Evaluation of the field-protective effectiveness of seasonal influenza vaccine among Korean children aged < 5 years during the 2014–2015 and 2015–2016 influenza seasons: a cohort study

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ABSTRACT

Background: A field effectiveness evaluation of the influenza vaccine among children younger than five years is important due to the high burden of influenza in this age group. The epidemiology of influenza virus changes rapidly each year. Moreover, the development of a new type of influenza vaccine is accelerating, necessitating a new field effectiveness evaluation.

Methods: This multi-center, open-label cohort study was conducted in the northern part of Seoul from December 2014 to May 2015 and in Gyeong-gi Province from December 2015 to May 2016. The cohort comprised an influenza vaccinated group and non-vaccinated group. During the influenza seasons, we conducted influenza rapid tests and polymerase chain reaction assays for individuals with suspected influenza and checked for the presence of influenza virus. We calculated the influenza vaccine effectiveness by comparing the incidence rates of influenza between the vaccinated and non-vaccinated groups.

Results: During the 2014–2015 season, the field effectiveness of the influenza vaccine was 38.4%. In particular, the vaccine effectiveness against type A influenza virus was 50.7%. During the 2015–2016 season, the vaccine effectiveness reached 23.8% and the vaccine effectiveness against type A influenza virus was 48.5%. The vaccine effectiveness against influenza B virus was markedly reduced in both seasons.

Conclusion: The influenza vaccine was supposed to be effective against influenza A, but may have a limited effectiveness against influenza B among Korean children aged < 5 years.

Introduction

Influenza is an infectious disease with a high burden and is known to have seasonal epidemic activity.1,2

Influenza is a viral disease that causes high fever, headache, and myalgia in healthy individuals and causes serious social problems.3,4

This infection can cause fatal complications in high-risk individuals including children and the elderly.5,6 Severe courses of influenza are often observed in children who have chronic cardiopulmonary diseases such as congenital or acquired cardiac diseases, bronchopulmonary dysplasia, and asthma; and neuromuscular diseases that involve the respiratory muscles.6,7

Children play a major role in the spread of influenza in their families and communities, as their secretions have higher concentrations of the influenza virus. The management of children’s personal hygiene is difficult, and they exhibit more frequent respiratory symptoms than adults do.8

Therefore, in controlling influenza, many developed countries like the United States of America recommend the administration of influenza vaccine to all children aged six months and older.9

Moreover, the Korea Centers for Disease Control and Prevention (KCDC) recommend that all children younger than five years should be given the influenza vaccine first because it is the most effective method of preventing influenza.10

According to the Korea National Health and Nutrition Examination Surveys report released in 2016, the influenza vaccination rate among children aged one to 11 years old was 63.5%, while that among those older than 12 years was 23.0%.11

Although the number of children who received the influenza vaccine was higher in South Korea than in other countries,12,13 the effectiveness and immunogenicity of this vaccine have not been successfully verified.

The epidemiology of influenza changes rapidly each year. Influenza remains highly unusual among infectious diseases in the rapid evolutionary rate of its causative viruses. A new influenza vaccine is required each year because the influenza virus has the ability to undergo antigenic drift. The vaccine is prepared according to the antigenic variation in the influenza virus, which can cause epidemic influenza.14 Many new types of influenza vaccine have recently been developed and added; previous field effectiveness evaluations cannot represent the current situation.

Therefore, a new field effectiveness evaluation is required every season due to seasonal changes in the vaccine composition. A field effectiveness evaluation among children younger than
five years is important due to the high burden of influenza in this age group. This study aimed to evaluate the effectiveness of influenza vaccine among Korean children younger than 5 years.

**Materials and methods**

This multi-center, open-label cohort study (carried out at the Korea Cancer Center Hospital, Eulji Hospital, and Jungnang-gu Health Center) was conducted in the northern part of Seoul from December 2014 to May 2015 and in the Gyeonggi Province from December 2015 to May 2016. The study involved healthy children aged six months to < 5 years. An open-label cohort study is a type of study in which both patients and healthy people are aware of the treatment being given. The cohort comprised an influenza vaccinated group and a non-vaccinated group. The vaccination criteria were based on voluntary intention. During the epidemic influenza season, we conducted influenza rapid tests and polymerase chain reaction (PCR) assays for individuals with suspected symptoms of influenza and checked for the presence of the influenza virus. We calculated the influenza vaccine effectiveness by comparing the incidence rates of influenza, based on the type of influenza virus identified, between the two cohorts.

**Subject recruitment and selection**

We informed the designated health care professionals in Korea Cancer Center Hospital, Eulji Hospital and Jungnang-gu Health Center about case definition, influenza-like illness, study procedure, etc.

The participants were recruited from the hospital or health center through announcements or by sending out letters to the caregivers in daycare centers. Written consent was obtained from all participants of the study.

We selected healthy children aged six months to < 5 years who voluntarily provided written consent through a legal representative. Those who were deemed unsuitable after history taking, who were suspected or confirmed of having immunosuppression or immunodeficiency disorders including tumors, and human immunodeficiency virus infection, who received adrenocortical hormone or immunosuppressive drugs within eight weeks before the start of the study (continuous systemic administration of more than 0.5 mg/kg/day of prednisone or an equivalent agent for more than one week), who had marked nutritional disorder, chronic diseases that could impede the progress of or require the need to terminate the study, severe asthmatic patients at risk of collecting respiratory specimens, or all patients with hemorrhagic tendencies were excluded from the study.

**Consent procedure**

The purpose and process of the study were explained to the participants and their legal representatives, and the participants’ legal representatives provided the consent on their behalf. There was a gap between when an explanation was provided regarding the study and written consent was obtained, that is, written consent was obtained within seven days after the study process was explained to participants and their legal representatives. In order to minimize unreasonable effects on the patients, the explanations were based on the written content, and it was emphasized that the patients were free to leave at any time during the trial period. If a certain term was not understood by the participants or legal representative within the course of the explanation, additional explanation was provided before obtaining the informed consent. The following information was provided to the participants: the purpose of the study, procedure of the study, signs and symptoms of influenza-like illness (ILI), risks and benefits when participating in this study.

ILI is characterized by fever of more than 38°C and one or more of the following symptoms: rhinorrhea (nasal stuffiness), sore throat, cough, headache, myalgia, arthralgia, and general weakness.

Participants with ILI were requested to visit the hospital for the influenza virus confirmatory test. The two respiratory specimens per subject were collected through throat or nasal swab. One of the specimens was immediately stored in a freezer at a temperature of ~70°C after being planted in a virus-specific medium (BD Universal Viral Transport for viruses, Becton, Dickinson and Company Sparks), and the other was used as a specimen for the influenza rapid test.

Moreover, we investigated those patients who did not visit the clinical trial center although they were suspected of having influenza or were diagnosed with influenza at a medical center other than the clinical trial center by a caregiver through a phone call during the epidemic influenza season.

**Diagnosis of influenza**

We chose two methods of diagnosing influenza: the rapid test kit (BD Veritor System for Rapid Detection of Flu A + B) and PCR assay. After obtaining the RNA from the respiratory specimens, C-DNA was prepared and the influenza virus was confirmed through PCR. PCR assay was performed using the Seeplex® Influenza A/B One Step Typing to distinguish between H1N1 and seasonal influenza A (H1 and H3). Influenza was defined as positivity of at least one of the two results.

**Evaluation of effectiveness**

Vaccine effectiveness was defined as a reduction in the incidence of influenza virus infection in the vaccinated group compared to the non-vaccinated group. It is calculated using the following formula:

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\text{Effectiveness} \% = 1 - (\text{relative risk} \times 100)
\]

The relative risk is the ratio of the incidence of influenza virus infection in the vaccinated group to that in the unvaccinated group. A definite diagnosis was made if the result of the rapid test kit was positive; if the respiratory specimens were positive for H3N2, H1N1, and B influenza as confirmed by PCR assay; if a definite diagnosis was confirmed using the above assessment methods in other centers; and if the patient brought documentary evidence regarding his or her diagnosis.
**Promoting patients’ participation**

In order that the participants with clinical symptoms actively visit the hospital to undergo the test, we regularly informed them about the signs and symptoms of ILI, study procedure, when to visit the hospital, and taught them how to participate by sending mobile text messages (once per week from January to March, and once every two weeks after April).

**Statistical analysis**

Using descriptive statistics, the demographic data and health statuses of the participants were assessed. Continuous variables were expressed as mean, standard deviation, and median, while categorical variables were expressed as frequency count. To compare the statistical difference between groups, continuous data were analyzed using the t-test, while categorical data were analyzed using the chi-squared test.

**Results**

Of the 568 participants enrolled during the 2014–2015 season, 464 (81.69%) were vaccinated, 55.63% of whom were men. During the 2014–2015 season, the mean age of vaccinated participants was 2.522 and the standard deviation was 1.532; the median age was two years. Of the 818 participants enrolled during the 2015–2016 season, 646 (78.97%) were vaccinated, 53.11% of whom were men. During the 2015–2016 season, the mean age of the vaccinated participants was 2.685 and the standard deviation was 1.691; the median age three years (Table 1).

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Of the 568 subjects, 464 received the influenza vaccine while 104 did not receive the vaccine during the 2014–2015 season. Of the 54 subjects, 62 cases of ILI occurred and visited the hospital to undergo influenza rapid test from January 15 to May 31, 2015.

Among the 464 vaccinated children, 25 cases occurred among 22 children with definite diagnoses of influenza, 11 cases among 11 children infected with the type A influenza virus and 14 cases among 14 children infected with the type B influenza virus. Three children of the subjects were infected with types A and B influenza virus simultaneously.

The influenza vaccine effectiveness was 38.4% (relative risk: 0.616, 95% confidence interval (CI): 0.282, 1.346). The protective effectiveness against type A influenza virus was 50.7% (relative risk: 0.493, 95% CI: 0.175, 1.389), and the preventive effect of the vaccine against type B influenza virus was lower (Table 2).

**Table 1. Characteristics of enrolled patients with or without influenza virus vaccination.**

| Characteristics   | Vaccinated 2014–2015 | Unvaccinated 2014–2015 | P Value | Vaccinated 2015–2016 | Unvaccinated 2015–2016 | P Value |
|-------------------|----------------------|------------------------|---------|----------------------|------------------------|---------|
| Sex               | n = 464              | n = 104                |         | n = 646              | n = 172                |         |
| Male              | 55.63 %              | 47.06 %                | 0.146*  | 53.11 %              | 53.8 %                 | 0.124*  |
| Female            | 44.37 %              | 52.94 %                |         | 46.89 %              | 46.2 %                 |         |
| Mean age          | 2.522                | 2.635                  |         | 2.685                | 2.594                  |         |
| (Standard deviation) | (1.532)            | (1.541)                | 0.534** | (1.691)              | (1.968)                | 0.598** |
| Median age        | 2                    | 3                      |         | 3                    | 2.5                    |         |

*P Value from chi-square statistic.  
**P Value from t-test statistic.

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The protective effectiveness of influenza vaccine through 2015

| Flu Positive | Flu Negative | Subtotal | Relative Risk | VE* |
|--------------|--------------|----------|---------------|-----|
| 22           | 442          | 464      | 0.616         | (1 – 0.616) |
| 22           | 442          | 464      | (95% CI** 0.282, 1.346) | x 100 = 38.4% |

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*VE, vaccine effectiveness.**CI, confidence intervals.

Table 3. The protective effectiveness of influenza vaccine through 2015–2016 influenza seasons.

| Flu Positive | Flu Negative | Subtotal | Relative Risk | VE* |
|--------------|--------------|----------|---------------|-----|
| 63           | 583          | 646      | 0.762         | (1 – 0.762) |
| 63           | 583          | 646      | (95% CI** 0.484, 1.202) | x 100 = 23.8% |

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From December 2015 to May 2016

*VE, vaccine effectiveness.**CI, confidence intervals.

0.515, 95% CI: 0.282, 0.938), and the preventive effect of the vaccine against type B influenza virus was lower (Table 3).

Discussion

According to this study, the total effectiveness of the influenza vaccine was 38.4% during the 2014–2015 influenza season. The vaccine effectiveness against type A influenza virus was 50.7%, and the effectiveness of the vaccine against type B influenza virus was reduced during the 2014–2015 influenza season. During the 2015–2016 influenza season, the total effectiveness of the influenza vaccine was 23.8%. The vaccine effectiveness against type A influenza virus was 48.5%, and the effectiveness of the vaccine against type B influenza virus was reduced during the 2015–2016 influenza season.

According to the United States Centers for Disease Control and Prevention (CDC) report during the 2015–2016 season, the rates of vaccine effectiveness against H1N1, all subtypes of influenza B viruses, and Yamagata lineage were 51%, 76%, and 79%, respectively. However, the report did not include an evaluation of the effectiveness of the vaccine against type B influenza virus of the Victoria lineage.

According to the United States CDC report, during the 2014–2015 season, the effectiveness of the influenza vaccine for all ages was estimated at approximately 23%, and the effectiveness of the vaccine against H3N2 type A influenza virus was approximately 18%. During the 2014–2015 season, more than 80% of reported influenza cases in the United States were caused by H3N2. The effectiveness of the vaccine was remarkably low because the antigenicity in two-thirds of H2N3 influenza was different from that of the vaccine. However, the antigenicity in one-third of H3N2 cases matched with that of the vaccine, as did the antigenicity of H1N1 and type B influenza. The antigenic drift of H3N2 during the 2014–2015 season was identified in the World Health Organization (WHO) surveillance in March 2014. The WHO had recommended the composition of influenza vaccine for use in the northern hemisphere influenza season in mid-February 2014.

According to the 2014–2015 KCDC report, influenza A(H1N1)pdm09, H3N2 and B were found to be 10.9%, 52% and 37.2% respectively in Korea. Moreover, according to the 2015–2016 KCDC report, influenza A(H1N1)pdm09, H3N2 and B were found to be 44.1%, 4.7% and 51.1% respectively in Korea.

In this study, the effectiveness of the influenza vaccine against all types of influenza virus during the 2014–2015 season was estimated to be approximately 30–40%. In particular, the effectiveness of the vaccine against type A influenza virus was more than 50%, but the vaccine had a limited effect against type B influenza virus. These results, especially the effect on type B influenza virus, were different from those shown in foreign reports. The seasonal variation in vaccine effectiveness was generally consistent with the degree of antigenic match between viruses isolated from patients and vaccine strains.

Several reasons could be given for the lower effectiveness of the vaccine against type B influenza virus in this study. First, the
epidemic type B influenza season is concentrated between March and May. Therefore, it is possible that the influenza vaccine is less effective against type B influenza virus as vaccine immunity wanes over time. The KCDC recommended that the influenza vaccine be administered from October to December. However, the epidemic season of the type B influenza virus occurs 6 months later. Therefore, during the epidemic season of influenza type B, the vaccine immunity might be reduced, rendering the vaccine in effective.

Second, the fact that the trivalent vaccine was administered to a greater proportion of participants could be one of the reasons for the limited effect of the vaccine on the type B influenza virus. In Korea, the quadrivalent influenza vaccination is contraindicated for children younger than three years. Among the influenza B strains, both Yamagata and Victoria types were in circulation during the 2013–2014 season in Korea, but the vaccine only covered the Yamagata strain. As a result, the vaccine effectiveness against influenza B virus was relatively low.

Two different lineages of type B influenza virus have been circulating globally for many years. They have distinct antigens, and there is evidence, especially among very young children, that vaccination or infection with one lineage produces little antibodies against the other virus strain. The inability to predict which type B virus will circulate in a particular year, as well as mixed outbreaks, has resulted in the development of, as yet unreleased, the quadrivalent vaccine containing both type B virus lineages.

According to a recent study in Korea, the 2015–2016 northern hemisphere formulation of IIV4 was highly immunogenic in adults aged 18–60 years. Comparing quadrivalent vaccines with trivalent vaccines, immunogenicity was comparable in three shared strains of influenza virus and appeared higher in the quadrivalent vaccine than in the trivalent vaccine of the Victoria lineage.

However, McLean et al. reported that vaccination with a trivalent vaccine containing influenza B/Yamagata was effective against infection caused by influenza B/Victoria, indicating a significant cross-lineage protection. Cross-lineage protection was also observed in Canada during the 2012–2013 season and in the United States during the 2011–2012 season. In contrast, data from Canada during the 2011–2012 season showed limited or no cross-lineage protection. Choi et al. reported that cross-reactivity was found in trivalent vaccines, but at a much weaker level than the immune response induced by quadrivalent vaccines among adults in Korea. These discussions are still underway, and further studies on the effectiveness of each type of influenza vaccine are needed.

Moreover, antigenic variants may have reduced the protective effect of vaccine against influenza. Antigenic variants from human influenza virus have been recently identified. This process occurred through antigenic evolution, and this transformation drives the emergence of strain replacements. In this study, although we did not identify mutant strains, we cannot rule out the possibility that the presence of such strains may have affected the vaccine effectiveness.

The strength of this study lies in the use of reverse transcription PCR in addition to influenza rapid test in the detection of the influenza virus. This study was conducted prospectively. In most vaccine-related studies, vaccine effectiveness was evaluated retrospectively as the process is simpler because there is no dropout problem and researcher can save time, money, effort due to using existing data. However, retrospective studies have selection and recall biases because they first confirm virus infection before obtaining the vaccination history. Thus, we prospectively evaluated the effectiveness of vaccine to reduce these biases.

This study had some limitations. Because this study was performed only in small towns in Seoul and Gyeong-gi do, it is difficult to conclude that the result is representative of the general population in South Korea. Another limitation was the recruitment period. The recruitment was conducted approximately two months before the study. During the year, seasonal influenza epidemics usually start in October, peak in January and February, and then wanes through March. In addition, this study was limited in its inability to distinguish among the kinds of vaccine injected. We calculated vaccine effectiveness without distinguishing among injected vaccines, be they trivalent, quadrivalent and split type or subunit type.

The assessment of vaccine effectiveness against laboratory-confirmed influenza in populations for whom annual influenza vaccination is recommended may influence influenza control recommendations if results are already available while the influenza season is still underway. The increased use of influenza diagnostic tests and antiviral agents may be recommended if the vaccine effectiveness is reduced as a result of poor antigenic match.

In conclusion, the influenza vaccine was supposed to be effective against type A influenza virus in the 2014–2015 and 2015–2016 influenza seasons, but may have a limited effect against type B influenza virus in Korean children aged < 5 years. Thus, further studies and measures are needed to support these findings.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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