Published in final edited form as:

Vaccine. 2017 March 27; 35(14): 1758–1763. doi:10.1016/j.vaccine.2017.02.030.

Adverse Events Following Quadrivalent Meningococcal CRM-Conjugate Vaccine (Menveo®) Reported to the Vaccine Adverse Event Reporting System (VAERS), 2010–2015

Tanya R. Myers, PhD MSc^{a,b,*}, Michael M. McNeil, MD MPH^a, Carmen S. Ng, MSPH^a, Rongxia Li, PhD^a, Paige W. Lewis, MSPH^a, and Maria V. Cano, MD MPH^a

^aImmunization Safety Office, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333, USA

^bRollins School of Public Health, Emory University, 1518 Clifton Road, Atlanta, GA 30322, USA

Abstract

Background—Limited data are available describing the post-licensure safety of meningococcal vaccines, including Menveo®. We reviewed reports of adverse events (AEs) to the Vaccine Adverse Event Reporting System (VAERS) to assess safety in all age groups.

Methods—VAERS is a national spontaneous vaccine safety surveillance system co-administered by the Centers for Disease Control and Prevention and the US Food and Drug Administration. We searched the VAERS database for US reports of adverse events in persons who received Menveo from 1 January 2010 through 31 December 2015. We clinically reviewed reports and available medical records for serious AEs, selected pre-specified outcomes, and vaccination during pregnancy. We used empirical Bayesian data mining to identify AEs that were disproportionately reported after receipt of Menveo.

Results—During the study period, VAERS received 2614 US reports after receipt of Menveo. Of these, 67 were classified as serious, including 1 report of death. Adolescents (aged 11–18 years) accounted for 74% of reports. Most of the reported AEs were non-serious and described AEs consistent with data from pre-licensure studies. Anaphylaxis and syncope were the two most common events in the serious reports. We did not identify any new safety concerns after review of AEs that exceeded the data mining threshold, although we did observe disproportionate reporting for terms that were not associated with an adverse event (e.g., “incorrect drug dosage form administered”, “wrong technique in drug usage process”). Although reports were limited, we did not find any evidence for concern regarding the use of Menveo during pregnancy.

*Correspondence: Tanya R. Myers, PhD MSc, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS D-26, Atlanta, GA 30333, USA (vje9@cdc.gov).

Disclaimer: The views, findings and conclusions of this paper are solely those of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention, the NAIAD, or the National Institutes of Health.

Potential conflicts of interest: All authors: no potential conflicts.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions—In our review of VAERS reports, findings of AEs were consistent with the data from pre-licensure studies. Vaccine providers should continue to emphasize and adhere to proper administration of the vaccine.

Keywords

meningococcal disease; meningitis vaccine; vaccines; vaccine safety; epidemiology; Vaccine Adverse Event Reporting System (VAERS)

INTRODUCTION

To protect against invasive meningococcal disease caused by *Neisseria meningitidis* groups A, C, W-135, and Y, the Advisory Committee on Immunization Practices (ACIP) currently recommends that adolescents receive quadrivalent meningococcal conjugate vaccine (MCV4) at 11–12 years followed by a booster dose at 16 years and that persons at increased risk receive a dose series and recommended vaccine product depending upon age and condition [1]. Coverage in the adolescent population is nearing 80% for at least one dose [2], indicating that a substantial proportion of this population is electing to receive MCV4 vaccine, of which two brands are currently available in the United States (US). The most recently licensed MCV4 vaccine, Menveo®, was approved in 2010 for use among persons aged 11–55 years [3] with subsequent approvals for use in children and infants as young as 2 months [4–5].

Pre-licensure studies of Menveo found adverse events (AEs) that were mainly mild and quickly resolved. In infants and children between 2 and 23 months of age, the most frequently reported AEs were tenderness, erythema, induration, irritability, and sleepiness [6–9]. In children aged 2–10 years, the most frequently reported AEs were injection site pain, erythema, irritability, induration and sleepiness [9–11]. The most frequently reported AEs from adolescents and adults were injection site pain, headache, erythema and myalgia [9,12]. Reports of post-licensure data in the US are limited. A recent review of reports to VAERS following improperly prepared doses of Menveo found AEs similar to those reported in preclinical studies [13]. Although the Menveo label includes events that have been reported voluntarily since licensure, frequency of occurrence and causal relationships have not been determined [9]. To provide additional information on post-licensure safety, we reviewed reports to the Vaccine Adverse Events Reporting System (VAERS) for subjects of any age receiving Menveo during January 1, 2010 through December 31, 2015.

METHODS

VAERS

We utilized data reported to a spontaneous reporting system – the Vaccine Adverse Event Reporting System (VAERS), co-administered by the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) – to summarize US reports following immunization with Menveo. Health care providers, vaccine recipients, vaccine manufacturers and others submit reports to VAERS, including data on demographic information about the recipients, vaccine(s) and date received, adverse event(s) experienced,

and medical history. Once a report is received, trained personnel apply the Medical Dictionary for Regulatory Activities (MedDRA) coding to reported signs and symptoms, assigning 1 or more preferred terms (PTs) to each report [14]. Reports do not always include an adverse event (e.g., medication errors). Reports are classified as serious or non-serious, using the definition for serious based on the Code of Federal Regulations, 21CFR800.60. This definition specifies classification of an adverse event if it results “death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital/birth defect”; additionally, the definition specifies that important medical events that do not meet the above definition may also be classified as serious if they “may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition” [15]. VAERS personnel routinely request and review medical records for serious reports submitted by the public. Vaccine manufacturers are responsible for requesting and reviewing medical records for reports as described in 21CFR800.60 [14, 15]. VAERS personnel do not perform causality assessments regarding the relationship between a particular vaccine and a temporally-associated adverse event.

We included all domestic reports to VAERS for subjects of any age vaccinated with Menveo through December 31, 2015 and received by March 31, 2016. Descriptive statistics were calculated, including mean and median age of vaccinated individuals, onset interval from date of vaccination to first symptom(s), and most commonly reported PTs. SAS (version 9.3, SAS Institute, Inc., Cary, NC, USA) was used for the data analysis.

Clinical Review

We reviewed the medical records available for the majority of serious AE reports to VAERS after vaccination with Menveo (for two of the public reports only the initial report form was filed) or in summarized form for all manufacturer’s reports. For each report, we determined the primary event (and corresponding MedDRA term) that prompted the report and its respective MedDRA System Organ Class (SOC).

In addition, we prespecified conditions for clinical review based on previous studies of meningococcal and other adolescent vaccines and on clinical judgement. These prespecified conditions were anaphylaxis, facial nerve palsy (including Bell’s palsy), Guillain-Barré syndrome (GBS) and vaccine administered during pregnancy. For each report of a prespecified condition, we reviewed VAERS reports and medical records. Reports of anaphylaxis, facial nerve palsy and GBS were classified using Brighton Collaboration case definitions when possible [16–18]. For reports of vaccination during pregnancy, we reviewed available information to determine maternal trimester of vaccination and whether any pre- or post-natal adverse event was reported.

Data Mining

We used empirical Bayesian (EB) data mining methods to identify MedDRA PTs that were reported at least twice as frequently as expected (i.e., lower bound of the 90% CI surrounding the EB geometric mean [EB05] >2) after adjusting for sex and year received

[19,20]. Reports for PTs exceeding this predetermined limit and not described in the package insert were considered for further clinical review.

Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to institutional review board and informed consent requirements.

RESULTS

VAERS received a total of 2614 U.S. reports following vaccination with Menveo from January 1, 2010 through December 31, 2015. In 1380 (53%) of these reports, other vaccines were given concomitantly with Menveo. The most commonly co-administered vaccines varied depending upon age including pneumococcal (9 [27%]) and measles, mumps and rubella (8 [24%]) in children less than 2 years of age, tetanus, diphtheria, and pertussis (Tdap) in children aged 2–10 years (32 [41%]), Tdap (776 [40%]) and human papillomavirus (608 [31%]) in adolescents (aged 11–18 years), and Tdap in adults (>18 yrs, 43 [11%]). Median age of all vaccinees was 12 years (range 0–89 years) and the median onset interval was 0 days (range 0–734 days), with day 0 set as the day of vaccination. Reports were nearly equally distributed between males and females (47% each), with the remainder missing information on sex. Dose number was recorded for 57% of the reports and ranged from Dose 1 to Dose 7, suggesting a lack of reliability for reported dose.

Most reports (n=1932, 74%) were in the adolescent population, including 1 death and 45 serious, non-death reports (Table 1). Among 2–23 month olds, a total of 33 reports were received, including 4 serious, non-death reports. Among 2–10 year olds, a total of 79 reports were received, including 4 serious, non-death reports. In adults, 379 reports were received (12 serious, non-death). Of the reports for which age was missing (n=191), one was a serious, non-death report. The most frequent PTs (those reported in greater than 5% of the reports after vaccination with Menveo) are shown in Table 2. The most frequently reported AEs were related to local reactions (erythema, injection site swelling, injection site warmth, and injection site pain), dizziness, pyrexia (fever), headache, or syncope.

Serious Reports

The SOC and PTs determined after individual review of the 67 serious reports are shown in Table 3. Of these, 19 were received from the manufacturer, and the remainder from the public. In 42 (63%) of these reports, Menveo was administered concomitantly with one or more other vaccines. The most common presenting SOC was nervous system disorders (16 reports), including diagnoses or presentations of GBS and seizures (4 each). The next most common presenting SOC was immune system disorders (10 reports), including anaphylaxis (7) and non-anaphylactic allergic reactions (2). Five cases of syncope were reported, contributing to a total of 7 reports in the cardiac disorders class. Tradename and manufacturer could not be confirmed for one report.

Anaphylaxis

We identified 9 reports of possible anaphylaxis. Three reports met the definition for Brighton level 1, one report met the definition for Brighton level 2, and three reports did not meet Brighton criteria but were physician-diagnosed anaphylaxis (one of which did not

include tradename or manufacturer); all of these reports were classified as serious and all included epinephrine administration in the descriptions of treatment. Two non-serious reports lacked sufficient information to classify according to the Brighton criteria.

Five cases reported symptom onset within 30 minutes of vaccination, while two (one Brighton level 1 and one Brighton level 2) experienced onset of symptoms 24 hours or more after vaccination. For the remainder of cases, timing was not precisely specified. Median onset interval of symptoms was 0 days (range 0–1 days). In one Brighton level 1 case, the patient had experienced a similar response immediately following receipt of an unknown vaccine 6 years earlier. Eight of the 9 reports described concomitant administration of other vaccines.

Facial Nerve Palsy

We identified 9 reports of possible idiopathic facial nerve palsy. Three reports were excluded based on coincident diagnosis of an underlying conditions (thyroid tumor, polyneuritis) or infection associated with facial palsy (otitis media). One report of idiopathic facial nerve palsy met the definition for Brighton level 1, one report met the definition for Brighton level 2, and two reports met the definition for Brighton level 3. Two reports lacked sufficient information to classify according to Brighton criteria. Median onset interval of symptoms was 1 day (range 1–21 days). None of the reports of idiopathic facial nerve palsy were classified as serious.

Guillain Barré Syndrome (GBS)

We identified 6 reports of possible GBS. One report met the definition for Brighton level 1, and three reports met the definition for Brighton level 2; all were classified as serious. After review of medical records, the remaining two reports were determined not to be cases of GBS (one was determined to be undergoing repeated treatment for chronic inflammatory demyelinating polyneuropathy (CIDP) and the other had a diagnosis of migraine with orthostatic hypotension dysautonomic syndrome). Three of the four classified reports were documented as fully recovered at 1 year, while the fourth reported unresolved symptoms of neuropathy in both feet. The median onset interval of symptoms was 11 days (range 1–55 days).

Viral illness prior to onset of symptoms was noted for two of the reports. In one case, records indicated that the patient experienced severe gastroenteritis followed by lower extremity weakness in the weeks immediately before vaccination, although symptoms had improved before receiving Menveo. In three of the four reports, the patients had received Menveo alone; the fourth also received trivalent influenza vaccine.

Vaccination in Pregnancy

We identified 14 reports of vaccination with Menveo during pregnancy, and we were able to determine trimester of vaccination in 12 of these reports (10 were in the first trimester, 1 was in the second trimester and 1 was in the third trimester). In 11 of these reports, it was noted that the vaccination was inadvertent or that the pregnancy test occurred after the vaccination. Three reports did not include verification of tradename or manufacturer.

In the majority of the pregnancy reports (13/14), no AEs were reported. There was one report of fever and muscle soreness following vaccination. The majority of reports (11/14) had no information on birth outcomes due to loss to follow-up. Three reports included limited information on birth outcome: one noted that the mother and infant were “fine”, one described normal ultrasounds throughout pregnancy followed by an uncomplicated vaginal delivery, and one described a normal delivery at term with no maternal complications and normal APGAR scoring for the infant.

We also identified one report of accidental exposure to Menveo during pregnancy due to a syringe error. The reporter described that the vaccine administrator was pregnant and was splashed in the eye with vaccine during administration of the vaccine to a patient after the needle detached from the syringe. No AE was experienced as a result of the exposure. No information was available regarding infant outcome.

Deaths

We identified one death in the reports to VAERS following administration of Menveo. We were unable to review medical records, autopsy reports or a death certificate for this report. The report indicated receipt of Menveo concomitantly with Gardasil® and Havrix® 2 months prior to symptom onset, with a diagnosis of a brain tumor approximately 5 months after vaccination.

Data mining

The data mining findings for all reported PTs by age group are shown in Table 4. The disproportionately reported terms were predominantly related to handling or administration errors, and in nearly all age groups, “no adverse event” was disproportionately reported. In adults aged 19–44 years, an elevated EB05 was also observed for “syncope”, a finding that is described in the manufacturer’s package insert.

When data mining was conducted for PTs in serious reports at any age, there were no disproportionately reported AEs.

DISCUSSION

We completed a comprehensive review of AEs reported in the US after receipt of Menveo from January 1, 2010 through December 31, 2015. Many of the most frequent AEs were consistent with the data from pre-licensure trials of Menveo. These included injection-site reactions (erythema, induration, pain) and selected systemic reactions (fever, irritability, headache, nausea, and sleepiness). The majority of reports were received following vaccination of adolescents (74%), the group for which meningococcal vaccine is routinely recommended.

After clinical review of all serious reports, we found that anaphylaxis (7 reports) and syncope (5 reports) were the two most common events reported; syncope was also one of the most frequently observed MedDRA PTs in adults. While syncope is usually viewed as a temporary and non-threatening condition, we found that the serious reports of syncope in this study were labeled as such due to hospitalization for observation or to monitor for

potential concussions sustained during the syncopal episode. Both anaphylaxis and syncope are known risks following any vaccine, and post-vaccination syncope (irrespective of vaccine type) is more common in the adolescent and young adult age groups that are the major recipients of meningococcal vaccines [21]. The most frequently observed SOC was nervous system disorders, where we found 4 reports each of GBS and seizures. We did not observe disproportionate reporting for either of these conditions in the data mining analysis.

To our knowledge, this is the first study to investigate AEs in women who have been vaccinated with Menveo while pregnant. In the majority of the reports, women had been vaccinated during the first trimester (often prior to knowledge of the pregnancy) and experienced no AEs. Although the number of reports was small (n=14), the findings did not provide any evidence for concern, as only one report noted a mild adverse event while the remainder recorded inadvertent vaccination during pregnancy. Menveo is not contraindicated during pregnancy. Our findings are consistent with a review of 80 reports to VAERS following maternal immunization with another meningococcal conjugate vaccine, which did not find any concerning patterns of AEs [1].

Multiple non-adverse event terms were frequently reported for Menveo and/or disproportionately reported in the data mining analysis. These included “no adverse event”, “drug administration error”, “incorrect drug dosage form administered”, “incorrect product formulation administered”, “incorrect product storage”, “incorrect storage of drug”, “wrong drug administered”, and “wrong technique in drug usage process”. A recent publication describing reports to VAERS of administration errors after Menveo found that in 346 of the 407 reported errors, no adverse event was experienced [13]. The frequency of similar findings in our study highlights the importance of vaccine providers adhering to the proper administration of this vaccine as described in the package insert.

In recent years, concerns have arisen regarding dysautonomic syndromes such as postural orthostatic tachycardia syndrome (POTS) following HPV vaccine [22]. In our study, one case of POTS was reported following vaccination with Menveo, TDaP and HPV vaccines and one case of orthostatic hypotension dysautonomic syndrome was reported following vaccination with Menveo and TDaP. In addition, the data mining analysis did not find disproportionate reporting of PTs suggestive of dysautonomic syndromes, which is a reassuring finding.

Strengths of VAERS include its national scope and ability to process reports in a timely manner, making it potentially useful for detection of vaccine safety signals for further investigation. Limitations include those inherent to passive surveillance systems, including under- or over-reporting, biased reporting, and inconsistency of quality and completeness of reports. Additionally, reports may not contain sufficient detail for verification or classification of certain outcomes which require very specific and complete medical records (for example, acute disseminated encephalomyelitis). Finally, VAERS data do not include an unvaccinated comparator group, therefore preventing an assessment of causality.

From 2010 through 2015, approximately 8.2 million doses of Menveo were distributed for use within the US (data shown with permission of GSK, personal communication). The

calculated crude reporting rate was approximately 32 per 100,000 doses distributed for all reports and 0.8/100,000 doses distributed for serious reports. Our analysis did not reveal any unexpected findings or patterns of AEs after Menveo. This represents the first comprehensive, published assessment of post-licensure safety of Menveo and adds to the existing knowledge base regarding the safety of meningococcal vaccines.

Acknowledgments

Financial support: This study was supported by the CDC. Dr. Myers was supported by Award Number T32AI074492 from the National Institute of Allergy and Infectious Diseases (NAIAD).

We would like to acknowledge Dr. Brock Stewart for technical assistance with data mining methods, and Dr. Frank DeStefano for his helpful review of early drafts of the manuscript.

References

- Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2013; 62:1–28. [PubMed: 23302815]
- Reagan-Steiner S, Yankey D, Jeyarajah J, Elam-Evans LD, Singleton JA, Curtis CR, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years—United States, 2014. MMWR Morb Mortal Wkly Rep. 2015; 64:784–792. [PubMed: 26225476]
- Centers for Disease Control and Prevention. Licensure of meningococcal conjugate vaccine (Menveo) and guidance for use – Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep. 2010; 59:273. [PubMed: 20224545]
- Centers for Disease Control and Prevention. Licensure of a meningococcal conjugate vaccine for children aged 2 through 10 years and updated booster dose guidance for adolescents and other persons at increased risk for meningococcal disease – Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep. 2011; 60:1018–1019. [PubMed: 21814165]
- Centers for Disease Control and Prevention. Use of MenACWY-CRM vaccine in children aged 2 through 23 months at increased risk of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2013. MMWR Morb Mortal Wkly Rep. 2014; 63:527–530. [PubMed: 24941332]
- Abdelnour A, Silas PE, Valdés Lamas MR, Grazioso Aragón CF, Chiu NC, Chiu CH, et al. Safety of a quadrivalent meningococcal serogroups A,C, W, and Y conjugate vaccine (MenACWY-CRM) administered with routine infant vaccinations: results of an open-label, randomized, phase 3b controlled study in health infants. Vaccine. 2014; 32:965–72. [PubMed: 24397906]
- Klein NP, Reisinger KS, Johnston W, Odrlijn T, Gill C, Bedell L, et al. Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly with routine vaccinations in infants. Pediatr Infect Dis J. 2012; 31:64–71. [PubMed: 22094635]
- Klein NP, Shepard J, Bedell L, Odrlijn T, Dull P. Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine administered concomitantly with measles, mumps, rubella, varicella vaccine in health toddlers. Vaccine. 2012; 30:3929–36. [PubMed: 22504039]
- U.S. Food and Drug Administration. [accessed 26.7.2016] Package insert - Menveo®. 2013. <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201349.pdf>
- Black S, Klein NP, Shah J, Bedell L, Karsten A, Dull PM. Immunogenicity and tolerability of a quadrivalent meningococcal glycoconjugate vaccine in children 2–10 years of age. Vaccine. 2010; 28:657–63. [PubMed: 19895922]
- Halperin SA, Gupta A, Jeanfreau R, Klein NP, Reisinger K, Walter E, et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2–10 years of age. Vaccine. 2010; 28:7865–72. [PubMed: 20943209]

12. Jackson LA, Baxter R, Reisinger K, Karsten A, Shah J, Bedell L, et al. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. *Clin Infect Dis*. 2009; 49:e1–e10. [PubMed: 19476428]
13. Su JR, Miller ER, Duffy J, Baer BM, Cano MV. Notes from the field: administration error involving a meningococcal conjugate vaccine – United States, March 1, 2010 – September 22, 2015. *MMWR Morb Mortal Wkly Rep*. 2016; 65:161–2. [PubMed: 26890604]
14. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2015; 33:4398–405. [PubMed: 26209838]
15. U.S. Code of Federal Regulations. [accessed 12.12.2016] 21 CFR 600.80. Postmarketing reporting of adverse experiences. 2014. Available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80>
16. 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]
17. Rath B, Gidudu JF, Anyoti H, Bollweg B, Caubel P, Chen YH, et al. Facial nerve palsy including Bell's palsy: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine*. 2016; Epub ahead of print. doi: 10.1016/j.vaccine.2016.05.023
18. Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, 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]
19. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Stat*. 1999; 53:177–90.
20. 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]
21. Sutherland A, Izurieta H, Ball R, Miller ER, Braun MM, Broder KR, et al. Syncope after vaccination – United States, January 2005 – July 2007. *MMWR*. 2008; 57:457–60. [PubMed: 18451756]
22. Chandler RE, Juhlin K, Fransson J, Caster O, Edwards JR, Norén GN. Current safety concerns with human papillomavirus vaccine: a cluster analysis of reports in Vigibase. *Drug Saf*. 2017; 40:81–90. [PubMed: 27638661]

Table 1

Characteristics of VAERS reports following Menveo, 2010–2015

	2 mo – 23 mo Total=33 n (%)	2 yr – 10 yr Total=79 n (%)	11 yr – 18 yr Total=1932 n (%)	>18 yr Total=379 n (%)	All ages ^a Total=2614 n (%)
Male ^b	16 (48)	40 (51)	992 (51)	147 (39)	1232 (47)
Serious	4 (12)	4 (5)	46 (2)	12 (3)	67 (3)
Age, median	12 mo	10 yr	12 yr	25 yr	12 yr
Onset interval, median, d (range)	0 (0–126)	1 (0–732)	0 (0–734)	0 (0–365)	0 (0–734)
Menveo given alone	14 (42.4)	32 (41)	749 (38.8)	256 (68)	1234 (47)
Type of Reporter					
Vaccine Provider	5 (15)	41 (52)	1107 (57)	161 (42)	1320 (51)
Manufacturer	19 (58)	21 (27)	460 (24)	123 (32)	804 (31)
Patient/parent	6 (18)	7 (9)	70 (4)	42 (11)	125 (5)
Other	3 (9)	10 (13)	295 (15)	53 (14)	365 (14)

^a includes reports missing age, n=191

^b data missing for n=140

Table 2

Most frequent MedDRA preferred terms for all reports

2 mo – 23 mo		2 yr – 10 yr		11 yr – 18 yr		>18 yr	
MedDRA preferred term	n (%) ^a	MedDRA preferred term	n (%)	MedDRA preferred term	n (%)	MedDRA preferred term	n (%)
No Adverse Event	17 (51.5)	Injection Site Erythema	29 (37)	Injection Site Erythema	422 (22)	No Adverse Event	89 (24)
Drug Administered to Patient of Inappropriate Age	5 (15)	Erythema	16 (20)	No Adverse Event	329 (17)	Injection Site Erythema	55 (14)
Pyrexia	5 (15)	Injection Site Swelling	15 (19)	Injection Site Swelling	323 (17)	Pyrexia	54 (14)
Wrong Drug Administered	5 (15)	Injection Site Warmth	15 (19)	Erythema	254 (13)	Injection Site Swelling	49 (13)
Injection Site Swelling	3 (9)	No Adverse Event	12 (15)	Injection Site Warmth	204 (11)	Headache	47 (12)
Irritability	3 (9)	Injection Site Pain	10 (13)	Dizziness	187 (10)	Injection Site Pain	42 (11)
Erythema	2 (6)	Skin Warm	10 (13)	Injection Site Pain	181 (9)	Dizziness	38 (10)
Incorrect Drug Dosage Form Administered	2 (6)	Oedema Peripheral	8 (10)	Syncope	141 (7)	Erythema	37 (10)
Injection Site Mass	2 (6)	Pain	8 (10)	Headache	136 (7)	Nausea	32 (8)
Injection Site Warmth	2 (6)	Pyrexia	8 (10)	Skin Warm	129 (7)	Pain	29 (8)
Oedema Peripheral	2 (6)	Induration	7 (9)	Pyrexia	123 (6)	Syncope	24 (6)
Somnolence	2 (6)	Peripheral Swelling	6 (8)	Incorrect Drug Dosage Form Administered	109 (6)	Pain In Extremity	24 (6)
		Pruritus	6 (8)	Administered		Chills	24 (6)
		Drug Administered to Patient of Inappropriate Age	5 (6)			Injection Site Warmth	24 (6)
		Injection Site Induration	5 (6)				
		Rash	5 (6)				
		Swelling	5 (6)				

^a each report may have one or more preferred terms

Table 3

Medical conditions for 67 serious reports following Menveo, VAERS 2010–2015

Medical Conditions	Total n=67 n (%)
Nervous system disorders	16 (23.9)
Guillain-Barre Syndrome	4
Seizure	4
Intracranial hypertension	2
Acute disseminated encephalomyelitis	1
Chronic inflammatory demyelinating polyradiculopathy	1
Hypotonia/motor delay	1
Migraine without aura combined with orthostatic hypotension	1
Neuromyopathy	1
Polyneuritis	1
Immune system disorders	10 (14.9)
Anaphylaxis	7
Allergic reaction	2
Drug eruption	1
Cardiac disorders	7 (10.4)
Vasovagal syncope	5
Myocarditis and pericarditis	1
Postural orthostatic tachycardia syndrome	1
Infections and infestations	6 (9.0)
Appendicitis	1
Headache	1
Streptococcal pneumonia	1
Viral meningitis	1
Multiple symptoms ^a	2
Skin and subcutaneous tissue disorders	6 (9.0)
Cellulitis	4
Erythema multiforme	1
Steven Johnson syndrome	1
General disorders and administration site conditions	5 (7.5)
Injection site reaction	3
Multiple symptoms ^b	2
Musculoskeletal and connective tissue disorders	4 (6.0)
Fibromyalgia	1
Juvenile idiopathic arthritis	1
Muscular weakness	1
Pyomyositis	1

Medical Conditions	Total n=67 n (%)
Psychiatric disorders	4 (6.0)
Abnormal behavior	2
Major depression	1
Psychogenic seizure	1
Gastrointestinal disorders	3 (4.5)
Abdominal pain	1
Intestinal obstruction	1
Irritable bowel syndrome	1
Neoplasms benign, malignant and unspecified	2 (3.0)
Glioma	1
Osteosarcoma	1
Blood and lymphatic system disorders	1 (1.5)
Idiopathic thrombocytopenic purpura	1
Endocrine disorders	1 (1.5)
Hyperthyroidism	1
Injury, poisoning and procedural complications	1 (1.5)
Inadvertent exposure to vaccine ^c	1
Vascular disorders	1 (1.5)
Kawasaki's disease	1

^a one report of fever of unknown origin accompanied by headache, neck pain and gastritis; one report of fever accompanied by headache

^b one report of headache accompanied by dizziness, fatigue and fever; one report of diarrhea, itching (at injection site), nose bleed, somnolence and upset stomach

^c although report noted that no adverse event was reported following the administration error, the report was classified as serious due to a later hospitalization

Table 4

Data mining findings in VAERS after vaccination with Menveo

MedDRA PTs with increased EB05* (>2)	n
< 2 years of age	
No Adverse Event	13
2 to <9 years of age	
No Adverse Event	6
9 to <19 years of age	
Incorrect drug dosage form administered	108
Incorrect product formulation administered	31
Incorrect product storage	71
Incorrect storage of drug	71
Wrong technique in drug usage process	89
19 to <45 years of age	
Drug administration error	4
Expired product administered	7
Incorrect drug dosage form administered	18
Incorrect product formulation administered	8
Incorrect route of drug administration	6
No adverse event	56
Syncope	23
Wrong technique in drug usage process	12
45 to <65 years of age	
Drug administered to patient of inappropriate age	6
No adverse event	13
65 years of age and greater	
Drug administered to patient of inappropriate age	6
No adverse event	6

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