ORIGINAL ARTICLE

Influenza vaccine effectiveness in primary school children in Japan: a prospective cohort study using rapid diagnostic test results

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Abstract A low-cost, prospective cohort study using the results of rapid diagnostic test performed at local clinics was conducted to estimate influenza vaccine effectiveness (VE) in school children (6–12 year-olds). All children in four primary schools in Tsuchiura City, Ibaraki, Japan were enrolled ($n = 2607$). Vaccination status and other risk factors were obtained with a baseline questionnaire. Participants were encouraged to visit a clinic to have a rapid test when they developed an influenza-like illness during the winter season in 2006–2007, and 88.6% of those who reported influenza to the school had been tested. The result of the test was obtained with another questionnaire. The attack rate of influenza A and B was 5.4% and 11.9%, respectively. Logistic regression was used to model the association between influenza vaccination and rapid-test-confirmed influenza after adjusting for potential confounders. Influenza VE was calculated as (1– adjusted odds ratio) × 100. VE for total influenza was 21% (95% confidence interval −8 to 42), which was a combination of VE for influenza A (44%, 8–66) and VE for influenza B (5%, −37 to 34). Among several possibilities that would account for rather low VE estimates in this study, low sensitivity of the rapid test, and differential propensity to seek vaccination or medical care between the vaccinated and nonvaccinated were considered to be important. This study was able to estimate influenza VE at very low cost with high specificity in case ascertainment by collecting the readily available data on influenza rapid test with questionnaires.

Keywords Influenza · Vaccine effectiveness · Children · Rapid test

Introduction

Influenza vaccination is the most effective method for preventing influenza virus infection and its potentially severe complications [1]. The vaccine effectiveness (VE) of trivalent inactivated vaccine to laboratory-confirmed influenza in healthy children has been reported as 59% [95% confidence interval (CI) 41–71] [2] or 67% (51–78) [3]. But influenza VE varies considerably by time, place, and the degree of antigenic distance between the vaccine strain and circulating strain. Therefore, it is important to take every opportunity to assess influenza VE to monitor the performance of a vaccination program.

In many studies assessing VE for influenza, influenza-like illness (ILI) has been used as the primary endpoint [2]. This is usually because virological confirmation of influenza infection is costly and logistically difficult. But ILI is not a specific case definition including other similar illnesses, and VE tend to be underestimated with such a low specific endpoint because of the diluting effect [4]. Influenza rapid diagnostic test (rapid test) has been used in routine medical practice in Japan since 1999. It has been reported to be more specific than clinical diagnosis during the influenza epidemic seasons [5]. However, there have been few reports on the use of rapid test for estimating influenza VE [6–8]. This would be because not all patients with ILI seek medical care, and not all those who attended a clinic are actually tested with a rapid test during influenza

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seasons, which makes it almost impossible to assess influenza VE with a facility-based prospective cohort study. On the other hand, the Law of School Health in Japan prohibits a schoolchild who caught influenza from coming to school until 2 days after the febrile period, and this regulation gives a strong motivation to parents to take their febrile child to a clinic for a rapid test in winter. It is also of note that the cost of rapid test is mostly covered by public health insurance in Japan.

However, whereas most children with influenza are tested, those results have not been systematically collected for epidemiological purposes. This has been a waste of valuable information, and it could be corrected by involving school administrations into epidemiological practices for collection of these data. Therefore, we established a collaboration model in which several primary schools were invited to collect information on vaccination status and other risk factors of the children, as well as results of the rapid test from those who reported influenza, by using questionnaires. Here we report the results of estimated VE and the strength and limitations of the use of rapid test in assessing influenza VE in school children.

Methods

Study design and participants

This study was a prospective cohort study conducted during the 2006–2007 influenza season. To detect a significant effect of 50% VE when the incidence of influenza was assumed to be 6% and the vaccination coverage 50%, the required sample size was calculated as 1068 for each group (95% significance level with 90% power). Taking the average size of each school into account, the number of required schools was determined as four. Therefore, all pupils in four primary schools that were randomly selected from a total of 18 primary schools in Tsuchiura City (60 km northeast of Tokyo; population 143000), Ibaraki, Japan, were enrolled in the study ($n = 2607$).

Information collection and vaccination

A questionnaire for the baseline survey was sent to parents or guardians via school administrations in early January 2007, which inquired about potential confounders (age, sex, number of siblings, presence of underlying illness, and influenza disease history in the previous season) and vaccination status in the previous and current season. Influenza disease history in the current season up to the time of the baseline survey was also obtained. The vaccine contained A/New Caledonia/20/99(H1N1), A/Hiroshima/52/ 2005(H3N2), and B/Malaysia/2506/2004, and the antigen

level for each strain was 30 μg/ml. Vaccine dosage was given according to the standard Japanese recommendation (i.e., 0.3 ml for schoolchildren aged 6–12 years). Two doses of vaccine were commonly administered subcutaneously 4 weeks apart between October and December 2006. Those who were vaccinated at least once during this period were considered as vaccinated in this study.

Case surveillance and definition

When a child was diagnosed as having influenza with a positive rapid test at a clinic, the child was forced to stay at home until 2 days after the febrile period according to the Law of School Health. When the child resumed school, the parent of the child was asked to submit an Influenza Reporting Form to the school administration for exemption purpose. At this time, another questionnaire was also given to the parent to collect information on the result of the rapid test. The primary endpoint of this study was a case of influenza confirmed by a positive rapid test (total influenza). A case was further classified as influenza A or B according to the test result, which was the secondary endpoint of this study. Those who were diagnosed as influenza without a rapid test (clinical influenza) were excluded from the main analysis, but they were included in a sensitivity analysis to assess the magnitude of their exclusion. This study was terminated at the end of the semester in March 2007.

Statistical analysis

Statistical analysis was performed with SAS 9.1 for Windows (SAS Institute, Cary, NC, USA). Univariate analysis was performed with a logistic regression model that included "vaccination of the current year" as an independent variable and "development of influenza" as a dependent variable. Adjusted VE was calculated as 1 minus odds ratio (OR) that was obtained from a logistic regression analysis accounting for potential confounders. Two models of logistic regression analysis were calculated. Model 1 was an unconditional logistic regression that included school, grade, sex, number of siblings, underlying illness, vaccination in the previous season, and corresponding type of influenza disease history in the previous season as potential confounders. Model 2 was a conditional logistic regression analysis that matched the individuals by school, grade and class while adjusting for the other confounders.

Ethical considerations

This study was approved by the board committee of the Tsuchiura City Medical Society and the Board of