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Safety surveillance of meningococcal group B vaccine (Bexsero®), Vaccine Adverse Event Reporting System, 2015–2018

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Abstract

Background: Bexsero® (GlaxoSmithKline) is a four-component *Neisseria meningitidis* serogroup B vaccine (MenB-4C). It was licensed in the United States in 2015 for use among individuals ages 10–25 years. We aimed to assess the post-licensure safety profile of MenB-4C by examining reports received in the Vaccine Adverse Event Reporting System (VAERS).

Methods: VAERS is a national passive surveillance system for adverse events (AEs) following immunization that uses the Medical Dictionary for Regulatory Activities to code reported AEs and the Code of Federal Regulations to classify reports by seriousness. In this case series, we analyzed U.S. reports involving MenB-4C received between January 23, 2015 through December 31, 2018. We used Empirical Bayesian data mining to identify MenB-4C/AE combinations reported at least twice as often as expected.

Results: VAERS received 1,867 reports following MenB-4C administration, representing 332 reports per million doses distributed. Most reports were for females (59%), with a median age of 17 years (interquartile range: 16–18 years); 40% of reports described simultaneous administration

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Declaration of Competing Interest

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.

Disclaimer

The findings and conclusions in this report are those of the authors and not necessarily represent the official position of the Department of Health and Human Services, the U.S. Food and Drug Administration, or the Centers for Disease Control and Prevention.

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of other vaccines. The majority of reports were classified as non-serious (96%). The most commonly reported AEs were injection site pain (22%), pyrexia (16%), and headache (16%). Data mining identified disproportionate reporting for “injected limb mobility decreased” secondary to injection site reactions, including extensive swelling of the vaccinated limb and injection site pain.

Conclusions: Analysis of passive surveillance data from over 5.6 million doses of MenB-4C distributed in the United States did not reveal new safety concerns. The large majority of reports were classified as non-serious and the reported AEs were generally consistent with the safety experience described in clinical studies and the product’s package insert. While our results are reassuring, continued post-marketing surveillance is warranted.

Keywords

4CMenB vaccine; Meningococcal vaccines; Neisseria meningitidis serogroup B; Pharmacovigilance; Vaccine Adverse Event Reporting System

1. Introduction

Meningococcal disease is caused by *Neisseria meningitidis* and may result in death or major long-term sequelae even with appropriate antimicrobial therapy. In the United States, during 2006–2015, serogroup B was the most frequently isolated serogroup causing meningococcal disease, with an estimated incidence of 0.07 cases per 100,000, with the highest rates observed in infants less than 1 year of age, adolescents, and young adults [1]. Bexsero® (Glaxo SmithKline Biologicals, Siena, Italy) is an aluminum hydroxide-adjuvanted *N. meningitidis* serogroup B vaccine (MenB-4C) that contains four antigens: three outer-membrane recombinant proteins (factor H binding protein, Neisseria adhesin A, and Neisserial Heparin Binding Antigen) and detoxified outer-membrane vesicles derived from the New Zealand epidemic strain NZ98/254. In January 2015, the U.S. Food and Drug Administration (FDA) approved a two-dose series of MenB-4C for active immunization to prevent invasive disease caused by *N. meningitidis* serogroup B in individuals ages 10–25 years under accelerated approval regulations [2]. Prior to its approval, the Centers for Disease Control and Prevention (CDC) received permission from FDA, under an expanded access investigational new drug (IND) protocol, to sponsor mass vaccination campaigns using MenB-4C at two U.S. universities which experienced unrelated outbreaks [3,4]. The safety data submitted in support of the license application included data from 3,139 subjects enrolled in randomized clinical trials who received at least one dose of MenB-4C and 15,351 subjects who participated in the CDC’s vaccination campaigns. The nature and frequency of adverse events (AEs) following MenB-4C reported in subjects ages 10–25 years were consistent with events commonly observed following other vaccinations administered to adolescents and young adults in the United States. These data did not raise any serious safety concerns [5]. The CDC’s Advisory Committee on Immunization Practices (ACIP) recommends the use of meningococcal B vaccines in individuals aged ≥ 10 years at increased risk for serogroup B meningococcal disease, including persons with persistent complement component deficiencies or taking a complement inhibitor, those with anatomic or functional asplenia, those identified as at increased risk because of a serogroup B meningococcal disease outbreak, and microbiologists routinely exposed to

isolates of *N. meningitidis*. Meningococcal B vaccination is not routinely recommended for individuals who are not at increased risk, although ACIP recommends a meningococcal B series for adolescents and young adults ages 16–23 years, on the basis of shared clinical decision-making, to provide short-term protection against disease [6–8]. We aimed to assess the safety profile of MenB-4C as reported to the U.S. Vaccine Adverse Event Reporting System (VAERS).

2. Methods

VAERS is a national passive surveillance system jointly administered by FDA and CDC since 1990 for AEs following immunization [9,10]. Besides vaccine manufacturers that are required to report to VAERS AEs that come to their attention, anyone can submit reports, regardless of clinical relevance or likelihood of causal association [10]. VAERS uses the Medical Dictionary for Regulatory Activities (MedDRA) to code reported AEs and the Code of Federal Regulations to define seriousness. A serious AE is one that is life-threatening, results in death, permanent disability, congenital anomaly, hospitalization, or requires medical or surgical intervention to preclude one of aforementioned outcomes [11,12]. VAERS reports vary considerably in quality, although all U.S. serious reports include medical records or information derived from medical records [10].

In this case series, we reviewed U.S. MenB-4C reports received by VAERS between January 23, 2015 through December 31, 2018, including follow-up information received through March 1, 2019. This VAERS safety review did not require institutional review board approval because it met the Department of Health and Human Services regulations for exemption, which was granted by the Office for Protection from Research Risks.

2.1. Descriptive analyses

We calculated frequencies for categorical variables and medians, interquartile ranges (IQR), and ranges for continuous variables. We summarized the most common MedDRA Preferred Terms (PTs) for non-serious and serious non-fatal AEs. We also calculated VAERS AE reporting rates by dividing the number of reports received in VAERS by the number of vaccine doses distributed in the United States according to data provided by the manufacturer.

We performed detailed case report reviews for death reports and those potentially representing selected AEs, including injection site reactions (ISRs) described in serious reports, syncope, hypersensitivity reactions, chronic fatigue syndrome, selected autoimmune diseases, and selected renal conditions. We also individually reviewed reports of MenB-4C administered shortly before or during pregnancy, in temporal association with a complement inhibitor (eculizumab; Soliris®, Alexion Pharmaceuticals, Inc.), and those reporting vaccine failures, vaccine administration errors, and shoulder injuries. We identified these reports through MedDRA PTs, text mining, or a combination of text mining and discrete variables in the VAERS form. When available, we used Brighton Collaboration case definitions to confirm the diagnosis of case reports [13–17]. During the review process, we excluded duplicate reports and those with coding discrepancies that could not be resolved.

We used Stata/IC 13.1 (StataCorp LLC, College Station, TX, United States) to conduct the analyses.

2.2. Data mining (disproportionality analyses)

We conducted Empirical Bayesian data mining analyses to assess disproportionality in AE reporting for MenB-4C compared to all vaccines in VAERS by using the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm [18,19]. We restricted our primary analyses to U.S. reports received from January 23, 2015 through December 31, 2018 and to the age range for which MenB-4C is approved for use in the United States (10–25 years). We controlled for age group (10–17, 18–25 years), sex, and year in which the report was received in VAERS. We conducted additional analyses further restricting to U.S. serious reports. Because we identified reports with age outside of the 10–25 years range, we conducted an additional analysis for the broader age group (≤9, 10–17, 18–25, 26–64, ≥65 years) adjusted for sex and year in which the report was received in VAERS. We estimated Empirical Bayes Geometric Mean (EBGM) and the 5th and 95th percentiles of the posterior distribution (EB05, EB95), which are interpreted as the lower and upper bound of a 90% confidence interval, respectively [19,20]. We used an EB05 ≥ 2.0 as a criterion for considering a potential signal, because this threshold suggests a high probability of the vaccine-event pair occurring at least twice as often as expected under the assumption that vaccine-events are randomly paired [19]. For serious events, we used an EB05 > 1.0 to identify AEs that occurred at least at a higher-than-expected ratio [21,22]. Elevated data mining statistics should not be interpreted as evidence of a causal relationship between a vaccine-event pair, but as a potential signal that may need to be assessed through well-designed controlled studies [23,24].

We conducted our data mining analyses using Oracle©'s Empirica Signal.

3. Results

3.1. Descriptive analyses

We identified a total of 1,867 U.S. MenB-4C reports (59% female) [Table 1]. The manufacturer reported a total of 5,623,800 MenB-4C doses distributed during our assessment period, representing 332 reports per million doses distributed. Among reports that specified age (84%), the median age was 17 (IQR: 16–18) years, with 80% of individuals being between 10 and 25 years of age. Overall, 40% of reports described simultaneous administration of other vaccines, most commonly meningococcal serogroups A, C, W, and Y (MenACWY), human papillomavirus (HPV), influenza, and hepatitis A vaccines. The median time from MenB-4C administration to symptom onset was 0 days (IQR: 0–1 days). The most commonly reported AEs included injection site pain (22%), pyrexia (16%), headache (16%), injection site erythema (15%), and pain in extremity (15%) [Table 2].

3.1.1. Non-serious reports—The majority of reports (96%) were classified as non-serious. The most frequently reported AEs were injection site reactions, pyrexia, headache, nausea, dizziness, chills, fatigue, syncope, and vomiting [Table 2].

3.1.2. Serious non-fatal reports—We identified a total of 80 (4%) serious non-fatal reports (50% females), representing 14 serious reports per million MenB-4C doses distributed. The median patient age was 17 (IQR: 16–18) years. Most reports (55%) described onset of symptoms related to the AE on the day of (day 0) or the day after (day 1) vaccination (Table 1). The most commonly reported AEs were pyrexia, headache, nausea, asthenia, chills, vomiting, dizziness, hypoesthesia, paresthesia, gait disturbance, dyspnea, and pain in extremity (Table 2).

3.1.3. Death reports—VAERS received two (0.1%) death reports for MenB-4C. The first report, which was previously published, described a death in a 16-year-old female who started treatment with a complement inhibitor (eculizumab) 190 days after her second dose of MenB-4C and died 14 days later. The autopsy was consistent with Waterhouse-Friderichsen syndrome. The organism isolated from the meninges was found to be a non-groupable meningococcal strain, which rarely causes disease in healthy individuals [25]. The other report described meningitis as the reported cause of death in a male of unknown age vaccinated with MenB-4C (dose number unknown). The reporter (consumer) did not include additional information.

3.1.4. Adverse events of interest

3.1.4.1. Injection site reactions (serious reports).: Our search identified a total of 673 reports describing ISRs. We individually reviewed the 12 reports (1.8%) classified as serious. Six reports described ISRs accompanied by systemic events, including fever and/or chills. Three of these reports additionally described: (1) tingling, muscle spasms, vomiting, headache, and pallor; (2) syncope and nausea; and (3) viral infection. We classified five of these ISRs as Level 1 and one as Level 2 of the Brighton Collaboration case definition. We classified the three serious reports describing ISRs not accompanied by systemic symptoms as meeting Brighton Level 1 criteria (n = 2) and Level 2 criteria (n = 1). Two of these cases reported injected limb mobility decreased. Additionally, two reports described ISRs that coincided with multiple apparently unrelated systemic events whose outcomes were the reason for the reports to be classified as serious. One remaining report described cellulitis at the vaccination site of non-MenB-4C.

3.2. Syncope

A total of 145 reports (61% female) described syncope or near-syncope; most were non-serious (n = 136, 94%), included a physician/healthcare provider diagnosis (n = 136, 94%), and described simultaneous vaccination with at least one other vaccine (n = 103; 71%). Only two (1%) reported a blood draw after vaccination. The median age of patients at vaccination was 17 years (IQR: 16–18 years). Among 138 reports in which time to event was available, 62% described the syncopal event within 15 min of vaccination. Twelve (8%) reports described an injury and one a possible injury, with eight individuals requiring urgent/emergent care or an additional office visit. A total of 19 (13%) reports (58% female) described seizure-like activity, with 17 (89%) classified as non-serious, and 16 (84%) noting concomitant vaccinations.

3.3. Hypersensitivity reactions

Nine reports (67% males) described anaphylaxis among individuals 13–20 years of age, with all events occurring within eight hours following MenB-4C vaccination. Six reports (67%) described receipt of a concomitant vaccine. Six cases (67%) met the Brighton Collaboration case definition (i.e., Levels 1–3).

Five reports described other serious hypersensitivity reactions among individuals ages 16–36 years. Two did not clearly describe allergic reactions. The other three noted (1) small urticarial lesions and mouth swelling two hours after vaccination with the first dose of MenB-4C and the third dose of HPV vaccine in a male with sickle cell disease, asthma, and history of bone marrow transplant complicated by graft-versus-host disease; (2) generalized urticaria occurring five days after vaccination with the first dose of MenB-4C in a female with atopic dermatitis, keratosis pilaris, and food allergies; and (3) possible allergic reaction manifested by nausea and intractable vomiting one hour after receiving MenB-4C in a female with a history of similar symptoms after receiving three vaccines simultaneously.

3.4. Chronic fatigue syndrome

Our search did not identify any reports of chronic fatigue syndrome.

3.5. Immune-mediated diseases

Our search identified a total of nine cases of immune-mediated diseases reported among individuals ages 15–47 years of the two reports of GBS, one with Brighton Level 3 diagnostic certainty described a female whose symptoms started one day after she received MenB-4C (dose number not reported) and two weeks following an upper respiratory infection. The second report, which did not include sufficient information to assign a Brighton classification, described a male who experienced GBS a few weeks after he received his first dose of MenB-4C.

We identified two reports of immune thrombocytopenia (ITP). The first report described a case in a female with history of chronic ITP and splenectomy five years prior who maintained a baseline platelet count of 30,000–50,000 on active treatment with eltrombopag, a thrombopoietin receptor agonist. The patient also had recurrent sinus infections and developed low grade fever, sore throat, sinus pressure, and ear pain four days after vaccination with MenB-4C, at which time the platelet count was 38,000. She was treated with azithromycin for acute sinusitis. Eight days after vaccination, she presented with increased bruising and petechiae and was found to have a platelet count of 9,000 requiring hospital admission. The second ITP report referred to a male with trisomy 21 who presented with petechiae and mild bleeding and was found to have new onset, acute thrombocytopenia eight days after receipt of MenB-4C and influenza vaccines. Consistent with the diagnosis of presumed ITP, his platelet count steadily improved to normal range following a two-day course of high dose intravenous gammaglobulin. Both cases met Brighton Level 1 criteria for thrombocytopenia.

We found one report of multiple sclerosis (MS) in a male who was diagnosed seven days after being vaccinated with MenB-4C, HPV, and hepatitis A vaccines. As per the

report, there was no MS diagnosis prior to vaccination, but the MS plaque visualized on imaging was thought to be preexisting. There was also a report of a female diagnosed with acute disseminated encephalomyelitis (ADEM) versus MS who began having symptoms 3–5 days after being vaccinated with MenB-4C and HPV vaccine. The report did not include sufficient details to allow for classification according to Brighton Collaboration case definition. Additionally, there was a report of a male vaccinated with MenB-4C, HPV, and hepatitis A vaccines who developed acute progressive numbness below the waist approximately nine days post-vaccination. The magnetic resonance imaging (MRI) revealed new and preexisting inflammatory lesions, suggestive of MS, although it was unknown if the patient had a prior history of MS. The differential diagnosis included transverse myelitis, herpes encephalitis, and ADEM.

We identified a case of optic neuritis/neuroretinitis in a male who experienced symptom onset four weeks after receiving his first MenB-4C dose. We also noted a report of a female diagnosed with rheumatoid arthritis 14 days after being vaccinated with her first dose of MenB-4C. Based on her anamnesis, the possibility of Lyme disease-associated arthritis was also considered, but she had not been tested for Lyme disease at the time the report was submitted to VAERS. We did not identify any reports of autoimmune renal disease occurring after vaccination with MenB-4C.

3.6. Potential shoulder injury

We identified three reports consistent with shoulder injury involving the arm in which MenB-4C was administered. All individuals were females receiving their first MenB-4C dose, and none received simultaneous vaccines. Physician diagnoses included bursitis (n = 2) and tendinitis (n = 1). In one case of bursitis, the vaccine was reported to have been inadvertently injected into the joint capsule. The symptoms resolved in less than 42 days in the two cases of bursitis, and the tendinitis case was reported as improving on day four post-vaccination, but the total symptom duration was not specified.

3.7. Vaccine failures

There were six reports coded as vaccination failure or meningococcal infection. Of the five reports of meningococcal disease, two were previously published: one with a non-groupable meningococcal strain [25] and one with a suspected serogroup B strain identified during an outbreak, but for which laboratory testing was inconclusive [26]. Another report described an individual with meningococcal B disease, but no documentation of laboratory testing was provided; this case occurred in a person who had only received one dose of MenB-4C and, thus, was not considered a vaccine failure by the reporter. The other two reports did not mention the serogroup; one occurred two years and 74 days after the second MenB-4C dose, and the other occurred at an unknown time after an unspecified number of doses.

3.8. Vaccine administration errors

We reviewed 108 reports with codes that could potentially represent a vaccine administration error; 24 did not report an error and 20 reported an error involving another vaccine given concurrently with MenB-4C. Among the remaining 64 vaccine administration error reports, the most common AE was wrong vaccine administered (n = 18; 28%), representing cases

in which MenB-4C was inadvertently administered instead of another intended vaccine (Table 3). Among the 26 (41%) vaccine administration error reports that included an AE, 19 described common AEs such as ISR.

4. Special populations

4.1. Complement inhibitor (eculizumab) use

We identified one VAERS report that mentioned eculizumab (described above under death reports) [25].

4.2. Pregnancy

Six reports described inadvertent exposure to MenB-4C shortly before or during pregnancy among women ages 16–29 years. A pregnancy in a 29-year-old female diagnosed with Grave's disease who was undergoing treatment with propylthiouracil ended in spontaneous abortion 12 days after vaccination. None of the other pregnancy-related reports described an AE.

4.3. Data mining (disproportionality analyses)

The data mining analyses with age restriction (10–25 years) included a total of 19,300 VAERS reports; of these, 1,201 were MenB-4C reports. We identified disproportionate reporting for injected limb mobility decreased (n = 70) [EBGM: 2.80; EB05, EB95: 2.23, 3.53]. The data mining analyses without age restriction included 143,469 total reports (1,494 MenB-4C reports). In these analyses, we also identified disproportionate reporting for injected limb mobility decreased (n = 40) in individuals ages 10–17 years (EBGM: 4.18; EB05, EB95: 2.88, 5.53).

When we restricted the analyses to serious reports (1,086 total reports; 52 MenB-4C reports), we did not identify disproportionate reporting for any MenB-4C/event combinations.

5. Discussion

Our case series, comprehensively examining U.S. passive surveillance data from over 5.6 million doses of MenB-4C distributed, did not reveal new safety concerns. The large majority of reports submitted to VAERS were classified as non-serious, and the reported AEs were generally consistent with the safety experience identified in clinical studies and those described in the U.S. package insert.

The most commonly reported AEs were ISRs, including injection site pain, erythema, swelling and warmth, and pain in extremity, with reporting rates ranging from 19 to 74 per million doses distributed. In the pre-licensure clinical trials, the most consistently reported local reactions across all MenB-4C studies was injection site pain, with rates as high as 90%. Up to 20–29% of subjects reported severe injection site pain after a MenB-4C dose. Other common local reactions reported in clinical trials included injection site erythema and less frequently induration [5]. Our data mining analyses identified disproportionate reporting for "injected limb mobility decreased." These cases were secondary to ISRs, including extensive

swelling of the vaccinated limb and injection site pain. On October 12, 2017, the sponsor revised the package insert to include extensive limb swelling and injection nodule among adverse reactions identified during post-approval use [27]. This change was based on data from the sponsor's worldwide post-marketing surveillance programs of 170 cases observed following vaccination, many within 24 hours. Most of these events occurred in infants and toddlers, below the age range for which Men4C-B is approved for use in the United States. There was no dose effect noted and the events were often transient [28]. In our review, in which underreporting of mild and labeled events is expected, less than 2% of reports describing local ISRs were classified as serious and less than 1% described local ISRs accompanied by systemic events.

Overall, pyrexia, headache, fatigue, nausea and related signs and symptoms were among the most frequently reported systemic events among those receiving MenB-4C vaccine. Myalgia was also among the most commonly reported systemic events among individuals who received only MenB-4C. In the pre-licensure clinical trials, the most commonly reported solicited systemic reactions included myalgia, fatigue, headache, nausea, and malaise, with severe myalgia reported more frequently when compared to other systemic reactions [29]. Although subjects did not often report fever, there was frequent use of antipyretic/analgesic medications after vaccination (up to 20% in some studies) [5].

In VAERS reports, syncope, another labeled event, was another frequently reported systemic AE following MenB-4C administration. The reporting rate (24 per million doses distributed) was approximately 3.4 times lower than what was found for the quadrivalent HPV vaccine during the first few years post-licensure [30]. However, although the age groups for which HPV vaccine was indicated for use in the United States at that time were similar to those for MenB-4C, HPV vaccine was indicated only for women, whose rates of syncope might be higher, especially among those under age 20 years [31]. Despite the majority (94%) of syncope reports being non-serious, at least 8% of total syncope reports resulted in injury. Moreover, approximately 13% described seizure-like activity, suggestive of convulsive syncope [32]. The relatively high rates of injury and convulsive syncope suggest a need to raise health care provider awareness and revisit adherence to existing safety protocols for both syncope prevention and case management.

The reporting rates for anaphylaxis in our analyses are similar to reporting rates in VAERS for other injectable vaccines [11,33]. Other serious hypersensitivity reactions mostly occurred among patients with predisposing conditions. The serious non-fatal reports that included unlabeled events, such as hypoesthesia, paresthesia, neck pain, and/or dyspnea, corresponded to a diversity of cases with AEs closely related to events, signs, or symptoms included in the current U.S. package insert; with information that did not suggest MenB-4C as the cause or the sole cause of the AE; or with insufficient information to suggest a causal relationship to MenB-4C.

We did not identify any reports of select renal diseases occurring after vaccination with MenB-4C. Active safety surveillance conducted during a mass vaccination campaign in Canada identified an unexpected increased incidence of nephrotic syndrome following MenB-4C vaccination among children ages 2–5 years [34]. A theoretical safety concern

for certain autoimmune diseases had previously been proposed based on detection of Factor H autoantibodies following immunization with MenB-4C [35]. Factor H autoantibodies have been found in persons with complement-mediated diseases such as membranoproliferative glomerulonephritis, C3 glomerulopathies, and membranous nephropathy [36,37]. We did identify nine cases of non-renal immune-mediated diseases temporally associated with MenB-4C administration, including GBS, ITP, MS, ADEM/transverse myelitis, optic neuritis/neuroretinitis, and rheumatoid arthritis. While these cases highlight the difficulty of establishing a causal association in the presence of other relevant concurrent exposures or pre-existing conditions, at this time, the VAERS data do not suggest an increased occurrence of any of these events following MenB-4C administration.

The two deaths reported following MenB-4C administration could not be attributed to the vaccine. The death due to a non-groupable strain of *N. meningitidis* in a patient with paroxysmal nocturnal hemoglobinuria was likely a result of increased susceptibility to meningococcal disease due to treatment with eculizumab [25]. By blocking C5, eculizumab inhibits meningococcal serum bactericidal activity, leaving patients with up to 2000-fold higher risk of meningococcal disease than the general population [38]. Accordingly, the U.S. package insert for eculizumab includes a boxed warning regarding increased risk for meningococcal disease and recommends vaccination with meningococcal vaccines at least two weeks prior to administering the first dose of eculizumab, unless the risks of delaying eculizumab therapy outweigh the risks of developing meningococcal infection [39]. In May 2018, the U.S. package insert for MenB-4C was updated to clarify the increased risk of invasive disease caused by *N. meningitidis* serogroup B in individuals treated with eculizumab even if they develop serum bactericidal antibodies following vaccination with MenB-4C [40]. The U.S. package insert for ravulizumab, another terminal complement inhibitor approved by FDA in December 2018, also includes a boxed warning regarding serious meningococcal infections consistent with that of the eculizumab package insert [41]. In 2020, the ACIP recommended booster vaccination against meningococcal B in persons at increased risk for meningococcal disease; they should receive a dose of the same meningococcal B vaccine one year after completing the primary series and every two to three years thereafter [8].

In our review, the most commonly identified vaccine administration errors included MenB-4C inadvertently administered instead of another intended vaccine. A few reports also described errors related to an inappropriate route or site of administration, extra doses administered, interchange of vaccine products or inappropriate administration. Although vaccine administration errors frequently do not cause AEs, some do and these errors are preventable. Vaccine administration errors have an impact in terms of additional costs, possible effect on immunological protection, patient/parent inconvenience, and loss of confidence in the health care delivery system [42]. We also identified a few reports consistent with shoulder injury. When injecting a vaccine into the deltoid muscle, care should be taken to ensure that the injection is placed in the thick, centrally located portion of the muscle, away from the upper third of the deltoid where the risk of over penetration into underlying structures of the shoulder is greatest [43].

Strengths of our study include the use of VAERS, which has a national scope and proven ability to detect rare AEs. However, VAERS shares the inherent limitations of all passive surveillance systems, including underreporting, selective reporting (serious events and events occurring in close proximity with vaccination are more likely to be reported), lack of a control group, inadequate denominator data to calculate AE rates, diagnostic uncertainty of events, and duplicate reporting. More importantly, consistent with the purpose of VAERS in generating (not testing) hypotheses, an established or probable causal relationship between a vaccine and an AE is not required for reporting. VAERS reports are not formal case reports, but non-standardized descriptions of signs and symptoms temporally associated with vaccination. Whereas some AEs reported to VAERS are likely caused by the vaccine of interest, others may be related to an underlying disease or condition, to drugs or other vaccines given concurrently, or to a chance occurrence shortly after vaccination [10]. Although we made efforts to exclude duplicate and miscoded reports identified during the review process, reports that were not included in the manual review may have included duplicates.

6. Conclusions

Our review of VAERS data in the four years after U.S. MenB-4C licensure did not reveal new safety concerns. The vast majority of reports were classified as non-serious and reported AEs that were generally consistent with the safety experience described in clinical studies and the U.S. package insert. While our results are reassuring, continued post-marketing surveillance is warranted. The relatively increased sequelae of syncopal episodes suggest that health care systems and providers should increase adherence to the ACIP recommendations for a routine 15-minute waiting period following vaccination and implement strategies to improve case management of syncope.

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Abbreviations:

ADEM	Acute disseminated encephalomyelitis
AEs	Adverse events
ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
EBGM	Empirical Bayes Geometric Mean
GBS	Guillain-Barré syndrome

ITP	Immune thrombocytopenia
IND	Investigational new drug
IQR	Interquartile range
ISR	Injection site reaction
MRI	Magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal serogroups A, C, W, and Y
MS	Multiple sclerosis
MenB-4C	Four-component Neisseria meningitidis serogroup B vaccine
MGPS	Multi-Item Gamma Poisson Shrinker
PTs	Preferred Terms
FDA	U.S. Food and Drug Administration
VAERS	Vaccine Adverse Event Reporting System
HPV	Human papillomavirus

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Table 1

Description of U.S. MenB-4C reports received by the Vaccine Adverse Event Reporting System (VAERS) from January 23, 2015 through December 31, 2018.

	Reports; n (%)[$]			
	All	**Non-serious**	**Serious non-fatal[¥]**	**MenB-4C only**
Total reports[e]	1,867 (100)	1,785 (100)	80 (100)	1,122 (100)
Age group (years)				
≤9	13 (1)	12 (1)	1 (1)	8 (1)
10–17	832 (45)	795 (45)	36 (45)	373 (33)
18–25	667 (36)	642 (36)	25 (31)	450 (40)
≥26	47 (3)	43 (2)	4 (5)	25 (2)
Unknown	308 (16)	293 (16)	14 (18)	266 (24)
Sex				
Female	1,094 (59)	1,053 (59)	40 (50)	680 (61)
Male	609 (33)	572 (32)	36 (45)	300 (27)
Unknown	164 (9)	160 (9)	4 (5)	142 (13)
Adverse event onset (days)				
0	866 (46)	830 (46)	36 (45)	451 (40)
1	327 (18)	319 (18)	8 (10)	181 (16)
≥2	199 (11)	177 (10)	22 (28)	107 (10)
Unknown	475 (25)	459 (26)	14 (18)	383 (34)
Year received in VAERS				
2015	50 (3)	45 (3)	5 (6)	33 (3)
2016	559 (30)	533 (30)	26 (33)	346 (31)
2017	595 (32)	569 (32)	24 (30)	343 (31)
2018	663 (36)	638 (36)	25 (31)	400 (36)

Abbreviations: MenB-4C, Four-component meningococcal group B vaccine; Tdap, Tetanus-diphtheria-acellular pertussis.

[$]Percentages may not add up to 100% due to rounding.

[¥]Excludes death reports (n = 2).

[e] Based on information included in initial reports

Table 2

Most frequently reported MedDRA Preferred Terms (PTs) in U.S. MenB-4C reports received by the Vaccine Adverse Event Reporting System (VAERS) from January 23, 2015 through December 31, 2018.

	n(%)				Reporting rate (all)[£]
	All	Non-serious	Serious non-fatal[¥]	MenB-4C only	
Total reports	1,867 (100)	1,785 (100)	80 (100)	1,122 (100)	-
MedDRA Preferred Term[C]					
Injection site pain	414 (22)	406 (23)	8 (10)	286 (25)	74
Pyrexia	306 (16)	279 (16)	27 (34)	199 (18)	54
Headache	297 (16)	275 (15)	21 (26)	175 (16)	53
Injection site erythema	276 (15)	272 (15)	*	177 (16)	49
Pain in extremity	272 (15)	261 (15)	10 (13)	158 (14)	48
Nausea	257 (14)	236 (13)	20 (25)	149 (13)	46
Injection site swelling	237 (13)	233 (13)	*	152 (14)	42
Pain	227 (12)	218 (12)	8 (10)	151 (13)	40
Dizziness	223 (12)	209 (12)	14 (18)	106 (9)	40
Chills	161 (9)	146 (8)	15 (19)	97 (9)	29
Fatigue	159 (9)	149 (8)	9 (11)	104 (9)	28
Syncope	136 (7)	129 (7)	*	*	24
Erythema	134 (7)	132 (7)	*	83 (7)	24
Vomiting	132 (7)	116 (6)	15 (19)	74 (7)	23
Injection site warmth	105 (6)	103 (6)	*	69 (6)	19
Myalgia	*	*	*	66 (6)	17
Asthenia	*	*	19 (24)	*	16
Malaise	*	*	*	*	14
Hypoesthesia	*	*	12 (15)	*	11
Paresthesia	*	*	12 (15)	*	14
Dyspnea	*	*	11 (14)	*	7
Gait disturbance	*	*	11 (14)	*	4
Neck pain	*	*	8 (10)	*	12

	n(%)				Reporting rate (all)[£]
	All	Non-serious	Serious non-fatal[¥]	MenB-4C only	
Vaccination complication	*	*	8 (10)	*	9

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; MenB-4C, Four-component meningococcal group B vaccine

[*] Adverse events not among the ten most frequently reported.

[£] Reports per million doses distributed.

[¥] Excludes death reports (n = 2).

[c] Based on information included in initial and follow-up reports.

Table 3

Types of vaccine administration errors reported involving MenB-4C reports received by the Vaccine Adverse Event Reporting System (VAERS) from January 23, 2015 through December 31, 2018.

Type of vaccine administration error	n
Total	64
Wrong vaccine administered; MenB-4C given instead of:	18
MenACWY (n = 10)	
Other vacine not specified (n = 3)	
Tdap (n = 2)	
Hepatitis A (n = 1)	
Hepatitis B (n = 1)	
Pneumococcal (n = 1)	
Extra doses administered (>2 doses of MenB-4C)	10[§]
Inappropriate site of administration	8
Arm, but not deltoid muscle (n = 6)	
Leg (n = 2)	
Inappropriate age	7[¥]
Storage and handling	6
Deviation from storage temperature (n = 6)	
Inappropriate vaccine schedule	5
Second dose given sooner (n = 3) or later (n = 2) than indicated	
Incorrect route of administration	4
Subcutaneous (n = 4)	
Interchange of meningococcal vaccines	3
MenB-4C given after a previous dose of MenB-FHbp (n = 3)	
Expired product administered	2
Contraindication or warning/precaution to vaccination	
Pre-existing latex allergy (n = 1)	1

Abbreviations: MenACWY, Meningococcal serogroups A, C, W, and Y vaccine; MenB-FHbp, Bivalent meningococcal group B vaccine; MenB-4C, Four-component meningococcal group B vaccine; Tdap, Tetanus-diphtheria-acellular pertussis.

[§]Five reports from the same provider.

[¥]Three reports with vaccine administered to individuals for whom the vaccine is not indicated in the U.S. (ages 5, 28, 58 years) and four to individuals younger (ages 11–14 years) than recommended by the Advisory Committee on Immunization Practices.