





RESEARCH PAPER



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

Young Kyung Kang ^a, Hea Lin Oh ^a, Jung Sub Lim ^a, Jun Ah Lee ^a, Yun Kyung Kim ^b, Byung Wook Eun ^c, Dae Sun Jo ^d, and Dong Ho Kim^a

^aDepartment of Pediatrics, Korea Cancer Center Hospital, Seoul, Korea; ^bDepartment of Pediatrics, Korea University Ansan Hospital, Ansan, Korea; ^cDepartment of Pediatrics, Eulji Medical Center, Seoul, Korea; ^dDepartment of Pediatrics, Chonbuk National University Hospital, Jeonju, Korea

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.

ARTICLE HISTORY

Received 6 June 2018
Revised 11 September 2018
Accepted 22 September 2018

KEYWORDS

Influenza virus; influenza vaccine; vaccine effectiveness; field protective evaluation; Korean child

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:

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

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).

Evaluation of the field protective effectiveness of the seasonal influenza vaccine among Korean children aged < 5 years during the 2014–2015 influenza season

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).

Evaluation of the field protective effectiveness of seasonal influenza vaccine among Korean children aged < 5 years during the 2015–2016 influenza season

A total of 818 children were recruited as a cohort from October 2015. The influenza-vaccinated group comprised 646 children, while the non-vaccinated group comprised 172 children. Among the 646 vaccinated children, 133 underwent the influenza rapid antigen test, and 52 children were diagnosed with influenza. Of these children who had a definitive influenza diagnosis, 19 children tested positive for the type A influenza virus only, 30 children tested positive for type B influenza virus only, and three children were co-infected with types A and B influenza viruses. 11 cases with negative rapid test results yielded positive PCR assay findings, seven children of whom were infected with type A influenza virus and four children with type B influenza virus. Among the 646 vaccinated children, 66 cases occurred among 63 children with definitively diagnosed influenza, 29 cases among 29 children infected with the type A influenza virus and 37 cases among 37 children infected with the type B influenza virus. Three children among the subjects were simultaneously infected with types A and B influenza viruses. Of the 172 unvaccinated children, 28 children underwent an influenza rapid antigen test and 20 children were diagnosed with influenza. 14 children of the unvaccinated children were diagnosed with influenza caused by type A influenza virus and six children were diagnosed with influenza caused by type B influenza virus. Three cases with negative rapid test results yielded positive PCR assay findings, two of whom tested positive for the type A influenza virus, and while the other tested positive for the type B influenza virus. Among the 172 unvaccinated children, 23 cases occurred among 22 children with definitively diagnosed influenza, 16 cases among 15 children infected with type A influenza virus, and seven cases among seven children infected with type B influenza virus. One of the subjects was infected with two influenza A virus subtypes (H1N1 and H3N2) at different times.

Eventually, the influenza vaccine effectiveness reached 23.8% (relative risk: 0.762, 95% CI: 0.484, 1.202). The effectiveness of vaccine against type A influenza virus was 48.5% (relative risk:

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

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

*P Value from chi-square statistic.

**P Value from t-test statistic.

In Korea Cancer Center Hospital, Eulji Hospital, Jungnang-gu Health Center

Table 2. The protective effectiveness of influenza vaccine through 2014–2015 influenza seasons.

	Vaccinated	Unvaccinated	Subtotal	Relative Risk	VE*
Flu Positive	22	8	30	0.616	(1 – 0.616)
Flu Negative	442	96	538	(95% CI** 0.282, 1.346)	x 100 = 38.4%
Subtotal	464	104	568		
Incidence (%)	4.74	7.69	5.28		
Flu A Positive	11	5	16	0.493	(1 – 0.493)
Flu A Negative	453	99	552	(95% CI	x 100 = 50.7%
Subtotal	464	104	568	0.175, 1.389)	
Incidence (%)	2.37	4.81	2.82		
Flu B Positive	14	3	17	1.05	
Flu B Negative	450	101	566	(95% CI	
Subtotal	464	104	568	0.306, 3.574)	
Incidence (%)	3.02	2.88	2.99		

In Korea Cancer Center Hospital, Eulji Hospital, Jungnang-gu Health Center
From December 2014 to May 2015

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

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

	Vaccinated	Unvaccinated	Subtotal	Relative Risk	VE*
Flu Positive	63	22	85	0.762	(1 – 0.762)
Flu Negative	583	150	733	(95% CI** 0.484, 1.202)	x 100 = 23.8%
Subtotal	646	172	818		
Incidence (%)	9.75	12.79	10.39		
Flu A Positive	29	15	44	0.515	(1 – 0.515)
Flu A Negative	617	157	774	(95% CI	x 100 = 48.5%
Subtotal	646	172	818	0.282, 0.938)	
Incidence (%)	4.49	8.72	5.38		
Flu B Positive	37	7	44	1.408	
Flu B Negative	609	165	774	(95% CI	
Subtotal	646	172	818	0.639, 3.101)	
Incidence (%)	5.73	4.07	5.38		

In Korea Cancer Center Hospital, Eulji Hospital, Jungnang-gu Health Center
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 H3N2 and type B influenza virus of the Victoria lineage.¹⁵

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 2014.¹⁶

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.¹⁷ 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.¹⁸

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.^{19–21} The seasonal variation in vaccine effectiveness was generally consistent with the degree of antigenic match between viruses isolated from patients and vaccine strains.²²

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.²³ 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 ineffective.

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.²⁴ 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.²⁵

According to a recent study in Korea, the 2015–2016 northern hemisphere formulation of IIV4 was highly immunogenic in adults aged 18–60 years.²⁶ 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.²⁶

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.²⁷ Cross-lineage protection was also observed in Canada during the 2012–2013 season and in the United States during the 2011–2012 season.²⁷ In contrast, data from Canada during the 2011–2012 season showed limited or no cross-lineage protection.²⁷ 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.²⁶ 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.²⁸ 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.²⁹ However, retrospective studies have selection and recall biases because they first confirm virus infection before obtaining the vaccination history.^{30,31} 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.²²

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.

Funding

This study was supported by a grant from Transgovernmental Enterprise for Pandemic Influenza in Korea (TEPIK) which is a part of the Korea Healthcare Technology R&D Project by Ministry of Health and Welfare, Republic of Korea (grant No. A103001).

ORCID

Young Kyung Kang  <http://orcid.org/0000-0002-5504-9624>

Hea Lin Oh  <http://orcid.org/0000-0002-6583-8993>

Jung Sub Lim  <http://orcid.org/0000-0001-9560-8921>

Jun Ah Lee  <http://orcid.org/0000-0003-3310-9566>

Yun Kyung Kim  <http://orcid.org/0000-0003-4396-8671>

Byung Wook Eun  <http://orcid.org/0000-0003-3147-9061>

Dae Sun Jo  <http://orcid.org/0000-0002-3141-9539>

References

1. Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. *Am J Epidemiol.* 1980 Dec;112(6):798–811. doi:10.1093/oxfordjournals.aje.a113052.
2. Neuzil KM, Zhu Y, Griffin MR, Edwards KM, Thompson JM, Tollefson SJ, Wright PF. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. *J Infect Dis.* 2002 Jan 15;185(2):147–152. doi:10.1086/338363.

3. Heikkinen T, Silvennoinen H, Peltola V, Ziegler T, Vainionpaa R, Vuorinen T, Kainulainen L, Puhakka T, Jartti T, Toikka P, et al. Burden of influenza in children in the community. *J Infect Dis.* 2004 Oct 15;190(8):1369–1373. doi:10.1086/424527.
4. Poehling KA, Edwards KM, Griffin MR, Szilagyi PG, Staat MA, Iwane MK, Snively BM, Suerken CK, Hall CB, Weinberg GA, et al. The burden of influenza in young children, 2004–2009. *Pediatrics.* 2013 Feb;131(2):207–216. doi:10.1542/peds.2012-1255.
5. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, McGeer AJ, Neuzil KM, Pavia AT, Tapper ML, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the infectious diseases society of america. *Clin Infect Dis.* 2009 Apr 15;48(8):1003–1032. doi:10.1086/598513.
6. Chaves SS, Aragon D, Bennett N, Cooper T, D’Mello T, Farley M, Fowler B, Hancock E, Kirley P D., Lynfield R, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010–2011 influenza season: exploring disease severity by virus type and subtype. *J Infect Dis.* 2013 Oct 15;208(8):1305–1314. doi:10.1093/infdis/jit316.
7. Burton C, Vaudry W, Moore D, Bettinger JA, Tran D, Halperin SA, Scheifele DW. Burden of seasonal influenza in children with neurodevelopmental conditions. *Pediatr Infect Dis J.* 2014 Jul;33(7):710–714. doi:10.1097/INF.0000000000000272.
8. Lee BY, Shah M. Prevention of influenza in healthy children. *Expert Rev Anti Infect Ther.* 2012 Oct;10(10):1139–1152. doi:10.1586/eri.12.106.
9. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Bresee JS, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2017–18 Influenza Season. *MMWR Recomm Rep.* 2017 Aug 25;66(2):1–20. doi:10.15585/mmwr.rr6602a1.
10. Korea Centers for Disease Control and Prevention. [accessed 2017 Apr 8]. <http://cdc.go.kr/CDC/notice/CdcKrTogether0302.jsp?menuIds=HOME001-MNU1154-MNU0005-MNU0088&cid=71428>
11. Ministry of Health and Welfare, Korea Centers for Disease Control and Prevention, Korea Health Statistics 2016: Korea National Health and Nutrition Examination Survey(KNHANES VII-1), Sejong: Korea Centers for Disease Control and Prevention; 2017.
12. Flu Vaccination CDC. Coverage, United States, 2016–17 Influenza Season. Available at: <https://www.cdc.gov/flu/fluview/coverage-1516estimates.html>
13. European Centre for Disease Prevention and Control. Seasonal influenza vaccination in Europe. Vaccination recommendations and coverage rates in the EU member states for eight influenza seasons: 2007–2008 to 2014–2015. Stockholm: ECDC; 2017
14. Kilbourne ED. Influenza immunity: new insights from old studies. *J Infect Dis.* 2006 Jan 1;193(1):7–8. doi:10.1086/498984.
15. Flu vaccine nearly 60 percent effective [news release]. Atlanta, GA: Centers for Disease Control and Prevention. Published February 24, 2016. Accessed February 26, 2016.
16. Centers for Disease Control and Prevention, Flannery B, Clippard J, Zimmerman RK, Nowalk MP, Jackson ML, Jackson LA, et al. Early estimates of seasonal influenza vaccine effectiveness - United States, January 2015. *MMWR Morb Mortal Wkly Rep.* 2015;64(1):10–5. PMID:25590680
17. Ki HO, Kim IH, Cho EH, Kang MG, Chu H, Lee JY. Korean influenza sentinel surveillance report, 2014–2015. *Public Health Wkly Rep* 2015;8:1096–106. [Internet]. [accessed on 25 August 2016]. Available at http://www.cdc.go.kr/CDC/info/CdcKrInfo0301.jsp?menuIds=HOME001-MNU1132-MNU1138-MNU0037-MNU1380&q_type=&year=2015&cid=66230&pageNum=%20
18. In HK, Lee DH, Kang MG, Chu H, Lee JY, Kim KS. Influenza Korea and Respiratory Surveillance Report, 2015–2016 *Public Health Wkly Rep* 2017;8:185–93. [Internet]. [accessed on 27 February 2017] http://www.cdc.go.kr/CDC/info/CdcKrInfo0301.jsp?menuIds=HOME006-MNU3003-MNU2950-MNU2951&q_type=&year=2017&cid=73282&pageNum=
19. Buchan SA, Booth S, Scott AN, Simmonds KA, Svenson LW, Drews SJ, Russell M L., Crowcroft N S., Loeb M., Warshawsky B F., et al. Effectiveness of live attenuated vs inactivated influenza vaccines in children during the 2012–2013 through 2015–2016 influenza seasons in Alberta, Canada: a Canadian Immunization Research Network (CIRN) Study. *JAMA Pediatr.* 2018 Jul;e181514. doi:10.1001/jamapediatrics.2018.1514.
20. Sugaya N, Shinjoh M, Nakata Y, Tsunematsu K, Yamaguchi Y, Komiyama O, Takahashi H, Mitamura K, Narabayashi A, Takahashi T. Three-season effectiveness of inactivated influenza vaccine in preventing influenza illness and hospitalization in children in Japan, 2013–2016. *Vaccine.* 2018 Feb 14;36(8):1063–1071. doi:10.1016/j.vaccine.2018.01.024.
21. Valdin HL, Begue RE. Influenza vaccines effectiveness 2013–14 through 2015–16, a test-negative study in children. *Vaccine.* 2017 Jul 24;35(33):4088–4093. doi:10.1016/j.vaccine.2017.06.050.
22. Belongia EA, Kieke BA, Donahue JG, Greenlee RT, Balish A, Foust A, Lindstrom S, Shay D. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004–2005 season to the 2006–2007 season. *J Infect Dis.* 2009 Jan 15;199(2):159–167. doi:10.1086/595861.
23. Ferdinands JM, Fry AM, Reynolds S, Petrie J, Flannery B, Jackson ML, Cox A L., Dore G., Grebely J., Kim A Y., et al. Intraseason waning of influenza vaccine protection: evidence from the US influenza vaccine effectiveness network, 2011–12 through 2014–15. *Clin Infect Dis.* 2017 Mar 1;64(5):544–550. doi:10.1093/cid/ciw816.
24. Ki HO, Kim IH, Cho EH, Kang MG, Chu H. Korean influenza sentinel surveillance report, 2013–2014. *Public Health Wkly Rep* 2014;7:1089–98. [accessed on 4 December 2014] http://www.cdc.go.kr/CDC/info/CdcKrInfo0301.jsp?menuIds=HOME006-MNU3003-MNU2950-MNU2951&fid=31&q_type=title&q_value=%EC%9D%B8%ED%94%8C%EB%A3%A8%EC%97%94%EC%9E%90&cid=60812&pageNum=1
25. Ohmit SE, Thompson MG, Petrie JG, Thaker SN, Jackson ML, Belongia EA, Zimmerman R K., Gaglani M., Lamerato L., Spencer S M., et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. *Clin Infect Dis.* 2014 Feb;58(3):319–327. doi:10.1093/cid/cit736.
26. Choi WS, Noh JY, Lee J, Choi JY, Lee JS, Kim MS, Kim HS, Bang J, Lavis N, Kim WJ. Immunogenicity and safety of a split-virion quadrivalent influenza vaccine in adults 18–60 years of age in the Republic of Korea. *Hum Vaccin Immunother.* 2018 Mar 4;14(3):587–592. doi:10.1080/21645515.2017.1381808.
27. McLean HQ, Thompson MG, Sundaram ME, Kieke BA, Gaglani M, Murthy K, Piedra PA, Zimmerman RK, Nowalk MP, Raviotta JM, et al. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. *J Infect Dis.* 2015 May 15;211(10):1529–1540. doi:10.1093/infdis/jiu647.
28. Bedford T, Suchard MA, Lemey P, Dudas G, Gregory V, Hay AJ, McCauley JW, Russell CA, Smith DJ, Rambaut A. Integrating influenza antigenic dynamics with molecular evolution. *Elife.* 2014 ;3(3):e01914. doi:10.7554/eLife.01914.
29. Lytras T, Kossyvakis A, Melidou A, Exindari M, Gioula G, Pogka V, Malisiovas N, Mentis A. Influenza vaccine effectiveness against laboratory confirmed influenza in Greece during the 2013–2014 season: A test-negative study. *Vaccine.* 2015 Jan 3;33(2):367–373. doi:10.1016/j.vaccine.2014.11.005.
30. Jimenez-Jorge S, Pozo F, de Mateo S, Delgado-Sanz C, Casas I, Garcia-Cenoz M, Castilla J, Sancho R, Etxebarriarteun-Aranzabal L, Quiñones C, et al. Influenza vaccine effectiveness in Spain 2013/14: subtype-specific early estimates using the cycEVA study. *Euro Surveill.* 2014 Mar 6;19(9). doi:10.2807/1560-7917.ES2014.19.9.20727.
31. Skowronski D, Chambers C, Sabaiduc S, De Serres G, Dickinson J, Winter A, Fonseca K, Gubbay JB, Charest H, Petric M, Kraiden M. Interim estimates of 2013/14 vaccine effectiveness against influenza A(H1N1)pdm09 from Canada’s sentinel surveillance network, January 2014. *Euro Surveill.* 2014 Feb 6;19(5):20690. doi:10.2807/1560-7917.ES2014.19.5.20690.