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Influenza Vaccine is Protective Against Laboratory-Confirmed Influenza in Obese Children

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Abstract

Background—Obesity emerged as a novel risk factor for severe disease during the 2009 H1N1 influenza pandemic. Murine studies indicate that obesity is associated with ineffective response to influenza vaccine, but few human studies exist. We aimed to determine if influenza vaccine is protective against laboratory-confirmed influenza in obese children.

Methods—Body mass index (BMI), vaccination status, and laboratory-confirmed influenza data were analyzed from a previously conducted prospective study in which active surveillance for influenza-like illness (ILI) was conducted in eight elementary schools in Los Angeles County during the 2010–2011 influenza season. Polymerase-chain reaction (PCR) was performed on combined nose/throat swabs collected from children with ILI at presentation to the school nurse or during absenteeism.

Results—Of 4,260 children with height/weight data, 1,191 (28.0%) were obese (BMI ≥95th percentile). Respiratory specimens were obtained from 858 (20.1%) children. Unvaccinated obese compared with vaccinated obese children acquired three times more PCR-confirmed influenza (62 vs. 17 per 1000 children, $p=0.003$) and missed more school days (4.6 vs. 3.2 per 100 school days, $p<0.001$) during influenza season. Obese children with PCR-confirmed influenza were more likely to present with cough (86.2 vs. 72.4%, $p=0.030$) and missed more school per episode (2.4 vs. 1.9 days, $p=0.023$) compared with non-obese children. Among vaccinated children, rates of PCR-confirmed influenza were similar in obese and non-obese children (17 vs. 20 per 1000 children, $p=0.77$).

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Conclusions—Obese children with PCR-confirmed influenza suffered from more cough and missed more school days than their non-obese peers. Influenza vaccination protected obese children against PCR-proven influenza illness.

Keywords

Influenza; Influenza Vaccine; Obesity; School-located influenza vaccination

INTRODUCTION

Obesity is a worldwide pandemic. The World Health Organization estimates that 500 million adults and more than 40 million children under 5 years of age are obese (1). Nearly one in five children under 20 years of age in the United States is obese (2). Several studies documented an association of obesity with poor outcome following infection with the 2009 H1N1 influenza pandemic strain that continues to circulate worldwide (3–9). Body mass index (BMI) over 30 was associated with a greater risk of hospitalization, admission to the intensive care unit, and death. The Centers for Disease and Control and Prevention (CDC) now consider persons who are morbidly obese (BMI ≥ 40) to be at risk for medical complications from influenza (10).

Annual vaccination is the primary strategy for influenza disease prevention (10). However, data on the clinical effectiveness of influenza vaccine in protecting obese individuals against influenza disease is lacking. Impaired antibody response has been seen following hepatitis B vaccine and tetanus toxoid in obese humans (11–13). Murine studies found that vaccinated diet-induced obese (DIO) mice were not protected from challenge with the 2009 H1N1 influenza. DIO mice had lower vaccine-induced influenza-specific antibodies, higher lung virus titers, greater lung inflammation, and higher mortality compared with vaccinated lean mice (14). One human study of adults and children found no significant differences in hemagglutination inhibition antibody titers on day 21 following two doses of 2009 pandemic influenza A (H1N1) vaccine (15). Another human adult study showed similar robust antibody response initially but faster decline in titers in obese compared with normal weight individuals (16). Investigators also showed impaired CD8⁺ T cells responses in obese individuals (16). The influence of BMI on actual rates of laboratory-confirmed influenza in vaccinated individuals has not been studied. We sought to determine if influenza vaccine is protective against laboratory-confirmed influenza in obese children.

MATERIALS AND METHODS

Study Design and Weight Categories

Data were analyzed from a previously conducted prospective study to evaluate the impact of school-located influenza vaccination (SLV) programs on influenza rates and absenteeism (17). The original study group consisted of 4,455 children enrolled in eight elementary schools in two Los Angeles County (LAC) school districts. Children were included in this study if age, gender, height and weight data were available. The BMI and BMI-for-age percentiles were calculated using the CDC's Children's BMI Tool for Schools based on a child's age and sex (18). The BMI percentile determined classification into one of four

weight status categories: obese defined as a BMI at or above the 95th percentile, overweight defined as a BMI at or above the 85th percentile and lower than the 95th percentile, healthy weight defined as a BMI at or above the 5th percentile and lower than the 85th percentile and underweight defined as a BMI below the 5th percentile (19, 20). Outcomes in obese children were compared to non-obese children including healthy, over- and underweight children.

Influenza Vaccination

Trivalent influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV), as recommended for the 2010–11 season (A/California/7/2009 [H1N1]-like virus, A/Perth/16/2009 [H3N2]-like virus, B/Brisbane/60/2008-like virus) (21), were offered free-of-charge to children attending the four schools that conducted SLV programs of the eight participating schools. The vaccine matched 94.0–99.8% of strains circulating in LAC that season (22, 23). SLV clinics were held on site at each intervention school between October and December 2010. Vaccination status was recorded in the California Immunization Registry (CAIR) for the Los Angeles-Orange County Region. Children were considered “vaccinated” if they received influenza vaccine through the SLV program or if vaccination at a community site was documented in CAIR between August 2010 and May 2011. CAIR was used by 62% and 45% of providers in the surrounding communities of districts 1 and 2, respectively.

Influenza Surveillance and Virus Identification

Prospective active ILI surveillance was conducted during the period in which at least 5% of specimens from nine sentinel community surveillance sites located throughout LAC tested positive for influenza (17). ILI was defined as fever (temperature $\geq 100.4^{\circ}\text{F}$ [38.0°C]) or feverishness and at least one of the following: cough, sore throat, runny nose, nasal congestion, headache, earache, wheezing, muscle aches, chills, anorexia, vomiting, or diarrhea (24). Respiratory specimens were obtained from all children who presented with ILI to the school nurses’ office. Absent children were called to obtain the reason for absence and a same-day home visit was scheduled for swabs if the child’s symptoms met the ILI case definition. Children missed during absence were swabbed upon return to school if they returned within three days of fever onset. Specimens were collected and analyzed for each distinct ILI episode, defined as no symptom overlap for ≥ 7 days. A short parent interview was conducted on the day of specimen collection to assess symptoms, date of onset, and household characteristics.

Multiplex reverse transcription-polymerase chain reaction (PCR) (Luminex xTAG[®] respiratory virus panel, Luminex Corporation, Austin, Texas) was performed on combined nose and throat specimens for 12 viruses including influenza A (with subtype H1 and H3, neuraminidase component not identified), influenza B, respiratory syncytial virus (subgroups A and B), parainfluenza virus (types 1, 2, and 3), rhinovirus, adenovirus, and human metapneumovirus as previously described (17). Specimens positive for influenza A and negative for subtype H1 and H3 was presumed to be 2009 H1N1 based on the epidemic strains in LAC during the surveillance period (22).

Absenteeism

Each school provided absence logs. The first two months of the school year (September and October) were used to define the baseline absentee rates. For school administrative purposes, days of absence did not include the day a child was sent home early from school with illness.

Statistical Analysis

Categorical variables were compared using Pearson chi-square or Fisher's exact test. Independent sample two-tailed T-tests were used for comparison of continuous variables. ILI rates and PCR-confirmed influenza rates were calculated per 1000 children. Point estimates of risk ratios (RR) with 95% confidence intervals (CI) were calculated between vaccinated and non-vaccinated children in the obese and non-obese BMI groups. Vaccine effectiveness (VE) estimates were calculated using $(1-RR) \times 100\%$ among obese and non-obese children. Statistical analyses were performed using SPSS Version 19.0 (IBM Corp., Armonk, NY). All tests were two-tailed with significance level of 0.05.

Parents were notified of the influenza study at their child's school by a letter announcement sent home three times between September and December. Informed consent was obtained for influenza vaccination and respiratory virus testing. The study was approved by both school districts, and the institutional review boards at LAC Department of Public Health and Children's Hospital Los Angeles.

Results

Study Participant Characteristics and Influenza Vaccination

Height, weight, gender and age data were available for 4263 (95.7%) of 4455 children who participated in the SLV study. Three children were excluded for height or weight recorded as higher or lower than is considered biologically possible based on the CDC Children's BMI Tool for Schools (18). Therefore, we included in the analysis 4260 (95.6%) children for whom we were able to calculate BMI-for-age percentile. Nearly 30% were obese (Figure 1). Characteristics of the children are shown in Table 1. Obese children were more likely to be male and/or Hispanic and missed more days of school at baseline. One fifth of the children received influenza vaccine through the SLV programs or at a community site as documented in CAIR (Table 2). Most (83.1%) received LAIV, which the SLV program gave preferentially (17). We compared outcomes of obese children with different groupings of non-obese categories including: healthy weight alone, healthy weight and underweight, and overweight, healthy weight, and underweight. Because the results were similar, we present here the results of obese children compared to non-obese children of all other categories combined. In addition, no differences were seen based on age groups of 5–8 years and 9–13 years; therefore, we present the results without age stratification.

PCR-confirmed Influenza

During active surveillance conducted from January 1 to April 15, 2011, while influenza activity was present in LAC, ILI was detected in 858 (20.1%) children with known BMI for which respiratory swabs were obtained. Specimens were collected from 787 (69.5%) of

1133 children absent from school due to fever and respiratory symptoms. Of 856 (98.6%) respiratory specimens available for PCR testing, 198 (23.1%) were positive for influenza, including 62 (31.3%) influenza A 2009 H1N1, 16 (8.1%) influenza A H3, and 120 (60.6%) influenza B (Figure 2). One child tested positive for 2009 H1N1 and influenza B at the same time. None had influenza detected in more than one ILI episode.

Unvaccinated children were three times more likely to acquire PCR-confirmed influenza compared with vaccinated children regardless of BMI (RR 3.0, 95% CI: 1.8–4.9). Figure 3 shows protection against PCR-confirmed influenza by vaccination of both obese and non-obese children. Vaccine effectiveness against PCR-confirmed influenza was 72.7% (95% CI: 25.7–90.0%) in obese children and 63.5% (95% CI: 34.6–79.6%) in non-obese children; these values were not statistically different. Of the 16 vaccinated children who acquired PCR-confirmed influenza, 10 (62.5%) had influenza B, 5 (31.3%) had influenza A 2009 H1N1 and 1 (6.2%) had influenza A H3.

Among unvaccinated children, rates of influenza did not significantly differ in obese compared with non-obese children (61.8 vs. 54.7 per 1000 children, $p=0.418$). Frequency of influenza strains did not differ by obesity status. Cough at presentation of illness was more common in obese children with PCR-confirmed influenza compared with non-obese children (86.2 vs. 72.4%, $p=0.030$). The frequencies of all other ILI symptoms were similar between the two groups. Obese children missed a half day more school compared to non-obese children during their PCR-confirmed influenza episodes (2.4 vs. 1.9 days, $p=0.023$).

Influenza-like illness and other respiratory viruses

Vaccinated children had fewer episodes of ILI compared with unvaccinated children overall (169 vs. 204 cases per 1000 children, $p=0.017$). Influenza vaccination resulted in significantly less ILI in non-obese children, but this did not reach statistical significance in obese children (Figure 4). There were no significant differences in number of ILI episodes in obese children compared with non-obese children. Non-influenza respiratory viruses were detected in 111 (13.0%) samples. Eight children were infected with more than one respiratory virus during the same episode. There were no statistical differences in rates of non-influenza respiratory viruses by obesity status or immunization status.

Absenteeism

Children missed more school days during the influenza circulation period compared with the September/October baseline months regardless of obesity status (3.9 vs. 2.2 days per 100 school days, $p<0.001$). Unvaccinated children missed more days than vaccinated children during influenza surveillance period (4.3 vs. 2.8 days per 100 school days). Obese children missed more school days than non-obese children during influenza (4.3 vs. 3.8, $p=0.002$) and non-influenza periods (2.5 vs. 2.1 days per 100 school days, $p=0.004$). Figure 5 shows rates of missed school days broken down by time period, obesity category and vaccination status. Vaccinated obese and non-obese children missed less school days compared with their unvaccinated cohorts during influenza season.

Discussion

In this analysis of school-aged children, we found that influenza vaccine protected obese and non-obese children against PCR-confirmed influenza. This protective effect manifested most significantly in fewer PCR-confirmed influenza cases and improved school attendance regardless of weight category. The findings reinforce the value of immunization for influenza. Two human studies had shown that both obese and lean individuals produce robust hemagglutination inhibition antibody titers following vaccination,(15, 16) but murine studies found that obesity dramatically reduced vaccine efficacy against clinical infection. (14) Our study is the first, to our knowledge, to examine clinical effectiveness in obese children with PCR-confirmed influenza as the study endpoint. We found that vaccinated obese children suffered 3 times less influenza compared with unvaccinated obese children. Furthermore, vaccinated obese children missed less school days during influenza season compared with those unvaccinated. Vaccine protection and effect on absenteeism were similar to non-obese children.

Our study did not find that obese children were more susceptible to influenza compared to non-obese children. Among unvaccinated children, rates of PCR-confirmed influenza were similar in obese and non-obese children. Despite the evidence showing that obesity increases the risk of complications from influenza, the relationship between obesity and susceptibility to influenza infection in humans is less clear. A recent study showed a null relationship between obesity and medically attended, laboratory-confirmed influenza (25). Our study has an advantage in evaluating the question of susceptibility because we prospectively followed our cohorts during influenza season and tested any symptomatic children. Therefore, we captured influenza disease in children who otherwise may not have sought medical attention. In our pediatric cohort, we did not find an association between obesity and increased risk for influenza infection. However, we did not assess vaccination status for the prior season; it is possible that more obese children received influenza vaccination during the 2009 pandemic resulting in partial immunity.

Cough was more prevalent in obese children with confirmed influenza. They also missed more days of school during each influenza infection episodes suggesting that their symptoms lasted longer than their non-obese peers. Experience with the 2009 H1N1 pandemic showed that obese adults had worse outcomes when hospitalized.(3, 26–28) A meta-analysis found that obesity was a risk factor for complicated influenza even during non-2009 H1N1 influenza seasons (29). To our knowledge, no children in our cohort were hospitalized, but the results suggest that obesity might affect the course of illness even for influenza infection in outpatients. Investigators in Canada also found that risk for outpatient visits for acute respiratory infections was increased among obese adolescents and adults (30). Hypotheses for worse outcomes associated with obesity include constricted lung volumes due to excess adipose tissue, dysregulated cytokine production due to chronic inflammation, and defective cellular immune response (3, 31, 32). Obese animal models have shown defects of the innate and adaptive immune responses to influenza including type I interferon response, natural killer cell function, antigen presentation by dendritic cells and monocyte recruitment, and antigen-specific memory of CD8+ T cells (33–36). The relationship between BMI and immune responses in humans needs more investigation, but

the existing studies underscore the importance of influenza prevention in obese individuals by vaccination.

This study has several limitations. The study was conducted over a single influenza season. Our study population was heavily skewed toward Hispanic and Asian/Pacific Islander race/ethnicities, which may diminish its generalizability. We did not capture medication history or comorbidities of the children such as asthma or diabetes mellitus that may have affected respiratory illness incidence or outcome. Other information such as medically attended illnesses, hospitalizations, supplementary oxygen requirements, or prescribed antibiotics were not collected, which limited our ability to assess illness severity. We also did not collect any information about influenza antiviral treatment, which could affect illness severity and duration. We examined elementary school-aged children, but adolescents and adults may have distinct metabolic profile; their longer duration of living in an obese state and increasing chronic inflammation may result in different responses to vaccination and subsequent influenza exposure (37–39). We did not assess hemagglutination inhibition (HAI) antibody titers. Sheridan et al. described a robust HAI titer after influenza vaccination followed by a rapid decline by 12 months (16). In our cohort, vaccine protection against PCR-confirmed influenza was similar at the beginning and end of the influenza season; there was no evidence of rapid declining immunity among the vaccinated obese children. One hypothesis of lower vaccine response among obese individuals is that standard vaccine needle lengths do not penetrate the deltoid fat pad into the muscle of obese individuals (40). While other studies (15, 16, 39) have evaluated the response to intramuscular vaccine, the overwhelming majority of children in this study received LAIV for which needle length is not an issue. Furthermore, because studies have shown LAIV to be more effective in preventing influenza in children compared to TIV (41–43), the results of this study may not be generalizable to inactivated influenza vaccines. Our study was not designed, and therefore not powered, to compare differences in effectiveness between LAIV and TIV in obese children.

Vaccination of obese children is protective against PCR-confirmed influenza. Although obese children were not at increased risk for influenza infection in our study, they did suffer from more cough and a longer duration of illness when they were infected. Yearly vaccination is the most effective defense against infection and subsequent complications of influenza disease in obese children.

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Figure 1.
BMI-for age distribution of 4260 school children at participating elementary schools, Los Angeles County, 2011.

Figure 2. Distribution of respiratory viruses detected by PCR among 309 (36.1%) of 856 children with ILI. Influenza accounted for 65% of the respiratory viruses detected by RT-PCR in school children during the surveillance period, Los Angeles County, 2011. RT-PCR did not identify a respiratory virus in 547 (63.9%) children with ILI.

Figure 3.
PCR-confirmed influenza rates among 1191 obese and 3069 non-obese school children.
Rates were higher in non-vaccinated school children regardless of obesity status.

Figure 4.

Rates of Influenza-like illness (ILI) among 1191 obese and 3069 non-obese school children. ILI Rates were similar in obese and non-obese school children. Influenza vaccination resulted in less ILI in non-obese children but did not reach statistical significance in obese children.

Figure 5.

Absenteeism among 1191 obese and 3069 non-obese school children. Unvaccinated obese and non-obese school children missed more school days during influenza season compared to vaccinated children.

Table 1

Characteristics of 4260 school children by obesity category, Los Angeles, CA.

Characteristic	Non-obese (BMI 95%)	Obese (BMI>95%)	Total	p-value
No. of students [n(%)]	3069 (72.0)	1191 (28.0)	4260	
Grade (range)	K-6	K-6	K-6	NS
Age [years, mean (range)]	8.2 (5–13)	8.4 (5–13)	8.3 (5–13)	p=0.014
Male, [n (%)]	1508 (49.1)	707 (59.4)	2215 (52.0)	p<0.001
Race or Ethnic group [n(%)]				p<0.001
Hispanic	1929 (62.9)	942 (79.1)	2871 (67.4)	
Asian	977 (31.8)	185 (15.5)	1162 (27.3)	
White	62 (2.0)	27 (2.3)	89 (2.1)	
African American	21 (0.7)	4 (0.3)	25 (0.6)	
American Indian/Alaskan Native	11 (0.4)	3 (0.3)	14 (0.3)	
Mixed race/ethnicity	30 (1.0)	12 (1.0)	42 (1.0)	
Other/unknown	39 (1.3)	18 (1.5)	57 (1.3)	
Baseline absenteeism days* (mean, per 100 school days)	2.1	2.5	2.3	p=0.004

* Baseline absenteeism rate was calculated based on absent days of all enrolled children during September and October, 2010.

NS, not significant

Table 2

Influenza vaccination status in school children by school-located vaccination (SLV) and community physicians as documented in the Los Angeles-Orange County California Immunization Registry (CAIR), 2010–11. There was no significant difference in vaccination rates of type of vaccine given (TIV or LAIV) among obese versus non-obese children.

Vaccination Status	Non-obese (BMI <95%)	Obese (≥95%)	Total
Vaccinated, SLV	534 (17.4)	213 (17.9)	747 (17.5)
TIV	95 (17.8)	31 (14.6)	126 (16.9)
LAIV	439 (82.2)	182 (85.4)	621 (83.1)
Vaccinated, CAIR	67 (2.2)	24 (2.0)	91 (2.1)
Total vaccinated	601 (19.6)	237 (19.9)	838 (19.7)