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The effectiveness of influenza vaccination against medically-attended illnesses in Hong Kong across three years with different degrees of vaccine match, 2014–17

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ABSTRACT

Background: Influenza vaccination is the most effective intervention to prevent influenza virus infections. Vaccine effectiveness (VE) can vary due to factors such as matching between vaccine strains and prevailing strains, age and other characteristics of the vaccine recipients.
Objective: To evaluate influenza VE against medically-attended illness in different age groups and against specific influenza types/subtypes in Hong Kong.
Methods: A test-negative study was conducted from December 2014 through August 2017 in 20 outpatient clinics. Patients at least 6 months of age presenting with at least two symptoms of acute respiratory illness, ARI (fever ≥37.8 °C, cough, sore throat, runny nose, headache, myalgia and phlegm) within 72 h of onset were tested for influenza virus by reverse transcription polymerase chain reaction (PCR). Vaccination history was assessed by self-report or medical records at the clinics. VE against medically-attended illness was estimated using conditional logistic regression for influenza PCR result versus vaccination history, matching by calendar time and adjusting for age, age-squared, sex, and chronic medical illness. Additional analyses examined VE by age group and by influenza type/subtype.
Results: We enrolled 2566 patients, of whom 1118 (43.6%) tested positive for influenza A or B virus by PCR. Test-positive subjects were generally older, more likely to present with one of the symptoms of ARI, and less likely to receive vaccination against influenza. VE estimates for influenza A(H1N1), A (H3N2), B/Yamagata and B/Victoria were 61.6% (95% confidence interval, CI: 21.8%, 81.1%), 26.4% (95% CI: −1.3%, 46.6%), 67.0% (95% CI: 25.9%, 85.3%), 60.4% (95% CI: 0.3%, 84.3%), respectively. Estimates of VE by age group were generally higher in adults aged 50–64 and lower among children and older adults.
Conclusions: VE against medically-attended influenza was moderate in Hong Kong, confirming the impact of influenza vaccination in reducing disease burden. The reduced VE for influenza A(H3N2) is a continuing concern.

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1. Introduction

Influenza virus infections are associated with a substantial burden of morbidity and mortality worldwide [1]. In Hong Kong, a subtropical city with a population of 7.3 million, it has been estimated that influenza causes an average of 430 respiratory deaths and 12,700 respiratory hospitalizations each year [2]. Vaccination is generally recognised as the most effective intervention to prevent influenza virus infections. In Hong Kong, influenza circulates for most of the year with epidemics almost every winter, as well as spring or summer epidemics in many years [2]. Hong Kong uses the northern hemisphere formulation and conducts annual influenza vaccination campaigns each year in October through December, covering around 10% of the population in recent years [3]. The local government provides subsidized or free influenza vaccination for target groups including children aged 6 months to 5 years (extended to 11 years since 2016/17), pregnant women, persons with chronic medical conditions, people aged 65 years or above, and long-stay residents of institutions for persons with disability [4].

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Influenza vaccine effectiveness (VE) may vary from year to year and in different settings. Important factors that can affect VE include age and medical conditions of the vaccine recipients, and the degree of matching between vaccine strains and prevailing strains in the community [5–8]. Continuous monitoring of influenza VE can provide evidence to support vaccination policy. Locally, we have monitored influenza VE against hospitalization in children for almost 10 years [9–12], but there are no available data on VE against medically-attended illnesses in children outpatients, or illness of any severity in adults in Hong Kong. We therefore established a test-negative study in local private outpatient clinics from December 2014 to August 2017 to estimate influenza VE against medically-attended illness for children and adults.

2. Methods

2.1. Study design

We conducted this study in 20 private outpatient clinics in Hong Kong Island, Kowloon and the New Territories, i.e. spread geographically across the whole of Hong Kong. We enrolled patients ≥6 months of age who presented with at least two symptoms of acute respiratory illness (ARI) including fever ≥37.8 °C, cough, sore throat, runny nose, headache, myalgia and phlegm, within 72 h of illness onset. A nasal swab and a throat swab were obtained from each patient and maintained at 4–8 °C before delivery to a central laboratory within 24 h of collection. Specimens were preserved at −80 °C on receipt at the laboratory, and later thawed for testing in batches. Information regarding demographics, clinical signs and symptoms, influenza vaccination history, and history of chronic medical conditions were also collected in a structured interview.

2.2. Ethical approval

The study received ethical approval from the Institutional Review Board of Hong Kong University. Written informed consent was obtained from all patients aged 18 years and older, and proxy written informed consent was obtained from parents or legal guardians for their children before enrollment.

2.3. Ascertainment of vaccination history

Information on seasonal influenza vaccination, including the date and type of vaccination received for the previous and current year, was reported by all patients or by their parents or legal guardians, or obtained from patients' medical records at the clinics if available. Patients who received vaccination for the year of participation and with the last dose more than 2 weeks before participation were considered as vaccinated, or otherwise were classified as unvaccinated.

2.4. Laboratory testing

For patients enrolled between 22 December 2014 and 31 March 2017, nose and throat swabs were tested separately for influenza A and B by PCR, and a positive result on either specimen was taken as evidence of influenza virus infection. For patients enrolled after 31 March 2017, nose and throat swabs were pooled prior to testing by PCR. We used EasyMag (Biomerieux) for total nucleic acid extraction and tested for the presence of influenza A and influenza B viral RNA using one-step reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assays targeting the conserved region in matrix gene of influenza A and influenza B viruses. All influenza A and B positives detected were then subtyped for A(H1), A(H3), B/Yamagta and B/Victoria. Screening and subtyping RT-qPCR assays were performed according to the WHO protocol and influenza B M gene assay was performed according to our earlier study [13,14].

2.5. Statistical analysis

We used conditional logistic regression to compare the odds of influenza vaccination for the present season among patients with PCR-confirmed influenza overall and by influenza type/subtype versus those who tested negative for influenza, matched by calendar time (two-week interval) of the illness onset date, and adjusted for age, age-squared, sex, and presence of chronic medical illness. VE against medically-attended illness was then estimated as 100% multiplied by (one minus the adjusted conditional odds ratio). In further analyses, we stratified VE estimates by age group. VE estimates were regarded as "not available" for reporting when the 95% confidence interval of estimated VE is wider than 100%. All statistical analyses were performed using R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Six influenza epidemics were captured during the study period. Fig. 1 shows the timeline of subject recruitment in this study and a comparison with the local influenza virus activity from the Centre for Health Protection. A total of 2566 patients were recruited from 22 December 2014 through 31 August 2017, with patients recruited throughout the year and influenza detections almost year-round (Fig. 1). 1118 (43.6%) of the patients tested positive for influenza A or B by PCR. Patients testing positive were older, more likely to present within a shorter interval since illness onset, and to present with one of the symptoms of fever ≥37.8 °C, cough, sore throat, runny nose, headache, myalgia and phlegm than patients testing negative. All the influenza vaccinations that the patients received for the seasons of participation were inactivated, with 197 (54.6%) of the patients known to have received quadrivalent vaccine and 71 (19.7%) received trivalent vaccine. Influenza vaccination uptake was higher in older adults and among test-negative patients. A detailed comparison of characteristics between test-positive and test-negative patients is shown in Table 1. Among the 2566 patients, 14 (0.5%) who had uncertain vaccination status were excluded from further analysis. Therefore, 2552 patients (99.5%) were retained in the analyses for VE.

Over the entire study period, the overall VE against influenza A and B combined was estimated to be 37.9% (95% CI: 19.3%, 52.2%). The VE estimates for influenza A(H1N1), A(H3N2), B/Yamagata and B/Victoria were 61.6% (95% CI: 21.8%, 81.1%), 26.4% (−1.3%, 46.6%), 67.0% (25.9%, 85.3%), 60.4% (0.3%, 84.3%), respectively (Table 2). For A(H3N2), the subtype-specific VE were generally higher for the years 2015–2016 (39.9%, 95% CI: −50.6, 76.0) and 2016–2017 (27.9%, 95%CI: −11.0, 53.2) comparing with 2014–2015 (18.0%, 95%CI: −46.4, 54.0). By comparing the epidemic strains in northern hemisphere reported in literature with the influenza vaccine strains recommended by the WHO for northern hemisphere each year, the vaccine strains generally matched with the epidemic strains, except when there was a major mismatch between the recommended vaccine strain and the prevailing epidemic strain, causing a large local epidemic between January and March in 2015 (Table 3). Influenza vaccine recommended for southern hemisphere summer in 2015 was provided to local older adults aged 75 or above in May and June 2015 [15], but only 16 patients in our study reported receipt of this vaccine. The age-related pattern of VE for each influenza type and subtype is shown in Table 4. The age-stratified point estimates suggested that VE was generally

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