Practice Guideline: Immunization and Multiple Sclerosis


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14 DISCLOSURE

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

J. Correale is a member of the Scientific Advisory Board of Merck-Serono LATAM, Novartis Argentina, Genzyme Argentina, Genzyme Global; has received funding for travel from Merck-
Serono Argentina; is a member of the editorial boards of Archivos de Neurología, Current Neurology and Neuroscience Reports, Frontiers in Multiple Sclerosis, Latin American Multiple Sclerosis Journal, Multiple Sclerosis, Multiple Sclerosis and Related Disorders, Neuropsiquiatría y Neuropsiquiatría and The Open Autoimmunity Journal; 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, and Novartis Argentina; and has received research support from Genzyme Argentina, Biogen-Idec Argentina, and Novartis Argentina.

M. J. Armstrong serves on the Level of Evidence Editorial Board for Neurology (not compensated financially); receives publishing royalties from Oxford University Press for co-editing Parkinson’s Disease: Improving Patient Care; received honoraria for teaching at the 2014, 2015, and 2016 AAN Annual Meetings and the 2013 and 2014 International Congresses of Parkinson’s Disease and Movement Disorders; serves as an 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 AHRQ (K08HS024159-03); and worked at the University of Maryland through August 2015, and works for the University of Florida.

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G. Gronseth receives funding for AAN sponsored travel to guideline-related meetings; serves as an associate editor of Neurology; and received honoraria for presentations given at the annual AAN meeting.
D. Michelson receives publishing royalties of $500 per year as co-author for one Up-to-Date article.

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J. Sejvar reports no disclosures.

P. Narayanaswami has received the Myobloc Vial Grant for teaching; is a member of the editorial board for the International Journal of Aging and Health Management; received honoraria from Harris Interactive, Health Products Research, TEVA neurosciences Parkinson’s round table advisory group; and is a member of the Blue Cross Blue Shield Pharmacy and Therapeutics Committee.

ABBREVIATIONS

AAN: American Academy of Neurology
Anti-HBc: hepatitis core antibody
BCG: bacille Calmette-Guérin
CIS: clinically isolated syndrome
CSF: cerebrospinal fluid
CI: confidence interval
1 COI: conflict of interest
2 EDDS: Expanded Disability Status Scale
3 GRADE: Grading of Recommendations Assessment, Development and Evaluation
4 Gd: gadolinium
5 GDDI: Guideline Development Dissemination and Implementation
6 HC: healthy control
7 HI: hemagglutination inhibition
8 Hib: *Haemophilus influenzae* type B
9 HMO: health maintenance organizations
10 HPV: human papillomavirus
11 IgA: immunoglobulin A
12 IgG: immunoglobulin G
13 IgM: immunoglobulin M
14 IFN-β: interferon-β
15 IQR: interquartile range
16 ISIM: immunosuppressive or immunomodulating
17 MMR: measles-mumps-rubella
18 MRI: magnetic resonance imaging
19 MS: multiple sclerosis
20 ON: optic neuritis
21 OR: odds ratio
22 PBMC: peripheral blood mononuclear cells
23 PPMS: primary progressive multiple sclerosis
24 PICO: patient, intervention, comparator, outcome
Objective: To update the 2002 American Academy of Neurology (AAN) guideline regarding immunization and multiple sclerosis (MS).

Methods: A systematic review was performed (January 1990 through February 2016) and articles were classified per the AAN evidence-based classification 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 obtain information regarding vaccination status as soon as possible after MS diagnosis and at initiation of treatment. Clinicians should recommend that patients with MS follow local vaccine standards and receive annual influenza vaccine, unless specifically contraindicated. Clinicians should counsel patients with MS about infection risks associated with specific immunosuppressive or
immunomodulating (ISIM) agents and treatment-specific vaccination recommendations. Clinicians should assess vaccination status before prescribing ISIM therapy and vaccinate patients, according to local standards and prescribing information, at least 4–6 weeks before ISIM therapy. Clinicians must screen patients with MS for latent tuberculosis, as per prescribing information, before initiating treatment with teriflunomide and also before starting treatment with other ISIM medications in populations at high risk of tuberculosis or in countries with a high tuberculosis burden (Level A) and should treat those with positive test results for tuberculosis before treating them with teriflunomide. Clinicians should recommend against using live attenuated vaccines in patients with MS who are receiving or have recently discontinued ISIM therapies.

INTRODUCTION
Since the publication of the previous AAN guideline “Immunization in Multiple Sclerosis”¹ in 2002, several major studies have been published regarding the effects of infections and immunizations on the course of multiple sclerosis (MS). Additionally, several new vaccines (e.g., the human papillomavirus [HPV] vaccine) have been developed or approved. New disease-modifying therapies in MS with novel mechanisms of action have been developed. The influence of these newer immunosuppressive or immunomodulating (ISIM) therapies on the efficacy of immunization has not been systematically evaluated. Immunization against a disease may be achieved by natural infection or by vaccination against a specific agent or agents. In this guideline, we use the terms immunization and vaccination interchangeably to refer to immunity developed in response to vaccines.
The pathology of MS is characterized by the infiltration of immune cells from the circulatory system into the central nervous system. These immune cells including lymphocytes, monocytes, natural killer cells, and autoreactive T cells that are thought to be directed against myelin antigens. There is now increasing evidence to suggest a central role for migrating B cells in MS pathogenesis, with fundamental contributions both to T cell activation and direct tissue injury.\textsuperscript{2,3} There is some evidence that infections may trigger MS relapses, increase MS radiologic and immunologic activity, and accelerate disease progression.\textsuperscript{4,5} Likewise, there have been reports linking some immunizations to clinical exacerbations of MS.\textsuperscript{6} Thus, it is understandable that patients may have concerns about receiving recommended immunizations.

Another concern is that patients with MS are often treated with a variety of drugs that suppress or modulate normal immune function.\textsuperscript{7,8} These are commonly referred to as ISIM agents, although there is no clearly accepted definition of these categories. These drugs may increase susceptibility to infections in patients with MS and may reduce vaccine effectiveness because of a decreased ability to mount an immune response. The effectiveness of immunization in patients with MS who are receiving disease modifying agents was not evaluated in the previous guideline.

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?
3a. Does vaccination increase the risk of developing MS?

3b. Does vaccination increase the risk of exacerbations of MS?

4a. Are attenuated live vaccines as effective in patients with MS as they are in the general population?

4b. Are inactivated vaccines as effective in patients with MS as they are in the general population?

4c. Does ISIM treatment of MS with corticosteroids, interferons, glatiramer acetate, mitoxantrone, natalizumab, alemtuzumab, or fingolimod reduce the effectiveness of vaccinations in people with MS? In December 2016, the panel decided to include dimethyl fumarate, teriflunomide, and daclizumab to this list, and the literature search for this question was updated in January 2017.

DESCRIPTION OF THE ANALYTIC PROCESS

This guideline was developed according to the 2011 American Academy of Neurology (AAN) guideline development process as amended. In January 2012, a multidisciplinary panel, consisting of nine physicians, one patient representative (MB), and three AAN staff members (TG, EH, JC), was recruited to develop this systematic review (SR). The physicians included content experts (JC, MFF, AR-G, NK, and DJ), AAN Guideline Development, Dissemination, and Implementation (GDDI) committee members (PN, DG, DM, DD, and YH), methodology experts (GG, MJA), and an expert on immunization (JS). Conflict of Interest (COI) disclosures
were obtained from all panel members and reviewed by the AAN methodologist, AAN staff, and GDDI leadership before work on the SR commenced. Although some of the authors of the SR (JC, MF, ARG) reported COI that may be related to MS treatments, the topic of this guideline is MS and Immunizations, not MS treatments, except for question 4c, which relates to evaluation of the effects of MS treatments on immunization efficacy. As specified in the GDDI process manual, more than one half of the panel did not have a relevant COI. This panel was solely responsible for the final decisions about the design, analysis, and reporting of the guideline. The full panel participated in development of the questions to be addressed in the SR. Three content experts (JC, MFF, AR-G) and GDDI committee members performed data extraction and developed the SR. Data analysis for the SR was performed by PN and MJA.

The panel included randomized controlled trials (RCTs) and cohort and case-control studies from January 1990 to February 2016 in which the incidence, prevalence, and effect of vaccine-preventable disease and their associated immunizations on the risk of MS causation and relapses were described. Because of new literature available regarding the effects of some of the newer immunosuppressive/immunomodulating drugs on response to immunization, the search with the original search terms was updated in January 2017, and all abstracts pertaining to question 4c were reviewed and relevant full-text articles selected for data extraction and inclusion in the SR. Studies that evaluated the role of MS disease-modifying therapies on the effectiveness of immunizations were also included. The panel considered studies published in English and in other languages. Case reports and case series were excluded, except when they pertained to safety of vaccines or used a specific laboratory reference standard.

The population of interest was adults (people aged 18 years and older) in whom MS was
diagnosed according to Poser or any of the McDonald Committee’s published and revised
criteria.9 Initially, we planned to include only studies in which cases of MS were diagnosed by a
neurologist. However, we changed this criterion to include studies of cases with a diagnosis of
MS as stated by the study authors because many of the studies were from computerized
databases. Accepted control groups varied by question. For questions referencing the general
population, studies with only neurologic disease (non-MS) control groups were excluded. All
immunizations currently recommended by the United States Centers for Disease Control (CDC)
10 for children, adults, and travelers as well as vaccines suggested by panel members or during
protocol public comment (tuberculosis, bacille Calmette-Guérin [BCG], and Japanese
encephalitis vaccines) were included. The search strategy (Appendix e-1) was validated by its
ability to retrieve several key articles as determined by the content experts (JC, MFF, AR-G).

Two authors independently reviewed all titles and abstracts for relevance. Abstracts were
included if either reviewer rated them as relevant, and the full-text articles were obtained. AAN
staff sorted the titles and abstracts by clinical question and distributed the full-text manuscripts
randomly for review. The full-text articles were independently screened for inclusion by two
authors. Differences were reconciled by discussion; when disagreements arose, a methodologist
on the panel (GG, MJA) adjudicated. Following full-text screening, all included articles were
independently reviewed by two authors who extracted key data and elements from each article
and determined the article’s class according to the AAN prognostic or therapeutic rating schemes
(Appendix e-2),11 using a standardized data extraction form that was developed for each clinical
question by the AAN methodologists (MJA, GG), with input from the content experts (JC, MFF
and AR-G). Differences were resolved as previously described.
Studies in which patients with a wide range of MS severity were not included, as measured by the Expanded Disability Status Scale (EDSS) or other accepted scales, or in which the spectrum of disability was not mentioned were systematically downgraded for spectrum bias for questions 2, 3b, 4a and 4b. For questions 1a, 1b, 3a, and 4c in which the risk factor was development of MS or influence of MS treatments on vaccine effectiveness respectively, spectrum bias was not considered to be applicable because development of MS is an all-or-none phenomenon, and the influence of MS treatments on vaccine effectiveness should not be dependent on the severity of MS, respectively. When the history of infection or vaccination was determined from patient surveys, the a priori decision was to treat this as an objective outcome. Because most of these studies evaluated more than one infection or vaccination, it was felt that patients with MS would be unlikely to respond in the affirmative to all of the infections and vaccines. Unless stated as provided in the study, Bonferroni corrections for multiple outcomes were performed by the author panel. When the number of events was 0 or 100%, the Sweeting continuity correction was applied to calculate the odds ratio (OR). Data that did not provide information regarding individual diseases or vaccines were excluded.

When conclusions could not be drawn based on the available studies because of imprecision or inconsistent results between studies, we performed random effects meta-analyses when appropriate to increase precision and formulate conclusions. The random effects model was selected because it takes into account the differences between studies and provides a measure of the heterogeneity between studies ($I^2$). According to the AAN methodology, the strength of the conclusion resulting from a meta-analysis is based on whether the included studies could independently drive conclusions. If the studies included in the meta-analysis could
not independently drive a conclusion, the meta-analysis was considered equivalent to the lowest study classification included in the meta-analysis as that drives the risk of bias. That is, if no study could independently drive a conclusion and the meta-analysis included Class II studies, the meta-analysis would be equivalent to a single Class II study.

After data extraction, we synthesized the evidence and developed conclusions according to the AAN’s modified form of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process, considering precision, consistency, directness, plausibility, magnitude of effect, and dose response, where relevant. Recommendations were drafted and revised by the panel and subjected to up to three rounds of modified Delphi voting to achieve consensus and determine the strength of the recommendation. Recommendations are anchored to the evidence, 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 cost. Infections and vaccines are described in alphabetical order in the respective sections. Tables 1 and 2 summarize all conclusions by disease and vaccine as well as MS treatment and vaccine, respectively.

ANALYSIS OF EVIDENCE

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

Initially, the panel developed two questions relating to vaccine-preventable infectious diseases and MS, one relating to frequency and one relating to causation:
1. Are vaccine-preventable infectious diseases more frequent in patients with MS than in the general population?

2. Do vaccine-preventable infectious diseases increase the risk of developing MS?

However, after data extraction it was noted that all studies identified for the two questions evaluated a history of past exposure to vaccine-preventable infectious diseases in patients with MS versus controls, and this data did not inform the causation question. Hence, the two questions were collapsed into one.

A history of vaccine-preventable infections was assessed by variable methods including surveys, interviews, review of medical records, and antibody titers (serum or cerebrospinal fluid [CSF]). The prognostic schema was used for rating the risk of bias of these studies to evaluate the association between vaccine-preventable infections and the development of MS. Hence these conclusions only reflect an association and do not imply causation. Table 3 summarizes the diseases with insufficient evidence.

**Diphtheria**

A Class II case-control study investigated the Faroe Island epidemic of MS, which began in 1943, attributed to the occupation of the islands by British troops in World War II and the resultant introduction of an unknown infectious agent. Surveys were returned by 23 MS patients, 69 siblings and relatives, 37 neighbor controls or patients' spouses, and 21 distant matched controls and their spouses. Several environmental and socioeconomic factors and history of prior infectious illness and vaccinations were compared between patients with MS and controls. Two
percent of controls (3 of 127) and none of the patients with MS reported a history of diphtheria (odds ratio [OR] with Sweeting continuity correction 0.0139; 95% confidence interval [CI], 0.00 to 2.87).

Conclusion

There is insufficient evidence to support or refute whether a history of diphtheria is more frequent in patients with MS than in the general population (very low confidence in the evidence; one Class II study with decreased confidence in the evidence because of insufficient precision.

Hepatitis (unknown type)

Two Class II studies were identified.\textsuperscript{12,13}

In a Class II case-control study,\textsuperscript{12} 8 of 127 (6\%) controls and none of the 23 cases reported a history of hepatitis (OR with Sweeting correcting 0.005; 95\% CI, 0.00 to 2.873).

In a Class II case-control study,\textsuperscript{13} 140 patients with MS (relapsing remitting MS [RRMS], secondary progressive MS [SPMS], or primary progressive MS [PPMS]; mean age 42.1 ± 10.2 years; and mean disease duration 10.9 ± 7.5 years) and 131 age- and sex-matched blood donor controls were surveyed, with the use of a structured questionnaire, by masked interviewers in a face-to-face interview. In a univariate logistic regression analysis, antecedent infection with hepatitis was not associated with MS (4 of 140 [2.8\%] cases and 8 of 131 controls [6\%] [OR 0.5; 95\% CI, 0.1 to 1.5]).

Because neither Class II study had sufficient precision, a random effects meta-analysis was performed, resulting in an OR of 0.075, 95\% CI, 0 to 6.28, $I^2=78$, with CIs including the possibility of clinically important increased or decreased odds of prior exposure to hepatitis in
Conclusion

There is insufficient evidence to support or refute whether a history of hepatitis is more frequent in patients with MS than controls (very low confidence in the evidence; two Class II studies with decreased confidence in the evidence because of insufficient precision and a random effects meta-analysis of 2 Class II studies showing a lower history of exposure to hepatitis in patients with MS but lacking the precision to exclude clinically important effects in either direction).

Hepatitis B

In a Class II case-control study, 675 patients with various autoimmune diseases were matched with a control cohort for age, gender, ethnicity, and socioeconomic status. All serum samples were tested for hepatitis B core antibodies (anti-HBc). Among the 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; CI, 0.04 to 0.84).

Conclusion

It is possible that a history of Hepatitis B is less frequent in patients with MS compared to the general population (OR 0.19; 95% CI, 0.04 to 0.84) (low confidence in the evidence, one Class II study).
Measles

Ten Class II studies were identified (Table 4). 12,13,15–22

In the previously described Class II case control study,12 83% of MS subjects and 93% of controls reported a history of measles (OR 0.37; 95% CI, 0.15 to 0.93).

In another previously described Class II case control study,13 a univariate logistic regression analysis found that antecedent infection with measles was not associated with MS. (126 of 140 [90%] cases and 110 of 131 [83.9%] controls [OR 1.3; 95% CI, 0.6 to 3).

In a Class II retrospective twin cohort study,15 all twin pairs with at least one affected member with MS were identified from the nationwide Finnish Twin Cohort, linked to the International Statistical Classification of Diseases, Injuries, and Causes of Death (where the diagnosis of MS was coded). Serum samples from 17 discordant twins (8 monozygotic and 9 dizygotic) were assayed for antibodies against 21 viral antigens, Toxoplasma, Mycoplasma pneumoniae, and Chlamydia. MS duration ranged from 2 years to 49 years, with a mean of 17.9 years. Mean differences in measles antibody titers were no different between MS subjects and their healthy twins. Raw mean difference [RMD] of geometric mean complement-fixing antibody titers between twins with MS and twin controls was 0.06 (95% CI, -2.78 to 2.90). In 6 of 17 patients with MS and 2 of 17 healthy subjects, the measles titer was at least fourfold higher. This difference was significant, but the CI lacked precision to exclude important effects in either direction (OR 4.09; 95% CI, 0.69 to 24). The serum concentration of immunoglobulin G (IgG) (RMD -0.1; 95% CI, -2.14 to 1.94), immunoglobulin A (IgA) (RMD 0; 95% CI, -1.079 to
1.079), and immunoglobulin M (IgM) (RMD 0.2; 95% CI, -0.283 to 0.683) did not differ between patients and their healthy twins.

In a Swedish Class II case-control study, authors linked an MS registry database to 2 serum sample databases. Serum samples from 234 MS cases and matching controls were available. Cases without any possible MS symptoms before the date of serum collection were defined as “prospective,” and the cases whose serum was collected after the onset of MS were defined as “retrospective.” The prospective cohort consisted of 73 cases of definite MS (age range 17–59, [median 28 years], duration between symptom onset and blood serum collection 1 to more than 15 years, and 67 of the participants were female). The retrospective cohort consisted of 161 MS cases (age range 19–68 years, [median 40 years], duration between symptom onset and serum collection 1–15 years, and 125 of the participants were female). Three controls matched for serum bank, sex, age, and year of blood serum collection were selected for each case.

All 73 prospective cases and 219 controls were positive for measles, thus precluding the detection of any association between infection and risk of developing MS (OR using Sweeting correction 1; 95% CI, 0.0002 to 10161.82, imprecise). A multivariate logistic regression revealed no significant association between measles and the risk of developing MS. In the retrospective cohort, the prevalence of seropositivity to measles was comparable in the cases and controls, and thus did not show an association between measles and the risk of MS (100% of cases and 99.2% of controls were antibody positive [OR 0.57; 95% CI, 0 to 4.5, imprecise]). A multivariate analysis revealed that high antibody titers against measles were associated with increased risk of MS (OR 1.9; 95% CI, 1.1 to 3.3). The significance of the association of high antibody titers to
measles in MS cases in the absence of a difference between cases and controls is uncertain. Because this is a database study, it is difficult to be certain that samples were collected before MS onset; symptoms may not have been reported at the time of serum collection.

A Class II case-control study compared the seroprevalence of measles IgG and IgM antibodies in 60 patients with RRMS (McDonald criteria, 52 female, mean age 32±17 years) who had not received any immunosuppressant or corticosteroid treatment or vaccination for 1 year before the study with 61 healthy controls (HCs) who were matched for age, gender, and socioeconomic status. The MS patients had a higher seroprevalence of measles IgM than the HCs (54% vs 27% [OR 3.2; 95% CI, 1.5 to 6.9]). There was no difference in measles IgG (84% of patients with MS vs 88% of controls [OR 0.67; 95% CI, 0.24 to 1.9, imprecise). The authors did not mention how they excluded immunization in the year before the study (recall and other biases may occur if patient history was used), and therefore it is not possible to definitively attribute the antibody positivity to prior infection or immunization. The presence of IgM antibodies in the absence of immunization in the year before the study raises the possibility of infection rather than immunization.

Another Class II retrospective case-control study reported the seroprevalence of measles antibodies in a cohort of 166 patients MS (124 RRMS Poser criteria and 42 clinically isolated syndrome [CIS]) compared with 50 HC (blood donors with paired serum and CSF samples). Histories of measles infection and vaccination in all subjects were obtained. The majority of controls reported measles infection; only 6 of 50 reported vaccination. There were no significant differences in the proportion of patients with MS/CIS and HCs who were seropositive (94% of patients with MS vs 92% of HCs [OR 1.36; CI, 0.45 to 4.07, imprecise). Antibodies to
measles in CSF were more likely to be detected in patients with MS than in HCs (74% vs 34% [OR 5.52; 95% CI, 3 to 10]). Additionally, the patients with MS/CIS had significantly higher measles antibody titers in serum and CSF than HCs, (serum median: 3,200 vs 1,600 [Bonferroni corrected $p <0.01$] and CSF median [interquartile range (IQR)]: 20, [<10–80] vs <10 [<10–10], Bonferroni corrected $p <0.01$). When comparing vaccinated subjects to those who had natural infection, measles vaccination induced antibodies in CSF in fewer MS/CIS patients than natural measles infection did (62% of those who were vaccinated vs 87% of those who were naturally infected [relative risk (RR), 0.71; 95% CI, 0.6 to 0.84]), but antibody levels in serum and CSF were higher in the vaccinated group compared with the natural-infection group (median levels in serum: 6,400 vs 1,600 [Bonferroni corrected $p <0.01$]; median levels in CSF: 40 vs 10, Bonferroni corrected $p <0.01$). Antibody titers in the serum of vaccinated MS/CIS patients were no different than those in HCs (median in both groups was 1,600, $p=0.056$), whereas antibody levels in the CSF of vaccinated MS/CIS patients were significantly higher than in HCs (median 10 [IQR: <10–40] vs <10 [IQR: >10–10], Bonferroni corrected $p <0.01$). This study included patients who reported natural infection or receiving the immunization or both, and this may have influenced the results. MS and CIS data were not provided separately. Hence, it is difficult to draw any conclusions regarding the prevalence of measles in MS subjects compared to HC.

A Class II case-control study evaluated the seroprevalence of measles antibodies in 25 patients with MS (21 with RRMS, 2 with PPMS, 1 transitioning to progressive MS, and 1 with CIS). The mean age of these patients was 36.2±10.7 years, and 64% of them were female. Forty-six siblings were used as controls (mean age 36.3±12.8 years). There was no difference in the seroprevalence of measles antibodies between cases and controls (100% in both groups). Mean
antibody titers to measles were also not significantly different (raw means and standard deviation [SD] not provided, means appear similar in the figure provided in the study, calculation from the figure yields OR of 0.548; 95% CI, 0.0217 to 13.9). There is no report on the prevalence of immunization. Measles immunization was added to the mandatory immunization scheme in 1978, and it is likely that a high proportion of cases and controls were immunized against measles.

In a Class II case control study,20 81 patients with MS (Poser criteria) were compared with 81 HCs (friends/neighbors), matched by age, gender and birthplace. A standardized questionnaire was used for face-to-face interviews with all study participants. A forward conditional logistic regression model found that a history of measles was not significantly different between cases with MS and HCs (56 of 81 [68.4%] cases with MS had a history of measles vs 54 of 81 [66.2%] HCs [OR 1.2; 95% CI, 0.6 to 2.7]).

In a Class II study in which a longitudinal population based cohort identified from a Canadian database was used,21 14,362 MS index cases (mean age 49 years ± 9.6 years, 58% with RRMS) and 7,671 spouse controls (mean age 52.9 years ± 11.9 years) were asked about history of childhood infections (as well as history of vaccination). Logistic regression showed no significant age-and sex-adjusted difference between cases with MS and controls for history of measles (OR 0.97; 95% CI, 0.91 to 1.05). The authors point out limitations, including reporting and recall bias. Males in this study were more likely than females to report “unknown” as an answer to virus or vaccination exposures (19.3% vs 16.2%, \( p < 0.001 \)).

A Class II case-control study22 evaluated the risk of infectious diseases for individuals
with MS in 2 cohorts. The first cohort included individuals born after 1940 (455 cases and 1,801 controls), and the second cohort included individuals born after 1950 (182 cases and 690 controls). The age range of all participants was 15–56 years (the mean was 35 years), the ratio of males to females was 1:1.9, and MS was diagnosed by Allison or Poser criteria. School records that contained information on measles, pertussis, and scarlet fever for the first cohort and rubella, mumps and varicella for the second cohort were reviewed. A history of measles was reported in 78% of cases and 80% of controls (OR 0.8; 95% CI, 0.6 to 1.1). The difference remained nonsignificant when stratified by age at infection.

When considering methods for ascertainment of either history of measles or measles antibody titers, six studies \(^{12, 15, 19-22}\) showed no difference in measles exposure between patients with MS and controls, and 4 studies \(^{13, 16, 17, 18}\) were imprecise to exclude a higher or lower frequency of measles exposure in MS patients. To increase precision, all 10 Class II studies were combined in a random-effects meta-analysis assuming that all methods of assessing measles exposure were measuring similar underlying phenomena. When multiple laboratory methods were reported by studies, testing of IgG was used preferably over IgM, and serum antibody levels were used over CSF antibody levels. The random effects meta-analysis found no significant difference in the history of measles exposure in MS patients vs controls (OR 0.957; 95% CI, 0.88 to 1.038; \(I^2=1\)%).

**Conclusion**

It is probable that a history of measles is similar in patients with MS compared with the general population (moderate confidence in the evidence; meta-analysis of 10 Class II studies with no
significant difference in the history of measles exposure in MS patients versus controls [OR 0.957; 95% CI, 0.88 to 1.038; I²=1%]).

Meningitis, type unspecified:

In a previously described Class II case-control study,¹² none of the 23 patients or 127 controls reported a history of meningitis (OR with Sweeting correction 1; 95% 0.0006–3342.36, imprecise).

Conclusion

There is insufficient evidence to support or refute whether a history of meningitis (type uncertain) is more frequent in patients with MS than in the general population (very low confidence in the evidence; one Class II study, with decreased confidence in the evidence because of imprecision).

Mumps:

Seven Class II studies were identified.¹²,¹⁵,¹⁷,²⁰–²³

In the previously described Class II case-control study,¹² 70% of MS cases and 84% of controls reported a history of mumps (OR 0.45; 95% CI, 0.25–0.88).

In the previously described Class II retrospective twin cohort study,¹⁵ mean differences in mumps antibody titers were no different between patients with MS and their healthy twins (RMD
of geometric mean complement-fixing antibody titers in patients with MS vs controls: -0.59; 95% CI, -5.036 to 3.856). A fourfold increase in IgG antibody titers was noted in one control twin and one twin with MS (OR 1; 95% CI, 0.06 to 17.4).

In the previously described Class II case-control study, patients with MS had higher seroprevalence for mumps IgM antibodies than HCs (MS: 64% vs HC: 30% [OR 4.1; 95% CI, 1.9 to 8.8]) and mumps IgG (MS: 93% vs HC: 60% [OR 9.5; 95% CI, 3 to 29.6]). As mentioned above, it is not possible to definitively attribute the antibody positivity to prior infection or immunization, although the presence of IgM antibodies in the absence of immunization in the year before the study increases the possibility of infection rather than immunization.

In another previously described Class II case-control study, a forward conditional logistic regression model found that a history of mumps was not different between the cases and controls (history of mumps in 52 of 81 cases [68.4%] vs history of mumps in 55 of 81 [71.4%] [OR 1.1; 95% CI, 0.5 to 2.3]).

In the previously described Class II study, logistic regression showed no significant age- and sex-adjusted difference between cases and controls for history of mumps (OR 0.98; 95% CI, 0.92 to 1.05).

In the previously described Class II case-control study, a history of mumps was reported in 35% of cases and 41% of controls (OR 0.8; 95% CI, 0.6 to 1.1, imprecise). There was no association between mumps and the future risk of developing MS. The difference remained nonsignificant when stratified by age at infection.

A Class II case-control study, available only as abstract, reported an increased risk of
MS with past mumps infection (OR 1.5; 95% CI, 1.0 to 2.2).

The seven Class II studies evaluating a history of mumps infection in MS patients versus controls included five studies with insufficient precision to detect an effect or exclude an important effect in either direction \textsuperscript{15,17,20,22,23} and two studies showing a less frequent history of mumps in MS cases compared with controls, according to responses on questionnaires.\textsuperscript{12,21} The heterogeneous methods for detecting infection history may have resulted in the disparate results, but there is no clear way to reconcile the findings. In a random-effects meta-analysis of the seven studies, the OR for a history of mumps infection in patients with MS was 1.09 (95% CI, 0.76 to 1.55, \(I^2=78\%\)), with CIs including potentially clinically important effects in both directions and with very high heterogeneity in the model.

Conclusion

There is insufficient evidence to support or refute whether a history of mumps is more frequent in patients with MS than in the general population (very low confidence in the evidence; seven Class II studies with a meta-analysis with decreased confidence in the evidence because of insufficient precision [OR 1.09; 95% CI, 0.76 to 1.55; \(I^2=78\%\)].

Pertussis

Two Class II studies were identified.\textsuperscript{12,22}

In the previously described Class II case-control study,\textsuperscript{12} 83% of patients and 80% of controls reported a history of pertussis (OR 1.2; 95% CI, 0.6 to 2.5, imprecise).
In another previously described Class II case-control study, a history of pertussis was reported in 50% of cases and 52% of controls (OR 0.9; 95% CI, 0.7 to 1.1, imprecise). The difference remained nonsignificant when stratified by age at infection.

Because both studies were limited by statistical precision, a random-effects meta-analysis was performed. This showed no significant difference in a history of pertussis infection in patients with MS vs controls (OR 0.925; 95% CI, 0.75 to 1.15, I²=0%), but the CIs included ORs that could suggest either higher or lower exposure history in people with MS.

**Conclusion**

There is insufficient evidence to support or refute whether a history of pertussis is more frequent in patients with MS (very low confidence in the evidence; two Class II studies and a meta-analysis with decreased confidence in the evidence because of insufficient precision [OR 0.925; 95% CI, 0.75 to 1.15, I²=0%]).

**Polio**

In the previously described Class II case-control study, none of the 23 patients with MS or the 127 controls reported a history of polio. (OR with Sweeting correction 1; 95% CI, 0.0006 to 3342.36, imprecise).

**Conclusion**

There is insufficient evidence to support or refute whether a history of polio is more frequent in
patients with MS than in the general population (very low confidence in the evidence; one Class II study with decreased confidence because of imprecision).

Rubella

Six Class II studies were identified.\textsuperscript{12,13,15,20–22}

In the previously described Class II case-control study,\textsuperscript{12} rubella was less frequent in the MS cases than in controls (61\% vs 79\% [OR 0.42; 95\% CI, 0.22 to 0.78]).

In another previously described Class II case-control study,\textsuperscript{13} a univariate logistic regression analysis found that antecedent infection with rubella was not associated with MS (75 of 140 [53.5\%] cases vs 74 of 131 [56.4\%] controls [OR 0.8; 95\% CI, 0.5 to 1.3]).

In the previously described Class II retrospective twin cohort study,\textsuperscript{15} mean differences in rubella antibody titers were no different between MS cases and their healthy twins (RMD of geometric mean antibody titers between twins with MS and controls 0.29; 95\% CI, -1.65 to 2.23, imprecise). A fourfold increase in rubella antibody titers was noted in one control and two cases (OR 2.13; 95\% CI, 0.18 to 26, imprecise).

In the previously described Class II prospective case-control study,\textsuperscript{20} a forward conditional logistic regression model found that rubella was less frequent in patients with MS than in controls (16 of 81 [20.5\%] cases vs 30 of 81 [39\%] controls; OR 0.4; 95\% CI, 0.2 to 0.9).

In another previously described Class II study,\textsuperscript{21} logistic regression showed no significant age- and sex-adjusted difference between cases and controls for history of rubella (OR 0.93; 95\%
In a previously described Class II case-control study,\textsuperscript{22} a history of rubella was reported in 45% of cases and 45% of controls (OR 1.0; 95% CI, 0.7 to 1.4). The difference remained nonsignificant when stratified by age at infection.

Of the six Class II studies, only one showed a higher odds of MS in patients with a history of rubella, but it was imprecise, with CIs including ORs that could suggest either a higher or lower risk of exposure to rubella in people with MS.\textsuperscript{15} Two studies showed a reduced odds of developing MS in the rubella exposed population,\textsuperscript{12,20} 2 studies yielded point estimate showing reduced odds (ORs < 1) but with CIs crossing unity,\textsuperscript{13,21} one study showed an OR of 1 with 95% CI ranging from 0.7 to 1.4, hence unable to exclude a higher or lower odd of MS in the rubella exposed patients.\textsuperscript{22} As in the case of measles, the heterogeneous methods for detecting infection history may have resulted in the disparate results. A random effects meta-analysis combining all the six Class II studies yielded an OR of 0.78 (95% CI, 0.59 to 1.02, I\textsuperscript{2}=57%).

**Conclusion**

There is insufficient evidence to support or refute whether a history of rubella is more frequent in patients with MS (very low confidence in the evidence; six Class II studies and a random effects meta-analysis with decreased confidence in the evidence because of insufficient precision [OR 0.78; 95% CI, 0.59 to 1.02; I\textsuperscript{2}=57%].
Small pox

In a previously described Class II case-control study,\textsuperscript{12} none of the patients or controls reported a history of small pox (OR with Sweeting correction 1; 95% CI, 0.0006 to 3342.36).

Conclusion

There is insufficient evidence to support or refute whether a history of small pox is more frequent in patients with MS than in the general population (very low confidence in the evidence; one Class II study with decreased confidence in the evidence due to imprecision).

Tuberculosis

Two Class II studies were identified.\textsuperscript{12,13}

In a previously described Class II case control study,\textsuperscript{12} 17% of cases and 11% of controls reported a history of tuberculosis (OR 1.66; 95% CI, 0.73 to 3.74).

In another previously described Class II case control study,\textsuperscript{13} a univariate logistic regression analysis found that antecedent infection with tuberculosis was not associated with MS (3 of 140 [2%] cases, 1 of 131 [0.7%] controls [OR 2.9; 95% CI, 0.3 to 28.5]).

Because both studies lacked precision, a random effects meta-analysis was performed; this showed higher odds of patients with MS having a history of tuberculosis compared with controls but with 95% CIs including potentially clinically important effects in both directions.
Conclusion

There is insufficient evidence to support or refute whether a history of tuberculosis is more frequent in patients with MS (very low confidence in the evidence; two Class II studies and a random effects meta-analysis with decreased confidence in the evidence because of insufficient precision [OR 1.77; 95% CI, 0.82 to 3.82; I²=0]).

Typhoid

In a Class II case-control study,12 4% of MS patients and 4% of controls reported a history of typhoid (OR 1; 95% CI, 0.24 to 4.11)

Conclusion

There is insufficient evidence to support or refute whether a history of typhoid is more frequent in patients with MS than in the general population (very low confidence in the evidence; one Class II study with decreased confidence in the evidence due to insufficient precision).

Varicella-zoster virus, chicken pox, herpes zoster
Seven Class II studies were identified.\textsuperscript{12,13,16,20–22,24} In the previously described Class II case-control study,\textsuperscript{12} chicken pox was more frequently reported by controls than by MS patients (cases 52\% vs controls 68\% [OR 0.5; 95\% CI, 0.29 to 0.9]).

In another previously described Class II case-control study,\textsuperscript{13} a univariate logistic regression analysis found that antecedent infection with varicella-zoster virus (VZV) was not associated with MS (111 of 140 [79\%] cases, 103 of 131 [78.6\%] controls [OR 1; 95\% CI, 0.5 to 1.7]).

In the previously described case-control study,\textsuperscript{16} in the prospective cohort, from which serum was collected before MS symptoms, VZV antibody was detected in 90.4\% of MS cases and 95.4\% of controls (OR 0.45; 95\% CI, 0.14 to 1.43). A multivariate logistic regression revealed no significant association between VZV infection and the risk of developing MS. In the retrospective cohort” also, the prevalence of seropositivity to VZV was comparable between the cases and controls (100\% of cases and 99.2\% of controls were positive). A multivariate analysis revealed that high VZV antibody titers were associated with an increased risk of MS (OR 2.6; 95\% CI, 1.5 to 4.6). The association of high antibody titers to measles in MS cases in the absence of a difference between cases and controls is uncertain.

In the previously described Class II case-control study,\textsuperscript{20} a forward conditional logistic regression model found that a history of chicken pox was not significantly different between cases and controls (55 of 81 [72.4\%] cases had a history of chicken pox vs 60 of 81 [77.9\%] controls [OR 0.7; 95\% CI, 0.3 to 1.7, imprecise).
In the previously described Class II study, \(^{21}\) logistic regression showed no significant age- and sex-adjusted difference between cases and controls for history of varicella (OR 1.07; 95% CI, 1 to 1.14).

In another previously described Class II case-control study,\(^ {22}\) a history of chicken pox was reported in 68% of cases and 67% of controls (OR 1.1; 95% CI, 0.7 to 1.5, imprecise). The difference remained nonsignificant when stratified by age at infection.

A Class II case-control study\(^ {24}\) evaluated the presence of VZV viral genomic material in the CSF of 38 patients with MS (Poser criteria, mean age of 38±12 years, disease duration of 1–14 years, 63% females, 23 with RRMS, 15 progressive MS) and 19 HC (mean age of 70±10 years, 11% females). VZV viral DNA was found in the CSF of 12 of 38 (32%) patients with MS, whereas none of the 19 HC had a detectable DNA viral load (OR with Sweeting correction 334.479; 95% CI, 1.968 to 49714.67, imprecise).

Only one Class II study had sufficient precision to show a difference in the history of varicella in patients with MS versus controls\(^ {12}\); all other studies lacked precision, although the ORs were <1. One study had a higher frequency of a history of varicella in patients with MS,\(^ {24}\) but had a very wide CI. Because of this, a random effects meta-analysis was performed showing essentially no difference in a history of varicella between patients with MS and controls (OR 1.017; 95% CI, 0.72 to 1.43; \(I^2=71\%\)). However, the CIs from this meta-analysis included ORs with potentially clinically important ORs in both directions (i.e., patients with MS could have a potentially higher or lower odds of a history of varicella compared with controls).
Conclusion

There is insufficient evidence to support or refute whether a history of varicella is more frequent in patients with MS than in the general population (very low confidence in the evidence; 7 Class II studies and a random effects meta-analysis with decreased confidence in the evidence because of insufficient precision [OR 1.017; 95% CI, 0.72 to 1.43; I²=71%]).

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

Influenza

One Class III case-control study (for spectrum bias) met inclusion criteria.25 Cases were patients with Poser criteria definite or laboratory supported MS attending an MS clinic in 1992 with their first exacerbation of the year. Each case was matched with a control patient who was attending the same clinic and had RRMS with a stable course in the previous 3 months, seen during the same period (matched for sex, age, EDSS score, and season of interview). Information on infectious disease exposure was obtained in a structured interview. The study included 89 cases (62 female mean age of 35.6 ±9.3 years, disease duration of 7.4±6.1 years, and mean EDSS of 1.7± 0.8) and 89 controls (62 female mean age of 35.3± 10.1 years, a mean MS duration of 7.9± 6.8 years, and a mean EDSS of 1.5± 1.0). There was no significant difference in exposure to influenza between the groups in the preceding 3 months (4 of 89 cases, and 8 of 89 controls [OR 0.5; 95% CI, 0.2 to 1.7]. The lack of a biological marker of recent influenza infection is a limitation of this study (directness/generalizability) because a diagnosis of influenza was based
on history, and other viral respiratory infections can mimic influenza. Additionally, the number of influenza cases in both groups was small.

Conclusion

There is insufficient evidence to support or refute whether a history of influenza increases the risk MS exacerbations (very low confidence in the evidence; one Class III study with decreased confidence in the evidence because of insufficient precision and indirectness).

Varicella-zoster virus, chicken pox, herpes zoster:

A Class II case-control study\textsuperscript{26} evaluated the presence of VZV DNA in peripheral blood mononuclear cells (PBMCs) from patients with MS during relapse (n=15) or remission (n=67), HC (n=20), and patients with other neurologic disorders (n=100). All subjects had RRMS (age range of 16–57 years, [mean 31± 9 years], EDSS range of 0–8, mean± SD of 3.6±2.4, 49 female). VZV DNA was found in the PBMCs of 13 of the 15 (87%) patients who were experiencing relapse, within the first week of a clinical relapse, whereas no VZV DNA was found in the PBMCs of any of these 15 patients when they were evaluated again 2 months after remission. VZV DNA was undetectable in all 67 patients with RRMS in remission. OR with Sweeting correction for detection of VZV DNA during relapse 6948.015; 95% CI, 71.819 to 414552.23. None of the 20 HCs had VZV DNA in their PBMCs.
Conclusion

The presence of viral VZV DNA in PBMCs is possibly associated with an increased risk of MS exacerbations (low confidence in the evidence; one Class II study).

3A) Does vaccination increase the risk of developing MS?

Diphtheria toxoid

Two Class II studies were identified.\textsuperscript{12,27}

In the previously described Class II case-control study,\textsuperscript{12} 35% of patients with MS and 55% of controls reported diphtheria vaccination (OR 0.44; 95% CI, 0.25 to 0.78).

Another Class II study\textsuperscript{27} used serum stored in the Department of Defense Serum Repository in a nested case-control study of 7 million military service members. Fifty-six cases of MS among active duty personnel in the US army occurring between Jan 1998 and July 2000 who had at least one serum sample collected before the onset of MS were compared with 2 controls (matched for age, sex, race, and date of collection (±30 days). No differences were found in mean levels of serum IgG antibodies against diphtheria toxoid between cases and controls (mean titers cases: 0.91 ± 0.89, controls: 0.89± 0.87 [RMD 0.02; 95% CI, -23.7 to 23.7]). The OR for MS associated with 1 SD difference in antibody titers was 1.03 (95% CI, 0.73 to 1.45). The CIs include the possibility that a history of diphtheria immunization may be either increased or decreased in MS patients compared with controls.
The inconsistent results between the two studies may be related to the method of determining exposure to diphtheria vaccination (from antibody titers in one\textsuperscript{27} and from survey responses in the other\textsuperscript{12}). The two studies combined in a random effects meta-analysis yielded an OR of 0.7 (95\% CI, 0.3 to 1.6), with very high heterogeneity in the model, $I^2 = 84\%$.

**Conclusion**

There is insufficient evidence to conclude whether diphtheria vaccination increases the risk of developing MS (very low confidence in the evidence; two Class II studies with decreased confidence in the evidence for inconsistency and imprecision; meta-analysis [OR 0.7; CI, 0.3 to 1.6; $I^2 = 84\%$]).

**Hepatitis B vaccination**

Six Class II studies were identified.\textsuperscript{21,28–32} One additional study\textsuperscript{33} was a subgroup analysis of a previous study.\textsuperscript{32}

In the previously described Class II study,\textsuperscript{21} logistic regression showed no significant age and sex adjusted difference between cases and controls for history of Hepatitis B vaccine (OR 0.92; 95\% CI, 0.84 to 1.01).

In a Class II nested case-control study,\textsuperscript{28} 192 women with MS (definite or probable Poser criteria) and 645 matched controls (534 HC and 111 controls with breast cancer) were asked their history of hepatitis B vaccination. Vaccination status was confirmed by medical record
review. To control for the recombinant hepatitis B vaccine that was introduced in 1987, another analysis was performed excluding women with onset of MS before 1987. Twenty-three of 190 (12.1%) women with MS and 54 of 543 (10.1%) HC controls were vaccinated against hepatitis B more than 2 years before onset of MS (OR for developing MS, 1.2; 95% CI, 0.73 to 2.1). Nine of 190 (4.7%) women with MS and 30 of 534 (5.6%) controls were vaccinated against hepatitis B 2 years or less before the index date (OR 0.8; 95% CI, 0.39 to 1.8). Thirty-two of 190 (16.8%) women with MS and 84 of 534 (15.7%) controls were vaccinated against hepatitis B any time before the index date (OR 1.08; 95% CI, 0.69 to 1.7). The results were similar in analyses restricted to women with MS with onset after the introduction of the recombinant hepatitis B vaccine. There was also no statistically significant association between the number of doses of vaccine received and the risk of MS. However, the CIs included ORs that were associated with a lower or higher frequency of exposure to hepatitis B vaccine in MS cases compared with controls.

In another Class II case-control study, electronic health records were utilized to identify 427 newly diagnosed MS cases (McDonald’s criteria) and a maximum of 5 controls (matched for age, sex, and socioeconomic status at the date of the case patient’s symptom onset). Only 3.3% of controls and 4.0% of cases had received hepatitis B vaccination. At 90 days, 180 days, 1 year, and 3 years before symptom onset, 1 (0.2%), 1 (0.2%), 4 (0.9%) and 18 (4.2%) cases and 11 (0.5%), 17 (0.8%), 31 (1.5%), and 66 (3.1%) controls, respectively, had received hepatitis B vaccination. The OR at 90 days, 180 days, and 1 year were 0.41 (95% CI, 0.05 to 3.58), 0.26 (95% CI, 0.03 to 2.07), and 0.69 (95% CI, 0.23 to 2.07), respectively. At 3 years the OR was 1.36 (95% CI, 0.77 to 2.42). Although the point estimate for the OR of developing MS was lower
in the cases at all time points except at 3 years, none of the results achieved statistical significance, and the study lacked the precision to exclude a significant effect in either direction.

In another Class II case-control study,30 163 adults with a diagnosis of MS (RR, SPMS, and PPMS, Poser criteria) and at least 3 years of computerized medical records in the British General Practice Research Database before the date of the first symptom of MS were compared with up to 10 age- and gender-matched controls (n= 1604). Eleven of 163 (6.7%) cases and 39 of 1604 (2.4%) controls had received hepatitis B vaccination (OR for developing MS, 3.1; 95% CI, 1.5 to 6.3). When the date of MS diagnosis was used as the index date, there was no significant association with hepatitis B vaccination exposure (OR 1.0; 95% CI, 0.5 to2.1). Most of the MS cases (93%) cases were unvaccinated. The proportion of MS cases that received at least one hepatitis B vaccination during the 3 years before the date of first symptoms was 6.7% (11 of 153), compared with 2.4% (39 of 1604) of controls (OR 3.1; 95% CI, 1.6 to 6.2).

In a Class II case-control study,31 cases of MS (Poser criteria) or optic neuritis (ON) (n=440, age range of 18–49 years) were identified from the computer records of three large health maintenance organizations (HMO). Exposure to several vaccinations was compared with exposure in age- and gender-matched controls (n=950). Paper records and telephone interviews, including self-reported vaccination history, were used to supplement data from the computerized database. On conditional logistic regression, associations between exposures to hepatitis B vaccinations and symptoms of MS were nonsignificant (34 of 440 [7.7%] of cases and 77 of 950 [8.1%] controls [OR, 0.8; 95% CI, 0.5 to 1.4) When the analyses were repeated, requiring more restrictive criteria for diagnosis (diagnosis by a specialist or only diagnoses clinically definite for MS or HMO documentation of vaccinations), the associations remained nonsignificant.
([neurologist/ophthalmologist diagnosed MS/ON OR, 0.9; 95% CI, 0.6 to 1.5] [clinically definite
MS OR, 0.8; 95% CI, 0.4 to 1.4] [MS/ON when vaccination was confirmed from records OR,
0.9; 95% CI, 0.5 to 1.6]). There was also no significant increase in risk of MS adjusted for the
time the vaccines were received (less than 1 year after receiving vaccination, the OR for
developing MS was 0.8 [95% CI, 0.4 to 1.8]; 1–5 years after vaccination, the OR was 1.6 [95%
CI, 0.8 to 3]; and more than 5 years after vaccination, the OR was 0.6 [95% CI, 0.2 to 1.4]).
However, the CIs included ORs that indicated either a higher or lower frequency of hepatitis B
vaccination in MS cases.

A Class II subgroup analysis of hepatitis B vaccination from the same dataset
previously discussed was presented in a subsequent abstract, in which the OR for developing
MS in a cohort of 226 MS subjects with data from medical records only was analyzed. Interview
information was excluded to minimize bias. This analysis also did not show an association
between hepatitis B vaccination and subsequent development of MS (OR 0.8; 95% CI, 0.4 to
1.4) but was imprecise. The timing of vaccination did not influence subsequent development of
MS (MS symptoms 0–1 year after vaccination: OR 0.7 [95% CI, 0.3 to 2.0]; MS symptoms 1–2
years after vaccination: OR 0.7 [95% CI, 0.2 to 2.5]; MS symptoms 2–3 years after vaccination:
OR 0.6 [95% CI, 0.1 to 3.1]; MS symptoms 3–4 years after vaccination: OR 2.2 [95% CI, 0.4 to
11.8]; MS symptoms 4–5 years after vaccination: OR 0.9 [95% CI, 0.2 to 4.5]; and MS
symptoms more than 5 years after vaccination: OR 0.7 [95% CI, 0.3 to 2.0]. These results were
imprecise with CIs, including potentially important effects in either direction.

In a Class II case-control study of 250 incident MS patients identified from the local
MS society and 250 age- and gender-matched controls, the association between hepatitis B
vaccination and MS development was evaluated by responses to a questionnaire survey administered to subjects by the study personnel. There was no difference in the hepatitis B vaccination frequency between cases and controls (101 of 204 [40.4%] cases and 108 of 250 [43.5%] controls [OR 1.29; 95% CI, 0.89 to 1.78]).

Only 1 study showed an increased risk of MS after hepatitis B vaccination; all other studies showed either no difference or reduced history of hepatitis B vaccination in patients with MS. However, all the studies except one lacked precision to exclude an important effect in either direction. Therefore, all six Class II studies were combined in a random effects meta-analysis. The random effects meta-analysis found that a history of exposure to hepatitis B vaccination was slightly lower in MS cases compared with controls (OR 0.9; 95% CI, 0.84 to 1, I² 0%).

**Conclusion**

It is probable that hepatitis B vaccination is not associated with an increased risk of developing MS (low confidence in the evidence, six Class II studies, with decreased confidence in the evidence for imprecision and a meta-analysis showing an OR of 0.9 [95% CI, 0.84 to 1; I² = 0%]).

**Human papillomavirus vaccination**

One Class I and one Class II study were identified.

A Class I prospective population cohort study evaluated risk of developing MS in all
Danish girls and women aged 10 years to 44 years between October 2006, and July 2013, and all
Swedish girls and women aged 10 years to 44 years between October 2006, and December 2012,
respectively, using data from the Civil Registration System in Denmark and Statistics Sweden
register. The cohort included 3,978,271 women and girls; 789,082 received HPV vaccination.
The crude incidence rate of MS was 21.54 (95% CI, 20.9 to 22.2) events per 100,000
person/years in unvaccinated women and 6.12 (95% CI, 4.86 to 7.69) in vaccinated women in
the two-year period after the last dose of HPV vaccine. The OR of developing MS after HPV
vaccination was 0.28 (95% CI, 0.12 to 0.7).

In a Class II case-control study of 92 cases and 459 controls, 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 symptom onset. The point estimate for the OR of developing MS was lower
in cases at all time points except at 3 years, but none of the results achieved statistical
significance. The ORs for developing MS was: 42 days: 3.25 (95% CI, 0.8 to 13.29); 90 days:
2.25 (95% CI, 0.76 to 6.65); 180 days: 1.44 (95% CI, 0.56 to 3.74); 1 year: 1.59 (95% CI, 0.72 to
3.49); 3 years: 1.6 (95% CI, 0.79 to 3.25) at 3 years. The overall OR for developing MS up to 3
years after HPV vaccination was 1.05 (95% CI, 0.62 to 1.78). Although the point estimate
suggests an increased risk of MS after HPV vaccination at some time points, the absolute number
of cases was small; the CI crosses unity and spans potentially clinically important effects in both
directions for each assessment.
Conclusion

It is probable that HPV vaccination is not associated with an increased risk of developing MS and is probably associated with a decreased risk of developing MS (moderate confidence in the evidence, one Class I study showing a lower risk\textsuperscript{34} and one Class II study with insufficient precision).

Influenza vaccination

Four Class II studies were identified.\textsuperscript{13,21,30,31}

In the previously described Class II case-control study,\textsuperscript{13} in a univariate logistic regression analysis, antecedent immunization with influenza vaccine was not associated with increased risk of MS (19 of 140 [13.5\%] cases and 12 of 131 [9\%] controls [OR 1.6; 95\% CI, 0.7 to 3.3, imprecise]).

In another previously described Class II study,\textsuperscript{21} logistic regression showed no significant age- and sex-adjusted difference between cases and controls for history of influenza vaccine (OR 1.02; 95\% CI, 0.96 to 1.09).

In the previously described Class II case-control study,\textsuperscript{30} 10 of 163 (6.1\%) cases and 153 of 1,604 (9.5\%) controls had received influenza vaccine (OR 0.62; 95\% CI, 0.3 to 1.2).

In another previously described Class II case-control study,\textsuperscript{31} on conditional logistic regression, the association between exposure to influenza vaccine and MS was nonsignificant (73 of 440 [16.6\%] cases and 177 of 950 [18.6\%] controls [OR 0.7; 95\% CI, 0.5 to 1.1]). When
the analyses were repeated, requiring more restrictive criteria for diagnosis, the associations remained nonsignificant (OR 0.9 [95% CI, 0.6 to 1.3] for neurologist/ophthalmologist diagnosed MS/ON; OR 1[95% CI, 0.6 to 1.4] for clinically definite MS; OR 0.9 [95% CI, 0.6 to 1.3] for MS/ON when vaccination was confirmed from records). There was no significant increase in risk of MS adjusted for timing of vaccination (symptom onset less than 1 year after vaccination, OR 0.8 [95% CI, 0.5 to 1.4]; symptom onset 1–5 years after vaccination, OR 1.1 [95% CI, 0.5 to 1.7]; and symptom onset more than 5 years after vaccination, OR 0.6 [95% CI, 0.3 to 1.1]).

Based on point estimates, two of the four studies showed a lower odds of MS in association with influenza vaccination, one showed no association, and one showed a higher odds of association. Because no study had sufficient precision to support a conclusion on its own, all four studies were combined in a random effects meta-analysis. The random effects meta-analysis found that persons with history of exposure to influenza vaccine had slightly lower odds of developing MS versus controls by point estimate (OR 0.91; 95% CI, 0.67 to 1.23; I² = 55%), but this was not significant because the CI included potentially clinically important effects in both directions.

Conclusion

There is insufficient evidence to conclude whether influenza vaccination increases the risk of developing MS (very low confidence in the evidence; 4 Class II studies with decreased confidence in the evidence because of insufficient precision and a meta-analysis with OR 0.91 [95% CI, 0.67 to 1.23; I² = 55%]).
Measles vaccination

Four Class II studies were identified.\textsuperscript{12,13,21,31}

In the previously described Class II case-control study,\textsuperscript{12} 4\% of MS patients and 9\% of controls reported measles vaccination (OR 0.42; 95\% CI, 0.13 to 1.42).

In another previously described Class II case control study,\textsuperscript{13} a univariate logistic regression analysis revealed that antecedent immunization with measles vaccine was associated with increased risk of MS (38 of 140 [27\%] cases and 1 of 131 [0.76\%] 0.7\% [OR 48.4; 95\% CI, 6.5 to 358.7]). This association remained significant after logistic regression adjusting for environmental, socioeconomic, and familial variables (OR 92.2; 95\% CI, 12.1 to 700.2).

In the previously described Class II study,\textsuperscript{21} logistic regression showed no significant age- and sex-adjusted difference between cases and controls for history of measles vaccine (OR 1.08; 95\% CI, 1 to 1.016). The OR is only marginally significant, and \textit{p} values were not significant when corrected for multiple outcomes per the authors.

In another previously described Class II retrospective case-control study,\textsuperscript{31} on conditional logistic regression, associations between exposures to measles vaccine and MS was nonsignificant (42 of 440 [9.6\%] cases and 102 of 950 [10.7\%] controls [OR 0.9; 95\% CI, 0.4–1.8]). Analyses requiring more restrictive criteria for diagnosis also did not reveal significant associations (OR 0.8 [95\% CI, 0.5 to 1.3] for neurologist/ophthalmologist diagnosed MS/ON; OR 0.9 [95\% CI, 0.5–1.7 for clinically definite MS; OR 0.9 [95\% CI, 0.5 to 1.4 for MS/ON
when vaccination was confirmed from records). There was no significant increase in risk of MS adjusted for timing of the vaccines (OR 0.9 [95% CI, 0.4 to 1.9] for symptom onset 1–5 years after vaccination and OR 0.8 [95%, CI, 0.5 to 1.3] for symptom onset more than 5 years after vaccination).

Because of inconsistency and lack of precision to support a conclusion, all four studies were combined in a random effects meta-analysis. The random effects meta-analysis found that the point estimate for the OR for developing MS was slightly higher for persons with a history of exposure to measles vaccine versus controls (OR 1.3; 95% CI, 0.5 to 3.4; I² 81%), but this was not statistically significant, and the CIs included both a higher and lower odds of developing MS after exposure to measles vaccine.

**Conclusion**

There is insufficient evidence to conclude whether measles vaccination increases the risk of developing MS (very low confidence in the evidence; 4 Class II studies with decreased confidence in the evidence because of insufficient precision and a random effects meta-analysis with OR 1.3 [95% CI, 0.5 to 3.4; I² =81%]).

**Mumps vaccination**

Four Class II studies were identified.¹²,¹³,¹⁷,²³

In the previously described Class II case-control study,¹² none of the 23 MS cases and 3 of 127 (2%) controls reported mumps vaccination (OR with Sweeting correction 0.0139; 95%...
In another previously described Class II case-control study, a univariate logistic regression analysis revealed that antecedent immunization with mumps vaccine was associated with increased risk of MS (39 of 140 [27.8%] cases and 1 of 131 [7.6%] controls [OR 51.4; 95% CI, 6.9 to 381.2]). After logistic regression adjusting for environmental, socioeconomic and familial variables, this association was no longer significant (data not provided).

In the previously described Class II study, logistic regression showed no significant age- and sex-adjusted difference between cases and controls for history of mumps vaccine (OR 1.09; 95% CI, 1.01 to 1.17). The OR was only marginally significant, and p values were not significant when corrected for multiple outcomes per the authors.

In the previously described Class II case-control study available only as abstract, risk of MS was lower with history of past vaccination against mumps (OR 0.15 [95% CI, 0.06 to 0.35], reciprocal of the data provided in the abstract, OR 6.9 [95% CI, 2.9 to 16.9]).

When considering point estimates, one study showed a reduced odds of developing MS after mumps vaccination, another suggested a lack of association or a slightly increased odds, one study showed a very high odds of developing MS after mumps vaccination, and one showed a lower odds but was imprecise. Combining these studies in a random effects meta-analysis yielded an OR of 0.91 (95% CI, 0.14 to 6.094; I² = 92%), reflecting very high heterogeneity and including ORs that suggest either an increased or decreased risk of MS after mumps vaccination.
Conclusion

There is insufficient evidence to conclude whether mumps vaccination increases the risk of developing MS (very low confidence in the evidence; 4 Class II studies with decreased confidence in the evidence because of insufficient precision and a random effects meta-analysis with OR 0.91 [95% CI, 0.14 to 6.094; I² = 92%]).

Measles-mumps-rubella vaccine

In the previously described Class II case-control study, on conditional logistic regression, associations between exposures to measles-mumps-rubella (MMR) vaccine and MS was nonsignificant (28 of 440 [6.4%] cases and 71 of 950 [7.5%] controls [OR 0.9; 95% CI, 0.4 to 1.8]). With analyses using more restrictive criteria for diagnosis, the associations remained nonsignificant (OR 0.8 [95% CI, 0.4 to 1.5] for neurologist/ophthalmologist diagnosed MS/ON; OR 0.8 [95% CI, 0.4 to 1.7] for clinically definite MS; and OR 0.8 [95% CI, 0.5 to 1.5] for MS or ON when vaccination was confirmed from records). There was no significant increase in risk of MS adjusted for timing of the vaccines (OR 0.9 [95% CI, 0.4 to 1.9] for symptom onset 1–5 years after vaccination and OR 0.8 [95% CI, 0.4 to 1.5] for symptom onset more than 5 years after vaccination. All these results were nonsignificant, with CIs crossing unity, suggesting a higher or lower frequency of MS after exposure to mumps vaccine.

Conclusion

There is insufficient evidence to conclude whether measles-mumps-rubella (MMR) vaccination
increases the risk of developing MS (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence because of insufficient precision).

Pertussis vaccine

Two Class II studies were identified.\textsuperscript{12,23}

In the previously described Class II case-control study,\textsuperscript{12} 9\% of MS patients and 19\% of controls reported pertussis vaccination (OR 0.42; 95\% CI, 0.18 to 0.98).

The previously described Class II case-control study available only as abstract,\textsuperscript{23} found a lower risk of MS with history of vaccinations against pertussis (OR 0.27 [95\% CI, 0.13 to 0.55], reciprocal of data provided in abstract, OR 3.7 [95\% CI, 1.8 to 7.7]).

To increase precision, both studies were combined in a random effects meta-analysis. The random effects meta-analysis found that persons with a history of exposure to pertussis vaccine had lower odds of developing MS versus controls (OR 0.3; 95\% CI, 0.2 to 0.56; I\(^2\) 0).

Conclusion

It is probable that pertussis vaccination is not associated with an increased risk of developing MS (moderate confidence in the evidence; 2 Class II studies and a meta-analysis with OR 0.3 [95\% CI, 0.2 to 0.56; I\(^2\) = 0\%]).
Poliomyelitis vaccine

Two Class II studies were identified.\textsuperscript{12,13}

In the previously described Class II case-control study,\textsuperscript{12} 61% of MS patients and 66% of controls reported polio vaccination (OR 0.81; 95% CI, 0.45 to 1.43).

In another previously described Class II case control study,\textsuperscript{13} a univariate logistic regression analysis found that antecedent immunization with poliomyelitis vaccine was not associated with increased risk of developing MS (118 of 140 [84\%] cases and 130 of 131 [99\%] controls [OR 0.8; 95\% CI, 0.07 to 2.8]).

Because neither study had the precision to support a conclusion on its own, they were combined in a random effects meta-analysis. The random effects meta-analysis found that persons with a history of exposure to polio vaccine had a lower odds of developing MS versus controls by point estimate, but this effect was not statistically significant (OR 0.81; 95\% CI, 0.47 to 1.4; I\textsuperscript{2} 0\%).

Conclusion

There is insufficient evidence to conclude whether polio vaccination increases the risk of developing MS (very low confidence in the evidence; 2 Class II studies with decreased confidence in the evidence because of insufficient precision and a meta-analysis with OR 0.81 [95\% CI, 0.47 to 1.41; I\textsuperscript{2} = 0\%]).
Rubella vaccination

Three Class II studies were identified.\textsuperscript{13,21,31}

In the previously described Class II case-control study,\textsuperscript{13} a univariate logistic regression analysis found that antecedent immunization with rubella vaccine was associated with increased risk of MS (31 of 140 [22\%] cases and 6 of 131 [4.5\%] controls [OR 6.2; 95\% CI, 2.3 to 15.3]). After logistic regression, adjusting for environmental, socioeconomic, and familial variables, this association was no longer significant (data not provided).

In another previously described Class II study,\textsuperscript{21} logistic regression showed no significant age- and sex-adjusted difference between cases and controls for history of rubella vaccination (OR 1.09; 95\% CI, 1 to 1.17). The OR is only marginally significant, and \( p \) values were not significant when corrected for multiple outcomes per the authors.

In the previously described Class II case-control study,\textsuperscript{31} on conditional logistic regression, association between exposures to rubella vaccine and MS was nonsignificant (45 of 440 [10.2\%] cases and 124 of 950 [13.1\%] controls [OR 0.7; 95\% CI, 0.4–1.2]). When the analyses were repeated, requiring more restrictive criteria for diagnosis, the associations remained nonsignificant (OR 0.7 [95\% CI, 0.4 to 1] for neurologist/ophthalmologist diagnosed MS/ON; OR 0.7 [95\% CI, 0.4 to 1.2] for clinically definite MS; and OR 0.7 [95\% CI, 0.4 to 1] for MS or ON when vaccination was confirmed from records). There was also no significant increase in risk of MS adjusted for timing of the vaccines (OR 0.9 [95\% CI, 0.5 to 2] for symptom onset 1–5 years after vaccination and OR 0.6 [95\% CI, 0.4 to 0.9] for symptom onset more than 5 years after vaccination).
Because of the imprecision of two studies\textsuperscript{21,31} to support a conclusion on their own and the inconsistency of results of the third study,\textsuperscript{13} all three studies were combined in a random effects meta-analysis. The random effects meta-analysis found that persons with histories of exposure to rubella vaccine had slightly higher odds of developing MS versus controls by point estimate, but this was not statistically significant (OR 1.47; 95% CI, 0.66 to 3.23; $I^2$ 87%), and the CI included both a higher and lower odds of developing MS after exposure to rubella vaccine.

Conclusion

There is insufficient evidence to conclude whether rubella vaccination increases the risk of developing MS (very low confidence in the evidence; 3 Class II studies with decreased confidence in the evidence because of insufficient precision and a meta-analysis with OR 1.47 [95% CI, 0.66 to 3.23; $I^2$=87%]).

Small pox vaccination

In the previously described Class II case-control study,\textsuperscript{12} 78% of MS patients and 94% of controls reported small pox vaccination (OR 0.23; 95% CI, 0.09 to 0.59).

Conclusion
It is possible that smallpox vaccination is not associated with an increased risk of developing MS (low confidence in the evidence; 1 Class II study).

**Tetanus toxoid**

Four Class II studies were identified.\(^{12,27,30,31}\)

In the previously described Class II case-control study,\(^{12}\) 35% of MS cases and 54% of controls reported tetanus vaccination (OR 0.46; 95% CI, 0.26 to 0.81).

In another previously described Class II study,\(^{27}\) no differences were found in mean blood serum IgG antibody levels against tetanus toxoid between MS cases and their matched controls (mean titer± SD: 3.7 ± 2.75 for cases and 4.46± 4.71 for controls [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 to 1.21).

In another previously described Class II case-control study,\(^{30}\) 19 of 163 (11.7%) cases and 279 of 1,604 (17.4%) controls had received tetanus toxoid (OR for developing MS 0.6; 95% CI, 0.4–1).

In the previously described Class II case-control study,\(^{31}\) on conditional logistic regression, there was a lower risk of association between exposure to tetanus vaccine and MS (155 of 440 [35.2%] cases and 449 of 950 [47.3%] controls [OR 0.6; 95% CI, 0.4 to 0.8]). On analyses with more restrictive criteria for diagnosis, the associations remained significant (OR 0.5 [95% CI, 0.4 to 0.7] for neurologist/ophthalmologist diagnosed MS/ON; OR 0.6 [95% CI,
0.4 to 0.8 for clinically definite MS; and OR 0.6 [95% CI, 0.4 to 0.8] for MS/ON when vaccination was confirmed from records). There was a reduced risk of MS developing more than 5 years after vaccination (<1 year post-vaccine: OR 1.2 [95% CI, 0.7 to 2]; 1–5 years: OR 0.8 [95% CI, 0.6 to 1.1]; and > 5 years: OR 0.5 [95% CI, 0.4 to 0.7]).

To increase precision, the four studies were combined in a random effects meta-analysis, yielding OR 0.61, 95% CI, 0.49 to 0.76, I²=0.

Conclusion

It is probable that vaccination with tetanus toxoid is not associated with an increased risk of developing MS (moderate confidence in the evidence, 4 Class II studies and a meta-analysis, yielding OR 0.61 [95% CI, 0.49 to 0.76; I=0²]).

Tuberculosis vaccine (BCG)

One Class I³⁵ and one Class II¹³ study were identified.

A Class I study³⁵ evaluated the effect of BCG on the progression of CIS to MS in 73 patients with CIS, 33 who received BCG and 40 who received placebo, followed for 12 months in a blinded study and then up to 60 months in an open extension. All subjects were receiving β-interferon (IFNβ)-1a. The cumulative mean number of total gadolinium (Gd)-enhancing lesions was lower in the group that received BCG vaccination (3.09 ±5.40) compared with the placebo group (6.62 ± 11.84); using a binomial regression model, the RR was 0.54 (95% CI, 0.31 to
Of the vaccinated subjects, 45.5%, compared with 75% of placebo subjects, developed 1 or more new Gd-enhancing lesions and met criteria of dissemination in time for MS (OR 0.28; 95% CI, 0.15 to 0.51). Relapse occurred in 5 of 40 (12.5%) subjects in the placebo group and 2 of 33 (6.06%) subjects who received the BCG vaccine (OR 0.45; 95% CI, 0.08 to 2.5).

In the previously described Class II case-control study, a univariate logistic regression analysis found that antecedent immunization with BCG was not associated with increased risk of MS (10 of 140 [7%] cases and 10 of 131 [7.6%] controls [OR 1; 95% CI, 0.4 to 2.6]).

Conclusions

1. It is probable that BCG is not associated with an increased risk of progression to MS in patients with CIS (moderate confidence in the evidence, 1 Class I study).

2. There is insufficient evidence to conclude whether BCG vaccination increases the risk of developing MS (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence due to lack of precision).

Typhoid vaccine

In the previously described Class II case-control study, 13% of MS patients and 18% of controls reported typhoid vaccination (OR 0.68; 95% CI, 0.31 to 1.48).
Conclusion

There is insufficient evidence to conclude whether typhoid vaccination increases the risk of developing MS (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence for lack of precision).

Yellow fever vaccine

In the previously described Class II case-control study,\textsuperscript{12} none of the 23 MS patients and 6 of the 127 (5\%) controls reported yellow fever vaccination (OR with Sweeting correction 0.07; [95\% CI, 0 to 4]).

Conclusion

There is insufficient evidence to conclude whether yellow fever vaccination increases the risk of developing MS (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence because of insufficient precision).

Varicella-zoster virus vaccination (chicken pox, herpes zoster)

Two Class II studies were identified.\textsuperscript{13,23} The vaccine type was not specified.

In the previously described Class II case-control study,\textsuperscript{13} a univariate logistic regression
analysis revealed that antecedent immunization with a VZV vaccine was associated with increased risk of MS (33 of 140 [23.5%] cases and 1 of 131 [7.6%] controls [OR 41.6; 95% CI, 5.6 to 309.6]). After logistic regression analysis adjusting for environmental, socioeconomic, and familial variables, this association was no longer significant (data not provided).

The previously described Class II case-control study available only as abstract reported a lower risk of MS with history of past vaccinations against chicken pox (OR 0.18 [95% CI, 0.08 to 0.4], reciprocal of the data provided in the abstract, OR 5.5 [95% CI, 2.5 to 12.7]).

Conclusion

There is insufficient evidence to conclude whether VZV (chicken pox) vaccination increases the risk of developing MS (very low confidence in the evidence; 2 Class II studies with decreased confidence in the evidence due to inconsistency between studies).

3B) Does vaccination increase the risk of exacerbations of MS?

BCG vaccination (tuberculosis)

A Class III crossover study evaluated the safety of BCG vaccination as an immunomodulator in MS (n=14, 10 women, definite RRMS, age range 21–40 years, [mean 30.6 years], mean disease duration 3.5 years [range 2-6 years], and EDSS mean score 1.3 [range 1–2.5]). Neurologic examination and Gd-enhanced brain MRI were performed at baseline and then at monthly intervals for a 6-month run-in period and for another 6 months after a single intracutaneous dose
of freeze-dried BCG. In the 12 analyzed subjects, there were nine clinical relapses during the run-in phase (75%) and 3 after BCG vaccination (25%) (OR 0.11; 95% CI, 0.02 to 0.70). The study was imprecise to detect a significant difference in the frequency of Gd-enhancing lesions (RMD 0.7; 95% CI, -0.69 to 2.09), the number of Gd-enhancing scans (RR 0.65; 95% CI, 0.005 to 80.22), the frequency of active lesions (RMD 1.29; 95% CI, -0.56 to 3.14), or the mean number of active scans (RR 0.58; 95% CI, 0.01 to 32.8).

Conclusion

There is insufficient evidence to support or refute whether BCG vaccination increases the risk of MS exacerbations (very low confidence in the evidence; one Class III study).

H1N1 (swine flu) vaccination

One Class I\textsuperscript{37} and one Class III\textsuperscript{38} studies were identified. A Class I double-blind RCT\textsuperscript{37} evaluated the response to a single intramuscular dose of inactivated swine influenza vaccine in MS patients older than 24 years who had not received corticosteroids or other immunomodulating drugs. Patients were classified as having clinically active disease (relapse within the previous 3 months or progressive worsening over 6 months before the study) and inactive disease, and patients in each group were randomized to vaccine or placebo. There were 3 arms: (1) 33 patients (eight with active disease) who received vaccine, (2) 33 patients (seven with active disease) who received a placebo injection, and (3) 33 patients (six with active disease) who were untreated.
Relapses were not significantly different between the three groups at 3 months (four relapses in the treatment group, with a combined 3-month annualized relapse rate of 0.5 in the vaccine group, 0.5 in placebo group, and 0.7 in the untreated group [OR 1; 95% CI, 0.23 to 4.4, imprecise]).

A class III study\textsuperscript{38} evaluated relapse rates in 30 consecutive MS patients who received influenza vaccine (3 [10%]), H1N1 vaccine (7 [23%]), both influenza and H1N1 vaccines (8 [27%]), or no vaccine (12 [40%]). Fifteen MS subjects received the H1N1 vaccine, with (n=8) or without (n=7) influenza vaccine. Relapse rates in the control group are not provided. Ten of 15 (66.6%) MS subjects who relapsed had received H1N1 vaccine in the immediate 3-week period before the relapse (reference period), whereas 5 of 15 (33.3%) had received H1N1 vaccine in three sequential 3-week periods preceding the reference period. However, 8 of these subjects had also received influenza vaccine and data are not provided separately for the H1N1 vaccine group.

From the figure provided, assuming that the remaining relapses occurred in the time frame preceding the reference period, the relapse rates after H1N1 vaccine alone were 6 of 7 (86%) in the reference period, 1 of 7 (14%) in the control period preceding vaccination (OR 36; 95% CI, 1.8 to 719).

\textbf{Conclusion}

There is insufficient evidence to support or refute whether H1N1 vaccination increases the risk of MS exacerbation (very low confidence in the evidence; 1 Class I study with markedly decreased confidence in the evidence due to precision [CIs include the possibility of either a clinically important increase in risk or a clinically important decrease in risk]).
Trivalent influenza vaccination

One Class II\textsuperscript{39} and two Class III studies\textsuperscript{38,40} were identified. A Class II (for spectrum bias) multicenter RCT\textsuperscript{39} evaluated influenza vaccination in clinically definite RRMS patients with EDSS <6.5. One hundred and four patients were randomized to receive standard influenza immunization or vaccine diluent placebo (vaccine 49, placebo 54). At 28 days after immunization, 3 of 49 (6%) vaccine-treated patients developed a relapse, compared with 2 of 54 (4%) placebo-treated patients (OR 1.7; 95% CI, 0.27 to 10.59, nonsignificant, imprecise). Over 6 months of follow-up, 11 attacks were noted in the vaccinated subjects (22%) and 6 attacks in the placebo subjects (11%) for an annual relapse rate of 0.45 and 0.22, respectively (OR for relapse rate, 2.3; 95% CI, 0.78 to 6.8 [statistically nonsignificant and imprecise, with CI including the possibility of either a clinically important increase or decrease in risk of MS exacerbations in patients vaccinated with influenza vaccine]).

In the previously described class III study,\textsuperscript{38} from the figure provided, 66.7% of relapses occurred in the reference period 3 weeks after vaccination with the influenza vaccine, with 33.3% presumably occurring outside of the reference period (OR 4; 95% CI, 0.13 to 119, nonsignificant and imprecise).

Another Class III case-control study (spectrum bias)\textsuperscript{40} evaluated trivalent influenza vaccine in 19 subjects with MS (ambulatory RRMS). The subjects had an age range of 28–60 years [mean 40.2±10.3 years], disease duration of 1–25 years [mean 6.6 ± 6.5 years], and an EDSS less than 6.5. Fourteen of the subjects were women. Eleven subjects received a single,
intramuscular dose of influenza vaccine and eight subjects received placebo. MS exacerbations (patient-reported and investigator-evaluated by EDSS changes) occurred over 6 months in 3 of 11 (27%) vaccinated subjects and in 2 of 8 (25%) MS subjects who received placebo (OR 1.12; 95% CI, 0.14 to 8.99, imprecise).

Because no study had sufficient precision to support a conclusion on its own, all three studies were combined in a random effects meta-analysis. The random effects meta-analysis found that immunization with influenza vaccine was associated with a higher OR point estimate for MS exacerbation (OR 1.64; 95% CI, 0.48 to 5.87; I² 0%), but this was not statistically significant. The CI included potentially clinically important effects in both directions, suggesting either an increased or decreased risk of MS exacerbations after trivalent influenza vaccination.

Conclusion

There is insufficient evidence to support or refute whether trivalent influenza vaccination increases the risk of MS exacerbations (very low confidence in the evidence; one Class II and 2 Class III studies with decreased confidence in the evidence due to insufficient precision and a meta-analysis with OR 1.64 (95% CI, 0.48 to 5.87; I² 0%).

Tick-borne encephalitis

A case-control study (Class III for narrow spectrum, Class IV for outcome of EDSS because of lack of stated blinding) evaluated new lesions, on brain MRI, or a clinical relapse in
15 MS patients after they received a single, intramuscular dose of tick-borne encephalitis (TBE) 
vaccine with Four men and 11 women with RRMS (Poser criteria) aged 19–60 years with EDSSs 
ranging between 1 and 3.5 were compared with matched MS controls. New Gd-enhancing 
lesions, were noted at 42±5 days compared with baseline in 2 of 15 (13%) vaccinated and 4 of 15 
(27%) control patients (OR, 0.42; 95% CI, 0.66 to 2.77, imprecise). Patient-reported clinical 
relapses were noted in 2 of 15 (13%) vaccinated subjects and 3 of 15 (20%) controls (OR 0.62; 
95% CI, 0.08 to 4.34 imprecise).

Conclusions

There is insufficient evidence to support or refute whether vaccination against tick borne 
encephalitis increases the risk of MS exacerbations (very low confidence in the evidence; one 
Class III study with decreased confidence in the evidence because of insufficient precision).

4A) Are live attenuated vaccines as effective in patients with MS as in the general population?
No studies were identified

4B) Are inactivated vaccines as effective in patients with MS as in the general population?

Trivalent influenza vaccine

Three Class III studies that evaluated trivalent influenza vaccine were identified40,42,43.
In the previously described Class III case-control study, flu-like systemic illness, presumed to be caused by influenza, occurred in 2 of 11 vaccinated MS patients and 1 of 9 age- and sex-matched normal vaccinated subjects (OR for developing flu-like illness 1.78; 95%, CI, 0.13 to 23.5; imprecise). A four-fold increase in antibody titers to the influenza AT strain was noted in the 11 vaccinated MS subjects and 9 normal subjects but not in MS subjects receiving placebo (mean difference in titers: vaccinated MS subjects, 665 [95% CI, 497 to 812]; vaccinated normal subjects, 337 [95% CI, 8 to 665]; MS subjects who received placebo, 15 [95% CI, -106 to 136]). Influenza AB strain antibody titers increased in vaccinated MS subjects and normal subjects. Influenza BP strain antibody titer responses were not significantly different but lacked statistical precision. In summary, a protective antibody response was noted in the MS subjects vaccinated against influenza that appeared to be substantially similar to normal subjects. There was no difference in the incidence of influenza in the vaccinated MS, nonvaccinated MS, or vaccinated control groups, but the wide CIs include effect sizes that include both a higher and lower antibody response in vaccinated MS patients.

In another Class III (spectrum bias) case-control study, 12 subjects with MS (7 RRMS, 5 SPMS [clinically definite according to Poser criteria], EDSS less than 7, without relapses or corticosteroids for 2 months and not receiving immunosuppressive agents at the time of vaccination) and 28 age- and sex-matched controls who received one intramuscular dose of trivalent subunit influenza vaccine during two vaccination periods (1998–1999 and 1999–2000), were followed for 4 months and 4 weeks, respectively. Six of 12 (50%) MS subjects and 4 of 28 (14%) controls had respiratory infections during the winter following the time they received vaccinations (OR for developing respiratory infection 6; 95% CI, 1.27 to 28.25). It is not
possible to be certain that the respiratory infections reported by the subjects were influenza.

In the final Class III case control study,\textsuperscript{43} 49 patients with MS and 73 HCs received trivalent seasonal influenza vaccine (Influvac or Vaxigrip). Sixty-nine percent of patients with MS who were vaccinated developed protective hemagglutination inhibition (HI) antibody titers compared with 71.2\% of controls (OR 0.9; 95\% CI, 0.5 to 1.7; imprecise). However, MS patients received different immunotherapies and the proportion of cases with protective HI titers varied by treatment. It is therefore not possible to separate the effect of MS from that of treatment in the differential effects to H1N1 vaccination.

**Conclusion**

There is insufficient evidence to conclude whether trivalent influenza vaccine is as effective in patients with MS as in the general population (very low confidence in the evidence; three Class III studies with decreased confidence in the evidence due to insufficient precision and indirectness).

**H1N1 influenza vaccine**

One Class III study (no MS spectrum provided) evaluating H1N1 vaccine was identified.\textsuperscript{43} This case-control study evaluated the immune response to H1N1 vaccine in 131 patients with MS and 216 health care workers (controls) during the 2009 pandemic. MS subjects were receiving treatment with IFN\(\beta\) (type unspecified), glatiramer acetate, natalizumab, or mitoxantrone. Only
27.4% of cases compared with 43.5% of controls had HI titer greater than 40, indicating protective effect of H1N1 vaccine (OR 0.5; 95% CI, 0.27 to 0.89). However, patients with MS had been receiving different immunotherapies, and the proportion of cases with protective HI titers varied by treatment. It is therefore not possible to separate the effect of MS from that of treatment in the differential effects to H1N1 vaccination.

Conclusion

There is insufficient evidence to conclude whether H1N1 influenza vaccine is as effective in patients with MS as in the general population (very low confidence in the evidence; one Class III study with decreased confidence in the evidence due to imprecision and indirectness).

4C) Does IMIS treatment of MS with corticosteroids, interferons, glatiramer acetate, mitoxantrone, natalizumab, alemtuzumab, fingolimod, dimethyl fumarate, daclizumab or teriflunomide reduce effectiveness of vaccinations in MS?

Influenza vaccines (Table 5)

Effect of IFN-β on response to influenza vaccines (H1N1 or trivalent influenza vaccine)

Three Class II studies and one Class III study were identified. The Class II studies evaluated IFN-β-1a and IFN-β, type unspecified. The Class III study evaluated IFN-β-1a and IFN-β-1b.
A Class II case-control study\(^4\) examined vaccination seroconversion in 113 patients with MS and 216 healthcare workers as controls after the pandemic H1N1 vaccination (2009 cohort) and 49 patients with MS and 73 healthcare workers as controls after the 2010 seasonal influenza vaccination (2010 cohort). In the 2009 cohort, 36 patients were receiving IFN-β. Forty-four percent of cases receiving IFN-β (95% CI, 29.5% to 60.4%) and 43.5% of HCs (95% CI, 37.1% to 50.2%) developed protective HI titers to H1N1 (OR 1.03; 95% CI, 0.5 to 2.1). In the 2010 cohort receiving trivalent influenza vaccine, 17 patients were receiving IFN-β. Seroprotection to H1N1 was noted in 88.2% of MS patients (95% CI, 65.6% to 96.7%) and 71.2% of normal controls (95% CI, 59.9% to 80.4%). The odds ratio for seroprotection in the patients treated with IFN-β was 3.3 (95% CI, 0.77 to 15.1). In the 2010 cohort, seroprotection to H3N2 was noted in 88.2% of patients treated with IFN-β (95% CI, 65.6% to 96.7%) and 79.5% of HCs (95% CI, 68.8% to 87.1% [OR 1.9; 95% CI, 0.45 to 8.7]) (Table 5).

A Class II prospective, nonrandomized open label study\(^4\) (n=123, RRMS, disease duration at least 1 year, EDSS 0–5.5) evaluated HI titers at day 0, 21, and 28 after influenza vaccination. Eighty-six of 163 (53%) had been taking IFN-β-1a (Rebif, Serono), 44 µg subcutaneously, three times per week for at least 6 months and continued treatment during the study. Seventy-seven (47%) were not receiving interferon treatment. Neither group had received immunosuppressive treatment or glatiramer acetate within 1 year or corticosteroids within 1 month. The primary endpoint, the proportion of participants achieving an HI titer of 40 or greater for the Panama strain 4 weeks after influenza vaccination, was no different between the two groups (93% [95% CI, 85.4% to 97.4%] for those treated with interferons and 90.9%, [95% CI, 82.2% to 96.3%] for those not treated with interferons [OR 1.3; 95% CI, 0.4 to 4.1; imprecise).
Similar findings were identified for the New Caledonia and Hong Kong strains (Table 5).

One hundred and forty-five adverse events were reported by 75 of 163 (46.0%) participants. The proportion of participants experiencing an adverse event was similar between the group that received IFNβ-1a (45.3%) and the group that did not receive interferons (46.8%) OR 0.9 (95% CI, 0.5 to 1.6). The most frequent adverse event was injection site pain (IFN β-1a, 12.8%; no interferon, 13.0%). Most adverse events were mild or moderate in severity (82 of 84 [98%] in the group receiving IFN-β-1a and 60 of 61 [98%] of the group not receiving interferons). Adverse events classified as very severe were not reported in either group. There were no relapses or clinically significant changes in vital signs, hematology, or chemistry.

A Class II case-control study evaluated the response to seasonal influenza vaccination with MutagripH. Twenty-six patients with definite RRMS who were receiving beta interferons and 33 HCs were evaluated. Blood was obtained from both groups 7, 14, and 28 days after vaccination, and antibody response was measured by ELISA and Enzyme-linked immuno-spot (ELISpot) assays. Following vaccination, concentrations of influenza type A- and influenza type B-specific IgM increased significantly and comparably in both groups by day 7 and remained increased on day 28 after vaccination. Before vaccination, 54% of patients treated with IFN-β and 64% of HCs fulfilled predefined seroprotection criteria (IgG ≥10 VE/mL). After vaccination, the proportion of individuals fulfilling seroprotection criteria at 28 days was higher in patients with MS who received IFN-β treatment compared with HCs for both influenza type A and influenza type B vaccination (Table 5). OR estimated after converting percentages provided in the figures of the paper to numbers is listed as follows:
Influenza type A—OR with Sweeting correction 86.89 (95% CI, 0.66 to 152)
Influenza type B—OR with Sweeting correction 191.84 (95% CI, 1.48 to 30281.68)

In a Class III cohort study, the multinational TERIVA study (no comparator group without immunomodulator, evaluates seroconversion from baseline after vaccine), 47 90 patients with RRMS who received either 7 mg or 14 mg per day of teriflunomide (n=82) or received IFN-β (n=46) for at least 6 months were screened for a 21-day period and then given a single dose (intramuscularly or intradermally) of the 2011/2012 inactivated trivalent seasonal influenza vaccines, either Vaxigrip or Mutagrip, and assessed for antibody status at 28±2 days after immunization. Of the IFN-β group, 34.8% received Avonex (IFN-β-1a), 28.3% received Rebif (IFN-β-1a), and 21.7% received Betaseron (IFN-β-1b). Of the remaining patients, 8.7% received Genfaxone (IFN-β-1a [Russia only]) and 6.5% received Rebif (IFN-β-1a ). The primary efficacy endpoint was the proportion of patients who achieved seroprotection. Between 44% and 70% of the study population had received influenza vaccination previously. The influenza vaccines used in this study included the same strains as those in the 2010/2011 vaccine. Hence, a high proportion of patients had baseline HI titers of 40 or greater. Seroprotection for each of the influenza strains was achieved in more than 90% of recipients (Table 5). The proportions of subjects with baseline titers less than 10 who achieved seroprotection at day 28 was 100%, 57%, and 100 % for H1N1, H3N2, and influenza B, respectively.

Although only one identified study 45 directly addressed the prespecified PICO (patient, intervention, comparator, outcome) question comparing the results of immunization in patients with MS who were and were not receiving interferon therapy, three studies report cohorts with seroconversion rates with influenza vaccines either compared with normal controls 43, 46 or as the
reference standard for other MS treatments. Given the imprecision for some of the comparisons (Table 5), a meta-analysis was performed combining influenza strains for a global estimate of effect. The underlying assumptions were that all types of interferon would have the same effect on the immune response and all influenza vaccines are largely similar. For the three studies with comparison groups (either normal controls or patients with MS not receiving IFN-β therapy), fixed effects meta-analyses were performed to combine the OR for response to each vaccine strain for each separate cohort, resulting in one combined measure for the cohort(s) in each study. The 2009 and 2010 cohorts of the fourth study were not combined in a meta-analysis because the cohorts and vaccines were different. However, the data for H1N1 and H3N2 in the 2010 cohorts were combined in a fixed-effects meta-analysis resulting in one combined measure for the 2010 cohort. All the combined measures and the results for the 2009 cohort were combined in a random effects meta-analysis resulting in an OR of 1.001 (95% CI, 0.97 to 1.03; I²=0%). This suggests that patients with MS receiving IFN-β therapy have the same odds of influenza seroprotection compared with varied controls.

Conclusion

The use of IFN-β probably does not meaningfully reduce the frequency of seroprotection in response to influenza vaccines with various strains (moderate confidence in the evidence; three Class II and 1 Class III studies and a meta-analysis without decreased odds of seroconversion; OR for seroconversion in patients with MS receiving IFN-β therapy compared with either normal controls or patients with MS not receiving therapy 1.001 (95% CI, 0.97 to 1.03; I²=0%).
Effect of fingolimod on response to trivalent influenza vaccine

One Class I and two Class III studies were identified.

In a Class I multicenter RCT, 136 patients with MS (RRMS, aged 18–55 years) were randomized in a 2:1 ratio to 0.5 mg of fingolimod (n=93) or placebo (n=43) for 12 weeks. At week 6, patients received trivalent influenza vaccine. Antibody titers were measured by HI at baseline and at 3 and 6 weeks after vaccination. Responder rate was defined as the proportion of patients showing seroconversion or a significant increase (4 fold or greater) in antibody titer from prevaccination to postvaccination periods for at least one of the three strains contained in the seasonal influenza vaccine. The primary efficacy variable was responder rate of 3 weeks postvaccination. The responder rates for influenza vaccine in the fingolimod and placebo groups were 54% and 85%, respectively, at 3 weeks (OR, 0.21; 95% CI, 0.08 to 0.54) and 43% and 75%, respectively, at 6 weeks (OR, 0.25; 95% CI, 0.11 to 0.57). A lower proportion of patients who received fingolimod attained seroprotection (postvaccination HI titer of 1:40 or greater) to two of the three strains of influenza virus at 3 weeks and 6 weeks after vaccination (48.4% of patients who received fingolimod compared with 72.1% who received placebo attained seroprotection to the California strain 3 weeks after vaccination [OR 0.33; 95% CI, 0.12 to 0.49]; 41.6% of patients who received fingolimod compared with 60.5% who received placebo attained seroprotection to the California strain 6 weeks after vaccination [OR 0.47; 95% CI, 0.26 to 0.82]; 76.9% of patients who received fingolimod compared with 95.3% who received placebo attained seroprotection to the Brisbane strain 3 weeks after vaccination [OR 0.16; 95% CI, 0.06 to 0.46]; and 67.4% of patients who received fingolimod compared with 90.7% who received placebo attained seroprotection to the Brisbane strain 6 weeks after vaccination [OR, 0.2; 95% CI, 0.1 to
A lower proportion of patients who received fingolimod developed a 4-fold or greater increase in antibody titers to the California and Brisbane strains at 3 weeks and 6 weeks.

**Conclusion**

For patients with RRMS, it is probable that treatment with fingolimod decreases the immune response to trivalent influenza vaccine as compared to patients with MS not on fingolimod.

(Moderate confidence in evidence, 1 Class 1 study)

*Effect of natalizumab on response to trivalent influenza vaccine:*

Two Class II studies were identified

In the previously described Class II case-control study, eight patients were receiving natalizumab in the 2010 cohort. Of these eight patients, 50% developed protective HI titers to H3N2 compared with 79.5% of HCs (OR, 0.09; 95% CI, 0.008 to 0.89). In the same study, in the 2009 cohort, 4 of 17 (23.5%) patients who were receiving natalizumab and 94 of 216 (43.5%) of HCs developed protective H1N1 antibodies (OR, 0.4; 95% CI, 0.13 to 1.26, imprecise). In the 2010 cohort, 6 of 8 (75%) patients who were receiving natalizumab developed protective antibodies to H1N1 compared with 52 of 73 (71%) HCs (OR, 1.22; 95% CI, 0.23 to 6.49; imprecise).

In a Class II nonrandomized study, 17 RRMS patients and 10 HCs received trivalent influenza vaccine. Patients with MS and HCs had similar increases in mean antibody levels at 4
weeks compared with baseline (49.5% increase for patients who were receiving natalizumab and 56.4% increase for HCs [OR, 0.76; 95% CI, 0.43 to 1.3). There was also no difference at 8 or 12 weeks. At 4 weeks, 56.3% of patients who were receiving natalizumab and 50% of HCs developed an increase in antibody titers to influenza B of more than 50% (OR, 1.28; 95% CI, 0.0738 to 2.2478; imprecise). At 4 weeks, 6.3% of patients who were receiving natalizumab and none of the HCs developed an increase in antibody titers to influenza A of more than 50% [OR with Sweeting correction, 12.49; 95% CI, 0.107 to 951.12; imprecise).

In both studies, the antibody response was compared with HCs and not with an MS control group (i.e., subjects with MS who were not receiving immunomodulatory treatments). Because of the imprecision of both studies, fixed effects meta-analysis was first performed for Influenza type A and influenza type B in the study by Vagberg and colleagues, yielding an OR of 1.33 (95% CI, 0.767 to 2.316; I² 0%). The result of the fixed effects meta-analysis was then combined with the results of the two cohorts of the study by Olberg and colleagues, and a random effects meta-analysis was performed, yielding an OR of 0.66 (95% CI, 0.25 to 1.786; I² 60%).

Conclusion

There is insufficient evidence to support or refute whether the use of natalizumab reduces the effectiveness of trivalent influenza vaccine compared with healthy controls (very low confidence in the evidence; two Class II studies, one with two cohorts with decreased confidence because of imprecision, and a meta-analysis with OR 0.66 [95% CI, 0.25 to 1.786; I² 60%].
Effect of glatiramer acetate on response to trivalent and H1N1 influenza vaccine:

In a previously described Class II study, in the 2010 cohort, twelve patients were receiving glatiramer acetate received trivalent influenza vaccine. Five of these twelve patients (41.7%) as well as 58 of the 73 (79.5%) HCs developed protective antibodies to H3N2 (OR, 0.19; 95% CI, 0.05 to 0.66). In the same study, in the 2009 cohort, 8 of 37 (21.6%) of patients who were receiving glatiramer acetate and received the H1N1 vaccine developed protective antibodies compared with 94 of 216 (43.5%) of HCs who received the H1N1 vaccine (OR, 0.36; 95% CI, 0.17 to 0.82). In the 2010 cohort, seven of 12 patients (58.3%) who were receiving glatiramer acetate developed protective antibodies to H1N1 compared with 52 of 73 (71.2%) HCs (OR, 0.57; 95% CI, 0.16 to 1.98, imprecise).

With the assumption that the response to all types of influenza vaccine is likely to be similar, a random effects meta-analysis was performed to increase precision, yielding an OR of 0.35 (95% CI, 0.19 to 0.63; I² 0%).

Conclusion

It is probable that the use of glatiramer acetate reduces the effectiveness of influenza vaccine compared with healthy controls (moderate confidence in the evidence; one Class II study with two separate cohorts and a random effects meta-analysis with OR 0.35 [95% CI, 0.19 to 0.63; I² =0%]).
Effect of mitoxantrone on response to trivalent and H1N1 influenza vaccine

In the previously described Class II study,\textsuperscript{43} in the 2010 cohort of 4 patients who were receiving mitoxantrone, only 1 (25%) developed protective antibodies to H3N2 compared with 58 of 73 (79.5%) HCs (OR, 0.09; 95% CI, 0.008 to 0.89). In the same study,\textsuperscript{43} in the 2009 cohort, none of the 11 patients who were receiving mitoxantrone developed H1N1 antibodies compared with 43.5% of HCs (OR with Sweeting correction, 0.0016; 95% CI, 0.000 to 0.4843). In the 2010 cohort, 1 of 4 (25%) patients who were receiving mitoxantrone developed protective antibodies to H1N1 compared with 52 of 73 (71.2%) HCs (OR, 0.13; 95% CI, 0.013 to 1.37; imprecise).

With the assumption that the response to all types of influenza vaccine is likely to be similar, a random effects meta-analysis was performed to increase precision, yielding an OR of 0.025 (95% CI, 0.001 to 0.46; $I^2=81\%$).

Conclusion

It is probable that the use of mitoxantrone reduces the effectiveness of influenza vaccine compared with healthy controls (moderate confidence in the evidence; one Class II study with two separate cohorts, and a random effects meta-analysis with OR 0.025 [95% CI, 0.001 to 0.46, $I^2=81\%$]).

Effect of teriflunomide on response to influenza vaccine:

In the previously described Class III TERIVA cohort study,\textsuperscript{47} patients receiving 7 mg of teriflunomide (group 1) and 14 mg of teriflunomide 14 mg (group 2) were compared with
patients who were receiving IFN-β, as a reference standard. For the primary outcome of seroprotection from H1N1, H3N2, and influenza type B at 28 days, the data are listed as follows:

- 42 of 43 (97.7%) patients who were receiving IFN-β achieved seroprotection from H1N1 compared with 39 of 40 (97.5%) patients who were receiving 7 mg of teriflunomide (OR, 1.07; 95% CI, 0.065 to 17.8; imprecise) and 38 of 39 (97.4%) patients who were receiving 14 mg of teriflunomide (OR, 1.1; CI, 0.067 to 18.3; imprecise).

- 39 of 43 (90.7%) patients who were receiving IFN-β achieved seroprotection from H3N2 compared with 36 of 40 (90%) patients who were receiving 7 mg of teriflunomide (OR, 0.92; 95% CI, 0.21 to 3.96; imprecise) and 30 of 39 (76.9%) patients who were receiving 14 mg of teriflunomide (OR, 0.3419; 95% CI, 0.096 to 1.22; imprecise).

- 40 of 43 (93%) patients who were receiving IFN-β achieved seroprotection from influenza type B compared with 39 of 40 (97.5%) patients who were receiving 7 mg of teriflunomide (OR, 2.93; 95% CI, 0.29 to 29.3; imprecise) and 38 of 39 (97.4%) of patients who were taking 14 mg of teriflunomide (OR, 2.85; 95% CI, 0.28 to 28.61; imprecise).

**Conclusion**

There is insufficient evidence to support or refute whether the use of teriflunomide reduces the effectiveness of trivalent influenza vaccine (very low confidence in the evidence; one Class III study with decreased confidence for imprecision). However, the high proportions of patients in the teriflunomide group who achieved seroprotection make an adequate response to vaccination in the context of teriflunomide plausible.
**Effect of daclizumab on response to trivalent influenza vaccine:**

One Class II\textsuperscript{51} and 1 Class III\textsuperscript{52} study were retrieved.

In a Class II study\textsuperscript{51} 23 patients with RRMS who were treated with daclizumab for a minimum of 36 months, 10 untreated patients with MS (EDSS 0-3), and four HCs received Afluria, a trivalent influenza vaccine. Fourteen of the 23 patients (60.9\%) had been treated previously with another formulation of daclizumab for up to 6 years. Neutralizing antibody titers and CD4\textsuperscript{1} cell, CD8\textsuperscript{1} cell, T cell, B cell, and natural killer cell proliferation to three strains of virus contained in the Afluria vaccine were assessed at 0 days, 1 day, and 180 days after vaccination, with an additional sample collected at day 7 in 17 patients and 14 controls. Data for Patients with untreated MS and HCs were not presented separately. Seroconversion rate was 43 of 51 (84.3\%) in the group treated with daclizumab and 33 of 42 (78.6\%) in controls (denominators represent the combination of all antibodies tested in the group) (OR, 1.47; CI, 0.51 to 4.2, imprecise). Seven out of 8 (87.5\%) patient/viral strain pairs without pre-existing immunity seroconverted compared with all 9 controls (100\%) (OR with Sweeting correction, 0.087; CI, 0.0014 to 3.73; imprecise).

In the Class III study\textsuperscript{52} (published historical normal control group), 90 patients with RRMS who had received daclizumab for 1–2 years were given the seasonal vaccine (Influvac\textsuperscript{®}/Imuvac\textsuperscript{®}) in a single intramuscular dose containing three inactivated influenza virus strains: (1) A/H1N1, (2) A/H3N2, and (3) influenza type B. At 28 days after vaccination, seroprotection from A/H1N1 was noted in 92\% of patients (95\% CI, 85\% to 97\%); seroprotection from A/H3N2 was noted in 91\% of patients (95\% CI, 83 to 96\%); and seroprotection from influenza
type B was noted in 67% of patients (95% CI, 56 to 76%). This was comparable with published rates of seroprotection in normal controls: seroprotection from A/H1N1 in 78% of normal controls, seroprotection from A/H3N2 in 81% of normal controls, and seroprotection from influenza type B in 75% of normal controls. The proportion of patients who seroconverted (a change from baseline titer of 10 or less to seroprotected or a four-fold increase in antibodies if baseline was 10 or greater) was 69% for A/H1N1 (95% CI, 58 to 78%); 69% for A/H3N2 (95% CI, 58 to 78%); and 44% for influenza (95% CI, 34 to 55%) for B, compared with 58%, 61%, and 51%, respectively, in historical controls.

Conclusion

There is insufficient evidence to support or refute whether the use of daclizumab reduces the effectiveness of trivalent influenza vaccine (very low confidence in the evidence; one Class II study with decreased confidence for imprecision and 1 Class III study). However, the high proportions of patients achieving seroconversion while treated with daclizumab make an adequate response plausible.

Effect of methotrexate and 6-mercaptopurine on response to influenza vaccine:

A Class II study compared the immune responses in subjects with MS who were receiving methotrexate and 6-mercaptopurine or placebo as part of a clinical trial, and 2 other control groups: 11 normal controls from Kansas City and 14 from Houston. Twenty-three patients received two subcutaneous injections of bivalent influenza vaccine, one month apart. Mean
postvaccination IgG levels were 1,463 mg/dL for controls and 1,208 mg/dL for patients with MS. Mean IgA levels were 275 mg/dL for controls and 173 mg/dL for patients with MS. Mean IgM levels were 206 mg/dL for controls and 192 mg/dL for patients with MS. Further data were not provided. Mean increase in HI titers for Hong Kong influenza was 2.8 for patients with MS and 1.6 for controls. Mean increase in HI titers for influenza type B was 1.2 for patients with MS and 2.0 for controls. Range and SD are not provided; hence, CI cannot be calculated to estimate the precision of these results.

Conclusion

There is insufficient evidence to support or refute whether the use of methotrexate and 6-mercaptopurine reduces the effectiveness of influenza vaccine (very low confidence in the evidence; one Class II study with insufficient statistical information to evaluate precision). The clinical relevance of this study to current MS management is uncertain because methotrexate and 6-mercaptopurine are not usually used to treat MS presently.

Tetanus toxoid

*Effect of fingolimod on response to tetanus toxoid*

In the previously described Class I multicenter RCT,48 patients received a tetanus toxoid (TT) booster dose at week 6. Antibody titers were measured by ELISA at baseline and at 3 weeks and 6 weeks after vaccination. The responder rates for TT at 3 weeks in the fingolimod group were 40% compared with the placebo response of 61% (OR, 0.43; 95% CI, 0.20 to 0.92) and 38%
compared with placebo response of 49% at 6 weeks (OR, 0.62; 95% CI, 0.29 to 1.33).

Sero protection rates were high for both groups at 3 weeks (fingolimod 92%, placebo 91% [OR, 1.14; CI, 0.42 to 3.1] and 6 weeks (fingolimod 92%, placebo 84% [OR, 2.2; CI, 0.9 to 5.3]).

Seroconversion at 3 weeks was higher in patients receiving fingolimod than in the placebo group (fingolimod group 66.7%, placebo group 60% [OR, 1.34; 95% CI, 0.75 to 2.38]). Seroconversion at 6 weeks was also higher in patients receiving fingolimod than in the placebo group (fingolimod group 72.2%, placebo group 50% [OR, 2.6; 95% CI, 1.4 to 4.7]). In contrast, a significant increase in TT antibody titer (a 4-fold or greater increase in titers from baseline) was seen in a lower proportion of fingolimod-treated patients treated at 3 weeks (fingolimod group 33.3%, placebo 60.6% [OR, 0.22; CI, 0.18 to 0.58) and 6 weeks (fingolimod group 28.6%, placebo group 48.5% [OR, 0.43; CI, 0.24 to 0.76).

**Conclusion**

There is insufficient evidence to support or refute whether the use of fingolimod reduces the effectiveness of tetanus toxoid (very low confidence in evidence, 1 Class I study, with decreased confidence in the evidence for imprecision and inconsistency between outcomes).

**Effect of natalizumab on response to tetanus toxoid:**

One Class II study was identified. This was a multicenter randomized study, in which patients aged 18–60 years with RRMS were randomized to a control group (n=30, delayed natalizumab for 2 months and received TT) and treatment group (n=30, natalizumab for 6 months, received
TT at the 7th month). Per-protocol analysis revealed that 24 of 24 controls (100%) and 15 of 16 natalizumab group (94%) were responders (two-fold or greater increase in anti-TT titers) at day 28 (OR with Sweeting correction, 0.0375; 95% CI, 0.0003 to 2.7601; imprecise). At day 56, 21 of 22 controls and 14 of 15 natalizumab subjects were responders (OR, 0.67; 95% CI, 0.04 to 11.6; imprecise).

Conclusions

There is insufficient evidence to support or refute whether the use of natalizumab reduces the effectiveness of tetanus toxoid (very low confidence in evidence, 1 Class I study, with decreased confidence in the evidence for imprecision).

Effect of dimethyl fumarate on response to tetanus-diphtheria vaccine and, pneumococcal and meningococcal vaccines

Only one Class IV study was available as a conference abstract, without results (ECTRIMS 2016).55

Effect of alemtuzumab on response to various vaccines

One Class III cohort study using historical controls56 evaluated the effect of alemtuzumab on response to various vaccines. Twenty-four patients with RRMS were given pneumococcal polysaccharide vaccine; diphtheria, tetanus, and poliomyelitis vaccine with polio types 1–3; Haemophilus influenzae type B (Hib) vaccine; and meningococcal group C vaccine. Control data
from the literature were used. Of 23 patients receiving meningococcal vaccine, 19 (83%) seroconverted at 4 weeks compared with 97.6 (100%) of historical controls (OR using historical control of 98%, 0.096; 95% CI, 0.012 to 0.57). Of the 19 patients in whom Hib vaccine seroconversion could be measured, 18 (95%) seroconverted compared with 82–90% of historical controls (OR using historical control of 86%, 3.1; 95% CI, 1.1 to 9). Of 15 patients in whom seroconversion to pneumococcal polysaccharide serotype A could be measured, 11 (73%) seroconverted compared with 35–47% of historical controls (OR using historical control of 41%, 4.3; 95% CI, 2.36 to 7.9). Of 20 patients in whom seroconversion to pneumococcal polysaccharide serotype B could be measured, 19 (95%) seroconverted compared with 81–85% of historical controls (OR using historical control of 83%, 3.9; 95% CI, 1.4 to 11). Eighteen of 21 (88%) mounted an adequate immune response by expert consensus definition.

Conclusion
There is insufficient evidence to support or refute whether the use of alemtuzumab has an impact on seroconversion after meningococcal, Hib, and pneumococcal vaccines (very low confidence in the evidence; one Class III study).

PUTTING THE EVIDENCE INTO CLINICAL CONTEXT
The results of this SR highlight important gaps in knowledge related to our clinical questions:

1. Is the development of MS associated with vaccine preventable infections or vaccines?
2. Are MS exacerbations associated with vaccine preventable infections or vaccines?
3. How effective are vaccines in patients with MS compared to the general population?
4. Do ISIM treatments of MS affect the immune response to vaccines?

Some consistent weaknesses in study methodology were observed across studies, constraining the strength of the evidence. Most of the association studies (questions 1 and 2) were case-control studies; very few prospective cohort studies were found. The methods of confirmation of infection or immunization varied across studies from surveys to registry data to direct testing of antibody responses to immunization. These varied ascertainment methods may have had an impact on the results. For studies evaluating the effectiveness of vaccines, only a few RCTs were found; most were cohort studies. For the questions regarding exacerbation of MS by infections or vaccines (questions 3a and 3b), several studies evaluated only ambulant or moderately affected patients, resulting in spectrum bias. This is understandable from a study design perspective and the difficulty of recruiting severely disabled patients, but reduces the generalizability and directness of the results, which cannot be extrapolated with confidence to more severely affected patients, who may have a different response to infections or vaccines.

The common live attenuated vaccines are BCG, oral polio, measles, mumps, rubella, small-pox, chicken-pox, rotavirus, yellow fever, influenza nasal spray, oral typhoid, and herpes zoster vaccines. We found no studies to evaluate the effectiveness of these vaccines in patients with MS (question 4a). Among the other weaknesses identified, statistical imprecision, likely cause by small sample sizes was an important factor limiting conclusions.

New IMIS treatments for MS are rapidly being developed. Some of these treatments have not been reviewed here. However, given similar mechanisms of action of some of these agents, we believe that the recommendations of this guideline are sufficiently broad. The product information of these agents should be reviewed before their use for specific immunization-
related recommendations from the manufacturer.

Below we summarize the conclusions for each question.

1. **Is a history of vaccine preventable infections more frequent in patients with MS than in the general population?**

The SR found that it is likely that a history of hepatitis B and measles is possibly not more frequent in patients with MS. The evidence available in our SR did not support either increased or decreased frequency of the following infections in patients with MS: diphtheria, meningitis (type unspecified), mumps, rubella, pertussis, polio, small-pox, tuberculosis, typhoid, and varicella.

2. **Do vaccine-preventable infectious diseases increase the risk of MS exacerbations?**

Evidence to inform this question was sparse. The evidence available did not support or refute an association between influenza increase in MS exacerbations. The evidence for VZV was indirect and related to the presence of VZV DNA in PBMCs during relapses and, hence, cannot be generalized to VZV infections. No evidence was available for other vaccine-preventable infections.

3A. **Does vaccination increase the risk of developing MS?**

3B. **Does vaccination increase the risk of exacerbations of MS?**

In addition to the previously mentioned limitations, evidence for these questions was limited by inconsistency between studies when multiple studies were available (diphtheria, influenza, measles, mumps, rubella, and VZV), and may be related to different methods of ascertaining exposure to vaccines (antibody titers, history obtained by medical record review or questionnaire surveys, etc). Our SR found that HPV vaccine, hepatitis B vaccine, pertussis vaccine, and tetanus
toxoid probably do not increase the risk of developing MS. Small pox vaccine possibly does not increase the risk of developing MS. BCG vaccination probably does not increase the risk of progression to MS in patients with CIS. There was no data for the association of the following vaccines and a risk of developing MS: diphtheria, influenza, measles, mumps, MMR, polio, rubella, BCG (for risk of developing MS de novo, without mention of prior CIS), typhoid, yellow fever, and VZV. The evidence for BCG, H1N1, trivalent influenza and TBE vaccinations was insufficient to inform question 3b regarding an effect on MS exacerbations. Studies evaluating other vaccines were not available for this question.

Two studies of BCG vaccination were identified. Both of these studies evaluated the effect of BCG vaccination as an immunomodulatory agent, not as an immunization, and conclusions regarding our questions were therefore indirectly inferred. The use of BCG vaccination in routine immunization schedules is limited and is not common in adults. BCG vaccination is recommended in the World Health Organization (WHO) immunization schedule in children as soon as possible after birth. In countries with a low burden of tuberculosis, BCG vaccination is limited to children and adults in specific situations. A position paper by the WHO does not recommend BCG vaccination of adults but states that it may be considered for tuberculin-negative persons in unavoidable and close contact with cases of multidrug-resistant tuberculosis. Intravesical BCG vaccination is also used in some protocols for immunotherapy of non–muscle-invasive bladder cancer.

For evidence regarding influenza vaccine, because the strains of influenza vaccine differ from year to year, the directness (generalizability) of the evidence regarding influenza vaccine may be slightly limited.
4B. Are inactivated vaccines as effective in patients with MS as in the general population?

The evidence for trivalent influenza vaccine and H1N1 vaccine was insufficient to inform this question. Studies of other inactivated vaccines were not available.

4c. Does immunomodulating treatment of MS with corticosteroids, interferons, glatiramer acetate, mitoxantrone, natalizumab, alemtuzumab or fingolimod reduce effectiveness of vaccines in MS?

Our SR found that beta interferons likely do not affect immune response to vaccinations. Fingolimod, glatiramer acetate and mitoxantrone probably reduce effectiveness of influenza vaccines. Although direct evidence was not available for teriflunomide and daclizumab, a large proportion of patients with MS who were receiving these treatments developed protective antibodies. No evidence was available for other agents or vaccines. In evaluating this evidence, we decided a priori to use direct comparisons of MS patients who were receiving and not receiving ISIM agents to evaluate whether these agents affected immune responses to vaccines. However, most studies used HCs instead of untreated MS controls, which is not surprising because it may not be ethical to not treat MS patients. Because of the importance of this information to the treating clinician and to patients, we evaluated all the available studies and clarified the comparator used in the conclusions.

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 evidence. Human papillomavirus vaccine, tetanus toxoid, hepatitis B, pertussis, and small pox vaccines had evidence for not
increasing the risk of developing MS (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, side effects, and coverage by insurance (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 the evidence regarding immunization in MS with their patients (Level
B).

Statement 1b
Clinicians should explore patient’s opinions, preferences, and questions regarding immunizations
at the clinical visit to be able to effectively address the optimal immunization strategy for each
patient, in keeping with their MS status, values, and preferences (Level B).

Recommendation 2
Rationale
All unvaccinated individuals are at a higher risk of acquiring vaccine-preventable infections
(PRIN). While there is no evidence that MS alone increases the risk of acquiring vaccine-
preventable infection (EVID), patients with MS have at least the same risk as unvaccinated
individuals without MS (PRIN). Patients receiving immunosuppressive therapy as part of the MS
treatment may be at an 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 personal benefits of vaccination, vaccination of the MS patient population contributes to the well-established phenomenon of “herd immunity” for the communities in which they live (RELA). 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 (i.e., from the Centers for Disease Control and Prevention, the WHO, and local regulatory bodies) unless there is a specific contraindication (eg, active treatment with immunomodulatory medication) (Level B based on importance of outcomes, variability in patient preferences, and cost relative to net benefit).

**Recommendation 3**

**Rationale**

Prevalence of vaccine-preventable diseases and seropositivity for vaccine-preventable diseases varies by country and region (PRIN). For example, BCG vaccination is recommended by the WHO but not by the CDC, except in special cases. This region-specific disease epidemiology informs the risk–benefit discussion of vaccination in MS (INFER, PRIN). In cases in which local risks of infection are particularly high, the benefits of vaccination in people with MS—even with live vaccines and immunomodulatory therapy—may outweigh the risks (INFER).

**Statement 3**
Clinicians should weigh local risks of vaccine-preventable diseases when counseling people with MS regarding vaccination (Level B).

Recommendation 4

Rationale

MS exacerbations are associated with increased short- and long-term disability (RELA). 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 our SR found that influenza infections increase exacerbation risk compared with vaccination (RELA). Influenza infections may also cause increased morbidity and mortality in 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 known risks of exacerbation and other morbidity with influenza infection and no identified risks of exacerbation with influenza vaccines, benefits of influenza vaccination outweigh the risks in most scenarios (INFER).

Statement 4

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

Recommendation 5

Rationale 5a–5b
Immunosuppressive or immunomodulatory medications now used to treat MS include fingolimod, natalizumab, mitoxantrone, alemtuzumab, daclizumab, rituximab, dimethyl fumarate and teriflunomide (PRIN). These treatments have been associated with severe occurrences or recurrences or both of vaccine-preventable infections, including varicella zoster and hepatitis B (RELA).  

While we identified no studies showing an increased risk associated with immunization with live vaccines in patients receiving ISIM medications (EVID), studies regarding the safety of live vaccines during treatment with ISIM medications are scarce (EVID). Many package inserts approved by the Food and Drug Administration provide specific guidance regarding immunization with live vaccines and treatment with these pharmacologic therapies. Prescribing information for fingolimod recommends VZV vaccination of antibody-negative patients with MS at least 1 month before treatment to allow for the immune response to develop (RELA). Fingolimod prescribing information also recommends avoiding live vaccines during treatment and for 2 months after discontinuation (RELA). Prescribing information for teriflunomide recommends against using live vaccines during treatment and for 6 months after discontinuation (RELA). The prescribing information for daclizumab recommends immunization before treatment and recommends avoiding live vaccines during treatment and up to 4 months after discontinuation of treatment (RELA). Prescribing information for alemtuzumab recommends against the use of live vaccines for 6 weeks before initiation of treatment, during treatment, and after “recent” treatment (RELA).

**Rationale 5c**
As we previously noted, ISIM medications now used to treat MS are associated with severe occurrences, severe recurrences, or both of vaccine-preventable infections, including varicella zoster and hepatitis B (RELA).\textsuperscript{58-63} and have treatment-specific guidance for immunization with live vaccines in their package inserts (RELA).\textsuperscript{64-67} 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 4–6-week delays between immunization with live vaccines and initiation of treatment with these medications [INFER].

\textbf{Statement 5a}

Clinicians should counsel patients with MS about infection risks associated with specific ISIM medications and treatment-specific vaccination guidance as per the prescribing instructions for ISIM medications when one of these treatments is being considered for use (Level B based on importance of outcomes and variation in patient preferences).

\textbf{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 prescribing information (Level B, based on importance of outcomes and variation in patient preferences).
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).

Recommendation 6

Rationale
Approach to vaccination against tuberculosis varies by country (PRIN). Because of occurrence of tuberculosis infections in studies of teriflunomide, the teriflunomide prescribing information advises clinicians to screen patients for latent tuberculosis before initiating treatment with teriflunomide (RELA). Prescribing information also recommends treatment for tuberculosis in patients who test positive for tuberculosis before initiating teriflunomide treatment (RELA). While prescribing information for other ISIM medications does not provide tuberculosis-specific guidance, given 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). 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 infrequent (eg, in North America and Europe) (PRIN), potentially resulting in an underestimate of the risk of activation of latent tuberculosis from the use of ISIM medications other than teriflunomide (INFER).

Statement 6a
Clinicians must screen for latent tuberculosis as per the prescribing information before initiating treatment with teriflunomide (Level A) and should treat patients testing positive for tuberculosis prior to teriflunomide treatment (Level B based on feasibility, patient preferences and costs).

**Statement 6b**

Clinicians must also screen for latent tuberculosis before starting MS treatment with ISIM medications other than teriflunomide, particularly in high risk populations or in countries with high tuberculosis burdens (Level A) and should treat patients who test positive for tuberculosis before treating them with ISIM medications other than teriflunomide (Level B).

**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), given biologically plausible risks of live vaccines in immunosuppressed patients, it is generally advised that patients who are receiving ISIM therapy avoid immunization with live vaccines (PRIN). Prescribing information in package inserts for fingolimod, daclizumab, alemtuzumab, and teriflunomide recommend against the use of live vaccines during treatment and immediately preceding treatment (RELA). Additionally, because the immunosuppressive effects of these medications may last for months after discontinuation of medication, prescribing information 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).
Rationale 7b

Although we recommend against routine the use of live attenuated vaccines in people with MS who are receiving or recently discontinuing ISIM therapies, circumstances can arise in which risks of infection are high (eg, endemic risks or local pandemics) (PRIN). Infections can result in morbidity and mortality in general and also increase the risk of exacerbation (RELA). Particularly given 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 7a

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

Statement 7b

When the risk of infection is high, clinicians may recommend using live attenuated vaccines if killed vaccines are unavailable in people with MS who are currently receiving ISIM therapies (Level C based on variation in patient preferences).

Recommendation 8

Rationale
We 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). Additionally, although data regarding the impact of steroids on vaccination response are limited, 1993 recommendations from the Centers for Disease Control and Prevention state, “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)64. 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 may delay vaccination of people with MS who are experiencing a relapse until clinical resolution or until the relapse is no longer active (eg, the relapse is associated with residual disability), often many weeks after relapse onset (Level C based on variation in patient preferences).

SUGGESTIONS FOR FUTURE RESEARCH
Our SR found few high-quality studies to inform the evidence. As more ISIM agents are developed to manage a chronic disease 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 post-marketing registries, with wide ascertainment of treated populations, can help to identify rare, emergent, and poorly characterized risks that are only recognized when the drugs are prescribed in practice. Funding, governance, physician and institutional involvement, and research protections are aspects that require attention while using this post-marketing data to inform clinical care and future research.

Tables/Figures

Table 1. Summary of conclusions for immunizations in patients with multiple sclerosis by disease and vaccine
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type of vaccine</th>
<th>Usual indication for adults (CDC)</th>
<th>H/O infection more frequent in MS patients?</th>
<th>Infection increases risk of risk of MS exacerbation?</th>
<th>Vaccination increases risk of MS?</th>
<th>Vaccination increases risk of MS exacerbation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria toxoid (as part of Tdap or Td)</td>
<td>Inactivated vaccine</td>
<td>Tdap: 1 dose at age 11 or 12, 1 dose anytime if not given at that age Td: booster every 10 years</td>
<td>There is insufficient evidence to support or refute whether a history of diphtheria is more frequent in patients with MS than in the general population (very low confidence in the evidence; one Class II study with decreased confidence in the evidence due to insufficient precision [OR with Sweeting continuity correction 0.0139; 95% CI, 0.00 to 2.87]).</td>
<td>There is insufficient evidence to conclude whether diphtheria vaccination increases the risk of developing MS (very low confidence in the evidence; two Class II studies with decreased confidence in the evidence for inconsistency and imprecision; meta-analysis OR 0.7, CI 0.3-1.6, I²= 84%).</td>
<td></td>
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<tr>
<td>Haemophilus influenzae type B (Hib)</td>
<td>Inactivated vaccine</td>
<td>Persons who have anatomical or functional asplenia or sickle cell disease or are undergoing elective</td>
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<tr>
<td>Hepatitis A</td>
<td>Inactivated vaccine</td>
<td>Any person seeking protection from hepatitis A virus infection and persons with high risk: 1) persons who use injection or noninjection illicit drugs; 2) persons working with hepatitis A virus-infected primates or with hepatitis A virus in a research laboratory setting; 3) persons with chronic liver disease and persons who receive clotting factor concentrates; 4) persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A; 5) unvaccinated persons who anticipate close personal contact with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity for hepatitis A.</td>
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<tr>
<td>Hepatitis B</td>
<td>Inactivated vaccine</td>
<td>Recommended for unvaccinated adults seeking protection from hepatitis B and high-risk groups: It is possible that a history of hepatitis B is less frequent in patients</td>
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<tr>
<td></td>
<td></td>
<td>It is probable that hepatitis B vaccination is not associated with an</td>
<td></td>
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</tr>
</tbody>
</table>
| HPV Inactivated Vaccine | People whose sex partners have hepatitis B.  
2) Sexually active persons who are not in a long-term monogamous relationship  
3) Persons seeking evaluation or treatment for a sexually transmitted disease  
4) People who share needles, syringes, or other drug-injection equipment  
5) People who have household contact with someone infected with the hepatitis B virus  
6) Health care and public safety workers at risk for exposure to blood or body fluids  
7) Persons in correctional facilities  
8) Victims of sexual assault or abuse  
9) Travelers to regions with increased rates of hepatitis B  
10) People with chronic liver disease, kidney disease, HIV infection, or diabetes | with MS compared to the general population (OR 0.19, 95% CI 0.04 to 0.84) (low confidence in the evidence, one Class II study).  
increased risk of developing MS (low confidence in the evidence, six Class II studies, with decreased confidence in the evidence for imprecision and a meta-analysis showing an OR of 0.9, 95% CI 0.84 to 1, $I^2 = 0\%$). | It is probable that HPV vaccination is not associated with an increased risk of developing MS and is probably |

| HPV | Females: recommended at age 11 or 12 and for those aged 13 through 26, if not previously vaccinated.  
Males: recommended at age 11 or 12 and for those aged 13 through 21, if not | It is probable that HPV vaccination is not associated with an increased risk of developing MS and is probably |
<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Vaccine</th>
<th>Dosage</th>
<th>Evidence Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Inactivated vaccine¹</td>
<td>1 dose annually</td>
<td>There is insufficient evidence to support or refute whether a history of influenza increases the risk of MS exacerbation (very low confidence in the evidence; one Class III study with decreased confidence in the evidence because of insufficient precision and indirectness [OR 0.5; 95% CI, 0.2 to 1.7]).</td>
</tr>
<tr>
<td>H1N1</td>
<td></td>
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<td>There is insufficient evidence to conclude whether H1N1 vaccination increases the risk of developing MS (very low confidence in the evidence; 1 Class I study with markedly decreased confidence in the evidence due to precision [CIs include the possibility of either a clinically important increase in risk or a clinically important decrease in risk]).</td>
</tr>
</tbody>
</table>
There is insufficient evidence to support or refute whether trivalent influenza vaccination increases the risk of MS exacerbation (very low confidence in the evidence; one Class II and 2 Class III studies with decreased confidence in the evidence due to insufficient precision and a meta-analysis with OR 1.64, 95% CI 0.48 to 5.87, I² 0%).

<p>| Japanese Encephalitis | Inactivated vaccine, live-attenuated | It is recommended for travelers to Asia who: plan to spend at least a month in areas where Japanese encephalitis occurs, plan to travel for less than a month, but will visit rural areas and spend a lot of time outdoors, travel to areas where there is a Japanese encephalitis outbreak, or... |</p>
<table>
<thead>
<tr>
<th>Measles (MMR)</th>
<th>Inactivated vaccine</th>
<th>Unvaccinated individuals (1 or 2 doses)</th>
<th>It is probable that a history of measles is similar in patients with MS compared with the general population (moderate confidence in the evidence; meta-analysis of 10 Class II studies with no significant difference in the history of measles exposure in MS patients versus controls (OR 0.957, 95% CI 0.88 to 1.038, $I^2=1%$)).</th>
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<tbody>
<tr>
<td></td>
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<td>There is insufficient evidence to conclude whether measles vaccination increases the risk of developing MS (very low confidence in the evidence; 4 Class II studies with decreased confidence in the evidence because of insufficient precision and a random effects meta-analysis with OR 1.3, 95% CI 0.5 to 3.4, $I^2=81%$).</td>
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<td>There is insufficient evidence to conclude whether MMR vaccination increases the risk of developing MS (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence because of insufficient precision and a random effects meta-analysis with OR 1.3, 95% CI 0.5 to 3.4, $I^2=81%$).</td>
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</table>

are not sure of their travel plans.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Status</th>
<th>Description</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis/meningococcal vaccination (MenACWY, MPSV4, MenB)</td>
<td>Inactivated vaccine</td>
<td>1) Adults with anatomical or functional asplenia or persistent complement component deficiencies, 2) Microbiologists who are routinely exposed to isolates of <em>Neisseria meningitides</em>; 3) Persons at risk because of a meningococcal disease outbreak; 4) Persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic; 5) Military recruits; 6) First-year college students aged ≤21 years who live in residence halls</td>
<td>There is insufficient evidence to support or refute whether a history of meningitis (type uncertain) is more common in patients with MS than in the general population (very low confidence in the evidence; one Class II study, with decreased confidence in the evidence because of imprecision [OR 1; 95% CI, 0.0006 to 3342.36]).</td>
</tr>
<tr>
<td>Mumps (MMR)</td>
<td>Inactivated vaccine</td>
<td>Unvaccinated individuals (1 or 2 doses)</td>
<td>There is insufficient evidence to conclude whether mumps vaccination increases the risk of developing MS (very low confidence in the evidence; 4 Class II studies).</td>
</tr>
<tr>
<td>Pertussis toxoid (as part of Tdap or Td)</td>
<td>Inactivated vaccine</td>
<td>Tdap: 1 dose at age 11 or 12, 1 dose anytime if not given at that age. Td: booster every 10 years</td>
<td>There is insufficient evidence to support or refute whether a history of pertussis is more frequent in patients with MS (very low confidence).</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Type</td>
<td>Population</td>
<td>Evidence</td>
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<tr>
<td>Pneumococcal vaccine (PCV13, PPSV23)</td>
<td>Inactivated vaccine</td>
<td>Adults aged ≥65 years who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23 6-12 months later. PCV13 in adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leak, or cochlear implants</td>
<td>Two Class II studies and a meta-analysis with decreased confidence in the evidence because of insufficient precision; OR 0.3, 95% CI 0.2 to 0.56, I² = 0%.</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>Inactivated vaccine</td>
<td>Inactivated poliovirus vaccine is not routinely recommended for U.S. residents aged 18 years or older.</td>
<td>There is insufficient evidence to support or refute whether a history of polio is more</td>
</tr>
<tr>
<td>Condition</td>
<td>Vaccine Type</td>
<td>Group Description</td>
<td>Evidence Description</td>
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<tr>
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<tr>
<td>Rubella (MMR)</td>
<td>Inactivated vaccine</td>
<td>Unvaccinated individuals (1 or 2 doses)</td>
<td>There is insufficient evidence to support or refute whether a history of rubella is more frequent in patients with MS (very low confidence in the evidence; six Class II studies and a random effects meta-analysis with decreased confidence in the evidence).</td>
</tr>
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<td></td>
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<td>Developing MS (very low confidence in the evidence; 2 Class II studies with decreased confidence in the evidence because of insufficient precision and a meta-analysis with OR 0.81, 95% CI 0.47 to 1.41, I² = 0%).</td>
</tr>
<tr>
<td></td>
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<td>There is insufficient evidence to conclude whether rubella vaccination increases the risk of developing MS (very low confidence in the evidence; 3 Class II studies with decreased confidence in the evidence because of insufficient precision and a meta-analysis).</td>
</tr>
<tr>
<td>Vaccine Type</td>
<td>Description</td>
<td>Evidence</td>
<td>Conclusion</td>
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<tr>
<td>Tetanus (as part of Tdap or Td)</td>
<td>Inactivated vaccine Tdap: 1 dose at age 11 or 12, 1 dose anytime if not given at that age Td: booster every 10 years</td>
<td>with OR 1.47, 95% CI 0.66 to 3.23, $I^2 = 87%$. There is insufficient evidence to conclude whether MMR vaccination increases the risk of developing MS (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence because of insufficient precision [OR 0.9; 95% CI, 0.4 to 1.8]).</td>
<td>It is probable that vaccination with tetanus toxoid is not associated with an increased risk of developing MS (moderate confidence in the evidence, 4 Class II studies and a meta-analysis, yielding OR 0.61, CI 0.49 to 0.76, $I^2 = 0%$).</td>
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<tr>
<td>Disease</td>
<td>Vaccine Type</td>
<td>Information</td>
<td>Probability</td>
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<tr>
<td>Tuberculosis (BCG)</td>
<td>Live Attenuated vaccine</td>
<td>Not routinely administered for U.S. residents.</td>
<td>There is insufficient evidence to support or refute whether a history of tuberculosis is more frequent in patients with MS (very low confidence in the evidence; two Class II studies and a random effects meta-analysis with decreased confidence in the evidence because of insufficient precision; OR 1.77, 95% CI 0.82 to 3.82, ( \chi^2=0 )).</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>Inactivated IM vaccine, oral live-attenuated</td>
<td>Routine typhoid vaccination is not recommended in the United States. Vaccination is recommended for the following groups: 1) Travelers to areas where there is a recognized</td>
<td>There is insufficient evidence to support or refute whether a history of typhoid is more frequent in patients.</td>
</tr>
<tr>
<td>VZV (chickenpox)</td>
<td>Live attenuated vaccine</td>
<td>All adults without evidence of immunity to varicella should receive 2 doses of single-antigen varicella vaccine or a second dose if they have received only 1 dose. Vaccination should be emphasized for those who have close contact with persons at high risk for severe disease (e.g., health care personnel and family contacts of persons with immunocompromising conditions) or are at high risk for exposure or transmission (e.g., teachers; child care employees; residents and staff members of institutional settings, including with MS than in the general population (very low confidence in the evidence; one Class II study with decreased confidence in the evidence due to insufficient precision [OR 1; 95% CI, 0.24 to 4.11]).</td>
<td>0.68; 95% CI, 0.31 to 1.48) (very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence for lack of precision).</td>
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<td>There is insufficient evidence to support or refute whether a history of varicella is more frequent in patients with MS than in the general population (very low confidence in the evidence; 7 Class II studies and a random effects meta-analysis with decreased confidence in the evidence).</td>
<td>The presence of viral VZV DNA in PBMCs is possibly associated with an increased risk of MS exacerbation (low confidence in the evidence; one Class II study [OR with Sweeting correction for detection of VZV DNA during relapse 6948.015; 95%CI, 71.819 to 414552.23]).</td>
</tr>
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<td>There is insufficient evidence to conclude whether VZV (chickenpox) vaccination increases the risk of developing MS (very low confidence in the evidence; 2 Class II studies with decreased confidence in the evidence due to inconsistency between studies [OR 41.6; 95% CI, 5.6 to 309.6] and [OR 0.18; 95% CI, 0.04 to 2.38]).</td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>Indications</td>
<td>Evidence</td>
<td>95% CI, 0.08 to 0.4).</td>
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<tr>
<td>VZV (Shingles)</td>
<td>Live attenuated vaccine</td>
<td>A single dose of zoster vaccine is recommended for adults aged ≥60 years regardless of whether they report a prior episode of herpes zoster.</td>
<td>There is insufficient evidence to support or refute whether a history of varicella is more frequent in patients with MS than in the general population (very low confidence in the evidence; 7 Class II studies and a random effects meta-analysis with decreased confidence in the evidence because of insufficient precision OR 1.017 95% CI 0.72 to 1.43 $I^2=71%$).</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Live attenuated</td>
<td>1) Persons 9 months through 59</td>
<td>There is insufficient</td>
</tr>
</tbody>
</table>
ed vaccine | years of age traveling to or living in an area where risk of yellow fever is known to exist, or traveling to a country with an entry requirement for the vaccination. 2) Laboratory personnel who might be exposed to yellow fever virus or vaccine virus. | evidence to conclude whether yellow fever vaccination increases the risk of developing MS (OR with Sweeting correction 0.07; 95% CI, 0 to 4 [very low confidence in the evidence; 1 Class II study with decreased confidence in the evidence because of insufficient precision]). |

1

Abbreviations: CI, confidence interval; OR, odds ratio; BCG, bacille Calmette-Guérin; Hib, *Haemophilus influenzae* type B; HPV, human papillomavirus; MMR, measles-mumps-rubella; MS, multiple sclerosis; Td, tetanus and diphtheria toxoids; Tdap, diphtheria and reduced tetanus toxoids and acellular pertussis vaccine; VZV, varicella-zoster virus

1There is an intranasal live attenuated vaccine, currently not recommended by the CDC for the 2016-2017 season.

Note: General contraindications are not indicated on this table. Please follow CDC guideline for contraindications or national guidelines, accordingly. For any untreated patient that did not receive corticosteroids or IV immunoglobulin for the past 30 days. For specific modifications according to treatment, see Table 2.
Table 2. Summary of Conclusions for immunizations in MS patients by treatment

<table>
<thead>
<tr>
<th>MS treatment</th>
<th>Mechanism of action</th>
<th>Affects vaccine response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon β</td>
<td>Cytokine that modulates immune response through various mechanisms</td>
<td>The use of IFN-β probably does not meaningfully reduce the frequency of seroprotection in response to influenza vaccines with various strains (moderate confidence in the evidence; three Class II and 1 Class III studies and a meta-analysis without decreased odds of seroconversion; OR for seroconversion in patients with MS receiving IFN-β therapy compared with either normal controls or patients with MS not receiving therapy 1.001 (95% CI, 0.97 to 1.03; I²=0%).)</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Binds to major histocompatibility complex molecules and competes with myelin antigens for their presentation to T cells.</td>
<td>It is probable that the use of glatiramer acetate reduces the effectiveness of influenza vaccine compared with healthy controls (moderate confidence in the evidence; 1 Class II study with two separate cohorts and a random effects meta-analysis with OR 0.35 [95% CI, 0.19 to 0.63; I²=0%]).</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>Mostly unknown, anti-inflammatory via the activation of the Nrf2 pathway.</td>
<td>Insufficient evidence.</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Inhibits pyrimidine biosynthesis affecting T cell proliferation.</td>
<td>There is insufficient evidence to support or refute whether the use of teriflunomide reduces the effectiveness of trivalent influenza vaccine (very low confidence in the evidence; one Class III study with decreased confidence for imprecision). However, the high proportions of patients in the teriflunomide group who achieved seroprotection make an adequate response to vaccination in the context of teriflunomide plausible (see text for data for each vaccine).</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Modulates the sphingosine-1-phosphate receptor, resulting in sequestration of lymphocytes in lymph nodes</td>
<td>For patients with relapsing remitting MS, it is probable that treatment with fingolimod decreases the immune response to trivalent influenza vaccine as compared to patients with MS not on fingolimod. (Moderate confidence in evidence, 1 Class 1 study [OR, 0.21; 95% CI, 0.08 to 0.54]) There is insufficient evidence to support or refute whether the use of fingolimod reduces the effectiveness of tetanus toxoid (very low confidence in evidence, 1 Class 1 study, with decreased confidence in the evidence for imprecision and inconsistency between outcomes [see text for data]).</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Monoclonal antibody against the alpha-4 subunit of integrin molecules. Natalizumab blocks integrin association with vascular receptors, limiting adhesion and</td>
<td>There is insufficient evidence to support or refute whether the use of natalizumab reduces the effectiveness of tetanus toxoid (very low confidence in evidence, 1 Class 1 study, with decreased confidence in the evidence for imprecision). There is insufficient evidence to support or refute whether the use of natalizumab reduces the effectiveness of trivalent influenza vaccine compared to healthy controls (very low confidence in the evidence; two Class II studies, one with two cohorts with decreased confidence because of imprecision, and a meta-analysis with OR 0.66, 95% CI 0.25 to 1.786, I² 50%). There is insufficient evidence to support or refute an effect of natalizumab on the response to H1N1 influenza vaccination in patients with MS compared to healthy controls (very low confidence in the evidence; one Class II study with...</td>
</tr>
</tbody>
</table>
transmigration of leukocytes. decreased confidence in the evidence due to imprecision [OR with Sweeting correction, 0.0375; 95% CI, 0.0003 to 2.7601]).

Alemtuzumab

Monoclonal antibody that causes depletion of CD52-expressing T cells, B cells, natural killer cells, and monocytes. There is insufficient evidence to support or refute whether the use of alemtuzumab has an impact on seroconversion after meningococcal, Hib, and pneumococcal vaccines (very low confidence in the evidence; one Class III study [see text for data]).

There is insufficient evidence to support or refute whether the use of natalizumab reduces the effectiveness of trivalent influenza vaccine compared with healthy controls (very low confidence in the evidence; two Class II studies, one with two cohorts \(^{1,3}\) with decreased confidence because of imprecision, and a meta-analysis with OR 0.66 [95% CI, 0.25 to 1.786; \(I^2 = 60\%\)].

Mitoxantrone

Intercalates into DNA resulting in cross-links and strand breaks, affecting lymphocyte replication. It is probable that the use of mitoxantrone reduces the effectiveness of influenza vaccine compared with healthy controls (moderate confidence in the evidence; one Class II study with two separate cohorts, and a random effects meta-analysis with OR 0.025 [95% CI, 0.001 to 0.46, \(I^2 = 81\%\)].

Daclizumab

Monoclonal antibody that binds to the high-affinity interleukin-2 receptor subunit (CD25), limiting T-cell activation and increasing the expansion of NK regulatory cells. There is insufficient evidence to support or refute whether the use of daclizumab reduces the effectiveness of trivalent influenza vaccine (very low confidence in the evidence; one Class II study with decreased confidence for imprecision [OR, 1.47; CI, 0.51 to 4.2] and 1 Class III study). However, the high proportions of patients achieving seroconversion while treated with daclizumab make an adequate response plausible.

1

Abbreviations: CI, confidence interval; IFN, interferon; Hib, *Haemophilus influenzae* type B; MS, multiple sclerosis; OR, odds ratio

Note: If more than one vaccine has to be administered, follow CDC guideline for spacing live and inactivated antigens: 1) two or more inactivated vaccines, may be administered simultaneously or at any interval between doses, 2) Inactivated and live, may be administered simultaneously or at any interval between doses, 3) Two or more live injectable, 28 days minimum interval, if not administered simultaneously, 4) Live oral vaccines may be administered simultaneously or at any interval before or after inactivated or live injectable vaccines.

---

**Table 3. Vaccine-Preventable Infection Data Insufficient to Support an Association with MS**

<table>
<thead>
<tr>
<th>Vaccine-Preventable Infection</th>
<th>Reference (Class)</th>
<th>OR for MS with history of infection (95% CI)</th>
<th>Conclusion</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Study Details</th>
<th>Odds Ratio (95% CI)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diptheria</td>
<td>Kurtzke 1997 (Class II)</td>
<td>0.0139 (0.00-2.87)</td>
<td>There is insufficient evidence to support or refute whether a history of diptheria is more common in patients with MS than in the general population (very low confidence in the evidence; one Class II study with decreased confidence in the evidence due to insufficient precision).</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Kurtzke 1997 (Class II), Zorzon 2003 (Class II)</td>
<td>0.0051 (0.00-2.873) 0.5 (0.1-1.5)</td>
<td>There is insufficient evidence to support or refute whether a history of hepatitis is more frequent in patients with MS than controls (very low confidence in the evidence; two Class II studies with decreased confidence in the evidence because of insufficient precision, and a random effects meta-analysis of 2 Class II studies showing a lower history of exposure to hepatitis in patients with MS but lacking the precision to exclude clinically important effects in either direction).</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Kurtzke 1997 (Class II)</td>
<td>1 (0.0006-3342.36)</td>
<td>There is insufficient evidence to support or refute whether a history of meningitis (type uncertain) is more frequent in patients with MS than in the general population (very low confidence in the evidence; one Class II study, with decreased confidence in the evidence because of imprecision).</td>
</tr>
<tr>
<td>Mumps</td>
<td>Bager 2004 (Class II), Da Silva 2009 (Class II), Harandi 2012 (Class II), Khaki 2001 (Class II), Kinnunen 1990 (Class II)</td>
<td>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) 0.45 (0.25-0.88) 0.98 (0.92-1.05)</td>
<td>There is insufficient evidence to support or refute whether a history of mumps is more frequent in patients with MS than in the general population (very low confidence in the evidence; seven Class II studies with a meta-analysis).</td>
</tr>
<tr>
<td>Disease</td>
<td>Study Details</td>
<td>Meta-analysis</td>
<td>Conclusion</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Bager 2004 (Class II) Kurtzke 1997 (Class II)</td>
<td>0.9 (0.7-1.1) 1.22 (0.6-2.5)</td>
<td>Meta-analysis: 0.925 (0.75-1.15), I²=0%</td>
</tr>
<tr>
<td>Polio</td>
<td>Kurtzke 1997 (Class II)</td>
<td>1 (0.0006-3342.36)</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>Bager 2004 (Class II) Da Silva 2009 (Class II) Kinnunen 1990 (Class II) Kurtzke 1997 (Class II) Ramagopalan 2009 (Class II) Zorzon 2003 (Class II)</td>
<td>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)</td>
<td>Meta-analysis: 0.78 (0.59-1.02), I²=57%</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Kurtzke 1997 (Class II)</td>
<td>1 (0.0006-3342.36)</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Studies</td>
<td>Odds Ratio with 95% CI</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Kurtzke 1997 (Class II) Zorzon 2003 (Class II)</td>
<td>1.66 (0.73-1.74) 2.9 (0.3-28.5)</td>
<td>1.77 (0.82-3.82), I²=0</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Kurtzke 1997 (Class II)</td>
<td>1 (0.24-4.11)</td>
<td></td>
</tr>
<tr>
<td>Varicella Zoster virus</td>
<td>Bager 2004 (Class II) Da Silva 2009 (Class II) Kurtzke 1997 (Class II) Mancuso 2007 (Class II) Ramagopalan 2009 (Class II) Sundstrom 2004 (Class II, serum collected before MS diagnosis) Sundstrom 2004 (Class II, serum collected after MS diagnosis) Zorzon 2003 (Class II)</td>
<td>1.1 (0.7-1.5) 0.7 (0.3-1.7) 0.51 (0.29-0.91) 334.479 (1.968-49714.67) 1.07 (1-1.14) 0.45 (0.14-1.43) 2.6 (1.5-4.6) 1 (0.5-1.7)</td>
<td>1.017 (0.72-1.43), I²=71%</td>
</tr>
</tbody>
</table>
Abbreviations: CI, confidence interval; MS, multiple sclerosis; OR, odds ratio
### Table 4. Studies Investigating an Association between Measles and MS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Key Study Design Features</th>
<th>Outcome OR for MS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahlgreen 2011</td>
<td>Class II case-control study. Measured seroprevalence of measles antibodies in a cohort of 166 patients, (124 relapsing remitting MS, and 42 CIS) compared to 50 healthy controls (blood donors with paired serum and CSF samples).</td>
<td>Seropositivity in MS/CIS patients overall and controls: 94% vs 92%, OR 1.36 (0.45-4.07). CSF measles antibodies: MS 74% vs. controls 34%, OR 5.52 (3-10)</td>
</tr>
<tr>
<td>Bager 2004</td>
<td>Class II case-control study (2 cohorts, first: born since 1940 cases n=455, controls n=1801; second cohort: born since 1950 cases n=182, controls n=690). School records were reviewed that contained information on measles, pertussis, and scarlet fever for the first cohort and rubella, mumps and varicella for the second.</td>
<td>History of measles in 78% of cases and 80% of controls. OR 0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Comabella 2010</td>
<td>Class II case-control study. Studied seroprevalence of antibodies against measles. The MS group included 25 patients (21 relapsing remitting MS, 2 primary progressive MS, 1 transitioning to progressive, 1 CIS). Forty-six siblings were used as controls.</td>
<td>Measles antibodies were detected in 100% of patients and 100% of controls. Mean antibody titers to measles no different (numbers not provided) OR 0.548 (0.0217-13.9)</td>
</tr>
<tr>
<td>Da Silva 2009</td>
<td>Class II case control study. 81 patients with MS (Poser criteria) from Rio de Janeiro were compared with 81 age, gender and birthplace matched healthy controls (friends/neighbors) and interviewed face-to-face using a standardized questionnaire.</td>
<td>History of measles: cases 56/81, 68.4%, controls 54/81, 66.7%, OR 1.2 (0.6-2.7).</td>
</tr>
<tr>
<td>Khaki 2011</td>
<td>Class II case-control study. Compared seroprevalence of measles IgG and IgM antibodies in 60 relapsing remitting MS patients (McDonald criteria), with age-, gender- and socio-economic status-matched healthy controls.</td>
<td>Seroprevalence for measles IgM: OR 3.2 (1.5-6.9) Seroprevalence for measles IgG: OR 0.67 (0.24-1.9)</td>
</tr>
<tr>
<td>Kinnunen 1990</td>
<td>Class II retrospective twin cohort study. All twins with at least one affected member with MS were identified from the nationwide</td>
<td>Fourfold higher measles HAI titer: OR 4.09 (0.69-24)</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Findings</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Finnish Twin Cohort, linked to the International Statistical Classification of Diseases, Injuries, and Causes of Death (where the diagnosis of MS was coded).</td>
<td>Kurtzke 1997 Class II case control study. Questionnaires surveys were returned by 23 MS patients, 69 siblings and relatives, 37 neighbor controls or patients’ spouses, and 21 distant matched controls and their spouses.</td>
<td>83% of MS subjects and 93% of controls reported a history of measles, OR 0.37, CI 0.15-0.93</td>
</tr>
<tr>
<td>Kurtzke 1997</td>
<td>Ramagopalan 2009 Class II study using a longitudinal population based cohort identified from a Canadian database. 14,362 MS index cases and 7,671 spouse controls were asked about history of childhood infections. Over half (58%) the subjects has relapsing remitting MS; MS type in the rest and level of disability were not mentioned.</td>
<td>No significant age and sex adjusted difference between cases and controls for history of measles (OR 0.97, CI 0.91 to 1.05)</td>
</tr>
<tr>
<td>Ramagopalan 2009</td>
<td>Sündstrom 2004 Class II case-control study, the authors linked an MS registry database to two serum sample databases of MS cases and controls. Cases without any possible MS symptoms before the date of serum collection were defined as “prospective”, and the cases whose serum was collected after the onset of MS were defined as “retrospective cases”. The “prospective” cohort consisted of 73 cases of definite MS. The “retrospective” cohort consisted of 161 MS cases.</td>
<td>IgG antibodies to measles (prospective cohort): OR 1 (0.0002-10161.82) Seropositivity to measles (retrospective cohort): OR 0.57 (0-4.5) Multivariate analysis including “high antibody activities against measles” (retrospective cohort): OR 1.9 (1.1-3.3)</td>
</tr>
<tr>
<td>Sündstrom 2004</td>
<td>Zorzon 2003 Class II case control study including 140 patients with MS and 131 age and sex matched controls. Structured questionnaire in face to face interview by masked investigators were performed.</td>
<td>History of measles was reported in 126/140, 90% cases, 110/131, 83.9% controls, OR 1.3, (0.6 to 3).</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CIS, clinically isolated syndrome; MS, multiple sclerosis; OR, odds ratio
Table 5. Frequency of influenza seroprotection in patients receiving MS treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>Vaccine/Infection</th>
<th>Frequency of seroprotection % (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment Group</td>
<td>Control Group*</td>
</tr>
<tr>
<td>Bar-Or 2013 (Class III)</td>
<td>H1N1</td>
<td>97.7% (93.9-100)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>H3N2</td>
<td>90.7% (83.4 to 98)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Influenza B</td>
<td>93% (86.6 to 99.4)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mehling 2013 (Class II) Olberg 2014 (Class II)</td>
<td>Influenza A</td>
<td>100% (87.1-100)</td>
<td>91% (76.4-96.9)</td>
<td>86.9 (0.66-15201.9, using Sweeting correction)</td>
</tr>
<tr>
<td></td>
<td>Influenza B</td>
<td>100% (87.1-100)</td>
<td>81.8% (65.6-91.4)</td>
<td>191.8 (1.5-20381.7, using Sweeting correction)</td>
</tr>
<tr>
<td></td>
<td>H1N1 (2009)</td>
<td>44.4% (29.5-60.4)</td>
<td>43.5% (37.1-50.2)</td>
<td>1.03 (0.5-2.1)</td>
</tr>
<tr>
<td>IFN-β Mehling 2013 (Class II)</td>
<td>H1N1 (2010)</td>
<td>88.2% (65.6-96.7)</td>
<td>69.4% (55.5-80.5)</td>
<td>3.3 (0.77-15.1)</td>
</tr>
<tr>
<td></td>
<td>H3N2 (2010)</td>
<td>88.2% (65.6-96.7)</td>
<td>79.5% (68.8-87.1)</td>
<td>1.9 (0.45-8.7)</td>
</tr>
<tr>
<td></td>
<td>Panama strain</td>
<td>93.0% [80/86] (85.4-97.4)</td>
<td>90.9% (82.2-96.3)</td>
<td>1.3 (0.4-4.1)</td>
</tr>
<tr>
<td></td>
<td>New Caledonia strain</td>
<td>88.4% [76/86]; (79.9-93.6)</td>
<td>79.2% [61/77] (68.9-86.8)</td>
<td>2 (0.9-4.3)</td>
</tr>
<tr>
<td></td>
<td>Hong Kong strain</td>
<td>51.2% [44/86] (40.8-61.5)</td>
<td>41.6% [32/77] (31.2-52.7)</td>
<td>1.5 (0.8-2.6)</td>
</tr>
<tr>
<td>Random effects meta-analysis</td>
<td>All influenza vaccines</td>
<td>1.001 (0.97 to 1.03), I²=0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Antigen</td>
<td>Percentage</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>---------</td>
<td>------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Olberg 2014 (Class II)</td>
<td>Glatiramer Acetate</td>
<td>Trivalent Influenza vaccine</td>
<td>41.7%</td>
<td>79.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H1N1 vaccine, 2009 cohort</td>
<td>21.6%</td>
<td>43.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H1N1 vaccine, 2010 cohort</td>
<td>58.3%</td>
<td>71.2%</td>
</tr>
<tr>
<td></td>
<td>Random effects meta-analysis</td>
<td>All influenza vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kappos 2015 (Class I)</td>
<td>Fingolimod</td>
<td>California Strain (3 weeks)</td>
<td>48.4%</td>
<td>72.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>California Strain (6 weeks)</td>
<td>41.6%</td>
<td>60.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brisbane Strain (3 weeks)</td>
<td>76.9%</td>
<td>95.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brisbane Strain (6 weeks)</td>
<td>67.4%</td>
<td>90.7%</td>
</tr>
<tr>
<td>Mehling 2011 (Class III)</td>
<td>Fingolimod</td>
<td>Influenza A (protective IgG)</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Influenza B (protective IgG)</td>
<td>87%</td>
<td>94%</td>
</tr>
<tr>
<td>Mehling 2014 (Class III)</td>
<td>Fingolimod</td>
<td>Influenza A (Mean differences between HCs and Fingolimod treated MS subjects)</td>
<td>Day 7: 0.02 (-0.2-0.24)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 14: 0.09 (-0.17-0.35)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 28: 0.06 (-0.28-0.4)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Influenza B (Mean differences between HC and Fingolimod treated MS subjects)</td>
<td>Day 7: 0.16 (-0.14-0.4)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 14: 0.2 (-0.15-0.55)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 28: 0.17 (-0.17-0.51)</td>
<td>N/A</td>
</tr>
<tr>
<td>Olberg 2014 (Class II)</td>
<td>Natalizumab</td>
<td>Trivalent influenza vaccine</td>
<td>50%</td>
<td>79.5%</td>
</tr>
<tr>
<td>Vagberg 2012 (Class III)</td>
<td></td>
<td>Trivalent influenza vaccine</td>
<td>49.5%*</td>
<td>56.4%*</td>
</tr>
<tr>
<td>Random effects meta-analysis</td>
<td></td>
<td>Trivalent influenza vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Year</td>
<td>Study Type</td>
<td>Vaccine Description</td>
<td>H1N1 Protection</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>---------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Daclizumab</strong></td>
<td>Lin 2016</td>
<td>Class II</td>
<td>Trivalent influenza vaccine (H1N1, H3N2, B strains)</td>
<td>84.3%</td>
</tr>
<tr>
<td></td>
<td>Mehta 2016</td>
<td>Class III</td>
<td>H1N1 strain</td>
<td>92% (85-97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H3N2 strain</td>
<td>91% (83-96)</td>
</tr>
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Abbreviations: CI, confidence interval; IFN, interferon; Ig, immunoglobulin; MS, multiple sclerosis

*The control group consisted of normal controls in Mehling 2013 and Olberg 2014 and MS*
patients not receiving IFN therapy in Schwid 2005. Bar-Or 2013 was a pre-post study without an external control group.

#Percentage of patients with increased titers

& Historical controls
Disclaimer

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Conflict of Interest Statement

The AAN’s Conflict of Interest Policy Implementation for AAN Guidelines is available at [web link]. All AAN guideline authors must meet the stipulations outlined in the policy in order to

Acknowledgments

Appendices

Appendix e1.

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### Embase 1988 to 2016 Week 01

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papillomavirus OR typhoid 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

Appendix e-2. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation

b. no more than 2 primary outcomes specified

c. exclusion/inclusion criteria clearly defined

d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).

iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A
description of major confounding differences between treatment groups that could affect outcome.**

Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

**Class IV**

Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer’s (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

**Diagnostic accuracy scheme**

**Class I**

A cohort study with prospective data collection of a broad spectrum of persons with the suspected condition, using an acceptable reference standard for case definition. The diagnostic test is objective or performed and interpreted without knowledge of the patient’s clinical status. Study results allow calculation of measures of diagnostic accuracy.

**Class II**

A case-control study of a broad spectrum of persons with the condition established by an acceptable reference standard compared with a broad spectrum of controls, or a cohort study with a broad spectrum of persons with the suspected condition where the data were collected.
retrospectively. The diagnostic test is objective or performed and interpreted without knowledge of disease status. Study results allow calculation of measures of diagnostic accuracy.

Class III

A case-control study or cohort study where either persons with the condition or controls are of a narrow spectrum. The condition is established by an acceptable reference standard. The reference standard and diagnostic test are objective or performed and interpreted by different observers. Study results allow calculation of measures of diagnostic accuracy.

Class IV

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Prognostic accuracy scheme

Class I

A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II

A case-control study of a broad spectrum of persons with the condition compared with a broad spectrum of controls, or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or
measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

*Class III*

A case-control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

*Class IV*

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

**Screening scheme**

*Class I*

A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients’ clinical presentations.

*Class II*

A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients’ clinical presentations.
Class III

A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

Class IV

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Causation scheme

Class I

Prospective cohort study design that satisfies all of these criteria:

a. groups studied are representative of population of interest (“broad spectrum”)

b. risk factors and outcomes are clearly defined with validated or generally accepted criteria, and measured independently or objectively

c. comparison groups are matched for known possible confounding risk factors, or the effects of such confounders are controlled in the study analysis

d. measures of association are expressed (or can be calculated) as rate ratios, risk ratios, relative risks (RRs), or population attributable risks with confidence intervals.

Class II

Retrospective cohort or case-control study designs that satisfy criteria a, b, and c above (see Class I), in which (d) the measure of association may also be expressed (or can be calculated) as an odds ratio (OR) with confidence intervals.
Class III

Other cohort or case-control study designs in which groups studied represent a narrow spectrum of the population of interest, or the measure of association does not include an RR or OR but does include an aggregate measure such as a correlation or group mean with standard deviation or p value. Criterion b (see Class I) above must still be satisfied. Obvious confounding is not evident.

Class IV

Studies not meeting criteria for Class I, II, or III. Specifically, studies that are noncomparative, unrepresentative of the population of interest, with major biases or confounding, lacking useful measures of effect, or lacking measures of effect estimate stability.

Notes:

1. In addition to the criteria above, any causal inference requires that exposure to the risk factor precede the development of the outcome. In addition, there may be need to allow for an induction period.

2. In translating evidence, a requirement of two or more studies implies that such studies should not include the same subjects.

3. Exploratory studies involving multiple comparisons of a variety of exposures and outcomes may be rated lower if it is evident that the study was designed without an a priori hypothesis or focus upon the specific exposure and outcome of interest.

4. Randomized clinical trials (RCTs) are equivalent to prospective cohort studies in which the risk of confounding has been minimized. Evidence from such studies may be considered Class I, provided it satisfies criteria a, b, and d above (see Class I). Note,
however, that it is preferable to apply the AAN criteria for therapeutic studies when classifying evidence pertaining to the experimental (treatment) variables of an RCT.
References


52. Mehta L, Umans K, Ozen G, Robinson RR, Elkins J. Immune Response to Seasonal Influenza Vaccine in Relapsing-Remitting Multiple Sclerosis Patients on Long-Term


2016.


