Safety and Immunogenicity of a Recombinant Influenza Vaccine: A Randomized Trial

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abstract

OBJECTIVES: The recombinant influenza vaccine is well established in adults ≥18 years of age for preventing seasonal influenza disease. In this randomized controlled trial, we compared the safety and immunogenicity of the quadrivalent, recombinant influenza vaccine (RIV4) versus the inactivated influenza vaccine in children and adolescents 6 to 17 years of age.

METHODS: Two age cohorts were enrolled sequentially: 159 subjects aged 9 to 17 years and, after reviewing for safety, 60 children aged 6 to 8 years. Enrollment of the younger children was halted prematurely at the onset of the influenza season. Subjects in each cohort were randomly assigned 1:1 to the RIV4 or inactivated vaccine. Hemagglutination inhibition antibody titers were obtained before and 28 days after vaccination. Tolerability and safety were monitored for 7 days and 6 months after vaccination, respectively.

RESULTS: Both vaccines were well tolerated in both age groups, and long-term follow-up revealed no vaccine-related adverse events. Overall, immunogenicity (geometric mean titers and seroconversion rate differences) provided comparable antibody responses to most antigens in both vaccines in the older subjects. Low responses to the influenza B Victoria lineage in both vaccines made interpretation difficult. Immunogenicity in younger children was similar, but the truncated sample size was insufficient to support noninferiority comparisons.

CONCLUSIONS: Despite low responses to influenza B lineages in both vaccines, the RIV4 provided safety and immunogenicity that were comparable to those of the licensed inactivated vaccine in pediatric subjects, which was most convincing in those aged 9 to 17 years. Future confirmatory clinical efficacy trials may be used to support the recombinant influenza vaccine as an alternative for the pediatric age group of ≥6 years.

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Dr Dunkle designed the study, wrote the protocol, oversaw the scientific conduct of the trial, and wrote the first draft of the manuscript; Dr Izikson selected the investigative sites, managed the operational aspects of study conduct, and reviewed the manuscript, subjecting it to careful quality control; Dr Goldenthal offered important insights into the study design and provided critical review of the manuscript; Dr Patriarca offered important insights into the study design, provided critical review of the manuscript, and participated in the external Data Monitoring Committee; Dr Cox provided critical insights at all steps of the project and critical review of the manuscript; Dr Treanor contributed important insight into the study design and chaired the external Data Monitoring Committee; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Vaccination provides the best protection against influenza and is recommended for all persons ≥6 months of age. More effective vaccines are needed to improve protection and public health. Recombinant influenza vaccine has provided better protection in older adults.

WHAT THIS STUDY ADDS: Recombinant influenza vaccine, well tolerated in subjects aged 6 to 17 years, provides comparable immunogenicity to inactivated vaccine. Further studies are needed to confirm the safety and protective efficacy of recombinant hemagglutinin as an alternative to egg-grown inactivated influenza vaccines.

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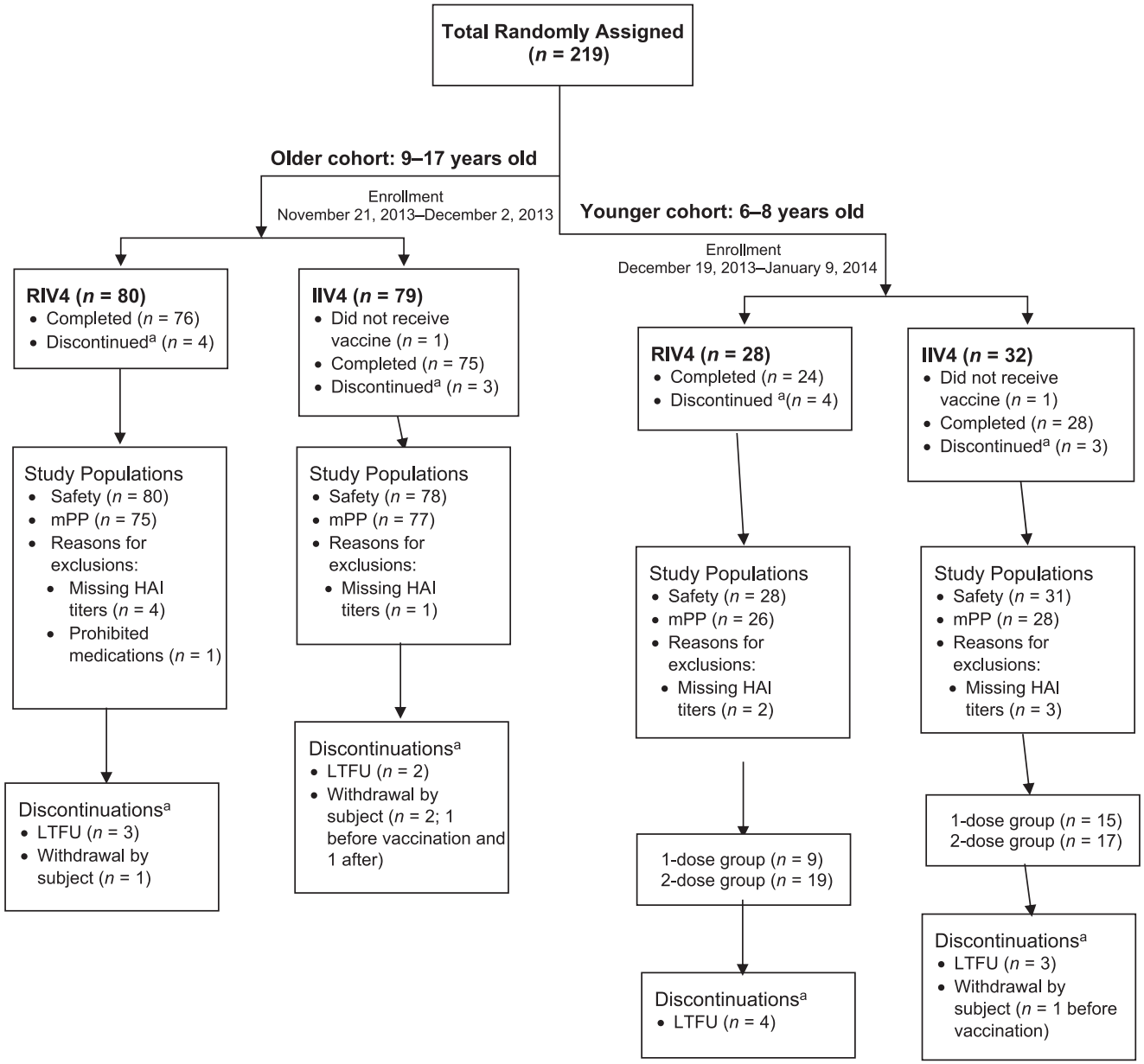

FIGURE 1
Study participant disposition. [a] Discontinued before the conclusion of the study. LTFU, lost to follow-up; mPP, modified per protocol.

Seasonal influenza vaccines have transitioned recently to quadrivalent formulations containing antigens representing both influenza B lineages (Yamagata and Victoria) as well as the conventional influenza A subtypes H1N1 and H3N2. The second influenza B lineage has been added to address the high frequency of circulation of both B lineages in a single season, and the common circulation of influenza B lineage mismatched with the vaccine strain.[1,2]

Because children are especially susceptible to complications of influenza B,[2] we therefore initiated the development of the quadrivalent, recombinant influenza vaccine (RIV4) in children aged 6 to 17 years.

An earlier phase 1 clinical trial of trivalent, recombinant influenza vaccine (RIV3) in a healthy pediatric population aged 6 to 59 months revealed that RIV3 was safe and well tolerated but yielded inferior levels of hemagglutination inhibition (HAI) antibody titers compared with those induced by the trivalent inactivated influenza vaccine (IIV3).[3] However, in the small subset of children 36 to 59 months of age (~20 per treatment group) in the same study, the RIV3 induced HAI antibody titers that were more comparable to the levels observed with the IIV3. This revealed that as they grew older, children became more responsive to the recombinant protein vaccine.

TABLE 1 Participant Demographics

Parameter	9–17 y		6–8 y		Total	
	RIV4	IIV4	RIV4	IIV4	RIV4	IIV4
	N = 80	*N* = 78	*N* = 28	*N* = 31	*N* = 108	*N* = 109
Age, y						
Mean	12.7	12.7	7.1	7.0	11.3	11.0
Range	9–17	9–17	6–8	6–8	6–17	6–17
Female sex, *n* (%)	42 (53)	40 (51)	17 (61)	12 (39)	59 (55)	52 (48)
Hispanic or Latino ethnicity, *n* (%)	13 (16)	8 (10)	6 (21)	6 (19)	19 (18)	14 (13)
Race, *n* (%)						
White	50 (63)	46 (59)	10 (36)	16 (52)	60 (56)	62 (57)
Black and/or African American	28 (35)	31 (40)	17 (61)	13 (42)	45 (42)	44 (40)
Multiracial	2 (3)	1 (1)	1 (4)	2 (7)	3 (3)	3 (3)

The safety population is shown.

TABLE 2 Immunogenicity (All Subjects 6–17 Years of Age) 28 Days After Last Dose of Study Vaccine

Antigen	RIV4 (*n* = 101)	IIV4 (*n* = 105)
A/California/7/2009 (H1N1)		
GMT (95% CI)	986.2 (777 to 1251.7)	596.5 (495.2 to 718.5)
GMT ratio (95% CI)	0.60 (0.45 to 0.82[a])	
SCR, % (95% CI)	87 (79.0[a] to 93.0)	70 (59.8[a] to 78.1)
SCR difference, % (95% CI)	−17 (−28.6 to −6.6[a])	
A/Texas/50/2012 (H3N2)		
GMT (95% CI)	904 (764.0 to 1069.7)	555.9 (479.1 to 645.1)
GMT ratio (95% CI)	0.6 (0.49 to 0.77[a])	
SCR, % (95% CI)	57 (47.2[a] to 67.2)	50 (39.6 to 59.5)
SCR difference, % (95% CI)	−7 (−21.5 to 5.7[a])	
B/Massachusetts 2/2012 (Yamagata lineage)		
GMT (95% CI)	146.4 (117.2 to 182.8)	120.7 (99.0 to 147.2)
GMT ratio (95% CI)	0.82 (0.61 to 1.11[a])	
SCR, % (95% CI)	71 (61.4[a] to 79.9)	67 (56.8[a] to 75.6)
SCR difference, % (95% CI)	−4 (−17.2 to 8.0[a])	
B/Brisbane/60/2008 (Victoria lineage)		
GMT (95% CI)	57.4 (45.5 to 72.5)	60.0 (49.2 to 73.2)
GMT ratio (95% CI)	1.05 (0.77 to 1.42[a])	
SCR, % (95% CI)	57 (46.4[a] to 67.7)	69 (57.8[a] to 78.0)
SCR difference, % (95% CI)	12 (−2.9 to 25.3)	

Modified per protocol population: day 56 for subjects assigned to receive 2 vaccine doses is shown.
[a] Meets the FDA regulatory criteria for noninferiority or accelerated approval on the basis of SCRs.[5]

Because the researchers in the phase 1 study of RIV3 had intentionally enrolled subjects who were naïve to previous influenza vaccination, it was postulated that the purified recombinant hemagglutinin (HA) antigens may be less immunogenic in individuals who were not immunologically primed by vaccination or infection.[4] It was for this reason that in the current phase 2 study, we targeted older children and adolescents 6 to 17 years of age.

The purpose of this exploratory phase 2 study was to assess the safety, reactogenicity, and immunogenicity of RIV4 compared with quadrivalent inactivated influenza vaccine (IIV4) in the pediatric population ≥6 years of age. The primary hypothesis was that the immunogenicity of all 4 strains of recombinant HA in RIV4 were noninferior to IIV4 on the basis of HAI geometric mean titers (GMTs) and the HAI seroconversion rates (SCRs).[5]

METHODS

Study Design and Oversight

This was an exploratory, observer-blind, parallel group, phase 2 trial in which pediatric subjects 6 to 17 years of age were randomly assigned 1:1 to receive RIV4 or IIV4 (protocol available in the Supplemental Information). At the time this study was initiated, RIV4 had not yet been studied in adults; therefore, subjects were enrolled in sequential age cohorts beginning with older children and adolescents 9 to 17 years of age followed by children 6 to 8 years of age. The older cohort of participants was enrolled from November 21, 2013, to December 2, 2013. Solicited reactogenicity data and any other available safety data collected during the 7 days after vaccination were reviewed by an unblinded, independent Data Monitoring Committee, leading to the recommendation that enrollment in the younger age cohort could commence. The enrollment of the younger cohort began on December 19, 2013, and was closed on January 9, 2014, with fewer than the planned 150 subjects because of the onset of the influenza season and the concern that the vaccine safety profiles might be confounded by the natural onset of influenza disease. Children in the younger cohort were assigned to 1 or 2 vaccine intramuscular injections 28 days apart on the basis of their vaccination histories and Centers for Disease Control and Prevention recommendations.[6] Vaccines were administered by unblinded study personnel (eg, a nurse or pharmacist who had no involvement in the evaluation of study participants).

The primary end point was HAI antibody titer 28 days after the completion of the assigned vaccine series (day 28 or day 56 for recipients of 1 or 2 doses, respectively). A secondary immunogenicity end point in children who received 2 vaccine injections was HAI antibody titer at day 28 before the second dose of the vaccine to assess the immune response to a single injection.

Study participants were healthy individuals in each age group with

TABLE 3 Immunogenicity by Age Cohort: Day 28 After Last Dose of Study Vaccine

Antigen	9–17 y		6–8 y	
	RIV4 (n = 75)	IIV4 (n = 77)	RIV4 (n = 26)	IIV4 (n = 28)
A/California/7/2009 (H1N1)				
GMT (95% CI)	915 (693 to 1207)	564 (450 to 708)	1224 (750 to 1999)	695 (501 to 963)
GMT ratio (95% CI)	0.62 (0.43 to 0.88[a])		0.57 (0.32 to 1.00[a])	
SCR, % (95% CI)	87 (76.8[a] to 93.4)	68 (55.9[a] to 77.8)	88 (69.8[a] to 97.6)	75 (55.1[a] to 89.3)
SCR difference, % (95% CI)	−19 (−32.1 to −6.2[a])		−13 (−33.7 to 6.7[a])	
A/Texas/50/2012 (H3N2)				
GMT (95% CI)	852 (698 to 1041)	531 (450 to 628)	1072 (776 to 1479)	629 (451 to 878)
GMT ratio (95% CI)	0.62 (0.48 to 0.81[a])		0.59 (0.37 to 0.92[a])	
SCR, % (95% CI)	59 (46.7[a] to 69.9)	49 (37.8 to 61.0)	54 (33.4 to 73.4)	50 (30.6 to 69.4)
SCR difference, % (95% CI)	−10 (−25.1 to 6.5[a])		−4 (−30.5 to 22.8)	
B/Massachusetts/2/2012 (Yamagata lineage)				
GMT (95% CI)	161 (125 to 208)	120 (95 to 151)	111 (70 to 177)	123 (82 to 184)
GMT ratio (95% CI)	0.75 (0.53 to 1.05[a])		1.11 (0.61 to 2.01)	
SCR, % (95% CI)	69 (57.6[a] to 79.5)	61 (49.2[a] to 72.0)	77 (56.4[a] to 91.0)	82 (63.1[a] to 93.9)
SCR difference, % (95% CI)	−8 (−23.4 to 6.8[a])		5 (−16.3 to 26.7)	
B/Brisbane/60/2008 (Victoria lineage)				
GMT (95% CI)	52 (40 to 67)	60 (47 to 75)	74 (45 to 121)	61 (40 to 91)
GMT ratio (95% CI)	1.15 (0.81 to 1.63)		0.82 (0.44 to 1.54)	
SCR, % (95% CI)	52 (39.4 to 65.1)	67 (53.7[a] to 78.0)	69 (48.2[a] to 85.7)	73 (52.2[a] to 88.4)
SCR difference, % (95% CI)	15 (−2.7 to 31.2)		4 (−20.8 to 28.5)	

Modified per protocol population day: 56 for subjects assigned to receive 2 vaccine doses is shown.
[a] Meets FDA criteria for noninferiority or accelerated approval on the basis of immunogenicity.

TABLE 4 Reactogenicity: Worst Severity Reported During Days 0–7 After First Study Vaccine Injection

Symptom Severity Grade	9–17 y		6–8 y		Total	
	RIV4 (N = 80)	IIV4 (N = 78)	RIV4 (N = 28)	IIV4 (N = 31)	RIV4 (N = 108)	IIV4 (N = 109)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pain: grades 1–2	35 (44)	35 (45)	12 (43)	13 (42)	47 (44)	48 (44)
Bruising: grades 1–2	7 (9)	5 (6)	3 (11)	2 (7)	10 (9)	7 (6)
Measurement of erythema						
Grades 1–2	7 (9)	4 (5)	1 (4)	3 (10)	10 (9)	11 (10)
Grade 3 (≥5 cm)	2 (3)	3 (4)	0 (0)	1 (3)	2 (2)	4 (4)
Measurement of induration						
Grades 1–2	8 (10)	4 (5)	3 (11)	5 (16)	12 (11)	12 (11)
Grade 3 (≥5 cm)	1 (1)	3 (4)	0 (0)	0 (0)	1 (1)	3 (3)
Fever						
None	80 (100)	77 (99)	27 (96)	30 (97)	107 (99)	106 (97)
Grades 1–2	0 (0)	1 (1)	1 (4)	1 (3)	1 (1)	3 (3)

The fever grading system is as follows: grade 0, <100.4; grade 1, 100.4–101.1; grade 2, 101.2–102.0; grade 3, 102.1–104; and grade 4, >104.

no serious underlying conditions, no acute febrile illness, no contraindication to either study vaccine, and who were not receiving any immunosuppressive therapy. The study was approved and monitored by a central institutional review board (Quorum Review Independent Review Board, Seattle, WA) and was conducted at 5 outpatient research centers in the United States according to international standards.[7] Written, informed consent was obtained from the parents or guardians, and assent was obtained from the study participants as required by the institutional review board before any study procedures. Randomization was accomplished according to schedules for each age group prepared by the contract research organization statisticians and provided to the unblinded personnel at each investigative site. Postvaccination, 7-day safety data from older participants were reviewed by the unblinded, independent Data Monitoring Committee on the basis of prespecified criteria for unacceptable frequency and severity of reactogenicity and serious adverse events before enrolling the younger children.

Serum samples were obtained from all study participants before and 28 days after vaccination. Children who received 2 vaccine injections had serum drawn 28 days after each injection. Solicited systemic and injection site reactions and body temperature were recorded daily for 7 days after each vaccination, and other adverse events were collected up to 28 days after the completion of the vaccination (day 28 or 56). Memory aids (ie, diary cards) with reactions recorded for 7 days after each vaccination were returned to the study sites at the time of the 28-day postvaccination visit. Serious and medically attended adverse events were collected via telephone interview through month 6 after the vaccination.

TABLE 5 Unsolicited Adverse Events From ≥2% of Any Age or Vaccine Group Through 28 Days After Last Study Vaccine Injection

Preferred Term	No. (%) Subjects								
	RIV4			IIV4			Total		
	9–17 y (*N* = 80)	6–8 y (*N* = 28)	Total (*N* = 108)	9–17 y (*N* = 78)	6–8 y (*N* = 31)	Total (*N* = 109)	9–17 y (*N* = 158)	6–8 y (*N* = 59)	Total (*N* = 217)
Subjects with ≥1 adverse event	19 (24)	13 (46)	32 (30)	26 (33)	15 (48)	41 (38)	45 (28)	28 (47)	73 (34)
Diarrhea	1 (1)	1 (4)	2 (2)	2 (3)	3 (10)	5 (5)	3 (2)	4 (7)	7 (3)
Vomiting	1 (1)	2 (7)	3 (3)	2 (3)	2 (6)	4 (4)	3 (2)	4 (7)	7 (3)
Oropharyngeal pain	3 (4)	0 (0)	3 (3)	4 (5)	0 (0)	4 (4)	7 (4)	0 (0)	7 (3)
Upper respiratory tract infection	0 (0)	0 (0)	0 (0)	1 (1)	4 (13)	5 (5)	1 (1)	4 (7)	5 (2)
Viral infection	1 (1)	2 (7)	3 (3)	0 (0)	1 (3)	1 (1)	1 (1)	3 (5)	4 (2)
Headache	0 (0)	1 (4)	1 (1)	2 (3)	1 (3)	3 (3)	2 (1)	2 (3)	4 (2)
Cough	0 (0)	1 (4)	1 (1)	1 (1)	3 (10)	4 (4)	1 (1)	4 (7)	5 (2)

Data from the memory aids and participant interviews were entered by study site personnel via online remote electronic data capture managed by the contract research organization, Icon plc., and Icon monitored and verified the data at the clinical sites.

Vaccines

Study participants in both age cohorts were randomly assigned 1:1 to receive RIV4 (Flublok Quadrivalent, Lot 50-13002; Protein Sciences Corporation, Meriden, CT) or IIV4 (Fluarix Quadrivalent, Lot 433FZ; GlaxoSmithKline, Research Triangle Park, NC). Vaccines were manufactured by using processes that have been described fully elsewhere.[8–10] RIV4 was produced by using recombinant DNA technology in a proprietary insect cell line and the baculovirus expression vector and contained 180 μg of purified influenza HA protein (45 μg of each strain) but no influenza neuraminidase. IIV4 was produced from the infectious influenza virus propagated in embryonated chicken eggs that was inactivated and partially purified to a split virus vaccine containing 60 μg (15 μg of each strain) HA and an unspecified quantity of neuraminidase per 0.5 mL intramuscular dose.

Study vaccines contained the HA antigens for the 4 influenza strains selected for the 2013–2014 season: A/California/7/2009 (H1N1) in the RIV4 or the antigenically similar A/Christchurch/16/2010 in the IIV4, A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

Study Populations

The 2 analysis populations included the safety population, which comprised all randomly assigned subjects in both age cohorts who received any dose of the study vaccine and provided any safety data after vaccination, and the evaluable immunogenicity population (modified per protocol, analysis population). The latter population included all randomly assigned subjects who received the assigned number of doses of the study vaccine and had HAI titers available from blood draws taken at baseline and ~28 days after the last dose of the study vaccine. For this primary analysis, day 28 HAI titers for subjects with 1 dose and day 56 HAI titers for subjects with 2 doses were pooled as the final postvaccination titers. Subjects with protocol violations, such as the use of systemic corticosteroids, were excluded from the immunogenicity analyses. The Safety Population was used for safety analyses, and tolerability was tabulated for subjects who returned memory aids.

The safety and immunogenicity populations were similarly defined for each age cohort separately. The primary immunogenicity analyses for the younger cohort were similarly used to pool the day 28 titers for subjects with 1 dose and day 56 titers for subjects with 2 doses as final postvaccination titers. Subjects in the younger cohort who were assigned to 2 vaccine doses were included in an analysis of the secondary end point in which we evaluated the day 28 immunogenicity after a single dose in unprimed children.

Statistical Analysis

The study was designated as an exploratory study; thus, the final sample size was not based on statistical calculations. We initially planned to enroll 150 subjects in each age cohort, randomly assign 1:1 to the RIV4 or IIV4, and pool the data from both age groups for the primary analysis. The planned sample size of 300 would have provided 80% power to conclude noninferiority of GMTs for each antigen without adjusting for multiple comparisons. The enrollment of the younger cohort, which was delayed for the planned safety review, was closed early to avoid confounding the safety data by the onset of the influenza season.

HAI assays were performed at Focus Diagnostics, subsidiary of Q2 Solutions (Cypress, CA), by using a validated assay and employing turkey red blood cells (Lampire Associates, Pipersville, PA) and HA antigens of egg origin (National Institute for Biological Standards and Control, London, United Kingdom). Serum samples, which were treated with a receptor-destroying enzyme, were diluted 1:10 and then serially in twofold dilutions. Reagents were qualified annually, and the assay

was validated with sensitivity within twofold dilution. HAI titers were reported as the inverse of the highest serum dilution at which hemagglutination was inhibited.

Noninferior immunogenicity was tested according to Food and Drug Administration (FDA) guidelines[5] by comparing GMTs and SCRs. A GMT was considered noninferior if the upper bound of the 2-sided 95% confidence interval (CI) around the ratio of the GMT of the IIV4 to the GMT of the RIV4 was ≤1.5. GMTs and their 95% CIs were computed by using serology results transformed to the natural logarithmic scale. The 95% CI for GMTs and ratios were calculated by using a test statistic on the mean or the difference of means, respectively, on the log scale under the assumption of asymptotic normality. The HAI immunogenicity data are presented as back transformed to the original titer scale.

The SCR was defined as the proportion of subjects in each group with a postvaccination titer that was greater than or equal to fourfold higher than a detectable prevaccination titer or ≥40 if the prevaccination titer was undetectable (<10). The SCR was considered noninferior if the upper bound of the 2-sided 95% CI around the difference of the SCR of IIV4 to the SCR of RIV4 was ≤10. The regulatory criterion for the acceptability of SCR for accelerated approval was a lower limit of the 95% CI for SCR ≥40%.[5] Solicited systemic and injection site reactions and body temperatures were tabulated for each treatment group for the entire study population and for each of the 2 age cohorts. Unsolicited adverse events (serious or nonserious) were coded by using Medical Dictionary for Regulatory Activities version 16.1 and tabulated by the preferred term.

RESULTS

A total of 219 subjects were enrolled, 159 in the older cohort and 60 in the younger cohort. One subject in each age cohort, both randomly assigned to the IIV4, withdrew without vaccination. Enrollment in the younger cohort was curtailed when the circulation of wild-type influenza became widespread. Most subjects (n = 203) completed the 6 months of follow-up after vaccination. There were no deaths or discontinuations because of an adverse event. The 2 vaccine groups were comparable in terms of their participation and completion of the study (Fig 1).

The demographics of study participants were well balanced between the 2 vaccine groups (Table 1). The study populations were evenly distributed regarding sex and race; subjects were predominantly not Hispanic or Latino. There were no participants who identified as Asian American, American Indian and/or Alaskan native, or Native Hawaiian and/or Pacific Islander.

The antibody response after the RIV4 was similar to that of the IIV4 for the entire study population and met FDA criteria for noninferior immunogenicity for the GMT ratios of all 4 antigens and for SCR differences for 3 of the 4 antigens (Table 2). The low HAI responses to influenza B–Brisbane in both vaccine groups have been observed in other studies of adults.[11,12] The immunogenicity of the RIV4 among participants 6 to 8 years of age was similar to that of the IIV4, although with wider CIs because of the smaller sample size (Table 3). For subjects 6 to 8 years of age assigned to 2 doses of the study vaccine, the antibody responses to the first injection were comparable between the 2 vaccine groups and similar to the magnitude of responses on day 56 after the second dose (Supplemental Information).

The safety profiles of the 2 vaccines were comparable in terms of reactogenicity (Table 4). The most common injection site reaction was pain, typically of mild-to-moderate severity. Injection site erythema, which was measured by participants or their parents or guardians, was reported to be >5 cm in diameter (grade 3) in <5% of subjects, without a clinically meaningful difference between the vaccine groups. The most commonly reported solicited systemic reactions of myalgia, fatigue, and headache were reported during days 0 to 7 with similar frequency in both vaccine groups; all complaints were self-limited, and most were of mild-to-moderate severity (data not shown). Body temperatures recorded daily during days 0 to 7 by participants or their guardians revealed infrequent fevers (<5%) in both vaccine groups, and none were >102°F. No participant experienced a febrile seizure.

All unsolicited adverse events during the 28 days and serious adverse events during the 6 months after the completion of the vaccination, respectively, were also similar in the 2 vaccine groups (Table 5). Unsolicited adverse events during the 28 days after the vaccination were approximately twofold more common in the younger participants but were of equal frequency in both vaccine groups. The most common events were various infections, diarrhea, and respiratory complaints; all were events that are common among children and adolescents during the winter season. There were no deaths among study participants, and only 1 serious adverse event occurred: a hospitalization of a 9-year-old child for treatment of a recrudescence of asthma 5 months after the IIV4. None of the unsolicited adverse events were considered related to the study vaccine or to an influenza infection during follow-up.

DISCUSSION

The recombinant influenza vaccine has been available in the United States for seasonal immunization in adults ≥18 years of age for >3 years, and the product was recently transitioned to a quadrivalent formulation.[13] Although this pediatric

study in 2013 and 2014 was the first clinical trial of the RIV4, 2 phase 3, active-controlled clinical trials in adults were conducted during the 2014–2015 season. The 2 adult trials were used to support the regulatory approval of the RIV4 and revealed that in adults ≥50 years of age, the RIV4 provided up to 43% better protection than the IIV4 against laboratory-confirmed, influenzalike illness[11] and noninferior immunogenicity in adults 18 to 49 years of age.[12] An earlier, placebo-controlled study revealed the RIV3's 45% absolute efficacy against predominantly mismatched, drifted influenza strains in adults 18 to 49 years of age.[13,14] The safety and immunogenicity of the RIV3 in comparison with the IIV3 in 159 influenza vaccine-naive pediatric subjects 6 to 59 months of age[3] revealed that the RIV3 was safe and well tolerated in comparison with the IIV3, but its immunogenicity in infants and toddlers 6 to 35 months of age was inferior to that of the IIV3.[3] HAI responses appeared to be more comparable in children 36 to 59 months of age (albeit a small number of subjects). Thus, further study of the RIV4 in 9- to 17-year-old subjects with stepdown to 6- to 8-year-old subjects was appropriate.

The immunogenicity of the RIV4 across the age group of 6 to 17 years was comparable to that of the IIV4. FDA criteria for noninferiority based on ratios of postvaccination GMTs were met for RIV4 recipients for all 4 antigens and differences in SCRs for 3 of 4 antigens. The HAI responses to the B–Victoria lineage (B/Brisbane/60/2011) failed to meet seroconversion criteria largely because the HAI titers in both vaccine groups were low, whereas the variability of the HAI assay may confound data interpretation. The low HAI antibody responses to influenza B antigens among pediatric subjects is well recognized and speculated to reflect poorer overall immunogenicity of the B antigens or the lesser role of HAI antibodies versus neutralizing antibodies in protecting against influenza B.[15–19] In a clinical trial of efficacy against laboratory-confirmed influenza disease in older adults, low titers against influenza B were not associated with different degrees of protection among RIV4 or IIV4 recipients.[11] By contrast, the GMTs to influenza A/Texas/50/2012 (H3N2) were significantly higher among RIV4 versus IIV4 recipients in this study. Higher immune responses to H3N2 in RIV3 or RIV4 recipients (versus IIV3 and IIV4 recipients, respectively) have been observed consistently in previous phase 3, active-controlled trials in adults.[11,12] Recent data reveal that HAI titers, especially to type A (H3N2), induced by egg-grown vaccines may provide reduced protective efficacy, further revealing that the noninferiority of titers generated by the RIV4 may be an incomplete assessment of potential protection.[20] Although HAI titers were similar in the children 6 to 8 years of age, the truncated sample size of this group limited the ability to interpret the data for the 2 age groups separately.

The safety and tolerability of the RIV4 in both age groups were similar to those of the IIV4. Most solicited events of injection site reactions in both age cohorts were of mild-to-moderate (grades 1–2) severity and reported with similar frequency in both vaccine groups. Grade 3 injection site erythema and induration were reported by a small number of subjects but slightly more frequently among IIV4 than RIV4 recipients. Fever was infrequent, not accompanied by febrile seizure, and not different between the vaccine groups.

The common unsolicited, spontaneously reported adverse events largely represented complaints that would be expected in children and adolescents during the winter season. Overall, there were more subjects reporting at least 1 adverse event among IIV4 recipients than among RIV4 recipients, although the difference was not significant. There were no vaccine-related serious or nonserious events in either vaccine group, and no deaths were reported among study participants.

There are several limitations to this study. This being a phase 2 study, we could only evaluate safety and immunogenicity of the RIV4 in an exploratory fashion before embarking on confirmatory efficacy trials, possibly to include more than a single influenza season. A major limitation is the lack of full enrollment because of the onset of the influenza season. Nevertheless, the data allow for a reasonable expectation of the likely comparable performance of the RIV4 to the IIV4 in pediatric subjects ≥6 years of age. Higher HAI titers in RIV4 recipients to influenza A subtypes may translate to improved clinical efficacy for these subtypes, as has been demonstrated in adults.[11,14]

CONCLUSIONS

The safety, reactogenicity, and immunogenicity of the RIV4 in pediatric subjects 6 to 17 years of age in this phase 2 exploratory trial are comparable to those in the profile of the IIV4 in pediatric subjects ≥6 years of age.

ABBREVIATIONS

CI: confidence interval
FDA: Food and Drug Administration
GMT: geometric mean titer
HA: hemagglutinin
HAI: hemagglutination inhibition
IIV3: trivalent inactivated influenza vaccine
IIV4: quadrivalent inactivated influenza vaccine
RIV3: trivalent, recombinant influenza vaccine
RIV4: quadrivalent, recombinant influenza vaccine
SCR: seroconversion rate

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