ORIGINAL ARTICLE

Response after One Dose of a Monovalent Influenza A (H1N1) 2009 Vaccine — Preliminary Report

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ABSTRACT

BACKGROUND

A novel influenza A (H1N1) 2009 virus is responsible for the first influenza pandemic in 41 years. A safe and effective vaccine is urgently needed. A randomized, observer-blind, parallel-group trial evaluating two doses of an inactivated, split-virus 2009 H1N1 vaccine in healthy adults between the ages of 18 and 64 years is ongoing at a single site in Australia.

METHODS

This preliminary report evaluates the immunogenicity and safety of the vaccine 21 days after the first of two scheduled doses. A total of 240 subjects, equally divided into two age groups (<50 years and ≥50 years), were enrolled and underwent randomization to receive either 15 μg or 30 μg of hemagglutinin antigen by intramuscular injection. We measured antibody titers using hemagglutination-inhibition and microneutralization assays at baseline and 21 days after vaccination. The co-primary immunogenicity end points were the proportion of subjects with antibody titers of 1:40 or more on hemagglutination-inhibition assay, the proportion of subjects with either seroconversion or a significant increase in antibody titer, and the factor increase in the geometric mean titer.

RESULTS

By day 21 after vaccination, antibody titers of 1:40 or more were observed in 116 of 120 subjects (96.7%) who received the 15-μg dose and in 112 of 120 subjects (93.3%) who received the 30-μg dose. No deaths, serious adverse events, or adverse events of special interest were reported. Local discomfort (e.g., injection-site tenderness or pain) was reported by 46.3% of subjects, and systemic symptoms (e.g., headache) by 45.0% of subjects. Nearly all events were mild to moderate in intensity.

CONCLUSIONS

A single 15-μg dose of 2009 H1N1 vaccine was immunogenic in adults, with mild-to-moderate vaccine-associated reactions. (ClinicalTrials.gov number, NCT00938639.)

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THE RAPID GLOBAL SPREAD OF A NOVEL influenza A (H1N1) 2009 virus (2009 H1N1) prompted the World Health Organization (WHO), on June 11, 2009, to declare the first influenza pandemic in 41 years.[1] In the Southern Hemisphere, 2009 H1N1 infection has been dominant during the current influenza season.[2] In the Northern Hemisphere, the incidence of 2009 H1N1 infection is likely to increase substantially during the approaching influenza season, with major public health ramifications. Early availability of safe and effective vaccines is a critical component of efforts to prevent 2009 H1N1 infection and mitigate the overall effect of the pandemic.[3,4]

Shortly after the identification of 2009 H1N1, influenza vaccine manufacturers, in conjunction with public health and regulatory agencies, started developing a 2009 H1N1 vaccine.[5] The sense of urgency was particularly notable in the Southern Hemisphere, where the timing of the pandemic coincided with the onset of winter. Ideally, clinical trials are needed to establish the safety and adverse-effect profiles of the new vaccines and to confirm the optimal dose and regimen.[6]

We undertook a clinical trial in healthy adults to examine the immunogenicity, safety, and tolerability of two different doses of a monovalent, split-virus 2009 H1N1 influenza vaccine (H1N1 vaccine). The vaccine was manufactured with the same procedures that have been used for the production of the company's seasonal trivalent inactivated vaccine. We examined a two-dose regimen of either 15 μg or 30 μg of hemagglutinin antigen, because there was uncertainty as to whether a higher antigen content or a two-dose series might be required to produce a satisfactory immune response. We enrolled equal numbers of subjects 50 years of age or older and below the age of 50 years to explore potential age-related differences in immune response that might result from previous exposure to H1N1 viruses that were displaced from circulation by the H2N2 subtype in the 1957–1958 influenza pandemic.[7]

In the current pandemic, rapid sharing of clinical-trial findings is critical, since such data may assist in the planning of national vaccination programs. This preliminary report includes results that are available to date from our ongoing Australian study in healthy adults after the first of two scheduled vaccinations.

METHODS

STUDY DESIGN

This phase 2, prospective, randomized, observer-blind, parallel-group clinical trial is ongoing at a single site in Adelaide, Australia (CMAX, a division of the Institute of Drug Technology). The purpose of this study is to evaluate the immunogenicity and safety of two different doses of the H1N1 vaccine in healthy adults between the ages of 18 and 64 years in a two-dose regimen. All subjects provided written informed consent.

The randomization code was prepared by a statistician, employed by CSL Limited, with the use of SAS software (version 9.1.3) and JMP (version 8.0.1) (SAS Institute); permuted-block randomization was used. The randomization code was provided to the vaccine administrator, who was aware of study-group assignments, as a list in a sealed envelope, although all subjects and investigators were unaware of such assignments.

The study was approved by the Bellberry Human Research Ethics Committee (Adelaide, Australia) and was conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice (as defined by the International Conference on Harmonization), and Australian regulatory requirements. All authors contributed to the content of the manuscript, had full access to all study data, and vouch for the completeness and accuracy of the data.

VACCINE

The H1N1 vaccine, a monovalent, unadjuvanted, inactivated, split-virus vaccine, was produced by CSL Biotherapies (Parkville, Australia). The seed virus was prepared from the reassortant vaccine virus NYMC X-179A (New York Medical College, New York), derived from the A/California/7/2009 (H1N1) virus, one of the candidate reassortant vaccine viruses recommended by the WHO.[8,9] The vaccine was prepared in embryonated chicken eggs with the same standard techniques that are used for the production of seasonal trivalent inactivated vaccine[10] and was presented in 10-ml multidose vials with thimerosal added as a preservative (final concentration, 0.01% weight per volume). The two doses were 15 μg of hemagglutinin antigen per 0.25-ml dose and 30 μg of hemagglutinin antigen per 0.5-ml dose.

SUBJECTS AND STUDY PROCEDURES

Healthy, nonpregnant adults between the ages of 18 and 64 years were eligible for enrollment. We excluded subjects with confirmed or suspected 2009 H1N1 infection and those who had received an experimental influenza vaccine during the preceding 6 months.

A total of 240 eligible subjects underwent randomization to receive either 15 μg or 30 μg of hemagglutinin antigen in a 1:1 ratio. An equal number of subjects from 18 to 49 years of age and from 50 to 64 years were included. Each dose was administered intramuscularly into the deltoid muscle. Since the injection volume differed between the two study doses, personnel who prepared and administered the study vaccine had no further involvement in the study.

SAFETY ASSESSMENTS

We collected solicited reports of local and systemic adverse events, using a 7-day diary card. All solicited local adverse events were considered to be related to the H1N1 vaccine, whereas the investigator assessed the causality of solicited systemic adverse events. Subjects used a standard scale to grade adverse events during the 7-day period.

Because of the novelty of the pandemic H1N1 strain, we prospectively collected data relating to the occurrence of select adverse events of special interest. These events included several neurologic (e.g., Guillain–Barré syndrome), immune-system, and other disorders. Any adverse events of special interest or serious adverse event was to be reported within 24 hours.

A safety-review committee monitored the safety of the study. Stopping rules were in place during the 7 days after vaccination but were not met, and all doses were given.

ASSESSMENT OF INFLUENZA-LIKE ILLNESS

Subjects who reported having an influenza-like illness were asked to provide specimens of nasal and throat swabs for virologic testing. An influenza-like illness was defined as an oral temperature of more than 38°C (100.4°F) or a history of fever or chills and at least one influenza-like symptom.

LABORATORY ASSAYS

Anti-influenza antibody titers were measured at enrollment and 21 days after each vaccination. The immunogenicity of the H1N1 vaccine was evaluated with the use of hemagglutination-inhi-bition and microneutralization assays with methods that have been described previously[11,12] (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Virologic testing of nasal- and throat-swab specimens was performed with the use of the protocol of the Centers for Disease Control and Prevention for real-time reverse-transcriptase–polymerase-chain-reaction assay for 2009 H1N1 virus.[13] All laboratory assays were performed by Focus Diagnostics.

PRIMARY AND SECONDARY END POINTS

The three coprimary immunogenicity end points after vaccination were chosen according to international guidelines used to evaluate influenza vaccines.[14,15] The coprimary immunogenicity end points were the proportion of subjects with antibody titers of 1:40 or more on hemagglutination-inhibition assay, the proportion of subjects with either seroconversion or a significant increase in antibody titer, and the factor increase in the geometric mean titer.

The secondary safety end points were the frequency, duration, and intensity of solicited adverse events during the 7 days after vaccination and the incidence of serious adverse events and adverse events of special interest during the study period.

STATISTICAL ANALYSIS

A sample size of 120 subjects per study group was chosen because it provided sufficient power to assess the primary immunogenicity end points. The primary and secondary end-point analyses were descriptive and consisted of an assessment of the lower confidence bounds of each end point for each study group. On the assumption of a population seroconversion rate of 53%, the study had a power of at least 80% with 120 subjects per group to show the seroconversion rate to be significantly more than 40%. For categorical variables, statistical summaries included counts and percentages relative to the appropriate population. The safety population included all subjects who received a dose of H1N1 vaccine. The population that could be evaluated included all subjects in the safety population who provided serum samples at baseline and after vaccination. The 95% confidence intervals, which were calculated on the basis of the binomial distribution, are provided for descriptive statistics.

RESULTS

STUDY SUBJECTS

From July 22 to July 26, 2009, we enrolled 240 subjects, who underwent randomization (Table 1 and Fig. 1). All subjects received a dose of H1N1 vaccine and were included in the safety population. All subjects provided a blood sample before and after vaccination and were included in the population that could be evaluated. All subjects returned the 7-day diary; there were no withdrawals from the study. Of the 240 subjects, 45.0% reported having received a 2009 Southern Hemisphere seasonal trivalent inactivated vaccine. The proportion of subjects who received the 2009 seasonal vaccine did not differ between the age groups (P=0.24 by Fisher's exact test).

IMMUNOGENICITY

At baseline, 76 of 240 subjects (31.7%) had antibody titers of 1:40 or more on hemagglutination-inhibition assay (Table 2 and Fig. 2A and 2C), with no significant differences between either age groups (P=0.21) or dose groups (P=0.68). Similarly, there were no significant differences in baseline geometric mean titers (GMTs) between age groups or dose groups (Table 3). Of note, baseline titers of 1:40 or more on hemagglutination-inhibition assay were observed in 48 of 108 subjects who had received the 2009 seasonal vaccine (44.4%; 95% confidence interval [CI], 35.4 to 53.8), as compared with 28 of 132 subjects who had not received the seasonal vaccine (21.2%; 95% CI, 15.1 to 28.9; P<0.001 by Fisher's exact test).

A single 15-μg or 30-μg dose of the H1N1 vaccine produced a robust immune response in a majority of subjects (Table 2 and Fig. 2). Postvaccination titers of 1:40 or more on hemagglutination-inhibition assay were observed in 96.7% (95% CI, 91.7 to 98.7) of recipients of the 15-μg dose and in 93.3% (95% CI, 87.4 to 96.6) of the recipients of the 30-μg dose (Table 2 and Fig. 2). Seroconversion or a significant increase in titer on hemagglutination-inhibition assay occurred in 74.2% of subjects, and the effect was similar between the two study groups (Table 2).

After vaccination, there was a substantial rise in GMTs, with no significant differences in factor increases between the two groups (Table 3). However, we observed age-related differences. Subjects who were 50 years of age or older had a numerically lower factor increase in the GMT

Characteristic	15-μg Vaccine Dose (N=120)			30-μg Vaccine Dose (N=120)			All Subjects (N=240)
	18–49 Yr (N=58)	50–64 Yr (N=62)	All Ages (N=120)	18–49 Yr (N=62)	50–64 Yr (N=58)	All Ages (N=120)	
Age — yr							
Mean	31.0±9.7	57.3±4.3	44.6±15.1	29.8±9.7	56.8±3.6	42.9±15.4	43.7±15.3
Median	28	58	50	26	56	48	50
Range	18–49	50–64	18–64	18–49	50–64	18–64	18–64
Sex — no. (%)							
Male	24 (41.4)	29 (46.8)	53 (44.2)	24 (38.7)	29 (50.0)	53 (44.2)	106 (44.2)
Female	34 (58.6)	33 (53.2)	67 (55.8)	38 (61.3)	29 (50.0)	67 (55.8)	134 (55.8)
Race — no. (%)†							
White	50 (86.2)	61 (98.4)	111 (92.5)	54 (87.1)	57 (98.3)	111 (92.5)	222 (92.5)
Other	8 (13.8)	1 (1.6)	9 (7.5)	8 (12.9)	1 (1.7)	9 (7.5)	18 (7.5)
Received 2009 Southern Hemisphere seasonal influenza vaccine — no. (%)‡	25 (43.1)	30 (48.4)	55 (46.0)	24 (38.7)	29 (50.0)	53 (44.0)	108 (45.0)

* Plus–minus values are means ±SD.
† Race was self-reported.
‡ The 2009 Southern Hemisphere seasonal influenza vaccine contained 15 μg of hemagglutinin antigen of each of the following strains: A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/4/2006 (B).

than those under the age of 50 years. This age-related effect was reflected in all measures of immunogenicity.

In general, the pattern of antibody responses, as measured by the microneutralization assay, was similar to those observed with the hemagglutination-inhibition assay (Table 3 and Fig. 2E through 2H). Baseline microneutralization GMTs in the younger age group were significantly higher than those in the older age group (P<0.001). Postvaccination microneutralization GMTs were also significantly higher in the younger age group than in the older age group, regardless of dose (P<0.001).

We performed an additional analysis examining the effect of baseline serostatus on the immune response to H1N1 vaccination. Subjects who were seronegative at baseline (with a hemagglutination-inhibition or microneutralization titer of <1:10) had lower postvaccination GMTs than those with baseline titers of 1:10 or more. However, subjects who were seronegative at baseline had significantly higher factor increases in the GMT (P<0.001 for both hemagglutination-inhibition and microneutralization assays) (Table 3 in the Supplementary Appendix). The proportion of subjects who were seronegative at baseline and who achieved seroconversion exceeded 86% on the hemagglutination-inhibition assay and 70% on the microneutralization assay. Among subjects with a baseline titer of 1:10 or more, the proportion of those achieving seroconversion exceeded 60% on the hemagglutination-inhibition assay and 70% on the microneutralization assay.

ADVERSE EVENTS

No deaths, serious adverse events, or adverse events of special interest were reported. Stopping rules were not triggered, and no subjects withdrew from the study. Since the study is ongoing and individual study-group assignments remain blinded, data regarding solicited adverse events are presented as aggregate totals of both study-dose groups. Data regarding unsolicited adverse events are being collected but are unavailable for this preliminary report.

Solicited local adverse events were reported by 46.3% (95% CI, 40.1 to 52.6) of subjects (Table 4). The most commonly reported events were injection-site tenderness (36.7% of subjects) and pain (21.7% of subjects). Solicited local adverse

Figure 1. Enrollment and Outcomes.
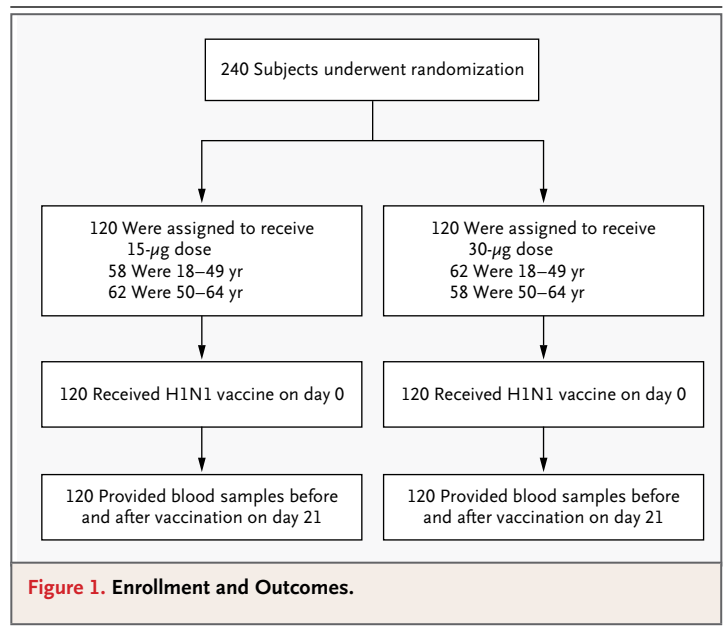
events were graded as mild by 105 of 111 subjects who reported having such an event (94.6%), with no severe local adverse events reported.

Solicited systemic adverse events were reported by 45.0% (95% CI, 38.8 to 51.3) of subjects (Table 4). The most commonly reported events were headache, malaise, and myalgia. Solicited systemic adverse events that were considered to be related to the H1N1 vaccine were reported by 30.4% of subjects. Of the subjects who had a solicited systemic adverse event, the majority reported events that were mild to moderate in intensity. Two subjects reported adverse events that were graded as severe: vaccine-related myalgia, malaise, and nausea that resolved within 5 days with standard treatment in one subject and non-vaccine-related nausea from day 6 through day 10 after vaccination in the other.

Three subjects had an influenza-like illness, one of whom tested positive for 2009 H1N1 on day 8 after vaccination. The remaining two subjects tested negative for 2009 H1N1.

DISCUSSION

A single 15-μg dose of unadjuvanted 2009 H1N1 vaccine resulted in titers of 1:40 or more on hemagglutination-inhibition assay in 96.7% of adult subjects, despite the prevailing assumption that two doses of vaccine would be required. These results will help to inform pandemic planning,

Table 2. Immune Response after One Dose of the H1N1 Vaccine, as Measured on Hemagglutination-Inhibition (HI) Assay.*

Immunogenicity End Point	15-μg Vaccine Dose (N=120)			30-μg Vaccine Dose (N=120)			All Subjects (N=240)
	18–49 Yr (N=58)	50–64 Yr (N=62)	All Ages (N=120)	18–49 Yr (N=62)	50–64 Yr (N=58)	All Ages (N=120)	
Baseline							
Subjects with HI titer ≥1:40 — % (95% CI)	32.8 (22.1–45.6)	33.9 (23.3–46.3)	33.3 (25.5–42.2)	38.7 (27.6–51.2)	20.7 (12.3–32.8)	30 (22.5–38.7)	31.7 (26.1–37.8)
Geometric mean titer — value (95% CI)	21.4 (14.8–30.8)	19.3 (13.8–26.9)	20.3 (15.9–25.9)	19.9 (13.7–28.9)	13.2 (9.7–17.9)	16.3 (12.8–20.8)	18.2 (15.3–21.6)
After vaccination							
Subjects with HI titer ≥1:40 — % (95% CI)	100 (93.8–100)	93.5 (84.6–97.5)	96.7 (91.7–98.7)	98.4 (91.4–99.7)	87.9 (77.1–94.0)	93.3 (87.4–96.6)	95.0 (91.5–97.1)
Subjects with seroconversion or significant increase in titer — % (95% CI)	75.9 (63.5–85.0)	66.1 (53.7–76.7)	70.8 (62.2–78.2)	82.3 (71.0–89.8)	72.4 (59.8–82.2)	77.5 (69.2–84.1)	74.2 (68.3–79.3)
Geometric mean titer — value (95% CI)	306.9 (228.2–412.7)	157.0 (120.8–204.2)	217.1 (177.1–266.1)	513.7 (401.2–657.7)	174.0 (116.0–260.9)	304.4 (237.0–391.0)	257.1 (218.7–302.2)
Factor increase in geometric mean titer	14.3±5.06	8.1±4.89	10.7±5.06	25.8±5.63	13.2±5.36	18.6±5.64	14.1±5.45

* Plus–minus values are means ±SD. The immunogenicity end points were the proportion of subjects who had an antibody titer of 1:40 or more, the proportion of subjects who had either seroconversion (a prevaccination titer of less than 1:10 with a postvaccination HI antibody titer of 1:40 or more) or an increase by a factor of four or more in antibody titer, and the factor increase in the geometric mean titer.

especially in light of widespread concern about vaccine availability because of low manufacturing yields.[16] The high level of immune protection afforded by a single 15-μg dose should improve the coverage and logistics of mass H1N1 vaccination programs.

The robust immune response to the H1N1 vaccine after a single dose was unanticipated. Much of the current global pandemic planning is predicated on previous experience that two doses of vaccine are required to elicit a protective immune response in populations that are immunologically naive to a new influenza strain.[17-21]

The initiation of the study coincided with the peak of the first pandemic wave in Australia. The weekly age-standardized H1N1 notification rate in South Australia, the state in which the study site is located, was higher than the national average at that time (113.6 per 100,000 population in South Australia, and 81.8 per 100,000 population in Australia).[22] However, we do not believe that intercurrent infection significantly contributed to the postvaccination response, since we monitored all subjects for influenza-like illness, and only one subject tested positive for 2009 H1N1 during the 21 days after vaccination.

The proportion of subjects with titers of 1:40 or more on hemagglutination-inhibition assay at baseline was higher than expected. Among subjects who were 50 years of age or older, this finding could be attributed to the presence of preexisting antibodies from exposure to H1N1 viruses circulating before 1957.[23] It was surprising, however, to see similar baseline antibody titers in the younger age group. A number of factors could have contributed to the observed titers in both age groups at baseline. It is probable that there was some degree of previous 2009 H1N1 infection in the study population, despite stringent exclusion criteria. Cross-reactive antibodies

Figure 2 (facing page). Reverse Cumulative Distribution Curves of Antibody Titers in Serum before and 21 Days after a Single Dose of H1N1 Vaccine, According to the Type of Assay.

Shown are levels of antibody titer against the 2009 H1N1 virus on hemagglutination-inhibition (HI) assay before vaccination (Panel A) and after vaccination (Panel B) and in the two age groups in the study (18 to 49 years and 50 to 64 years) (Panels C and D). Also shown are levels of antibody titer against the 2009 H1N1 virus on microneutralization (MN) assay before vaccination (Panel E) and after vaccination (Panel F) and in the two age groups (Panels G and H).
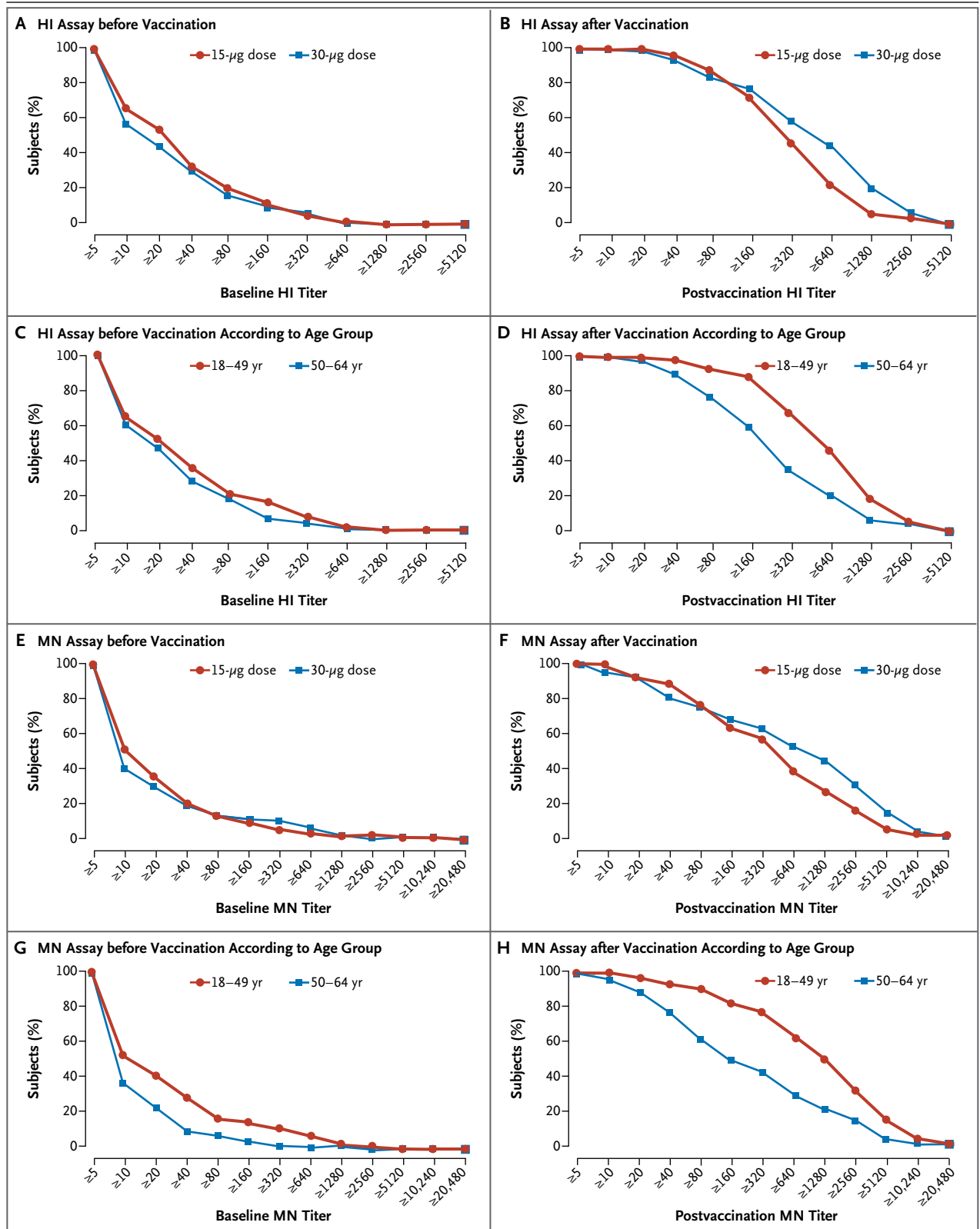
Table 3. Geometric Mean Titers and Factor Increases in the Geometric Mean Titer after One Dose of the H1N1 Vaccine, as Measured on Hemagglutination-Inhibition Assay and Microneutralization Assay.

Assay, Dose, and Age Group	Geometric Mean Titer		Factor Increase in Geometric Mean Titer
	Baseline	After Vaccination	
		value (95% confidence interval)	
Hemagglutination-inhibition assay			
15-µg dose	20.3 (15.9–25.9)	217.1 (177.1–266.1)	10.7 (8.0–14.3)
Age 18–49 yr	21.4 (14.8–30.8)	306.9 (228.2–412.7)	14.3 (9.4–22.0)
Age 50–64 yr	19.3 (13.8–26.9)	157.0 (120.8–204.2)	8.1 (5.4–12.2)
30-µg dose	16.3 (12.8–20.8)	304.4 (237.0–391.0)	18.6 (13.6–25.5)
Age 18–49 yr	19.9 (13.7–28.9)	513.7 (401.2–657.7)	25.8 (16.6–40.0)
Age 50–64 yr	13.2 (9.7–17.9)	174.0 (116.0–260.9)	13.2 (8.5–20.5)
Microneutralization assay			
15-µg dose	14.7 (11.4–18.9)	357.1 (256.5–497.0)	24.3 (17.2–34.3)
Age 18–49 yr	18.5 (12.1–28.3)	647.7 (413.6–1014.1)	35.0 (20.9–58.6)
Age 50–64 yr	11.9 (9.0–15.8)	204.6 (130.3–321.2)	17.2 (10.8–27.3)
30-µg dose	13.8 (10.3–18.4)	513.8 (344.7–766.1)	37.3 (24.9–55.9)
Age 18–49 yr	21.9 (13.8–34.7)	1203.5 (771.6–1877.0)	55.0 (31.5–96.2)
Age 50–64 yr	8.4 (6.2–11.4)	206.9 (113.1–378.6)	24.6 (13.7–44.2)

to 2009 H1N1 may also have played a role. In this issue of the *Journal*, a study by Hancock et al. that analyzed stored-serum samples from trials of seasonal trivalent inactivated vaccine predating the current pandemic showed the presence of cross-reactive antibodies to 2009 H1N1 in adults.[24] The same study showed that vaccination with the seasonal vaccine resulted in a doubling in titers of these cross-reactive antibodies. The latter finding is particularly relevant, given that 45% of the subjects in our study had received the 2009 seasonal vaccine.

Even in subjects with no measurable antibodies at baseline, a single dose of vaccine elicited a robust immune response. The question remains: Why did these subjects have such a brisk response? The 2009 H1N1 pandemic differs from previous pandemics in that although the virus is antigenically very distant from recently circulating H1N1 viruses, it is still of the same H1N1 subtype.[25] Cross-protection that was afforded by exposure to antigenically drifted strains of the same influenza subtype has been described.[19] In addition, the 2009 H1N1 virus shares three gene sequences with the recently circulating seasonal H1N1 virus and three sequences with the current seasonal H3N2 virus.[23] Perhaps there is

more immunotypic similarity between the 2009 H1N1 virus and recent seasonal strains than has been recognized previously.

The side-effect profile of the H1N1 vaccine, particularly the frequency and severity of solicited adverse events, is consistent with our previous experience with seasonal influenza vaccines in adults.[10] The full safety profile of H1N1 vaccine has not yet been elucidated. Population-based postlicensure surveillance will be required for all H1N1 vaccines, especially to assess rare outcomes, such as the Guillain–Barré syndrome.

Several important questions remain unanswered in this trial. First, since we studied healthy adults, trials need to be conducted in other populations that may have different responses to the vaccine, such as the elderly, children, and those with impaired immunity. Second, given the robust immune response to a 15-µg dose, lower antigen doses should be explored. Third, although our study is being carried out in one locality in Australia during winter in the Southern Hemisphere, our findings need to be borne out by studies in locations where the epidemiology of the pandemic may be different. Finally, estimates of the true effect of the vaccine when used in mass immunization

Table 4. Proportion of 240 Subjects Who Reported Having a Solicited Local or Systemic Adverse Event within 7 Days after Receiving One Dose of the H1N1 Vaccine.

Adverse Event	Mild	Moderate	Severe	All Grades
	percent (95% confidence interval)			
Solicited local event				
Any	43.8 (37.6–50.1)	2.5 (1.2–5.3)	0	46.3 (40.1–52.6)
Pain	20.8 (16.2–26.4)	0.8 (0.2–3.0)	0	21.7 (16.9–27.3)
Tenderness	35.0 (29.2–41.2)	1.7 (0.6–4.2)	0	36.7 (30.8–42.9)
Redness	8.8 (5.8–13.0)	0.4 (0.1–2.3)	0	9.2 (6.1–13.5)
Induration	8.8 (5.8–13.0)	0	0	8.8 (5.8–13.0)
Ecchymosis	4.6 (2.6–8.0)	0.4 (0.1–2.3)	0	5.0 (2.9–8.5)
Solicited systemic event				
Any	35.8 (30.0–42.1)	8.3 (5.5–12.5)	0.8 (0.2–3.0)	45.0 (38.8–51.3)
Fever	2.1 (0.9–4.8)	1.7 (0.7–4.2)	0	3.8 (2.0–7.0)
Headache	27.1 (21.9–33.0)	4.2 (2.3–7.5)	0	31.3 (25.7–37.4)
Malaise	14.2 (10.3–19.1)	2.9 (1.4–5.9)	0.4 (0.1–2.3)	17.5 (13.2–22.8)
Myalgia	13.8 (10.0–18.7)	2.9 (1.4–5.9)	0.4 (0.1–2.3)	17.1 (12.8–22.4)
Chills	5.8 (3.5–9.6)	0.8 (0.2–3.0)	0	6.7 (4.1–10.6)
Nausea	5.0 (2.9–8.5)	1.3 (0.4–3.6)	0.8 (0.2–3.0)	7.1 (4.5–11.0)
Vomiting	0	0.8 (0.2–3.0)	0	0.8 (0.2–3.0)

programs will come from vaccine-effectiveness studies.

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