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Surveillance of Adverse Events After the First Trivalent Inactivated Influenza Vaccine Produced in Mammalian Cell Culture (Flucelvax®) Reported to the Vaccine Adverse Event Reporting System (VAERS), United States, 2013-2015

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Abstract

Background: In November 2012, the first cell cultured influenza vaccine, a trivalent subunit inactivated influenza vaccine (Flucelvax®, ccIIV3), was approved in the US for adults aged ≥18 years.

Objective: To assess adverse events (AEs) after ccIIV3 reported to the US Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

Methods: We searched VAERS for US reports after ccIIV3 among persons vaccinated from July 1, 2013-March 31, 2015. Medical records were requested for reports classified as serious (death, hospitalization, prolonged hospitalization, disability, life-threatening-illness), and those suggesting anaphylaxis and Guillain-Barré syndrome (GBS). Physicians reviewed available information and assigned a primary clinical category using MedDRA system organ classes (SOC) to each report. Empirical Bayesian data mining was used to identify disproportional AE reporting following ccIIV3.

Results: VAERS received 629 reports following ccIIV3 of which 313 were for administration of vaccine to persons < 18 years.; Among 309 reports with an AE documented, 19 (6.1%) were serious and the most common categories were 152 (49.2%) general disorders and administration site conditions (mostly injection site and systemic reactions) and 73 (23.6%) immune system disorders with two reports of anaphylaxis. Four reports of GBS were submitted. Disproportional reporting was identified for 'drug administered to patient of inappropriate age.'

Conclusions: Review of VAERS reports did not identify any concerning pattern of AEs after ccIIV3. Injection site and systemic reactions were the most commonly reported AEs, similar to the pre-licensure clinical trials. Reports following ccIIV3 in persons <18 years highlight the need for education of healthcare providers regarding approved ccIIV3 use.

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Keywords

adverse event; cell culture; surveillance; trivalent inactivated influenza vaccine; vaccine safety

Introduction

On 20 November, 2012, the Food and Drug Administration (FDA) approved the trivalent subunit inactivated influenza vaccine (Flucelvax®, ccIIV3) for adults aged ≥18 years [1]. Flucelvax® is prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells. Cell culture-derived technology for production of influenza vaccines may present a number of advantages over egg-derived vaccine technology which include shorter production time, a more reliable supply of substrate, less risk of contamination, and minimization of egg passage-dependent antigenic changes [2]. The manufacturing process for ccIIV3 does not use eggs but the vaccine is not considered egg-free because the seed virus strains supplied by the World Health Organization were passaged in eggs [3]. The Advisory Committee on Immunization Practices (ACIP) included Flucelvax® for adults aged ≥18 years in its recommendations for the influenza seasons 2013–14 and 2014–15 [3,4]. The safety of ccIIV3 was evaluated in seven randomized, controlled studies in the United States, Europe, and New Zealand and involved a study population of 6,281 adults aged ≥18 years [5]. The most common (≥10%) solicited adverse reactions within 7 days of vaccination were local reactions (e.g., pain, erythema at the injection site). The most common (≥10%) systemic reactions included headache, fatigue, and malaise [5]. The rate of adverse events (AEs) after ccIIV3 was found to be comparable to that of IIV3 (Agriflu®). Although the safety data for ccIIV3 in pre-licensure studies was re-assuring, the small sample size of these studies makes it difficult to evaluate rare adverse events. We assessed the safety of ccIIV3 in the Vaccine Adverse Event Reporting System (VAERS) during the first two influenza seasons (2013–2015) following licensure to identify possible safety concerns which may not have been detected during pre-licensure trials.

Methods

Vaccine Adverse Events Reporting System (VAERS)

VAERS is a national vaccine safety surveillance system, co-administered by the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) that receives spontaneous reports of AEs following immunization [6]. VAERS accepts reports from healthcare providers, vaccine recipients, vaccine manufacturers, and other reporters. The VAERS report form collects information on age, sex, vaccines administered, the AE experienced, medical conditions at the time of vaccination and medical history. Signs and symptoms of AEs are coded by trained personnel and entered into a database using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized medical terminology [7]. A VAERS report may be assigned one or more MedDRA preferred terms (PT). A PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic [8]. Reports are classified as serious based on the Code of Federal Regulations if one of the following is reported: death, life-

threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or a congenital anomaly [9]. For non-manufacturer serious reports, medical records are routinely requested and made available to VAERS personnel. Reports with no AE (e.g., drug administered to patient of inappropriate age) may also be reported and are assigned MedDRA PTs.

We analyzed US VAERS reports for persons vaccinated with ccIIV3 during July 1, 2013 and March 31, 2015, with reports received by April 30, 2015. We excluded non-US reports and duplicate reports. Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to Institutional Review Board review and informed consent requirements.

Clinical review of reports

We conducted clinical review of all reports which involved review of all documentation (VAERS reports, medical records, autopsy report) on the AE and an assessment of the clinical characteristics of the medical event, condition/s following vaccination which motivated its reporting to VAERS. For serious reports and reports with a clinical presentation suggestive of anaphylaxis and Guillain-Barré syndrome (GBS), we also reviewed associated medical records. Reports suggestive of anaphylaxis or GBS were verified using the Brighton Collaboration criteria or a physician's diagnosis [10,11]. The Brighton Collaboration is a network of vaccine safety experts who have developed standardized, validated case definitions for certain AEs [12]. A primary diagnostic category was assigned to each report using MedDRA system organ classes (SOC), which is the highest level of the MedDRA hierarchy that provides the broadest classification for AEs [8]. Proportions of AEs under each SOC were calculated using only reports that report an AE. Cause of death was determined from information documented in the autopsy report, the death certificate, or the medical record. In this review we made no attempt to assess causality of the reported AEs.

Data mining

We used Empirical Bayesian (EB) data mining [13] to identify AEs reported more frequently than expected following ccIIV3 in the VAERS database. EB data mining can address the inherent limitation of absent denominator data (e.g., number of overall relevant doses administered) in VAERS by screening for vaccine-event pairs that are reported more frequently than expected. Furthermore, EB data mining can minimize false-positive signals resulting from the algorithm's shrinkage towards the null when observed and/or expected counts are low. EB05 is defined as the lower 95% CI limit of the adjusted ratios of the observed counts over expected counts [14]. Through this data-mining analysis, ccIIV3 reports were compared with all other vaccines in the VAERS database. We used published criteria [14,15] to identify, with a high degree of confidence, ccIIV3 vaccine-event pairs reported at least twice as frequently as would be expected (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] >2). We clinically reviewed those ccIIV3 reports containing preferred terms which exceeded the data mining threshold noted above to characterize and verify the signal.

Reporting rates

Pooled reporting rates for both GBS and anaphylaxis were calculated by totaling the number of reports of each of these conditions received over the first 2 influenza seasons of ccIIV3 distribution and diving by the total number of doses distributed during those 2 seasons.

Results

VAERS received 629 reports after ccIIV3 administered during the study period (Table 1); Only 309 of the 629 reports (49.1%) described an AE. Nineteen (6.1%) reports were classified as serious. Of all reports, 326 (51.8%) described vaccination errors; of these 313 were in persons aged <18 years (10 of which reported an AE), 10 were in adults and 3 in persons of unknown age. The median age in all reports was 18 years (range 0.7−85 years). In 585 (93.0%) reports, ccIIV3 was administered alone without any other vaccines. Most reports, 389 (61.8%), were submitted for persons vaccinated during the 2013–2014 influenza season; most of these (271 of 389;69.7%) were vaccination errors of the MedDRA preferred term ‘drug administered to patient of inappropriate age’.

Clinical Review

The most frequent AE diagnostic category was “general disorders and administration site conditions” in 152 (49.2%) reports. This system organ class included 74 (23.9%) reports of injection site reactions. Immune system disorders, which included hypersensitivity reactions, accounted for 73 (23.6%) reports which included two reports of anaphylaxis. One report in a 24- year-old male met Brighton criteria level 2, and a second report in a 43 year-old female did not meet Brighton criteria but the attending physician diagnosed it as an anaphylactic reaction. Both patients recovered fully. Of the 14 (4.5%) reports of nervous system disorders, four included reports of GBS. We were able to verify three of the GBS reports in males aged 49, 54, and 44 years that met Brighton level criteria 1, 2 and 3, respectively; the onset intervals from vaccination to onset of neurological symptoms were 6, 22 and 9 days. A history of respiratory or gastrointestinal infections prior to vaccination was present only in the 54 year-old male, who had watery diarrhea and fever before the onset of neurological symptoms. The one unverified report of GBS involved a 47-year-old female who had a history of GBS after a trivalent inactivated influenza vaccine in 1999 and presented with paralysis below her waist and in her arms 1 day after ccIIV3 vaccination.

Among the 19 serious reports, which included the four GBS reports described above, there was one death which occurred 12 days after vaccination in a 77-year-old female with a history of diabetes, chronic obstructive pulmonary disease, arthritis, and depression. Cause of death on the death certificate was noted as “cardiovascular disease due to diabetes”. Other serious reports included seven reports that required hospitalization with diagnoses of myocarditis, post-viral myalgia, pneumonia, generalized weakness and paresthesias, stroke, cardiac insufficiency, and arm pain where a pneumococcal vaccine was administered. Seven serious reports were classified as such because the reporter documented in the report that the AE resulted in permanent disability or was a life threatening illness. These conditions included influenza-like-illness, knee swelling with eye blurriness, myalgias with nausea and

vomiting, vertigo and an injection site reaction, systemic reactions (headache, fever, chills), and two reports of injection site pain.

Data mining

Disproportionality analysis revealed an elevated EB05 (>2) for the MedDRA preferred term ‘drug administered to patient of inappropriate age’, which denotes a vaccination error whereby persons received ccIIV3 at ages for which the vaccine is not approved. This signal was first detected during the 2013–2014 influenza season. For both seasons, we identified 313 reports of off-label use in persons of inappropriate age (271 during the 2013–2014 initial season of ccIIV3 use). Only 10 reports described an AE, none of which were serious. The AEs included reports of arm pain, or an injection site reaction (3), nausea and/or vomiting (2), non-anaphylaxis allergic reaction (2), and one report each of asthma attack, syncope, and fever with nasal congestion.

Crude reporting rate

During the first two influenza seasons (2013–2014 and 2014–2015) following licensure of ccIIV3, approximately 5.6 million doses of vaccine were distributed in the US [Dr. James Mansi, Novartis, personal communication]. The crude reporting rate for GBS cases was 0.7 per million doses distributed and for anaphylaxis 0.4 per million doses distributed. The crude reporting rate for non-anaphylaxis allergic reactions was 12.7 cases per million doses distributed.

Discussion

During the 2013–2014 and 2014–2015 influenza seasons, the first ccIIV3 was introduced in the United States for use in persons aged ≥18 years [3,4]. Post-licensure surveillance data from VAERS during this period were reassuring on the safety of ccIIV3. We noted disproportionate reporting for the MedDRA preferred term ‘drug administered to patient of inappropriate age’ which represents ccIIV3 being administered to persons aged <18 years, an age group in whom this vaccine is not approved or recommended. Only 3% of these reports, however, described an AE, all of which were mild. Moreover, most (86%) of these off-label or vaccination error reports occurred during the 2013–2014 season when the vaccine was first introduced. Other than this signal, we did not identify any other safety concerns among ccIIV3 reports reported to VAERS.

We found that 50% of the AEs were mild and comprised injection site or self-limited systemic reactions, consistent with the safety profile of ccIIV3 in pre-licensure clinical trials [5]. The European counterpart for ccIIV3, Optaflu, made by Novartis, was approved by the European Medicines Agency (EMEA) in June 2007 for use in all 27 member states of the European Union, Iceland and Norway [2]. Pre-licensure studies for Optaflu also found that injection site reactions were the most common reactions observed [2,16,18]. However, a small but statistically significant increase in injection site reactions following Optaflu in patients 18 – 64 years of age was observed [18].

In our study, hypersensitivity reactions accounted for almost 25% of reports after ccIIV3 submitted to VAERS, but only two met the criteria for anaphylactic reactions and the crude

reporting rate was similar to or less than what has been observed for other influenza vaccines [19]. Anaphylactic reactions, are potentially life-threatening immediate hypersensitivity reactions that rarely can be causally associated with influenza vaccination [20]. Anaphylaxis is closely monitored in VAERS especially following recommendations for use of newly licensed vaccines in the United States. For example, close monitoring of Flublok®, a cell-based vaccine which does not use chicken eggs for vaccine production, identified a notable number of reports describing hypersensitivity reactions, including one anaphylaxis reaction during its first year postlicensure [21]. This finding prompted a change in the vaccine label noting the presence of these adverse events [22].

GBS is an acute, immune-mediated paralytic disorder of the peripheral nervous system [23]. GBS is most commonly associated with *Campylobacter jejuni* and other infectious agents [23]. Influenza vaccines have been traditionally monitored for GBS risk since an increased risk of GBS after influenza vaccination was first observed with the 1976–1977 A/New Jersey (‘‘swine influenza’’) vaccine [24]. However, most subsequent studies have shown a small or no increased risk of GBS after influenza vaccination [25–26]. For ccIIV3, we identified four cases of GBS reported to VAERS, three of which were verified through review of medical records, all during the 2014–2015 influenza season. The crude reporting rate of 1.0 GBS cases per million ccIIV3 doses distributed was comparable to the background rate for this condition [19]. Moreover, no disproportionate reporting for GBS was observed in our study using EB data mining.

Data mining represents an analytical strategy to assess for disproportionate reporting in the VAERS database [13,14]. Through EB data mining we screen the VAERS database for ccIIV3-event pairs reported disproportionally more frequently compared to all other vaccine-event pairs contained in the VAERS database.. Moreover, data mining runs can be adjusted and/or stratified by possible confounding variables such as age, gender, season of administration, years of administration or reporting, and type of vaccines such as live or inactivated [15]. Through EB data mining the only disproportionality of importance was the administration of ccIIV3 to an age group for whom it was not approved which accounted for half of all reports to VAERS and highlights the need for education of healthcare providers regarding the approved ages and recommendations for ccIIV3 use.

While VAERS has a number of strengths, such as its broad national scope and timely reporting, it is a spontaneous reporting system that has limitations, including over- or under-reporting, biased reporting, and inconsistency in quality and completeness of reports [6]. VAERS generally cannot assess causality between an AE and receipt of a vaccine. Although we estimated crude reporting rates for anaphylaxis and GBS using doses of vaccine distributed as a denominator, these estimates should be interpreted with caution since the number of doses of vaccine distributed and administered and the completeness of anaphylaxis and GBS reporting to VAERS are not known.

Other than the finding of disproportionate reporting for the MedDRA preferred term ‘drug administered to patient of inappropriate age,’ we did not observe any new or unexpected safety concerns during the first two influenza seasons of ccIIV3 use in the United States. The safety profile is consistent with that observed during the pre-licensure trials. As more

persons receive ccIIV3 in future influenza seasons, VAERS may be able to detect other rare AEs. CDC and FDA will continue to monitor the safety of ccIIV3 during the 2015–2016 influenza season and beyond.

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References

1. Food and Drug Administration. 11 20, 2012 Approval Letter - Flucelvax. Available at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm328684.htm. Accessed March 23, 2015.
2. Doroshenko A, Halperin SA. Trivalent MDCK cell culture-derived influenza vaccine Optaflu (Novartis Vaccines). Expert Rev Vaccines 2009 6;8(6):679–88 [PubMed: 19485748]
3. Centers for Disease Control and Prevention (CDC). Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2013–2014. MMWR Recomm Rep 2013 9 20;62(RR-07):1–43. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6207a1.htm. Accessed March 23, 2015.
4. Grohskopf LA, Olsen SJ, Sokolow LZ, Bresee JS, Cox NJ, Broder KR, Karron RA, Walter EB; Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) -- United States, 2014–15 influenza season. MMWR Morb Mortal Wkly Rep 2014 8 15;63(32):691–7. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm. Accessed March 23, 2015 [PubMed: 25121712]
5. Food and Drug Administration, Flucelvax. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM329134.pdf Accessed on March 23, 2015.
6. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015. pii: S0264–410X(15)00982–2. [Epub ahead of print]
7. Medical Dictionary for Regulatory Activities. Available at: http://www.meddramsso.com/. Accessed April 28, 2011.
8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals. http://www.ich.org/products/meddra.html
9. Food and Drug Administration. 21 CFR Part 600.80. Postmarketing reporting of adverse experiences. Vol 62: Federal Register, 1997:52252–52253.
10. Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675–84. [PubMed: 17448577]
11. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011 29:599–612. [PubMed: 20600491]
12. Brighton Collaboration. https://brightoncollaboration.org/public
13. DuMouchel W Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat 1999;53:177–90.

14. 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;25:381–92. [PubMed: 12071774]
15. Martin D, Menschik D, Bryant-Genevier M, Ball R. Data Mining for Prospective Early Detection of Safety Signals in the Vaccine Adverse Event Reporting System (VAERS): A Case Study of Febrile Seizures after a 2010–2011 Seasonal Influenza Virus Vaccine. Drug Saf 2013 5 9. [Epub ahead of print]
16. European Medicines Agency. Optaflu. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000758/WC500046957.pdf Accessed on April 6, 2015
17. Manini I, Domnich A, Amicizia D, Rossi S, Pozzi T, Gasparini R, Panatto D, Montomoli E. Flucelvax (Optaflu) for seasonal influenza. Expert Rev Vaccines. 2015 6;14(6):789–804. [PubMed: 25968069]
18. Food and Drug Administration. Pharmacovigilance Review Memorandum, August 1, 2912. Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE). Pharmacovigilance Plan Review, Influenza vaccine (cell-culture derived trivalent influenza vaccine, cTIV), formerly Optaflu. http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm332467.pdf
19. Greene SK, Kulldorff M, Lewis EM, Li R, Yin R, Weintraub ES, et al. Near Real-Time Surveillance for Influenza Vaccine Safety: Proof-of-Concept in the Vaccine Safety Datalink Project. Am J Epidemiol 2010;171:177–188 [PubMed: 19965887]
20. Institute of Medicine. Influenza vaccines In: Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press, 2011:257–368.
21. Woo EJ. Allergic reactions after egg-free recombinant influenza vaccine: reports to the US Vaccine Adverse Event Reporting System. Clin Infect Dis 2015 3 1;60(5):777–80. [PubMed: 25428412]
22. Protein Science Corporation. Flublok package insert. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM336020.pdf Accessed April 6, 2015.
23. Harrison's Principles of Internal Medicine, 18th edition. Eds. Longo Dan L., Fauci Anthony S., Kasper Dennis L., Hauser Stephen L., Larry Jameson J, Loscalzo Joseph. Chapter 385. Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies. Chronic inflammatory demyelinating polyneuropathy. The McGraw-Hill Companies, Inc 2012.
24. Fenichel GM. Assessment: Neurologic risk of immunization: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1999;52:1546–52. [PubMed: 10331677]
25. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain–Barré syndrome in the United States, 1979–80 and 1980–81—lack of an association with influenza vaccination. JAMA 1982;248:698–700. [PubMed: 7097920]
26. Lasky T, Terracciano GJ, Magder L, Coski CL, Ballesteros M, Nash D, et al. The Guillain–Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. N Engl J Med 1998;339(25):1797–802. [PubMed: 9854114]
27. Baxter R, Bakshi N, Fireman B, Lewis E, Ray P, Vellozzi C, et al. Lack ofassociation of Guillain–Barré syndrome with vaccinations. Clin Infect Dis2013;57(2):197–204. [PubMed: 23580737]

Table 1.

Characteristics of Flucelvax® (ccIIV3) reports to VAERS among persons vaccinated July 1, 2013 through March 31, 2015 (reports received by April 30, 2015)

Characteristics	N (%)
Total Reports	629
Reports with an adverse event	309
Serious	19 (6.1)[a]
Reports during 2013-2014 influenza season	389 (61.8)
Reports during 2014-2015 influenza season	240 (38.2)
Median age (range) years [b]	18.5 (0.7 – 85)
Age groups (years)	
<18	313 (49.8)[c]
18 – 29	43 (6.8)
30 – 49	113 (17.9)
50 – 64	106 (16.9)
≥65	41 (6.5)
Female[d]	349 (55.5)
Median onset interval (range) days[e]	0 (0 – 115)
ccIIV3 was given alone	585 (93.0)
Type of reporter	
Manufacturer	283 (44.9)
Vaccine provider	191 (30.4)
Other	81 (12.9)
Patient	74 (11.8)

[a] Among reports with adverse events

[b] Age unknown in 29 (4.6%) reports

[c] Vaccination error reports containing MedDRA preferred term “Drug administered to patient of inappropriate age”

[d] Sex not reported in 27 (4.3%) reports

[e] Onset interval (the time between vaccination and onset of symptoms) not reported in 14 (4.5%) of 309 reports with AEs

Table 2.

Diagnostic categories for the 309 reports of adverse events after Flucelvax® (ccIIV3) in VAERS among persons vaccinated July 1, 2013 through March 31, 2015 (reports received by April 30, 2015)

MedDRA System Organ Class	N (%)
General disorders and administration site conditions	152 (49.2)
Local reactions[a]	74
Immune system disorders	73 (23.6)
Anaphylaxis[b]	2
Musculoskeletal and connective tissue disorders	35 (11.9)
Nervous system disorders	14 (4.5)
Guillain-Barré syndrome[c]	4
Bell's palsy	2
Respiratory, thoracic and mediastinal disorders	11 (3.6)
Gastrointestinal disorders	5 (1.6)
Cardiac disorders	5 (1.6)
Skin and subcutaneous tissue disorders	3 (1.0)
Infections and infestations	3 (1.0)
Ear and labyrinth disorders	2 (0.6)
Other[d]	4 (1.3)

[a] Local reactions comprised 48.7% of adverse events in this group

[b] One report met Brighton criteria for level 2, and one that did not meet Brighton criteria but was physician diagnosed

[c] One report met Brighton criteria level (BL) 1, one BL 2, one BL 3, and one was not verified as a GBS case

[d] Other includes one report each of endocrine disorder, psychiatric disorder, an unspecified adverse event, and a death due to cardiovascular disease secondary to diabetes