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Inactivated influenza vaccine effectiveness and an analysis of repeated vaccination for children during the 2016/17 season

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ABSTRACT

Objectives: We assessed the vaccine effectiveness (VE) of inactivated influenza vaccine (IIV) in children 6 months to 15 years of age during the 2016/17 season. In addition, we estimated the impact of repeated vaccination in children on VE.
Methods: Our study for VEs in preventing influenza and admission due to influenza were conducted according to a test-negative case-control design (TNCC) based on influenza rapid diagnostic test results. We also analyzed the VE by vaccine status in the current and previous seasons for the impact of repeated vaccination.
Results: During the 2016/17 season, the quadrivalent IIV was used in Japan. The adjusted VE in preventing influenza illness was 38% (95% CI, 29–46) against influenza A and 39% (95% CI, 18–54) against influenza B. Infants showed no significant VE. The VE in preventing hospitalization was not demonstrated. For the analysis of repeated vaccination, the vaccine was effective only when immunization occurred in the current season. The children who were immunized in two consecutive seasons were more likely to develop influenza compared to those immunized in the current season only (odds ratio, 1.58 [95% CI, 1.05–2.38], adjusted odds ratio, 1.53 [95% CI, 0.99–2.35]). However, the odds ratio of repeated vaccination was not significant when the analysis excluded those who developed influenza in the previous season.
Conclusions: VE in children in the 2016/17 season was similar to values previously reported. Repeated vaccination interfered with the VE against any influenza infection in the 2016/17 season. The results of our study suggest that decreased VE by repeat vaccination phenomenon was associated with immunity by influenza infection in the previous season. However, the influenza vaccine should be recommended every season for children.

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1. Introduction

In the 2016/17 season in Japan, the most dominant circulating influenza virus was type A, and the major strain was A(H3N2). According to FluNet, 97.1% (6757/6958) and 2.9% (201/6958) of the influenza A viruses isolated in Japan (44th week in 2016 to 13th week in 2017) were the A(H3N2) strains and A(H1N1) pdm09, respectively, and 40.8% (367/899) and 59.2% (532/899) of the influenza B were Yamagata and Victoria lineages, respectively [1,2]. All of the analyzed H3N2 isolates (N = 487) belonged to genetic clade 3C.2a [3,4].

Annual estimates of the effectiveness of influenza vaccines assessed by a test-negative case-control (TNCC) design have been reported in recent years, and the TNCC design has become the standard design for assessing vaccine effectiveness (VE). However, because most of the subjects of these recent studies were adults and the elderly, few studies clearly confirmed the VE of inactivated influenza vaccine (IIV) in children, especially the VE by age groups [5,6]. Since almost all children with a fever during an influenza epidemic in Japan receive a rapid influenza diagnostic test (RIDT) [7–11], we used the results of these RIDTs as a basis for estimating the VE in children using the TNCC design employed in our previous studies. As a result, we were able to enroll much larger numbers of children with influenza-like illness than many other published studies, thereby providing an opportunity to compare the age-specific VE and estimate the VE in preventing hospitalization [7–9].

Previous results have consistently confirmed a moderate VE in the 1- to 12-year-old group but have shown low or non-significant VE in infants and adolescents [7–9]. Moreover, the results of our previous studies demonstrated that influenza vaccination was highly effective in reducing the hospitalization of children with influenza A and B infections [9]. In our studies, adjusted VE for any influenza in children 6 months to 15 years old was 45% (95% CI: 39–52, N = 4727), 38% (95% CI: 28–46, N = 3752), and 49% (95% CI: 42–55, N = 4409) in the 2013/14, 2014/15, and 2015/16 seasons, respectively [7–9]. It is reasonable to calculate VE every season in a similar way because influenza VE varies based on study design [12].

Although annual immunization with the influenza vaccine is recommended [13], several reports have recently pointed out that repeated vaccination has attenuated VE [14–16]. The antigenic distance hypothesis has been the major theoretical immune mechanism for repeat influenza VE [17]. In contrast, several reports have argued against repeat immunization [18,19]. A recent meta-analysis showed that they had found no overall evidence that prior season vaccination negatively impacted current season VE [20]. For the analysis of repeated vaccination in our serial studies, we confirmed the vaccine status for the previous season (the last season only) as well as for the current season.

The purpose of this study was to measure the seasonal VE of the 2016/2017 season and to measure the VE in children with a repeated vaccination history.

2. Methods

Similar methods including enrollment and location, diagnosis of influenza, case and control patient identification, and TNCC design for VE were used as reported [7–9].

2.1. Influenza vaccine in the 2016/17 seasons

A quadrivalent inactivated subunit-antigen vaccine (A/California/7/2009[X-179A] [H1N1] pdm09, A/Hong Kong/4801/2014[X-263] [H3N2, genetic clade 3C.2a], B/Phuket/3073/2013 [Yamagata type] and B/Texas/2/2013 [Victoria type]) was used in Japan during the 2016/17 season. In Japan, two doses of vaccine are recommended for children aged 6 months to 12 years. Two 0.25 ml doses of vaccine 2–4 weeks apart are recommended for children aged 6 months to 2 years, and two 0.5 ml doses 2–4 weeks apart are recommended for children aged 3–12 years. Only one 0.5 ml dose is recommended for children aged 13 years and over.

2.2. Diagnosis of influenza

Nasopharyngeal swabs were obtained from all of the enrollees. Several different RIDT kits capable of differentiating between influenza A and influenza B were used in the hospitals. According to the manuals, all of the RIDT kits have high sensitivity (approximately 90–95%) and specificities (up to 100%) (Table 1) [7]. The minimum viral titers required for a positive reaction of RIDTs used in Japan were 3–4 $TCID_{50}$ [21]. Because most patients are tested within 48 h after the onset of illness in Japan [11] and the viral infection titer in the upper respiratory tract of patients is 5–6 $TCID_{50}$ within 48 h after onset, all patients theoretically show RIDT-positive results if they have an influenza virus infection. None of the patients were treated with a neuraminidase inhibitor (NAI) before enrollment.

2.3. Case and control patient identification

The RIDT-positive patients were enrolled as cases, and the RIDT-negative patients as controls. All of their medical charts were reviewed, and information regarding symptoms, influenza vaccination including vaccine history the previous year, number of vaccine doses (one or two), influenza complications and hospitalizations, sex, age, comorbidities, and treatment with NAIs was collected and recorded. Children were excluded if definite information on influenza vaccination was found to be unavailable. When a child was brought to one of our pediatric outpatient clinics, the parents or guardians were asked about the child's influenza vaccination status, and the child's influenza status was then usually confirmed by consulting the Maternal and Child Health Handbook provided by local governments, in which vaccinations are recorded by the physicians in charge.

2.4. VE in the 2016/17 seasons

Children aged 6 months to 15 years with a fever of 38 °C or over and who had received an RIDT in outpatient clinics of 21 hospitals mainly located in the Greater Tokyo Metropolitan area between 1 November 2016 (44th week) and 31 March 2017 (13th week) were enrolled in this study. A TNCC design was used to estimate VE based on RIDT results. We also calculated the VE in the more restricted period when approximately 95% of influenza A and B cases were reported (1st to 9th weeks of 2017 for any influenza, 49th weeks of 2016 to 9th weeks of 2017 for influenza A, and 1st to 13th weeks of 2017 for influenza B) and VE by age-groups and vaccine doses (6 months to 12 years old).

The VE in preventing hospitalization due to influenza was estimated by three different TNCC methods: 1. RIDT-positive hospitalized patients as cases and RIDT-negative hospitalized patient as controls, 2. RIDT-positive hospitalized patients as cases and RIDT-positive non-hospitalized patients as controls, and 3. RIDT-positive hospitalized patients as cases and non-hospitalized patients (irrespective of whether they were RIDT-positive or RIDT-negative) as controls. We also performed an analysis among non-hospitalized patients: RIDT-positive non-hospitalized patients as cases and RIDT-negative non-hospitalized patient as controls.

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