Randomized, Multicenter Trial of a Single Dose of AS03-adjuvanted or Unadjuvanted H1N1 2009 Pandemic Influenza Vaccine in Children 6 Months to <9 Years of Age

Safety and Immunogenicity

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Background: During the 2009–2010 influenza pandemic, we evaluated the immunogenicity and safety of different H1N1 2009 pandemic influenza vaccines delivering various viral hemagglutinin (HA) doses with or without AS03 (a tocopherol oil-in-water emulsion–based adjuvant system) in children (NCT00976820).

Methods: Three hundred twenty-two healthy children 6 months to <9 years of age were randomized to receive 2 doses of nonadjuvanted (15 μg or 7.5 μg HA) or adjuvanted vaccine (3.75 μg HA/$AS03_A$ or 1.9 μg HA/$AS03_B$), 21 days apart. Blood samples before and after each dose were tested for immune responses using hemagglutination inhibition and microneutralization assays. Safety assessments were done up to day 385.

Results: The first dose of both AS03-adjuvanted vaccines elicited strong immune responses (seroprotection rates: 98.3%/99.0%; seroconversion rates: 94.9%/97.0%; geometric mean fold rises: 36.2/33.6), which were higher post-dose 2 (seroprotection rate: 100.0%/100%; seroconversion rate: 100.0%/98.8%; geometric mean fold rise: 157.1/151.6), meeting European regulatory criteria on days 21 and 42. The nonadjuvanted 15 μg HA vaccine also met the regulatory criteria after each dose; the 7.5 μg HA vaccine met them only post-dose 2. Six months post-dose 1, all vaccines except the nonadjuvanted 7.5 μg HA vaccine met European regulatory criteria. Neutralizing antibody response paralleled the hemagglutination inhibition immune response after each dose. Pain at the injection site, lasting 2–3 days, was more common following adjuvanted than nonadjuvanted vaccination.

Conclusions: AS03-adjuvanted H1N1 2009 pandemic influenza vaccine (3.75 μg or 1.9 μg HA), administered as 2 doses, was highly immunogenic, induced long-term immune response to 6 months, with a clinically acceptable safety profile in children aged 6 months to <9 years of age.

Key Words: influenza vaccine, pandemic, adjuvant

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Young children have high rates of hospitalization and medical visits for influenza and have been identified as a priority for annual immunization programs.[1] In addition, they serve as a major source of viral transmission in the community.[2,3] The highest attack and hospitalization rates for the H1N1 2009 pandemic virus were reported in children,[4,5] particularly those <12 months of age[6] and 32% of all H1N1 2009 hospitalizations in the United States were in the pediatric population.[7]

Immunization was seen as the most important factor to mitigate the 2009 influenza pandemic.[8] Over 30 pandemic vaccines were developed worldwide[9] of which about 30% contained oil-in-water adjuvants. Before the implementation of national influenza vaccine programs, data on the safety and immunogenicity of H1N1 vaccines, unadjuvanted or adjuvanted, were limited. In addition, it was not known if 1 or 2 doses would be needed. Given the known immunological naivety/lack of priming of young children, the number of doses of H1N1 2009 pandemic vaccine that might be required in this population was particularly relevant.

In Canada, the vaccine used for the universal pandemic influenza vaccine program in 2009−2010 was an oil-in-water adjuvanted ($AS03_A$) dose-sparing influenza vaccine. This study in children 6 months to <9 years of age sought to determine whether 1 or 2 doses of the AS03-adjuvanted or nonadjuvanted vaccines of this pandemic influenza vaccine [containing 3.75 μg hemagglutinin (HA) or 1.9 μg HA], administered 21 days apart, could meet the immunogenicity guidance criteria of the Committee for Medicinal Products for Human Use (CHMP) for the evaluation of pandemic influenza vaccines and to describe the persistence of this immune response to 6 months. In addition, the neutralizing antibody response 21 days after each of the 2 vaccine doses in a subset of subjects and the safety and reactogenicity of the H1N1 2009 vaccines up to 1 year were assessed.

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MATERIALS AND METHODS

Study Design and Participants

This was a randomized, controlled multicenter study to determine the safety and immunogenicity of 1 and 2 doses of adjuvanted and nonadjuvanted pandemic influenza A H1N1 2009 vaccines in children 6 months to <9 years of age. Enrollment was initiated at 12 Canadian centers in October 2009.

Enrollment was conducted in 2 phases. In the first phase, healthy subjects (target sample size: 240) were randomized using a blocking scheme of 1:1:1:1 to receive 21 days apart, 2 doses of either adjuvanted or nonadjuvanted vaccines of H1N1 2009 vaccine as follows: group 3.75 μg HA/$AS03_A$: 3.75 μg A/California H1N1 influenza antigen plus $AS03_A$ (11.86 mg tocopherol); group 1.9 μg HA/$AS03_B$: 1.9 μg Ag plus $AS03_B$ (5.93 mg tocopherol); group 7.5 μg HA: 7.5 μg plain A/California H1N1 influenza antigen; group 15 μg HA: 15 μg plain A/California H1N1 influenza antigen. Treatment was allocated by an Internet-based central randomization system that used a minimization procedure accounting for center, age and history of seasonal influenza vaccination. Within each group, the subjects were to be stratified by age (1:1:2) into 6 to 11 months, 12 to 35 months and 3 to <9 years. This was followed by safety assessments in the first 120 randomized subjects, within the 7-day postvaccination follow-up period after the first vaccine dose. The second phase of enrollment occurred after the completion of the safety review. The target sample size for this phase was 120 subjects, to be enrolled in an open-label manner to receive the $AS03_B$-adjuvanted 1.9 μg HA vaccine. The design of the second enrollment phase was amended to: (1) ensure compliance with the recommendations of Health Canada for the then newly licensed study vaccine in children,[10] and (2) to adjust for the lower than anticipated number of volunteers owing to the ongoing mass vaccination programs in Canada at the time of this study.

The subjects, parents/guardians and study personnel evaluating the safety and immunogenicity endpoints were blinded during the first enrollment phase. Study personnel responsible for vaccine preparation and administration were unblinded but were not involved in the evaluation of endpoints.

Exclusion criteria were a history of physician-diagnosed H1N1 2009 pandemic influenza infection, previous receipt of a vaccine against this strain, suspected or confirmed immunosuppressive condition, receipt of immunoglobulins within 3 months of study start, a history of allergic reactions to any of the constituents of influenza vaccines, elevated liver enzymes or an abnormal complete blood count.

Written informed consent was obtained from parents or guardians of all subjects prior to conducting any study-related procedures. The study was conducted in accordance with good clinical practice, the Declaration of Helsinki, the US Code of Federal Regulations for the Protection of Human Subjects, the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans and all relevant local regulations. All study-related documents and procedures were approved by the appropriate Ethics Committees. This trial is registered with ClinicalTrials.gov; Identifier: NCT 00976820.

Study Vaccines

The H1N1 viral seed was prepared from the reassortant virus NYMC X-179A (New York Medical College, New York) generated from the A/California/07/2009 strain, based on the recommendations of the World Health Organization and propagated in embryonated hen's eggs.

$AS03_A$ is an adjuvant system containing α-tocopherol and squalene in an oil-in-water emulsion [DL-α-tocopherol (11.86 mg), squalene (10.69 mg) and polysorbate 80 (4.86 mg)]. $AS03_B$ is an adjuvant system containing α-tocopherol and squalene in an oil-in-water emulsion (5.93 mg tocopherol). The antigen suspension and adjuvant emulsion were made available in separate multidose vials; the vaccines were reconstituted by mixing the 2 components prior to administration. The adjuvanted vaccine is marketed by GSK Biologicals as Arepanrix (GSK Biologicals, Wavre, Belgium). The vaccines were administered intramuscularly in the deltoid (anterolateral thigh for subjects aged <12 months).

The AS03-adjuvanted vaccines were prepared from the 15 μg HA/mL antigen suspension, and the nonadjuvanted vaccines were prepared from the 30 μg/mL antigen suspension. Each 0.5 mL dose of the H1N1 2009 vaccine contained 5 μg of thimerosal as preservative.

Laboratory Assays

Blood samples for immunogenicity testing were collected before vaccination (at screening or day 0), 21 days post-dose 1 (day 21), post-dose 2 (day 42) and at month 6. Samples were analyzed at GSK Biologicals Central laboratory (Dresden, Germany) using a validated in-house micro-titer hemagglutination inhibition (HI) assay (cutoff: ≥1:10), using chicken erythrocytes as previously described by Hehme et al.[11] The A/California/7/2009 strain was used as the antigen strain.

The viral microneutralization assay was performed at Viroclinics BioSciences, Rotterdam, The Netherlands, using the A/Netherland/602/2009 strain as the reference strain, as described previously[12,13]; the 50% neutralization titer of a serum was calculated by the Reed and Muench method.[14] The assay cutoff was 1:8. The laboratories performing the assays for evaluating immune responses were blinded to treatment assignment.

Immunogenicity Assessments

The primary objective was to assess whether HI response in subjects 21 days post-dose 1 (day 21) and post-dose 2 (day 42) met the immunogenicity guidance criteria formulated by the CHMP for pandemic influenza vaccines [point estimates for HI antibody seroconversion rate (SCR): >40%, seroprotection rate (SPR): >70% and geometric mean fold rise (GMFR): >2.5].[15] The SCR was defined as the proportion of subjects with a prevaccination HI titer <1:10 and a postvaccination titer ≥1:40, or a prevaccination HI titer >1:10 and a 4-fold increase in postvaccination titer, the SPR as the proportion of subjects with postvaccination HI titer ≥1:40, and the GMFR as the geometric mean of the within-subject difference of the postvaccination reciprocal HI titer and the prevaccination reciprocal titer. The secondary immunogenicity assessments included assessment of neutralizing antibody immune response in terms of vaccine response rates (VRRs) and geometric mean titers (GMTs), before vaccination and 21 days after each vaccine dose and persistence of HI immune response at month 6 for the different age strata (6 to 11 months, 12 to 35 months and 3 to <9 years). The impact of previous seasonal influenza vaccination on the immune response was also assessed.

Safety and Reactogenicity Assessments

Subject's parents used diary cards to record the occurrence and intensity of solicited local adverse events (AEs) (pain, redness and swelling) and solicited general AEs [subjects 6 months to <6 years of age: drowsiness, fever, irritability/fussiness and loss of appetite; subjects ≥6 years to <9 years of age: fatigue, fever, gastrointestinal symptoms, headache, joint pain, muscle ache, shivering (chills) and sweating] during each 7-day postvaccination follow-up period.

Intensity of solicited symptoms was graded on a standard scale of 0–3 (except fever which was graded on a scale of 0–4),

with grade 3 symptoms being those that prevented normal daily activities. Grade 3 redness and swelling were defined as those with a diameter of >100 mm; fever was defined as body temperatures ≥38.0°C (≥100.4°F); grade 3 fever: body temperatures ≥39.0–40.0°C (≥102.2–104.0°F); grade 4 fever: body temperatures >40.0°C (>104.0°F). The occurrence of unsolicited AEs was recorded through the 42-day postvaccination follow-up period up to day 84, while the occurrence of medically attended unsolicited AEs, potential immune-mediated diseases (subset of AEs that include both autoimmune diseases and other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology, a subject of interest for public health authorities) and serious adverse events (SAEs) were recorded during the entire study period (up to day 385). An assessment of causality was done by the investigator for all reported AEs except for solicited local symptoms (which were assumed to be vaccine related). Clinical laboratory evaluations were performed on subjects before vaccination and at visits at days 7, 21, 42 and 182.

Statistical Analyses

The sample size was calculated taking into consideration the objective to meet or exceed the CHMP immunogenicity guidance criteria for HI endpoints following each vaccine dose.[15] Approximately 360 evaluable subjects (including subjects enrolled during both enrollment phases) were estimated to give a power of >99.99%, assuming 90% as reference for SPR and SCR, respectively.

The primary analyses of immunogenicity were performed on the according-to-protocol (ATP) cohort for immunogenicity, and the analyses of safety were performed on the total vaccinated cohort (TVC). All immunogenicity and safety parameters were calculated with 95% confidence intervals.

RESULTS

Demographics Characteristics

A total of 375 subjects were enrolled, of which 322 subjects received at least 1 dose of vaccine and were considered the TVC. The reasons for elimination of subjects from the ATP cohorts for immunogenicity assessment at different time points are presented in Figure 1.

The overall demographic profile of the 4 study groups was comparable. The mean age of subjects in the TVC before vaccination was 4.2 years (range: 0.5−9.6 years); 54.0% of the subjects were male. The study population was predominantly of Caucasian/European heritage (66.5%).

Immune Responses

HI Immune Response

The HI antibody responses before vaccination, 21 days after each of the 2 vaccine doses and at month 6 for the ATP cohorts are presented in Table 1. The first dose of the 2 AS03-adjuvanted vaccines (3.75 μg HA/$AS03_A$ and 1.9 μg HA/$AS03_B$) elicited strong immune responses that met the CHMP immunogenicity guidance criteria for pandemic influenza vaccines (SPRs: 98.3%/99.0%; SCRs: 94.9%/97.0%; GMFR: 36.2/33.6, respectively). The first dose of the nonadjuvanted 15 μg HA met all 3 CHMP criteria, whereas the 7.5 μg HA vaccine while meeting the CHMP criteria for SCR and GMFR, failed to meet the CHMP criteria for SPR. Among the nonadjuvanted vaccines, following 1 vaccination dose, the 15 μg HA dose was more immunogenic than the 7.5 μg HA dose (SPRs: 77.8%/64.9%; SCRs: 75.9%/59.6%; GMFR: 13.8/7.6, respectively).

The first dose of adjuvanted vaccines (both 3.75 μg HA/$AS03_A$ and 1.9 μg HA/$AS03_B$) elicited strong immune responses in all 3 age strata (Table 2). In contrast, the first dose of nonadjuvanted 15 μg HA vaccine failed to elicit a sufficiently strong immune response in the 6–11 months age stratum, whereas the nonadjuvanted 7.5 μg HA vaccine was insufficiently immunogenic in the 6–11 months and 12–35 months age strata. This trend toward reduced responses in younger age cohorts to the first dose of the nonadjuvanted vaccines was not observed in subjects who received the adjuvanted vaccines, although it should be noted that there was a modest number of subjects in the younger age strata.

Following the second dose, both the adjuvanted and nonadjuvanted vaccines elicited strong immune responses that met CHMP guidance criteria for pandemic influenza vaccines. The SPRs following the second dose of the adjuvanted vaccines and the 15 μg HA nonadjuvanted vaccine were 100% across all age strata. The groups receiving the AS03-adjuvanted vaccines of the H1N1 2009 vaccine had higher GMTs and GMFRs than the groups receiving nonadjuvanted vaccines.

Six months after the first vaccine dose, overall, all vaccines still met all CHMP criteria (Table 1); however, age-stratified data showed that the CHMP guidance criteria was not met for all 3 age strata (6 to 11 months, 12 to 35 months and 3 to <9 years) for subjects who received the nonadjuvanted 7.5 μg HA vaccine (Table 2).

The CHMP guidance criteria were met at all time points across all 3 age strata only by the AS03-adjuvanted vaccines (Table 2).

Neutralizing Antibody Response

Neutralizing antibody VRRs were generally higher in subjects who received the 2 AS03-adjuvanted vaccines (post-dose 1: 91.1%/81.4%; post-dose 2: 96.9%/100%, following 3.75 μg HA/$AS03_A$ and 1.9 μg HA/$AS03_B$, respectively) than those who received the nonadjuvanted vaccines (post-dose 1: 73.0%/55.8%; post-dose 2: 86.7%/67.6%, following 15 μg HA and 7.5 μg HA vaccines, respectively). The corresponding neutralizing antibody GMTs and neutralizing antibody VRRs by age strata are presented in Table 3.

Impact of Previous Seasonal Influenza Vaccination History

A history of previous vaccination with trivalent seasonal influenza vaccine did not appear to influence the immune response elicited by the adjuvanted or nonadjuvanted vaccines, as evident from the similar HI antibody SPR, SCR and GMFR and neutralizing antibody VRRs and GMTs in subjects who had previously received any seasonal influenza vaccine compared to those who were influenza vaccine naive (Table 4).

Safety and Reactogenicity

The frequency of reporting for all solicited local and general symptoms by age strata are presented in Figures 2 and 3, respectively. Overall, during the 7-day postvaccination period, injection site pain was the most frequently recorded solicited local symptom in all age strata and was reported more frequently in subjects who received the AS03-adjuvanted vaccines (54.3–84.6%) compared to those who received the nonadjuvanted vaccines (39.1–70.6%). Similarly, grade 3 injection site pain was more frequently reported among subjects who received the AS03-adjuvanted vaccines (5.6−19.2%) compared to those who received the nonadjuvanted vaccines (4.2−5.9%). The overall incidence of solicited local AEs appeared to be higher in subjects who received the AS03-adjuvanted vaccines with a similar incidence for both

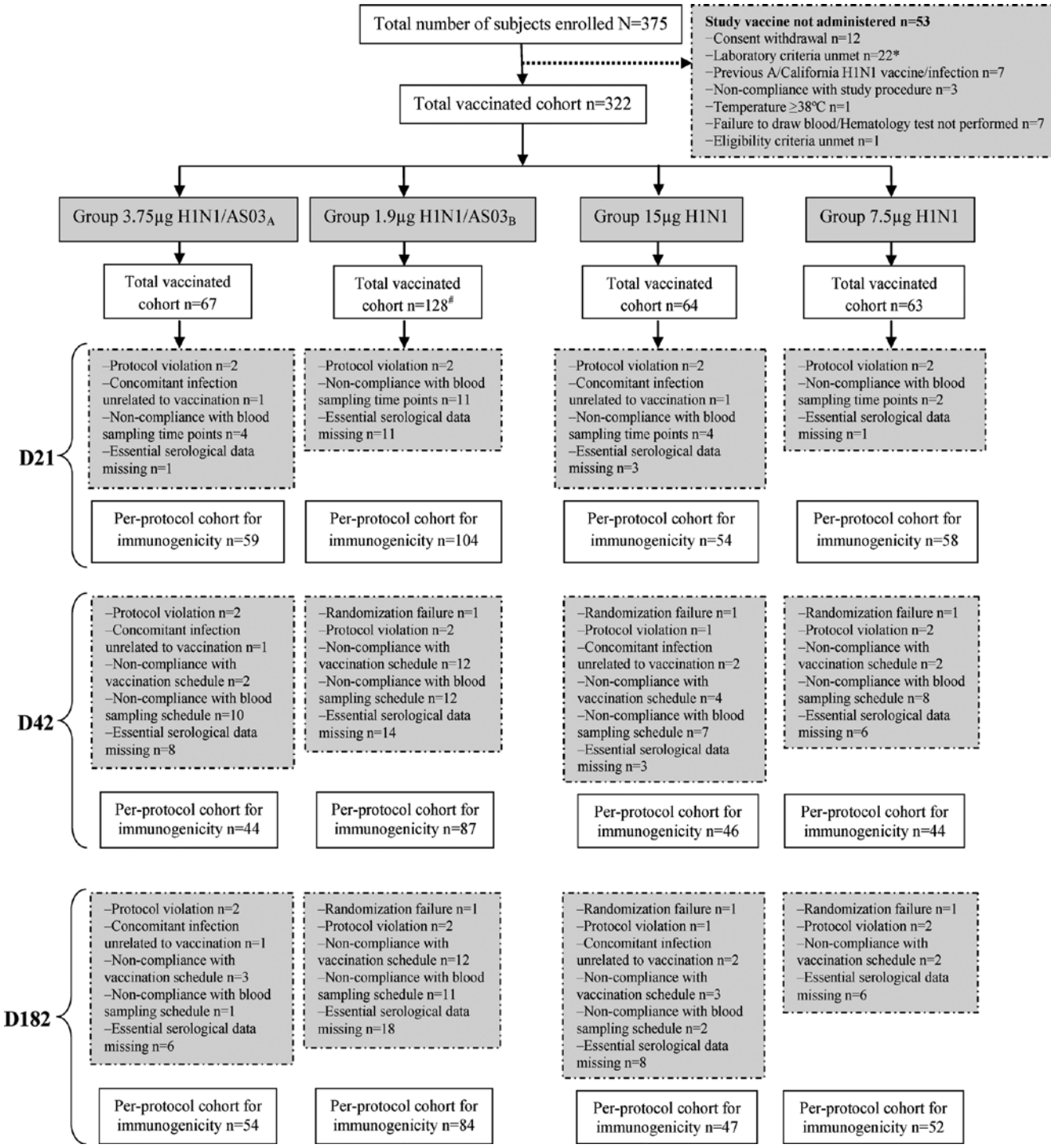

FIGURE 1. Study design. *Laboratory criteria unmet: Twenty-two subjects who were enrolled in the study were excluded from subsequent participation because of complete blood counts that were outside specified reference ranges at screening. #Additional 64 subjects were enrolled in group 1.9 µg H1N1/AS03$_B$ during the second enrollment phase.

3.75 µg HA/AS03$_A$ and 1.9 µg HA/AS03$_B$ HA-adjuvanted vaccines (Fig. 2).

During the 7-day postvaccination period, irritability and loss of appetite were the most frequently reported solicited general AEs in subjects 6 months through 5 years of age who received the AS03-adjuvanted vaccines (36.0−86.4%; 35.8−68.2%, respectively) as well as in those who received the nonadjuvanted vaccine (23.8−58.3%; 9.5−39.1%, respectively). In subjects 6 to <9 years of age who received the AS03-adjuvanted vaccines, fever and headache (34.6−50.0%; 46.2−50.0%, respectively) were most frequently reported, while in subjects who received the nonadjuvanted vaccines fatigue, headache and gastrointestinal symptoms

TABLE 1. Hemagglutination inhibition (HI) antibody response to the A/California/7/2009 (H1N1v) strain 21 days after each dose and at Month 6 (ATP cohort for immunogenicity)

Immune Response (CHMP Criteria)	Time Point	ATP Cohort	3.75 µg/AS03$_A$	ATP Cohort	1.9 µg/AS03$_B$	ATP Cohort	15 µg	ATP Cohort	7.5 µg
			Value or % (95% CI)						
Seroconversion rate (point estimate >40%)	Day 21	59	94.9 (85.9–98.9)	101	97.0 (91.6–99.4)	54	75.9 (62.4–86.5)	57	59.6 (45.8–72.4)
	Day 42	44	100 (92.0–100)	84	98.8 (93.5–100)	46	100 (92.3–100)	44	86.4 (72.6–94.8)
	Month 6	54	92.6% (82.1–97.9)	82	95.1% (88.0–98.7)	47	74.5% (59.7–86.1)	52	65.4% (50.9–78.0)
Seroprotection rate (point estimate >70%)	Day 0	59	20.3 (11.0–32.8)	102	23.5 (15.7–33.0)	54	22.2 (12.0–35.6)	58	24.1 (13.9–37.2)
	Day 21	59	98.3 (90.9–100)	103	99.0 (94.7–100)	54	77.8 (**64.4**–88.0)	57	64.9 (**51.1**–77.1)*
	Day 42	44	100 (92.0–100)	87	100 (95.8–100)	46	100 (92.3–100)	44	93.2 (81.3–98.6)
	Month 6	54	98.1% (90.1–100)	84	100% (95.7–100)	47	91.5% (79.6–97.6)	52	82.7% (**69.7**–91.8)
Geometric mean titer	Day 0	59	10.5 (7.3–15.1)	102	10.8 (8.2–14.3)	54	10.7 (7.2–15.8)	58	10.9 (7.5–15.8)
	Day 21	59	379.4 (277.9–518.0)	103	377.3 (299.6–475.3)	54	142.7 (92.4–234.3)	57	83.4 (52.9–131.4)
	Day 42	44	1440.5 (1149.0–1805.8)	87	1671.6 (1471.8–1898.4)	46	413.5 (296.6–576.4)	44	228.0 (156.9–331.3)
	Month 6	54	296.2 (230.5–380.8)	84	267.9 (219.5–327.0)	47	122.7 (86.4–174.3)	52	82.8 (59.5–115.2)
Geometric Mean Fold Rise (point estimate >2.5)	Day 21	59	36.2 (26.8–48.9)	101	33.6 (27.3–41.3)	54	13.8 (9.7–19.6)	57	7.6 (5.4–10.6)
	Day 42	44	157.1 (107.8–228.9)	84	151.6 (114.0–201.6)	46	44.2 (30.6–63.9)	44	24.1 (15.9–36.5)
	Month 6	54	31.0 (22.7–42.4)	82	26.6 (20.6–34.3)	47	10.3 (7.1–14.8)	52	7.8 (5.5–10.9)

*Values did not meet CHMP immunogenicity guidance criteria.
CI indicates confidence interval; bolded value, did not meet Center for Biologics Evaluation and Research criteria.

TABLE 2. Immune Response Stratified by Age: Hemagglutination Inhibition (HI) Antibody Response to the A/California/7/2009 (H1N1v) Strain 21 Days After Each Dose and at Month 6 (ATP Cohort for Immunogenicity)

Age Group	Immune Response (CHMP criteria)	Time Point	ATP Cohort	3.75 µg/AS03$_A$	ATP Cohort	1.9 µg/AS03$_B$	ATP Cohort	15 µg	ATP Cohort	7.5 µg
				Value or % (95% CI)						
6–11 months	Seroconversion rate (point estimate >40%)	Day 21	5	100% (47.8–100)	13	100% (75.3–100)	6	50.0% (**11.8**–88.2)	4	25.0% (**0.6**–80.6)*
		Day 42	3	100% (**29.2**–100)	11	100% (71.5–100)	5	100% (47.8–100)	3	66.7% (**9.4**–99.2)
		Month 6	4	100% (39.8–100)	11	90.9% (58.7–99.8)	4	75.0% (19.4–99.4)	3	33.3% (0.8–90.6)
	Seroprotection rate (point estimate >70%)	Day 0	5	0% (0.0–52.2)	14	14.3% (1.8–42.8)	6	0.0% (0.0–45.9)	4	25% (0.6–80.6)*
		Day 21	5	100% (**47.8**–100)	13	100% (75.3–100)	6	50.0% (**11.8**–88.2)*	4	25% (**0.6**–80.6)
		Day 42	3	100% (**29.2**–100)	12	100% (**73.5**–100)	5	100% (**47.8**–100)	3	66.7% (**9.4**–99.2)*
		Month 6	4	100% (39.8–100)	11	100% (71.5–100)	4	75.0% (19.4–99.4)	3	33.3% (0.8–90.6)*
	Geometric mean titers	Day 0	5	5 (5.0–5.0)	14	8.4 (3.8–18.5)	6	5 (5.0–5.0)	4	10.9 (0.9–130.3)
		Day 21	5	367.5 (178.7–755.5)	13	365.8 (179.4–745.9)	6	67.1 (11.8–380.6)	4	36.5 (1.9–709.9)
		Day 42	3	1015.9 (375.9–2745.4)	12	1863.2 (1467.7–2365.3)	5	368.2 (68.6–1975.7)	3	80.8 (0.8–7613.5)
		Month 6	4	319.9 (97.2–1053.1)	11	582.3 (378.6–895.5)	4	79.9 (19.2–333.1)	3	20.0 (0.6–626.1)
	Geometric mean fold rise (point estimate >2.5)	Day 21	5	73.5 (35.7–151.1)	13	41.8 (24.2–72.3)	6	13.4 (2.4–76.1)	4	3.3 (0.9–12.4)
		Day 42	3	203.2 (75.2–549.1)	11	290.4 (145.2–580.6)	5	73.6 (13.7–395.1)	3	16 (0.2–1522.7)
		Month 6	4	64.0 (19.4–210.6)	11	60.1 (25.0–144.3)	4	16.0 (3.8–66.6)	3	4.0 (0.1–125.2)
12–35 months	Seroconversion rate (point estimate >40%)	Day 21	15	93.3% (68.1–99.8)	22	95.5% (77.2–99.9)	14	71.4% (41.9–91.6)	16	56.3% (**29.9**–80.2)
		Day 42	13	100% (75.3–100)	20	100% (83.2–100)	11	100% (71.5–100)	11	90.9% (58.7–99.8)
		Month 6	14	92.9% (66.1–99.8)	18	94.4% (72.7–99.9)	12	75.0% (42.8–94.5)	14	64.3% (35.1–87.2)

(*Continued*)

TABLE 2. (*Continued*)

Age Group	Immune Response (CHMP criteria)	Time Point	ATP Cohort	3.75 µg/AS03$_A$	ATP Cohort	1.9 µg/AS03$_B$	ATP Cohort	15 µg	ATP Cohort	7.5 µg
				Value or % (95% CI)						
	Seroprotection rate (point estimate >70%)	Day 0	15	13.3% (1.7–40.5)	22	22.7% (7.8–45.4)	14	21.4% (4.7–50.8)	16	0% (0.0–20.6)
		Day 21	15	100% (78.2–100)	22	100% (84.6–100)	14	78.6% (**49.2**–95.3)	16	56.3% (**29.9**–80.2)*
		Day 42	13	100% (75.3–100)	20	100% (83.2–100)	11	100% (71.5–100)	11	90.9% (**58.7**–99.8)
		Month 6	14	92.9% (66.1–99.8)	18	100% (81.5–100)	12	91.7% (61.5–99.8)	14	64.3% (35.1–87.2)
	Geometric Mean Titers	Day 0	15	8.3 (3.9–17.7)	22	12.1 (5.8–25.2)	14	11.6 (4.4–30.9)	16	5 (5.0–5.0)
		Day 21	15	242.5 (127.1–462.4)	22	411.6 (245.2–690.8)	14	121.9 (41.4–358.8)	16	40.9 (22.4–74.6)
		Day 42	13	1810.0 (982.7–3333.7)	20	2267.4 (1789.1–2873.7)	11	481.9 (203.1–1143.2)	11	170.4 (76.7–378.8)
		Month 6	14	371.3 (204.5–674.1)	18	380.5 (258.0–561.4)	12	127.1 (50.6–319.4)	14	55.2 (26.5–114.9)
	Geometric mean fold rise (point estimate >2.5)	Day 21	15	29.2 (16.0–53.2)	22	34.1 (19.7–58.8)	14	10.5 (4.6–24.1)	16	8.2 (4.5–14.9)
		Day 42	13	284.8 (145.7–556.5)	20	171.9 (82.4–358.5)	11	49.7 (20.9–118.2)	11	34.1 (15.3–75.8)
		Month 6	14	59.4 (35.1–100.7)	18	37.3 (21.2–65.9)	12	9.5 (4.0–22.9)	14	11.0 (5.3–23.0)
3–<9 years	Seroconversion rate (point estimate >40%)	Day 21	39	94.9% (82.7–99.4)	66	97.0% (89.5–99.6)	34	82.4% (65.5–93.2)	37	64.9% (47.5–79.8)
		Day 42	28	100% (87.7–100)	53	98.1% (89.9–100)	30	100% (88.4–100)	30	86.7% (69.3–96.2)
		Month 6	36	91.7% (77.5–98.2)	53	96.2% (87.0–99.5)	31	74.2% (55.4–88.1)	35	68.6% (50.7–83.1)
	Seroprotection rate (point estimate >70%)	Day 0	39	25.6% (13.0–42.1)	66	25.8% (15.8–38.0%)	34	26.5% (12.9–44.4)	38	34.2% (19.6–51.4)
		Day 21	39	97.4% (86.5–99.9)	68	98.5% (92.1–100)	34	82.4% (**65.5**–93.2)	37	73.0% (**55.9**–86.2)
		Day 42	28	100% (87.7–100)	55	100% (93.5–100)	30	100% (88.4–100)	30	96.7% (82.8–99.9)
		Month 6	36	100% (90.3–100)	55	100% (93.5–100)	31	93.5% (78.6–99.2)	35	94.3% (80.8–99.3)
	Geometric mean titers	Day 0	39	12.6 (7.8–20.2)	66	11.0 (8.0–15.3)	34	11.8 (7.1–19.4)	38	15.1 (9.0–25.4)
		Day 21	39	452.6 (303.1–675.8)	68	369.1 (276.0–493.6)	34	182.7 (103.0–323.9)	37	124.1 (67.9–227.0)
		Day 42	28	1344.9 (1062.0–1703.3)	55	1461.1 (1233.2–1731.2)	30	398.5 (269.1–590.2)	30	281.7 (183.1–433.3)
		Month 6	36	269.0 (198.5–364.6)	55	204.5 (160.8–260.1)	31	127.9 (84.1–194.7)	35	109.9 (77.3–156.4)
	Geometric mean fold rise (point estimate >2.5)	Day 21	39	35.9 (24.3–53.2)	66	32.0 (24.9–41.1)	34	15.5 (10.3–23.4)	37	8.0 (5.1–12.6)
		Day 42	28	116 (70.9–189.6)	53	126.4 (90.0–177.4)	30	38.9 (24.7–61.3)	30	22.1 (13.0–37.4)
		Month 6	36	22.2 (15.1–32.6)	53	20.0 (15.0–26.6)	31	10.0 (6.3–15.8)	35	7.2 (4.8–10.8)

*Values did not meet CHMP immunogenicity guidance criteria.
CI indicates confidence interval; bold value, did not meet Center for Biologics Evaluation and Research criteria.

(23.5−44.4%; 23.5−27.8%; 17.6−38.9%, respectively) were most frequently reported. The frequency of grade 3 solicited general AEs in the respective age strata were comparable in subjects who received either the AS03-adjuvanted or nonadjuvanted vaccines, except for grade 3 fever, which was reported only in subjects who received the AS03-adjuvanted vaccines; the highest incidence of grade 3 fever was reported in subjects who received the 3.75 µg HA/AS03$_A$ vaccine (6 months to 5 years: 8.0−18.2%; 6 years to <9 years: 11.1%, including 2 subjects with fever >40°C).

No significant difference was observed across study groups in the percentage of subjects with at least 1 unsolicited AE (46.9–59.4%), the percentage of subjects with at least 1 unsolicited AE of grade 3 intensity (1.6−4.7%), the percentage of subjects with unsolicited AEs that were causally related to vaccination (9.0–15.9%) during the 84-day postvaccination period. None of the unsolicited AEs were reported in >14.8% of subjects in each study group. The most frequently reported unsolicited AEs were cough (4.5−9.5% of subjects), nasopharyngitis (4.7−9.5% of subjects), pyrexia (6.0−7.8% of subjects), upper respiratory tract infection (3.2−7.5% of subjects) and vomiting (3.1−9.5% of subjects), none of which appeared to have any association with vaccination. Owing to the modest number of subjects in each treatment group, the data on unsolicited AEs should be interpreted with caution. The percentage of subjects with unsolicited AEs occurring up to day 385 that required medical attention ranged between 54.0% and 68.0% across the 4 study groups.

A total of 5 SAEs were reported in 4 subjects during the entire study period; all 4 subjects received AS03-adjuvanted vaccines. The SAEs included convulsions (2 events in 2 subjects, occurring 266 days and 105 days, respectively, following the second

TABLE 3. Immune Response Stratified by Age: Neutralizing Antibody Response to the A/Netherland/602/2009 (H1N1v) Strain 21 Days After Each Dose (ATP Cohort for Immunogenicity)

Group	Age Group	Time Point	ATP Cohort	GMT	ATP Cohort	VRR
			Value or % (95% CI)			
3.75 μg/AS03$_A$	6–11 months	Day 0	2	4.0 (4.0–4.0)	—	
		Day 21	4	128.0 (13.1–1247.6)	2	100 (15.8–100)
		Day 42	1	763.0 (—)	—	
	12–35 months	Day 0	13	14.2 (4.7–42.8)	—	
		Day 21	12	189.7 (54.4–662.2)	10	70.0 (34.8–93.3)
		Day 42	9	1849.9 (556.5–6149.5)	9	100 (66.4–100)
	3–<9 years	Day 0	37	23.3 (11.7–46.5)	—	
		Day 21	35	648.5 (332.1–1266.5)	33	97.0 (84.2–99.9)
		Day 42	24	1279.5 (689.4–2374.5)	23	95.7 (78.1–99.9)
1.9 μg/AS03$_B$	6–11 months	Day 0	9	11.6 (2.2–60.5)	—	
		Day 21	10	104.7 (20.7–529.0)	7	71.4 (29.0–96.3)
		Day 42	5	1566.6 (450.3–5449.9)	2	100 (15.8–100)
	12–35 months	Day 0	18	15.9 (5.4–46.7)	—	
		Day 21	17	234.3 (71.2–771.4)	14	78.6 (49.2–95.3)
		Day 42	14	1792.4 (775.8–4141.1)	13	100 (75.3–100)
	3–<9 years	Day 0	57	13.5 (8.2–22.1)	—	
		Day 21	55	384.6 (214.2–690.3)	49	83.7 (70.3–92.7)
		Day 42	44	1812.1 (1171.2–2803.5)	39	100 (91.0–100)
15 μg	6–11 months	Day 0	4	4.0 (4.0–4.0)	—	
		Day 21	2	640.1 (68.7–5962.3)	1	100 (2.5–100)
		Day 42	3	155.2 (0.0–1396743)	1	100 (2.5–100)
	12–35 months	Day 0	11	23.5 (5.2–107.1)	—	
		Day 21	11	95.9 (12.8–718.1)	10	40.0 (12.2–73.8)
		Day 42	7	429.2 (31.2–5908.6)	7	85.7 (42.1–99.6)
	3–<9 years	Day 0	27	15.1 (7.2–31.7)	—	
		Day 21	31	295.6 (132.9–657.5)	26	84.6 (65.1–95.6)
		Day 42	26	481.5 (234.1–990.2)	22	86.4 (65.1–97.1)
7.5 μg	6–11 months	Day 0	4	14.1 (0.3–767.2)	—	
		Day 21	1	4.0 (—)	1	0.0 (0.0–97.5)
		Day 42	2	20.7 (0.0–2.419E10)	2	50.0 (1.3–98.7)
	12–35 months	Day 0	14	6.7 (2.9–15.3)	—	
		Day 21	10	40.3 (8.8–183.8)	10	30.0 (6.7–65.2)
		Day 42	10	84.4 (28.0–254.5)	8	62.5 (24.5–91.5)
	3–<9 years	Day 0	37	21.1 (10.3–43.3)	—	
		Day 21	32	227.2 (91.8–562.1)	32	65.6 (46.8–81.4)
		Day 42	24	216.2 (90.0–518.9)	24	70.8 (48.9–87.4)

CI indicates confidence interval.

dose of vaccine), tonsillitis, appendicular abscess (twice in the same subject). All SAEs resolved by the end of the study period. The investigators assessed all SAEs to be unrelated to vaccination. No potential immune-mediated diseases were reported. No laboratory findings were judged to be clinically significant by investigators.

DISCUSSION

In this comparison of the immunogenicity and safety of adjuvanted and nonadjuvanted vaccines of H1N1 2009 pandemic influenza vaccines in children, the AS03-adjuvanted dose-sparing vaccines produced strong immune responses after the first dose across all age strata which met CHMP regulatory criteria for immunogenicity. Immune responses for the nonadjuvanted 15 μg vaccine also met the European regulatory criteria for the entire pediatric age group after 1 dose, but not for infants 6−11 months of age. This youngest age group, and 12−35 month olds, had inferior responses to the first 7.5 μg unadjuvanted dose. However, it should be noted that there were very few subjects in the younger age strata. A 2-dose schedule of all vaccines met the European regulatory criteria. In addition, the immune responses following vaccination persisted to 6 months after the first vaccine dose, although the CHMP guidance criteria were met across all 3 age strata only in subjects who received the AS03-adjuvanted vaccines and the nonadjuvanted 15 μg HA vaccine. Overall, only the AS03-adjuvanted vaccines met CHMP guidance criteria at all time points in subjects from all age strata. The neutralizing antibody immune response paralleled the HI antibody immune response across the study groups. All vaccines were well tolerated, but injection site pain and systemic responses were more common after adjuvanted vaccines.

This trial took place in a unique context. The aim was to provide decisive data to the public health authorities in Canada (Health Canada), who were beginning the rollout of a universal pandemic influenza vaccine program. The trial safety summaries based on uncleaned data at day 7 and immunogenicity and safety summary reports at day 21 were provided promptly to decision makers. This information was used to inform policy including dosage recommendations and public messages and was publicly disseminated through the Public Health Agency of Canada Web site. Based on the evolving epidemiology of disease in late 2009 and trial results showing strong immunogenicity data, Canadian public health authorities recommended 1 dose (3.75 μg HA) of adjuvanted vaccine for children over 10 years of age, and 1 or 2 doses (1.9 μg HA), 21 days apart for younger children or those with certain chronic health conditions.[16]

Unadjuvanted seasonal trivalent inactivated influenza vaccines have lower efficacy in younger children, who may have no prior priming experience with infection or vaccine.[17] While studies

TABLE 4. Hemagglutination Inhibition (HI) and Neutralizing Antibody Response to the A/California/7/2009 (H1N1v) Strain 21 Days After Each Dose and at Month 6 by Previous Seasonal Influenza Vaccination History (ATP Cohort for Immunogenicity)

Group	Time Point	Seasonal Influenza Vaccination History	HI Antibody Response						Neutralizing Antibody Response			
			ATP Cohort	SPR	ATP Cohort	SCR	ATP Cohort	GMFR	ATP cohort	GMT	ATP cohort	VRR
			Value or % (95% CI)									
3.75 µg/ $AS03_A$	Day 21	No flu	42	100% (91.6–100)	42	95.2% (83.8–99.4)	42	33.9 (24.1–47.6)	37	372.8 (187.1–1742.7)	31	90.3% (74.2–98.0)
		Flu	17	94.1% (71.3–99.9)	17	94.1% (71.3–99.9)	17	42.6 (21.8–83.3)	14	614.7 (220.0–1717.3)	14	92.9% (66.1–99.8)
	Day 42	No Flu	30	100% (88.4–100)	30	100% (88.4–100)	30	137.2 (84.6–222.5)	23	1479.0 (758.1–2885.6)	21	95.2% (76.2–99.9)
		Flu	14	100% (76.8–100)	14	100% (76.8–100)	14	210.2 (111.9–394.9)	11	1219.0 (504.1–2948.1)	11	100% (71.5–100)
	Month 6	No flu	37	97.3% (85.8–99.9)	37	91.9% (78.1–98.3)	37	28.3 (19.1–42.0)	—	—	—	—
		Flu	17	100% (80.5–100)	17	94.1% (71.3–99.9)	17	37.7 (21.6–65.8)	—	—	—	—
1.9 µg/ $AS03_B$	Day 21	No flu	70	100% (94.9–100)	68	97.1% (89.8–99.6)	68	35.3 (27.2–45.7)	59	397.3 (216.6–728.5)	52	80.8% (67.5–90.4)
		Flu	33	97.0% (84.2–99.9)	33	97.0% (84.2–99.9)	33	30.4 (21.2–43.5)	23	139.3 (65.1–298.4)	18	83.3% (58.6–96.4)
	Day 42	No flu	58	100% (93.8–100)	55	98.2% (90.3–100)	55	147.0 (100.8–214.5)	44	2537.9 (1680.1–3833.5)	37	100% (90.5–100)
		Flu	29	100% (88.1–100)	29	100% (88.1–100)	29	160.7 (103.5–249.6)	19	793.0 (460.0–1366.9)	17	100% (80.5–100)
	Month 6	No flu	54	100% (93.4–100)	52	92.3% (81.5–97.9)	52	27.3 (19.0–39.1)	—	—	—	—
		Flu	30	100% (88.4–100)	30	100% (88.4–100)	30	25.4 (18.3–35.3)	—	—	—	—
15 µg	Day 21	No flu	36	75.0% (57.8–87.9)	36	72.2% (54.8–85.8)	36	14.4 (9.2–22.4)	29	364.0 (146.2–906.7)	25	80.0% (59.3–93.2)
		Flu	18	83.3% (58.6–96.4)	18	83.3% (58.6–96.4)	18	12.7 (6.7–23.9)	15	96.0 (28.8–319.7)	12	58.3% (27.7–84.8)
	Day 42	No flu	30	100% (88.4–100)	30	100% (88.4–100)	30	56.4 (36.3–87.5)	24	478.0 (193.5–1180.9)	20	90.0 (68.3–98.8)
		Flu	16	100% (79.4–100)	16	100% (79.4–100)	16	28.1 (14.4–54.8)	12	344.1 (86.6–1367.4)	10	80.0% (44.4–97.5)
	Month 6	No flu	32	96.9% (83.8–99.9)	32	81.3% (63.6–92.8)	32	11.3 (7.7–16.6)	—	—	—	—
		Flu	15	80.0% (51.9–95.7)	15	60.0% (32.3–83.7)	15	8.4 (3.5–19.9)	—	—	—	—
7.5 µg	Day 21	No flu	32	68.8% (50.0–83.9)	32	65.6% (46.8–81.4)	32	9.4 (6.2–14.3)	24	155.5 (51.1–473.0)	24	66.7% (44.7–84.4)
		Flu	25	60.0% (38.7–78.9)	25	52.0% (31.3–72.2)	25	5.7 (3.2–10.1)	19	119.4 (36.0–396.0)	19	42.1% (20.3–66.5)
	Day 42	No flu	24	91.7% (73.0–99.0)	24	87.5% (67.6–97.3)	24	30.6 (17.6–53.3)	20	163.8 (58.3–460.4)	19	63.2% (38.4–83.7)
		Flu	20	95.0% (75.1–99.9)	20	85.0% (62.1–96.8)	20	18.0 (9.3–35.0)	16	126.7 (49.5–324.9)	15	73.3% (44.9–92.2)
	Month 6	No flu	28	89.3% (71.8–97.7)	28	75.0% (55.1–89.3)	28	9.0 (5.7–14.1)	—	—	—	—
		Flu	24	75.0% (53.3–90.2)	24	54.2% (32.8–74.4)	24	6.6 (3.9–11.4)	—	—	—	—

CI indicates confidence interval.

with nonadjuvanted H1N1 2009 pandemic influenza vaccines in the pediatric population have shown that 1 dose may not elicit a satisfactory immune response in children, an observation that is already established for seasonal influenza vaccines,[18–21] there are limited data on the immunogenicity and safety of adjuvanted H1N1 2009 pandemic influenza vaccines in the pediatric population. A previous study with similar adjuvanted H1N1 2009 vaccines, as used in the present study conducted in children aged 6–35 months (3.75 µg and 1.9 µg HA), reported 100% SPR following the first dose.[22] However, these studies did not have a comparator treatment arm with a nonadjuvanted vaccine. Another study in children aged 6 months to <13 years that compared a similar 1.9 µg HA/$AS03_B$ vaccine and a nonadjuvanted 7.5 µg HA vaccine from another manufacturer reported a higher SCR in subjects who received the adjuvanted vaccine following 2 doses (99.3% versus 78.2% for the nonadjuvanted vaccine).[23] A study using a different oil-in-water (MF59) adjuvanted seasonal influenza vaccine in unprimed children 6–35 months of age also showed that the adjuvanted vaccine was more immunogenic than the unadjuvanted vaccine.[24]

In the present study, the 2 AS03-adjuvanted H1N1 2009 pandemic influenza vaccines elicited strong immune responses in the pediatric population following a single dose that exceeded

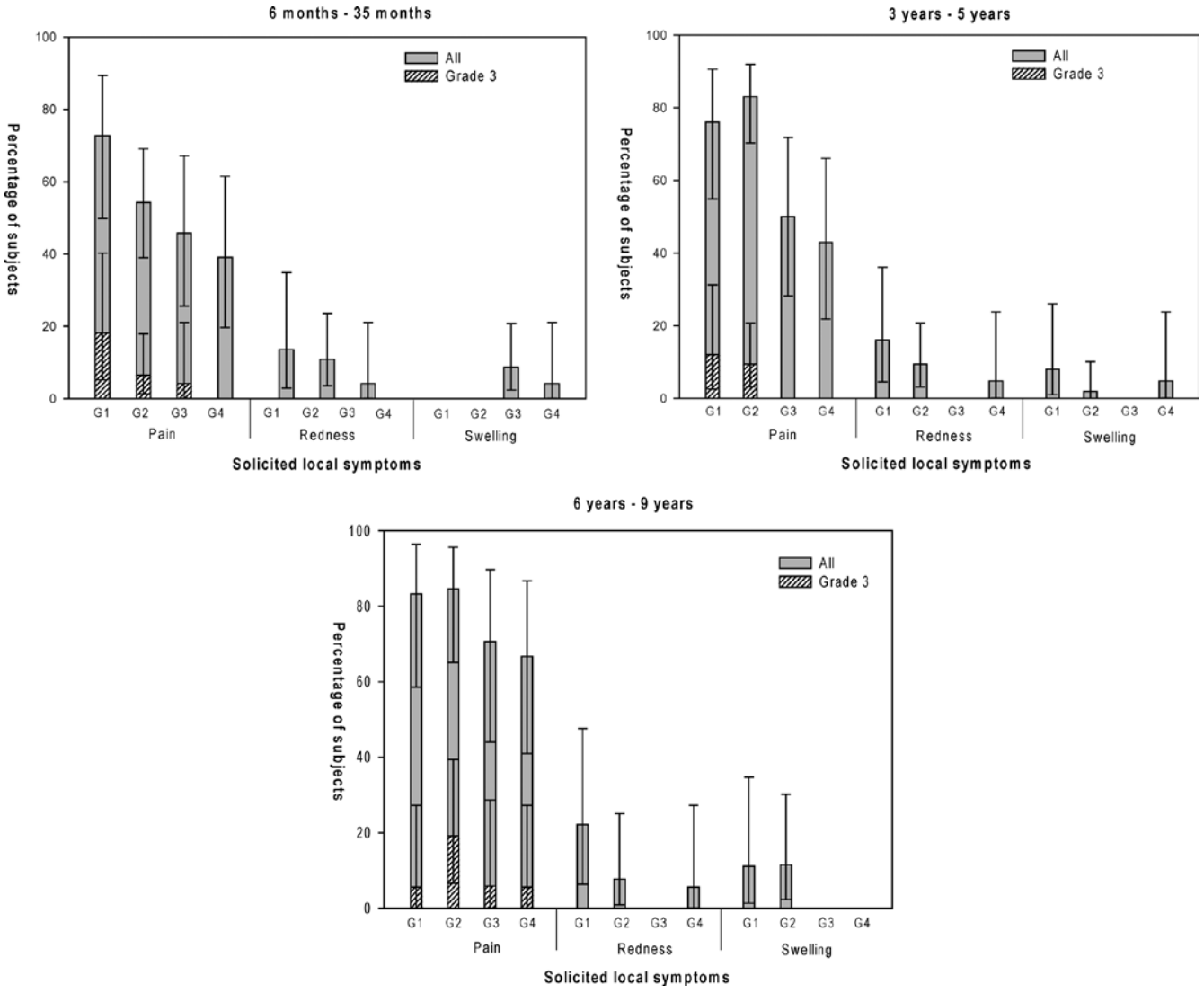

FIGURE 2. Percentage of subjects reporting solicited local adverse events during the 7-day postvaccination follow-up period following each dose, stratified by age (total vaccinated cohort).

the CHMP criteria for pandemic influenza vaccines (SPRs: 98.3%/99.0%; SCRs: 94.9%/97.0%; GMFR: 36.2/33.6, respectively). Following the second dose of both AS03-adjuvanted vaccines, SPRs increased to 100% and SCRs were 100% and 98.8%, respectively. As observed in previous studies,[22] the 3.75 μg HA/$AS03_A$ vaccine did not appear to further optimize the immune responses when compared with the 1.9 μg HA/$AS03_B$ vaccine. Of the 2 nonadjuvanted vaccines, the 15 μg HA vaccine elicited a stronger immune response, with SPRs and SCRs reaching 100%, following the second dose.

The safety profile of the 4 influenza vaccines, adjuvanted and unadjuvanted, was similar to that of seasonal trivalent inactivated influenza vaccines in children.[25,26] Injection site tenderness is usually the most common symptom, beginning 6–12 hours after vaccination and lasting for 1–2 days. Fever can occur in up to 5% of children receiving trivalent inactivated influenza vaccines and can be more frequent in children exposed for the first time to influenza antigens. Although a comparable incidence of all general solicited AEs was seen across all study groups receiving these monovalent pandemic vaccines, it was noted that children receiving the higher dose adjuvanted vaccine (3.75 μg HA/$AS03_A$ vaccine) appeared to have an increased incidence of fever following the second dose and fever ≥39°C was reported in 2 subjects. This difference in the reporting of solicited general symptoms has also been observed in a previous pediatric study with a similar vaccine.[22]

Superior immune responses were elicited by the AS03-adjuvanted vaccines when compared with the nonadjuvanted vaccines, using substantially low antigen content. This is especially important at the time of a pandemic when a sufficient number of doses of pandemic influenza vaccine must be made available. The assessment of the Center for Biologics Evaluation and Research licensure criteria for pandemic influenza vaccines was not a secondary endpoint[27]; however, the lower bounds of the immunogenicity parameters indicated that the adjuvanted vaccines induced HI immune responses that met them after the first and second doses and at month 6, although for the nonadjuvanted vaccines the Center for Biologics Evaluation and Research criteria were met only following the second dose.

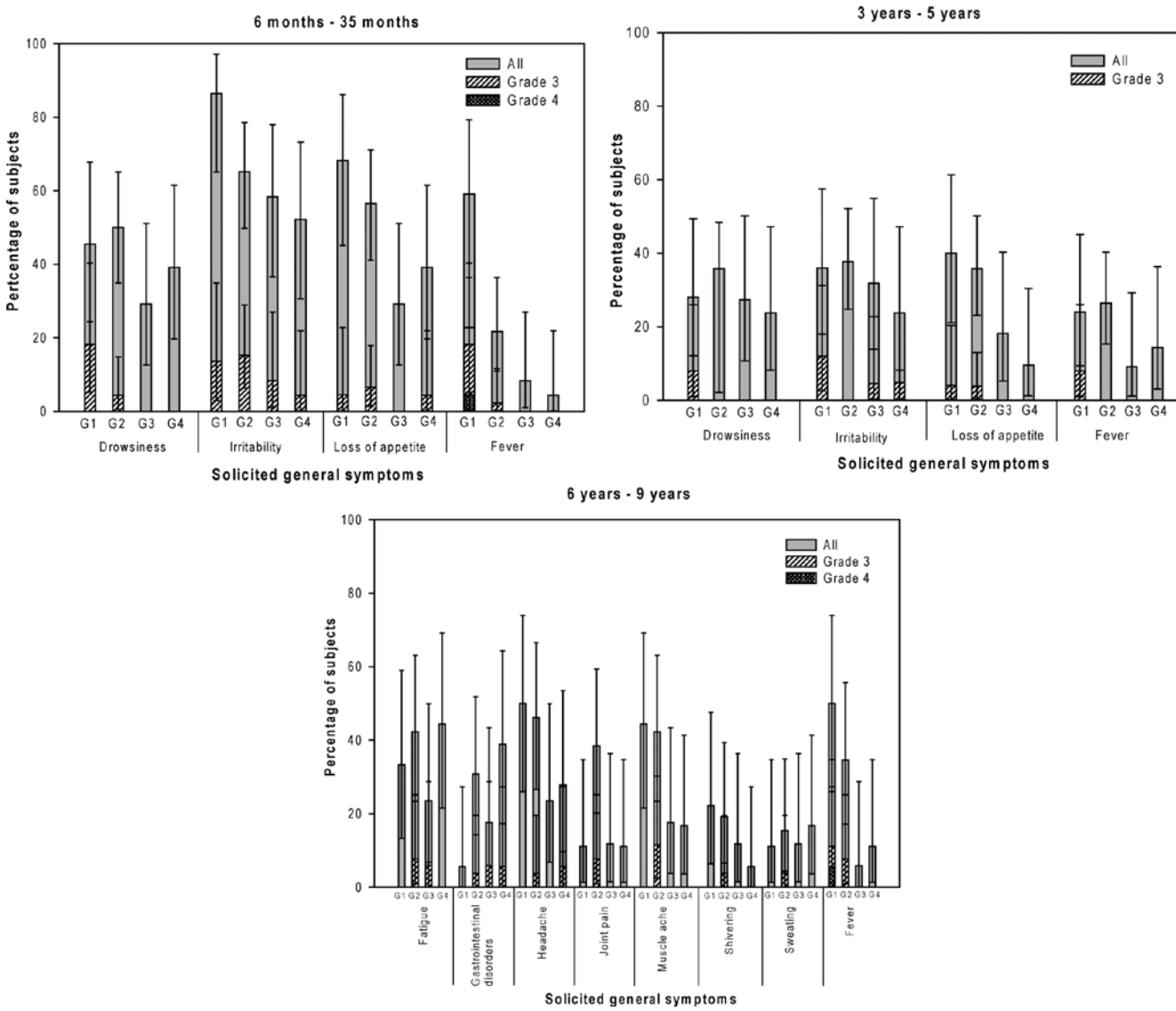

FIGURE 3. Percentage of subjects reporting solicited general adverse events during the 7-day postvaccination follow-up period following each dose, stratified by age (total vaccinated cohort).

Although the immunogenicity data obtained for the adjuvanted study vaccine are encouraging, further assessment of the duration of immunity following 1 or 2 doses is necessary. In this study, it was observed that the immune responses persisted up to 6 months after the first vaccine dose; 2 doses of all vaccines except the nonadjuvanted 7.5 μg HA induced immune responses in subjects across all 3 age strata (6 to 11 months, 12 to 35 months and 3 to <9 years) that met CHMP guidance criteria for pandemic vaccines at month 6. A case-control study done in one Canadian province using the same adjuvanted vaccine (1.9 μg HA) estimated the vaccine efficacy at 96% after 1 dose in children <10 years of age.[28] The role of 1 or 2 doses in priming with subsequent annual booster vaccination is also not yet known, although the 6-fold increase induced by the second vaccination does suggest priming after 1 dose. Of note, booster vaccination with AS03-adjuvanted H5N1 vaccine at 6 or 12 months from primary vaccination has been shown to be effective in adults irrespective of whether 1 or 2 primary doses were given.[29]

TRADEMARK STATEMENT

Arepanrix is a trade mark of GlaxoSmithKline group of companies.

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Evaluation of *Haemophilus influenzae* Type b Vaccine for Routine Immunization in Nepali Infants: ERRATUM

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