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Adverse events following quadrivalent meningococcal CRM-conjugate vaccine (Menveo®) reported to the Vaccine Adverse Event Reporting system (VAERS), 2010–2015

Tanya R. Myers [a,b,*], Michael M. McNeil [a], Carmen S. Ng [a], Rongxia Li [a], Paige W. Lewis [a], Maria V. Cano [a]

[a] Immunization Safety Office, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333, USA
[b] Rollins School of Public Health, Emory University, 1518 Clifton Road, Atlanta, GA 30322, USA

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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.
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.

1. 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

* Corresponding author at: Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS D-26, Atlanta, GA 30333, USA.
E-mail address: vje9@cdc.gov (T.R. Myers).

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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 the Vaccine Adverse Event Reporting System (VAERS) following improperly prepared doses of Menveo found AEs similar to those reported in pre-licensure 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 VAERS for subjects of any age receiving Menveo during January 1, 2010 through December 31, 2015.

2. Methods

2.1. 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 one 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 in "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.

2.2. 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.

2.3. 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.

3. 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 (n = 9, 27% of all Menveo reports in age group) and measles, mumps and rubella (8, 24%) in children less than 2 years of age, tetanus, diphtheria, and acellular 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 aged 19 and older (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 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.

3.1. Serious reports

The SOCs 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

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