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Effectiveness of influenza vaccination for children in Japan: Four-year observational study using a large-scale claims database

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ABSTRACT

Background: To date, few large-scale comparative effectiveness studies of influenza vaccination have been conducted in Japan, since marketing authorization for influenza vaccines in Japan has been granted based only on the results of seroconversion and safety in small-sized populations in clinical trial phases not on the vaccine effectiveness. We evaluated the clinical effectiveness of influenza vaccination for children aged 1–15 years in Japan throughout four influenza seasons from 2010 to 2014 in the real world setting.

Methods: We conducted a cohort study using a large-scale claims database for employee health care insurance plans covering more than 3 million people, including enrollees and their dependents. Vaccination status was identified using plan records for the influenza vaccination subsidies.

The effectiveness of influenza vaccination in preventing influenza and its complications was evaluated. To control confounding related to influenza vaccination, odds ratios (OR) were calculated by applying a doubly robust method using the propensity score for vaccination.

Results: Total study population throughout the four consecutive influenza seasons was over 116,000. Vaccination rate was higher in younger children and in the recent influenza seasons. Throughout the four seasons, the estimated ORs for influenza onset were statistically significant and ranged from 0.797 to 0.894 after doubly robust adjustment. On age stratification, significant ORs were observed in younger children. Additionally, ORs for influenza complication outcomes, such as pneumonia, hospitalization with influenza and respiratory tract diseases, were significantly reduced, except for hospitalization with influenza in the 2010/2011 and 2012/2013 seasons.

Conclusions: We confirmed the clinical effectiveness of influenza vaccination in children aged 1–15 years from the 2010/2011 to 2013/2014 influenza seasons. Influenza vaccine significantly prevented the onset of influenza and was effective in reducing its secondary complications.

1. Introduction

Because children are considered the primary infection center of influenza epidemics in the community, influenza vaccination, especially in the group aged less than 6 years, is recommended by WHO [1–4]. Influenza vaccination for children has been shown to effectively prevent the onset and spread of influenza by establishing herd immunity [5]. Currently, although influenza vaccination is highly recommended in Japan for school-aged children, it is available only through medical institutions on a voluntary basis at the vaccinees' own expense. Some employee health insurance plans subsidize influenza vaccination in children, especially in those aged under 16 years.

Although large-scale studies of the effectiveness of influenza vaccination have been conducted in many countries [6–9], evidence generated from large-scale studies using the vaccines available in Japan is lacking. Only inactivated, non-adjuvanted products are manufactured by a limited number of domestic suppliers, and supply is controlled under the Health Authority's vaccine policy [10]. Marketing authorization for influenza vaccines in Japan is normally granted based on the results of seroconversion

Abbreviations: DR, doubly robust method; OR, odds ratio; PS, propensity score; RTD, respiratory tract diseases.

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and safety in small-sized populations in clinical trial phases. These marketing authorization holders of influenza vaccines have long been reluctant to submit clinical evidence affirming the effectiveness of vaccination. From a public health perspective, it is therefore essential to evaluate the clinical effectiveness of vaccination in the post-marketing stage. Partly due to the absence of a nationwide vaccine registry, no large-scale effectiveness study of childhood influenza vaccination has yet been reported in Japan, although some hospital- or community-based studies have been reported [11,12].

Here, we evaluated the clinical effectiveness of influenza vaccination for children in Japan across four influenza seasons using a large-scale claims database.

2. Methods

2.1. Study design and population

We conducted a cohort study using a large-scale claims database which covered more than 3 million enrollees of employee health care insurance plans and their dependents, and contained enrollee claims records for ambulatory care, hospitalization and pharmacy benefits. The database was provided by JMDC (Japan Medical Data Center Co., Ltd., Tokyo, Japan) [13]. The present subjects were children aged 1–15 years who were the dependents of employees covered by the health plans and eligible for the insurers' vaccine subsidiary programs. Total study duration covered four consecutive influenza seasons, from October 2010 to May 2014. Influenza season for the analysis was determined to extend from October 1, the start date of influenza vaccination at medical institutes in Japan for each year according to the Health Ministry's policy, to the following May 31, when less than one influenza case per week per sentinel site on national average was reported after the peak, according to the weekly reports of infectious diseases published by the National Institute of Infectious Diseases [14,15].

Before data were retrieved from the health plan databases and transferred to the JMDC claims database, all identifiable personal data were anonymized and study subjects were coded with a unique identifier. Ethical approval for the study and waiver of informed consent by study subjects were obtained from the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (No. E-1822).

2.2. Outcome definition

The primary outcome was the effectiveness of influenza vaccination in preventing the onset of influenza. For this, a diagnosis of influenza was based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes (J101, J110, J111 and J118). To test the robustness of influenza diagnosis, sensitivity analyses were performed using three different outcome definitions for influenza occurrence: (1) combination of the above defined ICD-10 codes with records for the use of a rapid-testing kit; (2) combination of these ICD-10 codes with the prescription of antiviral drugs; or (3) combination of the J101 code "influenza due to identified seasonal influenza virus" with the use of a rapid-testing kit [16]. Antiviral drugs were determined using the Anatomical Therapeutic Chemical J05B4 classification of the European Pharmaceutical Marketing Research Association: laninamivir, oseltamivir, peramivir and zanamivir, and use of a rapid testing was identified by claim records for the influenza virus antigen (High-sensitive) test.

The secondary outcome was the effect of influenza vaccination on complications of influenza infection. Patients with diagnosis codes for pneumonia (J12-J18) and respiratory tract diseases (RTD: J00-J22, except for the above codes for influenza) were identified. Hospitalized cases met the following criteria: hospitalized within three days before or after the date of influenza diagnosis (hospitalization with influenza); and hospitalized within seven days after the diagnosis date of RTD (hospitalization with RTD).

2.3. Influenza vaccination

Seasonal trivalent inactivated, non-adjuvanted influenza vaccines were available for children aged 6 months or older during the study period in Japan. Influenza A(H1N1pdm09) was the most prevalent circulating strain in the 2010/2011 (52%) and 2013/2014 (43%) seasons, and A(H3N2) was the most prevalent circulating strain in the 2011/2012 (71%) and 2012/2013 (76%) seasons [15] (Table 1). Antigenic characteristics of vaccine strains are shown in Table 1. The dose of vaccine for children aged under 13 years was increased from the 2011/2012 season to be equivalent to the world standard dose (Appendix 1). Vaccination status and dates were identified from the records for influenza vaccination subsidies of the health plan. Subjects who were vaccinated after the onset of an outcome of concern were censored at the time of outcome diagnosis and classified as non-vaccinees.

2.4. Confounding factors

Covariates considered for adjustment of potential confounders were influenza vaccination status in the immediately preceding season, age group (low-age group, 1–5 years old; high-age group, 6–15 years old), sex, the presence of siblings aged 0–15 or over 15 years, preceding onset of influenza among siblings aged 1–15 years during each influenza season, a history of high-risk medical conditions, emergent hospitalization, and number of outpatient visits during or out of office hours in the preceding influenza off-season (June to September). High-risk medical conditions were defined in accordance with the definition of the US Center for Disease Control and Prevention [17]. Siblings were identified by having the same insurance number for dependents. "Preceding onset of influenza among siblings" was defined as the risk of second infection to which a subject was exposed when his/her siblings aged 1–15 years had had any influenza diagnosis code prior to his/her first influenza occurrence, or during the influenza season in the case of no occurrence; this was considered only in the analyses of the primary outcome and in the secondary outcome for hospitalization with influenza.

2.5. Statistical analysis

Subject characteristics during the four seasons were summarized with descriptive statistics. Comparison of continuous variables between vaccinees and non-vaccinees was tested with the Mann-Whitney test. The chi-square test was used for comparison of categorical variables.

The primary analysis was odds ratios (ORs) of outcome events for influenza vaccination, with a lower OR indicating better effectiveness. First, ORs for influenza vaccination and other covariates were calculated by conventional multivariate logistic regression for whole subjects and age groups. Next, a doubly robust method (DR) using inverse probability treatment weighting (IPTW) by propensity score (PS) was applied to calculate the OR_{DR}s to adjust confounding related to influenza vaccination [18,19]. Whether to be vaccinated is known to be strongly associated with health-seeking behaviors, and PS implementation has an advantage in adjusting the channeling bias that health-seeking behaviors involve [20,21]. However, it is known that PS adjustment methods yield biased estimates when the model used to specify the PS is misspecified, and the IPTW estimator