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Effectiveness of trivalent inactivated influenza vaccines in children during 2017–2018 season in Korea: Comparison of test-negative analysis by rapid and RT-PCR influenza tests

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ABSTRACT

Objectives: In Korea, the National Immunization Program provided trivalent inactivated influenza vaccines (IIV3) to all children aged 6–59 months during the 2017–2018 season. In this study, we aimed to evaluate the vaccine effectiveness (VE) of IIV3 in children during the 2017–2018 season.
Methods: Children aged 6–59 months who were tested for influenza for their acute respiratory illness in four hospitals during the 2017–2018 influenza season were included. We estimated the VE of IIV3 by test-negative case-control design based on the rapid influenza diagnostic test (RIDT) or reverse transcription polymerase chain reaction (RT-PCR) test results.
Results: A total of 4738 children were included in this study. The number of laboratory-confirmed influenza cases was 845 (17.8%), and there were 478 cases of influenza A and 362 cases of influenza B. The adjusted VE based on RT-PCR was 53.4% (95% CI, 25.3–70.5) against any influenza, 68.8% (95% CI, 38.7–84.1) against influenza A, and 29.7% (95% CI, −35.1 to 61.8) for influenza B. The adjusted VE based on RIDT was 14.8% (95% CI, −4.4 to 30.0) against any influenza, 24.2% (95% CI, 3.1–40.2) against influenza A, and −5.1% (95% CI, −42.6 to 21.4) against influenza B. Age-specific VE based on RT-PCR against any influenza was 44.1% (95% CI, −0.2 to 67.8) in children aged 6 months to 2 years and 59.3% (95% CI, 8.8–81.9) in children aged 3–<5 years.
Conclusion: Our results suggest moderate protection (53.4%) of IIV3 against RT-PCR laboratory-confirmed influenza in children in the 2017–2018 influenza season. However, the RIDT hampered the validity to assess VE during influenza season. Caution is needed when interpreting an RIDT-based test negative design influenza VE study.

Introduction

Influenza is an acute respiratory illness that causes local outbreaks and seasonal epidemics worldwide (Paules and Subbarao, 2017). Globally, the disease burden of influenza-associated respiratory mortality is as high as 290,000–650,000 annual deaths (Iuliano et al., 2018). Approximately 15–45% of children are known to be infected with influenza during a given season. High viremic titers and long periods of viral shedding in children represent a

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critical source in the transmission of influenza in the community (Nair et al., 2011; Paules and Subbarao, 2017). The influenza vaccine is the most effective public health measure for preventing influenza.

The performance of the vaccine could be evaluated by estimating the vaccine effectiveness (VE) (Sullivan et al., 2017; Skowronski et al., 2018, 2019; Rolfes et al., 2019). A previous study on VE of live attenuated influenza vaccines showed less effectiveness that led to alteration in the recommendation of this vaccine (CDC, 2016). The VE appears to have a wide range by age group, regional difference, and season. This discrepancy in VE may be attributable to various factors, such as vaccine coverage rate, season, manufacturing of vaccines, host factor and investigational bias (Mameli et al., 2019). In children aged 5 years and younger, this variability may increase to 15–85% (Shen et al., 2013; Blyth et al., 2014; Su et al., 2015).

Seasonal influenza generally occurs from November to April of the following year in Korea. In the 2017–2018 season, the Korean National Immunization Program for influenza is recommended for people who are at a high risk for developing complications from influenza. Since the 2017–2018 influenza season, Korea Centers for Disease Control and Prevention has provided free inactivated trivalent influenza vaccines (IIV3) for all children aged 6–59 months. In this study, we aimed to estimate the VE of IIV3 in preventing laboratory-confirmed influenza in children during the 2017–2018 influenza season when lineage-mismatched influenza B virus circulated. In addition, we compared the VE based on the rapid influenza diagnostic test (RIDT) or reverse transcription polymerase chain reaction (RT-PCR) test results.

Methods

Study design

This study setting included Seoul National University Children's Hospital (Seoul), Seoul National University Bundang Hospital (Seongnam), Chungbuk National University Hospital (Cheongju), and Jeju National University Hospital (Jeju). We enrolled children from 6 months to 59 months old who visited the four hospitals for influenza-like illness from November 2017 to April 2018. Children were excluded if they had an immunodeficiency disorder, received long-term use of high-dose steroids, or received quadrivalent inactivated influenza vaccines (IIV4). Only the first episode was included when more than one test was positive for the same influenza subtype. Vaccination within 2 weeks was not considered valid. Clinical information was collected from retrospective medical records and vaccination status (date of vaccination, vaccine type, and number of vaccinations) was confirmed from the National Immunization Registry Information System.

A rapid influenza diagnostic test (RIDT) and reverse transcription polymerase chain reaction (RT-PCR) were used for the diagnosis of influenza. Both tests were done when the patient presented the influenza like illness. RIDTs were mainly used to identify the influenza rapidly in the emergency room, and most RT-PCRs were used to differentiate from other respiratory infections for inpatients. Nasopharyngeal specimens were collected either by the swab method using flocked swabs or aspiration. RIDT was performed with the Sofia influenza A+B FIA Kit (Quidel, San Diego, CA, USA), BD Veritor™ Plus system (BD Diagnostics, Sparks, MD, USA), or Standard F Influenza A/B FIA (SD Biosensor Inc., Suwon, Korea). RT-PCR was performed by the Allplex™ Respiratory Panel Assays (Seegene Inc., Seoul, Korea), One-Step RV Detection Kit (BioSewoom Inc., Seoul, Korea), or in-house method according to the manufacturer's instructions.

Data analysis

VE against laboratory-confirmed influenza was estimated by using a test-negative case-control design. Cases were defined as children who were confirmed to have influenza by laboratory tests either by RIDT or by RT-PCR. Controls were children who were negative as per the influenza tests. The VE was calculated as: [1 − odds ratio (OR) × 100]%, and 95% confidence interval (CI) was calculated for each estimate.

The statistical analysis was performed using R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Logistic regression models were adjusted for age, and week of visit.

Results

Patient characteristics

A total of 4738 children were enrolled in this study. Clinical characteristics of enrolled subjects according to participating hospitals are shown in Table 1. In total, 2143 (45.2%) children were female and the median age was 19.6 months. The numbers of respiratory specimens collected by each hospital were 3837 (81.0%) at emergency units, followed by 572 (12.1%) at outpatient clinics and 517 (10.9%) at general wards. There were no fatal cases. The proportion vaccinated was 82.1% (3889/4738).

One thousand one hundred ninety patients were tested for influenza by RT-PCR, 4012 patients by RIDT, and 464 patients by both RT-PCR and RIDT (Table 2). Influenza was detected in 845 children (17.8%), leaving the other 3893 children (82.2%) to serve as controls. Sixty-two (7.3%) children were hospitalized. In detail, 478 (56.6%) had influenza A, 362 (42.8%) had influenza B, and 5 (0.6%) had influenza A and B. Eight hundred four patients were diagnosed with RIDT, 80 with RT-PCR and 57 with both tests.

Table 1
Clinical characteristics, test for influenza, and influenza cases at four hospitals in Korea.

Characteristic	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Total
Total patients	1173 (24.8)	1138 (24.0)	1133 (23.9)	1294 (27.3)	4738
Gender, male: female	635:538	618:520	642:491	700:594	2595:2143
Median age, yr ± SD	1.81 ± 1.20	1.80 ± 1.17	1.48 ± 1.08	1.54 ± 1.10	1.64 ± 1.14
Hospital visit					
Inpatient	179	104	41	193	517
Outpatient	44	45	394	89	572
Emergency room	1077	989	698	1012	3837
Test for influenza (RIDT/RT-PCR)	1115/222	971/296	761/398	1164/274	4012/1190
Influenza cases	261 (22.3)	196 (17.2)	126 (11.1)	262 (20.2)	845 (17.8)

Data are No. (%) of patients, unless otherwise indicated. Hospital 1: Seoul National University Hospital, Hospital 2: Seoul National University Bundang Hospital, Hospital 3: Chungbuk National University Hospital, Hospital 4: Jeju National University Hospital.
SD, standard deviation; RT-PCR, real time polymerase chain reaction; RIDT, rapid influenza diagnostic test.

Table 2
The prevalence of influenza according to diagnostic methods.

	No. (%) of tests		
	RT-PCR	RIDT	Both tests
Tested number of patients	1190	4012	464
Any influenza	87 (7.3)	804[a] (20.0)	57[b] (12.3)
Influenza A	37	469	25
Influenza B	50	340	32

RT-PCR: real time polymerase chain reaction, RIDT: rapid influenza diagnostic test.
[a] Five children coinfected with had both influenza A and B.
[b] Among 57 children, 46 had positive results by both RT-PCR and RIDT.

Among the 845 children who were confirmed to have influenza, 669 (79.2%) were vaccinated during the corresponding season. Of the 3893 children who were negative for influenza, 3220 (82.7%) were vaccinated. Among vaccinated children, 17.2% had influenza compared to 20.7% among unvaccinated children.

Vaccine effectiveness using RT-PCR

Applying only the RT-PCR test, adjusted VE was 53.4% (95% CI, 25.3 to 70.5) against any influenza, 68.8% (95% CI, 38.7 to 84.1) against influenza A, and 29.7% (95% CI, −35.1 to 61.8) for influenza B. Among 464 patients who were tested by both RIDT and RT-PCR, adjusted VE against any influenza was 36.7% (95% CI, −20.2 to 65.8) using the RT-PCR method. In detail, adjusted VE was 58.7% (95% CI, 41.9 to 84.6) against influenza A, and 14.9% (95% CI, −100.6 to 61.0) against influenza B.

Comparison of vaccine effectiveness using RIDT to RT-PCR

Applying the RIDT, adjusted VE based on the RIDT test was 14.8% (95% CI, −4.4 to 30.0) against any influenza, 24.2% (95% CI, 3.1–40.2) against influenza A, and −5.1% (95% CI, −42.6 to 21.4) against influenza B. Comparison of VE between RIDT and RT-PCR was shown in Figure 1. Among the patients who were tested by both tests, adjusted VE against any influenza was 15.6% (95% CI, −59.6 to 56.0) using RIDT. RIDT based VE was lower than RT-PCR based VE (Figure 2). In detail, adjusted VE based on RIDT was 50.5% (95% CI, −17.8 to 78.4) against influenza A, and −17.8% (95% CI, −229.7 to 51.5) against influenza B. Comparison of VE by each hospital is shown in Table 3.

Vaccine effectiveness according to age group

VE was subanalyzed after children were stratified into two age groups (6–35 months age: group 1, 36–59 months age: group 2). When using RT-PCR, VE against influenza was estimated as 44.1% (95% CI −0.2 to 67.8) in group 1 and 59.3% (95% CI, 8.8 to 81.9) in group 2 (Figure 3A). VE using RIDT against influenza was estimated as 14.3% (95% CI, −10.9 to 33.3) in group 1 and −3.4% (95% CI, −41.4 to 23.9) in group 2 (Figure 3B).

Discussion

In this study, we estimated the VE of IIV3 in children during the 2017–2018 influenza season when the mismatched influenza B strain circulated. The VE of the season estimated as 32–38% in Australia, Canada, and the US (Sullivan et al., 2017; Skowronski et al., 2018; Rolfes et al., 2019). However, VE was higher in children at 52% in Louisiana, US and 56% in Israel (Powell and Bégué, 2019; Segaloff et al., 2019). In the studies conducted in Asia, VE against influenza was estimated as 59% to 69% in Hong Kong and China (Chan et al., 2019; Luo et al., 2019). However, in our study, VE varied according to the diagnostic testing method; adjusted VE based on

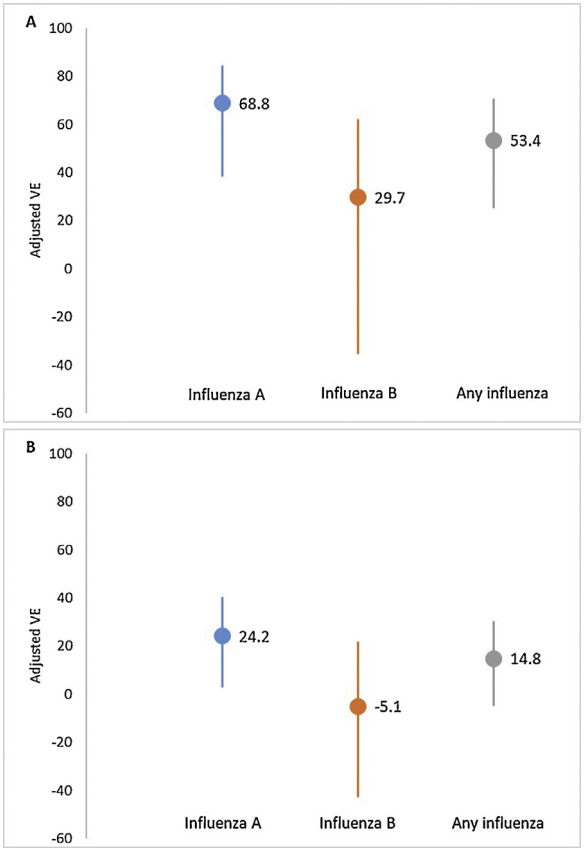

Figure 1. Adjusted vaccine effectiveness (VE) against influenza according to influenza type. (A) Influenza confirmed by real-time polymerase chain reaction (RT-PCR). (B) Influenza confirmed by rapid influenza diagnostic test (RIDT). Data are shown with dot (VE) and 95% confidence interval error bar.

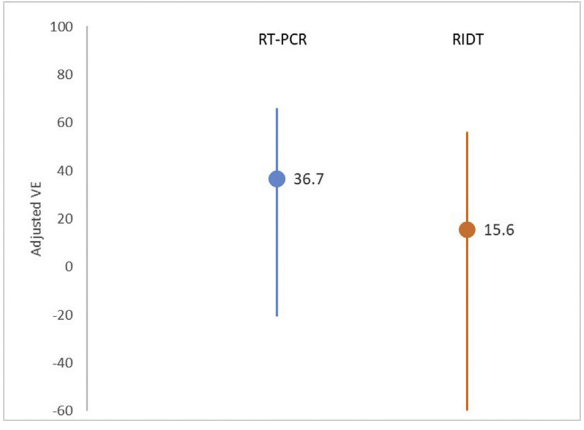

Figure 2. Adjusted vaccine effectiveness (VE) against influenza according to the testing method among the children who were tested by both real-time polymerase chain reaction (RT-PCR) and rapid influenza diagnostic test (RIDT). Data are shown with dot (VE) and 95% confidence interval error bar.

RT-PCR was 53.4% (95% CI, 25.3–70.5) for any influenza, while adjusted VE using RIDT was 14.8% (95% CI, −4.4 to 30.0) for any influenza, suggesting the role of diagnostic sensitivity in affecting VE results. Given the similarity of the study design, the influenza vaccine in our study was similarly effective against influenza as in other studies.

In many countries, RT-PCR is regarded as the standard test for influenza when estimating the VE against all influenza due to the

Table 3
Comparison of vaccine effectiveness by hospitals.

	Hospital 1	Hospital 2	Hospital 3	Hospital 4	Total
Vaccinated, *n* (%)	934 (79.6)	855 (75.1)	1016 (89.7)	1084 (83.8)	3889 (82.1)
Vaccine effectiveness (VE)					
Crude VE by RT-PCR(95% CI)	78.3(43.2, 92.6)	59.8(−48.0, 89.1)	57.6(−5.6, 81.3)	38.2(−66.0, 75.5)	54.5(28.1, 70.8)
Adjusted VE by RT-PCR[a] (95% CI)	74.3(31.4, 91.4)	51.7(−86.8, 87.4)	54.8(−15.7, 80.6)	36.3(−77.5, 74.9)	53.4(25.3, 70.5)
Crude VE by RIDT(95% CI)	2.1(−40.8, 30.9)	12.3(−27.2, 38.8)	13.8(−68.9, 52.9)	26.7(4.3, 48.6)	19.3(1.7–33.5)
Adjusted VE by RIDT[a] (95% CI)	−8.8(−60.0, 24.9)	−2.3(−51.0, 29.8)	−6.0(−112.0, 43.4)	25.3(0.0, 48.1)	14.8(−4.4, 30.0)

Hospital 1: Seoul National University Hospital, Hospital 2: Seoul National University Bundang Hospital, Hospital 3: Chungbuk National University Hospital, Hospital 4: Jeju National University Hospital.
RT-PCR, real time polymerase chain reaction; RIDT, rapid influenza diagnostic test; CI, confidence interval.
[a] Adjusted for age and week of visit.

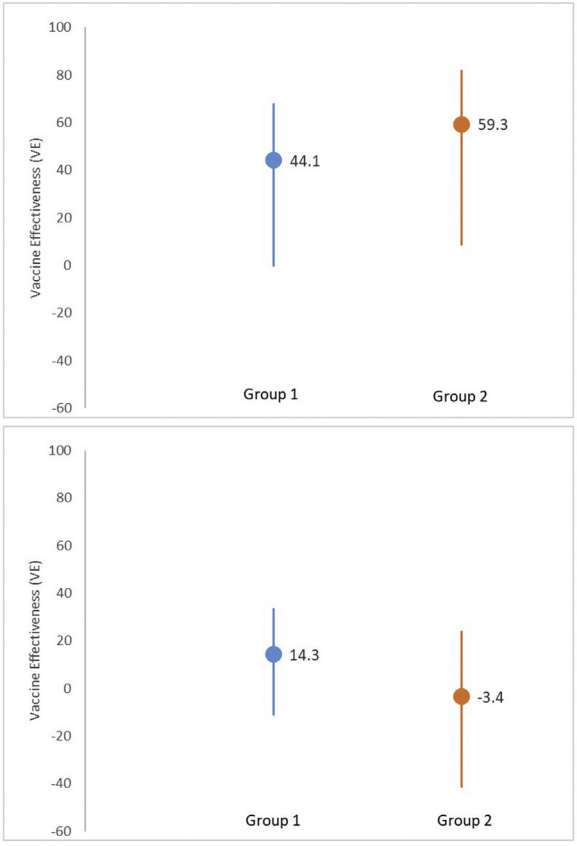

Figure 3. Vaccine effectiveness (VE) against influenza according to age group. Group 1 was from 6 months to 2 years old and group 2 was from 3 to <5 years old. (A) Influenza confirmed by real-time polymerase chain reaction (RT-PCR). (B) Influenza confirmed by rapid influenza diagnostic test (RIDT). Data are shown with dot (VE) and 95% confidence interval error bar.

possible underestimation of VE from the low diagnostic sensitivity of RIDT (Ferdinands and Shay, 2011). Previous reports indicate that the sensitivity and specificity of RIDT is comparable to that of RT-PCR, as in the cases in Japan (Suzuki et al., 2014; Sugaya et al., 2016, 2018). In our study, the sensitivity and specificity of RIDT using RT-PCR as gold standard were 73.7% and 97.6% among the patients who were tested by both tests. However, there was a substantial difference in the estimated VE between RT-PCR and RIDT. The ratio of controls to influenza cases was approximately 4:1. Lower estimates of VE by RIDT may be due to the fact that the test could detect influenza virus only for a narrower window period when the virus titer was sufficiently high. Children are also susceptible to various respiratory viruses other than influenza virus, for example, respiratory syncytial virus (RSV), rhinovirus, and coronavirus, which may cocirculate during the given influenza season. Attempts to test for influenza may have been made for children with other respiratory viruses. Although there was no difference in the age distribution between the RIDT and RT-PCR groups, indications for RIDT and RT-PCR were not identical in our study. Most RT-PCR tests were done in hospitalized patients as expected. In the subgroup analysis of the 464 patients who were examined by both tests, we demonstrated that VE using RT-PCR was higher than RIDT for all influenza as was shown in the separate analysis by each test method (Figure 2). Although the ratio of using both tests was not significantly different among four hospitals, the difference of VEs by diagnostic methods in hospital 4 was small compared with other hospitals (Table 3). Multifactorial factors may have contributed to the difference, such as unique epidemiology and pattern of seeking medical service related to the location of the Hospital 4 in Jeju Island. Further study is needed to explain the difference.

We also found difference in VE rates between virus subtypes. Using the RT-PCR test, the VE was 68.8% against influenza A and 29.7% against influenza B. In the 2017–2018 influenza season, the recommended vaccine constitution of trivalent vaccines consisted of an A/Michigan/45/2015(H1N1)pdm09-like virus, an A/Hong Kong/4801/2014(H3N2)-like virus, and a B/Brisbane/60/2008-like virus (Victoria lineage) (WHO, 2017). However, most influenza virus B circulated in the 2017-2018 season was influenza B/Yamagata lineage, resulting in vaccine-virus mismatch (Adlhoch et al., 2018; Skowronski et al., 2019). In the 2017–2018 season, influenza A (H3N2) accounted for approximately 80% of influenza A (Rolfes et al., 2019). According to the Korea Centers for Disease Control and Prevention laboratory sentinel surveillance system, influenza A and B were responsible for 44.6% and 55.4%, respectively, in the 2017–2018 influenza season (KCDC, 2018). In Korea, this predominance of influenza B in the 2017–2018 influenza season was unusual compared to the previous influenza seasons. Moreover, influenza A (H3N2) was 86.8% of influenza A, suggesting that the influenza activity in Korea was similar with other countries in the Northern Hemisphere in the given season (KCDC, 2018). Compared to influenza A, we found a limited VE of IIV3 against influenza B (Figure 1). This lower VE can be explained by the influenza B mismatch between IIV3 and circulating strains. This lower VE against influenza B has been observed worldwide (Skowronski et al., 2018; Chan et al., 2019; Rolfes et al., 2019). In the age subgroup analysis, VE in the older age group was higher than that in the younger age group (Figure 3). As children in the younger age group generally express symptoms inadequately, the criteria of influenza-like illness might have been broader and even children with RSV infection might have been included in this age group.

There are several limitations in this study. Given the retrospective design of the study, we were not able to apply

uniform inclusion criteria for testing eligible children. Tests for influenza were made by clinical decision, resulting in possible ascertainment bias. We analyzed our data based on the crude numbers assuming that the clinical practices across all four hospitals were stable during the season. However, there may be detection bias since healthcare providers may not have thought of performing tests for influenza in certain periods or in a specific hospital. Furthermore, RIDT and RT-PCR test was not simultaneously examined, and so the comparison between two tests has limitations considering other prospective simultaneous study (Chon et al., 2019). Finally, our data were from four large hospitals, possibly limiting the generalizability of these results. A more diverse pool of children and easily accessible primary medical institution might give the generalizability to this study. Despite these limitations, this is the first study that assessed the VE of influenza vaccine in Korean children. We included the largest number of pediatric population pools from diverse areas in Korea. We used two different diagnostic methods (RIDT and RT-PCR) as the numerators of the study, providing additional information on assessing VE using different testing methods. Lastly, by applying the test-negative design, a modified case-control study, we aimed to minimize confounders, such as health care-seeking behavior, and reduce disease misclassification as an outcome measure.

In conclusion, we found a moderated effectiveness of IIV3 against influenza confirmed by RT-PCR in Korean children during the 2017–2018 season. Compared with RT-PCR, the substantial difference in estimated VE and known low sensitivity of RIDT showed that RIDT is an unsuitable assay for test-negative design of estimating VE. Given the limited effect of IIV3 against influenza B, discussion on including IIV4 in the Korean National Immunization Program should be in place. Continuous assessment of VE of influenza vaccine is needed to provide evidence required for making appropriate policies for the prevention of influenza.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence this research.

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Ethical approval

This study was approved by the Institutional Review Board of all four participating hospitals. Written consent was exempted. There are no potential conflicts of interest relevant to this article.

References

Adlhoch C, Snacken R, Melidou A, Ionescu S, Penttinen P, Mook P, et al. Dominant influenza A(H3N2) and B/yamagata virus circulation in EU/EEA, 2016/17 and 2017/18 seasons, respectively. Euro Surveill 2018;23(13), doi:http://dx.doi.org/10.2807/1560-7917.ES.2018.23.13.18-00146 pii:18-00146.

Blyth CC, Jacoby P, Effler PV, Kelly H, Smith DW, Robins C, et al. Effectiveness of trivalent flu vaccine in healthy young children. Pediatrics 2014;133(5):e1218–25.

https://www.cdc.gov/media/releases/2016/s0622-laiv-flu.htmlCenters for Disease Control and Prevention (CDC). Advisory committee on immunization practice votes down use of LAIV for 2016-2017 flu season. Available from: [accessed 21.05.20].

Chan Y wai D, Wong M ling, Au K wing, Chuang S kwan. Seasonal influenza vaccine effectiveness at primary care level, Hong Kong SAR, 2017/2018 winter. Hum Vaccines Immunother 2019;15(1):97–101, doi:http://dx.doi.org/10.1080/21645515.2018.1514222.

Chon I, Saito R, Hibino A, Yagami R, Dapat C, Odagiri T, et al. Effectiveness of the quadrivalent inactivated influenza vaccine in Japan during the 2015-2016 season: a test-negative case-control study comparing the results by real time PCR, virus isolation. Vaccine X 2019;1:100011, doi:http://dx.doi.org/10.1016/j.jvacx.2019.100011.

Ferdinands JM, Shay DK. Magnitude of potential biases in a simulated case-control study of the effectiveness of influenza vaccination. Clin Infect Dis 2011;54(1):25–32, doi:http://dx.doi.org/10.1093/cid/cir750.

Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 2018;391(10127):1285–300, doi:http://dx.doi.org/10.1016/S0140-6736(17)33293-2.

Korea Centers for Disease Control and Prevention (KCDC). Influenza weekly surveillance report, week 20. 2018 Available from: http://www.cdc.go.kr/npt/biz/npp/portal/nppPblctDtaView.do?pblctDtaSeAt=2&pblctDtaSn=621 [accessed 21.05.20].

Luo SY, Zhu JL, Lyu MZ, Hu YQ, Cheng H, Zhang GM, et al. Evaluation of the influenza vaccine effectiveness among children aged 6 to 72 months based on the test-negative case control study design. Zhonghua Yu Fang Yi Xue Za Zhi 2019;53(6):576–80, doi:http://dx.doi.org/10.3760/cma.j.issn.0253-9624.2019.06.007.

Mameli C, Cocchi I, Fumagalli M, Zuccotti G. Influenza vaccination: effectiveness, indications, and limits in the pediatric population. Front Pediatr 2019;7, doi:http://dx.doi.org/10.3389/fped.2019.00317.

Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet 2011;378(9807):1917–30, doi:http://dx.doi.org/10.1016/S0140-6736(11)61051-9.

Paules C, Subbarao K. Influenza. Lancet 2017;390:697–708, doi:http://dx.doi.org/10.1016/S0140-6736(17)30129-0.

Powell LN, Bégué RE. Influenza vaccine effectiveness among children for the 2017–2018 season. J Pediatr Infect Dis Soc 2019;, doi:http://dx.doi.org/10.1093/JPIDS/PIZ077 piz077.

Rolfes MA, Flannery B, Chung JR, O'Halloran A, Garg S, Belongia EA, et al. Effects of influenza vaccination in the United States during the 2017–2018 influenza season. Clin Infect Dis 2019;69(11):1845–53, doi:http://dx.doi.org/10.1093/cid/ciz075.

Segaloff HE, Leventer-Roberts M, Riesel D, Malosh RE, Feldman BS, Shemer-Avni Y, et al. Influenza vaccine effectiveness against hospitalization in fully and partially vaccinated children in Israel: 2015–2016, 2016–2017, and 2017–2018. Clin Infect Dis 2019;69(12):2153–61, doi:http://dx.doi.org/10.1093/cid/ciz125.

Shen S, Campitelli MA, Calzavara A, Guttmann A, Kwong JC. Seasonal influenza vaccine effectiveness in pre- and full-term children aged 6–23 months over multiple seasons. Vaccine 2013;31(29):2974–8, doi:http://dx.doi.org/10.1016/j.vaccine.2013.05.011.

Skowronski DM, Chambers C, De Serres G, Dickinson JA, Winter A-L, Hickman R, et al. Early season co-circulation of influenza A(H3N2) and B(Yamagata): interim estimates of 2017/18 vaccine effectiveness, Canada. Euro Surveill 2018;23(5):18–00035, doi:http://dx.doi.org/10.2807/1560-7917.ES.2018.23.5.18-00035.

Skowronski DM, Chambers C, De Serres G, Sabaiduc S, Winter AL, Dickinson JA, et al. Vaccine effectiveness against lineage-matched and -mismatched influenza B viruses across 8 seasons in Canada, 2010–2011 to 2017–2018. Clin Infect Dis 2019;68:1754–7, doi:http://dx.doi.org/10.1093/cid/cjy876.

Su WJ, Chan TC, Chuang PH, Liu YL, Lee PI, Liu MT, et al. Estimating influenza vaccine effectiveness using routine surveillance data among children aged 6–59 months for five consecutive influenza seasons. Int J Infect Dis 2015;30:115–21, doi:http://dx.doi.org/10.1016/j.ijid.2014.11.011.

Sugaya N, Shinjoh M, Kawakami C, Yamaguchi Y, Yoshida M, Baba H, et al. Trivalent inactivated influenza vaccine effective against influenza A(H3N2) variant viruses in children during the 2014/15 season, Japan. Euro Surveill 2016;21(42):30377, doi:http://dx.doi.org/10.2807/1560-7917.ES.2016.21.42.30377.

Sugaya N, Shinjoh M, Nakata Y, Tsunematsu K, Yamaguchi Y, Komiyama O, et al. Three-season effectiveness of inactivated influenza vaccine in preventing influenza illness and hospitalization in children in Japan, 2013–2016. Vaccine 2018;36(8):1063–71, doi:http://dx.doi.org/10.1016/j.vaccine.2018.01.024.

Sullivan SG, Chilver MB, Carville KS, Deng Y-M, Grant KA, Higgins G, et al. Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017. Euro Surveill 2017;22(43):17–00707, doi:http://dx.doi.org/10.2807/1560-7917.ES.2017.22.43.17-00707.

Suzuki M, Minh LN, Yoshimine H, Inoue K, Yoshida LM, Morimoto K, et al. Vaccine effectiveness against medically attended laboratory-confirmed influenza in Japan, 2011–2012 season. PLoS One 2014;9(2):e88813, doi:http://dx.doi.org/10.1371/journal.pone.0088813.

World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2017–2018 northern hemisphere influenza season. Available from: https://www.who.int/influenza/vaccines/virus/recommendations/2017_18_north/en/ [accessed 21.05.20].