

Practice guideline update summary: Vaccine-preventable infections and immunization in multiple sclerosis

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Abstract

Objective

To update the 2002 American Academy of Neurology (AAN) guideline regarding immunization and multiple sclerosis (MS).

Methods

The panel performed a systematic review and classified articles using the AAN system. Recommendations were based on evidence, related evidence, principles of care, and inferences according to the AAN 2011 process manual, as amended.

Major recommendations (Level B except where indicated)

Clinicians should discuss the evidence regarding immunizations in MS with their patients and explore patients' opinions, preferences, and questions. Clinicians should recommend that patients with MS follow all local vaccine standards, unless there are specific contraindications and weigh local vaccine-preventable disease risks when counseling patients. Clinicians should recommend that patients with MS receive the influenza vaccination annually. Clinicians should counsel patients with MS about infection risks associated with specific immunosuppressive/immunomodulating (ISIM) medications and treatment-specific vaccination guidance according to prescribing information (PI) and vaccinate patients with MS as needed at least 4–6 weeks before initiating patients' ISIM therapy. Clinicians must screen for infections according to PI before initiating ISIM medications (Level A) and should treat patients testing positive for latent infections. In high-risk populations, clinicians must screen for latent infections before starting ISIM therapy even when not specifically mentioned in PI (Level A) and should consult specialists regarding treating patients who screen positive for latent infection. Clinicians should recommend against using live-attenuated vaccines in people with MS receiving ISIM therapies. Clinicians should delay vaccinating people with MS who are experiencing a relapse.

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Podcast

Dr. Stacey Clardy talks with Dr. Mauricio Farez about his practice guideline update summary on vaccine-preventable infections and immunization in multiple sclerosis.

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This practice guideline was endorsed by the Multiple Sclerosis Association of America on January 11, 2019, and by the Consortium of Multiple Sclerosis Centers on February 1, 2019.

Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on October 20, 2018; by the Practice Committee on May 4, 2019; and by the AAN Institute Board of Directors on July 3, 2019.

Glossary

BCG = bacille Calmette-Guérin; **CI** = confidence interval; **DMT** = disease-modifying therapy; **HC** = healthy control; **ISIM** = immunosuppressive or immunomodulating; **MS** = multiple sclerosis; **OR** = odds ratio; **PI** = prescribing information; **RCT** = randomized controlled trial; **REMS** = Risk Evaluation and Mitigation Strategy; **SR** = systematic review; **TT** = tetanus toxoid; **VZV** = varicella zoster virus.

In 2002, the American Academy of Neurology (AAN) published the guideline “Immunization in multiple sclerosis: a summary of published evidence and recommendations.”¹ The purpose of the current update is to systematically evaluate and incorporate new evidence, vaccines, and disease-modifying therapies (DMTs). Immunization against a disease may be achieved by natural infection or by vaccination against specific agents. In this guideline update, the guideline panel uses the terms “immunization” and “vaccination” interchangeably to refer to immunity developed in response to vaccines.

Multiple sclerosis (MS) is characterized by the infiltration of immune cells from the circulation into the CNS. These immune cells (B and T lymphocytes, monocytes, and natural killer cells) are thought to target myelin antigens. Increasing evidence suggests a role for migrating B cells in MS pathogenesis, with contributions to T-cell activation and direct tissue injury.^{2,3} Some evidence suggests that infections may trigger MS relapses, increase MS radiologic and immunologic activity, and accelerate disease progression.^{4,5} Likewise, select reports link immunizations to clinical exacerbations of MS.⁶ Thus, it is understandable that patients with MS may have concerns about receiving recommended immunizations.

Another concern is that immunosuppressive or immunomodulating (ISIM) agents used to treat MS suppress or modulate normal immune function.^{7,8} These drugs may increase susceptibility to infections and may reduce vaccine effectiveness because of a decreased ability to mount an immune response. The effectiveness of immunization in patients with MS who are receiving DMTs was not evaluated in the previous guideline.

This guideline addresses the following clinical questions:

1. (a) Are vaccine-preventable infectious diseases more frequent in patients with MS than in the general population? (b) Do vaccine-preventable infectious diseases increase the risk of developing MS?
2. Do vaccine-preventable infectious diseases increase the risk of MS exacerbations?
3. Does vaccination increase the risk of (a) developing MS or (b) MS exacerbation?
4. Are (a) attenuated live and (b) inactivated vaccines as effective in patients with MS as they are in the general population? (c) Does treatment of MS with alemtuzumab,

corticosteroids, daclizumab, dimethyl fumarate (DMF), fingolimod, glatiramer acetate, interferons, mitoxantrone, natalizumab, rituximab, and teriflunomide reduce the effectiveness of vaccinations in people with MS?

Description of the analytic process

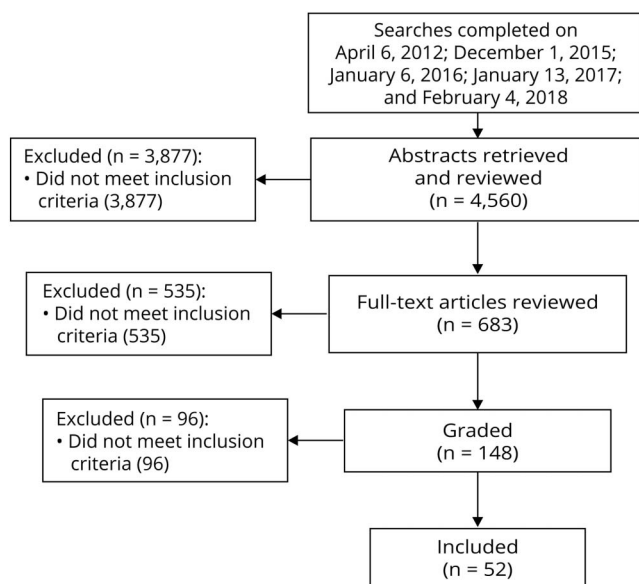
This systematic review (SR) and practice guideline were developed according to the 2011 AAN guideline development process, as amended.⁹ The full guideline is available on the AAN website (aan.com/guidelines). The full guideline provides a description of the exact methodology followed, including the processes of convening the author panel, performing the literature search, reviewing the evidence, and applying a modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process.⁹ Recommendations were based not only on the evidence in the SR but also on strong related evidence, established principles of care, and inferences. The level of obligation for each recommendation was based on the strength of these premises and the risk-benefit ratio of following the recommendation, with adjustments based on importance of outcomes, variation in patient preferences, feasibility/availability, and patient costs. Consensus was determined by a modified Delphi voting process in accordance with prespecified rules.⁹

The panel evaluated randomized controlled trials (RCTs), cohort studies, and case-control studies published from 1990 to March 2018 that described the incidence, prevalence, and effect of vaccine-preventable disease and their associated immunizations on the risk of MS causation and relapses (minimum sample size 10, any language) (figure). Studies evaluating the role of DMTs on the effectiveness of immunizations were included. Case reports and case series were excluded, except studies providing safety data or using a laboratory reference standard. Dual reviewers assigned classification of evidence using the prognostic rating scheme.⁹ The full guideline provides study details, measures of association, additional meta-analysis results, forest plots, and references for studies determined to have insufficient evidence to drive conclusions.

Data availability

Appendices e-4 (evidence profile tables) and e-5 (evidence synthesis tables), described in the full-length guideline, are available from the AAN, upon request.

Figure MS immunization flowchart of evidence review



Analysis of evidence

Question 1: Is a history of vaccine-preventable infectious diseases more frequent in patients with MS than in the general population?

The panel developed 2 questions relating to vaccine-preventable infectious diseases and MS, 1 relating to frequency and 1 to causation, but no studies informed the causation question. Hence, the 2 questions were combined. Conclusions reflect associations and do not imply causation. Data were insufficient to support or refute an association between development of MS and a history of diphtheria, hepatitis (unknown type), measles, meningitis, mumps, pertussis, polio, rubella, smallpox, tuberculosis, typhoid, and zoster (varicella zoster virus [VZV], chicken pox, and herpes zoster).

Hepatitis B

It is possible that patients with MS have lower odds of previous hepatitis B infection compared with healthy controls (HCs) (odds ratio [OR] 0.19; 95% confidence interval [CI] 0.04–0.84; low confidence in the evidence, 1 Class II study¹⁰).

Question 2: Do vaccine-preventable infectious diseases increase the risk of MS exacerbations?

Data for this question were identified only for influenza and zoster. There was insufficient evidence to support or refute an association between influenza and MS exacerbation.

Varicella zoster (VZV, chicken pox, or herpes zoster)

It is probable that individuals with active MS exacerbations have higher odds of VZV viral DNA present in peripheral blood mononuclear cells than individuals with MS in

remission (OR 2,795.76, 95% CI 124.64–62,709.36, $I^2 = 0\%$; moderate confidence in the evidence, 2 Class II studies^{11,12}). These calculations were performed using the Sweeting continuity correction; see full guideline for details. The implication of these findings for an association between VZV infection and MS exacerbation is uncertain.

Question 3a: Does vaccination increase the risk of developing MS?

Most vaccines included in this SR were part of childhood vaccination series. Vaccine administration was assumed to precede the development of MS. Data were insufficient to support or refute an association between development of MS and a history of vaccination for diphtheria, hepatitis B, influenza, measles, mumps, measles-mumps-rubella, poliomyelitis, rubella, typhoid, yellow fever, and VZV/chicken pox.

Human papillomavirus vaccination

Human papillomavirus vaccination is probably associated with a lower likelihood of a subsequent MS diagnosis (moderate confidence in the evidence, 1 Class I study,¹³ and 1 Class II study¹⁴ showing lower odds of subsequent diagnosis [OR 0.28, 95% CI 0.12–0.70, and OR 0.31, 95% CI 0.13–0.73, respectively] and 1 Class II¹⁵ study with insufficient precision [OR 1.05, 95% CI 0.62–1.78]).

Pertussis vaccination

Pertussis vaccination is probably associated with a lower likelihood of a subsequent MS diagnosis (meta-analysis OR 0.30; 95% CI 0.20–0.56, $I^2 = 0\%$; moderate confidence in the evidence, 2 consistent Class II studies^{16,17}).

Smallpox vaccination

Smallpox vaccination is possibly associated with a lower likelihood of a subsequent MS diagnosis (OR 0.23, 95% CI 0.09–0.59; low confidence in the evidence; 1 Class II study¹⁷).

Tetanus toxoid vaccination

Tetanus toxoid (TT) vaccination is probably associated with a lower likelihood of a subsequent MS diagnosis (meta-analysis OR 0.61, 95% CI 0.49–0.76, $I^2 = 0\%$; moderate confidence in the evidence, 4 Class II studies^{17–20}).

Tuberculosis (bacille Calmette-Guérin) vaccination

Bacille Calmette-Guérin (BCG) vaccination is probably not associated with an increased likelihood of progression to MS in patients with clinically isolated syndrome (OR 0.28, 95% CI 0.15–0.51; moderate confidence in the evidence, 1 Class I study²¹). There is insufficient evidence to conclude whether individuals with MS have higher odds of previous BCG vaccination than HCs (meta-analysis OR 0.70; 95% CI 0.30–1.70; $I^2 = 16\%$; very low confidence in the evidence, 2 imprecise Class II studies,^{22,23} with decreased confidence in the evidence due to insufficient precision).

Question 3b: Does vaccination increase the risk of exacerbations of MS?

Data were insufficient to support or refute an association between MS exacerbation and history of BCG (tuberculosis), influenza, or tick-borne encephalitis vaccination.

Question 4a: Are live-attenuated vaccines as effective in patients with MS as in the general population?

No identified studies answered this question.

Question 4b: Are inactivated vaccines as effective in patients with MS as in the general population?

Influenza vaccines

Data were identified only for influenza vaccines. Influenza vaccine types (e.g., trivalent and H1N1) were considered together. It is possible that patients with MS have a higher likelihood of an insufficient response to influenza vaccination vs controls (low confidence in the evidence; 3 Class III studies,^{24–26} 1 of which included 2 separate cohorts²⁶ [2 with sufficient precision individually], and a meta-analysis showing increased odds of an insufficient response [OR 1.87, 95% CI 1.07–3.27, $I^2 = 27\%$] but with CIs including values of limited clinical significance).

Question 4c: Does treatment of MS reduce effectiveness of vaccinations?

Influenza vaccines and IFN- β

Six studies (2 Class I,^{27,28} 3 Class II,^{26,29,30} and 1 Class III³¹) were identified. Only 2 of the studies^{28,30} directly addressed the clinical question comparing the effectiveness results of immunization in patients with MS who were or were not receiving IFN therapy. The other 4 studies reported cohorts with seroconversion rates to influenza vaccine in participants with MS receiving IFNs compared with seroconversion rates either in HCs^{26,27,29} or in participants with MS receiving other ISIM treatments.^{27,31} A meta-analysis was performed for a global estimate of effect, with the assumption that all IFN types have a similar effect on immune response and that influenza vaccines are largely similar. It is probable that individuals with MS receiving IFN- β therapy do not have a meaningful reduction in the likelihood of seroprotection in response to influenza vaccination (moderate confidence in the evidence; 2 Class I studies,^{27,28} 3 Class II studies,^{26,29,30} and 1 Class III study,³¹ with 1 of the Class II studies including 2 separate cohorts²⁶; meta-analysis of Class I and II studies without meaningfully decreased odds of seroconversion [OR 1.51; 95% CI 0.79–2.90, $I^2 = 55\%$]).

Influenza vaccines and glatiramer acetate

It is possible that individuals with MS receiving glatiramer acetate therapy have a reduced likelihood of seroprotection from influenza vaccine compared with various controls (low confidence in the evidence; 1 Class I study²⁸ and 1 Class II study²⁶ with 2 separate cohorts; only the Class II study has

sufficient precision to drive a conclusion on its own; meta-analysis OR 0.39; 95% CI 0.21–0.74; $I^2 = 0\%$).

Influenza vaccines and fingolimod

It is probable that individuals with MS receiving fingolimod therapy have a reduced likelihood of seroprotection from influenza vaccine compared with individuals with MS not receiving treatment (moderate confidence in the evidence; 2 Class I studies,^{28,32} 1 with sufficient precision and 1 with insufficient precision; meta-analysis OR 0.35; 95% CI 0.21–0.57; $I^2 = 0\%$).

Influenza vaccines and mitoxantrone

It is probable that individuals with MS receiving mitoxantrone have a lower likelihood of response to influenza vaccination compared with HCs (moderate confidence in the evidence; 1 Class II study²⁶ with 2 separate cohorts, each showing a reduced response; meta-analysis OR 0.11, 95% CI 0.03–0.45, $I^2 = 0\%$).

Influenza vaccines and therapies for which there is insufficient evidence

There is insufficient evidence to support or refute whether individuals with MS receiving natalizumab, daclizumab, teriflunomide, methotrexate/6-mercaptopurine, or BCG therapy differ in likelihood of response to influenza vaccination compared with various controls. For some of these therapies, high rates of seroprotection or seroconversion in treatment groups make an adequate response plausible.

TT and fingolimod

It is probable that individuals with MS receiving fingolimod have a lower likelihood of response to a TT booster at 3 weeks after vaccination compared with individuals with MS receiving placebo (OR 0.43; 95% CI 0.20–0.92). There is insufficient evidence to support or refute a difference in the likelihood of a response at 6 weeks (OR 0.62; 95% CI 0.29–1.33) or seroprotection rates at 3 weeks (OR 1.22; 95% CI 0.35–4.20) or 6 weeks (OR 2.10; 95% CI 0.70–6.00) because of limited precision for those outcomes (1 Class I study³² with insufficient precision for some outcomes). The high proportions of participants in the fingolimod group who achieved seroprotection (3 weeks: 92%, 6 weeks: 92%) suggest that an adequate response to vaccination in the context of fingolimod is plausible.

Additional vaccine-treatment pairs for which there is insufficient evidence

There is insufficient evidence to support or refute whether individuals with relapsing-remitting multiple sclerosis receiving natalizumab are likely to differ in response to TT compared with individuals with MS not receiving such treatment.³³ There is insufficient evidence to support or refute whether individuals with MS receiving DMF are likely to differ in response to TT, diphtheria toxoid, pneumococcal, or meningococcal vaccination compared with participants with MS receiving IFN- β .³⁴ There is insufficient evidence to

support or refute whether individuals with MS receiving alemtuzumab are likely to differ in response to *Haemophilus influenzae* type b, meningococcal, or pneumococcal polysaccharide vaccines compared with HCs.³⁵ There is insufficient evidence to support or refute whether individuals with MS receiving IFN- β therapy are likely to differ in response to BCG vaccination compared with individuals with MS not receiving such treatment.²²

Putting the evidence into clinical context

This document updates the 2002 AAN guideline “Immunization in multiple sclerosis.”¹ Conclusions differ from those in the previous guideline because of updated guideline methodology,⁹ exclusion of case series and publications with fewer than 10 participants, systematic assessment of spectrum bias, use of a literature search starting in 1990, and incorporation of interim publications.

The results of this SR highlight important knowledge gaps that persist since the previous guideline. The guideline panel noted some consistent weaknesses in study methodology across studies. Most of the association studies used a case-control design; very few prospective cohort studies were found. The variation in ascertainment methods for infection and immunization (surveys, registries, and antibody responses) may have affected results. For evaluation of vaccine effectiveness, only a few RCTs were found; most were cohort studies. Several studies evaluating MS exacerbation by infections or vaccines were limited by spectrum bias, including only participants who were ambulatory or moderately affected, thereby reducing generalizability. Statistical imprecision, often related to low sample size, was an important factor limiting conclusions.

New ISIM treatments for MS are rapidly being developed. Some of these treatments have no immunization evidence to date. However, because some of these agents have similar mechanisms of action, the guideline panel believes that the recommendations here are sufficiently broad. The panel encourages review of manufacturer product information before the use of specific agents for immunization-related recommendations.

Practice recommendations

Recommendation rationales are presented; tables summarize recommendation statements (n.neurology.org/content/91/10/450; tables 1–3).

Recommendation 1 rationale

There is no definite evidence suggesting that vaccination increases the risk of MS, although a link cannot be completely excluded, given the paucity of relevant data. Vaccinations against HPV, TT, pertussis, and smallpox 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.

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 patients with MS live.³⁶ Thus, vaccination of patients with MS is expected to have personal and population-level benefits.

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 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.³⁷ 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 (IGRA), (2) have no evidence of previous infection, and (3) live in settings with high incidence of tuberculosis or leprosy or both, are moving to such settings, or work in occupations that put them at risk (e.g., health care, laboratory, and prison settings).³⁸ The CDC recommendations for BCG are limited to children and adults in specific clinical situations.³⁹ 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.

Recommendation 4 rationale

MS exacerbations are associated with increased short- and long-term disability.⁴⁰ Although the SR found insufficient evidence to support or refute an association between a history of influenza infection and MS exacerbations, 1 study not

Table 1 Recommendation statements^a for general care for individuals with multiple sclerosis when considering immunization and vaccine-preventable infections

Recommendation number	Recommendation statement and level
1	1a. Clinicians should discuss with their patients the evidence from the systematic review regarding immunization in MS (Level B). 1b. 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 (Level B).
2	Clinicians should recommend that patients with MS follow all local vaccine standards (e.g., from the US CDC, WHO, and local regulatory bodies), unless there is a specific contraindication (e.g., active treatment with ISIM agents) (Level B).
3	Clinicians should weigh local risks of vaccine-preventable diseases when counseling individuals with MS regarding vaccination (Level B).
4	Clinicians should recommend that patients with MS receive the influenza vaccination annually, unless there is a specific contraindication (e.g., previous severe reaction) (Level B).

Abbreviations: CDC = Centers for Disease Control and Prevention; ISIM = immunosuppressive or immunomodulating; MS = multiple sclerosis; WHO = World Health Organization.

^a Level A is the strongest recommendation level and is denoted by the use of the helping verb must. These recommendations are rare. Level B corresponds to the helping verb should. Such recommendations are more common, as the requirements are less stringent but are still associated with confidence in the rationale and a favorable benefit-risk profile. Level C corresponds to the helping verb may. These recommendations represent the lowest allowable recommendation level that the American Academy of Neurology considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

meeting the criteria for the SR found that influenza infections increase exacerbation risk compared with vaccination.⁴¹ 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, and mitoxantrone) may have

Table 2 Recommendation statements regarding immunization in the setting of immunosuppressive or immunomodulating medication use

Recommendation number	Recommendation statement and level
5	5a. 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). 5b. 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 4–6 weeks before initiating ISIM therapy as advised by specific prescribing information (Level B). 5c. 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 (Level C based on variation in patient preferences).
6	6a. Clinicians must screen for certain infections (e.g., hepatitis, tuberculosis, and 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 and tuberculosis) before MS treatment according to individual ISIM prescribing information (Level B based on feasibility and cost relative to benefit). 6b. In high-risk populations or in countries with high burden (in the case of tuberculosis), clinicians must screen for latent infections (e.g., hepatitis and 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).
7	7a. Clinicians should recommend against using live-attenuated vaccines in people with MS who currently receive ISIM therapies or have recently discontinued these therapies (Level B based on importance of outcomes). 7b. 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 (Level C based on variation in patient preferences, benefit relative to harm, and importance of outcomes).

Abbreviations: ISIM = immunosuppressive or immunomodulating; MS = multiple sclerosis; VZV = varicella zoster virus.

Table 3 Recommendation statement regarding immunization for individuals with multiple sclerosis during a relapse

Recommendation number	Recommendation statement and level
8	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 (Level B).

Abbreviation: MS = multiple sclerosis.

a reduced response to influenza vaccination. Although the SR identified no evidence regarding vaccine response in individuals with MS receiving rituximab, evidence regarding rituximab use in neuromyelitis optica spectrum disorders²⁷ and in rheumatoid arthritis⁴² suggests that rituximab can be associated with reduced influenza vaccine responsiveness.

Recommendation 5 rationale

Rationale for recommendations 5a and 5b

Immunosuppressive or immunomodulatory medications now used to treat MS include alemtuzumab, DMF, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, and teriflunomide. These treatments have been associated with severe occurrences or recurrences or both of vaccine-preventable infections, including VZV and hepatitis B.^{43–48} 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 1 month before treatment to permit the immune response to develop.⁴⁹ Fingolimod PI also recommends avoiding live vaccines during treatment and for 2 months after discontinuation.⁴⁹ The PI for teriflunomide recommends against using live vaccines during treatment and for 6 months after discontinuation.⁵⁰ For alemtuzumab, the PI recommends against the use of live vaccines for 6 weeks before treatment initiation, during treatment, and after “recent” treatment.⁵⁰ The PI for ocrelizumab recommends vaccinating according to immunization guidelines at least 4 weeks before starting ocrelizumab for live or live-attenuated vaccines and at least 2 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.⁵¹

Rationale for recommendations 5c

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,^{43–48} and their manufacturers’ PIs have treatment-specific guidance for immunization with live vaccines.^{49–52} 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 4- to 6-week delays between immunization with live vaccines and initiation of treatment with these medications.

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.^{53–56} 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.⁵⁰ The PI also recommends treatment for tuberculosis in patients who test positive for tuberculosis before initiating teriflunomide treatment.⁵⁰ The PI for alemtuzumab recommends tuberculosis screening according to local guidelines.⁵² 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.⁵⁷ 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.⁵¹ 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.⁵² 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.⁵² 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 6 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 2 months following treatment completion or until the CD4⁺-lymphocyte count is ≥ 200 cells per microliter, whichever occurs later.⁵²

Recommendation 7 rationale

Rationale for recommendation 7a

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 recommends against the use of live vaccines during and immediately preceding treatment.^{49–52} 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 2–6 months after treatment to immunize with live vaccines, depending on the half-life of the specific therapy being used.^{49–52}

Rationale for recommendation 7b

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.^{41,58} 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.

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 3 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 2 weeks.”⁵⁹ Immunization is not typically an urgent need and, in most cases, can be temporarily delayed without a marked increase in infection risk.

Suggestions for future research

The SR found few high-quality studies to inform recommendations. As more ISIM agents are developed to manage chronic diseases such as MS, long-term prospective cohort studies are required to evaluate both the safety and effectiveness of immunizations in MS. Simultaneous prospective cohort studies to evaluate the risks of infections in patients with MS and the effect of infections on short-term and long-term disability in patients with MS will help the risk-benefit analysis of immunization in this population.

Risk Minimization Action Plan (Risk-MAP) and Risk Evaluation and Mitigation Strategy (REMS) data collection protocols aim to ensure safe use of medications. The reporting of serious adverse effects is not yet a part of the REMS programs. However, these postmarketing registries, with wide ascertainment of treated populations, can help to identify rare, emergent, and poorly characterized risks that are recognized only when the drugs are prescribed in practice. Funding, governance, physician and institutional involvement, and research protections are aspects that require attention while using these postmarketing data to inform clinical care and future research.

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Conflict of interest statement

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this evidence-based document. Management and disclosure of document developer relationships is conducted in compliance with the 2011 AAN process manual section titled, “Revealing Conflicts of Interest.”⁹

Author contributions

M.F. Farez and J. Correale: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, and critical revision of the manuscript for important intellectual content. M.J. Armstrong: acquisition of data, analysis or interpretation of data, and drafting/revising the manuscript. A. Rae-Grant: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, and critical revision of the manuscript for important intellectual content. D. Gloss: study concept and design, analysis or interpretation of data, and drafting/revising the manuscript. D. Donley: analysis or interpretation of data, drafting/revising the manuscript, and critical revision of the manuscript for important intellectual content. Y. Holler-Managan: analysis or interpretation of data and drafting/revising the manuscript. N.J. Kachuck: study concept and design, analysis or interpretation of data, and drafting/revising the manuscript. D. Jeffery: analysis or interpretation of data, drafting/revising the manuscript, and critical revision of the manuscript for important intellectual content. M. Beilman: drafting/revising the manuscript and critical revision of the manuscript for important intellectual content. G. Gronseth and D. Michelson: study concept and design, analysis or interpretation of data, and drafting/revising the manuscript. E. Lee: study concept and design, acquisition of data, analysis or interpretation of data, and drafting/revising the manuscript. J. Cox: drafting/revising the manuscript and critical revision of the manuscript for important intellectual content. T. Getchius and J. Sejvar: study concept and design, drafting/revising the manuscript, and critical revision of the manuscript for important intellectual content. P. Narayanaswami: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, and study supervision.

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for travel from the AAN and serves on the editorial advisory board for *Brain & Life*. N.J. Kachuck has served on speakers' bureaus for Teva Pharmaceuticals and Acorda Therapeutics; serves as medical director for Glycominds Laboratories, Inc.; and assisted in the preparation of a patent extension appeal by Acorda Therapeutics. D. Jeffery serves on scientific advisory boards for Teva, Novartis, Biogen, Acorda, and Bayer; serves as an editor for the *Journal of the Neurological Sciences*; has received honoraria and serves on speakers' bureaus for Teva, Novartis, Biogen, Bayer, and Acorda; has received research support from Teva, Serono, Pfizer, Novartis, Sanofi, Roche, Biogen, continuing medical education companies, the University of South Florida, and the University of Massachusetts; and has provided expert testimony as a defense expert witness. M. Beilman reports no disclosures relevant to the manuscript. G. Gronseth serves as an associate editor of *Neurology*; serves on the editorial advisory board for *Brain & Life*; served as a paid evidence-based medicine methodologist for the AAN; and received honoraria for presentations given at the AAN annual meeting. D. Michelson receives publishing royalties of \$500 per year as coauthor for 1 UpToDate article. E. Lee and J. Cox are currently full-time employees of the AAN. T. Getchius was a full-time employee of the AAN when he made his contribution to this guideline. J. Sejvar reports no disclosures relevant to the manuscript. P. Narayanaswami has received grant support from the AHRQ, the Patient-Centered Outcomes Research Institute, and Merz Pharmaceuticals; has consulted for Momenta Pharmaceuticals; served on an advisory board of Alexion Pharmaceuticals; is an associate editor for *Muscle & Nerve*; and serves on the editorial boards of the *Journal of Clinical Neuromuscular Disease* and *Annals of Neurology*. Go to Neurology.org/N for full disclosures.

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