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REVIEW

Vaccine Considerations for Multiple Sclerosis in the COVID-19 Era

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ABSTRACT

People with multiple sclerosis (MS) are at risk for infections that can result in amplification of baseline symptoms and possibly trigger clinical relapses. Vaccination can prevent infection through the activation of humoral and cellular immune responses. This is particularly pertinent in the era of emerging novel vaccines against severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019 (COVID-19). MS disease-modifying therapies (DMTs), which affect the immune system, may impact immune responses to COVID-19 vaccines in people with MS. The objective of this article is to provide information on immune system responses to vaccinations and review previous studies of vaccine responses in people with MS to support the safety and importance of receiving currently available and emerging COVID-19 vaccines. Immunological studies have shown that coordinated interactions between T and B lymphocytes of the adaptive immune system are key to successful generation of immunological memory and production of neutralizing antibodies following recognition of vaccine antigens by innate immune cells. $CD4^+$ T cells are essential to facilitate $CD8^+$ T cell and B cell activation, while B cells drive and sustain T cell memory. Data suggest that some classes of DMT, including type 1 interferons and glatiramer acetate, may not significantly impair the response to vaccination. DMTs—such as sphingosine-1-phosphate receptor modulators, which sequester lymphocytes from circulation; alemtuzumab; and anti-CD20 therapies, which rely on depleting populations of immune cells—have been shown to attenuate responses to conventional vaccines. Currently, three COVID-19 vaccines have been granted emergency use authorization in the USA on the basis of promising interim findings of ongoing trials. Because analyses of these vaccines in people with MS are not available, decisions regarding COVID-19 vaccination and DMT choice should be informed by data and expert consensus, and personalized with considerations for disease burden, risk of infection, and other factors.

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Key Summary Points

People with multiple sclerosis (MS) may be at increased risk for infection, which can lead to relapses or pseudo-relapses.

Vaccines are an important health measure to prevent infections and require activation of humoral and cellular immune responses.

Some disease-modifying therapies (DMTs) for MS—including sphingosine-1-phosphate receptor modulators, which sequester lymphocytes from circulation; alemtuzumab (anti-CD52); anti-CD20 therapies; and cladribine (impairs DNA synthesis)—exert effects on humoral and cellular immune activity that may affect the response to available and emerging coronavirus disease 2019 (COVID-19) vaccines.

Coordinated interactions between T and B lymphocytes of the adaptive immune system are integral to the successful generation of immunological memory and the production of neutralizing antibodies.

Risks versus benefits of timing vaccinations to ensure maximum vaccine efficacy, as outlined in vaccination guidance and guidelines developed by national and international MS groups, should be considered in the decision to receive a COVID-19 vaccine—even if efficacy may be compromised—when disease burden is high.

DIGITAL FEATURES

This article is published with digital features, including an educational video, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14459775.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, demyelinating, neurodegenerative disease of the central nervous system that causes significant and irreversible neurological disability [1, 2]. An estimated 2.8 million people are living with MS worldwide, including almost 1 million people in the USA; global prevalence in 2020 was 35.9 per 100,000 persons and is expected to rise [3, 4]. Although the etiology of MS is unknown, a number of environmental, genetic, and epigenetic factors are believed to contribute to immunopathogenesis of MS [5].

People with MS are at increased risk for acquiring certain types of infections, including respiratory and other viral and bacterial infections [6–8]. Additionally, certain disease-modifying therapies (DMTs), which suppress or alter the immune system, have been associated with increased risk of upper respiratory tract infections, urinary tract infections, and other infections [9]. This is relevant for people with MS because bacterial and viral infections have been shown to be associated with new or worsening baseline MS symptoms in the form of relapses or pseudo-relapses [10]. Upper respiratory tract infections can double the risk for relapse [11]. Furthermore, increased rates of influenza in the general population are temporally associated with a greater occurrence of relapses in people with MS [12]. It is speculated that relapses associated with an infection can be more neurologically damaging than those unrelated to infection [13]. Therefore, measures to prevent infection are particularly important for people with MS.

Over the years, there have been numerous iterations of consensus statements regarding the risks and benefits of vaccination in people with MS [14–20]. National and international guidance and guidelines generally agree that the benefits of vaccination outweigh any potential risks. The only exception is with live attenuated vaccines, which should not be used in people

who are currently receiving or have recently discontinued immunosuppressive or immunomodulating DMTs, unless the risk of infection is elevated and nonlive vaccines are not available. The reason for this is that a live virus or bacteria has the potential to cause an infection and if the vaccine is administered during treatment with a MS DMT, the ability of the immune response to clear the infection could be impaired, which could possibly result in worsening of MS symptoms. Some DMTs exert effects on humoral and cellular immune activity that may affect the response to vaccination [21, 22].

Data on the efficacy of vaccinations in people with MS receiving immunosuppressive or immunomodulatory DMTs are still lacking, leading to a great deal of variability at the local, national, and international level with regard to vaccine guidance and guidelines [15–17, 19]. A better understanding of how DMTs for MS may influence vaccine safety and efficacy has become even more urgent given the current coronavirus disease 2019 (COVID-19) pandemic and recent authorization of vaccines specific for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19.

The incidence of COVID-19 in people with MS ranges from below 1% to 11% (including suspected but not confirmed cases) in studies that included a cross-sectional mixed method study, retrospective cohort analysis, and a prospective observational cohort study compared with World Health Organization (WHO) estimates of 1432 per 100,000 globally, and 8424 per 100,000 in the USA in the general population [23–26]. COVID-19-related MS mortality has been reported to be approximately 1–4% overall (compared with a case–fatality ratio in the general population of 0.0–9.2% in the 20 countries most affected by COVID-19, including the USA, which has a rate of 1.8% [according to Johns Hopkins University]), and more than 50% of deaths have occurred in people not receiving MS DMTs [27–29]. An analysis of data in people with MS from 28 countries who had suspected or confirmed COVID-19 found that treatment with ocrelizumab or rituximab was associated with significantly increased risk of hospitalization and admission to the intensive care unit compared with other pooled DMTs (including alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon, natalizumab, and teriflunomide) [30]. Rituximab was also associated with significantly increased risk of artificial ventilation [30]. In a recent retrospective study from electronic health records, interferons and glatiramer acetate were shown to be associated with reduced COVID-19 risk, whereas anti-CD20 therapies were associated with increased risk, within the treated MS cohort [31]. In contrast, an analysis of COViMS registry data from 1626 patients with MS found that poorer clinical COVID-19 outcomes (including mortality) were associated with older patient age and greater disability whereas use of rituximab was associated with increased risk of hospitalization [32]. These findings suggest that the use of these anti-CD20 agents could be a risk factor for more severe infection.

Up to 98% of neurologists surveyed were concerned about their patients with MS contracting COVID-19, and 80% thought that certain DMTs would not permit a protective response to a COVID-19 vaccine [33]. Clinicians were most concerned about vaccine response and concomitant treatment with ocrelizumab (84%), rituximab (83%), and alemtuzumab (78%) [33], suggesting that prolonged T and B cell depletion is an important consideration. However, there may be an optimal timing of vaccination with some DMTs in order to achieve the best vaccine immune response.

This review will discuss the immune system, immunological effects of vaccination, existing data on the effects of DMTs on vaccination efficacy, and vaccine considerations in people with MS as they relate to currently available and emerging COVID-19 vaccines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Table 1 Types of vaccines

Vaccine type	MOA/effect	Examples
Major types [47]		
Live attenuated [40, 48]	Weakened version of the pathogen Cause $CD8^+$ cytotoxic T cell generation and recruitment of antigen-specific $CD4^+$ T helper cells (i.e., a T-dependent antibody response) Confer immunity that lasts for decades Generally contraindicated in those with weakened immune systems	Smallpox Yellow fever Measles Chicken pox Oral polio vaccine
Inactivated whole cell [36, 48, 49]	More stable and safer than live vaccines, as dead microbe cannot mutate back to its virulent form Often poorly immunogenic and require additives or adjuvants, such as aluminum salts, oil-in-water emulsions, and saponins to help stimulate antibody and effector T cell immune functions Protection may be of shorter duration; booster vaccinations may be required	Inactivated polio Whole cell polio
Subunit (purified antigen) [40, 47–51]	Include protein-based, polysaccharide, and conjugate types Often poorly immunogenic and require additives or adjuvants, such as aluminum salts, oil-in-water emulsions, and saponins to help stimulate antibody and effector T cell immune functions Can contain up to 20 antigenic determinants, i.e., epitopes of the antigen that are recognized by antibodies and T cells Reversion to a virulent form cannot occur Determination of antigen combinations must be made to elicit effective immune response	Acellular pertussis (aP) *Haemophilus influenzae* type b (Hib) Pneumococcal (PCV-7, PCV-10, PCV-13) Hepatitis B (HepB) COVID-19

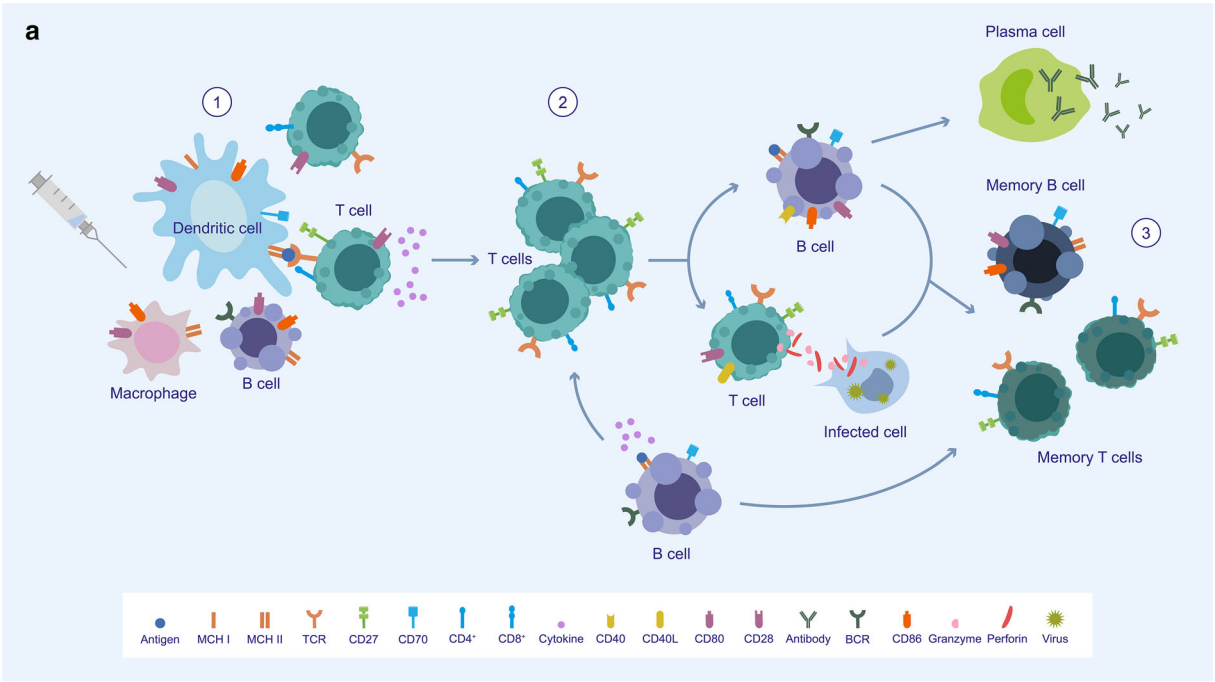
Table 1 continued

Vaccine type	MOA/effect	Examples
Toxoid (inactivated toxins) [40, 48, 49]	Contain inactivated toxins	Diphtheria
	Often poorly immunogenic and require additives or adjuvants, such as aluminum salts, oil-in-water emulsions, and saponins to help stimulate antibody and effector T cell immune functions	Tetanus
	Administration induces high-affinity antitoxoid antibodies, which bind and neutralize the toxin and develop an immune memory for the toxin	
	Used in diseases in which the toxin causes illness	
Others		
Nucleic acid [52, 53]	Consist of mRNA or plasmid DNA that codes for the antigen of interest, mimicking a live infection by causing the person immunized to produce the antigen, thereby priming both B cell and T cell responses	In development for a number of infectious diseases and for cancer, where preclinical and human studies have demonstrated encouraging results [54]
		COVID-19
Replication-deficient/defective viral vectors [55–59]	Mutant viruses that lack the functions needed for viral genome replication and assembly of progeny viruses within host cells	HIV
		Malaria
	Antigen of interest is integrated into the replication-incompetent virus	Chronic viral infections
		Cancer
	Have the potential to induce a strong T cell response	COVID-19
Recombinant [60–62]	Based on an engineered viral genome comprising genes for RNA replication machinery	Rabies (oral vaccine for wildlife)
		Shingles
	Vectors are able to direct self-replication and, once introduced into a host cell as a viral particle, cause production of antigens as would viral pathogens, triggering both B cell and T cell responses	

MOA mechanism of action, *mRNA* messenger RNA

THE IMMUNE SYSTEM

The immune system is composed of two arms: the innate system and the adaptive or acquired system. It is the complex interplay between these two arms that comprises the normal immunological response to foreign antigens. The innate immune system is the first line of defense against infection; it plays a crucial role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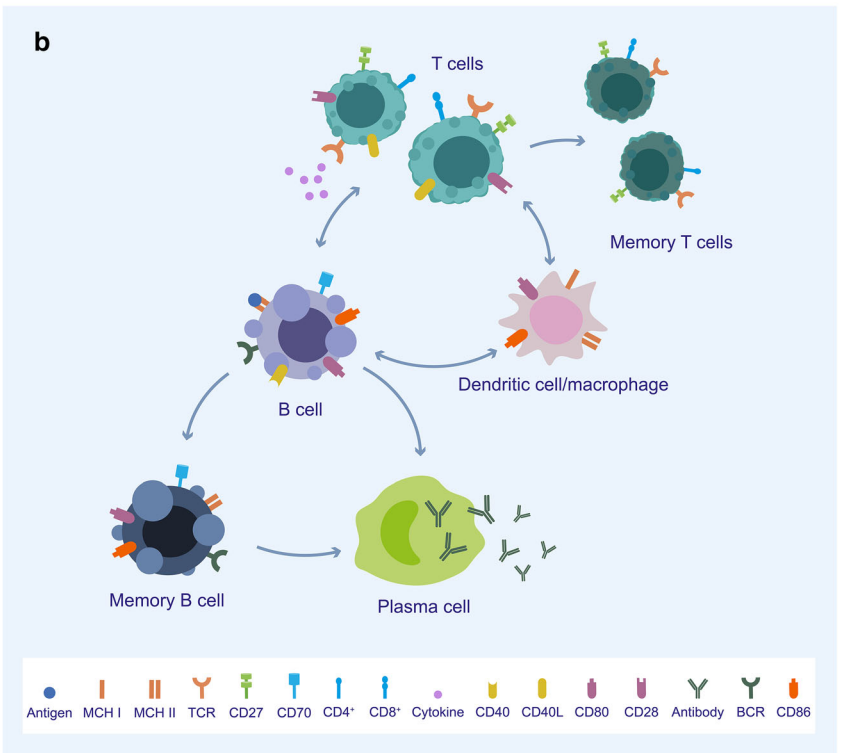
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CD8+
Cytokine
CD40
CD40L
CD80
CD28
Antibody
BCR
CD86

◀ **Fig. 1** Immune response to vaccination. **a** Occurs in multiple steps: (1) An APC (e.g., dendritic cells, macrophage, or B cell) recognizes vaccine antigen, resulting in local inflammation; and internalizes, processes, and presents antigen to $CD4^+$ T cell in MHC class II. (2) Antigen-specific T cell becomes activated, differentiates, and secretes cytokines to support B cell activation. B cells become activated via interaction with T cells (contact-dependent or contact-independent [involving cytokines]) and differentiate into plasma cell/plasma blast, which produces neutralizing antibodies that can prevent future infection. T ($CD4^+$ and $CD8^+$) and B cells proliferate, but dendritic cells become limited to support continued differentiation. B cells take over to help continued differentiation and proliferation of T cells by providing late co-stimulatory signals and secretion of cytokines/survival signals that enhance T cell memory formation. (3) Optimal immune memory results (i.e., more memory $CD8^+$ T cells, better survival, and enhanced cytotoxicity). Approximately 10% of activated B and T cells become memory cells to help prevent disease in the future. Without B cells, suboptimal memory results (fewer cells, poor survival, and decreased cytotoxicity in cells that remain). **b** B and T cell interactions are bidirectional and form an integral part of the immune response to vaccination. APC antigen-presenting cell, MHC major histocompatibility complex

in the initial recognition of pathogens and in the activation of the cells of the adaptive immune system. Cells that are involved in innate immune responses include monocytes/macrophages, dendritic cells, mast cells, neutrophils, eosinophils, natural killer cells, and natural killer T cells [34]. These cells express receptors such as pattern recognition receptors, which are not specific to any particular pathogen and allow the cells to react to microbes containing common molecular structures, and pathogen-associated molecular patterns, including liposaccharides, other bacterial cell wall components, and virus-derived double-stranded RNA [35]. Innate immune responses occur more rapidly than adaptive immune responses and are generated within minutes to hours of infection [36]. However, subsequent encounters with the same pathogen will not elicit a faster or stronger response (i.e., no innate immunological memory is created) [36].

The Adaptive Immune System

The adaptive immune system is activated 4–7 days after exposure to a pathogen [37] in response to interactions between antigens, antigen receptor-bearing lymphocytes (T cells), and antigen-presenting cells (APCs); the latter-most can be specific cells of the innate immune system or B cells (Fig. 1) [37, 38]. The coordinated interactions between T and B lymphocytes of the adaptive immune system are integral to the immune system's response when called into action by the innate immune cells [39]. Both T and B cells express unique antigen-binding receptors on their cell membranes [35]. Each cell expresses a single type of receptor and has the ability to rapidly proliferate and differentiate when activated.

Cellular Response

T cells mediate the cellular immune response [40–42]. They are activated by APCs that have digested an antigen and are displaying a peptide from the antigen on their membrane (bound by major histocompatibility complex molecules) [35]. Specific subtypes of T cell are produced and have differentiated functions, including $CD8^+$ (cytotoxic T cells), $CD4^+$ (helper T cells), and follicular T helper cells, among others [40]. $CD8^+$ T cells reduce, control, and eliminate intracellular pathogens by directly (via release of perforin, granzyme, etc.) or indirectly (via antimicrobial cytokine release) killing infected cells [40]. $CD4^+$ T cells are involved in the reduction, control, and clearance of extracellular and intracellular pathogens. This occurs through the release of cytokines that support the activation and differentiation of B cells, $CD8^+$ T cells, and macrophages, contributing to defense against bacteria and viruses on mucosal surfaces [40]. Subsets of $CD4^+$ T cells include T helper 1, 2, 9, and 17 cells; regulatory T cells; and, as mentioned previously, follicular T helper cells [43], which provide an intricate and highly specific response to the pathogen.

Humoral Response

The cellular immunity that is achieved by the differentiation and production of antigen-specific T cell populations is important, but it is only one part of the adaptive immune response. The other part is humoral immunity, which is composed of B cells, the complement system, and antibodies [38, 40, 44].

B cells are activated by cytokines released by T helper cells (e.g., interleukin [IL]-4, IL-5, IL-5, IL-13) and upon activation differentiate into plasma cells, which produce antibodies [37, 40, 45]. B cells can also recognize antigens directly, without the involvement of APCs of the innate immune system [35]. Antibodies stop or reduce infections via clearance of extracellular pathogens through binding to the enzymatic active sites of toxins or preventing their diffusion, by neutralizing viral cell entry, promoting phagocytosis of extracellular bacteria, and activating the complement cascade [40]. Additionally, B cells play a role in the further activation of T cells and are involved in both antigen presentation to T cells and the generation of immunological memory [46]. Immunological memory is the capability of the immune system to respond more quickly and effectively to pathogens encountered earlier, and is based on persistent populations of clonally expanded, specialized memory T and B cells [37]. Complement factors opsonize antigens, which can then stimulate the complement receptor 2 expressed on B cells and lower the threshold for producing neutralizing antibodies [44].

Vaccine-Related Immune Response

Vaccines exert their effects through the immune system and rely on both the innate and adaptive arms interacting in a complex and complementary fashion with the goal of generating immunological memory [35]. A variety of vaccine types exist, as shown in Table 1, and they elicit varying degrees of long-term immunological response.

In response to vaccination, the innate, humoral (B cell mediated), and cellular (T cell mediated) immune pathways are activated through multiple steps (Fig. 1) [42, 45]. Initially, inflammation occurs at the site of administration, which can be intramuscular, subcutaneous, oral, or pulmonary/nasal, and is followed by activation of the innate system [45, 63]. The site of administration can affect the immune response [64]. For example, immunization via parenteral administration can fail to induce mucosal immunity [63], while pulmonary/nasal administration of experimental nanoparticle vaccination has resulted in high-frequency, long-lasting, antigen-specific effector memory T cell response at mucosal sites and increased antigen transport [65].

Following vaccine administration, the delivery of vaccine antigens by APCs to activate and recruit $CD4^+$ T cells results in T and B cell interaction and the first step of the antibody response: B cell proliferation, maturation, and differentiation into plasma cells [40, 45]. However, the resulting antibodies have low affinity for the antigen, and the response is short-lived. This is followed by the effector phase of the response, which involves the production of higher-affinity antibodies by B cells, differentiation and proliferation of effector T cells [40], and generation of immunological memory, allowing a more rapid and efficient response when the target pathogen is encountered at a later time [37]. B cells are then involved in modulating the contraction of $CD8^+$ T cell responses following immunization and in generating memory T cells [46]. Follicular T helper cells are integral to B cell activation or differentiation into memory and plasma cells and in the generation of long-lived antibody responses [66]. The role of follicular T helper cells in the response to vaccination is especially important in the context of therapies for MS that alter or deplete certain immune cell populations. If the follicular T helper cell response is suppressed, complete seroprotection is unlikely to be achieved with a vaccine or even repeated vaccination. Nevertheless, partial seroprotection could still be enough to prevent contracting the infection of interest and/or preventing severe complications from the infection.

The US Centers for Disease Control and Prevention frequently updates the recommendations for adults receiving routine

vaccinations to prevent 17 vaccine-preventable diseases [67]. Recommendations are made on the basis of the effectiveness of the vaccines, which is assessed by humoral response (i.e., the presence of antigen-specific antibody titers) [68]. The hemagglutination inhibition assay, which measures the presence of antibodies to hemagglutinins (which are glycoproteins on the surface of influenza viruses), is one way to measure influenza vaccine response [68, 69]. Typical outcomes seen in clinical trials for vaccines include assessment of antibody titers, seroconversion rates, seroprotection rates (percentages of people developing neutralizing antibodies), functional antibodies (by flow cytometric opsonophagocytosis assays), antibody avidity, B cell and T cell activation, lymphoproliferation, and cytokine responses [70].

However, systems for measuring cellular responses to vaccination are not typically utilized in clinical trials or clinical practice for a number of reasons, including the complexity and cost associated with such assays. For example, US Food and Drug Administration guidelines for influenza vaccine development rely on hemagglutination-inhibiting (HI) antibody titers, i.e., percentage of subjects achieving an HI antibody titer of at least 1:40 and rates of seroconversion (change in titer from less than 1:10 to at least 1:40 or fourfold rise in HI antibody titer) [71]. T cells have been demonstrated to play a role in the immune response to SARS-CoV-2 [72, 73], but such responses are difficult to measure, which has prevented a full understanding of the role of T cells in an effective vaccine response against SARS-CoV-2. Because these data on cellular responses to vaccination are limited, the extent to which any one individual or group of individuals responds to vaccination is difficult to ascertain. In the future, systems biology may be used to analyze early human immune responses to vaccination. Using such approaches, individuals who have been vaccinated may display noticeable and characteristic changes in the gene expression profiles of their peripheral blood leukocytes, allowing for an understanding of the immune response beyond just antibody titers [74].

As treatment of MS evolves toward a personalized approach, immune correlates and how vaccine response is measured—including not only humoral immune responses but also cellular immune responses—may help determine the true differential impact of MS DMTs on vaccine immune response. Moreover, the management of MS may prove to be an incremental burden revolving around treatment choices and timing, if a yearly COVID-19 vaccine or booster becomes necessary.

Individuals may experience diminished protection from vaccines for various reasons. For example, inadequate responses have been reported in people aged over 64 years [75], which may result from immunosenescence stemming from thymic involution, a decrease in naïve T cells, increased T cell memory defects, and impaired ability of B cells to undergo class-switch recombination (i.e., isotype switching), resulting in less diversity of antibodies and decreases in naïve B cells [76]. Other factors that may affect response include sex, obesity, behavior, comorbidities, pregnancy, immunosuppression, and possibly ethnicity [70, 77, 78]. All of these considerations will apply to people with MS as well, and may impact vaccine responsiveness in this population.

GUIDANCE AND GUIDELINES ON VACCINES FROM MS-RELATED SOCIETIES AND ORGANIZATIONS

A number of organizations have made recommendations regarding vaccination for people with MS (Table 2) and, importantly, most point to the lack of high-quality data that can support recommendations [16–18]. The only recommendation by the American Academy of Neurology (AAN) based on the strongest level of evidence (level A) is to screen for certain infections, according to the prescribing information of the particular immunosuppressive or immunomodulating DMT being considered as treatment, and for latent infections in high-risk populations or in countries where specific infections are common [16].

A Delphi consensus statement from a panel of experts and the French Multiple Sclerosis Society (Société Francophone de la Sclérose en

Table 2 Vaccine guidance and guidelines for people with MS

Guidance/guideline	AAN [16, 79]	MSIF [19][a]	NMSS [14, 15, 80][b]	MSAA [20][b]	SFSEP [17, 81][c]	ABN [82][d]
Live attenuated and killed vaccines						
Infection screening	✔	No guidance	✔	✔	No guidance	No guidance
Discuss available information and patients' opinions to determine optimal strategy	✔	No guidance	✔	✔	No guidance	No guidance
Follow all local vaccine standards[e]	✔	No guidance	✔	✔	✔	No guidance
Influenza vaccination should be received annually[e]	✔	✔	✔	✔	✔	No guidance
Patients should be counseled about infection risks associated with ISIM therapy and ISIM-specific vaccination guidance	✔	No guidance	✔	✔	✔	No guidance
Vaccination status should be assessed before prescribing ISIM therapy	✔	No guidance	✔	✔	✔	No guidance
Vaccination should occur ≥ 4–6 weeks before ISIM therapy initiation[f]	✔	No guidance	✔	✔	No guidance	No guidance
Live attenuated vaccines should be avoided while on ISIM therapy or if recently discontinued; if a patient is at high risk of infection and killed vaccines are unavailable, live attenuated vaccines may be considered	✔	No guidance	✔	✔	✔	No guidance
Vaccination during MS relapse should be delayed	✔	No guidance	✔	✔	✔[g]	No guidance
COVID-19 mRNA vaccines[h]						
Discuss available information and patients' opinions to determine optimal strategy	No guidance	✔	✔[i]	No guidance	No guidance	✔[d]
Most people with MS should be vaccinated; vaccination unlikely to trigger MS relapse or worsen chronic symptoms	No guidance	✔	✔	No guidance	No guidance	✔[d]
Vaccination can occur while on ISIM therapy	No guidance	✔	✔[h]	No guidance	✔	✔[d]

Table 2 continued

Guidance/guideline	AAN [16, 79]	MSIF [19][a]	NMSS [14, 15, 80][b]	MSAA [20][b]	SFSEP [17, 81][c]	ABN [82][d]
Both doses of vaccine should be taken, even if side effects temporarily exacerbate MS symptoms	No guidance	✔	✔	No guidance	No guidance	✔[d]
Data to support evidence-based recommendations on the implications of vaccination for specific neurologic diseases are not yet available	✔	✔	✔	No guidance	✔	✔[d]

AAN American Academy of Neurology, *ABN* Association of British Neurologists, *ISIM* immunosuppressive or immunomodulating, *MS* multiple sclerosis, *MSIF* Multiple Sclerosis International Federation, *NMSS* National Multiple Sclerosis Society, Multiple Sclerosis Association of America, *S1P* sphingosine-1-phosphate, *SFSEP* Société Francophone de la Sclérose En Plaques (French Multiple Sclerosis Society)

[a] COVID-19 mRNA vaccine guidance relates to Pfizer-BioNTech and Moderna

[b] Refers to AAN guidelines on live attenuated and killed vaccines

[c] Guidance is associated with immunosuppressive therapy, but no restrictions on vaccination associated with immunomodulators are indicated

[d] Recommendations are not specific for MS

[e] Unless there is a specific contraindication

[f] According to local regulatory standards, guided by treatment-specific infectious risks, and as advised by specific prescribing information

[g] If relapse treatment requires high-dose steroid therapy

[h] Information current as of February 11, 2021

[i] NMSS guidance on timing of medications [80]: S1P receptor modulators: consider getting fully vaccinated (defined as 2 doses of the mRNA [Pfizer BioNTech or Moderna] or 1 dose of the vector vaccine [Janssen]) ≥ 2–4 weeks before starting. If already on an S1P receptor modulator, continue medication and get vaccinated when a vaccine is available. Alemtuzumab: consider getting fully vaccinated ≥ 4 weeks before starting. If already on alemtuzumab, wait ≥ 24 weeks after the last dose of alemtuzumab before getting vaccinated. If due for next treatment course, when possible, resume alemtuzumab ≥ 4 weeks or more after getting fully vaccinated. Cladribine: consider getting fully vaccinated ≥ 2–4 weeks before starting. If due for the next cladribine treatment, resume cladribine 2–4 weeks after getting fully vaccinated. Ocrelizumab/rituximab: consider getting fully vaccinated ≥ 2–4 weeks before starting treatment. If already on ocrelizumab or rituximab, consider getting fully vaccinated ≥ 12 weeks after the last dose. When possible, resume ocrelizumab or rituximab ≥ 4 weeks after getting fully vaccinated. Ofatumumab: consider getting fully vaccinated ≥ 2–4 weeks before starting treatment. If already on ofatumumab, when possible resume ofatumumab 2–4 weeks after getting fully vaccinated. High-dose steroids: consider getting the vaccine injection(s) 3–5 days after the last dose

Plaques) agree with AAN regarding limited studies; and the French Multiple Sclerosis Society recommendations regarding preventative methods are generally similar to those of AAN [17, 18]. The National Multiple Sclerosis Society and Multiple Sclerosis Association of America currently reference AAN and US Centers for Disease Control and Prevention guidance and guidelines and use language from DMT product labels regarding vaccination recommendations [15, 20].

Although robust data to support evidence-based recommendations on COVID-19 vaccinations are not yet available, the Multiple Sclerosis International Federation and the National Multiple Sclerosis Society have

recently advised vaccination for most people with MS, which can occur while treatment with DMTs is ongoing [14, 19, 79]. Both have also recently made recommendations regarding the timing of DMTs with COVID-19 vaccination (Table 2) [19, 80].

These COVID-19 vaccination guidance and guidelines are living documents based on what has been learned from previous vaccine studies, DMT prescribing information, ongoing studies and registries such as the COViMS registry, and expert consensus, and will be updated over time as more data become available and as more vaccines are approved for use.

VACCINE EFFICACY AND DMTS

Because DMTs have immunosuppressive and/or immunomodulating effects, data on vaccination efficacy in people with MS treated with DMTs may help inform how the immune response may be impacted and whether there should be considerations about optimal timing of vaccine administration with DMTs. Most reports have been on the response to influenza vaccination. People with MS are able to mount a cellular immune response following influenza vaccination [83]. However, increases in influenza-specific T cells following vaccination are higher in people with MS than in healthy controls and, importantly, no increases in T cell responses to central nervous system myelin proteins (i.e., human myelin basic protein or recombinant human myelin oligodendrocyte protein) were seen [83]. A meta-analysis of studies on influenza vaccination in patients with MS found no statistical difference in immune responses versus healthy controls and that most immunotherapies did not affect the immune response [84].

As previously mentioned, the different mechanisms of action for DMTs (summarized in Table 3) have been shown to impact immune responses to vaccination with administration of different DMTs. This has been demonstrated in clinical studies, case reports, and some preclinical data (Table 4). Several reports on interferon beta products indicate that people with MS treated with interferon beta can generate protective levels of response to influenza, tetanus-diphtheria toxoid, pneumococcal vaccine polyvalent, and meningococcal vaccines [85–90], with no evidence for a reduction in tetanus toxoid-induced T cell responses [91]. Endogenous interferon betas are part of the type I interferon family, which play an important role in antiviral response [92, 93]. The binding of interferons to their receptors causes a signaling cascade leading to upregulation of genes that results in production of antiviral molecules such as myxovirus resistance proteins, adenosine deaminase acting on RNA (ADAR1), oligoadenylate synthetase, and RNase L nuclease [93–96]. Postmarketing surveillance data showing no increased risk of infection suggest therapeutic interferon betas may have some protective antiviral effects [97].

For all other DMTs, data suggest a diminished immune response to vaccination, usually influenza vaccination. Glatiramer acetate may also impact the immune response, though most studies indicate adequate responses [87, 130, 131]; in one study, patients on glatiramer acetate had slightly lower responses to influenza vaccination compared with healthy controls [90]. Teriflunomide was found to cause a mild dose-dependent reduction in the efficacy of influenza and rabies vaccines [86, 134]; higher doses of teriflunomide induced a lower response to at least one strain of influenza in the vaccines [86].

Among sphingosine-1-phosphate (S1P) receptor modulators, most data were available for fingolimod. Patients treated with fingolimod had reduced response rates to influenza vaccination versus patients treated with interferon or placebo or versus healthy controls and no increase in avidity (binding) of influenza-specific immunoglobulin (Ig) G was seen [87, 130, 136, 137]. Studies and case reports also indicate that fingolimod affected responses to varicella zoster and pneumococcal polysaccharide vaccines [138–141]. The few data available for the other S1P receptor modulators, including a pooled analysis of two trials of ozanimod ($n = 2659$), suggest similar reductions in responses to vaccination [145, 146].

A study on dimethyl fumarate found adequate seroprotection and no reduction in

Table 3 DMTs and vaccination recommendations for people with MS

DMT category	Proposed mechanism of action	Vaccine recommendations from USPI
Interferons [98–102]		
Interferon beta-1b (Betaseron®) Interferon beta-1b (Extavia®) Interferon beta-1a SC (Rebif®) Interferon beta-1a IM (Avonex®) Peginterferon beta-1a (Plegridy®)	Unknown, but hypotheses include [103, 104] Promote shift from Th1 to Th2 Reduce trafficking across blood–brain barrier Restore T_{reg} function Inhibit antigen presentation Enhance apoptosis of autoreactive T cells	No vaccine-specific language
Glatiramer acetate [105]		
Copaxone®	Not fully understood, but hypotheses include [103, 106] Promote differentiation in Th2 and T_{reg} cells, leading to bystander suppression in the central nervous system Increase release of neurotrophic factors from immune cells Cause deletion of myelin-reactive T cells May inhibit Th17 immune response by direct influence on T cells [107]	No vaccine-specific language
DHODH inhibitor		
Teriflunomide [108]	Unknown; has been shown to [109] Has a cytostatic effect on rapidly dividing T and B lymphocytes in the periphery Inhibits de novo pyrimidine synthesis	No clinical data on the efficacy/safety of live vaccinations in patients taking teriflunomide Live vaccines are not recommended Long half-life needs to be taken into consideration after stopping treatment and before administration of a live vaccine Advise patients that use of some vaccines should be avoided during treatment with teriflunomide and for 6 months after stopping treatment

Table 3 continued

DMT category	Proposed mechanism of action	Vaccine recommendations from USPI
S1P receptor modulators		
Fingolimod [110]	Unknown, but Active metabolite binds with high affinity to S1P receptor on lymphocytes, thus preventing their egress from lymph organs [111, 112] Increases CD39-expressing T_{reg} cells and decreases B cells and $CD4^+$ cells [113]	Patients without confirmed history of chicken pox or documentation of full course of vaccination against VZV should be tested for VZV Abs before starting treatment. VZV vaccination is recommended in VZV Ab-negative patients before starting treatment, and initiation of fingolimod treatment should be delayed for 1 month to allow full effect of vaccination to take effect Vaccination against HPV should be considered before initiating treatment, taking into account vaccine recommendations Reduces immune response to vaccination, based on results from 2 placebo-controlled studies Vaccination may be less effective during and for up to 2 months after discontinuation of treatment Avoid use of live attenuated vaccines during and for 2 months after treatment because of the risk of infection Pediatric patients should complete all immunizations in accordance with current immunization guidelines before initiating treatment
Siponimod [114]	Unknown, but binds S1P receptors 1 and 5 with high affinity, blocking lymphocyte egress from lymph nodes	Avoid use of live attenuated vaccines during treatment and for 4 weeks after stopping treatment because of the risk of infection Before initiating treatment, patients should be tested for VZV Ab; VZV vaccination is recommended in VZV Ab-negative patients before starting treatment Patients without an HCP-confirmed history of chicken pox or documentation of a full course of vaccination against VZV should be tested for VZV Ab before initiating treatment. A full course of vaccination with varicella vaccine is recommended for Ab-negative patients before starting treatment; initiation of treatment should be postponed for 4 weeks to allow the full effect of vaccination to occur Vaccinations may be less effective if administered during treatment Vaccinations may be less effective during and for up to 1 month after discontinuation of treatment Treatment discontinuation 1 week before and until 4 weeks after a planned vaccination is recommended

Table 3 continued

DMT category	Proposed mechanism of action	Vaccine recommendations from USPI
Ozanimod [115]	Unknown, but binds with high affinity to S1P receptors 1 and 5, thereby blocking lymphocyte egress from lymph nodes and reducing the number of lymphocytes in peripheral blood	Avoid use of live attenuated vaccines during and for 3 months after treatment If live attenuated vaccine immunizations are required, administer ≥ 1 month prior to initiation treatment Patients without an HCP-confirmed history of chicken pox or documentation of a full course of vaccination against VZV should be tested for VZV Ab before initiating treatment. A full course of vaccination with varicella vaccine is recommended for Ab-negative patients before starting treatment; initiation of treatment should be postponed for 4 weeks to allow the full effect of vaccination to occur No clinical data available on the efficacy or safety of vaccinations in patients taking ozanimod Vaccinations may be less effective if administered during treatment Vaccinations may be less effective during and for up to 3 months after discontinuation of treatment Live attenuated vaccines may carry the risk of infection and should therefore be avoided during treatment and for up to 3 months after discontinuation of treatment
Ponesimod [116]	Unknown but binds with high affinity to S1P receptor 1, thereby blocking the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood	Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV before initiating ponesimod treatment. A full course of vaccination for Ab-negative patients with varicella vaccine is recommended prior to commencing treatment with ponesimod, following which initiation of treatment with ponesimod should be postponed for 4 weeks to allow the full effect of vaccination to occur No clinical data are available on the efficacy and safety of vaccinations in patients taking ponesimod. Vaccinations may be less effective if administered during ponesimod treatment If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ponesimod. Avoid the use of live attenuated vaccines during and for 1–2 weeks after treatment with ponesimod During, and for up to 1–2 weeks after discontinuation of, treatment with ponesimod, vaccinations may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during ponesimod treatment and for 1–2 weeks after discontinuation of treatment with ponesimod

Table 3 continued

DMT category	Proposed mechanism of action	Vaccine recommendations from USPI
Fumarates		
Dimethyl fumarate (DMF) [117]	Unknown; thought to promote anti-inflammatory and cytoprotective activities mediated by the Nrf2 pathway [118]	Concomitant exposure to DMF did not attenuate Ab responses to tetanus toxoid-containing vaccine, pneumococcal polysaccharide, or meningococcal vaccines relative to Ab responses in patients treated with nonpegylated interferon in a randomized, open-label study in adults with relapsing forms of MS. The impact of these findings on vaccine effectiveness in this patient population is unknown Safety and effectiveness of concomitant administration of live and live attenuated vaccines have not been assessed
Diroximel fumarate [119]	Unknown; thought to promote anti-inflammatory and cytoprotective activities mediated by Nrf2 pathway, which is involved in cellular response to oxidative stress [USPI]	A randomized, open-label study examined the concomitant use of DMF (which has the same active metabolite as diroximel fumarate) and several nonlive vaccines in adults 27–55 years of age with relapsing forms of MS (38 subjects undergoing treatment with DMF at the time of vaccination and 33 subjects undergoing treatment with non-pegylated interferon at the time of vaccination). Concomitant exposure to DMF did not attenuate Ab responses to tetanus toxoid-containing vaccine, pneumococcal polysaccharide, and meningococcal vaccines relative to Ab responses in interferon-treated patients. The impact of these findings on vaccine effectiveness in this patient population is unknown The safety and effectiveness of live or live-attenuated vaccines administered concomitantly with diroximel fumarate or DMF have not been assessed
Monomethyl fumarate [120]	Unknown; activates Nrf2 pathway, which is involved in cellular response to oxidative stress [USPI]	No vaccine-specific language
High-efficacy DMTs		
Anti-VLA4		
Natalizumab [121]	Blocks α4 subunit of α4β1 and α4β7 integrins on lymphocytes, thus reducing trafficking of lymphocytes into the central nervous system [122]	No data are available on the effects of vaccination in patients receiving natalizumab[a] No data are available on the secondary transmission of infection by live vaccines in patients receiving natalizumab

Table 3 continued

DMT category	Proposed mechanism of action	Vaccine recommendations from USPI
Anti-CD20		
Ocrelizumab [123]	Unknown but thought to bind CD20, a cell surface antigen, on pre-B and mature B lymphocytes, causing Ab-dependent and complement-mediated cytolysis	Vaccination with live attenuated or live vaccines not recommended during treatment and after discontinuation until B cell repletion Administer all immunizations according to immunization guidelines $\geq$ 4 weeks before starting treatment for live or live attenuated vaccines and, whenever possible, $\geq$ 2 weeks before starting treatment for nonlive vaccines Ocrelizumab may interfere with the effectiveness of nonlive vaccines The safety of immunization with live or live attenuated vaccines following treatment has not been studied Confirm recovery of B cell counts, as measured by $CD19^{+}$ B cells, in infants born to mothers exposed to ocrelizumab during pregnancy before administering live or live attenuated vaccines to infants. Depletion of B cells in these infants may increase the risks from live or live attenuated vaccines. Inactivated vaccines may be administered before recovery of B cell depletion, but vaccine immune responses should be evaluated in consultation with a qualified specialist to ensure protective immune response was mounted Concomitant exposure to ocrelizumab attenuated Ab responses to tetanus toxoid-containing vaccine, pneumococcal polysaccharide, pneumococcal conjugate vaccines, and seasonal inactivated influenza vaccines in a phase 3b, open-label study of ocrelizumab vs no treatment in adults with relapsing forms of MS. The impact of the observed attenuation on vaccine effectiveness in this patient population is unknown The safety and effectiveness of live or live attenuated vaccines administered concomitantly with ocrelizumab have not been assessed The potential duration of B cell depletion in infants following maternal exposure to ocrelizumab has not been evaluated in clinical trials, and the impact of B cell depletion on vaccine safety and effectiveness is unknown

Table 3 continued

DMT category	Proposed mechanism of action	Vaccine recommendations from USPI
Ofatumumab [124]	Unknown, but presumed to involve binding to CD20, a cell surface antigen on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ofatumumab results in Ab-dependent cellular cytolysis and complement-mediated lysis	Live attenuated or live vaccines not recommended during treatment and after discontinuation, until B cell repletion The safety of immunization with live or live attenuated vaccines following ofatumumab treatment has not been studied All immunizations should be administered according to immunization guidelines ≥ 4 weeks before starting treatment for live or live attenuated vaccines and, when possible, ≥ 2 weeks before starting treatment for inactivated vaccines Ofatumumab may interfere with effectiveness of inactivated vaccines Confirm recovery of B cell counts in infants born to mothers treated with ofatumumab during pregnancy before administering live or live attenuated vaccines to infants. Inactivated vaccines may be administered before recovery of B cell depletion, but vaccine immune responses should be evaluated
Rituximab [125]	Targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes Upon binding to CD20, rituximab mediates B cell lysis Possible mechanisms of cell lysis include complement-dependent cytotoxicity and Ab-dependent cell-mediated cytotoxicity	The safety of immunization with live viral vaccines following rituximab therapy has not been studied, and vaccination with live virus vaccines is not recommended before or during treatment Patients should, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating rituximab, and administered nonlive vaccines at least 4 weeks prior to a course of rituximab
Anti-CD52		
Alemtuzumab [126]	Unknown, but presumed to involve binding to CD52, a cell surface antigen on T and B lymphocytes, and on natural killer cells, monocytes, and macrophages. This results in depletion of T and B lymphocytes after infusion [127]	Do not administer live viral vaccines following a course of alemtuzumab Patients treated with alemtuzumab have altered immunity and may be at increased risk of infection following administration of live viral vaccines Patients without confirmed history of VZV or documentation of VZV vaccination should be tested for VZV Abs before starting treatment. VZV vaccination is recommended in VZV Ab-negative patients before starting treatment; postpone starting treatment until ≥ 6 weeks after vaccination Patients should complete any necessary immunizations ≥ 6 weeks before starting treatment

Table 3 continued

DMT category	Proposed mechanism of action	Vaccine recommendations from USPI
DNA synthesis disrupters		
Cladribine [128]	Thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes	Vaccination of patients who are Ab-negative for VZV recommended before starting treatment Administer all immunizations according to immunization guidelines before starting treatment Administer live attenuated or live vaccines ≥ 4–6 weeks before starting treatment, because of a risk of active vaccine infection Avoid vaccination with live attenuated or live vaccines during and after treatment while the patient's white blood cell counts are not within normal limits
Mitoxantrone [129]	Intercalates into DNA through hydrogen bonding, causing cross-links and strand breaks Interferes with RNA Inhibits topoisomerase II, an enzyme responsible for uncoiling and repairing damaged DNA Inhibits B cell, T cell, and macrophage proliferation in vitro and impairs antigen presentation and secretion of interferon gamma, tumor necrosis factor alpha, and interleukin-2	No vaccine-specific language

Ab antibody, *CD* cluster of differentiation, *DHODH* dihydroorotate dehydrogenase, *DMT* disease-modifying therapy, *HCP* healthcare provider, *HPV* human papillomavirus, *MS* multiple sclerosis, *S1P* sphingosine-1-phosphate, *Th1/2* type 1/2 helper T cells, *Th17* T helper 17 cell, T_{reg} regulatory T cell, *USPI* United States prescribing information, *VLA4* very late antigen 4, *VZV* varicella zoster virus

[a] The EU label states there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet hemocyanin) in patients treated with natalizumab for 6 months compared with an untreated control group. Live vaccines have not been studied

Table 4 Studies on effect of DMTs on response to vaccination

DMT	Study groups[a]	Vaccine	Outcome	AEs
IFN				
IFN beta-1b (Betaseron®)	IFN beta-1, $N = 46$	2011/2012 influenza	> 90% achieved antibody titers ≥ 40 for all strains [86]	Injection site pain ($n = 3$)
	IFN, $N = 45$	2010/2011 and 2011/2012 influenza	> 84% seroprotection rate [87]	Flu-like symptoms ($n = 4$); headache ($n = 1$); feeling weak ($n = 1$)
IFN beta-1b (Extavia®)	IFN beta, $n = 26$	2008/2009 and 2009/2010 influenza	Comparable frequencies of influenza-specific T cells and concentrations of anti-influenza A and B IgM and IgG [88]	Not studied
IFN beta-1a SC (Rebif®)	HCs, $n = 33$			
	IFN beta-1a, $n = 86$	2002/2003 influenza	No difference in antibody titer response [89]	Not studied
IFN beta-1a IM (Avonex®)	No IFN beta-1a, $n = 77$			
PegIFN beta-1a (Plegridy®)	IFN beta, $n = 36$	2009 swine flu (H1N1)	Similar protection rates [90]	7.9% and 7.8% MS exacerbations with 2009 and 2010 vaccine
	HCs, $n = 216$	2010 influenza		
	IFN beta, $n = 17$			
	HCs, $n = 73$			
	IFN beta-1a/1b, $n = 25$	2012/2013 influenza	Comparable protection rates against H1N1 at 3, 6, and 12 months [130]	Not studied
	HCs, $n = 53$			
	Nonpegylated IFN, $n = 33$	TT-containing	Similar antibody responses [85]	Vaccination-emergent AEs in 55%, nonpegylated IFN; 42%, DMF
		Pneumococcal polysaccharide		
	DMF, $n = 38$	Meningococcal		
	IFN beta, $n = 10$	Tick-borne encephalitis	Increased antibody titers in 9 [131]	Local side effects (pain, induration) but DMT not specified
	IFN beta, $N = 14$	TT	Reduced IFN-gamma and IL-4 responses to TT; no change in TT-induced $CD4^+$ T cell proliferation [91]	Not studied
	High titer IFN alpha/beta, mouse model	Influenza	Th1 type of immune response and protection against virus challenge [132]	Not applicable
	IFN beta, mouse model	Recombinant vaccinia viruses followed by fowlpox virus recombinants at 2-week intervals	Robust anti-HA $CD8^+$ T cell response [133]	Not applicable

Table 4 continued

DMT	Study groups[a]	Vaccine	Outcome	AEs
Glatiramer acetates				
Copaxone®	Glatiramer acetate, *n* = 37	2009 swine flu (H1N1)	Reduced response in glatiramer acetate group (21.6% vs 43.5%) [90]	Not studied
	HCs, *n* = 216			
	Glatiramer acetate, *n* = 12	2010 influenza	Reduced response in glatiramer acetate group (58.3% vs 71.2% H1N1; 41.7% vs 79.5% H3N2) [90]	Not studied
	HCs, *n* = 73			
	Glatiramer acetate, *n* = 23	2012/2013 influenza	Similar protection rates against H1N1 at 3, 6, and 12 months [130]	Not studied
	HCs, *n* = 53			
	Glatiramer acetate, *n* = 26	2010/2011 and 2011/2012 influenza	> 73.1% seroprotection rate to 3 different strains [87]	Flu-like symptoms (*n* = 3); temperature increase (*n* = 2); nightly sweating (*n* = 1)
	Glatiramer acetate, *n* = 5	Tick-borne encephalitis	3 had protective titers before vaccination and developed 2- to 9.6-fold increases in antibody titers [131]	Local side effects (pain, induration); DMT not specified
DHODH inhibitor				
Teriflunomide	Teriflunomide, 7 mg, *n* = 41	2011/2012 influenza	> 70% achieved antibody titers ≥ 40 for all strains; seroprotection to H3N2 was lower with 14 mg dose [86]	Injection site pain, *n* = 1 in each group
	14 mg, *n* = 41			
	Teriflunomide, *n* = 23	Rabies	Lower antibody titers in teriflunomide group; no adverse impact on recall antigen response [134]	Treatment-emergent AEs: teriflunomide, 17.4%; placebo, 30.4%
	HCs placebo, *n* = 23			
S1P receptor modulators				
Fingolimod	Fingolimod, *n* = 14	2008/2009 and 2009/2010 influenza	Cellular and humoral immune responses similar to controls [135]	Not studied
	HCs, *n* = 18			
	Fingolimod, *n* = 95	2010/2011 influenza	Fingolimod group had lower immune responses [136]	No new safety or tolerability signals
	Placebo, *n* = 43	TT booster (recall antigen)		

Table 4 continued

DMT	Study groups[a]	Vaccine	Outcome	AEs
	Fingolimod, $n = 10$ IFN beta, $n = 10$ HCs, $n = 15$	Influenza	Fingolimod group had no increases in avidity (binding) of influenza-specific IgG vs IFN beta or control [137]	Comparable tolerability across groups
	Fingolimod, $n = 6$	2010/2011 and 2011/2012 influenza	Low protective antibody titers to H3N2 [87]	Exanthema, $n = 2$
	Fingolimod, $n = 15$ HCs, $n = 53$	2012/2013 influenza	Lower protection rates were seen in fingolimod group at 3, 6, and 12 months [130]	Not studied
	Fingolimod, $n = 11$	VZV	7/11 patients had lower IgG-VZV antibody titers 2.4 years after starting fingolimod [138]	3/7 patients stopped treatment because of an AE
	Fingolimod, $n = 2$	Tick-borne encephalitis	Lowest increase in antibody titer compared with other DMTs [131]	Local side effects (pain, induration) but DMT not specified
	Fingolimod, $n = 48$ HCs placebo, $n = 24$	KLH Pneumococcal polysaccharide (PPV-23) TT	Mild to moderate decreases in anti-KLH and anti-PPV-23 IgG and IgM levels, indicating mild to moderate decrease in humoral and cellular immune responses to neoantigens; no effect on recall antigen (TT) response [139]	Most common AEs: headache, injection site pain, and dizziness, which occurred across all treatment groups
	Fingolimod, 1 patient with MS and childhood history of chicken pox [case report]	VZV	Response to vaccination diminished [140]	Patient infected daughter with chicken pox and had 2 bouts of shingles
	Fingolimod, 1 patient with MS and chicken pox as a child [case report]	VZV (shingles vaccine 6 months before initiating fingolimod)	Developed VZV encephalitis after 6 months of fingolimod and 5 days of high-dose systemic corticosteroids [141]	Not applicable
	Fingolimod Mouse model	BCG	Reduced protection against TB infection; administration during infectious challenge did not. Suggests memory T lymphocytes that migrate to the lung following vaccination are sufficient for protection [142]	Not applicable
	Fingolimod Mouse model	Ovalbumin plus CpG oligodeoxynucleotide adjuvant; priming via nasal route	Greater buildup of more extensively divided T cells within draining lymph nodes; in distal lymph nodes percentage of divided transgenic cells was mostly reduced [143]	Not applicable

Table 4 continued

DMT	Study groups[a]	Vaccine	Outcome	AEs
	Fingolimod	Influenza A	Protected against TB by $CD4^+$ memory T cells [144]	Not applicable
	Mouse model	Treated with fingolimod before and during *Mycobacterium tuberculosis* challenge		
Siponimod	Siponimod, *n* = 90 across 3 groups of HCs	Pneumococcal polysaccharide (PPV-23)	No effect on PPV-23 antibody response. Response criteria were also met for influenza, but lower titers at time of vaccination [145]	Similar incidence of AEs between siponimod and placebo
	Placebo, *n* = 30	Influenza		
Ozanimod	Ozanimod, *n* = 2659 with positive VZV IgG antibody status or VZV vaccination 30+ days before randomization	VZV	5 (0.6%) VZV cases reported with ozanimod 1 mg and 3 (0.3%) with ozanimod 0.5 mg [146]	No patient discontinued treatment because of VZV
	Pooled data from 2 phase 3 trials			
Fumarates				
Dimethyl fumarate (DMF)	DMF, *n* = 38	TT-containing	Concomitant exposure to DMF did not diminish antibody responses versus antibody responses in patients treated with nonpegylated IFN [85]	Vaccination-emergent AEs occurred in 42% with DMF and in 55% with nonpegylated IFN
	Nonpegylated IFN, *n* = 33	Pneumococcal polysaccharide		
		Meningococcal		
High-efficacy DMTs				
Anti-VLA4				

Table 4 continued

DMT	Study groups[a]	Vaccine	Outcome	AEs
Natalizumab	Natalizumab, n = 30	TT Neoantigen (KLH)	Protective levels of anti-TT IgG antibodies achieved and demonstrated primary immunization responses to a neoantigen [147]	No unexpected events observed
	Natalizumab, n = 17 HCs, n = 10	Influenza A (H1N1/A-H3N2/B)	Significant increases in anti-influenza B IgG following influenza A and B vaccination; humoral response was comparable to HCs [148]	Not studied
	Natalizumab, n = 17 HCs, n = 216	2009 swine flu (H1N1)	Reduced (23.5%) response compared with HCs (43.5%) [90]	Not studied
	Natalizumab, n = 8 HCs, n = 73	2010 influenza (including H1N1, H3N2, and B strains)	H1N1 protection: natalizumab, 75.0%; controls, 71.2% H3N2 protection: natalizumab, 50.0%; controls, 79.5% [90] Note: limited sample size and no adjustment for disease factors	Not studied
	Natalizumab, n = 12 HCs, n = 53	2012/2013 influenza	Reduced response at 3 and 6 months post vaccination; comparable response to HCs at 12 months [130]	Not studied
	Natalizumab, n = 14	2010/2011 and 2011/2012 influenza	Low response rates (14.3% seroprotection, all strains) [87] Note: small sample size is a limitation of this study	Not studied
Anti-CD20				
Ocrelizumab	Ocrelizumab, n = 68 [patients with MS] HCs, n = 34	TT Pneumococcal KLH Influenza	Reduced response compared with controls [149]	No new safety signals
	Patient with MS who received VZV vaccine 4 months before first dose of ocrelizumab [case report], n = 1	VZV	VZV IgG negative 5 months later; remained VZV IgG negative despite additional varicella vaccination [150]	Not applicable
Anti-CD52				
Alemtuzumab	Alemtuzumab, n = 24	Pneumococcal polysaccharide Diphtheria, TT, and poliomyelitis HiB and meningococcal group C	Humoral response was normal, but when vaccination occurred $\leq$ 6 months after treatment, smaller proportions responded (2/5 vs 12/15 vaccinated $>$ 6 months after alemtuzumab) [151]	Not studied

Table 4 continued

DMT	Study groups[a]	Vaccine	Outcome	AEs
DNA synthesis disrupter				
Mitoxantrone	Mitoxantrone, $n = 11$	2009 swine flu	Those treated with mitoxantrone failed to respond (unprotected) [90]; 1 patient treated with mitoxantrone was protected against H1N1 and 1 against H3N2 [90]	Not studied
	HCs, $n = 216$			
	Mitoxantrone, $n = 4$	2010 influenza		
	HCs, $n = 73$			

AE adverse event, *BCG* Bacillus Calmette–Guérin, *DHODH* dihydroorotate dehydrogenase, *DMF* dimethyl fumarate, *DMT* disease-modifying therapy, *HA* hemagglutinin, *HC* healthy control, *HiB Haemophilus influenzae* type b, *HPV* human papillomavirus, *IFN* interferon, *Ig* immunoglobulin, *IM* intramuscular, *KLH* keyhole limpet hemocyanin, *MS* multiple sclerosis, *PPV* pneumococcal polysaccharide vaccine, *S1P* sphingosine-1-phosphate, *SC* subcutaneous, *TB* tuberculosis, *TT* tetanus toxoid, *VZV* varicella zoster virus

[a] Unless indicated otherwise, all study groups are people with MS

immune responses to tetanus toxoid, pneumococcal polysaccharide, or meningococcal vaccines compared with interferon [85]. In addition, in the 96-week PROCLAIM study, antibody (IgA, IgG, IgM, and IgG1–4) subclass levels were stable with long-term (96-week) dimethyl fumarate treatment, though lymphocyte levels decreased (i.e., naïve $CD4^+$ and $CD8^+$ T cell increases, $CD4^+$ and $CD8^+$ central and effector memory T cell decreases) [152]. This indicated a shift from an inflammatory to an anti-inflammatory cell profile without impairment of humoral immunity [152]. No data were available for the other fumarates.

Some information was available for several high-efficacy DMTs in people with MS. A randomized controlled study in patients with MS treated with natalizumab showed that all evaluated patients achieved protective levels of anti-tetanus toxin IgG antibodies, and a slightly lower proportion of responders to primary immunization with keyhole limpet hemocyanin with natalizumab compared to control group, suggesting that natalizumab may not significantly influence responses to primary or secondary immunization [147]. In several small studies, patients with MS treated with natalizumab achieved either comparable or lower responses to influenza vaccination versus those treated with interferons or versus healthy controls depending on the strain [87, 90, 130]. Although the studies were limited by small sample sizes with no adjustment for disease factors in the patients with MS, the responses were generally considered more than adequate to achieve seroprotection.

In a large study in patients with MS ($N = 102$), those treated with ocrelizumab were found to have substantially impaired responses to tetanus toxoid, influenza, and pneumococcal vaccines and to the neoantigen keyhole limpet hemocyanin compared with controls on interferon beta or no DMT [149]. Despite these attenuated immune responses, patients still mounted a humoral response, and the authors concluded that an adequate vaccine response is generated after ocrelizumab treatment that is seroprotective [149]. On the basis of these data, there may be an optimal timing of vaccine administration with this DMT. In phase 3 trials,

Table 5 Major COVID-19 vaccines in use or in development

Vaccine	Description	Administration	Efficacy (primary endpoint)	Safety
BNT162b2 (Pfizer/BioNTech)	LNP-encapsulated mRNA encoding SARS-CoV-2 spike protein modified by 2 proline mutations [168]	Two 30-μg doses, 21 days apart [169, 171]	95.0% efficacy ≥ 7 days after dose 2 (N = 36,523[a]): COVID-19 illness occurred in 162/18,325 with placebo vs 8/18,198 with BNT162b2 [171]	Adverse events reported 7 days after dose 2 of BNT162b2 (N = 8183[b]) Local: pain (78% in 16–55-year-olds; 66% in > 55-year-olds), redness (6%, 7%), and swelling (6%, 7%) Systemic: fever (16%, 11%), fatigue (59%, 51%), headache (52%, 39%), chills (35%, 23%), vomiting (2%, 1%), diarrhea (10%, 8%), muscle pain (37%, 29%), joint pain (22%, 19%), use of antipyretic medication (45%, 38%) Serious events in 0.6% and lymphadenopathy in 0.3% reported at any time (N = 21,621[c]) [171]
mRNA-1273 (Moderna)	LNP-encapsulated mRNA encoding SARS-CoV-2 spike protein altered by 2 proline substitutions [53]	Two 100-μg doses, 28 days apart [169, 170]	94.1% efficacy ($p < 0.001$) at 14 days after dose 2 (N = 28,207[d]): COVID-19 illness occurred in 185/14,073 with placebo vs 11/14,134 with mRNA-1273 [170]	Solicited adverse reactions (grade 3) reported 7 days after dose 2 of mRNA-1273 (N = 14,677[e]) [170] Local: pain (4.1%), erythema (2.0%), swelling (1.7%), axillary swelling/tenderness (0.5%) Systemic (grade 3/4): fever (1.4%/< 0.1%), headache (4.5%/0%), fatigue (9.7%/0%), myalgia (9.0%/0%), arthralgia (5.2%/0%), nausea/vomiting (0.1%/< 0.1%), chills (1.3%/0%) Bell's palsy[f] in 3 vaccine recipients > 28 days after injection

Table 5 continued

Vaccine	Description	Administration	Efficacy (primary endpoint)	Safety
Ad26.COV2.S (VAC31518; JNJ-78436735; Janssen Biotech)	Recombinant replication-deficient adenovirus vector vaccine encoding SARS-CoV-2 spike protein gene altered by 2 proline substitutions [58, 59]	One 0.5-mL dose, 5×10^{10} vp	66.9% efficacy at 14 days after administration (N = 39,321[g]) [59]: COVID-19 illness (PCR+; moderate to severe/critical) in 348/19,544 with placebo vs 116/19,514 with Ad26.COV2.S	Solicited AEs (grade 3) up to 28 days after administration of Ad26.COV2.S (N = 3356[h]) [59]: erythema (0.2%), pain (0.3%), swelling (0.2%), fatigue (0.1%), headache (0.7%), myalgia (1.0%), nausea (0.2%), pyrexia (0.2%); no grade 4 solicited AEs Serious AEs of special interest/related to vaccine: facial paralysis (n = 2), brachial radiculitis (n = 1), Guillain–Barré syndrome (n = 1), transverse sinus thrombosis (n = 1), postvaccination syndrome (n = 1) No severe anaphylactic reactions were reported in any study
ChAdOx1 nCoV-19 (AZD12222; AstraZeneca and Oxford Vaccine Group)	Single recombinant, replication-deficient adenovirus vector vaccine encoding unmodified SARS-CoV-2 spike protein [57]	Two 0.5-mL doses, 28–84 days apart; each dose contains 2.5×10^{8} infectious units [57]	70.4% efficacy at 14 days in all participants (N = 11,636[i]): COVID illness in 101/5829 with placebo and 30/5807 with ChAdOx1 nCoV-19 [172] 62.1% efficacy at 14 days in participants (n = 8895) who received 2 standard doses (5×10^{10} vp) 90.0% efficacy in participants (n = 2741) who received 1 low dose (2.5×10^{10} vp) and 1 standard dose	AE at any time during study with ChAdOx1 nCoV-19 (N = 12,021[j]) [172] Any serious AE (n = 79; 0.7%) including diarrhea (n = 1; < 0.1%), pain (0), pyrexia (n = 1; < 0.1%), vomiting (n = 1; < 0.1%) AEs of special interest: anaphylactic reaction (n = 1; < 0.1%), neuralgia (n = 2; < 0.1%), neuritis (n = 1; < 0.1%), neuropathy peripheral (n = 1; < 0.1%), facial paralysis (n = 3; < 0.1%), MS (n = 1; < 0.1%), myelitis transverse (n = 1; < 0.1%)

Table 5 continued

Vaccine	Description	Administration	Efficacy (primary endpoint)	Safety
NVX-CoV2373 (Novavax)	Subunit recombinant SARS-CoV-2 nanoparticle vaccine, constructed from the full-length wild-type SARS-CoV-2 spike protein altered by 2 proline substitutions; in Matrix M adjuvant [50, 51]	5–50 μg doses; 1 or 2 doses (administered 21 days apart) in clinical trial [51]	No efficacy data available At day 35 after first vaccination, two 5-μg doses (n = 29) induced geometric mean anti-spike IgG ELISA levels and higher neutralization responses than those in convalescent serum from COVID-19 patients (mostly symptomatic) Adjuvanted regimens induced $CD4^+$ T cell responses [51]	AEs (n = 83[k]) occurring after dose 2 included [51] Local: pain (grade 2, 7.7–12.5%), erythema or redness (grade 2, 3.8–33.3%), induration or swelling (grade 2, 3.8%), tenderness (grade 2, 23.1–33.3%; grade 3, 4.2%) Systemic: joint pain/arthralgia (grade 2, 3.8–4.8%; grade 3, 3.8–8.3%), fatigue (grade 2, 4.8–19.2%; grade 3, 3.8–8.3%), malaise (grade 2, 4.8–16.7%; grade 3, 8.3%), headache (grade 2, 4.8–16.7%; grade 3, 4.0%), muscle pain/myalgia (grade 2, 8.3–11.5%; grade 3, 3.8–8.3%), nausea or vomiting (grade 3, 4.0%)

Additional vaccine candidates are in various stages of clinical development and details can be found on the World Health Organization website [159]
AE adverse event, *ELISA*, enzyme-linked immunosorbent assay, *LNP* lipid nanoparticle, *mRNA* messenger RNA, *PCR*, polymerase chain reaction, *vp* virus particles

[a] Participants who received BNT162b2 or placebo as randomly assigned had no evidence of infection within 7 days after second dose and no major protocol deviations

[b] Reactogenicity subset; includes recipients of either BNT162b2 or placebo

[c] Includes participants who received ≥ 1 dose of BNT162b2, irrespective of follow-up or follow-up time

[d] Per-protocol population

[e] Solicited safety set

[f] Incidences of 20.2/100,000 person-years over 5 years to cumulative incidence of 53.3/100,000 per year in the general population [173, 174]

[g] Per-protocol at risk set (excludes participants who had a positive PCR test between day 1 and day 14)

[h] Safety subset

[i] Primary efficacy population

[j] Participants who received ≥ 1 dose of vaccine

[k] Participants who received 1 or 2 doses of NVX-CoV2373 with or without adjuvant

patients with MS treated with ocrelizumab also experienced decreases in IgG and IgM antibodies below the lower limit of normal 96–120 weeks after starting treatment with ocrelizumab, which is predictable on the basis of the mechanism of action of this therapy [123]. A single case report of loss of vaccinal immunity against varicella zoster virus suggests that ocrelizumab may impair varicella vaccines; however, this finding needs to be replicated in a larger cohort [150].

Interest in off-label treatment with rituximab for MS has increased [153, 154], but vaccination studies in patients with MS have not occurred to date. However, registry data (N = 822) show that 3% of patients with MS experience reductions in IgG below the lower limit of normal at some point during treatment [155]. Two systematic review and meta-analysis studies found

a reduced response to pneumococcal vaccination [156, 157] and influenza vaccine [157] in patients with rheumatoid arthritis treated with rituximab but not for those who received anti-tumor necrosis factor alpha (TNFα) agent. Similarly, in a systematic review of studies in patients with rheumatoid arthritis or other inflammatory rheumatic diseases, rituximab also significantly decreased responses to an influenza vaccine, with tenfold lower hemagglutination inhibition assay titers observed in those administered rituximab less than 12 weeks before vaccination versus those administered rituximab more than 24 weeks before vaccination [158]. A second dose of the vaccine was needed to achieve responses comparable to those achieved with a single dose in healthy controls. No studies on vaccines are available for ofatumumab.

Data on alemtuzumab suggest vaccination should occur at least 6 months before starting treatment because depletion of T and B cells, as occurs with alemtuzumab treatment, would diminish response to vaccination [151].

The one study that included the DNA disrupter mitoxantrone reported an almost complete lack of response to influenza vaccination [90]. No studies on vaccines are available for cladribine.

COVID-19 VACCINE TRIALS AND CONSIDERATIONS FOR PEOPLE WITH MS

Multiple COVID-19 vaccines are in development [159] and a number are already being administered worldwide. Many target the spike protein of SARS-CoV-2, a protein expressed on the surface of the virus that facilitates entry into host cells, with the goal of generating robust humoral and T cell responses [160, 161]. This protein binds to a receptor on the host cell surface and then causes the virus and host cell membranes to fuse [53, 162].

Three vaccines, BNT162b2 (developed by Pfizer and BioNTech), mRNA-1273 (developed by Moderna), and Ad26.COV2.S (VAC31518; JNJ-78436735; developed by Janssen Biotech), have received emergency use authorization but have not yet received approval from the US Food and Drug Administration at the time of this publication [163–165]. BNT162b2, mRNA-1273, and another vaccine, ChAdOx1 nCoV-19 (AZD12222; developed by AstraZeneca and Oxford Vaccine Group), have received conditional marketing authorization in the European Union [166, 167]. BNT162b2 and mRNA-1273 contain lipid nanoparticle-formulated nucleoside-modified mRNA that encodes the SARS-CoV-2 full-length spike protein but modified by two proline mutations [53, 168], and are administered in two doses [169]. Ad26.COV2.S (VAC31518; JNJ-78436735), administered in a single dose, and ChAdOx1 nCoV-19, administered in two doses, are recombinant replication-deficient adenovirus vector vaccines encoding the spike protein gene [57–59].

Efficacy and safety data for these vaccines are shown in Table 5. Adverse events reported for all the vaccines included local reactions, such as pain at the site of administration, and systemic reactions that included headache, fever, and fatigue. Bell's palsy ($n = 3$) was reported with mRNA-1273 and facial paralysis ($n = 2$), brachial radiculitis ($n = 1$), Guillain–Barré syndrome ($n = 1$), transverse sinus thrombosis ($n = 1$); postvaccination syndrome ($n = 1$) was reported with Ad26.COV2.S (VAC31518; JNJ-78436735) [59, 170]. Another candidate of interest is NVX-CoV2373 (developed by Novavax), a subunit recombinant nanoparticle created from the spike protein [50, 51]. No efficacy data are available yet; however, a small study showed inducement of anti-spike antibody and T cell responses [51] (Table 5).

Members of the MS community have expressed an interest in COVID-19 vaccination. A US online survey of people with MS in the spring of 2020, before any COVID-19 vaccines were available, found that approximately two-thirds of respondents were willing or moderately willing to be vaccinated [175]. However, analyses focusing specifically on MS subgroups have yet to occur, and it is unknown how many people with MS have participated in COVID-19 vaccine studies. Thus, current knowledge pertaining to COVID-19 vaccination in patients with MS is based on conventional vaccines and anecdotal experience in those who have

received the vaccine thus far. The percentage of seroconversion that is deemed sufficient for "protection" varies on the basis of what the vaccine/pathogen is, and people receiving certain DMTs may be able to mount some, albeit diminished, antibody response to vaccination. Duration of disease may also affect response to vaccination. Longer disease duration ($p = 0.040$; odds ratio = 0.910) has been associated with an insufficient response to influenza vaccine in people with MS treated with interferons, glatiramer acetate, natalizumab, fingolimod, and other DMTs [87]. These findings may be impacted not only by DMT but also by age, comorbidities, and other factors.

When thinking about the potential impact of MS DMTs on vaccine efficacy, the role of specific immune cell populations may be considered. For example, T cell signatures may be a more sensitive measure of past SARS-CoV-2 infection than antibody assays, as individuals with symptomatic infections or who required hospitalization had higher T cell responses [176]. This suggests that disease-specific memory T cells, in addition to antibody titers, may be measurable and reliable correlates of protection [176]. However, SARS-CoV-2-reactive $CD4^+$ T cells have been reported in 35–60% of unexposed individuals, suggesting possible cross-reactive T cell recognition between other coronaviruses (e.g., common cold viruses) and COVID-19 [177–179]; the protective effect of such cross-reactive T cells is unclear.

Coronavirus-specific T cells from Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) have been shown to have long-term persistence and contribute to protection [176, 180, 181]. Hence, DMTs that deplete or significantly impact T cells may affect the efficacy of potential COVID-19 vaccines. Moreover, the National Multiple Sclerosis Society advises waiting at least 12 weeks after the last dose of B cell-depleting treatment before vaccinating [80], as anti-CD20 antibodies (i.e., ocrelizumab) have been found to induce rapid and prolonged (up to 24 weeks) B cell depletion and attenuated humoral immune responsiveness to vaccination in people with MS [149]. Many clinicians advise their patients that if given a choice, they should receive a vaccine when available and worry about timing later. More data are needed to fully understand the necessity of the memory B cell population, an important target of anti-CD20 therapies, to drive persistent antibody responses for extended periods of time following vaccination. Delaying therapy to allow for a more robust B cell response to the COVID vaccine, only to potentially diminish this response when therapy is resumed, may be counterproductive. Lastly, the impact that B cell-depleting therapies may have on other components of the immune system, including T cells, may also need to be a consideration for vaccine administration.

Because of their persistence (as opposed to declining levels of antibodies), T cells may be the more important measure for determining the efficacy of COVID-19 vaccines. However, antibodies still clearly have a role in preventing future infection through neutralization of a virus before it can infect a cell. Indeed, vaccines are traditionally designed to elicit a very robust humoral immune response, in addition to a cellular immune response, to convey both protection from infection and prevention of disease. The COVID-19 vaccines are not an exception to this. Moreover, even if antibody titers decline, this does not negate the fact that memory B cells should still be present and able to contribute significantly to the prevention of future infection, highlighting the importance of maintaining adequate levels of both B cells and T cells during the vaccination period and beyond [45].

Although the evidence clearly demonstrates the importance of measuring and generating a T cell or cell-mediated response to COVID-19 vaccines (as evidenced by the detection of SARS-CoV-2-specific T cells in convalescent patients [182]), it is important to remember that the immune response is a coordinated effort that must be orchestrated by both T cells and B cells (or cell-mediated and humoral immunity), as evidenced by the essential role that B cells have been shown to play in the generation of T cell memory [39, 183].

SUMMARY/CONCLUSION

Infections can be associated with an increased risk of relapses or pseudo-relapses in people with MS. For this reason, vaccination is an important tool that should be utilized, whenever possible, to limit infection in this population. However, the use of DMTs, which alter various components of the immune response, may also reduce the vaccine immune response in people with MS. In light of the current COVID-19 global pandemic and the recent authorization of novel vaccines against COVID-19, a better understanding of how MS DMTs may alter the immune response to vaccination is greatly needed. This review highlights previous studies of vaccine response in people with MS and focuses on how immunological impairment driven by various DMTs may impact successful vaccination strategies against COVID-19 in this patient population.

Immunological studies have shown that the coordinated interactions between T and B lymphocytes of the adaptive immune system are integral to the successful generation of immunological memory and production of neutralizing antibodies, following recognition of vaccine antigens by innate immune cells. $CD4^+$ T cells play an essential role in facilitating both $CD8^+$ T cell and B cell activation, but the inverse is also true, with B cells playing an important role in driving and sustaining T cell memory.

Previous studies of the immune response to vaccines other than COVID-19 in people with MS receiving various DMTs (Table 2) have shed some light on the key question of how each DMT or class of DMTs might affect the efficacy of a COVID-19 vaccine. Indeed, the data suggest that type 1 interferons, glatiramer acetate, and possibly teriflunomide may not significantly impair the response to vaccination, as opposed to those DMTs that rely on sequestration or depletion of large populations of immune cells, including S1P receptor modulators, alemtuzumab, cladribine, and anti-CD20 therapies. Other factors that could impact vaccine efficacy, including age and comorbidities, are beyond the scope of this review but should be considered. Benefits of vaccination, as outlined in guidance and guidelines from national and international MS groups, should be considered—even if vaccine efficacy may be compromised—when disease burden is high.

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