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ORIGINAL RESEARCH ARTICLE

An 8-Year Prospective, Observational, Multi-centre Post-Marketing Safety Surveillance Study Conducted in South Korea (2014–2022) Following the Introduction of GSK's Inactivated Quadrivalent Seasonal Influenza Vaccine (*Fluarix Tetra*) for Subjects Aged 6 Months and Older

Gaël Dos Santos[1] · **Raghavendra Devadiga**[2] · **Chun Soo Kim**[3] · **Joon Bang**[4]

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Abstract

Introduction Seasonal influenza is associated with substantial public health burden. The objective of this study was to assess the safety of inactivated quadrivalent seasonal influenza vaccine (IIV4, *Fluarix Tetra*, GSK, Belgium) in subjects aged ≥ 6 months in Korea.

Methods This prospective, observational, non-comparative, multi-centre post-marketing surveillance study was conducted in Korea in subjects aged ≥ 3 years for 6 years (2014–2020) and extended to subjects aged 6–35 months for 4 years (2018–2022). Subjects received IIV4 in routine clinical practice according to local prescribing information. Adverse events (AEs) were recorded over 21 days post-vaccination.

Results The group aged ≥ 3 years included 701 subjects (mean 31.97 years, range 3–86 years, 46.36% male), and the group aged 6–35 months included 687 subjects (mean 16.31 months, 47.02% male). In the group aged ≥ 3 years, 98 subjects (13.98%) reported 140 AEs, of which 42 events in 34 subjects (4.85%) were adverse reactions to vaccine (ARVs). Most of the ARVs were expected, mainly administration site reactions. There were seven mild unexpected ARVs. In the group aged 6–35 months, 248 AEs were reported in 149/687 subjects (21.69%). ARVs were reported in 25/687 subjects (3.64%, 29 events); one was considered unexpected. There were five serious AEs overall, none of which were considered related.

Conclusion No safety concerns were found during this surveillance study of IIV4 in subjects aged ≥ 6 months in Korea. The findings of this study suggest IIV4 is safe and well tolerated for use in all age groups with a vaccine indication.

✉ Gaël Dos Santos
gael.x.dossantos@gmail.com

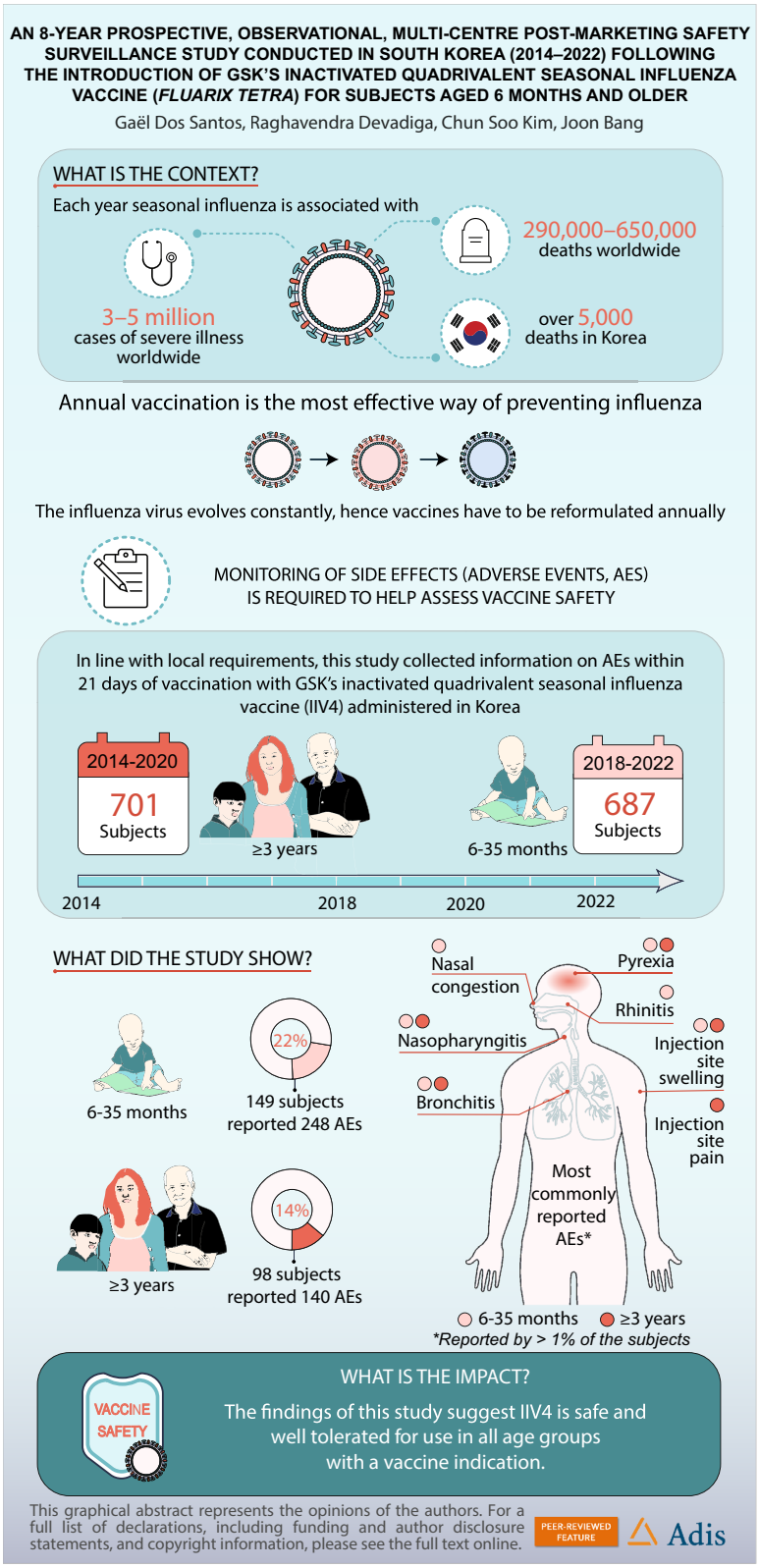
1 GSK, Wavre, Belgium

2 GSK, Bangalore, India

3 Department of Pediatrics, Keimyung University School of Medicine, Daegu, South Korea

4 GSK, Seoul, South Korea

Graphical Abstract



Plain Language Summary

Seasonal influenza is associated with over 5000 deaths annually in Korea, mainly in older adults. Annual vaccination is the most effective way of preventing seasonal influenza. The influenza virus strains in the vaccine are updated each year as the strains circulating change constantly. Monitoring of any unwanted medical incidents (adverse events) after vaccination is required to help assess vaccine safety. In this study, we monitored adverse events reported within 21 days of administration of *Fluarix Tetra* seasonal influenza vaccine (IIV4) in participants aged 6 months and older in Korea over a period of 4–6 years. Of the participants aged ≥ 3 years, 98 (14%) reported 140 adverse events, most commonly infections and infestations (most commonly nasopharyngitis such as the common cold), or general disorders and administration site conditions (most commonly pain or swelling at the injection site). In the participants aged 6–35 months, 149 (22%) reported 248 adverse events, also most commonly infections and infestations (such as the common cold) or general disorders and administration site conditions (most commonly fever or swelling at the injection site). There were five serious adverse events in total (adverse events that are life threatening or require hospitalization), but none of them were related to IIV4. In this study, we did not find any safety concerns for IIV4 in participants aged ≥ 6 months in Korea. The findings of this study suggest IIV4 is safe and well tolerated in all age groups with a vaccine indication.

Key Points

This study assessed safety within 21 days of GSK's seasonal influenza vaccine in subjects from 6 months onwards in Korea.

In Korean subjects, GSK's influenza vaccine was safe and well tolerated.

1 Introduction

Seasonal influenza is associated with a substantial public health burden, with an estimated 3–5 million cases of severe illness and 290,000–650,000 respiratory deaths worldwide each year [1]. Most influenza deaths in industrialised countries occur in the population aged 65 years or older; for example, in the European Union (EU), 88% of respiratory deaths associated with seasonal influenza occurred in this age group, and mortality was approximately 35 times higher than in the group aged < 65 years [2]. In an analysis using data from 33 countries, the influenza-associated excess mortality rate was estimated at 0.1–6.4 per 100,000 individuals in the group aged < 65 years, 2.9–44.0 per 100,000 for the group aged 65–74 years and 17.9–223.5 per 100,000 for the group aged 75 years or older [3]. In the World Health Organization (WHO) Western Pacific region, the rates were 0.4–1.7 per 100,000, 7.4–27.7 per 100,000 and 45.3–133.2 per 100,000, respectively [3]. In Korea, during the 2013–2014 influenza season, the estimated incidence of laboratory-confirmed influenza-related hospitalisation was 57.9 per 100,000 adults aged 20 years or older, and the estimated incidence of laboratory-confirmed influenza-related death was 3.1 per 100,000 adults [4]. As many influenza cases are not laboratory confirmed, the real burden is expected to be underestimated [4]. An analysis of national mortality data and laboratory surveillance data for the period 2009–2016 estimated that there were 5313 influenza-associated deaths per year in Korea over that period, with mortality rates of 10.59 per 100,000 population and 74.12 per 100,000 population aged ≥ 65 years [5].

The most effective way to prevent seasonal influenza is through vaccination, and WHO recommends annual vaccination for pregnant women, children aged 6 months–5 years, older adults aged 65 years or older, people with chronic medical conditions and healthcare workers [1]. Influenza vaccines are typically either trivalent, containing two influenza A virus strains and one influenza virus B lineage, or quadrivalent, containing two influenza A virus strains and both influenza virus B lineages. Quadrivalent influenza vaccines (QIVs) contain both influenza B lineages, potentially providing more stable vaccine effectiveness, and are now recommended by some health authorities [6].

The influenza virus constantly evolves through antigenic drift and shift [7]. Seasonal influenza vaccines, therefore, uniquely, are regularly reformulated in advance of each influenza season to maintain effectiveness [8]. The WHO regularly issues updated recommended influenza vaccine compositions [9]. The frequent updates of influenza vaccine composition in response to the changing influenza virus indicates a need for benefit–risk monitoring of seasonal influenza vaccines. Regularly monitoring for adverse events (AEs) experienced after vaccination is an important component of routine pharmacovigilance and vaccine safety assessments.

GSK's inactivated quadrivalent seasonal influenza vaccine (IIV4), *Fluarix Tetra*, was registered in Korea in December 2014, indicated for the population aged 3 years and older. In line with Korean Ministry of Food and Drug Safety (MFDS) requirements, this drug use investigation as a part of post-marketing surveillance (PMS) was conducted to collect safety information on the use of IIV4 over a period of 6 years. In response to the extension of the age indication for

IIV4 to include the population aged 6–35 months, additional drug use investigation for this new age group was conducted to collect safety information on the use of IIV4 for a period of 4 years according to the MFDS requirement.

The objective of this prospective, observational, non-comparative, multi-centre PMS study was to assess the safety of IIV4 pre-filled syringe, in terms of frequency and intensity of AEs and serious AEs (SAEs), when administered according to the local prescribing information (PI) in Korea in adults and children aged 3 years and above and in infants and children aged 6–35 months. To meet the requirement of the MFDS requesting that at least 600 subjects are followed after IIV4 administration according to the approved PI in Korea, around 720 subjects in each study group (aged 3 years or more, and aged 6–35 months) were intended to be enrolled, with safety information collected within 21 days (day 0–20) post-vaccination.

2 Methods

2.1 Purpose of Surveillance

This surveillance study was conducted to investigate the frequency and severity of AEs, adverse reactions to vaccine (ARVs), SAEs and serious ARVs (SARVs) occurring within 21 days of administration of IIV4 in individuals aged 6 months or older in Korea, and to explore factors that might affect safety in individuals receiving this vaccine.

2.2 Study Design and Population

The study design is summarised in Fig. 1. This was a prospective, observational, non-comparative, multi-centre study conducted in hospitals and private clinics in Korea. Subjects were included if they received IIV4 in routine clinical practice according to the local PI. The initial study included subjects aged 3 years or older and was conducted between 26 December 2014 and 25 December 2020 (6 years) at five hospitals and five clinics. The study was extended to include a second study group of infants and children aged 6 months to < 3 years, investigated between 27 April 2018 and 26 April 2022 (4 years) at two hospitals and 12 clinics. Pregnant or lactating women could receive IIV4 according to the PI if there was a clear need.

For adults and previously vaccinated children aged 6 months or older, IIV4 was administered as a single dose and, for previously unvaccinated children aged 6 months to 9 years, two doses were administered with the second dose at least 4 weeks after the first. The IIV4 vaccination was not part of the investigation. Administration of other vaccines and medications were allowed in the study and recorded.

In addition to the safety assessments, data were also collected on subjects' demographic characteristics, medical history, vaccination history, concomitant medications, concomitant vaccinations, and the presence of hepatic and renal disorders. Concomitant medications were categorised using the Korean index of medical specialties (KIMS), and concomitant vaccinations using WHODrug 2020-1Q.

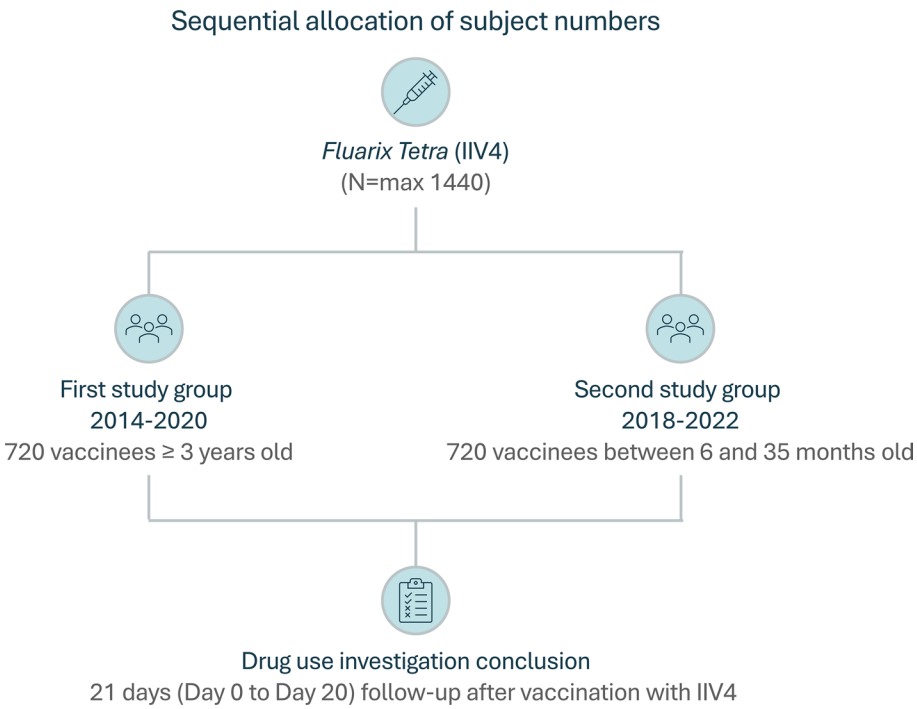


Fig. 1 Study design overview. Drug use investigation conclusion depended on the 21 days contact of the subject in the drug use investigation. Definition of conclusion of drug use investigation for a subject: a subject who is available for the concluding follow-up contact 21 days (day 0 to day 20) after receiving IIV4 is considered to have completed the drug use investigation. IIV4, inactivated quadrivalent seasonal influenza vaccine; *N*, number of subjects planned to be enrolled

2.3 Safety Assessment

Any AE occurring in the 21 days post-vaccination was recorded using diary cards, and the investigator transcribed the collected information into the case report form (CRF) in English. Parents of children aged 6 months to < 12 years were contacted to provide details of any AEs experienced by the child 21 days after the child received the vaccination. All subjects who received at least one dose of IIV4 and could be evaluated for AEs were included in the safety population. Any subjects who were pregnant at the time of IIV4 vaccination or became pregnant within 21 days were followed up for pregnancy outcome (whether full-term or premature, information on the status of the mother and child) at 6–8 weeks after the expected delivery date.

An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product (in this case, the vaccine of study). AEs were categorised using the Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class (SOC) and Preferred Terms. AEs were classified by GSK as expected or unexpected based on the locally approved PI. An expected AE was one that would be expected during the post-vaccination follow-up period as described in the locally approved PI, and an unexpected AE was any AE in addition to those reflected in the approved Korean PI.

Each AE was rated by the investigator as mild (easily tolerated by the subject, causing minimal discomfort and not interfering with normal everyday activities), moderate (sufficiently discomforting to interfere with normal everyday activities, or fever between 38°C and 39°C) or severe (prevents normal everyday activities, or fever > 39°C). A SAE was defined as one that resulted in death, was life threatening, required hospitalisation or prolongation of an existing hospitalisation, resulted in disability/incapacity or was a congenital abnormality/birth defect in the offspring of a study subject. The relationship of each AE to IIV4 was assessed by the investigator using clinical judgment. Following MFDS requirements, causality was classed as certain, probable/likely, possible, not related, conditional/unclassified or unassessable/unclassifiable. AEs for which a causal relationship with IIV4 could not be ruled out were categorised as ARVs. ARVs represent adverse, unintended reactions from normal administration/use of pharmaceuticals for which a causal relationship with the pharmaceutical cannot be excluded based on the investigator's assessment.

The outcome of any SAE reported at any time during the study period and any non-serious AE reported during the 21 days post-vaccination was assessed as recovered/resolved, not recovered/not resolved, recovering/resolving, recovered with sequelae/resolved with sequelae, fatal (SAEs only) or unknown.

2.4 Statistical Methods

According to MFDS requirements, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, allowing for a 20% drop-out rate, about 720 vaccinees aged 3 years and older, and about 720 vaccinees aged between 6 and 35 months were intended to be enrolled during the study period, making an intended total of 1440 across both study groups.

Descriptive analyses of demographic characteristics [age, height, weight, body mass index (BMI), gender and ethnicity] of the study cohort were conducted for each study group. Mean, standard deviation (SD), median, minimum and maximum were calculated for continuous variables such as age, and frequencies and percentages for categorical variables such as gender. Previous medical history (MedDRA), vaccination history within the three previous seasons (yes/no) and concomitant medication/vaccination received at least once during the 21 days were recorded.

All subjects who were vaccinated with at least one dose of IIV4 and provided post-vaccination safety data were included in the safety population. The number and percentage, with exact 95% confidence interval of any AEs, ARVs and SAEs occurring within 21 days were tabulated by SOC and preferred term.

2.5 Ethics Considerations

The study was conducted according to the local rules and regulations of the Korean MFDS. The study was reviewed and approved by the independent review board (IRB) at participating institutions where an IRB was available. Ethics approval numbers for these sites are presented in Supplementary Table 1. All subjects or their parent/legally accepted representative provided signed informed consent for the collection and handling of the personal and safety information before enrolment. The study is on the GSK clinical trial register, GSK Study ID 204687.

3 Results

3.1 Demographics

Data were assessed for safety from 701 subjects in the study group aged 3 years or older and 687 subjects in the study group aged 6–35 months. Within the group aged 3 years or older, the paediatric and adolescent population (aged 3–19 years) comprised 246 individuals, and the elderly population

Table 1 Demographic data

Variable	Study group aged 3 years or older ($N = 701$)	Study group aged 6–35 months ($N = 687$)
Male, *n* (%)	325 (46.36)	323 (47.02)
Female, *n* (%)	376 (53.64)	364 (52.98)
Korean, *n* (%)	701 (100.00)	686 (99.85)
Age		
Mean ± SD	31.97 ± 21.38 years	16.31 ± 9.04 months
Median	35.00 years	13.00 months
Range	3.00–86.00 years	6.00–35.00 months
Age groups, *n* (%)	3–9 years: 167 (23.82) 10–19 years: 89 (12.70) 20–29 years: 56 (7.99) 30–39 years: 108 (15.41) 40–49 years: 104 (14.84) ≥ 50 years: 177 (25.25)	6–11 months: 275 (40.03) 12–23 months: 233 (33.92) 24–35 months: 179 (26.06)
BMI		
Mean ±SD, kg/m^2	3–11 years ($n = 173$): 16.75 ± 2.42 12–18 years ($n = 37$): 21.20 ± 3.45 ≥ 19 years ($n = 283$): 23.30 ± 3.46	($n = 644$): 17.25 ± 1.81
Median, kg/m^2	3–11 years ($n = 173$): 16.23 12–18 years ($n = 37$): 20.74 ≥ 19 years ($n = 283$): 22.98	($n = 644$): 17.12
Range, kg/m^2	3–11 years ($n = 173$): 11.16–26.22 12–18 years ($n = 37$): 14.95–32.04 ≥ 19 years ($n = 283$): 15.96–42.51	($n = 644$): 11.94–24.79
Pre-existing disease, *n* (%)		
Yes	193 (27.53)	26 (3.78)[a]
No	508 (72.47)	661 (96.22)
Concurrent illness, *n* (%)		
Yes	303 (43.22)	109 (15.87)[a]
No	398 (56.78)	578 (84.13)
Renal impairment, *n* (%)		
Yes	2 (0.29)	0 (0.00)
No	699 (99.71)	687 (100.00)
Hepatic impairment, *n* (%)		
Yes	9 (1.28)	0
No	692 (98.72)	687 (100.00)
Influenza vaccination history, *n* (%)		
Yes	380 (54.21)	539 (78.46)
No	246 (35.09)	147 (21.40)
Unknown	75 (10.70)	1 (0.15)

BMI body mass index, *N*, total number of subjects in the given study group, *n* (%), number (and percentage) of subjects in given category, *SD* standard deviation

[a]Nine subjects were duplicated because they had both pre-existing diseases and concurrent illness when collecting medical history

(aged 65 years or older) comprised 36 individuals. Demographic characteristics are summarised in Table 1. All participants were ethnically Korean except for one participant in the group aged 6–35 months. There were no women who became pregnant within 21 days after vaccination with IIV4. The two paediatric groups could not be combined because the data were collected over different time periods. Non-influenza vaccination history of the study groups as well as heights and weights of the participants are summarised in Supplementary Table 2.

In the group aged 3 years or older, concomitant medication was received by 304 individuals (43.37%) and among these, the most commonly used class was systemic anti-infectives (46.71%) (Supplementary Table 3). Concomitant vaccination was received by 37 subjects (5.28%) (Supplementary Table 4). In the group aged 6–35 months, 203/687

Table 2 Incidence of adverse events (AEs) and adverse reactions to vaccine (ARVs) in subjects aged 3 years or older by system organ class (SOC)

	Adverse event[a]			Adverse reaction to vaccine[a]		
	Number of subjects with AE (%)	95% confidence interval (lower, upper)	Number of AEs	Number of subjects with ARV (%)	95% confidence interval (lower, upper)	Number of ARVs
Infections and infestations	45 (6.42)	(4.72, 8.50)	55	2 (0.29)	(0.03, 1.03)	2
General disorders and administration site conditions	32 (4.56)	(3.14, 6.38)	33	28 (3.99)	(2.67, 5.72)	29
Respiratory, thoracic and mediastinal disorders	13 (1.85)	(0.99, 3.15)	16	3 (0.43)	(0.09, 1.25)	5
Gastrointestinal disorders	10 (1.43)	(0.69, 2.61)	12	0 (0.00)	(0.00, 0.52)	0
Musculoskeletal and connective tissue disorders	5 (0.71)	(0.23, 1.66)	5	1 (0.14)	(0.00, 0.79)	1
Nervous system disorders	5 (0.71)	(0.23, 1.66)	6	2 (0.29)	(0.03, 1.03)	3
Skin and subcutaneous tissue disorders	3 (0.43)	(0.09, 1.25)	4	1 (0.14)	(0.00, 0.79)	2
Injury, poisoning and procedural complications	2 (0.29)	(0.03, 1.03)	2	0 (0.00)	(0.00, 0.52)	0
Psychiatric disorders	2 (0.29)	(0.03, 1.03)	3	0 (0.00)	(0.00, 0.52)	0
Ear and labyrinth disorders	1 (0.14)	(0.00, 0.79)	1	0 (0.00)	(0.00, 0.52)	0
Eye disorders	1 (0.14)	(0.00, 0.79)	1	0 (0.00)	(0.00, 0.52)	0
Metabolism and nutrition disorders	1 (0.14)	(0.00, 0.79)	1	0 (0.00)	(0.00, 0.52)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.14)	(0.00, 0.79)	1	0 (0.00)	(0.00, 0.52)	0
Total	98 (13.98)	(11.50, 16.77)	140	34 (4.85)	(3.38, 6.71)	42

AE adverse event, *ARV* adverse reaction to vaccine

[a] The list of detailed AEs and ARVs by SOC and preferred term is presented in Supplementary Table 7

Number of subjects with AE (%) = (Number of subjects with AE in each category) / (Number of subjects in safety analysis set) x 100

Number of subjects with ARV (%) = (Number of subjects with ARV in each category) / (Number of subjects in safety analysis set) x 100

95% confidence interval for the percentage of subjects with AE/ARV was calculated by exact methods

Coding dictionary: Medical Dictionary for Regulatory Activities (MedDRA) 23.0

(29.55%) subjects received concomitant medication, of which the most common category was respiratory system (156/203 subjects, 76.85%) (Supplementary Table 5). Concomitant vaccination was received by 165/687 (24.02%) subjects (Supplementary Table 6).

3.2 Safety Assessment, Age 3 Years and Older

Among the 701 subjects in the safety population, 98 subjects (13.98%) reported a total of 140 AEs during the 6 year surveillance period (Table 2 and Supplementary Table 7). The most common SOC AE categories were infections and infestations [6.42% (45/701) subjects, 55 events] followed by general disorders and administration site conditions [4.56% (32/701) subjects, 33 events] (Table 2). The most common AE by preferred term was nasopharyngitis [2.43% (17/701) subjects, 17 events]. The list of all AEs within SOC is presented in Supplementary Table 7.

Of the AEs, 42 were ARVs for which a causal relationship with IIV4 could not be ruled out by the investigators, reported by 34 subjects (4.85%) (Table 2). The most common ARV SOC was general disorders and administration site conditions [3.99% (28/701) subjects, 29 events] (Table 2). The most common ARVs by preferred term were administration site pain and administration site swelling, each of which was reported in 1.28% subjects (9/701 subjects, 9 events). The list of all ARVs within SOC is presented in Supplementary Table 7.

Of the AEs, 85 (reported by 62 subjects, 8.84%) were classed as unexpected according to the PI. The most common SOC categories for unexpected AEs were infections and infestations [5.85% (41/701) subjects, 50 events] followed by respiratory, thoracic and mediastinal disorders [1.85% (13/701) subjects, 16 events] and gastrointestinal disorders [1.00% (7/701) subjects, 7 events] (Supplementary Table 8). Seven unexpected ARVs were reported by five

Table 3 Incidence of adverse events (AEs) and adverse reactions to vaccine (ARVs) in subjects aged 6–35 months by system organ class (SOC)

	Adverse event[a]			Adverse reaction to vaccine[a]		
	Number of subjects with AE (%)	95% confidence interval (lower, upper)	Number of AEs	Number of subjects with ARV (%)	95% confidence interval (lower, upper)	Number of ARVs
Infections and infestations	98 (14.26)	(11.74, 17.11)	126	0 (0.00)	(0.00, 0.54)	0
General disorders and administration site conditions	43 (6.26)	(4.57, 8.34)	50	24 (3.49)	(2.25, 5.15)	28
Respiratory, thoracic and mediastinal disorders	24 (3.49)	(2.25, 5.15)	32	0 (0.00)	(0.00, 0.54)	0
Gastrointestinal disorders	19 (2.77)	(1.67, 4.29)	19	0 (0.00)	(0.00, 0.54)	0
Skin and subcutaneous tissue disorders	15 (2.18)	(1.23, 3.58)	15	1 (0.15)	(0.00, 0.81)	1
Psychiatric disorders	3 (0.44)	(0.09, 1.27)	3	0 (0.00)	(0.00, 0.54)	0
Injury, poisoning and procedural complications	1 (0.15)	(0.00, 0.81)	1	0 (0.00)	(0.00, 0.54)	0
Nervous system disorders	1 (0.15)	(0.00, 0.81)	1	0 (0.00)	(0.00, 0.54)	0
Vascular disorders	1 (0.15)	(0.00, 0.81)	1	0 (0.00)	(0.00, 0.54)	0
Total	149 (21.69)	(18.66, 24.96)	248	25 (3.64)	(2.37, 5.33)	29

AE adverse event, *ARV* adverse reaction to vaccine

[a]The list of detailed AEs and ARVs by SOC and preferred term is presented in Supplementary Table 9

Number of subjects with AE (%) = (Number of subjects with AE in each category) / (Number of subjects in safety analysis set) x 100

Number of subjects with ARV (%) = (Number of subjects with ARV in each category) / (Number of subjects in safety analysis set) x 100

95% confidence interval for the percentage of subjects with AE/ARV was calculated by exact methods.

Coding dictionary: Medical Dictionary for Regulatory Activities (MedDRA) 24.0

subjects (0.71%), which were cough (three events), rhinorrhoea (two events), nasopharyngitis (one event) and pharyngitis (one event) (Supplementary Table 8).

One subject reported a SAE, gastroenteritis. This was not considered a SARV.

About 96.43% of the reported AEs (135/140 events) were considered resolved during the follow-up period. Four AEs with the event terms hyperlipidaemia, pyrexia, rhinorrhoea and pharyngotonsillitis were not resolved during the course of the study, but none were considered to be ARVs. One AE, classed as positional vertigo, was considered resolving and was also not regarded as an ARV. There were no fatal events. All the ARVs were resolved, and the majority (24/42 ARVs, 57.14%) were administration site reactions expected according to the PI [administration site pain and administration site swelling (each 9/42 events, 21.4%), administration site erythema and administration site pruritus (each 3/42 events, 7.1%)].

Of the 140 AEs reported, no medical attention was required for 74 (52.86%) events, and 63 (45.00%) events led to a visit to or from medical personnel (medical doctor). Two (1.43%) events required hospitalisation and one (0.71%) subject went to the emergency room; these events were not ARVs and all resolved during the surveillance period. Most of the reported AEs were mild (115/140, 82.14%), with 24/140 AEs (17.14%) graded as moderate and one event (0.71%) graded as severe. The severe event was a case of influenza.

In the paediatric and adolescent population (aged 3 to < 19 years), 72 AEs were reported by 48 subjects (19.51%), and in the elderly population (aged 65 years or older), four AEs were reported by four subjects (11.11%).

3.3 Safety Assessment, Age 6–35 Months

A total of 248 AEs were reported in 149 of the 687 subjects in the safety population (21.69%) during the 4 year surveillance period (Table 3 and Supplementary Table 9). The most frequent AEs by SOC were infections and infestations [14.26% (98/687) subjects, 126 events], and general disorders and administration site conditions [6.26% (43/687) subjects, 50 events] (Table 3). The most frequent preferred terms were nasopharyngitis [7.13% (49/687) subjects, 53 events] and pyrexia [4.80% (33/687) subjects, 35 events]. The list of all AEs within SOC is presented in Supplementary Table 9.

ARVs were reported in 25/687 participants (3.64%, 29 events). The most frequent SOC for ARVs was general disorders and administration site conditions [3.49% (24/687) subjects, 28 events] (Table 3). The most frequent preferred term was pyrexia [2.04% (14/687) subjects, 14 events]. The list of all ARVs within SOC is presented in Supplementary

Table 9. All the ARVs were mild and recovered during the study period.

Of the AEs, 180 events in 116 participants (16.89%) were categorised as unexpected (Supplementary Table 10). The most common SOC for unexpected AEs was infections and infestations [14.26% (98/687) subjects, 126 events], and the most common preferred term was nasopharyngitis [7.13% (49/687) subjects, 53 events]. There was one unexpected ARV, injection site warmth, which was assessed by the investigator as mild with certain causal relationship with the study vaccine, and which resolved during the study period.

Four SAEs were reported in 3/687 subjects (0.44%). One subject had pneumonia, one had Kawasaki's disease, and one subject reported exanthema subitum and febrile convulsion. All were categorised as unexpected, and none were considered a SARV. All four SAEs required hospitalisation, were graded as moderate and resolved within the study period.

Mild AEs accounted for 89.92%, moderate for 10.08% and there were no severe AEs. Regarding outcome, 93.15% (231/248 events) of AEs recovered, and the other AEs (6.85%, 17/248 events) were recovering/resolving. All of the recovering AEs were mild and were not evaluated as ARVs. There were no fatal events. Of the 248 AEs, 157 (63.31%) required a visit to or from medical personnel. Four (1.61%) required hospitalisation and were classed as SAEs; all resolved within the study period and were considered not related to the study vaccine. One subject went to the emergency room because of urticaria, but this event was not serious and was also assessed as not related to the study vaccine by the investigators.

4 Discussion

This surveillance study collected safety data for 21 days after receiving IIV4 from 701 subjects aged 3 years or older over a 6 year period and from 687 subjects aged 6–35 months over a 4 year period in Korea. The study did not conduct an efficacy analysis. The study design was similar to other PMS studies conducted in Korea for tetanus toxoid, reduced diphtheria toxoid and the acellular pertussis (Tdap) vaccine [10]; diphtheria; tetanus; acellular pertussis and the inactivated poliovirus (DTaP-IPV) vaccine [11]; meningococcal A, C, W and Y (MenACWY) vaccine [12]; and to PMS studies with similar design and larger sample sizes for MF59-adjuvanted trivalent inactivated influenza subunit vaccine [13] and rotavirus vaccine [14].

The overall incidence of AEs was 13.98% in the study group aged 3 years or older, and 21.69% in the study group aged 6–35 months. Most AEs were considered not related to the study vaccine; the incidence of ARVs, for which a causal relationship could not be ruled out, was 4.85% in the subjects aged 3 years or older and 3.64% in the subjects aged 6–35 months. In the group aged 3 years or older, most ARVs were expected according to the local PI, mainly administration site reactions (24 of 42 events). There were seven unexpected ARVs reported by five subjects (0.71%): cough (3 events), rhinorrhoea (2 events), nasopharyngitis (1 event) and pharyngitis (1 event). In the group aged 6–35 months, all the ARVs were expected according to the PI except for one unexpected ARV, injection site warmth. All ARVs resolved in both groups. One SAE (gastroenteritis) was reported in the study group aged 3 years or older, and four SAEs were reported in the study group aged 6–35 months (pneumonia, febrile convulsion, exanthema subitum and Kawasaki's disease). None of the SAEs were considered to be related to the study vaccine. Overall, the study results showed no major differences from the safety profile in the approved Korean PI, and no safety concerns were found.

The key strength of this study is that it collected real-world data on IIV4 used in routine clinical practice over a wide age range. Nevertheless, the study also has some limitations. Due to the limited number of participants enrolled, there is a possibility that the study would not be able to capture rare AEs. The follow-up period of 21 days post-vaccination may not capture any potential events that develop over a longer timescale. In addition, as a result of the observational study design, there was no control group and it was not possible to control for potential confounding factors, so the results should be interpreted with caution.

This study was the first PMS study conducted on IIV4 in Korea. In Europe, the European Medicines Agency began requiring annual enhanced safety surveillance for seasonal influenza vaccines in 2014 [15]. Following an initial feasibility study conducted in the 2015–2016 season [16], surveillance studies have been conducted for IIV4 in England in 2016–2017 [17] and 2017–2018 [18], and in Belgium, Germany and Spain in 2018–2019 [19, 20], 2019–2020 [21] and 2020–2021 [22]. All these surveillance studies reported no safety concerns with IIV4, supporting the acceptable safety profile of the vaccine. The present surveillance study in Korea also found no safety concerns for IIV4, consistent with the European surveillance results.

5 Conclusions

In this PMS study conducted in Korea in subjects aged ≥ 6 months, no safety concerns were observed during the surveillance period. The results were consistent with the local

PI, and reported AEs were within the scope of events and the expected event rates for the populations studied.

The findings of this study suggest IIV4 is safe and well tolerated for use in all age groups with a vaccine indication. The incidence of AEs and their potential causal relationship with IIV4 will continue to be monitored from spontaneous cases and literature reports through routine pharmacovigilance by GSK.

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Declarations

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Conflict of Interest Gaël Dos Santos was employed by GSK at the time of the study and holds shares in GSK. Raghavendra Devadiga and Joon Bang are employed by GSK. Chun Soo Kim discloses providing support for the present manuscript for provision of study materials and for medical writing of the study report. Joon Bang was employed by Sanofi Pasteur, Korea, until 5 January 2021. All authors declare no other financial or non-financial relationships and activities and no conflict of interest.

Availability of Data and Material Anonymised individual participant data and study documents can be requested for further research from https://www.gsk-studyregister.com/en/.

Ethics Approval The study was conducted according to the local rules and regulations of the Korean MFDS. The study was reviewed and approved by the independent review board (IRB) at participating institutions where an IRB was available. Ethics approval numbers for these sites are presented in Supplementary Table 1.

Consent to Participate All subjects or their parent/legally accepted representative provided signed informed consent for the collection and handling of the personal and safety information before enrolment.

Consent of Publication Not applicable.

Code Availability Not applicable.

Trademarks Fluarix Tetra is a trademark owned by or licensed to GSK.

Author Contributions GDS led and wrote the first draft of the manuscript. All authors participated in the design or implementation or analysis, and interpretation of the study, and the development of this manuscript. All authors had full access to the data and gave final approval before submission. The authors are solely responsible for the final content and received no financial support or other form of compensation related to the development of the manuscript. The material is original and has not been submitted elsewhere.

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