

1 **Influenza vaccination effectiveness in preventing influenza hospitalization in children,**
2 **Hong Kong, winter 2019/20**

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8 **ABSTRACT**

9 The winter influenza season 2019/20 in Hong Kong was predominated by influenza
10 A(H1N1)pdm09. We analysed an on-going test-negative design study consisting of 889
11 children admitted for febrile acute respiratory illness from 3 November 2019 (week 45) to 21
12 March 2020 (week 12). We estimated influenza vaccine effectiveness of 65% (95% CI: 46 –
13 78) against hospitalization due to influenza A and B combined, and 74% (95% CI: 54 – 85)
14 against hospitalization due to influenza A(H1N1)pdm09.

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16

17 Keywords: influenza, vaccine effectiveness, hospitalization, children

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19

20 **Introduction**

21 Hong Kong usually experiences year-round influenza activity, and influenza epidemics occur
22 most winters. In the 2019/20 winter influenza activity began to increase in December 2019,
23 and continued to rise through the first two weeks of January, peaking in late January, before
24 being curtailed as a consequence of the public health measures used to control the
25 coronavirus disease (COVID-19) pandemic [1]. The majority of detections in the Hong Kong
26 Public Health Laboratory Services were influenza A(H1N1), with some circulation of
27 A(H3N2) as well.

28

29 Children are recommended to receive influenza vaccination in Hong Kong. Children aged
30 <12 years are a priority group for influenza vaccination in Hong Kong, and can receive free
31 or heavily subsidised vaccination. Since October 2018, the government has provided free
32 vaccination to children including a school-based program, which has reached 34.5% coverage
33 among children aged 6 months to 5 years and 55.4% coverage among children aged 6 to 12
34 years in 2018/19 [2]. In October 2019, the school-based program was expanded to include
35 children in kindergartens and primary schools (usual enrollees about 3 to 11 years of age) to
36 increase vaccination coverage in this age group. Most vaccinated children have received the
37 Northern Hemisphere formulation of quadrivalent inactivated influenza vaccines, with a
38 small fraction receiving trivalent inactivated vaccine or the quadrivalent live attenuated
39 vaccine. The aim of this study was to provide an estimate of influenza vaccination
40 effectiveness (VE) against influenza associated hospitalization in children in Hong Kong in
41 the winter of 2019/20.

42

43 **Methods**

44 We continued an ongoing study to monitor influenza hospitalization VE in children in Hong
45 Kong using the test negative design [3-5]. We enrolled children 6 months to 17 years of age
46 in three public hospitals, namely Queen Mary Hospital, Princess Margaret Hospital and Yan
47 Chai Hospital, which together have a catchment area covering 17% of all children living in
48 Hong Kong. Children were eligible for inclusion in our study if they were admitted with a
49 febrile acute respiratory illness (ARI) defined as fever measured $\geq 38^{\circ}\text{C}$ plus any respiratory
50 symptom such as cough, runny nose or sore throat [3-5]. We collected nasopharyngeal
51 aspirates from all enrolled children and tested for influenza viruses by multiplex assay [3].

52

53 We obtained influenza vaccination history from parents or legal guardians of each parent
54 using a standardised questionnaire. Where possible we verified information on vaccination
55 status by reviewing vaccination cards and electronic medical records, and by contacting
56 private clinics. Children were categorised as vaccinated if they had received vaccination
57 within the 6 months prior to hospital admission, but at least 14 days prior to admission, and if
58 they had received the appropriate number of doses according to the Advisory Committee on
59 Immunization Practices [6]. Those who received influenza vaccination within 14 days of the
60 hospitalization or partially vaccinated were excluded from the analysis. Conditional logistic
61 regression models were used to estimate VE, matching by calendar week and adjusting for
62 age and age-squared. VE was estimated via 1 minus the adjusted odds ratio of vaccination.

63 All statistical analyses were performed in R version 3.6.2 (R Foundation for Statistical
64 Computing, Vienna, Austria).

65

66 The study protocol was approved by the Institutional Review Board of the Hospital Authority
67 Hong Kong West Cluster and the Hospital Authority Kowloon West Cluster Research Ethics
68 Committee. Verbal consent was obtained from parents or legal guardians of participants.

69

70 **Results**

71 We enrolled a total of 1039 children from 3 November 2019 (week 45) to 21 March 2020
72 (week 12) (Figure 1). We excluded children who did not have PCR results (n=29), failed to
73 receive the appropriate number of doses, or were vaccinated within 14 days prior to
74 admission (n=148), an influenza A patient with unknown subtype information, and included
75 1227 children in our analyses. A total of 198 (16.1%) children tested positive for influenza.
76 Of these, the number of children who tested positive for influenza A(H1N1)pdm09, A(H3N2)
77 and B were 132 (66.7%), 46 (23.2%) and 20 (10.1%), respectively. The proportion
78 vaccinated among influenza-negative children (28.4%, 292/1029) was higher than that among
79 influenza-positive children (18.7%, 37/198) (p=0.006) (Table 1). Similar findings were
80 observed across age groups but the difference was not significant in children 6 to 17 years of
81 age. Most of these vaccinated children received quadrivalent inactivated vaccine (n=256,
82 77.8%), a very small proportion received trivalent inactivated vaccine (n=7, 2.1%), while
83 vaccine type was unknown for 66 (20.1%) children.

84

85 The overall influenza VE against influenza A and B combined was 65% (95% confidence
86 interval (CI): 46 – 78) (Figure 2). We also estimated overall VE of 73% (95% CI: 53 – 85)
87 against influenza A(H1N1)pdm09, 12% (95% CI: -80 – 57) against influenza A(H3N2) and
88 85% (95% CI: 30 – 97). Age group-specific VE against influenza A and B combined was
89 71% (95% CI: 17 – 90) for children 6 months to 2 years of age, 64% (95% CI: 29 – 82) for
90 children 3 to 5 years of age and 44% (95% CI: -15 – 73) for children 6 to 17 years of age.

91 Similarly, age group-specific VE against influenza A(H1N1)pdm09 was estimated to be
92 higher in children 6 months to 2 years and 3 to 5 years of age, and lower in children 6 to 17
93 years of age. Age group-specific VE against influenza A(H3N2) and B was not estimated due
94 to small sample size.

95

96 **Discussion**

97 We estimated an overall VE of 74% against hospitalization due to the predominant influenza
98 A(H1N1)pdm09 strain, emphasizing the important role of influenza vaccine in preventing
99 hospitalization due to influenza A(H1N1)pdm09 in children during the 2019/20 winter season
100 in Hong Kong. Study reported that government initiated school-based vaccination program
101 has helped to increase vaccination coverage significantly in primary schools [7]. The
102 expansion of the program to kindergartens and child care centres could therefore boost
103 vaccination coverage in younger children. We could not demonstrate a significantly
104 protective VE for older children, which has also been reported in outpatients previously [8].
105 The small sample size in this age group may have limit the statistical power required to detect
106 a protective effect.

107

108 VE against influenza A(H1N1)pdm09 in season 2019/20 was comparable with previous years
109 VE (72%) in Hong Kong, estimated by pooling data from 2009/10 through 2012/13 [3]. It
110 was however lower than early VE (92%) estimated in 2018/19 [4]. Compared with VE
111 against A(H1N1)pdm09 reported by other regional VE networks, our estimate was generally
112 higher than VE reported in children outpatients in Canada (63%), US (51%) and Europe (46
113 – 51%) early this season [9-11]. Preliminary end-of-season VE by age group consistently
114 estimated lower VE in both younger and older children in the US [12].

115

116

117 Interpretation of our findings is limited by the lack of genetic or antigenic characterization
118 information. Serological data provided by the local public health agency shows that up to
119 94.4% among influenza A(H1N1) cases randomly selected during the peak of the season
120 were largely antigenically similar to the 2019/20 influenza A(H1N1) vaccine component
121 [13]. Genetic characterization indicating the emergence of A(H1N1)pdm09 strains belonging
122 to clade 6B.1A5 substantially distinct from 2019/20 vaccine strain which belongs to clade
123 6B.1A1 indicates the importance of continuous monitoring of VE [9, 14].

124

125 **Conclusions**

126 We estimated protective VE against hospitalization due to predominating influenza
127 A(H1N1)pdm09 in 2019/20. Dynamic influenza activity demands continuous surveillance in
128 order to inform public health measures.

129

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197

198 **Conflict of Interest**

199 BJC has received honoraria from Sanofi and Roche for advisory committees. The authors
200 report no other potential conflicts of interest. The funding bodies had no role in study design,
201 data collection and analysis, preparation of the manuscript, or the decision to publish.

202

203 **Contributors**

204 Authors SSC and BJC designed the study, author HC performed the statistical analyses of the
205 data, authors SSC, HC and BJC drafted the manuscript, all authors participated in the
206 interpretation of the analyses, read and approved the final version.

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209 **Figure Legends**

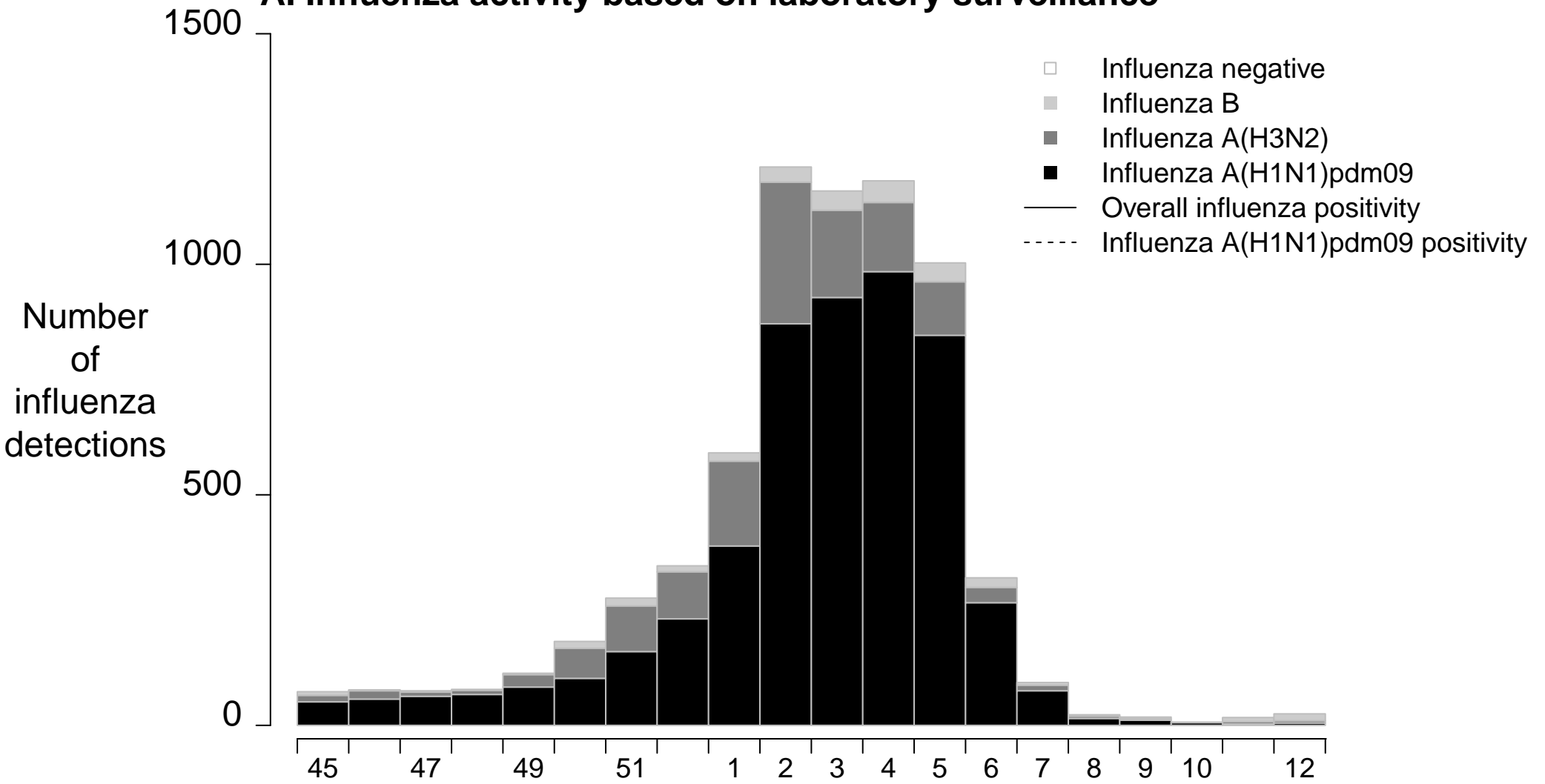
210 Figure 1. Local influenza activity by type/subtype based on laboratory surveillance in Hong
211 Kong [15] (A) and enrolment of hospitalized children into test-negative design study (B)
212 from 3 November 2019 (week 45) to 21 March 2020 (week 12).

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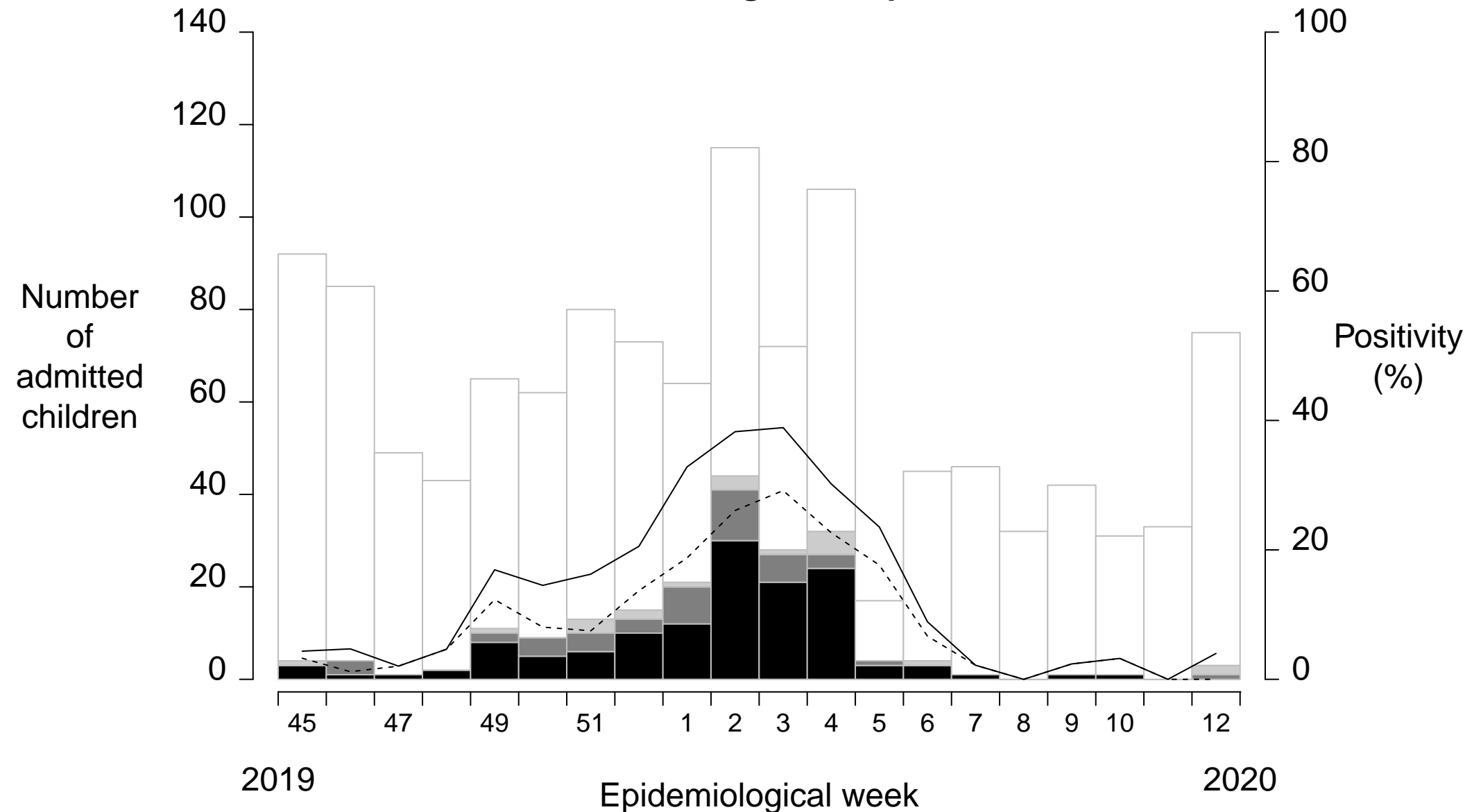
214 Figure 2. Influenza VE overall and by age strata against hospitalization due to influenza A
215 and B combined (top), and against hospitalization due to influenza A(H1N1)pdm09 (bottom).

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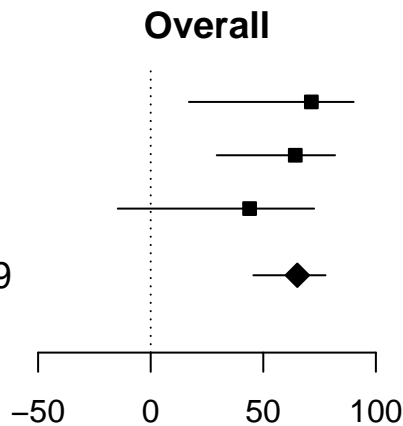
A. Influenza activity based on laboratory surveillance



B. Timeline of recruitment of eligible hospitalized children



Age group	Influenza-positive		Influenza-negative		VE (95% CI)
	Vax (%)	Total	Vax (%)	Total	
6m-2y	4 (5%)	74	88 (16%)	542	71 (17, 90)
3-5y	17 (25%)	67	104 (46%)	228	64 (29, 82)
6-17y	16 (28%)	57	100 (39%)	259	44 (-15, 73)
Overall	37 (19%)	198	292 (28%)	1029	65 (46, 78)



A(H1N1)pdm09					
Age group	Influenza-positive		Influenza-negative		VE (95% CI)
	Vax (%)	Total	Vax (%)	Total	
6m-2y	2 (4%)	57	88 (16%)	542	81 (19, 96)
3-5y	8 (19%)	43	104 (46%)	228	76 (42, 90)
6-17y	10 (31%)	32	100 (39%)	259	46 (-31, 77)
Overall	20 (15%)	132	292 (28%)	1029	74 (54, 85)

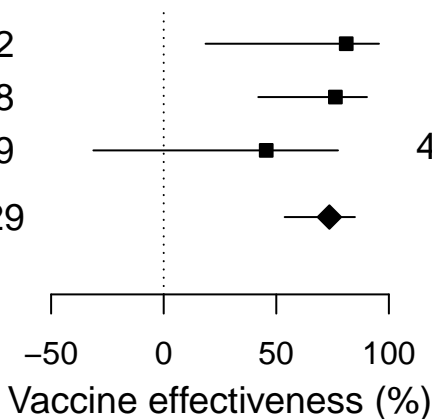


Table 1. Key characteristics of cases and controls.

Variable	Influenza-positive (n=198)	Influenza-negative (n=1029)	p-value*
Age group, n(%)			
6m – 2y	74 (37.4%)	542 (52.7%)	<0.001
3 – 5y	67 (33.8%)	228 (22.2%)	
6 – 17y	57 (28.8%)	259 (25.2%)	
Male, n(%)	104 (52.5%)	534 (51.9%)	0.932
Receipt of influenza vaccination, n(%)			
All ages	37 (18.7%)	292 (28.4%)	0.006
6m – 2y	4 (5.4%)	88 (16.2%)	0.014
3 – 5y	17 (25.4%)	104 (45.6%)	0.005
6 – 17y	16 (28.1%)	100 (38.6%)	0.179

Note: * p-value estimated by χ^2 or Fisher's exact tests whenever appropriate.