

Postlicensure Safety Surveillance for High-Dose Trivalent Inactivated Influenza Vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010–31 December 2010

Pedro L. Moro,¹ Jorge Arana,¹ Maria Cano,¹ David Menschik,² Xin Yue,¹ Paige Lewis,¹ Penina Haber,¹ David Martin,² and Karen Broder¹

¹Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; and ²Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland

Background. In December 2009, a new high-dose, trivalent, inactivated influenza vaccine (TIV-HD) was licensed for adults aged ≥ 65 years. We characterized clinical patterns of reports to the Vaccine Adverse Event Reporting System (VAERS) among older adults who received TIV-HD.

Methods. We searched VAERS for reports involving persons aged ≥ 65 years who received TIV-HD or TIV (standard dose) from 1 July 2010 through 31 December 2010. Medical records were requested for serious reports (ie, those associated with death, hospitalization or prolonged hospitalization, life-threatening illness, or disability). Clinicians reviewed information and assigned a diagnostic category to each report. Empirical Bayesian data mining was used to identify disproportional reporting following TIV-HD in VAERS. Reporting rates were calculated for reports of Guillain-Barré syndrome and anaphylaxis.

Results. VAERS received 606 reports after TIV-HD in persons aged ≥ 65 years (8.2% of reports involved serious events). The number of reports yielded by searches using the terms “ocular hyperemia” and “vomiting” exceeded the data mining threshold; $>80\%$ of these reports were nonserious. Clinical review of serious reports found that a greater proportion involving gastrointestinal events were made after TIV-HD receipt (5 of 51 [9.8%]) than after TIV receipt (1 of 123 [0.8%]). Four persons who received TIV-HD had gastroenteritis, and 1 had multiple gastrointestinal symptoms; all recovered. A higher proportion of cardiac events were noted after receipt of TIV-HD (9 of 51 [17.6%]) than after receipt of TIV (6 of 123 [4.9%]). No concerning clinical pattern was apparent. The reporting rates of Guillain-Barré syndrome and anaphylaxis after TIV-HD receipt were 1.4 and 1.0 reports per million doses distributed, respectively.

Conclusions. During the first year after US licensure of TIV-HD, no new serious safety concerns were identified in VAERS. Our analyses suggested a clinically important imbalance between the reported and expected number of gastrointestinal events after TIV-HD receipt. Future studies should assess this potential association.

Received 29 December 2011; accepted 16 February 2012; electronically published 22 March 2012.

Presented in part: Meeting of the Advisory Committee on Immunization Practices, Atlanta, Georgia, 23 June 2011; 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Chicago, Illinois, 14–17 August 2011.

Correspondence: Pedro L. Moro, MD, MPH, Immunization Safety Office, Centers for Disease Control and Prevention, 1600 Clifton Rd, NE, MS-D26, Atlanta, GA 30333 (psm9@cdc.gov).

Clinical Infectious Diseases 2012;54(11):1608–14

© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cis256

On 23 December 2009, the Food and Drug Administration (FDA) licensed a new high-dose, trivalent, inactivated influenza vaccine (TIV-HD) (Fluzone High Dose; Sanofi Pasteur) for use in adults aged ≥ 65 years, which contained 4 times the standard concentration of hemagglutinin, an influenza virus protein that elicits the formation of antibodies that inhibit viral attachment to cells [1–6]. Subsequently, the Advisory Committee on Immunization Practices included the TIV-HD formulation for adults aged ≥ 65 years in its

recommendations for the influenza 2010–2011 season [1]; the advisory committee has not stated a preference for TIV (standard dose) or TIV-HD for this age group.

Although prelicensure trials have shown that TIV-HD has an acceptable safety profile, rare adverse events may not have been adequately evaluated because of sample size limitations. To identify potential safety concerns that may not have been detected during prelicensure trials, we conducted surveillance of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) after receipt of TIV-HD by adults during the 2010–2011 influenza season.

MATERIALS AND METHODS

VAERS Background and Reporting

VAERS is a national spontaneous reporting system co-administered by the Centers for Disease Control and Prevention and the Food and Drug Administration that receives reports of adverse events that occur after vaccination [7]. VAERS generally cannot assess whether the adverse event is causally associated with vaccine receipt, but it may be useful for detecting signals of potential vaccine safety problems. VAERS accepts reports from vaccine manufacturers, health-care providers, vaccine recipients, and others. The VAERS report form collects information that includes the type of vaccine(s) received and the adverse event experience. Signs and symptoms of adverse events are coded by trained personnel and entered into a database, using the Medical Dictionary for Regulatory Activities (MedDRA) [8]. A VAERS report may be assigned ≥ 1 MedDRA preferred term. A report is classified as serious on the basis of the Code of Federal Regulations if one of the following events is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [9]. For serious reports from sources other than manufacturers, medical records are routinely requested by VAERS personnel for review.

We analyzed VAERS reports received by 28 February 2011 that involved individuals who received TIV-HD or TIV during 1 July 2010 through 31 December 31. Non-US reports and duplicate reports were excluded.

Clinical Review of Reports

We reviewed all reports of adverse events that occurred after receipt of TIV-HD. We also reviewed all serious reports among persons aged ≥ 65 years who received TIV during the study period, as well as a random sample of nonserious reports in this group.

Medical records were requested for all serious reports from nonmanufacturers and for persons with a clinical presentation suggestive of Guillain-Barré syndrome (GBS) or anaphylaxis (after TIV-HD receipt). Medical officers (P. M., J. A., and M. C.) reviewed the VAERS reports and, on the basis of the primary

event (ie, the event that appeared to trigger the reporter to report to VAERS), categorized reports into one of the following diagnostic categories modified from a system previously described [10]: allergic (including anaphylaxis); cardiovascular (including cerebrovascular accident); ear, nose, throat, gastrointestinal; local reaction at the injection site; musculoskeletal; neurologic (including GBS); psychiatric; respiratory (including influenza-like illness, pneumonia, and non-infectious upper/lower respiratory tract conditions); other infectious; other noninfectious (eg, syncope and diabetes); and death [10]. When discharge summaries were available, we used the primary diagnosis to assign the category.

For TIV-HD and TIV, reports that were suggestive of anaphylaxis or GBS were verified using the Brighton Collaboration criteria or a physician's diagnosis [11, 12]. Cause of death was determined from information documented in the autopsy report, the death certificate, or the medical record. We made no attempt to assess causality of the reported adverse events.

A sample of nonserious VAERS reports and all serious reports involving adults aged ≥ 65 years who received TIV during the 2010–2011 season were also reviewed and categorized into the same diagnostic categories. We used reporting odds ratios (RORs) and their 95% confidence intervals (CIs), an analytic method used in pharmacovigilance studies [13], to assess each diagnostic category for an imbalance in reports between adults aged ≥ 65 years who received TIV-HD and those who received TIV.

Data Mining

We used empirical Bayesian (EB) data mining [14] to identify adverse events reported more frequently than expected in the VAERS database following receipt of TIV-HD during the 2010–2011 influenza season by persons aged ≥ 65 years. All inactivated vaccines, including reports involving TIV but not TIV-HD, were used as the background for the data mining. Persons who received any live vaccine with the inactivated vaccines were excluded from the analysis. We used published criteria [15] to identify TIV-HD–adverse event pairs with reporting proportions greater than twice that of all other vaccines (ie, lower bound of the 90% confidence interval [EB05] > 2). Clinical reviews were conducted for MedDRA terms with an EB05 > 2 .

Reporting Rates

Crude reporting rates for GBS and anaphylaxis were estimated by dividing the number of verified reports of these conditions by the number of doses of TIV-HD distributed by the manufacturer during the 2010–2011 influenza season [16].

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.

Table 1. Characteristics of All Reports to the Vaccine Adverse Event Reporting System After Receipt of High-Dose Trivalent Inactivated Influenza Vaccine

Characteristics	Value
Total reports	622
Serious	51 (8.2)
Female sex ^a	407 (65.4)
Time to onset, days, median (range)	1 (0–95)
Type of reporter	
Provider	382 (61.4)
Other	159 (25.6)
Patient	64 (10.3)
Manufacturer	17 (2.7)
Age, years ^b	
Median (range)	71 (4–95)
≤65 ^c	15 (2.4)
65–69	228 (36.7)
70–74	183 (29.4)
75–79	93 (14.9)
80–84	60 (9.6)
≥85	42 (6.8)
Recovered by time of submission of VAERS form	409 (65.8)
TIV-HD given without other vaccines	576 (92.6)
Pneumococcal vaccine given on same date	39 (6.3)

Data are no. (%) of reports, unless otherwise indicated. Reports are for persons vaccinated from 1 July 2010 through 31 December 2010 and were received by 28 February 2011.

Abbreviations: TIV-HD, high-dose, trivalent, inactivated influenza vaccine; VAERS, Vaccine Adverse Event Reporting System.

^a Sex was unknown in 9 reports.

^b Age was unknown in 1 report.

^c Diagnoses included 4 reports of local reactions at injection site, 3 reports of systemic reactions, 2 reports of nonanaphylaxis allergic reactions, and 1 report each of neck pain, shoulder pain, nausea and vomiting, abdominal distention, diarrhea; 1 report had no adverse event. Three of 15 were pediatric patients aged 4, 7, and 10 years. Seven were aged 55–64 years.

RESULTS

VAERS received 622 reports after TIV-HD receipt; 606 (97.4%) involved persons aged ≥65 years (Table 1). Fifty-one (8%) of 622 reports were coded as serious, which included 3 deaths. In 49 (96%) of 51 serious reports, the primary diagnosis was verified by review of medical records. The median time between onset of the adverse event and submission as a serious report was 9 days (range, 1–80 days). The most frequent MedDRA-preferred terms associated with persons aged ≥65 years were vomiting and dyspnea, occurring in 37% and 35% of serious reports, respectively, and chills and fever, occurring in 25.4% and 25.2% of nonserious reports, respectively (Table 2)

Serious Reports

Serious reports after TIV-HD and TIV receipt among adults ≥65 years were similar in terms of sex and median age (Table 3).

Table 2. Serious and Nonserious Adverse Events in Persons Aged ≥65 Years Reported to the Vaccine Adverse Event Reporting System Following Influenza Vaccination, by Vaccine Type

MedDRA Code, Severity ^a	TIV-HD	Standard Dose =TIV
Serious	51 (100)	123 (100)
Increased blood glucose level	19 (37)	47 (38)
Vomiting	19 (37)	16 (13)
Dyspnea	18 (35)	31 (25)
Nausea	18 (35)	24 (20)
Abnormal chest radiograph finding	16 (31)	40 (33)
Pyrexia	16 (31)	28 (23)
Increased WBC count	16 (31)	42 (34)
Chills	15 (29)	18 (15)
Increased blood urea level	14 (28)	36 (29)
Asthenia	13 (26)	45 (37)
Nonserious	555 (100) ^b	1104 (100)
Chills	141 (25.4)	98 (8.9)
Pyrexia	140 (25.2)	106 (9.6)
Nausea	90 (16.2)	58 (5.3)
Pain	89 (16.0)	144 (13.0)
Headache	88 (15.9)	73 (6.6)
Vomiting	77 (13.9)	24 (2.2)
Dyspnea	67 (12.1)	50 (4.5)
Injection site pain	59 (10.6)	151 (13.7)
Pain in extremity	54 (9.7)	166 (15.0)
Asthenia	52 (9.4)	53 (4.8)

Data are no. (%) of reports. Reports are for persons vaccinated from 1 July 2010 through 31 December 2010 and were received by 28 February 2011.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TIV, standard-dose, trivalent, inactivated influenza vaccine; TIV-HD, high-dose, trivalent, inactivated influenza vaccine; WBC, white blood cell count.

^a The MedDRA codes reflect the 10 most frequent codes appearing in serious and nonserious reports made after receipt of TIV-HD. A report may contain >1 preferred term name.

^b One report with unknown age is not included.

Table 4 shows the main diagnosis for serious reports made after TIV-HD and TIV receipt among persons aged ≥65 years. Among the 3 deaths that occurred after TIV-HD receipt, the reported cause of death was sepsis in 1 and coronary artery disease in 2. A greater proportion of serious reports was observed for the diagnostic categories gastrointestinal (5 of 51 [10%] after TIV-HD vs 1 of 123 [1%] after TIV; ROR, 13.0 [95% CI, 1.4–632.2]) and cardiac (9 of 51 [18%] after TIV-HD vs 6 of 123 [5%] after TIV; ROR, 4.1 [95% CI, 1.2–15.0]). Four persons who received TIV-HD had gastroenteritis, and 1 had multiple gastrointestinal symptoms after vaccination; all recovered. All 9 patients for whom the serious report contained a cardiac diagnosis had preexisting cardiac conditions. No consistent cardiac diagnostic condition of concern was observed among these 9 reports (Table 4). Six of 9 cardiac patients had recovered by the time the VAERS form was submitted.

Table 3. Characteristics of Adults Aged ≥65 Years for Whom Serious Reports Were Submitted to the Vaccine Adverse Event Reporting System After Receipt of Influenza Vaccine, by Vaccine Type

Characteristic	TIV-HD ^a	TIV ^b
Reports, no.	51	123
Female sex	25 (49)	55 (45)
Time to AE onset, ^c days, median (range)	0 (0–95)	4.0 (0–137)
Age, years		
Median (range)	73 (65–92)	73 (65–95)
65–74	31 (61)	71 (58)
75–84	18 (35)	37 (30)
≥85	2 (4)	15 (12)

Data are no. (%) of reports, unless otherwise indicated. Reports are for persons vaccinated from 1 July 2010 through 31 December 2010 and were received by 28 February 2011.

Abbreviations: AE, adverse event; TIV, standard-dose, trivalent, inactivated influenza vaccine; TIV-HD, high-dose, trivalent, inactivated influenza vaccine.

^a A total of 606 reports involving vaccinees aged ≥65 years were made to VAERS.

^b A total of 1227 reports involving vaccinees aged ≥65 years were made to VAERS.

^c Defined as the interval between vaccination and onset of symptoms.

A higher proportion of serious reports of neurological conditions were made after TIV receipt (54 of 123 [44%]) than after TIV-HD receipt (7 of 51 [14%]; ROR, 0.2 [95% CI, .1–.5]); the most common neurological diagnosis in both the TIV and TIV-HD groups was GBS. Of the 5 reports of GBS after TIV-HD receipt, 3 were confirmed as Brighton level 2, and 2 were confirmed as Brighton level 3, one of which included a Miller-Fisher variant of GBS. In 4 of the 5 GBS reports, the interval between vaccination and onset of symptoms was ≤42 days. In one report, the interval was not clear but appeared to be <5 days. Higher proportions of serious reports were also observed after TIV-HD receipt, compared with after TIV receipt, under the diagnostic categories allergy and other noninfectious. Other noninfectious is a nonspecific category comprising diverse diagnoses (eg, syncope and renal failure). No pattern of concern was identified in either group.

Nonserious Reports After TIV-HD Receipt

Table 5 shows the distribution of diagnostic categories for all TIV-HD-associated nonserious reports and a random sample of 93 TIV-associated nonserious reports involving subjects aged ≥65 years. For TIV-HD, the predominant diagnostic categories were other noninfectious (eg, syncope and diabetes), local reactions, allergic, and respiratory, which together made up 86% of all reports. In the respiratory category, a greater proportion of reports (73 of 555 [13.2%]) were identified after

Table 4. Diagnostic Categories of Nonfatal Serious Reports Made to the Vaccine Adverse Event Reporting System After Receipt of Influenza Vaccine Among Persons Aged ≥65 Years, by Vaccine Type

Category ^a	TIV-HD (n = 51)	TIV (n = 123)	ROR (95% CI)
Other noninfectious	9 (18)	11 (9)	2.2 (.8–5.7)
Cardiac ^b	9 (18)	6 (5)	4.1 (1.2–15.0)
Respiratory	7 (14)	10 (8)	1.8 (.5–5.6)
Neurological	7 (14)	54 (44)	0.2 (.1–.5)
Guillain-Barré Syndrome	5	39	...
Other ^c	2	15	...
Allergic	6 (12)	6 (5)	2.6 (.7–10.2)
GI	5 (10)	1 (1)	13.0 (1.4–632.2)
Gastroenteritis	4	0	...
Multiple GI symptoms	1	1	...
Other infectious	3 (6)	13 (11)	0.5 (.1–2.1)
Deaths	3 (6)	9 (7)	0.8 (.1–3.4)
Musculoskeletal	2 (4)	7 (6)	0.7 (.1–3.7)
Ear, nose, and throat	0	2 (2)	...
Local reaction	0	4 (3)	...

Data are no. (%) of reports. Reports are for persons vaccinated from 1 July 2010 through 31 December 2010 and were received by 28 February 2011.

Abbreviations: CI, confidence interval; GI, gastrointestinal; ROR, reporting odds ratio; TIV, standard-dose, trivalent, inactivated influenza vaccine; TIV-HD, high-dose, trivalent, inactivated influenza vaccine.

^a Classified according to body system.

^b For TIV-HD: 3 reports of atypical chest pain and 1 each of myocardial infarction, idiopathic pericarditis, acute ischemic cerebrovascular accident, left carotid stenosis, hypertensive emergency, and cardiac syncope. For TIV: 2 reports of atrial fibrillation and 1 each of myocardial infarction, atypical chest pain, cardiac arrest, and subarachnoid hemorrhage.

^c For TIV-HD: 1 report of chronic inflammatory demyelinating polyneuropathy (CIDP); 1 of ischemic optic neuropathy. For TIV: 3 reports each of seizures and transverse myelitis, 2 of CIDP, and 1 each of dystonic reaction, acute disseminated encephalomyelitis, left arm neuropathy, acute confusional state, headache, dizziness, and meningoencephalopathy.

TIV-HD receipt than after TIV receipt (ROR, 3.4 [95% CI, 1.2–9.5]). The main diagnosis in 55 reports (75.3%) was influenza-like illness. Thirty-nine of 55 persons (71%) had recovered by the time the VAERS form was submitted.

Data Mining

In the data mining analysis, only the MedDRA-preferred terms “ocular hyperemia” and “vomiting” exceeded the EB05 threshold in reports made after TIV-HD receipt. Among the 34 reports of ocular hyperemia, 32 (94%) were nonserious. Twenty-eight of these 32 persons (88%) recovered by the time the VAERS form was submitted; cases in 17 of 32 were categorized as nonanaphylaxis allergic reactions. The 2 serious reports with the preferred term “ocular hyperemia” involved one patient who was hospitalized for experiencing syncope and subsequently recovered and another who had exacerbation of chronic obstructive pulmonary disease and an unknown recovery

Table 5. Diagnostic Categories of Nonserious Reports submitted to the Vaccine Adverse Event Reporting System After Receipt of Influenza Vaccine Among Persons Aged ≥ 65 Years, by Vaccine Type

Category ^a	TIV-HD (n = 555)	TIV ^b (n = 93)	ROR (95% CI)
Other noninfectious	178 (32.1)	26 (28)	1.2 (.7–1.9)
Local reactions	122 (21.9)	28 (30)	0.6 (.4–1.1)
Allergic	103 (18.6)	22 (24)	0.7 (.4–1.3)
Respiratory	73 (13.2)	4 (4)	3.4 (1.2–9.5)
Gastrointestinal	31 (5.6)	2 (2)	2.7 (.7–23.6)
Musculoskeletal	21 (3.8)	3 (3)	1.2 (.3–6.3)
Neurological	13 (2.3)	3 (3)	0.7 (.2–4.0)
Other infectious	10 (1.8)	3 (3)	0.6 (.1–3.2)
Cardiac	1 (0.2)	2 (2)	0.08 (.01–.9)
Unevaluable/no adverse event	3 (0.5)	0	...

Data are no. (%) of reports. Reports are for persons vaccinated from 1 July 2010 through 31 December 2010 and were received by 28 February 2011.

Abbreviations: CI, confidence interval; ROR, reporting odds ratio; TIV, standard-dose, trivalent, inactivated influenza vaccine; TIV-HD, high-dose, trivalent, inactivated influenza vaccine.

^a Classified according to body system.

^b Random sample from a total of 1219 standard TIV reports.

status. We assessed the 34 reports of ocular hyperemia for the potential presence of oculorespiratory syndrome, using a stringent Canadian case definition [17]. In an initial review, 16 reports were found to meet this definition of oculorespiratory syndrome. However, review of the 5 reports for which medical records were available showed that these patients received diagnoses of nonanaphylactic allergic reactions from physicians. Of the 99 VAERS reports made after TIV-HD receipt that contained the preferred term “vomiting,” 83 (84%) were nonserious. Sixty-two of these 83 persons (75%) recovered by the time the VAERS form was submitted. The main diagnostic categories for these nonserious reports, which were based on our classification system, included gastrointestinal in 36 (36%), other noninfectious in 25 (25%), nonanaphylaxis allergic type reactions in 14 (14%), and respiratory in 7 (7%). Sixteen of 99 reports (16%) with the preferred term “vomiting” were coded as serious reports. The primary diagnosis included gastroenteritis in 4 cases, nonanaphylaxis allergic reactions in 2, sepsis in 2, and chest pain, seizures, conjunctivitis, urinary tract infection, renal insufficiency, reactive airway disease, respiratory insufficiency, and anaphylaxis in 1 each.

Reporting Rates

From 1 July 2010 through 31 December 2010, 4 verified reports of GBS after TIV-HD receipt were reported for adults aged ≥ 65 years, with an onset interval of ≤ 42 days after vaccination. The crude reporting rate of GBS for this period was 1.4 reports per million doses distributed. During the study period, 3 reports

of anaphylaxis after TIV-HD receipt were reported to VAERS; the onset interval was < 24 hours after vaccination. Two were verified by review of medical records as Brighton level 1, and 1 was verified as Brighton level 2. The crude reporting rate for verified anaphylaxis after TIV-HD was 1.0 report per million doses distributed.

DISCUSSION

During the 2010–2011 influenza season, the first TIV-HD was introduced in the United States for use in persons aged ≥ 65 years [1–5]. Prelicensure studies had shown superior immunogenicity for TIV-HD, compared with TIV. However, rates of local reactions and fever were higher after TIV-HD than after TIV. Therefore, the safety of TIV-HD was closely monitored through VAERS. During the first year after licensure, 2.9 million doses of TIV-HD were distributed in the United States [16]. As of 28 February 2011, VAERS had received 622 reports following TIV-HD receipt. Most reports (91.8%) were coded as nonserious, generally self-limited events. Consistent with prelicensure experience, fever, pain, and headache were among the most frequent adverse events reported after TIV-HD receipt [5].

As part of postlicensure surveillance of TIV-HD, we conducted 3 levels of analysis: EB data mining, clinical review of VAERS reports, and reporting rate calculations for verified GBS and anaphylaxis reports. Through use of these complementary approaches, we identified clinical categories in which the VAERS data suggested the possibility that adverse event reporting may be unexpectedly higher after TIV-HD receipt than after TIV receipt.

Through EB data mining, we found that, among adults aged ≥ 65 years, a greater proportion of reports of vomiting were made after receipt of TIV-HD than after receipt of other inactivated vaccines; most were nonserious reports. Similarly, our clinical analysis of serious reports after TIV-HD receipt revealed an imbalance in reporting of gastrointestinal conditions, with a greater proportion of reports occurring after TIV-HD receipt than after TIV receipt. We noted that the MedDRA-preferred terms for vomiting and nausea were among the top 10 preferred terms after TIV-HD receipt, which is consistent with our clinical review and data mining findings. Gastrointestinal events were not described as occurring more frequently in prelicensure trials after TIV-HD receipt than after TIV receipt [5] and were not identified as a frequent coding term in a 15-year analysis of reports to VAERS after TIV receipt among adults [18]. Postmarketing surveillance done by the manufacturer revealed that nausea, vomiting, and diarrhea were among the top 10 most frequently observed adverse events after TIV-HD receipt, which is consistent with some of our observations [16]; however, there may be some overlap in the cases appearing in the VAERS and manufacturer databases.

Through data mining, we also found that, among adults aged ≥ 65 years, a greater proportion of reports containing the term “ocular hyperemia” were made after receipt of TIV-HD than after receipt of other inactivated vaccines; most reports were nonserious. Ocular hyperemia is one of the manifestations of oculorespiratory syndrome, which was first recognized in 2000 in Canada [19] and is characterized by the presence of bilateral red eyes and respiratory symptoms (ie, cough, dyspnea, and wheezing), with or without facial swelling, ≤ 24 hours after vaccination [17]. The symptoms described in 47% of reports with the coding term “ocular hyperemia” were compatible with this syndrome. However, we were not able to confirm this diagnosis in those reports for which medical records were not available.

While statistical data mining did not identify any disproportionate reporting for respiratory events, our clinical review revealed a higher proportion of respiratory conditions in nonserious reports made after TIV-HD receipt than after TIV receipt. Three-fourths of these reports involved mild influenza-like illness, and almost three-fourths of the affected individuals recovered by the time the VAERS form was submitted. Among serious reports, we also observed that the proportion in which cardiac conditions were specified was greater after TIV-HD receipt than after TIV receipt, but no specific clinical pattern of concern was observed among the cases. Because we did not identify a greater number of reports with a particular or specific cardiac diagnosis that were made after TIV-HD receipt than after TIV receipt, we did not deem this finding in the cardiac group to be a safety concern after TIV-HD receipt.

Anaphylaxis has a recognized causal association with influenza vaccines [20], and although it is a rare adverse event after vaccination, its postlicensure surveillance is important, especially for a newly licensed vaccine such as TIV-HD. Data mining analysis did not find a disproportionate number of reports of anaphylaxis that were made after TIV-HD receipt. The reporting rate of 1 case per million doses distributed after TIV-HD receipt is consistent with the observed incidence of anaphylaxis ≤ 2 days after TIV receipt (0.45–1.98 cases per million doses distributed) among all ages during the 2006–2008 influenza seasons, as specified in the Vaccine Safety Datalink [21].

GBS is an acute, immune-mediated paralytic disorder of the peripheral nervous system [22]. The background incidence of GBS among males aged ≥ 65 years in the United Kingdom and the United States was approximately 5.3 cases per 100 000 inhabitants during a 42-day period [23]. Despite its rarity, concerns about the risk of developing GBS following receipt of influenza vaccines have been present since an association was first noticed with the 1976–1977 A/New Jersey (“swine influenza”) vaccine [24]. Of the 5 verified GBS cases reported

after TIV-HD receipt, in 4 the interval between vaccination and symptom onset (42 days) was within the window of biologic plausibility if a causal association were suspected [22]. The crude reporting rate for GBS after TIV-HD receipt (1.4 reports per million doses distributed) is below the background rate for this neurological condition; however, it is expected that there would not be complete reporting of postvaccination GBS to VAERS. Data mining revealed no disproportionate reporting of GBS after receipt of TIV-HD. There is no clear explanation for the finding that the proportion of VAERS reports involving events that we categorized as neurological during clinical review was smaller after TIV-HD receipt than after TIV receipt. GBS was the most common neurological diagnosis in both groups. Our finding could be explained if the TIV-HD and TIV populations had differences in baseline health status that placed the 2 groups at different risks for neurological events, irrespective of vaccination. Another explanation could be that reporting practices for adverse events after TIV-HD receipt differed from those after TIV receipt. For example, if providers were more likely to report cardiac or gastrointestinal conditions that occurred shortly after the new vaccine than they were for TIV, this could lower the percentage of neurological reports in the overall sample. More information on health status of vaccinees aged ≥ 65 years receiving TIV-HD and practices for reporting adverse events after influenza vaccination in this population could be useful to interpret this and other medical conditions.

Any finding in VAERS needs to be interpreted with caution because of the inherent limitations of passive surveillance systems, such as overreporting or underreporting, biased reporting, and inconsistency in quality and completeness of reports. Through our clinical review of all TIV-HD reports, we attempted to obtain a more precise diagnosis of the adverse events experienced, categorizing the adverse events in each report into 1 primary diagnosis. Our use of RORs should be taken with caution because of the small number of reports involved and the inherent limitations of passive surveillance data. Their use is only to assess for potential imbalances between TIV-HD and TIV with regard to the diagnostic categories in the VAERS database, but in no way should they be interpreted as assessments of the level of risk or causality for these conditions. Although we estimated crude reporting rates for GBS and anaphylaxis by using doses of vaccine distributed as a denominator, these estimates should also be interpreted with caution since the number of doses administered is not known and the completeness of reporting for these conditions in VAERS is not known.

Fifteen TIV-HD nonserious reports occurred in subjects aged < 65 years. Although some of these reports may represent true medication errors (eg, inappropriate schedule of drug administration), it is possible the reporter may have mistakenly

reported TIV-HD when in fact TIV was really administered. It is also possible the vaccine administrator may have chosen to give TIV-HD to someone aged <65 years. Vaccine records were only available for 1 of the 15 reports (which involved a 61-year-old woman who mistakenly received TIV-HD), and therefore it is difficult to assess whether these were true medication errors.

This study describes the first year of postlicensure surveillance for adverse events following TIV-HD receipt that were reported to VAERS. We identified no new serious vaccine safety concerns among individuals who had received TIV-HD. Consistent with findings from prelicensure studies, we found conditions (eg, fever and pain) that were more frequently reported after TIV-HD receipt than after TIV receipt. However, taken together, our data suggest that clinically important gastrointestinal events, particularly vomiting, may be more likely to occur in persons aged ≥ 65 who receive TIV-HD, compared with TIV or other inactivated vaccines. Imbalances in the proportion of gastrointestinal events reported were not detected in prelicensure trials but were also observed in another analysis of postlicensure data [16]. Further studies to assess this potential association are warranted. In addition, further monitoring in VAERS and other systems for reports of adverse events following TIV-HD receipt during future seasons will be important as use of the vaccine increases.

Notes

Acknowledgments. We thank Drs Frank DeStefano, Claudia Vellozzi, and Jerry Tokars for their valuable comments and advice. We thank staff at the Centers for Disease Control and Prevention's Immunization Safety Office and the Food and Drug Administration's Center for Biologics Evaluation and Research, whose dedicated efforts allowed this activity to be conducted.

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 Food and Drug Administration.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Fiore AE, Uyeki TM, Broder K, et al. Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* **2010**; 59:1–62.
2. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA* **1994**; 272:1661–5.
3. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine* **2007**; 25:7656–63.
4. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med* **2006**; 166:1121–27.
5. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis* **2009**; 200:172–80.
6. Food and Drug Administration. Fluzone, fluzone high-dose and fluzone intradermal. Available at: <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm112854.htm>. Accessed 1 October 2011.
7. Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* **2004**; 23:287–94.
8. International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). Medical dictionary for regulatory activities (MedDRA). Available at: <http://www.meddrasso.com/>. Accessed 9 October 2010.
9. Food and Drug Administration. 21 CFR Part 600.80. Postmarketing reporting of adverse experiences. Vol 62. Washington, DC: Federal Register, **1997**; 52252–3.
10. Vellozzi C, Broder KR, Haber P, et al. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010. *Vaccine* **2010**; 28:7248–55.
11. Rugeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* **2007**; 25:5675–84.
12. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* **2011**; 29:599–612.
13. Bate A, Edwards IR. Data mining techniques in pharmacovigilance. In: Hartzema AG, Tilson HH, Chan KA, eds. *Pharmacoepidemiology and therapeutic risk management*. Cincinnati, OH: Harvey Whitney Books Company, **2008**: 239–72.
14. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Stat* **1999**; 53:177–90.
15. Szafrman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* **2002**; 25:381–92.
16. Advisory Committee on Immunization Practices. Presentation slides: June 2011 meeting. Fluzone® high-dose vaccine: one year post-approval. Available at: <http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-jun11/11-4-flu-high-dose.pdf>. Accessed 11 August 2011.
17. De Serres G, Skowronski DM, Guay M, et al. Recurrence risk of oculorespiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons. *Arch Intern Med* **2004**; 164:2266–72.
18. Vellozzi C, Burwen DR, Dobardzic A, Ball R, Walton K, Haber P. Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring. *Vaccine* **2009**; 27:2114–20.
19. Skowronski DM, Strauss B, Kendall P, Duval B, De Serres G. Low risk of recurrence of oculorespiratory syndrome following influenza re-vaccination. *CMAJ* **2002**; 167:853–8.
20. Institute of Medicine. Influenza vaccines. In: *Adverse effects of vaccines: evidence and causality*. Washington, DC: The National Academies Press, **2011**: 257–368.
21. Greene SK, Kulldorff M, Lewis EM, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am J Epidemiol* **2010**; 171:177–88.
22. Marks JS, Halpin TJ. Guillain-Barré syndrome in recipients of A/New Jersey influenza vaccine. *JAMA* **1980**; 243:2490–4.
23. Black S, Eskola J, Siegrist CA, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandemic H1N1 influenza vaccines. *Lancet* **2009**; 374:2115–22.
24. Fenichel GM. Assessment: Neurologic risk of immunization: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **1999**; 52:1546–52.