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Assessment Of H1n1 Vaccine Effectiveness In Preventing Hospitalization In Children

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Abstract

Assessment of H1N1 vaccine effectiveness in preventing hospitalization in children

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In 2009, the first influenza epidemic of the new millennium emerged. H1N1 disproportionately infected, hospitalized and killed pediatric patients, but the bulk of research on effective prevention was centered on the adult population. In order to address this gap, we conducted a matched case-control study to investigate the effectiveness of H1N1 vaccination in preventing hospitalization due to influenza-related illness in children and adolescents aged 6 months to 17 years of age. We found that one dose of H1N1 vaccine is only 30.5% effective in protecting against hospitalization for H1N1 influenza and identified several risk factors for an increased likelihood of hospitalization for influenza that can be used to guide future immunization policy.

Assessment of H1N1 vaccine effectiveness in preventing hospitalization in children

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Table of Contents

List of Tables

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CHAPTER 1

INTRODUCTION

1.1 Motivation

Three times in the last century, and for the first time during the new millennium in 2009, a pandemic influenza strain emerged: H1N1. By altering the subtype of flu virus that predominates globally, H1N1 exacted a large toll of morbidity and mortality via the introduction of unfamiliar, mutated cell surface antigens, the molecules that allow a host immune system to recognize and repel viral invaders. Vaccines are crucial in preventing widespread epidemics of seasonal flu, which has comparatively fewer differences from strains previously experienced by humans than pandemic flu. Therefore, vaccines are even more important in containing pandemics because they train the immune system to recognize and respond to novel pathogenic threats, thereby enabling prevention of disease—when a vaccine is effective-- whereas otherwise the body would only have more limited defenses.

Similarities to previously circulating strains of influenza, a rapid response by the healthcare community, and more advanced healthcare technologies for individuals who contracted influenza and experienced influenza-related complications, restrained the morbidity and mortality of this pandemic in older adults. But in children, lack of exposure to previous strains of H1N1 flu dealt a harsher hand and

led to unusually high attack rates, hospitalizations and deaths. As we look to the future, it is ever more critical that our prevention methods are effective, particularly in children whose immune systems are less developed compared to adults, having been exposed to a smaller number of immunologic threats. Accordingly, evaluation of vaccine effectiveness in pediatric patients contributes significantly to our preparedness for future pandemics by identifying gaps in effectiveness, which will help save lives during subsequent outbreaks.

1.2 Influenza

Influenza, commonly called "the flu," is a contagious respiratory illness caused by influenza viruses, single-stranded RNA viruses of the Orthomyxoviridae family, which includes types A, B and C flu (1). Infections with the A or B types of this virus are most common and can result in illness ranging from mild to severe with life-threatening complications, with severity correlated to which viral surface molecules are expressed for Type A influenza. There is only one subtype of Influenza B, although there are two lineages (2). However, Type A viruses express two variable hallmark surface antigens: hemagglutinin and neuramidinase.

Hemagglutinins are antigenic glycoproteins that facilitate binding of the virus to cells, cause red blood cell aggregation *in vitro*, and are the primary targets of host immune systems. Glycoside hydrolase enzymes called neuraminidases allow penetration through the respiratory tract mucosa and are a common antiviral target

(3). Seventeen hemagglutinins have been identified in human and avian influenza A viruses, as well as 9 forms of influenza neuraminidase, leading to substantial variation in the types of viruses that can cause disease. H1-3 and N1 and N2 are far more common in human strains of the flu virus, and worldwide pandemics have thus far been caused by only four of the subtypes: H1N1, H1N2, H2N2 and H3N2 (1,4,5).

There is a particularly high rate of point mutation in the hemagglutinin gene, which allows the virus to evade recognition by the host immune system via antigenic drift – small evolutionary changes over time in response to selection pressures. Less frequent, but more dramatic, is a phenomenon known as antigenic shift, which is a reassortment of viral genomes due to either cross-species transmission or concurrent infection by multiple viruses in the same host which leads to gene fracture and recombination (6,7). Type B viruses mutate much more slowly and are therefore substantially less likely to cause pandemics, though they occasionally cause epidemics. In addition to being classified by type, influenza viruses are also subclassified according to the location and year they were first isolated , for example A/California/2009 H1N1 (1,5).

1.3 Epidemiology

Although each season is unique, the Centers for Disease Control and Prevention (CDC) estimate that every year, 10% of U.S. residents contract influenza and approximately 200,000 persons are hospitalized for flu-related complications. Nationally, the total annual mortality due to influenza ranges from 3,000-49,000, usually due to complications of the illness; mortality also tends to be much more severe in years when an H3N2 virus predominates (8). The influenza viruses are spread from person to person via respiratory droplets. On occasion, they are also transferred species to species, mutating swiftly in the process. Several times per century, strains sufficiently immunologically distinct emerge, eluding crossover recognition by both B- and T-cells, and resulting in pandemics (1).

There were three influenza pandemics during the 20th century: an H1N1 variant in 1918 that is estimated to have cost more lives than the Great War, an H2N2 strain in 1957, and a H3N2 strain in 1968 that predominated until recently (9,10,11). The most recent pandemic influenza, 2009 H1N1, was notable not only because its death toll of at least 30,000 Americans was over five times the expected mortality from an H1N1 virus, but also because instead of preying most heavily on the elderly and immunocompromised, it was particularly virulent in the young and in persons with intact immune systems. Consistent with previous pandemics, it is likely that 2009 H1N1's much higher attack rates, mortality rates, and hospitalization rates in young

children and adolescents than what is typically observed with seasonal flu was due to an epidemiologic shift in the susceptible population because older adults had been previously exposed to H1N1 strains, which provided protection through antibody production with a residual memory effect (1, 5, 12, 13, 56).

Sixty percent of H1N1 cases occurred in children or adolescents under the age of 18 (14). In contrast to the seasonal flu trend of influenza-associated deaths occurring almost exclusively in individuals >65 years, 2009 H1N1 claimed more than 90%of its mortalities in persons <65 years (15), and ten times as many pediatric victims as seasonal flu in the preceding years (16). Pandemic 2009 H1N1 influenza is a type A influenza virus first diagnosed in the United States in April 2009 after being identified in Mexico as causing an outbreak of respiratory illness (17). Within weeks, it had spread across North America and in June 2009, the World Health Organization (WHO) upgraded the novel influenza virus to a Grade 6 alert, signifying it had become a global pandemic (9,18). Its emergence substantially altered the predominant subtypes of flu since the 1970s from >90% H3N2 globally to >98% H1N1 as of the 2011-2012 influenza season (see Figure 2) (6, 19). Seropositivity studies suggest that more than 20% of the US population, and 53% of U.S. children aged 5-17, had been infected with H1N1 by December 2009 (20).

1.4 Prevention Techniques

The best prevention against influenza infection is annual vaccination, which several large retrospective cohort studies have found to be protective against all-cause mortality (21, 22, 23). The CDC recommends that all children and adolescents be vaccinated with influenza vaccine as a protective measure against flu-related disease. For children from 6 months to nine years of age, the first time a vaccinee is immunized against influenza, it is recommended to receive two doses at least one month apart.

Some of the more serious complications caused by influenza include bacterial pneumonia, dehydration, and worsening of chronic medical conditions, such as congestive heart failure, asthma, or diabetes. Children may also develop sinus problems, ear infections and gastrointestinal distress (1). Although it is more difficult to measure health care demands associated with influenza infections not requiring hospitalization, Neuzil et al found, on average, a fifteen percent increase in outpatient provider visits, and a 3-9 percent increase in (unnecessary) antibiotic prescriptions for patients ultimately found to have the flu (24). Since children shed live virus for longer periods of time than adults, they function as a riskier vector population, which makes prevention particularly cost-effective among this group (25). Since vaccination is the best and most cost-effective prevention strategy for influenza—savings are estimated between $8,000 and $52,000 per successful

immunization—investigating the effectiveness of the H1N1 vaccine in this age group is particularly relevant to global public health efforts (26, 27).

Unfortunately, inactivated influenza virus vaccine is poorly immunogenic in children younger than six months of age and is not approved for children in this age group, even though children < 6 months of age are at highest risk for influenza-related complications (28). A promising study addressing this issue found that vaccinating pregnant mothers protects their infants until the children are of age to be safely and effectively vaccinated themselves (57). Another strategy is to employ cocooning by vaccinating individuals who may potentially transmit the influenza virus to a susceptible neonate or infant (58).

1.5 Vaccine Effectiveness

In mid-October 2009, H1N1 vaccine became available only to priority groups in the United States due to limited supplies (29). Priority vaccines included pregnant women, household contacts of children younger than six months of age, healthcare workers, children and young adults aged six months to 24 years, and persons aged 25-64 with chronic medical conditions increasing their risk of complications from influenza. The bulk of influenza vaccines are grown on chicken eggs, so supply is constrained and resources had to be diverted from seasonal flu vaccine production to pandemic vaccine production (30). CDC recommendations for initial influenza immunization in children dictate receiving two doses spaced one month apart, and early predictions were that the H1N1 vaccine would require two doses for all vaccines in order to confer immunity to H1N1 influenza. However, a study published in September 2009 in the New England Journal of Medicine suggested that one dose would be sufficient, effectively doubling the number of doses available to the population (5). This early study only assessed immunization of adults and concluded that due to well-documented differences in the immune response of children, further research was needed. The priority list for the limited initial supply of vaccine included children and adolescents between the ages of 6 months and 24 years of age (rather than individuals over age 65) in response to observations that previous cases of H1N1 influenza had caused more serious complications in this age

group. Children and adults were administered the vaccine although little data on efficacy were available.

While subsequent studies have shown good efficacy of the live attenuated vaccine in provoking an adequate immune response as measured by antigen-antibody titers when adjuvanted (5), the United States has not yet licensed adjuvanted influenza vaccines (1, 27, 31). Non-adjuvanted preparations are not equally efficacious at stimulating a measurable immune response indicated by a >40:1 antibody titer (12). And even if a vaccine in efficacious, that does not necessarily mean it will be effective, as measured by preventing clinical disease. There have been conflicting reports on the *effectiveness* of the vaccine in preventing clinically significant flu, with several studies finding that the vaccine is effective in this age group being funded or conducted by vaccine manufacturers and using adjuvants not otherwise available (32, 33). The ability to mount a measurable immune response has been found to vary by age, with a significantly smaller proportion of 3-11 year olds (younger children were not studied) mounting satisfactory hemagglutinin-inhibition titers than individuals >12 years of age after one dose of both alum-adjuvanted and unadjuvanted vaccines (34). One study published in Lancet in 2010 found that fewer than half of children under the 3 years of age mounted a protective antibody titer to one dose of the non-adjuvated live attenuated vaccine licensed in the United States (35). Despite this evidence of a lack of measurable immunoprotection from the licensed vaccine after one dose, and the

longstanding CDC recommendation for children to receive two doses of influenza vaccine, in practice few children receive both doses. Therefore, continued evaluation of the clinical *effectiveness* of the US-licensed unadjuvanted vaccine – showing that not only does the vaccine not stimulate a protective immune response, but that this lack of efficacy also decreases the unadjuvanted vaccine's effectiveness at preventing hospitalizations for influenza – is crucial to public health efforts to alter policy in order to provide the vulnerable pediatric population with effective vaccination coverage – either by increasing efforts to ensure children complete both doses, or by licensing adjuvanted vaccines that are effective at lower and fewer doses – and to help guide vaccination efforts during future seasons and similar pandemics.

The effectiveness of attenuated viral vaccines in preventing disease depends not only on the age and immunocompetence of the vaccine recipient, but also on the degree of similarity between the viruses in the vaccine and those in circulation (1). The majority of vaccinated children and young adults develop high post-vaccination antibody titers that are protective against illness caused by strains similar to those in the vaccine, although attaining a particular titer level is not absolutely correspondent to immunity and does not translate directly to a measure of a vaccine's effectiveness (31). Children aged as young as 6 months can develop protective levels of antibody after influenza vaccination, although the antibody response among children at high risk of influenza-related complications might be

lower than among healthy children (36, 37). Recommendation to give influenza vaccine routinely to children over the age of 6 months is based on an assumption that influenza vaccine will be as effective in preventing hospitalization in these children as it is in the elderly. However, it may not be reasonable to assume that influenza vaccine is as efficacious or effective in these children, especially because existing immunological data suggests a less robust immune response to typical vaccine doses in individuals younger than twelve years of age (34). The safety of the pandemic H1N1 influenza vaccine in children and adolescents has been established, but it is still not clear what immunization schedule is necessary for effective vaccination against H1N1 influenza with the licensed unadjuvanted vaccine (38, 39).

1.6 Hypothesis

H1N1 vaccine is effective in preventing hospitalization due to H1N1 influenza-related illness in a pediatric population.

CHAPTER 2

MATERIALS AND METHODS

2.1 Matched Case-control Study

Thesis writer Felicity Lenes-Voit designed the study in conjunction with and under the guidance of Dr. Vázquez, conducted all of the medical records reviews, helped to (but did not primarily) identify case and control subjects, interview and consent them and add their information to the database. She checked data in the database and conducted statistical analysis with SAS code written by Alexandra Grizas and edited by Emily Bucholz, as well as conducting a literature review and writing this manuscript.

A matched case-control study was developed to study the effectiveness of H1N1 vaccine in preventing hospitalization due to laboratory-confirmed H1N1 influenza in children. Potential subjects were identified retrospectively for the 2009-2010 flu season using the existing hospital infectious disease virology surveillance tool, then enrolled prospectively for the 2010-2011 and 2011-2012 seasons. Cases were identified in one of the following ways:

1. From an existing active surveillance program conducted by the Connecticut Emerging Infections Program at Yale (EIP: Multi-state Population Based surveillance for Influenza-Associated Hospitalizations in Children). This surveillance includes all children admitted to Yale-New Haven Hospital (YNHH), an urban academic hospital in the Northeastern United States, due to influenza and has been in place since 2003.

2. From the daily list of pediatric admissions to YNHH. This list is compiled by the admitting resident in Pediatrics.

3. Via surveillance of respiratory specimens submitted to the clinical virology laboratory from children and adolescents hospitalized at YNHH. Policy at YNHH dictates that all children or adolescents with respiratory complaints of symptoms during flu season have a specimen sent to virology for analysis.

4. From data from YNHH's infection control surveillance for influenza—conducted routinely at YNHH every influenza season.

2.2 Case Subject Definition

A case subject was defined as a child aged 6 months to 17 years who was hospitalized at Yale-New Haven Hospital (YNHH) due to or with a diagnosis of H1N1 novel influenza tested by Direct Fluorescence Antibody (DFA) test and confirmed as

novel H1N1 by RT-PCR lab tests any time between November 1, 2009 and May 2012. This interval began two weeks after the H1N1 vaccine became available to account for the lag time necessary to mount an immune response to a vaccine. The age of 6 months was chosen because that is the minimum recommended age for the vaccine owing to immunological development in infants.

Prospective cases provided a nasal wash for laboratory testing if their influenza had not already been typed by the hospital's clinical virology laboratory.

Medical records of identified case-subjects were reviewed to collect demographic information including race and ethnicity and to confirm that clinical symptoms at time of diagnosis were consistent with influenza (the combination of fever, respiratory difficulty, and cough within 48 hours of development of symptoms is a validated multivariate predictor). The medical records of the case subjects were also reviewed to gather necessary information to complete a validated influenza clinical severity score that assessed heart rate, respiratory rate, oxygen saturation, signs of difficulty breathing (including wheezing, retractions, nasal flaring), whether mechanical intubation was required, whether the patient's condition merited admission to the intensive care unit (ICU), and whether or not there was a documented abnormal chest radiograph. We obtained informed consent and conducted interviews to obtain information related to disease processes, household statistics, and demographics. Otherwise eligible subjects were excluded if they were

immunocompromised or informed consent could not be obtained. Nosocomial infections were also excluded.

2.2 Control Subjects

Control subjects were children matched on admit date (+/- 14 days of case admission) and date of birth (+/- 28 days for subjects >6 months -<5 years; +/- one year for patients 5 -<18 years) to case subjects. Put another way, control subjects were patients hospitalized with non-respiratory complaints at YNHH of similar age as their matched case subjects and admitted within two weeks of their matched case subject who did NOT have positive RT-PCR for H1N1. At least two matched controls were recruited per case, with up to seven matched controls. Controls were also excluded if they were immunocompromised or informed consent could not be obtained.

2.3 Informed Consent

Written informed consent was obtained from all study subjects. Participants completed a short questionnaire by phone providing information about items deemed to be possible confounders, such as comorbid health conditions, living conditions, day care or school attendance, second hand smoke exposure, household

size and vaccination status. Vaccination status was confirmed from healthcare provider records. Study subjects were considered vaccinated if they had received a documented dose of H1N1 influenza vaccine 14 or more days prior to hospital admission.

2.4 Data Management and Statistical Analysis

A database was created in Microsoft Access. Data were entered twice and multiple data checks were done to correct and check errors. Data were exported to Microsoft Excel for statistical analysis in the SAS statistical programs for personal computers [SAS® for Personal Computers. SAS Institute, Inc., Cary, NC: 1999, version 9.2] The protective efficacy (PE) of a vaccine, which is the proportional reduction in the risk of infection among vaccinees that is attributable to the vaccine, is calculated with data from clinical trials as:

$$\textbf{PE} = \frac{\text{risk of infection in controls - risk of infection in vaccines}}{\text{risk of infection in controls}}$$

This equation reduces to:

$$1 - \frac{\text{risk of infection in vaccinees}}{\text{risk of infection in controls}} \quad \text{or} \quad 1 - \text{the relative risk.}$$

For case-control studies, the standard measure of association is the odds ratio. We performed a matched analysis, since the controls were matched individually to the cases based on date of birth and date of hospitalization, with at least two and up to seven controls per case. Since for this type of study the matched odds ratio closely approximates the relative risk that would be observed in a prospective interventional clinical trial, the matched odds ratio can be substituted for the relative risk in the above equation and the vaccine's protective efficacy is estimated as: 1 - the matched odds ratio.

Matched odds ratios, with both their associated statistical significance (assessed with the Mantel-Haenszel χ^2 for matched triplets) and their 95% confidence intervals were calculated with the use of conventional techniques. In addition, conditional logistic regression was used to adjust these estimates.

A 30 percent vaccine coverage rate was used to construct the statistical models because the CDC and Committee on Infectious Disease estimated 32 percent coverage (26, 40). It is not clear from existing research precisely what percentage of coverage is required to establish herd immunity, with computer models predicting from 80-98% (45). Loeb et al. have demonstrated that it is possible to induce herd immunity to flu in small communities using the inactivated vaccine (46) but different yearly strains and vaccines of varying effectiveness present different coverage demands to reduce outbreaks through the herd effect.

Table 1

Power calculations

With 90% power and α = 0.05

Assuming 30% Vaccine Coverage			
Ratio of Cases to Controls	VE = 60%	VE = 70%	VE = 80%
1:1	177	109	67
1:5	97	61	39
1:10	88	56	35
Assuming 40% Vaccine Coverage			
Ratio of Cases to Controls	VE = 60%	VE = 70%	VE = 80%
1:1	145	88	53
1:5	79	49	30
1:10	71	44	27

With 80% power and α = 0.05

Assuming 30% Vaccine Coverage			
Ratio of Cases to Controls	VE = 60%	VE = 70%	VE = 80%
1:1	135	84	53
1:5	75	48	31
1:10	68	44	28
Assuming 40% Vaccine Coverage			
Ratio of Cases to Controls	VE = 60%	VE = 70%	VE = 80%
1:1	111	68	42
1:5	60	38	24
1:10	54	34	21

CHAPTER 3

RESULTS

3.1 Case and control identification

We identified 85 case subjects, 79 of which were retrospective and 6 of which were prospective. One of the prospective cases resided out of state and was lost to follow up. Nine retrospective cases refused to be interviewed, one refused to sign consent, five were ineligible (3 hospitalized for non-respiratory complaint with influenza an incidental finding, 1 admitted for a nosocomial infection and one resided out of state.) 16 were not able to be contacted. 47 were interviewed and consented, with medical record reviews completed. We then obtained their vaccination records for 45 patients from their healthcare providers. Of the 755 identified possible age- and date of admission-matched controls, 175 were interviewed; 124 gave consent; 25 refused to be interviewed; 2 were excluded and 140 medical record reviews were completed for documentation of vaccinations. The remaining identified possible control subjects have not been able to be contacted currently.

3.2 Demographics

Of the case subjects, 57.8% were female and 46.2% were male, while the control subjects were 48.5% female and 51.5% male. 22.2% of the case subjects were two

years of age or younger, whereas in the control population, 17.5% were two or under. 42.2% of the case subjects were non-Hispanic white; 31.1% were Hispanic; 26.7% were black or other non-white race. The control subjects were 74.2% white, 16.5% Hispanic and 9.3% black or other non-white race. 52.3% of the case subjects were breastfed, while 66% of the control subjects were breastfed. Our data shows significant associations between hospitalization for influenza and lower parental education. Families in which one or both parents were college graduates had a lower rate of hospitalization for influenza. In our study, 40% of the children hospitalized due to H1N1 had parents or caregivers who were college graduates, while 58.5% of control subjects were cared for by college graduates. This difference was statistically significant ($p=0.049$). Having a lower household income was also significantly associated with an increased likelihood of being hospitalized with H1N1, with 58.8% of case subjects living in households making less than $30,000 per year, but only 35.7% of control subjects living in low-income households ($p=0.021$). Preterm birth was not found to be a significant predictor of likelihood for hospitalization with H1N1 influenza, with 18.6% of the case subjects born before term and 14.7% of control subjects delivered early. There was also no significant difference between case and control groups in regards to school or daycare attendance, with 75% of case subjects attending school or daycare and 80.4% of control subjects attending school or daycare. Respiratory comorbidities were found to be correlated with a higher rate of influenza severe enough to warrant

hospitalization, with 52.3% of the case subjects reporting a respiratory comorbidity and 32% of control subjects. The severity of respiratory comorbidities was consistent across groups. Other comorbidities did not affect the likelihood of hospitalization for influenza, with 54.5% of case subjects with a non-respiratory comorbidity and 42.1% of control subjects. 22.2% of case subjects were only children, whereas 24.7% of control subjects had no siblings. Regarding housing arrangements, 20% of case subjects lived in single family dwellings or duplexes whereas 80% lived in multiple family dwellings like apartments. Among control subjects, 26% lived in stand-along housing. Vaccination status was not significantly different between those with and without influenza, with 11.1% of the case subjects being vaccinated and 19.6% of the control subjects.

3.3 Vaccination Status

There were several demographic characteristics that predicted vaccination with at least one dose of live attenuated H1N1 influenza vaccine in our sample. Younger children under the age of two were statistically significantly more likely to be vaccinated than older children, with 41.7% of those who were vaccinated two years of age or under, and only 14.4% of the unvaccinated study subjects two or younger. ($p=0.002$). 41.7% of the study subjects who were vaccinated were female, whereas 53.4% of the unvaccinated were female. 66.7% of those vaccinated were white, 20.8% were black or other non-white race. 12.5% were Hispanic. Of the

unvaccinated, 63.5% self-identified as white, 12.7% as black or other non-white race, and 22.8% as Hispanic. 62.5% of the vaccinated were breastfed, whereas 61.4% of the unvaccinated were breastfed by caregiver report. Of those study subjects whose caregivers were college graduates, there was no statistical difference in likelihood to be vaccinated, with 56.5% of vaccinated study subjects having a parent or caregiver with a college degree, and 52.3% of the unvaccinated. Higher household income did not increase statistical likelihood to vaccinate either: 65.2% of study participants who were vaccinated lived in households with annual income exceeding $30,000, whereas 55.8% of the unvaccinated study subjects lived in these households. Preterm birth narrowly missed statistical significance as a predictor of vaccination status. 29.2% of the vaccinated were preterm, whereas 13.2% of the unvaccinated were delivered before term. Similar percentages of individuals attended daycare and/or school among both the vaccinated (66.7%) and unvaccinated (81.2%). 37.5% of vaccinees had a respiratory comorbidity reported in their medical records, but that did not differ from the unvaccinated, 38.5% of whom carried diagnoses of comorbid respiratory conditions. There was also no difference between the vaccinated (50%) and unvaccinated (45.2%) in terms of incidence of other comorbidities. 29.2% of the vaccinated were only children, and 22.9% of the unvaccinated had no siblings. As for housing arrangements, 37.5 of the vaccinated lived in stand-alone single-family homes or duplexes, compared to 22.0% of the unvaccinated.

In the univariate, matched bivariate and multivariate analyses, vaccination status was not associated with a lower likelihood to be hospitalized for influenza (see tables 1, 3, 4 and 5). In the matched conditional logistic regression, respiratory comorbidities, non-White race and household income <$30,000 annually each bore odds ratios indicating an increased risk for hospitalization with H1N1 in our sample. However, in the multivariate analysis, none of these factors were independently significant. The odds ratio for the matched, adjusted multivariate analysis comparing vaccination status with likelihood to be hospitalized due to H1N1 influenza crossed one, but would yield a vaccine protective efficacy of only 30.5%. (1-0.695).

Table 2

Comparison of case subjects hospitalized with laboratory proven H1N1 versus matched case controls hospitalized with non-respiratory complaints

Patients hospitalized with laboratory-proven H1N1			
Variable (N=142)	**Yes[b] 45 (%)**	**No 97 (%)**	**p-value**
Age at Hospitalization*			0.507
> 2 years	35 (77.8)	80 (82.5)	
≤ 2 years	10 (22.2)	17 (17.5)	
Gender			0.301
Female	26 (57.8)	47 (48.5)	
Male	19 (46.2)	50 (51.5)	
Race/Ethnicity[⊥*]			0.002
Hispanic	14 (31.1)	16 (16.5)	
Black/other non-white	12 (26.7)	9 (9.3)	
White	19 (42.2)	72 (74.2)	
Breastfed (self-reported)			0.124
Yes	23 (52.3)	62 (66.0)	
No	21 (47.7)	32 (34.0)	
Caregiver education			0.049
College graduate	16 (40.0)	55 (58.5)	
Some college or less	24 (60.0)	39 (41.5)	
Household income			0.021
> $30K	14 (41.2)	54 (64.3)	
< $30K	20 (58.8)	30 (35.7)	
Preterm			0.565
Yes	8 (18.6)	14 (14.7)	
No	35 (81.4)	81 (85.7)	
School/daycare attendance			0.467
Yes	33 (75.0)	78 (80.4)	
No	11 (25.0)	19 (19.6)	
Respiratory comorbidity			0.022
Yes	23 (52.3)	31 (32.0)	
No	21 (47.7)	66 (68.0)	
Other comorbidity✧			0.171
Yes	24 (54.5)	40 (42.1)	
No	20 (45.5)	55 (57.9)	
Siblings			0.744
0	10 (22.2)	24 (24.7)	
+1	35 (77.8)	73 (75.3)	
Housing			0.381
Single family/duplex	9 (20.0)	26 (26.8)	
Multifamily (items 3-8)	36 (80.0)	71 (73.2)	
Vaccinated			0.210
1+ doses vaccine	5 (11.1)	19 (19.6)	
0 doses	40 (88.9)	78 (80.4)	

Table 2 Footnotes

[a] Column values are n (column %). May not sum to 100% due to rounding and/or missing data.

[b] Includes only study eligible subjects as described in Materials and Methods.

* Statistically significant at the $\alpha = 0.05$ level for chi-square test for categorical variables and t-test or Wilcoxan Rank Sum test for continuous variables.

$^{\perp}$ Other includes multiracial, other race, Asian, American Indian, Native Hawaiian/Pacific Islander. Other, Black, and White are all non-Hispanic

✧ Other comorbidities include sickle cell disease, renal disease, heart problems, immune deficiencies, birth defects, spinal cord injury, epilepsy, mental retardation, neurologic or neuromuscular diseases, metabolic or endocrine diseases, other chronic illnesses.

Table 3

Comparison of vaccinated and unvaccinated study subjects

Comparison by Vaccination Status			
Variable (N=142)	**Vaccinated[b] 24 (%)**	**Not vaccinated 118 (%)**	**p-value**
Age at Hospitalization*			0.002
> 2 years	14 (58.3)	101 (85.6)	
≤ 2 years	10 (41.7)	17 (14.4)	
Gender			0.295
Female	10 (41.7)	63 (53.4)	
Male	14 (58.3)	55 (46.6)	
Race/Ethnicity			0.443
White	16 (66.7)	75 (63.5)	
Black or other	5 (20.8)	15 (12.7)	
Hispanic	3 (12.5)	27 (22.8)	
Breastfed (self-reported)			0.920
Yes	15 (62.5)	70 (61.4)	
No	9 (37.5)	44 (38.6)	
Caregiver education			0.709
College graduate	13 (56.5)	58 (52.3)	
Some college or less	10 (43.5)	53 (47.7)	
Household income			0.412
>$30K	15 (65.2)	53 (55.8)	
<$30K	8 (34.8)	42 (44.2)	
Preterm			0.052
Yes	7 (29.2)	15 (13.2)	
No	17 (70.8)	99 (86.8)	
School/daycare attendance			0.113
Yes	16 (66.7)	95 (81.2)	
No	8 (33.3)	22 (18.8)	
Respiratory comorbidity			0.930
Yes	9 (37.5)	45 (38.5)	
No	15 (62.5)	72 (61.5)	
Other comorbidity✧			0.669
Yes	12 (50.0)	52 (45.2)	
No	12 (50.0)	63 (54.8)	
Siblings			0.512
0	7 (29.2)	27 (22.9)	
1+	17 (70.8)	91 (77.1)	
Housing			0.109
Single family/duplex	9 (37.5)	26 (22.0)	
Multifamily (items 3-8)	15 (62.5)	92 (78.0)	

Table 3 Footnotes

[a] Column values are n (column %). May not sum to 100% due to rounding and/or missing data.

[b] Received 1 or more doses of non-adjuvanted nasal or live attenuated vaccine >14 days before hospital admission.

* Statistically significant at the $\alpha = 0.05$ level for chi-square test for categorical variables and t-test or Wilcoxan Rank Sum test for continuous variables.

[⊥] Other includes multiracial, other race, Asian, American Indian, Native Hawaiian/Pacific Islander. Other, Black, and White are all non-Hispanic

✧ Other comorbidities include sickle cell disease, renal disease, heart problems, immune deficiencies, birth defects, spinal cord injury, epilepsy, mental retardation, neurologic or neuromuscular diseases, metabolic or endocrine diseases, other chronic illnesses.

Table 4

Matched conditional logistic regression

Bivariate analysis with Odds Ratio predicting likelihood to be hospitalized for influenza

Variable	Odds Ratio	N
Female gender	0.679 (0.319-1.454)	138
Breastfed	0.608 (0.297-1.244)	138
Preterm	1.344 (0.516-3.497)	141
Respiratory Comorbidities	**2.743 (1.229-6.119)**	**139**
Other comorbidities	1.949 (0.860-4.419)	111
Non-white race	**5.511 (1.481-20.508)**	**141**
Hispanic ethnicity	2.074 (0.879-4.891)	142
Vaccinated	0.408 (0.126-1.319)	134
Caregiver graduated college	0.479 (0.222-1.033)	118
Income >30K	**0.375 (0.145-0.970)**	**142**
Siblings	1.189 (0.445-3.178)	142
Housing (apartment, multi-family)	1.534 (0.603-3.900)	92

Table 5

Multivariate Odds Ratio predicting likelihood to be hospitalized due to H1N1

Controlled for Respiratory Comorbidity, non-white race and income.

Variable	Odds Ratio	N
Vaccination	3.327 (0.607-18.242)	120
Respiratory Comorbidity	5.705 (0.897-36.274)	120
Non-White race	5.515 (0.329-92.446)	120
Income >30K	0.259 (0.013-5.201)	120

Table 6

Adjusted Matched Multivariate Analysis with Odds Ratio of Vaccination status for H1N1 influenza versus hospitalization due to laboratory-confirmed H1N1 influenza

Vaccination Status versus hospitalization for influenza			
Variable (N=120)	**Vaccinated[b] (%)**	**Not vaccinated (%)**	**p-value**
Hospitalization Diagnosis			0.374
H1N1 influenza (case subject)	22 (33.3)	15 (27.8)	
Non-respiratory (control subject)	44 (41.7)	39 (72.2)	
			Odds Ratio: 0.695 (0.645-3.218)

CHAPTER 4

DISCUSSION

Vaccination with one dose of unadjuvanted H1N1 vaccine was only 30.5% protective against hospitalization for H1N1 influenza-related illness in our sample. Existing immunological research suggests there is an age-related difference in the ability to mount a robust response to vaccine antigen required for effective immunization (34, 35, 48, 50), and that even older children and adolescents—despite their more competent immune systems compared to younger children—have lower baseline protection from cross-reactive antibodies due to lack of exposure to previously circulating H1N1 subtype influenza viruses (1, 19, 40, 55). Effectiveness studies and long-term immunogenicity studies that found an influenza vaccine effectiveness of >80% in young children and adolescents, or persistently elevated protective antibody titers, were conducted using vaccines with adjuvants (33, 41, 52), which are not licensed for flu vaccines in the United States (1, 36). Further, head-to-head studies of adjuvanted flu vaccines versus conventional vaccines have found markedly poorer results in the unadjuvanted vaccines in achieving a protective antibody titer (>1:40) (42). In 2011, The World Health Organization in its Seventh Meeting on Evaluation of Pandemic Influenza Vaccines in

Clinical Trials explicitly stated that unadjuvanted vaccines and very-low dose adjuvanted vaccines were not capable of eliciting reliable seroprotection in children (17).

Adjuvanted vaccines have suffered a poor public relations image secondary to concerns that vaccine preservatives such as thimerosal and other additives including MF59 and AS03 adjuvants, lead to an increased risk of autism in children despite lack of scientific evidence to support this claim. It is possible that the strong lobbying efforts by anti-vaccine groups involved in vaccinations has resulted in adjuvants not being embraced for influenza vaccines in the United States despite their proven value in producing highly effective vaccines. With every vaccine administration, there is a risk-reward ratio – and adjuvants are perceived to contribute substantial risk without commensurate reward, when the evidence points to the opposite being true. In fact, safety studies have not thus far shown statistical differences in side effects or serious events in conventional versus adjuvanted vaccines (39, 43, 44) or in multiple doses of vaccine (38), rendering safety concerns about vaccine adjuvants without teeth.

Since we found that one dose of unadjuvanted H1N1 influenza vaccine is not highly protective in young children, possible solutions include bolstering current recommendations for young children to receive a second dose (up to nine years old with certain preparations according to immunological research) (39), a higher

initial dose of antigen (47), and/or introducing adjuvanted vaccines for influenza. These options taken together or separately could serve to reduce the toll on the healthcare system currently observed due to influenza related illnesses, as well as enable a better risk-reward profile to vaccination. Additionally, research shows that consumers of influenza vaccines, or in the case of pediatric patients, their parents, have diminished safety concerns with each subsequent vaccination, and they are overall more likely to be vaccinated subsequently once they have been initiated into receiving influenza vaccinations (49, 52).

Other areas of improvement identified by our research include issues of disparity. Individuals of lower socioeconomic status and minority status are at greater risk of hospitalization from influenza, and should be priority targets for effective vaccination programs. Given the average savings to the healthcare apparatus of an average of $8-52,000 per flu hospitalization prevented (26, 53), it would be a sound policy choice to subsidize influenza vaccines for individuals not able to afford them.

It does appear that certain high-risk patients are being targeted for immunization, as the younger children in our study were significantly more likely to be vaccinated than those over the age of two. Especially vulnerable groups such as children and adolescents with respiratory comorbidities including asthma were

disproportionately hospitalized for influenza complications in our sample, and would receive particular benefit from effective prevention strategies.

Our study did have some weaknesses. Although we computed a provisional vaccine efficacy based on our data, we were not powered to detect such a small protective effectiveness of the vaccine because we designed our study based on published data from previous influenza vaccines for seasonal influenza which are typically in excess of 80% effective in preventing influenza infection. Therefore, with a larger sample size we might detect a different vaccine efficacy. Future research in partnership with the Connecticut Children's Medical Center to combine sample sizes may further elucidate this issue, and will likely alter the protective efficacy of the vaccine in our sample. Since we were adequately powered to detect an 80% protective effect of the H1N1 vaccine in preventing hospitalization due to influenza in pediatric patients, we do know that it is <80% effective and that further study is warranted to help articulate vaccine policy and promote effective vaccine preparations and vaccine dosing regimens in order to encourage responsible and prudent use of preventative healthcare resources.

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