Efficacy, Immunogenicity, and Safety Evaluation of an MF59 Adjuvanted Quadrivalent Influenza Virus Vaccine Compared to Non-adjuvanted Influenza Vaccine in Children

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BACKGROUND

Children are at increased risk for influenza virus–induced morbidity.[1-3] Young children, particularly those younger than 2 years, have immature immune systems, which respond poorly to standard influenza vaccines. Enhanced influenza vaccines may help address this need in this most vulnerable population.

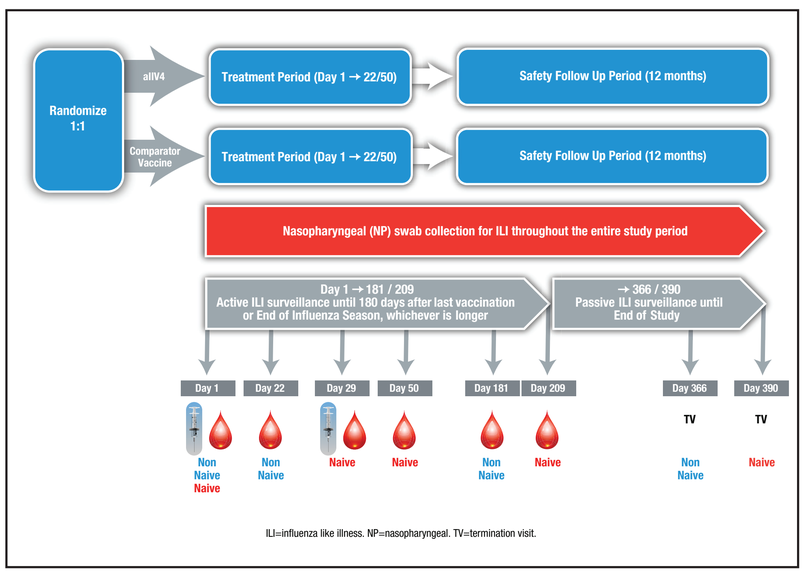
STUDY AIM

This phase III study evaluated the relative vaccine efficacy (rVE) of MF59 adjuvanted quadrivalent inactivated influenza vaccine (aIIV4) with a non-adjuvanted influenza vaccine comparator against influenza disease in children 6 months to 5 years of age.

METHODS

- In this phase III, observer-blind, active-controlled, relative efficacy study, children aged 6 months to 5 years were randomized 1:1 to receive 1 or 2 doses of aIIV4 or non-adjuvanted comparator vaccine (Fluzone®) (see **Figure 1** for design).
- As comparator, trivalent inactivated influenza vaccine [IIV3] was used in Season 1 and quadrivalent inactivated influenza vaccine [IIV4] in Season 2. For both efficacy and immunogenicity, results from B/Victoria from Season 1 were not included in the analyses in view of this strain lacking in the comparator vaccine in Season 1.
- Endpoints included reverse transcriptase polymerase chain reaction (RT-PCR)–confirmed, culture-confirmed, and antigenically matched influenza A and/or B and immunogenicity against homologous and heterologous strains.
- All endpoints were prespecified for the overall age group and for the subgroup of children aged 6 to 23 months.
- The study was conducted during the 2013/2014 and 2014/2015 seasons in 9 countries: Finland, United States, and Canada in Seasons 1 and 2, and Italy, Poland, Spain, Philippines, Thailand, and Taiwan in Season 2.

FIGURE 1. Study Design.

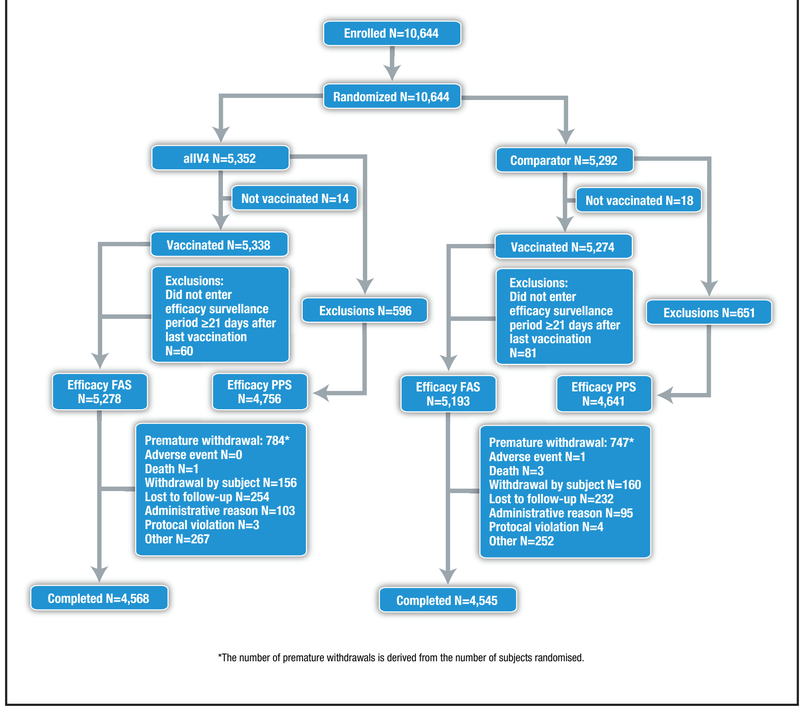


ILI=influenza like illness. NP=nasopharyngeal. TV=termination visit.

PATIENT DISPOSITION

- A total of 10644 subjects were enrolled in the study (1486 subjects in 2013/2014 [Season 1] and 9158 subjects in 2014/2015 [Season 2]). Of these, 5338 were randomly assigned to receive aIIV4 and 5274 were assigned to receive a comparator vaccine across the 2 seasons (**Figure 2**).
- A quarter of the overall study population (n=2686) in the efficacy full analysis set (FAS) was <2 years old.
- In both the efficacy and immunogenicity FAS, demographic and baseline characteristics including the proportion of subjects with baseline haemagglutination inhibition (HI) titres ≥1:10 were similar between vaccine groups.

FIGURE 2. Enrolment and Subject Disposition.



*The number of premature withdrawals is derived from the number of subjects randomised.

RESULTS

- Significantly greater rVE was demonstrated in the 6- to 23-month age group (rVE 31.4% [95% CI: 3.1, 51.4]), although not in the overall study population (overall rVE -0.7 [95% CI: -19.8, 15.4]) (**Table 1**).
- In vaccine-naïve subjects aged 6 months to 5 years, rVE was 54.7 (95% CI: 18.1, 74.9) and 70.6 (35.2, 86.6) ≥7 and ≥14 days after the first dose until second vaccination, respectively, demonstrating benefit of aIIV4 in preventing early cases of influenza (**Table 2**).
- In all ages, aIIV4 elicited a superior immunogenic response relative to comparator vaccine for all 4 vaccine strains (**Figure 3**). In addition, aIIV4 elicited a superior immune response against 3 heterologous strains, including A/Hong Kong/4801/2014 (H3N2) (data not shown).
- The highest ratios of geometric mean titres (GMT) were observed in children 6 to 23 months of age, consistent with higher relative efficacy observed in this age group (**Figure 3**).

TABLE 1. First-occurrence RT-PCR-confirmed and Culture-confirmed Influenza and Relative Vaccine Efficacy in Subjects 6 Months to 5 Years of Age.

	6 months to 5 years			6 to 23 months		
Strain	aIIV4 (n=5278)	Comparator (n=5193)	rVE (95% CI)	aIIV4 (n=1299)	Comparator (n=1339)	rVE (95% CI)
RT-PCR-confirmed influenza (primary endpoint)						
No. cases, any strain*	256 (4.9%)	252 (4.9%)	-0.7 (-19.8, 15.4)	55	79	31.4 (3.1, 51.4)
A/H1N1	7 (0.1%)	17 (0.3%)	59.4 (2.1, 83.2)	2	5	Not calculated
A/H3N2	200 (3.8%)	196 (3.8%)	-1.3 (-23.4, 16.8)	44	66	34.5 (4.1, 55.3)
B/Yamagata	36 (0.7%)	36 (0.7%)	2.1 (-55.4, 38.3)	5	9	Not calculated
B/Victoria	14 (0.3%)	9 (0.2%)	-54.5 (-256.9, 33.1)	4	0	Not calculated
Culture-confirmed influenza (secondary endpoint)						
No. cases, any strain*	140 (2.7%)	146 (2.8%)	5.2 (-19.5, 24.8)	31	48	36.0 (-0.6, 59.3)
Matched†	74 (1.4%)	80 (1.5%)	8.4 (-25.6, 33.3)	19	32	40.9 (-4.3, 66.5)
Unmatched†	65 (1.2%)	62 (1.2%)	-3.5 (-46.6, 26.9)	12	14	13.5 (-87.1, 60.0)

Data are n (%) or rVE (95% CI). aIIV4=adjuvanted quadrivalent inactivated influenza vaccine. CI=confidence interval. rVE=relative vaccine efficacy. *For any subject who had multiple confirmed influenza infections, only the first-occurrence confirmation was included under any strain. †Strain match was determined using HI or microneutralization inhibition. For some A/H3N2 isolates, HI was performed using ferret antisera raised against an exclusively cell-grown H3N2 virus and an egg-propagated A/H3N2 standard. For H3N2 isolates that did not bind red blood cells yet could be grown, a standard microneutralization inhibition assay was performed using egg-propagated A/H3N2 to both raise ferret antisera and as the reference standard. Matched strains were determined to be those with <8-fold difference in titre and unmatched strains are those with ≥8-fold difference in titre compared to the vaccine strain.

TABLE 2. First-occurrence of RT-PCR-confirmed Influenza and Relative Vaccine Efficacy in Subjects 6 Months to 5 Years Within 21 Days After Last Vaccination.

	aIIV4	Comparator	rVE (95% CI)
Any strain, vaccine-naïve subjects	**n=3559**	**n=3535**	
≥7 days after first and up to second vaccination	16	35	54.7 (18.1, 74.9)
≥14 days after first and up to second vaccination	8	27	70.6 (35.2, 86.6)
Any strain, all subjects	**n=5286**	**n=5208**	
≥7 days and ≤21 days after last vaccination	4	15	Not calculated

Data are n (%) or rVE (95% CI). aIIV4= adjuvanted quadrivalent inactivated influenza vaccine. CI=confidence interval. rVE=relative vaccine efficacy.

FIGURE 3. Geometric Mean HI Titres and Vaccine Group Ratios Against Homologous Vaccine Strains 21 Days After Last Vaccination.

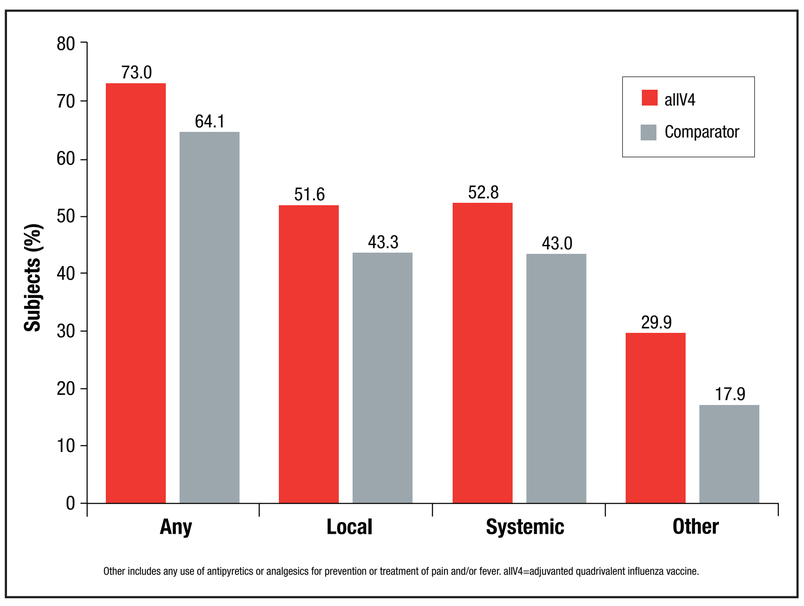
Homologous Strains	GMT		GMT Ratio (95% CI)		N	
FAS immunogenicity	aIIV4	Comparator	aIIV4: Comparator		aIIV4	Comparator
Subjects (6 months to 5 years)				*Superiority Bound*		
A/H1N1	996.40	522.50	1.91 (1.8, 2.0)		1362	1307
A/H3N2	1153.4	674.01	1.71 (1.6, 1.8)		1362	1307
B/Yamagata	198.89	90.68	2.19 (2.0, 2.4)		1362	1307
B/Victoria	315.52	138.82	2.27 (2.0, 2.6)		745	738
				0 1 6		
Subjects (6 to 23 months and 2 to 5 years)				*Superiority Bound*		
A/HINI						
6 to 23 months	654.99	223.88	2.93 (2.5, 3.5)		378	384
2 to 5 years	1110.84	692.98	1.60 (1.5, 1.8)		984	923
A/H3N2						
6 to 23 months	982.98	380.79	2.58 (2.2, 3.0)		378	384
2 to 5 years	1261.91	862.17	1.46 (1.3, 1.6)		984	923
B/Yamagata						
6 to 23 months	130.25	35.89	3.63 (3.1, 4.3)		378	384
2 to 5 years	200.09	111.83	1.79 (1.6, 2.0)		984	923
B/ Victoria						
6 to 23 months	292.45	76.07	3.84 (2.9, 5.0)		167	179
2 to 5 years	322.52	168.31	1.92 (1.6, 2.2)		578	559
				0 1 6		

Superiority defined as a lower bound of the 95% CI >1. aIIV4=adjuvanted quadrivalent inactivated influenza vaccine. CI=confidence interval. FAS=full analysis set. GMT=geometric mean titre.

SAFETY

- The overall vaccine safety profiles were similar except for the expected higher incidence of solicited adverse events (AEs) for aIIV4 (**Figure 4**).
- The proportion of subjects with any unsolicited AE was similar for the aIIV4 and comparator vaccine groups (68.2% vs 68.6%). The same pattern was also observed for possibly related AEs, any unsolicited serious AEs, adverse events of special interest, unsolicited AEs leading to death, unsolicited AEs leading to withdrawal from study or vaccine, hospitalisation, and new-onset chronic disease for subjects 6 months to 5 years of age.

FIGURE 4. Overview of Adverse Events Occurring Within 7 Days After Any Vaccination in Subjects 6 Months to 5 Years of Age.



Other includes any use of antipyretics or analgesics for prevention or treatment of pain and/or fever. aIIV4=adjuvanted quadrivalent influenza vaccine.

CONCLUSION

In this study, aIIV4 provided additional clinical benefit over non-adjuvanted influenza vaccine, with significantly greater efficacy in children aged 6 to 23 months. In addition, aIIV4 resulted in greater early efficacy in vaccine-naïve children after the first up to the second vaccination. Relative to comparator vaccine, aIIV4 was associated with superior immunogenicity and a similar safety profile in all children.

REFERENCES

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