HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2019 June 03.

Published in final edited form as:

Vaccine. 2016 May 27; 34(25): 2841–2846. doi:10.1016/j.vaccine.2016.04.021.

Post-licensure safety surveillance of 23-valent pneumococcal polysaccharide vaccine in the Vaccine Adverse Event Reporting System (VAERS), 1990–2013

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Abstract

Background: 23-Valent pneumococcal polysaccharide vaccine, trade name Pneumovax®23 (PPSV23), has been used for decades in the Unites States and has an extensive clinical record. However, limited post-licensure safety assessment has been conducted.

Objective: To analyze reports submitted to the Vaccine Adverse Event Reporting System (VAERS) following PPSV23 from 1990 to 2013 in order to characterize its safety profile.

Methods: We searched the VAERS database for US reports following PPSV23 for persons vaccinated from 1990 to 2013. We assessed safety through: automated analysis of VAERS data, crude adverse event (AE) reporting rates based on PPSV23 doses distributed in the US market, clinical review of death reports and reports involving vaccine administered to pregnant women, and empirical Bayesian data mining to assess for disproportional reporting.

Results: During the study period, VAERS received 25,168 PPSV23 reports; 92% were non-serious, 67% were in females and 86% were in adults aged ≥19 years. When PPSV23 was administered alone, fever (43%), injection site erythema (28%) and injection site pain (25%) were the most commonly reported non-serious AEs in children. Injection site erythema (32%), injection site pain (27%) and injection site swelling (23%) were the most commonly reported non-serious AEs in adults. Of serious reports (2129,8% of total), fever was most commonly reported in both children (69%) and adults (39%). There were 66 reports of death, four in children and 62 in adults. Clinical review of death reports did not reveal any concerning patterns that would suggest a causal association with PPSV23. No disproportional reporting of unexpected AEs was observed in empirical Bayesian data mining.

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Financial disclosure

None of the authors have any financial relationships to disclose.

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 US Food and Drug Administration (FDA).

Conflict of interest

None of the authors have a conflict of interest.

Conclusions: We did not identify any new or unexpected safety concerns for PPSV23. The VAERS data are consistent with safety data from pre-licensure clinical trials and other post-licensure studies.

Keywords

23-Valent pneumococcal polysaccharide; vaccine; Vaccines; Immunizations; Vaccine safety; Surveillance; Vaccine Adverse Event Reporting System; (VAERS)

1. Introduction

The US Food and Drug Administration (FDA) licensed 23-valent pneumococcal polysaccharide vaccine (PPSV23) (Pneumovax®23, Merck & Co, Inc., Whitehouse Station, NJ) in 1983 [1]. PPSV23 replaced 14-valent pneumococcal polysaccharide vaccine. Another licensed 23-valent pneumococcal polysaccharide vaccine, Pnu-Imune®23 (Wyeth Lederle), was used from 1983 to 2002. Pneumovax®23 is the only licensed pneumococcal polysaccharide vaccine currently available in the United States. The Advisory Committee on Immunization Practices (ACIP) recommends PPSV23 for individuals aged 2 through 64 years who are immunocompetent with chronic conditions, have functional or anatomic asplenia or are immunocompromised; and for all adults aged >65 years regardless of previous medical history [2–7]. Although no human or animal pre-licensure data are available on the safety of PPSV23 in pregnancy [1], pregnancy is neither a contraindication nor a precaution for vaccination [8]. In pre-licensure trials, the most frequently reported adverse events (AEs) after PPSV23 included injection site reactions like pain, swelling and redness at the injection site, and headache, fatigue, and myalgia. Injection site reactions were higher in persons receiving a second dose of the vaccine compared to persons receiving the first dose – pain was observed in 60% of primary vaccinations versus 77% of revaccinations, injection site swelling or induration was reported in 20% versus 40%, and injection site erythema was reported in 16% versus 35% respectively. Serious AEs were rare [1].

PPSV23 has been used for decades and has an extensive clinical record. However, limited post-licensure safety assessment has been conducted [9–11]. We analyzed reports submitted to the Vaccine Adverse Event Reporting System (VAERS) following PPSV23 for the period 1990 through 2013.

2. Methods

VAERS is a national vaccine safety monitoring system jointly administered by the Centers for Disease Control and Prevention (CDC) and the FDA that accepts spontaneous reports of AEs following vaccination [12]. VAERS accepts reports from patients, parents, healthcare providers, vaccine manufacturers, and others. The VAERS report form collects information on the patient, vaccines administered and the AE experienced. Signs and symptoms of AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology [13]. VAERS may also receive reports of vaccination errors (e.g., incorrect dose administered) not describing an AE. A VAERS report may be assigned one or more MedDRA preferred terms (PT). Reports are classified as serious based on the Code of Federal Regulations if one or more of the following is reported:

death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability [14]. For non-manufacturer serious reports, medical records are routinely requested and made available to VAERS personnel; for reports of deaths, efforts are made to obtain autopsy reports and death certificates to ascertain cause of death.

We analyzed the safety of PPSV23 using four methods: (1) automated analysis of VAERS data, including comparisons of PPSV23 reports and trivalent inactivated influenza vaccine (IIV3) reports, (2) crude AE reporting rates based on PPSV23 doses distributed in the US market for all reports, serious reports, and reports of cellulitis and anaphylaxis, (3) clinical review of death reports and reports involving vaccine administered to pregnant women, and (4) empirical Bayesian (EB) data mining to assess for disproportional reporting of any AE after PPSV23 compared to AEs after other vaccines in the VAERS database.

2.1. Automated analysis

We searched the VAERS database for US reports following brand name Pneumovax®23 for persons vaccinated from January 1, 1990 through December 31, 2013, with a report receipt date through January 31, 2014. We excluded foreign reports. We also excluded vaccine brand name Pnu-1mune®23 reports since it was not the focus of our analysis. We included reports of pneumococcal polysaccharide vaccine with brand name not reported or unknown that were received after 2002, since the only pneumococcal polysaccharide vaccine available in the US after 2002 was Pneumovax®23.

We analyzed reports by age, sex, “serious” status and most common MedDRA PTs. We also compared PPSV23 reports to reports following IIV3 gathered using similar search criteria. We summarized reports of anaphylaxis and cellulitis, and reports in which PPSV23 was given during pregnancy. MedDRA PTs for anaphylaxis reports included: ‘anaphylactic reaction’, ‘anaphylactic shock’, ‘anaphylactoid reaction’, or ‘anaphylactoid shock.’ MedDRA PTs for cellulitis included: ‘cellulitis’, ‘cellulitis staphylococcal’, ‘cellulitis streptococcal’, ‘injection site cellulitis’, ‘vaccination site cellulitis’ or ‘post procedural cellulitis.’ Pregnancy reports were identified using a combination of: (a) MedDRA PTs for ‘drug exposure during pregnancy’, ‘exposure during pregnancy’, or’ maternal exposure during pregnancy’; (b) MedDRA System Organ Class groupings ‘pregnancy, puerperium and perinatal conditions’, or ‘congenital, familial and genetic disorders’; and (c) a text string search for “preg” in the fields for symptoms, pre-existing conditions and medical history.

2.2. Adverse event reporting rates

We calculated AE crude reporting rates for all reports and serious reports by dividing the number of reports by PPSV23 vaccine doses distributed for the US market from 1990 through 2013. We also calculated crude reporting rates for anaphylaxis and cellulitis.

2.3. Clinical review of death and pregnancy reports

We reviewed all death reports and accompanying medical records, autopsy reports and death certificates when available to determine cause of death. Deaths were classified using previously described body systems categories [15]. We also reviewed reports involving vaccine administered to pregnant women.

2.4. Data mining

We performed disproportionality analysis using EB data mining [16] to identify AEs reported more frequently than expected following PPSV23 compared to all other US-licensed vaccines. We used published criteria [17] to identify PPSV23–AE pairs reported at least twice as frequently as expected (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05 >2]). We reviewed reports with AEs that exceeded this data mining threshold and were not already listed in the package insert as known and expected AEs.

VAERS is a routine surveillance program conducted as a public health function and does not meet the definition of research; therefore, it is not subject to Institutional Review Board review and informed consent requirements.

3. Results

During the study period, VAERS received 25,168 PPSV23 reports (Table 1); 92% were non-serious, 67% were in females and 86% of were in adults aged ≥19 years. Healthcare providers submitted 42% of reports. The percentages of serious reports were higher in children aged 2–18 years compared to adults, but did not exceed 20% (Tables 2a and 2b). Based on an estimate of just over 108 million PPSV23 doses distributed in the United States from 1990 to 2013 (CDC unpublished data), the AE reporting rate for all reports was 23 per 100,000 doses distributed and for serious reports 2 per 100,000 doses distributed.

The most commonly reported AEs in children aged 2–18 years were pyrexia and various injection site reactions (Table 3). PPSV23 was given alone in 45% of reports in this age group. Among children who received other concomitant vaccines with PPSV23, 50% received IIV3, 10% received diphtheria, tetanus, and pertussis (DTaP) vaccine and 2% received monovalent 2009-H1N1 pandemic influenza vaccine. The most commonly reported AEs in adults aged ≥19 years were injection site erythema, injection site pain and pyrexia (Table 4). PPSV23 was given alone in 52% of reports in adults. Among adults who received other concomitant vaccines with PPSV23, 81% received IIV3.

When comparing PPSV23 reports to IIV3 reports when the vaccines were given alone, the percent of serious reports in children was greater for PPSV23 than for IIV3: in children aged 2–5 years, 20% versus 9%; 6–12 years, 20% versus 7%; 13–18 years, 18% versus 10%. However, in individuals aged ≥65 years, the percent of serious reports was greater for IIV3 compared to PPSV23,16% versus 8%.

3.1. Cellulitis and anaphylaxis reports

We identified 2725 reports of cellulitis, with 94% having onset within 7 days of vaccination. The reporting rate for cellulitis was 2.5 per 100,000 PPSV23 doses distributed. In 43% of the PPSV23 reports to VAERS, the vaccine dose number was not reported.

We also identified 62 reports of anaphylaxis, with all cases occurring either on the day of vaccination (87%) or within one day of vaccination (10%), with the exception of one report which stated the AE occurred within 4 days of vaccination. In one anaphylaxis report, the

onset interval could not be determined. The reporting rate for anaphylaxis was 0.06 per 100,000 (0.6 per million) PPSV23 doses distributed.

3.2. Pregnancy reports

We identified 17 reports of women vaccinated with PPSV23 during pregnancy. Seven were vaccinated in the first trimester; four were vaccinated in the second trimester, and in six reports trimester was not stated. In six of the reports, the woman was known to be pregnant at the time of vaccination; in the remaining reports, pregnancy status was unknown or insufficient information was provided to determine if pregnancy status was known. AEs included cellulitis ($N = 5$), injection site reactions ($N = 5$), gestational diabetes and chlamydia ($N = 1$), spontaneous abortion ($N = 2$), and no AE documented ($N = 4$).

3.3. Deaths

We identified 66 reports of death following PPSV23 (Tables 2a and 2b); in one report age was not included. Four deaths were reported in children aged 2–18 years. Causes of death included *Neisseria meningitides* septicemia occurring 32 days after vaccination; accidental asphyxiation in a child with a history of lissencephaly, microcephaly and seizure disorder occurring 3 days after vaccination; and two cases of pneumococcal sepsis in children with sickle cell disease occurring more than three years after vaccination. Sixty-one deaths were reported in adults aged ≥19 years. Ages at time of death ranged from 27 to 98 years (median 69 years). The median time from vaccination to death was 32 days, with a range from the day of vaccination to 1869 days (just over 5 years). Cause of death could not be confirmed in 17 adult reports due to lack of availability of medical records, death certificates or autopsy reports. The most common causes of death among the 44 reports where records were available included cardiovascular conditions ($N = 16$), infections ($N = 9$), and respiratory conditions ($N = 9$). One reported death occurred the day of vaccination in a 50-year-old male who had a prolonged and complicated hospitalization, with a diagnosis of metastatic renal cell carcinoma and multiple abdominal surgeries. “Anaphylactic Shock” was listed on the death certificate as the immediate cause of death and “Pneumococcal Polysaccharide Vaccine (PPV) Administration” as an underlying cause.

3.4. Data mining

Disproportionality analysis detected EB05 >2 for the AEs: cellulitis, injection site cellulitis, local reaction, skin warm, injected limb mobility decreased, skin striae, local swelling, injection site streaking. These AEs are listed or are consistent with listed AEs in the PPSV23 package insert [1] and are not considered new safety concerns that warranted clinical review. Routine laboratory-associated MedDRA terms consistent with testing or results withEB05 >2 included: ‘blood culture,’ ‘blood culture negative,’ ‘leuko-cytosis,’ and ‘white blood cell count increased.’ Reports with the PTcodes ‘blood culture’ and ‘blood culture negative’ correlated with reports of fever (73%), white blood cell count increased (60%) and cellulitis (46%).

4. Discussion

In our VAERS review of PPSV23, we found that fever and injection site reactions were the most commonly reported AEs after PPSV23 in both children and adults. Cellulitis, an AE that has been observed in the post-marketing experience and is listed in the package insert [1,18,19], was a commonly reported serious AE. Cellulitis and cellulitis-like reactions can be difficult to distinguish from local reactions that involve pain, swelling, erythema, streaking and warmth, all of which occur after PPSV23. We did not detect any new or unexpected safety concerns in our analysis of PPSV23 reports.

Injection site reactions are known to occur more frequently after revaccination than after the initial dose [1,19]. In our data, 43% of PPSV23 reports did not include dose number. Prior experience also indicates that dose number is inconsistently reported on the VAERS form for many vaccines. Because of these limitations, we were not able to assess injection site symptoms by PPSV23 dose number. PPSV23 can be administered by intramuscular or subcutaneous injection [1]. There is evidence to suggest that the intramuscular route is associated with less injection site reactions than the subcutaneous route [20–22]. However, we are not able to compare AEs for intramuscular versus subcutaneous PPSV23 administration in VAERS due to data completeness and quality issues.

The AE reporting rate for all PPSV23 reports was 23 per 100,000 doses distributed and for serious reports 2 per 100,000 doses distributed. This is higher than that observed in a review of IIV3 reports to VAERS from 1990 to 2005, which showed a reporting rate of 2.44 per 100,000 doses administered for all reports and for serious reports 0.4 per 100,000 [23]. To further evaluate differences between PPSV23 and IIV3 reports, we conducted post hoc analysis that showed when the vaccines were administered alone, the percent of serious reports in children was greater for PPSV23 compared to IIV3, but in individuals aged ≥65 years the percent of serious reports was greater for IIV3 compared to PPSV23. When considering the recommendations for PPSV23 [2–7], these findings might be due to the epidemiologic phenomenon of confounding by indication [24]. In children, PPSV23 is recommended for those with certain chronic illnesses and functional or anatomic asplenia (e.g., sickle cell disease, splenectomy); illnesses that are generally risk factors for significant adverse health events. In contrast, annual seasonal influenza vaccination has been recommended for all children regardless of health status [25]. For most of the study period, in the elderly PPSV23 had generally been recommended as a onetime single dose for all individuals at age 65 years [26], while annual seasonal influenza vaccination has been recommended for all individuals aged ≥65 years [25]. The post hoc analysis also revealed differences between the two vaccines in the distribution of reports within the ≥65 years old age group, with the percent distribution of IIV3 reports weighted toward older individuals within this elderly age group compared to PPSV23 reports, which conversely were weighted toward younger individuals. Therefore, differences in percentage of serious reports between PPSV23 and IIV3 might best be explained by the different indications and recommendations for these vaccines.

We did not compare data for PPSV23 with the pneumococcal conjugate vaccine (PCV) in VAERS. During the study period, 1990–2013, PPSV23 and PCV were approved and

recommended for very different groups [2–4,26]. A comparison between PPSV23 and PCV vaccines in VAERS would be confounded by indication and difficult to interpret.

Our specific reviews of anaphylaxis, pregnancy, and deaths found no concerning patterns. Our reporting rate of anaphylaxis after PPSV23, 0.6 cases per million doses of vaccine distributed, is lower than a published estimate of approximately 1 case per million doses of any type of vaccine administered to children and adolescents [27]. This is reassuring; however, under-reporting in VAERS likely explains the lower reporting rate observed [28]. Although PPSV23 is not specifically recommended for pregnant women, pregnancy is neither a contraindication nor a precaution [8]; only 17 pregnancy-related reports were submitted to VAERS during the study period. Most of these reported non-pregnancy-specific AEs, such as injection site reactions, or no AE; there were only two reports of fetal demise, both spontaneous abortions. For the four deaths reported in children, non-vaccine-related causes were listed in the autopsy reports, death certificates, and/or medical records. Clinical reviews of death reports did not reveal any concerning patterns that would suggest a causal association with PPSV23 in children or adults. One death was attributed to anaphylaxis following PPSV23, however, medical records indicate the patient had a complicated hospitalization with a diagnosis of metastatic renal cell carcinoma and major abdominal surgeries and died in the hospital shortly after receiving PPSV23. Our finding that few deaths were reported after PPSV23, and the lack of causal association between vaccination and deaths, is consistent with a larger study of death reports submitted to VAERS following all vaccines. In that study, as in ours, causes of death were consistent with the most common causes of death in the US population [29].

5. Limitations

Our study had several limitations. Although VAERS has broad national scope and the ability to rapidly detect safety signals and rare adverse events, it is subject to the limitations of spontaneous reporting systems, such as under-reporting, reporting biases, inconsistency in quality and completeness of reports, and lack of an unvaccinated comparison group [12]. A parent or patient may report the wrong vaccine (e.g., PPSV23 maybe reported when pneumococcal conjugate vaccine or another vaccine was received), or may report pneumococcal vaccine type unknown; in which case the vaccine was entered in VAERS as PPSV23. Both of these situations could lead to misclassification of the vaccine. Generally, we cannot determine if the reported AEs were causally related to receipt of PPSV23. Furthermore, estimates of crude reporting rates using doses of PPSV23 vaccine distributed as a denominator should be interpreted with caution, since the actual number of doses administered and to whom those doses were administered are not known, and the rate of underreporting is unknown. Despite these limitations, VAERS is a valuable monitoring system to detect potential vaccine safety problems that might require further investigations in more controlled studies. The present study detected no such concerns.

6. Conclusion

We did not identify any new or unexpected safety concerns in our study of PPSV23 reports to VAERS from 1990 through 2013. Our findings from VAERS data are consistent with findings from pre-licensure clinical trials [1] and other post-licensure studies [9–11,18,19].

Acknowledgments

Funding

No external sources of funding.

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Table 1

Characteristics of 23-valent pneumococcal polysaccharide vaccine (PPSV23) reports submitted to VAERS, 1990–2013.[a]

Report characteristics	*N* (%)
Total reports	25,168
Serious[b]	2129(8)
Female	16,871 (67)
PPSV23 given alone[c]	13,113(52)
Type of reporter	
Healthcare provider	10,462 (42)
Other	6319(25)
Manufacturer	5152(20)
Patient/parent	2576 (10)
Not reported orunknown	659 (3)
Age groups (years)	
0<2[d]	940 (4)
2–5	427 (2)
6–12	550 (2)
13–18	390 (2)
19–64	11,040(44)
>65	10,546 (42)
Not reported or unknown	1275 (5)

[a] Vaccinated January 1, 1990 through December 31, 2013; reports received by January 31, 2014.

[b] Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

[c] When PPSV23 was given concomitantly with other vaccines, the most common vaccines included in children aged 2–18 years – trivalent inactivated influenza(50%), DTaP(10%)and monovalent H1N1 pandemic influenza (2%); in adults aged ≥19 years – trivalent inactivated influenza (81%), hepatitis B (1%) and hepatitis A (1%).

[d] PSV23 is not approved for this age group.

Table 2a

Age groups and serious status (all PPSV23 reports) among 23-valent pneumococcal polysaccharide vaccine (PPSV23) reports submitted to VAERS, 1990–2013.[a,b]

Age group (years)	Deaths *N* (%)	Non-death serious[c] *N* (%)	Non-serious *N* (%)	Total reports
2–5	1(0.2)	66(15)	360 (84)	427
6–12	2(0.4)	102(19)	446(81)	550
13–18	1(0.3)	66(17)	323(83)	390
19–64	23(0.2)	997 (9)	10,020(91)	11,040
≥65	38(0.4)	696 (7)	9812(93)	10,546

[a]Vaccinated January 1,1990 through December 31, 2013; reports received by January 31, 2014.

[b]Not shown are reports with age not reported or unknown and reports with age <2 years for which PPSV23 is not approved.

[c]Includes life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

Table 2b

Age groups and serious status (limited to reports where PPSV23 was given alone) among 23-valent pneumococcal polysaccharide vaccine (PPSV23) reports submitted to VAERS, 1990–2013.[a,b]

Age group (years)	Deaths *N* (%)	Non-death serious[c] *N* (%)	Non-serious *N* (%)	Total reports
2–5	1 (0.5)	39(19)	161 (80)	201
6–12	1 (0.4)	52 (20)	213(80)	266
13–18	0(0)	26(18)	120(82)	146
19–64	11(0.2)	532(10)	4820 (90)	5363
≥65	27 (0.5)	425 (7)	5471 (92)	5923

[a]Vaccinated January 1,1990 through December 31, 2013; reports received by January 31, 2014.

[b]Not shown are reports with age not reported or unknown and reports with age <2 years for which PPSV23 is not approved.

[c]Includes life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

Table 3

Most commonly reported adverse events among children aged 2–18years following 23-valent pneumococcal polysaccharide vaccine (PPSV23) in VAERS, 1990–2013.[a]

Adverse event[b] (all PPSV23 reports)	*N* (%)	Adverse event[b] (limited to reports in which PPSV23 was given alone)	*N* (%)
Non-serious	1129	Non-serious	494
Pyrexia	476 (42)	Pyrexia	210(43)
Injection site erythema	344 (30)	Injection site erythema	138(28)
Injection site pain	269 (24)	Injection site pain	125(25)
Injection site swelling	219(19)	Injection site swelling	98 (20)
Erythema	183(16)	Erythema	78 (16)
Pain	167(15)	Pain	73 (15)
Injection site edema	123(11)	Injection site edema	60 (12)
Injection site warmth	105 (9)	Edema peripheral	50 (10)
Edema peripheral	101 (9)	Injection site warmth	39 (8)
Vomiting	93 (8)	Swelling	39 (8)
Serious[c]	238	Serious[c]	119
Pyrexia	172(72)	Pyrexia	82 (69)
White blood cell count increased	95 (40)	Injection site pain	42 (35)
Cellulitis	93 (39)	Cellulitis	41 (34)
Injection site pain	87 (37)	White blood cell count increased	40 (34)
Injection site erythema	82 (34)	Injection site erythema	31 (26)
Injection site swelling	67 (28)	Injection site swelling	31 (26)
C-reactive protein increased	49 (21)	Pain	26 (22)
Erythema	46 (19)	Erythema	24 (20)
Vomiting	44 (18)	Edema Peripheral	19(16)
Edema peripheral	43 (18)	C-reactive protein increased	16(13)

[a] Vaccinated January 1, 1990 through December 31, 2013; reports received by January 31, 2014.

[b] A single report may contain more than one adverse event (i.e., not mutually exclusive).

[c] Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.

Table 4

Most commonly reported adverse events among adults aged ≥19 years following 23-valent pneumococcal polysaccharide vaccine (PPSV23) in VAERS, 1990–2013.[a]

Adverse event[b] (all PPSV 23 reports)	***N* (%)**	**Adverse event[b] (limited to reports in which PPSV23 was given alone)**	***N* (%)**
Non-serious	19,832	Non-serious	10,291
Injection site erythema	6119(31)	Injections site erythema	3279 (32)
Injection site pain	5161 (26)	Injections site pain	2821 (27)
Erythema	4498(23)	Injections site swelling	2356 (23)
Pyrexia	4418 (22)	Erythema	2273 (22)
Injection site swelling	4389 (22)	Pyrexia	1923(19)
Pain	3795(19)	Pain	1855(18)
Edema peripheral	2624(13)	Injections site warmth	1297(13)
Injection site warmth	2529(13)	Edema peripheral	1297(13)
Pain in extremity	2522(13)	Pain in extremity	1142(11)
Injection site edema	1906(10)	Injection site edema	1128(11)
Serious[c]	1754	Serious[c]	995
Pyrexia	770 (44)	Pyrexia	391 (39)
Injection site erythema	520 (30)	Injections site erythema	292 (29)
Cellulitis	515(29)	Injections site pain	287 (29)
Injection site pain	512(29)	Cellulitis	273 (27)
White blood cell count increased	454 (26)	Injections site swelling	203 (20)
Pain	373(21)	Pain	199(20)
Injection site swelling	369(21)	White blood cell count increased	198(20)
Chills	353 (20)	Erythema	184(18)
Erythema	323(18)	Chills	164(16)
Pain in extremity	272(16)	Edema peripheral	143(14)

[a]Vaccinated January 1,1990through December31, 2013; reports received by January 31, 2014.

[b]A single report may contain more than one adverse event (i.e., not mutually exclusive).

[c]Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.