Curr Neurol Neurosci Rep (2016) 16: 36
DOI 10.1007/s11910-016-0637-6

Vaccines in Multiple Sclerosis

Eric M. L. Williamson[1] · **Salim Chahin**[1] · **Joseph R. Berger**[1]

Published online: 27 February 2016

Abstract Vaccinations help prevent communicable disease. To be valuable, a vaccine's ability to prevent disease must exceed the risk of adverse effects from administration. Many vaccines present no risk of infection as they are comprised of killed or non-infectious components while other vaccines consist of live attenuated microorganisms which carry a potential risk of infection—particularly, in patients with compromised immunity. There are several unique considerations with respect to vaccination in the multiple sclerosis (MS) population. First, there has been concern that vaccination may trigger or aggravate the disease. Second, disease-modifying therapies (DMTs) employed in the treatment of MS may increase the risk of infectious complications from vaccines or alter their efficacy. Lastly, in some cases, vaccination strategies may be part of the treatment paradigm in attempts to avoid complications of therapy.

Keywords Vaccination · Multiple sclerosis · Immunity · Varicella zoster · Influenza · Disease-modifying therapy

This article is part of the Topical Collection on *Demyelinating Disorders*

✉ Eric M. L. Williamson
ericwilliamsonmd@gmail.com

Salim Chahin
salim.chahin@uphs.upenn.edu

Joseph R. Berger
joseph.berger@uphs.upenn.edu

[1] Department of Neurology, Division of Neuroimmunology, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA, USA

Introduction

This paper highlights the importance of avoiding infections in multiple sclerosis (MS), reviews the safety of vaccinations in patients with MS, and highlights several important issues pertaining to disease-modifying treatments (DMTs) and the use of vaccines.

Vaccines are biologic products administered to elicit an immune response resulting in protective and hopefully, long-term immunity. In healthy individuals, the benefits of most vaccines greatly outweigh their risks—this is also true for MS patients in the absence of DMT or advanced disability. The immune response mounted by patients with MS to antigenic stimulation is similar to otherwise healthy individuals, and any increased risk of infection is chiefly as a consequence of immune compromise secondary to therapy or sequelae of advanced disease like poor bladder function, impaired respiratory clearance, or skin breakdown from paraplegia.

While some studies suggest that MS patients have a higher incidence of certain other autoimmune diseases [1•] and a higher incidence of autoantibodies [2–4], there is no evidence of a significant alteration in cell-mediated immunity or increased incidence of infections in MS [5]. Nonetheless, infections may affect the disease process and the avoidance of infection in MS patients is desirable [6•, 7–9], highlighting the importance of safe vaccines for these patients.

Vaccines have been responsible for saving innumerable lives and preventing disability. The discovery and success of vaccination practices are considered one of the most important medical breakthroughs in history. It is important to be knowledgeable about the type of vaccine being administered, the intended use, the target population, and possible effects and complications. Current vaccine recommendations for children ages 0–18 and adults can be readily accessed at the Center for

Disease Control's website (http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html#printable and http://www.cdc.gov/vaccines/schedules/hcp/adult.html).

Types of Vaccines

Vaccines for the same infectious agent may be prepared in several ways and are attended by different benefits and risks (Table 1). Inactivated vaccines are comprised of microorganisms that have been rendered non-infectious by chemical or physical means; toxoid vaccines are made from inactivated toxic compounds rather than the microorganism, subunit vaccines contain a fragment of the infectious agent, and conjugate vaccines are comprised of linked polysaccharide outer coats of the microorganism. None of these types of vaccines carry risk of infection. In contrast, live attenuated vaccines (Table 1), which are derived from disease-causing viruses or bacteria and engineered to have substantially reduced virulence, may carry a potential risk of infection or reversion to a virulent form, particularly in immunocompromised individuals. As a rule, live attenuated vaccines should be avoided in immunocompromised patients.

Using live vaccines may present a real or potential risk of disease with certain immunotherapies used in the treatment of MS—particularly when the therapy potentially affects the immune response to the relevant microorganism. Extra precaution is necessary when vaccines are considered in this setting. There may also be risks to patients on certain DMTs when close family members receive live vaccines as the immunized individual may shed these live attenuated pathogens.

Vaccination and the Risk of Triggering or Aggravating MS

Several studies have associated infectious illnesses with disease activity in MS, with fear that infections can lead to exacerbation of symptoms or illnesses [6•, 7–9]. In theory, vaccine use should presumably decrease burden of disease and/or disease activity by preventing infectious illness [7].

There have been concerns about vaccine administration triggering disease or activity in MS. This has prompted countless studies on this topic. Most studies that have purported an increased risk of MS or MS relapse with vaccination have been small case series [10•, 11–13]. Importantly, there has been no substantiation to reports suggesting a link between vaccination and the development of MS. An extensive review by the US Institute of Medicine found no evidence of a causal relationship between onset of MS and vaccination against measles, mumps and rubella, influenza, hepatitis, human papilloma virus, diphtheria, tetanus, pertussis, or meningococcal disease [14]. Similarly, a review of the complete electronic health records of Kaiser Permanente Southern California members failed to reveal any causal association between vaccination and multiple sclerosis or other CNS demyelinating syndrome [15]. In 2001, the New England Journal of Medicine published the VACCIMUS study that assessed the risk of relapse associated with vaccines in patients with MS. This case crossover study of 643 patients followed from 1993 to 1997 concluded that vaccine use did not increase risk of relapse in MS patients [16]. A handful of studies have also demonstrated decreased disease activity in MS patients after certain vaccinations [17, 18].

Of note, special consideration is given to vaccinating patients with ongoing disease activity and there may be a reason to avoid further immune perturbation following a recent relapse [7]. According to the National Multiple Sclerosis Society (NMSS) and American Academy of Neurology (AAN), vaccination should be avoided when vaccines may be interpreted to pose an increased risk and patients with serious relapses should defer vaccination for 4–6 weeks, presumably until they recover or return to baseline [19].

Table 1 Examples of vaccines, by type

Inactivated vaccines	Injected influenza, cholera, bubonic plague, intramuscular polio (Salk vaccine), hepatitis A, rabies
Toxoid vaccines	Tetanus, diphtheria
Subunit vaccines	Hepatitis B, human papilloma virus, influenza
Conjugate vaccines	Hemophilus influenza type B
Live attenuated vaccines	Intranasal influenza, varicella zoster virus (Zostavax and Varivax), oral polio (Sabin vaccine), yellow fever, measles, rubella, mumps, typhoid, BCG, *Yersinia pestis*

Vaccination Efficacy and Safety in Patients on DMTs

Injectable Therapies

The injectable therapies for MS (glatiramer acetate and the interferon-βs) have now been in widespread use for over two decades and have not been associated with impairment of immune response or increasing risk of infections. There is no observed risk or safety concerns for vaccination of MS patients on these agents regardless of the nature of the vaccine (whether live attenuated, inactivated, toxoid, subunit, or conjugate). As there is no increased risk of vaccination in these patients, recommendations for vaccination in this population are no different than they would be for any other individual.

Oral and Infusion Therapies

The two primary concerns with respect to vaccination of MS patients on oral or infusion therapies are (1) is a sufficient immune response mounted to render the vaccine effective and (2) does the therapy increase the risk of converting an attenuated infectious agent into one capable of causing significant clinical disease. These concerns vary by the infectious agent and vaccine type as well as the individual DMTs. While data is limited for certain vaccines and DMTs, we will present data on individual vaccines followed by a review of studies for specific DMTs, when available.

Influenza Vaccine

There are two types of influenza vaccine, the inactivated injectable form and live attenuated nasal spray [20•]. The current CDC recommendation is for all individuals aged 6 months or older to receive vaccine. Infection with influenza has been shown to increase relapse risk in patients with MS [21], and most studies have shown no increased disease activity following vaccination [22, 23]. A randomized, double-blind, placebo-controlled trial of influenza vaccination in MS showed no significant difference in the rate of relapses [24]. Noting that patients with MS are at a higher risk for influenza-related hospitalization [25] and MS deaths peak coincident with pneumonia, vaccination against influenza is of a greater importance in MS patients [20•].

The standard dose inactivated injectable influenza vaccine is the most thoroughly researched vaccine in MS and is recommended and considered safe for all MS patients irrespective of treatment [7, 19, 20•]. The high-dose, inactivated influenza vaccine has not been studied sufficiently to recommend in MS [7, 19]. The live attenuated vaccine, because of the small risk of producing influenza, is also not recommended for patients with MS [7, 19].

The inactivated influenza vaccine, in contrast to the live attenuated vaccine, is considered safe even in MS patients on immunosuppressive therapy [20•]. The ability of the vaccine, however, to produce an adequate response may differ depending on the therapeutic agent administered [20•]. Multiple studies have shown comparable efficacy for the influenza vaccine for MS patients treated with beta-interferons and healthy controls [20•, 26–28]. One study showed that patients on glatiramer acetate did not mount as strong an immune response following vaccination with the influenza vaccine as did healthy controls [26], but little data exist for glatiramer acetate and the influenza vaccine [20•]. Patients treated with natalizumab had lower rates of protection in one study [26] and no significant difference in another [29] when compared to healthy controls. Patients on fingolimod had similar response rates as did healthy controls when receiving influenza vaccine in some studies [30, 31]; however, a recent randomized trial showed that although patients on fingolimod were able to mount immune responses against influenza, response rates were reduced at 3 and 6 weeks following vaccination when compared to placebo-treated patients [32]. Similarly, patients on teriflunomide mounted a slightly diminished response to the vaccine [33] and mitoxantrone has demonstrated interference with the influenza vaccine [20•]. Although no studies have assessed the effect of the influenza vaccine in patients treated with alemtuzumab, the National MS society recommends that the vaccine be given at least 6 weeks prior to receiving alemtuzumab [19] due to concerns about mounting on appropriate response to vaccination.

Hepatitis B Vaccine

The hepatitis B vaccine is an inactivated vaccine produced through recombinant DNA methodology that contains the viral envelope protein. The vaccine is recommended for all children, adolescents, and high-risk adults. The vaccine is considered safe for patients with MS [10•, 15, 19, 34]. Initially, there was concern over an association between the vaccine and CNS demyelination [10•]. However, more recent studies have refuted this and also did not show any increased risk for relapses following vaccination [15, 35]. It has been recently suggested that MS patients may be at a higher risk for hepatitis B-related complications; furthermore, MS patients have increased osteoponin and IL-17, two factors associated with worse outcomes for patients with hepatitis B—all of which may highlight the importance of this vaccine in patients with MS [34].

HPV Vaccine

The human papilloma virus (HPV) vaccine is an inactivated vaccine. It has been given to females and males to prevent cervical and anal cancer, as well as genital warts. It is available in three types: bivalent, quadrivalent, and 9-valent. It is recommended for both female and male adolescents 11 years and older. Earlier studies suggested an increased risk of CNS demyelinating diseases, including MS and neuromyelitis optica (NMO), following vaccination with the HPV vaccine [11, 12]; but, recent larger case-control [36] and population-based [37] studies did not identify an association between the quadrivalent vaccine and the risk for MS. The vaccine is probably safe in MS as initial reports of immune-mediated complications appear not to be true [12, 37].

Tetanus Vaccine

The tetanus vaccine is an inactivated vaccine that is recommended for all children and is often administered in combination with other vaccines for diphtheria and pertussis; a booster vaccination is also recommended every 10 years for adults.

Several studies have shown no increased risk for MS or relapse following vaccination [16, 17, 38]; in fact, vaccination may actually be associated with a reduced risk of relapses in patients with MS [16, 18].

The response to tetanus vaccination has been evaluated in several studies. For example, in a study evaluating the response to tetanus in natalizumab-treated patients, the proportion of responders to the vaccine was similar with or without natalizumab [39]. In fingolimod-treated patients, one study found no difference in the response rate to tetanus for fingolimod vs. placebo [31]; whereas a randomized clinical trial showed that the response rate to the tetanus vaccine was reduced at 3 and 6 weeks post vaccination when compared to placebo [32]. Alemtuzumab-treated patients were able to mount an adequate response to the tetanus vaccine [40] when compared to historical controls.

Yellow Fever Vaccine

The Yellow fever vaccine, a live attenuated vaccine against the mosquito-borne illness, is recommended for travelers to areas where the disease is endemic. Rarely, complications of encephalitis and/or meningitis may occur with this live vaccine and it is relatively contraindicated with immunomodulatory therapies. A small study of seven patients found an increased risk of MS relapses and MRI activity following vaccination [13]; thus, the risk of contracting this potentially fatal disease needs to be weighed against the possible risk of increased relapses in MS patients traveling to endemic areas. In all, the vaccine should be avoided in patients on immunosuppressive agents given that it is a live attenuated vaccine [10•].

Measles, Mumps, and Rubella vaccine

The measles, mumps, and rubella (MMR) vaccine is a live attenuated vaccine recommended for children and certain at-risk adults. Data on the safety of the MMR vaccine in MS is limited, but it is not thought to be associated with an increased incidence of MS [14, 38, 41]. Because the MMR vaccine is a live attenuated vaccine, it should be avoided in patients receiving immunosuppressive therapy due to concern about the risk of developing overt vaccine-associated disease [10•].

Varicella zoster Vaccine

Both the varicella zoster virus (VZV) vaccine recommended for patients without any prior exposure to the virus and the zoster vaccine indicated for patients previously infected by VZV are live attenuated vaccines. Because varicella vaccine is a live attenuated vaccine, it is best to avoid its use in patients on immunosuppressive agents. In a pilot study of seropositive progressive MS patients, the majority remained stable or improved following vaccination [42]. Furthermore, the vaccine is recommended prior to starting immunosuppressive treatment and is explicitly required prior to treatment with fingolimod and alemtuzumab, as will be addressed separately.

Bacille Calmette-Guerin Vaccine

Bacille Calmette-Guerin (BCG) is a vaccine for tuberculosis (TB) used in some high-prevalence countries. It is a live attenuated vaccine. Overall, studies have found no association between the vaccine and increased risk of MS [43]. Furthermore, a pilot study in 1999 found that the vaccine was not only safe in MS but also reduced MRI activity in patients with relapsing-remitting MS [44], and a recent double-blind, placebo-controlled trial [45] of patients with clinically isolated syndrome (often the initial demyelinating event of MS) showed the vaccine significantly reduced enhancing MRI lesions during 6 months prior to starting DMT [45].

Rabies Vaccine

The rabies vaccine is recommended for high-risk individuals and as part of the post exposure prophylaxis regimen following close contact with a suspected rabid animal. While very few studies have addressed the risk of MS following rabies vaccination [43], none found an association [43].

Bar-Or et al. showed that healthy subjects treated for 1 month with teriflunomide were able to mount an adequate immune response to the rabies vaccination but had lower antibody levels compared to subjects on placebo [46].

Other Vaccines The live version of the polio virus vaccine, no longer used in the USA, would be contraindicated in patients on immune suppression, while studies of the inactivated polio virus showed no increased risk of developing MS [43]. Aside from that reviewed above, sufficient evidence is scarcely available on the safety of other vaccines in patients with MS.

Additional Concerns with Vaccine Use in MS Immune suppression raises special concerns, and the effects of vaccines have not been tested in all situations. But, the profound effect of alemtuzumab on B and T cells as pertains to vaccine efficacy has been studied in some cases. In addition to the comments above regarding the influenza and tetanus vaccines, in a case-control study of alemtuzumab, McCarthy et al. [40] showed that patients treated with alemtuzumab retained humoral immunity in the form of responses to common viruses (mumps, rubella, varicella zoster, and Epstein-Barr virus), and mounted normal responses to diphtheria and inactivated polio as well as tetanus vaccines. Furthermore, following treatment, patients were able to mount a response against meningococcal and pneumococcal vaccines [40]. Although no safety issues were reported, these were all inactivated vaccines and the authors did caution against the use of live attenuated vaccines.

Lastly, there is a suggestion that vaccination within 2 months of treatment with alemtuzumab may not be as effective.

The available data as well as clinical experience suggests that the immune response following vaccination is sufficiently robust in MS patients to be protective in most instances; however, live vaccines are best avoided in patients on immunosuppressive therapy due to safety concerns.

As mentioned above, large studies and meta-analyses have proven the safety of vaccines such as tetanus, hepatitis B, influenza, measles, rubella, polio, BCG, and typhoid fever [16, 38, 43] and dispelled any concerns about the risk of causing multiple sclerosis [14]. Recently, a large nested case-control study showed no long-term association of vaccines (hepatitis B, HPV, or any vaccine) with MS or any other CNS demyelinating disease [15].

Current specific vaccination recommendations for MS patients are illustrated in Table 2.

Vaccines to Decrease the Risk of Zoster Reactivation and Other Infectious Disease Complications in MS Patients Treated with DMTs

In reviewing the established guidelines for the use of vaccination in MS patients and vaccines to avoid in patients on immunosuppressive regimens, one should also consider how and when to utilize vaccination strategies to prevent complications associated with the use of DMTs.

All the non-platform therapies appear to be associated with an increased risk of herpetic infections, including varicella zoster virus (VZV) [6•]. Although the concern has chiefly focused on the association of zoster reactivation with fingolimod, reactivation of VZV resulting in zoster (shingles) is a significant concern with other DMTs as well. Alemtuzumab may carry even a greater risk of VZV reactivation [6•] and other rare cases of varicella zoster complications have been reported with natalizumab [47–50]. Given the reduced risk of varicella zoster reactivation following vaccination, it has been recommended that VZV antibody status be obtained in patients about to be started on fingolimod [51] and alemtuzumab [52]. Given the relative safety of zoster vaccination and the perceived increased risk of varicella zoster reactivation with many of the non-platform DMTs, serious consideration needs to be given to assessment of VZV antibody status and prophylactically administering VZV vaccine in these situations.

In those who have no history of prior chickenpox and are VZV antibody negative, Varivax is recommended to be administered by two doses at least 4 weeks apart [53]. Seroconversion rates are higher when the second dose is separated by 8 weeks rather than 4 weeks, but there may be a trade-off between waiting and the delay of starting a DMT. In older patients with a history of prior chickenpox, but negative VZV antibody levels, treatment with a single dose of Zostavax has been recommended. Whether these measures are effective in reducing subsequent zoster outbreaks remains uncertain. Presumed shedding of the attenuated virus was observed in report of infection of contact of a woman who received a short course of fingolimod followed by VZV vaccination—despite recurrent bouts of shingles, the patient interestingly never mounted a detectable antibody response [54].

Several other infections have also been known to complicate treatment with certain DMTs [6•], but the guidelines on prevention, when available, are not always clear. For example, the risk of HPV-associated cervical cancer is increased in patients treated with alemtuzumab [52] and annual cervical pap smears are recommended. To date, however, there are no specific recommendations for HPV vaccination in MS patients prior to, or after, treatment with certain DMTs, including alemtuzumab. Herpes viral reactivation appears to occur with higher frequency on alemtuzumab [52], and while we do not have vaccinations against the herpes virus, antiherpetic medications are recommended for at least 2 months after alemtuzumab dosing (or until CD4 levels return to baseline) to prevent infection [52].

Concerns about complications of tuberculosis have led to suggestions to screen for latent illness, and positive testing should preclude the use of alemtuzumab or teriflunomide [52, 55]. Even with reports that the BCG vaccine showed efficacy in reducing MRI activity in MS [44, 45], the idea of vaccinating against tuberculosis in MS patients would be a novel and unproven safety measure to avoid complication of infection—particularly in light of the fact that the BCG vaccine is a live attenuated vaccine with controversial efficacy in preventing TB.

Natalizumab-associated progressive multifocal leukoencephalopathy (PML) is the most publicized and discussed infectious complication associated with DMTs in MS [6•, 56]. While we may hope for a vaccine in the future, preventative strategies focus on monitoring for PML risk factors and consideration of discontinuing therapy in high-risk patients [56].

We add screening for human immune deficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) prior to the use of alemtuzumab, noting the medication can effectively suppress immune responses and this is another infection without vaccination strategy to date. The long-term effects of the drug on immunity raises concern about screening measures just as it does about the safety of using live vaccines or the efficacy of vaccinating when appropriate immune responses may be altered.

Questions about boosters or new immunizations for tetanus and diphtheria, whooping cough, influenza, and pneumonia vaccines are also worth consideration in the MS population as patients already on therapy may consider these preventative health measures. Additional queries

Table 2 Current vaccination recommendations and safety for MS patients

Vaccine	Type	Recommendation in general population	Safety in MS
Injectable influenza	Inactivated	All individual 6 months and older	Considered safe in MS
Flu-mist	Live attenuated		Not recommended in MS. Live attenuated vaccines should be avoided in patients on immunosuppressants.
Hepatitis B	Inactivated	All children, adolescents, and at-risk adults.	Considered safe in MS
HPV	Inactivated	Boys and girls 11 years and older, also recommended for unvaccinated immunocompromised patients	Probably safe in MS
Tetanus	Inactivated	All children (in combination with diphtheria and pertussis). Booster dose recommended every 10 years	Considered safe in MS. Evidence also suggest the possibility of reduced relapses.
MMR	Live attenuated	All children and at-risk adults	Probably safe in MS. Live attenuated vaccines should be avoided in patients on immunosuppressants.
Yellow fever	Live attenuated	Travelers to endemic areas	Concern over safety in MS. Live attenuated vaccines should be avoided in patients on immunosuppressants.
Varicella	Live attenuated	Patients without exposure, given in two doses	Probably safe in MS. Live attenuated vaccines should be avoided in patients on immunosuppressants. Vaccination required before treatment with certain DMTs: including fingolimod and alemtuzumab.
Zoster	Live attenuated	Older adults to protect against shingles may be given in single dose for those aged 60 and older	
Bacille Calmette-Guerin (BCG)	Live attenuated	Used in some high risk countries	Probably safe in MS. Potentially reduces MRI activity in MS
Rabies	Inactivated	Post exposure prophylaxis (with immunoglobulin) and to individuals at high risk for exposure.	Probably safe in MS (very few studies done). Benefit likely outweighs any risk.
Polio vaccine	Inactivated (live-attenuated oral vaccine used in some countries)	All children.	Probably safe in MS

about vaccinations for particular patient populations that may have MS—such as immunizing against hepatitis for healthcare workers with the disease, taking preventative shots for those traveling to areas with illnesses not typically encountered like Yellow Fever, or even providing standard pediatric vaccinations in younger patients already on treatment for multiple sclerosis (not to exclude such newer issues such as vaccinating for HPV)—can all be viewed in light of the above recommendations.

Conclusion

Suggestions about how or when to utilize immunizations in MS parallel the general population with highlighted concerns (Table 2). Efficacy is one part of the equation, while risk associated with the practice of vaccinating is the other. Inactivated vaccines are generally considered safe while live ones may require further analysis of risk and benefit, especially for patients on immunosuppressive agents. Answering how long one should wait after a vaccination before starting a therapy is a valid question but not easy to answer, given that little data exists to guide practice. Conversely, how long after the discontinuation of an immunosuppressive therapy before a live vaccine can be used is difficult to know, but consideration of half-life of drug and/or recovery of immune effects may be worth consideration when there is a question. Lastly, measuring the efficacy of the vaccine in this patient population through antibody levels or other methods is worth considering.

Ongoing research may help to answer additional questions about the use of individual vaccines, but where there is lack of experience, we rely on theoretical or more generalized ideas about immunity in relationship to DMTs. Defining concerns based on drug or class, such as associating some degree of immune suppression with the newer DMTs, is one way to consider vaccination issues. We have outlined recommendations for most situations, but every case is different. Admittedly, a number of interesting questions about whether and how to utilize immunizations for otherwise unrelated illnesses in light of therapeutic use remain unanswered. When in doubt, further consideration of provided information or consultation with the manufacturer of the drug and/or vaccine may be helpful.

We highlighted some of the experience with infectious illness as a complication or potential risk of treatments, including recommendations to immunize for varicella prior to the use of a select few of our medications. We might hypothesize there will be similar guidelines with additional vaccinations and for emerging therapies in the future.

The use of vaccination in MS patients is a preventive health measure that we consider in a similar fashion to how we think of it for the general population, with noted caveats related to certain DMT use and vaccine types. The presumed benefit of vaccinating must outweigh any perceived risk in any population and each individual patient. With respect to vaccinations and consideration of DMT use, as a general rule, injectable therapies do not alter immune response and vaccines are thus considered relatively safe in patients taking them while live vaccines are typically recommended to be avoided when patients are on non-platform therapies.

Compliance with Ethics Guidelines

Conflict of Interest Salim Chahin declares no conflict of interest.

Eric M. L. Williamson has served on advisory boards for EMD Serono, Inc., and Teva Pharmaceutical Industries Ltd., with compensation in the past year.

Joseph R. Berger reports grants from PML Consortium, Biogen Idec, and Novartis. Dr. Berger has also received personal fees from Amgen, Astra-Zeneca, Bristol Myers Squibb, Eisai, Janssen, Millennium, Parexel, Pfizer, Roche, Takeda, Genentech, Genzyme, Incyte, Inhibikase, Johnson and Johnson, Novartis, the American Academy of Neurology, and the Consortium of MS Centers.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1.• Langer-Gould A, Albers KB, Van Den Eeden SK, Nelson LM. Autoimmune diseases prior to the diagnosis of multiple sclerosis: a population-based case-control study. Mult Scler. 2010;16(7):855–61. **Recent review of a large health system's records that failed to reveal any causal association between vaccination and multiple sclerosis or CNS demyelinating disease, further adding credence to 2011 Institute of Medicine Report**.
2. Dore-Duffy P, Donaldson JO, Rothman BL, Zurier RB. Antinuclear antibodies in multiple sclerosis. Arch Neurol. 1982;39(8):504–6.
3. Singh VK. Detection of antinuclear antibody in the serum of patients with multiple sclerosis. Immunol Lett. 1982;4(6):317–9.
4. Roussel V, Yi F, Jauberteau MO, Couderq C, Lacombe C, Michelet V, et al. Prevalence and clinical significance of anti-phospholipid antibodies in multiple sclerosis: a study of 89 patients. J Autoimmun. 2000;14(3):259–65.
5. Mourik J, The TH, Nater JP, Minderhoud JM. Cell-mediated immune reactivity in multiple sclerosis. Neurology. 1981;31(8):1036–8.
6.• Williamson EM, Berger JR. Infection risk in patients on multiple sclerosis therapeutics. CNS Drugs. 2015;29(3):229–44. **Comprehensive review of infections encountered in multiple sclerosis to date, including understanding of how infection may worsen the disease**.
7. Rutschmann OT, McCrory DC, Matchar DB, Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines. Immunization and MS: a summary of published evidence and recommendations. Neurology. 2002;59(12):1837–43.
8. Correale J, Fiol M, Gilmore W. The risk of relapses in multiple sclerosis during systemic infections. Neurology. 2006;67(4):652–9.
9. Buljevac D, Flach HZ, Hop WC, Hijdra D, Laman JD, Savelkoul HF, et al. Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain. 2002;125(Pt 5):952–60.
10.• Loebermann M, Winkelmann A, Hartung HP, Hengel H, Reisinger EC, Zettl UK. Vaccination against infection in patients with multiple sclerosis. Nat Rev Neurol. 2011;8(3):143–51. **Another review of vaccinations use in MS, highlights the concern of using live vaccines in concert with immune suppressing agents**.
11. Sutton I, Lahoria R, Tan I, Clouston P, Barnett M. CNS demyelination and quadrivalent HPV vaccination. Mult Scler. 2009;15(1):116–9.
12. Pellegrino P, Carnovale C, Pozzi M, Antoniazzi S, Perrone V, Salvati D, et al. On the relationship between human papilloma virus vaccine and autoimmune diseases. Autoimmun Rev. 2014;13(7):736–41.
13. Farez MF, Correale J. Yellow fever vaccination and increased relapse rate in travelers with multiple sclerosis. Arch Neurol. 2011;68(10):1267–71.
14. Medicine). IIo. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press; 2012.
15. Langer-Gould A, Qian L, Tartof SY, Brara SM, Jacobsen SJ, Beaber BE, et al. Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating diseases. JAMA Neurol. 2014;71(12):1506–13.
16. Confavreux C, Suissa S, Saddier P, Bourdes V, Vukusic S, Vaccines in Multiple Sclerosis Study Group. Vaccinations and the risk of relapse in multiple sclerosis. N Engl J Med. 2001;344(5):319–26.
17. De Keyser J. Safety of tetanus vaccination in relapsing-remitting multiple sclerosis. Infection. 1998;26(5):319.
18. Hernan MA, Alonso A, Hernandez-Diaz S. Tetanus vaccination and risk of multiple sclerosis: a systematic review. Neurology. 2006;67(2):212–5.
19. Society NMS. Living Well With MS. Available from: http://www.nationalmssociety.org/Living-Well-With-MS.
20.• Pellegrino P, Carnovale C, Perrone V, Pozzi M, Antoniazzi S, Radice S, et al. Efficacy of vaccination against influenza in patients with multiple sclerosis: the role of concomitant therapies. Vaccine. 2014;32(37):4730–5. **Excellent discussion of the flu vaccine and illustration of the rationale for administering influenza vaccine in patients with MS**.
21. De Keyser J, Zwanikken C, Boon M. Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. J Neurol Sci. 1998;159(1):51–3.
22. Salvetti M, Pisani A, Bastianello S, Millefiorini E, Buttinelli C, Pozzilli C. Clinical and MRI assessment of disease activity in patients with multiple sclerosis after influenza vaccination. J Neurol. 1995;242(3):143–6.
23. Michielsens B, Wilms G, Marchal G, Carton H. Serial magnetic resonance imaging studies with paramagnetic contrast medium: assessment of disease activity in patients with multiple sclerosis before and after influenza vaccination. Eur Neurol. 1990;30(5):258–9.
24. Miller AE, Morgante LA, Buchwald LY, Nutile SM, Coyle PK, Krupp LB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. Neurology. 1997;48(2):312–4.
25. Michiels B, Govaerts F, Remmen R, Vermeire E, Coenen S. A systematic review of the evidence on the effectiveness and risks

of inactivated influenza vaccines in different target groups. Vaccine. 2011;29(49):9159–70.
26. Olberg HK, Cox RJ, Nostbakken JK, Aarseth JH, Vedeler CA, Myhr K-M. Immunotherapies influence the influenza vaccination response in multiple sclerosis patients: an explorative study. Multiple Sclerosis J. 2014;20(8):1074–80.
27. Mehling M, Fritz S, Hafner P, Eichin D, Yonekawa T, Klimkait T, et al. Preserved antigen-specific immune response in patients with multiple sclerosis responding to IFNβ-therapy. PLoS ONE. 2013;8(11), e78532.
28. Schwid SR, Decker MD, Lopez-Bresnahan M, Rebif-Influenza Vaccine Study Investigators. Immune response to influenza vaccine is maintained in patients with multiple sclerosis receiving interferon beta-1a. Neurology. 2005;65(12):1964–6.
29. Vågberg M, Kumlin U, Svenningsson A. Humoral immune response to influenza vaccine in natalizumab-treated MS patients. Neurol Res. 2012;34(7):730–3.
30. Mehling M, Hilbert P, Fritz S, Durovic B, Eichin D, Gasser O, et al. Antigen-specific adaptive immune responses in fingolimod-treated multiple sclerosis patients. Ann Neurol. 2011;69(2):408–13.
31. Boulton C, Meiser K, David OJ, Schmouder R. Pharmacodynamic effects of steady-state fingolimod on antibody response in healthy volunteers: a 4-week, randomized, placebo-controlled, parallel-group, multiple-dose study. Int J Clin Pharmacol. 2012;52(12):1879–90.
32. Kappos L, Mehling M, Arroyo R, Izquierdo G, Selmaj K, Curovic-Perisic V, et al. Randomized trial of vaccination in fingolimod-treated patients with multiple sclerosis. Neurology. 2015;84(9):872–9.
33. Bar-Or A, Freedman MS, Kremenchutzky M, Menguy-Vacheron F, Bauer D, Jodl S, et al. Teriflunomide effect on immune response to influenza vaccine in patients with multiple sclerosis. Neurology. 2013;81(6):552–8.
34. Mormile R. Hepatitis B, virus (HBV) infection and multiple sclerosis: one more reason to undergo vaccination? Immunol Lett. 2015;165(1):60–1.
35. Martínez-Sernández V, Figueiras A. Central nervous system demyelinating diseases and recombinant hepatitis B vaccination: a critical systematic review of scientific production. J Neurol. 2013;260(8):1951–9.
36. Grimaldi-Bensouda L, Guillemot D, Godeau B, Bénichou J, Lebrun-Frenay C, Papeix C, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med. 2014;275(4):398–408.
37. Scheller N, Svanström H, Pasternak B, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA. 2015;313(1):54–61.
38. DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. Arch Neurol. 2003;60(4):504–9.
39. Kaufman M, Pardo G, Rossman H, Sweetser MT, Forrestal F, Duda P. Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis. J Neurol Sci. 2014;341(1–2):22–7.
40. McCarthy CL, Tuohy O, Compston DA, Kumararatne DS, Coles AJ, Jones JL. Immune competence after alemtuzumab treatment of multiple sclerosis. Neurology. 2013;81(10):872–6.
41. Ahlgren C, Odén A, Torén K, Andersen O. Multiple sclerosis incidence in the era of measles-mumps-rubella mass vaccinations. Acta Neurol Scand. 2009;119(5):313–20.
42. Ross RT, Nicolle LE, Cheang M. The varicella zoster virus: a pilot trial of a potential therapeutic agent in multiple sclerosis. J Clin Epidemiol. 1997;50(1):63–8.
43. Farez MF, Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. J Neurol. 2011;258(7):1197–206.
44. Ristori G, Buzzi MG, Sabatini U, Giugni E, Bastianello S, Viselli F, et al. Use of Bacille Calmette-Guerin (BCG) in multiple sclerosis. Neurology. 1999;53(7):1588–9.
45. Ristori G, Romano S, Cannoni S, Visconti A, Tinelli E, Mendozzi L, et al. Effects of Bacille Calmette-Guerin after the first demyelinating event in the CNS. Neurology. 2014;82(1):41–8.
46. Bar-Or A, Wiendl H, Miller B, Benamor M, Truffinet P, Church M, et al. Randomized study of teriflunomide effects on immune responses to neoantigen and recall antigens. Neurol Neurophysiol Neurosci. 2015;2(2), e70.
47. Fragoso YD, Brooks JB, Gomes S, de Oliveira FT, da Gama PD. Report of three cases of herpes zoster during treatment with natalizumab. CNS Neurosci Ther. 2013;19(4):280–1.
48. Bourdette D, Gilden D. Fingolimod and multiple sclerosis: four cautionary tales. Neurology. 2012;79(19):1942–3.
49. Bourre B, Lefaucheur R, Ahtoy P, Travers F, Fetter D. Varicella zoster virus acute myelitis in a patient with MS treated with natalizumab. Neurology. 2013;81(22):1966–7.
50. Yeung J, Cauquil C, Saliou G, Nasser G, Rostomashvili S, Adams D, et al. Varicella zoster virus acute myelitis in a patient with MS treated with natalizumab. Neurology. 2013;80(19):1812–3.
51. Novartis. Gilenya [package insert]. Stein SDbNPCEH, New Jersey. Revised August 2015.
52. Genzyme. Lemtrada [package insert]. Cambridge MG, 2015.
53. Merck. Varivax PI. Merck.
54. Berger JR. Varicella vaccination after fingolimod: a case report. Mult Scler Relat Disord. 2013;2(4):391–4.
55. Genzyme. Aubagio prescribing information. Cambridge MG, 2015.
56. Chahin S, Berger JR. A risk classification for immunosuppressive treatment-associated progressive multifocal leukoencephalopathy. J Neurovirol. 2014.