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## Editorial

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# Eculizumab package insert recommendations for meningococcal vaccinations: call for clarity and a targeted approach for use of the drug in neuromyelitis optica spectrum disorder

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The Food and Drug Administration (FDA) recently approved Soliris (Eculizumab) for the treatment of neuromyelitis optica spectrum disorder (NMOSD). The approval of eculizumab came with a black box warning for serious meningococcal infections and a mandated Risk Evaluation and Mitigation Strategy. To mitigate the risk of meningococcal meningitis with the use of eculizumab, 2 vaccine types which cover different serogroups, MenB and MenACWY, respectively, ought to be administered prior to administration of the drug. Neither the package insert for eculizumab nor the Soliris Risk Evaluation and Mitigation Strategy Prescriber Safety Brochure specify which of these vaccines a patient should receive or whether the vaccine schedule must be completed prior to therapy or if the patient ought to receive only the first dose. Alexion, the manufacturer of eculizumab has instead deferred the vaccination protocol to the Advisory Committee on Immunization Practice (ACIP) guidelines on the product label. This potentially leads to confusion when there are separate guidelines for each vaccine and multiple revisions of each. Additionally, it does not seem clear that the protocols used in the clinical trials used to approve eculizumab reflect current ACIP guidelines. Given the risk for morbidity and mortality associated with meningococcal infections, we urge Alexion to provide clarity and accuracy in their product labeling regarding vaccine requirements because the only FDA-approved drug for aquaporin-4 antibody disease, eculizumab, must not risk being discarded or sidelined owing to potential complications arising out of poorly defined vaccination guidelines.

In June 2019, the U.S. Food and Drug Administration (FDA) approved Soliris (Eculizumab) for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who have antibodies to aquaporin-4 (AQP4). In a phase 3, randomized, double-blind, placebo-controlled, time-to-event trial Prevention of Relapses in Neuromyelitis Optica (PREVENT), the efficacy and safety of eculizumab were evaluated in patients with AQP4-IgG–positive NMOSD. Eculizumab met its primary endpoint of prolonging time to first adjudicated relapse as well as reducing the risk of relapse.[1] The FDA approval followed an expedited 6-month prioritized review. Eculizumab, a first-in-class complement inhibitor and a humanized monoclonal antibody, targets complement C5 inhibiting cleavage into C5a and C5b preventing the formation of the membrane attack complex (MAC) that destroys cell membranes. Given the high proportion (73%) of AQP4-IgG positive patients that comprise NMOSD, physicians and patients alike welcomed the FDA approval of a drug for use in an orphan disease.[2] However, vaccination guidelines must be succinct and precise to mitigate risks inherent to complement inhibition that eculizumab administration potentially engenders.

The use of eculizumab can be associated with life-threatening and fatal meningococcal infection. Meningococcal meningitis is caused by *Neisseria meningitidis* which may be encapsulated or unencapsulated. The most invasive *N. meningitidis* organisms are encapsulated, or surrounded by a polysaccharide capsule which is used to classify the organism into 1 serogroups. Most infections are caused by 1 of 6 serogroups, A, B, C, W135, X, and Y.[3] In the United States, serogroups B and C are the most common (Figure 1). Because this is a life-threatening complication warranting a black box warning in the package insert for the drug, the FDA requires that physicians and patients participate in a Risk Evaluation and Mitigation Strategy (REMS) program to ensure mitigate the risks. The drug increases a patient's susceptibility to serious meningococcal infections such as septicemia and meningitis, and increases the risk of meningococcal disease by 1000- to 2000-fold, compared to the general U.S. population annual rate of meningococcal disease.[4] Of note, between the years 2008 and 2016, 16 cases of meningococcal disease were identified in eculizumab-treated patients and fourteen had received at least 1 dose of meningococcal vaccine before disease onset.[5] This should give pause to the theory of administering just 1 dose of the vaccine prior to initiation of eculizumab—in a pilot study for eculizumab, patients received only 1 dose of MenACWY prior to starting therapy. The protocol for the phase 3 trial does not specify which vaccines were used or how many doses were given.[1,6]

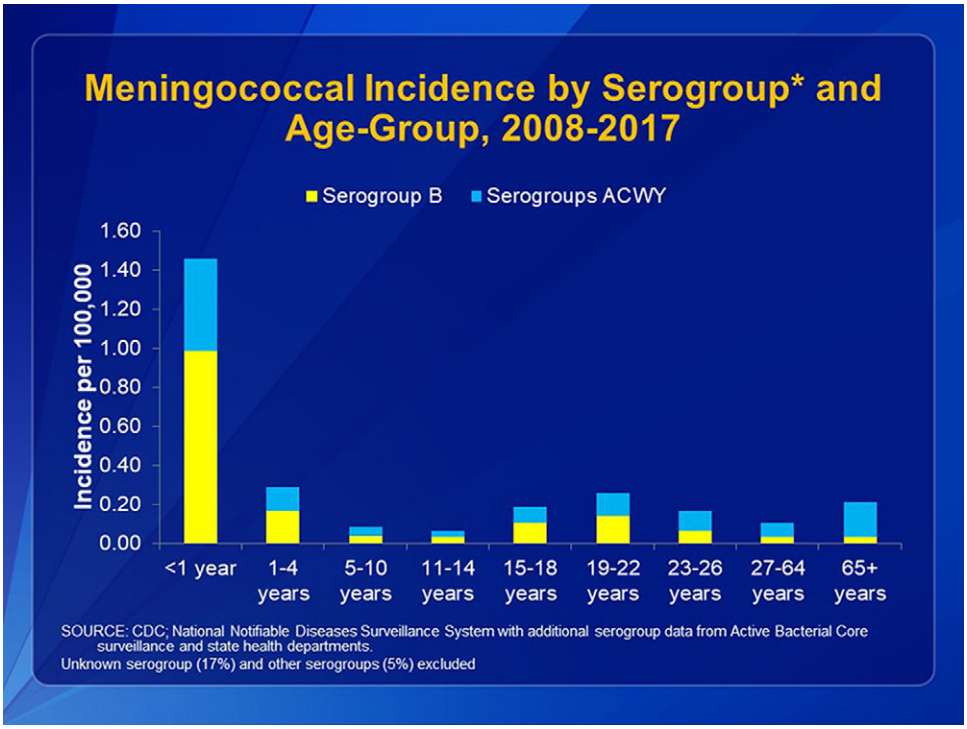


**Figure 1.** Incidence rates (per 100 000 persons) of meningococcal disease caused by serogroup B compared to serogroups A, C, W, and Y by age group from 2007 to 2017 (adapted from CDC disease trends).

Physicians are aware that NMOSD is a devastating disease that can cause irreversible disability, but meningococcal infections can be deadly and hence the specifics of meningococcal vaccinations must be laid out in no uncertain terms for eculizumab use in NMOSD.

In the original package drug insert put out by Alexion Pharmaceuticals, the company that makes eculizumab, advises physicians that vaccination protocols as recommended by the Advisory Committee on Immunization Practices (ACIP) be followed. However, it does not specify which publication carries such recommendations. In short, there is no single reference that one can check or verify to arrive at a reasonable decision. According to the package insert, vaccination is mandatory at least 2 weeks prior to receiving the first dose of the drug. Revaccination is recommended according to ACIP recommendations for meningococcal vaccination for vaccine use. What those guidelines entail remain unclear. More clarity on the exact bibliography would certainly be of help. For instance, in 1 publication, ACIP recommends routine vaccination with 1 of 2 serogroup B meningococcal (MenB) vaccines, in persons 10–25 years, using MenB-FHbp (Trumenba) and MenB-4C (Bexsero). Furthermore, vaccination is recommended in persons aged >10 years who are at increased risk for serogroup B meningococcal disease (category A recommendation) including those who have persistent complement component deficiencies. Further ACIP recommendations include either a 3-dose series of MenB-FHbp or a 2-dose series of MenB-4C.[7] To summarize, ACIP guidelines may not provide information on the use of both MenACWY and MenB vaccines unless one references the "correct version" and the recommendations found in these references may not have been followed in the protocols/studies which brought the drug to market for NMOSD.

Additionally, Alexion pharmaceuticals generated another separate guidance on their website for generalized myasthenia gravis (https://solirisgmg.com) to advise physicians specifically about meningococcal vaccinations, separate and removed from the original package insert. This link recommends the use of 2 types of meningococcal vaccinations—MenACWY and MenB because each vaccination type protects against different meningococcus serogroups. The recommendations include completion of 2 doses of at least 2 months apart for MenACWY vaccination. For MenB vaccination, either MenB-4C consisting of 2 doses at least 1 month apart or MenB-FHbp, 3 doses at 0, 1–2, and 6 months, respectively, is recommended. All adult patients undergoing complement inhibition receive MenACWY booster every 5 years. This additional and specific information is absent in the package insert and physicians who go by the recommendations of the original package insert may miss vaccinating their patients against MenACWY.

## Conclusions and Recommendations

The issues described herein are threefold: (1) Alexion pharmaceuticals deferred vaccine recommendations to ACIP but the company itself did not follow these recommendations in clinical trials leaving the true risk of meningococcal infection unknown; (2) Alexion pharmaceuticals does not reference which ACIP guidelines to follow and theses guidelines are spread across multiple recommendation statements; (3) Alexion pharmaceuticals has deferred the vaccination issues to the treating physician—which serogroups should be covered, which schedules to follow, and whether or not the schedule must be completed prior to therapy initiation are at the discretion of the provider. To avoid confusion about specific recommendations, Alexion pharmaceuticals should publish package inserts that are updated and current. The specifics of vaccine requirements should also be described in the REMS program for the medication. Any additional material added should be linked to the original document to avoid confusion. When administering, the drug warrants a black

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box warning and requires a REMS program therefore, guidelines must be written and followed very accurately. In the interest of patient safety and concern that eculizumab may fail if used incorrectly without proper vaccination protocols, we urge Alexion pharmaceuticals to reevaluate product labeling for eculizumab and update the vaccine requirements accordingly.

Finally, a final recommendation would be that akin to the use of eculizumab in transplanted kidney patients,[8] which recommends use of the drug only in those with confirmed C5 activation and deposition of MAC in transplanted kidney tissue, patients with NMOSD too must be stratified based on C5 activation and MAC deposition. Such a targeted approach is possible with the use of novel assays that use patient sera to study C5 convertase activity and MAC formation.[9] If validated in prospective studies the use of such an assay would help identify subpopulations of AQP4-positive NMOSD patients who are likely to benefit from the use of eculizumab, optimizing its use.

**Disclosure.** The authors do not have anything to disclose.

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