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Original Article

Influenza vaccine effectiveness in adults based on the rapid influenza diagnostic test results, during the 2015/16 season

Yuki Seki [a, *], Akira Onose [b], Norio Sugaya [c]

[a] Department of Internal Medicine, Keiyu Hospital, Japan
[b] Department of Internal Medicine, Nanashima Clinic, Japan
[c] Department of Pediatrics, Keiyu Hospital, Japan

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ABSTRACT

We assessed the influenza vaccine effectiveness (VE) of an inactivated quadrivalent influenza vaccine in adult patients, in our test-negative case-control design study based on the results of a rapid influenza diagnostic test. During the 2015/16 season in Japan, influenza A(H1N1)pdm09 virus and influenza B virus were epidemic. The overall adjusted VE was 44% (95% confidence interval [CI]: 13.6%-63.7%). The adjusted VE was 52.9% (95%CI: 20%-72.3%) against any influenza virus among those < 65 years of age and −5% (95% CI: 136%-53.5%) among the elderly ≧ 65 years of age.

The adjusted VE against influenza A was 49.1% (95%CI: 13.9%-69.9%). Although the VE was 55.5% (95% CI: 14.8%-76.8%) among those <65 years of age, it was only 15.3% (95%CI: 120%-67.4%) among the elderly ≧ 65 years of age.

The adjusted VE against influenza B was 33.8% (95%CI: 25%-64.8%) among adult patients (≧16 years of age) and 46.8% (95%CI: 13%-75%) among those < 65 years of age, the VE against influenza B could not be estimated in those ≧65 years of age because of the low number of elderly patients with that virus.

1. Introduction

Since the approval of zanamivir in 1999, and oseltamivir in 2000 for treating influenza virus infection in Japan, the rapid influenza diagnostic test (RIDT) has been routinely performed by clinicians in patients with an influenza-like illness (ILI). Those with positive test results, including otherwise healthy adults and children without any underlying illness, are usually treated with neuraminidase inhibitor (NAI) [1,2]. The influenza vaccine effectiveness (VE) was recently estimated in a test-negative design (TND) study based on RIDT results in Japan [3–5].

TND is now the standard method for estimating influenza VE worldwide. In this design, VE is calculated as 100% × (1-odds ratio [OR]) for vaccine receipt in influenza cases versus test-negative controls [6]. The first TND study was published in 2005 by Canadian investigators who reported the VE in British Columbia during the 2004/05 season [7]. Since then, many reports have been published regarding the estimation of the VE by TND studies.

VE as assessed in TND studies is usually based on polymerase chain reaction (PCR) data, the present study, however, was based on the results of RIDT results. Suzuki et al. detected no difference between the VE estimated by TND on the basis of RIDT results and that on the basis of PCR data [8].

In the 2015/16season in Japan, an inactivated quadrivalent influenza vaccine (IIV4) was introduced for the first time instead of an inactivated trivalent influenza vaccine (IIV3). This is the first report of the effectiveness of IIV4 in adult patients evaluated in a TND study based on RIDT data in Japan.

2. Materials and methods

2.1. Study enrollment location

Adult patients ≧16 years of age with an ILI who received an RIDT at an outpatient clinic of our hospital, between November 1, 2015 and March 31, 2016 were enrolled in this study. We received a report of a mass outbreak of influenza in our city (Yokohama-City)

* Corresponding author. Keiyu Hospital, 3-7-3, Minatomirai, Nishi-ku Yokohama-City, Kanagawa, 220-0012, Japan. fax: +81 45 681 9665.
E-mail address: seracyukka@yahoo.co.jp (Y. Seki).

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in October 2015, and we started this study in November, 2015. ILI was defined as the acute onset of respiratory illness (ARI) with a fever (based on a physician's assessment or self-reported by the patient) and cough and one or more of the following symptoms: arthralgia, myalgia, prostration or sore throat. A fever was not required for patients ≧65 years of age in this study [9].

2.2. Diagnosis of influenza

Nasopharyngeal swabs were obtained from all of the enrollees and tested using an Espline influenza A&B-N kit (Fujirebio Inc.,Tokyo, Japan). This RIDT kit is capable of detecting and differentiating between influenza A and influenza B. It has high sensitivity (86.6%-90.8%) and specificity (98.8%) [10], compared with PCR or virus isolation.

2.3. Case and control patient identification

Case patients were patients who were RIDT-positive, and, control patients were patients who were RIDT-negative. Both case and control patient's medical charts were reviewed, and information regarding the symptoms, influenza vaccination status, influenza complications and hospitalizations, sex, age, comorbidities (chronic disease of the heart, lungs, kidneys or liver, diabetes mellitus, neurological disease affecting the patient's lung function and immunosuppression caused by a disease or treatment), and treatment with NAIs was recorded [3,4]. Patients in whom definite information on their influenza vaccination history was unavailable were excluded from this study.

2.4. Vaccination status

Patients were considered vaccinated if they had received the seasonal 2015/16 influenza vaccine (IIV4) at least two weeks before the sample was taken; otherwise they were considered unvaccinated [11].

2.5. Vaccine

The IIV4 was used in Japan starting in the 2015/16 season. The vaccine strains of the 2015/16 season were A/California/7/2009 (X-179A) for A (H1N1) pdm09, A/Switzerland/9715293/2013(NIB-88) for H3N2, B/Phuket/3073/2013 for Yamagata lineage and B/Texas/2/2013 for Victoria lineage.

2.6. Test-negative case-control design

Influenza VE was assessed using a TND study. Case patients were patients who were RIDT-positive, and, control patients were patients who were RIDT-negative [3,4]. This study compared the odds of vaccination among outpatients with ILI who tested positive for influenza infection with the odds of vaccination among outpatients with ILI who tested negative for influenza infection. The VE was calculated as "1−OR" [6]. In addition, the test-negative case applied to minimize bias related to access to health care and to minimize the misclassification of influenza cases [12].

2.7. Statistical analyses

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user for R (the R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [13]. The VE was adjusted for age group (<65 years of age.vs.≧65 years of age), sex, comorbidity (yes or no) and month of onset of illness calculated using multivariate logistic regression analysis.

2.8. Ethics

This study was approved by the Keiyu Hospital Ethics Committee in 2015, No.H27-24 and the Institutional Review Board (IRB). Eligible patients were informed about the study objectives and methods verbally at the outpatient departments. We recorded the necessary information from patients using standardized question sheets, after obtaining their consent to be enrolled to this study. The requirement for obtaining written consent was waived by the IRBs because testing patients with RIDTs is standard practice in Japan.

3. Results

3.1. Influenza epidemic in the 2015/16 season

In the 2015/16 season in Japan, the dominant circulating strain was influenza A(H1N1)pdm09, which was antigenically matched to the vaccine strain [14].According to Flu Net [15], of the influenza A viruses detected in Japan, 87% were A(H1N1)pdm09 virus, and 12.9% were A/H3N2 during the study period. Of the influenza B viruses detected, 45.5% were B/Yamagata lineage, and 46.9% were B/Victoria lineage. The influenza epidemic peaked during early February 2016.

In the 2015/16season at our hospital, the number of patients tested by RIDT peaked in February 2016 (200/610, 35%). The first patients with influenza A were diagnosed on November 10, 2015. The number of influenza A patients peaked in February 2016 and then began to decrease in March. While the number of influenza B patients was smaller than that of influenza A patients in January and February, the numbers exceeded those of influenza A patients in March (Fig. 1).

3.2. Characteristics of the enrollees

A total of 629 patients were enrolled in this study. Nineteen patients were subsequently excluded from the analysis for the following reasons: 16 had an unclear influenza vaccination history, and 3 did not offer their consent.

Because the vaccination day was less than 14 days before the ILI onset, the vaccinated record was considered "unvaccinated" for 6 patients.

Of the remaining 610 patients eligible for the analysis in this study, 91 had influenza A virus infection and 53 had influenza B infection. The remaining 466 patients were RIDT-negative (Fig. 2).

Among RIDT positive patients, there were six hospitalized patients.

Regarding the cause of hospitalization, five cases were complicated with bacterial pneumonia, and the remaining case had sever dehydration. Among the admitted patients, the median age was 77 years old (inter-quartile-range: [IQR]:68−81years) in 4 males, and 2 females.5 patients had comorbidities (83.3%), and many patients had respiratory disease. Regarding the vaccination status, one patient was vaccinated, and five were not. Because of the small sample size, we could not analyze the VE of prevention.

Overall 26.4% (n = 24) of influenza A infected patients, 32% (n = 17) of influenza B infected patients and 37.8% (n = 176) of influenza negative patients were confirmed to be vaccinated (Table 1).

3.3. VE against influenza

In the 2015/16 season, the overall VE was 44% (95%confidence interval [CI]: 13.6% -63.7%) in all patients. The adjusted VE against