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

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

Mauricio F. Farez, MD, MPH,[1] Jorge Correale, MD,[1,2] Melissa J. Armstrong, MD, MSc,[3] Alexander Rae-Grant, MD,[4] David Gloss, MD,[5] Diane Donley, MD,[6] Yolanda Holler-Managan, MD,[7] Norman J. Kachuck, MD,[8] Douglas Jeffery, MD,[9] Maureen Beilman,[10] Gary Gronseth, MD,[11] David Michelson, MD,[12] Erin Lee,[13] Julie Cox, MFA,[13] Tom Getchius,[13] James Sejvar, MD,[14] Pushpa Narayanaswami, MD[15]

1. Centro para la Investigación de Enfermedades Neuroinmunológicas, FLENI, Buenos Aires, Argentina
2. Servicio de Neuroinmunología y Enfermedades Desmielinizantes, Departamento de Neurología, FLENI, Buenos Aires, Argentina
3. Department of Neurology, University of Florida, Gainesville
4. Mellen Center, Cleveland Clinic, OH
5. Department of Neurology, Charleston Area Medical Center, WV
6. Northern Michigan Neurology, Traverse City
7. Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago
8. MS Comprehensive Care Center, Keck School of Medicine of University of Southern California, Los Angeles
9. Lake Norman Neurology, Piedmont HealthCare, Mooresville, NC
10. The Marriage and Family Institute, Saint Louis, MO
11. Department of Neurology, Kansas University Medical Center, Kansas City
12. Department of Pediatrics, Neurology Division, Loma Linda University Health Care, CA
13. American Academy of Neurology, Minneapolis, MN
14. US Centers for Disease Control and Prevention, Atlanta, GA
15. Department of Neurology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA

Address correspondence and reprint requests to
American Academy of Neurology:
guidelines@aan.com

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.

AUTHOR CONTRIBUTIONS

Dr. Farez: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Correale: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Armstrong: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript.

Dr. Rae-Grant: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Gloss: study concept and design, analysis or interpretation of data, drafting/revising the manuscript.

Dr. Donley: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Holler-Managan: analysis or interpretation of data, drafting/revising the manuscript.

Dr. Kachuck: study concept and design, analysis or interpretation of data, drafting/revising the manuscript.

Dr. Jeffery: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

M. Beilman: drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Gronseth: study concept and design, analysis or interpretation of data, drafting/revising the manuscript.

Dr. Michelson: study concept and design, analysis or interpretation of data, drafting/revising the manuscript.

E. Lee: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript.

J. Cox: drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

T. Getchius: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. Sejvar: study concept and design, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.

Dr. 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, study supervision.

STUDY FUNDING

This practice guideline was developed with financial support from the American Academy of Neurology (AAN). Authors who serve or served as AAN subcommittee members or as methodologists (M.J.A., A.R.G., D.G., D.D., Y.H.M., G.G., D.M., P.N.), or who are or were AAN staff members (E.L., J.C., T.G.), were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

DISCLOSURE

M. Farez has received funding for travel from Teva Argentina, Novartis Argentina, and Merck-Serono Argentina and has received research support from Biogen-Idec.

J. Correale is a member of the scientific advisory boards of Merck-Serono LATAM, Novartis Argentina, Genzyme Argentina, and Genzyme Global; has received funding for travel from Merck-Serono Argentina; is a member of the editorial boards of *Current Neurology and Neuroscience Reports*, *Frontiers in Multiple Sclerosis and Neuroimmunology*, and *Multiple Sclerosis and Related Disorders*, *Latin American Multiple Sclerosis Journal*; serves as associate editor for the *Multiple Sclerosis Journal* and *Multiple Sclerosis Journal – Experimental, Translational and Clinical*; served on the editorial board of *Neurología Argentina*; has received honoraria from Merck-Serono Argentina, Merck-Serono LATAM, Genzyme Argentina, Genzyme LATAM, Genzyme-Global, Biogen-Idec Argentina, Ivax-Teva Argentina, Roche Argentina, and Novartis Argentina; and has received research support from Genzyme Argentina, Biogen-Idec Argentina, and Novartis Argentina.

M. Armstrong serves on the Level of Evidence Editorial Board for *Neurology*® (not compensated financially); receives publishing royalties from Oxford University Press for coediting *Parkinson's Disease: Improving Patient Care*; received honoraria for teaching at the 2014, 2015, and 2016 American Academy of Neurology (AAN) Annual Meetings and the 2013 and 2014 International Congresses of Parkinson's Disease and Movement Disorders; serves as a paid evidence-based medicine methodologist for the AAN; serves as faculty on the AAN online course "EBM Online"; has served as a local investigator for studies sponsored by AbbVie, the Parkinson Study Group (PSG), PSG/Biotie, the Huntington Study Group, CHDI Foundation, Inc., and Insightec, Inc., and is currently supported by a career development award from the Agency for Healthcare Research and Quality (K08HS024159-03); and worked at the University of Maryland through August 2015 and currently works for the University of Florida.

A. Rae-Grant received royalties from publishing, including *Multiple Sclerosis and Related Disorders* from Demos Medical Publishing; and serves as a deputy editor for DynaMed, an online medical textbook, and as a part-time employee of EBSCO Industries.

D. Gloss has served as a paid evidence-based medicine consultant for the AAN.

D. Donley serves as a reviewer of child neurology cases for Physicians Review Organization of Michigan and serves as a blinded rater for multiclinic clinical drug trials for MS, Parkinson disease, dementia, and epilepsy. Her spouse reviews adult cases for the Physician Review Organization of Michigan and serves as a principal investigator.

Y. Holler-Managan receives funding for travel from the AAN and serves on the editorial advisory board for *Brain & Life*.

N. 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.

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 one UpToDate article.

E. Lee is currently a full-time employee of the AAN.

J. Cox is currently a full-time employee 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.

P. Narayanaswami has received grant support from 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*.

GLOSSARY

AAN: American Academy of Neurology

Anti-HBc: hepatitis B core antibodies

BCG: bacille Calmette-Guérin

CDC: Centers for Disease Control and Prevention

CIS: clinically isolated syndrome

CIs: confidence intervals

COI: conflict of interest

DMTs: disease-modifying therapies

EDSS: Expanded Disability Status Scale

Gd: gadolinium

GDDI: Guideline Development, Dissemination, and Implementation Subcommittee

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HCs: healthy controls

HI: hemagglutination inhibition

Hib: *Haemophilus influenzae* type B

HPV: human papillomavirus

IFNs: interferons

IFN-β: interferon-β

IgA: immunoglobulin A

IgG: immunoglobulin G

IgM: immunoglobulin M

IQR: interquartile range

ISIM: immunosuppressive or immunomodulating

MMR: measles−mumps−rubella

MS: multiple sclerosis

ON: optic neuritis

OR: odds ratio

PBMC: peripheral blood mononuclear cells

PPMS: primary progressive multiple sclerosis

RCTs: randomized controlled trials

REMS: risk evaluation and mitigation strategies

Risk-MAPs: risk minimization action plans

RMD: raw mean difference

RR: relative risk

RRMS: relapsing–remitting multiple sclerosis

SPMS: secondary progressive multiple sclerosis

SR: systematic review

TBE: tick-borne encephalitis

TT: tetanus toxoid

VZV: varicella-zoster virus

WHO: World Health Organization

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 and vaccinate patients with MS as needed at least 4–6 weeks before initiating patients' ISIM therapy. Clinicians must screen for latent infection according to prescribing information 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 prescribing information (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.

INTRODUCTION

In 2002, the American Academy of Neurology (AAN) published the guideline "Immunization in multiple sclerosis: a summary of published evidence and recommendations."[1] Since then, several major studies have investigated the effects of infections and immunizations on the course of multiple sclerosis (MS). Furthermore, medicine has seen the development and approval of new vaccines and new disease-modifying therapies (DMTs) with novel mechanisms of action. The influence of these newer immunosuppressive or immunomodulating (ISIM) therapies on the efficacy of immunization has not been systematically evaluated. This guideline updates the evidence from the previous guideline and reviews new information regarding the effectiveness of vaccines in people with MS and the role of DMTs on vaccine effectiveness.

Immunization against a disease may be achieved by natural infection or by vaccination against a specific agent or agents. In this guideline, the guideline panel uses the terms *immunization* and *vaccination* interchangeably to refer to immunity developed in response to vaccines. Multiple sclerosis 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 be directed against myelin antigens. There is increasing evidence to suggest 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 patients with MS are typically treated with ISIM agents that 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. This guideline addresses the following clinical questions:

1a. Are vaccine-preventable infectious diseases more frequent in patients with MS than in the general population?

1b. 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?

4c. Does ISIM treatment of MS with alemtuzumab, corticosteroids, daclizumab, dimethyl fumarate (DMF), fingolimod, glatiramer acetate, interferons (IFNs), mitoxantrone, natalizumab, rituximab, and teriflunomide reduce the effectiveness of vaccinations in people with MS (daclizumab, DMF, and teriflunomide added after updated search in January 2017; rituximab

added after updated literature search in March 2018)?

Because daclizumab was recently recalled from the market,[9] it is omitted from recommendation statements.

DESCRIPTION OF THE ANALYTIC PROCESS

This practice guideline was developed according to the 2011 AAN guideline development process, as amended to include the processes of topic nomination prioritization and a change in the order of steps for external review.[10] In January 2012, the AAN guidelines subcommittee (appendices e-1 and e-2) recruited a multidisciplinary panel of participants consisting of physicians, AAN staff members, and a patient representative. Additional participants joined over the course of the project such that the participants at various project time points included 13 physicians (M.F.F., J.C., M.J.A., A.R.G., D.G., D.D., Y.H.M., N.J.K., D.J., G.G., D.M., J.S., P.N.), one patient representative (M.B.), and 3 AAN staff members (E.L., J.C., T.G.). Physicians included content experts (M.F.F., J.C., A.R.G., N.J.K., D.J.), current and former AAN Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) members (A.R.G., D.G., D.D., D.M., Y.H.M., P.N.; A.R.G. is also a content expert), current and former methodology experts (M.J.A., G.G.), and an expert on immunization (J.S.). Each potential author was required to submit an online conflict of interest (COI) form and a copy of his or her curriculum vitae (CV). The panel was in compliance with AAN conflict of interest (COI) policies. The GDDI leadership and 2 AAN staff persons (E.L., T.G.) reviewed the COI forms and curriculum vitae for financial and intellectual COI. As required by AAN policy, the lead author (M.F.) had no COIs at defined at project initiation. Three (J.C., N.J.K., D.J.) of the 17 authors were determined to have relevant COI, which were judged to be not significant enough to preclude them from authorship. The entire panel was responsible for decisions concerning the design, analysis, and reporting of the proposed systematic review (SR), which was then submitted for approval to the AAN GDDI.

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). Studies evaluating the role of DMTs on the effectiveness of immunizations were included. Case reports and case series were excluded, except where safety data were provided or a laboratory reference standard was used.

The population was adults in whom MS was diagnosed according to Poser[11] or McDonald[12] criteria. Initially, the panel included only cases of MS diagnosed by a neurologist but later revised this requirement because many studies used computerized databases. Accepted control group criteria varied by question. For questions referencing the general population, studies with only neurologic disease control groups were excluded.

The panel included immunizations recommended by the US Centers for Disease Control and Prevention (CDC)[13] and vaccines suggested by individual panel members or public comment respondents (tuberculosis, bacille Calmette-Guérin [BCG], and Japanese encephalitis vaccines).

After a comprehensive search of the medical literature, the panel retrieved and reviewed 4,560 abstracts for potential inclusion (see appendix e-3 for the complete search strategy). Of these, 683 abstracts were identified as potentially relevant and their associated articles obtained and reviewed in full. Of these reviewed articles, the panel selected 148 for data extraction and evidence rating. After article rating, the panel determined 52 articles met the minimum class of evidence required and were included in the review (see figure e-1).

The methodologic process included dual review of abstracts and articles, with reconciliation by methodologists if needed. Classification of evidence was assigned using the prognostic rating scheme[10] and a standardized data extraction form completed by 2 panelists. Differences in ratings were resolved by consensus or using a third rater. The prognostic rating scheme requires a broad spectrum of patients for Class I or II ratings. Studies lacking either a description of MS disability or a wide range of MS severity (e.g., as measured by the Expanded Disability Status Scale [EDSS] or other accepted scales) were systematically downgraded for spectrum bias for questions 2, 3b, 4a, and 4b. Spectrum bias was not relevant for questions 1a, 1b, or 3a where the presence or development of MS was a dichotomous variable. For question 4c, the panel considered the influence of ISIMs on vaccine effectiveness to be largely independent of MS severity. Furthermore, the panel considered patient survey report of infection or vaccination to be objective, an a priori decision stemming from the inclusion of many infections/vaccines on each survey such that patients would be unlikely to respond in the affirmative to all queries.

Panel members extracted information to calculate the odds ratio (OR) and associated confidence intervals (CIs) for each study from provided data, unless already supplied. The extracted numbers are included in the evidence profile tables (appendix e-4). Unless study authors indicated that they adjusted for multiple outcomes, the panel performed Bonferroni corrections for such outcomes. The Sweeting continuity correction was used for calculating the OR and associated CIs when the number of events was 0 or 100%.[14] This continuity correction methodology is less prone to bias than other approaches and results in wide CIs, accurately reflecting the uncertainty when no events occur or when events occur 100% of the time. The senior author (P.N.) and methodologist (M.J.A.) performed the random-effects meta-analyses. The statistic I^2 was provided as a measure of heterogeneity in the meta-analysis. Confidence intervals ranging from 0.8−1.25 were considered acceptable for concluding there was no difference in the odds of an outcome between 2 groups.

The guideline panel performed data synthesis using the AAN's modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) process[10] considering precision, consistency, directness, biological plausibility, magnitude of effect, and dose response. Random-effects meta-analyses were used to obtain a single estimate of effect, and confidence in the evidence was driven by the lowest class of included studies. The process manual delineates the rules for formulating confidence in the evidence.[10] The panel anchored recommendations to

the evidence strength, with consideration of strong related evidence, principles of care, inferences, benefits relative to harms, importance of outcomes, variation of patient preferences, feasibility and availability of the intervention, and patient cost. A modified Delphi voting process was used to achieve consensus and determine the strength of the recommendations.[10]

Infections and vaccines are described in alphabetical order in the respective sections. A table describing vaccine types, indications, and conclusions is available from the AAN, by request. Varicella zoster virus (VZV) refers to chicken pox vaccination; data for either killed or live inactivated shingles vaccine were not available.

Data availability

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

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, one relating to frequency and one to causation, but no studies informed the causation question. Hence, the 2 questions were combined. Included studies assessed history of vaccine-preventable infections using surveys, interviews, medical record review, and serum antibody titers. Conclusions reflect associations and do not imply causation.
Further detail is provided in the evidence synthesis tables (appendix e-5) and in the forest plot (figure e-2).

Data were insufficient to support or refute an association between development of MS and a history of diphtheria (one Class II study[15] with insufficient precision, OR 0.0139; 95% CI, 0.00–2.87), hepatitis, unknown type (2 imprecise Class II studies[15, 16] and a meta-analysis with insufficient precision, OR 0.075; 95% CI, 0–6.28; I^2 = 78%), measles (12 inconsistent Class II studies[15-26] and a meta-analysis with insufficient precision, OR 1.09; 95% CI, 0.86–1.37; I^2 = 56%; table e-1), meningitis (one Class II study[15] with insufficient precision, OR 1; 95% CI, 0.0006–3,342.36), mumps (9 inconsistent Class II studies[15, 17, 20-23, 25-27] and a meta-analysis with insufficient precision, OR 1.22; 95% CI, 0.89–1.67; I^2 = 84%), pertussis (2 Class II studies[15, 25] and a meta-analysis with insufficient precision, OR 0.93; 95% CI, 0.75–1.15, I^2 = 0%), polio (one Class II study[15] with insufficient precision, OR 1; 95% CI, 0.0006–3,342.36), rubella (8 inconsistent Class II studies[15-17, 21-23, 25, 26] and a meta-analysis with insufficient precision, OR 0.86; 95% CI, 0.66–1.11; I^2 = 66%), smallpox (one Class II study[15] with insufficient precision, OR 1; 95% CI, 0.0006–3,342.36), tuberculosis (2 Class II studies[15, 16] and a meta-analysis with insufficient precision, OR 1.77; 95% CI, 0.82–3.82; I^2 = 0), typhoid (one Class II study[15] with insufficient precision, OR 1; 95% CI, 0.24–4.11), and zoster (varicella-zoster virus [VZV],

chicken pox, and herpes zoster; 10 inconsistent Class II studies[15-17, 22-26, 28, 29] and a meta-analysis with insufficient precision, OR 1.03; 95% CI, 0.80–1.32, $I^2 = 83\%$) (table e-2).

Hepatitis B

In a Class II case-control study,[30] 675 patients with various autoimmune diseases were matched with healthy controls (HCs) for age, sex, ethnicity, and socioeconomic status. Serum was tested for hepatitis B core antibodies (anti-HBc). Of 98 patients with MS (type and other details unspecified), 2 (2%) had anti-HBc in their sera, compared with 15 of 140 (10.7%) controls (OR 0.19; 95% CI, 0.04–0.84).

Conclusion

It is possible that patients with MS have lower odds of prior hepatitis B infection compared with HCs (low confidence in the evidence, one Class II study OR 0.19; 95% CI 0.04–0.84).

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 based on one Class III case-control study (downgraded for spectrum bias).[31] In this study, 89 cases with relapsing−remitting MS (RRMS) and their first exacerbation of 1992 were matched to 89 controls with RRMS and a stable course in the preceding 3 months. Exposure to influenza (assessed by a structured interview) between groups was not significantly different (4/89 cases vs 8/89 controls, OR 0.5; 95% CI, 0.2–1.7).[31]

For VZV (VZV, chicken pox, or herpes zoster), 2 Class II studies were identified.[32, 33] One Class II case-control study[33] evaluated the presence of VZV DNA in peripheral blood mononuclear cells (PBMCs) from participants with RRMS during relapse (n = 15) or remission (n = 67). Varicella-zoster virus DNA was found in the PBMCs of 13/15 (87%) participants during relapse. No VZV DNA was found in the PBMCs of any of the participants on reevaluation after 2 months of remission post relapse. Varicella-zoster virus DNA was undetectable in all 67 participants with RRMS in remission (OR with Sweeting correction 6,948; 95% CI, 72–414,552). A subsequent study by the same authors[32] evaluated the presence of VZV DNA in PBMCs in 15 participants with MS during relapses and 19 during remission. All 15 participants during relapse and 4/19 participants in remission showed viral DNA in PBMCs (OR with Sweeting correction 1,060; 95% CI, 14–105,220). Combining these studies in a random-effects meta-analysis resulted in an OR of 2,796 (95% CI, 125–62,709, $I^2 = 0\%$).

Odds ratios are shown graphically in the forest plot (figure e-2).

Conclusion

It is probable that individuals with active MS exacerbations have higher odds of VZV viral DNA present in PBMCs than individuals with MS in remission (moderate confidence in the evidence, 2 Class II studies and a random-effects meta-analysis with OR of 2,796, 95% CI 125–62,709, I^2 = 0%). However, 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 (2 inconsistent Class II studies,[15, 34] and a meta-analysis with insufficient precision, OR 0.7; 95% CI 0.3–1.6; I^2 = 84%), hepatitis B (6 inconsistent Class II studies,[26, 35-39] one subgroup analysis of a prior study[40] and a meta-analysis with insufficient precision, OR 1.17; 95% CI, 0.89–1.55; I^2 = 69%), influenza (4 inconsistent Class II studies,[16, 26, 36, 38] and a meta-analysis with insufficient precision, OR 0.91; 95% CI, 0.67–1.23; I^2 = 55%), measles (4 inconsistent Class II studies,[15, 16, 26, 36] and a meta-analysis with insufficient precision, OR 1.3; 95% CI, 0.5–3.4; I^2 = 81%), mumps (4 inconsistent Class II studies,[15, 16, 26, 27] and a meta-analysis with insufficient precision, OR 0.91; 95% CI, 0.14–6.09; I^2 = 92%), measles−mumps−rubella (MMR) (one Class II study[36] with insufficient precision, OR 0.9; 95% CI; 0.4–1.8), poliomyelitis (2 Class II studies[15, 16] and a meta-analysis with insufficient precision, OR 0.81; 95% CI, 0.47–1.4; I^2 = 0%), rubella (3 inconsistent Class II studies[16, 26, 36] and a meta-analysis with insufficient precision, OR 1.47; 95% CI, 0.66–3.23; I^2 = 87%), typhoid (one Class II study[15] with insufficient precision, OR 0.68; 95% CI, 0.31–1.48), yellow fever (one Class II study[15] with insufficient precision, OR with Sweeting correction 0.07; 95% CI, 0–4), and VZV/chicken pox (3 inconsistent Class II studies[16, 27, 41] and a meta-analysis with insufficient precision, OR 1.37; 95% CI, 0.013–14.2; I^2 = 92%) (appendix e-4). Odds ratios are shown graphically in the forest plot (figure e-2).

Human papillomavirus vaccination

One Class I[42] and 2 Class II[39, 43] studies were identified.

A Class I prospective population cohort study[42] using the Civil Registration System in Denmark and Statistics Sweden register evaluated risk of MS development in girls and women aged 10–44 years over a 4- to 5-year period (2006–2012/2013). The cohort included 3,978,271 women and girls; 789,082 received HPV vaccination. The crude MS incidence rate was 21.54 (95% CI, 20.9–22.2) events per 100,000 person-years in nonvaccinated women and 6.12 (95% CI, 4.86–7.69) in vaccinated women in the 2-year period after the last dose of HPV vaccine. The OR of developing MS after HPV vaccination was 0.28 (95% CI, 0.12–0.7).
In a Class II case-control study[39] of 92 cases and 459 HCs, 4 (8.3%) cases and 8 (3.3%) controls, 6 (12.5%) cases and 15 (6.3%) controls, 8 (16.7%) cases and 30 (12.5%) controls, 13 (27.1%) cases and 50 (20.8%) controls, and 21 (43.8%) cases and 83 (34.6%) controls received HPV

vaccination at 42 days, 90 days, 180 days, 1 year, and 3 years, respectively, before MS symptom onset. The overall OR for developing MS up to 3 years after HPV vaccination was 1.05 (95% CI, 0.62–1.78). In another Class II case-control study,[43] 7/113 (6.2%) patients with MS or central demyelination (type and diagnostic criteria unspecified) and 173/863 (20%) HCs matched for age and place of residence had a history of HPV vaccination (OR 0.31; 95% CI, 0.13–0.73).

Conclusion

Human papillomavirus vaccination is probably associated with a lower likelihood of a subsequent MS diagnosis (moderate confidence in the evidence, one Class I study[42] and one Class II study[43] showing lower odds and one Class II[39] study with insufficient precision).

Pertussis vaccine

Two Class II studies were identified.[15, 27] In the first,[15] 9% of participants with MS and 19% of HCs reported pertussis vaccination (OR 0.42; 95% CI, 0.18–0.98). The second[27] also showed lower odds of MS with a history of pertussis vaccination compared with HCs (OR 0.27; 95% CI, 0.13–0.55). A random-effects meta-analysis found that a history of exposure to pertussis vaccination was associated with lower odds of developing MS (OR 0.3; 95% CI, 0.2–0.56; I^2 = 0).

Conclusion

Pertussis vaccination is probably associated with a lower likelihood of a subsequent MS diagnosis (moderate confidence in the evidence, 2 consistent Class II studies and a random-effects meta-analysis with OR 0.3; 95% CI, 0.2–0.56; $I^2 = 0$).

Smallpox vaccination

In a previously described Class II case-control study,[15] 78% (18/23) of participants with MS and 94% (119/127) of HCs reported smallpox vaccination (OR 0.23; 95% CI, 0.09–0.59).

Conclusion

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

Tetanus toxoid

Four Class II studies were identified.[15, 34, 36, 38] In a case-control study,[15] 35% of MS cases and 54% of HCs reported tetanus vaccination (OR 0.46; 95% CI, 0.26–0.81). In another study,[34] no differences were found in mean serum tetanus toxoid (TT) immunoglobulin G (IgG) antibody levels between MS cases and their matched HCs (mean titers ± SD: 3.7 ± 2.75 for cases, 4.46 ±

4.71 for controls; raw mean difference [RMD], 0.76; 95% CI, -0.6 to 2.12). The OR for MS associated with 1 SD difference in antibody titers in the baseline sample was 0.76 (95% CI, 0.48–1.21). In another case-control study,[38] 19/163 (11.7%) cases and 279/1,604 (17.4%) HCs had received TT (OR for developing MS, 0.6; 95% CI, 0.4–1). In the final case-control study,[36] on conditional logistic regression, 155/440 (35.2%) MS cases and 449/950 (47.3%) HCs were exposed to tetanus toxin (OR 0.6; 95% CI, 0.4–0.8); the association remained significant with analyses using more restrictive MS diagnostic criteria. A random-effects meta-analysis of the 4 studies yielded an OR of 0.61 (95% CI, 0.49–0.76, $I^2 = 0$).

Conclusion

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

Tuberculosis vaccine (bacille Calmette Guerin)

One Class I[44] and 2 Class II[16, 45] studies were identified. The Class I study[44] evaluated the effect of BCG on the progression of clinically isolated syndrome (CIS) to MS in 73 participants with CIS, 33 receiving BCG and 40 receiving placebo, observed blinded for 12 months and then up to 60 months in an open extension. All participants received IFNβ-1a from 6 months after BCG to 18 months after BCG (12 months). In the open-label extension, they received DMTs as advised by their neurologists. The cumulative mean number of total gadolinium (Gd)-enhanced MRI-detected lesions at 6 months was lower in the group that received BCG vaccination (3.09 ± 5.40) compared with placebo (6.62 ± 11.84) (relative risk using a binomial regression model: 0.54; 95% CI, 0.31–0.96). At 6-month follow-up, 45.5% of vaccinated participants developed one or more new Gd-enhanced MRI-detected lesions and met MS criteria of dissemination in time vs 75% of participants receiving placebo (OR 0.28; 95% CI, 0.15–0.51). In the (Class IV) open-label follow-up study, the cumulative probability of clinically definite MS at 60 months was lower in the group receiving BCG plus DMT vs the group receiving placebo plus DMT (hazard ratio 0.52; 95% CI, 0.27–0.99).

In a previously described Class II case-control study,[16] in a univariate logistic regression analysis, antecedent immunization with BCG was not associated with increased risk of MS (10/140 cases, 10/131 HCs; OR 1; 95% CI, 0.4–2.6). In another Class II case-control study,[45] 51 participants with MS and 34 matched HCs were evaluated for antibody reactivity to BCG. Anti-BCG IgG antibodies were found in 4/51 participants with MS and 6/34 HCs (OR 0.4; 95% CI, 0.1–1.5). A random-effects meta-analysis combining the 2 Class II studies found that individuals with MS had no higher odds of having a history of BCG vaccination than HCs (OR 0.7; 95% CI, 0.3–1.7; $I^2 = 16\%$).

Conclusions

Bacille Calmette-Guérin vaccination is probably not associated with an increased likelihood of progression to MS in patients with CIS (moderate confidence in the evidence, one Class I study, OR 0.28, 95% CI 0.15−0.51). There is insufficient evidence to conclude whether individuals with MS have higher odds of prior BCG vaccination than HCs (very low confidence in the evidence, 2 imprecise Class II studies and random-effects meta-analysis OR 0.7; 95% CI, 0.3–1.7; $I^2 = 16\%$, 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 any vaccination. For BCG (tuberculosis) vaccination, one Class I study[44] had insufficient precision (OR for relapse after vaccination 0.45; 95% CI, 0.08–2.5), and one Class III crossover study[46] found decreased odds of relapse after vaccination (OR 0.11; 95% CI, 0.02–0.70); however, one Class III study is insufficient to drive conclusions.

One Class II[47] study and one Class III[48] study evaluated risk of relapse after influenza vaccination in individuals with MS. Individual studies were insufficient to drive conclusions. A Class I study included in the original guideline (rated as Class II in the original guideline and Class I during update process) was not included in this update because it was published before 1990. The study also had insufficient precision to drive conclusions. When the Class II and Class III studies with replicable results were combined,[47, 48] precision remained insufficient to drive a conclusion (OR 1.04, 95% CI 0.31–3.46, $I^2 = 0$). Odds ratios are shown graphically in the forest plot (figure e-2).

A Class III study,[49] which evaluated a single IM dose of tick-borne encephalitis (TBE) vaccine, had insufficient precision to drive a conclusion (OR 0.62; 95% CI, 0.08–4.34).

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?

Data were identified only for influenza vaccines. Three Class III case-control studies evaluated the trivalent influenza vaccine,[48, 50, 51] one of which also evaluated the 2009 H1N1 vaccine.[51] In the first study,[48] presumed influenza occurred in 2/11 vaccinated participants with MS and in 1/9

matched vaccinated HCs (OR 1.78; 95% CI, 0.13–23.5). A 4-fold increase in antibody titers to the influenza A/Texas strain was noted in the vaccinated participants with or without MS but not in participants with MS receiving placebo. In the next study,[50] 12 participants with MS and 28 matched HCs received one IM dose of trivalent subunit influenza vaccine during 2 vaccination periods (1998–1999, 1999–2000). Six of 12 participants with MS and 4/28 controls had respiratory infections during the subsequent winter (OR 6; 95% CI, 1.27–28.25). In the final study,[51] 49 participants with MS and 73 HCs received trivalent seasonal influenza vaccine (Influvac or Vaxigrip). Sixty-nine percent of vaccinated participants with MS developed protective hemagglutination inhibition (HI) antibody titers to H1N1 compared with 71% of controls (OR of successful vaccination 0.9; 95% CI, 0.5–1.7; OR of insufficient titers 1.09; 95% CI, 0.50–2.39). Participants with MS received different immunotherapies, and titers varied by treatment. The same study evaluated H1N1 vaccination in 131 participants with MS receiving various therapies and 216 HCs during the 2009 pandemic.[51] Only 27.4% of cases vs 43.5% of HCs had evidence of a protective effect (HI titer >40) (OR of protective titers 0.5; 95% CI, 0.27–0.89; OR of evidence of insufficient titers 2.04; 95% CI, 1.25–3.34). Data for the 4 cohorts (from 3 studies) were combined in a meta-analysis to assess the odds of an insufficient response in participants with MS (as suggested by subsequent infection or insufficient titers), yielding an OR of 1.87 (95% CI, 1.07–3.27, $I^2 = 27\%$). Odds ratios are shown graphically in the forest plot (figure e-2).

Conclusion

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, one of which included 2 separate cohorts [2 with sufficient precision individually], and a meta-analysis showing increased odds but with CIs including values of limited clinical significance: OR 1.87 (95% CI, 1.07–3.27, $I^2 = 27\%$).

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

Most of the data for this question result from studies investigating the impact of ISIM treatment on influenza vaccines, with a few studies investigating the effect on other vaccines. Additional study details are available in the evidence profile tables (appendix e-4) and in the forest plot (figure e-2).

Influenza vaccines

IFN-β

Six studies (2 Class I,[52, 53] 3 Class II,[51, 54, 55] and one Class III[56]) were identified. Control groups varied by study (table e-3). Only 2 of the studies[53, 55] directly addressed the clinical question

comparing the effectiveness results of immunization in patients with MS who were receiving IFN with those not receiving IFN. 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[51, 52, 54] or in participants with MS receiving other ISIM treatments.[52, 56] 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. For the studies evaluating multiple influenza strains in the same cohort,[53-56] fixed-effects meta-analyses combined responses to obtain a single measure for each cohort to use in the random-effects meta-analysis. For the study[51] including multiple years, data for H1N1 and H3N2 in the 2010 cohorts were combined in a fixed-effects meta-analysis but data from the 2009 cohort were maintained separately because of the inclusion of different individuals. Data from first follow-up were used to minimize bias from attrition. This approach to meta-analysis was also used for all other analyses in this section. The final random-effects meta-analysis resulted in an OR of 1.51 (95% CI, 0.79–2.90; I^2 =55%; see table e-3).

Conclusion

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, 3 Class II studies, and one Class III study, with one of the Class II studies including 2 separate cohorts; 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%]).

Glatiramer acetate

The panel identified 2 studies of seroprotection in people with MS receiving glatiramer acetate. The first study (Class I)[53] compared seroprotection in participants with MS receiving glatiramer acetate with seroprotection in participants with MS not receiving ISIM therapy, and the second study (Class II)[51] compared seroprotection in participants with MS receiving glatiramer acetate with seroprotection in HCs (table e-3). Meta-analysis yielded an OR for seroprotection of 0.39 (95% CI, 0.21–0.74; I^2 = 0%).

Conclusion

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; one Class I study and one Class II study 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%).

Fingolimod

Two Class I[53, 57] and 2 Class III studies[58, 59] were identified. Because there are 2 Class I studies, the Class III studies are not reviewed here. For rates of protection in participants with MS receiving fingolimod vs no treatment[53] and fingolimod vs placebo,[57] a meta-analysis yielded odds of 0.35 (95% CI, 0.21–0.57; I^2 = 0%) for seroprotection in participants with MS receiving

fingolimod.

Conclusion

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, one with sufficient precision and one with insufficient precision; meta-analysis OR 0.35; 95% CI, 0.21–0.57; $I^2 = 0\%$).

Natalizumab

One Class I[53] and 2 Class II studies were identified[51, 60] (table e-3), with one of the Class II studies reporting the percentage of participants with MS and HCs achieving a greater than 50% increase in antibodies after vaccination rather than seroprotection rates.[60] No study had sufficient precision to inform conclusions on its own. A meta-analysis of all 3 studies yielded odds of 0.57 (95% CI, 0.30–1.07; $I^2 = 0\%$) for a response to influenza vaccination (either seroprotection or greater than 50% increase in antibody titers) in participants with MS receiving natalizumab compared with various controls.

Conclusion

There is insufficient evidence to support or refute whether individuals with MS receiving natalizumab therapy differ in likelihood of response to influenza vaccination compared with various controls (very low confidence in the evidence; one Class I and 2 Class II studies [one of which had 2 cohorts], each with imprecision on its own, and a meta-analysis with OR 0.57 [95% CI, 0.30–1.07; $I^2 = 0\%$]. However, the low point estimate makes a decreased response plausible.

Daclizumab

One Class II[61] study and one Class III[62] study were identified. In the Class II study,[61] 23 participants with RRMS treated with daclizumab were compared with 10 untreated participants with MS and 4 HCs (combined control group). All participants in the treated and untreated groups had baseline immunity to at least one of the 3 viral strains; 9/42 possible participant−variant combinations in the control group and 8/51 in the daclizumab-treated group did not fulfill criteria for seroprotection on day 0 (denominators represent the combination of antibodies to all 3 virus strains tested in the group). After treatment with a trivalent influenza vaccine (Afluria), 7/8 participant−viral strain pairs without preexisting immunity in the daclizumab-treated group seroconverted compared with all 9 participant−viral strain pairs for controls (OR with Sweeting correction 0.087; 95% CI, 0.0014–3.73). In the Class III study,[62] 90 participants with RRMS receiving daclizumab received the seasonal vaccine (Influvac/Imuvac) in a single IM dose; seroprotection rates were compared with rates for a historical HC group from a published meta-analysis[63] (table e-3). A meta-analysis of the 2 studies yielded odds of seroprotection in response to influenza vaccine of 0.68 (95% CI, 0.1−4.57; $I^2 = 36\%$).

Conclusion

There is insufficient evidence to support or refute whether individuals with MS receiving daclizumab therapy differ in likelihood of response to influenza vaccination compared with

normal controls (very low confidence in the evidence; one imprecise Class II study and one Class III study; meta-analysis OR 0.68; 95% CI, 0.1–4.47; $I^2 = 36\%$). However, the high proportion of participants achieving seroconversion/seroprotection while treated with daclizumab make an adequate response plausible.

Teriflunomide

In the previously described Class III TERIVA cohort study,[56] participants with MS receiving teriflunomide (7 or 14 mg) were compared with those receiving IFN-β as a reference standard (table e-3). Odds ratios for the 2 doses were combined in fixed-effect meta-analyses and then in a random-effects meta-analysis for both doses and all vaccines (H1N1, H3N2, influenza B), which resulted in an OR of 0.86 (95% CI, 0.42–1.75; $I^2 = 0\%$) for a vaccination response in individuals receiving teriflunomide vs a response in those receiving IFN–β.

Conclusion

There is insufficient evidence to support or refute whether individuals with MS receiving teriflunomide differ in likelihood of response to influenza vaccination compared with individuals with MS receiving IFN-β therapy (very low confidence in the evidence; one Class III study with decreased confidence for imprecision, OR 0.86, 95% CI, 0.42–1.75; $I^2 = 0\%$). The high proportions of participants in the teriflunomide group who achieved seroprotection (>90%) suggest that an adequate response to vaccination in the context of teriflunomide is plausible.

Mitoxantrone

One Class II study was identified.[51] Results of seroprotection rates to H1N1 and H3N2 from the 2010 cohort were combined in a fixed-effects meta-analysis, which was then combined with data for the 2009 cohort of seroprotection rates to H1N1 in a random-effects meta-analysis. The odds were 0.11 (95% CI, 0.026–0.45; $I^2 = 0\%$) for a response to influenza vaccination in participants receiving mitoxantrone compared with HCs (table e-3).

Conclusion

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; one Class II study with 2 separate cohorts, each showing a reduced response, random-effects meta-analysis OR 0.11, 95% CI, 0.026–0.45; $I^2 = 0\%$).

Methotrexate, 6-mercaptopurine

A Class II study[64] compared the immune responses of individuals with MS receiving methotrexate and 6-mercaptopurine with those receiving placebo as part of a clinical trial and with 2 HC groups. Twenty-three participants received 2 subcutaneous injections of bivalent influenza vaccine 1 month apart. Mean increase in HI titers for Hong Kong influenza/influenza B were 2.8/1.2 for participants with MS and 1.6/2.0 for HCs. Confidence intervals could not be calculated.

Conclusion

There is insufficient evidence to support or refute whether individuals with MS receiving methotrexate/6-mercaptopurine therapy differ in likelihood of response to influenza vaccination compared with various controls (very low confidence in the evidence; one Class II study with insufficient statistical information to evaluate precision).

BCG vaccine

IFN-β. In the previously described Class II case-control study,[45] 0/8 participants with MS receiving IFN-β mounted an IgG response to BCG and 4/43 participants not receiving IFN-β had IgG antibodies to BCG (OR 1.6; 95% CI, 0.1–17).

Conclusion

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 (very low confidence in the evidence; one imprecise Class II study).

Tetanus toxoid

Fingolimod. In a previously described Class I multicenter RCT,[57] participants with MS received a TT booster dose at week 6. Individuals with MS receiving fingolimod had a significantly lower TT responder rate (the primary outcome) than that of participants with MS receiving placebo at 3 weeks (40% vs 61%; OR 0.43; 95% CI, 0.20–0.92), but the difference at 6 weeks was not significant (38% vs 49%; OR 0.62; 95% CI, 0.29–1.33). Seroprotection rates were high for both groups at 3 weeks (fingolimod group 92%, placebo group 91%; OR 1.22; 95% CI, 0.35–4.2) and 6 weeks (fingolimod group 92%, placebo group 84%; OR 2.1; 95% CI, 0.7–6.0).

Conclusion

It is probable that individuals with MS receiving fingolimod have a lower likelihood of response to a TT booster at 3 weeks post 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, 0.35–4.2) or 6 weeks (OR 2.1; 95% CI, 0.7–6.0) because of limited precision for those outcomes (one Class I study[57] with insufficient precision for some outcomes). The high proportions of participants in the fingolimod group who achieved seroprotection (>90%) suggest that an adequate response to vaccination in the context of fingolimod is plausible.

Natalizumab. One Class II study[65] randomized participants with RRMS to a control group (n = 30, no ISIM treatments) or to natalizumab for 6 months followed by TT immunization in month 7. Per-protocol analysis revealed that 24/24 controls and 15/16 participants treated with natalizumab were responders (2-fold or greater increase in anti−TT titers) at day 28 (OR with Sweeting correction 0.0375; 95% CI, 0.0003–2.7601). At day 56, 21/22 controls and 14/15 participants treated with natalizumab were responders (OR 0.67; 95% CI, 0.04–11.6).

Conclusions

There is insufficient evidence to support or refute whether individuals with RRMS receiving natalizumab are likely to differ in response to TT compared with individuals with MS not receiving such treatment (very low confidence in the evidence, one imprecise Class I study). The high proportions of participants in the natalizumab group who were responders (>90%) suggest that an adequate response to TT vaccination in the context of natalizumab is plausible.

Dimethyl fumarate. One Class I study was available.[66] Thirty-eight participants with RRMS treated for at least 6 months with DMF 240 mg/d were compared with 33 participants treated for at least 3 months with nonpegylated IFN-β. Twenty-six of 38 participants receiving DMF vs 24/33 participants treated with IFN-β had a 2-fold rise in antibody titers to TT at 4 weeks (OR 0.81; 95% CI, 0.30–2.21).

Conclusion
There is insufficient evidence to support or refute whether individuals with MS receiving DMF are likely to differ in response to TT vaccination compared with participants with MS receiving IFN-β (very low confidence in the evidence; one imprecise Class I study).

Diphtheria toxoid

Dimethyl fumarate. In a Class I study,[66] 22/38 participants with RRMS receiving DMF responded to diphtheria toxoid (≥2-fold antibody titer rise) compared with 20/33 participants treated with IFN-β (OR 0.89; 95% CI, 0.35–2.31).

Conclusion
There is insufficient evidence to support or refute whether individuals with MS receiving DMF are likely to differ in response to diphtheria vaccination compared with individuals with MS receiving IFN-β therapy (very low confidence in the evidence; one imprecise Class I study).

Pneumococcal vaccine

Dimethyl fumarate. In a Class I study,[66] 25/38 participants treated with DMF responded to pneumococcal vaccine serotype 3 (≥2-fold antibody titer rise) vs 26/33 participants treated with IFN-β (OR 0.52; 95% CI, 0.18–1.5). For pneumococcal serotype 8, responses were seen in 36/38 participants treated with DMF and 29/33 participants treated with IFN-β (OR 2.5; 95% CI, 0.48–13.4).

Conclusion
There is insufficient evidence to support or refute whether individuals with MS receiving DMF are likely to differ in response to pneumococcal polysaccharide vaccines compared with individuals with MS receiving IFN-β therapy (very low confidence in the evidence; one imprecise Class I study).

Alemtuzumab. One Class III cohort study[67] using historical HCs evaluated the effect of alemtuzumab on response to various vaccines. Seroconversion to pneumococcal polysaccharide serotype 3 was noted in 11/15 participants with MS compared with 50/106 historical HCs[68] (OR 3.08; 95% CI, 0.98–9.92). Seroconversion to pneumococcal polysaccharide serotype 8 was noted in 19/20 participants compared with 90/106 historical HCs[68] (OR 3.38; 95% CI, 0.55–22.17). Eighteen of 21 (88%) participants mounted an adequate immune response by expert consensus definition.[69]

Conclusion
There is insufficient evidence to support or refute whether individuals with MS receiving alemtuzumab are likely to differ in response to pneumococcal polysaccharide vaccines compared with HCs (very low confidence in the evidence; one Class III study with varying precision).

Meningococcal vaccine

Dimethyl fumarate. In a Class I study,[66] 20/38 participants receiving DMF responded to meningococcal vaccine serogroup C (≥2-fold antibody titer rise) compared with 17/32 participants receiving IFN-β (OR 0.98; 95% CI, 0.38–2.50).

Conclusion
There is insufficient evidence to support or refute whether individuals with MS receiving DMF are likely to differ in response to meningococcal vaccination compared with individuals with MS receiving IFN-β therapy (very low confidence in the evidence; one imprecise Class I study).

Alemtuzumab. In a Class III study[67] of 23 participants receiving alemtuzumab and meningococcal vaccine, 19 seroconverted at 4 weeks compared with 41/42 adult historical HCs[70] (OR 0.12; 95% CI, 0.012– 1.1).

Conclusion
There is insufficient evidence to support or refute whether individuals with MS receiving alemtuzumab are likely to differ in response to meningococcal vaccination compared with historical HCs (very low confidence in the evidence; one Class III study).

Haemophilus influenzae *type b*
Alemtuzumab. In a Class III study,[67] 18/19 participants seroconverted to *Haemophilus influenzae* type b (Hib) compared with 60/73 historical HCs[71] (OR 3.9; 95% CI, 0.62–25.27).

Conclusion

There is insufficient evidence to support or refute whether individuals with MS receiving alemtuzumab are likely to differ in response to Hib vaccination compared with historical HCs (very low confidence in the evidence; one Class III study with insufficient precision).

PUTTING THE EVIDENCE INTO CLINICAL CONTEXT

This document updates the 2002 AAN guideline "Immunization in multiple sclerosis: a summary of published evidence and recommendations."[1] Conclusions differ from those in the prior guideline because of updated guideline methodology,[10] 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 prior guideline. The 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, antibody responses) may have affected results. For evaluation of vaccine effectiveness, only a few RCTs were found; most studies used a cohort design. 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, as 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 use of specific agents for immunization-related recommendations.

PRACTICE RECOMMENDATIONS

In this section, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

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 (EVID). Vaccine-preventable infections can be associated with morbidity and mortality (PRIN). 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 (INFER). An ongoing dialogue regarding immunization will help clinicians to understand patients' beliefs and preferences and help patients make choices regarding immunizations (PRIN).

Statement 1a

Clinicians should discuss with their patients the evidence from the SR regarding immunization in MS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 6	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 3	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 1	Usually 2	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 7	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 2	Modest 3	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 2

Rationale

All unvaccinated individuals are at a higher risk of acquiring vaccine-preventable infections (PRIN). Although there is no evidence that MS alone increases the risk of acquiring vaccine-preventable infection (EVID), individuals with MS have at least the same risk as unvaccinated individuals without MS (PRIN). Individuals with MS receiving immunosuppressive therapy as part of MS treatment may be at increased risk of infections (PRIN). There is no evidence that vaccination increases the risk of MS exacerbation, although the literature is sparse (EVID). 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 (RELA).[72] Thus, vaccination of patients with MS is expected to have personal and population-level benefits (INFER).

Statement 2

Clinicians should recommend that patients with MS follow all local vaccine standards (e.g., from the CDC, the World Health Organization [WHO], and local regulatory bodies) unless there is a specific contraindication (e.g., active treatment with ISIM agents) (Level B*).

* No consensus due to disagreement on variation in patient preferences. However, the majority of panel members rated variation in patient preferences as minimal, whereas a minority rated it moderate. Because only one or 2 panelists rated it modest (the in-between category), there is less than 80% of votes within 1 ordinal rank. Being conservative (i.e., making assumptions in a direction toward a weaker recommendation), the panel would have attained consensus if the voters judging "minimal" judged

"modest" (more conservative). This still would justify a Level B recommendation.

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 0	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 3	Modest 2	Minimal 6	No
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 3

Rationale

Prevalence of vaccine-preventable diseases and seropositivity for them vary by country and region (PRIN), 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.[73] 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 (TST) or IFN-γ release assay (IGRA), (2) have no evidence of prior 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, prison settings) (RELA).[74] The CDC recommendations for BCG are limited to children and adults in specific clinical situations.[75] This region-specific disease epidemiology informs the risk–benefit discussion of vaccination in MS (INFER, PRIN). 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 (INFER).

Statement 3

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

*No consensus due to disagreement on variation in patient preferences. However, the

majority of panel members rated variation in patient preferences as minimal, whereas a minority rated it moderate. Because only 1 or 2 rated it modest (the in-between category), there is less than 80% of votes within 1 ordinal rank. Being conservative (i.e., making assumptions in a direction toward a weaker recommendation), the panel would have attained consensus if the voters judging "minimal" judged "modest" (more conservative). This still would justify a Level B recommendation.

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 5	Yes
Variation in preferences	Large 1	Moderate 2	Modest 1	Minimal 7	No
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 4

Rationale

Multiple sclerosis exacerbations are associated with increased short- and long-term disability (RELA).[76] Although the SR found insufficient evidence to support or refute an association between a history of influenza infection and MS exacerbations (EVID), one study not meeting criteria for the SR found that influenza infections increase exacerbation risk compared with vaccination (RELA).[77] Influenza infections may also cause increased morbidity and mortality for individuals on whom chronic diseases have had a severe impact (PRIN). There is also insufficient evidence to support or refute an association between influenza vaccination and MS exacerbations (EVID). 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 (INFER), although patients with MS receiving some ISIM treatments (fingolimod, glatiramer acetate, mitoxantrone) may have a reduced response to influenza vaccination (EVID). Although the SR identified no evidence regarding vaccine response in individuals with MS receiving rituximab (EVID), evidence regarding rituximab use in neuromyelitis optica spectrum disorders[52] and in rheumatoid arthritis[78] suggest that rituximab can be associated with reduced influenza vaccine responsiveness (RELA).

Statement 4

Clinicians should recommend that patients with MS receive the influenza vaccination annually,

unless there is a specific contraindication (e.g., prior severe reaction) (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 10	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 2	Modest 5	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 4	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 5

Rationale for 5a and 5b

Immunosuppressive or immunomodulatory medications now used to treat MS include alemtuzumab, DMF, fingolimod, mitoxantrone, natalizumab, ocrelizumab, rituximab, and teriflunomide (PRIN). These treatments have been associated with severe occurrences or recurrences or both of vaccine-preventable infections, including VZV and hepatitis B (RELA).[79-84] Although the panel identified no studies showing an increased risk associated with immunization with live vaccines in patients with MS receiving ISIM medications (EVID), studies regarding the safety of live vaccines during MS treatment with ISIM medications are scarce (EVID). 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 (RELA).[85] Fingolimod PI also recommends avoiding live vaccines during treatment and for 2 months after discontinuation (RELA).[85] The PI for teriflunomide recommends against using live vaccines during treatment and for 6 months after discontinuation (RELA).[86] For alemtuzumab, the PI recommends against the use of live vaccines for 6 weeks before treatment initiation, during treatment, and after "recent" treatment (RELA).[87] 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 (RELA).[88]

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 0	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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 PI (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 1	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Rationale 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 (RELA),[79-84] and their manufacturers' PIs have treatment-specific guidance for immunization with live vaccines (RELA).[85-88] 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 (PRIN). 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 (INFER).

Statement 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).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 6	Critically important 5	Yes
Variation in preferences	Large 1	Moderate 2	Modest 3	Minimal 6	No
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

* Failed to meet consensus because of variation in patient preferences. Recommendation downgraded to Level C.

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 (PRIN, RELA).[89-92] 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 (RELA).[86] The PI also recommends treatment for tuberculosis in patients who test positive for tuberculosis before initiating teriflunomide treatment (RELA).[86] The PI for alemtuzumab recommends tuberculosis screening according to local guidelines.[87]

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 (PRIN). Severe active/chronic infections such as tuberculosis and hepatitis infection are listed as contraindications to fingolimod by the European Medicines Agency (RELA).[93] The risk of latent tuberculosis varies by country (PRIN). 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) (PRIN), potentially resulting in an underestimation of the activation risk of latent tuberculosis from the use of ISIM medications other than teriflunomide (INFER).
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 (RELA).[88] 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 (RELA).[87] 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 (RELA).[87] 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 (RELA).[87]

Statement 6a

Clinicians must screen for certain infection (e.g., hepatitis, tuberculosis, VZV) according to the PI 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 PI (Level B based on feasibility and cost relative to benefit).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 1	Modest 1	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 1	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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, tuberculosis) before starting MS treatment with ISIM medications even when not specifically mentioned in PI (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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 8	Yes
Variation in preferences	Large 1	Moderate 1	Modest 3	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 3	Usually 5	Always 3	No
Cost relative to net benefit	Very large 0	Large 1	Moderate 4	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 7

Rationale 7a

Although there is no evidence that patients with MS who are receiving ISIM therapy have increased risk with immunization with live vaccines (EVID), 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 (PRIN). Prescribing information in package inserts for alemtuzumab, fingolimod, ocrelizumab, and teriflunomide recommend against the use of live vaccines during and immediately preceding treatment (RELA).[85-88] 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 (RELA).[85-88]

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 7	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Rationale 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) (PRIN). Infections can result in morbidity and mortality in general and also increase the risk of MS exacerbation (RELA).[77, 94] Particularly because of the lack of evidence proving increased risks with the use of live vaccines in individuals using ISIM agents (EVID), circumstances of high infection risk should prompt reconsideration of the pros and cons of immunization with live vaccines in individuals receiving ISIM therapy (INFER).

Statement 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).*

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 5	Critically important 4	Yes
Variation in preferences	Large 2	Moderate 1	Modest 6	Minimal 2	No
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 7	Yes
Cost relative to net benefit	Very large 1	Large 0	Moderate 4	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

* Failed to meet consensus because of variation in patient preferences, benefit relative to harm, and importance of outcomes. Recommendation downgraded to Level C.

Recommendation 8

Rationale

The guideline panel identified no evidence that vaccines increase the risk of relapse or worsen relapse severity, but studies are limited (EVID). Experts remain concerned that vaccines may worsen relapse severity if given to patients who are actively experiencing an MS relapse (PRIN). 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" (RELA).[95] Immunization is not typically an urgent need and, in most cases, can be temporarily delayed without a marked increase in infection risk (PRIN).

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 6	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

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 plans (Risk-MAPs) and risk evaluation and mitigation strategies (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.

Table e-1. Studies investigating an association between measles and multiple sclerosis

Reference	Study design, method for ascertaining history of measles[a]	Cohort with MS	Controls	OR for diagnosis of MS with history of measles[a] in participants with MS vs controls
Ahlgren 2011	Case-control study Measured prevalence of measles antibodies in serum, CSF	N = 166 (124 RRMS, 42 CIS)	50 healthy controls	Serum: OR 1.36 (95% CI, 0.45–4.07). CSF: MS 74% vs controls 34%, OR 5.52 (95% CI, 3–10)
Bager 2004	Case-control study School vaccination records (Cohort 1 born since 1940, cohort 2 born since 1950)	Cohort 1: N = 455 Cohort 2: N = 182	Cohort 1: N = 1,801 Cohort 2: N = 690	OR 0.8 (95% CI, 0.6–1.1)
Comabella 2010	Case-control study Seroprevalence of antibodies against measles	N = 25 (21 RRMS, 2 PPMS, 1 SPMS, 1 CIS)	46 siblings	Measles antibodies present in 100% of participants, controls OR 0.548 (95% CI, 0.0217–13.9)
da Silva 2009	Case-control study Face-to-face interviews using a standardized	N = 81	81 matched controls (friends/neighbors)	OR 1.2 (95% CI, 0.6–2.7)

	questionnaire			
Khaki 2011	Case-control study Seroprevalence of measles IgG and IgM antibodies	N = 60 (RRMS)	61 matched controls	Seroprevalence for IgM: OR 3.2 (95% CI 1.5–6.9) Seroprevalence for IgG: OR 0.67 (95% CI, 0.24–1.9)
Kinnunen 1990	Retrospective twin cohort study Seropositivity	N = 17 Twins with MS	17 paired twins without MS	4-fold higher measles HI titer: OR 4.09 (95% CI, 0.69–24)
Kurtzke 1997	Case-control study Questionnaires/surveys	N = 23	69 siblings/relatives 37 spouses/ neighbors 21 distant matched controls and their spouses	OR 0.37 (95% CI, 0.15–0.93)
Ramagopalan 2009	Canadian database, longitudinal population–based cohort Questions about history of childhood infections	14,362 MS index cases (58% RRMS)	7,671 spouse controls	OR 0.97 (95% CI, 0.91–1.05)
Sündstrom 2004	Case-control study using MS registry database, serum sample databases Seropositivity Prospective cohort: serum collection before MS;	Prospective cohort: N = 73 Retrospective cohort: N = 161	219 matched controls	IgG antibodies to measles (prospective cohort): OR 1 (95% CI, 0.0002–10,161.82)

	retrospective cohort: serum collection after definite MS			Seropositivity to measles (retrospective cohort): OR 0.57 (95% CI, 0–4.5)
Zorzon 2003	Case-control study Face-to-face interviews by masked investigators using structured questionnaire	N = 140	131 matched controls	OR 1.3 (95% CI 0.6–3)
Abbasi 2017	Case-control study Questionnaire in face-to-face interview	N = 660	421 matched controls	OR 1.6 (95% CI, 1.05–2.45)
Shaygannejad 2016	Case-control study Questionnaire survey	N = 536 (RRMS, SPMS, PPMS, progressive–relapsing MS, PRMS)	399 matched controls	OR 1.57 (95% CI, 1.12–2.20)

[a]History of measles as defined by study (e.g., serum titers, survey responses)

Abbreviations: CI = confidence interval; CIS = clinically isolated syndrome; HI = hemagglutination inhibition; IgG = immunoglobulin G; IgM = immunoglobulin M; MS = multiple sclerosis; OR = odds ratio; PPMS = primary progressive MS; RRMS = relapsing−remitting MS; SPMS = secondary progressive MS.

Table e-2. Vaccine-preventable infection data insufficient to support an association with MS

Vaccine-preventable infection	Reference (class)	OR for MS with history of infection (95% CI)	Conclusion
Diphtheria	Kurtzke 1997 (Class II)	0.0139 (0.00-2.87)	Data were insufficient to support or refute an association between development of MS and a history of diphtheria (very low confidence in the evidence; one imprecise Class II study
Hepatitis (unknown type)	Kurtzke 1997 (Class II) Zorzon 2003 (Class II)	0.0051 (0.00-2.873) 0.5 (0.1-1.5) Meta-analysis: 0.075 (0-6.28), I^2 = 78%	Data were insufficient to support or refute an association between development of MS and a history of hepatitis of unknown type (very low confidence in the evidence; two imprecise Class II studies and a meta-analysis with insufficient precision
Meningitis (type unspecified)	Kurtzke 1997 (Class II)	1 (0.0006-3,342.36)	Data were insufficient to support or refute an association between development of MS and a history of meningitis, type unspecified (very low confidence in the evidence; one imprecise Class II study
Mumps	Bager 2004 (Class II) da Silva 2009 (Class II) Harandi 2012 (Class II) Khaki 2001 (Class II) Kinnunen 1990 (Class	0.8 (0.6-1.1) 1.1 (0.5-2.3) 1.5 (1-2.2) 9.5 (3-29.6) 1 (0.06-17.4)	Data were insufficient to support or refute an association between development of MS and a history of mumps (very low confidence in the evidence; 9 inconsistent Class II studies and a meta-analysis with insufficient precision)

	II) Kurtzke 1997 (Class II) Ramagopalan 2009 (Class II) Abbasi 2017 (Class II) Shaygannejad 2016 (Class II)	0.45 (0.25-0.88) 0.98 (0.92-1.05) 1.85 (1.22−2.78) Meta-analysis: 1.22 (0.89-1.67), I^2 = 84%	
Pertussis	Bager 2004 (Class II) Kurtzke 1997 (Class II)	0.9 (0.7-1.1) 1.22 (0.6-2.5) Meta-analysis: 0.93 (0.75-1.15), I^2 = 0%	Data were insufficient to support or refute an association between development of MS and a history of pertussis (very low confidence in the evidence; 2 Class II studies and a meta-analysis with insufficient precision)
Polio	Kurtzke 1997 (Class II)	1 (0.0006-3,342.36)	Data were insufficient to support or refute an association between development of MS and a history of polio (very low confidence in the evidence; one imprecise Class II study)
Rubella	Bager 2004 (Class II) da Silva 2009 (Class II) Kinnunen 1990 (Class II) Kurtzke 1997 (Class II) Ramagopalan 2009 (Class II)	1 (0.7-1.4) 0.4 (0.2-0.9) 2.13 (0.18-26) 0.42 (0.22-0.78) 0.93 (0.87-1) 0.8 (0.5-1.3)	Data were insufficient to support or refute an association between development of MS and a history of rubella (very low confidence in the evidence; 9 inconsistent Class II studies and a meta-analysis with insufficient precision) confidence in the evidence; 6 Class II studies and a random-effects meta-analysis with

	Zorzon 2003 (Class II) Abbasi 2017 (Class II) Shaygannejad 2016 (Class II)	Meta-analysis: 0.86 (0.66-1.11), I^2 = 66%	decreased confidence in the evidence because of insufficient precision; OR 0.78, 95% CI, 0.59 to 1.02, I^2 = 57%).
Smallpox	Kurtzke 1997 (Class II)	1 (0.0006-3,342.36)	Data were insufficient to support or refute an association between development of MS and a history of smallpox (very low confidence in the evidence; one imprecise Class II study)
Tuberculosis	Kurtzke 1997 (Class II) Zorzon 2003 (Class II)	1.66 (0.73-1.74) 2.9 (0.3-28.5) Meta-analysis: 1.77 (0.82-3.82), I^2 = 0	Data were insufficient to support or refute an association between development of MS and a history of mumps (very low confidence in the evidence; 2 Class II studies and a meta-analysis with insufficient precision)
Typhoid	Kurtzke 1997 (Class II)	1 (0.24-4.11)	Data were insufficient to support or refute an association between development of MS and a history of typhoid (very low confidence in the evidence; one imprecise Class II study)
Varicella-zoster virus (chicken pox, herpes zoster)	Bager 2004 (Class II) da Silva 2009 (Class II) Kurtzke 1997 (Class II)	1.1 (0.7-1.5) 0.7 (0.3-1.7) 0.51 (0.29-0.91) 334.479 (1.968-	Data were insufficient to support or refute an association between development of MS and a history of varicella zoster infection (very low confidence in the evidence; 10

	Mancuso 2007 (Class II) Ramagopalan 2009 (Class II) Sündstrom 2004(Class II, serum collected before MS diagnosis) Sündstrom 2004 (Class II, serum collected after MS diagnosis) Zorzon 2003 (Class II) Abbasi 2017 (Class II) Shaygannejad 2016 (Class II) Bager 2004 (Class II)	49,714.67) 1.07 (1-1.14) 0.45 (0.14-1.43) 2.6 (1.5-4.6) 1 (0.5-1.7) Meta-analysis: 1.03 (0.80-1.32), I^2 = 83%	inconsistent Class II studies and a meta-analysis with insufficient precision)

Abbreviations: CI = confidence interval; MS = multiple sclerosis; OR = odds ratio.

Table e-3. Frequency of influenza seroprotection in patients receiving MS treatment

Treatment	Reference	Vaccine/Infection	Frequency of seroprotection % (95% CI)		OR for seroprotection in patients with MS receiving treatment vs controls (95% CI)
			Treatment group	Control group	
IFN–β	Bar–Or 2013[56] (Class III)	H1N1	97.7% (93.9–100)	N/A	N/A
		H3N2	90.7% (83.4–98)	N/A	N/A
		Influenza B	93.0% (86.6–99.4)	N/A	N/A
	Kim 2013[52] (Class I)	*H1N1*	*87.5% (52.9–97.8)*	*100% (67.6–100)*	*0.10[a] (0.0016–4.1285)*
	Olberg 2018[53] (Class I)	H1N1	88.0% (72.8–96.3)	92.9% (68.5–98.7)	0.56 (0.06–4.50)
		H3N2	44.0% (26.7–62.9)	42.9% (21.4–67.4)	1.05 (0.29–3.70)
	Mehling 2013[54] (Class II) Olberg 2014[51] (Class II)	*Influenza A*	*100% (87.1–100)*	*91% (76.4–96.9)*	*86.9[a] (0.66–15202)*
		Influenza B	*100% (87.1–100)*	*81.8% (65.6–91.4)*	*191.8[a] (1.5–20382)*
		H1N1 (2009)	*44.4% (29.5–60.4)*	*43.5% (37.1–50.2)*	*1.03 (0.5–2.1)*
	Mehling 2013[54]	*H1N1 (2010)*	*88.2% (65.6–96.7)*	*69.4% (55.5–80.5)*	*3.3 (0.77–15.1)*

	(Class II)	*H3N2 (2010)*	*88.2% (65.6–96.7)*	*79.5% (68.8–87.1)*	*1.9 (0.45–8.7)*
	Schwid 2005[55] (Class II)	Panama strain	93.0% (85.4–97.4)	90.9% (82.2–96.3)	1.3 (0.4–4.1)
		New Caledonia strain	88.4% (79.9–93.6)	79.2% (68.9–86.8)	2 (0.9–4.3)
		Hong Kong strain	51.2% (40.8–61.5)	41.6% (31.2–52.7)	1.5 (0.8–2.6)
	Random-effects meta-analysis of Class I and II studies	All influenza vaccines			1.51 (0.79–2.90), I^2 = 55%
Glatiramer acetate	Olberg 2018[53] (Class I)	H1N1	91.3% (73.2–97.6)	92.9% (68.5–98.7)	0.81 (0.08–7.32)
		H3N2	26.1% (12.6–46.5)	42.9% (21.4–67.4)	0.47 (0.12–1.8)
	Olberg 2014[51] (Class II)	*H1N1 (2009 cohort)*	*21.6% (11.4–37.2)*	*43.5% (37.1–50.2)*	*0.36 (0.17–0.8)*
		H1N1 (2010 cohort)	*58.3% (32.0–80.7)*	*71.2% (60.0–80.4)*	*0.57 (0.16–1.98)*
		H3N2 (2010)	*41.7% (19.3–68.1)*	*79.5% (68.8–87.1)*	*0.19 (0.05–0.66)*
	Random-effects meta-	All influenza vaccines			0.39 (0.21–0.74), I^2 = 0%

	analysis				
Fingolimod	Olberg 2018[53] (Class I)	H1N1	71.4% (45.4–88.3)	92.9% (68.5–98.7)	0.19 (0.02–1.50)
		H3N2	21.4% (7.6–48.6)	42.9% (21.4–67.4)	0.36 (0.08–1.78)
	Kappos 2015[57] (Class I)	California strain	48.4% (38.4–58.5)	72.1% (57.3–83.3)	0.36 (0.17–0.78)
		Brisbane strain	76.9% (67.3–84.4)	95.3% (84.5–98.7)	0.16 (0.04–0.65)
		Perth strain	97.8% (92.3–99.4)	100% (91.8–100.0)	0.01 (0.00–3.99)
	Random-effects meta-analysis	All influenza vaccines			0.35 (0.21–0.57), $I^2 = 0\%$
Natalizumab	Olberg 2018[53] (Class I)	H1N1	72.7% (43.4–90.3)	92.9% (68.5–98.7)	0.21 (0.02–1.74)
		H3N2	30.0% (10.8–60.3)	42.9% (21.4–67.4)	0.57 (0.11–2.95)
	Olberg 2014[51] (Class II)	*H1N1 (2009 cohort)*	*23.5% (9.6–47.3)*	*43.5% (37.1–50.2)*	*0.39 (0.13–1.21)*
		H1N1 (2010 cohort)	*75.0% (40.9–92.9)*	*71.2% (60.0–80.4)*	*1.21 (0.26–5.86)*
		H3N2 (2010 cohort)	*50.0% (21.5–78.5)*	*79.5% (68.8–87.1)*	*0.09 (0.008–0.89)*

	Vagberg 2012[60] *(Class II)*	*Anti-influenza B IgG-U (>50% increase)*	*56.3% (33.2–76.9)*	*50.0% (23.7–76.3)*	*1.29 (0.28–5.75)*
		Anti-influenza B IgG-U (>50% increase)	*6.3% (1.1–28.3)*	*0.0%* *(0.0–27.8)*	*11.7[a] (0.10–857.09)*
	Random-effects meta-analysis	All influenza vaccines			0.57 (0.30–1.07), $I^2 = 0\%$
Daclizumab	*Lin 2016[61]* *(Class II)*	*Trivalent influenza vaccine (H1N1, H3N2, influenza B strains)*	*87.5% (52.9–97.8)*	*100.0% (70.1–100.0)*	*0.087[a] (0.0014–3.73)*
	Mehta 2016[62] *(Class III)*	*H1N1*	*92% (85–97)*	*78% (74–82)[b]*	*3.34 (1.57–7.12)*
		H3N2	*91% (83–96)*	*81% (77-85)[b]*	*1.40 (0.68–2.86)*
		Influenza B strain	*67% (56–76)*	*75% (69-80)[b]*	*0.67 (0.43–1.03)*
	Random-effects meta-analysis	All influenza vaccines			0.68 (0.10–4.57), $I^2 = 36\%$
Teriflunomide	Bar–Or 2013[56] (Class III)	H1N1	7 mg: 97.5% (87.1–99.6) 14 mg: 97.4% (86.8–99.6)	97.7% (93.9–100)[b]	7 mg: 0.93 (0.08–11.15)[c] 14 mg: 0.90 (0.075–10.9)[c]
		H3N2	7 mg: 90% (77.0–96.0) 14 mg: 76.9%	90.7% (83.4–98)[c]	7 mg: 0.92 (0.23–3.75)[c] 14 mg: 0.34 (0.10–1.15)[c]

			(61.7– 87.4)		
		Influenza B	7 mg: 97.5% (87.1–99.6) 14 mg: 97.4% (86.8–99.6)	93.0% (86.6–99.4)[c]	7 mg: 2.93 (0.38–24.50)[c] 14 mg: 2.85 (0.37–23.88)[c]
	Random-effects meta-analysis	All influenza vaccines			0.86 (0.42–1.75), $I^2 = 0\%$
Mitoxantrone	Olberg 2014[51] (Class II)	*H1N1 (2009 cohort)*	*0% (0–25.9)*	*43.5% (37.1–50.2)*	*0.0005[a] (0.00–0.47)*
		H1N1 (2010 cohort)	*25.0% (4.6–69.9)*	*71.2% (60.0–80.4)*	*0.13 (0.019–1.04)*
		H3N2 (2010 cohort)	*25.0% (4.6–69.9)*	*79.5% (68.8–87.1)*	*0.09 (0.012–0.68)*
	Random-effects meta-analysis	All influenza vaccines			0.11 (0.026–0.45), $I^2 = 0\%$

Abbreviations: CI = confidence interval; IFN = interferon; Ig = immunoglobulin; MS = multiple sclerosis.

Italics indicate the use of a normal control group (as opposed to a control group consisting of patients with MS either receiving no treatment or an alternate treatment). Bar–Or 2013[56] used a pre–post study design without an external control group.

[a]Calculated using Sweeting correction.

[b]Historical controls from: Seidman JC, Richard SA, Viboud C, et al. Quantitative review of antibody response to inactivated seasonal influenza vaccines. Influenza Other Respir Viruses 2012;6:52–62.

[c]Controls represent patients with MS receiving IFN–β therapy.

Figure e-1. Evidence review flow diagram

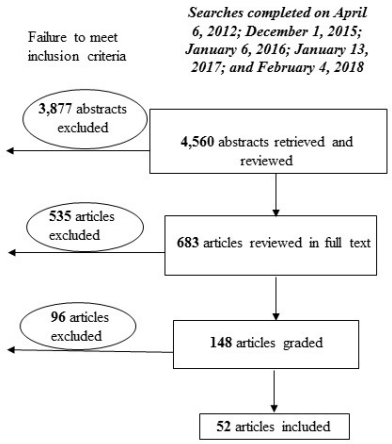
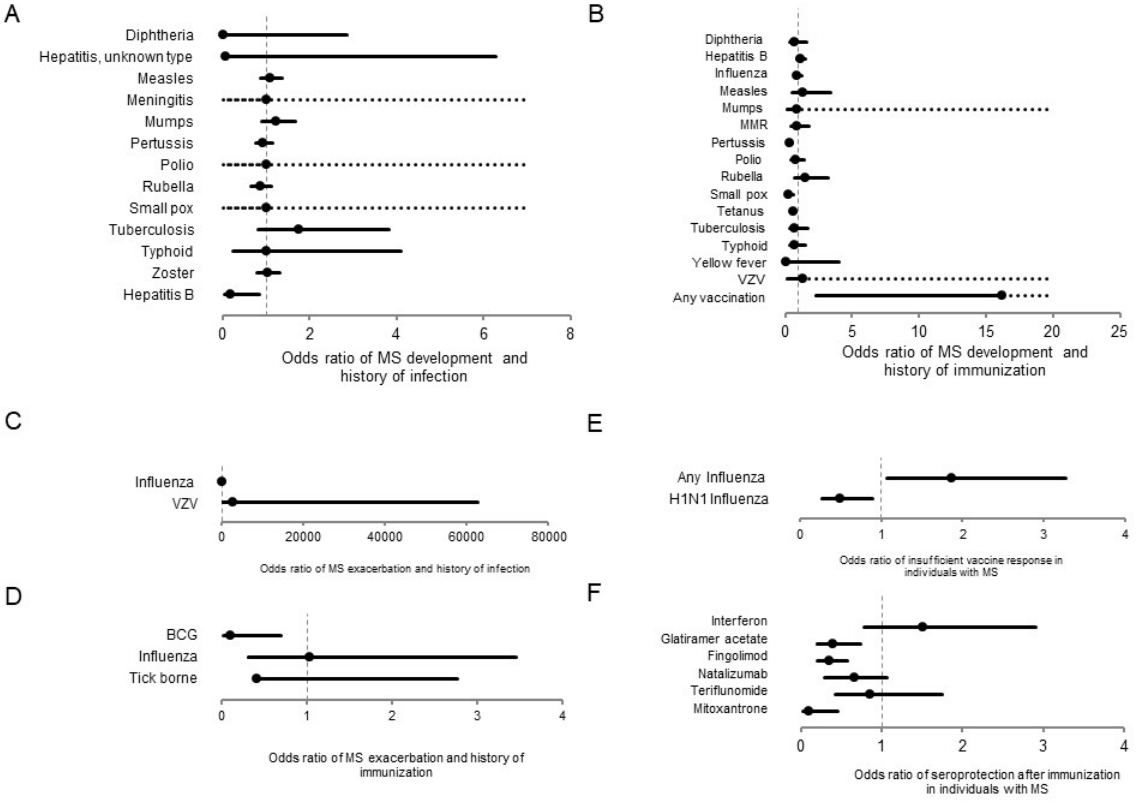


Figure e-2. Odds ratios of the analyzed evidence



DISCLAIMER

Practice guidelines, practice advisories, comprehensive systematic reviews, and other guidance published by the American Academy of Neurology (AAN) and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. The AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. The AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. The AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

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 he 2011 AAN process manual section titled, "Revealing Conflicts of Interest."[10]

Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders. The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2017–2019

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair), Steven R. Messé, MD (Co-Vice-Chair), Sonja Potrebic, MD, PhD (Co-Vice-Chair), Stephen Ashwal, MD, Lori L. Billinghurst, MD, Brian Callaghan, MD, Gregory S. Day, MD, MSc, Diane Donley, MD, Richard M. Dubinsky, MD, MPH, Jeffrey Fletcher, MD, Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert), Michael Haboubi, DO, John J. Halperin, MD, Yolanda Holler-Managan, MD, Koto Ishida, MD, Annette M. Langer-Gould, MD, PhD, Nicole Licking, DO, Mia T. Minen, MD, Pushpa Narayanaswami, MBBS, DM, Maryam Oskoui, MD, Allison M. Pack, MD, Alejandro A. Rabinstein, MD, Alexander Rae-Grant, MD, Navdeep Sangha, MD, Kevin Sheth, MD, Kelly Sullivan, PhD, Eric J. Ashman, MD (Ex-Officio), Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix e-3. Complete search strategy

Ovid MEDLINE(R) 1946 to April Week 1 2012 # Searches Results Search Type

1 multiple sclerosis/ or "multiple sclerosis".tw. or ms.tw. 181104 Advanced

2 exp hepatitis b/ or exp hepatitis a/ or exp diphtheria/ or exp tetanus/ or exp influenza/ or exp chickenpox/ or exp measles/ or exp mumps/ or exp rubella/ or exp haemophilus/ or exp streptococcus pneumoniae/ or exp neisseria meningitidis/ or exp papillomaviridae/ or exp typhoid fever/ or exp paratyphoid fever/ or exp encephalitis, japanese/ or exp rabies/ or exp rotavirus/ or exp yellow fever/ or exp tuberculosis/ 348207 Advanced

3 (tuberculosis or "hepatitis b" or "hepatitis a" or dipheria or tetanus or influenza or chickenpox or measles or mumps or rubella or haemophilus or "streptococcus peumonia*" or "neisseria meningitidis" or papillomavirus or typhoid or paratyphoid or "japanese encephalitis" or "yellow fever" or rotavirus).ti,ab. 330218 Advanced

4 1 and (2 or 3) 2305 Advanced

5 exp diphtheria-tetanus-acellular pertussis vaccines/ or exp diphtheria-tetanus-pertussis vaccine/ or exp diphtheria-tetanus vaccine/ or exp haemophilus vaccines/ or exp meningococcal vaccines/ or exp pertussis vaccine/ or exp streptococcal vaccines/ or exp tuberculosis vaccines/ or exp toxoids/ or exp vaccines, attenuated/ or exp vaccines, combined/ or exp vaccines, inactivated/ or exp influenza vaccines/ or exp japanese encephalitis vaccines/ or exp measles-mumps-rubella vaccine/ or exp measles vaccine/ or exp mumps vaccine/ or exp papillomavirus vaccines/ or exp rabies vaccines/ or exp rotavirus vaccines/ or exp rubella vaccine/ or exp smallpox vaccine/ or exp viral hepatitis vaccines/ or exp yellow fever vaccine/ 86500 Advanced

6 exp Vaccination/ or exp Pneumococcal Vaccines/ 53844 Advanced

7 ((bcg or "hepatitis b" or "hepatitis a" or "diphtheria tetanus" or diphtheria or "tetanus toxoid" or tetanus or influenza or chickenpox or "measles mumps rubella" or haemophilus or pnneumococcal or meningococcal or papillomavirus or "thyphoid parathyroid" or encephalitis or "yellow fever" or rotavirus) adj2 (vaccin* or immuni*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 62452 Advanced

8 1 and (5 or 6 or 7) 552 Advanced

9 4 or 8 2589 Advanced

10 limit 9 to (humans and yr="1990 - 2012") 1077 Advanced

11 exp immunization/ or vaccination/ or vaccine*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 256204 Advanced

12 1 and 11 1442 Advanced

13 ..l/ 12 hu=y and yr=1990-2012 665 Advanced

14 10 or 13 1382 Advanced

15 14 and ((co or ae).fs. or relaps*.mp. or exacerbat*.mp. or risk*.mp. or reactiv*.mp. or progress*.mp. or trigger*.mp. or worsen*.mp. or harm*.mp. or ep.fs. or incidence/ or odds ratio/ or proportional hazards model/ or multivariate analysis/) 778

16 14 not 15 604 Advanced

17 multiple sclerosis/ or "multiple sclerosis".tw. 46076 Advanced

18 16 and 17 250 Advanced

19 15 or 18 1028

15 limit 14 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or practice guideline or randomized controlled trial or "review" or validation studies) 347

16 exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/ or exp intervention studies/ 1385144

17 14 and (16 or relaps* or exacerbat* or risk*.mp. or reactiv*.mp. or progress*.mp. or trigger*.mp. or worsen*.mp. or harm*.mp. or ep.fs. or incidence/ or odds ratio/ or proportional hazards model/ or multivariate analysis/) 481

18 15 or 17 602

Cochrane = 40
EMBASE = 1418
ISI Web of Science = 501
.
Web of Science Strategy #1
Topic=("multiple sclerosis" AND (vaccin* OR immunis* OR immuniz* OR toxoid* OR bcg or hepatitis or diphtheria or "tetanus toxoid" or tetanus or influenza or chickenpox or measles OR mumps OR rubella or haemophilus or pneumococcal or meningococcal or papillomavirus or thyphoid or encephalitis or "yellow fever" or rotavirus OR rabies)) Refined by: Topic=(relaps* OR remit* OR remission* OR exacerbat* OR adverse* OR risk* OR react* OR interact* OR progress* OR trigger* OR worsen* OR harm*) Databases=SCI-EXPANDED Timespan=1990-2012

The short search yielded 80 new abstracts (polio , herpes)

1765 once all duplicates were removed.

PubMED
"multiple sclerosis" AND ((polio OR poliovirus OR poliomyelitis OR "herpes zoster" OR shingles) AND (vaccin* OR immunization)) = 25 (excluding pre 1990, not human)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present # Searches Results Search Type
1 "multiple sclerosis".mp. or multiple sclerosis/ [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 49373 Advanced
2 Poliomyelitis/ 14334 Advanced
3 (2 or polio*.mp.) and (exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/) [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 10379 Advanced
4 3 or poliovirus vaccines, inactivated/ 10379 Advanced
5 1 and 4 33 Advanced
6 ("herpes zoster".mp. or exp herpes zoster/ or shingles.mp.) and (exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/) [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 1196 Advanced
7 Herpes Zoster Vaccine/ 253 Advanced
8 1 and (6 or 7) 5 Advanced
9 5 or 8 38 Advanced
10 limit 9 to (humans and yr="1990 - 2012") 19

EMBASE 1988 to 2012 Week 29 # Searches Results Search Type
1 "multiple sclerosis".mp. or multiple sclerosis/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 60834 Advanced
2 Poliomyelitis/ 8295 Advanced
3 (2 or polio*.mp.) and (exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10720 Advanced
4 3 or poliovirus vaccines, inactivated/ 10720 Advanced
5 1 and 4 120 Advanced
6 ("herpes zoster".mp. or exp herpes zoster/ or shingles.mp.) and (exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 2337 Advanced
7 Herpes Zoster Vaccine/ 1376 Advanced
8 1 and (6 or 7) 40 Advanced
9 5 or 8 150 Advanced

10 limit 9 to (humans and yr="1990 - 2012") 140

Web of Science
Topic=("multiple sclerosis" AND (polio* OR zoster OR shingles) AND (immuni* OR vaccin*))
Timespan=1990-2012. Databases=SCI-EXPANDED. 42

SCOPUS
TITLE-ABS-KEY("multiple sclerosis" AND (polio* OR zoster OR shingles) AND (immuni* OR vaccin*)) AND PUBYEAR > 1989 = 2012

Ovid MEDLINE(R) 1946 to April Week 1 2012 # Searches Results Search Type
1 multiple sclerosis/ or "multiple sclerosis".tw. or ms.tw. 181104 Advanced
2 exp hepatitis b/ or exp hepatitis a/ or exp diphtheria/ or exp tetanus/ or exp influenza/ or exp chickenpox/ or exp measles/ or exp mumps/ or exp rubella/ or exp haemophilus/ or exp streptococcus pneumoniae/ or exp neisseria meningitidis/ or exp papillomaviridae/ or exp typhoid fever/ or exp paratyphoid fever/ or exp encephalitis, japanese/ or exp rabies/ or exp rotavirus/ or exp yellow fever/ or exp tuberculosis/ 348207 Advanced
3 (tuberculosis or "hepatitis b" or "hepatitis a" or dipheria or tetanus or influenza or chickenpox or measles or mumps or rubella or haemophilus or "streptococcus peumonia*" or "neisseria meningitidis" or papillomavirus or typhoid or paratyphoid or "japanese encephalitis" or "yellow fever" or rotavirus).ti,ab. 330218 Advanced
4 1 and (2 or 3) 2305 Advanced
5 exp diphtheria-tetanus-acellular pertussis vaccines/ or exp diphtheria-tetanus-pertussis vaccine/ or exp diphtheria-tetanus vaccine/ or exp haemophilus vaccines/ or exp meningococcal vaccines/ or exp pertussis vaccine/ or exp streptococcal vaccines/ or exp tuberculosis vaccines/ or exp toxoids/ or exp vaccines, attenuated/ or exp vaccines, combined/ or exp vaccines, inactivated/ or exp influenza vaccines/ or exp japanese encephalitis vaccines/ or exp measles-mumps-rubella vaccine/ or exp measles vaccine/ or exp mumps vaccine/ or exp papillomavirus vaccines/ or exp rabies vaccines/ or exp rotavirus vaccines/ or exp rubella vaccine/ or exp smallpox vaccine/ or exp viral hepatitis vaccines/ or exp yellow fever vaccine/ 86500 Advanced
6 exp Vaccination/ or exp Pneumococcal Vaccines/ 53844 Advanced
7 ((bcg or "hepatitis b" or "hepatitis a" or "diphtheria tetanus" or diphtheria or "tetanus toxoid" or tetanus or influenza or chickenpox or "measles mumps rubella" or haemophilus or pnneumococcal or meningococcal or papillomavirus or "thyphoid parathyroid" or encephalitis or "yellow fever" or rotavirus) adj2 (vaccin* or immuni*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 62452 Advanced
8 1 and (5 or 6 or 7) 552 Advanced
9 4 or 8 2589 Advanced
10 limit 9 to (humans and yr="1990 - 2012") 1077 Advanced
11 exp immunization/ or vaccination/ or vaccine*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 256204 Advanced
12 1 and 11 1442 Advanced

13 ..l/ 12 hu=y and yr=1990-2012 665 Advanced
14 10 or 13 1382 Advanced
15 14 and ((co or ae).fs. or relaps*.mp. or exacerbat*.mp. or risk*.mp. or reactiv*.mp. or progress*.mp. or trigger*.mp. or worsen*.mp. or harm*.mp. or ep.fs. or incidence/ or odds ratio/ or proportional hazards model/ or multivariate analysis/) 778
16 14 not 15 604 Advanced
17 multiple sclerosis/ or "multiple sclerosis".tw. 46076 Advanced
18 16 and 17 250 Advanced
19 15 or 18 1028

Same strategies, translated into EMBASE, and text words for Web of Science and Scopus.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results	Search Type
1	multiple sclerosis/ or "multiple sclerosis".tw. or ms.tw.	272565	Advanced
2	exp hepatitis b/ or exp hepatitis a/ or exp diphtheria/ or exp tetanus/ or exp influenza/ or exp chickenpox/ or exp measles/ or exp mumps/ or exp rubella/ or exp haemophilus/ or exp streptococcus pneumoniae/ or exp neisseria meningitidis/ or exp papillomaviridae/ or exp typhoid fever/ or exp paratyphoid fever/ or exp encephalitis, japanese/ or exp rabies/ or exp rotavirus/ or exp yellow fever/ or exp tuberculosis/	413443	Advanced
3	(tuberculosis or "hepatitis b" or "hepatitis a" or dipheria or tetanus or influenza or chickenpox or measles or mumps or rubella or haemophilus or "streptococcus peumonia*" or "neisseria meningitidis" or papillomavirus or typhoid or paratyphoid or "japanese encephalitis" or "yellow fever" or rotavirus).ti,ab.	430703	Advanced
4	exp diphtheria-tetanus-acellular pertussis vaccines/ or exp diphtheria-tetanus-pertussis vaccine/ or exp diphtheria-tetanus vaccine/ or exp haemophilus vaccines/ or exp meningococcal vaccines/ or exp pertussis vaccine/ or exp streptococcal vaccines/ or exp tuberculosis vaccines/ or exp toxoids/ or exp vaccines, attenuated/ or exp vaccines, combined/ or exp vaccines, inactivated/ or exp influenza vaccines/ or exp japanese encephalitis vaccines/ or exp measles-mumps-rubella vaccine/ or exp measles vaccine/ or exp mumps vaccine/ or exp papillomavirus vaccines/ or exp rabies vaccines/ or exp rotavirus vaccines/ or exp	105012	Advanced

	rubella vaccine/ or exp smallpox vaccine/ or exp viral hepatitis vaccines/ or exp yellow fever vaccine/		
5	exp Vaccination/ or exp Pneumococcal Vaccines/	66616	Advanced
6	((bcg or "hepatitis b" or "hepatitis a" or "diphtheria tetanus" or diphtheria or "tetanus toxoid" or tetanus or influenza or chickenpox or "measles mumps rubella" or haemophilus or pnneumococcal or meningococcal or papillomavirus or "thyphoid parathyroid" or encephalitis or "yellow fever" or rotavirus) adj2 (vaccin* or immuni*)).mp.	80990	Advanced
7	poliomyelitis/ or polio*.mp. or "herpes zoster".mp. or exp herpes zoster/ or shingles*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	46024	Advanced
8	7 and (exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	13561	Advanced
9	poliovirus vaccines, inactivated/ or herpes zoster vaccine/	471	Advanced
10	or/2-6	646335	Advanced
11	1 and (8 or 9 or 10 or exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/)	5062	Advanced
12	limit 11 to ("in data review" or in process or "pubmed not medline")	281	Advanced
13	12 and (human* or patient* or men or women).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	143	Advanced
14	..l/ 11 hu=y	2987	Advanced
15	13 or 14	3130	Advanced
16	..l/ 15 yr=2012-2016	686	Advanced

17	remove duplicates from 16	636	

EMBASE 1988 to 2016 Week 01

#	Searches	Results	Search Type
1	multiple sclerosis/ or "multiple sclerosis".tw. or ms.tw.	344316	Advanced
2	exp hepatitis b/ or exp hepatitis a/ or exp diphtheria/ or exp tetanus/ or exp influenza/ or exp chickenpox/ or exp measles/ or exp mumps/ or exp rubella/ or exp haemophilus/ or exp streptococcus pneumoniae/ or exp neisseria meningitidis/ or exp papillomaviridae/ or exp typhoid fever/ or exp paratyphoid fever/ or exp encephalitis, japanese/ or exp rabies/ or exp rotavirus/ or exp yellow fever/ or exp tuberculosis/	380437	Advanced
3	(tuberculosis or "hepatitis b" or "hepatitis a" or dipheria or tetanus or influenza or chickenpox or measles or mumps or rubella or haemophilus or "streptococcus peumonia*" or "neisseria meningitidis" or papillomavirus or typhoid or paratyphoid or "japanese encephalitis" or "yellow fever" or rotavirus).ti,ab.	362682	Advanced
4	exp diphtheria-tetanus-acellular pertussis vaccines/ or exp diphtheria-tetanus-pertussis vaccine/ or exp diphtheria-tetanus vaccine/ or exp haemophilus vaccines/ or exp meningococcal vaccines/ or exp pertussis vaccine/ or exp streptococcal vaccines/ or exp tuberculosis vaccines/ or exp toxoids/ or exp vaccines, attenuated/ or exp vaccines, combined/ or exp vaccines, inactivated/ or exp influenza vaccines/ or exp japanese encephalitis vaccines/ or exp measles-mumps-rubella vaccine/ or exp measles vaccine/ or exp mumps vaccine/ or exp papillomavirus vaccines/ or exp rabies vaccines/ or exp rotavirus vaccines/ or exp rubella vaccine/ or exp smallpox vaccine/ or exp viral hepatitis vaccines/ or exp yellow fever vaccine/	223778	Advanced
5	exp Vaccination/ or exp Pneumococcal Vaccines/	113997	Advanced
6	((bcg or "hepatitis b" or "hepatitis a" or "diphtheria tetanus" or diphtheria or "tetanus toxoid" or tetanus or influenza or chickenpox or "measles mumps rubella" or haemophilus or pnneumococcal or meningococcal or papillomavirus or "thyphoid parathyroid" or encephalitis or "yellow fever" or rotavirus) adj2 (vaccin* or immuni*)).mp.	95031	Advanced

7	poliomyelitis/ or polio*.mp. or "herpes zoster".mp. or exp herpes zoster/ or shingles*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	38658	Advanced
8	7 and (exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/) [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	15849	Advanced
9	poliovirus vaccines, inactivated/ or herpes zoster vaccine/	1890	Advanced
10	or/2-6	641461	Advanced
11	1 and (8 or 9 or 10 or exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/)	8098	Advanced
12	limit 11 to (human and yr="2012 - 2016")	1899	Advanced
13	*multiple sclerosis/	53969	Advanced
14	"multiple sclerosis".tw.	70552	Advanced
15	(13 or 14) and 12	748	Advanced
16	remove duplicates from 15	733	Advanced
17	16 not case report/	688	

TS=("multiple sclerosis" AND (polio* OR shingles OR herpes* OR vaccin* OR immunis* OR immuniz* OR toxoid* OR bcg OR hepatitis OR diphtheria OR "tetanus toxoid" OR tetanus OR influenza OR flu OR chickenpox OR measles OR mumps OR rubella OR haemophilus OR pneumococcal OR meningococcal OR papillomavirus OR thyphoid OR encephalitis OR "yellow fever" OR rotavirus OR rabies))

Refined by: TOPIC: (complicat* OR relaps* OR remit* OR remission* OR exacerbat* OR adverse* OR risk* OR react* OR interact* OR progress* OR trigger* OR worsen* OR harm*) AND**DOCUMENT TYPES:** (ARTICLE OR REVIEW) AND **TOPIC:** (vaccin* OR immuni*)

Timespan: 2012-2016. **Indexes:** SCI-EXPANDED. 409

The reason for the difference between MEDLINE and EMBASE is that EMBASE includes conference abstracts. There is also a systematic review on teriflunomide in mid-2016. The strategies look quite different because the focus was on the vaccines, vaccinat*.

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

#	Searches
1	multiple sclerosis.mp. or exp multiple sclerosis/
2	exp vaccine/
3	exp vaccination/
4	(2 or 3 or vaccin*.mp.) and 1 [mp=title, abstract, original title, name of substance word, su keyword heading word, protocol supplementary concept word, rare disease supplementary unique identifier]
5	limit 4 to yr="2012 - 2017"
6	1 and teriflunomide.mp. [mp=title, abstract, original title, name of substance word, subject keyword heading word, protocol supplementary concept word, rare disease supplementary unique identifier]
7	4 and 6
8	limit 7 to yr="2012 - 2017"
9	5 or 8
10	remove duplicates from 9
11	remove duplicates from 9
12	1 and exp vaccines/
13	1 and (3 or vaccin*.mp.) [mp=title, abstract, original title, name of substance word, subjec keyword heading word, protocol supplementary concept word, rare disease supplementary unique identifier]
14	12 or 13

15	..l/ 14 yr=2012-2017
16	remove duplicates from 15

EMBASE

#	Searches	Results	Type
1	multiple sclerosis.mp. or exp multiple sclerosis/	100786	Advanced
2	exp vaccine/	262365	Advanced
3	exp vaccination/	136038	Advanced
4	(2 or 3 or vaccin*.mp.) and 1 [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	2136	Advanced
5	limit 4 to yr="2012 - 2017"	617	Advanced
6	1 and teriflunomide.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]	1130	Advanced
7	4 and 6	58	Advanced
8	limit 7 to yr="2012 - 2017"	34	Advanced
9	5 or 8	617	Advanced
10	remove duplicates from 9	562	Advanced

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search history sorted by search number ascending

#	Searches	Results	Type

1	multiple sclerosis.mp. or exp multiple sclerosis/	71881	Advanced
2	exp vaccines/	208316	Advanced
3	exp vaccination/	75224	Advanced
4	(2 or 3 or vaccin*.mp.) and 1	996	Advanced
5	4 and (2017* or 2018$).dc.	0	Advanced
6	4 and (2017* or 2018$).dt.	50	

EMBASE <1988 to 2018 Week 05>

Search history sorted by search number ascending

#	Searches
1	multiple sclerosis.mp. or exp multiple sclerosis/
2	exp vaccines/
3	exp vaccination/
4	(2 or 3 or vaccin*.mp.) and 1
5	4 and (2017* or 2018$).dc.

Scopus

TITLE-ABS-KEY ("multiple sclerosis" AND (vaccin*)) AND PUBYEAR > 2016 – 96

MS-Immunity 2016-2018

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search history sorted by search number ascending

#	Searches	Results	Type
1	exp multiple sclerosis/ or "multiple sclerosis".mp.	71881	Advanced
2	exp hepatitis b/ or exp hepatitis a/ or exp diphtheria/ or exp tetanus/ or exp influenza/ or exp chickenpox/ or exp measles/ or exp mumps/ or exp rubella/ or exp haemophilus/ or exp streptococcus pneumoniae/ or exp neisseria meningitidis/ or exp papillomaviridae/ or exp typhoid fever/ or exp paratyphoid fever/ or exp encephalitis, japanese/ or exp rabies/ or exp rotavirus/ or exp yellow fever/ or exp tuberculosis/	443433	Advanced
3	(tuberculosis or "hepatitis b" or "hepatitis a" or diphtheria or tetanus or influenza or chickenpox or measles or mumps or rubella or haemophilus or "streptococcus pneumonia*" or "neisseria meningitidis" or papillomavirus or typhoid or paratyphoid or "japanese encephalitis" or "yellow fever" or rotavirus).ti,ab,kw.	496013	Advanced
4	exp diphtheria-tetanus-acellular pertussis vaccines/ or exp diphtheria-tetanus-pertussis vaccine/ or exp diphtheria-tetanus vaccine/ or exp haemophilus vaccines/ or exp meningococcal vaccines/ or exp pertussis vaccine/ or exp streptococcal vaccines/ or exp tuberculosis vaccines/ or exp toxoids/ or exp vaccines, attenuated/ or exp vaccines, combined/ or exp vaccines, inactivated/ or exp influenza vaccines/ or exp japanese encephalitis vaccines/ or exp measles-mumps-rubella vaccine/ or exp measles vaccine/ or exp mumps vaccine/ or exp papillomavirus vaccines/ or exp rabies vaccines/ or exp rotavirus vaccines/ or exp rubella vaccine/ or exp smallpox vaccine/ or exp viral hepatitis vaccines/ or exp yellow fever vaccine/	115838	Advanced
5	exp vaccination/ or exp immunization/ or exp pneumococcal vaccines/	164103	Advanced
6	((bcg or "hepatitis b" or "hepatitis a" or "diphtheria tetanus" or diphtheria or "tetanus toxoid" or tetanus or influenza or chickenpox or "measles mumps rubella" or haemophilus or pneumococcal or meningococcal or papillomavirus or "typhoid parathyroid" or encephalitis or "yellow fever" or rotavirus) adj2 (vaccin* or immuni*)).mp.	95154	Advanced
7	poliomyelitis/ or polio*.mp. or "herpes zoster".mp. or exp herpes zoster/ or shingles*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	48385	Advanced

8	7 and (exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	14576	Advanced
9	poliovirus vaccines, inactivated/ or herpes zoster vaccine/	567	Advanced
10	or/2-6	776151	Advanced
11	1 and (8 or 9 or 10 or exp vaccination/ or exp vaccines/ or vaccin*.mp. or exp immunization/ or immuniz*.mp. or immunis*.mp.)	3668	Advanced
12	limit 11 to ("in data review" or in process or "pubmed not medline")	212	Advanced
13	12 and (human* or patient* or men or women).mp.	134	Advanced
14	..l/ 11 hu=y	2267	Advanced
15	13 or 14	2400	Advanced
16	..l/ 15 yr=2016-2018	168	Advanced
17	15 and (2016* or 2017* or 2018*).dt.	163	Advanced
18	16 or 17	173	

Web of Science

# 6	**430**	#5 OR #3 *Indexes=SCI-EXPANDED, ESCI Timespan=2016-2018*	Edit
# 5	**324**	#4 AND #1 *Indexes=SCI-EXPANDED, ESCI Timespan=2016-2018*	Edit
# 4	**37,652**	TS=(immunis* OR immuniz* OR vaccin*)	Edit

		Indexes=SCI-EXPANDED, ESCI Timespan=2016-2018	
# 3	**161**	#2 AND #1 *Indexes=SCI-EXPANDED, ESCI Timespan=2016-2018*	Edit
# 2	**8,634**	TI=("multiple Sclerosis") *Indexes=SCI-EXPANDED, ESCI Timespan=2016-2018*	Edit
# 1	**741**	TS=("multiple sclerosis" AND (polio* OR shingles OR herpes* OR vaccin* OR immunis* OR immuniz* OR toxoid* OR bcg OR hepatitis OR diphtheria OR "tetanus toxoid" OR tetanus OR influenza OR flu OR chickenpox OR measles OR mumps OR rubella OR haemophilus OR pneumococcal OR meningococcal OR papillomavirus OR typhoid OR encephalitis OR "yellow fever" OR rotavirus OR rabies)) *Indexes=SCI-EXPANDED, ESCI Timespan=2016-2018*	Ed

(TS=("multiple sclerosis" AND (polio* OR shingles OR herpes* OR vaccin* OR immunis* OR immuniz* OR toxoid* OR bcg OR hepatitis OR diphtheria OR "tetanus toxoid" OR tetanus OR influenza OR flu OR chickenpox OR measles OR mumps OR rubella OR haemophilus OR pneumococcal OR meningococcal OR papillomavirus OR typhoid OR encephalitis OR "yellow fever" OR rotavirus OR rabies OR herpes)))*AND* **DOCUMENT TYPES:** (Article OR Review)

Refined by: TOPIC: ((complicat* OR relaps* OR remit* OR remission* OR exacerbat* OR adverse* OR risk* OR react* OR interact* OR progress* OR trigger* OR worsen* OR harm*)) AND**TOPIC:** (Vaccin* OR immuni*)

Timespan: 2016-2018. **Indexes:** SCI-EXPANDED, ESCI.

216

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search history sorted by search number ascending

#	Searches	Results
1	exp multiple sclerosis/ or "multiple sclerosis".ti,ab,kw.	71868
2	ocrelizumab.mp.	175
3	rituximab.mp. or RITUXIMAB/	18807
4	1 and (2 or 3)	399
5	exp vaccines/ or vaccin*.mp. or exp immunizations/ or immuniz*.mp. or immunis*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	442482
6	4 and 5	14

CENTRAL – 3 (all dups)

EMBASE <1988 to 2018 Week 06>

Search history sorted by search number ascending

#	Searches
1	exp *multiple sclerosis/ or "multiple sclerosis".ti,ab,kw.
2	ocrelizumab.mp.
3	rituximab.mp. or RITUXIMAB/
4	1 and (2 or 3)
5	exp vaccine/ or vaccin*.mp. or exp immunizations/ or immuniz*.mp. or immunis*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6	4 and 5

7	remove duplicates from 6	129

("multiple sclerosis" AND (rituximab OR ocrelizumab))

Refined by: TOPIC: (vaccin* OR immuni*)

Timespan: All years. **61**

Appendix e-4. Evidence profile tables

Evidence profile tables are available from the AAN, by request.

Appendix e-5. Evidence synthesis tables

Evidence synthesis tables are available from the AAN, by request.

REFERENCES

1. Rutschmann OT, McCrory DC, Matchar DB; for the Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines. Immunization and MS: a summary of published evidence and recommendations. Neurology 2002;59:1837-1843.
2. Sospedra M, Martin R. Immunology of multiple sclerosis. Annu Rev Immunol 2005;23:683-747.
3. Li R, Rezk A, Healy LM, et al. Cytokine-defined B cell responses as therapeutic targets in multiple sclerosis. Front Immunol 2015;6:626.
4. Buljevac D, Flach HZ, Hop WC, et al. Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain 2002;125:952-960.
5. Correale J, Fiol M, Gilmore W. The risk of relapses in multiple sclerosis during systemic infections. Neurology 2006;67:652-659.
6. Geier DA, Geier MR. A case-control study of serious autoimmune adverse events following hepatitis B immunization. Autoimmunity 2005;38:295-301.
7. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938-952.
8. Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin Proc 2014;89:225-240.
9. Food and Drug Adminstration. FDA working with manufacturers to withdraw Zinbryta from the market in the United States [online]. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm600999.htm. Accessed July 21, 2018.
10. American Academy of Neurology. Clinical Practice Guideline Process Manual. St. Paul, MN: American Academy of Neurology, 2011.
11. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227-231.
12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
13. Centers for Disease Control and Prevention. Adult Immunization Schedule [online]. Available at: https://www.cdc.gov/vaccines/schedules/hcp/adult.html. Accessed July 21, 2018.
14. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004;23:1351-1375.
15. Kurtzke JF, Hyllested K, Arbuckle JD, et al. Multiple sclerosis in the Faroe Islands. 7. Results of a case control questionnaire with multiple controls. Acta Neurol Scand 1997;96:149-157.
16. Zorzon M, Zivadinov R, Nasuelli D, et al. Risk factors of multiple sclerosis: a case-control study. Neurol Sci 2003;24:242-247.
17. Abbasi M, Nabavi SM, Fereshtehnejad SM, et al. Multiple sclerosis and environmental risk factors: a case-control study in Iran. Neurol Sci 2017;38:1941-1951.
18. Ahlgren C, Oden A, Haghighi S, Andersen O, Bergstrom T, Lycke J. The effect of live, attenuated measles vaccine and measles infection on measles antibody levels in serum and CSF of patients with multiple sclerosis or clinically isolated syndrome. J Neuroimmunol 2011;235:98-103.
19. Comabella M, Montalban X, Horga A, et al. Antiviral immune response in patients with multiple sclerosis and healthy siblings. Mult Scler 2010;16:355-358.

20. Khaki M, Ghazavi A, Ghasami K, et al. Evaluation of viral antibodies in Iranian multiple sclerosis patients. Neurosciences (Riyadh) 2011;16:224-228.
21. Kinnunen E, Valle M, Piirainen L, et al. Viral antibodies in multiple sclerosis. A nationwide co-twin study. Arch Neurol 1990;47:743-746.
22. Shaygannejad V, Rezaie N, Paknahad Z, Ashtari F, Maghzi H. The environmental risk factors in multiple sclerosis susceptibility: A case-control study. Adv Biomed Res 2016;5:98.
23. Silva KR, Alvarenga RM, Fernandez YFO, Alvarenga H, Thuler LC. Potential risk factors for multiple sclerosis in Rio de Janeiro: a case-control study. Arq Neuropsiquiatr 2009;67:229-234.
24. Sundstrom P, Juto P, Wadell G, et al. An altered immune response to Epstein-Barr virus in multiple sclerosis: a prospective study. Neurology 2004;62:2277-2282.
25. Bager P, Nielsen NM, Bihrmann K, et al. Childhood infections and risk of multiple sclerosis. Brain 2004;127:2491-2497.
26. Ramagopalan SV, Valdar W, Dyment DA, et al. Association of infectious mononucleosis with multiple sclerosis. A population-based study. Neuroepidemiology 2009;32:257-262.
27. Harandi AA, Pakdaman H, Sahraian MA. Infectious diseases, related vaccines and the risk of muliple sclerosis later in life: A case-control study (P03.242). Neurology 2012;78 (1 Supplement). April 24, 2012.
28. Eftekharian MM, Ghannad MS, Taheri M, et al. Frequency of viral infections and environmental factors in multiple sclerosis. Hum Antibodies 2016;24:17-23.
29. Mancuso R, Delbue S, Borghi E, et al. Increased prevalence of varicella zoster virus DNA in cerebrospinal fluid from patients with multiple sclerosis. J Med Virology 2007;79:192-199.
30. Ram M, Anaya JM, Barzilai O, et al. The putative protective role of hepatitis B virus (HBV) infection from autoimmune disorders. Autoimmun Rev 2008;7:621-625.
31. Gasperini C, Grasso MG, Fiorelli M, et al. A controlled study of potential risk factors preceding exacerbation in multiple sclerosis. J Neurol Neurosurg Psychiatry 1995;59:303-305.
32. Sotelo J, Martinez-Palomo A, Ordonez G, Pineda B. Varicella-zoster virus in cerebrospinal fluid at relapses of multiple sclerosis. Ann Neurol 2008;63:303-311.
33. Ordonez G, Pineda B, Garcia-Navarrete R, Sotelo J. Brief presence of varicella-zoster vral DNA in mononuclear cells during relapses of multiple sclerosis. Arch Neurol 2004;61:529-532.
34. Massa J, Munger KL, O'Reilly EJ, Levin LI, Ascherio A. Serum titers of IgG antibodies against tetanus and diphtheria toxoids and risk of multiple sclerosis. J Neuroimmunol 2009;208:141-142.
35. Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. N Engl J Med 2001;344:327-332.
36. DeStefano F, Verstraeten T, Jackson LA, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. Arch Neurol 2003;60:504-509.
37. Eftekharian MM, Mousavi M, Hormoz MB, Roshanaei G, Mazdeh M. Multiple sclerosis and immunological-related risk factors: results from a case-control study. Hum Antibodies 2014;23:31-36.
38. Hernan MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. Neurology 2004;63:838-842.

39. Langer-Gould A, Qian L, Tartof SY, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. JAMA Neurol 2014;71:1506-1513.
40. deStefano F, Weintraub E, Chen RT. Determining the risk of multiple sclerosis after hepatitis B vaccine: Time since vaccination and source of data. Pharmacoepidemiol Drug Saf 2004;13:S143.
41. Lai YC, Yew YW. Severe autoimmune adverse events post herpes zoster vaccine: A case-control study of adverse events in a national database. J Drugs Dermatol 2015;14:681-684.
42. Scheller NM, Svanstrom H, Pasternak B, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015;313:54-61.
43. Grimaldi-Bensouda L, Rossignol M, Kone-Paut I, et al. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. J Autoimmun 2017;79:84-90.
44. Ristori G, Romano S, Cannoni S, et al. Effects of Bacille Calmette-Guerin after the first demyelinating event in the CNS. Neurology 2014;82:41-48.
45. Cossu D, Yokoyama K, Tomizawa Y, Momotani E, Hattori N. Altered humoral immunity to mycobacterial antigens in Japanese patients affected by inflammatory demyelinating diseases of the central nervous system. Sci Rep 2017;7:3179.
46. Ristori G, Buzzi MG, Sabatini U, et al. Use of Bacille Calmette-Guerin (BCG) in multiple sclerosis. Neurology 1999;53:1588-1589.
47. Miller AE, Morgante LA, Buchwald LY, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. Neurology 1997;48:312-314.
48. Mokhtarian F, Shirazian D, Morgante L, Miller A, Grob D, Lichstein E. Influenza virus vaccination of patients with multiple sclerosis. Mult Scler 1997;3:243-247.
49. Baumhackl U, Franta C, Retzl J, Salomonowitz E, Eder G. A controlled trial of tick-borne encephalitis vaccination in patients with multiple sclerosis. Vaccine 2003;21 Suppl 1:S56-S61.
50. Moriabadi NF, Niewiesk S, Kruse N, et al. Influenza vaccination in MS: absence of T-cell response against white matter proteins. Neurology 2001;56:938-943.
51. Olberg HK, Cox RJ, Nostbakken JK, Aarseth JH, Vedeler CA, Myhr KM. Immunotherapies influence the influenza vaccination response in multiple sclerosis patients: an explorative study. Mult Scler 2014;20:1074-1080.
52. Kim W, Kim SH, Huh SY, et al. Reduced antibody formation after influenza vaccination in patients with neuromyelitis optica spectrum disorder treated with rituximab. Eur J Neurol 2013;20:975-980.
53. Olberg HK, Eide GE, Cox RJ, et al. Antibody response to seasonal influenza vaccination in patients with multiple sclerosis receiving immunomodulatory therapy. Eur J Neurol 2018;25:527-534.
54. Mehling M, Fritz S, Hafner P, et al. Preserved antigen-specific immune response in patients with multiple sclerosis responding to IFNbeta-therapy. PLoS One 2013;8:e78532.
55. Schwid SR, Decker MD, Lopez-Bresnahan M, Rebif-Influenza Vaccine Study I. Immune response to influenza vaccine is maintained in patients with multiple sclerosis receiving interferon beta-1a. Neurology 2005;65:1964-1966.

56. Bar-Or A, Freedman MS, Kremenchutzky M, et al. Teriflunomide effect on immune response to influenza vaccine in patients with multiple sclerosis. Neurology 2013;81:552-558.
57. Kappos L, Mehling M, Arroyo R, et al. Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. Neurology 2015;84:872-879.
58. Mehling M, Hilbert P, Fritz S, et al. Antigen-specific adaptive immune responses in fingolimod-treated multiple sclerosis patients. Ann Neurol 2011;69:408-413.
59. Mehling M, Eichin D, Hafner P, Honger G, Kappos L, Hess C. Avidity of vaccine-induced influenza IgG fails to increase in fingolimod-treated patients with MS. Neurol Neuroimmunol Neuroinflamm 2014;1:e28.
60. Vagberg M, Kumlin U, Svenningsson A. Humoral immune response to influenza vaccine in natalizumab-treated MS patients. Neurol Res 2012;34:730-733.
61. Lin YC, Winokur P, Blake A, et al. Patients with MS under daclizumab therapy mount normal immune responses to influenza vaccination. Neurol Neuroimmunol Neuroinflamm 2016;3:e196.
62. Mehta L, Umans K, Ozen G, Robinson RR, Elkins J. Immune response to seasonal influenza vaccine in patients with relapsing-remitting multiple sclerosis Receiving long-term daclizumab beta: A prospective, open-label, single-arm study. Int J MS Care 2017;19:141-147.
63. Seidman JC, Richard SA, Viboud C, Miller MA. Quantitative review of antibody response to inactivated seasonal influenza vaccines. Influenza Other Respir Viruses 2012;6:52-62.
64. Davis LE, Hersh EM, Curtis JE, et al. Immune status of patients with multiple sclerosis. Analysis of primary and established immune responses in 24 patients. Neurology 1972;22:989-997.
65. Kaufman M, Pardo G, Rossman H, Sweetser MT, Forrestal F, Duda P. Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis. J Neurol Sci 2014;341:22-27.
66. von Hehn C, Howard J, Liu S, et al. Immune response to vaccines is maintained in patients treated with dimethyl fumarate. Neurol Neuroimmunol Neuroinflamm 2018;5:e409.
67. McCarthy CL, Tuohy O, Compston DA, Kumararatne DS, Coles AJ, Jones JL. Immune competence after alemtuzumab treatment of multiple sclerosis. Neurology 2013;81:872-876.
68. Mair S, Fiquet A, Meghlaoui G, Thomas S, Ledesma E. Immunogenicity and safety of PNEUMOVAX II manufactured by a new process in older adults. Hum Vaccin 2009;5:608-613.
69. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94:S1-S63.
70. Borrow R, Southern J, Andrews N, et al. Comparison of antibody kinetics following meningococcal serogroup C conjugate vaccine between healthy adults previously vaccinated with meningococcal A/C polysaccharide vaccine and vaccine-naive controls. Vaccine 2001;19:3043-3050.
71. Dentinger CM, Hennessy TW, Bulkow LR, et al. Immunogenicity and reactogenicity to Haemophilus influenzae type B (Hib) conjugate vaccine among rural Alaska adults. Hum Vaccin 2006;2:24-28.
72. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. Clin Infect Dis 2011;52:911-916.
73. World Health Organization Immunization Schedules [online]. Available at:

http://www.who.int/immunization/policy/Immunization_routine_table1.pdf?ua=1. Accessed July 21, 2018.
74. World Health Organization. BCG vaccines: WHO position paper [online]. Available at: http://apps.who.int/iris/bitstream/handle/10665/260306/WER9308.pdf;jsessionid=D4D8642D60B01D90FB1195350A992830?sequence=1. Accessed July 21, 2018.
75. Centers for Disease Control and Prevention. CDC Fact Sheets - BCG Vaccine [online]. Available at: https://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm. Accessed July 21, 2018.
76. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology 2003;61:1528-1532.
77. De Keyser J, Zwanikken C, Boon M. Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. J Neurol Sci 1998;159:51-53.
78. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2014;66:1016-1026.
79. Aksoy S, Harputluoglu H, Kilickap S, et al. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 2007;48:1307-1312.
80. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012;380:1829-1839.
81. Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. Clin Infect Dis 2013;57:849-852.
82. Ratchford JN, Costello K, Reich DS, Calabresi PA. Varicella-zoster virus encephalitis and vasculopathy in a patient treated with fingolimod. Neurology 2012;79:2002-2004.
83. Uccelli A, Ginocchio F, Mancardi GL, Bassetti M. Primary varicella zoster infection associated with fingolimod treatment. Neurology 2011;76:1023-1024.
84. Yeung J, Cauquil C, Saliou G, et al. Varicella-zoster virus acute myelitis in a patient with MS treated with natalizumab. Neurology 2013;80:1812-1813.
85. Fingolimod prescribing information [online]. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf. Accessed July 21, 2018.
86. Teriflunomide prescribing information [online]. Available at: http://products.sanofi.us/aubagio/aubagio.html. Accessed July 21, 2018.
87. Alemtuzumab prescribing information [online]. Available at: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf Accessed January 4, 2019.
88. Ocrelizumab prescribing information [online]. Available at: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed January 4, 2019.
89. Wallin MT, Kurtzke JF. Reply to: 'multiple sclerosis: variation of incidence of onset over time in the Faroe Islands'. Mult Scler 2011;17:1395; author reply 1396.
90. Wallin MT, Kurtzke JF. Comments on familial multiple sclerosis in the Faroe Islands. Acta Neurol Scand 2010;121:429-431; author reply 432.
91. Wallin MT, Heltberg A, Kurtzke JF. Multiple sclerosis in the Faroe Islands. 8. Notifiable

diseases. Acta Neurol Scand 2010;122:102-109.
92. Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol 2001;54:1-22.
93. European Medicines Agency: Fingolimod [online]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf. Accessed July 21, 2018.
94. Panitch HS. Influence of infection on exacerbations of multiple sclerosis. Ann Neurol 1994;36 Suppl:S25-S28.
95. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Use of Vaccines and Immune Globulins in Persons with Altered Immunocompetence [online]. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00023141.htm. Accessed July 21, 2018.