Adverse events of 2009 novel pandemic influenza (A/H1N1) vaccination - comparison with seasonal and simultaneous vaccination -

Masahiro MATSUSHIMA, Hajime HINENOYA, Shigeko FUSHIMI
Hironobu KATSUYAMA

Department of Public Health, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-1092, Japan

ABSTRACT Vaccination against novel pandemic influenza (A/H1N1) is available in Japan since October 2009. During the 2009－10 influenza pandemic, this vaccine was administered either separately or simultaneously with seasonal influenza vaccine. In the present study, we investigated the adverse events associated with novel pandemic influenza vaccination, and compared these events with those of seasonal influenza vaccination and simultaneous vaccination. We also investigated the factors associated with the incidence of adverse events.

Although no serious adverse events were observed in any case (total cases, 470 ; 95 received pandemic, 134 received seasonal, and 241 received simultaneous vaccinations), some subjects developed local and systemic reactions. Local reactions like erythema and swelling and systemic reaction like fatigue were observed. Among the subjects who experienced local reactions, those who received novel pandemic vaccination showed significantly lower incidence of adverse events than those who received other vaccinations; among the subjects who experienced systemic reactions, no statistical difference was observed.

Odds ratios influencing the incidence of adverse events were calculated according to the potential risk factors using multiple logistic regression analysis. Among the subjects who received the novel pandemic influenza vaccination, females exhibited higher odds ratio (8.29 times) than males. With regard to the age groups, the odds ratios of subjects of all age groups were higher (3.74－9.28 times) than that of subjects over 50 years who received simultaneous vaccination. Moreover, the odds ratios of past adverse events were significantly high (10.9－15.9 times), regardless of the type of vaccination.

(Accepted on July 1, 2010)

Key words：**Novel pandemic influenza (A/H1N1) , Influenza vaccination , Adverse event , Local reaction , Systemic reaction**

Corresponding author
Masahiro Matsushima
Department of Public Health, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan
Phone : 81 86 462 1111
Fax : 81 86 462 1199
E-mail : masm@med.kawasaki-m.ac.jp

INTRODUCTION

After the pandemic caused by the novel influenza (A/H1N1) virus in early 2009, World Health Organization (WHO) promoted the development of treatment strategies for this pandemic influenza since September 2009[1]. Although people were exposed to different strains of influenza virus every year, no one had developed immunity to the novel pandemic influenza strain. Hence, there was a public health demand to develop a novel pandemic influenza vaccine as soon as possible[2], for which advanced planning and evaluation of safety and efficacy data were essential. Studies on this aspect are required because there is no conclusive data about the safety of the novel pandemic influenza vaccination.

Both influenza A and B viruses are important respiratory pathogens, and influenza has caused large epidemics with high mortality rate for patients and aged in Japan[3]. Therefore, the Ministry of Health, Labor and Welfare (MHLW) implemented vaccination programs for both seasonal influenza A and B vaccines[4] every year. Further, for the pandemic caused by novel influenza, MHLW administrated novel pandemic influenza vaccination since October 2009[5]. MHLW gave priority to medical personnel in novel pandemic influenza vaccination, and also conducted simultaneous vaccination programs of novel pandemic vaccine and seasonal vaccine[6], because both vaccination was required to reduce the incidence and mortality of influenza. It was recommended that a person should receive both the vaccines in different arms.

Novel pandemic influenza vaccination was administered to the staff members of Kawasaki Medical School Hospital between October and November, and subsequently, seasonal influenza vaccination was administered separately or simultaneously. We compared the adverse events associated with novel pandemic influenza vaccination and those with seasonal influenza vaccination. Further, we investigated the factors related to the incidence of adverse events.

SUBJECTS AND METHODS

Subjects

Influenza vaccination was administered to 3,932 subjects working at the Kawasaki Medical School Hospital. The novel pandemic influenza vaccination was administered to around 1,700 subjects. An anonymous self-administered questionnaire was distributed to 2,438 subjects, of which only 547 subjects returned the completed questionnaire (response rate, 22.4%).

This study was reviewed and approved by the Ethical Committee on Kawasaki Medical School and Kawasaki Medical School Hospital.

Types of vaccines

The novel pandemic influenza vaccine[5] contained A/California/7/2009(H1N1) virus and the seasonal vaccine[4] was composed of A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007(H3N2), and B/Brisbane/60/2008 strains. Medical staff personnel, including doctors and nurses, received simultaneous vaccinations. Other staff members, including radiologists, medical technologists, and medical clerks were first injected with the seasonal influenza vaccine in October and then with the novel pandemic influenza vaccine in November.

Anonymous self-administered questionnaire

A survey was conducted after vaccination using an anonymous self-administered questionnaire. The questions were related to baseline characteristics such as gender, age groups and occupation; type of vaccine; past history, including illness, allergy, influenza vaccination, and adverse events due to past influenza vaccination; and present illness.

Definition of adverse events

Adverse events are defined as undesirable health

events that occur after vaccination, regardless of whether there is an obvious relationship between vaccination and adverse events. MHLW has defined that the criteria of adverse events that occur after novel pandemic and seasonal influenza vaccinations include 17 clinical conditions[8]. And local and systemic reactions that develop after vaccine administration are described in the report of MHLW[7]. Local reactions include erythema, swelling, calor, pain, and itching, and systemic reactions include fatigue, itchiness, headache, fever (body temperature >37.5℃), and nausea.

Statistical analysis

χ^2 test was performed to compare the differences in the odds ratios of each type of vaccination. Odds ratios that influence the estimated risk with 95% confidence intervals were calculated by multiple logistic regression analysis by using JMP8.0 (SAS Corp.). The risks were determined by gender, age group, presence of past and present illness, history of allergy, past influenza vaccination, and adverse events due to past influenza vaccination.

Table 1. Characteristics of subjects

	Type of vaccine		
	Pandemic (n=95)	Seasonal (n=134)	Simultaneous (n=241)
Gender			
male	29	35	48
female	66	99	193
Age groups			
20's	15	21	92 *
30's	20	29	68
40's	25	32	49
Over 50's	35	50	32 *
Missing	-	2	-
Occupation			
Doctor	6	1	58 *
Nurse	4	7	162 *
Others	81	110	7 *
Missing	4	16	14

Data are number.
In gender, there was no difference in each type of vaccine. In age groups, those who received simultaneous vaccination showed significantly lower in 20's and higher in over 50's than those who received other vaccinations (*: P<0.01). In occupation, those who received simultaneous vaccination showed significantly higher in doctor and nurse and lower in others than those who received other vaccinations (*: P<0.01).

RESULTS

Among the 547 subjects who responded to the questionnaire, 470 replied with effective answers (85.9%). Among the 470 subjects, 95 had received the novel pandemic influenza vaccination, 134 seasonal influenza vaccination, and 241 (approximately 50%) simultaneous vaccination (Table 1). About 75% of the subjects were females. The subjects in the age groups of 20's and 30's mainly received simultaneous vaccination. Most doctors and nurses received simultaneous vaccination, while other medical personnel first received the seasonal vaccination and then the novel pandemic influenza vaccination.

The subjects did not exhibit any of the 17 clinical conditions defined by MHLW[8] after vaccination. Although no serious adverse events were observed, some subjects developed local and systemic reactions (Table 2). Many subjects complained of erythema and swelling (local reactions) as well as fatigue (systemic reaction). Among the subjects who developed local reactions, those who received novel pandemic vaccination showed significantly lower incidence of adverse events than those who received other vaccinations; among the subjects

Table 2. Number of local and systemic reactions in each type of vaccine

	Type of vaccine		
	Pandemic (n=95)	Seasonal (n=134)	Simultaneous (n=241)
Local reaction			
Erythema	20 *	61	150
Swelling	14 *	57	118
Calor	8 *	33	98
Pain	5 *	29	56
Itching	3 *	20	27
Systemic reaction			
Fatigue	7	15	30
Itching	3	7	27
Headache	5	4	15
Fever (>37.5℃)	2	4	7
Nausea	2	-	4

Data are number.
In each of local reactions, those who received novel pandemic vaccination showed significantly lower incidence of adverse events than those who received other vaccinations (*: P<0.01). In systemic reactions, no statistical difference was observed.

who developed systemic reactions, no statistical difference was observed (Fig. 1).

Odds ratios influencing the incidence of adverse events (any local and systemic reaction) were calculated according to the potential risk factors using multiple logistic regression analysis (Table 3). Among the subjects who received the novel pandemic influenza vaccination, females exhibited higher odds ratio (8.29 times) than males. With regard to age groups, the odds ratios of subjects of each age group were higher (3.74－9.28 times) than that of subjects over 50 years who received simultaneous vaccination. Moreover, the odds ratios of past adverse events were significantly high (10.9－15.9 times), regardless of the type of vaccination.

DISCUSSION

There have been several reports on the safety and adverse events related to novel pandemic influenza vaccination. According to a report from Japan[9], the incidence of adverse events in October 2009 among 20,000 staff members of national hospitals was as follows: non-serious events, 2%, and serious events, 0.03%. However, the incidence of adverse

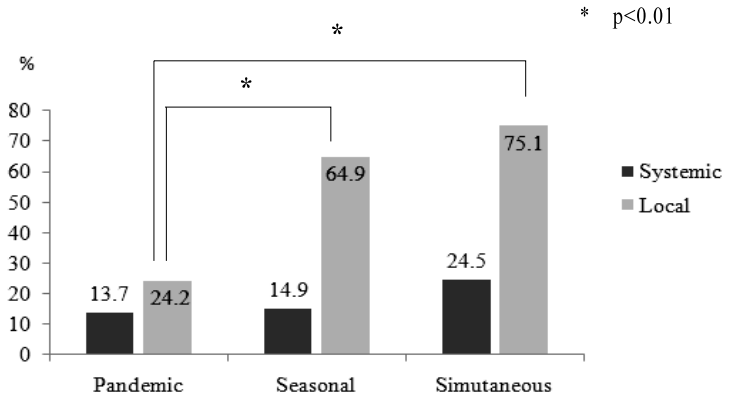

Fig. 1. Incidence of local and systemic reaction in each type of vaccine. In local reaction, incidence of adverse events in novel pandemic vaccine was significantly lower than other types of vaccines, but no statistical difference in systemic reaction was observed between each vaccine.

Table 3. Risk determinants for adverse event divided by each vaccine

	Type of vaccine		
	Pandemic	Seasonal	Simultaneous
Gender (female/male)	8.29* (1.73-58.1)	2.65 (0.96-7.63)	0.87 (0.34-2.18)
Age groups			
20's	0.84 (0.14 -4.54)	2.62 (0.64-12.3)	6.09* (1.86-22.2)
30's	1.87 (0.46 -7.91)	1.17 (0.36-3.83)	9.28* (2.65-36.7)
40's	0.23 (0.035-1.17)	0.94 (0.30-2.98)	3.74* (1.10-13.9)
Over 50's	reference	reference	reference
Adverse events in past influenza vaccination (yes/no)	15.9* (4.65-70.2)	12.0* (4.09-45.3)	10.9* (4.30-33.2)

Data are odds ratio (95% confidence interval).
Odds ratios were calculated according to the potential risk factors using multiple logistic regression analysis. In gender, the odds ratio (female/male) was significantly high in pandemic influenza vaccination. In age groups, the odds ratios of all age groups were higher than that of subjects over 50 years who received simultaneous vaccination. And the odds ratios of adverse events in past influenza vaccination were significantly high, regardless of the type of vaccination.

events in subjects who received novel pandemic influenza vaccination in Japan from October 19, 2009 to March 9, 2010, these values have reduced to 0.01% for non-serious and 0.002% for serious events, and are consistent with the incidence of adverse events in subjects who received seasonal influenza vaccination the incidence of adverse events in subjects who received seasonal influenza vaccination in Japan[10]. Further, according to a report from Centers for Disease Control and Prevention (CDC)[11], the incidence of serious adverse events related to novel pandemic influenza vaccination was not higher than that of seasonal influenza vaccination. In Israel, Grotto reported that the incidence of adverse events related to novel pandemic influenza vaccination was very less, and the incidence of mild and transient adverse events was similar to that observed in seasonal influenza vaccination[12]. In the present study, no serious adverse events were observed in novel pandemic influenza vaccination, and the incidence ratios of both local and systemic reactions were around 20% respectively, lower than other vaccinations. The novel pandemic influenza vaccination was concluded to be safe.

Since the novel pandemic influenza vaccine is a new vaccine, clinical trials for investigating simultaneous vaccination of this vaccine with other vaccines are currently in progress. Both the novel pandemic influenza vaccine and seasonal influenza vaccine are used as inactivated vaccines in Japan[4-7]. According to the information released by MHLW on October 19, 2009, the abovementioned vaccines are safe and simultaneous vaccination of these vaccines is permitted[6]. Moreover, the Strategic Advisory Group of Experts (SAGE) on Immunization of WHO found no evidence that indicated increase in risk of adverse events due to simultaneous vaccination[13]. Recently, in their randomized examination of 355 healthy adults and elderly patients, Vajo *et al*. reported that both novel pandemic influenza vaccination alone and simultaneous vaccination were associated with few adverse events[14]. In the present study, simultaneous vaccination did not show serious or non-serious adverse events. Further, no statistical difference was observed between seasonal and simultaneous vaccination in both local and systemic reactions. Thus, simultaneous vaccination also appeared safe.

About the factor associated with adverse events in seasonal influenza vaccination, the following factors are associated with local and systemic reaction, such as gender, age, and past influenza vaccination[15, 16]. In the present study, gender in novel pandemic influenza vaccination and age groups in simultaneous vaccination are associated with adverse events. However, multiple logistic regression analysis revealed that past influenza vaccination was not related to adverse events but adverse events in past influenza vaccination had high odds ratios in all types of vaccinations. This result indicated that the adverse events were related to the adverse events in past influenza vaccination.

Our study had several limitations. First, this was a questionnaire-based study and participants in this study were voluntary; the response rate was also very low. Second, when adverse events were observed in simultaneous vaccination, it was unknown which vaccine was affected to adverse event. In spite of these shortcomings and small sample size, we clarified the safety of novel pandemic influenza vaccination and simultaneous vaccination in this study. Further studies are required to confirm the adverse events on a large scale.

REFERENCES

1）WHO. DG statement following the meeting of the Emergency Committee. http://www.who.int/csr/disease/swineflu/4th_meeting_ihr/en/index.html (2010.4.22)

2）WHO. Pandemic (H1N1). http://www.who.int/csr/don/2009_09_25/en/index.html (2010.4.22)

3）Infectious Disease Surveillance Center, NIID (National Institute of Infection Disease), Japan. The excess mortality due to influenza in 2002/03 season, Japan. IASR (Infectious Agents Surveillance Report) 24:281-282, 2003

4）Ministry of Health, Labor and Welfare, Japan. Decision of subgroups in influence HA vaccine in 2009. (in Japanese). http://idsc.nih.go.jp/iasr/rapid/pr3533.html (2010.4.22)

5）Ministry of Health, Labor and Welfare, Japan. Guideline of novel pandemic influenza (A/H1N1) vaccination for medical institution, October 13, 2009. (in Japanese). http://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/10/dl/info1013-05.pdf (2010.4.22)

6）Ministry of Health, Labor and Welfare, Japan. Information of revise of the packaging insertion of novel pandemic influenza vaccine (A/H1N1), October 19, 2009. (in Japanese). http://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/10/dl/info1019-02.pdf (2010.4.22)

7）Ministry of Health and Welfare, Japan. Report of effect concerning vaccination of influenza vaccine. (in Japanese). http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do (2010.4.22)

8）Ministry of Health, Labor and Welfare, Japan. Requirement of report of adverse events concerning vaccination of novel pandemic influenza vaccine (A/H1N1). (in Japanese). http://www.mhlw.go.jp/kinkyu/kenkou/influenza/hourei/2009/10/dl/info1019-01.pdf (2010.4.22)

9）Ministry of Health, Labor and Welfare, Japan. Report of intermediate result of investigation intended for 20,000 person novel pandemic influenza vaccine (A/H1N1) in 2009. (in Japanese). http://www.mhlw.go.jp/shingi/2009/11/dl/s1121-3a01.pdf (2010.4.22)

10）Ministry of Health, Labor and Welfare, Japan. Report of the number of vaccination and adverse events for novel pandemic influenza (A/H1N1) vaccination. (in Japanese). http://www.mhlw.go.jp/shingi/2010/03/dl/s0312-12a.pdf (2010.4.22)

11）CDC. Safety of Influenza A (H1N1) 2009 Monovalent Vaccines - United States, October 1-November 24, 2009. MMWR58: 1351-1356, 2009

12）Grotto I, Engelhard D: The safety and immunogenicity of the vaccines against pandemic (H1N1) 2009 influenza. Harefuah 148: 799-803, 2009

13）Experts advise WHO on pandemic vaccine policies and strategies. Pandemic (H1N1) 2009 briefing note 14. http://www.who.int/csr/disease/swineflu/notes/briefing_20091030/en/ (2010.4.22)

14）Vajo Z, Tamas F, Sinka L, Jankovics I: Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre randomised controlled trial. Lancet 375: 49-55, 2010

15）Sugiyama Y, Nagashiba K, Hayashi Y, Mori K, Baba K, Yamaguchi E, Ando H : Investigation of Adverse Effects Occurring with Inoculation of Influenza Vaccine from 2003-2004. Japanese journal of pharmaceutical health care and sciences 31: 307-312, 2005

16）Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA: Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ 307: 1213-1214, 1993