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Original Article

Effectiveness of quadrivalent influenza vaccine based on the test-negative control study in children during the 2016–2017 season☆

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ABSTRACT

To estimate the vaccine effectiveness (VE) of quadrivalent influenza vaccine, I conducted a test-negative case control study in children, based on the rapid influenza diagnostic test (RIDT), during the 2016–2017 season. Overall, the adjusted VE was significant for any influenza (influenza A + B); VE: 30.2% (95% confidence interval [CI]: 5.4–48.4) and influenza B: 48.2% (95% CI: 11.3–69.7).

The participants were divided into three age groups (group A: 0–4 years old, group B: 5–9 years old, and group C: 10–15 years old); in group A, the adjusted VE of quadrivalent influenza vaccine was significant for any influenza (A + B): 58.6% (95% CI: 28.8–76.0), influenza A: 53.9% (95% CI: 16.4–74.6), and influenza B: 78.6% (95% CI: 23.6–94.0). In both groups B and C, VE was not observed for any of the types of influenza. In only group A, two doses of vaccines provided significantly better VE against any influenza, as well as both influenzas A and B, than single-dose vaccines and cases in which vaccination was not administered. In conclusion, quadrivalent influenza vaccine showed significant VE and dose-dependent VE against any influenza and both influenzas A and B, in children aged 0–4 years during the 2016–2017 season. Both the VE and dose-dependent VE were almost not observed in older group. However, this may due to low rate of vaccination, particularly in children aged 10–15 years.

1. Introduction

The World Health Organization (WHO) recommended the use of quadrivalent influenza vaccines in the southern hemisphere during the 2013 influenza season [1]. In Japan, quadrivalent influenza vaccines replaced trivalent vaccines in the 2015–2016 season. The vaccine effectiveness (VE) against influenza was recently estimated in a test-negative case control study [2,3]. In Japan, two reports have described the efficacy of influenza vaccines, using the test-negative case control design [4,5]. While one focused on the effectiveness of trivalent influenza vaccines in children, the other report centered on the effectiveness of quadrivalent influenza vaccines in adults in 2015–2016 [4,5]. To complement these previous reports, the present study explored the effectiveness of quadrivalent influenza vaccines in children during the 2016–2017 season, based on a test-negative case control design.

2. Materials and methods

2.1. Patients

All patients at the Ando Clinic (Narashino City, Chiba, Japan) who underwent the rapid influenza diagnostic test (RIDT) due to a suspicion of influenza infection in the 2016–2017 season were informed of the study concept; all patients provided informed consent and were enrolled in the study. Among them children (6 months-15 years old) fulfilling criteria of influenza-like illness (ILI) were analyzed. The following clinical information was obtained: sex, age, vaccination status for quadrivalent influenza vaccine, comorbidities and month of influenza infection onset. Comorbidities were defined as chronic pulmonary, cardiovascular (excluding hypertension), renal, liver, hematologic, and neurological disorders, diabetes mellitus, autoimmune disorders, and cancer. To analyze the age effect, participants were divided into three groups (group A: 6 months-4 years old, group B: 5–9 years old, and group C: 10–15 years old), according to an annual report [6].

☆ All authors meet the ICMJE (International Committee of Medical Journal Editors) authorship criteria.

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2.2. Eligibility criteria

1) Children (6 months-15 years old) who underwent the RIDT due to an ILI, in the 2016–2017 season. ILI was defined based on the WHO's definition [7] as follows:
   a) Patients with a fever (body temperature (BT) ≥38.0 °C).
   b) Patients in whom influenza infection was suspected, evidenced by symptoms like acute onset, nasal discharge, sore throat, cough, arthralgia, myalgia, etc.

   Fulfillment of both a) and b).

2) The interval from the time quadrivalent inactivated influenza vaccination was administered was ≥14 days and <5 months [8].
3) If patients had multiple episodes, they should have been at least one week apart:
   a) For patients with any influenza-negative episodes, I employed the episode where the highest BT was observed.
   b) For patients with both influenza-positive and negative episodes, I employed the positive episode.
   c) For patients with both influenza A and B-positive episodes, I employed both episodes.

2.3. Exclusion criteria

1) Patients ≥16 years of age.
2) An influenza infection in the 2016–2017 season.
3) If the RIDT was negative, the neuraminidase inhibitor had already been given before presentation.
4) Influenza case did not meet the ILI criteria.
5) The interval from the time of quadrivalent inactivated influenza vaccination was <14 days and ≥5 months.

2.4. Diagnosis of influenza

Nasopharyngeal swabs were obtained from all patients and tested using Alsonic® Flu (Alfresa Pharma Co., Osaka, Japan). This RIDT kit can detect and differentiate between influenzas A and B, with high positive concordance (influenza A: 90.8%, influenza B: 88.8%) and negative concordance rates (influenza A: 98.1%, influenza B: 100%) with a viral isolation culture (package insert first edition, July 2015, Alsonic® Flu, Alfresa Pharma Co., Osaka, Japan).

2.5. Vaccine

The quadrivalent influenza vaccine contained influenza A/California/7/2009 (X-179A) (H1N1) pdm09, A/Hong Kong/4801/2014 (X-263) (H3N2), B/Phuket/3073/2013 (Yamagata lineage), and influenza B/Texas/2/2013 (Victoria lineage) viral strains.

At 2–4-week intervals, two 0.25 ml and 0.5 ml doses of vaccine were administered to children aged 6 months to 2 years and 3–12 years, respectively. Although a single 0.5-ml dose of vaccine was administered to children aged 13 years and older, some patients chose to be inoculated with two 0.5-ml doses of vaccine.

2.6. Test-negative case control study

VE was estimated by a test-negative case control design: patients who were ILI- and RIDT-positive for influenza infection were considered cases, and patients who were ILI and RIDT-negative for influenza infection were considered controls. VE was defined as {1-odds ratio (OR)} × 100 (%) and the OR was calculated as (number of influenza-positive among vaccinated patients × influenza-negative among unvaccinated patients)/(number of influenza-negative among vaccinated patients × influenza-positive among unvaccinated patients) [4,5,9]. The OR was calculated using the Wald test.

2.7. Statistical analysis

Student's *t*-test was used to compare continuous variables (i.e., time from onset, age) between participants with and without influenza infection. χ^2 tests were used to compare nominal variables (i.e., sex, comorbidities, month of onset). The VE was adjusted for sex, age group (6 months-4 years old, 5–9 years old, 10–15 years old), presence/absence of comorbidities, and month of onset of influenza infection [4,5]. Considering the effect of age, I performed both a stratified analysis and an analysis treating both vaccine doses and age groups as continuous variables, using the unit OR (i.e., the OR for an increase of 1 unit = 1 of vaccine dose and rank of age group). The adjusted OR was calculated, and the unit OR was adjusted for other continuous variables (age, body temperature, time from onset, and vaccine doses). Differences in the time from onset, between the age groups, were tested by the Wilcoxon/Kruskal-Wallis test. Two-sided *P* values < 0.05 were considered significant. Statistical analyses were performed using JMP® 13.2 (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA).

2.8. Ethics

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients, their parents, or both. Participants were recruited prospectively. The study design was retrospectively approved by the Joint Institutional Review Board (approval number: 14000050.20171020–4517).

3. Results

3.1. Enrollment

From January to May 2017, a total of 1526 episodes were enrolled; 786 were excluded (289: BT < 38.0 °C, 63: overlapped episodes, 10: already had influenza infection in the 2016–2017 season, 9: timing of vaccination was uncertain, 7: interval from the time of vaccination was >5 months, and 408: ≥16 years old). In total, 740 patients were finally analyzed.

3.2. Patients characteristics

The patients' characteristics are summarized in Table 1. A total of 372 patients were RIDT-positive (case) and 368 were RIDT-negative (control). The mean age of the RIDT-positive patients was significantly higher than that of the RIDT-negative patients (mean age±standard error; 7.6 ± 0.2 vs 5.9 ± 0.2, *P*-value<0.0001). The sex distribution and frequency of comorbidities were not significantly different between the cases and controls. Comorbidities included bronchial asthma (n = 34), febrile convulsions (undergoing treatment) (n = 18), epilepsy (n = 3), food allergy (undergoing treatment) (n = 3), hypothyroidism (n = 2), neuroblastoma (n = 1), Down syndrome (n = 1), myositis (n = 1), autoimmune neutropenia (n = 1), severe headache (undergoing treatment) (n = 1), active scarlet fever (undergoing treatment), and active impetigo (undergoing treatment) (n = 1) (Overlapping: yes). The rate of vaccination was significantly lower in the RIDT-positive group than the RIDT-negative group (% (vaccinated/vaccinated + unvaccinated case)/any influenza (influenza A + B): influenza A: influenza B vs not-influenza case = 40.6 (151/372): 42.1 (122/290): 35.4 (29/82) vs 52.2 (192/368), *P*-value = 0.0019, 0.0118, and 0.0070, respectively). Although the time from onset was significantly longer for the

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