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Current Safety Issues with Quadrivalent Meningococcal Conjugate Vaccines

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Abstract

Invasive meningococcal disease, although rare, can present as sudden, life-threatening disease with high risk of mortality or severe long-term sequelae. The main prevention strategy for invasive meningococcal disease in the United States is the routine vaccination of adolescents and other persons at increased risk of meningococcal disease with quadrivalent meningococcal conjugate vaccines. Two such vaccines are currently licensed and available in the United States, Menactra® (Sanofi Pasteur) and Menveo® (Glaxo Smith Kline), and usage in the adolescent population have steadily increased since their introduction. Although early reports raised concerns about a possible association of Menactra with Guillain-Barré syndrome, a comprehensive safety review determined that if such risk existed it was no more than 0.66 cases per 1 million vaccinations. More recently, a study found an elevated risk of Bell's palsy when Menveo was administered concomitantly with other vaccines but no association was found when the vaccine was administered alone. In this commentary, we describe the current state of knowledge with respect to the safety of quadrivalent meningococcal conjugate vaccines, and we identify potential areas for safety research for these vaccines.

Keywords

meningococcal vaccines, immunization safety, meningococcal quadrivalent conjugate vaccines

Introduction

Quadrivalent meningococcal polysaccharide-protein conjugate vaccine (MenACWY) has been in use in the United States for over a decade as a key component of the public health strategy to prevent meningococcal disease. The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with MenACWY as part of an adolescent vaccination platform to be administered at 11 to 12 years of age, along with vaccines to prevent pertussis, human papillomavirus-associated cancers, and influenza (if the timing of the adolescent visit falls within seasonal influenza vaccine availability). Recently, an additional adolescent immunization platform has been proposed as a means to improve pre-college coverage by increasing uptake of the MenACWY booster recommended at age 16 years, to provide an opportunity for healthcare providers to discuss vaccination with meningococcal serogroup B vaccine, and to identify prior missed opportunities for other vaccines thereby allowing an opportunity for "catch up" to the recommended schedule.[1] All vaccines which are currently licensed and available for use in the United States for protection against meningococcal disease are shown in Table 1; however, this review will discuss only the quadrivalent meningococcal conjugate vaccines.

With the current renewed emphasis on increasing the uptake of MenACWY, it is timely to review knowledge gaps in the safety of MenACWY vaccines. In addition to guiding future research efforts, this serves not only to refine our understanding of the risk/benefit profile of MenACWY vaccine, but also to inform healthcare providers and policy makers as well as parents and vaccinees.

Pre-licensure Safety Data

As described in Table 1, two MenACWY vaccines are currently licensed and available in the United States: Menactra® (approved for use in individuals 9 months to 55 years of age, manufactured by Sanofi Pasteur) and Menveo® (approved for use in individuals 2 months through 55 years of age, manufactured by Glaxo Smith Kline). Safety data collected during the pre-licensure studies did not indicate any major safety signals for either vaccine.[2,3] The tolerability profile of both vaccines was considered to be adequate. Patients experienced

similar frequencies of solicited local reactions and systemic adverse events when compared to either a previously approved meningococcal polysaccharide vaccine or to other approved routine vaccines.[2,3]

Post-licensure Safety Experience

Reports to VAERS

The Vaccine Adverse Event Reporting System (VAERS) is a spontaneous reporting system co-administered by the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Reports are accepted from any source, and the data collected include demographic information, vaccine(s) and date of receipt, adverse event experienced, and medical history.[4] Reviews of reports to VAERS following receipt of Menactra and Menveo have discussed mainly findings of local injection site reactions and systemic adverse events.[5,6] The most frequently reported adverse events for Menactra were fever, headache, injection site erythema, and dizziness.[5] For Menveo, injection site erythema, swelling, warmth and pain were most commonly reported as well as dizziness.[6] For both vaccines, syncope was also one of the most frequently reported adverse events[5,6]; this is not an unexpected finding, as syncope following vaccination is a known risk particularly in the adolescent population that is recommended for routine vaccination against meningococcal disease.[7] Limited numbers of reports have been submitted for vaccination during pregnancy, but review of these has thus far not indicated any cause for concern.[6,8]

Guillain-Barré syndrome

In the year following the recommendation of Menactra for routine vaccination in adolescents, VAERS received eight reports of Guillain-Barré syndrome (GBS) following vaccination with Menactra.[9,10] Following this safety signal, two retrospective cohort studies evaluated the risk of GBS after vaccination with Menactra in adolescent populations.[11,12] No incident cases of GBS were observed in either study in the 6 weeks following vaccination after a total of 2.3 million doses of vaccine. The attributable risk of GBS following vaccination in the combined populations of these two studies was estimated not to exceed 0.66 case per 1

million vaccinations, if such a risk exists.[12] This compares with estimates of the annual population incidence of GBS which range from 0.4 – 4 per 100,000 persons, depending on population, geographic location, and age.[13,14]

To address the lack of evidence regarding the risk of recurrent GBS following vaccination, a retrospective cohort study of vaccination in persons with a history of GBS was conducted in a large, integrated managed care setting.[15] Over the 11 year study period, the risk of recurrent GBS was low with only one recurrent episode of GBS found in an individual who had received measles-mumps-rubella vaccine 4 months prior; of the seven patients who had histories of GBS and subsequently received MenACWY in the study (unspecified, but likely Menactra as it was the only marketed MenACWY during the study period), there was no evidence of recurrence of GBS.[15]

Bell's palsy

Recently, Tseng et al. reported a post-marketing study which utilized a self-controlled case-series analysis conducted at Kaiser Permanente Southern California (SCK) during September 2011 to June 2013.[16] These investigators evaluated 26 pre-specified adverse events identified through electronic medical records 1 year after receipt of Menveo vaccination in a cohort aged 11 to 21 years. This study found a statistically significant association with Bell's palsy when Menveo was administered concomitantly with other vaccines but no association was found when the vaccine was administered alone; attributable risks were not reported. The study employed a longer risk interval (84 days) than utilized in previous studies, where risk windows were set to days 1--14, 1--28, or 29--56.[17,18] Tseng et al. did not specify whether a cluster analysis was performed on the entire risk period.[16]

Annually in the overall VSD data we observe a marked uptake of MenACWY in August, coincident with adolescents return to school after the summer break (CDC unpublished). With added potential for seasonality in the occurrence of Bell's palsy, a finer adjustment for seasonality in the analysis may be needed to clarify the actual risk of Bell's palsy following receipt of Menveo (and Menactra). As noted by Tseng and

colleagues, disentangling the effect of concomitant vaccines versus single administration of Menveo presents a methodologic challenge given that MenACWY is often administered with other vaccines on the adolescent schedule.[16]

Administration Errors

Vaccination administration errors reported soon after the introduction of new vaccines can be a consequence of unfamiliarity of healthcare providers with requirements for appropriate administration of new products. Although vaccination errors are rarely the cause of a serious safety problem, patients may remain unprotected against disease. Additional doses, if indicated, may lead to more vigorous local reactions, additional cost and inconvenience to the patient (or parent), and a loss of trust in the provider.

During the first year of Menactra's licensure in the United States, clusters of inadvertent subcutaneous (SC) misadministration of Menactra were reported involving 101 persons in seven states.[19] The subsequent investigation of these clusters included a telephone survey of vaccinees as well as a serologic assessment of responses in those having received Menactra via SC injection as compared to the licensed intramuscular (IM) route; results indicated that persons vaccinated by the SC route were sufficiently protected, that revaccination was not necessary, and that misadministration of Menactra was due to providers' unfamiliarity with administering Menactra by the licensed IM route compared with long experience with the SC administration of Menomune® (quadrivalent meningococcal polysaccharide vaccine, Sanofi Pasteur).[19]

For Menveo, administration errors have occurred due to incorrect preparation of the vaccine. The vaccine is provided in two vials, one containing the serogroup A component in lyophilized form and one containing serogroups C, Y, and W-135 components in liquid form; prior to injection, the liquid component must be drawn into a syringe and used to reconstitute the lyophilized component.[4] After a targeted search for reports of single component administration of Menveo in VAERS, 390 reports were found of this type of administration error during March 2010-September 2015.[20] The authors of the report of these findings advised that a properly prepared, repeat dose of Menveo should be administered to those having received

incorrect preparations; this dose can be given at any time.[20] Occurrence of vaccine administration errors were also identified in a statistical analysis of all Menveo reports to VAERS.[6]

Further Research Needs

The post-marketing assessments of the two MenACWY vaccines to date have been reassuring; however, the data are sparse and a more comprehensive safety assessment is indicated for each of the vaccines. For Menactra, while there was an early focus on reports of GBS, there has not been a formal descriptive summary of VAERS reports nor any further evaluation specific outcomes following Menactra since the end of real time surveillance (rapid cycle analysis) in VSD.[5] Therefore, VSD has initiated a comprehensive study to improve knowledge of the Menactra's safety profile. As for Menveo, the recently published review of VAERS reports and a published post-marketing study, both mentioned above, are collectively reassuring.[6,16] However, as the investigators of the latter study commented, the association between vaccination and Bell's palsy needs further investigation.[16] With substantial doses of Menveo now included in the VSD database, such an analysis is now being planned.

Additional areas that warrant consideration for research with respect to safety outcomes include receipt of MenACWY concomitant with other vaccines and receipt of MenACWY during pregnancy. As the adolescent immunization platform expands, it will be useful to understand better the risk of adverse events following vaccination with MenACWY administered concurrently with other vaccines in the adolescent schedule; the Bell's palsy finding for Menveo is one example of this need. MenACWY is not routinely recommended during pregnancy; however, it may be administered when indicated. While the limited number of reports to VAERS thus far have not indicated concerns, additional review of the safety of MenACWY administration during pregnancy is needed. Addressing these knowledge gaps will provide a more complete picture of the safety profile of these quadrivalent meningococcal conjugate vaccines that are widely administered to adolescents and other populations at-risk of meningococcal disease.

Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1. Current US-licensed Meningococcal Vaccines

Trade Name	Serogroup	Type of Vaccine	Original Licensure Year	Approved Usage
Menactra	A, C, W, Y	Conjugate – diphtheria toxoid	2005	9 months – 55 years
Menveo	A, C, W, Y	Conjugate – CRM_{197}	2010	2 months – 55 years
Trumenba	B	Recombinant	2014	10 years – 55 years
Bexsero	B	Recombinant	2015	10 years – 55 years