

Impact of Body Mass Index on Immunogenicity of Pandemic H1N1 Vaccine in Children and Adults

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Obesity emerged as a risk factor for morbidity and mortality related to 2009 pandemic influenza A (H1N1) infection. However, few studies examine the immune responses to H1N1 vaccine among children and adults of various body mass indices (BMI). Pooling data from 3 trials of unadjuvanted split-virus H1N1 A/California/07/2009 influenza vaccines, we analyzed serologic responses of participants stratified by BMI grouping. A single vaccine dose produced higher hemagglutination inhibition antibody titers at day 21 in obese compared to nonobese adults, but there were no significant differences in responses to H1N1 vaccine among children or adults of various BMI following 2 doses.

Keywords. body mass index; influenza vaccine; immune response; obesity.

In both children and adults, obesity emerged as an important risk factor for morbidity and mortality during the 2009 influenza A(H1N1) pandemic [1]. It was hypothesized that obese individuals had diminished respiratory reserve and an increased incidence of both cardiac disease and metabolic syndromes, such as diabetes mellitus, making them more susceptible to influenza-related complications. However, epidemiologic studies suggested that there were more complications associated with obesity alone, independent of other comorbidities [2]. In light of these observations, the Advisory Committee on

Immunization Practices (ACIP) added morbid obesity (body mass index [BMI] ≥ 40 kg/m²) to the list of priority groups for vaccination against pandemic influenza [3].

There are few studies regarding the impact of obesity on immune responses to influenza vaccine in general and specifically to pandemic H1N1 vaccine. Sheridan and colleagues found no significant differences in seroconversion rates to the H1N1 component of trivalent inactivated influenza vaccine (IIV3) among obese and nonobese vaccinees, although this H1N1 strain was not the pandemic one [4]. Similarly, in a study of adults ≥ 50 years, Talbot et al found no association between obesity and seroconversion to a different H1N1 component of IIV3 [5]. In animal models, Kim et al reported that monovalent H1N1 vaccine was protective against an influenza challenge in lean mice, but that diet-induced obese mice had markedly diminished antibody responses that were not protective against an influenza challenge [6].

Similarly, there are few studies of the immunogenicity of H1N1 vaccine among underweight children and adults. A pilot study of immunogenicity of H1N1 vaccination among 10 adults with anorexia nervosa found antibody levels at 2 and 3 weeks to be similar to published data, but the study lacked a control group and the persistence of immune response was not evaluated [7]. Starvation, as seen in eating disorders like anorexia nervosa, has been shown to alter B-cell and T-cell responsiveness, although the implications for the immunogenicity of vaccines are unknown [8].

Given that one-third of the United States population are obese and 2%–5% are underweight, it is important to assess the impact of elevated and low BMI on the immunogenicity of the pandemic H1N1 vaccine in children and adults [9, 10]. Thus, the specific aims of this study were to compare the serologic responses to pandemic H1N1 vaccine among children and adults of various BMI.

METHODS

Study Design

Pooled data were analyzed from 3 independently conducted NIH-supported phase 2, multicenter clinical trials of monovalent, unadjuvanted split-virus pandemic H1N1 A/California/07/2009 influenza vaccines conducted from August 2009 to March 2010 at 8 Vaccine and Treatment Evaluation Units (VTEUs). Study details are available in the literature or at ClinicalTrials.gov (NCT00943488, NCT00943631, and NCT00944073) [11].

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Vaccine

One trial enrolled children and adolescents (ages 6 months to 17 years inclusive) using vaccine manufactured by Sanofi Pasteur (Swiftwater, PA) and provided by the Biomedical Advanced Research and Development Authority (BARDA). Two trials with identical study designs enrolled nonpregnant adults (≥ 18 years) and used vaccine manufactured by either Sanofi Pasteur or CSL Biotherapies (Parkville, Australia) and provided by BARDA [11]. Study participants were randomly assigned to receive 2 intramuscular injections of study vaccine containing either 15 μg or 30 μg of hemagglutinin (HA) as determined by high-performance liquid chromatography spaced 21 days apart. For the studies using the Sanofi Pasteur vaccine, final potency testing by single radial immunodiffusion (SRID) assay showed a HA content of 22–25 μg for the 15 μg dosage (2 different lots were used to conduct the study) and 47 μg for the 30 μg dosage. Data regarding age, comorbid medical conditions, gender, race, and prior receipt of seasonal influenza vaccine were collected at study entry.

Determination of BMI

Height and weight were measured by research staff, and BMI was calculated as weight (kg)/height (m)². All subjects age ≥ 2 years with BMI data were included. For subjects age 2–19 years, age- and gender-specific *z*-scores for BMI were calculated using software available from the Centers for Disease Control and Prevention (CDC) based on the 2000 CDC growth charts to define BMI categories of underweight (<5th percentile), normal weight (5–84th percentile), overweight (85–94th percentile), and obese (≥ 95 th percentile) [12]. Subjects ≥ 20 years of age were grouped according to clinical guidelines into BMI categories of underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obese (30.0–39.9 kg/m²), and morbidly obese (≥ 40 kg/m²) [13].

Immunogenicity

Serum samples were obtained immediately before and on days 8 and 21 after each vaccination and were analyzed at Southern Research Institute (Birmingham, AL) for hemagglutination inhibition antibody (HAI) titers. Geometric mean titers (GMT) of HAI were determined. Seroconversion was defined as a 4-fold rise in HAI if the prevaccine HAI titer was $\geq 1:10$ or a postvaccination HAI titer $\geq 1:40$ if the prevaccination HAI titer was $< 1:10$. Seroprotection was defined as a postvaccination HAI titer $\geq 1:40$. Results for children, adolescents, and adults were stratified by BMI grouping.

Analyses

Serum HAI antibody responses 21 days after each vaccine dose were compared in a pair-wise manner for normal weight subjects vs each of the other weight groups. Unless explicitly noted, results were adjusted for multiple comparisons using

the Sidak method. Analysis of covariance of log transformed titers was used both without controlling for covariates and controlling for race, age, and baseline titers. Contrasts were used within these analyses to examine the pair-wise differences. The nonparametric Kruskal–Wallis test was also used as a check on the direct comparisons of normal and nonnormal weight groups. Seroprotection and seroconversion for normal weight subjects were similarly compared without controlling for covariates using Fisher exact test and controlling for race, age, and baseline titers using logistic regression. Separate models were created for children (ages 2–11), adolescents (ages 12–19), and adults (ages ≥ 20) corresponding to CDC growth parameters and approximating prepubertal, pubertal, and adult development, respectively. Note that 18–19 year olds in the adolescent group were enrolled in the 2 adult trials and not in the pediatric study.

The current study was approved by the Institutional Review Board of Vanderbilt University and the clinical studies from which the data were derived were each individually approved by the Institutional Review Boards of the academic medical centers conducting the trials.

RESULTS

Children and Adolescents

Subject characteristics and serologic responses to pandemic H1N1 vaccine for 178 children and 160 adolescents are presented in Table 1. Seven percent of children and 13% of adolescents were obese, whereas 6% of children and 1% of adolescents were underweight.

Prevaccination GMT were significantly higher for children in the overweight category compared to children in the normal weight category ($P = .03$; Table 1). After vaccine dose 1, children in the underweight category had lower GMT than those in the normal weight category, although the difference was not statistically significant after adjusting for multiple comparisons ($P = .03$ unadjusted; $P = .08$ adjusted). There were no significant differences in postvaccination GMT in the children between weight categories following dose 1 or 2 after controlling for age, race, and prevaccine GMT. After dose 1, rates of seroconversion and seroprotection were lower for underweight children compared to children in the normal weight category (20% vs 52%); however, due to the small number of underweight children, this did not reach statistical significance ($P = .10$, uncorrected Fisher exact test). For all children, seroconversion and seroprotection rates after dose 1 and dose 2 were 51% and 87%, respectively. There were no significant differences in rates of seroconversion or seroprotection by weight category after dose 2 or after controlling for age, race, and prevaccination titers after either dose.

Table 1. Characteristics and Immune Response to One or Two Doses of Monovalent H1N1 Vaccine in Children (A) 2–11 Years and (B) 12–19 Years by BMI percentile grouping

BMI Percentiles	Underweight (<5)	Normal Weight (5–84.9)	Overweight (85–94.9)	Obese (≥95)	Total
(A) Children 2–11 y					
N (row %)	10 (6)	137 (77)	18 (10)	13 (7)	178 (100)
Mean Age (SD), years	5.1 (2.5)	6.6 (2.8)	6.8 (3.5)	5.9 (2.5)	6.5 (2.8)
Gender					
Female n (row %)	2 (3)	61 (88)	4 (6)	2 (3)	69 (100)
Male n (row %)	8 (7)	76 (70)	14 (13)	11 (10)	109 (100)
Race					
White n (%)	6 (4)	120 (83)	11 (8)	8 (6)	145 (100)
Non-white n (%)	4 (12)	17 (52)	7 (21)	5 (15)	33 (100)
Prior receipt of IIV3 n (%)	8 (80)	116 (85)	13 (72)	12 (92)	149 (84)
Hemagglutination Inhibition (HAI)					
GMT (CI), prevaccine ^a	5.0 (.) ^b	5.7 (5.1, 6.3)	7.8 (5.0, 12.8)	7.1 (5.0, 11.8)	5.9 (5.3, 6.5)
Post Dose 1					
GMT (CI), postvaccine ^a	10 (5, 20)	38 (28, 52)	61 (20, 190)	60 (14, 250)	38 (29, 51)
Seroconversion ^c n (%)	2 (20)	71 (52)	11 (61)	7 (54)	91 (51)
Seroprotection ^d n (%)	2 (20)	71 (52)	11 (61)	7 (54)	91 (51)
Post Dose 2					
GMT (CI), postvaccine ^a	120 (57, 240)	150 (115, 195)	170 (76, 390)	320 (170, 590)	158 (126, 198)
Seroconversion ^c n (%)	10 (100)	116 (85)	15 (83)	13 (100)	154 (87)
Seroprotection ^d n (%)	10 (100)	117 (86)	15 (83)	13 (100)	155 (87)
(B) Children 12–19 y					
N (%)	2 (1)	110 (69)	27 (17)	21 (13)	160 (100)
Mean Age (SD), years	12 (0)	14 (2)	14 (2)	15 (2)	14 (2)
Gender					
Female n (%)	1 (1)	50 (62)	17 (21)	12 (15)	80 (100)
Male n (%)	1 (1)	60 (75)	10 (12)	9 (11)	80 (100)
Race					
White n (%)	1 (1)	93 (74)	18 (14)	14 (11)	126 (100.0)
Nonwhite n (%)	1 (3)	17 (50)	9 (26)	7 (21)	34 (100)
Prior receipt of IIV3 n (%)	1 (50)	71 (65)	16 (59)	10 (48)	98 (61)
Hemagglutination Inhibition (HAI)					
GMT (CI), prevaccine ^a	5.0 (.) ^b	7.4 (6.1, 8.8)	11.7 (6.2, 21.8)	9.2 (4.6, 18.2)	8.2 (6.8, 9.8)
Post Dose 1					
GMT (CI), postvaccine ^a	190 (5, >5000)	464 (356, 605)	368 (202, 674)	534 (266, 1070)	450 (360, 562)
Seroconversion ^c n (%)	2 (100)	102 (93)	24 (89)	18 (86)	146 (91)
Seroprotection ^d n (%)	2 (100)	104 (95)	25 (93)	19 (90)	150 (94)
Post Dose 2					
GMT (CI), postvaccine ^a	190 (5, >5000)	561 (476, 661)	528 (326, 854)	718 (456, 1130)	566 (487, 657)
Seroconversion ^c n (%)	2 (100)	109 (99)	25 (93)	20 (95)	156 (98)
Seroprotection ^d n (%)	2 (100)	110 (100)	26 (96)	21 (100)	159 (99)

BMI, body mass index (kg/m²).

Abbreviations: CI, 95%, confidence interval; GMT, geometric mean titers; SD, standard deviation.

^a Reciprocal titers <10 were imputed to 5.

^b All values = 5 for this cell.

^c Seroconversion (≥4 fold increase in HAI titer, post/prevaccine and postvaccination titer ≥1:40).

^d Seroprotection (HAI titer ≥1:40).

Among adolescents (Table 1), there were no significant differences by weight category in prevaccination or postvaccination GMT, or in seroconversion or seroprotection rates after either

vaccine dose 1 or 2. Seroconversion rates among all adolescents after dose 1 and dose 2 were 91% and 98%, respectively, and seroprotection rates were 94% and 99%, respectively.

Table 2. Characteristics and Immune Response to One or Two Doses of Monovalent H1N1 Vaccine Adults (≥20 Years) by BMI Grouping

BMI	Underweight (<18.5)	Normal Weight (18.5–24.9)	Overweight (25.0–29.9)	Obese (30.0–39.9)	Morbid Obesity (≥40.0)	Total
N (%)	6 (1)	264 (33)	293 (37)	201 (25)	30 (4)	794 (100)
Mean Age (SD), years	63 (10)	57 (18)	60 (16)	61 (14)	49 (17)	59 (16)
Gender						
Female n (%)	6 (1)	179 (42)	123 (29)	102 (24)	17 (4)	427 (100)
Male n (%)	0 (0)	85 (23)	170 (46)	99 (27)	13 (4)	367 (100)
Race						
White n (%)	5 (1)	243 (34)	273 (38)	180 (25)	22 (3)	723 (100)
Nonwhite n (%)	1 (1)	21 (30)	20 (28)	21 (30)	8 (11)	71 (100)
Prior receipt of IIV3 n (%)	5 (83)	220 (83)	256 (87)	178 (89)	21 (70)	680 (86)
Hemagglutination Inhibition (HAI)						
GMT (CI), prevaccine ^a	10.0 (4.0, 25.1)	10.6 (9.2, 12.2)	10.0 (8.8, 11.4)	9.9 (8.4, 11.6)	8.2 (5.7, 11.8)	10.1 (9.3, 10.9)
Post Dose 1						
GMT (CI), postvaccine ^a	269 (33, 2181)	140 (113, 172)	134 (109, 166)	184 (147, 230)	273 (154, 485)	152 (135, 172)
Seroconversion ^b n (%)	5 (83)	79 (73)	206 (70)	158 (79)	24 (80)	586 (74)
Seroprotection ^c n (%)	5 (83)	214 (81)	228 (78)	172 (86)	26 (87)	655 (81)
Post Dose 2						
GMT (CI), postvaccine ^a	170 (27, 1100)	151 (125, 182)	143 (119, 172)	181 (146, 224)	257 (149, 442)	158 (142, 176)
Seroconversion ^b n (%)	5 (83)	204 (77)	217 (74)	162 (81)	26 (87)	614 (77)
Seroprotection ^c n (%)	5 (83)	224 (85)	240 (82)	175 (87)	28 (93)	672 (85)

BMI, body mass index (kg/m²).

Abbreviations: CI, 95%, confidence interval; GMT, geometric mean titers; SD, standard deviation.

^a Reciprocal titers <10 were imputed to 5.

^b Seroconversion (≥4 fold increase in HAI titer, post/prevaccine and postvaccination titer ≥1:40).

^c Seroprotection (HAI titer ≥1:40).

Adults

Table 2 displays characteristics and serologic response to H1N1 vaccine for 794 adult subjects. Nearly 30% of subjects were obese or morbidly obese, 37% were overweight, and only 1% was underweight. Morbidly obese adults were younger than obese or overweight adults ($P < .01$ adjusted for multiple comparisons) and morbidly obese and obese adults were significantly more likely to be nonwhite ($P = .02$). Adults in the normal weight category were significantly more likely to be female ($P < .001$).

Subjects in the morbidly obese category had significantly higher GMT than subjects in the normal weight category after dose 1 ($P = .04$). This difference persisted even after adjusting for age, race, and baseline GMT ($P = .04$). There was no significant difference between subjects of various BMI in GMT after dose 2. In analyses not shown, we compared results for male and female subjects separately and found no significant differences in GMT by weight category for either gender. Seroconversion rates among all adults after dose 1 and dose 2 were 74% and 77%, respectively, and seroprotection rates were 81% and 85%, respectively. Rates of seroconversion and seroprotection did not significantly differ by weight category in adults.

DISCUSSION

In this analysis of pooled data from 1 trial of children and adolescents and 2 trials of adults using 2 different monovalent, unadjuvanted pandemic H1N1 vaccines, we found significantly higher serologic response to 1 dose of H1N1 vaccine among obese adults compared to adults of normal weight. However, we found no significant differences in serologic response after 2 doses of vaccine among children, adolescents, or adults by weight categories. These findings are consistent with 2 studies of IIV3 in obese adults and extend prior research to include data on children and adolescents [4, 5]. Together, these results demonstrate robust serologic responses of individuals of various BMI to pandemic H1N1 vaccine.

After controlling for age, race, and prevaccination GMT, obese adults had significantly higher GMT than peers in the normal weight category following 1 dose of vaccine. These findings are of interest because the recommended usage of H1N1 monovalent vaccine in adults was 1 dose. Our observation is similar to Sheridan and colleagues who reported higher GMT among obese adults following 1 dose of seasonal IIV3 containing a nonpandemic H1N1 strain [4]. In the Sheridan study,

obese subjects had greater decline in HAI titers at 12 months postvaccination than subjects of normal weight. Moreover, these authors found that CD4⁺ and CD8⁺ T-cell activation to an ex vivo challenge with H1N1 at 12 months postvaccination was significantly lower in obese relative to normal weight individuals [4, 14]. The mechanisms mediating their findings, and the clinical implications are unknown. It is reassuring that initial HAI antibody response to H1N1 vaccine among obese individuals was robust; however, more studies are needed to determine the longevity of this response.

We observed lower GMT following dose 1 of vaccine among children in the underweight category when compared to those in the normal weight category; however, the difference was not statistically significant, likely due to the small number of underweight participants. Only 4% of the adolescent population in the United States is underweight; but globally the percentage of children and adolescents who are underweight is much higher, particularly in low- and middle-income countries [15]. Given that children who are underweight and/or undernourished may be more susceptible to infection, the response to vaccines by underweight individuals represents an important area for future research.

Our study has a number of limitations. First, it evaluated the serologic responses to only a monovalent influenza vaccine, and it is possible that immune responses may differ for trivalent or quadrivalent influenza vaccines. Second, relatively small numbers of underweight and morbidly obese subjects limited our ability to detect differences in these specific groups. The strengths of this study include its large sample size (including large numbers of individuals whose BMI places them in the obese category), multiple study sites, and the inclusion of individuals of various ages.

In conclusion, we found that a single dose of the vaccine produced higher HAI GMT at day 21 in obese adults compared to other BMI groups. However, we found no significant differences in the serum HAI antibody responses following immunization with 2 doses of unadjuvanted, inactivated, monovalent 2009 H1N1 influenza vaccines when administered to children, adolescents, and adults of various BMI.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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