of an inactivated vaccine among children less than 1 year of age, and they mentioned that there was a lower immune response to the influenza vaccine for those less than 1 year of age.[14]

Maeda *et al*.[12] showed, with a prospective cohort study in Japan, that the risk of an influenza-like illness was insignificantly reduced in the group receiving the inactivated vaccine of age strata from 1 year to 7 years of age. Similar to this study's results, they found a significantly decreased risk of the inactivated vaccine on influenza infection in the total number of children aged 1–7 years. As explained by Hirota *et al*.,[19] the variety in results comes from the fact that efficacy or effectiveness of the vaccine is influenced by the designs or conditions in the fields, such as a mixed epidemic with different strains, antigenic similarity between the vaccine strains and epidemic viruses, and inter-individual variation in the antibody response to the vaccine.

Table 3 HR and its 95%CI of trivalent inactive vaccine on influenza incidence in 2011–2012 season, after adjusting potential confounding variables†

Age	HR	95%CI	*P*-value
0 years	2.47	0.08, 73.63	0.602
1 year	0.22	0.09, 0.54	0.001
2 years	0.60	0.28, 1.28	0.185
3 years	0.66	0.35, 1.27	0.215
4 years	0.75	0.36, 1.54	0.427
5 or 6 years	1.37	0.62, 3.04	0.438
Total	0.72	0.52, 0.99	0.042

†Distribution of day-care center, presence of comorbidity, size of household, number of siblings, and number of smokers in home, were adjusted in addition to sex and age. HR, hazard ratio.

The efficacy of the influenza vaccine has been reported to be higher in fully vaccinated children with two doses than in partially vaccinated children with one dose.[20,21] However, Gruber *et al*.[10] showed that a single dose of TIV produced a sufficient serologic rise to influenza viral antigen, and might protect against viral infection. It should be mentioned that the research by Gruber *et al*.[10] was performed among school-age children, and immunological backgrounds may be different from pre-school children. Because a majority of the vaccinated subjects (93.2%) were fully vaccinated with two doses of TIV, it was not possible to compare the effectiveness between one and two doses in this study.

The influenza incidence was defined as that diagnosed by a pediatrician, although information was not obtained about either cultural confirmation or the subtype of influenza. A report about the sampling study on the cultural confirmation of suspected specimen from clinics in Sapporo City showed that 91.4% of them were the influenza virus.[18] Furthermore, according to surveillance by Sapporo City Hygiene Research Center,[22] endemic of the influenza virus A/H3N2 was observed from the 51st week of 2011 to the 14th week of 2012, and its peak was at the 4th week of 2012. In addition, the spread of the influenza virus B was observed from the 3rd week of 2012 to the 20th week of 2012. The proportion of patients with influenza was reported to be about 71% in influenza A/H3N2 and about 28% in influenza B in the entire 2011–2012 season. We considered that the endemic of influenza in the study population was consistent with endemic of influenza in the entire Sapporo City. In addition, it was reported that the antigenicity of 2011–2012 endemic influenza A (H3N2) and B strains were concordant with those of 2011–2012 vaccine strains in around 60% and 70%, respectively (IASR 33: 288–294, 2012).

Although the amount of influenza vaccine given to children increased in the 2011–2012 season from 0.1 mL to 0.25 mL for those aged 0 years, from 0.2 mL to 0.25 mL for those aged 1–2 years, and from 0.2 mL to 0.5 mL for those aged 3–5 years, it was not possible for us to evaluate the effect of these increments, because the appropriate comparative population could not be obtained. Although we set the initial date of observation at 1 October 2011, the initial date of observation for each subject with or without vaccination is controversial for analysis with the Cox model. Therefore, we applied analysis by the logistic regression model in addition to analysis by the Cox model. As a result, we could obtain the similar risk estimates in association of influenza vaccination with influenza infection between these two analyses (the odds ratios obtained with the logistic regression analysis are not shown in this article).

As a limitation of this study, only 40% of study candidates responded to the request to participate in this study. Accordingly, a selection bias might exist in this study. Ideally the incidence of influenza should be confirmed by observing protocols at every medical institution, or observing records of high fever in every day-care center. However, it was not practical for us to access medical records at all medical institutions or records of high fever at the day-care centers. It was thought that distribution of the day-care centers, size of household, number of siblings, and the number of smokers in home were all potential confounding factors in the association between vaccination and influenza incidence. Especially, different status of influenza endemic was observed in 10 day-care centers as shown in Table 1, and one day-care center showed a significantly increased risk of influenza infection (HR = 2.53, 95%CI 1.48–4.34). However, it was not the case in this study, because HR of TIV on the influenza incidence were not altered even after adjusting all of them, as shown in Table 3.

In conclusion, HR of TIV on the influenza incidence was significantly reduced in the subjects aged 1 year and in the total subjects, but not in the subjects aged 0 years, or 2–6 years. Further studies are necessary in different seasons, places, and populations to clarify the effectiveness of the influenza vaccine in children.

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