Vaccine 27 (2009) 2114–2120

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety of trivalent inactivated influenza vaccines in adults: Background for pandemic influenza vaccine safety monitoring

Claudia Vellozzi[a,b,*], Dale R. Burwen[c], Azra Dobardzic[c], Robert Ball[c], Kimp Walton[a], Penina Haber[a]

[a] Immunization Safety Office (ISO), Office of the Chief Science Officer (OCSO), Centers for Disease Control and Prevention, Atlanta, GA, United States
[b] National Center for HIV, Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, United States
[c] Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration (FDA), Rockville, MD, United States

ARTICLE INFO

Article history:
Received 5 December 2008
Received in revised form 22 January 2009
Accepted 29 January 2009
Available online 6 February 2009

Keywords:
Influenza vaccines
Vaccine safety
Post-marketing surveillance

ABSTRACT

In preparation for pandemic vaccine safety monitoring, we assessed adverse events reported to the Vaccine Adverse Event Reporting System following receipt of trivalent inactivated influenza vaccines among adults from 1990 through 2005. We calculated reporting rates for nonserious, serious, and neurological adverse events. We reviewed reports of recurrent events and deaths, as well as reports identified through advanced signal detection. The most frequently reported events were local reactions and systemic symptoms. Guillain-Barré syndrome was the most frequently reported serious event (0.70 reports per million vaccinations). Adverse event reporting rates have been reasonably constant over time. No new safety concerns emerged after our review of 15 years of post-licensure surveillance data. These findings provide useful information if pandemic vaccine is rapidly distributed and pre-licensure data are limited.

Published by Elsevier Ltd.

1. Background

Influenza vaccines are the primary method for the control of influenza and its complications and the most widely used type of vaccine for adults in the United States (US). The US and much of the world is preparing for the use of pandemic influenza vaccines [1]. However, even with extensive planning, limited safety data will be available for these vaccines prior to use. Safety profile highlights of the seasonal trivalent inactivated influenza vaccines (TIV) can provide a background for interpretation of adverse events that can be anticipated if pandemic influenza vaccines must be employed in the future. In addition, special importance for TIV safety monitoring stems from the 1976–1977 influenza season, when a mass vaccination effort in the US against swine influenza was halted after the vaccines appeared to be associated with an elevated risk of Guillain-Barré syndrome (GBS) [2].

Placebo-controlled trials among older and healthy young adults have demonstrated that TIV administration is not associated with an increased risk of systemic symptoms (e.g., fever, malaise, myalgia); the most frequent adverse effect following vaccination is pain at the injection site [3]. Immediate hypersensitivity reactions, including anaphylaxis can occur [3], but the latter is rare [4]. A pre-licensure study of the recently licensed H5N1 vaccine identified headache, malaise, and myalgia as the most frequent systemic symptoms but also identified these at similar rates among placebo recipients [5].

Clinical trials are generally not large enough to detect rare adverse events. Post-licensure safety data provide examples of adverse event experiences among a larger and more diverse population, and reporting of adverse events following receipt of seasonal TIV to the US Vaccine Adverse Event Reporting System (VAERS) is an important source of this information. We examined 15 years of VAERS data among adults aged ≥18 years to describe patterns of adverse events after seasonal vaccines and to identify possible safety concerns that might merit intensified monitoring or evaluation. Although pandemic influenza vaccines will differ from current TIV products, at least in their antigenic composition, reported adverse events following several annual TIV products probably provide the best currently available information for the types of adverse events that might be anticipated following administration of pandemic influenza vaccines.

2. Methods

2.1. Data sources

VAERS is a passive surveillance system established in 1990 that accepts reports of adverse events following any US licensed vaccine from providers, health care workers, and the public. It is operated

Abbreviations: CV, cardiovascular; DIG, digestive; ENDO, endocrine; HAL, heme and lymphatic; MAN, metabolic and nutritional; MS, musculoskeletal; NER, nervous; RES, respiratory; SKIN, skin; SS, special.

* Corresponding author at: 1600 Clifton Road, MS E-45, Atlanta, GA 30333, United States. Tel.: +1 404 639 6175; fax: +1 404 639 6127.
E-mail addresses: bno1@cdc.gov (C. Vellozzi), PHaber@cdc.gov (P. Haber).

0264-410X/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.vaccine.2009.01.125

jointly by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) [6–9]. Although VAERS cannot usually prove causal associations between vaccines and adverse events, it can detect signals to be tested with more rigorous methods [10].

Symptoms recorded on a VAERS report were assigned to one or more coding terms using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) [11]. This process does not employ standardized case definitions. Reports of death, hospitalization or prolongation of hospitalization, life-threatening illness, persistent or significant disability/incapacity, or certain other medically important conditions are classified as serious [12] and followed up by nurses to obtain additional medical information. All other reports are coded as nonserious. Each COSTART code was also linked to one or more body systems which we used to summarize the distribution of adverse events by body system category.

2.2. Reporting rates

We defined an influenza season as July 1–June 30 and searched for all domestic TIV-related initial reports among persons aged ≥18 years with vaccination between July 1, 1990 and June 30, 2005. We grouped persons by age (18–49, 50–64, and ≥65 years) and by reports classified as nonserious and serious. We used influenza vaccination coverage data from the National Health Interview Survey (NHIS) to estimate the proportion of people receiving TIV by age group and season [13–15] and multiplied these proportions by the census estimates of the population [16] for the same age groups to derive the number of people vaccinated in each group as denominators for reporting rates. We calculated age-specific and seasonal adverse event reporting rates for serious and nonserious reports. We also calculated rates for the most commonly reported events among nonserious and serious reports. Due to the close attention given to neurological adverse events [17] we calculated age-specific adverse event reporting rates for the 10 most frequently reported neurological events. With a neurologist we reviewed all neurological COSTART symptom codes and, where appropriate, combined codes (e.g., the codes ataxia and cerebellar ataxia are considered together as ataxia). Headache, which is often a systemic symptom, was not included. Coding terms suggestive of stroke or transient ischemic attack,[1] which are often classified under the circulatory system, were considered separately and not included as neurological adverse events in this analysis. We used SAS (version 9.01, SAS Institute, Inc., Cary, NC) to generate reporting rates.

2.3. Positive rechallenge reports

To identify positive rechallenge reports (i.e., an adverse event that followed receipt of TIV and recurred after a subsequent dose, suggesting, but not confirming, a causal association with TIV), we used the coding term "POS RECHAL" and completed a text search using phrases consistent with a repeat event. All positive rechallenge reports were reviewed individually by two physicians and assigned to one of the following categories: local reaction, allergic reaction, respiratory, dermatologic, neurological, systemic, musculoskeletal, cardiovascular, or gastrointestinal illnesses.[2]

2.4. Death reports

We reviewed each death report and, when available, documented the cause of death from the autopsy report, death certificate, and/or hospital records. We identified reported comorbid conditions that might have increased an individual's risk of death regardless of vaccination. As a crude risk adjuster, we adapted risk categories previously used for potential influenza-related morbidity and mortality and classified persons as high-risk (heart disease, lung disease, or late stage malignancy), intermediate-risk (diabetes, renal disease, rheumatologic disease, stroke, or dementia), or low-risk (other or none) [18].

2.5. Advanced signal detection (data mining)

To screen serious VAERS reports among US adults aged ≥18 years for further individual review, we calculated the ratio of the proportion of a particular COSTART term among serious reports following TIV to the proportion of the same term among serious reports following all other vaccines (proportional reporting ratios [PRR]) [19–21]. The PRR was adjusted for age (<65, ≥65 years). We used the proposed criteria for significant disproportionality [20] (coding terms identified in at least three reports, with a PRR > 2.0 and chi square > 4.0) to guide selection of VAERS reports for further review. We also employed empirical Bayesian data mining methodology [22], with similar age adjustment, to identify reports for further review using criteria outlined by Szarfman et al. [23]. Both of these data mining methods used WebVDME (Lincoln Technologies, Inc., Waltham, MA). To evaluate transverse myelitis (a coding term identified for review), we used a hypothetical risk period of 30 days to compare the reporting rate with published estimates of background incidence (1.3–4.6 per million per year) [24,25].

3. Results

3.1. Reporting rates

From July 1, 1990, through June 30, 2005, an estimated 747.1 million doses of TIV were administered, and VAERS received 18,245 US reports among persons aged ≥18 years, resulting in an overall adverse event reporting rate of 24.4 per million TIV vaccinations; 14% (2518/18,245) were classified as serious reports. When stratified by age group, we found the highest reporting rate for serious events was among people aged 50–64 years (4.2 per million vaccinations). For nonserious reports, the highest rate was among people aged 18–49 years, more than twice the rate found among people aged ≥65 years (28.3 and 13.1 per million vaccinations, respectively)(Table 1). Seventy-nine percent (14,480/18,245) of all reported adverse events followed TIV given alone, and 15% (2721/18,245) followed TIV and pneumococcal vaccines given simultaneously. The remainder of reports included TIV given with one or more other vaccines.

The vaccine doses administered steadily increased over time from an estimated 24.3 to 71.1 million doses from 1990–1991 to 2003–2004; during the 2004–2005 season, there was a shortage of TIV [26], and doses administered decreased by nearly 24 million doses. During the first few years after the inception of VAERS in 1990, the reporting rates for nonserious reports tended to increase, and by 1994–1995 through 2004–2005, the rates remained fairly steady. The reporting rates of serious reports ini-

[1] COSTARTs included were CEREBROVASC ACCID, EMB CAROTID, EMB CEREBR, HEM CEREBR, HEM INTRACRAN, HEM SUBARACHNOID, INFARCT CEREBR, ISCHEMIA CEREBR, OCCLUS CAROTID, THROM CAROTID, THROM CEREBR, THROM CEREBR ART.

[2] *Local reaction*: Induration, redness, edema, pain, swelling, burning, mass at injection site; *allergic reaction*: urticaria, angioedema, pruritis, asthma; *respiratory*: cough, rhinitis, pharyngitis, laryngitis; *dermatologic*: rash, vasculitis, alopecia; *neurological*: paresthesia, numbness, vertigo, nystagmus, ataxia, confusion, GBS, optic neuritis; *systemic*: fever, myalgia, malaise, headache, asthenia; *musculoskeletal*: arthralgia, joint pain; *cardiac*: irregular pulse, tachycardia, vasovagal reaction, hypertension; *gastrointestinal*: nausea, diarrhea, vomit.

Table 1
Adverse event reports following trivalent inactivated influenza vaccine in adults age ≥18 years, by age-group and severity, VAERS[a], July 1, 1990 through June 30, 2005, United States.

	All ≥18 years	18–49 years	50–64 years	≥65 years
Serious reports[b]				
N (rate)[c]	2518 (3.4)	752 (2.9)	718 (4.2)	1048 (3.4)
% Male	43	37	43	46
% TIV alone	86	83	87	88
Mean (median) age	58 (60)	36 (38)	57(57)	75 (74)
Mean (median) onset interval[d]	19 (3)	20 (2)	15 (4)	21(3)
Nonserious reports				
N (rate)[c]	15,727 (21.1)	7452 (28.3)	4197 (24.3)	4078 (13.1)
% Male	24	21	22	30
% TIV alone	78	84	79	67
Mean (median) age	52 (51)	37 (39)	56 (56)	73 (72)
Mean (median) onset interval[d]	5 (1)	6 (0)	5 (1)	2 (1)
All reports				
N (rate)[c]	18,245 (24.4)	8204 (31.1)	4915 (28.5)	5126 (16.5)

[a] Vaccine Adverse Event Reporting System.
[b] Serious reports include deaths, life-threatening events, hospitalizations or prolongations of hospitalization, and persistent or significant disabilities.
[c] Reporting rate calculated per 1,000,000 TIV doses administered; total doses administered for all age groups combined = 747,070,979; 18–49 age group = 263,696,575; 50–64 age group = 172,364,441; ≥65 age group = 311,009,963.
[d] Number of days from the date of vaccination to the first reported symptom onset date.

tially generally declined and then remained mostly steady from 1994–1995 through 2004–2005 (Fig. 1).

We identified 15,727 nonserious VAERS reports which included 55,757 coded symptoms, or a mean of 3.7 coded symptoms per report (median 3.0, range 1.0–22.0). As demonstrated in Fig. 2, 40% of these terms linked to the general body system category (including nonspecific symptoms and injection site reactions). Among the 2518 serious VAERS reports, 12,592 coded symptoms were included in our analysis; the mean, median and range of coded symptoms per serious report was 5.0, 4.0, and 1.0–25.0, respectively. Twenty-eight percent of the codes from serious reports were linked to the nervous system category (Fig. 2).

3.2. Most commonly reported events—nonserious reports

The most frequent coding term in the nonserious reports to VAERS was injection site reaction (9561; 12.8 per million vaccinations); pain, fever, myalgia and headache were also among the top 10 most frequently identified coding terms in nonserious reports (Table 2). The 10 most common coding terms comprise 49% (27,504/55,757) of the terms included in the nonserious reports.

3.3. Most commonly reported events—serious reports

GBS was the most frequently identified coding term among serious reports (522), with a reporting rate of 0.70 per million vaccinations. Among the 10 most common coding terms found in serious reports, four were symptoms frequently associated with GBS (paresthesia, asthenia, myasthenia and hypokinesia in 42%, 30%, 26% and 17% of reports with the coding term GBS). The 10 most common coding terms comprise 26% (3260/12,592) of all codes included in the serious reports (Table 2).

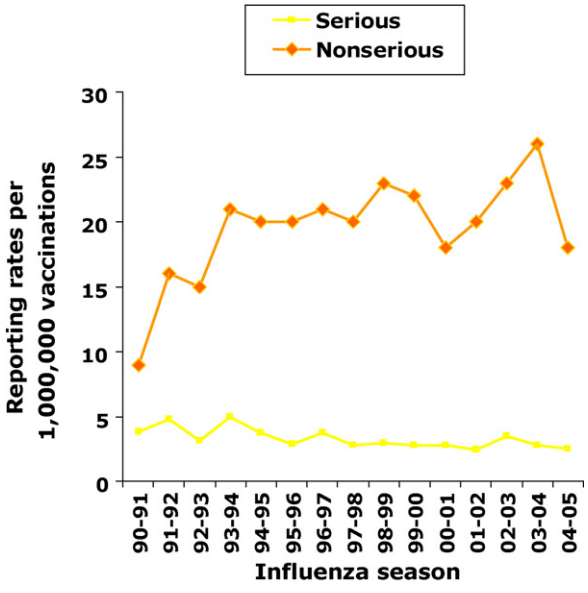

Fig. 1. Reporting rates of serious and nonserious adverse event reports following trivalent inactivated influenza vaccine, VAERS, July 1, 1990 through June 30, 2005, United States. Serious reports include deaths, life-threatening events, hospitalizations or prolongations of hospitalization, and persistent or significant disabilities.

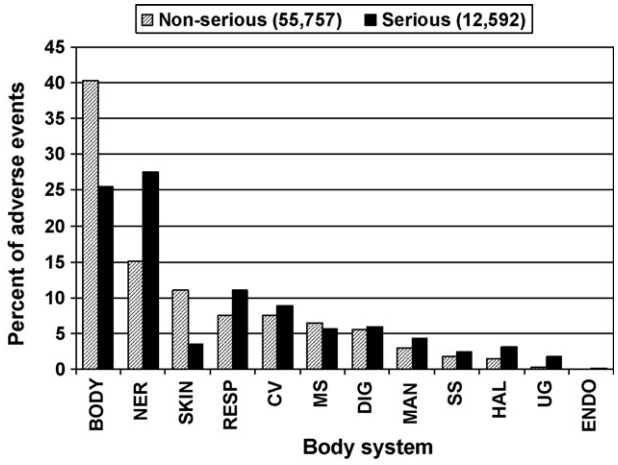

Fig. 2. Percent of reported serious and nonserious adverse events after receipt of trivalent inactivated influenza vaccine attributed to each body system, VAERS, 1990–2005, United States. In the COSTART body system classification, some coding terms are mapped to more than one body system, and can be counted more than once; analysis of 55,757 adverse event coding terms among 15,727 nonserious reports, and 12,592 adverse event coding terms among 2518 serious reports reported to VAERS. Abbreviations: BODY, Body as a whole or non-specific (includes also injection site reactions); CV, cardiovascular; DIG, digestive; ENDO, endocrine; HAL, heme and lymphatic; MAN, metabolic and nutritional; MS, musculoskeletal; NER, nervous; RES, respiratory; SKIN, skin; SS, special.

Table 2
Most common coding terms (COSTART)[a] following trivalent inactivated influenza vaccine in adults age ≥18 years, VAERS[b], July 1, 1990 through June 30, 2005, United States.

	All ≥18 years *N* (rate)[c]	18–49 years *N* (rate)[c]	50–64 years *N* (rate)[c]	≥65 years *N* (rate)[c]
COSTART[a] for serious reports[d]				
Guillain-Barré syndrome	522 (0.70)	132 (0.50)	213 (1.24)	177 (0.57)
Asthenia	446 (0.60)	133 (0.50)	133 (0.77)	180 (0.58)
Paresthesia	413 (0.56)	166 (0.63)	139 (0.81)	108 (0.35)
Fever	398 (0.53)	121 (0.46)	96 (0.56)	181 (0.58)
Dyspnea	297 (0.40)	104 (0.39)	81 (0.47)	112 (0.36)
Pain	278 (0.37)	88 (0.33)	97 (0.56)	93 (0.30)
Myasthenia	254 (0.34)	79 (0.30)	96 (0.56)	79 (0.25)
Injection site reactions[e]	243 (0.33)	100 (0.38)	60 (0.35)	83 (0.27)
Hypokinesia	208 (0.30)	54 (0.20)	69 (0.40)	85 (0.27)
Headache	201 (0.27)	100 (0.38)	56 (0.32)	45 (0.14)
COSTART[a] for nonserious reports				
Injection site reactions[e]	9561 (12.8)	4560 (17.3)	2583 (14.9)	2418 (7.8)
Pain	2500 (3.35)	1102 (4.18)	734 (4.25)	664 (2.13)
Vasodilatation	3111 (4.16)	1519 (5.76)	832 (4.830	760 (2.44)
Fever	2468 (3.30)	1182 (4.48)	635 (3.68)	651 (2.09)
Myalgia	2334 (3.12)	1126 (4.27)	670 (3.89)	538 (1.73)
Pruritus	2079 (2.78)	1110 (4.21)	552 (3.20)	417 (1.34)
Headache	1474 (1.97)	747 (2.83)	436 (2.53)	291 (0.94)
Rash	1411 (1.89)	716 (2.72)	362 (2.10)	333 (1.07)
Asthenia	1344 (1.80)	632 (2.40)	360 (2.09)	352 (1.13)
Urticaria	1222 (1.64)	677 (2.57)	306 (1.78)	239 (0.77)

[a] Each adverse event report may have more than one COSTART code.
[b] Vaccine Adverse Event Reporting System.
[c] Reporting rate calculated per 1,000,000 TIV doses administered; total doses administered for all age groups combined = 747,070,979; 18–49 age group = 263,696,575; 50–64 age group = 172,364,441; ≥65 age group = 311,009,963.
[d] Serious reports include deaths, life-threatening events, hospitalizations or prolongations of hospitalization, and persistent or significant disabilities.
[e] Includes: injection site reaction, injection site hypersensitivity, edema, mass, pain, cyst, atrophy, fibrosis, rash, necrosis, inflammation, abscess, hematoma, granuloma, induration.

3.4. Neurological events

Among all reports (both serious and nonserious) paresthesia was the most commonly reported neurological adverse event for all age groups, with a rate of 1.80 per million vaccinations; it was reported more than twice as often as any other neurological coding term and more than twice as often among persons aged <65 years compared to those aged ≥65 years. GBS followed as the next most common code at a rate of 0.78 per million vaccinations (including serious and nonserious reports). We identified GBS in reports from persons aged 50–64 years nearly twice as often as among both the elderly (≥65 years) and younger adults (18–49 years) (Table 3). Multiple sclerosis (reporting rate = 0.03 per million vaccinations) was not among the top 10 most frequently reported neurological adverse events. Coding terms suggestive of stroke or transient ischemic attack (considered cardiovascular rather than neurological) had a reporting rate of 0.09 per million vaccinations.

3.5. Positive rechallenge events

One hundred nine of 18,245 reports (0.6%) included a positive rechallenge symptom. The most frequently reported adverse events among these reports were local (23) and allergic reactions (19) and systemic illness (16). We found 12 reports describing a neurological illness, three of which were serious: GBS, optic neuritis, and a transient episode of slurred speech and mental confusion associated with vomiting and hypertension. Three other serious positive rechallenge adverse event reports included vasculitis, gastroenteritis, and psychosis.

3.6. Death reports

We identified 371 death reports to VAERS after TIV vaccination (0.5 per million doses administered), representing two percent of all adverse event reports (371/18,245). Only 31 reports indicated that

Table 3
Most common neurological coding terms (COSTART)[a] following trivalent inactivated influenza vaccine, in adults age ≥18 years old, VAERS[b], July 1, 1990 through June 30, 2005, United States.

COSTART code[a]	All ≥18 years *N* (rate)[c]	18–49 years *N* (rate)[c]	50–64 years *N* (rate)[c]	≥65 years *N* (rate)[c]
Paresthesia	1343 (1.80)	730 (2.77)	368 (2.14)	245 (0.79)
Guillain-Barré syndrome	581 (0.78)	155 (0.59)	231 (1.34)	195 (0.63)
Peripheral neuritis/neuritis/neuropathy	339 (0.45)	136 (0.52)	118 (0.68)	85 (0.27)
Facial paralysis	215 (0.29)	93 (0.35)	72 (0.42)	50 (0.16)
Convulsion/convulsion grand mal	118 (0.16)	73 (0.28)	14 (0.08)	31 (0.10)
Ataxia	117 (0.16)	42 (0.16)	32 (0.19)	43 (0.14)
Encephalitis/encephalopathy	92 (0.12)	39 (0.15)	18 (0.10)	35 (0.11)
Myelitis	88 (0.12)	41 (0.16)	25 (0.15)	22 (0.07)
Meningitis/meningism	40 (0.05)	25 (0.09)	10 (0.06)	5 (0.02)
Optic neuritis	33 (0.04)	16 (0.06)	12 (0.07)	5 (0.02)

[a] Each adverse event report may have more than one COSTART code.
[b] Vaccine Adverse Event Reporting System.
[c] Reporting rate calculated per 1,000,000 TIV doses administered; total doses administered for all age groups combined = 747,070,979; 18–49 age-group = 263,696,575; 50–64 age-group = 172,364,441; ≥65 age-group = 311,009,963.

autopsies had been performed. The median age was 73 years (range, 18–104). The median interval between vaccination and date of death was nine days (range <1–530 days). Thirty-five reports (9.4%) described death on the day of vaccination, including four reported as anaphylaxis and six others with death shortly after vaccination (within approximately 1 h based on time or text description) but no specified cause of death. We identified co-morbidities in 283 death reports (76%), and we categorized 245 as high or intermediate-risk for morbidity/mortality; only 38 of the deaths were associated with persons having low-risk co-morbidity.

Among all the reported causes of death, 152 (41%) were due to cardiovascular events, including myocardial infarction/atherosclerotic heart disease (62), heart failure (39), sudden death (35), cerebrovascular accident (7), endocarditis (3), myocarditis (2), and other conditions (4); 70 (19%) were respiratory events, including pneumonia/pneumonitis (31), respiratory failure (22), chronic obstructive pulmonary disease (9), pulmonary embolism (3), and others (5); 39 (11%) were neurological events (GBS (26), myelitis (3), acute disseminated encephalomyelitis (2), encephalitis/encephalopathy (3), and others (5)). Malignancy (11), sepsis (8), anaphylaxis (4), Stevens Johnson syndrome (SJS) (3), liver failure (3), and various other conditions (20) were also reported as causes of death. We were unable to find a cause of death for sixty-one reports (16%). Reports of death due to cardiac causes were proportionately higher among the older age group (11 [28%], 18 [37%] and 120 [43%] among ages 18–49, 50–64 and ≥65 years); conversely, reports indicating a neurological cause of death were proportionately higher among the younger ages (8 [21%], 5 [10%] and 26 [9%]). Four of the eight death reports among the youngest age group stated GBS was the cause of death.

3.7. Advanced signal detection (data mining)

GBS, myelitis (and related clinical findings such as paralysis, cerebral spinal fluid abnormality), apnea, respiratory disorder, rhinitis, SJS and dermatomyositis (all classified as serious reports) met the criteria for closer review based on signal detection using a PRR ($n \geq 3$, PRR > 2 and chi square > 4). We also reviewed nonserious reports having coding terms suggestive of uncommon diagnoses, such as myelitis, SJS, and dermatomyositis. The median number of serious reports with any of these coding terms was 13, ranging from four to more than 500 (GBS). We did not include a review of GBS reports in this analysis, since this has been recently published [27]. In the text of 70 reports coded as "myelitis" we found a diagnosis of transverse myelitis or a description of myelitis with signs/symptoms attributable to the spinal cord [28]. Among 60 reports that did not describe a potential etiology for transverse myelitis, such as inflammatory arthritis, infection, or multiple sclerosis, the median onset interval was seven days (range: 0–109; 6 unknown). Using these criteria, the reporting rate of transverse myelitis within 30 days after vaccination was 0.064 per million doses administered (48/747,070,979).

Our review of reports with apnea or respiratory disorder revealed a variety of conditions that may have these symptoms, including GBS. Rhinitis was usually a coexistent symptom in a report for a more serious adverse event. Among 14 reports of SJS, nine patients were taking concomitant medications, and three had additional vaccinations. There were six reports of dermatomyositis; all involved women, and five occurred within a week after vaccination (one occurred 298 days following vaccination). After reviewing the reports for the remaining coding terms identified through PRR screening we did not find unexpected patterns associated with clinical characteristics, demographics, or onset intervals. Finally, no coding term met the criteria for further review using empirical Bayesian data mining methodology (results not shown).

4. Discussion

We used a variety of methods to systematically search for unusual patterns of adverse events following receipt of TIV among adults in 15 years of VAERS data. Nearly 750 million TIV vaccinations were administered to adults during the period of this review, and it would be expected that a variety of serious medical conditions may occur coincidentally after vaccination. While we did identify a broad range of serious adverse events reported after receipt of TIV, it is reassuring that no clear new safety concern emerged.

A review by an Institute of Medicine committee of neurological adverse events following TIV [17] prompted us to focus part of our review on this topic. Some of the neurological events identified in our review have previously been observed. GBS was the most common serious event reported and second only to paresthesia for all reported neurological events. The 1976–1977 swine influenza vaccines were associated with an increased risk of GBS at a rate of one case per 100,000 persons vaccinated [2,17]. This finding may continue to contribute to ongoing concerns and stimulated reporting of GBS to VAERS. However, controlled studies of TIV formulations since that time have demonstrated either no or only slightly elevated risk [17,29–33]. A previous review of VAERS data revealed reporting rates of GBS following receipt of TIV have decreased four-fold from 1994 through 2003 [27].

A causal association of Bell's palsy following receipt of TIV has been hypothesized from reports to VAERS [34], but a self-controlled observational study in the United Kingdom did not support this association [35]. The Institute of Medicine committee reviewed the hypothesized association between TIV and certain demyelinating conditions such as optic neuritis and incident multiple sclerosis and concluded that evidence was inadequate to accept or reject this association [17]. In our examination of reports of transverse myelitis, we found 60 with no alternative etiology, most with onset within a few weeks after vaccination (median 7 days). Despite this pattern, the reporting rate of transverse myelitis without an identified etiology and with onset within 30 days after vaccination (0.064 per million) was less than the background rate (0.107–0.378 per million per 30 day period) [24,25]. Sensitivity analyses using a less restricted subset from VAERS still yielded a reporting rate within the range of the background rate (data not shown). However, recent estimates of background incidence are not available, and because VAERS is limited by underreporting, the true incidence of transverse myelitis or other adverse events after TIV is unknown.

A previously published review found a number of SJS reports following a variety of vaccines without other identified etiologies [36]. We found a limited number of SJS reports following influenza vaccinations, most with competing etiologies or insufficient information. Our analysis did not identify SJS or transverse myelitis as clear safety concerns, but due to the limitations of VAERS and the seriousness of these conditions, continued monitoring is important.

Dyspnea was one of the most commonly reported adverse events among serious reports. One data mining method (but not the other method) also highlighted the coding terms for respiratory disorder and apnea, but review of these reports did not reveal any unexpected patterns. These symptoms reflect many conditions (e.g., hypersensitivity reactions, GBS, pneumonitis) and may also be more common due to confounding by indication, i.e., persons with chronic respiratory conditions are advised to receive TIV. An "oculorespiratory syndrome", defined as respiratory symptoms or facial edema or red eyes within 24 h following receipt of TIV, has been described in Canada [37–41]. However these symptoms have high background rates (3.4% among placebo recipients in one study [41]), and it is difficult to assess their possible association with vaccination from spontaneous reporting. These symptoms would best be assessed within clinical trials.

The causes of death reported (primarily cardiovascular) and the ages of the vaccinees in death reports, are largely consistent with what is seen in the general population [42]. In addition, there was a substantial variation in causes of death. Together, these findings do not suggest causation by TIV. We found neurological events comprised the second largest proportion of death reports among persons aged 18–49 years, even though neurological conditions are not among the leading causes of death in US adults aged <65 years [42]. However, the total number of neurological death reports for this age group (18–49 years) is small (8), with half indicating GBS as the cause of death and no pattern among the others. Although VAERS data are likely limited by underreporting, this particular finding may reflect stimulated reporting for GBS.

Four reports of deaths shortly after vaccination identified anaphylaxis as the cause. Anaphylaxis is a recognized risk of influenza and other vaccines [43,44]. Another six reports described deaths within approximately 1 h after vaccination; we could not assess from available data whether these vaccinees had unrecognized anaphylactic reactions or some other event, such as arrhythmia, either not detected or not included in the report.

The most frequently reported symptoms among nonserious reports were linked to the general body system category (e.g., local reactions, fever, fatigue, and headache) (Fig. 2). Positive rechallenge reports, which may provide some support for a causal relationship between a vaccine and an adverse event, were mostly local and systemic reactions although some serious adverse events were reported. Positive rechallenges might represent a reasonable basis for further assessment; they do not by themselves prove relationships to vaccination.

To our knowledge this is the largest comprehensive review of post-licensure adverse event reports following receipt of TIV, yet the adverse events described and shown in Table 2 represent only 26% and 49% of the coding terms in serious and nonserious reports. There are a multitude of other adverse events temporally associated with TIV, some of which have been described in published reports or listed in product labeling, though causality is generally uncertain [45–60]. Due to the vast accumulation of symptom codes and medical conditions in VAERS, and in order to concisely summarize and present highlights of the safety profile, we limited our review. Adverse events did not appear in our report if they were infrequently reported, not associated with death or positive rechallenge, or not found to be disproportionately reported after TIV as compared to other vaccines in VAERS.

VAERS is subject to underreporting, biased reporting (as it relates to severity, publicity or timing of the adverse event) and inconsistency in the quality and completeness of reports. Serious events or events that occur shortly after vaccination, are highly visible in the media or follow a recently marketed vaccine are more likely to be reported to VAERS [6,7,10]. However, VAERS provides valuable information for a larger and more diverse population than what is attainable during pre-licensure trials and has been demonstrated to be useful for early detection of potential safety issues [61,62].

The 15 year period of our review included whole virus (not currently distributed), split, and purified subunit TIV manufactured using egg based technology. In the future, incorporation of new technologies into the development of pandemic and seasonal vaccines (e.g., adjuvants, cell culture) may result in changes in the safety profile; post-licensure monitoring will continue to be crucial [1].

5. Conclusion

Our review of VAERS data did not identify any clear new safety concerns, but some rare serious events may warrant further investigational studies (e.g., case–control or prospective analyses), and, due to its association with the 1976–1977 vaccines, GBS requires continued monitoring. The most frequently reported adverse events were not severe, consistent with data from clinical trials. In the event of influenza pandemic when vaccines may need to be rapidly distributed, only limited safety data from pre-licensure trials may be available. This safety profile from 15 years of post-marketing surveillance for TIV may provide a reference for reported adverse events and a context to help identify new adverse event patterns.

Acknowledgments

We wish to thank Peng-Jun Lu, MPH, PhD, James Singleton, MS and Barry Sirotkin, MS for help with data analysis; James Sejvar, MD for help with categorizing and grouping neurological codes; and John Iskander, MD, MPH, and Robert P. Wise, MD, MPH for review of critical content.

Disclosures: No authors have a conflict of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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.

References

[1] Iskander J, Broder K. Monitoring the safety of annual and pandemic influenza vaccines: lessons from the US experience. Expert Rev Vaccines 2008;7(February (1)):75–82.
[2] Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States 1976–1977. Am J Epidemiol 1979;110(2):105–23.
[3] Fiore AE, Shay DK, Haber P, Iskander J, Uyeki TM, Mootrey G, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP) 2007. MMWR Morb Mortal Wkly Rep 2007;56(RR-6):1–60.
[4] Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, et al. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics 2003;112:815–20.
[5] Treanor JJ, Campbell JD, Zangwill KM, Rowe T, Wolff M. Safety and immunogenicity of an inactivated subvirion influenza a (H5N1) vaccine. N Engl J Med 2006;354:1343–51.
[6] Chen RT, Rastogi SC, Mullen JR, Hayes SW, Coch SL, Donlon JA, et al. The vaccine adverse event reporting system (VAERS). Vaccine 1994;12:542–50.
[7] Ellenberg SS, Chen RT. The complicated task of monitoring vaccine safety. Public Health Rep 1997;112(1):10–20.
[8] Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J 2004;23:287–94.
[9] Iskander J, Miller E, Chen R. The role of the Vaccine Adverse Event Reporting system (VAERS) in monitoring vaccine safety. Pediatr Ann 2004;33(9):599–606.
[10] Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. MMWR 2003:1–24.
[11] COSTART: coding symbol for thesaurus of adverse reaction terms. 5th ed. Rockville, MD: Food and Drug Administration, Center for Drugs and Biologics, Division of Drug and Biological Product Experience; 1989.
[12] Food and Drug Administration. 21 CFR Part 600.80. Postmarketing reporting of adverse experiences: Federal Register; 1997, p. 52252–53.
[13] Centers for Disease Control and Prevention NCHS. National Health Interview Survey Datasets, Available from: http://www.cdc.gov/nchs/about/major/nhis/quest_data_related_doc.htm; 2008 [cited 2009 January 15, 2009].
[14] Lu P, Bridges C, Euler G, Singleton J. Influenza vaccination of recommended adult populations, U.S., 1989–2005. Vaccine 2008;26:1786–93.
[15] Massey JT, Moore TF, Parsons VL, Tadros W. National health interview survey, 1985–1994: design and estimation. Vital and health statistics, Series 2: data evaluation and methods research. No. 110. Public Health Service, DHHS; 1989.
[16] United States Government Census Report, Available from: http://www.census.gov; 2000 [cited April 8, 2008].
[17] Institute of Medicine (IOM). Immunization safety review. Influenza vaccines and neurological complications. Washington, DC: National Academies Press; 2004.
[18] Nichol KL, Wuorenma J, Von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Int Med 1998;158:1769–76.
[19] Banks D, Woo E, Burwen DR, Perucci P, Braun MM, Ball R. Comparing data mining methods on the VAERS database. Pharmacoepidemiol Drug Saf 2005;14(September (9)):601–9.

[20] Evans SJ, Aller PC, Davis S. Use if proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf 2001;10:483–6.
[21] Woo E, Ball R, Burwen DR, Braun MM. Effects of stratification on data mining in the Vaccine Adverse Event Reporting System (VAERS). Drug Saf 2008;31:667–74.
[22] DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Statistician 1999;53:177–90.
[23] Szarfman 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(6):381–92.
[24] Berman M, Feldman S, Alter M, Zilber N, Kahana E. Acute transverse myelitis: incidence and etiologic considerations. Neurology 1981;31:966–71.
[25] Jeffery DR, Mandler RN, Davis LE. Transverse myelitis: retrospective analysis of 33 cases, with differentiation of cases associated with multiple sclerosis and parainfectious events. Arch Neurol 1993;50:532–5.
[26] Updated interim influenza vaccination recommendations—2004-05 influenza season. MMWR Morb Mortal Wkly Rep 2004:1183–4.
[27] Haber P, DeStefano F, Angulo F, Iskander J, Shadomy SV, Weintraub E, et al. Guillain-Barre syndrome following influenza vaccination. JAMA 2004;292(20):2478–81.
[28] Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute transverse myelitis. Neurology 2002;59:499–505.
[29] Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barré syndrome and the 1992-93 and 1993-94 influenza vaccines. N Engl J Med 1998;339(25):1797–802.
[30] Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979–1980 and 1980–1981. Lack of an association with influenza vaccination. JAMA 1982;248(6):698–700.
[31] Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barre syndrome and the 1978–1979 influenza vaccine. N Engl J Med 1981;304(26):1557–61.
[32] Hughes RA, Charlton J, Latinovic R, Gulliford MC. No association between immunization and Guillain-Barré Syndrome in the United Kingdom, 1992 to 2000. Arch Int Med 2006;166:1301–4.
[33] Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain-Barré Syndrome after influenza vaccination in adults: a population-based study. Arch Int Med 2006;166:2217–21.
[34] Zhou W, Pool V, DeStefano F, Iskander J, Haber P, Chen RT. A potential signal of Bell's palsy after parenteral inactivated influenza vaccines: reports to the Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. Pharmacoepidemiol Drug Saf 2004;13(8):505–10.
[35] Stowe J, Andrews N, Wise L, Miller E. Bell's palsy and parenteral inactivated influenza vaccine. Hum Vaccine 2006;2:110–2.
[36] Ball R, Ball L, Wise RP, Braun MM, Beeler JA, Salive ME. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J 2001;20:219–23.
[37] King A, Galanis E. National Advisory Committee on Immunization (NACI), Supplementary statement on influenza vaccination: continued use of Fluviral influenza vaccine in the 2000–2001 influenza season. Can Commun Dis Rep 2001;27(ACS-1):1–7.
[38] DeSerres G, Boulianne N, Duval B, Rochette L, Grenier JL, Roussel R, et al. Oculo-respiratory syndrome following influenza vaccination: evidence for occurrence with more than one influenza vaccine. Vaccine 2003;21(19–20):2346–53.
[39] DeSerres G, Toth E, Menard S, Grenier JL, Roussel R, Tremblay M, et al. Oculo-respiratory syndrome after influenza vaccination: trends over four influenza seasons. Vaccine 2005;23:3726–32.
[40] National Advisory Committee on Immunization (NACI). Supplementary statement for the 2002–2003 influenza season: update on oculo-respiratory syndrome in association with influenza vaccination. Can Commun Dis Rep 2002;28(ACS-6):1–8.
[41] Scheifele DW, Duval B, Russell ML, Warrington R, DeSerres G, Skowronski DM, et al. Ocular and respiratory symptoms attributable to inactivated split influenza vaccine: evidence from a controlled trial involving adults. Clin Infect Dis 2003;36(7):850–7.
[42] Minino AM, Heron MP, Murphy SL, Kochanek KD. Deaths: final data for 2004. Natl Vital Stat Rep 2007 21;55(August (19)):1–119.
[43] Bierman CW, Shapiro GG, Pierson WE, Taylor JW, Foy HM, Fox JP. Safety of influenza vaccination in allergic children. J Infect Dis 1977;136:S652–5.
[44] Stratton KR, Howe CJ, Johnston RB. Adverse events associated with childhood vaccines other than pertussis and rubella: summary of a report from the Institute of Medicine (IOM). JAMA 1994;271(20):1602–5.
[45] Biasi D, Carletto A, Caramaschi P, Tonoli M, Bambara LM. A case of reactive arthritis after influenza vaccination. Clin Rheumatol 1994;13:645.
[46] Blanche P, Decrette C, Sicard D. Development of uveitis following vaccination for influenza. Clin Infect Dis 1994;19:979.
[47] Boutros N, Keck BP. Delirium following influenza vaccination. Am J Psychiatry 1993;150:1899.
[48] Downs AM, Lear JT, Bower CP, Kennedy CT. Does influenza vaccination induce bullous pemphigoid? A report of four cases. Br J Dermatol 1998;138:363.
[49] Finsterer J, Artner C, Kladosek A, Kalchmayr R, Redtenbacher S. Cavernous sinus syndrome due to vaccination-induced giant cell arteritis. Arch Int Med 2001;161:1008–9.
[50] Hamdy RC, Micklewright M, Beecham VF, Moore SW. Influenza vaccine may enhance theophylline toxicity. A case report and review of the literature. J Tenn Med Assoc 1995;88:463–4.
[51] Kelsall JT, Chalmers A, Sherlock CH, Tron VA, Kelsall AC. Microscopic polyangiitis after influenza vaccination. J Rheumatol 1997;24:1198–202.
[52] Kielstein JT, Termuhlen L, Sohn J, Kliem V. Minimal change nephrotic syndrome in a 65-year-old patient following influenza vaccination. Clin Nephrol 2000;54:246–8.
[53] Liozon E, Ittig R, Vogt N, Michel JP, Gold G. Polymyalgia rheumatica following influenza vaccination. J Am Geriatr Soc 2000;48:1533–4.
[54] Mader R, Narendran A, Lewtas J, Bykerk V, Goodman RCJ, Dickson JR, et al. Systemic vasculitis following influenza vaccination—report of 3 cases and literature review. J Rheumatol 1993;20:1429–31.
[55] Marti J, Anton E. Polymyalgia rheumatica complicating influenza vaccination. J Am Geriatr Soc 2004;52:1412.
[56] May S, Netto G, Domiati-Saad R, Kasper C. Cutaneous lymphoid hyperplasia and marginal zone B-cell lymphoma following vaccination. J Am Acad Dermatol 2005;53:512–6.
[57] Ramakrishnan N, Parker LP. Thrombotic thrombocytopenic purpura following influenza vaccination—a brief case report. Conn Med 1998;62:587–8.
[58] Solomon A, Frucht-Pery J. Bilateral simultaneous corneal graft rejection after influenza vaccination. Am J Ophthalmol 1996;121:708–9.
[59] Tavadia S, Drummond A, Evans CD, Wainwright NJ. Leukocytoclastic vasculitis and influenza vaccination. Clin Exp Dermatol 2003;28:154–6.
[60] Tishler M, Levy O, Amit-Vazina M. Immune thrombocytopenic purpura following influenza vaccination. Isr Med Assoc J 2006;8:322–3.
[61] Update: Guillain-Barré Syndrome among recipients of Menactra® meningococcal conjugate vaccine—United States, June 2005–September 2006. Morb Mortal Wkly Rep 2006:1120–4.
[62] Zanardi LR, Haber P, Mootrey GT, Niu MT, Wharton M. Intussusception among recipients of rotavirus vaccine: reports to the vaccine adverse event reporting system. Pediatrics 2001;107(6):E97.