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Influenza vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings: A test-negative case-control study in Beijing, China, 2016/17 season

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ABSTRACT

Background: The objective of this study was to estimate influenza vaccine effectiveness (VE) for the 2016/17 epidemic of co-circulating influenza A(H1N1)pdm09 and A(H3N2) viruses in Beijing, the capital of China.

Methods: The surveillance-based study included all swabbed patients through influenza virological surveillance, between November 2016 and April 2017. A test-negative case-control design was used to estimate influenza VE against medically-attended laboratory-confirmed influenza in outpatient settings. Cases were influenza-like illness (ILI) patients who tested positive for influenza, and controls were influenza negative patients.

Results: A total of 10,496 ILI patients were enrolled and swabbed. Among them, 735 tested positive for influenza A(H1N1)pdm09, 1851 for A(H3N2), and 40 for type B. Of the 45 randomly selected specimens out of 1851 influenza A(H3N2) viruses, 2(4.4%) belonged to the H3N2 3C.2a1 clade, and 43(95.6%) belonged to A/Hong Kong/4801/2014-like 3C.2a clade. Among the 43 viruses of the 3C.2a clade, 32 viruses clustered in one subgroup carrying T131K, R142K and R261Q substitutions. The adjusted VE against all influenza was low at 25% (95% confidence interval (CI): 0–43%), with 54% (95%CI: 22–73%) for influenza A(H1N1)pdm09, and 2% (95%CI: −35% to 29%) for influenza A(H3N2).

Conclusions: Our study suggested a moderate VE against influenza A(H1N1)pdm09, but low VE against influenza A(H3N2) in Beijing, 2016/17 season. Amino acid substitutions in the hemagglutinin may contribute to the low VE against influenza A(H3N2) for this season.

1. Introduction

Influenza vaccination is the most effective way to minimize influenza-related mortality and morbidity [1]. People in most regions of China bear the full cost of the vaccine, thus this led to a very low influenza vaccination coverage rate in China [2]. Since 2007, the Beijing government, ahead of most of other Chinese cities, has provided free seasonal influenza vaccines to older adults aged ≥60 years and primary, middle and high school students [3]. The policy greatly increased the influenza vaccination coverage rate in the targeted population [4]. As in previous years, a mass vaccination campaign was conducted to provide free influenza vaccines to the targeted population in Beijing, from October 15 to November 30, 2016. A trivalent inactivated influenza vaccine was used in the 2016/17 season. The composition of this vaccine for use in the 2016/17 northern hemisphere recommended by WHO included an A/California/7/2009 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus [5].

Beijing, the capital of China, is the largest city in Northern China. In 2016/17, influenza A(H1N1)pdm09 and A(H3N2) viruses co-circulated in Northern China, whereas influenza A(H3N2) viruses were dominant in Europe and North America, with influenza A(H1N1)pdm09 and influenza B viruses circulated at very low levels [6]. Therefore, influenza VE studies from these countries

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focused on influenza A(H3N2), but VE against influenza A(H1N1) pdm09 were absent for the 2016/17 season [7–12]. Regarding VE against A(H3N2) viruses, a meta-analysis indicated that reduced VE was observed for both antigenically matched (33%, 95%CI: 22–43%) and variant A(H3N2) viruses (23%, 95%CI: 22–43%) in the past decade [13]. In 2016/17, low VE was also reported in some Northern Hemisphere countries with a predominance of A(H3N2) viruses belonging to subclade 3C.2a1 [7–12,14]. However, there is limited information regarding VE against influenza A(H3N2) in China in 2016/17, where the clade 3C.2a with amino acid substitutions were the majority of influenza A(H3N2) viruses.

In the present study, we performed a test-negative case-control study for estimating influenza VE in preventing medically-attended influenza-like-illness (ILI) associated with laboratory-confirmed influenza virus infection in outpatient settings in Beijing, 2016/17 season. Influenza VE estimates were stratified by age groups (6–35 months, 3–17 years, 18–59 years, and ≥ 60 years) and influenza subtypes (influenza A(H1N1) pdm09, A(H3N2), and B).

2. Methods

2.1. Participants and laboratory detection

The test-negative case-control design was used to estimate VE [15]. Cases were ILI patients who tested positive for influenza, and controls were influenza negative patients. Influenza positive and negative patients were identified through influenza virological surveillance in Beijing, from November 1, 2016 to April 30, 2017 [16]. As previously described [17], the influenza virological surveillance system, designed and managed by Beijing Center for Disease Prevention and Control (BJCDC), consisted of 23 sentinel hospitals and 17 collaborating laboratories in the 2016/17 season. Under this system, clinicians in outpatient settings (including internal medicine, emergency department, fever clinic, and pediatric clinic) were required to diagnose all ILI cases by using a standard ILI definition (patients presenting with fever ≥38 °C and cough or sore throat). Trained clinicians collected pharyngeal swab specimens from a convenience sample of 10–20 outpatient ILI cases per sentinel hospital per week. The specimens were transported to collaborating laboratories in viral transport medium at 4 °C for detection by polymerase chain reaction (PCR) following the procedures recommended by the WHO Collaborating Center for Reference and Research on Influenza in China.

Sanger sequencing of the viral haemagglutinin (HA) gene was undertaken on a subset of original specimens to access the contribution of genetic clades to VE estimates. A total of 45 A(H3N2) strains isolated in 2016/17 were randomly selected and sequenced. Viral RNA was extracted using QIAmp Viral Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instruction. For strains, reverse transcription and amplication of HA gene were carried out as described previously [18]. Then PCR products were sequenced by ABI Prism 3130xl automated sequencer (Applied Biosystems, Foster City, USA). Other A(H3N2) HA sequences were retrieved from Global Initiative for Sharing All Influenza Data (GISAID) EpiFlu influenza sequence database and then screened by CD-HIT program [19]. Nucleotide sequences were assembled and then aligned by MEGA software (ver. 6.0.4) [20]. Neighbor-joining (NJ) phylogeny trees were inferred with 1000 bootstrap replications. The circular tree was prepared with the iTOL (ver. 4).

2.2. Data collection

Nurses at the sentinel hospitals collected the epidemiological information using a standardized questionnaire. Variables included age, sex, presence of chronic diseases, date of symptom onset and interval onset to enrollment for swabbed patients. Presence of chronic diseases was defined as having any one of the following diseases: asthma, tuberculosis, pulmonary fibrosis, chronic tracheitis or bronchitis, emphysema, chronic obstructive pulmonary disease, diabetes, anemia, oncological diseases, diseases of the immune system, cardiovascular and cerebrovascular diseases, renal diseases, hepatopathy and neurological diseases. The questionnaires were sent along with the specimens to collaborating laboratories. The laboratory staffs input data from the questionnaires and then sent data sets to BJCDC.

A trivalent inactivated influenza vaccine containing antigens of two influenza A strains, A(H1N1)pdm09 and A (H3N2), and an influenza B/Victoria strain was used in the 2016/17 season. Influenza vaccination records were obtained from the Beijing Management System of Information for the Immunization Program. Vaccination services are provided by the staffs from the points of vaccination (POV) located at the community health centers. Local regulation requires that demographic information and vaccination history are deposited in the Management System by the staffs from the POV clinics. In this study, participants aged ≥3 years were considered to be vaccinated if they received influenza vaccination ≥14 days before onset of symptoms, and participants aged 6–35 months who received 2 doses of the influenza vaccine ≥14 days before illness onset were regarded as vaccinated. The other participants were considered to be unvaccinated.

2.3. Statistical analysis

Data entry was performed using Epidata software Version 3.1 (The EpiData Association, Odense Denmark), while the statistical analyses were carried out using SPSS Version 20.0 (IBM Corporation, New York, United States). Descriptive analysis was performed to generate frequency distributions of the survey variables, and differences between the subgroups were tested using Pearson's chi-square test. Univariable and multivariable logistic regression models were performed to examine the association between vaccination status and laboratory-confirmed influenza, and the odds ratio (OR) and 95% confidence intervals (95%CI) were used as measures of association. The adjustment variables included sex, age groups (6–35 months, 3–17 years, 18–59 years, ≥60 years), presence of chronic diseases, interval onset to enrollment, and time of onset of symptoms (by week). VE was estimated as (1-OR) × 100%. VE estimates were stratified by age groups and influenza subtypes. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

3. Results

3.1. Influenza virus activity

From November 1, 2016 (week 44 in 2016) to April 30, 2017 (week 17 in 2017), a total of 10,496 specimens were tested for influenza virus. Around 25.0% specimens tested positive for influenza, and influenza A(H1N1)pdm09 and A(H3N2) viruses co-circulated during the study period. Influenza virus activity increased from week 44 of 2016, peaked in week 1 of 2017 and decreased afterwards. Regarding the differences between the subtypes, influenza A(H3N2) peaked in week 1 of 2017, and influenza A(H1N1)pdm09 peaked in week 12 of 2017 (Fig. 1).

This study sequenced 45 randomly selected specimens out of 1851 influenza A(H3N2) viruses. Of these, 2(4.4%) belonged to the H3N2 3C.2a1 clade, 43(95.6%) belonged to A/Hong Kong/4801/2014-like 3C.2a clade, and 0(0%) clustered in A/Switzerland/9715293/2013-like 3C.3a clade. Among the 43 viruses of the

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