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The reporting sensitivity of the Vaccine Adverse Event Reporting System (VAERS) for anaphylaxis and for Guillain-Barré syndrome

Elaine R. Miller[*], **Michael M. McNeil**, **Pedro L. Moro**, **Jonathan Duffy**, **John R. Su**

Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, United States

Abstract

Background: Underreporting is a limitation common to passive surveillance systems, including the Vaccine Adverse Event Reporting System (VAERS) that monitors the safety of U.S.-licensed vaccines. Nonetheless, previous reports demonstrate substantial case capture for clinically severe adverse events (AEs), including 47% of intussusception cases after rotavirus vaccine, and 68% of vaccine associated paralytic polio after oral polio vaccine.

Objectives: To determine the sensitivity of VAERS in capturing AE reports of anaphylaxis and Guillain-Barré syndrome (GBS) following vaccination and whether this is consistent with previous estimates for other severe AEs.

Methods: We estimated VAERS reporting rates following vaccination for anaphylaxis and GBS. We used data from VAERS safety reviews as the numerator, and estimated incidence rates of anaphylaxis and GBS following vaccination from the Vaccine Safety Datalink (VSD) studies as the denominator. We defined reporting sensitivity as the VAERS reporting rate divided by the VSD incidence rate. Sensitivity was reported as either a single value, or a range if data were available from >1 study.

Results: VAERS sensitivity for capturing anaphylaxis after seven different vaccines ranged from 13 to 76%; sensitivity for capturing GBS after three different vaccines ranged from 12 to 64%. For anaphylaxis, VAERS captured 13–27% of cases after the pneumococcal polysaccharide vaccine, 13% of cases after influenza vaccine, 21% of cases after varicella vaccine, 24% of cases after both the live attenuated zoster and quadrivalent human papillomavirus (4vHPV) vaccines, 25% of cases

[*]Corresponding author at: Immunization Safety Office, Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, MS-V18-4, Atlanta, GA 30329, United States. EMiller@cdc.gov (E.R. Miller).

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after the combined measles, mumps and rubella (MMR) vaccine, and 76% of cases after the 2009 H1N1 inactivated pandemic influenza vaccine. For GBS, VAERS captured 12% of cases after the 2012–13 inactivated seasonal influenza vaccine, 15–55% of cases after the 2009 H1N1 inactivated pandemic influenza vaccine, and 64% of cases after 4vHPV vaccine.

Conclusions: For anaphylaxis and GBS, VAERS sensitivity is comparable to previous estimates for detecting important AEs following vaccination.

Keywords

Adverse event; Vaccine Adverse Event Reporting System (VAERS); Passive surveillance; Vaccine; Vaccine safety

1. Background

The Vaccine Adverse Event Reporting System (VAERS) was authorized by the National Childhood Vaccine Injury Act of 1986 [1]. Co-administered by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA), VAERS is a national spontaneous reporting (passive surveillance) system for monitoring U.S.-licensed vaccines. VAERS accepts reports of adverse events (AEs) following vaccination from healthcare providers, vaccine manufacturers, and the general public [1].

The proportion of AEs occurring after vaccination that are reported to VAERS (i.e., the sensitivity or VAERS reporting completeness) is often unknown but as with all passive surveillance systems, underreporting is considered an important limitation. There is limited data on VAERS sensitivity: In a 1995 study that compared VAERS reports for specific AEs with data from published studies, investigators found that the reporting sensitivity for vaccine-associated poliomyelitis (a serious, potentially life-threatening event) after receipt of the oral polio vaccine was 68% in VAERS, whereas rash (a non-serious event) after the combined measles, mumps, and rubella (MMR) vaccine had a reporting sensitivity of under 1% [2]. In a 2001 study that used a capture-recapture method, investigators found that VAERS reporting sensitivity for capturing intussusception after rotavirus vaccine was 47% [3].

Since these studies were published, efforts have been made to expand awareness of VAERS to increase reporting of AEs. For example, information on VAERS has been made more prominent on Vaccine Information Statements (VIS) that are provided when administering vaccines on the CDC recommended childhood immunization schedule [4]. During the 2009 H1N1 influenza pandemic, VAERS information was included on immunization report cards, and CDC collaborated with the American Academy of Neurology to promote VAERS reporting of Guillain-Barré syndrome (GBS) [5]. Additionally, state health departments designated an on-site Vaccine Safety Coordinator in each state to promote reporting as well. One responsibility of the coordinator is to promote VAERS reporting in their state; that collaboration continues today [6].

To provide a current assessment of VAERS reporting sensitivity and determine if the assessed sensitivity is comparable to previous estimates, we estimated reporting sensitivities

for two potentially serious outcomes that have been the subject of extensive vaccine safety surveillance and research: anaphylaxis and Guillain-Barré syndrome (GBS).

2. Methods

In the current analysis, we estimate VAERS reporting sensitivity, meaning the percentage of actual vaccine AEs that VAERS is able to capture. We calculated VAERS reporting sensitivity for two distinct AEs which are very different in terms of the expected onset intervals: 1) anaphylaxis after seven different vaccines, and 2) Guillain-Barré syndrome (GBS) after the 2009 H1N1 inactivated pandemic vaccine, the quadrivalent human papillomavirus vaccine (4vHPV) and the 2012–2013 inactivated seasonal influenza vaccine. We chose anaphylaxis because anaphylaxis is a potentially life-threatening event; is an important vaccine safety concern for all patients; can occur after any vaccine; and has published rates after vaccination available [7]. We chose GBS after the 2009 H1N1 inactivated pandemic vaccine because GBS was thoroughly studied due to concerns for a potential causal association [5]. We chose GBS after 4vHPV and the 2012–2013 seasonal influenza vaccines because GBS cases are of interest after influenza vaccine and after any newly licensed vaccine. GBS is of interest because in 1976 there was an increased risk of GBS after swine flu vaccine [5]. Additionally, although anaphylaxis and GBS are not necessarily representative of all AEs that occur after vaccination, publications exist with data on the reported rates of these AEs specifically after vaccination. While we considered other potential AEs for analysis, rate data after vaccination for those AEs is lacking; without such data, we were unable to include those AEs in this analysis.

2.1. VAERS reporting rate

We obtained VAERS reporting rates for AEs based on published safety reviews. These studies generally use VAERS reports as the numerator and doses of vaccine distributed as the denominator. Doses distributed is used as a surrogate for doses administered and generally this proprietary information must be requested from individual vaccine manufacturers. Additionally, as described below, in some cases, denominators for VAERS reporting rates rely on vaccine coverage survey data.

2.2. Estimates of actual or “true” incidence rates

We obtained estimates of AE incidence rates from published studies of the Vaccine Safety Datalink (VSD). We used these rates to represent what is believed to be the actual or true rate at which these events occur following vaccination. The VSD is a collaboration between the CDC and several integrated healthcare organizations. VSD uses patient electronic health records to link vaccination data to health outcome data. VSD rates of AEs use medically attended events as the numerator, and vaccine doses administered as the denominator [8].

2.3. VAERS reporting sensitivity

We defined reporting sensitivity as the VAERS reporting rate divided by the VSD reference incidence rate from published studies. We multiplied this number by 100 to express the sensitivity as a percentage of the VSD rate.

2.4. Data sources for anaphylaxis after vaccination

To determine how well VAERS captures cases of anaphylaxis after vaccination, we obtained anaphylaxis rates after seven different vaccines (MMR, 23 valent pneumococcal polysaccharide [PPSV23], live attenuated varicella, zoster vaccine live [ZVL], 4vHPV, 2009 H1N1 inactivated, and seasonal influenza vaccines), based on a VSD study published in 2016 [7]. Then we determined the reporting rate in VAERS for similar years, based on published data from VAERS safety reviews (Table 1).

We used reported anaphylaxis rates from the VSD as our referent group [7]. For the VSD analysis, numerator data were chart validated cases occurring within 0–2 days after vaccination that were identified initially by screening for specific International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9) codes and searching among nonspecific hypersensitivity codes with site algorithms identifying receipt of epinephrine. These cases were then adjudicated as vaccine-related cases and all met level 1 or 2 Brighton Collaboration Case Definition criteria [9]; the denominator was the 25,173,965 vaccine doses administered to the cohort of approximately 9.3 million enrollees during the study period of 2009–2011 (Table 1) [7].

For the comparison data from VAERS, we used published VAERS analyses in which reporting rates of anaphylaxis were available (Table 1). For the data on MMR, PPSV23, varicella, and seasonal influenza vaccines, methods for identifying anaphylaxis reports for a recent VAERS safety review have been described [10]. Briefly, symptoms in VAERS reports are coded using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) [11]. Su et al searched for MedDRA PTs indicating anaphylaxis, and reviewed non-serious reports with medical records available and all serious reports (defined as those that resulted in hospitalization or prolongation of an existing hospitalization, life threatening illness, permanent disability, or death) [12] to determine if the case either met the Brighton Collaboration Case definition for anaphylaxis, or if the case was diagnosed by a physician. Su et al included cases if the onset of symptoms occurred within one day of vaccination. Vaccine manufacturers provided data for doses distributed for MMR, PPSV23, and varicella vaccines; the denominator was calculated based on population estimates and vaccine coverage data for influenza vaccines [10]. We estimated VAERS reporting sensitivity for each vaccine separately (Table 1).

For VAERS reporting rates for MMR and PPSV23 vaccines, we used the data from a publication for the years 1990 to 2016 by Su et al [10], but we recalculated the reporting rate using only the VAERS data for 2006–2016 to reflect more recent reporting patterns.

Using another VAERS PPSV23 publication by Miller et al which covered the years 1990–2013 [13] (Table 1), we also recalculated rates based on VAERS data for the more recent period of 2004–2013; however, the methods were different from those of Su et al and have been previously described [13]. Briefly, rates of anaphylaxis were calculated based on specific MedDRA PTs, but medical records were not reviewed to determine if Brighton Collaboration criteria for anaphylaxis were met (not all reports had medical records available for review).

For VAERS reporting rates for anaphylaxis after ZVL and 4vHPV vaccines (Table 1), the methods for case finding are also described in detail elsewhere [14,15]. Briefly, MedDRA PTs for anaphylaxis were used and all reports that met the MedDRA PT search criteria were included, regardless of whether they met the Brighton Collaboration criteria for anaphylaxis (not all reports had medical records available for review).

For VAERS anaphylaxis reporting rates for the 2009 H1N1 inactivated pandemic influenza A vaccine Table 1, we obtained rates from a published safety review on reports received during the first 4 months (October 2009 to January 2010) of 2009 H1N1 pandemic vaccine use [16], when an estimated 62.4 million doses of the vaccine were administered; the Brighton Collaboration Case definition for anaphylaxis [9] was used to verify the diagnosis for reports suggestive of anaphylaxis.

2.5. Data sources for Guillain-Barré syndrome (GBS) after vaccination

To determine how well VAERS captures cases of GBS after vaccination, we obtained published rates of GBS with onset within 42 days after receipt of the 2009 H1N1 inactivated pandemic influenza A vaccine during the 2009–2010 season from a VSD study [17]. We compared these rates to the published reporting rate of GBS cases in VAERS after the same vaccine. We performed a similar comparison between VAERS and VSD data for reported GBS after the 4vHPV vaccine, and after the 2012–2013 seasonal influenza vaccine (Table 2).

We used reported GBS rates after the 2009 H1N1 inactivated pandemic vaccine from the VSD as our referent group [17]. For the VSD analysis, numerator data were chart validated cases occurring within 1–42 days after vaccination with the 2009 H1N1 inactivated pandemic influenza A vaccine; these cases were identified initially by screening for specific ICD-9 codes. These cases were then adjudicated by neurologists with GBS expertise as incident cases that met level 1, 2 or 3 Brighton Collaboration Case Definition criteria [18] or were reported cases but had insufficient evidence to meet the Brighton Criteria. The denominator was 1,480,135 vaccine doses administered to the cohort of approximately 9 million enrollees during the study period of 2009–2010 [17].

For GBS rates after the 2009 H1N1 inactivated pandemic influenza A vaccine (Table 2), we used 2 different VAERS analyses: a summary by Vellozzi, et al of all VAERS reports received during the first 4 months (October 2009 to January 2010) of 2009 H1N1 pandemic vaccine use [16], and a summary by Bardenheier, et al of VAERS reports received August 1, 2009 through December 31, 2010 among persons aged 17–44 years [19]. Methods for both analyses are detailed in their respective publications. Briefly, in both analyses, medical records were requested and the Brighton Collaboration case definition for GBS [18,20] was applied. GBS was considered confirmed if the Brighton Collaboration case definition for GBS was met or if medical records indicated that a neurologist had diagnosed GBS. Vaccine doses administered for the Vellozzi et al safety review were estimated based on national survey data. For the non-military population, Bardenheier et al also estimated doses administered based on national survey data; for the military population, actual doses administered data were available.

For GBS rates after the 4vHPVvaccine (Table 2), we used a VSD study for our referent group [21]. For the VSD analysis, numerator data were incident cases occurring within 1–42 days after vaccination that were identified by screening for specific ICD-9 codes. These cases were then adjudicated with medical record review by medical epidemiologists using the Brighton Collaboration Case Definition criteria [18]. The denominator was the total number of vaccine doses administered to males and females aged 9–26 years during the study period of August 1, 2006 – December 31, 2015.

For the comparison data from VAERS (Table 2), we used a published VAERS analyses in which reporting rates of GBS after 4vHPV vaccine in VAERS among persons vaccinated 2009–2015. The methods for case finding are described in detail elsewhere [15]. Briefly, MedDRA PTs for GBS were used and all reports that met the GBS MedDRA PT search criteria were reviewed to determine whether they met the Brighton Collaboration criteria. Vaccine doses distributed in the United States during the review period was the denominator. Cases were included that occurred more than 42 days after vaccination.

For GBS rates after the 2012–2013 seasonal influenza vaccine (Table 2), we used VSD as our referent group. For the VSD analysis, numerator data were incident cases of GBS occurring within 1–42 days after inactivated influenza vaccination (IIV) that were identified by screening for specific ICD-9 codes. The denominator was the number of first doses of seasonal IIV doses administered during the 2012–2013 influenza season [22].

For the comparison data from VAERS (Table 2), we used the number of GBS reports in VAERS among IIV doses distributed as reported by the manufacturer for the 2013–2014 season. MedDRA PTs for GBS were used and all IIV reports that met the GBS PT search criteria were included [23].

3. Results

3.1. Anaphylaxis

Table 1 shows published rates from VSD of anaphylaxis after specific vaccines for 2009–2011 [7], with corresponding reporting rates of anaphylaxis from VAERS [10,13–16]. VAERS reporting sensitivity for anaphylaxis after the seven vaccines studied ranged from 13% to 76% (Table 1).

3.2. Guillain-Barré syndrome

The VSD published rate of GBS with symptom onset within 42 days after administration of the 2009 H1N1 inactivated pandemic vaccine included 9 cases that met Brighton Collaboration GBS criteria levels 1–3 or were probable cases (defined as a reported case with insufficient evidence to meet Brighton Collaboration GBS criteria) out of 1,480,135 doses given for a rate of 6.08 per million doses administered (Table 2) [17].

VAERS published data included 86 reports that either met Brighton Collaboration criteria for GBS, or were diagnosed by a neurologist as GBS, after the 2009 H1N1 inactivated pandemic vaccine, (but the publication is unclear as to whether all cases occurred within 42 days after vaccination) over a time period during which 64.6 million doses of 2009 H1N1

inactivated pandemic vaccine were administered, for a reporting rate of 1.33 cases of GBS per million doses of vaccine administered (Table 2) [16].

An additional analysis of reports to VAERS of AEs after the 2009 H1N1 inactivated pandemic vaccine found 5 reports of GBS within 42 days of vaccination that either met the Brighton Collaboration case definition or were diagnosed by a neurologist as GBS among males in the US military aged 17–44 years, out of 1,494,377 males vaccinated. These data yield a reporting rate of 3.35 cases per million doses administered (Table 2) [19]. This same analysis found 8 reports of GBS within 42 days of vaccination that met the Brighton Collaboration case definition of GBS or were diagnosed by a neurologist as GBS among civilian males aged 17–44 years out of 8,592,313 males vaccinated for a reporting rate of 0.93 per million doses of 2009 H1N1 inactivated pandemic vaccine administered [19]. VAERS reporting sensitivities for GBS after the 2009 H1N1 inactivated pandemic vaccine ranged from 15% to 55% (Table 2).

The VSD published rate of GBS with symptom onset within 42 days after administration of the 4vHPV vaccine included 1 case that met Brighton Collaboration GBS criteria out of 2,773,185 doses given for a rate of 0.36 per million doses administered [21].The VAERS published rate of GBS after 4vHPV vaccine included 14 cases that met the Brighton Case Collaboration criteria after 60,461,220 doses distributed for a rate of 0.23 per million [15]. The study excluded VAERS cases that did not have sufficient information to make a determination (number not stated) and included cases that had an onset of 2–200 days with a median onset of 21 days. VAERS reporting sensitivity for GBS after the 4vHPV vaccine was 64% (Table 2).

The VSD published incident rate of GBS with symptom onset within 42 days after administration of the 2012–2013 IIV included 14 incident cases within 1–42 days after vaccination out of 2,832,064 first doses administered for a rate of 4.94 per million doses administered [22]. VAERS data for the 2012–2013 season included 72 reports of GBS among approximately 121.9 million doses of IIV, for an estimated reporting rate of 0.59 cases per million doses of IIV distributed [23]. It was not reported whether these reports met the GBS Brighton Collaboration case definition or had an onset of within 42 days after vaccination. VAERS reporting sensitivity for GBS after the 2012–13 IIV was 12% (Table 2).

4. Discussion

For the clinically serious AEs of anaphylaxis and GBS, estimated VAERS capture of overall cases is comparable to previous estimates of case capture sensitivity for other important AEs. Previous reports showed VAERS' case capture at 68% for vaccine associated polio disease and 47% for intussusception after rotavirus vaccine [2–3].

For anaphylaxis after the vaccines included in this review, VAERS captured 13–76% of cases, with the highest percent captured after the 2009 H1N1 inactivated pandemic influenza A vaccine (Table 1). This percentage of case capture might be related to the efforts to promote VAERS reporting during the H1N1 pandemic [5,6]. The percent of case capture among the other vaccines in this review was consistently between 13 and 27% (Table 1),

and while not necessarily generalizable to other vaccines, might suggest some uniformity in VAERS' ability to capture cases.

For GBS after the vaccines included in this review, a high percent of cases captured (55%) was also after the 2009 H1N1 inactivated pandemic influenza vaccine, specifically among U.S. military cases (Table 2). This percentage of case capture might be related to the military policy regarding reporting to VAERS [24]. VAERS also captured a substantial proportion (64%) of GBS cases reported among 4vHPV vaccine recipients (Table 2). 4vHPV vaccine was recommended and approved for people aged 9–26 years [25–26], an age group among whom GBS is rare [27]: the attention such an uncommon event would likely receive might have increased the likelihood of its report to VAERS and contributed to case capture. Additionally, the VAERS study included cases that had onset of greater than 42 days. This likely also contributed to the higher numbers found in VAERS. The comparatively low case capture of GBS after the 2012–13 inactivated seasonal influenza vaccine (12%) (Table 2) is likely an underestimate, as doses distributed can overestimate doses administered, thus inflating the denominator. Additional reasons for the low case capture of GBS after the 2012–13 inactivated seasonal influenza vaccine may be because GBS is generally a serious condition that results in treatment by specialists in neurology, critical care, and pulmonology. These specialists are usually not involved with ordering and administering vaccinations, so they may not be aware of the patient's recent immunization receipt and therefore would not have reported their patient's GBS as a vaccine adverse event.

4.1. Strengths and limitations

VAERS is a national passive surveillance system; the sensitivity of such systems allows detection of rare AEs that other surveillance systems are not likely to detect [1]. Also, we used published VSD studies as our reference group. These studies likely had excellent (albeit not complete) capture of anaphylaxis and GBS cases in the VSD population. Additionally, VSD's use of doses administered as denominators provided accurate rates. The VSD population is also a representative sample of the United States, suggesting these data can be generalized to a broader population [28].

Limitations of this analysis include methodological differences among the studies used, possibly contributing to the broad range of estimated VAERS sensitivities. These differences include identifying reports using automated search criteria instead of review of medical records [13–15] to determine if Brighton Collaboration Case Definition criteria were met, and including reports of GBS more than 42 days after vaccine receipt. Some studies estimated doses administered from survey data [16,19,29]. Also, our estimated case capture for anaphylaxis and GBS might not be generalizable to other AEs.

4.2. Conclusions

Our analysis indicates that for several vaccines, estimated VAERS sensitivity was at least 13% for anaphylaxis and 12% for GBS, with a sensitivity as high as 76% for anaphylaxis and 64% for GBS. These estimates exceed the <1% reporting sensitivity previously observed for mild non-serious adverse events [2]. For the clinically serious outcomes of

anaphylaxis and GBS, VAERS sensitivity is comparable to previous estimates of important AEs following vaccination.

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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 (CDC) or the U.S. Food and Drug Administration (FDA). Mention of a product or company name is for identification purposes only and does not constitute endorsement by the CDC or FDA.

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Table 1

VAERS reporting sensitivity for anaphylaxis after seven vaccines.

Vaccine	Incidence Rate in Vaccine Safety Datalink (VSD)[1,2]	Reporting Rate in Vaccine Adverse Event Reporting System (VAERS)	VAERS Reporting Sensitivity
Measles, Mumps & Rubella (MMR)	5.14 per million doses administered 2009–2011 [7]	1.31 per million doses distributed 2006–2016 [10][3]	25%
Pneumococcal Polysaccharide 23 valent (PPSV23)	2.86 per million doses administered 2009–2011 [7]	0.38 per million doses distributed 2006–2016 [10] [3]	13%
		0.77 per million doses distributed 2004–2013 [13] [4]	27%
Varicella	5.77 per million doses administered 2009–2011 [7]	1.2 per million doses distributed 2006–2016 [10] [3]	21%
Zoster live (ZVL)	6.58 per million doses administered 2009–2011 [7]	1.6 per million doses distributed 2006–2015 [14] [4]	24%
Human papillomavirus vaccine, quadrivalent (4vHPV)	2.58 per million doses administered 2009–2011 [7]	0.63 per million doses distributed 2009–2015 [15] [4]	24%
2009 H1N1 inactivated pandemic influenza A	2.11 per million doses administered 2009–2011 [7]	1.6 per million doses estimated to have been given from Oct. 2009 to Jan. 2010 [16] [5]	76%
Influenza (all types)	1.53 per million doses administered 2009–2011 [7]	0.2 per million doses administered 2010–2016 [10] [3]	13%

[1] All VSD anaphylaxis cases met level 1 or 2 Brighton Collaboration Case Definition criteria and on case review were determined to be vaccine triggered and occurred 0 to 2 days after vaccination [7].

[2] The total number of doses administered in the VSD for the vaccines listed: MMR = 584,103; PPSV23 = 698,482; varicella = 866,129; zoster live = 304,001; 4vHPV = 775,833; 2009 H1N1 inactivated pandemic influenza A = 1,422,921; any influenza = 11,119,652 [7].

[3] All cases occurred within one day of vaccination AND either met the Brighton Collaboration Case definition for anaphylaxis, or anaphylaxis was diagnosed by a physician [10].

[4] All reports that met search criteria for anaphylaxis were included, regardless of whether they met the Brighton Collaboration criteria since not all reports had medical records available for review [13–15].

[5] All cases either met the Brighton Collaboration Case definition for anaphylaxis, or the case was diagnosed by a physician and occurred within 24 h of vaccination [16].

Table 2

VAERS reporting sensitivity for Guillain-Barré Syndrome (GBS) after three vaccines.

Vaccine	Rate in VSD within 42 days of vaccination	Rate in Vaccine Adverse Event Reporting System (VAERS)	VAERS Reporting Sensitivity
2009 H1N1 inactivated pandemic vaccine	6.08 per million doses administered during the 2009–2010 season [17]	1.33 per million doses estimated to have been given Oct. 2009-Jan. 2010 [16][1]	22%
		3.35 per million doses administered in military population for ages 17–44 years with report date of Aug. 2009-Dec. 2010 [19][2]	55%
		0.93 per million doses estimated to have been given in non-military population for ages 17–44 years with report date of Aug. 2009-Dec. 2010 [19][3]	15%
Human papillomavirus vaccine, quadrivalent (4vHPV)	0.36 cases per million doses administered 2006–2015 [21]	0.23 cases per million doses distributed 2009–2015 [15][4]	64%
2012–2013 influenza season inactivated influenza vaccine (IIV)	4.94 cases per million doses administered during the 2012–2013 season [22]	0.59 cases per million doses distributed [23] [5]	12%

[1] All cases either met the Brighton Collaboration case definition for GBS or had neurologist diagnosis of GBS, but unclear if onset for all cases was within 42 days of vaccination [16].

[2] All cases either met the Brighton Collaboration case definition for GBS or had neurologist diagnosis of GBS, and all cases had onset within 42 days onset of vaccination [19].

[3] All cases either met the Brighton Collaboration case definition for GBS or had neurologist diagnosis of GBS, and all cases had onset within 42 days onset of vaccination [19].

[4] All cases either met the Brighton Collaboration case definition Level 1 or Level 2 criteria for GBS and the median onset was 21 days with a range of 2–200 days [15].

[5] Unclear of the onset interval or whether the cases met the Brighton Collaboration case definition [23].