Original Article

Post-marketing Surveillance Study of an Inactivated Split-Virion Influenza Vaccine in Korea

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Purpose : This post-marketing surveillance study (NCT00750360) assessed the safety and reactogenicity of an inactivated, trivalent split-virion influenza vaccine licensed for use in the Korea since 2002.
Methods : Eight hundred and eighty three subjects aged ≥6 months received a single dose of the vaccine; an additional dose was administered to those aged <9 years and unprimed with an influenza vaccine. Four hundred and eleven subjects used diary cards to record safety information; this report presents data from these subjects. Incidence of solicited local, general and unsolicited adverse events (4-days and 21-days post-vaccination follow-up periods, respectively) were recorded. Serious adverse events (SAEs) were recorded throughout the study period.
Results : Injection site pain (subjects aged <6 years: 12.6% of subjects, ≥6 years: 34.7%), fever (<6 years: 1.3%) and myalgia (≥6 years: 13.9%) were the most frequently recorded solicited local and general adverse events. Grade 3 solicited adverse events were reported by ≤4.0% subjects. No vaccine-related SAEs were recorded (KFDA criteria).
Conclusion : Considering the vaccine's well-established immunogenicity and its favourable safety and reactogenicity profile across all age groups and its high coverage rate in Korea, it may be recommended as a candidate to facilitate annual seasonal influenza vaccination for all ages as part of the Korean National Immunization Program. **(Korean J Pediatr Infect Dis 2011;18:68-79)**

Key Words : Influenza vaccine, Reactogenicity, Safety

Conflict of Interest:

B Gunapalaiah and HL Bock are/were employees of GlaxoSmithKline (which sponsored this study) at the time of study conduct. The investigators have received investigator fees from GlaxoSmithKline for conducting the study.

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*Trademarks : *Fluarix* is a trademark of the GlaxoSmithKline group of companies.
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Introduction

Influenza is a highly communicable acute respiratory febrile disease that occurs around the world [1]. Influenza spreads through seasonal outbreaks and epidemics, whose occurrences are estimated to be between three and five million cases of severe illness and between 250,000 and 500,000 deaths annually[2]. Influenza has an estimated attack rate of 20.0-30.0% in children and 5.0-10.0% in adults[1]. While the highest infection rate has been observed in the 5-9 year age group, the elderly population and specific high risk groups are most susceptible to influenza-related morbidity and mortality[1]. The incidence of influenza-related complications and hospitalizations has been found to be similar in children and the elderly[3]. Precise data on influenza-related morbidity and mortality are available from industrialized countries and assist in an actual assessment of the socioeconomic impact of the disease. However, limited data are available from the tropics and subtropics and it is believed that the true impact of influenza is greatly underestimated in these regions[3].

Vaccination against influenza is considered to be the most efficient, cost-effective and safe method of preventing and controlling influenza[1, 4, 5]. Vaccination can prevent 70.0-90.0% of laboratory-confirmed illnesses and substantially reduce the risk of pneumonia, which can result in hospitalization and influenza-related deaths[1]. In the United States (US), influenza vaccination has brought about a drastic reduction in the number of influenza cases reported annually[6]. Following this success, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) has recommended annual vaccination for all US children between 6 months and 18 years of age[6].

In Korea, the influenza virus is one of the major

etiological agents for viral respiratory infections[7]. It is responsible for nearly 19.0% of all respiratory illnesses and related complications observed in Korea; influenza A and B separately account for 11.0−19.0% and 4.6−8.0% of these cases, respectively[7−9]. Published data indicate that influenza vaccination significantly reduced the incidence of influenza-like illness (32.0%) among the elderly in Korea[10]. Taking into consideration the threat from influenza and adapting from the experience of influenza vaccination in Korea and other countries, in 2008 the Korean Pediatric Society recommended influenza vaccination for children between 6 months and 23 months of age[11].

The study vaccine, *Fluarix*™, an inactivated, trivalent split-virion influenza vaccine, has been licensed in Korea since 2002 and indicated for use by all aged 6 months or older (Prescribing Information, *Fluarix*™, November 2008). Influenza vaccination is part of the National Immunization Program in Korea, for priority groups and has a coverage rate of 34.3% in the total adult population, 61.3% in the high risk group and 79.7% in the elderly population (65 years and above)[12]. Priority groups include persons aged 50−64 years, subjects with chronic illness, pregnant women, healthcare personnel including those dealing with SARS (Severe Acute Respiratory Syndrome) and children aged 6−23 months[12]. Considering that the study vaccine has a considerably wide coverage across all age groups in Korea, it is imperative that the safety of this vaccine should be assessed under routine clinical settings.

This post-marketing surveillance (PMS) study evaluated the safety of the study vaccine administered according to the Prescribing Information in terms of occurrence of severe unsolicited adverse events reported after each vaccination in a Korean population aged >6 months at the time of vaccination. This report presents the results of those subjects who used diary cards to record the adverse events.

Materials and Methods

1. Study design and subjects

This open-label, non-randomized, single group PMS study was conducted across 47 centres (located in Seoul and surrounding suburbs and other regions of Korea. The study was conducted according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki and complied with the Korean Food and Drugs Administration (KFDA) regulations (eTrack clinical study ID: 218352/054; Clinicaltrials.gov identifier: NCT00750360). All necessary study-related approvals were obtained from the Independent Ethics Committees of the respective study centres. Written informed consent was obtained from all the subjects or parents of subjects (for those aged <18 years) before enrolment into the study.

The study was conducted between July 2003 and December 2007 and enrolled healthy volunteers aged more than six months of age at the time of first vaccination. Volunteers were not considered for enrolment if they had any signs of febrile illness, previous history of allergic reactions to influenza vaccines or egg-based products or if they were under treatment with immunosuppressive drugs.

All subjects participating in this study received at least one dose of the study vaccine, according to the Korean Pediatrics Immunization Guidelines[13]

and Package Insert. Subjects who were younger than 9 years and had not been previously vaccinated against influenza received an additional dose of the study vaccine with an interval of at least 4 weeks between the doses.

The data from these subjects were categorized based on their age as follows:

· Group UND6: subjects aged >6 months and <6 years, unprimed with any seasonal influenza vaccine, receiving two doses of the study vaccine,

· Group PRI6: subjects aged >6 months and <6 years, already primed with a seasonal influenza vaccine, receiving one dose of the study vaccine,

· Group PRI6-8: subjects aged ≥6 years and <9 years, already primed with a seasonal influenza vaccine, receiving one dose of the study vaccine,

· Group ALL9-17: subjects aged ≥9 years and <18 years, receiving one dose of the study vaccine

· Group ALL18+: subjects aged ≥18 years, receiving one dose of the study vaccine.

Some unprimed subjects aged ≥6 years and <9 years, received two doses of the study vaccine, however, data from these subjects were not presented in this report as diary cards were not used to record adverse events during the follow-up periods.

The first set of subjects or their parents retrospectively, passively reported post-vaccination adverse events at the next visit following vaccination. However, diary cards were subsequently introduced in 13 centres. Necessary amendments were made to the protocol and other study-related documents to facilitate the introduction of diary cards and the corresponding approvals were obtained from the appropriate authorities. This report presents the data obtained from those subjects who used diary cards to record adverse events. Group UND6, who received two shots of vaccines, recorded diary card after the 1st shot only. The results from 472 subjects, who did not use diary cards for reporting of adverse events, will be presented in a separate report that will compare safety reporting with or without the use of diary cards.

2. Vaccines

GSK Biologicals' *Fluarix*™ is an inactivated, trivalent purified split-virion influenza vaccine produced from whole viruses cultivated in embryonated eggs. The vaccine (0.5 mL dose) used in this study contained 15 μg hemagglutinin (HA) for each of the yearly WHO-recommended strains during 2003-2007 as shown in Table 1.

Subjects aged >6 months and <3 years received 0.25 mL dose(s) of the study vaccine, while subjects aged ≥3 years received 0.5 mL dose(s) of the study vaccine.

The vaccine was administered as an intramuscular injection, whereas for subjects with thrombocyto-

Table 1. World Health Organization Approved Reference Influenza Strains used in *Fluarix*™ between 2003 and 2007

Year	Strains (15 μg HA of each)
2003/2004	A/New Caledonia/20/99 (H1N1); A/Panama/2007/99 (H3N2); B/Shangdong/7/97
2004/2005	A/New Caledonia/20/99 (H1N1); A/Wyoming/3/2003 (X-147); B/Jiangsu/10/2003
2005/2006	A/New Caledonia/20/99 (H1N1); A/New York/55/2004 (X-157); B/Jiangsu/10/2003
2006/2007	A/New Caledonia/20/99 (H1N1); A/Wisconsin/67/2005 (X-161) or A/Wisconsin/67/2005 (X-161B); B/Malaysia/2506/2004
2007/2008	A/Solomon Islands/3/2006 (H1N1); A/Wisconsin/67/2005 (X-161B); B/Malaysia/2506/2004

penia or any bleeding disorder, the administration was done by subcutaneous injection.

3. Assessment of safety

The subjects or subjects' parents were given a diary card and instructed to record the occurrence and intensity of any local solicited symptoms (pain, redness, swelling, or induration) or general solicited symptoms (<6 years: fever, shivering, or sweating; ≥6 years: fever, shivering, sweating, myalgia, arthralgia, fatigue, malaise, or headache) during the 4-day post-vaccination follow-up period. The intensity of the adverse events was graded on a three-point scale [0-3]. Pain that prevented normal daily activities was categorized as Grade 3, while redness, swelling and induration >30 mm and >50 mm (for subjects <6 years and ≥6 years, respectively) were considered Grade 3. Axillary temperature >39.0℃ was defined as Grade 3 fever, while for all other general adverse events (shivering, sweating, myalgia, arthralgia, fatigue, malaise, or headache) that prevented normal daily activities were considered Grade 3. All general adverse events and serious adverse events (SAEs) were assessed by the investigator for causality in relation to vaccination, as per the KFDA and GSK criteria (Table 2). Unsolicited symptoms were recorded during the 21-day follow-up period after each vaccination. Serious

Table 2. Korean Food and Drugs Administration (KFDA) and GlaxoSmithKline (GSK) Criteria for Assessment of Causality of Unsolicited and Serious Adverse Events

	Causality assessment	Criteria
KFDA criteria	Definitely related	-Evidence of exposure to the drug -Temporal sequence of the onset of adverse event (AE) relative to administration of the drug is reasonable -AE is more likely explained by the drug than by another cause -AE subsides or disappears on withdrawing the drug -Rechallenge (if feasible) is positive -AE shows a pattern consistent with previous knowledge of the drug or the drug class
	Probably related	-Evidence of exposure to the drug -Temporal sequence of the onset of adverse event (AE) relative to administration of the drug is reasonable -AE is more likely explained by the drug than by another cause -AE subsides or disappears on withdrawing the drug
	Possibly related	-Evidence of exposure to the drug -Temporal sequence of the onset of adverse event (AE) relative to administration of the drug is reasonable -AE could have been due to another equally likely cause -AE subsides or disappears on withdrawing the drug (if performed)
	Probably not related	-No evidence of exposure to the drug -Another more likely cause of the AE -AE does not disappear even after the withdrawal of the drug (if performed) or is ambiguous
	Unknown	
GSK criteria	Yes	-A reasonable possibility that the vaccine contributed to the AE
	No	-AE is not causally related to administration of the study vaccine -There are other more likely causes and administration of the study vaccine is not suspected to have contributed to the AE

adverse events (SAEs) occurring during the 21-day follow-up period after each vaccination were recorded; in addition, SAEs related to participation in the study or related to concurrent medication were recorded throughout the period during which the subject was in the study.

4. Statistical analyses

In line with the requirements of the Korean regulatory authorities, at least 600 subjects were to be enrolled to have at least 95% probability to observe the occurrence of at least one severe (Grade 3) adverse event within the 21-day post-vaccination follow-up period, with a true incidence of 0.5%. Enrolled subjects were stratified by age for the purpose of safety assessment.

The primary end point was defined as the occurrence of Grade 3 unsolicited adverse events during the 21-day follow-up period after vaccination.

In this paper, primary analyses of safety and reactogenicity were performed on the total vaccinated cohort who used diary cards to record and report adverse events: 411 subjects out of 883 subjects. All analyses were performed as per pre-defined age groups and pooled age group. Percentage of doses followed by and percentage of subjects reporting at least one solicited or unsolicited local and general adverse event during the 4-day post-vaccination follow-up and percentage of doses followed by each local and general symptom by type, severity and relationship were tabulated with exact 95% confidence interval (CI). The study was also tabulated with exact 95% CI, the percentage of subjects reporting each individual solicited symptom during the 4-day follow-up period and those reporting at least one unsolicited adverse event during the 21-day follow-up period along with the intensity and relationship.

All analyses were performed using Statistical Analysis System (SAS) version 9.1 and all 95% CI were calculated using Proc StatXact 7.0. A P value <0.05 was considered statistically significant.

Results

1. Study population

A total of 883 subjects were enrolled from July 2003 to December 2007, of which 411 subjects used diary cards (UND6 [N=55], PRI6 [N=255], PRI6-8 [N=55], ALL9-17 [N=25]), ALL18+ [N=21]).

Median age of these subjects using diary cards was 4 years (range: 6 months to 73 years); 51.3% of subjects were males. All subjects (99.8%) except one (who was Caucasian) were of East Asian or Korean origin.

2. Safety and reactogenicity

Overall, solicited and unsolicited local adverse events were recorded in 27.0% of subjects and general adverse events were recorded in 16.5% of subjects across all age groups during the 4-day post-vaccination follow-up period. The percentage of subjects with local adverse reactions was highest in the PRI6-8 group (47.3%), while the percentage of subjects with general adverse events was highest in the ALL18+ group (33.3%).

Pain at the injection site was the most frequently recorded solicited local adverse event across all age groups; 12.6% of subjects aged <6 years and 34.7 % of subjects ≥6 years reported injection site pain.

Correspondingly, Grade 3 pain was recorded in 0.3 % and 4.0% of subjects aged <6 years and ≥6 years, respectively. Incidence of solicited local adverse events is presented by age group in Fig. 1.

Fever (overall 1.3% of subjects) and myalgia (overall 13.9% of subjects) were the most frequently recorded solicited general adverse events in the <6 years and ≥6 years age groups, respectively. None of the subjects reported Grade 3 fever, while Grade 3 myalgia was reported by 1.0% of subjects in the same age groups. Age-wise incidence of solicited general adverse events is presented in Fig. 2. For those subjects aged <6 years and ≥6 years who received two vaccine doses, none of the subjects reported any solicited local or general symptoms after the second dose.

Assessment of causality:

GSK assessment: Solicited general adverse events (fever, shivering and sweating) assessed by the investigator to be causally related to vaccination were recorded in 0.6% of subjects aged <6 years. None of the Grade 3 adverse events in this age

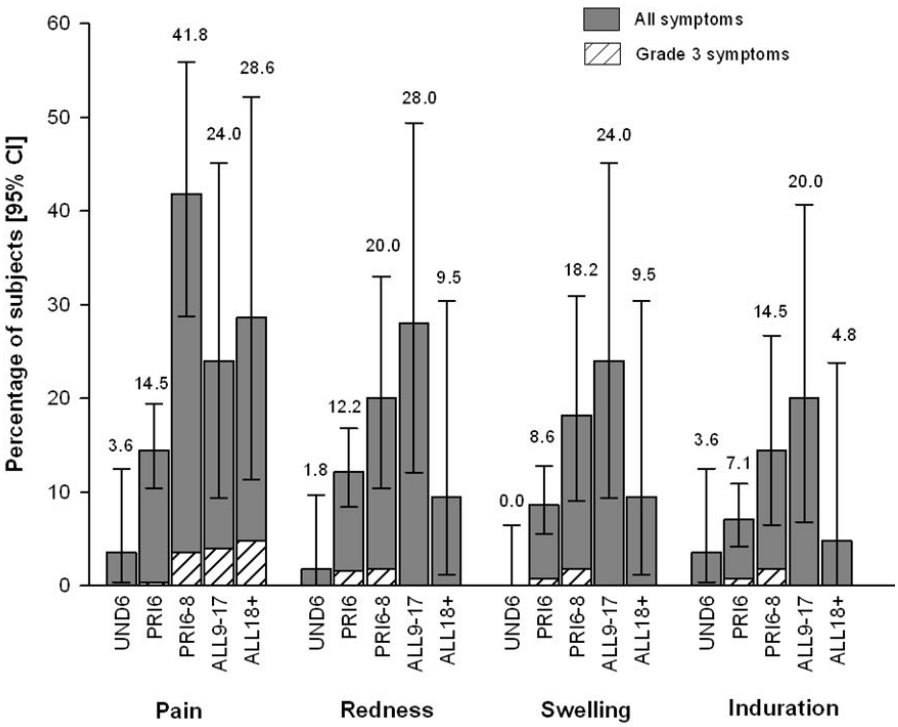

Fig. 1. Incidence of solicited local adverse events recorded within the 4-day post-vaccination follow-up period, in each age group (Total vaccinated cohort)
Footnotes: UND6: subjects >6 months-<6 years unprimed with the study vaccine and receiving two doses of the study vaccine
PRI6: subjects >6 months-<6 years primed with the study vaccine and receiving one dose of the study vaccine
PRI6-8: subjects ≥6-<9 years primed with the study vaccine and receiving one dose of the study vaccine
ALL9-17: subjects ≥9-<18 years receiving one dose of the study vaccine
ALL18+: subjects ≥18 years receiving one dose of the study vaccine
Note: The shaded portion indicates the Grade 3 symptoms. The error bars represent the 95% confidence intervals

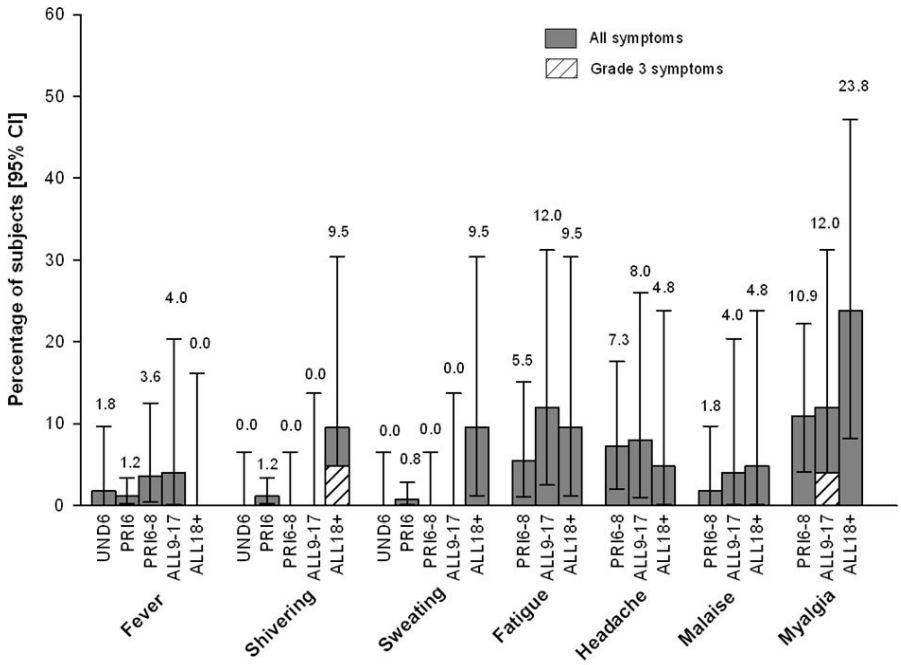

Fig. 2. Incidence of solicited general adverse events recorded within the 4-day post-vaccination follow-up period, in each age group (Total vaccinated cohort)
Footnotes: UND6: subjects >6 months-<6 years unprimed with the study vaccine and receiving two doses of the study vaccine
PRI6: subjects >6 months-<6 years primed with the study vaccine and receiving one dose of the study vaccine
PRI6-8: subjects ≥6-<9 years primed with the study vaccine and receiving one dose of the study vaccine
ALL9-17: subjects ≥9-<18 years receiving one dose of the study vaccine
ALL18+: subjects ≥18 years receiving one dose of the study vaccine
Note: The shaded portion indicates the Grade 3 symptoms. The error bars represent the 95% confidence intervals

group was assessed to be vaccination-related. In subjects ≥6 years of age, vaccination-related causality varied between 1.0% (fever) and 12.9% (myalgia) of subjects; myalgia and shivering of the Grade 3 intensity were determined to be vaccination-related in 0.1% of subjects.

KFDA assessment: None of the solicited general adverse events reported in any of the age groups was "definitely" related to vaccination.

At least one unsolicited adverse event was recorded in 25.8% of subjects during the 21-day post-vaccination follow-up. Overall, upper respiratory tract infection (5.8% of subjects) and asthma (4.6% of subjects) were the most frequently recorded unsolicited adverse events. The most frequently recorded unsolicited adverse events in each age group are presented in Table 3. None of the subjects reported unsolicited symptoms of Grade 3 severity during the 21-day post-vaccination follow-up period. Three of the unsolicited adverse events were considered by the investigator to be vaccination-related ("definitely related" in terms of KFDA assessment criteria) (one case of injection site pruritus in each of the PRI6, ALL9-17 and ALL18+

Table 3. Most Frequently Reported Unsolicited Adverse events in Each Age Group, During the 21-day Post-vaccination Follow-up (Total Vaccinated Cohort)

Age group	Symptom	Percentage (95% CI)
UND6*	Upper respiratory tract infection	16.4 (7.8-28.8)
PRI6†	Asthma	5.1 (2.7-8.6)
PRI6-8‡	Asthma	5.5 (1.1-15.1)
ALL9-17∫	Injection site pruritus	8.0 (1.0-26.0)
	Rhinitis	8.0 (1.0-26.0)
ALL18+‖	Injection site pruritus	4.8 (0.1-23.8)
	Rhinitis	4.8 (0.1-23.8)
	Upper respiratory tract infection	4.8 (0.1-23.8)

*UND6: subjects >6 months-<6 years unprimed with the study vaccine and receiving two doses of the study vaccine
†PRI6: subjects >6 months-<6 years primed with the study vaccine and receiving one dose of the study vaccine
‡PRI6-8: subjects ≥6-<9 years primed with the study vaccine and receiving one dose of the study vaccine
∫ALL9-17: subjects ≥9-<18 years receiving one dose of the study vaccine
‖ALL18+: subjects ≥18 years receiving one dose of the study vaccine
95% CI: Exact 95% confidence interval

groups). All subjects reporting unsolicited adverse events were recovering at the time of conclusion of this study.

Overall, one SAE was reported throughout the study period. This 15 month-old male subject was diagnosed with Kawasaki disease five days after vaccination; the event resolved within five days. The relationship to vaccination was considered as "unknown" in terms of KFDA causality assessment, while being considered as "possibly related" when assessed in terms of GSK criteria. No fatal events were reported.

Exploratory analyses indicated that there was no statistically significant difference in the incidence of solicited and unsolicited adverse events across the various age groups; *P*-values for occurrence of adverse events between pairs of groups ranged between 0.104 and 0.882. However, there appeared to be a statistically significant difference between females (52.0%) and males (41.2%) in experiencing solicited and unsolicited adverse events during the study period (*P*-value=0.028).

Discussion

Previous studies have confirmed the susceptibility of the Korean population to influenza, influenza-like infections (ILIs) and influenza-related afflictions like pneumonia and bronchiolitis[8, 9, 14, 15]. Some Korean studies have reported that the influenza cases and ILIs have been recorded most commonly in children, while others suggest that children and adults >50 years are equally affected by ILIs[15, 16]. Children have been found to be more susceptible to influenza infections than adults[7, 16]. Published reports indicate that pre-school and school-going children (i.e. children aged <6 years) were susceptible to influenza B virus infections, while influenza A virus infections predominantly occurred in children <2 years of age [17]. Considering that there is a need for safe and effective vaccines against influenza in Korea and the vaccine used in the present study has a high coverage rate in Korea, this study investigated whether the study vaccine has a favourable safety profile across all age groups in Korea, as requested

by the KFDA.

The seasonal influenza vaccine used in this study has a well-established safety profile in infants, children, adults (18-60 years) and the elderly (60 years and above)[3, 18, 19]. In the present study, the vaccine was well-tolerated in Korean subjects. No new vaccination-related adverse events were reported in this study, compared to previous studies with the same vaccine[3, 18]. The overall incidence of solicited local and general adverse events (27.0% and 16.5%, respectively) in this study was similar to that observed in previous studies, while SAEs were far rarer than previously observed[18]. No Grade 3 unsolicited adverse events was reported in any age group in this study. Based on the exploratory analyses, the incidence of adverse events appeared to be independent of age but not gender. These differences in reporting of injection site pain were also observed by Treanor et al, in a study with the same vaccine conducted in American subjects aged 18-64 years[18].

Previous studies have demonstrated that not only does the study vaccine have a favourable safety and reactogenicity profile (even in pregnant women), but it also has a good immunogenicity profile[3, 19-21]. In addition to immunogenicity against the vaccine strains, the study vaccine has demonstrated cross-clade immunogenicity against homologous drifted variants[22].

The close proximity of Korea to countries that have previously reported frequent outbreaks of influenza in poultry and cases of influenza in birds and humans increases its susceptibility towards influenza outbreaks[15]. Hence, in line with the WHO recommendations to implement surveillance systems to monitor influenza-related developments in the regions[1], Korea launched a nationwide influenza surveillance system called the Korean Influenza Surveillance Scheme (KISS) during the 2000-2001 influenza season in order to closely monitor influenza activity and circulating influenza virus strains and contribute to the development of influenza control measures[15]. However, it is also essential that the influenza surveillance program is supplemented with annual vaccination against seasonal influenza.

The Pediatric Society of Korea recommends influenza vaccination for all infants and children aged 6-23 months[13]. In this context, *Fluarix*™ could be a suitable option for mass vaccination in the Korean population owing to its established immunogenicity and acceptable safety and reactogenicity profile and high coverage rate in Korea.

This study was originally not designed with the aim to use diary cards for safety reporting. However, with the aim to provide validated safety and reactogenicity data on the vaccine to the Korean health authorities, diary cards were introduced midway during the conduct of the study. The number of subjects using diary cards (411 subjects) was lower than KFDA requirements (at least 600 subjects). In addition, the data presented on the differences between age groups and genders are purely exploratory. However, considering the fact that the number of PMS studies on any vaccine conducted by vaccine manufacturers in Korea is limited and availability of data from real-life settings is limited, the PMS data collected in this study using diary cards from a post-marketing clinical setting are valuable and crucial as they added a real-life perspective to the data available on the safety profile of the study vaccine in Korea. Importantly, the post-marketing data were collected using a metho-

dology similar to the one used in clinical trials.

In conclusion, *Fluarix*™ has an established immunogenicity and a clinically acceptable safety and reactogenicity profile in all age groups. In order to minimize chances of future influenza outbreaks in Korea, this vaccine which already has a high vaccine coverage rate can be a suitable option for mass vaccination in the Korean population.

요 약

불활화 분할 인플루엔자 백신의 국내 시판 후 조사 연구

플루아릭스 054 연구 그룹을 대표하여 허재원 마상혁*, 김현균†, 바바슈리 구나팔라이아†, 한스 복‡

부산 일신 기독병원 소아청소년과, 창원 파티마 병원 소아청소년과, 대구 미래연합 소아청소년과 의원†, 글라소스미스클라인‡*
플루아릭스 054 연구 그룹 참가자들은 영문본 서두에 상세히 기록되어 있음

목 적: 본 시판 후 조사(NCT00750360)는 2002년부터 국내에서 사용 허가된 정제불활화 3가 분할 인플루엔자 백신의 안전성 및 반응원성을 평가하기 위하여 시행되었다.

방 법: 생후 6개월 이상의 소아 및 성인 피험자 총 883명을 대상으로 평가대상 인플루엔자 백신을 1회 접종하였다. 이전에 인플루엔자에 감염되지 않았거나 인플루엔자 백신을 접종하지 않은 만 9세 미만의 소아의 경우에는 1회의 추가접종을 실시 하였다. 411명의 피험자가 일일 기록카드를 사용하여 안정성 정보를 기록하였으며 본 보고서에는 이들 피험자들로부터 수집된 자료가 포함되어 있다. 전신 및 투여부위에서의 명시된 이상반응 및 명시되지 않은 이상반응의 발생률을 기록하였다(백신접종 후 각각 4일 및 21일 동안 추적 관찰하였음). 또한 연구진행기간 전체에 걸쳐서 중대한 유해사례를 추적 관찰하여 기록하였다.

결 과: 가장 흔하게 관찰된 전신 및 투여부위에서의 명시된 이상반응은 접종부위 통증(만 6세 미만의 소아: 12.6%, 만 6세 이상의 소아: 34.7%), 발열(만 6세 미만: 1.3%) 그리고 근육통(만 6세 이상: 13.9%) 이었다. 등급 3의 명시된 이상반응은 전체 피험자의 4.0% 이하에서 보고되었다. 한국식품의약품 안전청의 기준에 따라 백신과 인과관계가 없는 중대한 유해사례도 기록하였다.

결 론: 평가대상 백신의 전 연령대에서의 확립된 면역원성 및 우수한 안정성, 반응원성 프로파일과 국내에서의 높은 접종률을 고려할 때, 본 백신을 국가예방접종사업에 포함시켜 모든 연령대에서 계절성 인플루엔자 예방접종을 증진시키기 위한 후보백신으로 추천할 수 있을 것이다.

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