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Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Seasonal Influenza Vaccine in Young Children at High Risk of Influenza-associated Complications: A Phase III, Randomized, Observer-blind, Multicenter Clinical Trial

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Background: Vaccination against seasonal influenza is recommended for all children with a history of medical conditions placing them at increased risk of influenza-associated complications. The immunogenicity and efficacy of conventional influenza vaccines among young children are suboptimal; one strategy to enhance these is adjuvantation. We present immunogenicity and safety data for an MF59-adjuvanted quadrivalent influenza vaccine (aIIV4) in healthy children and those at a high risk of influenza-associated complications, based on the results of a recently completed phase III study.

Methods: Children 6 months to 5 years of age (N = 10,644) were enrolled. The study was conducted across northern hemisphere seasons 2013–2014 and 2014–2015. Subjects received either aIIV4 or a nonadjuvanted comparator influenza vaccine. Antibody responses were assessed by hemagglutination inhibition assay against vaccine and heterologous strains. Long-term antibody persistence was assessed (ClinicalTrials.gov: NCT01964989).

Results: aIIV4 induced significantly higher antibody titers than nonadjuvanted vaccine in high-risk subjects. aIIV4 antibody responses were of similar magnitude in high-risk and healthy subjects. Incidence of solicited local and systemic adverse events (AEs) was slightly higher in aIIV4 than nonadjuvanted vaccinees, in both the healthy and high-risk groups. Incidence of unsolicited AEs, serious AEs and AEs of special interest were similar for adjuvanted and nonadjuvanted vaccinees in the healthy and high-risk groups.

Conclusion: aIIV4 was more immunogenic than nonadjuvanted vaccine in both the healthy and high-risk study groups. The reactogenicity and safety profiles of aIIV4 and the nonadjuvanted vaccine were acceptable and similar in 6-month- to 5-year-old high-risk and healthy children.

Key Words: influenza, vaccine, quadrivalent, adjuvant, pediatric

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The burden of seasonal influenza disease is higher in infants and young children than in other age groups, and specific pre-existing medical conditions, such as diabetes, immunosuppression and neurologic disorders, significantly increase the risk of severe influenza disease in children.[1–6] Annual vaccination is recommended for all children classified as being at a high risk of severe disease and influenza-associated complications.[1,2]

Two distinct influenza B strain lineages emerged in the 1980s, B/Yamagata and B/Victoria, which continue to co-circulate globally during every influenza season.[7] Children under 15 years of age suffer the highest burden of B strain influenza disease,[3,8,9] and as such, the development of quadrivalent vaccines containing antigen derived from both B lineages is of particular advantage to children, and even more so to children at a high risk of severe disease.

Immune responses to standard-dose, nonadjuvanted, seasonal influenza vaccines in infants and young children are known to be suboptimal, with low vaccine effectiveness (VE) observed, particularly in children under 2 years of age.[10] Strategies to enhance the levels of protection afforded by seasonal vaccines to children include that of adjuvantation. Many clinical trials have shown the squalene-based adjuvant, MF59 (Novartis International AG, Basel, Switzerland) to increase the immunogenicity of both seasonal and pandemic influenza vaccines, to enhance long-term antibody persistence, and importantly, to promote cross-reactive antibody responses.[11–20]

A phase III study was conducted during the 2013–2014 and 2014–2015 northern hemisphere influenza seasons to evaluate the efficacy, immunogenicity and safety of an MF59-adjuvanted quadrivalent influenza vaccine (aIIV4) compared with a nonadjuvanted influenza vaccine in children 6 months to 5 years of age.[21] The outcome of the study was mainly driven by relative vaccine efficacy (rVE) against mismatched A/H3N2 strains, because 78% of identified isolates were A/H3N2 and only 5% of culture-confirmed A/H3N2 strains were vaccine-matched. aIIV4 and the nonadjuvanted comparator were equally efficacious in the prevention of clinical influenza disease for any strain in subjects 6 months to 5 years of

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age, with similar attack rates observed in both vaccine groups, and a rVE of −0.67% [95% confidence interval (CI): −19.81 to 15.41). In children 6–23 months of age, representing the most vulnerable and influenza-naive population, higher efficacy was demonstrated for aIIV4 (rVE 31.37%; 95% CI: 3.14–51.38).[21]

In this article, we present immunogenicity and safety data for aIIV4 compared with a nonadjuvanted influenza vaccine in healthy and high-risk cohorts of 6-month- to 5-year-old children.

MATERIALS AND METHODS

Study Design and Subjects

This phase III, randomized, multicenter, observer-blind study was conducted over 2 consecutive northern hemisphere influenza seasons, and across 146 sites in the United States, Canada, Finland, Italy, Spain, Poland, Taiwan, the Philippines and Thailand. The protocol was approved by either central or local Institutional Review Boards, and the study conducted in accordance with the principles of the Declaration of Helsinki[22] and Good Clinical Practice.[23] Written informed consent was obtained from the parents or legal guardians of all participants before enrollment. Children (6 months to 5 years old; N = 10,644), either healthy or at high risk of influenza-associated complications (conditions defining high-risk status listed in Table 1, Supplemental Digital Content 1, http://links.lww.com/INF/D944, as determined by investigators during screening), were enrolled and randomly assigned (1:1) to receive either aIIV4 or nonadjuvanted influenza vaccine. Subjects having received <2 doses of seasonal influenza vaccine since July 1, 2010 were considered to be vaccine naïve on enrollment. Subject inclusion and exclusion criteria are provided as Table 2, Supplemental Digital Content 2, http://links.lww.com/INF/D944. All site personnel (except staff administering vaccines), subjects, parents/guardians and outcome assessors were blinded to the vaccines administered. Vaccine naïve subjects received 2 vaccine doses given 4 weeks apart (days 1 and 29). Nonvaccine naïve subjects received a single dose on day 1. All vaccines were administered in the deltoid muscle of the nondominant arm (or anterolateral thigh, if deltoid mass was insufficient). All subjects enrolled in season 1 were included in the immunogenicity subset. In season 2, subsets of high-risk (n = 356) and healthy (n = 1424) subjects receiving aIIV4 and nonadjuvanted vaccine were randomized into the immunogenicity subset at ratio of 1:1, respectively [stratified according to country, dose group (0.25 and 0.5 mL dose volumes for 6–35-month-old and 3–5-year-old children, respectively) and previous vaccination status].

Vaccines

One 0.5 mL dose of aIIV4 (Seqirus S.r.l., Rosia, Italy) used in seasons 1 and 2 contained a total of 60 μg hemagglutinin (HA) antigen; 15 μg antigen from each of the World Health Organization (WHO)-recommended strains for seasons 2013–2014 and 2014–2015 (northern hemisphere): A/California/7/2009 (H1N1)pdm09-like virus; A/Texas/50/2012 (H3N2); B/Massachusetts/2/2012 (B/Yamagata lineage) and B/Brisbane/60/2008 (B/Victoria lineage). One 0.5 mL dose of aIIV4 contained a standard quantity (9.75 mg squalene) of the oil-in-water emulsion adjuvant, MF59. One 0.5 mL dose of the nonadjuvanted, trivalent comparator vaccine used in season 1 (Fluzone; Sanofi Pasteur, Swiftwater, PA) contained a total of 45 μg HA antigen; 15 μg antigen from each of the strains: A/California/7/2009 (H1N1)pdm09-like virus; A/Texas/50/2012 (H3N2) and B/Massachusetts/2/2012. One 0.5 mL dose of the nonadjuvanted, quadrivalent comparator vaccine used in season 2 (Fluzone Quadrivalent; Sanofi Pasteur), contained 60 μg antigen; 15 μg from each strain identical to aIIV4. Children of 3–5 years old received 0.5 mL vaccine doses. Children of 6–35 months old received 0.25 mL doses (total 22.5 μg antigen per trivalent dose; total 30 μg antigen per quadrivalent dose). Trivalent nonadjuvanted comparator vaccine was used in season 1 because the nonadjuvanted quadrivalent comparator was not FDA-approved for children ≥6 months old until June 2013 and was therefore unavailable.

Immunogenicity and Safety Assessment

Immunogenicity endpoints included geometric mean [antibody] titers (GMTs) at baseline, and 3 weeks and 6 months after the last dose, as assessed by hemagglutination inhibition (HI) assay[24] (HI assays performed by Viroclinics Biosciences B.V., Rotterdam, the Netherlands). GMTs were also assessed 4 weeks after the first dose in subjects vaccine naïve at enrollment. Ratios of aIIV4 versus nonadjuvanted vaccine-induced GMTs were assessed at each timepoint. Parents/guardians were asked to record the use of antipyretic/analgesic medication, and any solicited local (tenderness, erythema, induration and ecchymosis) and systemic (irritability, sleepiness, altered eating habits, vomiting, diarrhea, chills and fever) adverse events (AEs) on diary cards. Solicited local and systemic AEs were assessed for 7 days after administration of each vaccine dose. Unsolicited AEs were assessed from days 1 to 50 for subjects vaccine naïve on enrollment, and from days 1 to 22 for nonvaccine naïve subjects. Serious AEs (SAEs), AEs leading to study withdrawal, the new onset of chronic diseases and AEs of special interest were monitored throughout the entire study period (days 1–366 and days 1–390 for nonvaccine naïve subjects and vaccine naïve subjects, respectively).

Statistical Analyses

aIIV4 was considered to be immunologically superior to a nonadjuvanted comparator if the lower bound 2-sided 95% CI for the ratio of GMTs was >1. All statistical analyses of HI data were performed on logarithmically transformed values (base 10). HI titers below the detection limit were assigned to half that limit for the purpose of analysis. Because IIV3 was used as a comparator vaccine in the first season, season 1 immunogenicity results for the B/Victoria strain were excluded from vaccine group comparisons within healthy and high-risk subjects. Immunogenicity full analysis set included all enrolled subjects selected for immunogenicity analysis during randomization, which were vaccinated and provided valid serum samples prevaccination and postvaccination. Safety analysis set included all vaccinated subjects that provided safety data. Statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC). ClinicalTrials.gov: NCT01964989.

RESULTS

A total of 10,644 subjects were enrolled, 1486 subjects (14.0%) during season 1 (November 2013–January 2014), and 9158 (86.0%) during season 2 (September 2014–March 2015). Of the 10,644 subjects enrolled, 10,612 (99.7%) received study vaccine; aIIV4 and nonadjuvanted comparator vaccine were administered to 5339 and 5273 subjects, respectively. Of all enrolled subjects, 927 children (8.7%) were classified as being at a high risk of influenza-associated complications and 9717 (91.3%) were classified as healthy. Of the 927 high-risk subjects, 473 (51%) and 454 (49%) were randomized to receive aIIV4 and nonadjuvanted vaccine, respectively. Of the 9717 healthy subjects, 4879 (50%) and 4838 (50%) were randomized to receive aIIV4 and nonadjuvanted vaccine, respectively. Mean age, gender distribution and vaccine naïve status on enrollment were evenly balanced between the vaccine groups in the high-risk and healthy cohorts. In general, high-risk subjects were slightly older and less likely to be vaccine naïve compared with healthy subjects (Table 1).

TABLE 1. Study Population Demographics: FAS - Immunogenicity and Safety Set data

	Immunogenicity Set				Safety Set			
	High Risk		Healthy		High Risk		Healthy	
	aIIV4 (n = 273)	Comparator (n = 234)	aIIV4 (n = 1208)	Comparator (n = 1171)	aIIV4 (n = 470)	Comparator (n = 452)	aIIV4 (n = 4869)	Comparator (n = 4820)
Age, Mean (mo; SD)	39 ± 19	38 ± 18	35 ± 19	35 ± 18	43 ± 18	42 ± 17	38 ± 18	38 ± 18
Male:female (%)	56:44	59:41	48:52	49:51	55:45	62:38	50:50	50:50
Vaccine naïve (%)	59	59	63	62	56	59	69	69
Caucasian (%)	64	59	69	70	55	49	39	39
African American (%)	25	26	20	20	23	26	12	12
Asian (%)	8	10	6	6	19	22	46	47
Native American* (%)	0.7	0.4	0.3	0.6	0.4	0.2	0.2	0.2
Hawaiian† (%)	0	1	0.7	0.4	0.2	0.7	0.3	0.3

FAS indicates full analysis set; mo, months; SD, standard deviation.
*Native American/Alaskan.
†Hawaiian/Pacific Islander.

TABLE 2. Medical History Events (Percentages of High-risk Subjects) Among Infants and Children (6 Months–5 Years of Age; n = 927) Defining High-risk Status for Influenza Complications (All Enrolled Set Data)

	aIIV4 (n = 473)	Comparator (n = 454)
Asthma and other RADs (%)	66	66
Neurologic and neurodevelopmental conditions (%)	2.5	3.1
Neurologic disorders	1.5	1.8
Developmental delay	0.6	1.1
Cerebral palsy	0.4	0.2
Chronic respiratory diseases* (%)	1.5	1.1
Cystic fibrosis	0.6	0
Chronic lung diseases	0.8	1.1
Heart diseases (%)	5.7	7.9
Cardiac disorders	0.8	2.2
Congenital cardiac disorders	4.4	5.3
Congenital disorders repair	0.4	0.4
Blood disorders (%)	1.3	2.2
Thalassemia†	0.2	0.8
Sickle cell anemia	1.1	1.1
Anemia	0	0.2
Endocrine disorders (%)	1.1	0.7
Kidney disorders (%)	1.5	2.6
Liver disorders (%)	0.4	0.2
Metabolic disorders (%)	0	0.2
Immune system disorders (%)	0.7	0.8
HIV infection	0.4	0.7
Congenital immunodeficiency	0.2	0.2
Morbid obesity (%)	25	21
Other medical conditions‡ (%)	4.2	6.8

RADs indicates reactive airway diseases.
*Excluding RADs.
†All cases classed as thalassemia minor.
‡Mainly congenital disorders, genetic disorders and recurrent respiratory infections.

A comprehensive medical history review was performed for all subjects classified as being at high risk of influenza-associated complications (Table 2). The most frequent conditions in high-risk subjects were classified as "asthma and other reactive airway diseases," occurring in 66% of the high-risk population (5.7% of all subjects enrolled); other chronic respiratory diseases were infrequent, occurring in 1.1%–1.5% of the high-risk subjects. Morbid obesity was the second most common condition, accounting for 21%–25% of high-risk subjects (2.0% of all subjects enrolled). Chronic cardiac disorders (mainly congenital defects) were identified in 5.7%–7.9% of high-risk subjects.

Immunogenicity data are presented in Table 3. At baseline, vaccine antigen-specific A/H1N1 and A/H3N2 antibody titers were slightly higher in high-risk than healthy subjects; B strain titers were similar in both groups. Antibody responses were assessed 3 weeks after the last study vaccination (ie, on day 22 for nonvaccine naïve subjects, and on day 50 for vaccine naïve subjects) by HI assay against all vaccine antigen (homologous) strains. Overall, the data presented in Table 3 demonstrate that MF59-adjuvanted vaccine induced considerably higher antibody titers than nonadjuvanted vaccine in both high-risk and healthy subjects. Across all groups, GMTs 3 weeks after the final dose (day 22/50) were higher in response to A strains than B strains. As a general trend, a comparison of day 22/50 GMTs in response to adjuvanted versus nonadjuvanted vaccines in high-risk and healthy subjects found antibody titers to be twice as high [GMT ratios (GMTrs) ranged from 1.6 to 2.3] in response to aIIV4 compared with nonadjuvanted vaccine, for all 4 vaccine strains. Antibody responses in the healthy and high-risk groups following vaccination with aIIV4 demonstrated no significant difference (lower bounds of CIs for the intergroup ratio < 1), for all 4 vaccine antigen strains (data not shown).

In vaccine naïve subjects, the differences in antibody titers between adjuvanted and nonadjuvanted groups were greatest on days 29 and 50, and decreased over time (Fig. 1). Six months after the last vaccination, GMTs against homologous vaccine strains remained statistically higher in healthy subjects and in subjects at high risk in the aIIV4 group than in the comparator vaccine group (data not shown). Cross-reactive antibody responses were also assessed by HI assay against heterologous A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains (Table 3, Supplemental Digital Content 3; http://links.lww.com/INF/D944). Overall, similar trends in antibody responses against heterologous strains were observed, with substantially higher GMTrs following aIIV4 compared with nonadjuvanted vaccine administration, both in the healthy and high-risk groups. Antibody responses against the heterologous A/H1N1 strain were close to baseline levels for all study groups.

Overall, no relevant differences in the safety profiles of aIIV4 and the nonadjuvanted vaccine were observed between the healthy and high-risk groups. Incidence of solicited local and systemic AEs was similar in the high-risk and healthy groups after any vaccine dose. The most common solicited local AEs following aIIV4 and nonadjuvanted vaccine administration were tenderness and erythema (Table 4), in both healthy and high-risk subjects. The most frequent solicited systemic AEs among both healthy and high-risk groups in response to aIIV4 and nonadjuvanted vaccine were

TABLE 3. Immunogenicity Results in High-risk and Healthy Subjects

	High-risk aIIV4	High-risk Comparator	High-risk GMTr (95% CI)	Healthy aIIV4	Healthy Comparator	Healthy GMTr (95% CI)
A/H1N1						
GMT: day 1	59 (n = 273)	62 (n = 234)	–	37 (n = 1208)	35 (n = 1171)	–
GMT: day 22/50	1023 (n = 258)	626 (n = 223)	1.6 (1.3–2.0)	945 (n = 1104)	474 (n = 1084)	2.0 (1.8 – 2.2)
GMR: (day 22/50)/day 1	17 (n = 258)	10 (n = 223)	–	25 (n = 1104)	14 (n = 1084)	–
A/H3N2						
GMT: day 1	86 (n = 273)	67 (n = 234)	–	49 (n = 1208)	48 (n = 1171)	–
GMT: day 22/50	1316 (n = 258)	774 (n = 223)	1.7 (1.4–2.0)	1147 (n = 1104)	660 (n = 1084)	1.7 (1.6–1.9)
GMR: (day 22/50)/day 1	14 (n = 258)	11 (n = 223)	–	23 (n = 1104)	14 (n = 1084)	–
B/Yamagata						
GMT: day 1	13 (n = 273)	13 (n = 234)	–	11 (n = 1208)	10 (n = 1171)	–
GMT: day 22/50	195 (n = 258)	96 (n = 223)	2.0 (1.6–2.5)	174 (n = 1104)	77 (n = 1084)	2.3 (2.0–2.5)
GMR: (day 22/50)/day 1	15 (n = 258)	7.3 (n = 223)	–	16 (n = 1104)	7.4 (n = 1084)	–
B/Victoria						
GMT: day 1	12 (n = 161)	11 (n = 165)	–	10 (n = 636)	10 (n = 615)	–
GMT: day 22/50	316 (n = 155)	142 (n = 158)	2.2 (1.6–3.0)	315 (n = 590)	138 (n = 580)	2.3 (2.0–2.7)
GMR: (day 22/50)/day 1	26 (n = 155)	13 (n = 158)	–	31 (n = 590)	13 (n = 580)	–

Antibody responses against homologous vaccine strains assessed by HI assay 3 weeks after administration of last vaccine dose (FAS - immunogenicity data). HI analyses 3 weeks after the last dose occurred on day 22 for nonvaccine naïve subjects (vaccinated on day 1); HI analyses 3 weeks after the last dose occurred on day 50 for vaccine naïve subjects (vaccinated on days 1 and 29). B/Victoria data from season 2 only are presented for both aIIV4 and comparator to allow vaccine group comparison analyses.

FAS indicates full analysis set; GMR, geometric mean ratio; GMT, geometric mean titer; GMTr, geometric mean titer ratio.

irritability, sleepiness and altered eating habits. Generally, solicited AEs resolved within 3–4 days. Severe local and systemic AEs were rare. Rates of mild-to-moderate fever appeared to be higher in aIIV4 vaccinees; in high-risk subjects, 15% and 9.6% of aIIV4 and nonadjuvanted vaccine recipients experienced fever; 20% and 11% of healthy aIIV4 and nonadjuvanted vaccine recipients experienced fever, respectively. Rates of severe fever (≥39°C) were also slightly higher in aIIV4 recipients. The percentages of subjects experiencing any unsolicited AEs were also similar in the high-risk and healthy cohorts, for both adjuvanted (65% vs. 69%) and nonadjuvanted vaccines (68% vs. 69%, respectively). Incidents of SAEs were low in all groups. Vaccine-related SAEs were experienced by 7 subjects (<0.07% of enrolled participants), none of whom were classified as high risk.

DISCUSSION

Here, we present aIIV4 immunogenicity and safety data in a subset of children at high risk of developing influenza-related complications, compared with healthy subjects. This study demonstrated antibody responses in high-risk subjects to be significantly higher against all 4 vaccine strains following aIIV4 compared with nonadjuvanted vaccine. In addition, aIIV4 was demonstrated to be equally immunogenic in high-risk and healthy subjects, inducing similar antibody titers in both groups 3 weeks after the last vaccination. Moreover, in high-risk vaccine naïve children, high antibody titers were rapidly generated 4 weeks after a first vaccine dose; long-term antibody persistence was evident, with high antibody titers detected in the peripheral blood 6 months after the last dose. Cross-reactive antibody responses were also demonstrated by HI assay against nonvaccine heterologous strains. Vaccine safety profiles were similar in high-risk and healthy subjects, with predictably higher frequencies of mild-to-moderate AEs experienced after aIIV4 administration.[25]

The higher and broader antibody responses to aIIV4 are due to the ability of MF59 to: activate monocytes, macrophages and dendritic cells at the injection site; increase the transportation of vaccine antigen to the lymph nodes[26]; activate T cells and increases B-cell expansion within the lymph nodes.[15,27] The ability of MF59 to promote enhanced and cross-reactive antibody responses in recipients of all ages is well documented,[11–20] and the induction of such potential cross-protection during seasons of antigenic drift and vaccine mismatch, as well as in a pandemic setting, is of the utmost importance. Recent analysis of MF59-adjuvanted trivalent influenza vaccine (aIIV3) responses in high-risk children mirror the general trends of the aIIV4 immunogenicity and safety data observed during the present study,[28] with both demonstrating the immunologic benefits of adjuvantation, and similar immunogenicity and safety profiles in at-risk and healthy children under 6 years of age. Similarly, higher responses to aIIV3 as compared with conventional nonadjuvanted influenza vaccine have been observed in adults with underlying chronic diseases.[29–31]

Asthma and obesity were the most common conditions among the high-risk population assessed in this study. Asthma is the most common underlying disease in both adults and children admitted to healthcare facilities, and is a risk factor for hospitalizations during the influenza season.[32] Despite the recognized need for subjects at increased risk of influenza complications to be vaccinated, coverage in children with asthma is low, with rates of ~18%–20% in Spain, ~15% in France and 2.5%–20% in Italy, compared with ~50% in the United States.[32] Morbid obesity has been associated with increased influenza disease in some adult studies,[33–35] and may also be a risk factor for children,[36] although it may not be an independent factor for influenza complications requiring hospitalization or resulting in death.[4,37] Because this study was conducted in young children across North America, Europe and Asia, morbid obesity was defined according to the judgment of the investigators, rather than by uniform criteria based on body mass index.

Although the study inclusion criteria allowed for the enrollment of immunocompromised subjects, only a few immunocompromised individuals were assessed; therefore, no definite conclusions for this population can be drawn from this study. Trials of aIIV3 suggest similar or even higher antibody responses compared with nonadjuvanted vaccine in immunocompromised subjects. In a study of pediatric juvenile idiopathic arthritis patients treated with disease-modifying antirheumatic drugs (DMARDs) or etanercept, similar immune responses were observed to aIIV3 in patients treated with DMARDs and healthy controls; despite significantly lower immune responses in patients treated with etanercept, 95% of these subjects were

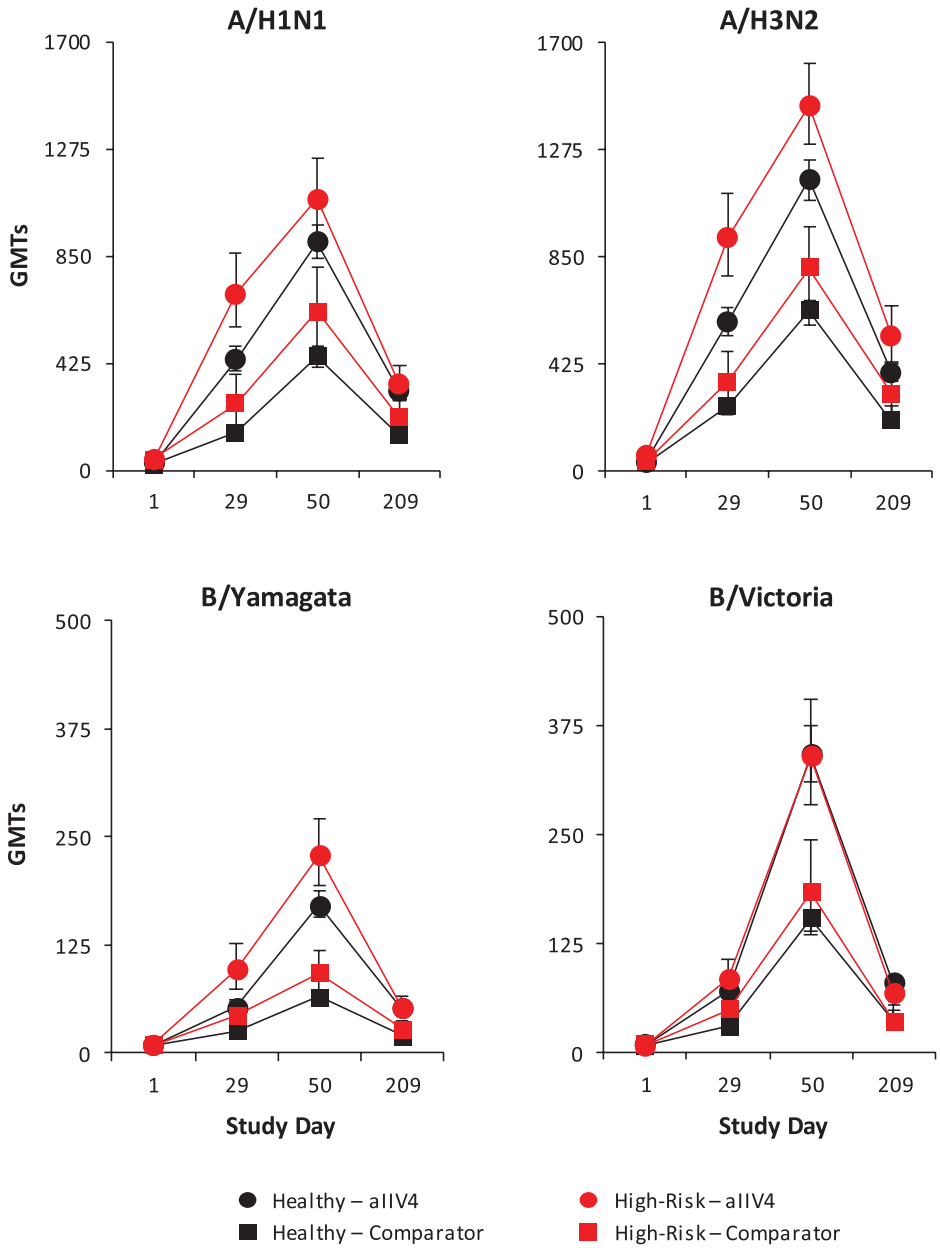

FIGURE 1. Geometric mean antibody titers (95% CI) in vaccine naïve subjects (6 months–5 years of age) against homologous vaccine strains. Assessment by HI assay (FAS - immunogenicity data). Note, A and B strain data presented on different y-axis scales. B/Victoria data from seasons 1 and 2 (aIIV4), and season 2 only (comparator) are presented. FAS indicates full analysis set.

seroprotected following receipt of aIIV3.[13] Likewise, MF59-adjuvated A/H1N1 2009 monovalent vaccine elicited an adequate immune response in pediatric solid organ transplant patients[38]; the vaccine was considered safe, and no subjects experienced acute allograft rejection. Higher immune responses to aIIV3 than nonadjuvanted vaccine were also observed in adult renal transplant patients,[39] as well as in adult HIV patients receiving highly active antiretroviral therapy.[40] A similar response to aIIV3 and nonadjuvanted vaccine was observed in a smaller study of adult renal transplant patients[41]; aIIV3 was considered safe, and did not result in increased levels of human leukocyte antigen alloantibodies. Together, the data from these studies suggest that immune responses in immunocompromised subjects are variable, and are likely to depend on the condition of the individual and levels of immunosuppression.

Although this study collected vaccine efficacy data, the number of polymerase chain reaction-confirmed influenza cases in the at-risk population was too low to allow for reliable rVE estimates; therefore, the extent to which enhanced antibody titers translated into increased VE cannot be known. Given that subjects with a history of asthma and morbid obesity accounted for a combined 91% of all high-risk subjects, caution is advised in extrapolating conclusions from this study data to all high-risk individuals in general. Few immunocompromised subjects were enrolled, and definite conclusions cannot be drawn regarding this population. Only subjects 6 months to 5 years of age were recruited; therefore, the benefit of adjuvanted vaccine in high-risk subjects over 5 years of age requires further investigation.

Causal factors for the low rates of vaccination observed among high-risk individuals include a general lack of awareness, a limited understanding of influenza disease and the benefits of

TABLE 4. Percentages of Subjects Experiencing Any Solicited and Unsolicited Adverse Events After Any Vaccination

	High-risk aIIV4	High-risk Comparator	Healthy aIIV4	Healthy Comparator
Observation period: day 1–7	n = 450	n = 421	n = 4688	n = 4635
Any solicited systemic AEs (%)	51	43	53	43
Any solicited local AEs (%)	54	46	51	43
Tenderness* (%)	46 (1.1)	37 (1.0)	43 (1.7)	34 (0.6)
Erythema* (%)	23 (0.9)	18 (1.7)	21 (0.9)	17 (0.4)
Induration* (%)	19 (0.9)	15 (1.0)	14 (0.5)	10 (0.1)
Ecchymosis* (%)	12 (0)	10 (0)	7.3 (<0.1)	7.0 (<0.1)
Irritability† (%)	30 (1.6)	23 (1.0)	27 (1.3)	23 (0.8)
Sleepiness† (%)	25 (2.0)	22 (0.5)	26 (0.6)	21 (0.4)
Altered eating habits† (%)	21 (1.3)	19 (1.7)	23 (0.9)	17 (0.9)
Diarrhea† (%)	11 (0.7)	12 (0.5)	12 (0.7)	12 (0.5)
Vomiting† (%)	8.9 (0)	6.4 (0)	10 (0.4)	8.4 (0.3)
Chills† (%)	7.6 (0.2)	5.0 (0.2)	6.8 (0.2)	4.0 (0.1)
Fever ≥ 38°C† (%)	15 (3.3)	9.6 (2.6)	20 (4.7)	11 (2.5)
Observation period: day 1–390	n = 462	n = 439	n = 4781	n = 4722
Any unsolicited AE (%)	65	68	69	69
Any vaccine-related AE (%)	14	11	13	10
Any SAE (%)	3.9	7.3	4.5	4.2
Any vaccine-related SAE (%)	0	0	0.1	<0.1
Any AE leading to withdrawal (%)	0.4	0.7	0.2	0.1
Any vaccine-related AE leading to withdrawal (%)	0.4	0.5	0.1	<0.1
Any AE leading to death (%)	0	0.2	<0.1	<0.1
Any AE of special interest (%)	0	0.2	0.1	<0.1
Any new onset of chronic disease (%)	2.0	3.4	1.6	1.7

Severe (grade 3) solicited adverse events are shown in parentheses (safety analysis set). Severe fever defined as body temperature ≥ 39°C.
AE, adverse event; SAE, serious adverse event.
*Local AEs.
†Systemic AE.

vaccination (both in parents and primary care pediatricians), and concerns about side effects.[42] The higher antibody responses to aIIV4 and the acceptable safety profile described in this article may help to influence attitudes toward influenza vaccination.

This study indicates that aIIV4 induces significantly higher antibody titers against all 4 vaccine antigen strains than nonadjuvanted vaccine, and that aIIV4 has an acceptable safety profile in healthy and high-risk 6-month- to 5-year-old children.

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