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Adverse Events Following Quadrivalent Meningococcal Diphtheria Toxoid Conjugate Vaccine (Menactra®) Reported to the Vaccine Adverse Event Reporting System (VAERS), 2005–2016

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Abstract

Background: Post marketing safety evaluations of quadrivalent meningococcal diphtheria-toxoid conjugate vaccine (MenACWY-D) have focused on post-vaccination risk of Guillain Barré Syndrome (GBS), adverse events (AEs) after maternal vaccination, and comparative studies with the newer quadrivalent meningococcal CRM_{197} conjugate vaccine (MenACWY-CRM). To provide an updated general safety assessment, we reviewed reports of AEs following MenACWY-D submitted to the Vaccine Adverse Event Reporting System (VAERS).

Methods: VAERS is a national spontaneous reporting vaccine safety surveillance system co-administered by the Centers for Disease Control and Prevention and the U.S. Food and Drug Administration. We searched the VAERS database for U.S. reports of AEs after administration of MenACWY-D from January 2005 through June 2016. We conducted clinical reviews of serious reports after MenACWY-D administered alone, reports of MenACWY-D use during pregnancy, and reports of selected pre-specified outcomes. We screened for disproportionate reporting of AEs after MenACWY-D using empirical Bayesian data mining.

Results: VAERS received 13,075 U.S. reports after receipt of MenACWY-D; most (86%) described vaccination in adolescents, were classified as non-serious (94%), and described AEs

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

consistent with pre-licensure studies. We did not find any evidence that reported deaths were related to vaccination. In serious reports, GBS and meningococcal infection were the most commonly reported medical conditions. Many reports of MenACWY-D use during pregnancy described inadvertent vaccination; most (61%) did not report any AE.

Conclusions: Findings from our comprehensive review of reports to VAERS following MenACWY-D are consistent with data from pre-licensure studies and provide further reassurance on the safety of MenACWY-D.

Keywords

meningococcal vaccine; vaccine safety; adolescent; surveillance

INTRODUCTION

On January 14, 2005, the first quadrivalent meningococcal conjugate vaccine (Menactra®, MenACWY-D) was approved in the United States for protection against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y. Pre-licensure studies of MenACWY-D in adolescents and adults demonstrated an acceptable safety profile, similar rates of systemic adverse events (AEs) as the comparator meningococcal polysaccharide vaccine and slightly higher rates of local AEs, which were hypothesized to be due to the diphtheria toxoid component of MenACWY-D [1]. Additional clinical trials were conducted in children and infants to support later approvals of the vaccine for use in younger ages; rates of serious AEs after MenACWY-D were similar to rates after other childhood vaccines, and the most common solicited local and systemic AEs were injection site tenderness and irritability, respectively [2,3]. MenACWY-D is currently approved for use in individuals 9 months through 55 years of age [4].

Shortly after the initial approval of MenACWY-D for use in persons aged 11–55 years, the Advisory Committee on Immunization Practices (ACIP) recommended routine adolescent vaccination with MenACWY-D at 11–12 years of age. For adolescents not vaccinated previously, ACIP recommended vaccination before high-school entry (at approximately 15 years). ACIP also recommended routine vaccination for first-year college students living in dormitories, military recruits, microbiologists routinely exposed to *N. meningitidis* isolates, persons residing in or traveling to countries where *N. meningitidis* is hyperendemic or endemic, and persons at increased risk of invasive meningococcal disease due to specific medical conditions (terminal complement component deficiencies, anatomic or functional asplenia) [1]. These initial recommendations for quadrivalent meningococcal vaccine have since been expanded to reflect approval of a quadrivalent meningococcal CRM_{197} conjugate vaccine (Menveo®, MenACWY-CRM), include vaccination with a 2-dose primary series for children 2 months to 10 years of age at increased risk of meningococcal disease, a booster dose for adolescents at age 16 years, repeated booster doses every 5 years for persons who remain at increased risk of meningococcal disease, and inclusion of persons with human immunodeficiency virus infections among those considered at high risk of invasive meningococcal disease [5,6].

In October 2005, reports to the Vaccine Adverse Event Reporting System (VAERS) indicated a possible safety signal for Guillain-Barré syndrome (GBS) following vaccination with MenACWY-D, and three publications subsequently described 17 reports to VAERS of GBS after MenACWY-D occurring between June 2005 and September 2006 [7–9]. These reports described onset of symptoms of GBS ranging from 2 to 33 days after vaccination in persons 11–43 years of age. While the available data suggested a small increased risk of GBS after MenACWY-D vaccination, the authors concluded that uncertainty regarding background incidence rates for GBS and the inherent limitations of the data source (a passive surveillance system) warranted additional evaluation in a more robust data source such as the Vaccine Safety Datalink (VSD) [9]. After review of the data, ACIP determined that the protection provided by MenACWY-D against meningococcal disease outweighed a possible small increased risk of GBS [5].

To investigate the possible association between MenACWY-D and GBS, two separate large cohort studies were conducted, one using medical claims data from five U.S. healthcare plans and the other in the VSD (10–11). Neither study identified any cases of GBS in the 6 weeks following vaccination with MenACWY-D. Furthermore, a combined analysis of the two studies estimated that the attributable risk of GBS in the 42 days after vaccination was likely less than 1 case per million adolescents vaccinated with MenACWY-D [11]. After reviewing these new findings, ACIP determined that the data continued to support their previous determination that benefits of vaccination outweighed the small risk of GBS, and the committee voted to remove the precaution for persons having a history of GBS [5].

Post-licensure safety studies of MenACWY-D in infants 9–23 months of age, in children 2–10 years of age and in adolescents and adults 11–55 years of age have not identified any new safety concerns [12,13], although these studies may have been underpowered to detect rare safety outcomes. A retrospective study of MenACWY-D and other vaccines containing diphtheria toxoid in adolescents and young adults found a low risk of medically attended local reactions and did not detect any differences when these vaccines were administered concomitantly as compared to sequentially [14]. In addition, a recent application of a novel data mining analysis for detection of potential adverse events following MenACWY-D in the VSD detected several statistical signals for expected safety outcomes (diseases of the skin and subcutaneous tissue, fever, urticaria) but did not find any new safety concerns [15].

MenACWY-D has now been in use for over a decade in the United States. A substantial number of doses have been administered to adolescents and others recommended to receive the vaccine. The 2016 national coverage survey for the adolescent population estimated that 82% of teens aged 13–17 years had received at least one dose of a quadrivalent conjugate meningococcal vaccine and that 39% had received at least two doses [16]. To assess whether any new safety concerns have emerged, we conducted a comprehensive review of reports following MenACWY-D to VAERS.

METHODS

VAERS is a spontaneous reporting system for AEs following vaccination that is co-administered by the Centers for Disease Control and Prevention (CDC) and the U.S. Food

and Drug Administration (FDA). Anyone can submit a report to VAERS, including health care providers, patients, parents of patients and others; vaccine manufacturers are required to report AEs that come to their attention. Reports include demographic information on the vaccine recipient, data on the vaccine(s) received, a description of the AE(s) experienced, and any relevant medical history. Trained personnel assign one or more Preferred Terms (PTs) to the signs and symptoms described in each report using the standard Medical Dictionary for Regulatory Activities (MedDRA) [17]. Reports are classified as serious or non-serious according to the Code of Federal Regulations definition, which specifies that events describing death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability must be classified as serious [18]. For serious reports, VAERS personnel request follow up medical records for further review, excepting those submitted by vaccine manufacturers which are subject to separate follow-up procedures [17,18]. Some reports may not include a description of an adverse health event (e.g., vaccine administration errors with no adverse consequences for a patient's health).

We described all U.S. reports to VAERS submitted for persons of any age who were vaccinated with MenACWY-D during the period January 2005 through June 2016 and received by September 2016. We calculated descriptive statistics, including median age of vaccinated individuals, interval from date of vaccination to onset of first symptom(s), and most commonly reported PTs. Reports can describe more than one reported PT. We used SAS (version 9.3, SAS Institute, Inc., Cary, NC, USA) for the data analysis.

A crude MenACWY-D AE reporting rate was calculated for all reports and serious reports by dividing the number of such reports received during the analytic period by the total number of doses of MenACWY-D distributed in the United States during the analytic period.

Clinical Review

We reviewed all reports that described deaths after MenACWY-D vaccination and all reports of serious AEs after vaccination with MenACWY-D given alone, including medical records when these were available. For each report, we identified the main event that prompted the report and the respective MedDRA System Organ Class (SOC) and PT for the main event. In addition, we reviewed reports and accompanying medical records where available for the pre-specified conditions of anaphylaxis, facial nerve palsy (including Bell's palsy), GBS and vaccine administered during pregnancy. For anaphylaxis, facial nerve palsy, and GBS, we applied case definitions developed by the Brighton Collaboration when possible [19–21]. For reports of vaccination during pregnancy, we identified the trimester during which vaccination occurred and whether any pre- or post-natal maternal or infant AE was described.

Data Mining

To identify MenACWY-D-AE pairings that might be disproportionally reported (i.e., in excess compared to all other vaccines in the VAERS database), we used an empirical Bayesian (EB) data mining method to generate EB geometric mean (EBGM) values and their corresponding 90% confidence intervals (EB05–EB95). The EBGM provides an estimate of the true ratio of actual events reported over expected events after vaccination. We

identified MedDRA PTs reported after MenACWY-D and having a lower bound of the 90% confidence interval of the EBGM greater than 2 after adjusting for sex and year received [22,23]. Reports of PTs exceeding this predetermined threshold and not previously identified and described in the package insert based on pre-licensure clinical trial data were considered for further clinical review, unless they were included in our prespecified list of outcomes for review as described above. Elevated EB05 results do not necessarily imply a causal relationship between a vaccine exposure and the reported AE (PT), but they can suggest potential safety signals that may require further assessment.

This surveillance review was not subject to institutional review board and informed consent requirements because VAERS is considered a routine surveillance program that does not meet the definition of research.

RESULTS

VAERS received a total of 13,075 U.S. reports following receipt of MenACWY-D during the analytic period, January 2005 through June 2016 (Table 1). The median age of vaccinees was 14 years (range 0–85 years), and most reports described receipt of MenACWY-D in the adolescent population. The median interval from time of vaccination to time of onset of AE was 1 day (range 0–2630 days). The majority of reports were from females (55%) compared to males (43%), with the remainder not specifying sex. During the analytic period, VAERS received 846 (6%) reports that were classified as serious, including 36 reports of death. Among all reports, the most frequently reported PTs included injection site erythema (2058, 16%), pyrexia (1929, 15%), headache (1901, 15%), dizziness (1779, 14%), and injection site swelling (1556, 12%). The ten most frequent PTs for non-serious and serious reports are shown in Table 2.

The majority of reports (79%) described receipt of at least one vaccine simultaneously administered with MenACWY-D. The most commonly co-administered vaccines varied in accordance with age-based recommendations in the immunization schedule. For adolescents, tetanus, diphtheria, and acellular pertussis (Tdap, 48%), human papillomavirus (HPV, 35%), and varicella (25%) were the most common vaccines administered with MenACWY-D. Of the 2790 reports describing receipt of MenACWY-D alone, 219 (8%) were classified as serious.

During the analytic period, 70,312,683 MenACWY-D doses were distributed in the United States (Sanofi, personal communication, 2017). The overall crude reporting rate to VAERS was 18.6 reports per 100,000 doses distributed. For serious reports, the crude reporting rate was 1.2 per 100,000 doses distributed.

Deaths

VAERS received 36 death reports following receipt of MenACWY-D; autopsy reports, death certificates, and/or medical records were available for 35 of these reports. Complications from *N. meningitidis* infection (meningitis meningococcal or meningococcal bactaeremia) were the most commonly cited cause of death (13, 36%). Of these, 11 were seroconcordant with the vaccine (8 reports described serogroup C infection and 3 described serogroup Y

infection). Two reports described deaths after infection with *N. meningitidis* serogroup B, for which MenACWY-D offers no protection. For those infections identified as due to serogroups C and Y, the median age at death was 18 years (IQR: 17–20), and the median onset interval after vaccination was 972 days (IQR: 349–764). None of these reports described infection after receipt of a booster dose, although we did not have the ability to verify dose in series. Cause of death for all 36 reports are listed in Table 3.

Serious Reports

The SOCs and most frequently reported medical conditions described by PTs after MenACWY-D alone are shown in Table 4. The most common SOC was nervous system disorders, including diagnoses of GBS (32 reports), seizures (8 reports), acute disseminated encephalomyelitis (ADEM, 7 reports), transverse myelitis (TM, 6 reports), and chronic inflammatory demyelinating polyneuropathy (4 reports). The second most common SOC was infections and infestations, including 27 reports of meningococcal infection; of these, 11 reported serogroup C infection, 11 reported serogroup Y infection, 3 reported serogroup B infection, with the remainder either untyped or not reported. One report of serogroup Y infection included medical records indicating the patient was diagnosed with C3 complement deficiency after infection. Another 18 reports described meningitis that was not attributed to *N. meningitidis* infection. The third most frequent SOC was cardiac disorders, and 6 (50%) of these reports were post-vaccination syncope. Lastly, the majority of reports in the immune systems disorders SOC comprised hypersensitivity and anaphylactic reactions.

Pre-specified outcomes

Anaphylaxis—We identified 37 reports of possible anaphylaxis with onset 0–1 days after receipt of MenACWY-D. After applying the Brighton Collaboration case definition, 15 reports were classified as level 1 (the highest level of diagnostic certainty), 6 reports were level 2, and 1 report was level 3. Another 10 reports did not meet the Brighton Collaboration criteria but were reported as diagnosed by a physician, and 5 reports did not describe anaphylaxis. Eight reports documented onset of anaphylaxis symptoms within 30 minutes of vaccination (8 Brighton level 1, 1 Brighton level 3, and 7 physician-diagnosed). Four reports indicated a likely or possible alternative trigger for anaphylaxis, including food, drug, and insect bite exposures. Most reports described anaphylaxis after receipt of multiple vaccines, with only three reports describing the outcome following receipt of MenACWY-D alone (one Brighton level 2, one Brighton level 3, and one physician diagnosis).

Facial Nerve Palsy—We identified 121 reports of possible idiopathic facial nerve palsy. After exclusion of 48 reports due to alternative diagnoses or coincident diagnosis of an underlying condition or disease associated with facial palsy, 5 reports met the Brighton Collaboration case definition level 1, 9 reports met level 2, and 17 reports met level 3. The remaining reports (n=42) lacked sufficient information to classify them according to Brighton Collaboration criteria. Median interval from time of vaccination until onset of symptoms was 4 days (range 0–281 days). Five reports were classified as serious.

Guillain Barré Syndrome (GBS)—We identified 144 reports of possible GBS, of which 24 were excluded due to alternative diagnoses or no evidence of GBS. Of the remaining 120, 24 reports met the Brighton Collaboration case definition level 1, 56 reports met level 2, 14 reports met level 3, and 26 reports described GBS-like illness that could not be classified according to Brighton Collaboration criteria (mainly due to incomplete medical records). The median onset interval of symptoms was 15 days (range 0–259 days). Most of the confirmed reports described GBS after receipt of more than one vaccine, with 42 reports describing GBS following receipt of MenACWY-D alone.

Vaccination in Pregnancy—We identified 132 reports that described vaccination with MenACWY-D during pregnancy. We were able to determine trimester of vaccination in 99 of these reports (72 reported vaccination in the first trimester, 24 in the second trimester, 1 in late first trimester or early second trimester, and 2 in the third trimester). One third of reports (n=44) included information indicating that the provider was unaware of the patient's pregnancy status at the time of vaccination. The majority of reports did not describe an AE for either the mother or the infant (n=81, 61%); 16 of these non-AE reports included follow-up through a normal birth outcome.

The main AEs reported in pregnant women and infants after maternal vaccination with MenACWY-D are described in Table 5, selected after review to identify the predominant medical concern in the report to VAERS. The most common pregnancy specific AE's were spontaneous abortion, preterm delivery, and elective termination of pregnancy. There was one report of stillbirth after vaccination with MenACWY-D. Non-pregnancy specific AE's were rare and included two reports of urinary tract infection and two reports describing maternal depression. The reported infant outcomes included several distinct congenital defects, intrauterine growth restriction, infection with respiratory syncytial virus and seizure.

Data mining

The data mining results for all reports by age group and for all serious reports are shown in Table 6. Data mining conducted for the age group at which MenACWY-D is recommended for routine use (11–18 years) found no disproportionately reported terms. In other age groups, disproportionately reported terms described incorrect usage of the vaccine (inappropriate schedule of drug administration, incorrect route of drug administration, medication error, wrong drug administered), local and systemic reactions commonly reported after vaccines (arthralgia, dizziness, fatigue, induration, nausea, myalgia, tenderness), and terms used in describing syncopal episodes (dyskinesia, muscle rigidity). In persons 19–54 years of age, disorientation, convulsion and grand mal seizure, GBS and photophobia were also disproportionately reported after MenACWY-D. In serious reports (all ages), disproportionately reported terms included ADEM, atelectasis, facial paresis, and meningococcal infection. Upon review, most serious reports of atelectasis were related to intubation following other diagnoses and most (19) of the facial paresis reports included diagnosis or suspicion of GBS.

DISCUSSION

This comprehensive review describes U.S. reports to VAERS after receipt of MenACWY-D during January 2005 through June 2016. Most reports described vaccination of adolescents (86%), the group for which meningococcal vaccine is routinely recommended. Overall, AEs reported were consistent with those observed during the vaccine's pre-licensure trials and early post-approval studies and included injection-site reactions (erythema, swelling, pain) and systemic reactions such as fever, headache, fatigue, nausea, and syncope. Our evaluations of selected pre-specified AEs and safety in pregnant women, together with the most frequently reported PTs (considered separately for all serious and non-serious reports), were also generally consistent with available data from pre- and post-licensure safety studies [5]. Crude reporting rates were consistent with those previously reported for other vaccines routinely recommended for adolescents [24–27].

The most frequently reported cause of death after receipt of MenACWY-D was infection with *N. meningitidis*. Because VAERS does not always have complete medical histories, we were unable to determine if any of these reports were in persons having medical conditions that increase the risk of meningococcal infection (such as complement deficiency disorder, functional/anatomic asplenia, or HIV infection). None of these reports described receipt of a booster dose after the initial vaccine dose, although our access to full vaccination records may have been incomplete. The remainder of the reported deaths identified a broad range of assigned causes of death with no observable pattern or other evidence to suggest the deaths were related to vaccination.

The most frequently reported SOC after receipt of MenACWY-D alone was nervous system disorders, driven largely by the number of reports received for GBS. GBS was the most commonly reported AE after receipt of MenACWY-D alone (32 reports). Meningococcal infection was the second most commonly reported AE (27 reports), with 21 reports concordant with the serogroups included in MenACWY-D.

Our findings for reports to VAERS following maternal vaccination with MenACWY-D were consistent with a previously published report reviewing this vaccine's safety during pregnancy [28]. The findings continue to support the ACIP recommendation that MenACWY-D vaccine should be considered for pregnant women at increased risk for meningococcal infection [29]. More broadly, our findings may be informative for endemic countries considering maternal meningococcal vaccination [30].

The data mining findings for MenACWY-D across the age group analyses included terms consistent with known local and systemic reactions as well as incorrect usage of the vaccine, with the strongest signals for terms indicating incorrect usage. Nervous system disorders reported disproportionately included seizure related terms and GBS (in adults 19–54 years of age) and ADEM and facial paresis (in all serious reports), all of which are mentioned in the MenACWY-D package insert as having been reported after vaccination but for which causal association is unknown [4]. Our data mining findings in the adult age group may be subject to bias because the population used to calculate the expected number of events may represent a healthier population than those receiving MenACWY-D at this age. Reassuringly,

these terms did not signal in the adolescent analysis (11–18 years of age) representing the majority of reports to VAERS. A recent study applied a different data mining technique, tree-temporal scan statistic analysis, to explore AEs after MenACWY-D in the VSD population using administrative healthcare data; no new safety concerns were identified, and no signals were observed for nervous system disorders [15]. A case-centered analysis of TM and ADEM in the VSD population did not find evidence for a causal association of either outcome with MenACWY-D [31]. In addition to these data, CDC and its partners are completing a study of selected safety outcomes in the VSD population [32].

The strengths of using VAERS to assess AEs following MenACWY-D are its national scope, ability to accept reports from a variety of sources (healthcare providers, patients and others), rapid signal detection and ability to detect rare AEs. Limitations are those inherent to passive surveillance systems, including reporting bias, under reporting, inconsistent data quality and completeness, lack of an unvaccinated comparison group and lack of denominator data for rate calculations. Because doses distributed were used as a proxy for MenACWY-D doses administered and the level of underreporting of AEs is unknown, the crude reporting rate must be interpreted with caution. Collectively, these limitations prevent a rigorous assessment of cause and effect; however, VAERS data are well suited to hypothesis generation and further follow up in more robust databases, such as VSD, which is better suited for more rigorous statistical testing of causal associations.

We did not observe any trends or patterns of concern in this comprehensive assessment of post-licensure safety of MenACWY-D. While CDC continues to assess safety of the vaccine in an ongoing research study in the VSD, these findings from VAERS expand the existing knowledge base on the safety of meningococcal vaccines.

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Table 1.

Characteristics of VAERS reports following MenACWY-D, 2005–2016

	<2 yr Total=93 n (%)	**2 yr – 10 yr Total=251 n (%)**	**11 yr – 18 yr Total=11,215 n (%)**	**>18 yr Total=1188 n (%)**	**All ages[a] Total=13,075 n (%)**
Sex[b]					
Female	42 (45)	114 (45)	6282 (56)	676 (57)	7234 (55)
Male	42 (45)	129 (51)	4828 (43)	496 (42)	5575 (43)
Median age[b]	7 mo	10 yr	13 yr	26 yr	14 yr
Onset interval[b], median in days (range)	0 (0–365)	1 (0–2193)	1 (0–2630)	1 (0–1287)	1 (0–2630)
MenACWY-D given alone	20 (22)	38 (15)	2187 (20)	417 (35)	2790 (21)
Serious[c]/non-serious status					
Non-serious	90 (97)	240 (96)	10518 (94)	1085 (91)	12229 (94)
Serious, non-death	3 (3)	10 (4)	666 (6)	100 (8)	810 (6)
Serious, death	0 (0)	1 (0)	31 (0)	3 (0)	36 (0)
Type of Reporter[b]					
Vaccine Provider					
Manufacturer	44 (47)	157 (63)	6931 (62)	635 (53)	7801 (60)
	16 (17)	16 (6)	986 (9)	134 (11)	1405 (11)
Patient/parent		13 (5)	548 (5)	81 (7)	652 (5)
Other	9 (10)	65 (26)	2747 (25)	338 (28)	3214 (25)
	24 (26)				

[a] includes reports missing age

[b] data missing for sex (n=266), age (328), date of onset (1296), and type of reporter (3)

[c] serious reports are those describing death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability

Table 2.

Most frequent MedDRA Preferred Terms[a] for serious[b] and non-serious reports (n=13,075) following MenACWY-D, 2005–2016

MedDRA Preferred Term	n (%)
Non-serious reports	**12229**
Injection site erythema	2016 (16)
Pyrexia	1648 (13)
Dizziness	1629 (13)
Headache	1568 (13)
Injection site swelling	1524 (12)
Erythema	1370 (11)
Syncope	1281 (10)
Injection site pain	1041 (9)
Nausea	1032 (8)
Pain	916 (7)
Serious reports	**846**
Headache	333 (39)
Pyrexia	281 (33)
Nausea	213 (25)
Vomiting	207 (24)
Fatigue	185 (22)
Asthenia	176 (21)
Muscular weakness	170 (20)
Paraesthesia	157 (19)
Dizziness	150 (18)
Hypoaesthesia	140 (17)

[a] a report may have one or more assigned MedDRA Preferred Terms

[b] serious reports are those describing death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability

Table 3.

Cause of death among 36 death reports after MenACWY-D in VAERS, 2005–2016

Cause of Death[a]	**n (%)**
Neisseria meningitidis infection[b]	13 (36)
Complications related to seizure disorder	3 (8)
Myocarditis[c]	3 (8)
Sudden cardiac death	2 (6)
Suicide	2 (6)
Acute hemorrhagic leukoencephalitis	1 (3)
Acute myeloblastic leukemia	1 (3)
Cardiogenic shock	1 (3)
Cardiopulmonary failure	1 (3)
Diabetes mellitus	1 (3)
Hepatic necrosis	1 (3)
Hypertrophic cardiomyopathy	1 (3)
Infection - unspecified	1 (3)
Lymphohistiocytosis	1 (3)
Polymyositis	1 (3)
Septic shock	1 (3)
Toxic shock syndrome (streptococcal)	1 (3)
Undetermined	1 (3)

[a] Confirmed by review of death certificate, autopsy report, or medical records, when available

[b] Serogroup B (2), serogroup C (8), serogroup Y (3)

[c] Eosinophilic myocarditis (1), idiopathic myocarditis (1), lymphocytic myocarditis (1)

Table 4.

Medical conditions for 219 serious[a] reports following MenACWY-D given alone, 2005–2016

Medical Conditions	n (%)
Nervous system disorders	**86 (39.3)**
GBS	32
Seizure	8
Acute disseminated encephalomyelitis	7
Transverse myelitis	6
Chronic inflammatory demyelinating polyradiculoneuropathy	4
Dizziness	3
Facial paralysis	3
Headache	3
Neuropathy peripheral	3
Infections and infestations	**64 (29.2)**
Meningococcal infection	27
Meningitis, non-meningococcal	19
Pneumonia	4
Cardiac disorders	**12 (5.5)**
Syncope	6
Immune system disorders	**11 (5.0)**
Hypersensitivity	4
Anaphylactic reaction	3
General disorders and administration site conditions	**8 (3.7)**
Gastrointestinal Disorders	**7 (3.2)**
Psychiatric disorders	**7 (3.2)**
Skin and subcutaneous tissue disorders	**6 (2.7)**
Cellulitis	3
Blood and lymphatic system disorders	**4 (1.8)**
Immune thrombocytopenia	3
Musculoskeletal and connective tissue disorders	**4 (1.8)**
Respiratory, thoracic and mediastinal disorders	**2 (0.9)**
Congenital, familial and genetic disorders	**1 (0.5)**
Ear and labyrinth disorders	**1 (0.5)**
Eye disorders	**1 (0.5)**
Hepatobiliary disorders	**1 (0.5)**
Metabolism and nutrition disorders	**1 (0.5)**
Neoplasms benign, malignant and unspecified	**1 (0.5)**
Renal and urinary disorders	**1 (0.5)**
Vascular disorders	**1 (0.5)**

[a] serious reports are those describing death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability

Table 5.

Main adverse events in pregnant women and infants following maternal vaccination with MenACWY-D reported to the Vaccine Adverse Event Reporting System (VAERS), United States, 2005–2016

Main Adverse Event[a]	**n (%)**
Pregnancy-specific AEs	
Spontaneous abortion	17 (13)
Preterm delivery (<37 weeks)	8 (6)
Elective termination	7 (5)
Failure to progress	3 (2)
Preeclampsia	2 (2)
Severe anemia	2 (2)
Chorioamnionitis	1 (1)
Eclampsia	1 (1)
Gestational diabetes	1 (1)
Gestational hypertension	1 (1)
Polyhydramnios	1 (1)
Stillbirth (>20 weeks gestation)[b]	1 (1)
Syncope	1 (1)
Non-pregnancy specific AEs	
Urinary tract infection	2 (2)
Depression	1 (1)
Fever with concomitant vomiting and abdominal pain	1 (1)
Major depressive disorder	1 (1)
Pyelonephritis	1 (1)
Rash on extremities	1 (1)
Tonsillitis	1 (1)
Infant outcomes	
Respiratory distress	3 (2)
Polydactyly	2 (2)
Umbilical hernia	2 (2)
Aqueductal stenosis with severe ventriculomegaly	1(1)
Hereditary spherocytosis	1(1)
Hypovolemia	1(1)
Intrauterine growth restriction	1(1)
Mild jaundice	1(1)
Multiple congenital anomalies incompatible with life	1(1)
Necrotizing enterocolitis	1(1)
Patent ductus arteriosus	1(1)

Main Adverse Event[a]	**n (%)**
Respiratory syncytial virus with bronchiolitis[c]	1(1)
Seizure[d]	1(1)
Sepsis	1(1)
No adverse event	81 (61)

[a]Adverse events are based on main reported diagnoses identified during clinical review. A report may have more than one main adverse event if multiple AEs are reported for the pregnant woman and/or her infant.

[b]Exact date of fetal demise was unknown and vaccination may have occurred afterward. Documented as a missed abortion after an HCG test result of 0.0 at 2 weeks post-vaccination.

[c]Infant treated for respiratory syncytial virus at 2 weeks of age.

[d]Seizure documented during post-birth hospitalization; follow-up at 2 months post-birth indicated no further seizure activity.

Table 6.

Data mining findings[a] for reports to VAERS after vaccination with MenACWY-D, by age group and by serious classification

MedDRA PTs with increased EB05* (>2)	n	E	O/E	EBGM	EB05
All reports (by age group)					
< 2 years of age					
Medication error	18	0.76	23.54	18.34	12.31
Wrong drug administered	19	1.61	11.82	10.28	6.57
Unevaluable event	5	0.20	24.70	6.99	2.30
No adverse event	4	0.08	49.89	6.71	2.06
2 to <11 years of age					
Inappropriate schedule of drug administration	28	2.63	10.67	9.63	7.00
Dizziness[a]	20	2.34	8.56	7.62	5.14
Syncope[a]	15	2.00	7.49	6.40	3.81
Nausea	13	1.64	7.93	6.55	3.71
Loss of consciousness[a]	8	0.69	11.61	7.84	3.61
Wrong drug administered	13	2.12	6.13	4.95	2.78
Chills[a]	6	0.54	11.18	6.38	2.46
Oedema peripheral	27	7.28	3.71	3.26	2.35
Fall	7	0.88	7.93	5.10	2.26
Neck pain	4	0.17	24.18	7.09	2.13
Pallor	11	2.24	4.90	3.69	2.12
Tenderness[a]	8	1.31	6.10	4.16	2.08
Induration[a]	10	2.04	4.91	3.60	2.03
11 to <19 years of age					
No findings	---	---	---	---	---
19 to <55 years of age					
Incorrect route of drug administration	15	2.19	6.85	5.88	3.61
Muscle rigidity	6	0.39	15.57	7.85	3.33
Upper respiratory tract infection	13	1.91	6.80	5.67	3.29
Productive cough	9	1.03	8.74	6.40	3.26
Guillain-Barré syndrome[a,b,c]	27	6.02	4.49	4.11	2.86
Dyskinesia	10	1.42	7.05	5.48	2.85
Disorientation	10	1.43	6.99	5.43	2.82
Fall	23	5.10	4.51	4.06	2.73
Balance disorder	16	3.29	4.86	4.17	2.56
Photophobia	17	3.69	4.61	3.98	2.49

MedDRA PTs with increased EB05* (>2)	n	E	O/E	EBGM	EB05
Speech disorder	8	1.11	7.19	5.14	2.44
Hypotonia	5	0.34	14.50	6.62	2.42
Sensory disturbance	8	1.15	6.96	4.99	2.37
Dysarthria	11	2.02	5.44	4.34	2.36
Aphasia	5	0.39	12.82	6.16	2.28
Hyperaesthesia	7	0.96	7.33	4.94	2.23
Cold sweat	12	2.49	4.81	3.89	2.22
Loss of consciousness[a]	49	16.89	2.90	2.73	2.15
Unresponsive to stimuli	12	2.61	4.59	3.70	2.14
Gaze palsy	5	0.45	11.09	5.61	2.12
Convulsion[a]	14	3.40	4.12	3.40	2.08
Grand mal convulsion[a]	4	0.20	19.69	6.31	2.06
Staring	4	0.21	18.83	6.19	2.03
55 years of age and older					
Inappropriate schedule of drug administration	13	0.54	23.95	19.90	12.32
Medication error	7	0.19	36.29	22.91	11.59
Wrong drug administered	9	0.40	22.33	17.32	9.48
Arthralgia[a]	7	0.67	10.42	5.98	2.44
Fatigue[a]	7	0.76	9.23	5.07	2.27
Lymphadenopathy[a]	4	0.15	27.13	9.25	2.14
Myalgia[a]	9	1.52	5.94	3.67	2.10
Serious reports only (all ages)					
Injection site oedema[a]	9	1.62	5.56	3.80	2.35
Productive cough	21	5.97	3.52	3.22	2.30
Papule	5	0.41	12.10	4.04	2.22
Ear infection	6	0.79	7.60	3.85	2.19
Atelectasis	8	1.60	5.01	3.53	2.11
Blister	8	1.62	4.95	3.51	2.10
Meningococcal infection	12	3.13	3.83	3.24	2.09
Acute disseminated encephalomyelitis[a]	21	6.73	3.12	2.94	2.08
Facial paresis[a,b]	24	8.20	2.93	2.80	2.03

n=observed number of reports containing both the vaccine and the MedDRA Preferred Term

E=expected number of reports containing both the vaccine and the MedDRA Preferred Term

OE=ratio of n/E

EBGM=empirical Bayes geometric mean estimate of OE (using the DuMouchel model)

EB05=lower bound of the 90% confidence interval surrounding the empirical Bayesian geometric mean

[a] MedDRA Preferred Terms having EB05 >2

[b] mentioned in package insert for MenACWY-D

[c] reviewed as a selected outcome