Vaccine 36 (2018) 1063–1071

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Three-season effectiveness of inactivated influenza vaccine in preventing influenza illness and hospitalization in children in Japan, 2013–2016

Norio Sugaya [a,*], Masayoshi Shinjoh [b], Yuji Nakata [c], Kenichiro Tsunematsu [d], Yoshio Yamaguchi [e], Osamu Komiyama [f], Hiroki Takahashi [g], Keiko Mitamura [h], Atsushi Narabayashi [i], Takao Takahashi [b], on behalf of the Keio Pediatric Influenza Research Group [1]

[a] Department of Pediatrics, Keiyu Hospital, Yokohama, Kanagawa, Japan
[b] Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan
[c] Department of Pediatrics, Nippon Kokan Hospital, Kawasaki, Kanagawa, Japan
[d] Department of Pediatrics, Hino Municipal Hospital, Hino, Tokyo, Japan
[e] Department of Pediatrics, National Hospital Organization, Tochigi Medical Center, Utsunomiya, Tochigi, Japan
[f] Department of Pediatrics, National Hospital Organization, Tokyo Medical Center, Tokyo, Japan
[g] Department of Pediatrics, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan
[h] Department of Pediatrics, Eiju General Hospital, Tokyo, Japan
[i] Department of Pediatrics, Kawasaki Municipal Hospital, Kawasaki, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 12 June 2017
Received in revised form 27 December 2017
Accepted 10 January 2018

Keywords:
Influenza vaccine
Child
Effectiveness
Hospitalization
Test-negative case control design

ABSTRACT

Objectives: We assessed the vaccine effectiveness (VE) of inactivated influenza vaccine (IIV) in children 6 months to 15 years of age in 2015/16 season. In addition, based on the data obtained during the three seasons from 2013 to 2016, we estimated the three-season VE in preventing influenza illness and hospitalization.

Methods: Our study was conducted according to a test-negative case-control design (TNCC) and as a case-control study based on influenza rapid diagnostic test results.

Results: During 2015/16 season, the quadrivalent IIV was first used in Japan. The adjusted VE in preventing influenza illness was 49% (95% confidence interval [CI]: 42–55%) against any type of influenza, 57% (95% CI: 50–63%) against influenza A and 34% (95% CI: 23–44%) against influenza B. The 3-season adjusted VE was 45% (95% CI: 41–49%) against influenza virus infection overall (N = 12,888), 51% (95% CI: 47–55%) against influenza A (N = 10,410), and 32% (95% CI: 24–38%) against influenza B (N = 9232). An analysis by age groups showed low or no significant VE in infants or adolescents. By contrast, VE was highest in the young group (1–5 years old) and declined with age thereafter. The 3-season adjusted VE in preventing hospitalization as determined in a case-control study was 52% (95% CI: 42–60%) for influenza A and 28% (95% CI: 4–46%) for influenza B, and by TNCC design, it was 54% (95% CI: 41–65%) for influenza A and 34% (95% CI: 6–54%) for influenza B.

Conclusion: We demonstrated not only VE in preventing illness, but also VE in preventing hospitalization based on much larger numbers of children than previous studies.

1. Introduction

Annual estimates of the effectiveness of influenza vaccine assessed by a test-negative case-control (TNCC) design have been reported in recent years [1–7], 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, none of these studies clearly confirmed the VE of inactivated influenza vaccine (IIV) in children, especially the VE by age groups of children.

Since almost all children with a fever during an influenza epidemic in Japan receive an influenza rapid diagnostic test (IRDT) [8], in our previous studies we used the results of IRDTs as a basis for estimating the VE in children by the TNCC design [9,10]. As a result, we were able to enroll much larger numbers of children with influenza-like illness—4727 in the 2013/14 season [9] and

* Corresponding author at: Department of Pediatrics, Keiyu Hospital, 3-7-3 Minatomirai, Nishi-ku, Yokohama 220-0012, Kanagawa, Japan.
E-mail address: sugaya-n@za2.so-net.ne.jp (N. Sugaya)
[1] See complete list of the Keio Pediatric Influenza Research Group co-authors in the online version.

https://doi.org/10.1016/j.vaccine.2018.01.024
0264-410X/

3752 in the 2014/15 season [10]—than many other published studies, thereby providing an opportunity to compare the age-specific VE and estimate the VE in preventing hospitalization. Previous results have consistently confirmed a moderate VE in the 1- to 12-year-old group but shown low or no significant VE in infants and adolescents.

Although a meta-analysis did not yield convincing evidence that the influenza vaccine reduces mortality, hospitalizations, or serious complications in children [11], the results of our previous studies demonstrated that influenza vaccination was highly effective in reducing hospitalization of children with influenza A infection in the 2013/14 season [9] and 2014/15 season [10].

In this study, we investigated the VE of quadrivalent IIV during the epidemic caused by influenza A(H1N1)pdm09 and influenza B viruses in 2015/16 season, and based on the data obtained in over 12,000 children during the 3 consecutive seasons of 2013/14 [9], 2014/15 [10], and 2015/16, we estimated the 3-season VE in preventing influenza illness, especially the VE by age groups of children, and the VE in preventing hospitalization.

2. Methods

2.1. Epidemiology in the 2015/16 season

Influenza A(H1N1)pdm09 viruses, influenza A(H3N2) viruses, and influenza B viruses circulated in Japan in the 2015/16 season, and the dominant circulating influenza A strain was A(H1N1)pdm09, which was antigenically matched to the vaccine strain in Japan, A/California/7/2009. According to FluNet [12], 87.1% of the influenza A viruses isolated in Japan during the study period were the A(H1N1)pdm09 strain. All A(H1N1)pdm09 viruses belonged to clade 6B, and most of them (80%) were classified into subclade 6B.1 [13].

Of the influenza B viruses isolated, 45.5% were Yamagata lineage in clade 3, represented by B/Phuket/3073/2013, and 46.9% were Victoria lineage in clade 1A, represented by B/Texas/2/2013. Both influenza B viruses were included in the 2015/16 quadrivalent vaccine.

2.2. Vaccine strains in the 2015/16 season

A quadrivalent inactivated subunit-antigen vaccine was used to vaccinate children in Japan during the 2015/16 season. The vaccine strains used to produce the vaccine were: A/California/7/2009(X-179A) for protection against A(H1N1)pdm09, A/Switzerland/9715293/2013 (NIB-88) for protection against A(H3N2), B/Phuket/3073/2013 for protection against the Yamagata lineage, and B/Texas/2/2013 for protection against the Victoria lineage.

In Japan, 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.

2.3. Study enrolment and location in the 2015/16 season

Twenty-two hospitals that had both pediatric outpatient clinics and pediatric wards participated in this study. All children of 6 months to 15 years of age with a fever of 38 °C and cough and/or rhinorrhea and who had received an IRDT in the pediatric outpatient clinic of any of the 22 hospitals between November 1, 2015 and March 31, 2016 were enrolled in the present study. Our hospitals were located in six (Gunma, Tochigi, Saitama, Tokyo, Kanagawa, and Shizuoka) of the 47 prefectures in Japan, and they are mainly located in the Greater Tokyo Metropolitan area.

Patients who met the symptom criteria and IRDT criterion during the study period were eligible for enrollment of this study. Patients who had been vaccinated against influenza less than 14 days before illness onset were excluded from this study. A TNCC design was used to estimate VE based on IRDT results as previously described [9,10].

2.4. Diagnosis of influenza

Nasopharyngeal swabs were obtained from all of the enrollees. Several different IRDT kits capable of differentiating between influenza A and influenza B were used in the hospitals [9,10]. According to their respective manuals, all of the IRDT kits used in this study have similar sensitivities (88–100%) and specificities (94–100%), as compared with reverse transcription-polymerase chain reaction (RT-PCR) [14]. More than 90% of the outpatients with ILI visited pediatric clinics within 48 h after the onset of illness and were tested with an IRDT (Table 1). None of the patients were treated with a neuraminidase inhibitor (NAI) before enrollment.

2.5. Case and control patient identification

The IRDT-positive patients were enrolled as case patients, and the IRDT-negative patients as control patients. 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 all vaccinations are recorded by the physicians in charge.

2.6. Test-negative case–control design

We estimated VE by using a TNCC design. VE was defined as 1 - OR (odds ratio).

2.7. Statistical analysis

The statistical analysis was performed by using SPSS 22.0 software (IBM, U.S.A.) and the Ekuseru-Toukei 2015 for Windows software program (Social Survey Research Information Co., Ltd., Tokyo, Japan).

VE was adjusted for age group (6–11 months, 1–2 years, 3–5 years, 6–12 years, and 13–15 years), presence of a comorbidity (yes or no), area of the Kanto Region of Japan, i.e., north area: Gunma Prefecture and Tochigi Prefecture; middle area: Saitama Prefecture and Tokyo Prefecture; and south area: Kanagawa Prefecture and Shizuoka Prefecture, and month of illness onset.

The sensitivity analysis was performed by modifying the sensitivity or specificity of the IRDT to investigate the effects on the VE results. The sensitivity and specificity of the IRDT kits used in this study were reported to be 88–100% and 94–100%, respectively. Thus, the respective VE was estimated by changing the sensitivity from −10% to +10%, and changing the specificity from −5% to +5%.

2.8. Vaccine effectiveness in preventing hospitalization

The effectiveness of this vaccine in preventing children from being hospitalized due to influenza virus infection was estimated by two different methods: a case-control study and TNCC design.

In the case-control study (Tables 3a and 4a), the outpatients who visited the pediatric clinics of our hospitals due to ILI but