Dose-range Study of MF59-adjuvanted Versus Nonadjuvanted Monovalent A/H1N1 Pandemic Influenza Vaccine in Six- to Less Than Thirty-Six-month-old Children

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Background: The successful vaccination of children 6 to 36 months of age against 2009 A/H1N1 influenza was essential to help reduce the burden of pandemic disease in both the pediatric and adult populations.

Objectives: We compared the immunogenicity and safety of 4 alternative monovalent vaccine formulations to identify which provided optimal levels of seroprotection according to the US and European Union (EU) licensure criteria.

Subjects and Methods: A total of 654 healthy subjects (6 to <36 months old) were given 2 vaccine doses 3 weeks apart. Participants were assigned to 1 of the 4 immunization groups, receiving MF59-adjuvanted (Novartis Vaccines, Marburg, Germany) vaccine either containing 3.75 μg or 7.5 μg of A/H1N1 California/7/2009 antigen, or nonadjuvanted vaccine containing 7.5 μg or 15 μg of antigen. Antibody titers were assessed by hemagglutination inhibition assay 3 weeks, 3 months and 1 year after immunization. Vaccine safety was monitored throughout the study.

Results: After 1 dose, both adjuvanted formulations met the US and EU criteria for seroconversion; the 15 μg nonadjuvanted vaccine met the EU criterion for seroconversion alone. The US and EU criteria for seroprotection were only met by adjuvanted groups. MF59-adjuvanted formulations alone resulted in clinically significant persisting antibody titers after 12 months. All vaccines were well tolerated.

Conclusions: A single dose of MF59-adjuvanted vaccine containing 3.75 μg A/H1N1 antigen was highly immunogenic, met both the US and EU licensure criteria and was well tolerated. These data support the suitability of this monovalent vaccine formulation for pandemic use in children 6 to <36 months of age.

Key Words: influenza, H1N1, pandemic, pediatric, MF59, adjuvant

(*Pediatr Infect Dis J* 2012;31: e92–98.)

The 1918 to 1920 H1N1 influenza pandemic was the most severe in recent history, resulting in ~45 million deaths. Although partially sharing the same H1 antigenicity, the A/H1N1 virus responsible for the 2009 to 2010 pandemic is much less virulent than the 1918 virus.[1] The pediatric population was disproportionally affected by the 2009 to 2010 influenza pandemic,[2] with infection rates 4 times greater in the children of the United Kingdom than in adults.[3,4] Globally, the majority of severe pandemic A/H1N1 influenza infections initially reported occurred in children.[5] The pediatric population plays a major role in the transmission of the influenza virus within a community[6,7] and is therefore, considered a high-priority group for vaccination against pandemic influenza.[8] Modeling analyzes suggest that the mass immunization of children is essential for optimal disease control,[9–11] reducing infection rates and viral transmission within families and consequently the wider community.[12] Based on prior experience with trivalent, seasonal influenza vaccines, the Advisory Committee on Immunization Practices recommended that all children <9 years of age should be given 2 doses of monovalent A/H1N1 influenza vaccine at least 3 weeks apart in the 2009 to 2010 influenza season.[8]

Young children and infants have relatively limited exposure to influenza and usually remain immunologically naive to viral antigens. It has been shown that previous receipt of seasonal influenza vaccine does not result in the production of cross-reactive antibodies able to provide heterologous immunity to the A/H1N1 pandemic virus.[13,14] Such poor immunogenicity can be overcome with the use of oil-in-water emulsion adjuvants, such as MF59 (Novartis Vaccines, Marburg, Germany). The use of such adjuvants for 2009 A/H1N1 pandemic vaccines was endorsed by the World Health Organization.[15] MF59 has a well-established safety profile,[16] supported by >13 years of postmarketing and clinical safety data, with >158 million doses of MF59-adjuvanted vaccine distributed to date.[17]

This phase II/III, randomized study was conducted in healthy children to evaluate antibody responses to 4 different A/H1N1 vaccine formulations, varying in adjuvant and antigen content, to identify the vaccine formulation and administration schedule that offered optimal levels of seroprotection against pandemic A/H1N1 influenza in children from 6 to <36 months of age.

MATERIALS AND METHODS

Study Design and Objectives

This phase II/III, randomized, multicenter, observer-blind study was conducted across 29 sites in the United States and Mexico, between October 2009 and December 2010. The protocol was approved by a central Institutional Review Board for all study centers in the United States. For study centers in Mexico, the protocol was approved by the National Institute of Medical Sciences and Nutrition and the Federal Commission for Protection Against Health Risks. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Before enrollment, written informed consent was obtained from the legal guardians of each participant. The primary objective of this study was to assess the immunogenicity of 4 distinct A/H1N1 vaccine formulations in pediatric subjects according to the criteria defined by the US Center for Biologics Evaluation and Research

Accepted for publication March 20, 2012.
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Supported by a research grant provided by Novartis Vaccines and Diagnostics (to S.L.B.). This project has been funded in whole or in part with Federal funds from the Office of Public Health Emergency Preparedness, Office of Research and Development Coordination, under Contract Number HHSO100200700030C. J.B, V.S and S.J.H are permanent employees of Novartis Vaccines and Diagnostics. The authors have no other funding or conflicts of interest to disclose.
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ISSN: 0891-3668/12/3107-e92
DOI: 10.1097/INF.0b013e318257644f

(CBER) and the European Committee for Medicinal Products for Human Use (CHMP). Secondary objectives were to demonstrate superior antibody titers in response to MF59-adjuvanted vaccines compared with nonadjuvanted formulations, to assess long-term antibody persistence and to evaluate the reactogenicity and safety profiles for each vaccine.

Subjects

The exclusion criteria were laboratory-confirmed influenza disease within 6 months before study day 1; any acute illness within 3 days before vaccination; hypersensitivity to any vaccine component; an impaired or altered immune system; receipt of any inactivated or live vaccines within 2 weeks and 4 weeks before study day 1, respectively; fever (axillary ≥37.5°C, oral ≥38.0°C, rectal ≥38.5°C, tympanic membrane ≥37.7°C) within 3 days before vaccination; use of analgesic/antipyretic medication within 24 hours of vaccination; and receipt of influenza or routine childhood vaccines 7 days before or after the administration of investigational vaccine.

Vaccines and Subject Groups

The investigational, monovalent, influenza vaccine, Rexibel (Novartis Vaccines, Liverpool, United Kingdom), contains hemagglutinin and neuraminidase surface antigens derived from the influenza strain A/H1N1 California/7/2009. The vaccine seed A/H1N1 virus was prepared from the reassortant virus NYMC X-179A (New York Medical College, New York) generated from the A/California/7/2009 strain, as recommended by the World Health Organization.[18] The 4 vaccination groups were group A (3.75-Half MF59) received two 0.25 mL MF59 (Novartis Vaccines)-adjuvanted doses containing 3.75 μg A/H1N1 antigen; group B (7.5-No MF59) received two 0.25 mL nonadjuvanted doses containing 7.5 μg antigen; group C (7.5-Half MF59) received two 0.38 mL MF59-adjuvanted doses containing 7.5 μg antigen and group D (15-No MF59) received two 0.5 mL nonadjuvanted doses containing 15 μg antigen. A standard dose of MF59 contains 9.75 mg of squalene, as found in the licensed, seasonal, trivalent influenza vaccine, Fluad (Novartis Vaccines). In this study, subjects in groups A and C received vaccine containing half a standard dose of MF59 (4.88 mg squalene per dose). Adjuvanted vaccines were prepared by premixing prefilled syringes containing A/H1N1 antigen and separate vials of MF59 adjuvant. The preferred sites of vaccine administration were the anterolateral thigh and the deltoid muscle of the nondominant arm for children <24 months and 24 to <36 months of age, respectively.

Immunogenicity Assessment

Blood samples were centrifuged immediately after collection; sera were stored at a temperature of −18°C or below and shipped to the Novartis Vaccines Clinical Serology Laboratory in Marburg, Germany, where antibody responses were assessed by hemagglutination inhibition (HI) assay. The HI assay was based on the method of Stephenson et al.[19] HI titer is expressed as the reciprocal of the highest dilution at which hemagglutination was totally inhibited. For subjects seronegative (titer <10) at baseline (day 1), seroconversion or a significant increase in HI antibody titer was defined as a postvaccination titer ≥40. For subjects seropositive (≥10) at baseline, seroconversion or a significant increase in HI antibody titer was defined as a >4-fold increase. Assays were performed using the vaccine antigen strain A/H1N1 California/7/2009.

Safety Assessment

The subjects' parents or legal guardians were provided with diary cards and asked to record the occurrence of any adverse local or systemic reactions. The frequency and severity of all solicited or unsolicited adverse reactions were recorded for 6 days after the day of each vaccination. Information on any serious adverse events, adverse events necessitating the nonroutine consultation of a physician or adverse events leading to withdrawal from the study were collected throughout the entire study period (days 1–387). Vaccinees were observed for 30–60 minutes after each immunization to monitor for immediate adverse reactions. All subjects were physically assessed for general well-being at each clinic visit. The investigator used a standard scale to grade adverse events, in which symptoms were defined as mild, moderate or severe if they resulted in no limitation of, some limitation of or inability to perform normal daily activities, respectively.

Statistical Analyses

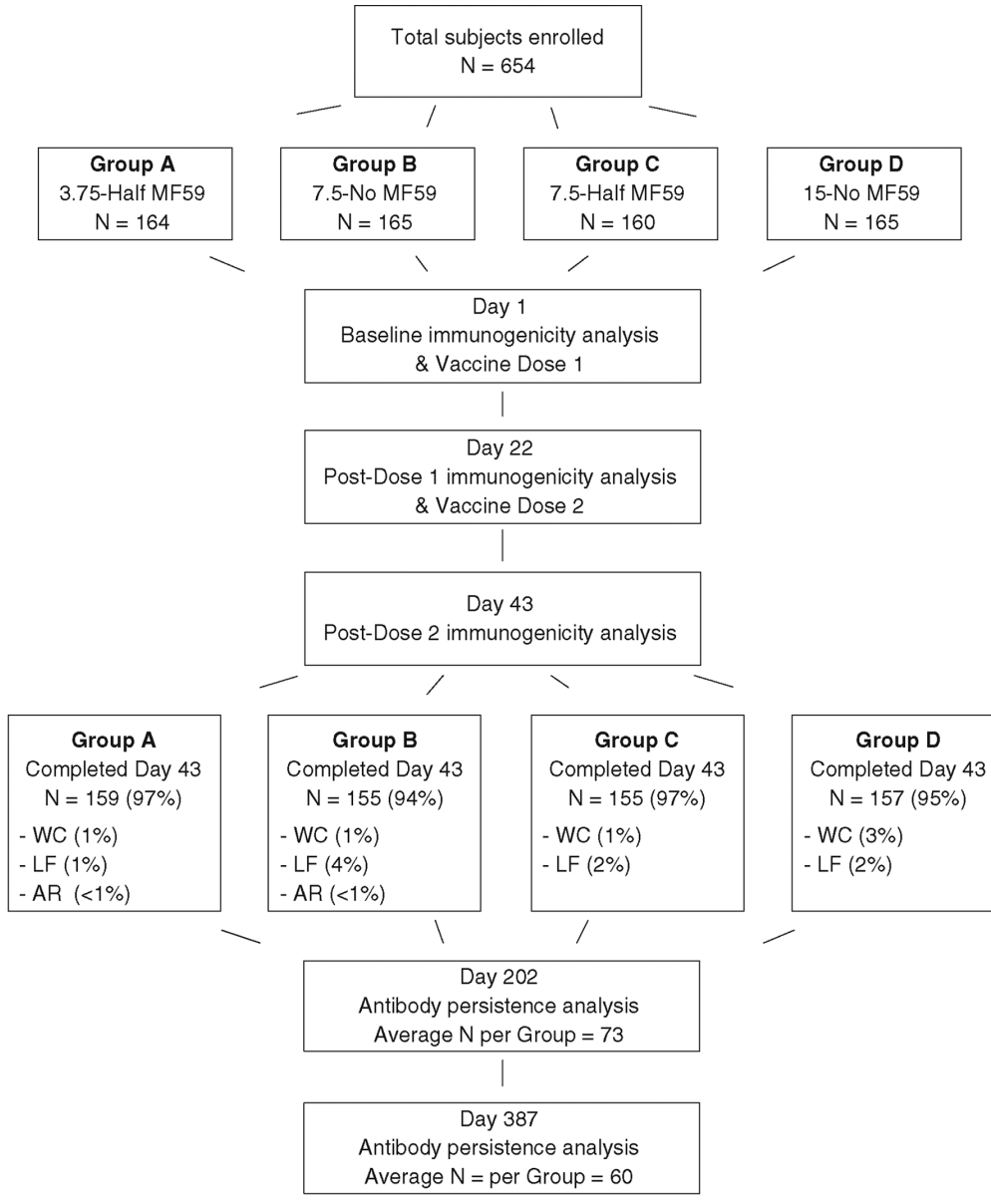
A sample size of at least 150 subjects per vaccination group was estimated to provide sufficient power to examine the primary study objective. No assumptions and power considerations were made for secondary objectives. No formal statistical hypothesis associated with the immunogenicity objectives of this study was tested, immunogenicity endpoints being based on licensure criteria established by CBER and CHMP. The following CBER criteria for pandemic influenza vaccines applied: the lower bound of the 2-sided 95% confidence interval (CI) for the percent of subjects achieving seroconversion for HI antibody should be ≥40% (seroconversion criterion); and the lower bound of the 2-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥40 should be ≥70% (seroprotection criterion). No CHMP criteria were established for subjects <18 years of age, therefore, the following adult CHMP criteria were applied: the percentage of subjects achieving seroconversion for HI antibody should be ≥40% (seroconversion criterion); geometric mean ratio should be >2.5 and the percentage of subjects achieving an HI antibody titer ≥40% should be >70% (seroprotection criterion). To assess the superiority/noninferiority of antibody responses to MF59-adjuvanted compared with nonadjuvanted vaccine, pairwise comparisons were performed for geometric mean antibody titer (GMT) ratios between vaccine groups. For each pairwise vaccine group compared, least squares GMT and associated 2-sided 95% CI, and median, minimum and maximum HI titer values were determined. Log_{10}-transformed antibody responses were modeled using analysis of variance including a factor for vaccine group and study centre. CIs were calculated and assessed against the margins of 0.5 for noninferiority, and 0.667 for superiority. The superiority hypothesis was tested using a margin of 1. No statistical null hypothesis was associated with the safety objective, which was analyzed descriptively.

RESULTS

A total of 654 healthy children 6 to <36 months of age were enrolled. Of the 164, 165, 160 and 165 subjects assigned to vaccination groups A, B, C and D, 159 (97%), 155 (94%), 155 (97%) and 157 (95%) completed the study on day 43, respectively (Fig. 1). The demographic and baseline characteristics of subjects enrolled into each of the 4 vaccine groups are described in Table 1. Because there was a >10% difference (12%) between full analysis set (FAS) and per protocol set (PPS) subject numbers, immunogenicity was analyzed using CBER and CHMP criteria in both population sets and the respective subgroups. Superiority and noninferiority analyses were performed using full analysis set and per protocol set data, respectively.

Immunogenicity

Analysis of antibody responses against the vaccine influenza antigen A/H1N1/California/7/2009 by HI assay is shown in Table 2. At baseline (day 1), HI titers against the vaccine antigen



WC, withdrew consent; LF, lost to follow-up, AR, administrative reasons/unclassified

FIGURE 1. Enrolled subjects from 6 to <36 months of age (n = 654) were assigned to 1 of 4 vaccination groups to receive a total of 2 vaccine doses, the first dose administered on day 1, the second on day 22. Immunogenicity was assessed 3 weeks after the administration of each vaccine dose. Long-term antibody persistence was analyzed approximately 6 and 12 months after immunization.

strain were low, with titers >40 observed in 9%–19% of subjects across all vaccination groups. Three weeks (day 22) after the administration of a first vaccine dose on day 1, only the adjuvanted vaccine groups A (74%) and C (80%) met the CBER criterion for seroconversion, with 32% and 44% of subjects achieving seroconversion in the nonadjuvanted groups B and D, respectively. Three weeks (day 43) after the administration of a second vaccine dose on day 22, the CBER criterion for seroconversion was met by all vaccination groups (98%, 68%, 98% and 76% in groups A, B, C and D, respectively). The CHMP criterion for seroconversion was met on day 22 by both adjuvanted vaccine groups A and C, and the nonadjuvanted/high antigen dose group D. On day 43, all vaccine groups met the CHMP criterion for seroconversion. On day 22, HI antibody titers ≥40 were achieved by 79%, 37%, 86% and 50% of subjects in groups A, B, C and D, respectively. Therefore, only those groups receiving adjuvanted vaccine met the CBER and CHMP criteria for seroprotection on day 22. On day 43, the CBER and CHMP criteria for seroprotection were met by the adjuvanted vaccine groups A and C (both 100%), and the nonadjuvanted/high antigen dose group D (81%); the nonadjuvanted/low antigen dose group B did not meet either licensure criteria, with 70% of subjects achieving an HI titer >40. Analysis of long-term antibody persistence found that only subject groups immunized with the MF59-adjuvanted vaccine

TABLE 1. Study Population Demographics

	Group A 3.75-Half MF59 (n = 164)	Group B 7.5-No MF59 (n = 165)	Group C 7.5-Half MF59 (n = 160)	Group D 15-No MF59 (n = 165)
Age (months, SD)	21.2 ± 7.9	21.6 ± 8.8	21.1 ± 8.4	21.3 ± 8.9
Female (%)	46	48	50	47
Weight (kg, SD)	12.1 ± 2.2	12.3 ± 2.6	12.0 ± 2.4	12.1 ± 2.8
Height (cm, SD)	83.6 ± 9.1	84.1 ± 9.8	83.3 ± 9.5	83.6 ± 9.4
BMI (kg/m², SD)	17.5 ± 4.8	17.5 ± 2.7	17.6 ± 4.9	17.3 ± 2.9
Previous influenza vaccination (%)	51	52	43	52
Asian (%)	0	<1	1	1
Black (%)	16	16	18	22
Caucasian (%)	52	56	54	50
Hispanic (%)	26	22	24	23
Other (%)	5	5	3	4

SD indicates standard deviation; BMI, body mass index.

TABLE 2. Immunogenicity Analyses (95% Confidence Interval) by Hemagglutination Inhibition Assay Against the A/H1N1 Vaccine Strain California/7/2009 at Baseline (Day 1), 3 Weeks After First (Day 22) and Second (Day 43) Doses, and Approximately 6 (Day 202) and 12 (Day 387) Months After Vaccination

	Group A 3.75-Half MF59	Group B 7.5-No MF59	Group C 7.5-Half MF59	Group D 15-No MF59
	% Seroconversion (HI titer ≥40)			
Day 22	74 (65–81) n = 129	32 (24–41) n = 124	80 (72–87) n = 127	44 (35–53) n = 129
Day 43	98 (93–100) n = 129	68 (59–76) n = 124	98 (94–100) n = 127	76 (68–83) n = 129
Day 202	89 (76–96) n = 45	50 (33–67) n = 38	91 (79–98) n = 46	39 (24–57) n = 38
Day 387	76 (61–87) n = 46	22 (10–38) n = 37	76 (60–89) n = 38	25 (12–42) n = 36
	Geometric mean ratio			
Day 22:1	8.0 (5.9–11) n = 129	2.8 (2.1–3.8) n = 124	10 (7.4–13) n = 127	3.4 (2.6–4.6) n = 129
Day 43:1	62 (45–85) n = 129	11 (8.0–15) n = 124	67 (49–92) n = 127	14 (10–19) n = 129
Day 202:1	23 (14–39) n = 45	7.0 (4.0–12) n = 38	25 (16–40) n = 46	5.5 (3.2–9.7) n = 38
Day 387:1	12 (6.9–21) n = 46	2.4 (1.3–4.5) n = 37	11 (6.1–19) n = 38	3.0 (1.6–5.7) n = 36
	% Seroprotection (≥70% with HI titer ≥40)			
Day 1	19 (12–26) n = 129	9 (5–15) n = 124	16 (10–23) n = 127	19 (13–27) n = 129
Day 22	79 (71–86) n = 129	37 (29–46) n = 124	86 (79–91) n = 127	50 (41–59) n = 129
Day 43	100 (97–100) n = 129	70 (61–78) n = 124	100 (97–100) n = 127	81 (74–88) n = 129
Day 202	96 (85–99) n = 45	50 (33–67) n = 38	100 (92–100) n = 46	55 (38–71) n = 38
Day 387	85 (71–94) n = 46	27 (14–44) n = 37	84 (69–94) n = 38	36 (21–54) n = 36

formulations displayed persisting antibody titers sufficient to meet the CBER licensure criterion for seroprotection (Table 2). Both 3.75 μg and 7.5 μg adjuvanted formulations resulted in persisting, seroprotective antibody titers of clinical significance on day 202 (96% and 100%, respectively) and day 387 (85% and 84%, respectively).

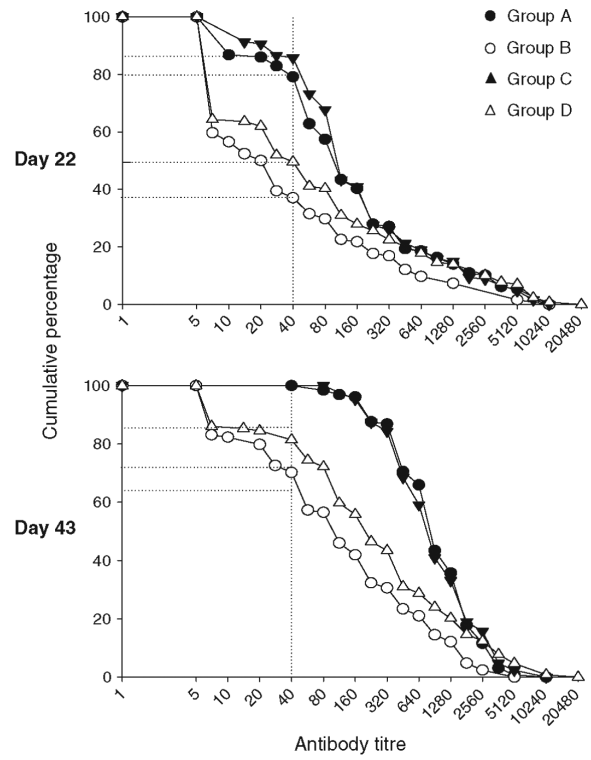


FIGURE 2. Reverse cumulative distribution of HI antibody titers against the A/H1N1 vaccine strain California/7/2009, measured 3 weeks after the administration of first (day 22) and second (day 43) vaccine doses.

The distribution of HI antibody titers against the vaccine strain A/H1N1/California/7/2009 is illustrated in Figure 2. Median antibody responses show adjuvanted vaccine formulations (groups A and C) elicited considerably higher antibody titers after first and second immunizations. The heightened antibody response to adjuvanted vaccine resulted in >95% of subjects receiving MF59 having an HI titer ≥120 on day 43. Both adjuvanted groups had similar antibody distribution, showing the 3.75 μg and 7.5 μg formulations to be equally immunogenic. The steeper slopes observed for the adjuvanted vaccine groups indicate less variability in antibody distribution among those receiving MF59. In the nonadjuvated vaccine groups, higher HI antibody titers were consistently observed in response to the 15 μg antigen dose.

Administration of the first vaccine dose resulted in ~9- and 3-fold increases (day 1 to day 22) in GMTs for adjuvanted and nonadjuvanted groups, respectively (Fig. 3). Three weeks after the second vaccine dose, GMTs were increased from baseline values by ~65-fold for adjuvanted and 13-fold for nonadjuvanted groups. GMTs in response to the adjuvanted vaccines were superior to GMTs in response to the nonadjuvanted formulations after both first and second doses; the 3.75-Half MF59 vaccine was noninferior to the 7.5-Half MF59 formulation. Further subgroup analysis showed that antibody responses were higher in those subjects with seropositive (≥10) compared with seronegative (<10) baseline titers and that recent immunization with seasonal influenza vaccine did not influence the immune response to the investigational vaccines. Persisting antibody GMTs up to 1 year after vaccination are illustrated in Figure 3. Increased antigen dose was found to have little impact on antibody persistence (days 202 and 387) within both the adjuvanted and nonadjuvanted groups. Long-term GMTs were considerably higher in response

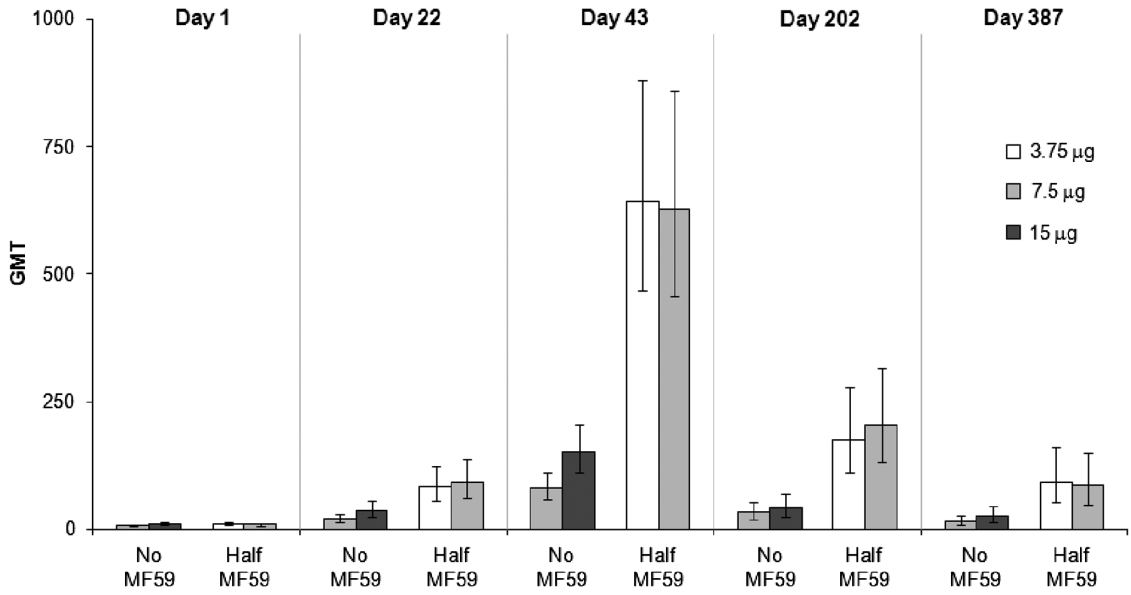


FIGURE 3. GMT against the A/H1N1 vaccine strain California/7/2009, measured by HI assay at baseline (day 1), 3 weeks after the administration of first (day 22) and second (day 43) vaccine doses, and approximately 6 (day 202) and 12 (day 387) months after immunization.

TABLE 3. Percentage of Subjects Experiencing Mild (Open Figures) and Severe (Brackets) Solicited Local* and Systemic Adverse Reactions Occurring Within 1 Week of Vaccination

	Dose 1				Dose 2			
	Group A 3.75-Half MF59 (n = 161)	Group B 7.5-No MF59 (n = 161)	Group C 7.5-Half MF59 (n = 161)	Group D 15-No MF59 (n = 163)	Group A3.75-Half MF59 (n = 155)	Group B 7.5-No MF59 (n = 148)	Group C 7.5-Half MF59 (n = 157)	Group D 15-No MF59 (n = 157)
Ecchymosis*	0	0	0	0	0	0	1 (0)	0
Erythema*	1 (0)	0	1 (0)	1 (0)	1 (0)	1 (0)	3 (0)	1 (0)
Swelling*	3 (1)	5 (1)	1 (1)	3 (1)	1 (0)	1 (0)	5 (0)	4 (0)
Induration*	5 (0)	4 (0)	8 (0)	5 (0)	3 (0)	2 (0)	8 (0)	6 (0)
Tenderness*	30 (0)	26 (0)	33 (0)	26 (0)	23 (0)	18 (0)	24 (0)	19 (1)
Sleepiness	22 (0)	17 (0)	23 (1)	16 (2)	18 (0)	14 (0)	13 (0)	10 (1)
Diarrhea	19 (1)	16 (1)	22 (1)	15 (0)	12 (1)	13 (0)	13 (0)	10 (0)
Vomiting	8 (0)	6 (0)	7 (0)	5 (1)	7 (0)	6 (0)	9 (0)	3 (0)
Irritability	24 (1)	23 (1)	28 (0)	25 (0)	23 (0)	25 (1)	19 (1)	15 (0)
Altered eating habits	13 (0)	9 (1)	12 (0)	10 (1)	13 (0)	12 (0)	9 (0)	7 (0)
Persistent crying	21 (0)	22 (0)	21 (1)	20 (1)	14 (0)	14 (1)	15 (0)	11 (0)
Fever	3 (0)	3 (0)	5 (1)	4 (0)	5 (0)	2 (1)	3 (0)	4 (0)
Analgesic/antipyretic	11	18	22	18	13	15	10	11

to MF59-adjuvanted vaccines when compared with nonadjuvanted formulations.

Safety

The percentages of subjects reporting local and systemic adverse reactions were similar for all 4 groups following first (57%–64%) and second (42%–53%) vaccine doses (Table 3). No trend toward increased local or systemic reactions was observed in those subjects receiving MF59-adjuvanted vaccines. Across all groups, the most commonly reported local reaction was tenderness at the site of injection, experienced by 26%–33% and 18%–24% of subjects after first and second vaccine doses, respectively. The majority of local reactions were mild and transient, severe local reactions were only reported after administration of the first vaccine dose (1% of subjects). The most commonly reported systemic reactions were irritability, reported by 24%–28% and 15%–26% of subjects and sleepiness, reported by 18%–24% and 11%–18% of subjects after first and second vaccine doses, respectively. Severe systemic reactions were experienced by <2% of subjects in each vaccine group. Adverse events were reported by 56%–72% of subjects across all 4 vaccination groups, <30% of which were considered to be vaccine-related. Three subjects experienced serious adverse events (intussusception, subcutaneous abscess and staphylococcal abscess), none of which were vaccine-related. During the 12-month follow-up period, 22 subjects reported serious adverse events (16 in the nonadjuvanted vaccine groups and 6 in the adjuvanted groups), none of which were considered to be vaccine-related.

DISCUSSION

The relatively poor performance of nonadjuvanted A/H1N1 vaccines in children 6–36 months of age, and therefore, the need for adjuvanted formulations in this age group is well documented. The relationship between age and levels of seroprotection resulting from A/H1N1 vaccination is evident in a recent report from Plennevaux et al.[20] Seroprotection rates of 45%, 69%, 95% and 94% were observed in subjects 6–35 months, 3–9 years, 18–64 years and ≥65 years of age, respectively, 3 weeks after receiving 1 dose of nonadjuvanted vaccine containing 7.5 μg of A/California/07/2009 antigen; a similar pattern was also observed with a 15 μg antigen dose. This earlier study found 1 vaccine dose to be sufficient for adults, but not for 6- to 36-month-old subjects, suggesting the need for adjuvant in this age group. Clark et al[21] also demonstrated that there is no requirement for adjuvant in the adult population, finding little difference in numbers achieving seroconversion after receiving nonadjuvanted (72%) and MF59-adjuvanted (73%) A/H1N1 vaccine. The present trial found that 2 doses of nonadjuvanted vaccine containing 7.5 μg of antigen were required to meet the CBER and CHMP criteria for seroconversion. A similar trial conducted in 6- to <36-month-old children also found that 2 doses of nonadjuvanted vaccine containing 7.5 μg of A/California/07/2009 antigen were required to meet the licensure criteria, with 6% and 56% of subjects achieving seroconversion after first and second doses, respectively.[22]

A study by Waddington et al[23] provides further evidence of the benefits of adjuvanted A/H1N1 vaccine in the 6- to 36-month-old age group. Two doses of either adjuvanted or nonadjuvanted vaccine were administered, containing 1.9 μg or 7.5 μg of A/California/07/2009 antigen, respectively. Despite the nonadjuvanted vaccine containing a much higher antigen dose, considerably higher antibody titers were observed in response to the adjuvanted vaccine. Trials of an AS03-adjuvanted monovalent A/H1N1 vaccine also found the administration of a single adjuvanted vaccine dose to be sufficient to induce adequate levels of seroprotection in subjects under 3 years of age[24]; 2 vaccine doses containing either 1.9 μg or 3.75 μg of A/California/07/2009 antigen were given 3 weeks apart and immunogenicity assessed 21 days after each immunization. Following the first vaccine doses, 99% and 98% of subjects were found to achieve seroconversion in response to 1.9 and 3.75 μg vaccine formulations, respectively.

The identification of an MF59-adjuvanted vaccine formulation as optimal has 3 major benefits. First, MF59 allows for reduced antigen content,[25–28] ensuring dose-sparing and therefore, the widest possible vaccine supply from the limited manufacturing capacity. Second, as well as heightening the homologous antibody response against vaccine strain antigen, MF59 has been shown to enhance levels of heterologous immunity by increasing cross-reactive antibody production,[25,27,29–31] a quality of great importance during the later stages of a pandemic, when viral mutation is a major concern. Third, these data and other studies demonstrate that MF59 increases long-term antibody persistence,[31,32] promoting the presence of antibody titers sufficient to meet seroprotection licensure criterion for as long as 1 year after immunization. All study participants were deemed healthy on enrollment, and therefore, the results of this trial cannot be applied to children affected by any chronic disease or the immunocompromised. The observed levels of long-term antibody persistence were the result of a 2-dose vaccination schedule; further investigation is required to confirm that persisting antibody titers are not significantly decreased following the single dose administration schedule identified as optimal.

ACKNOWLEDGMENTS

All authors participated in the conception, design and implementation of this clinical trial. All authors were involved in the interpretation of analyzed data and approved the final draft manuscript for submission. The authors thank Jamie Stirling, Robert Baldwin Mboizi, and Maithili VN Dokuparti (Novartis Vaccines and Diagnostics), Patricia de Groot (CHC Europe), and Bilal Bham (Scripsi Scriptum Ltd) for providing advice and editorial assistance in the preparation of this manuscript.

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