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SHORT REPORT

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Safety of a quadrivalent influenza vaccine in Vietnamese healthy subjects aged 6 months and older

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ABSTRACT

Quadrivalent influenza vaccines (QIVs) provide protection against the two influenza A viruses (H1N1 and H3N2) and both co-circulating influenza B lineages. QIVs have been found safe, immunogenic, and efficacious in several phase III clinical trials. Here we assess the safety of QIV after vaccination in Vietnamese infants, children, and adults. Participants (n = 228) were asked to report any solicited adverse events (AEs) occurring within 7 days, unsolicited non-serious AEs occurring within 28 days post-vaccination, and serious adverse events (SAEs) at any time during the study. The study was completed by 224 participants (97.4%). Thirty-one children (39.7%) aged 6 – 35 months, 32 children (40.0%) aged 3 – 8 years, 2 participants (9.0%) aged 9 – 17 years, 5 participants (17.9%) aged 18 – 60 years, and 3 participants (15.0%) aged ≥60 years reported ≥1 solicited reaction within 7 days following vaccination. The most frequent-solicited AEs were injection-site tenderness or pain, appetite loss, fever, and abnormal crying in 6 – 35 month-olds, and fever, headache, and myalgia in other age groups. No severe-unsolicited AEs or vaccine-related SAEs were reported. These results suggest that QIV is well tolerated across age groups in Vietnam, and can be safely used to protect the Vietnamese population against influenza and its potentially serious complications.

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Influenza vaccine; seasonal influenza; clinical trial; adverse reaction; adverse event; Vietnam

Influenza is a highly contagious, acute respiratory disease caused by influenza viruses that infect the nose, throat, and lungs.[1] Influenza type A and B viruses are the predominant virus types that cause disease in humans.[1,2] Vaccination is the most effective method of controlling seasonal influenza outbreaks and is recommended by the World Health Organization for at-risk populations.[1,2] Trivalent influenza vaccines (TIVs), which contain inactivated strains of two A viruses (H1N1 and H3N2) and a single B virus (either B/Victoria or B/Yamagata lineage) were used to provide coverage against influenza.[3] However, the two antigenically distinct B lineages, B/Victoria and B/Yamagata, co-circulate globally, making it difficult to predict which lineage should be used in the trivalent formulation. This complication led to the development of quadrivalent influenza vaccines (QIVs), which contain a second B virus strain to provide simultaneous protection against both co-circulating B-lineages.[4] QIV has been found to be immunogenic and efficacious in several phase III trials in infants, children, and adults, with similar reactogenicity and safety to TIV despite the inclusion of the additional B strain.[5-7]

Vietnam is a country of 97 million people[8] and is without a steady supply of influenza vaccine.[9] Influenza A and B viruses co-circulate throughout the year in Vietnam,[10,11] and the country is a hotspot for the evolution of new seasonal strains and zoonotic variants with pandemic potential due to an abundance of poultry farming, dense human population, and other topographical features.[12,13] TIV is the most frequently used influenza vaccine in Vietnam, and a locally produced TIV is available as part of a recent government initiative to prevent influenza transmission.[9] However, both B/Yamagata and B/Victoria lineages have circulated in Vietnam in recent years, and the B lineage in the TIV was mismatched with the predominant B lineage in circulation in 2007, 2009, and 2014.[14] Introducing QIV in Vietnam could therefore improve protection against influenza against both B lineages circulating in the country.

The objective of this study was to assess the safety of QIV in individuals aged 6 months and older in Vietnam. This was an open-label, single-arm, single-center, safety assessment study conducted between 15 January and 17 March, 2019 in Viet Tri City, Phu Tho province, Vietnam, under the management of the Center for Clinical Trials, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam (WHO Universal Trial Number: U1111-1183-6274; EudraCT Number: 2019–00221838; and ClinicalTrials.gov: NCT03765437). Participants aged ≥9 years received one 0.5-mL dose of QIV (VaxigripTetra™, Sanofi Pasteur) intramuscularly. Participants aged 6 months to 8 years were vaccinated with one 0.5-mL dose if they had previously received ≥2 doses of an influenza vaccine since birth (not required to be received during the same season or consecutive seasons), or with two 0.5-mL doses 28 days apart if not. The vaccine dose was administered intramuscularly or deep subcutaneously into the

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deltoid muscle of the upper arm in participants aged ≥3 years, and either into the deltoid muscle of the upper arm or into the anterolateral area of the thigh in children aged 6 – 35 months. Diary cards were provided to the participants, or their parents or legal guardians, to report any solicited injection-site reactions or systemic reactions occurring within 7 days of post-vaccination, unsolicited non-serious AEs in the first 28 days of post-vaccination, and SAEs (including Adverse Events of Special Interest [AESIs]) at any time during the study. Investigators assessed whether the unsolicited local and systemic AEs were vaccine-related. Investigators also recorded any immediate unsolicited systemic AEs occurring in the 30 minutes following vaccine administration.

The study included 230 subjects: 79 participants aged 6 – 35 months, 81 participants aged 3 – 8 years, 22 participants aged 9 – 17 years, 28 participants aged 18 – 60 years, and 20 participants aged >60 years. Of the 230 individuals, 228 participants were included in the safety analysis (one child aged 6 – 35 months met the exclusion criteria, and one child aged 3 – 8 years was withdrawn from the study before the first vaccine injection), and 224 (97.4%) completed the study (Supplemental Table 1). Six participants did not complete the study: one child aged 3 – 8 years withdrew due to an SAE unrelated to the vaccine (hospitalized due to multiple injuries from a car accident); five children (two children aged 6 – 35 months, and three children aged 3 – 8 years) were withdrawn voluntarily.

All age groups had more female than male participants, except the age groups 3 – 8 years and 9 – 17 years, which had more male than female participants. Forty-three (54.4%) children aged 6 – 35 months and 40 (49.4%) children aged 3 – 8 years were previously vaccinated (Supplemental Table 1). Most vaccinated children aged 6 – 35 months (97.7%) and 3 – 8 years (100%) received one QIV injection; and most unvaccinated children aged 6 – 35 months (97.2%) and 3 – 8 years (92.7%) received two vaccine injections as planned.

Thirty-one children (39.7%) aged 6 – 35 months, 32 children (40.0%) aged 3 – 8 years, 2 participants (9.1%) aged 9 – 17 years, 5 participants (17.9%) aged 18 – 60 years, and 3 participants (15.0%) aged ≥60 years reported ≥1 solicited reaction within 7 days following any vaccine dose. Twenty-five children (32.1%) aged 6 – 35 months, 31 children (38.8%) aged 3 – 8 years, 2 participants (9.1%) aged 9 – 17 years, 5 participants (17.9%) aged 18 – 60 years, and 2 participants (10.0%) aged ≥60 years reported at least one injection-site reaction. Seventeen children (21.8%) aged 6 – 35 months, 9 children (11.3%) aged 3 – 8 years, 2 participants (7.1%) aged 18 – 60 years, and 2 participants (10.0%) aged ≥60 years reported at least one systemic reaction (Table 1).

Table 1. Safety overview.

Subjects experiencing ≥1:	6– 35 months (N = 78)		3– 8 years (N = 80)		9– 17 years (N = 22)		18– 60 years (N = 28)		>60 years (N = 20)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Immediate unsolicited AE	0	0.0 (0, 4.6)	0	0.0 (0, 4.5)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0 (0, 16.8)
Vaccine-related	0	0.0 (0, 4.6)	0	0.0 (0, 4.5)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0 (0, 16.8)
Any solicited reaction	31	39.7 (28.8, 51.5)	32	40.0 (29.2, 51.6)	2	9.1 (1.1, 29.2)	5	17.9 (6.1, 36.9)	3	15.0 (3.2, 37.9)
Grade 3	2	2.6 (0.3, 9.0)	2	2.5 (0.3, 8.7)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0 (0, 16.8)
Any solicited injection site reaction	25	32.1 (21.9, 43.6)	31	38.8 (28.1, 50.3)	2	9.1 (1.1, 29.2)	5	17.9 (6.1, 36.9)	2	10.0 (1.2, 31.7)
Grade 3	0	0.0 (0, 4.6)	0	0.0 (0, 4.5)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0 (0, 16.8)
Any solicited systemic reaction	17	21.8 (13.2, 32.6)	9	11.3 (5.3, 20.3)	0	0.0 (0, 15.4)	2	7.1 (0.9, 23.5)	2	10.0 (1.2, 31.7)
Grade 3	2	2.6 (0.3, 9.0)	2	2.5 (0.3, 8.7)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0 (0, 16.8)
Unsolicited AE*	26	33.3 (23.1, 44.9)	5	6.3 (2.1, 14.0)	0	0.0 (0, 15.4)	1	3.6 (0.1, 18.3)	0	0.0 (0, 16.8)
Unsolicited AR	0	0.0 (0, 4.6)	0	0.0 (0, 4.5)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
AE leading to discontinuation	0	0.0 (0, 4.6)	1	1.3 (0, 6.8)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
SAE	0	0.0 (0, 4.6)	1	1.3 (0, 6.8)		0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Grade 3	0	0.0 (0, 4.6)	1	1.3 (0, 6.8)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Death	0	0.0 (0, 4.6)	0	0.0 (0, 4.5)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)

This was an open-label, single-arm, single-center, safety assessment study conducted between 15 January and 17 March, 2019 at the request of the Drug Administration of Vietnam. Participants had to be aged 6 months or older. All children less than 2 years enrolled in the study had to be born at full term of pregnancy (≥37 weeks) or with a birth weight ≥2.5 kg. Details of ethics and informed consent, exclusion criteria, vaccine formulation, and calculation of study size are provided in the **Supplemental materials**. Previously unvaccinated children aged 6 months to 8 years received two 0.5 mL doses of QIV given 28 days apart. Previously vaccinated children and participants ≥9 years of age received one 0.5 mL dose of QIV. Children aged 6 – 35 months received vaccination into either the upper arm or thigh, and participants aged ≥3 years received vaccination into the upper arm. Safety was assessed in all participants who received at least one dose of vaccine. All statistical analyses were descriptive; 95% confidence intervals (CIs) were calculated using the Clopper Pearson method of exact binomial distribution for percentage.

Abbreviations: AE, adverse event; AR, adverse reaction; CI, confidence interval; SAE, serious adverse event

* Four children in aged 3 –8 years experienced unsolicited non-serious systemic AEs

Across age groups, injection-site tenderness or pain was the most frequently reported injection-site reaction (Table 2). The frequencies of these adverse reactions were lower in children aged 3 – 8 years (32.5%) compared to previous clinical trials (62.4%).[6] This trend was considered non-significant due to the small size of the study. Among children aged 6 – 35 months, injection-site tenderness or pain were generally more frequent after the first vaccine dose than after the second dose (26.9% vs 8.6%) (Supplemental Table 2). Erythema also tended to be more frequent after the first dose in children 6 – 35 months and 3 – 8 years. Similar to previous studies of QIV,[6,7,16] all solicited injection-site reactions were mild or moderate (grade 1 or 2) in intensity, started within 3 days after vaccine injection, and lasted 1 – 3 days and there was a trend of lower incidence of adverse reactions after the second injection compared to the first one in children aged 6 – 35 months.

The most common solicited systemic reactions included appetite loss, fever, and abnormal crying in 6 – 35 month-olds; fever, headache, and myalgia in participants aged ≥3 years (Table 2). No differences were seen between the first and the second vaccine dose in children (Supplemental Table 2). No severe (grade 3) systemic reactions were reported in participants aged ≥9 years. Consistent with previous QIV studies,[6,7,16] most systemic reactions were mild or moderate (grade 1 or 2) in intensity, started within 7 days after vaccine injection, and lasted 1 – 7 days. In previously unvaccinated children, four severe (grade 3) solicited systemic reactions were reported within 7 days after the first vaccine injection: two children aged 6 – 35 months and two children aged 3 – 8 years experienced high fever (39.5°C to 39.7°C) after the first vaccine injection. No severe solicited systemic reactions were observed after the second vaccine injection (Table 1 and Supplemental Table 2). None of the participants experienced severe (grade 3) solicited injection-site reactions.

None of the participants experienced any immediate unsolicited systemic AEs, vaccine-related unsolicited AEs, or AESIs during the study. Twenty-six children (33.3%) aged 6 – 35 months, four children (5.0%) aged 3 – 8 years, and one participant (3.6%) aged 18 – 60 years experienced one or more unsolicited non-serious systemic AEs (Table 1). Thirteen participants experienced nasopharyngitis (16.7%), the most common unsolicited non-serious AE, and six participants experienced pharyngitis (7.7%). One child aged 3 – 8 years reported an SAE that led to study discontinuation (multiple injuries due to a car accident); this was considered unrelated to the vaccine.

This study provides safety data for QIV in Vietnamese population. Although these findings are limited, they are consistent with clinical trials of QIV that showed this vaccine to be

Table 2. Solicited injection site and systemic reactions within 7 days of any vaccination.

Subjects experiencing ≥1:	6– 35 months (N = 78)		3– 8 years (N = 80)		9– 17 years (N = 22)		18– 60 years (N = 28)		>60 years (N = 20)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Injection-site reactions	25	32.1 (21.9, 43.6)	31	38.8 (28.1, 50.3)	2	9.1 (1.1, 29.2)	5	17.9 (6.1, 36.9)	2	10.0 (1.2, 31.7)
Tenderness or Pain	22	28.2 (18.6, 39.5)	26	32.5 (22.4, 43.9)	2	9.1 (1.1, 29.2)	5	17.9 (6.1, 36.9)	1	5.0 (0.1, 24.9)
Erythema	7	9.0 (3.7, 17.6)	8	10.0 (4.4, 18.8)	0	9.1 (1.1, 29.2)	0	0.0 (0, 12.3)	1	5.0 (0.1, 24.9)
Swelling	0	0.0 (0, 4.6)	4	5.0 (1.4, 12.3)	0	9.1 (1.1, 29.2)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Induration	0	0.0 (0, 4.6)	5	6.3 (2.1, 14.0)	0	9.1 (1.1, 29.2)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Ecchymosis	0	0.0 (0, 4.6)	3	3.8 (0.8, 10.6)	0	9.1 (1.1, 29.2)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Systemic reactions[a]	17	21.8 (13.2, 32.6)	9	11.3 (5.3, 20.3)	0	0.0 (0, 15.4)	2	7.1 (0.9, 23.5)	2	10 (1.2, 31.7)
Fever	7	9.0 (3.7, 17.6)	4	5 (1.4, 12.3)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Headache	2	5.9 (0.7, 19.7)	4	5 (1.4, 12.3)	0	0.0 (0, 15.4)	1	3.6 (0.1, 18.3)	1	5 (0.1, 24.9)
Malaise	2	5.9 (0.7, 19.7)	3	3.8 (0.8, 10.6)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Myalgia	0	0.0 (0, 10.3)	4	5 (1.4, 12.3)	0	0.0 (0, 15.4)	1	3.6 (0.1, 18.3)	1	5 (0.1, 24.9)
Shivering	0	0.0 (0, 10.3)	1	1.3 (0, 0.8)	0	0.0 (0, 15.4)	0	0.0 (0, 12.3)	0	0.0 (0, 16.8)
Vomiting	2	4.5 (0.6, 15.5)	0	–	0	–	0	–	0	–
Crying abnormally	5	11.4 (3.8, 24.6)	0	–	0	–	0	–	0	–
Drowsiness	2	4.5 (0.6, 15.5)	0	–	0	–	0	–	0	–
Appetite loss	6	13.6 (5.2, 27.4)	0	–	0	–	0	–	0	–
Irritability	2	4.5 (0.6, 15.5)	0	–	0	–	0	–	0	–

Safety was assessed in all study participants who received the vaccine. AEs were defined according to the International Conference on Harmonization E2A guideline for Clinical Safety Data Management and Definitions and Standards for Expedited Reporting.[16] Abbreviations: AE, adverse event; AR, adverse reaction; CI, confidence interval; SAE, serious adverse event

[a]Headache, malaise, myalgia, and shivering were assessed only in participants ≥24 months of age. Vomiting, crying abnormally, drowsiness, appetite loss, and irritability were assessed only in children ≤23 months of age. Fever was assessed in all participants.

safe in all populations.[5-7,16] QIV was well tolerated by all age groups, and the observed solicited injection site and systemic reactions are consistent with the frequencies observed in other populations.[5-7,16] One limitation of this study could be the relatively small size of the study population, especially in older adults aged >60 years (N = 20) for whom annual influenza vaccination is recommended.[2] However, the safety profile for the elderly population is expected to be consistent, as for other age groups, with phase III studies of QIV in which this study population is well represented.[5-7,16] As this is a single-center, open-label trial, reporting of AEs may not be sufficiently representative of the actual safety profile, and rare adverse events may not be addressed adequately due to the small sample size. However, larger safety studies for QIV have been conducted globally for initial vaccine registration and the safety profile of QIV is consistent with these other studies. Further, QIV is increasingly replacing TIV worldwide as the standard seasonal influenza vaccine. This study showed that QIV is well tolerated by individuals aged 6 months and older, suggesting that this vaccine is safe for use in Vietnamese population as well.

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Disclosure of potential conflicts of interest

M.S. was employed by Sanofi Pasteur at the time of this study and is currently employed by Takeda Pharmaceuticals International. A.L.C, M.F, and N.L are employees of Sanofi Pasteur. N.D.Q, V.H.H and V.D.T are employed by the National Institute of Hygiene and Epidemiology.

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