Original Article

Safety and immunogenicity profiles of an adjuvanted seasonal influenza vaccine in Guatemalan children

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Abstract

Introduction: The efficacy of non-adjuvanted seasonal influenza vaccine in young children is considered to be suboptimal. This study compared the safety and immunogenicity profiles of MF59-adjuvanted, trivalent, influenza vaccine (ATIV) and non-adjuvanted, trivalent, influenza vaccine (TIV) in Guatemalan children (N = 360) between 6 and < 60 months of age.

Methodology: Children received two doses of ATIV or TIV administered four weeks apart. Solicited adverse reactions were recorded for seven days after each vaccination. Serious adverse events were recorded throughout the entire study period. Antibody responses were assessed by hemagglutination inhibition (HI) assay at baseline, four weeks after administration of the first vaccine dose, and three weeks after administration of the second dose.

Results: Both ATIV and TIV were well tolerated, with similar rates of solicited reactions and adverse events observed in response to both vaccines. MF59-adjuvanted vaccine induced considerably higher antibody titers than did TIV. After two doses, the B strain-specific antibody response to TIV was insufficient to meet the Center for Biologics Evaluation and Research (CBER) licensure criterion for seroprotection, whereas responses to the MF59-adjuvanted vaccine met the seroprotection criterion against all three strains. Cross-reactive antibody responses to MF59-adjuvanted vaccine met the CBER seroprotection criterion against all three strains after two doses; B strain-specific heterologous responses to non-adjuvanted TIV were inadequate.

Conclusions: The MF59-adjuvanted seasonal influenza vaccine was well-tolerated and highly immunogenic in children 6 to < 60 months of age, inducing seroprotective antibody titers against both the vaccine strains and antigenically distinct heterologous strains.

Key words: influenza; vaccine; seasonal; trivalent; MF59; pediatric.

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Introduction

Young children and infants have the highest rates of seasonal influenza disease and are at increased risk of hospitalization for influenza-related conditions [1,2]. Epidemiological studies have demonstrated high rates of influenza-related hospitalizations and outpatient visits in the pediatric population [3,4]. Children play a major role in the spread of influenza disease within communities [5,6]. Immunization of children against influenza not only protects the individual, but inhibits viral transmission among the wider population [7,8]. Therefore, safe and effective vaccines for the pediatric population are essential to minimize the socio-economic impact of seasonal influenza disease.

Following the lead of the United States (US) [9], routine vaccination against seasonal influenza in children from six months of age is increasingly being recommended by health authorities in other countries [10]. However, the efficacy of non-adjuvanted, trivalent influenza vaccines (TIV) in young and unprimed children is inadequate. Meta-analyses have shown the efficacy of non-adjuvanted TIV to be as low as 59% in children above two years of age, and to be unproven in children under two years of age [11,12]. The immunogenicity of non-adjuvanted TIV is particularly poor against B strain influenza virus [13,14].

Vaccine adjuvants, such as MF59 (Novartis Vaccines and Diagnostics), serve to potentiate the

immunogenicity of vaccines, and offer a solution to the suboptimal antibody titers observed in response to non-adjuvanted TIV in the pediatric population. As well as decreasing required antigen content per dose and promoting long-term antibody persistence [15], MF59 has been shown to enhance levels of heterologous immunity by heightening cross-reactive antibody responses in vaccinees of all ages [16-23]. The good safety profile of MF59-adjuvanted influenza vaccines is well established [24-27].

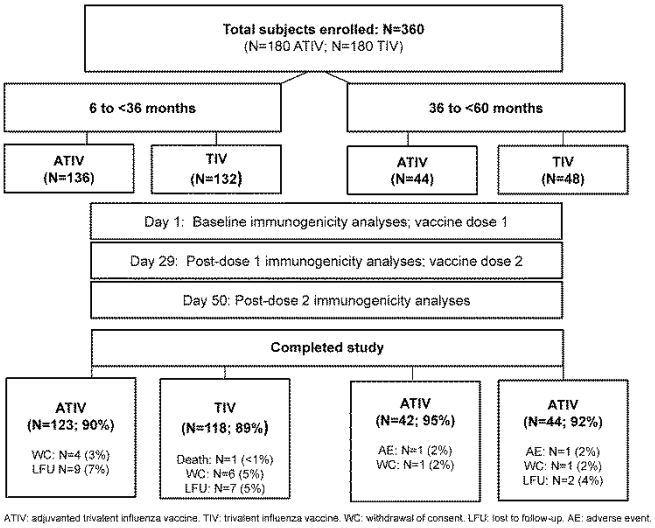
In order to evaluate the possible benefits of adjuvanted seasonal influenza vaccine in children under five years of age compared with non-adjuvanted vaccine, this study assessed the safety and immunogenicity profiles of ATIV compared with non-adjuvanted, split TIV in healthy Guatemalan children. Vaccine antigen-specific (homologous) and cross-reactive (heterologous) antibody responses were analyzed after first and second vaccine doses by hemagglutination inhibition (HI) assay according to the US Center for Biologics Evaluation and Research (CBER) licensure criteria for seasonal influenza vaccines [28].

Methodology

Study design and objectives

This phase II, randomized, multicenter, observer-blind study was conducted across five sites in Guatemala between January and October 2008. The study protocol was approved by an independent Guatamalan ethics committee, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Before enrolment, written informed consent was obtained for all subjects from their parents or legal guardians. The primary objective of this study was to evaluate the safety and tolerability of one and two doses of either ATIV or TIV in children under three years of age. The secondary objective of this study was to evaluate the immunogenicity of one and two doses of either ATIV or TIV by HI assay in children under five years of age. Subjects were randomly assigned in equal numbers to receive two doses of either ATIV or TIV. Children 36 to < 60 months of age group were enrolled first; enrolment of children 6 to < 36 months of age began only after the reactogenicity data for the older children had been found to be acceptable by an independent safety data monitoring committee. Vaccines were prepared and administered by designated, non-blinded study personnel who did not participate in the evaluation of data. Blood samples (5 mL) were obtained by venipuncture for immunogenicity analysis

Figure 1. Study design and subject disposition



ATIV: adjuvanted trivalent influenza vaccine. TIV: trivalent influenza vaccine. WC: withdrawal of consent. LFU: lost to follow-up. AE: adverse event.

at baseline (day 1), four weeks after administration of the first vaccine dose (day 29), and three weeks after the second vaccine dose (day 50).

Subjects

A total of 360 healthy children from 6 to < 60 months of age were enrolled in the study (Figure 1). Exclusion criteria were: any serious illness; history or likelihood of anaphylaxis or adverse reaction to any vaccine component; known or suspected impairment of the immune system; history of Guillain-Barré syndrome or bleeding diathesis; receipt of inactivated or live vaccine two and four weeks prior to enrolment, respectively; receipt of influenza vaccine six months prior to enrolment; laboratory-confirmed influenza disease six months prior to enrolment; receipt of any investigational agent 90 days prior to enrolment; previous receipt of two doses of influenza vaccine, either in a single previous influenza season or two previous consecutive seasons; a rectal temperature ≥ 38°C; and acute illness within the three days prior to enrolment.

Vaccines

The MF59-adjuvanted, egg-derived, seasonal, trivalent influenza vaccine (ATIV) contained hemagglutinin (HA) surface antigen from each of the three World Health Organization (WHO) recommended influenza strains for the 2007–2008 season in the northern hemisphere: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. Children 6 to < 36 months of age received ATIV in a volume of 0.25 mL per dose. A 0.25 mL dose of ATIV contained 7.5

µg of HA antigen from each of the three strains (total 22.5 µg antigen per dose) and half the standard dose of MF59 (4.88 mg squalene). Children 36 to < 60 months of age received ATIV in a volume of 0.50 mL per dose. A 0.50 mL dose of ATIV contained 15 µg of HA antigen from each of the three strains (total 45.0 µg antigen per dose) and a standard dose of MF59 (9.75 mg squalene). The antigen content of the non-adjuvanted, seasonal, trivalent influenza vaccine (TIV), US licensed Fluzone (Sanofi Pasteur Inc., One Discovery Drive, Software, PA 18370), was identical to the ATIV in terms of quantities and viral strains. Children 6 to < 36 months of age received TIV in a volume of 0.25 mL per dose (total 22.5 µg antigen per dose). Children 36 to < 60 months of age received TIV in a volume of 0.50 mL per dose (total 45.0 µg antigen per dose). All vaccines were supplied in monodose (0.50 mL), and the pre-filled syringes containing the 0.5 mL dose were provided with a pediatric line for administering the 0.25 mL dose. The vaccine was administered in the deltoid muscle of the non-dominant arm, or the anterolateral aspect of the thigh if deltoid muscle mass was insufficient.

Safety analyses

All subjects were monitored for ~30 minutes after vaccination for possible immediate adverse reactions. Solicited local and systemic adverse reactions were recorded on diary cards for seven consecutive days following first and second dose vaccinations by the subjects' parents or legal guardians. Unsolicited adverse events (AEs) were recorded from study days 1–50. Serious adverse events (SAEs), medically attended visits, and AEs leading to withdrawal were recorded throughout the entire study period (days 1–211). All SAEs were immediately reported to the study sponsor. Solicited local adverse reactions were ecchymosis, erythema, induration, swelling, and pain (defined as tenderness or pain at injection site in children 6 to < 36 months age and 36 to < 60 months of age, respectively). In children 6 to < 36 months of age, solicited systemic adverse reactions were sleepiness, diarrhea, vomiting, irritability, altered eating habits, shivering, and unusual crying. In children 36 to < 60 months of age, solicited systemic adverse reactions were chills, malaise, myalgia, arthralgia, headache, sweating, and fatigue. Other solicited indicators of reactogenicity were fever (≥ 38°C), severe fever (≥ 40°C), the use of analgesic or antipyretic medication, and the decision to stay at home due to adverse reactions. AEs were classified as mild, moderate, or severe if they resulted in no limitation of, some limitation of, or an inability to perform normal daily activities, respectively. AEs were judged to be either non-related, possibly related, or probably related to vaccination by the investigator.

Immunogenicity analyses

Blood samples were centrifuged, and sera were stored at -18°C until being shipped to the Novartis Vaccines Clinical Serology Laboratory in Marburg, Germany, for analysis. Antibody responses to vaccination were measured by HI assay, according to standard methods [29]. HI titer was expressed as the reciprocal of the highest dilution at which hemagglutination was totally inhibited. Homologous antibody responses were tested against the vaccine antigen strains A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. Cross-reactive (heterologous) antibody responses were tested against influenza strains A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2), and B/Florida/4/2006. For subjects seronegative (HI titer < 10) at baseline, seroconversion was defined as a pre-vaccination HI titer < 10 to a post-vaccination titer ≥ 40. For subjects seropositive (HI titer ≥ 10) at baseline, seroconversion was defined as a ≥ fourfold increase in HI titer following vaccination. HI titers below the detection limit of 1:10 were arbitrarily assigned to half that limit (1:5) for the purpose of analysis. Per protocol set (PPS) immunogenicity data are reported throughout.

Statistical analyses

No formal statistical hypothesis was tested. Sample sizes were chosen to provide adequate estimates for immunogenicity endpoints based on CBER licensure criteria [28], assuming a 10% dropout rate. The CBER criterion for seroconversion was that the lower bound of the two-sided 95% confidence interval (CI) for the percentage of subjects achieving seroconversion for HI antibody should be ≤ 40%. The CBER criterion for seroprotection was that the lower bound of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥ 40 should be ≤ 70%. Geometric mean antibody titers (GMTs), and geometric mean ratios (GMRs) as well as corresponding two-sided 95% CIs were calculated for each vaccine group. Log_{10}-transformed antibody titers were modeled using analysis of variance (ANOVA) for each strain with vaccine groups and study centers as factors. Safety data were evaluated descriptively and expressed as the numbers and percentages of subjects experiencing AEs in each vaccination group.

Statistical analyses were performed by the Statistics Department of Novartis Vaccines and Diagnostics using SAS 9.1 software (SAS Institute, Cary, NC, USA).

Results

Across age and vaccination groups, 89%–96% of subjects completed the study on day 211 (Figure 1). The reasons for subjects not completing the study were withdrawal of consent (n = 12), subjects being lost to follow-up (n = 18), AE (n = 2), and non-vaccine-related death (n = 1). The baseline demographics of the enrolled study population are presented in Table 1. Groups were similar with respect to subjects' weights, heights, and ethnicities within the 6 to < 36 month-old and 36 to < 60 month-old age groups.

Safety analyses

In the 6 to < 36 month-old age group, rates of solicited adverse reactions were slightly higher in subjects who received ATIV compared with subjects who received TIV. The majority of reactions were mild in severity and transient in nature. Local adverse reactions were experienced by 32% and 24% of ATIV vaccinees, and by 29% and 17% of TIV vaccinees after first and second doses, respectively. The most commonly reported solicited local adverse reactions in both ATIV and TIV groups were pain at the site of injection and erythema (Table 2). No subjects experienced severe local adverse reactions. Systemic adverse reactions were experienced by 28% and 22% of ATIV vaccinees, and by 25% and 21% of TIV vaccinees after first and second doses, respectively. The most commonly reported solicited systemic adverse reaction in both ATIV and TIV groups was unusual crying (Table 2). Fever (≥ 38°C) was reported in 32% and 23% of subjects in the ATIV and TIV groups, respectively. No subjects experienced severe fever (≥ 40°C) at any time during the study.

In the 36 to < 60 month-old age group, rates of solicited local adverse reactions were generally higher in subjects who received ATIV compared with those who received TIV. The majority of reactions were mild in severity and transient in nature. Local adverse reactions were experienced by 60% and 54% of ATIV vaccinees, and by 46% and 45% of TIV vaccinees after first and second doses, respectively. Pain at the site of injection and erythema were the most commonly reported local adverse reactions (Table 3). Rates of systemic adverse reactions were similar in the ATIV and TIV groups; systemic adverse reactions were experienced by 34% and 23% of ATIV vaccinees, and by 32% and 21% of TIV vaccinees after first and second doses, respectively. Malaise and headache were the most commonly reported systemic reactions (Table 3). One subject in the ATIV group and one subject in the TIV group experienced severe malaise. Rates of fever (≥ 38°C) were similar in the ATIV (18%) and TIV (22%) groups. Severe fever (≥ 40°C) was experienced by one subject in the TIV group after the first vaccine dose.

Rates of AEs were similar between ATIV and TIV groups. Between study days 1–50, AEs were reported by 36%–42% of 6 to < 36 month-old children, and by 36%–48% of 36 to < 60 month-old children; 2%–4% of these events were considered to be at least possibly related to vaccination. The most commonly reported AEs among all subjects by preferred term were nasopharyngitis (5%–7% across ATIV and TIV groups), upper respiratory tract infection (6%–7% across both groups), and cough (6%). During the primary study period (days 1–50), one 36 to < 60 month-old ATIV vaccinee and one 36 to < 60 month-old TIV vaccinee experienced non-vaccine-related AEs (both varicella-zoster infection), leading to withdrawal from the study. No SAEs were reported during the primary study period. Two non-vaccine-related SAEs were reported during the six-month safety follow-up period (days 50–211): one 11-month-old female TIV vaccinee died due to falling down stairs, and one 18-month-old male ATIV vaccinee was hospitalized due to lobar pneumonia.

Immunogenicity analyses

In the 6 to < 36 month-old age group, MF59-adjuvanted vaccine consistently induced higher homologous GMTs (Figure 2) and higher GMRs (Table 4) than did non-adjuvanted TIV after first (day 29) and second (day 50) doses. In the 36 to < 60 month-old age group, first and second MF59-adjuvanted vaccine doses induced higher homologous GMTs (Figure 2) than did non-adjuvanted TIV against A/H1N1 and B strains, but not against A/H3N2; GMRs were consistently higher in response to MF59-adjuvanted vaccine after both first and second doses (Table 4). For both age groups, antibody responses to one dose of ATIV and TIV were sufficiently high against A/H1N1 and A/H3N2 strains to meet the CBER licensure criteria for seroconversion (Table 4) and seroprotection (Figure 3); seroconversion and seroprotection criteria were not met after one dose of ATIV or TIV against the B strain.

Table 1. Population demographics of study participants receiving adjuvanted, trivalent, influenza vaccine (ATIV) and non-adjuvanted, trivalent, influenza vaccine (TIV)

	6 to < 36 months of age		36 to < 60 months of age	
	ATIV (n = 136)	**TIV** (n = 132)	**ATIV** (n = 44)	**TIV** (n = 48)
Mean age (years, SD)	1.2 ± 0.7	1.2 ± 0.7	3.4 ± 0.5	3.5 ± 0.5
Male (%)	53	52	64	52
Mean weight (kg, SD)	11 ± 2.5	11 ± 2.2	16 ± 2.6	16 ± 2.7
Mean height (cm, SD)	81 ± 8.8	79 ± 8.2	100 ± 7.1	100 ± 7.1
Hispanic (%)	100	100	95	98
Caucasian (%)	0	0	5	2

SD: standard deviation

Table 2. Percentages of subjects 6 to < 36 months of age experiencing solicited local* and systemic adverse reactions within one week of vaccination

	Subjects 6 to < 36 months of age			
	1st dose ATIV (n = 130)	**1st dose TIV** (n = 130)	**2nd dose ATIV** (n = 124)	**2nd dose TIV** (n = 121)
Ecchymosis*	8	11	9	7
Erythema*	15	11	15	7
Induration*	5	2	8	2
Swelling*	5	2	2	2
Tenderness*	18	15	11	9
Altered eating habits	12	12	9	5
Sleepiness	5	5	3	2
Unusual crying	16	17	15	12
Irritability	11	10	11	12
Vomiting	8	4	2	2
Diarrhea	8	4	6	4
Shivering	3	1	2	1
Fever ≥ 38°C	18	12	19	17
Stayed home	14	8	15	15
Analgesics/antipyretics	19	15	25	16

ATIV: adjuvanted trivalent influenza vaccine; TIV: trivalent influenza vaccine

Table 3. Percentages of subjects 36 to < 60 months of age experiencing solicited local* and systemic adverse reactions within one week of vaccination

	Subjects 36 to > 60 months of age			
	1st dose ATIV (n = 50)	**1st dose TIV** (n = 50)	**2nd dose ATIV** (n = 48)	**2nd dose TIV** (n = 47)
Ecchymosis*	18	10	8	13
Erythema*	27	22	33	28
Induration *	24	10	29	23
Swelling*	12	4	13	11
Pain*	43	27	46	30
Chills	8	8	6	2
Malaise	16	16	17	17
Myalgia	8	6	13	6
Arthralgia	4	2	4	0
Headache	12	18	13	9
Sweating	4	2	2	6
Fatigue	8	6	10	6
Fever ≥ 38°C	6	4	15	21
Stayed home	6	4	11	9
Analgesics/antipyretics	22	12	17	19

ATIV: adjuvanted trivalent influenza vaccine; TIV: trivalent influenza vaccine

Table 4. Immunogenicity analyses (95% CI) by HI assay against the vaccine strains A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 at baseline (day 1), four weeks after administration of the first vaccine dose (day 29), and three weeks after administration of the second dose (day 50). Bold text indicates CBER licensure criterion was met.

	6 to < 36 months of age						**36 to < 60 months of age**					
	ATIV (n = 97)			**TIV** (n = 102)			**ATIV** (n = 23)			**TIV** (n = 20)		
	H1N1	H3N2	B strain	H1N1	H3N2	B strain	H1N1	H3N2	B strain	H1N1	H3N2	B strain
GMR day 29 : 1	41 (33–52)	26 (20–35)	4.0 (3.2–5.0)	29 (23–36)	11 (8.4–15)	2.0 (1.6–2.5)	37 (23–59)	21 (12–37)	8.6 (4.3–17)	23 (14–39)	16 (8.5–30)	4.3 (2.1–9.2)
GMR day 50 : 1	113 (84–153)	69 (47–100)	34 (28–42)	97 (72–129)	30 (21–44)	9.9 (8.2–12)	69 (33–142)	25 (13–46)	29 (17–51)	51 (23–113)	19 (9.8–38)	22 (12–40)
SC day 29 (%)	**97 (91–99)**	**95 (88–98)**	32 (23–42)	**97 (92–99)**	**85 (77–92)**	9.0 (4.0–16)	**100 (85–100)**	**91 (72–99)**	61 (39–80)	**95 (75–100)**	**90 (68–99)**	30 (12–54)
SC day 50 (%)	**99 (94–100)**	**98 (93–100)**	**95 (88–98)**	**98 (93–100)**	**89 (82–94)**	**75 (65–83)**	**96 (78–100)**	**91 (72–99)**	**96 (78–100)**	**95 (75–100)**	**95 (75–100)**	**80 (56–94)**

ATIV: adjuvanted trivalent influenza vaccine; TIV: trivalent influenza vaccine; GMR: geometric mean ratio; SC: seroconversion

Table 5. Analyses (95% CI) of cross-reactive (heterologous) antibody responses by HI assay at baseline (day 1), four weeks after administration of the first vaccine dose (day 29), and three weeks after administration of the second dose (day 50). Bold text indicates CBER licensure criterion was met.

	6 to < 36 months of age						**36 to < 60 months of age**					
	ATIV (n = 97)			**TIV** (n = 102)			**ATIV** (n = 23)			**TIV** (n = 20)		
	H1N1	H3N2	B strain	H1N1	H3N2	B strain	H1N1	H3N2	B strain	H1N1	H3N2	B strain
GMT day 1	43 (36–53)	19 (13–28)	15 (13–17)	45 (37–54)	16 (11–23)	14 (12–16)	39 (25–62)	40 (20–81)	16 (12–22)	61 (37–100)	64 (30–138)	36 (25–51)
GMT day 29	207 (143–300)	168 (104–273)	25 (21–30)	157 (109–225)	56 (35–90)	18 (16–22)	430 (189–977)	393 (167–925)	57 (35–94)	381 (155–933)	827 (325–2107)	53 (31–92)
GMT day 50	394 (298–522)	475 (346–651)	55 (47–65)	279 (213–367)	141 (103–192)	25 (21–29)	458 (259–809)	629 (363–1091)	73 (45–119)	426 (228–793)	1014 (566–1850)	80 (47–136)
GMR day 29 : 1	4.8 (3.5–6.5)	8.9 (6.5–12)	1.7 (1.4–2.0)	3.5 (2.6–4.7)	3.5 (2.6–4.7)	1.3 (1.1–1.6)	11 (5.4–22)	9.8 (5.8–17)	3.6 (2.4–5.4)	6.3 (2.9–14)	13 (7.2–23)	1.5 (1.0–2.3)
GMR day 50 : 1	9.1 (7.1–12)	25 (19–33)	3.7 (3.1–4.5)	6.2 (4.9–7.9)	8.7 (6.6–11)	1.8 (1.5–2.2)	12 (6.7–20)	16 (8.9–27)	4.6 (2.9–7.2)	7.0 (3.8–13)	16 (8.6–29)	2.2 (1.4–3.7)
SC day 29 (%)	47 (37–58)	**63 (52–72)**	9.0 (4.0–17)	45 (35–55)	43 (33–53)	6.0 (2.0–12)	**74 (52–90)**	**83 (61–95)**	43 (23–66)	**70 (46–88)**	**85 (62–97)**	20 (6.0–44)
SC day 50 (%)	**87 (78–93)**	**96 (90–99)**	**55 (44–65)**	**73 (63–81)**	**79 (70–87)**	19 (12–28)	**74 (52–90)**	**91 (72–99)**	**70 (47–87)**	**80 (56–94)**	**90 (68–99)**	45 (23–68)
SP day 29 (%)	**93 (86–97)**	63 (55–74)	34 (25–44)	**92 (85–97)**	48 (38–58)	21 (13–30)	**96 (78–100)**	**91 (72–99)**	52 (31–73)	**100 (83–100)**	**85 (72–97)**	45 (23–68)
SP day 50 (%)	**100 (96–100)**	**100 (96–100)**	**90 (82–95)**	**98 (93–100)**	**91 (84–96)**	56 (46–66)	**96 (78–100)**	**100 (85–100)**	78 (56–93)	**100 (83–100)**	**100 (83–100)**	80 (56–94)

ATIV: adjuvanted trivalent influenza vaccine; TIV: trivalent influenza vaccine; GMT: geometric mean titre; GMR: geometric mean ratio; SC: seroconversion; SP: seroprotection

After the second vaccine dose, the seroconversion criterion was met in response to ATIV and TIV against all three strains (Table 4) in both age groups. The seroprotection criterion was met against all three strains after two doses of ATIV in both age groups; two doses of TIV consistently failed to meet the seroprotection criterion against the B strain (Figure 3). Combined analysis for both age groups (6 to < 60 months) found that two doses of ATIV met the CBER licensure criteria for seroconversion and seroprotection against all three strains, whereas TIV failed to meet the seroprotection criterion against the B strain (data not shown).

Sera were analyzed by HI assay for the presence of vaccine-induced antibody able to cross-react with the non-vaccine strains A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2), and B/Florida/4/2006. Heterologous GMTs and GMRs were consistently higher in response to first and second doses of MF59-adjuvanted vaccine than to non-adjuvanted vaccine in both age groups, apart from anti-H3N2 responses, which were equal or higher in response to TIV for children 36 to < 60 months of age (Table 5). In children 6 to < 36 months of age, one dose of MF59-adjuvanted vaccine was sufficient to meet the licensure criterion for seroconversion against the A/H3N2 strain; one dose of non-adjuvanted TIV failed to meet this criterion. One dose of ATIV and TIV met the seroconversion criteria against both A strains in children 36 to < 60 months of age. Two doses of MF59-adjuvanted vaccine met the seroconversion criterion against all three strains in both age groups; two doses of non-adjuvanted TIV failed to meet the seroconversion criterion against the B strain in both age groups. The CBER criterion for seroprotection was met after one dose of ATIV and TIV against the A/H1N1 strain in children 6 to < 36 months of age, and against both A strains in children 36 to < 60 months of age. Two doses of MF59-adjuvanted vaccine met the seroprotection criterion against all three vaccine strains in children 6 to < 36 months of age; non-adjuvanted TIV failed to meet the seroprotection criterion against the B strain. In children 36 to < 60 months of age, two doses of ATIV and TIV met the seroprotection criterion against both A strains, but not against the B strain.

Figure 2. GMTs (95% CI) against A/H1N1, A/H3N2, and B strain vaccine antigens at baseline (day 1), four weeks after administration of the first dose (day 29), and three weeks after administration of the second dose (day 50)

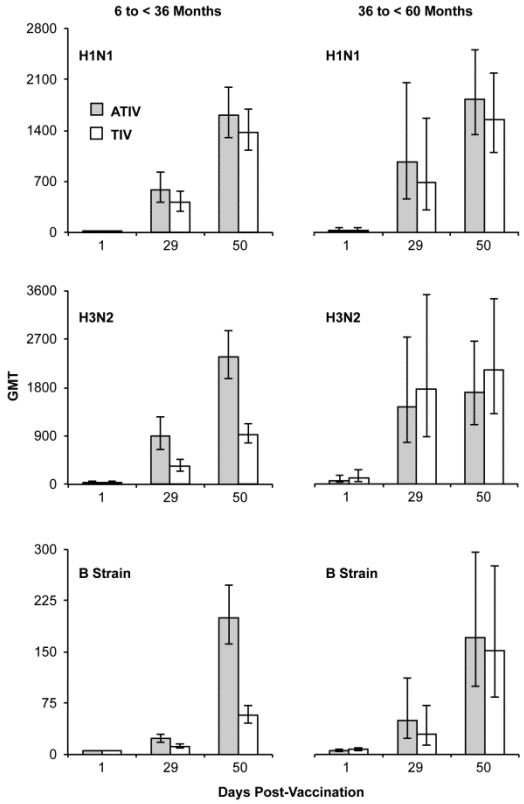
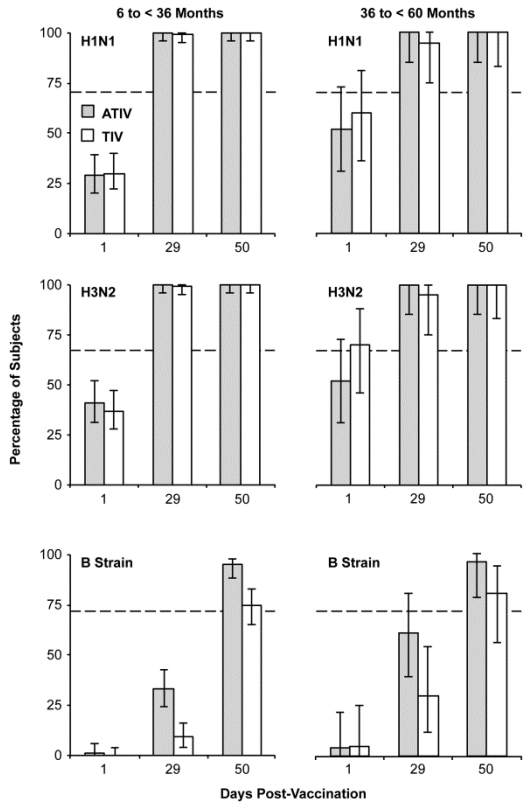


Figure 3. Seroprotection rates (95% CI) against A/H1N1, A/H3N2, and B strain vaccine antigens at baseline (day 1), four weeks after administration of the first dose (day 29), and three weeks after administration of the second dose (day 50). Broken lines represent the CBER criterion for seroprotection



Discussion

Due to being immunologically naive for influenza antigens, the pediatric population is affected by particularly high rates of seasonal influenza disease and high rates of influenza-associated hospitalization [1-4]. Non-adjuvanted, seasonal TIVs do not induce adequate levels of seroprotection against influenza disease in unprimed young children [11,12]. Vaccine adjuvants offer a solution to the suboptimal antibody titers observed in response to non-adjuvanted TIV in the pediatric population. A recent study of the MF59-adjuvanted, trivalent influenza study vaccine (ATIV), Fluad, in 4,707 previously unvaccinated healthy children 6 to < 72 months of age, demonstrated ATIV to be 98% efficacious in preventing influenza disease, while non-adjuvanted TIV had a vaccine efficacy of only 45% [30]. The present study was conducted to assess vaccine safety and to determine whether immunization with MF59-adjuvanted trivalent influenza vaccine resulted in increased levels of homologous and heterologous seroprotection compared with a licensed, non-adjuvanted TIV.

Both adjuvanted and non-adjuvanted vaccines were generally well-tolerated in both age cohorts. Slightly more mild solicited adverse reactions were observed in subjects who received ATIV compared with those who received TIV. Rates of AEs were similar in the ATIV and TIV groups. These data are in agreement with previous studies of MF59-adjuvanted influenza vaccine in young children [14,25,30-32], and support the well-established safety profile of MF59 adjuvant [24-27]. The MF59-adjuvanted study vaccine induced considerably higher antibody titers than the non-adjuvanted comparator vaccine. In addition to increasing vaccine antigen-specific (homologous) antibody responses, MF59-adjuvanted vaccine was shown to enhance the production of anti-A and anti-B strain-specific cross-reactive antibodies. These data are in agreement with previous studies – the ability of MF59 to heighten levels of heterologous immunity against influenza is well-documented [16-23]. MF59-induced heterologous protection against antigenic drift is particularly advantageous in tropical regions of the world, where both northern and southern hemisphere influenza strains co-circulate.

Circulation of influenza A strains was reported in Guatemala during the time of this study [32]; this fact may explain the atypically high anti-A strain antibody levels observed at baseline and after the first vaccine dose in both ATIV and TIV groups. This study demonstrated MF59-adjuvanted vaccine to be particularly beneficial in terms of enhancing B strain-specific antibody responses. The CBER licensure criteria for B strain antibody responses were only met by MF59-adjuvanted vaccine, whereas non-adjuvanted TIV failed to meet the seroprotection criterion. B strain influenza is responsible for a significant proportion of the influenza-related hospitalizations that occur each year in the pediatric population [33,34], with proportionally more B strain infections occurring in children than in adults or the elderly [34,35].

The results of this study demonstrate that MF59-adjuvanted, trivalent influenza vaccine is well-tolerated and induces seroprotective antibody titers able to provide children from 6 to < 60 months of age with vaccine antigen-specific and heterologous immunity against seasonal influenza disease.

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Trial registration

www.clinicaltrials.gov (NCT00649883)

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