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Estimating influenza vaccine effectiveness using routine surveillance data among children aged 6–59 months for five consecutive influenza seasons

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SUMMARY

Objectives: We aimed to estimate the pooled vaccine effectiveness (VE) in children over five winters through data linkage of two existing surveillance systems.
Methods: Five test-negative case–control studies were conducted from November to February during the 2004/2005 to 2008/2009 seasons. Sentinel physicians from the Viral Surveillance Network enrolled children aged 6–59 months with influenza-like illness to collect throat swabs. Through linking with a nationwide vaccination registry, we measured the VE with a logistic regression model adjusting for age, gender, and week of symptom onset. Both fixed-effects and random-effects models were used in the meta-analysis.
Results: Four thousand four hundred and ninety-four subjects were included. The proportion of influenza test-positive subjects across the five seasons was 11.5% (132/1151), 7.2% (41/572), 23.9% (189/791), 6.6% (75/1135), and 11.2% (95/845), respectively. The pooled VE was 62% (95% confidence interval (CI) 48–83%) in both meta-analysis models. By age category, VE was 51% (95% CI 23–68%) for those aged 6–23 months and 75% (95% CI 60–84%) for those aged 24–59 months.
Conclusions: Influenza vaccination provided measurable protection against laboratory-confirmed influenza among children aged 6–59 months despite variations in the vaccine match during the 2004/2005 to 2008/2009 influenza seasons in Taiwan.

1. Introduction

Influenza viruses cause annual epidemics and the occasional pandemic of acute respiratory disease, which pose a threat to the health of the population.[1] Vaccination is considered a priority in public health departments and is an effective way to prevent influenza-associated morbidity, mortality, and expense.[2] Since 1998, the Department of Health in Taiwan has gradually endorsed annual influenza vaccination campaigns to encourage susceptible subjects, including the elderly, healthcare workers, poultry workers, and young children, to receive free influenza immunization, based on the recommendations of the Advisory Committee on Immunization Practices in Taiwan.

The recommendation of universal influenza vaccination of young children was not popular in many countries initially, probably because of the absence of studies providing solid evidence of effectiveness in the targeted population.[3,4] During the 2004/2005 influenza season, the Centers for Disease Control in Taiwan (Taiwan CDC) started to vaccinate groups of children aged 6–23 months; this program was extended to those aged 24–35

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months starting in 2008/2009. All vaccination target groups had the same opportunity to receive free influenza shots beginning in October each year. In addition to the recommended groups, all people could receive free influenza vaccination after December 1 each season in order to best utilize the influenza vaccine resources and to increase the vaccine coverage of the entire population.

It is important to determine the influenza vaccine effectiveness (VE) after the implementation of such a program. Previous studies have encouraged large studies to assess the impact of influenza vaccination on children in terms of specific outcome measurements.[5,6] Furthermore, multiyear studies are preferred for estimating robust influenza VE over time through a meta-analysis methodology.[7,8] The Taiwan CDC has successfully coordinated a laboratory-based surveillance network for influenza virus for all ages since 2000 and established the National Immunization Information System (NIIS) for children aged <6 years in 2003.[9] By using the retrospective laboratory-confirmed influenza surveillance data and linking these to individual vaccination records, we were able to rapidly and efficiently demonstrate the influenza VE in children for the 2004/2005 to 2008/2009 seasons.

Previous reports have demonstrated influenza VE using routinely collected laboratory and/or surveillance data and directly pooling results from multiple years to provide the overall VE.[10–12] In this study, we implemented a fixed-effects and a random-effects meta-analysis of case–control studies to estimate the pooled VE for children aged 6–59 months across the five consecutive influenza seasons, and considered the variation in antigenic match across seasons and epidemics year by year as the heterogeneity between studies. Such effectiveness studies of inactivated influenza vaccine among young children could assist public health sectors in reassessing the current national influenza vaccination strategy for the target groups, especially when vaccine match varies year to year.

2. Subjects and methods

2.1. Study population

Children aged 6–59 months with an influenza-like illness (ILI) during the November to February winter epidemics over five seasons from 2004/2005 to 2008/2009 were investigated. The Viral Surveillance Network required sentinel physicians to collect throat or nasal swabs among verbally consenting ILI patients regardless of the patient's influenza vaccination status and underlying medical conditions. ILI was defined as a body temperature ≥38 °C plus one of the following four clinical manifestations: cough, sore throat, hoarseness and running nose, or headache and myalgia/fatigue. This study was initiated as a public health response and used routinely collected surveillance data and vaccination records to assess influenza VE. The Taiwan CDC determined these activities to be non-research and thus the study did not require review by an institutional review board.

2.2. Viral surveillance network and virological testing

The Viral Surveillance Network coordinated by the Taiwan CDC was started in October 2000; it comprises 10–13 collaborating laboratories (the number is affected by the annual budget) and aims to survey and isolate nationwide circulating viruses related to respiratory tract infections year-round.[9] Clinical specimens obtained from nasal or throat swabs were collected by the sentinel physicians and sent to the local collaborating laboratories for virus identification using viral culture and/or reverse transcriptase PCR. Methods of virus isolation have been described previously.[13] The Taiwan CDC collected and analyzed these results on a weekly basis and posted this information on their website. The antigenic match between vaccine and circulating strains in each season was evaluated by hemagglutination inhibition (HAI) assay.

2.3. Determination of case and control subjects

Children whose specimens tested positive for laboratory-confirmed influenza infection during the study periods were defined as case subjects. Control subjects were those with the same symptoms but who were negative for influenza. For cases and controls, information about age, sex, week of symptom onset, and personal identifiers were obtained from the reports submitted by the sentinel physicians.

2.4. Influenza vaccination status

Information on the influenza vaccination status of the subjects was obtained from the NIIS, which was established by the Taiwan CDC to collect vaccination records for children at a national level. Children were classified as vaccinated if they had received one or more vaccine doses in the current influenza season and it was administered ≥14 days before the onset of ILI. Children were classified as unvaccinated for the given season if they were not vaccinated in that study season or if they had received the first vaccine dose within 14 days before respiratory tract infection. In this study, we did not define the status of partially vaccinated children because many influenza epidemic strains in Taiwan become the vaccine strains 2–3 years later, as shown by hemagglutination sequence comparisons.[9,14] Therefore, children aged 6–59 months were considered immunized if they had received one or more vaccine doses in the current influenza season regardless of previous influenza immunization history.

2.5. Statistical analysis

We linked the NIIS and National Viral Surveillance System using the personal identifier. We used a logistic regression model to adjust for age, gender, and week of symptom onset, with the first week including November 1 and the last week including February 28 in the five different epidemic seasons.[15,16] The adjusted odds ratio (aOR) was used to model the association between influenza vaccination and laboratory-confirmed influenza-related medical visits in each season. VE and 95% confidence intervals (CI) were estimated using the formula VE = $(1 - \mathrm{OR}) \times 100\%$. Stratified VE estimates were calculated according to age (6–23 months or 24–59 months) and adjusted for gender and week of symptom onset. We used both a fixed-effects model with inverse variance method and a random-effects model with DerSimonian–Laird weighting method[17] to run the synthesis results. A forest plot was used to display the estimated overall ORs and separate ORs in the five epidemic seasons according to the two age groups.[18] We used the 'meta' package for the R system for statistical computing to implement the meta-analysis.[19,20] Annual vaccination rates among control groups were examined using the Cochran–Armitage test for trend in SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

In Taiwan, five winter epidemics occurred between November 2004 and February 2009, which were dominated by influenza A H1N1 in 2005/2006, 2007/2008, and 2008/2009, influenza B in 2004/2005, and influenza B followed by influenza A H3N2 in 2006/2007 (Figure 1, Table 1). Information on influenza activity obtained from the Viral Surveillance Network demonstrated that positive rates of influenza isolates for 6–59-month-old children varied each winter; from high to low, these rates were 23.9% (189/791) in the