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The effectiveness of influenza vaccination in preventing hospitalizations in elderly in Beijing, 2016–18

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ABSTRACT

Background: Influenza vaccinations play an important role in preventing influenza related hospitalizations. The objective of this study was to estimate the effectiveness of vaccination in protecting Beijing residents aged ≥60 years from influenza related hospitalizations during the 2016/17 and 2017/18 influenza seasons.

Methods: Patients who met the definition of severe acute respiratory infection (SARI) and were hospitalized in the nine sentinel hospitals in Beijing during the 2016/17 and 2017/18 influenza seasons were identified as the study population. The vaccination status of patients was obtained from a vaccination registry. Real-time reverse transcription polymerase chain reaction (RT-PCR) experiments were conducted to test pharyngeal or lower respiratory tract samples collected from SARI patients for influenza A and B viruses. Vaccine effectiveness (VE) was examined using a test-negative design that compare the odds of vaccination among influenza positives and negatives, adjusting for calendar week of illness onset, age, and underlying medical conditions.

Results: We identified 50,364 patients in the study, in which there were 145 influenza cases and 528 influenza-negative controls aged ≥60 years in 2016/17 season and 149 cases and 358 controls aged ≥60 years in 2017/18 season. The most commonly identified subtype among participants was influenza A(H3N2) in 2016/17 and 2017/18 season (78.5% and 70.6%). Among the adults aged ≥60 years, the adjusted VE of vaccination against any influenza virus for serious acute respiratory infection (SARI) patients was 32.8% (95% confidence interval [CI]: −22.0 to 63.0%) in 2016/17 season. While the adjusted VE in 2017/18 season were 4.6% (95% CI: −72.4 to 47.2%) against any types of influenza, 29.2% (95% CI: −92.9 to 74%) against influenza A(H1N1)pdm09, −37.7% (95% CI: −293.8; 51.9%) against influenza A (H3N2) viruses, and 3.6% (95% CI: −113.8 to 56.5%) against influenza B.

Conclusion: The influenza vaccine provided moderate protection in 2016/17 season and mild protection in 2017/18 season for influenza related inpatients of adults aged ≥60 years in Beijing.

1. Introduction

The influenza vaccine is considered as the most effective way to protect against infection and laboratory confirmed illness caused by influenza virus during regional and widespread outbreaks [1]. Vaccination is also used as an efficient measure to protect cases admitted to hospital for influenza or pneumonia, regardless of vaccine match or mismatch to circulating viruses [2]. As a result, annual influenza vaccination programs have been implemented in many countries around the world to reduce the health burdens of seasonal influenza [3].

In China, influenza vaccination is recommended to all ages except infants less than 6 months old. However, coverage was reported to be as low as 2% [4], which is considerably lower than the coverage rate suggested by the World Health Organization [5]. Beijing is located in northeastern China where influenza epidemics occur seasonally, usually from late autumn through spring of the following year [6]. To encourage vaccination among residents, the Beijing government has provided subsidized trivalent inactivated vaccine (TIV) against influenza since 2007 to older adults (≥60 years) and all primary and secondary school students

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(normally aged 6–18 years) [7]. However, many factors can affect the influenza vaccine effectiveness (VE), such as the similarity between the vaccination strains and the viruses circulating during the influenza season. VE varies annually. For example, vaccinations in the 2013/14 season reduced influenza-associated hospitalizations by 47% [6]. While in 2014/15 and 2015/16 seasons, the overall VE fell to 5% and lower [6,8]. Although the influenza VE varied significantly by season, geographic location, influenza type/subtype and age [9–11], it was still the most effective preventative measure against influenza and is currently the primary recommendation for preventing seasonal influenza worldwide [12]. Small increases in influenza VE would dramatically decrease the number of hospitalizations related to influenza as well as other associated functional declines during a severe season [13]. It is important to conduct ongoing annual estimation of VE.

Commonly, the test-negative case control design (TND) that utilizes sentinel surveillance systems was widely used to assess influenza VE in influenza studies [14]. In this study, we used the TND methodology to estimate the influenza VE against laboratory-confirmed hospitalization in adults aged 60 years and over based on the data of 2016/17 and 2017/18 seasons from sentinel hospital influenza surveillance systems established in Beijing. This age group was selected for the reason that they are the target group for vaccination as well as the major population of inpatients.

2. Methods

2.1. Study period

The study period was determined from the week when laboratory confirmed diagnosis identified one or more positive cases of influenza A or B amongst severe acute respiratory infection (SARI) patients in two sequential weeks, till the week without any laboratory confirmed patients identified.

2.2. Population recruitment

This study was informed by data sourced from nine sentinel hospitals in nine districts in Beijing. Patients who were hospitalized in the respiratory care unit, pediatric ward, or intensive care unit (ICU) of sentinel hospitals were regarded as candidates for our study.

All inpatients aged $\geq$60 years and met the definition of severe acute respiratory infection (SARI) and hospitalized during the study period were enrolled. SARI was defined based on the WHO recommendation: an acute respiratory infection with (1) history of fever or measured fever of $\geq$38 °C, (2) cough, (3) onset within the last 10 days, and (4) requiring hospitalization. All hospitalized patients were screened for SARI by attending doctors. Within 24–48 h of hospital admittance, doctors interviewed SARI patients with standard questionnaires. Patient's demographics, medical history, clinical procedure, and treatment outcomes were also recorded. Pharyngeal swabs or lower respiratory tract samples were collected from SARI patients after receiving their verbal consent. Samples were then delivered to the respective district's Center for Diseases Control and Prevention (CDC) and tested for influenza A and B using real-time reverse transcription polymerase chain reaction (RT-PCR) experiments within 24 h of collection. In case of the delayed laboratory test, samples would be stored below −70 °C until being tested.

2.3. Confirmation of vaccination status

Only trivalent inactivated influenza vaccine (TIV) was available in Beijing during the 2016/17 and 2017/18 influenza seasons. The vaccination status of patients was acquired through a vaccination registry. Patients were identified as vaccinated if he or she had received a TIV at least 14 days prior to symptom onset in the respective season [15]. Patients who received at least one dose of influenza vaccine in the previous season were defined as vaccinated in the previous season. Patients would be excluded in either of the following situations: (1) having contraindications to influenza vaccination, (2) developing symptoms less than 14 days after vaccination, or (3) under immunosuppression status. In addition, as influenza vaccine inoculation in Beijing began from the 15th of October in both years, and it was commonly understood that the effect of vaccinations would not be sufficient until 14 days after inoculation, we excluded patients who experienced onset of illness before the 1st of November.

2.4. Statistical analysis

Conditional logistic regression models were adopted to assess the odds ratios (ORs) of vaccination among influenza positives and negatives, matching on week of onset and adjusting for presence of underlying medical conditions. VE was calculated as 100% × (1-adjusted OR). The overall VE against all influenza virus and virus type/sub-type (A(H1N1) pdm09, A(H3N2), and B) were presented separately. As vaccination status in previous influenza seasons was indicated to be able to influence the VE in current season [16], the effects of previous vaccination on seasonal influenza VE were evaluated using three categories: vaccinated only in the current season, vaccinated only in the previous season and receiving both vaccines. VE for these three groups were estimated using those who unvaccinated in both current and previous seasons as a reference. For all estimations, the adjusted VE was not further calculated for the actural vaccinated cases that were less than 5 after stratification. All statistical tests were 2-sided, and statistical significance was defined as $p < 0.05$ or the lower bound of the 95% CI for VE > 0.

2.5. Ethical consideration

The study design was approved by the Ethics Committee of Beijing CDC.

3. Results

3.1. Influenza season and demographics

During the study period, 50,364 patients were screened in nine sentinel hospitals in Beijing from 2016 to 2018. A total of 686 and 508 SARI patients aged $\geq$60 years were identified in 2016/17 and 2017/18 seasons respectively. Patients were excluded on the basis of the exclusion criteria shown in Fig. 1. Consequently, 673 patients in 2016/17 season and 507 patients in 2017/18 season were included in this study to estimate VE. The timeline of patients recruited in the study is shown in Fig. 2.

Of all the participants, 294 (24.9%) patients were tested positive for influenza A or/and B, and 886 (75.1%) were tested negative for influenza A or/and B. The characteristics of SARI patients are shown in Table 1. There were more male patients than female patients in both influenza-positive and negative patients. No significant differences were found regarding the distribution of sex and underlying medical conditions between influenza-positive and negative patients.

The proportion of patients that had been vaccinated was low, 12.8% (86/673) in 2016/17 season and 14.8% (75/507) in 2017/18 season (see Tables 2 and 3).

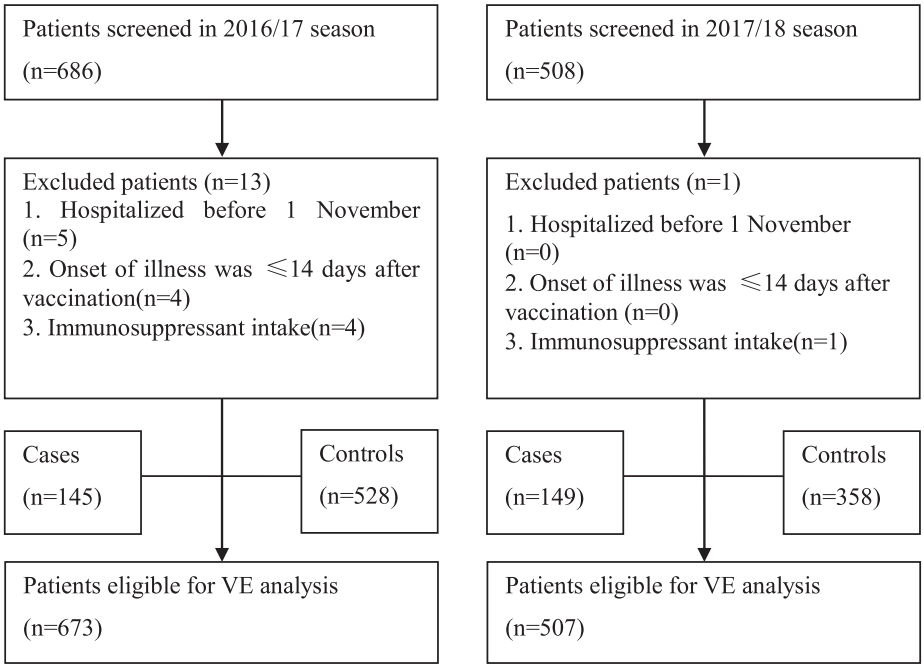

Fig. 1. Flowchart of hospital admissions included in the influenza vaccine effectiveness analysis.

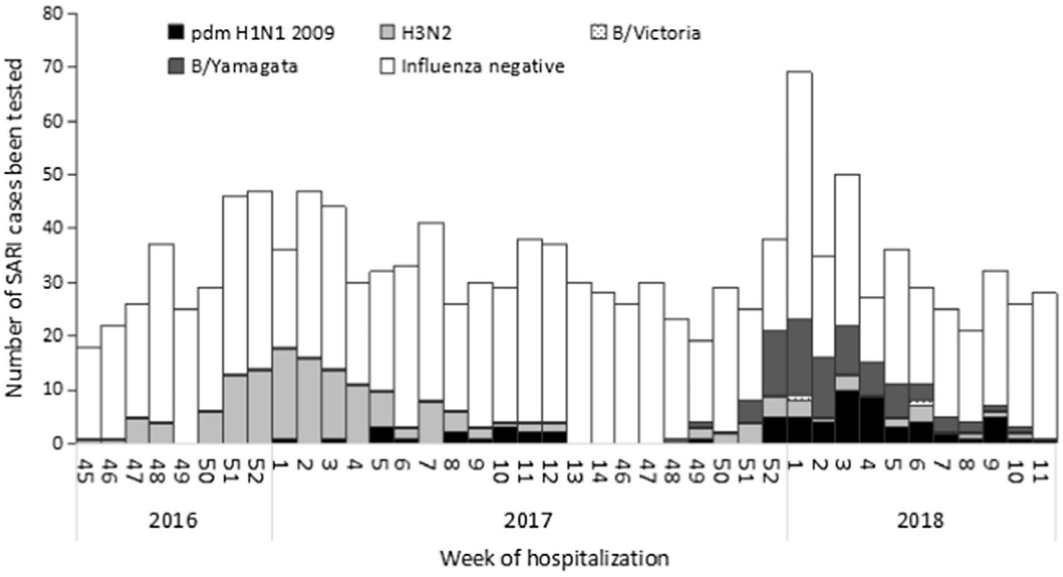

Fig. 2. Timeline of recruitment of inpatients with severe acute respiratory infection who tested positive or negative for influenza virus by type/subtype.

Table 1
Descriptive characteristics of enrolled inpatients with severe acute respiratory infection (SARI) in elderly, in 2016/17 and 2017/18 seasons, Beijing.

Characteristics	Total			2016/2017 season			2017/2018 season		
	Test-positive (n = 294) N(%)	Test-negative (n = 886) N(%)	*p*-value	Test-positive (n = 145) N(%)	Test-negative (n = 528) N(%)	*p*-value	Test-positive (n = 149) N(%)	Test-negative (n = 358) N(%)	*p*-value
Sex									
Male	157 (23.0%)	526 (77.0%)	0.073	78 (19.7%)	318 (80.3%)	0.163	79 (27.5%)	208 (72.5%)	0.293
Female	137 (27.6%)	360 (72.4%)		67 (24.2%)	210 (75.8%)		70 (31.8%)	150 (68.2%)	
Underlying medical conditions									
No	89 (25.1%)	266 (74.9%)	0.936	35 (20.6%)	135 (79.4%)	0.726	54 (29.2%)	131 (70.8%)	0.94
Yes	205 (24.9%)	620 (75.2%)		110 (21.9%)	393 (78.1%)		95 (29.5%)	227 (70.5%)	
Receipt of TIV in the current season									
No	259 (25.4%)	760 (74.6%)	0.316	129 (22.0%)	458 (78.0%)	0.478	130 (30.1%)	302 (69.9%)	0.404
Yes	35 (21.7%)	126 (78.3%)		16 (18.6%)	70 (81.4%)		19 (25.3%)	56 (74.7%)	

3.2. Influenza virus type/subtype distribution

In 2016/17 season, the number of patients who were tested positive and tested negative for influenza were 145 (21.5%) and 528 (78.5%) respectively. Among those who were tested positive, influenza A(H1N1) pdm09 and A(H3N2) accounted for 11.0% (16/145) and 89.0% (129/145),respectively.

In 2017/18 season, the number of patients that tested positive and negative for influenza were 149 (29.4%) and 358 (70.6%). Of the previous patients, 51 (35.1%), 27 (17.5%), 2 (1.3%) and 74 (48.1%) were tested positive for influenza A(H1N1) pdm09, A (H3N2), B/Victoria and B/Yamagata respectively. Among them, four patients were found to have co-infections with influenza A(H1N1) pdm09 and B/Yamagata, and two cases were identified as influenza A(H3N2) and B/Yamagata co-infected.

3.3. VE against hospitalization

In 2016/17 season, the overall adjusted VE against laboratory-confirmed influenza-related hospitalization in elderly was 32.8% (95% CI: −22.0, 63.0). The VE against A(H3N2) was 29.8% (95% CI: −30.4, 62.2). In the 2017/18 season, the total adjusted VE against hospitalization was 4.6% (95% CI: −72.4, 47.2). The VE against influenza type/subtype were 29.2% (95% CI: −92.9, 74.0) for influenza A(H1N1) pdm09, −37.7% (95% CI: −293.8, 51.9) for A(H3N2), and 3.6% (95% CI: −113.8, 56.5) for B (B/Victoria 2 (2.6%) and B/Yamagata 74 (97.4%)).

3.4. Sensitivity analysis

In both 2016/17 and 2017/18 seasons, the VE for patients who were vaccinated in the current season were not estimated as small number of influenza-positive cases that were vaccinated. The VE for patients vaccinated in 2015/16 and 2016/17 seasons were both higher than those only vaccinated in last seasons.

3.5. Genetic analysis of influenza viruses

Virus sequencing and genetic analysis of genes encoding hemagglutinin (HA) and neuraminidase (NA) were performed in our study. In the 2016/17 season, 100% (47/47) of circulating influenza A(H1N1)pdm09 belonged to clade 6B.1, which was close to the vaccine strains in genetic evolution relationship. 87.0% (39/45) of A(H3N2) circulating strains belonged to 3C.2a clade, which was the same as the clade of vaccine strain A/Hong Kong/4801/2014. While 13% (6/45) belonged to 3C.2a1 clade, which was different from vaccine strain in genetic evolutionary relationship. 100% (12/12) of the circulating strains of B/Victoria belonged to 1A clade, which was similar to vaccine strain B/Brisbane/60/2008. 100% (5/5) of the circulating strains of B/Yamagita belonged to 3 clade, which was the same as the clade of vaccine strain B/Phuket/3073/2013. However, it was not included in TIV in the 2016/17 season.

In the 2017/18 season, 95.7% (67/70) of the influenza A(H1N1) pdm09 circulating strains were similar to the vaccine strain A/Michigan/45/2015 in genetic evolutionary relationship. 62.0% (31/50) of influenza A(H3N2) circulating strains belonged to 3C.2a clade, which was the same as the vaccine stain A/HongKong/4801/2014, with 26.0% (13/50) of them belonging to 3C.2a1, and the remainder were 3C.2, 3C.3a and 3A clades. 100% (3/3) of the circulating strains of B/Victoria belonged to 1A clade, which was the same as vaccine strain B/Brisbane/60/2008. All circulating strains of B/Yamagita (39/39) belonged to the same clade as vaccine strains B/Phuket/3073/2013, which was not included in TIV in 2017/18 season.

4. Discussion

The influenza VE usually alters from year to year. In our study, the adjusted VE against influenza related hospitalization was moderate in 2016/17 season and weak in 2017/18 season.

The overall adjusted VE against laboratory-confirmed influenza-related hospitalization in adults ≥60 years differed between the two seasons. Although VE may be different from country to country, similar trends that the influenza VE dropped dramatically from 2016/17 season to 2017/18 season were observed in other studies [2,17]. Several factors influenced the protectiveness of influenza vaccination, among which the match between influenza viruses used in vaccine production and the viruses circulating in the influenza season was the most important. In our study, the match rates between circulating and vaccine strains in 2016/17 season were high for influenza A(H1N1) pdm09, A(H3N2) and B, which led to a moderate VE. Nevertheless, in 2017/18 season, the match rates of influenza A(H3N2) lowered. The proportion of B/Yamagata virus increased sharply to 42.5% among all the circulating strains, while the vaccine strain that matched the circulating strains was not included in TIV. Both factors above made great contributions to the observed weak VE in the 2017/18 influenza season. Hence, it is important to improve the accuracy of prediction for vaccine strains of the next influenza season. VE estimates against A (H3N2) viruses had been inferior to estimates against A(H1N1) pdm09 and B viruses for several years [18]. Studies showed that the VE against influenza A(H3N2) was low in both the northern and southern hemispheres for the 2016/17 and 2017/18 influenza seasons [18–20]. Analogously, in our study, the influenza VE estimates against A(H3N2) were the lowest among the estimates of all viruses in both seasons. The anti-genetic drift that was demonstrated could seriously affect the VE of seasonal influenza vaccines, and was considered as one of the vital reason for sub-optimal VE against A(H3N2) [21]. In the study, there were two kinds of A (H3N2) virus detected in circulating strains: clade 3C.2a that included the A/Hong Kong/4801/2014 vaccine strain, and subclade 3C.2a1 including virus evolved from the vaccine strain [22]. The subclade 3C.2a1 were reported as anti-genically like the vaccine virus [23], but VE estimated against it were moderate to low [24–26]. The A(H3N2) virus proportions of 3C.2a in the study

Table 2
Influenza vaccine effectiveness in preventing laboratory confirmed influenza inpatients in elderly in 2016/17 season, Beijing.

	Influenza positive		Influenza negative		Adjusted VE (95%CI)
	N	Vaccinated (%)	N	Vaccinated (%)	
All influenza	145	16 (11.0)	528	70 (13.3)	32.8% (−22.0%, 63.0%)
Subtypes					
H1	16	1 (6.3)	528	70 (13.3)	–
H3	129	15 (11.6)	528	70 (13.3)	29.8% (−30.4%, 62.2%)
Only current season	122	3 (2.5)	448	13 (2.9)	–
Only last season	129	10 (7.8)	458	23 (5.0)	−18.4% (−77.8%, 21.1%)
Both seasons	132	13 (9.9)	492	57 (11.6)	11.5% (−11.5%, 28.9%)

Table 3
Influenza vaccine effectiveness in preventing laboratory confirmed influenza inpatients in elderly in 2017/18 season, Beijing.

	Influenza positive		Influenza negative		Adjusted VE (95%CI)
	N	Vaccinated (%)	N	Vaccinated (%)	
All influenza	149	19 (12.8)	358	56 (15.7)	4.6% (−72.4%, 47.2%)
Subtypes					
H1	51	5 (9.8)	358	56 (15.7)	29.2% (−92.9%, 74.0%)
H3	27	5 (18.5)	358	56 (15.7)	−37.7% (−293.8%, 51.9%)
Influenza A	78	10 (12.8)	358	56 (15.7)	4.6% (−102.1%, 55.0%)
Influenza B	76	9 (11.8)	358	56 (15.7)	3.6% (−113.8%, 56.5%)
Only current season	128	2 (1.6)	299	11 (3.7)	–
Only last season	130	4 (3.1)	302	14 (4.6)	–
Both seasons	143	17 (11.9)	333	45 (13.5)	−0.9% (−24.6%, 18.3%)

was 87.0% in 2016/17 season, and fell to 62.0% in 2017/18 season, while the vaccine strains of A(H3N2) remained the same and belonged to the clade 3C.2a. In our study, the decrease in match rate between circulating and vaccine strains was thought to be a critical reason for the observed weak VE in 2017/18 season. In addition, according to the antigenic distance hypothesis [27], the prior vaccination may negatively interfer the current VE when the vaccine strains were the same in the two seasons and the antigenic distances between vaccine and epidemic strains were large. It was demonstrated that 82.7% of the vaccinated population in 2017/18 season were vaccinated in 2016/17 season, which might negatively affected the VE in 2017/18 season. Expectably, the A/Singapore/INFIMH-16–0019/2016 virus belonging to 3C.2a1 clade has been selected as influenza vaccines strain in the 2018 southern hemisphere and 2018/19 northern hemisphere [28] in hope of improving VE against A(H3N2). Another potential reason for the less effective vaccine immune response against circulating A (H3N2) viruses might be due to elicited genetic changes in the vaccine virus hemagglutinin protein that can arise during development in eggs [29]. For example, the mutation L194P in HA1 during the egg-based vaccine production process would shift the vaccine virus from the larger to the smaller cluster [30]. This might result in a smaller fraction of viruses inhibited by vaccines, and present with low VE [31]. Meanwhile, human serologic data in a VE study identified that the inhibition of circulating A(H3N2) viruses decreased among study population vaccinated with egg-based vaccines [2]. Therefore, greater efforts should be made to develop and enhance vaccines to improve influenza VE.

Previous influenza vaccination has been demonstrated to have certain extended effects on VE of the current season [32]. Because of the residual effects from previous seasons vaccination, the vaccination history was always considered to be indispensable in the VE assessment [24,33]. In our study, we tend to analyze the impact of repeated vaccination. However, the VE for those immunized in current season was not estimated because most immunized persons enrolled in this study were vaccinated in two consecutive seasons. Some previous studies showed that the protective effects of current season vaccination was reduced if a patient was vaccinated in the prior season. The original antigenic sin responses to influenza viruses and blunting of immune response due to repeated prior immunization were usually put forth as hypotheses of the phenomenon [34]. Nevertheless, influenza vaccination remained to be an important protective factor against influenza relating hospitalizations despite a patient's recent influenza vaccination history [33]. As the data in 2017/18 season showed that the VE for those vaccinated in both current and previous seasons was higher than those vaccinated in previous season only, and this finding is in line with the former published study [35]. It underlined the importance of current season vaccination, especially for those who were in high risk of serious complications caused by influenza infection.

Several limitations may exist in this study. First, vaccination coverage rates in both seasons were far below the average vaccination rates of the general Beijing population [7], as well as that recommended by the World Health Organization. It led to a small sample size, especially in some cases groups. The regression model might not obtain adequate statistical power to work out accurate VE estimates and confidence interval was large in our study. Second, the interval time between the onset of influenza infection and hospitalization might be quite long. This could lead to false negative results in influenza virus detection experiments. Third, there were usually several underlying medical conditions with hospitalized patients. The statistical adjustment in the regression model was usually unable to completely explain the potential impact of comorbidities on influenza-associated hospitalization. This may result in VE estimation bias.

5. Conclusion

We observe that influenza vaccinations provided moderate protection against influenza related hospitalization in elderly in the 2016/17 influenza season in Beijing. The influenza VE weakened in the following 2017/18 season. Nonetheless, influenza vaccination showed optimal protection against influenza relating hospitalization in Beijing. The authors recommend that it is vital to promote influenza vaccination coverage within the population.

Declarations of interest

None.

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