Seasonal Influenza Vaccination Status Among Children With Laboratory Evidence of Pandemic H1N1 Infection

Christina A. Nelson, MD, MPH, Eric K. France, MD, MSPH,† Susan M. Shetterly, MS,‡ and Jason M. Glanz, PhD‡§*

Background: The 2009 pandemic H1N1 influenza virus emerged in March 2009 and spread rapidly, causing many thousands of deaths worldwide. A case–control study of 60 Mexican adults with H1N1 suggested that the seasonal influenza vaccine protected against H1N1 infection (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.11–0.66), but subsequent studies have had varied results and few have addressed this question in children. The objective of this study was to evaluate the effect of 2008–2009 seasonal influenza vaccination on pandemic H1N1 infection in children.

Methods: Cases (n = 165) were Kaiser Permanente Colorado inpatients and outpatients aged between 18 months and 18 years, with laboratory-confirmed pandemic H1N1 infection from May to November 2009. Controls (n = 660) were pediatric Kaiser Permanente members without documented H1N1 infection who were matched by age and gender. Seasonal influenza vaccination status was recorded for all cases and controls; conditional logistic regression analyses were used to calculate matched odds ratios.

Results: Cases were more likely than controls to have underlying chronic health conditions (45% vs. 21%, $P < 0.0001$). Pandemic H1N1 cases were neither more nor less likely to have received the 2008–2009 seasonal influenza vaccine (OR, 1.31; 95% CI, 0.92–1.88). After adjustment for chronic medical conditions and health-seeking behavior, H1N1 cases were as likely as controls to have received the 2008–2009 seasonal influenza vaccine (OR, 1.08; 95% CI, 0.75–1.57).

Conclusions: There was no overall association—either protection or risk—between seasonal influenza vaccination and medically attended pandemic H1N1 infection in children. These results have important implications for understanding influenza immunity and future public health efforts to prevent pandemic influenza.

Key Words: influenza A virus, H1N1 subtype, influenza vaccines, immunization, public health practice

(*Pediatr Infect Dis J* 2011;30: 000–000)

The 2009 pandemic H1N1 influenza virus first emerged in Mexico in March 2009 and subsequently spread rapidly throughout the world, causing more than 18,000 laboratory-confirmed deaths worldwide by May 2010.[1] Initial surveillance and serologic analyses suggested that the 2008–2009 seasonal influenza vaccine would have little protective effect against pandemic H1N1 infection.[2] Subsequent research has yielded conflicting information about the effect of the 2008–2009 seasonal influenza vaccine on risk of H1N1 infection.

Soon after the H1N1 epidemic began, a vaccine trial conducted in Australia noted that many subjects had preexisting antibodies to pandemic H1N1, even though the study had strict exclusion criteria for previous confirmed or suspected H1N1 infection. Subjects with preexisting antibodies were significantly more likely to have received the 2008–2009 seasonal influenza vaccine, suggesting that the 2008–2009 seasonal influenza vaccine had produced cross-reactive antibodies to the pandemic H1N1 virus.[3]

A subsequent case–control study conducted at a Mexican respiratory hospital showed that pandemic H1N1 cases had 0.27 times the odds of having received the 2008–2009 influenza vaccine than controls (95% confidence interval [CI], 0.11–0.66), providing further support for a possible protective effect of the seasonal influenza vaccine against pandemic H1N1. The study was conducted only in hospitalized adults, however, and vaccination status was based solely on subject recall.[4] Additionally, a study of US military personnel found a protective association between 2008–2009 influenza vaccination and pandemic H1N1 infection, particularly for severe H1N1 disease.[5]

In contrast, others have hypothesized that the receipt of annual seasonal influenza vaccinations may actually increase susceptibility to pandemic influenza strains, particularly if the vaccines are given annually for multiple consecutive years. Since infection with influenza A viruses can induce heterosubtypic immunity to antigenically distinct influenza A strains, vaccination theoretically inhibits this response by preventing influenza infection.[6] A review of 4 observational studies conducted in Canada supported this hypothesis—3 of the 4 studies indicated that prior receipt of the 2008–2009 trivalent influenza vaccine was associated with an increased likelihood of medically attended pandemic H1N1 infection (odds ratio [OR] range, 1.4–2.5).[7]

The association between seasonal influenza vaccination and immunity to pandemic influenza strains has significant public health implications. An estimated 24% of all children in the United States received the seasonal influenza vaccine during the 2008–2009 season,[8] many of whom will likely be exposed to further H1N1 waves and/or other pandemic influenza strains in the future. Therefore, it is important to understand how seasonal influenza vaccination affects protection against pandemic influenza strains. To our knowledge, there have been few published studies to date on the relationship between seasonal influenza vaccination and pandemic H1N1 infection in children. We conducted this study to determine whether the 2008–2009 seasonal influenza vaccine

Accepted for publication December 15, 2010.
From the *Department of Preventive Medicine, Colorado School of Public Health, Aurora, CO; †Population and Prevention Services, Kaiser Permanente, Denver, CO; ‡Institute for Health Research, Kaiser Permanente, Denver, CO; and §Department of Epidemiology, Colorado School of Public Health, Aurora, CO.
Supported by the Kaiser Permanente Colorado Community Benefit Initiatives Committee; and in part from the Health Resources and Services Administration (HRSA) grant D33HP02610 for Preventive Medicine Residencies (to C.A.N.).
The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of HRSA.
Address for correspondence: Eric France, MD, MSPH, Kaiser Permanente-Legacy Highlands, 10065 E. Harvard Ave, Suite 250, Denver, CO 80231. E-mail: cnelson.medicine@gmail.com.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pidj.com).

ISSN: 0891-3668/11/3007-0001
DOI: 10.1097/INF.0b013e31820bb482

affected susceptibility to H1N1 infection in children during the 2009 pandemic.

MATERIALS AND METHODS

Study Population

Kaiser Permanente Colorado (KPCO) is an integrated health care delivery model which serves approximately 500,000 members and has used electronic medical records since 1998. KPCO members in the Denver and Boulder area who were aged between 18 months and 18 years on November 1, 2009 and were continuously enrolled from October 1, 2008 to November 1, 2009 were eligible for inclusion in the study. KPCO members who were less than 18 months old on November 1, 2009 were excluded from the study since they were too young to have received the seasonal influenza vaccine the prior year. To confirm that KPCO was a source of health care for potential subjects, eligible children were excluded if they did not have at least 1 health care visit within the past year if under 2 years of age or within the past 2 years if aged 2 to 18 years.

Definition and Selection of Cases and Controls

Using KPCO medical databases, we searched for cases of laboratory-confirmed pandemic H1N1 infection in pediatric patients from March 1, 2009 to November 30, 2009. Potential cases were selected if they had at least one of the following influenza diagnostic tests performed during the study period: real-time polymerase chain reaction, direct fluorescent antibody test, or rapid influenza test (RIT). All potential cases who were admitted to the hospital or had a medical encounter in the emergency department or outpatient setting were included in the study.

The medical charts of potential cases were reviewed by a trained abstractor to evaluate test results and confirm diagnosis of influenza A/H1N1 infection. Because there was little to no seasonal influenza circulating during the study period,[9,10] a positive RIT, direct fluorescent antibody test, or real-time polymerase chain reaction for influenza A (including nonsubtypeable influenza) was attributed to H1N1 infection. Due to variations in test reporting between hospitals, we were unable to determine the type of test performed for some subjects, only whether the result was positive or negative for influenza A.

For each case, the date of H1N1 diagnosis was the index date. Each case was matched to 4 randomly selected controls by gender and age at the index date within 7 days. Controls were selected from a pool of children continuously enrolled in the KPCO health plan from October 1, 2008 to November 1, 2009. Controls were assigned the same index date as their matched case. Eligible controls did not have a record of laboratory-confirmed H1N1 infection before the index date. Vaccination status was ascertained retrospectively from the index date (given later in the text).

Data Collection

Demographic information including age, gender, race, ethnicity, and insurance status (commercial vs. Medicaid) was collected electronically for all cases and controls. Self-reported race, ethnicity, and language preference information has been collected from patients by Kaiser Permanente since 2007. Subjects were identified as having an underlying medical condition if they had an ICD-9 code for conditions that increase risk of complications from influenza[11] (Appendix, Supplemental Digital Content 1, http://links.lww.com/INF/A733) or were listed in the KPCO asthma or diabetes registries. Additionally, to examine health-seeking behavior, we calculated the rate of health care provider (HCP) contacts for each subject which included the number of all primary care visits, telephone calls, and e-mail contacts during the entire index period. For comparison, we also calculated a visit count variable that included only in-person primary care visits during the index period. The index period began on October 1, 2008 for all subjects and ended 3 days before the index date.

Information on 2008–2009 seasonal influenza vaccination status of cases and controls was collected from the electronic medical record and confirmed with chart review by a trained abstractor who was blinded to case status. For subjects who did not have a 2008–2009 seasonal influenza vaccine recorded, abstractors also reviewed their medical encounters during influenza season and available records from external facilities to find evidence of influenza vaccination from an outside facility.

Both the H1N1 influenza vaccine and 2009–2010 seasonal influenza vaccine became available in Colorado near the end of the study period, in November 2009. To determine whether these vaccines significantly affected study findings, we also collected information on H1N1 and 2009–2010 seasonal influenza vaccination of cases and controls.

Statistical Analysis

We used univariate conditional logistic regression analyses to compare baseline characteristics of cases and controls and calculate unadjusted matched odds ratios. Multivariate conditional logistic regression analyses were used to calculate matched odds ratios, adjusting for chronic medical conditions and health-seeking behavior (measured by HCP contacts).

To determine whether the 2008–2009 seasonal influenza vaccine differentially affected moderate-to-severe H1N1 infection, we conducted a subset analysis of cases admitted to the hospital or seen in the emergency department.

In addition, we performed a sensitivity analysis of cases diagnosed only from September to November 2009, when H1N1 was epidemic in Colorado and the positive predictive value of rapid influenza tests was higher.[12]

Finally, we conducted sensitivity analyses excluding cases and controls who received the H1N1 vaccine or 2009–2010 seasonal influenza vaccine at least 4 days prior to the index date.

SAS version 9.1 was used for all statistical analyses (SAS Institute, Cary, NC). The study was powered to detect an OR <0.6 or >1.7 with 80% power and alpha 0.05, consistent with the effect size seen in other studies. Power calculations were performed using Power and Sample Size software (PASS, 2008).

Human Subjects Protection

This research was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

RESULTS

A total of 56,025 subjects comprised the initial study population; 7074 subjects (12.6%) were excluded because they did not have at least 1 health care visit during the specified time period. A total of 618 subjects were tested for influenza during the study period; of those, 165 (26.7%) were positive for influenza A/H1N1.

One hundred sixty-five laboratory-confirmed cases of pandemic H1N1 infection were identified from May to November 2009 (Fig. 1), along with 660 matched controls. No cases of laboratory-confirmed H1N1 infection were identified during March and April 2009. Of the cases, 13 were hospitalized, 66 were seen in the emergency department, and 86 were seen in the outpatient setting. One of the inpatients died; the remaining cases were discharged home.

Cases were evenly distributed across 3 age categories (18 months–6 years, 7–12 years, and 13–18 years). A higher proportion of cases had select chronic medical conditions compared with controls (44.9% vs. 21.1%, $P < 0.0001$). Cases and

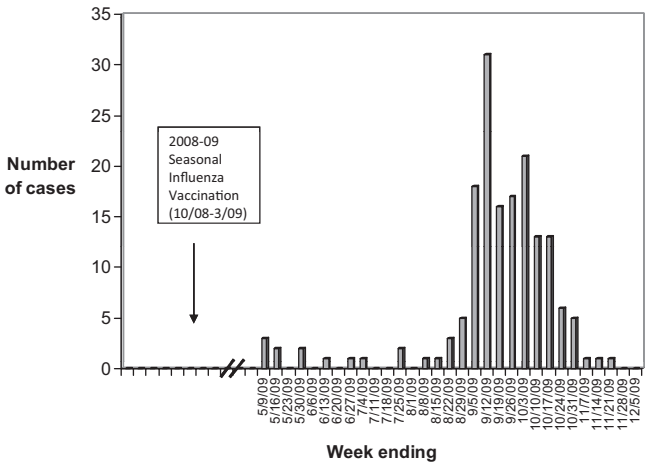

FIGURE 1. Timeline of laboratory-confirmed pH1N1 infections.

controls also differed significantly by number of HCP contacts and insurance status (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A734). There was no difference in prior season influenza vaccination status between cases and controls (47.9% vs. 41.7%, $P = 0.13$).

Table 1 summarizes the results of univariate and multivariate conditional logistic regression analyses. Univariate conditional logistic regression analysis showed that H1N1 cases were not significantly more or less likely to have received the 2008–2009 seasonal influenza vaccine (OR, 1.31; 95% CI, 0.92–1.88). After adjustment for chronic medical conditions and rate of HCP contacts, multivariate conditional logistic regression analyses showed no association between 2008–2009 seasonal influenza vaccination status and H1N1 infection (adjusted OR, 1.08; 95% CI, 0.75–1.57). As expected, both the presence of a chronic medical condition and a higher rate of HCP contacts were independently associated with laboratory-confirmed H1N1 infection in both univariate and multivariate conditional logistic regression analyses (chronic condition adjusted OR, 2.78; 95% CI, 1.90–4.07). Interestingly, presence of a chronic medical condition and rate of HCP contacts were not highly correlated (Pearson correlation coefficient, 0.14). The number of in-person primary care visits reflected total HCP contacts closely and thus was not included in final analyses.

When the effect of 2008–2009 seasonal influenza vaccination was examined in the 3 age subcategories (18 months–6 years, 7–12 years, and 13–18 years), adjusted ORs continued to show a lack of significant association.

Of the 165 total cases, 136 (82.4%) were diagnosed with H1N1 between September 1 and November 30, 2009. Univariate and multivariate conditional logistic regression analyses found that this subset of cases had no association between 2008–2009 seasonal influenza vaccination status and H1N1 infection (adjusted OR, 1.04; 95% CI, 0.69–1.56).

Seventy-nine (47.9%) of the cases were seen in the emergency department and/or admitted to the hospital. Univariate and multivariate conditional logistic regression analyses found that there was also no association between 2008–2009 seasonal influenza vaccination status and H1N1 infection in this subset of cases (adjusted OR, 1.13; 95% CI, 0.66–1.94).

None of the cases or controls received the H1N1 vaccine prior to the index date. Two cases and 14 controls received the 2009–2010 seasonal influenza vaccine at least 4 days prior to the index date. Sensitivity analyses excluding these subjects did not significantly change the study results (adjusted OR, 1.07; 95% CI, 0.74–1.56).

DISCUSSION

Although a possible protective effect of the 2008–2009 seasonal influenza vaccine has been reported in adults, we found no overall association—either protection or risk—between prior season influenza vaccination and medically attended pandemic H1N1 infection in children.

This is the first published clinical research on the effect of seasonal influenza vaccination on susceptibility to pandemic influenza infection in a large US pediatric population. Since 2008, the CDC's Advisory Committee on Immunization Practices has recommended vaccination for all children 6 months through 18 years of age against influenza, and seasonal influenza vaccination rates among children increased from 24% in 2008–2009[8] to more than 40% in 2009–2010.[13] Because millions of children receive the seasonal influenza vaccine each year and children are at significantly increased risk for pandemic influenza-related morbidity and mortality,[14,15] it is important to understand the effect of the seasonal influenza vaccine on immunity to other influenza strains.

There have been conflicting data on the relationship between seasonal influenza vaccination and susceptibility to pandemic influenza infection in adults. The variable results in adult studies may be attributable to unique effects of different vaccine types (ie, live attenuated vs. trivalent inactivated), differential bias related to various study designs, distinct study populations, or a true lack of association.

Our case-control study has advantages over previously published research on the topic. First, Kaiser Permanente is an inte-

TABLE 1. Association of 2008–2009 Seasonal Influenza Vaccination and Selected Variables With Laboratory-confirmed Pandemic H1N1 Infection

Explanatory Variable	Crude Matched Odds Ratio (95% CI)	*P*	Adjusted Matched Odds Ratio* (95% CI)	*P*
2008–2009 seasonal influenza vaccine	1.31 (0.92, 1.88)	0.13	1.08 (0.75, 1.57)	0.67
Chronic condition	3.09 (2.14, 4.46)	<0.001	2.78 (1.90, 4.07)	<0.0001
Health care provider contacts	1.09 (1.05, 1.14)	<0.001	1.07 (1.02, 1.11)	0.003
2008–2009 seasonal influenza vaccine: emergency room and inpatients only (n = 79)	1.33 (0.79, 2.24)	0.29	1.13 (0.66, 1.94)	0.66
2008–2009 seasonal influenza vaccine: September to November cases only (n = 136)	1.32 (0.89, 1.95)	0.17	1.04 (0.69, 1.56)	0.85

*Adjusted for chronic medical conditions and health care provider contacts during the index period.
CI indicates confidence interval.

grated health care delivery model with its own health care facilities, so most pediatric KPCO members are vaccinated and receive medical care at Kaiser Permanente-affiliated facilities. Second, in 2008 KPCO adopted the ACIP recommendation to vaccinate all children 6 months through 18 years of age and provided the vaccine free of charge, so pediatric vaccination rates during the 2008–2009 influenza season were slightly higher than the general pediatric population in Colorado.[16,17] Finally, complete electronic medical records allowed us to ascertain vaccination status for cases and controls. Subjects who received the 2008–2009 seasonal influenza vaccine had administration information clearly noted in the medical record; for subjects who did not have evidence of vaccine receipt, chart reviewers were able to assess clinic visit notes and external facility documents to determine whether the child received the vaccine at an outside facility.

This study had several limitations. Misclassification of disease was likely an issue since we relied in part on the RIT for diagnosis of H1N1 infection. The RIT has 99% specificity and a high positive predictive value but poor sensitivity (62% according to a recent study in children),[18] so some cases of H1N1 infection were likely not identified. A significant number of H1N1 cases in this study were diagnosed by RIT; however, due to variations in medical records, we do not have exact counts of which tests were used, only whether the result was positive for influenza A. Misclassification of disease due to testing bias was also possible, since many subjects with mild-to-moderate H1N1 infection were not seen by a health care provider and/or tested for H1N1.

Misclassification of the primary exposure (receipt of the 2008–2009 seasonal influenza vaccine) may have also contributed to bias, although misclassification was likely nondifferential between cases and controls. A recent study in adults found that vaccination status collected from electronic medical records is not completely accurate (sensitivity, 51%–89%; negative predictive value, 46%–87%).[19] However, misclassification of our pediatric subjects was probably less common compared with adults—school-based influenza vaccination of children in the Denver area was not widespread during the 2008–2009 season, and children do not typically receive influenza vaccines at other sites such as the workplace.

Confounding may have also affected the study results. Parents who consistently vaccinate their children against seasonal influenza likely have distinct health-seeking behavior patterns compared with those who do not. These parents may have also been more prone to seek medical care and diagnostic testing when their children displayed flu-like symptoms, potentially biasing our results toward the null. We attempted to address this source of confounding by adjusting for HCP contacts; however, this was an indirect measurement.

Previous studies related to this topic have reported estimated risk or odds ratios ranging from 0.27 to 2.5, and this study was powered to detect a similar effect. A more subtle association may exist between the 2008–2009 seasonal influenza vaccine and susceptibility to H1N1 infection, which may not have been detected in this and other similar studies.

This study showed that prior seasonal influenza vaccination likely did not induce clinically significant heterosubtypic immunity to medically attended pandemic H1N1 infection. Additionally, this study did not support previous hypotheses that annual seasonal influenza vaccination increases risk of pandemic influenza infection. Evidence that seasonal influenza vaccination neither increases nor decreases susceptibility to pandemic influenza has important implications for influenza vaccination guidelines, pandemic control, and future influenza-related research.

ACKNOWLEDGMENTS

The authors thank Mary Kershner, RN, BSN; Daniel Winn, BS; and Quynh Le, BA for their assistance with medical chart reviews; and also thank Carolyn DiGuiseppi, MD, PhD, MPH; Marci Sontag, PhD; Anna Baron, PhD; and Lucinda Bryant, PhD, MSHA for their guidance and helpful comments on early drafts of the manuscript.

REFERENCES

1. World Health Organization Pandemic (H1N1), 2009. Available at: http://www.who.int/csr/don/2010_07_23a/en/index.html. Accessed September 2, 2010.
2. Kelly H, Grant K. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. *Euro Surveill*. 2009;14(; pii):19288.
3. Greenberg ME, Lai MH, Hartel GF, et al. Response to a monovalent 2009 influenza A (H1N1) vaccine. *N Engl J Med*. 2009;361:2405–2413.
4. Garcia-Garcia L, Valdespino-Gomez JL, Lazcano-Ponce E, et al. Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico city. *Br Med J*. 2009;339:b3928.
5. Johns MC, Eick AA, Blazes DL, et al. Seasonal influenza vaccine and protection against pandemic (H1N1) 2009-associated illness among US military personnel. *PLoS One*. 2010;5:e10722.
6. Bodewes R, Kreijtz J, Rimmelzwaan G. Yearly influenza vaccinations: a double-edged sword? *Lancet Infect Dis*. 2009;9:784–788.
7. Skowronski DM, De Serres G, Crowcroft NS, et al. Association between the 2008–2009 seasonal influenza vaccine and pandemic H1N1 illness during Spring-Summer 2009: four observational studies from Canada. *PLoS Med*. 2010;7:e1000258.
8. Centers for Disease Control and Prevention. Influenza vaccination coverage among children and adults - United States, 2008–2009 influenza season. *Morb Mortal Wkly Rep*. 2009;58:1091–1095.
9. Colorado Department of Public Health and Environment: 2009–2010 Influenza Season Surveillance Report. Available at: http://www.cdphe.state.co.us/dc/Influenza/09_10_hospital.pdf. Accessed September 2, 2010.
10. Centers for Disease Control and Prevention. Update: influenza activity–United States, August 30, 2009–January 9, 2010. *Morb Mortal Wkly Rep*. 2010;59:38–43.
11. Centers for Disease Control and Prevention. High risk inpatient influenza vaccination module. 2009. Available at: http://www.cdc.gov/nhsn/PDFs/pscManual/pscManual_current.pdf. Accessed January 10, 2011.
12. Grijalva CG, Poehling KA, Edwards KM, et al. Accuracy and interpretation of rapid influenza tests in children. *Pediatrics*. 2007;119:e6–e11.
13. Centers for Disease Control and Prevention. Interim results: state-specific seasonal influenza vaccination coverage—United States, August 2009–January 2010. *Morb Mortal Wkly Rep*. 2010;59:477–484.
14. Centers for Disease Control and Prevention. Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection–United States, April–August 2009. *Morb Mortal Wkly Rep*. 2009;58:941–947.
15. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med*. 2009;361:1935–1944.
16. Centers for Disease Control and Prevention. Influenza vaccination coverage among children aged 6 months–18 years—Eight immunization information system sentinel sites, United States, 2008–2009 influenza season. *Morb Mortal Wkly Rep*. 2009;58:1059–1062.
17. Kaiser Permanente Colorado Population and Prevention Services Database. HealthTRAC (Health Tracking Registry and Alert Companion). Accessed May 2010.
18. Hawkes M, Richardson SE, Ipp M, et al. Sensitivity of rapid influenza diagnostic testing for swine-origin 2009 a (H1N1) influenza virus in children. *Pediatrics*. 2010;125:e639–e644.
19. Greene SK, Shi P, Dutta-Linn MM, et al. Accuracy of data on influenza vaccination status at four Vaccine Safety Datalink sites. *Am J Prev Med*. 2009;37:552–555.