

Vaccination of patients with mild and severe asthma with a 2009 pandemic H1N1 influenza virus vaccine

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Background: Asthma was the most common comorbidity of patients hospitalized with 2009 H1N1 influenza.

Objective: We sought to assess the immunogenicity and safety of an unadjuvanted, inactivated 2009 H1N1 vaccine in patients with severe versus mild-to-moderate asthma.

Methods: We conducted an open-label study involving 390 participants (age, 12-79 years) enrolled in October-November 2009. Severe asthma was defined as need for 880 µg/d or more of inhaled fluticasone equivalent, systemic corticosteroids, or both. Within each severity group, participants were randomized to receive intramuscularly 15 or 30 µg of 2009 H1N1 vaccine twice 21 days apart. Immunogenicity end points were seroprotection (hemagglutination inhibition assay titer ≥40) and seroconversion (4-fold or greater titer increase). Safety was assessed through local and systemic reactogenicity, asthma exacerbations, and pulmonary function.

Results: In patients with mild-to-moderate asthma (n = 217), the 2009 H1N1 vaccine provided equal seroprotection 21 days after the first immunization at the 15-µg (90.6%; 95% CI, 83.5% to

95.4%) and 30-µg (95.3%; 95% CI, 89.4% to 98.5%) doses. In patients with severe asthma (n = 173), seroprotection 21 days after the first immunization was 77.9% (95% CI, 67.7% to 86.1%) and 94.1% (95% CI, 86.8% to 98.1%) at the 15- and 30-µg doses, respectively (P = .004). The second vaccination did not provide further increases in seroprotection. Participants with severe asthma who are older than 60 years showed the lowest seroprotection (44.4% at day 21) with the 15-µg dose but had adequate seroprotection with 30 µg. The 2 dose groups did not differ in seroconversion rates. There were no safety concerns. **Conclusion:** Monovalent inactivated 2009 H1N1 pandemic influenza vaccine was safe and provided overall seroprotection as a surrogate of efficacy. In patients older than 60 years with severe asthma, a 30-µg dose might be more appropriate. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: H1N1, asthma, influenza, vaccine, seroprotection, severe asthma

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The names of the institutions and investigators who collaborated in the H1N1 vaccination study are shown in [Appendix 1](#).

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Abbreviations used

FVC: Forced vital capacity
 GMT: Geometric mean titer
 HAI: Hemagglutination inhibition
 ICS: Inhaled corticosteroid
 SAE: Serious adverse event
 TIV: Trivalent seasonal influenza vaccine

The US Centers for Disease Control and Prevention estimate that between April 2009 and March 2010, 8,720 to 18,050 deaths and 193,000 to 398,000 hospitalizations can be attributed to the 2009 H1N1 influenza virus pandemic.¹ The most common comorbidity for patients hospitalized as a result of the 2009 H1N1 virus infection was asthma,^{2,3} and the percentage of patients with asthma hospitalized because of the 2009 H1N1 virus was 4- to 5-fold higher than the prevalence of asthma in the general population.³⁻⁵

Viral infections are triggers of asthma exacerbations,^{6,7} although the role of influenza was not previously as clear as the epidemiologic data from the 2009 H1N1 pandemic now indicate. The Advisory Committee on Immunization Practices has recommended vaccination of patients with chronic disorders of the pulmonary system, including asthma.⁸ Similarly, immunization against influenza has been recommended for asthmatic patients by national and international asthma management guidelines^{9,10} and has been reported to be safe.¹¹

As the 2009 H1N1 influenza pandemic was developing, it was expected that asthma would be in the priority list for vaccination given the limited vaccine stock that was initially available. However, knowledge regarding the efficacy and safety of the newly developed 2009 H1N1 pandemic influenza vaccine in this high-risk population was unknown. Furthermore, based on suggestive data from a previous study testing a seasonal influenza vaccine,¹² the hypothesis was raised that optimal immunization rates might not be achieved in patients with severe asthma because of long-term, high-dose corticosteroid treatment.

This study was designed to assess the immunogenicity and safety of the 2009 H1N1 vaccine in 2 groups of patients with asthma: those with severe disease (receiving high-dose inhaled corticosteroids [ICSs], systemic corticosteroids, or both) and those with mild-to-moderate disease. The design of the study included 2 intramuscular vaccine doses (15 and 30 μ g), with each dose administered twice (3 weeks apart).

METHODS**Study population**

A total of 390 male and nonpregnant female participants aged 12 to 79 years were enrolled at 7 clinical centers of the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Eligibility was limited to participants who (1) had physician-diagnosed asthma, (2) had confirmed asthma symptoms within the last 12 months, and (3) did not have a known or suspected history of the 2009 H1N1 virus infection or treatment. Patients who had received the trivalent seasonal influenza vaccine (TIV) within 2 weeks before the study were not eligible for participation, nor was TIV vaccination allowed until 3 weeks after the second 2009 H1N1 virus vaccination. Participants receiving high doses of ICSs (≥ 880 μ g of fluticasone equivalent per day) or continuous or near-continuous (50% of year) systemic (oral or injectable) corticosteroids to maintain asthma control or whose symptoms were uncontrolled despite this treatment were classified as having severe asthma.¹³

The protocol was approved by all institutional review boards. Written informed consent was obtained from each participant or his or her parent or legal guardian. Adolescents aged 12 to 17 years provided assent.

Study design

This was a randomized, open-label study to investigate the safety and immunogenicity of 2 administrations of an unadjuvanted, inactivated 2009 H1N1 virus vaccine (Novartis Vaccines and Diagnostics Ltd, Speke, Liverpool, United Kingdom) delivered intramuscularly at 2 dose levels (15 or 30 μ g) 21 days apart. The 15- μ g dose was administered as 1 injection, and the 30- μ g dose was administered as 2 injections (15 μ g in each arm). A high-dose formulation for single injection was not available at the time of the study. At the initial clinic visit, asthma characterization was performed, and participants were randomized into one of 2 dose-level groups stratified by asthma severity (mild to moderate and severe), age (12-17, 18-64, and >64 years), and investigative site. The study consisted of 5 clinic visits (days 1, 8, 21, 28, and 41), as well as 2 interim and 3 follow-up telephone contacts for safety assessment (days 81, 141, and 201).

Solicited injection-site and systemic reactogenicity were assessed according to conventional vaccine trials.¹⁴ Asthma-related information was obtained from daily symptom diaries and participant reports. Specifically, in the diary participants recorded the use of albuterol in the previous 24 hours, the number of awakenings requiring albuterol treatment, and the presence and severity (on a 4-point scale) of chest tightness, wheeze, cough, and shortness of breath assessed each morning for overnight and each evening for daytime. In addition, at each study visit, information was obtained from each participant regarding asthma-related hospitalizations, unscheduled medical visits for asthma management, and initiation of an oral corticosteroid burst or increase in the regular dose of oral corticosteroids. Pulmonary function testing (spirometry) was conducted at each visit. Asthma exacerbations were defined as any of the following: (1) unscheduled medical visit for asthma management, (2) initiation or increase in the dose of oral corticosteroids, and (3) increase by 6 or more puffs or 2 nebulizations per day of albuterol for 2 consecutive days.

The following serum assays were performed on blood samples collected at each clinic visit: (1) 2009 H1N1 influenza virus hemagglutination inhibition (HAI) and (2) 2009 H1N1 influenza microneutralization. Both assays were performed at a central laboratory (Southern Research Institute, Birmingham, Ala) in accordance with World Health Organization–recommended standards.¹⁵ In addition, at baseline, total serum IgE and specific IgE levels for 9 common aeroallergens were measured. HAI titers against the viral components of the 2009 TIV were measured only at baseline in a subgroup of the study population who had received the 2009 seasonal influenza vaccine before entering our study. Each serum sample was tested against 3 influenza viruses (A/Brisbane/59/2007 [H1N1], A/Brisbane/10/2007 [H3N2], and B/Brisbane/60/2008), which matched the 2009-2010 TIV. The assays were conducted at the Center for Vaccine Research, University of Pittsburgh.¹⁵

Primary immunogenicity outcomes included the percentage of participants with putative seroprotection (HAI titers ≥ 40) and the percentage of participants with seroconversion (≥ 4 -fold increase in HAI titers) after 2 administrations of the vaccine (day 41). Secondary end points included the same data after the first vaccination (day 21). HAI titers on the viral components of the 2009 TIV were exploratory end points.

Statistical methods

A sample size of 150 participants in the group with severe asthma (75 per dose group) was chosen to provide at least 87% power to detect seroprotection differences of 20% or greater between dose groups (ie, 90% vs 70%). Categorical variables were summarized with enumerations and percentages, and exact 95% CIs (Clopper-Pearson method) were computed to describe seroprotection and seroconversion rates. All participants who received at least 1 vaccination and provided serum at day 1 and either days 21 or 41 were included in the analyses. Logistic regression modeling assessed associations between seroprotection and explanatory variables (eg, receipt of 2009 influenza vaccine), adjusting for covariates (eg, age and baseline HAI titers).

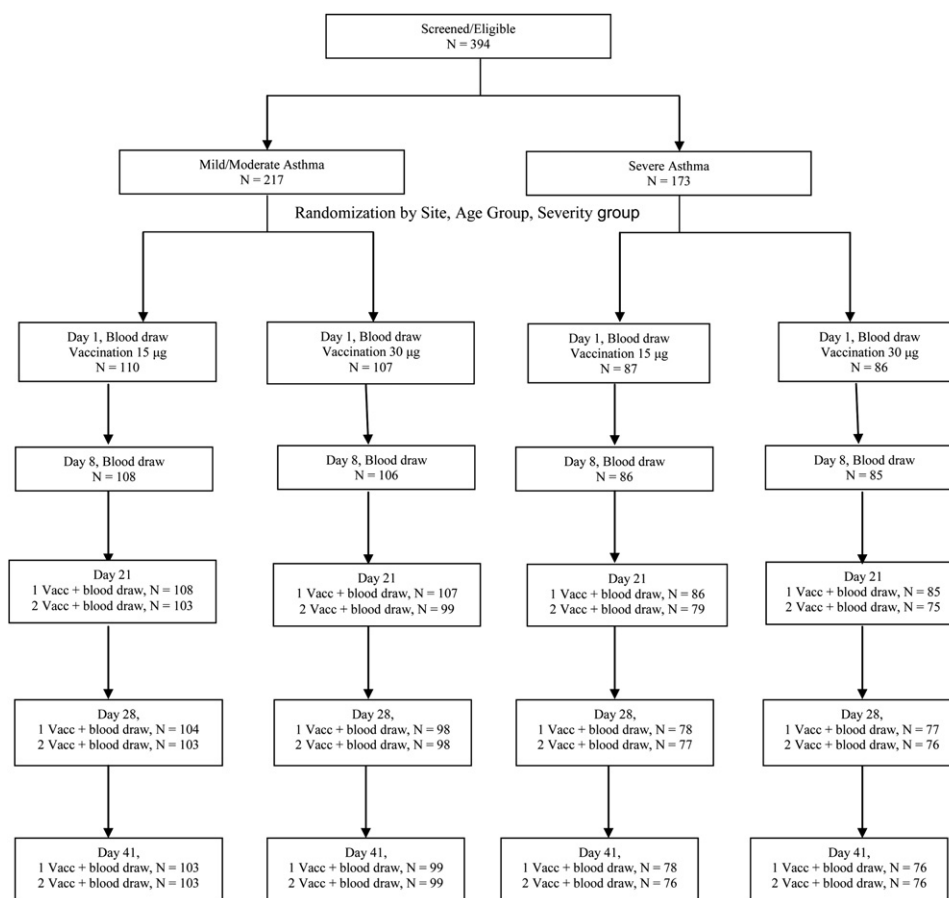


FIG 1. Consolidated Standard of Reporting Trials diagram. Panels representing days 21, 28, and 41 report 2 groups of participants. *First line*, Participants who had their first vaccination on day 1 and blood draw on the indicated study visit. *Second line*, Participants who had their first vaccination on day 1, second vaccination on day 21, and blood draw on the indicated study visit. The group in the second line is a subgroup of the group in the first line. Randomization was stratified by investigative site, asthma severity group, and age group.

RESULTS

Study participants

Study participants were enrolled from October 16 to November 13, 2009. Of the 394 enrolled and eligible subjects, 390 were randomized (Fig 1) and received 1 (15 µg) or 2 (30 µg) injections of vaccine on day 1. Of these, 357 received a second administration of the same vaccine dose on day 21.

Participant age was 12 to 79 years, and those with severe asthma were on average older than those with mild-to-moderate asthma (Table I). Of the randomized participants, 52.8% reported receiving the 2009 TIV at least 2 weeks before enrollment. Participants with severe asthma had lower baseline lung function and higher body mass index.

A total of 33 participants did not receive the second vaccination on day 21 because of adverse events ($n = 18$), asthma exacerbations ($n = 9$), not meeting eligibility criteria ($n = 4$), and participant withdrawal ($n = 2$). The percentage of participants who missed the second vaccination did not differ between the 2 asthma severity groups.

Immunogenicity

Fig 2 presents geometric mean titers (GMTs) for the HAI assay for all study participants. A single 15- or 30-µg dose of the 2009

H1N1 virus vaccine produced a robust immune response, with significant differences between the 2 dose levels in the severe asthma group. The second vaccination on day 21 produced no further increases in HAI GMTs. Consequently, other analyses presented herein focus on immunogenicity at day 21, 3 weeks after the first vaccination.

Table II presents seroprotection rates (percentage of participants with HAI titers ≥ 40) and seroconversion rates (percentage of participants with a ≥ 4 -fold increase from baseline in HAI titers), as well as absolute GMT values for all participants at baseline and day 21. At baseline, between 21.4% and 26.7% of subjects were seroprotected despite no clinical history of 2009 H1N1 virus infection; these rates were not different between study groups but were higher in younger participants (data not shown). After the first vaccination, seroprotection was greater than 90% in the mild-to-moderate asthma group, and no difference between the 15- and 30-µg doses was noted. In the severe asthma group seroprotection was 77.9% for participants who received the 15-µg dose and 94.1% for those who received the 30-µg dose ($P = .004$). When only participants without baseline seroprotection were analyzed, the difference in vaccine-induced seroprotection between the 15- and 30-µg doses became even larger in the severe asthma group (69.8% vs 92.3%, $P = .001$). The 2 vaccine doses did not differ in seroconversion rates.

TABLE I. Demographic characteristics of study participants, baseline spirometric results, and body mass index

	Mild-to-moderate asthma (n = 217)		Severe asthma (n = 173)	
	15- μ g Vaccine dose (n = 110)	30- μ g Vaccine dose (n = 107)	15- μ g Vaccine dose (n = 87)	30- μ g Vaccine dose (n = 86)
Current age (y)	39.1 $\pm$ 18.1	36.3 $\pm$ 17.0	45.2 $\pm$ 17.0	46.5 $\pm$ 17.3
Age at asthma onset (y)	17.1 $\pm$ 17.0	16.4 $\pm$ 14.9	21.9 $\pm$ 19.7	21.9 $\pm$ 20.1
Asthma duration (y)	21.9 $\pm$ 13.9	19.9 $\pm$ 13.4	23.3 $\pm$ 16.5	24.6 $\pm$ 17.8
Body mass index (kg/m ²)	29.5 $\pm$ 8.5	28.5 $\pm$ 6.8	31.8 $\pm$ 9.7	30.1 $\pm$ 8.0
FEV ₁ (% predicted)	83.8 $\pm$ 16.3	86.6 $\pm$ 17.6	72.6 $\pm$ 19.4	69.8 $\pm$ 20.8
FVC (% predicted)	92.6 $\pm$ 14.3	94.3 $\pm$ 16.1	85.0 $\pm$ 17.1	80.9 $\pm$ 18.7
FEV ₁ /FVC ratio ($\times$ 100)	74.5 $\pm$ 9.07	75.7 $\pm$ 8.99	68.4 $\pm$ 10.91	68.4 $\pm$ 11.76
Sex (% female)	65	58	60	52
Race (%)				
White	66	76	72	65
African American	28	20	25	34
Other	5	5	2	1
Ethnicity (%)				
Hispanic or Latino	4	4	3	0
Received 2009 seasonal TIV before H1N1 study (%)	44	51	62	57
Received 2009 seasonal TIV after vaccination (%)*	40	39	32	39

Values are presented as means $\pm$ SDs unless otherwise noted.

*TIV was offered to all participants 21 days after the second vaccination with the 2009 pandemic H1N1 influenza vaccine.

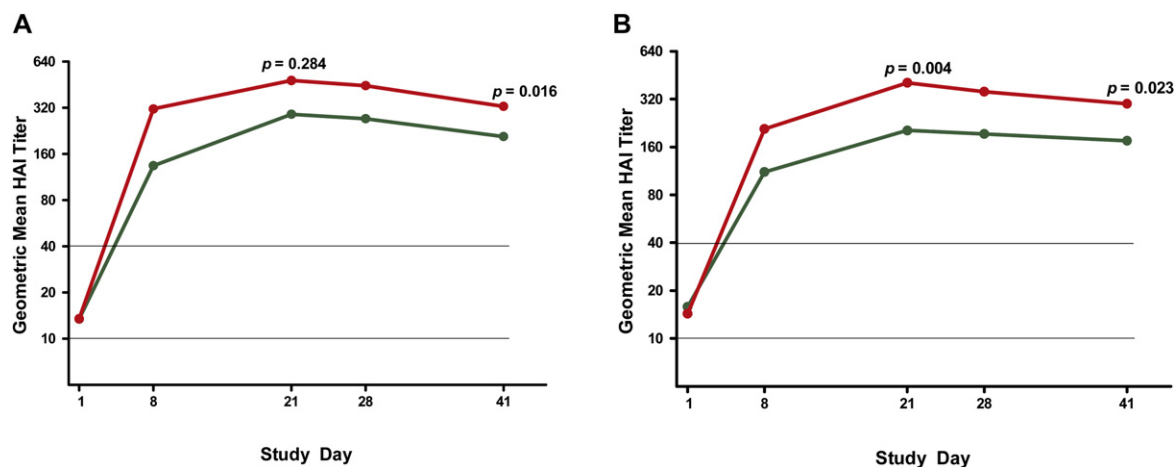


FIG 2. Geometric mean of 2009 pandemic H1N1 influenza virus serum HAI titers by asthma severity and vaccine dose groups. Horizontal lines represent the lower detection limit of the HAI assay (1:10), as well as the conventional seroprotection level (1:40). P values represent comparisons at days 21 and 41 between the 15- and 30- μ g dose groups. **A**, Mild-to-moderate asthma. **B**, Severe asthma. Green lines represent 15 μ g, and red lines represent 30 μ g.

Analysis of the microneutralization assay data did not reveal any qualitative discrepancies compared with the HAI data. Correlation coefficients between HAI GMTs and microneutralization GMTs ranged from 0.73 to 0.83 for days 1 through 41. Microneutralization GMTs were overall higher than HAI GMTs, as previously reported.^{16,17}

Age-related differences in HAI GMTs were observed. As previously mentioned, younger participants had higher GMTs at baseline (results not shown). After vaccination, participants 60 years or older displayed lower seroprotection rates than younger participants (Fig 3). This phenomenon was accentuated in the severe asthma group. At day 21, the seroprotection rate in older participants with severe asthma who received the 15- μ g dose was

44.4% (n = 18); the rate was 88.9%, however, in those participants receiving the 30- μ g dose (n = 18, P = .012).

Seroprotection rates at days 21 or 41 (3 weeks after the first and second H1N1 vaccination, respectively) were significantly lower in participants who had received the 2009 TIV before enrolling in the trial compared with those who had not (see Table E1 in this article's Online Repository at www.jacionline.org). The effect of TIV was significant (P < .001 by using the logistic regression model with seroprotection status as outcome) and remained significant after adjustment for baseline H1N1 HAI titers, age, H1N1 vaccine dose, severity group, dose $\times$ severity group interaction, body mass index, sex, and baseline FEV₁ percent predicted (P = .002). To test the hypothesis that antibodies against

TABLE II. Immune response at day 21 after 1 dose of the 2009 pandemic influenza H1N1 vaccine

Immunogenicity end point	Mild-to-moderate asthma (n = 214)			Severe asthma (n = 171)		
	15- μ g Vaccine dose (n = 107)	30- μ g Vaccine dose (n = 107)	30-15 μ g Difference	15- μ g Vaccine dose (n = 86)	30- μ g Vaccine dose (n = 85)	30-15 μ g Difference
Baseline						
Subjects with HAI titer $\geq$ 1:40 (seroprotected [%])	20.6	22.4	1.9	26.7	23.5	−3.2
95% CI	13.4 to 29.5	14.9 to 31.5	−11.9 to 15.6	17.8 to 37.4	15 to 34	−18.3 to 11.4
P value			.868			.725
GMT	13.0	13.8	1.1	15.5	14.4	0.9
95% CI	9.7 to 17.3	10.5 to 18.2	0.7 to 1.6	11.1 to 21.8	10.6 to 19.7	0.6 to 1.5
P value			.747			.748
After vaccination at day 21						
Subjects with HAI titer $\geq$ 1:40 (seroprotected [%])	90.7	95.3	4.7	77.9	94.1	16.2
95% CI	83.5 to 95.4	89.4 to 98.5	−9.2 to 18.4	67.7 to 86.1	86.8 to 98.1	1.4 to 30.8
P value			.284			.004
Subjects with seroconversion (%)	80.4	85.0	4.7	75.6	85.9	10.3
95% CI	71.6 to 87.4	76.9 to 91.2	−9.2 to 18.4	65.1 to 84.2	76.6 to 92.5	−4.5 to 25.2
P value			.470			.120
GMT	291.0	482.8	1.7	203.8	405.4	2.0
95% CI	218.4 to 387.8	378.3 to 616.3	1.1 to 2.4	141.9 to 292.6	306.5 to 536.1	1.3 to 3.1
P value			.008			.003
Factor increase in GMT	22.5	34.9	1.6	13.1	28.1	2.1
95% CI	16.3 to 31	25.5 to 47.8	1 to 2.4	9.2 to 18.6	19.8 to 39.8	1.3 to 3.5
P value			.054			.002

GMT, Geometric mean titer.

Statistical comparisons were made on log of HAI titers and then back-transformed for reporting purposes. The Fisher exact test was used for comparison of seroprotection and seroconversion rates between dose groups. Exact binomial CIs were computed to describe seroprotection and seroconversion rates, as well as differences in rates between dose groups.

the 3 viral components of the TIV might interfere with the H1N1 HAI assay (in which case an inverse relationship between TIV and 2009 H1N1 virus HAI titers would be expected), we measured, in a subgroup of participants who had received the TIV before entering our study, HAI titers against the TIV viruses (H1N1 Brisbane/59/2007, H3N2 Brisbane/10/2007, and B/Brisbane/3/2007) at baseline. We computed correlations between the antibody titers against the above TIV viruses and antibody titers against the 2009 pandemic H1N1 virus at day 21 after vaccination. We found no inverse relationship between the HAI titers for the 2009 H1N1 virus and any of the TIV viruses; in contrast, a positive correlation between the day 21 titers for the 2009 H1N1 and the day 1 titers for the H1N1 Brisbane/59/2007 viruses was observed (data not shown).

Atopy, evaluated for every participant by way of total serum IgE levels and the number of positive (class I or greater) serum allergen-specific IgE test results, had no influence on HAI GMTs or on seroprotection rates (data not shown). Similarly, we detected no effects of body mass index, systemic corticosteroid use for at least 6 of the previous 12 months, or ICS dose (fluticasone equivalents) at study entry (data not shown).

Safety (not asthma related)

After the first vaccination, 64% of participants experienced systemic adverse events (solicited), and this did not differ statistically between the 2 dose levels within the mild-to-moderate and severe asthma groups nor did participants with severe asthma experience a significantly higher rate of systemic

events (see Table E2 in this article's Online Repository at www.jacionline.org). After the second vaccination, less systemic reactivity was observed (46%). The percentage of participants who experienced injection-site adverse events (solicited) within the first 8 days of the first vaccination was higher after the 30- μ g dose compared with the 15- μ g dose in the severe asthma group ($P = .014$). A slightly higher but statistically significant rate of severe injection-site and systemic solicited reactions occurred with the 30- μ g dose in the mild-to-moderate asthma group. The severe asthma group tended to have less frequent severe solicited reactions with the 30- μ g dose.

Unsolicited, non-serious adverse events (non-SAEs) were reported by 49% of participants, with no significant differences between dose groups or between severity groups within each system organ class.

Three SAEs not associated with an asthma exacerbation occurred within 21 days of vaccination. Fifteen additional SAEs occurred during the telephone follow-up phase (days 42–201). None of these SAEs were characterized as vaccine associated, and there was no predilection for the higher vaccine dose or the severe asthma group.

Safety (asthma related)

Four asthma-related SAEs (hospitalizations), 3 in the severe asthma group, occurred within 21 days of vaccination. Only 1 of these participants had received the 30- μ g vaccine dose. Eight additional asthma-related SAEs occurred during the telephone follow-up phase of the study, all in the severe asthma group. One

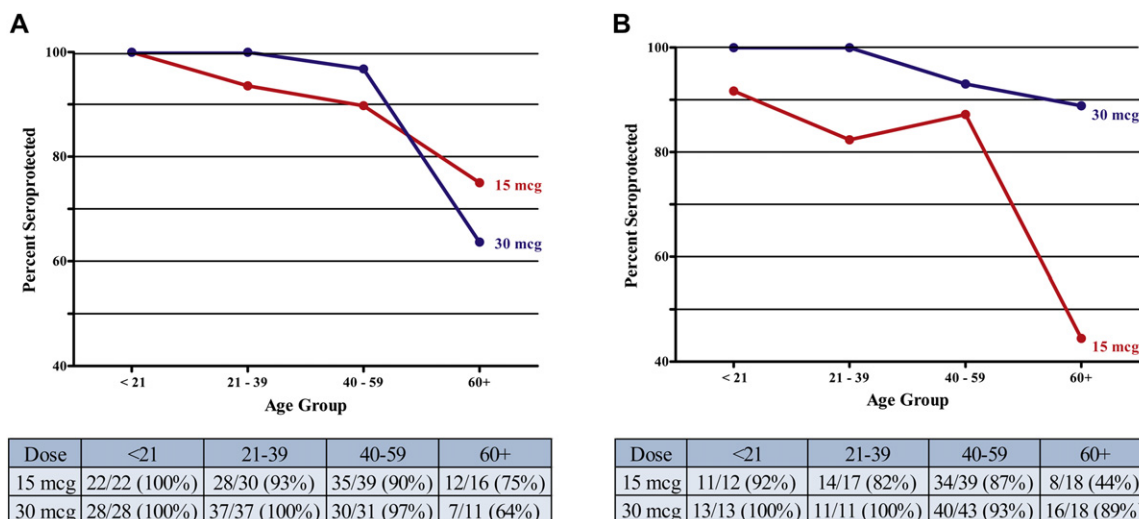


FIG 3. Age effect on seroprotection rates at day 21 by severity and dose-level group. **A**, Mild-to-moderate asthma. **B**, Severe asthma. Tables below each panel provide information on the number and percentage of participants per age group who were seroprotected.

of the SAEs was a fatality caused by status asthmaticus; the participant died at home approximately 2 months after the second vaccination.

Asthma exacerbations not resulting in hospitalization (non-SAEs) were recorded in 59 participants (total of 68 events), 38 in the severe asthma group. Thirty of the 68 exacerbations occurred in participants who received the 30- μ g dose.

Pulmonary function testing (FEV₁ percent predicted, forced vital capacity [FVC] percent predicted, and FEV₁/FVC ratio) results did not demonstrate significant changes from days 1 to 8 or from days 21 to 28 within any of the asthma severity/dose groups except for FVC percent predicted in the severe 30- μ g group, which decreased by an average of 1% from days 1 to 8 ($P = .017$) but returned to baseline levels on day 21 and did not decrease after the second vaccination.

DISCUSSION

The most common comorbidity in persons hospitalized because of the 2009 pandemic H1N1 influenza virus was asthma.² This is not surprising given that viral respiratory tract infections are believed to be the major cause of asthma exacerbations, even though rhinovirus is the dominant virus found in association with these events.⁶ Based on these experiences, asthmatic patients are a high-priority group for H1N1 vaccination.

Our study was designed to compare the immunogenicity and safety of 2 doses, 15 and 30 μ g, of an unadjuvanted 2009 H1N1 influenza virus vaccine administered intramuscularly in patients with mild-to-moderate and severe asthma. Severe asthma was a primary concern because of the presumed greater risk for loss of asthma control with H1N1 infection and the potential influence on vaccine immunogenicity of high doses of ICSs and, in some patients, systemic corticosteroids.

We found that both the 15- μ g (standard vaccine dose) and 30- μ g H1N1 vaccine doses generally provide excellent seroprotection 21 days after a single immunization in patients with mild-to-moderate asthma. In patients with severe asthma, the response

to the 15- and 30- μ g doses was significantly different, with 77.9% achieving seroprotection with the 15- μ g dose versus 94.1% with the 30- μ g dose. This difference in seroprotection rates was not seen in the mild-to-moderate asthma group, although HAI GMTs after the 15- μ g dose were significantly lower than those after the 30- μ g dose in both groups. Interestingly, in studies conducted in healthy adults, no differences between the 15- and 30- μ g doses of the 2009 H1N1 pandemic influenza vaccine (albeit from different manufacturers) were found.^{18,19}

We also observed that the vaccination response was less in participants 60 years and older, with the lowest response (44.4% seroprotection) in the 60-year-old or older group with severe asthma who received the 15- μ g dose (Fig 3). It is well known that the immunogenicity of TIV is diminished in older healthy adults.^{20,21} Our data, however, suggest an interaction between age and disease severity in that older participants with severe asthma receiving the 15- μ g dose had the lowest immunogenicity to the 2009 H1N1 vaccine. Although, within the severe asthma group, 23.3% of the participants were 60 years or older, their influence on the data was substantial: removal of these subjects changed the seroprotection rate of the 15- μ g severe asthma group from 77.9% (95% CI, 67.7% to 86.1%) to 86.8% (95% CI, 76.4% to 93.8%). An encouraging finding is that older participants with severe asthma attained adequate seroprotection with the 30- μ g dose, suggesting that older adults with severe asthma might need to be vaccinated with a higher-than-standard dose. Recent studies with high-dose (60 μ g) TIV have demonstrated higher immunogenicity than the standard dose for patients older than 65 years.^{22,23} In our study older participants with mild-to-moderate asthma sustained acceptable seroprotection 3 weeks after vaccination with the 15- μ g dose. However, 3 weeks after the second vaccination, seroprotection decreased from 75% to 56%, again suggesting that even in these patients the 30- μ g dose might need to be considered.

Limited studies have addressed the question of whether ICS or systemic corticosteroid use interferes with the antibody response to influenza immunization. The largest published study in asthma

was that of Hanania et al,¹² which compared the response to TIV in 148 patients receiving medium to high-dose ICSs versus 146 subjects receiving no or low-dose ICSs. The investigators found no difference between the 2 study groups in the responses to the influenza vaccine, except in a *post hoc* analysis, in which significantly lower antibody titers to influenza B were detected. In addition to having a larger number of participants, our study of the 2009 pandemic H1N1 vaccine tested various immunization schedules (15 vs 30- μ g dose and 1 vs 2 vaccinations) and used subjects with severe asthma who were receiving a considerably higher dose of ICSs (≥ 880 μ g/d fluticasone) and were, on average, 10 years older compared with the participants in the Hanania et al study.

An additional observation from this study is the clear lack of a booster response by the second vaccination (Fig 2). As in many other studies examining immunogenicity of influenza vaccines, the second vaccination was included in the study design to offer a possible solution to the potential problem of low immunogenicity after a single vaccination. Indeed, in several H1N1 vaccine studies in infants or young children, a second vaccination improved seroprotection rates, which were rather low after a single vaccine dose.^{18,24} In older adults (≥ 61 years) Zhu et al¹⁸ also found that the second vaccination resulted in better seroprotection rates. In our study participants 60 years and older, the age group with the lowest seroprotection rates after the first vaccination, did not benefit from the second vaccine dose.

Earlier studies have reported that postvaccination GMTs obtained with influenza vaccines can be lower in patients reporting previous vaccination compared with GMTs in those without previous vaccination.^{25,26} We have made similar observations in this study. The reasons for this vaccine interference effect are unclear. One possible explanation is that antibodies generated after TIV vaccination could bind to the 2009 H1N1 hemagglutinin vaccine component *in vivo* and alter its turnover, its uptake and presentation by antigen-presenting cells, or both. Another explanation could have been that serum antibodies against seasonal viral hemagglutinin bind to the pandemic H1N1 viral hemagglutinin protein in the HAI assay, thereby preventing the pandemic H1N1 anti-hemagglutinin antibodies in the assay from recognizing the pandemic H1N1 hemagglutinin protein. We indirectly tested this hypothesis in patients who had received the 2009 TIV before entering our study by examining whether baseline HAI titers against each of the 3 viruses in the TIV vaccine were inversely correlated with the titers against the 2009 pandemic H1N1 virus at days 21 or 41 after the first pandemic H1N1 vaccination. The lack of such correlations argues against the possibility that our observation reflects an *in vitro* artifact. In prior studies that reported similar vaccine interference, no differences in protection from influenza illness were observed.²⁵ We and others²⁶ also saw that this vaccine interference effect had little effect on the number of subjects achieving seroprotection against the 2009 pandemic H1N1.

We did not identify any safety concerns with the 2009 H1N1 vaccine. Injection-site, but not systemic, reactogenicity was overall higher in participants with severe asthma after the 30- μ g dose compared with the 15- μ g dose, this likely being secondary to the fact that the 30- μ g dose was delivered with 2 injections, one in each arm. On the other hand, solicited reactions ranked as "severe" by study participants were more common in the mild-to-moderate asthma group, regardless of vaccine dose. Overall, we can conclude that the severe asthma group tolerated the vaccine as well as the mild-to-moderate asthma group and that

the 30- μ g dose was equally well tolerated. In the severe asthma group the rate of asthma exacerbations and hospitalizations in the 21 days after each vaccination was not higher than the expected rate from historical data obtained by the Severe Asthma Research Program investigators in patients with asthma of similar severity.²⁷

Our study did not include a healthy control group because it was designed to compare the 2 vaccine doses in 2 phenotypically distinct groups of patients with asthma. However, we had the opportunity to exchange information with the vaccine manufacturer (Novartis Vaccines and Diagnostics Ltd), who has conducted immunogenicity and safety trials in healthy US adult populations using the same doses and vaccination intervals. Overall, the immunogenicity and safety of the 2009 H1N1 influenza virus vaccine in healthy subjects was similar to what we observed in patients with asthma.

Our findings should not be assumed to be automatically applicable to the live attenuated intranasal vaccine. Although intranasal administration of the seasonal influenza vaccine has shown efficacy and safety in persons with asthma,^{28,29} patients with severe airway disease have not been extensively tested, and some concern exists as to the potential of inducing an asthma exacerbation with the intranasal vaccine in this group.^{30,31} It is also not known whether the substantial nasal mucosal disease, which is characteristic of the vast majority of these patients,³² and the use of nasal corticosteroids can influence intranasal vaccine immunogenicity and safety.

In summary, adult and adolescent patients with asthma can be safely administered the 2009 H1N1 pandemic influenza vaccine (which is currently a component of the 2010 TIV) and will most likely experience seroprotection at a rate comparable with healthy subjects with a single 15- μ g dose. It is noteworthy that the 30- μ g dose of the vaccine led to a higher rate of seroprotection compared with the 15- μ g dose in the severe asthma group, this being primarily because of the low seroprotection in older participants. Indeed, older adults with severe asthma should be considered for the 30- μ g dose, which offers substantially better seroprotection.

Clinical implications: H1N1 vaccination is safe and produces robust antibody responses in patients with asthma. High-dose ICSs did not adversely affect seroprotection. Patients with severe asthma and older than 60 years might benefit from a higher vaccine dose.

REFERENCES

1. CDC estimates of 2009 H1N1 influenza cases, hospitalizations and deaths in the United States, April 2009–March 13, 2010. Atlanta: Centers for Disease Control and Prevention; 2010.
2. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009;361:1935–44.
3. 2009 H1N1 Flu: underlying health conditions among hospitalized adults and children. Centers for Disease Control and Prevention; February 24, 2010. Available at: http://www.cdc.gov/H1N1flu/eip_underlying_conditions.htm. Accessed September 17, 2009.
4. Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2008. National Center for Health Statistics. *Vital Health Stat* 2009;244):1–81.
5. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. National Center for Health Statistics. *Vital Health Stat* 2009;242):1–157.
6. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010;376:826–34.
7. Sears MR, Johnston NW. Understanding the September asthma epidemic. *J Allergy Clin Immunol* 2007;120:526–9.

8. Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep* 2008;57(RR-7):1-60.
9. National Heart, Lung, and Blood Institute. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma—full report 2007. August 28, 2007. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed December 7, 2009.
10. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA). Available at: <http://www.ginasthma.com/>. Accessed November 10, 2010.
11. The American Lung Association Asthma Clinical Research Centers. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;345:1529-36.
12. Hanania NA, Sockrider M, Castro M, Holbrook JT, Tonascia J, Wise R, et al. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. *J Allergy Clin Immunol* 2004;113:717-24.
13. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000;162:2341-51.
14. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: clinical data needed to support the licensure of pandemic influenza vaccines. Washington (DC): US Food and Drug Administration; 2007.
15. World Health Organization manual on animal influenza diagnosis and surveillance. Available at: http://whqlibdoc.who.int/hq/2002/WHO_CDS_CSR_NCS_2002.5.pdf. Accessed November 10, 2010.
16. Clark TW, Pareek M, Hoschler K, Dillon H, Nicholson KG, Groth N, et al. Trial of 2009 influenza A (H1N1) monovalent MF59-adjuvanted vaccine. *N Engl J Med* 2009;361:2424-35.
17. Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. Response to a monovalent 2009 influenza A (H1N1) vaccine. *N Engl J Med* 2009;361:2405-13.
18. Zhu FC, Wang H, Fang HH, Yang JG, Lin XJ, Liang XF, et al. A novel influenza A (H1N1) vaccine in various age groups. *N Engl J Med* 2009;361:2414-23.
19. Plennevaux E, Sheldon E, Blatter M, Reeves-Hoche MK, Denis M. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. *Lancet* 2010;375:41-8.
20. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine* 2006;24:1159-69.
21. McElhaney JE. The unmet need in the elderly: designing new influenza vaccines for older adults. *Vaccine* 2005;23(suppl 1):S10-25.
22. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis* 2009;200:172-80.
23. Keitel WA, Atmar RL, Cate TR, Petersen NJ, Greenberg SB, Ruben F, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med* 2006;166:1121-7.
24. Oh CE, Lee J, Kang JH, Hong YJ, Kim YK, Cheong HJ, et al. Safety and immunogenicity of an inactivated split-virus influenza A/H1N1 vaccine in healthy children from 6 months to <18 years of age: a prospective, open-label, multi-center trial. *Vaccine* 2010;28:5857-63.
25. Keitel WA, Cate TR, Couch RB. Efficacy of sequential annual vaccination with inactivated influenza virus vaccine. *Am J Epidemiol* 1988;127:353-64.
26. Treanor J, Keitel W, Belshe R, Campbell J, Schiff G, Zangwill K, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. *Vaccine* 2002;20:1099-105.
27. Moore WC, Peters SP. Severe asthma: an overview. *J Allergy Clin Immunol* 2006;117:487-95.
28. Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J* 2006;25:860-9.
29. Glezen WP. Asthma, influenza, and vaccination. *J Allergy Clin Immunol* 2006;118:1199-208.
30. Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatr Infect Dis J* 2004;23:138-44.
31. MedImmune, LLC. FluMist influenza vaccine live, intranasal. Highlights of prescribing information. Available at: http://www.medimmune.com/pdf/products/flumist_pi.pdf. Accessed November 10, 2010.
32. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;111:1171-84.

APPENDIX 1

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TABLE E1. Immune response at day 21 after 1 dose of 2009 pandemic influenza H1N1 vaccine according to prior receipt of 2009 seasonal trivalent influenza vaccine

Received 2009 seasonal influenza vaccine before study participation	Mild-to-moderate asthma (n = 101)			Severe asthma (n = 103)		
	15-μg Vaccine dose (n = 46)	30-μg Vaccine dose (n = 55)	30-15 μg Difference	15-μg Vaccine dose (n = 54)	30-μg Vaccine dose (n = 49)	30-15 μg Difference
Baseline						
Subjects with HAI titer $\geq 1:40$ (seroprotected [%])	19.6	20.0	0.4	22.2	22.4	0.2
95% CI	9.4 to 33.9	10.4 to 33	-19 to 19.7	12 to 35.6	11.8 to 36.6	-19.1 to 19.4
P value			>.99			>.99
GMT	13.6	13.6	1.0	13.1	13.7	1.0
95% CI	8.5 to 21.7	9.6 to 19.3	0.6 to 1.8	9.1 to 19	9.1 to 20.8	0.6 to 1.8
P value			>.99			.869
After vaccinations at day 21						
Subjects with HAI titer $\geq 1:40$ (seroprotected [%])	87.0	92.7	5.8	74.1	89.8	15.7
95% CI	73.7 to 95.1	82.4 to 98	-13.7 to 25	60.3 to 85	77.8 to 96.6	-3.8 to 34.2
P value			.506			.046

Did not receive 2009 seasonal influenza vaccine before study participation	Mild-to-moderate asthma (n = 113)			Severe asthma (n = 68)		
	15-μg Vaccine dose (n = 61)	30-μg Vaccine dose (n = 52)	30-15 μg Difference	15-μg Vaccine dose (n = 32)	30-μg Vaccine dose (n = 36)	30-15 μg Difference
Baseline						
Subjects with HAI titer $\geq 1:40$ (seroprotected [%])	21.3	25.0	3.7	34.4	25.0	-9.4
95% CI	11.9 to 33.7	14 to 38.9	-14.7 to 21.9	18.6 to 53.2	12.1 to 42.2	-32.8 to 14.6
P value			.661			.435
GMT	12.5	14.0	1.1	20.7	15.4	0.7
95% CI	8.5 to 18.2	9.1 to 21.7	0.6 to 2	10.5 to 40.8	9.4 to 25.3	0.3 to 1.7
P value			.682			.482
After vaccinations at day 21						
Subjects with HAI titer $\geq 1:40$ (seroprotected [%])	93.4	98.1	4.6	84.4	100.0	15.6
95% CI	84.1 to 98.2	89.7 to 100	-13.9 to 22.8	67.2 to 94.7	90.3 to 100	-8.3 to 38.5
P value			.372			.019

GMT, Geometric mean titer.

Statistical comparisons were made on log of HAI titers and then back-transformed for reporting purposes. The Fisher exact test was used for comparison of seroprotection rates between dose groups. Exact binomial CIs were computed to describe seroprotection rates, as well as differences in rates between dose groups.

TABLE E2. Systemic and local reactogenicity of 2009 pandemic H1N1 influenza vaccination

	Mild-to-moderate asthma		Severe asthma		All participants, both doses
	15 µg	30 µg	15 µg	30 µg	
After first vaccination	n = 110	n = 107	n = 87	n = 86	
With systemic event	58%	63%	64%	74%	64%
With local event	55%	54%	33%	52%*	49%
After second vaccination	n = 102	n = 99	n = 80	n = 76	
With systemic event	47%	47%	48%	42%	46%
With local event	46%	60%†	29%	38%	44%

*Comparison of 15 versus 30 µg within the severe asthma group ($P = .014$, Fisher exact test).

†Comparison of 15 versus 30 µg within the mild-to-moderate asthma group ($P = .05$, Fisher exact test).