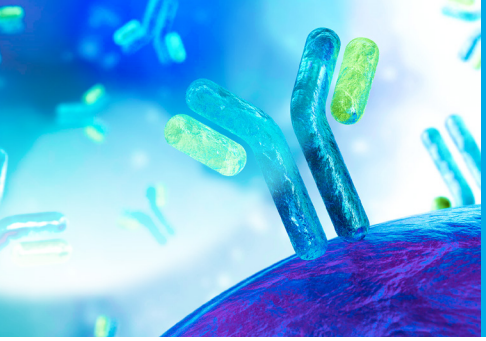

AAN Practice Guideline Summary for **Clinicians**

Practice Guideline Update: Vaccine-preventable Infections and Immunization in Multiple Sclerosis

This is a summary of the American Academy of Neurology (AAN) practice guideline, "Update: Vaccine-preventable Infections and Immunization in Multiple Sclerosis," which was published in *Neurology*® online on August 28, 2019, and appears in the September 24, 2019, print issue.

Please refer to the full guideline at AAN.com/guidelines for more information, including full descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

Note: Dimethyl fumarate, teriflunomide, and daclizumab were added January 2017 and rituximab in March 2018 (at literature search update). Because daclizumab was recently recalled from the market, it is omitted from recommendation statements.

Recommendation 1

Rationale

There is no definite evidence suggesting that vaccination increases the risk of multiple sclerosis (MS), although a link cannot be completely excluded given the paucity of relevant data. Vaccinations against human papillomavirus (HPV), tetanus toxoid, pertussis, and small pox were associated with a lower likelihood of a subsequent MS diagnosis. Vaccine-preventable infections can be associated with morbidity and mortality. Patients with MS are often concerned about the safety of immunizations and may have questions regarding immunizations, including their effect on MS, interactions with MS treatments, adverse effects, and payer coverage. An ongoing dialogue regarding immunization will help clinicians to understand patients' beliefs and preferences and help patients make choices regarding immunizations.

Level	Recommendation
Level B	Clinicians should discuss with their patients the evidence from the systematic review regarding immunization in MS. Clinicians should explore patients' opinions, preferences, and questions regarding immunizations at clinical visits to be able to effectively address the optimal immunization strategy for each patient, in keeping with the patient's MS status, values, and preferences.

Recommendation 2

Rationale

All unvaccinated individuals are at a higher risk of acquiring vaccine-preventable infections. Although there is no evidence that MS alone increases the risk of acquiring vaccine-preventable infection, individuals with MS have at least the same risk as unvaccinated individuals without MS. Individuals with MS receiving immunosuppressive therapy as part of MS treatment may be at an increased risk of infections. There is no evidence that vaccination increases the risk of MS exacerbation, although the literature is sparse. In addition to conferring personal benefits, vaccination of the MS patient population contributes to the well-established phenomenon of herd immunity for the communities in which they live.[1] Thus, vaccination of patients with MS is expected to have personal and population-level benefits.

Level	Recommendation
Level B	Clinicians should recommend that patients with MS follow all local vaccine standards (e.g., from the US Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and local regulatory bodies) unless there is a specific contraindication (e.g., active treatment with immunosuppressive or immunomodulating [ISIM] agents).

Recommendation 3

Rationale

Prevalence of vaccine-preventable diseases and seropositivity for them vary by country and region, and recommendations for immunization also vary. The use of bacille Calmette-Guérin (BCG) vaccination in routine immunization schedules is limited and is not common in adults. The WHO recommends that in countries or settings with a high tuberculosis incidence or high leprosy burden or both, a single dose of BCG vaccine should be given to all healthy neonates at birth.[2] If BCG vaccine cannot be given at birth, it should be given at the earliest opportunity thereafter. Countries with low incidence of tuberculosis or leprosy may choose to vaccinate neonates selectively in groups at high risk for tuberculosis or leprosy or both. The WHO recommends BCG vaccination in older age groups for unvaccinated individuals who (1) test negative on tuberculin skin test or interferon-γ release assay, (2) have no evidence of prior infection, and (3) live in settings with high tuberculosis or leprosy or both, are moving to such settings, or work in occupations that put them at risk (e.g., health care, laboratory, prison settings).[3] The CDC recommendations for BCG are limited to children and adults in specific clinical situations.[4] This region-specific disease epidemiology informs the risk–benefit discussion of vaccination in MS. In cases where local risks of infection are particularly high, vaccination benefits for people with MS—even with live vaccines and immunomodulatory therapy—may outweigh vaccination risks.

Level	Recommendation
Level B	Clinicians should weigh local risks of vaccine-preventable diseases when counseling individuals with MS regarding vaccination.

Recommendation 4

Rationale

MS exacerbations are associated with increased short- and long-term disability.[5] Although the systematic review found insufficient evidence to support or refute an association between a history of influenza infection and MS exacerbations, one study not meeting criteria for the systematic review found that influenza infections increase exacerbation risk compared with vaccination.[6] Influenza infections may also cause increased morbidity and mortality for individuals on whom chronic diseases have had a severe impact. There is also insufficient evidence to support or refute an association between influenza vaccination and MS exacerbations. With (1) known risks of exacerbation and other morbidity with influenza infection and (2) no identified risks of exacerbation with influenza vaccines, benefits of influenza vaccination outweigh the risks in most scenarios, although patients with MS receiving some ISIM treatments (fingolimod, glatiramer acetate, mitoxantrone) may have a reduced response to influenza vaccination. Although the systematic review identified no evidence regarding vaccine response in individuals with MS receiving rituximab, evidence regarding rituximab use in neuromyelitis optica spectrum disorders[7] and in rheumatoid arthritis[8] suggests that rituximab can be associated with reduced influenza vaccine responsiveness.

Level	Recommendation
Level B	Clinicians should recommend that patients with MS receive the influenza vaccination annually, unless there is a specific contraindication (e.g., prior severe reaction).

Recommendation 5

Rationale

Immunosuppressive or immunomodulatory medications now used to treat MS include alemtuzumab, dimethyl fumarate, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, and teriflunomide. These treatments have been associated with severe occurrences or recurrences or both of vaccine-preventable infections, including varicella zoster virus (VZV) and hepatitis B.[9–14] Although the panel identified no studies showing an increased risk associated with immunization with live vaccines in patients with MS receiving ISIM medications, studies regarding the safety of live vaccines during MS treatment with ISIM medications are scarce. Many package inserts approved by the US Food and Drug Administration provide specific guidance regarding immunization with live vaccines and treatment with these pharmacologic therapies. The prescribing information (PI) for fingolimod recommends VZV vaccination of patients with MS who are antibody-negative at least one month before treatment to permit the immune response to develop.[15] Fingolimod PI also recommends avoiding live vaccines during treatment and for two months after discontinuation.[15] The PI for teriflunomide recommends against using live vaccines during treatment and for six months after discontinuation.[16] For alemtuzumab, the PI recommends against the use of live vaccines for six weeks before treatment initiation, during treatment, and after "recent" treatment.[16] The PI for ocrelizumab recommends vaccinating according to immunization guidelines at least four weeks before starting ocrelizumab for live or live-attenuated vaccines and at least two weeks before starting ocrelizumab for non-live vaccines, when possible. The PI also recommends avoiding vaccination with live-attenuated or live vaccines during treatment and after discontinuation until B-cell repletion has occurred. Non-live vaccines can be administered if needed before recovery of B cells after depletion, but immune response to the vaccine should be assessed to confirm immunoprotection.[17]

Level	Recommendation
Level B	Clinicians should counsel patients with MS about infection risks associated with specific ISIM medications and treatment-specific vaccination guidance according to the prescribing instructions for ISIM medications when one of these treatments is being considered for use.
Level B	Physicians should assess or reassess vaccination status of patients with MS before prescribing ISIM therapy and should vaccinate patients with MS, according to local regulatory standards and guided by treatment-specific infectious risks, at least four to six weeks before initiating ISIM therapy as advised by specific prescribing information.

Rationale

As previously noted, ISIM medications now used to treat MS are associated with severe occurrences or severe recurrences or both of vaccine-preventable infections, including VZV and hepatitis B,[9–15] and their manufacturers' PIs have treatment-specific guidance for immunization with live vaccines.[15–18] Use of ISIM therapies to treat MS is increasing, and many patients with MS will require one of these treatments at some point in their disease course. Vaccination of patients with MS in advance of the decision to use ISIM therapy will prevent the four- to six-week delays between immunization with live vaccines and initiation of treatment with these medications.

Level	Recommendation
Level C	Clinicians may discuss the advantage of vaccination with patients as soon as possible after MS diagnosis, regardless of initial therapeutic plans, to prevent future delays in initiation of ISIM therapies.

Recommendation 6

Rationale

Because of inconsistencies in vaccination approaches, variations in vaccination standards by country (e.g., for tuberculosis), and increased infection risks with ISIM medications, PI for ISIM medications often recommends screening for latent vaccine-preventable infections.[19–22] Because of occurrence of tuberculosis infections in studies of teriflunomide, the teriflunomide PI advises clinicians to screen patients for latent tuberculosis before initiating treatment with teriflunomide.[16] The PI also recommends treatment for tuberculosis in patients who test positive for tuberculosis before initiating teriflunomide treatment.[23] The PI for alemtuzumab recommends tuberculosis screening according to local guidelines.[18] Although the PI for other ISIM medications does not provide tuberculosis-specific guidance, because of the mechanisms of action for these medications, other ISIM medications are also likely to be associated with an increased risk of activation of latent tuberculosis. Severe active/chronic infections such as tuberculosis and hepatitis infection are listed as contraindications to fingolimod by the European Medicines Agency.[24] The risk of latent tuberculosis varies by country.

Pivotal trials for many of these ISIM medications were performed at centers where latent tuberculosis is likely to be less frequent (e.g., in North America and Europe), potentially resulting in an underestimation of the activation risk of latent tuberculosis from the use of ISIM medications other than teriflunomide.

The PI for ocrelizumab requires hepatitis B virus screening before the first dose and states that active hepatitis B infection is a contraindication to use. For hepatitis B carriers, consultation with a liver disease specialist is recommended before treatment.[17] Alemtuzumab PI notes that no information on hepatitis B or C reactivation risk is available for patients with active or chronic hepatitis infection because those patients were excluded from alemtuzumab studies. The PI recommends consideration of screening patients at high risk of hepatitis B or C infection before initiating alemtuzumab and caution in prescribing alemtuzumab to carriers because of risks.[18] The alemtuzumab PI also notes a higher incidence of herpes viral infections in patients treated with alemtuzumab, including oral and genital herpes, herpes zoster, herpes simplex, primary varicella, and herpes meningitis.[18] The PI for alemtuzumab recommends assessment for a history of varicella or vaccination against VZV before treatment initiation and testing for VZV antibodies in the absence of a history of either disease or vaccination. The PI also recommends consideration of vaccination for those who are antibody-negative and to postpone treatment until six weeks after VZV vaccination. Antiviral agents for herpetic prophylaxis at suppressive doses are recommended starting on the first day of each treatment course and continuing for a minimum of two months following treatment completion or until the CD4+ lymphocyte count is ≥ 200 cells per microliter, whichever occurs later.[18]

Level	Recommendation
Levels A and B	Clinicians must screen for certain infections (e.g., hepatitis, tuberculosis, VZV) according to prescribing information before initiating the specific ISIM medication planned for use (Level A) and should treat patients testing positive for latent infections (e.g. hepatitis, tuberculosis) before MS treatment according to individual ISIM prescribing information (Level B).
Levels A and B	In high-risk populations or in countries with high burden (in the case of tuberculosis), clinicians must screen for latent infections (e.g., hepatitis, tuberculosis) before starting MS treatment with ISIM medications even when not specifically mentioned in prescribing information (Level A) and should consult infectious disease or other specialists (e.g., liver specialists) regarding treating patients who screen positive for latent infection before treating them with ISIM medications (Level B).

Recommendation 7

Rationale

Although there is no evidence that patients with MS who are receiving ISIM therapy have increased risk with immunization with live vaccines, because of biologically plausible risks of live vaccines in patients who are immunosuppressed, it is generally advised that patients who receive ISIM therapy avoid immunization with live vaccines. PI in package inserts for alemtuzumab, fingolimod, ocrelizumab, and teriflunomide recommend against the use of live vaccines during and immediately preceding treatment.[15–18] Furthermore, because the immunosuppressive effects of some of these medications and immunomodulatory effects of others may last for months after discontinuation of medication, PI recommends waiting for two to six months after treatment to immunize with live vaccines, depending on the half-life of the specific therapy being used.[15–18]

Level	Recommendation
Level B	Clinicians should recommend against using live attenuated vaccines in people with MS who currently receive ISIM therapies or have recently discontinued these therapies.

Rationale

Although the guideline panel recommends against the routine use of live attenuated vaccines in individuals with MS who are receiving or have recently discontinued ISIM therapies, circumstances can arise in which risks of infection are high (e.g., endemic risks or local pandemics). Infections can result in morbidity and mortality in general and also increase the risk of MS exacerbation.[6, 25] Particularly because of the lack of evidence proving increased risks with the use of live vaccines in individuals using ISIM agents, circumstances of high infection risk should prompt reconsideration of the pros and cons of immunization with live vaccines in individuals receiving ISIM therapy.

Level	Recommendation
Level C	When the risk of infection is high, clinicians may recommend using live attenuated vaccines if killed vaccines are unavailable for people with MS who are currently receiving ISIM therapies.

Recommendation 8

Rationale

The guideline panel identified no evidence that vaccines increase the risk of relapse or worsen relapse severity, but studies are limited. Experts remain concerned that vaccines may worsen relapse severity if given to patients who are actively experiencing an MS relapse. In addition, although data are limited regarding the effect of steroids on vaccination response, recommendations of the Advisory Committee on Immunization Practices state, "The immunosuppressive effects of steroid treatment vary, but many clinicians consider a dose equivalent to either 2 mg/kg of body weight or a total of 20 mg/day of prednisone as sufficiently immunosuppressive to raise concern about the safety of immunization with live-virus vaccines. Corticosteroids used in greater than physiologic doses also may reduce the immune response to vaccines. Physicians should wait at least three months after discontinuation of therapy before administering a live-virus vaccine to patients who have received high-dose, systemic steroids for greater than or equal to two weeks."[26] Immunization is not typically an urgent need and, in most cases, can be temporarily delayed without a marked increase in infection risk.

Level	Recommendation
Level B	Clinicians should delay vaccination of people with MS who are experiencing a relapse until clinical resolution or until the relapse is no longer active (e.g., the relapse is no longer progressive but may be associated with residual disability), often many weeks after relapse onset.

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This practice guideline was endorsed by the Consortium of Multiple Sclerosis Centers and by the Multiple Sclerosis Association of America.

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