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BRIEF REPORT

Influenza Vaccine Effectiveness Against Influenza-Associated Hospitalization in Hong Kong Children Aged 9 Months to 17 Years, March–June 2023

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In March–June 2023, we conducted a test-negative study in 1671 children who were hospitalized with acute respiratory illness in Hong Kong. Two hundred and eighty-six children (17.2%) were tested positive for influenza virus including 188 with A(H1N1). We estimated influenza vaccine effectiveness against influenza-associated hospitalization as 69.6% (95% confidence interval: 49.3%, 81.7%).

Key words. influenza; vaccination; vaccine effectiveness.

INTRODUCTION

Between March 2020 and February 2023, influenza laboratory detections in Hong Kong were limited to sporadic cases mostly in arriving travelers and children who had recently received live attenuated influenza vaccine [1, 2]. Public health measures used to suppress COVID-19 transmission during this period included travel restrictions, social distancing measures, and a mask mandate in public areas. The mask mandate was the last measure to be relaxed, on March 1, 2023, and influenza virus detections in the community began to increase shortly thereafter.

In Hong Kong, most influenza vaccines are administered through a public program which provides free or subsidized vaccination for target groups, which includes children from 6 months to 17 years of age. A school-based vaccination program began in 2018/19 for children aged 6–11 years. This program expanded in 2019/20 to children aged 3 years and older via kindergartens, and further expanded in 2022/23 to children aged 12–18 years via secondary schools. Ambulatory healthcare is largely delivered through the private sector, while most nonelective hospitalizations in children occur in the public sector. In our ongoing prospective study, we examined the effectiveness of influenza vaccination for preventing influenza-associated hospitalizations in children aged 9 months to 17 years in Hong Kong.

METHODS

Sources of Data

We used a test-negative study design [3] enrolling children admitted to three public hospitals: Queen Mary Hospital; Princess Margaret Hospital; and Yan Chai Hospital. These represent three of the five pediatric hospitals on Hong Kong Island and West Kowloon serving approximately 17% of children in Hong Kong. Children were eligible if they were aged 6 months to 17 years old and were admitted with febrile acute respiratory infection (those with at least one respiratory symptom and a fever measuring ≥38°C). In this study, we focus on the children at least 9 months of age rather than 6 months because the earliest a child can receive vaccination is 6 months followed by a second dose at 7 months, with additional weeks then needed for the resulting protection to accrue. We collected nasopharyngeal aspirates or nasopharyngeal swabs from all enrolled children and tested for influenza viruses and other respiratory viruses, including respiratory syncytial virus, enteroviruses/rhinoviruses, parainfluenza viruses, human metapneumoviruses, adenoviruses and coronaviruses using an in-house multiplex PCR assay, and the FilmArray Respiratory Panel (BioFire/bioMérieux, Salt Lake City, UT).

Influenza vaccination history was obtained from parents or guardians of patients using a standard questionnaire and further reviewed using available vaccination records. Quadrivalent inactivated and live attenuated influenza vaccines using the 2022/23 Northern Hemisphere formulation were available for

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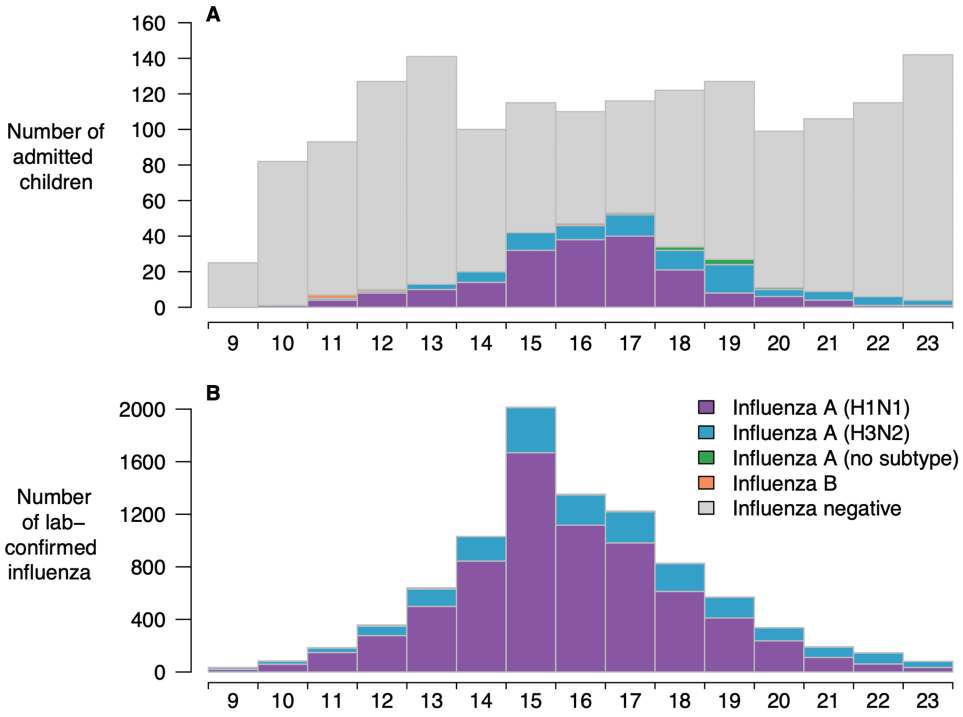

Figure 1. (A) Number of children admitted to hospital and included in our study, by influenza test result. (B) Influenza detections in the community as reported by the public health laboratory services in Hong Kong over the same period, March 1 through June 12, 2023.

use in children in Hong Kong. Children were considered vaccinated if they had received the appropriate number of vaccine doses [4] since August 2022 and more than 2 weeks before hospitalization. A small number of children <9 years of age who received one dose but had not previously been vaccinated were categorized as partially vaccinated and were removed from the analysis. We reviewed data in GISAID on influenza virus sequences over the corresponding study period to identify circulating virus clades. The study protocol was approved by the Institutional Review Board of the Hospital Authority Hong Kong West Cluster and the Hospital Authority Kowloon West Cluster Research Ethics Committee. Verbal consent was obtained from the parents or legal guardians of participants.

Statistical Analysis

We used conditional logistic regression models stratified by calendar time to estimate the odds of infection on vaccination status, adjusting for age, sex, underlying medical conditions, and prior vaccination. Influenza vaccine effectiveness (VE) was then estimated as one minus the adjusted conditional odds ratio, multiplied by 100%. We estimated VE against influenza A and B overall and against A(H1N1) specifically, with additional analyses stratified by age group. In a sensitivity analysis, we examined potential changes to estimates after removing test-negative controls who were positive for SARS-CoV-2 [5]. All statistical analyses were performed in R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From March 1, 2023 through June 12, 2023, there were 1817 children admitted who met the clinical case definition and were tested by PCR for influenza and other respiratory viruses. A total of 138 children were excluded as they were either partially vaccinated or younger than 9 months old, and eight children who tested positive for influenza C were also excluded. Among the 1671 children included in the analyses, 282 (16.9%) tested positive for influenza A, with 188 positive for A(H1N1), 87 for A(H3N2), and 4 (0.2%) tested positive for B/Victoria. Local laboratory surveillance also indicated influenza A(H1N1) was the predominant type/subtype in the general community (Figure 1).

Among the test-negative controls, the most frequently detected viruses were rhinovirus (35.2%) and respiratory syncytial virus (15.2%), while SARS-CoV-2 was detected in 6.6%. Of the 595 children that reported receipt of influenza vaccination in this study, 562 (94.4%) received the quadrivalent inactivated influenza vaccine, 27 (4.5%) received the quadrivalent live attenuated vaccine and we were unable to confirm the vaccination type for the remaining 6. Among the test-negative controls, 532 (38.4%) reported receipt of influenza vaccination (Table 1).

We estimated overall VE against influenza-associated hospitalization as 69.6% (95% confidence interval: 49.3%, 81.7%). When stratified by age, it was similar in children up to 3 years of age and in those 4–8 years of age (Table 2). We estimated

Table 1. Characteristics of Children Admitted to Hospital and Included in Our Study, By Influenza Test Result

Characteristic	Influenza Positive (n=286)	Influenza Negative (n=1385)	p-Value
Sex			
Male	156 (54.5%)	774 (55.9%)	0.73
Female	130 (45.5%)	611 (44.1%)	
Age group			
9 months to 3 years	109 (38.1%)	751 (54.2%)	<0.001
4 to 8 years	113 (39.5%)	491 (35.5%)	
9 to 17 years	64 (22.4%)	143 (10.4%)	
Underlying medical conditions			
Lung diseases[a]	7 (2.4%)	80 (5.8%)	0.004
Cardiac diseases	2 (0.7%)	7 (0.5%)	
Immunosuppressive disorders	1 (0.3%)	1 (0.1%)	
Other	0 (0.0%)	17 (1.2%)	
Receipt of influenza vaccination by age group			
9 months to 3 years	6 (5.5%)[b]	186 (24.8%)[b]	<0.001
4 to 8 years	35 (31.0%)[b]	272 (55.4%)[b]	
9 to 17 years	22 (34.4%)[b]	74 (51.7%)[b]	

[a]The most common lung disease was asthma.
[b]Denominators for age-specific vaccination coverage are the total number of children in each age group.

that VE against influenza A(H1N1) specifically was 71.4% (95% confidence interval: 47.3%, 84.5%) and similar in the age strata (Table 2). In a sensitivity analysis, noting that there was a strong correlation between receipt of COVID-19 vaccination and influenza vaccination ($P < 0.001$), we excluded SARS-CoV-2 positives from the influenza-negative comparison group, but this had a minimal influence on our VE estimates (Table 2). We identified 34 relevant virus sequences for influenza A(H1N1) uploaded to GISAID by the Public Health Laboratory Services in Hong Kong, all are from clade 6B.1A.5a.2a, the same genetic clade as the A/Victoria/2570/2019 (H1N1) vaccine virus.

DISCUSSION

We estimate high VE of 69.6% against influenza-associated hospitalization in children up to 17 years of age in Hong Kong in the 2022/23 winter, in an epidemic predominated by influenza A(H1N1) clade 6B.1A.5a.2a. Our estimates of relatively high influenza VE in children in 2022/23 are consistent with other recent reports, including against A(H1N1) in children in Europe [6] and the United States [7], while VE was also high in Canada where A(H3N2) predominated [8].

Prior to the COVID-19 pandemic, annual estimates of VE against A(H1N1) have tended to be high in this same

Table 2. Estimated Vaccine Effectiveness Against Influenza-Associated Hospitalization Against All Influenza and Against Influenza A(H1N1), By Age, and in a Sensitivity Analysis Removing Children Positive for SARS-CoV-2 From the Control Group

	Total	Influenza Positive			Influenza Negative			Vaccine Effectiveness[a]	
		n vac	N	%	n vac	N	%	%	95% CI
Any influenza									
All ages (9 m–17 y)	1671	63	286	22.0	532	1385	38.4	69.6	49.3 to 81.7
9 months to 3 years	860	6	109	5.5	186	751	24.8	81.7	53.5 to 92.8
4 to 8 years	604	35	113	31.0	272	491	55.4	61.8	12.6 to 83.3
9 to 17 years	207	22	64	34.4	74	143	51.7	60.0	−59.6 to 90
All influenza, removing controls positive for SARS-CoV-2									
All ages (9 m–17 y)	1580	63	286	22.0	510	1294	39.4	70.9	51.1 to 82.7
9 months to 3 years	810	6	109	5.5	179	701	25.5	82.2	55.0 to 93.0
4 to 8 years	584	35	113	31.0	265	471	56.3	67.6	22.9 to 86.4
9 to 17 years	186	22	64	34.4	66	122	54.1	53.4	−87.9 to 88.5
Influenza A(H1N1)									
All ages (9 m–17 y)	1573	39	188	20.7	532	1385	38.4	71.4	47.3 to 84.5
9 months to 3 years	832	4	81	4.9	186	751	24.8	82.4	46.9 to 94.2
4 to 8 years	565	22	74	29.7	272	491	55.4	66.0	6.2 to 87.7
9 to 17 years	176	13	33	39.4	74	143	51.7	65.3	−114.2 to 94.4

[a]Estimated as (1 − the adjusted conditional odds ratio) × 100%, with adjustment for age, sex, underlying medical conditions, prior vaccination and conditioned on calendar time.

prospective study [3]. Our point estimate for VE against A(H1N1) of 71.4% in 2022/23 is at the lower end of our annual point estimates for VE against A(H1N1) from 2010/11 through 2019/20 [3]. VE was highest in the youngest age group. Immunity from prior natural infections could "dilute" the effect of vaccination because unvaccinated children with prior infection would also have some degree of protection against infection. However, given that influenza did not circulate in Hong Kong between March 2020 and February 2023, unvaccinated children aged <3 years in our population are very unlikely to have had any natural exposure to influenza viruses, so our estimate of VE in children aged up to 3 years should be unaffected by any such dilution. This same benefit may not be conferred for older age groups, among whom a higher proportion of unvaccinated children could have some infection-induced immunity. Reduced VE in the youngest age groups could be attributable to waning post-vaccination immunity before the relatively late 2022/23 season [9].

In the past 5 years, a school-based vaccination program has substantially increased vaccination coverage in children in Hong Kong. Whereas vaccine uptake in the age group 3–5 years was approximately 10% in the winters of 2012/13 through 2016/17 [3], it has now risen above 50%. The school-based vaccination program also expanded to children between 12 and 18 years old during the 2022–23 season in Hong Kong with coverage about 40%. Our study focuses on estimating the direct effects of vaccination, and there should be an additional impact of this school-based vaccination program beyond the VE estimated in our study via the indirect benefits to unvaccinated children [10, 11].

There are a number of limitations to our study. We do not have an influenza vaccine registry in Hong Kong, and misclassification of vaccination history due to self-report could have biased our VE estimate. We made every effort to verify vaccination status from medical records as well as confirm the date and type of flu vaccination with schools for those children vaccinated in school. Influenza vaccination was correlated with COVID-19 vaccination in our study, potentially also reducing the risk of COVID-19 hospitalization and inclusion in our study as an influenza-negative control [5]. However there were very few children hospitalized with SARS-CoV-2 during our study period, and we did not find any effect of excluding these cases on our VE estimate (Table 2). We also excluded children who were partially vaccinated, the majority of which were in those <3 years old. Had we included them we might expect the VE estimates to be diluted. Finally, while influenza rapid tests are not yet widely used in the community, they are now available in Hong Kong and we cannot rule out that use of rapid tests at home could have affected the propensity to be admitted to hospital, for example, by facilitating earlier use of antivirals in the community.

In conclusion, in the first community influenza epidemic in Hong Kong after the COVID-19 pandemic, we estimated that influenza vaccination provided children aged 9 months to 17 years with a high level of protection against influenza-associated hospitalization. Vaccination continues to be an important public health measure to reduce the annual disease burden of influenza.

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Potential conflicts of interest. B. J. C. consults for AstraZeneca, Fosun Pharma, GSK, Haleon, Moderna, Novavax, Pfizer, Roche, and Sanofi Pasteur. S. G. S. has consulted for Moderna, Pfizer, and CSL Seqirus. The authors report no other potential conflicts of interest.

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