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The 2015–2016 influenza epidemic in Beijing, China: Unlike elsewhere, circulation of influenza A(H3N2) with moderate vaccine effectiveness

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ABSTRACT

Background: While the 2015–2016 influenza season in the northern hemisphere was dominated by A (H1N1)pdm09 and B/Victoria viruses, in Beijing, China, there was also significant circulation of influenza A(H3N2) virus. In this report we estimate vaccine effectiveness (VE) against influenza A(H3N2) and other circulating viruses, and describe further characteristics of the 2015–2016 influenza season in Beijing.
Methods: We estimated VE of the 2015–2016 trivalent inactivated vaccine (TIV) against laboratory-confirmed influenza virus infection using the test-negative study design. The effect of prior vaccination on current VE was also examined.
Results: Of 11,000 eligible patients included in the study, 2969 (27.0%) were influenza positive. Vaccination coverage was 4.2% in both cases and controls. Adjusted VE against all influenza was 8% (95% CI: −16% to 27%): 18% (95% CI: −38% to 52%) for influenza A(H1N1)pdm09, 54% (95% CI: 16% to 74%) for influenza A(H3N2), and −8% (95% CI: −40% to 18%) for influenza B/Victoria. The overall VE for receipt of 2015–2016 vaccination only, 2014–2015 vaccination only, and vaccinations in both seasons was −15% (95% CI: −63% to 19%), −25% (95% CI: −78% to 13%), and 18% (95% CI: −11% to 40%), respectively.
Conclusions: Overall the 2015–2016 TIV was protective against influenza infection in Beijing, with higher VE against the A(H3N2) viruses compared to A(H1N1)pdm09 and B viruses.

1. Introduction

Influenza contributes to high morbidity and mortality in China [1,2] and globally [3]. Annual influenza vaccination is considered to be the most effective way to prevent influenza virus infection and its complications [4]. Although the Chinese Center for Disease Control and Prevention (CDC) recommends annual influenza vaccination with the northern hemisphere trivalent influenza vaccine (TIV) for young children, older adults, and other high risk individuals, following World Health Organization (WHO) recommendations [5,6], vaccine coverage remains very low, with less than 2% vaccine uptake in the total Chinese population and around 10% among Beijing citizens [7], and there is limited information on vaccine effectiveness (VE) and impact of the vaccination programme in China.

Since Beijing is located in the northern temperate zone of China, it has one seasonal peak of influenza in winter/spring each year, which usually occurs in the months of December or January [8]. The 2015–2016 influenza season in Beijing started and peaked later than the previous season (2014–2015) [9]. Influenza activity remained low until late November, and peaked in early February 2016, following that season's general trend in the northern hemisphere [10]. However, the subtypes/lineages in China differed from those reported from most other countries in the northern hemisphere. In North America and Europe, influenza A(H1N1)pdm09 viruses predominated at the start of the season, followed by influenza B/Victoria lineage later in the season [11–17]. Activity of

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influenza A(H3N2) virus was extremely low in North America and Europe. In Northern China, Influenza A(H1N1)pdm09, influenza A (H3N2), and influenza B viruses co-circulated during the 2015–2016 season [18,19]. Influenza A(H3N2)strains were predominant from October to mid-January in Beijing, followed by influenza B/Victoria lineage as the predominant type until April 2016. The Beijing data, which has a large sample size from a single study site, therefore provide the opportunity to estimate VE against influenza A(H3N2), which was not possible in most of the northern hemisphere.

During the annual influenza vaccination campaigns, first launched in 2007, Beijing offers seasonal TIV free of charge to school-aged children (aged 6–17 years) and to adults aged ≥60 years prior to each year's wintertime influenza season. The vaccine is also available to other residents against out-of-pocket payment [11,20]. Children aged six to 35 months receive two doses of 0.25 ml TIV administered at least 4 weeks apart, while individuals aged 3 years and older receive a single 0.5 ml dose of TIV.

The composition of TIV used during the 2015–2016 campaign in Beijing followed recommendations of the World Health Organization (WHO) for the 2015–2016 influenza season in the northern hemisphere, including an A/California/7/2009 (H1N1)pdm09-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus, and a B/Phuket/3073/2013-like virus (of the B/Yamagata/16/88 lineage) [21]. However, global influenza surveillance showed circulation of influenza B/Victoria lineage rather than B/Yamagata in the mid and late season. Also, two newly emerging genetic clades 6B.1 and 6B.2 of influenza A(H1N1)pdm09 viruses predominated in the northern hemisphereas reported by WHO in February 2016 lay [10]. These mismatches could have affected the influenza VE in the 2015–2016 season.

In this study, influenza vaccination data were collected from an established electronic registry system of vaccination in Beijing [22]. We describe the genetic and antigenic features of representative strains circulating in Beijing in the 2015–2016 influenza season, and we assess the component-specific VE of the 2015–2016 TIV used in Beijing, accounting for the effects of prior immunization on current vaccine protection.

2. Methods

2.1. Enrollment of subjects and laboratory diagnosis

Details of the VE network design, sites, and enrollment procedures in Beijing have been described previously [8,23]. Influenza-like-illness (ILI) patients (i.e., temperature ≥ 38 °C and either cough or sore throat) aged ≥6 months seeking outpatient medical care were enrolled at 23 sentinel hospitals in Beijing. Convenience sampling was used to select subjects. According to the unified procedure and the sample size requirements stated in the documents issued by the national health administrative authority of China and the local health administrative authority of Beijing, in each sentinel hospital, pharyngeal swabs from 20 or more patients with ILI who visited the outpatient clinic were collected by trained nurses per week. Since ILI patients in Beijing were used to seek medical attention at hospitals rather than at private clinics, these patients may involved both mild and severe cases. Pharyngeal specimens collected were sent to 18 collaborating laboratories managed by Beijing CDC within 24 h, and were tested by real-time reverse transcription–polymerase chain reaction (rRT-PCR) using PCR procedures recommended by the WHO Collaborating Center for Reference and Research on Influenza at the Chinese National Influenza Center (CNIC).

Test-negative case-control design was used to estimate influenza VE. Cases were patients who tested positive for influenza viruses. Controls were patients who tested negative for influenza viruses. Since annual influenza immunization campaigns across Beijing typically commence in mid-October, with vaccinees considered immune 14 days after vaccination, and increased influenza virus circulation usually begins in early November, ILI patients with onset of medically attended ILI between November 1, 2015, and April 30, 2016, were eligible for inclusion in the primary VE analysis. According to the recommended immunization schedule, 1 dose of adult influenza vaccine was used in people aged ≥3 years, and 2 doses of the influenza vaccine for children were used in infants and young children aged 6–<36 months Participants aged ≥3 years were considered vaccinated if they received the 2015/16 influenza vaccine at least 14 days before illness onset, and those who did not receive influenza vaccine in the current season or received it <14 days before illness onset were considered unvaccinated; those aged 6–<36 months were considered vaccinated only if they received two doses of influenza vaccine at least 14 days before illness onset. Patients were excluded if they had been vaccinated within 14 days before symptom onset. The specifics of inclusion and exclusion criteria applied to the study are shown in Fig. 1.

2.2. Data collection

Information on enrolled patients was recorded by nurses using a standard questionnaire at the time of specimen collection, including demographic characteristics, onset date, specimen collection date, comorbidities and influenza vaccination status within the prior 6 months. Vaccination status was collected from the Beijing Management System of Information on Immunization Program. The reporting form was sent to the collaborating laboratory, along with the respiratory specimens. Comorbidities included asthma, pulmonary tuberculosis, pulmonary fibrosis, chronic obstructive pulmonary disease, diabetes mellitus, cardiac-cerebral vascular disease, cancer, anaemia, chronic hepatitis, chronic kidney disease, immune system disease, neurological disorders. Two strata were used for evaluating VE homogeneity: no high-risk comorbidities, and one or more high-risk comorbidities. Interval (days) between illness onset and specimen collection was stratified to two groups: ≤3 days and >3 days.

2.3. Virus characterization

Six A(H1N1) 09pdm, 16 A(H3N2), and three B/Victoria strains isolated in 2015–2016 were randomly selected and sequenced. Viral RNA was extracted using QIAmp Viral Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. For each strain, reverse transcription and amplification of HA gene were carried out as described previously [24,25]. PCR products were sequenced by ABI Prism 3130xl automated sequencer (Applied Bio systems, Foster City, USA). Another six HA genes from A (H1N1) 09pdm strains isolated in 2015–2016 and sequenced previously were also included in this study. Nucleotide sequences were assembled and then aligned by MEGA software (ver. 6.0.4). Neighbor-joining (NJ) phylogeny trees were inferred with 1000 bootstrap replications.

2.4. Data analysis

Questionnaire data were entered using EpiData software (version 3.1; The EpiData Association, Odense, Denmark), and data were analyzed using SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA). Participant characteristics and vaccination status of cases and controls were compared using $\chi 2$ tests. Univariable and multivariable logistic regression models were used to estimate odds ratios (ORs) comparing vaccination status of cases and con-

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