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Influenza vaccine effectiveness against hospitalizations associated with influenza A(H3N2) in Hong Kong children aged 9 months to 17 years, June-November 2023

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Abstract

A test negative study was carried out from 13 June through to 15 November 2023 enrolling 3183 children hospitalized with acute respiratory illness in Hong Kong. Influenza A and B viruses were detected in 528 (16.6%) children, among which 419 (79.4%) were influenza A(H3N2). The overall vaccine effectiveness against hospitalization associated with any influenza virus infection was

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POTENTIAL CONFLICTS OF INTEREST

BJC consults for AstraZeneca, Fosun Pharma, GSK, Haleon, Moderna, Novavax, Pfizer, Roche, and Sanofi Pasteur. SGS has consulted for Evo Health, Moderna, Pfizer and CSL Seqirus. The authors report no other potential conflicts of interest.

estimated as 22.4% (95% CI: −11.7%, 46.1%), and against influenza A(H3N2) specifically was 14.3% (95% CI: −29.2%, 43.2%). Despite the moderate to low VE estimated here, which could be a result of wanning immunity and antigenic drift, influenza vaccination remains an important approach to reduce the impact of influenza in children.

Keywords

influenza; vaccination; vaccine effectiveness; H3N2

INTRODUCTION

In Hong Kong, a subtropical city in the northern hemisphere, epidemics most frequently occur in the winter (January to March) and spring or summer but may circulate at other times as well [1]. However, influenza was absent from Hong Kong between March 2020 and March 2023 due to control measures and behavioral changes that occurred during the COVID-19 pandemic [2]. Upon relaxation of these measures, an influenza A(H1N1) epidemic occurred in April-May 2023 [3], and this was followed by a large A(H3N2) epidemic in August-September 2023.

The Hong Kong government vaccination program begins at the end of September each year, providing free or subsidized influenza vaccinations to eligible target groups, including a school outreach program that covers children aged up to 18 years. Inactivated and live attenuated quadrivalent vaccines with the Northern Hemisphere vaccine formulation were available for the 2022/23 influenza season. The objective of this study was to provide an estimate of influenza vaccine effectiveness (VE) against influenza-associated hospitalization in children in Hong Kong during an A(H3N2) epidemic in June-November 2023.

METHODS

Data sources

An ongoing test-negative study is being prospectively conducted in three large hospitals in Hong Kong [4, 5]. Each hospital enrolled children admitted to the pediatric ward with febrile acute respiratory illness defined as having a fever of ≥38°C and a respiratory symptom such as a runny nose, sore throat, or a cough with symptom onset within 72 hours. Children between six months up to nine years of age who have never been vaccinated before are advised to receive two doses, each administered at least four weeks apart [6]. Given the time required to ensure adequate immunity is developed, we excluded children below 9 months of age in this study. Nasopharyngeal aspirates or swabs were collected for all patients and tested for influenza and other respiratory viruses using a multiplex PCR assay and/or the FilmArray Respiratory Panel (BioFire/bioMérieux, Salt Lake City, UT) [7].

Information on the receipt of vaccination was obtained from parents or legal guardians using a standardized questionnaire. Vaccinated children were those that had received a vaccine from August 2022 onwards and were vaccinated more than two weeks before hospitalization. Vaccine doses within the two weeks before hospital admission were not counted because post-vaccination immunity would not yet have developed, and children

below nine years of age that should have received two doses but only received one dose were categorized as partially vaccinated and not included in statistical analyses.

Ethical approval

The study protocol was approved by the Institutional Review Board of the University of Hong Kong and the Kowloon West Cluster Research Ethics Committee. The nasopharyngeal aspirate or swab collection was part of the clinical management, and the questionnaire was voluntary, thus only verbal consent was obtained from parents or legal guardians.

Statistical analysis

The sample size was calculated assuming a 5% level of significance and 80% power. Taking the population vaccination coverage as 15% and a 20% influenza positivity, we aimed to enroll 1500 patients to detect a VE estimate of 40%. Consistent with previous years [4, 5], we used conditional logistic regression to model the association between influenza infection and vaccination status, adjusting for age, sex, underlying medical conditions, prior vaccination and matched by calendar time. VE was estimated as 1- aOR x 100%. We estimated the VE against any hospitalization associated with influenza virus infection, and also against influenza A(H3N2), specifically. A sensitivity analysis was carried out, removing those that tested positive for SARS-CoV-2 [8]. Statistical analyses were performed in R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From 13 June through 15 November 2023, 3183 children aged 9 months to 17 years of age were admitted to hospital, of which 528 (16.6%) were positive for influenza A or B. During this period, influenza A(H3N2) was the predominant influenza type/subtype with 419 (79.4%) cases, followed by 70 (13.3%) cases of influenza A(H1N1) and 31 (5.9%) cases of influenza B. A small number (n=8) of influenza A positives had an undetermined subtype (Figure 1).

The other respiratory viruses most frequently detected among the test negative controls were rhinoviruses (34.7%) and respiratory syncytial virus (11.0%) while 4.0% were positive for SARS-CoV-2. Of the 1186 patients that were vaccinated, 1152 (97.1%) received the quadrivalent inactivated influenza vaccine and 30 (2.5%) received the quadrivalent live attenuated influenza vaccine. Among the controls, 992 (37.4%) children reported receipt of an influenza vaccination, higher than the 194 (36.7%) reporting vaccination among influenza-positive cases (Table 1).

The VE against influenza A(H3N2) was estimated to be 14.3% (95%CI: −29.2%, 43.1%) which was similar to the overall VE estimate (Table 2). The age stratified VE estimates were similar between the age groups 9 month to 3 years and 4 to 8 years. The overall VE estimates and VE against influenza A(H3N2) were similar after the removal of children that tested positive for SARS-CoV-2 (Table 2).

DISCUSSION

While influenza can circulate throughout the year in Hong Kong, compared to previous years the 2023 influenza season began a few months late, overlapping with the beginning of the 2023/24 vaccination campaign. In this late influenza A(H3N2) season, we estimated a VE of 14.3% (95% CI: −29.2%, 43.1%) against pediatric hospitalizations associated with influenza A(H3N2). This estimate is similar to previous influenza seasons in Hong Kong [5]. It was lower than the range of estimates against influenza A(H3N2) from several European study sites for the 2022/23 season in children (62%–70%) [9] and lower than the influenza A(H3N2) VE reported in Chile for all ages (49%, 95% CI: 23%–67%) [10]. The 2022/23 influenza season in most of the 53 WHO European Region countries and in Chile occurred earlier than their pre-pandemic seasons and both studies reported that the circulating influenza A(H3N2) clade matched their respective vaccine formulations [9, 10].

In Hong Kong's delayed winter 2022/23 epidemic predominated by influenza A(H1N1) we also reported that the estimated VE for A(H1N1) in 2022/23 was similar to estimates of VE against A(H1N1) in the period 2010/11 through 2019/20 [3]. Natural immunity from prior infections in the unvaccinated can reduce VE estimates but given there was little to no influenza circulation for three years from March 2020 through to February 2023 in Hong Kong [2] we had anticipated higher VE estimates in 2022/23. One possible explanation for the low VE estimate against influenza A(H3N2) may be due to the late season, resulting in wanning immunity [11]. The majority (73%) of vaccinated children had received their vaccination more than six months before hospitalization. On the other hand, if many of these children were not recently infected, there may be a decreasing VE because there has been no natural protection or vaccine boosting of naturally acquired antibodies. During the study period, A(H3N2) viruses drifted away from the 2023/24 northern hemisphere vaccine antigen A/Darwin/9/2021 and the WHO has updated its recommendation to a A/Thailand/8/2022-like viruses (2a.3a.1) for the 2024 southern hemisphere formulation [12]. A majority of the sequences uploaded to GISAID by the Public Health Laboratory in Hong Kong corresponded to this new 2a.3a.1 clade. Globally, it was documented that circulating A(H3N2) viruses were becoming less well-inhibited by ferret antisera raised against egg-culture based A/Darwin/9/2021. Moreover, post-vaccination human serum panels also suggested reduced inhibition of 2a.3a.1 viruses [12]. Thus, it is possible that the vaccine provided reduced coverage of the viruses that circulated in Hong Kong during this time.

There were several limitations to this study. First, our sample size did not permit reliable VE estimation in subgroups such as age groups. Second, we were unable to estimate the VE by vaccine type, although, the majority of children in this study received the inactivated quadrivalent egg-based influenza vaccine. Vaccination history is reported by the parents or legal guardians of children and we cannot rule out misclassification of vaccination status. Every effort was made to check medical records or for the children vaccinated in schools we checked the dates and vaccination type with schools. In our study, the influenza vaccination coverage among controls was 40%, which was the same as that reported in early March for children up to 18 years old in Hong Kong [13]. Third, it has been reported that a correlation between receipt of influenza and COVID-19 vaccination could lead to bias in VE estimates [8], but in a sensitivity analyses we examined the effect of removing

SARS-CoV-2-positives and observed similar overall and subgroup VE estimates. Finally, children who were partially vaccinated were excluded from our analysis and the VE estimate might be reduced if they were included in the vaccinated group [14].

Carrying out test-negative studies in hospital settings can also be subject to limitations. Patients presenting at hospitals may be later in infection and as viral shedding decreases with time it may result in false negatives [15]. To minimize misclassification of test-positive cases and test-negative controls, we restricted enrolment in the study to within three days of symptom onset. A strength of the test-negative study design is enrolling cases and controls using the same clinical case definition, reducing the potential for differential healthcare seeking behaviors and ensuring the controls are reflective of the source population. However, biases may persist if those who do not usually engage in health seeking behaviors still seek hospital admission when severely ill [16]. Vaccination could also reduce the severity of influenza symptoms [17, 18]. In turn this could reduce the probability of being admitted to hospital among vaccinated cases [19] or reduce the detection of influenza due to reduced viral shedding [16]. If vaccination does not affect the probability of hospitalization among the controls (non-influenza ARI) the VE estimate could be overestimated [16]. Additionally, hospital admission criteria vary across countries. Admission can be judged by a clinician and may not always be related to severity, and in particular the clinical threshold for admission of younger children with influenza could be lower in Hong Kong than in some other locations, affecting the generalizability of our results.

In conclusion, we estimated a moderate to low influenza VE during a late summer influenza A(H3N2) epidemic in Hong Kong. Despite the moderate to low VE, which was suspected to be a result of waning immunity and antigenic drift, influenza vaccination remains an important approach to reduce the impact of influenza in children.

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Declaration of interests

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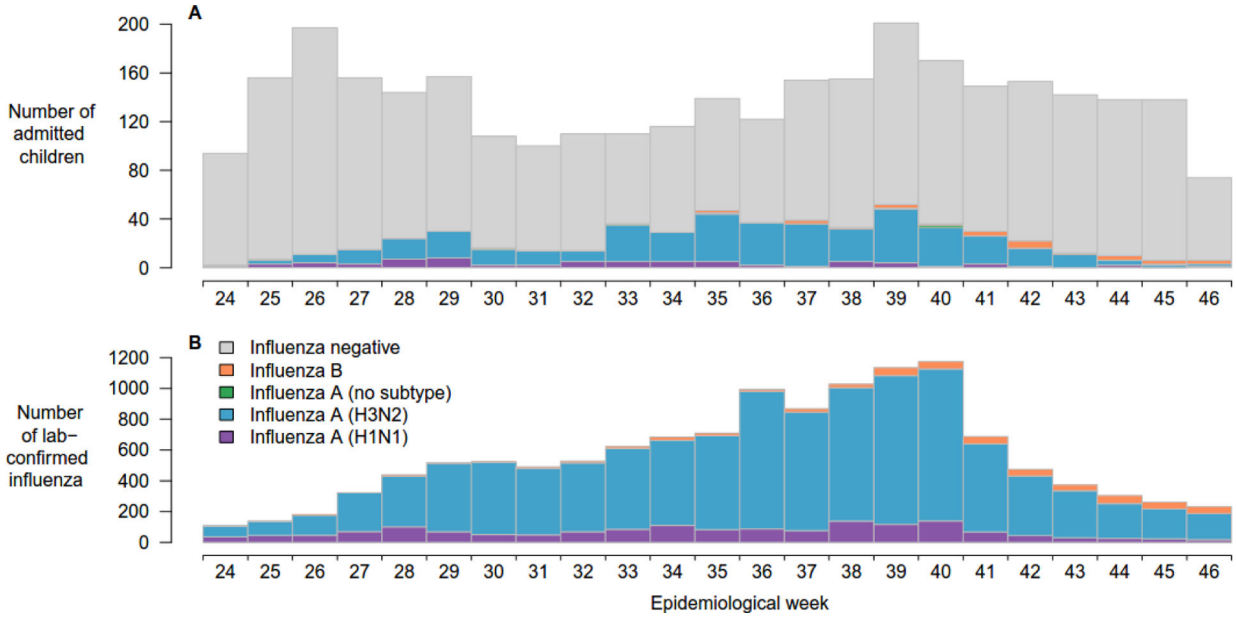

Figure 1.

Panel A shows the number of children aged 9 months to 17 years admitted to hospital between June and November in Hong Kong. Panel B shows the number of laboratory-confirmed influenza cases in the community reported by the public health laboratory services in Hong Kong for the same period.

Table 1.

Characteristics of children hospitalized and included in our study.

Variable	Influenza positive (n=528)	Influenza negative (n=2655)	p-value
Male n (%)	313 (59.3%)	1492 (56.2%)	0.208
Female	215 (40.7%)	1163 (43.8%)	
Age group n (%)			
9m-3y	146 (27.7%)	1255 (47.3%)	<0.001
4–8y	244 (46.2%)	1102 (41.5%)	
9–17y	138 (26.1%)	298 (11.2%)	
Underlying conditions			
Lung diseases *	13 (2.5%)	157 (5.9%)	0.062
Cardiac diseases	3 (0.6%)	11 (0.4%)	
Immunosuppressive disorders	0 (0.0%)	4 (0.2%)	
Other	6 (1.1%)	23 (0.9%)	
Receipt of influenza vaccine n (%)			
9m-3y	17 (11.6%)	242 (19.3%)	<0.001
4–8y	115 (47.1%)	598 (54.3%)	
9–17y	62 (44.9%)	152 (51.0%)	

* the most common lung disease was asthma

Table 2.

Vaccine effectiveness estimated against influenza-associated hospitalization against all influenza and against influenza A(H3N2), by age, and in a sensitivity analysis removing children positive for SARS-CoV-2.

	Total	Influenza positive			Influenza negative			Vaccine effectiveness*	
		nvac	N	Proportion vaccinated (%)	nvac	N	Proportion vaccinated (%)	%	95% CI
Any influenza									
All ages (9m-17y)	3183	194	528	36.7	992	2655	37.4	22.3	−11.9 to 46.0
9 months to 3 years	1401	17	146	11.6	242	1255	19.3	32.7	−28.7 to 64.9
4 to 8 years	1346	115	244	47.1	598	1102	54.3	13.2	−46.1 to 48.4
9 to 17 years	436	62	138	44.9	152	298	51.0	8.8	−129.8 to 63.8
All influenza, removing SARS-CoV-2 positives									
All ages (9m-17y)	3074	193	526	36.7	963	2548	37.8	24.4	−9.0 to 47.6
9 months to 3 years	1333	17	145	11.7	233	1188	19.6	34.9	−24.3 to 65.9
4 to 8 years	1328	115	244	47.1	584	1084	53.9	10.3	−51.3 to 46.8
9 to 17 years	413	61	137	44.5	146	276	52.9	26.3	−91.4 to 71.6
Influenza A(H3N2)									
All ages (9m-17y)	3074	164	419	39.1	992	2655	37.4	14.3	−29.3 to 43.1
9 months to 3 years	1362	14	107	13.1	242	1255	19.3	27	−53.0 to 65.2
4 to 8 years	1295	98	193	50.8	598	1102	54.3	−2.8	−86.7 to 43.4
9 to 17 years	417	52	119	43.7	152	298	51.0	11.3	−148.4 to 68.4
Influenza A(H3N2), removing SARS -CoV-2 positives									
All ages (9m-17y)	2965	163	417	39.1	963	2548	37.8	16.7	−26.0 to 44.9
9 months to 3 years	1294	14	106	13.2	233	1188	19.6	29.2	−47.8 to 66.1
4 to 8 years	1277	98	193	50.8	584	1084	53.9	−6.7	−94.4 to 41.5
9 to 17 years	394	51	118	43.2	146	276	52.9	31.5	−99.0 to 76.4

*Estimated as (1 minus the adjusted conditional odds ratio)x100%, with adjustment for age, sex, underlying medical conditions, prior vaccination and conditioning on calendar time.