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Adverse events after Fluzone® Intradermal vaccine reported to the Vaccine Adverse Event Reporting System (VAERS), 2011–2013☆

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Abstract

Background: In May 2011, the first trivalent inactivated influenza vaccine exclusively for intradermal administration (TIV-ID) was licensed in the US for adults aged 18–64 years.

Objective: To characterize adverse events (AEs) after TIV-ID reported to the US Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

Methods: We searched VAERS for US reports after TIV-ID among persons vaccinated from July 1, 2011–February 28, 2013. Medical records were requested for reports coded as serious (death, hospitalization, prolonged hospitalization, disability, life-threatening-illness), and those suggesting anaphylaxis. Clinicians reviewed available information and assigned a primary clinical category to each report. Empirical Bayesian data mining was used to identify disproportional AE reporting following TIV-ID. Causality was not assessed.

Results: VAERS received 466 reports after TIV-ID; 9 (1.9%) were serious, including one reported fatality in an 88-year-old vaccinee. Median age was 43 years (range 4–88 years). The most common AE categories were: 218 (46.8%) injection site reactions; 89 (19.1%) other non-infectious (comprised mainly of constitutional signs and symptoms); and 74 (15.9%) allergy. Eight reports (1.7%) of anaphylaxis were verified by the Brighton criteria or a documented physician diagnosis. Disproportional reporting was identified for three AEs: ‘injection site nodule’, ‘injection site pruritus’, and ‘drug administered to patient of inappropriate age’. The findings for the first two AEs were expected. Twenty-four reports of vaccinees <18 years or ≥65 years were reported, and 14 of 24 were coded with the AE ‘drug administered to patient of inappropriate age’.

Conclusions: Review of VAERS reports did not identify any new or unexpected safety concerns after TIV-ID. Injection site reactions were the most commonly reported AEs, similar to the pre-licensure clinical trials. Use of TIV-ID in younger and older individuals outside the approved age range highlights the need for education of healthcare providers regarding approved TIV-ID use.

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Keywords

Adverse event; Intradermal; Surveillance; Trivalent inactivated influenza vaccine; Vaccine safety

1. Introduction

On May 9, 2011 the Food and Drug Administration (FDA) licensed the first US trivalent inactivated influenza intradermal vaccine (TIV-ID) formulation (Fluzone® Intradermal, manufactured by Sanofi Pasteur), for use in adults 18–64 years. TIV-ID contains 9 μg of hemagglutinin per strain and is administered in a 0.1 ml/dose using a microinjection system [1]. By contrast, standard Fluzone® trivalent inactivated influenza vaccine (TIV) contains 15 μg of hemagglutinin per strain and is administered as an intramuscular injection of 0.5 ml/dose. The Advisory Committee on Immunization Practices (ACIP) included TIV-ID for adults aged 18–64 years in its recommendations for the 2011–12 and 2012–13 influenza seasons [2,3]. Effectiveness of TIV-ID was found to be non-inferior to that of Fluzone® (TIV) (IM); however, TIV-ID may be an appealing option for persons who have an aversion to intramuscular injections, and TIV-ID is antigen-sparing [4]. Pre-licensure clinical trials enrolled 2855 TIV-ID and 1421 TIV recipients and found that TIV-ID elicited a higher proportion of local reactions than TIV, with the exception of pain [5–7]. These local reactions after TIV-ID were also found to be greater in clinical severity as compared to TIV. However, most of these reactions were self-limited. No other clinically important differences were detected for adverse events (AEs) after TIV-ID, compared with TIV (Fluzone®). A similar intradermal inactivated influenza vaccine, Intanza®, was licensed for use in Europe, Canada, Australia, and New Zealand in 2009 and 2010 [8–10]. In these countries, two formulations of Intanza® were licensed: 9 μg of hemagglutinin per strain for use in adults 18–59 years, and 15 μg of hemagglutinin per strain for use in adults ≥60 years. Pre-licensure data for Intanza® 9 μg showed it had a similar safety profile as TIV-ID [11,12]. Although initial clinical trial experience with both Intanza® and TIV-ID suggest both vaccines had a good safety profile, these pre-licensure trials may not adequately identify rare AEs due to sample size limitations. We reviewed AEs reported to the Vaccine Adverse Event Reporting System (VAERS) involving individuals who received TIV-ID during the first two influenza seasons after licensure in order to identify possible safety concerns which may not have been detected during pre-licensure trials.

2. Methods

2.1. Vaccine Adverse Events Reporting System (VAERS)

VAERS is a national vaccine safety surveillance system, co-administered by the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA), that receives spontaneous reports of AEs following immunization [13]. VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients and others. The VAERS report form collects information on age, gender, vaccines administered, the AE experienced, and health 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, and entered into a database [14]. A VAERS report

may be assigned one or more MedDRA preferred terms. Reports are classified as serious or non-serious. A report is considered serious if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [15]. For non-manufacturer serious reports, medical records are routinely requested and made available to VAERS personnel. Reports with no AE may also be reported that describe an improper vaccine administration but where no adverse event took place. We analyzed VAERS reports received by March 15, 2013 for subjects vaccinated with TIV-ID during the first two influenza seasons of vaccine availability from July 1, 2011 through February 28, 2013. Non-US reports and duplicate reports were excluded.

2.2. Clinical review of reports

We conducted a clinical review of all VAERS reports and associated medical records for all serious reports, and for persons with a clinical presentation suggestive of anaphylaxis or Guillain–Barré syndrome (GBS), and for all pregnant women. A primary diagnostic category was assigned to each report based on the event that caused the reporter to report to VAERS, using a system previously described [16]. Reports suggestive of anaphylaxis were verified using the Brighton Collaboration criteria or a physician's diagnosis [17]. Cause of death was determined from information documented in the autopsy report, the death certificate, or the medical record. In this review we made no attempt to assess causality of the reported adverse events.

2.3. Data mining

We used empirical Bayesian (EB) data mining [18] to identify AEs reported more frequently than expected following TIV-ID in the VAERS database. We used published criteria [19,20] to identify, TIV-ID vaccine-event pairs reported at least twice as frequently as would be expected (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] >2). We clinically reviewed those TIV-ID reports containing preferred terms which exceeded the data mining threshold noted above.

2.4. Reporting rates

Crude reporting rates for all reports and anaphylaxis were estimated by dividing the number of all TIV-ID reports or verified reports of anaphylaxis by the number of doses of TIV-ID distributed by the manufacturer during the 2011–2012 and 2012–2013 influenza seasons combined [Sanofi Pasteur, personal communication].

2.5. Ethics

Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to Institutional Review Board review and informed consent requirements.

3. Results

VAERS received 466 reports after TIV-ID administered during July 1, 2011 through February 28, 2013, and received up to March 15, 2013 (Table 1). Nine (1.9%) reports were coded as serious. Among non-serious reports, 97 (20.6%) of 457 reported a visit to an

emergency department. The median age of vaccinees was 43 years (range 4 88) and 347 (74.5%) were female. In 438 reports (93.9%), TIV-ID was the only vaccine administered.

3.1. Clinical review

The most frequent AE diagnostic category was local injection site reactions, which accounted for 218 (46.8%) reports. The other non-infectious category, comprised mainly of constitutional signs and symptoms (e.g. syncope, fever) accounted for 89 (19.1%) reports, allergic type events accounted for 74 (16%) reports, including 8 reports of anaphylaxis. Among anaphylaxis reports, the onset interval for 7 of 8 reports was less than 24 hours and for one it was 2 days. Seven of the 8 anaphylaxis cases recovered by the time the VAERS form was submitted (Table 2). All 8 received only TIV-ID. Four reports met Brighton level 1 criteria, the category indicating the highest degree of diagnostic certainty, one met Brighton level 3 criteria, and three reports were physician-verified cases that did not meet Brighton criteria for anaphylaxis [17]. The three reports of physician-diagnosed anaphylaxis occurred among subjects who received TIV-ID from the same lot at an employee vaccination clinic in a healthcare facility. All three had a history of allergies to certain antibiotics (i.e., penicillin, cephalosporin), but none had a history of allergies or anaphylaxis to influenza or other vaccines. Two of the three were known to have received TIV in the past without any problems. None of the vaccinees in the other 5 reports of anaphylaxis had a history of severe allergies or anaphylaxis to any vaccine.

In all 9 serious reports TIV-ID was the only vaccine given. These serious reports included a fatal report of an 88-year-old female which occurred 16 days after vaccination. The death certificate listed “sudden cardiac death” as the cause of death. In two serious neurological reports, the main diagnoses were “cervical brachialgia,” and “headache.” Other diagnoses among serious reports included new onset fatigue and weakness, asthma exacerbation, neck swelling, anaphylaxis (Brighton level 1), arm pain, and multiple symptoms (e.g., fever, abdominal pain, nausea, fatigue, tachycardia). Although no reports were consistent with Guillain–Barré Syndrome after TIV-ID, one case of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in a 50-year-old female was reported. The patient had a history of diabetes mellitus and hypertension, but no recent history of respiratory or gastrointestinal infections. Seven non-serious reports involved pregnant women (median age 29 years; range 25–35 years of age). AEs in these reports involved injection site reactions in three, and one report each of systemic reactions (e.g., chills, myalgia), syncope, seizures, and injection site swelling in a patient with excessive bleeding during labor.

3.2. Data mining

Disproportionality analysis revealed an elevated EB05 (>2) for the AEs ‘injection site nodule’, ‘injection site pruritus’, and ‘drug administered to patient of inappropriate age’. The AE ‘drug administered to patient of inappropriate age’ denotes a vaccination error whereby individuals received TIV-ID at ages for which the vaccine is not approved. We identified 24 reports of use of TIV-ID in subjects of an age where TIV-ID is not indicated, 14 of which received the error code. In 16 reports, the vaccine recipient was aged <18 years; eight were aged ≥65 years. Twelve of the 24 reports did not describe an AE. The 12 AE reports among the inappropriate aged vaccinees included the death of the 88-year-old described above, and

a report of anaphylaxis in a 67-year-old male who recovered from the event. The other 10 reports included four injection site reactions, and one report each of: (i) pruritus and induration in the same arm where zoster vaccine was given; (ii) upper respiratory infection; (iii) non-anaphylactic allergic reaction; (iv) fever, cough, fatigue; (v) vertigo; and (vi) lymphadenitis.

3.3. Crude reporting rate

During the first two influenza seasons following licensure of TIV-ID, approximately 4.7 million doses of vaccine were distributed in the United States [Sanofi Pasteur, personal communication].

The overall crude reporting rate for TIV-ID was 99 reports per million doses of TIV-ID distributed. The crude reporting rate for anaphylaxis after TIV-ID in VAERS was 1.7 reports per million doses distributed during 2011–2013.

4. Discussion

During the 2011–2012 and 2012–2013 influenza seasons, the first TIV-ID was introduced in the United States for use in persons aged 18–64 years [2]. In this review, we found that almost half of the AEs reported to VAERS were mild and comprised injection site reactions, consistent with the safety profile of TIV-ID in pre-licensure clinical trials [2,3]. Our findings were also consistent with pre-licensure safety findings of Intanza® 9 μg which enrolled 2384 adults <60 years [11,12]. Erythema, induration, injection site swelling and pruritus were all significantly more common in recipients of Intanza® compared to Vaxigrip® (TIV) (IM) [11,12].

Although no cases of Guillain–Barré Syndrome were reported, a case of CIDP was observed in a 50-year-old female. CIDP is a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. Most cases occur in adults, and males are affected slightly more often than females. Although there is evidence of immune activation in CIDP, the precise mechanisms of pathogenesis are unknown. CIDP is closely related to Guillain–Barré syndrome, and it is considered the chronic counterpart of that acute disease [21]. The Institute of Medicine recently reviewed available scientific studies that looked at the association between influenza vaccination and CIDP and determined that the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and CIDP [22].

Using EB data mining, we noted disproportionate reporting for three adverse event terms: ‘injection site nodule’, ‘injection site pruritus’, and ‘drug administered to patient of inappropriate age’. The findings for the adverse event terms for local reactions were consistent with the product package insert and not unexpected. The third adverse event term denotes an error involving administration of TIV-ID to individuals whose ages were outside the approved age range. Use of TIV-ID in subjects outside the approved age range was observed in 5% of all TIV-ID reports, and highlights the need for education of healthcare providers regarding the approved ages and recommendations for TIV-ID use. Nevertheless, little harm was evident: just over half of these reports described no AE and of those that did,

most were mild, non-serious reports, with the only serious one being a fatal report of sudden cardiac death.

Anaphylaxis is a rare potentially life-threatening AE after vaccination that has an established causal association with influenza vaccines [22], making post-licensure surveillance warranted for newly licensed vaccines. In a previous study of data from 2006–2008, the observed incidence of anaphylaxis after TIV administration was 0.45–1.98 cases per million TIV doses administered for all ages [23]. We found no disproportionate reporting for anaphylaxis after TIV-ID in the VAERS database. The estimated crude reporting rate for anaphylaxis using doses distributed after TIV-ID was consistent with the incidence among TIV recipients [23].

While VAERS has a number of strengths, such as its broad national scope and timely reporting, it is a spontaneous reporting system. Limitations include over or under reporting, biased reporting, and inconsistency in quality and completeness of reports [13]. VAERS generally cannot assess causality between an AE and receipt of a vaccine. Although we estimated crude reporting rates for anaphylaxis using doses of vaccine distributed as a denominator, these estimates should be interpreted with caution since the number of doses administered and the completeness of anaphylaxis reporting to VAERS are not known. The regulatory definition of a serious report in VAERS can have limitations as it may not reflect the true severity of an outcome. For example, in our review, only one of 8 anaphylaxis reports was coded as serious because the patient was hospitalized, whereas the other 7 were coded as non-serious because although the patients were seen at the emergency department they were not hospitalized.

Our review of the safety of TIV-ID did not find any new or unexpected safety concerns that would warrant further study. However, as more vaccinees receive TIV-ID in future influenza seasons, rarer AEs may start to be reported more frequently to VAERS. CDC and FDA will continue to monitor the safety of TIV-ID during the 2013–2014 influenza season.

5. Conclusion

In this review of VAERS reports in persons who received TIV-ID during the first two influenza seasons post-licensure, we did not identify any new or unexpected safety concerns.

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Table 1

Characteristics of all intradermal trivalent inactivated influenza vaccine (TIV-ID) reports to VAERS among persons vaccinated July 1, 2011 through February 28, 2013 (reports received by March 15, 2013).

Characteristics	No. (%)
Total Reports	466
Serious	9 (1.9)
Reports during 2011–2012 influenza season	86 (18.5)
Reports during 2012–2013 influenza season	380 (81.5)
Female[a]	347 (74.5)
Median onset interval (range) days[b]	1 (0–87)
Reports where TIV-ID was given alone	438 (93.9)
Type of reporter	
Vaccine provider	224 (48.1)
Patient	124 (26.6)
Other	60 (12.9)
Manufacturer	58 (12.4)
Median age (range) years[c]	43 (4–88)
Age groups (years)	
<18	16 (3.4)
18–29	68 (14.6)
30–49	193 (41.4)
50–64	148 (31.8)
≥65	8 (1.7)
Subject recovered by the time the VAERS form was submitted	234 (50.2)

[a] Gender unknown in 19 (4.1%) reports.

[b] Onset interval (the time between vaccination and onset of symptoms) was unknown in 66 (14.1%) reports.

[c] Age unknown in 33 (7.1%) reports.

Table 2

Diagnostic categories for all reports of adverse events after intradermal trivalent inactivated influenza vaccine (TIV-ID) in VAERS among persons vaccinated July 1, 2011 through February 28, 2013.

Body system categories	**TIV-ID (*N* = 466) *N* (%)**
Local reactions[†]	218 (46.8)
Other non-infectious[‡]	89 (19.1)
Allergic	74 (15.9)
Non-anaphylaxis allergic reactions	66
Anaphylaxis[a]	8
Musculoskeletal	35 (7.5)
Neurological	13 (2.8)
Bell's palsy	2
Seizures	2
Chronic inflammatory demyelinating polyneuropathy	1
Other[b]	8
Respiratory	9 (1.9)
Digestive	4 (0.9)
Cardiac	3 (0.6)
Other[c]	21 (4.5)

[†]One report may contain more that one type of local reaction.

[‡]Other non-infectious is an unspecific category which includes diverse diagnoses (e.g. syncope, fever).

[a]Anaphylaxis reports include 4 reports of Brighton level 1, 3 reports of physician diagnosed anaphylaxis, and one Brighton level 3.

[b]Other neurological diagnoses include one report each of Parsonage Turner Syndrome, hearing loss, hypoesthesia/paresthesias, transverse myelitis, trigeminal neuralgia, cervical brachialgia, headache, and weakness.

[c]Other diagnoses include two reports each of the body system eye, nose and throat, and unspecified diagnosis, one report each of death, other infectious and psychiatric and 14 reports with no adverse events.