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# Monitoring the safety of high-dose, trivalent inactivated influenza vaccine in the vaccine adverse event reporting system (VAERS), 2011 – 2019

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ABSTRACT

*Background:* On 12/23/2009 a new high-dose trivalent inactivated influenza vaccine (IIV3-HD) was licensed for adults aged ≥65 years. We assessed the post-licensure safety data for IIV3-HD in the Vaccine Adverse Event Reporting System (VAERS) during 2011–2019.
*Methods:* We searched VAERS for reports after IIV3-HD during 1/1/2011–06/30/2019 in persons aged ≥65 years. Medical records were reviewed for all death reports and for certain pre-specified conditions (e.g. Guillain Barré Syndrome [GBS], anaphylaxis). We also reviewed certain groups who received IIV3-HD erroneously (e.g. pregnant women, children). Empirical Bayesian data mining was used to identify disproportional reporting.
*Results:* VAERS received 12,320 reports after IIV3-HD;723 reports (5.9%) were serious. The most common adverse events (AEs) among serious reports were pyrexia (30.2%), asthenia (28.9%), and dyspnea (24.9%), and among non-serious reports were injection site erythema (16.8%), pain in extremity (15.8%), and injection site pain (14.2%). Among 55 death reports, the most common causes of death were diseases of the circulatory system (n = 23;41.8%). Based on medical record review, there were 61 reports of GBS and 13 of anaphylaxis. There were 13 reports of pregnant-women who inadvertently received IIV3-HD; three reports described arm pain or local reactions, and 10 did not report any AE. Among 59 reports of children who erroneously received IIV3-HD, 31 experienced an AE (most commonly injection site or constitutional reactions) and the remaining 28 reports did not describe any AE.
*Conclusions:* Post-licensure safety data of IIV3-HD during 9 influenza seasons revealed no new or unexpected safety concerns among individuals ≥65 years. Inadvertent administration of IIV3-HD to children or pregnant women was observed, although with no serious AEs reported. Training and education of providers in vaccine recommendations and groups for whom the vaccine is indicated may help in preventing these vaccine administration errors. This review provides baseline information for future monitoring of the quadrivalent-high-dose influenza vaccine.

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## 1. Introduction

Older adults are more vulnerable to infection with influenza, and to subsequent influenza illness, hospitalization, and death, [1] which may be due to decreased immunity and comorbid conditions [2]. Improving the efficacy of influenza vaccines in this population has been an active area of research [3]. A high dose trivalent inactivated influenza vaccine (IIV3-HD) was licensed by the Food and Drug Administration (FDA) on December 23, 2009 [4,5]. The Advisory Committee on Immunization Practices (ACIP) has included the IIV3-HD formulation for adults aged ≥ 65 years in its recommendations since the 2010–2011 influenza season [1]. A previous post-licensure assessment of the safety of IIV3-HD in the Vaccine Adverse Event Reporting System (VAERS) during its first year after licensure did not reveal any new or unexpected safety concern [6]. Adverse events reported were consistent with injection site and constitutional reactions observed in pre-licensure studies [4,7]. The current review describes the post-licensure safety experience with IIV3-HD in VAERS during 9 influenza seasons since 2011.

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## 2. Material and methods

### 2.1. Vaers

VAERS is a U.S. national vaccine safety surveillance system created in 1990 and co-administered by the Centers for Disease Control and Prevention (CDC) and FDA [8]. It receives spontaneous reports of adverse events (AEs) following vaccination. Vaccination errors not describing an AE may also be reported [9]. VAERS data generally cannot be used to assess whether an AE is causally associated with vaccination, but may be useful for detecting potential vaccine safety problems [8]. VAERS accepts reports from healthcare providers, vaccine manufacturers, vaccine recipients, and other reporters. The VAERS report form collects information on sex, age, vaccines administered, dose and lot number, the AE experienced, and medical history. Signs and symptoms of AEs are coded by trained personnel using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology [10]. A VAERS report may be assigned one or more MedDRA Preferred Terms (PTs). A PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, or medical, social, or family history characteristic [10], but PTs are not necessarily medically confirmed diagnoses. A report is considered serious based on the Code of Federal Regulations (21-CFR) definition if one or more of the following are reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, congenital anomaly, permanent disability, or medical intervention to prevent the aforementioned outcomes [11]. For non-manufacturer serious reports, medical records are routinely requested and made available to VAERS personnel.

We searched the VAERS database for reports after IIV3-HD for persons given this vaccine from January 1, 2011 through June 30, 2019 (reports received by June 30, 2019). Non-U.S. reports were excluded, and duplicate reports were consolidated. We summarized the most common MedDRA PTs for serious and non-serious IIV3-HD reports and performed medical review for selected AEs, as described in the following section.

To provide context for our findings, we asked Sanofi Pasteur, the manufacturer of IIV3-HD, for permission to publicly disclose dose distribution information.

### 2.2. Clinical review of serious reports

All death reports after IIV3-HD were manually reviewed by physicians (PLM, EJW). The primary cause of death was obtained from the autopsy report, death certificate, and/or medical records. We also searched all reports and any available medical records for the following pre-specified conditions or populations: Guillain Barré Syndrome (GBS), anaphylaxis, pregnant women, and children. Reports of GBS were identified using the following MedDRA PTs: Guillain Barré Syndrome, Miller Fisher Syndrome, and demyelinating polyneuropathy. Anaphylaxis reports were identified using the following MedDRA PTs: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. Reports of GBS and anaphylaxis were classified using the Brighton Collaboration case definition, which uses three levels of diagnostic certainty, or a physician's diagnosis [12,13]. We searched for pregnancy reports by using a text string search for 'preg' in the variables for symptom text, pre-existing conditions, and medical history. We identified pediatric cases based on the age (≤18 years) reported on the VAERS form. In this review, we made no attempt to assess causality of the reported AEs.

### 2.3. Data mining

We used empirical Bayesian (EB) data mining to identify AEs that were reported more frequently than expected following IIV3-HD compared to other vaccines in VAERS, adjusting for age, sex, and the year in which reports were received [14]. We conducted the analyses using the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm [14,15] in Oracle's Empirica™ Signal System. The main statistical scores computed are EBGM, EB05, EB95, representing the Empirical Bayes Geometric Mean and the 90% confidence interval. We used published criteria to identify AEs that were reported at least twice as frequently as would be expected following IIV3-HD (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] > 2) [15] For PTs with elevated values, we clinically reviewed the VAERS reports. Elevated data mining statistics should not be interpreted as evidence of causal relationship between a vaccine and an AE; vaccine-event combinations identified as potential signals by data mining methods may be useful to generate hypothesis that can be tested with controlled studies [16,17].

## 3. Ethics

Because VAERS is a routine surveillance program designed to improve an immunization program, it does not meet the definition of research; therefore, this work was not subject to Institutional Review Board evaluation and informed consent requirements.

## 4. Results

During the period of this review, VAERS received 12,320 reports for IIV3-HD in adults aged ≥ 65 years; 723 reports (5.9%) were serious, including 55 deaths. Table 1 summarizes the demographic characteristics, and Table 2 summarizes the most common MedDRA PTs. Females accounted for almost ¾ of all reports and the most common PTs for serious and non-serious reports were pyrexia (30.2%) and injection site erythema (16.8%), respectively.

Through June 2019, 113.1 million doses of IIV3-HD have been distributed (data shown with permission from Sanofi Pasteur).

### 4.1. Deaths

There were 55 deaths, with age ranging from 65 to 95 years (median: 80 years); 21 were women (38%). On the whole, the causes of death were typical for individuals in this age group (Table 3). Cardiovascular conditions accounted for the largest cat-

**Table 1**
Characteristics of high-dose trivalent inactivated influenza vaccine (IIV3-HD) reports to VAERS among persons aged ≥ 65 years.

| Characteristics | n = 12,320[a] (%) |
|---|---|
| Serious | 723 (5.9) |
| Female[b] | 8,930 (72.5) |
| Median onset (range) days | 0 (0 – 1097) |
| Type of reporter | |
| Provider | 7,952 (64.6) |
| Other[c] | 2,222 (18.0) |
| Patient | 1,550 (12.6) |
| Manufacturer | 596 (4.8) |
| Median age (range) years | 71 (65 – 102) |
| IIV3-HD was the only vaccine listed on VAERS form | 8,454 (68.6) |
| Pneumococcal vaccine given on same date [d] | 3,502 (28.4) |

[a] In 646 reports after IIV3-HD (not included in this table), the vaccine was given to subjects less than 65 years of age, or with a missing value for age
[b] Gender unknown in 130 reports (x%); [c] Pharmacist
[d] Pneumovax, Prevnar, Prevnar 13, Pnu-Imune or no brand

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**Table 2**
Most frequent MedDRA Preferred Terms after high-dose trivalent inactivated influenza vaccine (IIV3-HD) reports for serious and non-serious reports in VAERS among person aged ≥ 65 years.

| Serious | IIV3-HD (n = 723) |
|---|---|
| Preferred Term[†] | n (%) |
| Pyrexia | 218 (30.2) |
| Asthenia | 209 (28.9) |
| Dyspnea | 180 (24.9) |
| Chills | 171 (23.7) |
| Nausea | 140 (19.4) |
| Pain | 125 (17.3) |
| Pain in extremity | 112 (15.5) |
| Dizziness | 108 (14.9) |
| Malaise | 107 (14.8) |
| Fatigue | 106 (14.7) |
| **Non-serious** | **IIV3-HD (n = 11,597)** |
| Injection site erythema | 1,947 (16.8) |
| Pain in extremity | 1,826 (15.8) |
| Injection site pain | 1,644 (14.2) |
| Pyrexia | 1,602 (13.8) |
| Pain | 1,561 (13.5) |
| Erythema | 1,553 (13.4) |
| Injection site swelling | 1,491 (12.9) |
| Chills | 1,385 (11.9) |
| Headache | 952 (8.2) |
| Injection site warmth | 900 (7.8) |

[†] One report may contain more than one PT.

**Table 3**
Causes of death after administration of high-dose trivalent inactivated influenza vaccine for reports submitted to VAERS.

| Body system | N (%) |
|---|---|
| **Diseases of the circulatory system** | 23 (41.8) |
| Coronary artery disease/myocardial infarction | 15 (27.3) |
| Hypertension/hypotension | 3 (5.4) |
| Rhythm alterations (e.g arrythmias) | 2 (3.6) |
| Cerebrovascular accidents | 2 (3.6) |
| Cardiovascular disease | 1 (1.8) |
| **Diseases of the respiratory system** | 8 (14.5) |
| Chronic obstructive pulmonary disease | 4 (7.3) |
| Pneumonia | 2 (3.6) |
| Acute respiratory distress syndrome | 1 (1.8) |
| Pulmonary fibrosis | 1 (1.8) |
| **Infectious diseases** | 5 (9.1) |
| Sepsis/septic shock | 5 (9.1) |
| **Neoplasms** | 5 (9.1) |
| **Diseases of the nervous system** | 3 (5.4) |
| Guillain-Barré Syndrome | 3 (5.4) |
| **Injury, poisoning and certain other consequences of external causes** | 2 (3.6) |
| Aspiration | 2 (3.6) |
| **Endocrine, nutritional and metabolic diseases** | 1 (1.8) |
| **Diseases of the genitourinary system** | 1 (1.8) |
| **Immune system disorders** | 1 (1.8) |
| **Unevaluable/no information** | 6 (10.9) |
| **Total** | 55 |

The average time from vaccination to death was 9.4 days (range 0–85 days) and the median time was 1 day.

egory, followed by respiratory diseases, infection/sepsis, and neoplasms.

### 4.2. Guillain-Barré Syndrome

Sixty-nine reports of GBS after IIV3-HD were reported to VAERS (0.6%; 69/12,320). Sixty-one met Brighton criteria or were considered as GBS by the attending physician. The onset interval was 0–42 days following vaccination in 52 of the 61 reports for which information was available. Sixteen cases were confirmed as Brighton level 1, 32 as Brighton level 2, and 8 as Brighton level 3. Five reports did not have sufficient information for Brighton classification, but were considered as GBS by the patient's physician.

### 4.3. Anaphylaxis

Thirty-nine reports had at least one PT suggestive of anaphylaxis (0.32%;39/12,320); 24 described likely or possible cases of anaphylaxis. Based on review of medical records, 13 were verified as anaphylaxis: Brighton level 1 (n = 7), Brighton level 2 (n = 1), Brighton level 3 (n = 2), or a diagnosis of anaphylaxis by the patient's physician (n = 3). In 11 additional reports, the description in the VAERS form suggested anaphylaxis, but medical records were not available. Of these 24 cases of likely or possible anaphylaxis, 18 received IIV3-HD as the only vaccine. Fifteen reports described allergic reactions that were not anaphylaxis.

### 4.4. Pregnancy

Thirteen reports stated that pregnant women had inadvertently received IIV3-HD. Median age was 29 years with a range of 18–37 years. Three reports described local reactions, and the other 10 did not report any AE. None of the reports described any adverse effects affecting the pregnancy itself.

### 4.5. Children

Fifty-nine reports stated that an individual < 18 years had inadvertently received IIV3-HD. Thirty-one reports described AEs, including: injection site reactions or arm pain (n = 12), constitutional symptoms (n = 4), non-anaphylaxis allergic reactions (n = 2), gastrointestinal symptoms (n = 3), and one report each of febrile seizures, post viral cerebellitis, upper leg/knee swelling, acute kidney injury, hypotonia, opening mouth as if to scream, difficulty breathing, shaking uncontrollably, torticollis, and autism/speech regression. Twenty-eight reports did not describe an AE.

## 5. Discussion

We conducted a review of AEs after IIV3-HD reported to VAERS during 9 influenza seasons. Our review included automated analyses of all reports, and clinical review of all death reports and prespecified conditions (GBS, anaphylaxis). We also analyzed certain groups of interest for whom this vaccine is not recommended (pregnant women and children) but who received the vaccine in error. Our findings were consistent with those from pre-licensure studies [4] and an initial post-licensure study of the VAERS database during its first season on the market [6]. The most common PTs observed among serious and non-serious reports were constitutional (e.g. fever, asthenia) and injection site reactions (e.g., injection site erythema, injection site pain), respectively, which are findings consistent with those from pre-licensure clinical trials [4].

Among death reports for which sufficient records were available for review, the leading causes of death were diseases of the circulatory system (e.g. coronary artery disease, myocardial infarction), respiratory conditions (e.g., chronic obstructive pulmonary disease), and sepsis, all of which are consistent with leading causes of death in older adults in the US [18].

Anaphylaxis is an acute hypersensitivity reaction that involves the release of mediators from mast cells, basophils and recruited inflammatory cells [19]. It involves multiple organ systems and can present with variable severity, ranging from mild to

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life-threatening [19]. Anaphylaxis is a rare adverse event after vaccination and its incidence after IIV3 vaccination was recently estimated to be 1.6 per million doses distributed among all ages [20]. Our finding of 13 reports of verified anaphylaxis after IIV3-HD is consistent with the rarity of this event after vaccination with other influenza vaccines.

Guillain Barré Syndrome (GBS) is an acute, immune-mediated paralytic disorder of the peripheral nervous system [21]. The background incidence of GBS varies and is higher with increasing age [22]. Among persons aged 80–89 years it has been reported at 2.66 cases per 100,00 person-years [22]. Although very rare, an increased risk of GBS was observed following vaccination with the 1976–1977 A/New Jersey ("swine influenza") vaccine [23]. In our review of 9 years of data for IIV3-HD, GBS was confirmed in 61 cases. For 52 of these cases, the onset was within 42 days of vaccination, the window of biological plausibility if an association with vaccination is suspected. However, during the time period of our study 113 million doses of IIV3-HD vaccine had been distributed, and our data mining analysis did not show disproportionate reporting for GBS.

Vaccination errors involving pregnant women and children were reported to VAERS but no concerning pattern of AEs was observed in these groups. Most of the reports did not describe an AE, and if one was present it was typically mild and non-serious. However, these findings highlight the need to provide education and training to providers on ACIP recommendations and package insert indications to help prevent these errors.

Strengths of VAERS include its broad national scope and timeliness [8]. VAERS may be particularly useful for detecting potential safety signals which can be further evaluated in larger datasets using controlled epidemiological methodologies [24]. As a passive surveillance system, VAERS has several inherent limitations which call for careful interpretation of its findings. Some of these limitations include over- or under-reporting, biased reporting, and inconsistency in quality and completeness of reports [8]. VAERS data generally cannot be used to assess if a vaccine caused an AE. VAERS does not collect data on number of vaccinees, therefore, it does not provide denominator data to calculate incidence rates of AEs.

## 6. Conclusion

Our assessment of post-licensure safety data for IIV3-HD did not identify any new or unexpected safety issues and is consistent with pre-licensure studies. With the introduction of quadrivalent high-dose influenza vaccine (IIV4-HD) [25], the information from this review may serve as a baseline for monitoring post-licensure safety of the new vaccine.

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 Food and Drug Administration.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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