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Immunogenicity and safety of a trivalent inactivated influenza vaccine produced in Shenzhen, China

Zhaojun Mo^a, Yi Nong^a, Shuzhen Liu^b, Ming Shao^b, Xueyan Liao^c, Kerry Go^d, and Nathalie Lavis^e

^aGuangxi Zhuang Autonomous Region Center for Disease Prevention and Control, Guangxi, China; ^bNational Institutes for Food and Drug Control, Beijing, China; ^cSanofi Pasteur, Beijing, China; ^dSanofi Pasteur, Swiftwater, PA, US; ^eSanofi Pasteur, Lyon, France

ABSTRACT

A split-virion trivalent inactivated influenza vaccine produced according to the Chinese pharmacopeia (Shz-IIV3) has been commercially available in China since 2014. Here, we describe the results of a phase IV open-label trial to describe the immunogenicity and safety of the 2014–2015 Northern Hemisphere formulation of Shz-IIV3 in individuals ≥ 6 months of age. Subjects 6–35 months of age received 2 half-doses of Shz-IIV3 (0.25 ml) 28 d apart, and subjects ≥ 3 y of age received a single full dose (0.5 ml). The study included 602 subjects. Except for the A (H3N2) strain in subjects 3–17 years, geometric mean hemagglutination inhibition titer ratios were ≥ 10 and rates of seroconversion/significant increase in titer were $\geq 78\%$ in all age groups. For the H3N2 strain in subjects 3–17 years, the geometric mean titer ratio was 3.8 and the rate of seroconversion/significant increase was 56%. Post-vaccination seroprotection rates were $\geq 88\%$ for all strains in all age groups. The most common solicited reactions were injection-site pain/tenderness and fever, most of which were grade 1 and resolved within 3 d. Vaccine-related unsolicited adverse events were reported only by subjects 6–23 months, most of which were mild abnormal crying and irritability. No vaccine-related serious adverse events and no deaths were reported. No new safety signals or unexpected safety events occurred, although an immediate anaphylactic skin reaction occurred in one subject. This study confirmed that the 2014–2015 Northern Hemisphere formulation of Shz-IIV3 was well tolerated and highly immunogenic in subjects ≥ 6 months of age.

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Introduction

Vaccination is the most effective way of preventing seasonal influenza and its complications.¹ The World Health Organization recommends influenza vaccination for individuals at high risk, including those ≥ 65 y of age, those with chronic medical conditions, pregnant women, children <5 years, and especially children <2 y of age.^{2–4}

In China, rates of hospitalization for severe acute respiratory infection due to influenza have been reported to be 61–142 per 100,000^{5,6} and rates of mortality due to influenza-related respiratory and circulatory diseases from 11.1–12.4 per 100,000.^{7,8} Seasonal influenza peaks in China at different times in different regions, with a peak in January or February in the temperate zone, 2 peaks in January to February and June to August in mid-latitude regions, and a peak in April to June in the southernmost regions.^{9,10}

Sanofi Pasteur has been producing an inactivated split-virion trivalent influenza vaccine (Vaxigrip[®]) since 1968.^{11,12} In compliance with World Health Organization recommendations, Vaxigrip contains 2 variants of influenza subtype A (H1N1 and H3N2) and one variant of type B. Vaxigrip reduces the incidence of influenza infection, decreases workplace absenteeism, and decreases hospitalization and mortality in the elderly and other at-risk populations.^{12–14} Long-term

experience has shown that this trivalent influenza vaccine is well tolerated.¹²

A split-virion trivalent inactivated influenza vaccine (Shz-IIV3) has been produced by Sanofi Pasteur's affiliate in China since 2013 and has been commercially available since 2014. Shz-IIV3 is made using the same method as Vaxigrip and is a bio-comparative vaccine, although in accordance with the Chinese pharmacopeia, it is produced without hydrocortisone during virus production. Here, we report the results of a phase IV study evaluating the immunogenicity and safety of the 2014–2015 Northern Hemisphere formulation of Shz-IIV3 in individuals ≥ 6 months of age.

Results

Subjects

Between September 5 and October 9, 2014, 602 subjects were enrolled ($n = 150$, 6–35 months; $n = 150$, 3–17 years; $n = 151$, 18–60 years; $n = 151$, ≥ 61 years), and the study ended on December 27, 2014. The study was completed by 84.0% subjects aged 6–35 months, 98.0% subjects aged 3–17 years, 98.7% subjects aged 18–60 years, and 98.0% subjects aged ≥ 61 y (Fig. 1). Just over half of subjects were male in the 6–35 month (54.7%) and 3–17 y (53.3%) age groups, whereas less than half

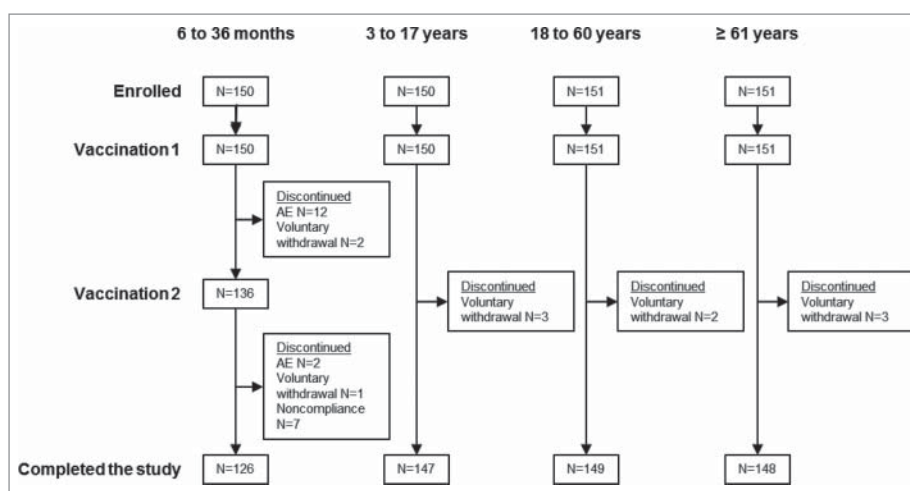


Figure 1. Subject disposition flowchart. Subjects 6–35 months received 2 half-doses 28 d apart of the study vaccine. All other subjects received a single full dose. Blood samples were collected before vaccination (day 0) and 28 d after the last vaccination.

were male in the 18–60 y (24.5%) and ≥ 61 y (47.7%) age groups. None of the subjects were vaccinated the previous year (2013–2014) for seasonal influenza and none had influenza disease diagnosed before study enrolment.

Immunogenicity

Post-vaccination seroprotection rates were $\geq 88.8\%$ for all strains in all age groups (Table 1). Geometric mean titer ratios were ≥ 10.9 for all strains in all age groups, except for the H3N2 strain in subjects 3–17 y for whom the ratio was 3.8. Rates of seroconversion/significant increase in hemagglutination inhibition (HAI) titer were $\geq 78.2\%$ for all strains and in all age groups, except for the H3N2 strain in subjects 3–17 y for whom it was 56.2%. No major differences in immunogenicity

were found between subjects 3–8 y and 9–17 y of age. Committee for Medicinal Products for Human Use (CHMP) criteria for subjects 18–60 and ≥ 61 y of age were met for all 3 vaccine strains.

Solicited injection-site and systemic reactions

Overall, the most common solicited reactions were pain/tenderness at the injection site and fever ($\geq 38.0^\circ\text{C}$) (Figs. 2 and 3). Most solicited reactions resolved within 3 d after vaccination (data not shown). Rates of solicited reactions were highest in the youngest age groups. Grade 3 reactions were reported for 8 subjects: in the 6–23 month age group, 3 subjects had grade 3 loss of appetite and one had grade 3 loss of appetite and drowsiness; in the 24–35 month age group, one subject had grade 3

Table 1. Humoral immunogenicity.

Measure	Time	Strain	Value (95% confidence interval)			
			6–35 mo (N = 150)	3–17 y (N = 150)	18–60 y (N = 151)	≥ 61 y (N = 151)
HAI GMT (dilution ⁻¹) ^a	Day 0	A(H1N1)	12.8 (10.5; 15.6)	24.3 (20.1, 29.4)	11.2 (9.49, 13.1)	9.0 (7.68, 10.5)
		A(H3N2)	14.3 (11.3; 18.1)	62.0 (51.5, 74.8)	12.2 (10.4, 14.4)	21.1 (16.9, 26.5)
	Day 28/56	A(H1N1)	152.2 (120; 193)	300.7 (243, 372)	188.3 (158, 224)	144 (116, 180)
		A(H3N2)	235.9 (191; 291)	236.2 (207, 270)	166.1 (140, 197)	237.8 (198, 285)
Seroconversion or significant increase (%) ^{a,c}	Day 0	B	5.9 (5.49, 6.30)	17.7 (15.0, 20.9)	16.3 (13.7, 19.5)	15.3 (12.8, 18.2)
		A(H1N1)	31.3 (24.0; 39.4)	45.3 (37.2, 53.7)	17.2 (11.6, 24.2)	14.6 (9.4, 21.2)
	Day 28/56	A(H1N1)	88.8 (81.9; 93.7)	94.5 (89.4, 97.6)	96.6 (92.3, 98.9)	89.7 (83.5, 94.1)
		A(H3N2)	32.0 (24.6, 40.1)	78.0 (70.5, 84.3)	21.9 (15.5, 29.3)	39.1 (31.2, 47.3)
GMTR ^a	Day 0	B	98.4 (94.3, 99.8)	99.3 (96.2, 100.0)	95.3 (90.6, 98.1)	95.9 (91.3, 98.5)
		A(H1N1)	1.3 (0.2, 4.7)	30.0 (22.8, 38.0)	29.8 (22.6, 37.8)	23.8 (17.3, 31.4)
	Day 28/56	A(H1N1)	93.5 (87.6, 97.2)	95.2 (90.4, 98.1)	98.7 (95.2, 99.8)	93.9 (88.8, 97.2)
		A(H3N2)	11.6 (9.69; 13.9)	12.1 (9.45, 15.6)	17.0 (13.8, 20.9)	15.8 (12.7, 19.6)
Day 28/56 vs. day 0	B	18.5 (15.9, 21.6)	12.1 (9.74, 15.1)	13.8 (11.1, 17.2)	10.9 (8.68, 13.7)	
	A(H1N1)	86.4 (79.1; 91.9)	79.3 (71.8, 85.6)	91.3 (85.5, 95.3)	84.1 (77.2, 89.7)	
	A(H3N2)	90.4 (83.8, 94.9)	56.2 (47.7, 64.4)	83.2 (76.2, 88.8)	78.2 (70.7, 84.6)	
Day 28/56 vs. day 0	B	93.5 (87.6, 97.2)	82.2 (75.0, 88.0)	85.9 (79.3, 91.1)	80.4 (73.1, 86.5)	

Abbreviations: GMT, geometric mean titer; GMTR, geometric mean of the day 28/56 vs. day 0 HAI titer ratio; HAI, hemagglutination inhibition

^aPost-vaccination assessments were on day 28 in subjects receiving a single dose of vaccine and day 56 in subjects receiving 2 doses of vaccine.

^bSeroconversion was defined as a HAI titer $\geq 1:40$

^cSeroconversion was defined as a pre-vaccination HAI titer $< 1:10$ and a post-vaccination titer $\geq 1:40$. Significant increase was defined as a pre-vaccination HAI titer $\geq 1:10$ and ≥ 4 -fold increase in post- vs. pre-vaccination HAI titer.

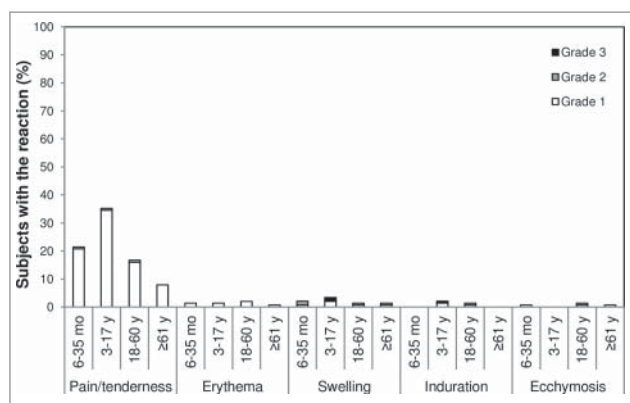


Figure 2. Frequency and severity of solicited injection-site reactions by age group.

fever and one had grade 3 malaise; and in the 3–17 y age group, one subject had grade 3 injection-site induration and swelling and one had grade 3 injection-site swelling. No grade 3 reactions were reported for subjects ≥ 18 y of age.

Unsolicited adverse events (AEs)

Proportions of subjects reporting unsolicited AEs were highest for the youngest age groups (Table 2). Serious adverse events (SAEs) were reported for 3 subjects, including one who had severe acute bronchitis, one who had severe hyperplasia of the prostate and severe lung infection, and one who had severe hand, foot, and mouth disease. None of these SAEs were considered to be vaccine-related. No deaths were reported.

Eleven subjects in the youngest age group (6–35 months) had unsolicited AEs considered related to the vaccination. Most of these related events were crying and irritability ($n = 6$; 4.0%) and decreased appetite ($n = 4$; 2.7%). Other less common unsolicited AEs considered related to vaccination included diarrhea and vomiting, sleepiness, upper respiratory tract infection, and agitation, all mostly mild (grade 1), and a grade 3 cutaneous anaphylactic reaction. Most of these AEs resolved spontaneously within 8 d. Vaccine-related unsolicited AEs (pruritus and diarrhea), all mild or moderate, were also reported for 3 subjects ≥ 61 y of age. None of the other age

Table 2. Adverse events within 28 d after vaccination.

Event	6–35 mo (N = 150)		3–17 y (N = 150)		18–60 y (N = 151)		≥ 61 y (N = 151)	
	n/M	%	n/M	%	n/M	%	n/M	%
Immediate unsolicited AE								
Vaccine-related	2/150	1.3	0/150	0.0	0/151	0.0	0/151	0.0
Solicited reaction	70/141	49.6	72/148	48.6	35/150	23.3	24/151	15.9
Solicited injection-site reaction	33/140	23.6	53/148	35.8	26/150	17.3	13/151	8.6
Solicited systemic reaction	60/140	42.9	39/148	26.4	16/150	10.7	14/151	9.3
Unsolicited AE	62/150	41.3	12/150	8.0	4/151	2.6	5/151	3.3
Vaccine-related	11/150	7.3	0/150	0.0	0/151	0.0	3/151	2.0
Non-serious	62/150	41.3	11/150	7.3	4/151	2.6	4/151	2.6
Non-serious vaccine-related	11/150	7.3	0/150	0.0	0/151	0.0	3/151	2.0
Injection-site non-serious vaccine related	0/150	0.0	0/150	0.0	0/151	0.0	0/151	0.0
AE leading to study discontinuation	14/150	9.3	0/150	0.0	0/151	0.0	0/151	0.0
SAE	1/150	0.7	1/150	0.7	0/151	0.0	1/151	0.7
Vaccine-related	0/150	0.0	0/150	0.0	0/151	0.0	0/151	0.0
Death	0/150	0.0	0/150	0.0	0/151	0.0	0/151	0.0

Abbreviations: AE, adverse event; SAE, serious adverse event

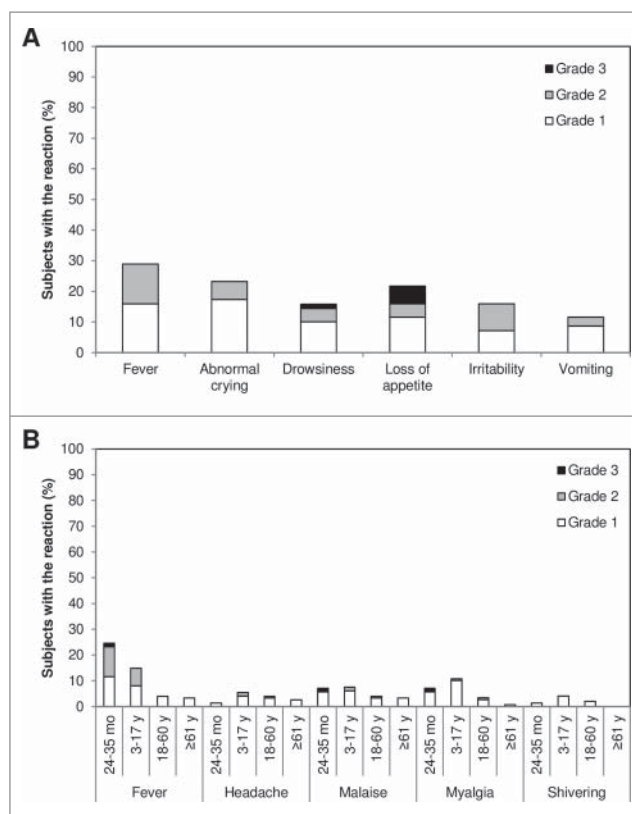


Figure 3. Frequency and severity of solicited systemic reactions by age group (A) Subjects 6–23 months of age. (B) Subjects ≥ 2 y of age.

groups had vaccine-related AEs, and none of the vaccine-related events were considered serious.

Unsolicited AEs led to discontinuation of the study for 14 subjects in the 6–35 month age group (12 subjects post-dose 1 and 2 subjects post-dose 2). None of the subjects in the other age groups discontinued because of an AE.

Immediate unsolicited AEs

Two subjects in the 6–35 month age group had immediate unsolicited AEs (within 30 min of vaccination). This included one subject who had a grade 3 cutaneous anaphylactic reaction

on the face and finger that lasted 24 days, was treated by medication, and led to discontinuation of the study. The other subject had mild abnormal crying that lasted 2 d and resolved spontaneously. Both of these events were considered to be related to the vaccination.

Discussion

This study, conducted at the request of the China Food and Drug Administration, showed that the 2014–2015 Northern Hemisphere formulation of Shz-IIV3 was highly immunogenic and well-tolerated in individuals ≥ 6 months of age. Post-vaccination seroprotection rates were at least 88% for all strains in all age groups, and seroconversion/significant increase rates were at least 78% for all strains in all age groups, except for the H3N2 strain in subjects 3–17 years, for whom the rate was 56%. This is similar to the seroprotection and seroconversion rates reported for Vaxigrip.¹³ For subjects ≥ 18 y of age, CHMP criteria were met for all 3 vaccine strains.

In this study, immunogenicity was assessed by measuring HAI titers, and seroprotection estimated using the standard definition of a HAI titer $\geq 1:40$. This value of this threshold and of specific correlates of protection based on serological responses continue to be debated.¹⁵ Accordingly, a specific threshold for estimating protection based on HAI titers is not included in the updated CHMP guidelines that became available in 2016.¹⁶ These issues, however, do not change the fact that IIV3 appeared highly immunogenic in all age groups.

Seroconversion/significant increase rates were at least 78% for all strains in all age groups, but the rate was only 56% for the H3N2 strain in subjects 3–17 y. This was due to high baseline titers against this strain—78% had a baseline HAI titer $\geq 1:40$ and the geometric mean ratio of post- to pre-vaccination HAI titer was only 3.80. In all other cases, less than 40% had a baseline HAI titer $\geq 1:40$ and geometric mean titer ratios were above 10. Because none of the subjects were vaccinated the previous year (2013–2014) for seasonal influenza, the high baseline titers for the H3N2 strain in subjects 3–17 y were probably due to exposure to this strain from a natural infection during a previous year.

Vaccine responses in older adults are typically lower than in younger adults due to aging of the immune system, commonly referred to as immunosenescence.¹⁷ This decrease in HAI titers with age can be seen for the A/H1N1 and B strains. The immune response for the A/H3N2 strain, on the other hand, decreased little with age. In all cases, however, seroprotection and seroconversion rates remained relatively high in the oldest subjects and immunosenescence appeared to have only a moderate effect on immunogenicity. This was most likely because none of the subjects were vaccinated for seasonal influenza the previous year.

Overall, the vaccine was well-tolerated with no unexpected events or new safety signals. As found in other studies of influenza vaccines,^{12,18} reactogenicity and rates of unsolicited AEs were highest in the youngest participants, and the most common solicited reactions were pain/tenderness at the injection site and fever. Fever is known to be associated with trivalent inactivated influenza vaccines but is not considered to be serious and is not associated with complications.¹⁹ One subject

24–35 months of age had an immediate cutaneous anaphylactic reaction on the face and finger after a first vaccination. Such immediate allergic reactions are rare and can be triggered by the hemagglutinin antigens themselves or other vaccine components.²⁰

A recent analysis found that the economic burden of influenza-associated outpatient and inpatient visits in mainland China is substantial.²¹ The average total costs were estimated at \$155 US for influenza-associated outpatient visits and \$1511 for influenza-associated inpatient visits. Costs were highest for children under 5 y of age, adults over 60 y of age, and individuals with underlying medical conditions. Results from other countries^{22,23} suggest that vaccination for seasonal influenza will be cost-effective or cost-saving in China, at least for these groups, although comprehensive cost-effectiveness studies have not yet been reported for mainland China. At the same time, influenza vaccination coverage rates in China remain very low, with overall national rates around 10%.^{24–27} Increasing influenza vaccination rates, using Shz-IIV3 or other seasonal influenza vaccines, would help to further reduce the significant burden of seasonal influenza in China.

Patients and methods

Study design and conduct

This was a phase IV, open-label, descriptive, single-arm study in healthy subjects ≥ 6 months of age conducted at a single center in the Province of Guangxi, China between September and December, 2014 (NCT02228980). The study was conducted to comply with a request from the China Food and Drug Administration. The objective was to describe the immunogenicity and safety of a single dose (subjects ≥ 3 y of age) or 2 doses (subjects 6–35 months of age) of Shz-IIV3. The study was approved by the Guangxi Institutional Review Board before the start of the trial, conducted according to the Declaration of Helsinki, and complied with the International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was obtained from subjects or their legal representatives.

Subjects

The study included subjects ≥ 6 months of age. Subjects aged 6–35 months of age had to have been born at full term of pregnancy (≥ 37 weeks) at a birth weight ≥ 2.5 kg, and they could not have had a previous vaccination against influenza (2 consecutive doses of influenza vaccine having the same seasonal strain composition) any time before study enrollment or have a history of prior exposure to influenza virus through natural infection. Subjects 3–8 y of age had to have previously received at least one dose of influenza vaccine or had to have had a history of prior exposure to influenza virus through natural infection. Subjects were excluded if they had received or planned to receive any vaccine within 2 weeks before the first trial vaccination or 2 weeks after the last trial vaccination; were vaccinated against influenza within the 6 months before the first trial vaccination or planned to receive a non-study influenza vaccine during the study; had received immune globulins, blood, or

Table 3. Grading of solicited reactions according to the China Food and Drug Administration scale.

Solicited reaction	Age group	Grade 1	Grade 2	Grade 3
Injection-site Tenderness	6–23 mo	Minor reaction when injection site is touched	Cries or protests when injection site is touched	Cries when injected limb is moved or movement of the injected limb is reduced
Pain	2–11 y	Easily tolerated	Sufficiently discomforting to interfere with normal behavior or activities	Incapacitating, unable to perform usual activities
	≥ 12 y	No interference with activity	Some interference with activity	Significant, prevents daily activity
Erythema, swelling, induration, ecchymosis	All	>0 to <15 mm	≥ 15 to ≤ 30 mm	>30 mm
Systemic Fever	All	≥ 37.1°C to ≤ 37.5°C	>37.5°C to ≤ 39°C	>39°C
Vomiting	6–23 mo	1 episode/24 h	2–5 episodes/24 h	≥ 6 episodes/24 h
Abnormal crying	6–23 mo	<1 h	1–3 h	>3 h
Drowsiness	6–23 mo	Sleepier than usual or less interested in surroundings	Not interested in surroundings or did not wake up for a feed/meal	Sleeping most of the time or difficult to wake
Loss of appetite	6–23 mo	Eating less than normal	Missed 1 or 2 feeds/meals completely	Refuses ≥ 3 feeds/meals or refuses most feeds/meals
Irritability	6–23 mo	Easily consolable	Requiring increased attention	Inconsolable
Headache, malaise, myalgia, shivering	≥ 2 y	No interference with activity	Some interference with activity	Significant, prevents daily activity

blood-derived products in the past 3 months that could interfere with assessment of the immune response; had a known or suspected congenital or acquired immunodeficiency or had received immunosuppressive therapy within the preceding 6 months; had received long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months); had thrombocytopenia, a bleeding disorder, or had received anticoagulants in the preceding 3 weeks; had known systemic hypersensitivity to eggs or to any of the vaccine ingredients; or were pregnant.

Vaccination

Shz-IIV3 was a trivalent split virion, inactivated influenza vaccine formulated for the 2014–2015 Northern Hemisphere influenza season. The vaccine was provided in pre-filled syringes of 0.25 ml (half dose containing 7.5 µg hemagglutinin per strain) or 0.5 ml (full dose containing 15 µg hemagglutinin per strain) of A/California/7/2009 (H1N1)pdm09, A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012. Shz-IIV3 does not contain thimerosal, preservatives, hydrocortisone, or adjuvants. Infants (6–12 months of age) were vaccinated by intramuscular injection in the anterolateral aspect of the thigh. All other subjects were vaccinated by intramuscular injection in the deltoid muscle. Subjects 6–35 months of age received 2 half-doses (0.25 ml) of Shz-IIV3 28 d apart. All other subjects received one full dose (0.5 ml).

Immunogenicity assessments

Immunogenicity was described in all age groups according to the recommendations of the CHMP Note for Guidance on Harmonization of Requirements for Influenza Vaccines.²⁸ Anti-hemagglutinin antibody levels were measured by HAI assay before vaccination (day 0) and 28 d after the last vaccination by the National Institutes for Food and Drug Control in China. Immunogenicity endpoints included HAI titer, post-

vaccination/pre-vaccination HAI titer ratio, seroprotection, and seroconversion/significant increase. Seroprotection was defined as a HAI titer ≥ 1:40; seroconversion as a pre-vaccination HAI titer <1:10 and a post-vaccination titer ≥ 1:40; and a significant increase as a pre-vaccination HAI titer ≥ 1:10 and ≥ 4-fold increase in post- vs. pre-vaccination HAI titer. In addition, the immunogenicity vs. all 3 vaccine strains was assessed according to the CHMP Note for Guidance criteria.²⁸ Specifically, for subjects 18–60 y of age, the criteria include a rate of seroconversion or significant increase in post-vaccination HAI titer >40%, a mean geometric increase in HAI titer between pre- and post-vaccination >2.5, and a rate of post-vaccination seroprotection >70%; for subjects ≥ 61 y of age, the criteria include a rate of seroconversion or significant increase in post-vaccination HAI titer >30%, a mean geometric increase in HAI titer between pre- and post-vaccination >2, and a rate of post-vaccination seroprotection >60%

Safety and tolerability

Safety was assessed according to International Conference on Harmonization E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.²⁹ Subjects or their parents or legal representatives recorded information about solicited reactions in a diary card for up to 7 d after each vaccination, about unsolicited AEs up to 28 d after each vaccination, and about SAEs throughout the trial. Solicited injection-site reactions included tenderness (6–23 months), pain (≥ 2 years), erythema, swelling, induration, and ecchymosis. Solicited systemic reactions included fever, vomiting, abnormal crying, drowsiness, loss of appetite, and irritability for subjects 6–23 months of age; and fever, headache, malaise, myalgia, shivering for subjects ≥ 2 y of age. The intensity of solicited reactions was graded as mild (1), moderate (2), or severe (3) according to the China Food and Drug Administration scale (Table 3). SAEs were collected by investigators throughout the trial. Immediate unsolicited AEs were defined

as those occurring within 30 min following vaccination. Investigators assessed unsolicited AEs and SAEs as unrelated or possibly related to the vaccination.

Sample size

As required by the China Food and Drug Administration, the sample size was set to have 500 evaluable subjects for safety evaluation at the end of the assessment period. Assuming that 17% of subjects would not be assessable, 600 subjects were enrolled (150 subjects in each group) to ensure that this sample size was met. For the 150 subjects 3–17 y of age, enrollment was stratified so that 75 subjects 3–8 y of age and 75 subjects 9–17 y of age would be enrolled. With 500 evaluable subjects overall, there was a 95% probability of observing an event that had a true incidence of 0.6%, and with 125 evaluable subjects in each age group (150 subjects enrolled), there was a 95% probability of observing an event that had an incidence of 2.4%.

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Missing data were not replaced and no search for outliers was performed. All analyses were descriptive. Immunogenicity was analyzed in all eligible subjects who were vaccinated according to protocol and who had valid serology results. Safety was analyzed in all subjects who received the study vaccine. Confidence intervals for single proportions were calculated using the exact binomial method (Clopper-Pearson method). Geometric mean HAI titers, geometric mean post-vaccination/pre-vaccination HAI titer ratios, and their 95% confidence intervals were calculated assuming that \log_{10} transformation of the titers followed a normal distribution.

Abbreviations

AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
HAI	hemagglutination inhibition titer
SAE	serious adverse event
Shz-IIIV3	bio-comparative split-virion inactivated trivalent influenza vaccine produced by Sanofi Pasteur's affiliate in China

Disclosure of potential conflicts of interest

X. Liao, K. Go, and N. Lavis are employees of Sanofi Pasteur. The other authors declare no conflicts of interest.

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