Effectiveness of partial and full influenza vaccination in children aged <9 years in Hong Kong, 2011-2019

Huiying Chua*[1], Susan S. Chiu*[2], Eunice L. Y. Chan[2], Shuo Feng[1], Mike Y. W. Kwan[3], Joshua S. C. Wong[3], J. S. Malik Peiris[1], Benjamin J. Cowling[1]

*Joint first authors

Affiliations

1. WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
2. Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital and Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
3. Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong Special Administrative Region, China

Corresponding author:

Prof. Benjamin J Cowling, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 7 Sassoon Road, Pokfulam, Hong Kong.

Tel: +852 3917 6711; Fax: +852 3520 1945; email: bcowling@hku.hk

Alternative corresponding author:

Susan S. Chiu, Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong

Tel: +852 2255 4203; Email: ssschiu@hku.hk

Running head: VE for partial influenza vaccination

Word Count (abstract): 199

Word Count (main text): 3,152

Summary (max 40 words):

Full vaccination was significantly more protective than partial vaccination in preventing children 6 months to 8 years of age against influenza-associated hospitalization, supporting the current ACIP recommendation of 2-dose regimen in previously unvaccinated children.

ABSTRACT

INTRODUCTION: Two doses of influenza vaccination are recommended for previously unvaccinated children aged <9 years, and receipt of one dose is sometimes termed "partial vaccination". We assessed the vaccine effectiveness (VE) against influenza hospitalization of partial and full influenza vaccination among children in Hong Kong.

METHODS: Using the test-negative design we enrolled 23,187 children aged <9 years admitted to hospitals with acute respiratory illness between September 2011 through to March 2019. Vaccination and influenza status were recorded. Fully vaccinated children included those vaccinated with two doses, or one dose if they were previously vaccinated. Partially vaccinated children included those who should receive two doses but received only one dose. We estimated VE using conditional logistic regression models matching on epidemiological week.

RESULTS: Overall VE estimates among fully and partially vaccinated children were 73% (95% confidence interval, CI: 69% ,77%) and 31% (95% CI: 8%, 48%), respectively. Consistently higher VE was observed in fully vaccinated children against each influenza type/subtype. VE of partial vaccination did not vary by age groups.

CONCLUSIONS: Partial vaccination was significantly less effective than full vaccination. Our study supports the current recommendation of two doses of influenza vaccination in previously unvaccinated children <9 years of age.

INTRODUCTION

Influenza is a major cause of morbidity and mortality worldwide. Children are at increased risk of influenza virus infection, and young children are at high risk of associated complications and sequelae, some of which require hospitalization [1]. Influenza in children is also associated with substantial medical costs, absenteeism from schools and loss of productivity due to care-giving by parents or guardians [2, 3].

Influenza vaccination is an essential component of the public health measures used to control influenza. A systematic review reported that vaccinated children are 43% to 69% less likely to have medically-attended influenza during the influenza season, compared with unvaccinated children, with some variation by influenza type/subtype [4]. The Advisory Committee of Immunization Practices recommends that children below 9 years of age receive two doses of influenza vaccine if they have never been vaccinated, and then one dose is sufficient in subsequent years [5-7]. The rationale for requiring two doses in the first year is because children of this age group may not yet have been exposed to natural influenza virus infections and may lack pre-existing antibodies against some or all influenza types/subtypes. Therefore, for previously unvaccinated children, the first dose of influenza vaccine is administered to prime or stimulate the immune response, followed by a second dose to achieve a protective antibody response [6, 8, 9].

The test-negative design (TND) is increasingly used for the routine monitoring of influenza vaccine effectiveness (VE), informing annual vaccination policy and facilitating scientific research into factors affecting variability in VE. Children who have been “partially vaccinated” (previously unvaccinated children who only receive one dose) are often excluded from annual VE estimation or included in analyses as unvaccinated or vaccinated [10-14]. In

tropical and subtropical locations, such as Hong Kong, where there are longer periods of influenza activity each year, we have hypothesized that children may be more frequently infected and more likely to have had one or more priming infections before the age of 9 than in other locations [15, 16]. Here, we aimed to examine the effectiveness of full and partial vaccination in children <9 years of age using data pooled across multiple seasons.

METHODS

We have been enrolling children 6 months to 17 years of age into a test-negative design (TND) study in Hong Kong since September 2011 [11, 17-20]. Between September 2011 and August 2015 we enrolled children in two public hospitals in Hong Kong: Queen Mary Hospital and Pamela Youde Nethersole Eastern Hospital. From September 2015 to present we enrolled children in three public hospitals in Hong Kong: Queen Mary Hospital, Princess Margaret Hospital and Yan Chai Hospital. These large general hospitals capture 90% of acute admissions from their surrounding local districts and provide a representative sample of children with acute respiratory illness requiring hospitalization in Hong Kong. In the present study we analyze data on children 6 months to 8 years of age admitted during the 7.5-year period from 4 September 2011 through to 15 March 2019.

Children who presented to one of these hospitals with fever (body temperature of at least 38℃) and at least one respiratory symptom such as cough, sore throat and runny nose with any duration of symptoms were eligible for recruitment. Upon enrollment, nasopharyngeal samples were collected, and influenza virus infection was confirmed by reverse-transcriptase polymerase-chain-reaction (PCR) and/or viral culture. Parents or legal guardians were interviewed to obtain vaccination status, including the dosage and type of vaccination, using

a standardized questionnaire. Vaccination records were subsequently verified using immunization records, electronic medical records, or by contacting vaccine providers.

Definition of vaccination status

Children 6 months to 8 years of age who were vaccinated with two doses of trivalent inactivated influenza vaccine (TIV) or quadrivalent inactivated influenza vaccine (QIV) at least four weeks apart, with the most recent dose received within 6 months and at least 14 days prior to admission were considered as fully vaccinated. Children who were vaccinated with at least one dose within 6 months and at least 14 days prior to admission were also considered as fully vaccinated if they have been previously vaccinated with at least one dose of seasonal influenza vaccines containing A(H1N1)pdm09 strains, regardless of changes in vaccine compositions. Most of the children who were previously vaccinated received two doses of vaccines in the subsequent season. Children who had never been vaccinated and therefore should have received two doses but instead only received one dose within 6 months and at least 14 days prior to admission were considered as partially vaccinated.

Statistical analyses

Children who were tested positive for influenza A(H1N1), A(H3N2) or B by PCR and/or viral culture were considered as influenza-positive cases, whereas those who were tested negative for influenza were considered as influenza-negative controls. Children who received the most recent vaccination dose within 14 days of admission or those with unknown vaccination status were excluded from analyses. In a sensitivity analysis we considered the former as unvaccinated. We also performed sensitivity analysis restricted to children tested using PCR.

We first compared the characteristics of cases and controls using χ^2 tests. We controlled for calendar time and age which had been identified as confounders using directed acyclic graphs [21]. To evaluate the vaccine effectiveness (VE) of full and partial vaccination, controls were matched to cases on epidemiological week to control for variations in vaccination coverage and infection risk over the influenza season. We then conducted conditional logistic regression by adjusting for age and age-squared, with the latter term allowing for potential non-linear effects of age. The exposure odds ratio is a direct estimate of the risk ratio because of the incidence density sampling approach used in the study design [22, 23]. VE was estimated as one minus the adjusted odds ratios of vaccination, multiplied by 100%. We estimated the overall VE of full and partial vaccination against influenza A and B combined, and performed subgroup analyses to estimate VE against influenza A(H1N1), A(H3N2) and B separately. VE was estimated for all children combined and by age strata: 6 months to 2 years, 3 to 5 years and 6 to 8 years of age. We compared whether there was significant difference between these two groups using an interaction test that compares the corresponding log-odds ratios in the regression model from which VEs were derived [24]. A p-value less than 0.05 indicates a significant difference between the two VE estimates.

Each influenza season was defined as the time period between the first epidemiological week in September and the last epidemiological week in August the following year, except for season 2018/19 where data up to 15 March 2019 were analyzed. All statistical analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 23,447 children aged between 6 months and 8 years old were admitted with fever and respiratory symptoms during the study period of 4 September 2011 through to 15 March

2019. After excluding 64 children without PCR or viral culture results on influenza, 181 children who received their most recent dose of influenza vaccination within 14 days of admission, and 15 children with undetermined vaccination status, there were 23,187 children remaining for inclusion in analyses including 3,852 (16.6%) children who were influenza-positive cases and 19,335 (83.4%) children who were influenza-negative controls. All except 3288 (14.2%) children were tested using PCR. Cases and controls were enrolled year-round, and there were prolonged influenza epidemics in most years, with ≥1 laboratory-confirmed influenza admission in 336/393 (85%) of weeks across the entire study period (Figure 1). In analyses we excluded the 57 weeks (1,563 controls) in which there were no influenza admissions. Among cases, children tested positive for influenza A(H1N1), A(H3N2), B, and more than one type/subtype were 1,543 (40.1%), 1,179 (30.6%), 1,119 (29.0%) and 11 (0.3%) respectively. Of 2,570 vaccinated children, 2,125 (82.7%) were classified as fully vaccinated while 445 (17.3%) were classified as partially vaccinated. The majority (n=1,602, 62.3%) were vaccinated with QIV, 204 (7.9%) were vaccinated with TIV, 6 (0.2%) were vaccinated with both TIV and QIV, and vaccine type was unknown for 758 (29.5%) vaccinated children. Because of the small number of children who received TIV, we were not able to conduct further analyses to compare TIV and QIV. As live-attenuated influenza vaccine (LAIV) was only offered during seasons 2011/12, 2012/13 and 2018/19 alongside inactivated vaccines, and the uptake of LAIV was low because it was only available in some private sector clinics.

The characteristics of influenza-positive cases were compared to the influenza-negative controls (Table 1). There were significant differences between cases and controls in terms of age and sex. The proportion of fully vaccinated cases (n=201, 5.2%) was significantly lower compared to that among controls (n=1,924, 10.0%) while no significant difference was

observed when comparing partially vaccinated cases (n=72, 1.9%) and controls (n=373, 1.9%). Among vaccinated controls, the proportion of children classified as fully vaccinated increased with age group (6 months to 2 years: 76.2%; 3 to 5 years: 89.3%; 6 to 8 years: 93.5%) while the proportion of children classified as partially vaccinated decreased with age group (6 months to 2 years: 23.8%; 3 to 5 years: 10.7%; 6 to 8 years: 6.5%).

The overall VE against influenza A and B combined was 73% (95% confidence interval, CI: 69%, 77%) for full vaccination and 31% (95% CI: 8%, 48%) for partial vaccination (Figure 2), and the protection conferred by full vaccination was significantly higher than that from partial vaccination ($p<0.001$). In children 6 months to 2 years of age, the risk of influenza-associated hospitalization was reduced by 74% (95% CI: 64%, 81%) among fully vaccinated children compared to unvaccinated children. However, statistically significant VE was not observed for partially vaccinated children of this age group (18%, 95% CI: -20%, 43%) ($p<0.001$). Similar results were observed in children 6 to 8 years of age though VEs for full and partial vaccination was not significantly different in this age group ($p>0.05$). Both full (74%, 95% CI: 68%, 80%) and partial vaccination (47%, 95% CI: 13%, 67%) provided statistically significant protection against influenza A and B combined in children 3 to 5 years of age, and in this age group we observed significantly higher protection provided by full vaccination ($p=0.01$).

In analyses by influenza type/subtype, the estimated VE for full vaccination was 85% (95% CI: 81%, 89%) against influenza A(H1N1), 55% (95% CI: 41%, 66%) against A(H3N2) and 66% (95% CI: 55%, 74%) against B virus (Figure 3). In contrast, no statistically significant effectiveness was observed for partial vaccination except against influenza A(H1N1) (48%, 95% CI: 20%, 66%). The protection conferred by full vaccination was significantly higher

than that from partial vaccination against each influenza type/subtype. Estimated VE was statistically significant against influenza A(H1N1), A(H3N2) and B in fully vaccinated children of all ages, except against influenza A(H3N2) in children 6 to 8 years of age (39%, 95% CI: -14%, 67%). Partial vaccination was only significantly effective in reducing hospitalization due to influenza A(H1N1) in children 3 to 5 years of age (56%, 95% CI: 8%, 79%). Full vaccination was significantly more protective than partial vaccination against influenza A(H1N1) and A(H3N2) in children 6 months to 2 years and 3 to 5 years of age, and also against influenza B in children 6 to 8 years of age.

In sensitivity analyses where children who received their most recent dose within 14 days prior to admission were considered as unvaccinated, similar results were observed (data not shown). Sensitivity analyses restricted to children tested by PCR also produced very similar results.

DISCUSSION

Applying the TND to multiple-season data, we demonstrated that overall protection from full vaccination against hospitalization due to influenza A and B combined was consistently higher than that from partial vaccination for children 6 months to 8 years of age in Hong Kong. Analysis by age group revealed that the effectiveness of partial vaccination was only statistically significant in children 3 to 5 years of age against influenza A and B combined, although estimates in the other age groups were less precise (Figure 2). Further subgroup analyses also showed that full vaccination protected children of all ages against influenza A(H1N1), A(H3N2) and B, except for influenza A(H3N2) in children 6 to 8 years of age, whereas partial vaccination was only protective against influenza A(H1N1) in children 3 to 5 years of age.

Our results show that full vaccination is more effective than partial vaccination in preventing influenza hospitalization in children <9 years of age. Cumulative incidence of infection increases with age, and younger children are less likely to have been immunologically primed to influenza particularly multiple types/subtypes [25]. Other studies have shown that vaccination in previously vaccinated or infected children could mount an improved immune responses compared to unvaccinated children, and it has been suggested that natural infection is more effective than vaccination in priming immune response [8, 26, 27]. However, our finding highlights the importance of the second dose to achieve a protective immune response following immunologic priming with the first dose among those who are vaccinated for the first time even up to the age of 9 years [6, 8]. We were unable to distinguish which children had previously been naturally infected, but we found no evidence that effectiveness of partial vaccination increased with age. Our findings of the differences in VE between full and partial vaccination are largely consistent with other reports where full vaccination is more protective than partial vaccination [28-44].

Although influenza A(H1N1), A(H3N2) and B often co-circulates in Hong Kong in most years [16], in subgroup analyses, we observed statistically significant VE in partially vaccinated children against influenza A(H1N1) only but not other influenza types/subtypes, but full vaccination was consistently more protective than partial vaccination against each influenza type/subtype. Our findings are consistent with a recent study that pooled data across multiple seasons and two other studies which apply the TND study to examine VE by influenza type in partially vaccinated children, though influenza A(H1N1) was not examined separately in these studies [41, 44, 45]. Contrary to our findings are some studies which reported higher VE against A(H3N2) among partially vaccinated children compared with

fully vaccinated children, possibly due to heterogeneity in prior vaccination status among partially vaccinated children [39, 40, 46]. Meanwhile, of two studies in Japan, one reported that one dose is sufficiently protective against both influenza A and B but not influenza A(H1N1) and a second dose did not confer additional protection against influenza B [38], while another reported significant VE against influenza A in partially vaccinated children though the confidence intervals overlaps with that of full vaccination and these estimates were likely confounded due to lack of adjustment for potential confounders such as age [43]. Together with a study by El Omeiri and colleagues, these 3 studies included only data from one influenza season and may have limited power to detect differences in subgroup analyses [42].

Our study shows no evidence of heterogeneity in VE among partially vaccinated children by age groups, although estimates were imprecise. The mean VE of partial vaccination against influenza A and B combined in children 3 to 5 years of age (47%) was higher than that in children 6 months to 2 years of age (18%), however these estimates were not significantly different (p=0.17). Although there is a lack of consensus on age group categorization, our findings are nonetheless consistent with many other studies which assessed age group-specific VE in partially vaccinated children [30-32, 37, 41, 44]. Similar to our studies, two studies have reported significant and higher VE in partially vaccinated children 2 to 5 years of age relative to children less than 2 years of age, but confidence intervals overlaps with each other [37, 40]. Survival analyses in a prospective study reported that VE in partially vaccinated children aged less than 2 was similar to the VE estimate including all partially vaccinated children 6 months to 8 years of age [28]. The only study that demonstrates clear differences in VE among partially vaccinated children by age group is an early case-control study where children 2 to 5 years of age were significantly better protected by partial

vaccination than children less than 2 years of age [46]. The authors suggested that older children are more likely to have a primed immune system, and were therefore sufficiently protected by one dose of influenza vaccination, while also emphasized the importance of two-dose vaccination in light of antigenic drift. However, as the proportion of partially vaccinated children decreases with age in our study, we may have limited power to detect protective VE in partially vaccinated children 6 to 8 years of age.

Our study relies on a large dataset of 23,187 children admitted to hospital across 7.5 years. However, our study is not without limitations. Despite the very large sample size, the number of partially vaccinated children of 6 to 8 years of age was small, and some age-specific estimates were uncertain particularly in type/subtype-specific analyses. Our definition of vaccination status based on a time frame of 6 months before hospitalization may lead to misclassification of vaccination status in children who were vaccinated more than 6 months before admission (e.g. vaccinated in October, admitted in July the following year), but the majority of our data are from winter epidemics (Figure 1) while most vaccines are administered between September and January and therefore any misclassification bias in VE should be minimal [47]. We did not consider potential confounders such as pre-existing medical conditions which may result in heterogeneity of VE, but we expect that children with higher risk are more likely to be fully vaccinated. Moreover, our results are consistent with a previous study which had adjusted for presence of comorbidity in their statistical model [44]. We did not have any information on prior exposure to influenza virus through natural infections which may affect immune response to vaccination. If future studies were able to collect blood samples before vaccination, this could be examined. Furthermore, VE study reporting that VE in children repeatedly vaccinated are often lower than that in children

vaccinated in current season only indicates the importance of understanding immune response in children [40].

In conclusion, full vaccination is more protective against influenza-associated hospitalization than partial vaccination. Our results support the current Advisory Committee of Immunization Practices recommendation where children below 9 years of age should receive 2 doses of influenza vaccine if they are vaccinated for the first time. While it remains a challenge to predict predominating seasonal influenza strains to be included in vaccine formulation to ensure a degree of antigenic match, efforts should be taken to encourage vaccination. Meanwhile, quite a number of children in our study had received only one dose of vaccination when they should have received two, and this high rate of partial (incomplete) vaccination should be addressed. Results from a survey conducted in Hong Kong suggested that partial vaccination in this age group is most commonly associated with unawareness of 2-dose recommendation [48], implying a potential avenue for improving compliance.

ACKNOWLEDGMENTS

We thank the doctors and nurses of Princess Margaret Hospital, and Ms Rose So at Queen Mary Hospital and Mr Wai Ting Hui at Princess Margaret Hospital for research support. The virological data were provided by the Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health, Hong Kong Special Administrative Region, China as part of the routine diagnostic service.

FUNDING

This work was supported by the Research Grants Council of the Hong Kong Special Administrative Region (project no. 17105414 and T11-705/14N) and a commissioned grant from the Health and Medical Research Fund (project no. HKS-19-E20). BJC is supported by the Harvard Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences (grant no. U54 GM088558). The funding bodies had no role in study design, data collection and analysis, preparation of the manuscript, or the decision to publish.

POTENTIAL CONFLICTS OF INTEREST

JSMP has received research funding from Crucell NV and serves as an ad hoc consultant for GlaxoSmithKline and Sanofi. BJC has received honoraria from Sanofi Pasteur and Roche. The authors report no other potential conflicts of interest.

REFERENCES

1. Gill PJ, Ashdown HF, Wang K, et al. Identification of children at risk of influenza-related complications in primary and ambulatory care: a systematic review and meta-analysis. Lancet Respir Med **2015**; 3:139-49.

2. Putri W, Muscatello DJ, Stockwell MS, Newall AT. Economic burden of seasonal influenza in the United States. Vaccine **2018**; 36:3960-6.

3. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med **2006**; 355:31-40.

4. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis **2016**; 16:942-51.

5. Frey SE, Bernstein DI, Gerber MA, et al. Safety and immune responses in children after concurrent or sequential 2009 H1N1 and 2009-2010 seasonal trivalent influenza vaccinations. J Infect Dis **2012**; 206:828-37.

6. Englund JA, Walter EB, Gbadebo A, Monto AS, Zhu Y, Neuzil KM. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. Pediatrics **2006**; 118:e579-85.

7. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018-19 Influenza Season. MMWR Recomm Rep **2018**; 67:1-20.

8. Neuzil KM, Jackson LA, Nelson J, et al. Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naive 5-8-year-old children. J Infect Dis **2006**; 194:1032-9.

9. Hurwitz ES, Haber M, Chang A, et al. Studies of the 1996-1997 inactivated influenza vaccine among children attending day care: immunologic response, protection against infection, and clinical effectiveness. J Infect Dis **2000**; 182:1218-21.

10. Jackson ML, Chung JR, Jackson LA, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 Season. N Engl J Med **2017**; 377:534-43.

11. Chiu SS, Kwan MYW, Feng S, et al. Interim estimate of influenza vaccine effectiveness in hospitalised children, Hong Kong, 2017/18. Euro Surveill **2018**; 23.

12. Blyth CC, Macartney KK, Hewagama S, et al. Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN). Euro Surveill **2016**; 21.

13. Wu S, Pan Y, Zhang X, et al. Influenza vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings: A test-negative case-control study in Beijing, China, 2016/17 season. Vaccine **2018**; 36:5774-80.

14. Flannery B, Chung JR, Monto AS, et al. Influenza Vaccine Effectiveness in the United States during the 2016-2017 Season. Clin Infect Dis **2018**.

15. Cowling BJ, Ng S, Ma ES, et al. Protective efficacy against pandemic influenza of seasonal influenza vaccination in children in Hong Kong: a randomized controlled trial. Clin Infect Dis **2012**; 55:695-702.

16. Wu P, Goldstein E, Ho LM, et al. Excess mortality associated with influenza A and B virus in Hong Kong, 1998-2009. J Infect Dis **2012**; 206:1862-71.

17. Cowling BJ, Chan KH, Feng S, et al. The effectiveness of influenza vaccination in preventing hospitalizations in children in Hong Kong, 2009-2013. Vaccine **2014**; 32:5278-84.

18. Cowling BJ, Kwan MY, Wong JS, et al. Interim estimates of the effectiveness of influenza vaccination against influenza-associated hospitalization in children in Hong Kong, 2015-16. Influenza Other Respir Viruses **2017**; 11:61-5.

19. Chiu SS, Kwan MYW, Feng S, et al. Influenza Vaccine Effectiveness Against Influenza A(H3N2) Hospitalizations in Children in Hong Kong in a Prolonged Season, 2016/2017. J Infect Dis **2018**; 217:1365-71.

20. Chiu SS, Kwan MY, Feng S, et al. Early season estimate of influenza vaccination effectiveness against influenza hospitalisation in children, Hong Kong, winter influenza season 2018/19. Euro Surveill **2019**; 24.

21. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Expert Rev Vaccines **2014**; 13:1571-91.

22. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd ed.: Lippincott Williams & Wilkins, **2008**.

23. Vandenbroucke JP, Pearce N. Case-control studies: basic concepts. Int J Epidemiol **2012**; 41:1480-9.

24. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ **2003**; 326:219.

25. Sauerbrei A, Langenhan T, Brandstadt A, et al. Prevalence of antibodies against influenza A and B viruses in children in Germany, 2008 to 2010. Euro Surveill **2014**; 19.

26. Ng S, Ip DK, Fang VJ, et al. The effect of age and recent influenza vaccination history on the immunogenicity and efficacy of 2009-10 seasonal trivalent inactivated influenza vaccination in children. PLoS One **2013**; 8:e59077.

27. Ito K, Mugitani A, Irie S, et al. Prior vaccinations improve immunogenicity of inactivated influenza vaccine in young children aged 6 months to 3 years: A cohort study. Medicine (Baltimore) **2018**; 97:e11551.

28. Ritzwoller DP, Bridges CB, Shetterly S, Yamasaki K, Kolczak M, France EK. Effectiveness of the 2003-2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. Pediatrics **2005**; 116:153-9.

29. Allison MA, Daley MF, Crane LA, et al. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003-2004 season. J Pediatr **2006**; 149:755-62.

30. Eisenberg KW, Szilagyi PG, Fairbrother G, et al. Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003-2004 and 2004-2005 influenza seasons. Pediatrics **2008**; 122:911-9.

31. Szilagyi PG, Fairbrother G, Griffin MR, et al. Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study. Arch Pediatr Adolesc Med **2008**; 162:943-51.

32. Staat MA, Griffin MR, Donauer S, et al. Vaccine effectiveness for laboratory-confirmed influenza in children 6-59 months of age, 2005-2007. Vaccine **2011**; 29:9005-11.

33. Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clin Infect Dis **2012**; 55:951-9.

34. Yang Z, Dong Z, Fu C. Seasonal influenza vaccine effectiveness among children aged 6 to 59 months in southern China. PLoS One **2012**; 7:e30424.

35. Shen S, Campitelli MA, Calzavara A, Guttmann A, Kwong JC. Seasonal influenza vaccine effectiveness in pre- and full-term children aged 6-23 months over multiple seasons. Vaccine **2013**; 31:2974-8.

36. Ferdinands JM, Olsho LE, Agan AA, et al. Effectiveness of influenza vaccine against life-threatening RT-PCR-confirmed influenza illness in US children, 2010-2012. J Infect Dis **2014**; 210:674-83.

37. Fu C, Xu J, Lin J, et al. Concurrent and cross-season protection of inactivated influenza vaccine against A(H1N1)pdm09 illness among young children: 2012-2013 case-control evaluation of influenza vaccine effectiveness. Vaccine **2015**; 33:2917-21.

441 38. Shinjoh M, Sugaya N, Yamaguchi Y, et al. Effectiveness of Trivalent Inactivated
442 Influenza Vaccine in Children Estimated by a Test-Negative Case-Control Design Study
443 Based on Influenza Rapid Diagnostic Test Results. PLoS One **2015**; 10:e0136539.
444 39. Thompson MG, Clippard J, Petrie JG, et al. Influenza Vaccine Effectiveness for Fully and
445 Partially Vaccinated Children 6 Months to 8 Years Old During 2011-2012 and 2012-2013:
446 The Importance of Two Priming Doses. Pediatr Infect Dis J **2016**; 35:299-308.
447 40. Buchan SA, Chung H, Campitelli MA, et al. Vaccine effectiveness against laboratory-
448 confirmed influenza hospitalizations among young children during the 2010-11 to 2013-14
449 influenza seasons in Ontario, Canada. PLoS One **2017**; 12:e0187834.
450 41. Ando S. Effectiveness of quadrivalent influenza vaccine based on the test-negative
451 control study in children during the 2016-2017 season. J Infect Chemother **2018**; 24:782-8.
452 42. El Omeiri N, Azziz-Baumgartner E, Thompson MG, et al. Seasonal influenza vaccine
453 effectiveness against laboratory-confirmed influenza hospitalizations - Latin America, 2013.
454 Vaccine **2017**; 36:3555-66.
455 43. Kimiya T, Shinjoh M, Anzo M, et al. Effectiveness of inactivated quadrivalent influenza
456 vaccine in the 2015/2016 season as assessed in both a test-negative case-control study design
457 and a traditional case-control study design. Eur J Pediatr **2018**; 177:1009-17.
458 44. Segaloff HE, Leventer-Roberts M, Riesel D, et al. Influenza Vaccine Effectiveness
459 Against Hospitalization in Fully and Partially Vaccinated Children in Israel; 2015-16, 2016-
460 17, and 2017-18. Clin Infect Dis **2019**.
461 45. Yeung KHT, Chan KCC, Chan PKS, et al. Influenza vaccine effectiveness in hospitalised
462 Hong Kong children: Feasibility of estimates from routine surveillance data. Vaccine **2018**;
463 36:3477-85.

46. Shuler CM, Iwamoto M, Bridges CB, et al. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004. Pediatrics **2007**; 119:e587-95.

47. Feng S, Chiu SS, Chan ELY, et al. Effectiveness of influenza vaccination on influenza-associated hospitalisations over time among children in Hong Kong: a test-negative case-control study. Lancet Respir Med **2018**; 6:925-34.

48. Lau JT, Mo PK, Cai YS, Tsui HY, Choi KC. Coverage and parental perceptions of influenza vaccination among parents of children aged 6 to 23 months in Hong Kong. BMC Public Health **2013**; 13:1026.

FIGURE LEGENDS

Figure 1. Distribution of enrolled cases (by influenza type/subtype) and controls across the study period (4 September 2011 through 15 March 2019).

Figure 2. Overall vaccine effectiveness (VE) estimates for full and partial vaccination against influenza A and B combined, for all ages combined, 6 months to 2 years, 3 to 5 years and 6 to 8 years of age.

Figure 3. Vaccine effectiveness (VE) estimates for full and partial vaccination against influenza A(H1N1), A(H3N2) and B separately by age groups.

Table 1. Comparison of characteristics between influenza-positive cases and influenza-negative controls.

Characteristics, n(%)	Influenza-positive cases (n=3,852)	Influenza-negative controls (n=19,335)	p-value
Age group			
6 months – 2 years	1600 (41.5)	11208 (58.0)	<0.001
3 – 5 years	1537 (39.9)	5886 (30.4)	
6 – 8 years	715 (18.6)	2241 (11.6)	
Male	2086 (54.2)	10944 (56.6)	0.005
Receipt of any vaccination in the preceding 6 months			
All ages	273 (7.1)	2297 (11.9)	<0.001
6 months – 2 years	87 (5.4)	1064 (9.5)	<0.007
3 – 5 years	128 (8.3)	956 (16.2)	
6 – 8 years	58 (8.1)	277 (12.4)	
Receipt of full vaccination in the preceding 6 months			
All ages	201 (5.2)	1924 (10.0)	<0.001
6 months – 2 years	48 (55.2)	811 (76.2)	<0.001
3 – 5 years	102 (79.7)	854 (89.3)	
6 – 8 years	51 (87.9)	259 (93.5)	

Receipt of partial vaccination			
in the preceding 6 months			
All ages	72 (1.9)	373 (1.9)	0.854
6 months – 2 years	39 (44.8)	253 (23.8)	0.052
3 – 5 years	26 (20.3)	102 (10.7)	
6 – 8 years	7 (12.1)	18 (6.5)	
Influenza season			
2011/12	213 (5.5)	1001 (5.2)	<0.001
2012/13	126 (3.3)	1461 (7.6)	
2013/14	163 (4.2)	953 (4.9)	
2014/15	163 (4.2)	1266 (6.5)	
2015/16	912 (23.7)	4073 (21.1)	
2016/17	775 (20.1)	4128 (21.3)	
2017/18	761 (19.8)	4270 (22.1)	
2018/19	739 (19.2)	2183 (11.3)	

488 Note: p-values were estimated using χ^2 tests.

489