Study GRC88

Safety and Immunogenicity of Fluzone® Quadrivalent Vaccine 0.5-mL Dose for Children 6 through 35 Months of Age

SANOFI PASTEUR

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Background

- **Use of half-dose (0.25 mL) inactivated influenza vaccine for young children based on reactogenicity data from studies of whole-virus vaccine**
  - Split-virus vaccines are less reactogenic
- **Data from recent studies suggest that in children 6–35 months of age, full-dose (0.5 mL) influenza vaccine generally induces higher antibody responses compared to those induced by a half-dose (0.25 mL) without causing materially higher rates of systemic or injection-site reactions**
- **Full-dose vaccine recommended for children 6–35 months of age in USA, Canada, United Kingdom, and Finland**

Aim and Objectives of Study GRC88

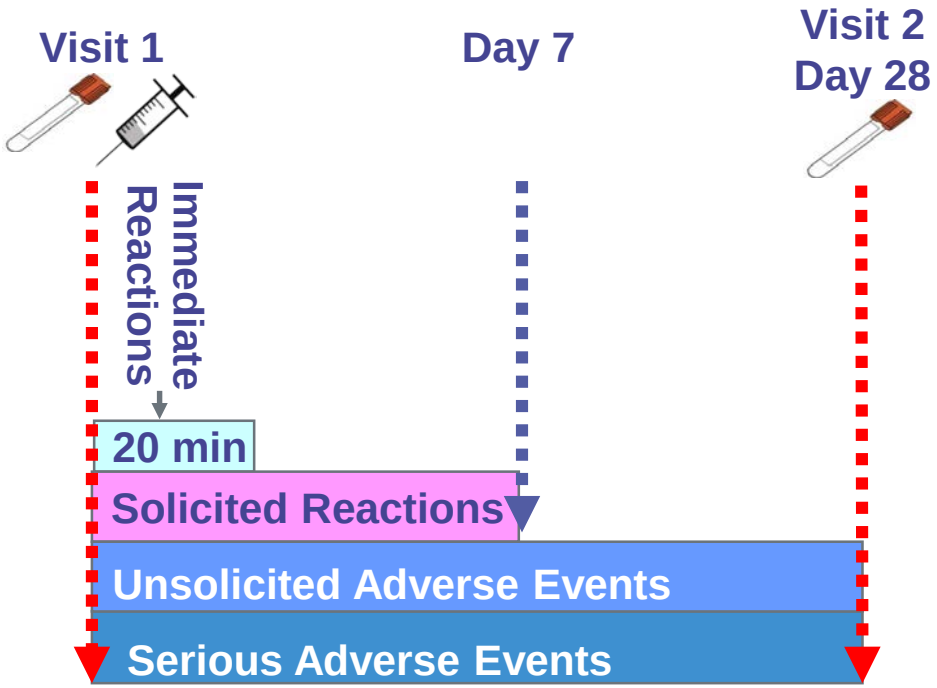
- **Aim: To evaluate the safety and immunogenicity of a 0.5-mL dose of Fluzone Quadrivalent vaccine compared to a 0.25-mL dose in children 6–35 months of age**
- **1° objective: To compare the rate of any fever (temperature ≥ 100.4°F) following a 0.5-mL dose to that following a 0.25-mL dose during the 7 days after vaccination**
- **2° objective: To compare antibody responses induced by a 0.5-mL dose to those induced by a 0.25-mL dose, as assessed by:**
  - Geometric mean titer (GMT) ratios
  - Seroconversion (SC) rate differences

Study design

- **Phase IV, randomized, observer-blinded, 2-arm, multi-center study conducted in the US**
- **Planned cohort of 2190 healthy children 6–35 months old**
- **Subjects randomly assigned 1:1 to receive Fluzone Quadrivalent vaccine administered in either a half- or full-dose volume**
  - Enrollment was stratified by age (6 to < 24 months vs 24–35 months) to achieve equal proportions of subjects in each age subgroup
- **A subset of subjects (1600 planned) were randomly selected to participate in the immunogenicity assessment**
- **Investigators, study site personnel, sponsor's research team and subjects were blinded to group assignment**
  - Exception was the unblinded study staff who administered the vaccine

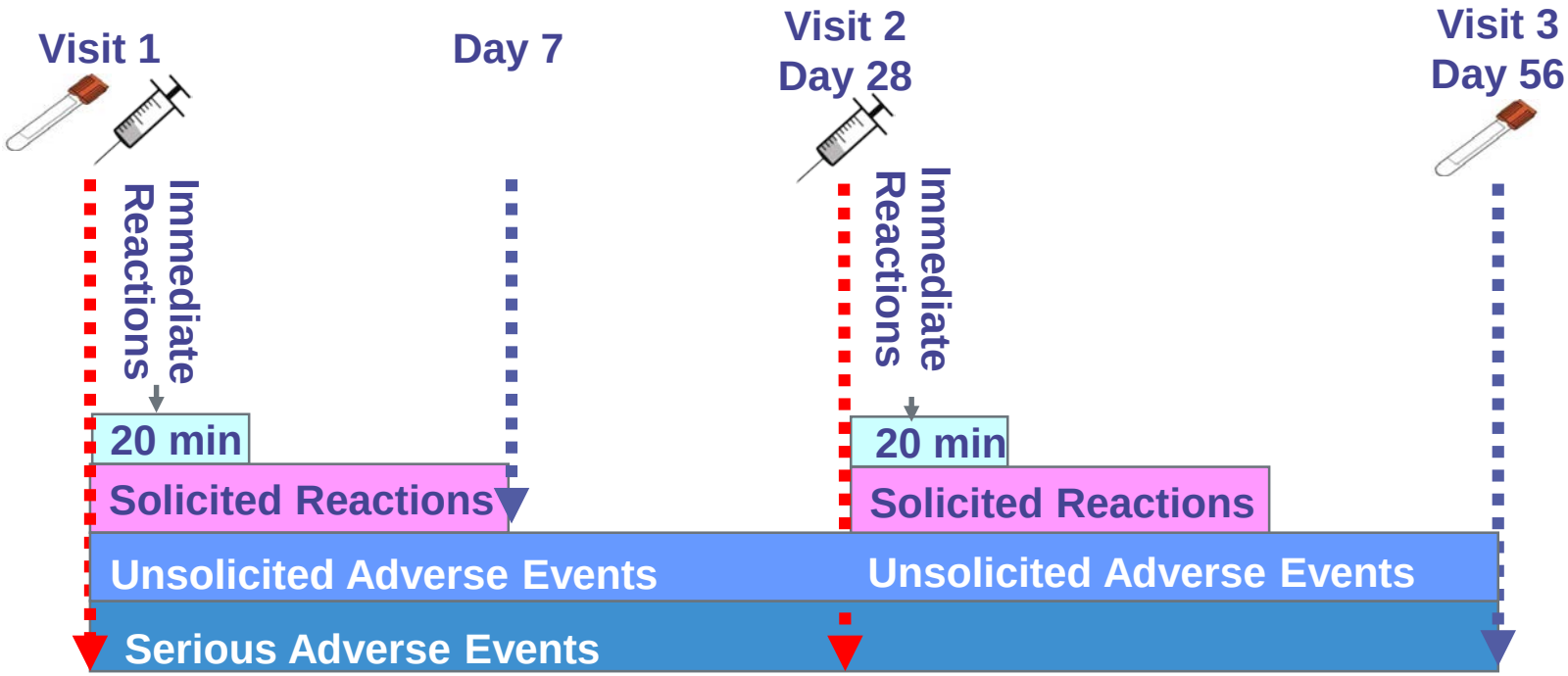
Safety data and sera collection

Subjects receiving 1 dose of vaccine (2 visits)



Safety data and sera collection

Subjects receiving 2 doses of vaccine (3 visits)



Summary of subject disposition – All randomized subjects

	0.25-mL Dose (N=955)		0.5-mL Dose (N=995)		All (N=1950)	
	n	%	n	%	n	%
Randomized but did not receive vaccine	6	0.6	3	0.3	9	0.5
Safety Analysis Set	949	50.6	992	50.1	1941	99.5
Received exactly 1 dose of vaccine	442	46.3	475	47.7	917	47.0
Received 2 doses of vaccine	507	53.1	517	52.0	1024	52.5
Subjects randomly assigned to the immunogenicity subset	715	74.9	745	74.9	1460	74.9

Baseline demographics – Safety Analysis Set[a] (N=1941)

	0.25-mL Dose (N=949)		0.5-mL Dose (N=992)	
Sex: n (%)				
Female	**469**	**(49.4)**	**495**	**(49.9)**
Male	**480**	**(50.6)**	**497**	**(50.1)**
Age in months (median)	**20.1**		**20.1**	
Race: n (%)				
White	**717**	**(75.6)**	**725**	**(73.1)**
Nonwhite	**228**	**(24.0)**	**261**	**(26.3)**
Ethnicity: n (%)				
Hispanic or Latino	**206**	**(21.7)**	**221**	**(22.3)**
Not Hispanic or Latino	**731**	**(77.0)**	**763**	**(76.9)**

[a]Safety Analysis Set: all subjects having received at least one dose of study vaccine

Fever rates

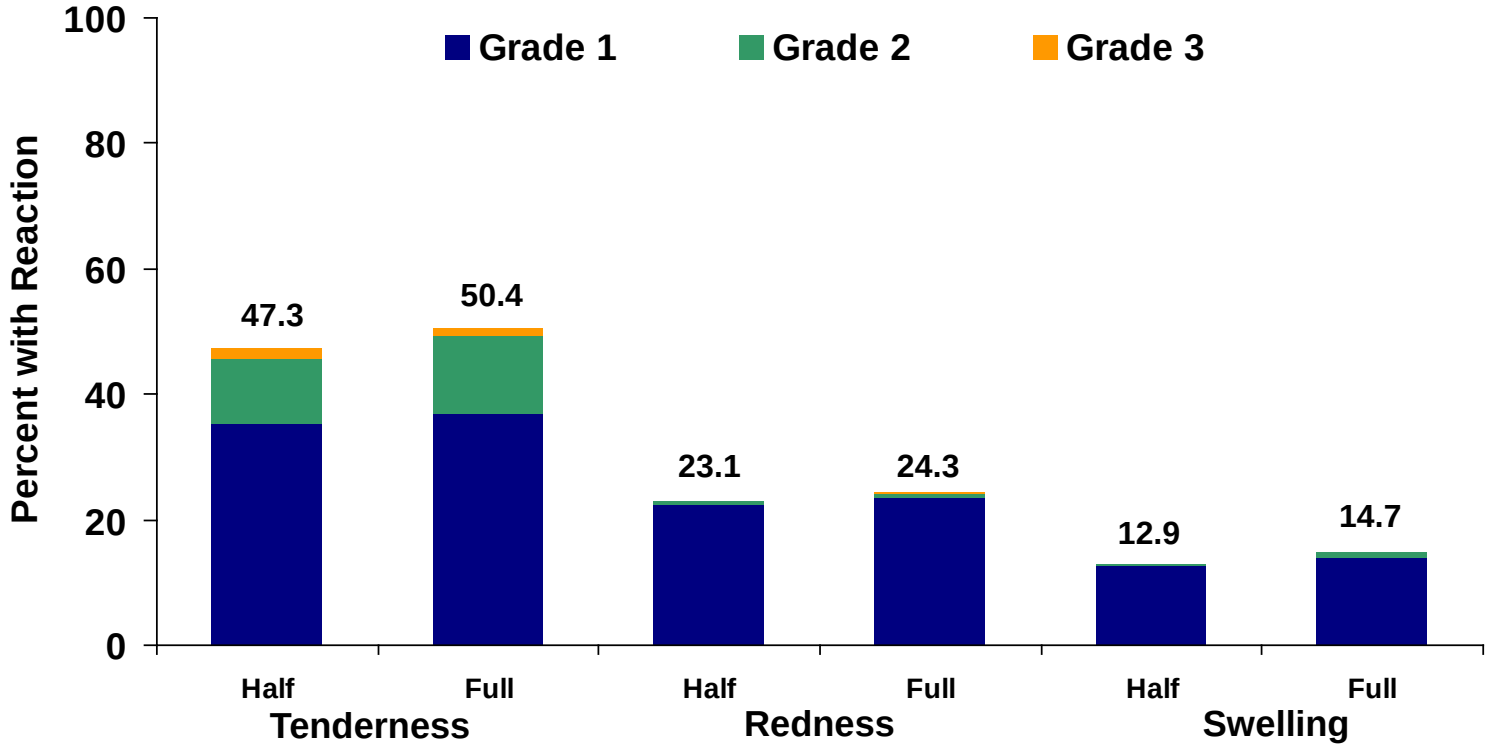
Overall (after Dose 1 and Dose 2 combined)

0.25-mL Dose of Fluzone Quadrivalent Vaccine N=949		0.5-mL Dose of Fluzone Quadrivalent Vaccine N=992		Difference in Fever Rates (95% CI)
n/M	Fever rate (95% CI)	n/M	Fever rate (95% CI)	
101/893	11.31% (9.31%; 13.57%)	113/930	12.15% (10.12%; 14.42%)	0.84 (-2.13; 3.80)

Pre-specified non-inferiority criterion: the upper limit of the 2-sided 95% CI of the difference in fever rates between groups had to be < 5%

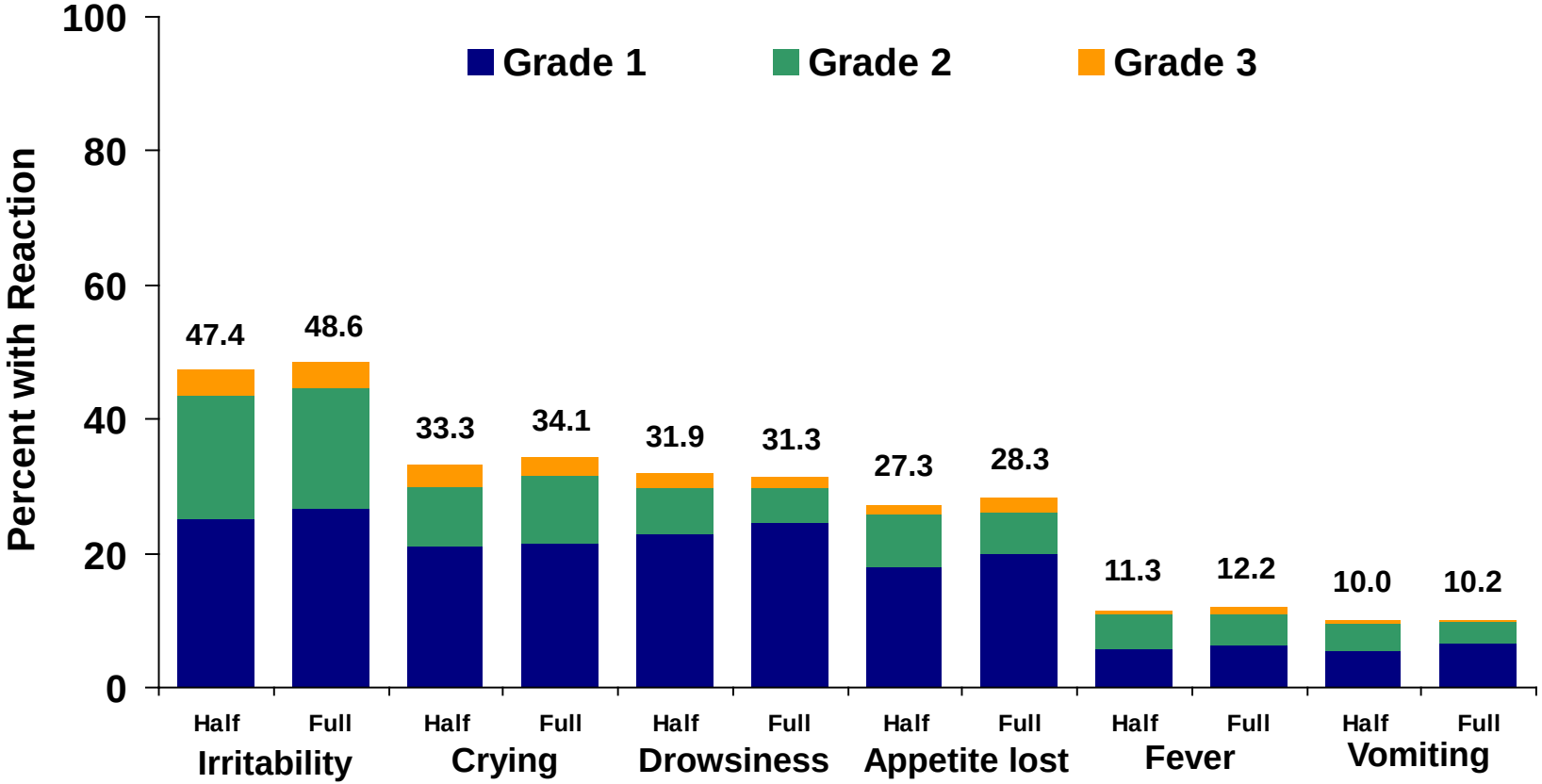
n: number of subjects experiencing the endpoint listed
M: number of subjects with available data for the relevant endpoint

Solicited injection-site reactions



Tenderness: Grade 1: Minor reaction when injection site is touched; Grade 2: Cries or protests when injection site is touched; Grade 3: Cries when injected limb is moved, or the movement of the injected limb is reduced
Erythema and swelling: Grade 1: > 0 to < 25 mm; Grade 2: ≥ 25 to < 50 mm; Grade 3: ≥ 50 mm

Solicited systemic reactions



Fever: Grade 1: ≥ 100.4°F to ≤ 101.3°F; Grade 2: > 101.3°F to ≤ 103.1°F; Grade 3: > 103.1°F

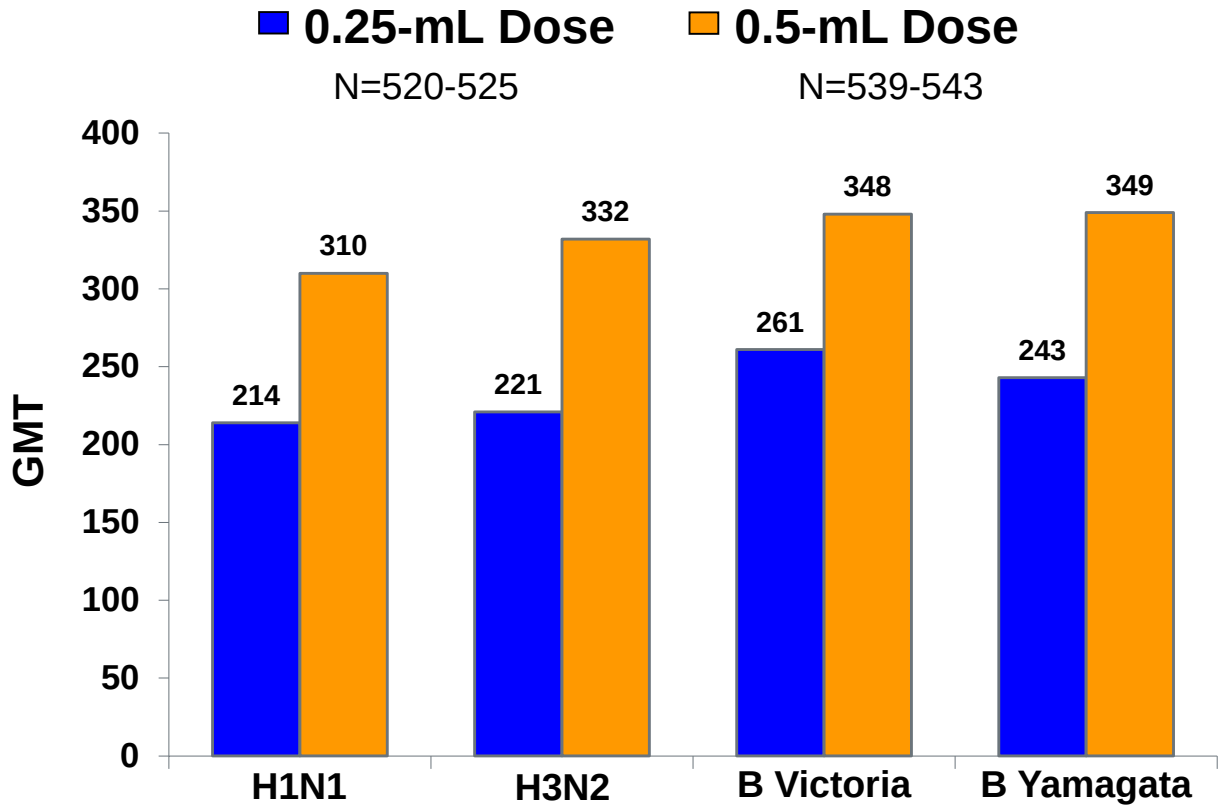
Irritability, crying, drowsiness, appetite loss, and vomiting: definitions available upon request

Unsolicited non-serious adverse events (AEs) and serious adverse events (SAEs)

	0.25-mL Dose (N=949)		0.5-mL Dose (N=992)	
Subjects experiencing at least one:	**n**	**%**	**n**	**%**
Immediate unsolicited AE	2	0.2	0	0.0
Immediate unsolicited adverse reaction (AR)	1	0.1	0	0.0
Unsolicited AE	420	44.3	395	39.8
Unsolicited AR	29	3.1	30	3.0
AE leading to discontinuation	3	0.3	0	0.0
AE of special interest (AESI)[a]	1	0.1	0	0.0
SAE	5	0.5	5	0.5
Death	0	0.0	0	0.0

[a]AESIs included new onset of Guillain-Barré syndrome (GBS), encephalitis/myelitis, neuritis (including Bell's palsy, optic neuritis, and brachial neuritis), thrombocytopenia, vasculitis, convulsions (including febrile), and anaphylaxis or other hypersensitivity/allergic reactions

Geometric mean titers, 28 days after final vaccination

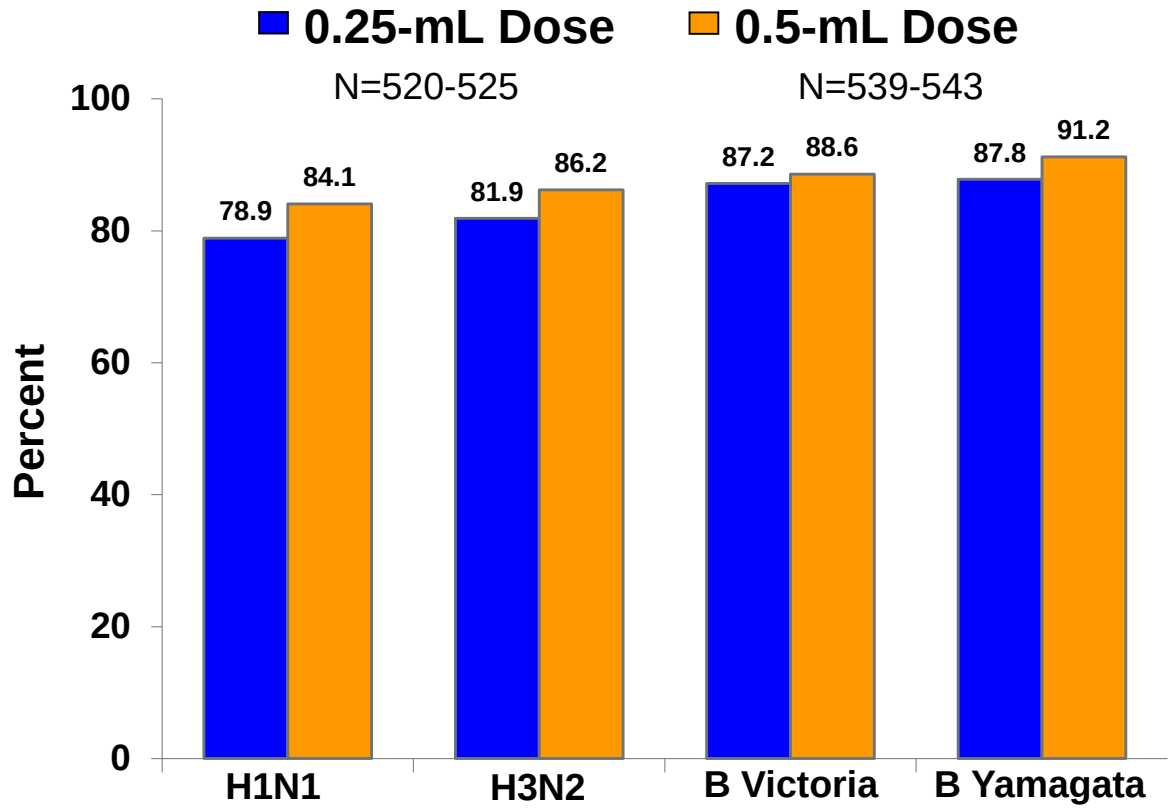


Comparison of GMTs, 0.25-mL dose vs. 0.5-mL dose

Strain/ Lineage	0.25-mL Dose GMT (N=520-525)	0.5-mL Dose GMT (N=539-543)	GMT Ratio (95% CI)	Statistical Comparison[a]
A/H1N1	214	310	1.45 (1.19; 1.77)	Noninferior
A/H3N2	221	332	1.50 (1.23; 1.83)	Noninferior
B Victoria	261	348	1.33 (1.10; 1.62)	Noninferior
B Yamagata	243	349	1.44 (1.20; 1.73)	Noninferior

GMT: geometric mean titer
Noninferiority: lower bound of 95% CI of GMT ratio > 0.667
[a]All comparisons are based on data from the Per-Protocol Analysis Set

Seroconversion rates, 28 days after final vaccination



Comparison of SC rates, 0.25-mL dose vs. 0.5-mL dose

Strain/ Lineage	0.25-mL Dose SC Rate (%) (N=470-475)	0.5-mL Dose SC Rate (%) (N=483-488)	Difference in SC Rates (95% CI)	Statistical Comparison[a]
A/H1N1	78.9	84.1	5.1 (0.189; 10.0)	Noninferior
A/H3N2	81.9	86.2	4.3 (-0.283; 8.99)	Noninferior
B Victoria	87.2	88.6	1.4 (-2.78; 5.56)	Noninferior
B Yamagata	87.8	91.2	3.4 (-0.465; 7.36)	Noninferior

SC=seroconversion
Noninferiority: lower bound of 95% CI of SC rate difference > -10%
[a]All comparisons are based on data from the Per-Protocol Analysis Set

Conclusions and Next Steps

- **This study in children 6–35 months of age affirms that a full (0.5-mL) dose of Fluzone Quadrivalent vaccine has a safety profile similar to that of a half-dose (0.25 mL) and may be more immunogenic**
- **These clinical trial results are consistent with findings from other studies**
- **An sBLA has been submitted to FDA to permit use of a 0.5-mL dose of Fluzone Quadrivalent vaccine in children as young as 6 months of age**
  - Action date: January 2019

Important Safety Information for Fluzone Quadrivalent Vaccine (1)

Fluzone Quadrivalent vaccine should not be administered to anyone who has had a severe allergic reaction (eg, anaphylaxis) to any vaccine component, including eggs, egg products, or thimerosal, or to a previous dose of any influenza vaccine.

If Guillain-Barré syndrome has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone Quadrivalent vaccine should be based on careful consideration of the potential benefits and risks.

Important Safety Information for Fluzone Quadrivalent Vaccine (2)

The most common local and systemic adverse reactions to Fluzone Quadrivalent vaccine include pain at the injection site (all ages) and redness and swelling at the injection site (in children); muscle aches, fatigue, and headache (irritability, abnormal crying, drowsiness, appetite loss, vomiting, and fever in young children). Other adverse reactions may occur. Vaccination with Fluzone Quadrivalent vaccine may not protect all individuals.

Indication for Fluzone Quadrivalent Vaccine

Fluzone Quadrivalent vaccine is indicated for active immunization against disease caused by Influenza A subtype viruses and type B viruses contained in the vaccine. Fluzone Quadrivalent vaccine is approved for use in persons 6 months of age and older.

Before administration please see full Prescribing information for Fluzone Quadrivalent vaccine.

THANK YOU

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