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ORIGINAL ARTICLE

Analysis of the Influenza A (H1N1) 2009 Pandemic Infection in Japanese Asthmatic Patients: Using a Questionnaire-Based Survey

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ABSTRACT

Background: Influenza infection is known to be an exacerbating factor in the control of asthma, therfore its prevention is critical in managing asthma. The aim of this study was to investigate the influenza A H1N1 2009 pandemic virus (H1N1 pdm09) infection in adult asthmatic patients.

Methods: Data were obtained from a questionnaire-based survey of asthmatic patients conducted from September to October 2010 in Niigata Prefecture. Patient background, H1N1 pdm09 infection, vaccination status, and asthma exacerbation due to influenza infection were analyzed.

Results: In total, 2,555 cases were analyzed. The incidence of the infection was 6.7% (95% confidence interval [CI]: 5.7-7.6), and the rate of vaccination was 63.9% (95% CI: 62.1-65.8). The odds ratio (OR) for vaccination against the infection among adult patients and younger patients (≤ the median age) were 0.61 (95% CI: 0.45-0.84) and 0.62 (95% CI: 0.42-0.90), respectively. However, OR among the older patient (> median age) were 1.38 (95%CI: 0.66-2.89). The rate of infection-induced asthma exacerbation was 23.2% (95% CI: 18.6-29.6), and the OR for vaccination against the infection-induced asthma exacerbation was 1.42 (95% CI: 0.69-2.92).

Conclusions: The effectiveness of the vaccination against the H1N1 pdm09 virus was confirmed during the first pandemic season, but it was limited. Further investigation on H1N1 pdm09 virus infection in asthmatics will be required.

KEY WORDS

A H1N1 pdm09, asthma, exacerbation, infection, vaccination

INTRODUCTION

As many factors exacerbate the symptoms of asthma, an important aspect of asthma management is to avoid these factors.[1] Among these are respiratory viral infections, such as those caused by seasonal influenza viruses, which can affect the nature of bronchial asthma; infection is is known to be a major cause of emergency room visits or hospital admissions for asthmatic patients.[2,3] Therefore, the prevention against seasonal influenza virus infection, for example by vaccination, is one of the most important strategies in the management of asthma.[4,5]

A novel strain of swine-origin influenza A virus, named A (H1N1) pandemic 2009 (pdm09) virus, first emerged in 2009 (H1N1 pdm09). In Japan, 1 month

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after the first cases were reported in the 19th week of 2009, it was estimated approximately 30 million cases were reported by the 11th week of 2010 as a result of this virus.[6,7] The H1N1 pdm09 infection accounted for 96% of the influenza cases in Japan.[8] As this infection was estimated to be associated with high disease activity and mortality in the early pandemic phase,[9-11] there was an increased need for vaccination. In Japan, vaccination was administrated by giving precedence to patients with diseases that could be exacerbated by influenza infection.[12,13] The aggressive use of antiviral agents resulted in milder disease activity and the lowered the mortality.[14]

In the Niigata Prefecture specifically, variations in H1N1 pdm09 infection were different from those in the whole of Japan. The case numbers reported as H1N1 pdm09 infection (/institute/week) was delayed in this region, but increased in the mid-October 2009 to beyond the warning standard (39.25/institute/week) during the 44th week, peaking in the 46th week. By the end of January 2010, the rate returned to below the warning standard.[15] However, vaccination of patients bearing diseases that could be exacerbated by influenza infection was started on November 2, 2009, and was inoculated in 90.2% of target patients by the end of March 2010.[15] Since 1998, the Niigata Asthma Treatment Study Group has been conducting annual or biennial questionnaire-based surveys in the Niigata Prefecture to investigate various concerns with asthma control and management.[16-23] On the basis of the variations of the pandemic season in the Niigata Prefecture, when planning the survey in May of 2010, we decided to include questions regarding the H1N1 pdm09 infection in order to investigate the relationship between this novel influenza virus infection and bronchial asthma in a clinical setting. The questionnaire-based survey was scheduled to be conducted between September and October of 2010, >6 months after the pandemic season had ended and before the start of the next influenza outbreak, although the timing of vaccination did not adequately match the pandemic phase of the infection. In this study, we investigated patient background, incidence of H1N1 pdm09 infection, H1N1 pdm09 vaccination status and H1N1 pdm09 infection-induced exacerbation of asthma in asthmatic patients. We also examined the effect of the influenza vaccine in preventing this infection.

METHODS

Participation in this study was open to all medical institutions in the Niigata Prefecture intending to join the Niigata Asthma Treatment Study Group. The study was performed with the approval of the Ethics Committee at the School of Medicine of Niigata University (#1090), Japan, in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki). Written informed consent was obtained from all patients. The study involved 24 large hospitals (200 beds or more), 16 small hospitals (less than 200 beds), and 56 clinics (no beds). In total, 4,662 questionnaires in Japanese were prepared, and 2,706 responses were received (response rate of 58.0%). The questionnaire-based survey was carried out between September and October 2010. The subjects were patients 16 years of age or older with bronchial asthma, who regularly visited the participating institutions for asthma management (typically once or twice a month). The recruited patients were asked to complete the questionnaire without assistance - thus, patients were expected to understand technical terms, such as "attack" used in the questionnaire.

All participating patients were asked about their medical condition and vaccination status against the H1N1 pdm09 virus as follows: "Have you received vaccination against the new-type of influenza?" and "Have you been infected with the new-type of influenza?" Patients infected with H1N1 pdm09 were also asked about the effect of this viral infection on their asthma, as follows: "When infected with the new-type of influenza, did your asthma become worse?" Questions about the onset time of this infection and the vaccination itself were not included in the survey. Using these data, incidence of the infection, rate of vaccination, rate of infection-induced asthma exacerbation, and odds ratio (OR) for vaccination against both the infection onset and the infection-induced asthma exacerbation were calculated.

The Asthma Control Test (ACT) has been validated as a clinical indicator of asthma control,[24-26] and the ACT Japanese version (ACT-J) was included in the questionnaire survey. In addition to the ACT-J, in order to evaluate their asthma management and control, patients were also asked about their peak flow meter use, smoking status, and the incidence of asthma attacks during the 2 weeks prior to answering the questionnaire. The questionnaire also requested information about asthma-related symptoms in the last 2 weeks, including cough and sputum production (morning and night), and sleep disturbances as a result of asthma. The patients were also asked to provide information about the frequency of their asthma attacks by selecting 1 of 3 options ("few attacks," "seasonal attacks," and "frequent attacks"), in order to evaluate their condition during the last year. In addition to monitoring questionnaire completion by the patients, physicians were asked to provide details on patients' current treatment, medication used for primary control, the type of asthma (atopic or non-atopic)- in accordance with serum total IgE elevation or the detection of a specific IgE for allergens, asthma severity in accordance with asthma guidelines by the Japanese Society of Allergology, and the complication of COPD.

Representative results for continuous variables

were expressed as arithmetic means and standard deviations (SD) and/or expressed as median values and the interquartile range (IQR). Intergroup differences with respect to continuous variables were evaluated using the Kruskal-Wallis test and Mann-Whitney U test with the Bonferroni correction. A Chi-square test with the Bonferroni correction was also used to detect significant differences in proportions between groups. All statistical analyses were performed with the statistical software StatView 5.0 PowerPC version (SAS Institute Inc., Cary, NC, USA). For all statistical analyses, a P value of <0.05 was considered as statistically significant.

RESULTS

PUPULATION AND EFFECT OF VACCINATION

Among the 2,706 asthmatic patients who answered the questionnaire, 2,555 also completed the ACT-J and answered the questions about the influenza infection. Infection of H1N1 pdm09, vaccination against H1N1 pdm09 and asthma exacerbation due to the influenza infection were analyzed. Demographic and clinical characteristics of the patients are shown in Table 1. The incidence of H1N1 pdm09 infection in the asthmatic patients was 6.7% (95% confidence interval [CI]: 5.7-7.6), and the rate of influenza vaccination in the asthmatic patients was 63.9% (95% CI: 62.1-65.8). The age (mean ± SD/median IQR), gender (male/female [%]), disease duration (mean ± SD), disease type (atopic/non-atopic [%]) and the rate of peak-flow meter use were 58.2 ± 17.8/61 [46-72] years, 41.7%/56.4%, 15.4 ± 14.7 years, 65.9%/28.3% and 22.5%, respectively. Rates of non-smokers, ex-smokers and current smokers were 51.0%, 31.5% and 14.2%, respectively. 1.8%, 1.9%, 12.9%, 13.4%, 5.8% and 3.3% of patients did not reply the question of age, sex, disease duration, rate of PEFM, type of asthma and smoking status, respectively. The rate of COPD complication was 9.9%, and 5.9% of patients did not provide the information about the COPD. The rates of few, seasonal and persistent attacks during the 1 year period prior to the questionnaire were 49.4%, 28.6% and 9.0%, respectively, and 13.0% of patients did not answered to this question. The attack rate during the 2 weeks prior to answering the questionnaire was 19.0%, and rates of morning symptoms, night symptoms and sleep disturbance were 39.3%, 27.5% and 12.0%, respectively. 7.4%, 2.6%, 3.8% and 5.4% of the patients did not reply the question of attacks, morning and night symptoms, and sleep disturbance.

The infected and non-infected cases in the non-vaccinated patients were 80 and 842, respectively, and 90 and 1543 in vaccinated patients, respectively. The ORs for vaccination against H1N1 pdm09 are summarized in Table 2. In all analyzed patients, the OR for infection was 0.61 (95% CI: 0.45-0.84). When patients were divided into 2 groups, younger (≤ the median age of the analyzed patients) and older (> the median

Table 1 Demographic and clinical characteristics of the study population

Number of cases	2,555
Incidence of the infection (%)	6.7
Vaccination rate (%)	63.9
Age (year, mean ± SD)	58.2 ± 17.0
Sex (%, male/female)	41.7/56.4
Duration (year, mean ± SD)	15.4 ± 14.7
Rate of PEFM use (%)	22.5
Type of asthma (atopic/non-atopic, %)	65.9/28.3
Smoking status	
Non-smoker (%)	51.0
Ex-smoker (%)	31.5
Current smoker (%)	14.2
COPD complication (%)	9.9
Frequency of asthma attacks (year†)	
Few attacks (%)	49.4
Seasonal attacks (%)	28.6
Persistent attacks (%)	9.0
Asthma attacks (%) (2 weeks‡)	19.0
Morning synptoms (%)	39.3
Night symptoms (%)	27.5
Sleep disturbance (%)	12.0
ACT (median, [IQR])	24 [21-25]
Severity (Mil/MiP/MoP/SP/mSP, %)	29.5/26.1/31.4/6.7/1.5
Medication	
Rate of ICS use (%)	87.7
Rate of OCS use (%)	4.9
Rate of LABA use (%)	46.0
Rate of LTRA use (%)	44.0
Rate of OSRT use (%)	39.5

†During the 1 year prior to answering the questionnaire, ‡During the 2 weeks prior to answering the questionnaire. SD, standard deviation; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long acting beta agonist; LTRA, leukotriene receptor antagonist; Mil, mild intermittent; MiP, mild persistent; MoP, moderate persistent; OCS, oral corticosteroid; OSRT, oral sustained-released theophylline; SP, severe persistent; mSP, severer persistent; PEFM, peak flow meter.

Table 2 Odds ratios for vaccination against influenza infection

Group	Number	Odds ratio (95% CI)
All	2555	0.61 (0.45-0.84)
Younger patients	1303	0.62 (0.42-0.90)
Older patients	1202	1.38 (0.66-2.89)

CI, confidence interval. Young group: age ≤ median of age (61 years old), Old group: age > median of age (61 years old).

age of the analyzed patients) patients, 50 cases were excluded because of the lack of age description, and the age (median [IQR]) was 61 [46-72]. The OR for infection in younger and older group were 0.62 (95% CI: 0.42-0.90) and 1.38 (95% CI: 0.66-2.89), respectively.

The exacerbated and non-exacerbated cases due to the infection in non-vaccinated and vaccinated patients were 16 and 64 cases, and 23 and 65 cases, respectively, because 2 cases did not answer about the asthma exacerbation. Therefore, the rate of infection-induced asthma exacerbation was 23.2% (95% CI: 18.6-29.6). When patients were divided into 2 groups, younger (≤ the median age of the analyzed patients) and older (> the median age of the analyzed patients) patients, 2 cases were excluded because of the lack of age description, and the age (median [IQR]) was 45 [32-62]. The OR for vaccination against the infection-induced asthma exacerbation is shown in Table 3. In the analysis of the 3 groups - the entire population of patients who responded, the younger group and the older group, OR for infection was 1.42 (95% CI: 0.69-2.92), 1.67 (95% CI: 0.60-4.66) and 1.71 (95% CI: 0.50-5.83), respectively.

Table 3 Odds ratios for vaccination against asthma exacerbation due to influenza infection

Group	Number	Odds ratio (95% CI)
All	168	1.42 (0.69-2.92)
Younger patients	84	1.67 (0.60-4.66)
Older patients	82	1.71 (0.50-5.83)

CI, confidence interval. Young group: age ≤ median of age (45 years old), Old group: age > median of age (45 years old).

COMPARISON BETWEEN H1N1 pdm09 NON-INFECTED AND INFECTED PATIENTS

The comparison between H1N1 pdm09 non-infected and infected patients is summarized in Table 4. The vaccination rate in the infected patients was significantly lower than that in the non-infected patients. Infected patients were significantly younger than the non-infected patients, although there were no significant differences in sex, disease duration, type of asthma, peak-flow meter use rate, and smoking status between these 2 groups.

The comparison of indicators for asthma control that had been evaluated >6 months after the end of the pandemic season is also shown in Table 4. There was a significant difference in the frequency of asthma attacks during the 1 year prior to answering

Table 4 Comparison between H1N1 pdm non-infected and infected patients

	Non-infected patients	Infected patients
Number of cases	2385	170
Vaccination rate	64.7	52.9**
Age (year, mean ± SD)	58.9 ± 16.6	47.4 ± 18.5***
Sex (%, male/female)	41.8/56.7	40.6/57.6
Duration (year, mean ± SD)	15.4 ± 14.9	15.9 ± 12.3
Rate of PEFM use (%)	22.6	21.8
Type of asthma (%, atopic/non-atopic, %)	65.5/28.7	71.2/21.8
Smoking status		
Non-smoker (%)	50.8	53.5
Ex-smoker (%)	31.5	32.4
Current smoker (%)	14.3	12.4
Frequency of asthma attacks (year†)		
Few attacks (%)	50.1	40.0*
Seasonal attacks (%)	28.2	34.1
Persistent attacks (%)	8.6	13.5
Asthma attacks (%) (2 weeks‡)	18.5	25.9*
Morning symptoms (%)	39.1	42.9
Night symptoms (%)	26.8	37.1**
Sleep disturbance (%)	11.3	21.8***
ACT (median, [IQR])	24 [21-25]	23 [20-25]
Severity (MiI/MiP/MoP/SP/mSP, %)	30.1/26.1/31.1/6.6/1.6	21.2/26.5/34.7/7.6/1.2

†During the 1 year prior to answering the questionnaire, ‡During the 2 weeks prior to answering the questionnaire. SD, standard deviation; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long acting beta agonist; LTRA, leukotriene receptor antagonist; MiI, mild intermittent; MiP, mild persistent; MoP, moderate persistent; OCS, oral corticosteroid; OSRT, oral sustained-released theophylline; SP, severe persistent; mSP, severer persistent; PEFM, peak flow meter. *$p < 0.05$, **$p < 0.01$, $p < 0.001$, ***$p < 0.001$ vs. non-infected patients.

Table 5 Comparison between non-vaccinated and vaccinated patients

	Non-vaccinated patients	Vaccinated patients
Number of cases	922	1633
Infection rate	8.7	5.5**
Age (year, mean ± SD)	52.5 ± 16.4	61.4 ± 16.5***
Sex (%, male/female)	47.9/49.8	38.2/60.1***
Duration (year, mean ± SD)	15.1 ± 14.3	15.6 ± 15.0
Rate of PEFM use (%)	14.9	26.8***
Type of asthma (%, atopic/non-atopic, %)	61.8/26.9	64.6/29.1
Smoking status		
Non-smoker (%)	45.2	54.3***
Ex-smoker (%)	32.8	30.9
Current smoker (%)	18.8	11.6***
Frequency of asthma attacks (year†)		
Few attacks (%)	43.2	53.0***
Seasonal attacks (%)	32.9	26.3***
Persistent attacks (%)	9.5	8.6
Asthma attacks (%) (2 weeks‡)	24.2	16.1***
Morning synptoms (%)	42.3	37.7*
Night symptoms (%)	30.3	26.0*
Sleep disturbance (%)	15.8	9.8***
ACT (median, [IQR])	23 [20-25]	24 [21-25]***
Severity (MiI/MiP/MoP/SP/mSP, %)	30.0/27.8/29.8/5.4/1.1	29.1/38.9/32.2/7.3/1.8

†During the 1 year prior to answering the questionnaire, ‡During the 2 weeks prior to answering the questionnaire. SD, standard deviation; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long acting beta agonist; LTRA, leukotriene receptor antagonist; MiI, mild intermittent; MiP, mild persistent; MoP, moderate persistent; OCS, oral corticosteroid; OSRT, oral sustained-released theophylline; SP, severe persistent; mSP, severer persistent; PEFM, peak flow meter. *$p < 0.05$, **$p < 0.01$, $p < 0.001$, ***$p < 0.001$ vs. non-vaccinated patients.

the questionnaire between the 2 patient groups. The proportion of patients that qualified their asthma attacks responding with "few attacks" was significantly lower in infected patients than that in non-infected patients. Although there was no significant difference in the rate of morning symptoms between the 2 groups, the frequencies of asthma attacks, rate of night symptoms and sleep disturbance during the 2 weeks prior to the survey was significantly higher in the infected patients compared to the non-infected patients. There was no significant difference in ACT-J scores and disease severity between the 2 groups.

COMPARISON BETWEEN NON-VACCINATED AND VACCINATED PATIENTS

The comparison between non-vaccinated and vaccinated patients is summarized in Table 5. As would be expected, the incidence of infection in the vaccinated patients was significantly lower than that in the non-vaccinated patients. Patients who were vaccinated were significantly older, and had a higher proportion of female patients and of peak-flow meter use than non-vaccinated patients. While there were no significant differences in disease duration and type of asthma between the 2 groups, there were significant differences in smoking status. The proportions of non-smokers and current smokers in the vaccinated patients were significantly higher and lower, respectively, than those in non-vaccinated patients.

The comparison of indicators for asthma control that had been evaluated >6 months after the end of the pandemic season is also shown in Table 5. There were significant differences in the frequency of asthma attacks during the 1 year prior to the survey between the 2 groups. The proportion of patients with "few attacks" and "seasonal attacks" among the vaccinated patients was significantly higher and lower, respectively, than those in the non-vaccinated patients. Among other indicators for asthma control, there was a significantly lower rate of asthma attacks, night symptoms, and sleep disturbance during the 2 weeks prior to the survey in the vaccinated patients compared to non-vaccinated patients. The ACT-J score in the vaccinated patients was significantly higher than that in the non-vaccinated patients. There was no significant difference of asthma disease severity between the 2 groups.

DISCUSSION

The aim of this study was to investigate the influenza A (H1N1) pdm09 virus infection in adult asthmatic patients in a clinical setting. Data on infection and

vaccination were obtained by conducting a questionnaire-based survey. During this pandemic season, vaccination against H1N1 pdm09, distinct to that against seasonal influenza, was administered. Moreover, the rate of H1N1 pdm09 infection, relative to all influenza virus infection, during this pandemic season was approximately 96% in Japan.[8] Therefore, the information on infection and vaccination from the questionnaire-based survey was relevant and important for investigation.

The incidence of H1N1 pdm09 infection in the Niigata Prefecture (Table 1) was 6.7% (95% CI: 5.7-7.6). The incidence of H1N1 pdm09 infection in all of Japan was reported to be approximately 7.1%, by statistics from the Ministry of Health, Labour and Welfare.[27] Considering the rate of vaccination and the OR for vaccination against infection, the incidence of the H1N1 pdm09 infection in this study on the Niigata Prefecture was not dissimilar from that of Japan as a whole. Furthermore, being asthmatic was not likely to have had a major influence on the incidence of infection in Japan; however, this relationship is difficult to accurately evaluate in our study because no other published study resembles ours. The only background factor that differed between the H1N1 pdm09 non-infected and infected asthmatic patients was age, with infected patients being younger than non-infected patients (Table 4). However, this characteristic was seen in all individuals infected with this virus during the pandemic season,[28] indicating that younger age was not a characteristic specific to asthmatic patients.

The rate of vaccination was 63.9% (95% CI: 62.1-65.8) in this Niigata Prefecture survey. According to the statistics of Niigata Prefecture, the vaccination rate of patients bearing various diseases that could be exacerbated by influenza infection was 90.2% of target patients by the end of March 2010.[15] Therefore, some asthmatic patients were not vaccinated, possibly due to themselves or their physicians not considering their disease to apply to this category.

An OR for vaccination against H1N1 pdm09 infection status (Table 2) clearly showed the effectiveness against the onset of this novel viral infection (0.61 [95% CI: 0.45-0.84]). Another study in England reported an OR of 0.38 for relative risk of the vaccination in high-risk patients.[29] However, there was reportedly a difference in the relative risk of the vaccination against seasonal influenza virus between patients with laboratory-confirmed influenza and those with clinical symptom-based diagnoses, and the relative risk was reported to be between 0.75 and 0.78 in patients with clinical symptom-based diagnoses.[30] These observations indicate that there is room for improvement in vaccination effectiveness against infection in the asthmatic patients of this study. If there had been a significant association between pandemic phase and vaccination time, more effectiveness could have been obtained. As shown in Table 2, this effectiveness was limited to the younger age group (≤ the median age, 61 years old). A possible explanation for this finding could be the antigenicity of the H1N1 pdm09 vaccine in older age groups (> the median age, 61 years old) being insufficient in generating adequate immunity to prevent infection. Another possibility is that an old pandemic virus with the same or similar immunogenicity to that of H1N1 pdm09 had been responsible for infection before the younger generation was born - i.e. the older age groups might have already acquired a degree of resistance to this new virus regardless of vaccination. The reasons were not confirmed by our data, and another approach will be required to elucidate the mechanisms responsible.

In the present investigation, one important yet discouraging finding, was that the vaccination did not appear to be effective in curbing asthma exacerbation due to influenza infection, as indicated in Table 3. There are some factors that may account for this result. Firstly, there was an important problem in the definition of asthma exacerbation due to influenza infection. It is not easy to distinguish the symptoms of influenza from those of asthma exacerbation, and medication for the influenza infection could exacerbate asthma. Bacterial infection following the influenza infection could be mistaken for asthma exacerbation. And this definition may have not been clear to the patients answering the questionnaire, and depended on the patients' judgments rather than physician diagnosis; the data were therefore subjective. Secondly, the timing of vaccination in the Niigata Prefecture was inappropriate, as mentioned above. Thirdly, the number of cases analyzed may not have been large enough to detect vaccine efficacy against asthma exacerbation by influenza virus infection. Further investigation will therefore be required.

As shown in Table 4, asthma control in infected patients >6 months after the end of the pandemic season was worse than that in non-infected patients, as a result of a lower incidence of few attacks and a higher incidence of night symptoms and sleep disturbance - although the difference in the ACT-J scores between the 2 groups was not statistically significance. These findings suggest that adequate asthma control could provide suitable protection against this influenza infection in asthmatic patients, although there is also a possibility that the presence of an influenza infection could adversely affect subsequent asthma control. Regarding the comparison between non-vaccinated and vaccinated patients, a reverse to the result from the comparison between non-infected and infected patients was observed. If the control of asthma indicated by the questionnaire survey could have reflex the asthma control at the vaccination period, asthmatic patients with poor asthma control had not been vaccinated with precedence compared with well-

controlled patients as shown in Table 5. These findings might suggest that precedence for subsequent vaccinations against this virus should be given to poorly controlled asthmatic patients. In our comparisons in Table 4, 5, there was an important problem in the frequency of asthma attacks that was decided by patients' sense. Even if the frequency of asthma attacks is same in patients, some patients feel "few", others feel "persistent", indicating that there is the limitation this indicator.

In summary, we conducted a survey to investigate the influence of the influenza A (H1N1) pdm09 virus infection on adult asthmatic patients. The results showed that, although the vaccination was effective in blocking the onset of infection during the first pandemic season of H1N1 pdm09, its effectiveness was limited to younger patients. Vaccination effectiveness against asthma exacerbation caused by influenza infection was not observed; however, the effect of the H1N1 pdm09 virus infection on asthmatic patients requires further investigation.

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