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Post-licensure surveillance of trivalent adjuvanted influenza vaccine (aIIV3; Fluad), Vaccine Adverse Event Reporting System (VAERS), United States, July 2016–June 2018

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ABSTRACT

Background: Trivalent adjuvanted influenza vaccine (aIIV3; Fluad®) was approved in the United States (U.S.) in 2015 for adults aged ≥65 years and has been in use since the 2016–17 influenza season.
Methods: We analyzed U.S. reports for aIIV3 submitted from July 1, 2016 through June 30, 2018 to the Vaccine Adverse Event Reporting System (VAERS), a national spontaneous reporting system. Medical records were reviewed for serious reports. Among individuals ≥65 years of age, the relative frequency of the most commonly reported adverse events (AEs) after aIIV3 were compared with non-adjuvanted inactivated influenza vaccines given to adults aged ≥65 years, high-dose trivalent influenza vaccine (IIV3-HD) and trivalent or quadrivalent vaccines (IIV3/IIV4). Data mining analyses were undertaken to identify whether AEs for aIIV3 occurred disproportionately more than expected compared to all influenza vaccines.
Results: VAERS received 630 reports after aIIV3, of which 521 (83%) were in adults aged ≥65 years; 79 (13%) in persons <65 years and in 30 (5%) reports age was missing; 19 (3%) reports were serious, including two deaths (0.4%) related to myocardial infarction and Sjogren's syndrome. The most common AEs reported in adults aged ≥65 years were injection site pain (21%) and erythema (18%), with similar proportions reported for IIV3-HD (17% and 19%, respectively) and for IIV3/IIV4 (15%, each). Except for reports related to vaccination of inappropriate age (n = 79) and syringe malfunction (n = 6), data mining did not identify other disproportionately reported AEs.
Conclusions: Although our review of aIIV3 in VAERS did not identify any unexpected health conditions of concern, we observed more than twice the expected number of reports with administration of the vaccine to persons outside of the age range for which the vaccine is approved in the U.S. Health care providers should be educated on the age groups for whom aIIV3 is recommended.

1. Introduction

On November 24, 2015, the United States (U.S.) Food and Drug Administration (FDA) approved Fluad® (aIIV3) (Seqirus), under accelerated approval, for the prevention of seasonal influenza in adults aged ≥65 years [1]. aIIV3, a trivalent vaccine produced from three influenza virus strains (two subtype A and one type B), is the first U.S. licensed seasonal adjuvanted influenza vaccine. On October 15, 2015, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of aIIV3 in adults aged ≥65 years during 2016–17 influenza season [2].

Adjuvants are incorporated into some vaccine formulations to enhance or direct the immune response of the vaccinated individuals [1,3,4]. aIIV3 is formulated using an egg-based process and the adjuvant MF59®, an oil-in-water emulsion of squalene oil. Squalene, a naturally occurring substance found in humans, animals, and plants, is highly purified for the vaccine manufacturing process. Safety and immunogenicity studies, on which current approval for aIIV3 is based, suggest that aIIV3 provides an alternative to other recommended non-adjuvanted inactivated influenza vaccines for adults aged ≥65 years [1,3].

aIIV3 was first approved for use in Italy in 1997 and is currently approved in 38 countries, including Canada and 15 European

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countries [2,5,6]. aIIV3 is approved also for pediatric use (6 through 24 months) in Canada and other European countries [5,6]. aIIV3 has been evaluated extensively in clinical trials in both young children and adults. In both groups, systemic reactions were comparable to trivalent influenza vaccines [3,7]. Safety of aIIV3 in elderly subjects has been assessed in 15 randomized controlled clinical studies and safety concerns were not identified [2–6].

Post-licensure safety studies of the elderly in Italy reported a similar safety profile among individuals receiving aIIV3 and non-adjuvanted influenza vaccines [5,8]. The most commonly reported adverse events (AEs) were injection site pain and tenderness, muscle aches, headache, and fatigue [1,8,9].

aIIV3 is the first adjuvanted influenza vaccine in the U.S. market. In this review, we analyzed the safety profile of aIIV3 by reviewing reports submitted to the U.S. Vaccine Adverse Event Reporting System (VAERS).

2. Methods

2.1. Data source

VAERS is a national, spontaneous reporting system co-administered by the Centers for Disease Control and Prevention (CDC) and the FDA for monitoring AEs following vaccination [10,11]. VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients and others (e.g., pharmacists). VAERS data include information on demographics of the vaccinee, vaccine administered, concurrent medications and vaccinations, medical history, reporter type (person submitting the report), the AE, and the outcome of the AE. For U.S. serious reports, medical records are routinely requested and reviewed, except for reports submitted by vaccine manufacturers. A report is considered serious if the AE results in death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability or birth defect [12].

Signs and symptoms of AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terms according to guidance from the International Conference on Harmonization [13]. MedDRA terms are arranged in categories that range from broad terms or System Organ Class (SOC) to more specific terms or Preferred Terms (PTs). A single VAERS report may be assigned one or more PTs within one or more SOCs. We searched the VAERS database for all aIIV3 reports received from July 1, 2016 through June 30, 2018. Foreign reports were excluded.

2.2. Descriptive analysis

We determined the frequency of MedDRA PTs and tabulated the most common relevant PTs. We also calculated the mean and median ages of individuals at time of vaccination and AE onset interval (time from vaccination [day 0] to date of onset of first symptoms related to AEs).

2.3. Clinical review of reports

We reviewed all serious VAERS reports and all available medical records, including death certificates and autopsy reports, if applicable, submitted for aIIV3 during July 1, 2016 through June 30, 2018 [14]. We also reviewed reports and medical records for the following pre-specified conditions: Guillain-Barré syndrome (GBS) and anaphylaxis. Additionally, we reviewed reports for MedDRA PTs of clinical or epidemiological importance that exceeded the data mining threshold (i.e. EB05 $\geq$ 2.0) using data mining techniques described below [15,16]. We excluded from the clinical review reports of AEs described in the aIIV3 package insert or those deemed as nonspecific, or general in nature as described elsewhere [17].

Cause of death was determined from information documented in the autopsy report, death certificate, or medical record. We did not assess causality of the AE following vaccination. Reports of GBS and anaphylaxis were verified using the Brighton Collaboration criteria or a physician's diagnosis documented on the medical records [18–20].

2.4. Comparative review

We compared the most common MedDRA PTs associated with aIIV3 reports with those reported for trivalent or quadrivalent inactivated influenza vaccines (IIV3/IIV4) and high-dose trivalent inactivated influenza vaccine (IIV3-HD) among adults $\geq$65 years of age during the same study period. We grouped the most commonly reported PTs and compared the proportions with those reported for IIV3-HD and IIV3/IIV4. Finally, we compared the proportion of GBS and anaphylaxis reports in these same vaccine groups.

2.5. Disproportionality analysis (data mining)

We used Empirical Bayesian (EB) data mining techniques [15] to identify AEs reported more often than expected following aIIV3 compared to AEs reported for all vaccines (other than influenza vaccines) and for all influenza vaccines. The primary statistic calculated with data mining is the Empirical Bayes Geometric Mean (EBGM) and its associated 90% confidence interval (EB05, EB95). An EB05 $\geq$ 2.0 is commonly used as a threshold for considering an AE as a potential signal because it suggests a high probability that a vaccine-event pair occurs at least twice as often as expected, with the underlying assumption that vaccine-event pairs are random [16]. AEs reported for aIIV3 were compared to AEs associated with all U.S. vaccine reports or all U.S. influenza vaccine reports in VAERS submitted during the study period. Analyses were adjusted for sex, age, and year report received. AEs were assessed overall (all ages, all events); overall, excluding individuals with unknown age; by age group (<65 years, $\geq$65 years, unspecified/unknown); and by seriousness (all events, serious events only). Of note, disproportionality analyses are intended to assess potential signals and do not imply causality between the vaccine-event pair.

3. Results

3.1. aIIV3 reports in VAERS

From July 1, 2016 through June 30, 2018, VAERS received a total of 630 U.S. reports of which 521 (82.7%) were for adults aged $\geq$65 years, 79 (12.5%) were for adults aged <65 years, and 30 (4.8%) had age unspecified. aIIV3 was administered alone, without a concurrent vaccine, in 325 (62%) reports. Pneumococcal polysaccharide vaccine (PPSV) was the most commonly co-administered vaccine (n = 115; 18%) followed by pneumococcal conjugate vaccine (PCV13) (n = 69; 11%) [Table 1].

Twenty-one (3%) were serious reports, including two death reports (0.3%). Three serious reports (14%) described AEs occurring in adults aged <65 years; one of them described a case of GBS in a 32-year-old female [Table 2].

3.2. Clinical review of all serious reports

Among serious, non-death reports, 16 were described in females and three in males. The median onset interval was within one day of vaccination (range 0–47 days). Table 2 lists the main diagnoses of these serious reports classified by SOCs. Neurological

Table 1
Characteristics of all aIIV3 reports submitted to VAERS during July 1, 2016–June 30, 2018.

	aIIV3 Reports, N = 630
Serious Status, n (%)[a]	
Death	2 (0.3)[b]
Serious, non-death	19 (3)
Non-serious	609 (97)
Age Group (years), n (%)	
0–18	11 (2)
19–64	68 (11)
≥65	521 (83)
Not specified	30 (5)
Concomitant Vaccines, n (%)	
None	325 (52)
PPSV	115 (22)
PCV13	69 (13)
Other	121 (19)
Sex, n (%)	
Male	196 (31)
Female	417 (66)
Unknown	17 (3)
Age (years), median (range)	71 (1–94)
AE Onset (days), median (range)	1 (0–56)

Abbreviations: AE, adverse event; n, number of reports; PCV13, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; VAERS, Vaccine Adverse Event Reporting System.
[a] Two death and 16 serious, non-death reports were reported in adults aged ≥65 years.
[b] Percentages may not sum to 100 due to rounding.

Table 2
Serious reports after all trivalent adjuvanted influenza vaccines (aIIV3) in adults according to System Organ Class, VAERS, July 1, 2016–June 30, 2018[a].

System Organ Class	No. of reports (N = 21)[a]
Neurological disorders	
Guillain-Barré syndrome	3
Bell's palsy	1
Bickerstaff's encephalitis	1
Weakness lower extremities	1
Musculoskeletal and connective tissue disorders	
Shoulder pain	3
Arm pain	2
General disorders and administration site conditions	
Fever, chills	3
Cellulitis, bursitis	2
Gastrointestinal disorders	
Acute diarrhea/gastroenteritis	1
Injury, poisoning and procedural complications	
Fall	1
Skin and subcutaneous tissue disorders	
Keratosis pilori rubra	1
Deaths	
Cause of death: Sjogren's syndrome	1
Cause of death: Myocardial infarction	1
Total	21

Abbreviations: VAERS, Vaccine Adverse Event Reporting System.
[a] Three serious, non-death reports in persons <65 years of age included one report each of cellulitis, fever/chills/myalgia, and unverified Guillain-Barré syndrome (GBS). The report of GBS (32-year-old female) was not classified as serious because the diagnosis could not be verified and therefore, is not included in this table.

and musculoskeletal conditions comprised the most common groups of serious AEs. Three serious reports involved persons aged <65 years: GBS in a 32-year-old female, left deltoid cellulitis in a 27-year-old female, and fever, chills, and myalgia in a 20-year-old female. Two deaths following aIIV3 vaccination were reported: a 75-year-old male with cause of death reported as Sjogren's syndrome and a 65-year-old male who died due to myocardial infarction [Table 2].

3.3. Comparative analysis

The most common PTs after aIIV3 were similar to those reported after IIV3-HD and IIV3/IIV4 among individuals ≥65 years of age. The most common AEs were injection site pain (21%) and erythema (18%), with similar proportions reported for IIV3-HD (17% and 19%, respectively) and for IIV3/IIV4 (15%, each) [Table 3a]. Among select, pre-specified conditions [Table 3b], there were no reports of anaphylaxis among 521 reports for aIIV3, and anaphylaxis accounted for 0.2% (8 out of 4383) and 0.4% (4 out of 1095) reports following IIV3-HD and IIV3/IIV4, respectively. Three cases (0.6%) of GBS were reported following aIIV3, a similar proportion following IIV3-HD (0.7%; n = 31), and a relatively higher proportion after IIV3/IIV4 (1.6%; n = 17).

3.4. Clinical review of pre-specified adverse events and conditions

3.4.1. Anaphylaxis

Among the 521 aIIV3 reports submitted for individuals ≥65 years of age, there were no cases of anaphylaxis [Table 3b].

3.4.2. Guillain-Barré syndrome

Four reports of GBS occurring after aIIV3 were submitted to VAERS during the review period. Three reports involved a single aIIV3 vaccine, and one report noted concurrent vaccination with aIIV3 and PCV13. In one report of GBS (32-year-old female), medical records were not available, and the diagnosis could not be verified. Among the verified reports, the affected individuals (2 males and 1 female) were aged 70, 73, and 74 years. The onset interval from vaccination to appearance of neurological symptoms ranged from 1 to 8 days. Two reports met Brighton level criteria 1 and 3, and a third did not meet Brighton criteria, but was considered as GBS by the attending physician. None of the three patients had a recent history of a respiratory or gastrointestinal infection.

3.4.3. Data mining

Serious AEs were not reported disproportionately for aIIV3 compared to all other vaccines nor compared to all influenza vaccines. Data mining analyses revealed disproportionate reporting for the PT's 'drug administered to patient of inappropriate age' (n = 62) and 'syringe issue' (n = 6). Among reports of drug administered to patient of inappropriate age, the median age at vaccination was 38 years (range 5–64 years). Seven were reports in children. Most reports (57 out of 62; 91.9%) did not describe an AE. The AEs in five reports were mild conditions including excessive sleeping, malaise, headache, fatigue, and injection site pain. Two reports with no AE were in pregnant women who received the vaccine at 15-weeks and 39-weeks gestation. Reports of 'syringe issue' were either leakage of the vaccine outside the syringe due to a problem with the syringe/needle attachment (n = 4), or difficulty pushing the plunger (n = 2). The age and sex of individuals involved in these six reports was unknown.

4. Discussion

This is the first VAERS-based post-marketing safety review of aIIV3 since U.S. licensure with an indication for use in adults aged ≥65 years. Our review of AEs following aIIV3 administration in the U.S. did not identify any unexpected health condition of concern. However, we did observe administration of the vaccine to persons <65 years of age in whom the vaccine is not recommended. Syringe issues were also reported disproportionately more often than with other vaccines, but review of these cases did not reveal any consistent patterns in reports nor an association with a specific lot number.

Table 3a
Most frequently reported Preferred Terms following aIIV3, IIV3-HD and IIV3/IIV4 in adults aged ≥65 years, VAERS, July 1, 2016–June 30, 2018.[a]

Preferred Terms according to vaccine					
aIIV3 (N = 521)[b]		IIV3-HD (N = 4383)[b]		IIV3/IIV4 (N = 1095)[b]	
Pain in extremity	110 (21)	Injection site erythema	833 (19)	Injection site pain	173 (16)
Injection site erythema	92 (18)	Pain in extremity	727 (17)	Pain in extremity	160 (15)
Pain	82 (16)	Injection site pain	686 (16)	Injection site erythema	159 (15)
Injection site pain	7 (15)	Erythema	684 (16)	Pain	138 (13)
Injection site swelling	68 (13)	Injection site swelling	656 (15)	Injection site swelling	124 (11)
Erythema	68 (13)	Fever	578 (13)	Erythema	115 (11)
Peripheral swelling	50 (10)	Pain	540 (12)	Fever	107 (10)
Fever	48 (9)	Peripheral swelling	477 (11)	Peripheral swelling	74 (7)
Injection site warmth	41 (8)	Chills	423 (10)	Injection site warmth	72 (7)
Chills	40 (8)	Injection site warmth	371 (8)	Fatigue	71 (6)

Abbreviations: aIIV3 Trivalent adjuvanted influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3/IIV4, trivalent or quadrivalent vaccines; N, number of reports; VAERS, Vaccine Adverse Event Reporting System.
[a] Preferred Terms (PTs) are not mutually exclusive (e.g., a report may include more than one PT).
[b] Results are presented for number of reports and percentage, as indicated, N (%).

Table 3b
Pre-specified medical conditions after aIIV3, IIV3-HD and IIV3/IIV4 in adults aged ≥65 years, VAERS, July 1, 2016–June 30, 2018.

Pre-specified events according to vaccine			
Pre-specified event	aIIV3[a]	IIV3-HD[a]	IIV3/IIV4[a]
Anaphylaxis	0	8 (0.2)	4 (0.4)
Guillain-Barré syndrome	3 (0.6)	31 (0.7)	17 (1.6)
Injection site reactions	183 (35)	1599 (36)	350 (32)

Abbreviations; aIIV3 Trivalent adjuvanted influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3/IIV4, trivalent or quadrivalent vaccines; N, number of reports; VAERS, Vaccine Adverse Event Reporting System.
[a] Results are presented for number of reports and percentage, as indicated, N (%).

Our findings were consistent with pre-licensure studies, which found that local reactions such as injection site pain and injection site erythema were the most common AEs [1]. In post-licensure meta-analysis of clinical trials in elderly adults, local reactions were slightly more common for aIIV3 than IIV3, but the occurrence of fever was comparable between these vaccines. Overall, AEs in pre-licensure studies were generally mild and transient [3,8]. Collective data from 1997 to 2010, including clinical trials and post marketing studies, encompassed 160 million people of all ages, and documented similar local reactions and a similar safety profile compared to non-adjuvanted influenza vaccines in the elderly [2,3,5,9].

In this review, the most common serious, non-death reports included neurological conditions. Four reports of GBS following aIIV3 were submitted, one in an adult <65 years of age. In all four reports, the interval between date of vaccination and symptom onset (1–8 days) was within the window of biologic plausibility [18,21–24]**.** GBS is an acute, immune-mediated paralytic disorder of the peripheral nervous system which was first linked to influenza vaccination during the vaccination campaign for the 1976 swine influenza A(H1N1) pandemic threat and has been shown to be associated with receipt of seasonal inactivated influenza vaccines in adults in some influenza seasons [21–23]. When an association has been noted, the attributable risk of GBS in adults after seasonal inactivated influenza vaccines has been approximately 1–3 additional cases per million vaccinees [24,25]. Data mining did not detect disproportionate reporting of GBS following aIIV3 compared with other vaccines or other influenza vaccines. The four reported cases of GBS [Table 2] should be interpreted in the context of nearly six million doses of aIIV3 distributed in the U.S. (Seqirus personal communication June 2018).

Anaphylaxis may be causally associated with influenza vaccination in rare instances [19,20]. Our review did not identify reports of anaphylaxis after aIIV3 and few reports after IIV3-HD or IIV3/IIV4.

The strength of this study is use of VAERS, a nationally representative, passive surveillance system which can help identify safety signals, especially for rare AEs. Following the introduction of new vaccines or issuance of new vaccination recommendations, safety data can be rapidly collected and assessed in near real-time [26]. Such advantages can be useful for a new vaccine such as aIIV3. However, spontaneous systems such as VAERS can have important limitations, including biased reporting, over- or under-reporting, and inconsistency in quality and completeness of reports [10,11]. Other limitations include the general inability to assess causality between an AE from a VAERS report and receipt of a vaccine, and limitations in comparing AEs for vaccines that have been available on the market for varying periods of time, because AE reporting to VAERS tends to peak within two years of vaccine approval and initial uptake [27]. While it is usually not possible to verify causal associations between vaccines and AEs, assessments in VAERS, including the current study, can help identify AEs that may warrant follow-up or evaluation in other databases.

In summary, we did not identify new safety concerns associated with aIIV3 among individuals ≥65 years, i.e. within the age range for which the vaccine is approved in the U.S. However, we identified disproportional reporting for 'drug administered to patient of inappropriate age'. AEs associated with these vaccination errors were non-serious reports with no obvious immediate effects; however, longer-term effects are not known. Nevertheless, these reports serve to alert health care providers to review the age group in whom this vaccine is recommended prior to vaccine administration [28,29]. Because aIIV3 has been available in the U.S. only since the 2016–17 influenza season, the data available in VAERS describing AEs temporally associated with the vaccine are limited. Thus, CDC and FDA will continue to monitor AE reports to assess the safety profile of aIIV3.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the U.S. Food and Drug Administration.

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