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National safety surveillance of quadrivalent recombinant influenza vaccine in Taiwan during NH 20/21

Szu-Ying Tsai [a,b,*], Ting-Yu Yeh [a], Nan-Chang Chiu [c,d], Ching-Tai Huang [e]

[a] Sanofi, Taipei, Taiwan
[b] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States
[c] Department of Pediatrics, Mackay Children's Hospital, Taipei, Taiwan
[d] Department of Medicine, Mackay Medical College, New Taipei City, Taiwan
[e] Division of Infectious Disease, Department of Internal Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan

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ABSTRACT

Background: During the COVID-19 pandemic, the need for influenza vaccine significantly increased in the initial weeks of the 2020–2021 influenza vaccination campaign season in Taiwan. To meet this demand, the Taiwanese government therefore purchased additional influenza vaccines via special import, including 350,000 doses of quadrivalent recombinant influenza vaccines (RIV4, Flublok Quadrivalent). Approved in the United States since 2016, there were limited numbers of published studies regarding RIV4 outside America. We utilized the national passive surveillance system consisting adverse event (AE) reports following RIV4 immunization to describe its safety profiles in Taiwan.
Methods: We obtained the database from the Taiwan National Adverse Drugs Reactions Reporting System and collected reports from January 2021 to July 2021, which was at least one month after RIV4 immunization. AE reporting rates were calculated based on the total administered doses.
Results: Eight AEs were reported among 200,287 administered doses, which led to a reporting rate of 3.99 AEs per 100,000 doses administered. The mean age of the reported individuals were 47.53 years, and women (75%) were the predominant gender. Most adverse events started within the first day after immunization, with one reported as starting 4 days after vaccination. Among the 8 cases, 75% (n = 6) were non-serious and the most common symptoms were erythematous skin rashes with pruritus. Two cases were listed as serious based on the criteria of "other clinically significant medical conditions", but neither was judged to have a causal relationship with RIV4 immunization.
Conclusion: The Taiwan national passive surveillance data supported the safety profiles of RIV4 in Taiwan population.

1. Introduction

Seasonal influenza contributes three to five million cases of severe illness worldwide, and is estimated to have caused 290,000–650,000 respiratory deaths per year [1]. Prior to the COVID-19 pandemic, around 1000–2000 severe cases and 100–275 mortalities were recorded in each influenza season in Taiwan [2,3]. Vaccination is one of the most effective methods to prevent influenza infection. Taiwan has adopted quadrivalent influenza vaccines in the government-funded programs offering free influenza shots to the eligible population since 2019 [4]. The people eligible to receive free influenza vaccine during the 2020–2021 influenza season included children and adolescents aged 6 months until 18 years, all adults aged 50 years and older, high-risk patients with underlying medical conditions, pregnant women, parents who had babies under 6 months of age, child-care workers, nursing home residents and staff, healthcare and public health personnel, poultry farmers and animal health inspectors [5].

COVID pandemic was also a prominent issue during the northern hemisphere (NH) 20/21 influenza season. The importance of influenza vaccination was emphasized due to concerns of co-circulation of influenza and COVID-19, resulting in a high burden for the healthcare system with severe disease for the high-risk groups [6,7]. Although there were only less than six-hundred [8] COVID-19 cases in Taiwan at the start of influenza vaccination campaign [9], the citizens, including a significant number of population who never received influenza vaccines, flocked to vaccination centers in the first two weeks, which had led to a shortage

* Corresponding author at: Sanofi, 7F, No. 3, Songren Rd, Xinyi District, Taipei City 11010, Taiwan.
E-mail address: Doris.Tsai@sanofi.com (S.-Y. Tsai).

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of vaccine shots, causing a pause in vaccination for the 50–64 years-old cohort [10]. The Taiwanese government therefore procured an additional 410,000 doses of influenza vaccine, 350,000 of which were quadrivalent recombinant influenza vaccines (RIV4, Flublok Quadrivalent, Protein Sciences Corporation) via special import before its full licensure. However, due to a series of adverse events (AEs) following influenza vaccinations in South Korea during late October time in 2020, which was overly exacerbated by media, the weekly immunization number dropped abruptly. When the additionally acquired influenza vaccines finally arrived in January 2021, due to the low immunization uptake, the government expanded the eligibility (of the free shots) to all people above 6 months old as of January 30, 2021[11].

Utilizing baculovirus vector in expresSF+ cells and recombinant DNA technology to produce hemagglutinin (HA) proteins instead of adapting influenza viruses in embryonated eggs, RIV4 provides genetically identical strains according to World Health Organization (WHO) predictions with no mutation and low bioburden [12]. The manufacture of RIV4 is scalable, and the process is accomplished within 6–8 weeks [13]. RIV4 contains 45 μg of recombinant HA (rHA) for each strain, and is currently indicated for adults aged 18 years and older. Although already approved and in the market of United States (US) since 2016[14], RIV4 was only formally licensed in the US and Brazil before the start of NH20/21 influenza season.

The safety profile of RIV4 was assessed with two randomized control trials [13,15], one included 998 adults in the 18–49 years old cohort, and the other one included 4328 adults in the 50 years and older cohort; both studies have limited numbers of participants other than Caucasian and African American descendants [13,15]. The safety data showed comparable reactogenicity, AEs and serious AEs versus standard-dose egg-based quadrivalent influenza vaccines, and the severe AEs were not related to study vaccine [13,15].

To better understand the safety profiles in an Asian/Pacific Islander population who received RIV4 from this special import in Taiwan, we captured the safety information that were submitted to Taiwan National Adverse Drugs Reactions (ADR) Reporting System and summarized the AEs reported in this study.

2. Materials and methods

Established in 1998, Taiwan National ADR Reporting System is a national passive surveillance system with single-window service governed by Taiwan Food and Drug Administration (TFDA) [16–19]. Reports of any AEs following medications or vaccinations at any interval from recipients, healthcare providers, manufacturers or other sources are encouraged without considering causality [16]. The reporters should submit online or via emails following a standardized reporting form, which requires minimal information including identifiable reporter, identifiable patient, suspected product, and detailed descriptions of AEs [16]. Due to concerns of patient privacy, medical records are not included in the reporting process [17]. The reports from healthcare institutions directly to the Vaccine Adverse Events Reporting System (VAERS) by Taiwan Centers for Disease Control (TCDC) were also incorporated in the ADR reporting system [17,18,20]. The characteristics and severity would be further determined for each individual report [16]; vaccinees could also be reported to Taiwan Vaccine Injury Compensation Program (VICP) for further causality assessments.

At the time of the special import to Taiwan, RIV4 was indicated for adults 18 years of age and older. The RIV4 doses were distributed from TCDC to local health authorities from January 22, 2021 to the end of the influenza vaccination campaign on June 30, 2021. We obtained de-identifiable AE reports between January 1, 2021 and July 31, 2021 from Taiwan National ADR Reporting System, which was at least one month post RIV4 immunization. The precise number of total administered doses was acquired from TCDC. Conducted as a routine public health surveillance based on existing documents, the study derived from ADR reporting system did not require additional intervention or exposure, besides, we were not able to identify subjects from the reports. Thus, institutional review board approval for informed consent from each subject was waived.

Taiwan National ADR Reporting System categorized each AE report by severity. AEs following immunization (AEFI) are defined as serious if they led to death, life-threatening illness, permanent disability, congenital anomaly, need for hospitalization or prolongation of hospitalization, or other clinically significant medical conditions [16], which is aligned with the WHO definition [21]. We reviewed all serious and non-serious adverse events, and integrated duplicate reports. Reporting rates of AEFIs were calculated per 100,000 doses administered during the half-year period. Demographic characteristics of the AEs and reported symptoms were also summarized with descriptive statistics.

3. Results

A total of 200,287 doses of RIV4 were administered during January 22, 2021 through June 30, 2021. Eight AEs were reported from that time until July 31, 2021, hence, at a reporting rate of 3.99 reports per 100,000 doses administered. Table 1 outlines the details of the AE reports. Of the 8 reported AEs, 6 of the AEFIs were considered as non-serious.

Two of the 8 reports were categorized as serious, which is at a rate of 1.00 reports per 100,000 doses administered. Both serious reports were based on the criteria of "other clinically significant medical conditions". The first one was a 53.6-year-old man who developed vomiting, dizziness, unsteady gait, and general weakness on the day after receiving RIV4 and visited ER with the symptoms. Brain CT scan was performed, he was discharged with oral medication and to be followed by otolaryngology outpatient clinic. The second individual was a 53.5-year-old woman who experienced severe cough on the same evening after RIV4 immunization, increased eye discharge and rhinorrhea were noted two days after, and severe low back pain with inability to move accompanied with cold sweats were noted on the third day post-RIV4. At this point, she visited a family medicine outpatient clinic in the hospital. She visited infectious disease clinic on the fourth day post-vaccination and was prescribed oral medication use and then the abovementioned symptoms gradually improved (Table 1). There was no report of death following RIV4 immunization, and neither of the serious AEs mentioned above were considered to have a causal relationship with the RIV4 immunization.

The mean age of those individuals reporting an AE was 47.53 years. Women accounted for the majority (75%) of the reporting individuals. Most adverse events started within the first day after immunization, with one AE reported as starting 4 days after vaccination (Table 2). Since concurrent vaccine/medication is not the mandatory item in the reporting system, we do not have data regarding co-administration of medication or vaccine.

Table 3 summarizes the reported symptoms. Erythematous skin rash with pruritus was the most common (3/8, 37.5%) reported symptoms, and 25% (2/8) of the reports mentioned cough or low back pain. The other symptoms reported include cold sweats, dizziness, diarrhea, fever, general soreness, general swelling, general weakness, increased eye discharge and rhinorrhea, injection site pain and numbness, myalgia, unsteady gait, and vomiting.

Table 1
Overview of RIV4 adverse event reports.

Case Number	Symptoms	Symptom Onset (days)	Sex	Age
Serious adverse events				
2	Vomiting, dizziness, unsteady gait, general weakness	1	M	53.6
5	Cough, increased eye discharge and rhinorrhea, severe low back pain with inability to move, cold sweats	0	F	53.5
Non-serious adverse events				
1	Erythematous skin rashes with pruritus over face, limbs and trunk	2	F	30.1
3	Left upper arm (injection site) pain and numbness, persistent for more than 7 days	0	F	37.8
4	General erythematous skin rashes with pruritus and swelling	4	M	47.8
6	Fever, dizziness, myalgia, general erythematous skin rashes with pruritus	0	F	63.3
7	Cough, low back pain	0	F	53.5
8	General soreness, diarrhea	0	F	40.6

Table 2
Demographics of the subjects reporting adverse events after RIV4.

Variable	All reports (n = 8)	Serious reports (n = 2)	Non-serious reports (n = 6)
Age (years)	47.53 ± 10.71	53.55	45.52 ± 11.89
Female sex	6 (75%)	1 (50%)	5 (83.3%)
Adverse event onset interval (days)			
Median	0	0.5	0
Mean ± SD	0.88 ± 1.46	0.5	1 ± 1.67
Interquartile range	0–1.5	NA	0–2
Range	0–4	0–1	0–4

SD: standard deviation; NA: non-available.

Table 3
Summary of symptoms reported after RIV4 immunization (n = 8).

Symptoms	Frequency
Erythematous skin rash with pruritus	3 (37.5%)
Cough	2 (25%)
Low back pain	2 (25%)
Cold sweats	1 (12.5%)
Dizziness	1 (12.5%)
Diarrhea	1 (12.5%)
Fever	1 (12.5%)
General soreness	1 (12.5%)
General swelling	1 (12.5%)
General weakness	1 (12.5%)
Increased eye discharge and rhinorrhea	1 (12.5%)
Injection site pain and numbness	1 (12.5%)
Myalgia	1 (12.5%)
Unsteady gait	1 (12.5%)
Vomiting	1 (12.5%)

4. Discussion

To our knowledge, this is the first real-world surveillance study in the Asian/Pacific Islander population with regards to safety of RIV4 via passive surveillance. Although RIV4 has not been formally approved by TFDA, this special import database contained over 200,000 doses nationwide with 8 reports of AEs, resulting in a reporting rate of 3.99 reports per 100,000 doses administered. This rate was lower than the reported NH20/21 influenza vaccine AEFIs in Taiwan before RIV4 distribution by about half (around 8.6 reports per 100,000 doses administered)[22], but slightly higher than the other recent influenza seasons in Taiwan (NH19/20: 1.9 reports per 100,000 doses; NH18/19: 3.6 reports per 100,000 doses; NH17/18: 2.0 reports per 100,000 doses) [22]. This could possibly be related to the increased awareness and reporting behaviors after the South Korea influenza vaccine AEFIs reported in October 2020 and suspected COVID-19 vaccine complications worldwide in 2021 [23,24]. Due to limited information provided by TFDA influenza vaccination weekly summaries, we do not have reporting rate of AEs of other influenza vaccines in the same adult age group, but only as a whole (aged 6 months and above). However, based on the published weekly summaries, 32 AEs were reported among around 298,000 influenza vaccines administered (10.7 reports per 100,000 doses administered) between January 2021 and June 2021 [22]; if we further deducted the RIV4 doses and related AEs, it would be 24 AEs among around 98,000 influenza vaccine doses (24.5 reports per 100,000 doses administered), which was significantly higher than our findings.

During the whole NH20/21 influenza season in Taiwan, a total of 6.229 million influenza vaccines were given, and over 70% (382/537) of the reported AEFIs were categorized as non-serious and included symptoms like fever, chills, dizziness, vomiting, skin rashes and injection site reactions [22]. Of these, as mentioned above, 6 (1.5%) of the vaccinees received RIV4, and the percentage and symptoms of non-serious AEs were similar.

Woo and Moro [25] consolidated the post-marketing surveillance data of RIV4 from VAERS in the US during the 2017–2020 influenza seasons. While there were 5% (39/849) of reports classified as serious, almost half of the serious AEFIs were neurological conditions, including 10 reports of Guillain-Barre syndrome and three seizures. There were only 8 AE reports in our study, therefore the percentage of serious AEs differed from the Woo and Moro study due to limited case numbers. Allergic reactions/anaphylaxis, injection site responses and respiratory conditions also accounted for more than 10% of serious AEFIs respectively. As for the non-serious reports, vaccination errors, injection site responses and skin rashes were the main reasons for reporting. Erythematous rashes and cough are also commonly reported symptoms in our study. Females were predominant in the VAERS reports following RIV4 [25], which was also observed in our study and consistent with the overall VAERS surveillance findings [26]. The mean and the median age in Woo and Moro study were 43.7 and 50.5 years old, respectively [25]; which were also similar to mean age 47.53 years in our study. In addition, both of the median AE onset interval in Woo and Moro study [25] and our study were 0 day.

As the only published study regarding RIV4 constituted by Asian cohorts, Cowling et al. [27,28] compared the reactogenicity and immunogenicity of four different influenza vaccines: standard-dose quadrivalent vaccine, MF59-adjuvanted trivalent vaccine, high-dose trivalent vaccine, and recombinant quadrivalent vaccine. The study was conducted in NH17/18 among the 65–82 years-old elderlies in Hong Kong. In this study, the RIV4 proved to have higher humoral response toward H3N2 while maintaining similar or lower rates of local and systemic reactogenicities [28] compared to standard-dose quadrivalent vaccine. It was noted that reactogenicity occurred in 44% of standard-dose influenza vaccine and 40% of RIV4 recipients in the Cowling study [28], which was much higher than the findings in our passive surveillance study due to its randomized controlled trial characteristics. The reactogenicity reporting was most common in the first day following immunization, and the most frequent symptoms were local reactions such as tenderness, pain and swelling [28].

ADR reporting system has the advantage of its national scale, timeliness, accessibility for both the public and the healthcare providers, and capability to monitor rare or unexpected AEs [18,25,29], however, our study derived from the voluntary reporting system has several limitations, including underreporting, biased or poor-quality reporting, incomplete information, difficulty in verification, and lack of comparison group [18,25,29]. It is also rather challenging to determine the causality based on the limited details shared from the AE reports alone. However, this passive surveillance data still provides valuable demographic and epidemiological information and observations for unexpected AEFIs.

5. Conclusion

Preventing influenza infection is crucial in the context of the COVID-19 pandemic, and vaccination remains to be one of the most effective methods in preventing disease. This study demonstrates that RIV4 is safe among the Taiwan population when compared to the overall safety profiles for influenza vaccine in this population.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S-YT and T-YY are currently employed by Sanofi and may hold shares and/or stock options in the company. N-CC and C-TH have no relevant conflict of interest to report.

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Author contributions

S-YT collected and analyzed data, drafted and finalized the manuscript, and designed the tables. T-YY devised the main conceptual ideas, finalized the manuscript, and supervised the work. N-CC and C-TH reviewed and revised the manuscript. All authors discussed the results and commented on the manuscript.

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