Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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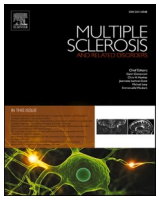

Review article

Vaccination of multiple sclerosis patients during the COVID-19 era: Novel insights into vaccine safety and immunogenicity

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ABSTRACT

Multiple sclerosis (MS) is an incurable autoimmune disease known to cause widespread demyelinating lesions in the central nervous system (CNS) and a host of debilitating symptoms in patients. The development of MS is believed to be driven by the breakdown of the blood brain barrier, subsequent infiltration by $CD4^+$ and $CD8^+$ T cells, and widespread CNS inflammation and demyelination. Disease modifying therapies (DMTs) profoundly disrupt these processes and therefore compose an essential component of disease management. However, the effects of these therapeutic agents on vaccine safety and immunogenicity in individuals with MS are not yet fully understood. As such, the primary objective of this review article was to summarize the findings of recently conducted studies on vaccine safety and immunogenicity in MS patients treated with DMTs, particularly in the context of the ongoing coronavirus disease 2019 (COVID-19) pandemic. Discussed in this review are vaccinations against influenza, yellow fever, human papillomavirus, measles, mumps, rubella, *Streptococcus pneumoniae*, hepatitis B, and COVID-19. This article additionally reviews our current understanding of COVID-19 severity and incidence in this patient population, the risks and benefits of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and vaccination guidelines set forth by MS societies and organizations.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease known to cause widespread demyelination and functional disruption of the central nervous system. Although MS is not a hereditary disease, several key genetic and environmental factors that predispose individuals to MS have been identified. A Canadian study confirmed a pattern of increased familial risk for this autoimmune disease (Sadovnick et al., 1996). According to their findings, the risk for developing MS is 300-fold greater in monozygotic twins when one sibling is affected and at least 20-fold greater in individuals with first-degree family members suffering from MS (Sadovnick et al., 1996). Of note, the disease is closely linked to certain major histocompatibility complexes including HLA-DRB1. Various environmental factors like vitamin D deficiency, teenage obesity, exposure to tobacco smoke, and infections by Epstein-Barr virus and Human Herpes Virus 6 have also been linked to a higher risk of MS development (Kamm et al., 2014; Guan et al., 2019; Olsson et al., 2017).

Though the mechanisms by which multiple sclerosis arises are still unclear, the disruption of the blood brain barrier (BBB) is thought to be one of the earliest events that initiate the disease process. With the breakdown of the BBB, various immune cells including $CD4^+$ and $CD8^+$ T lymphocytes are then able to gain access to the central nervous system (CNS) (Al-Badri and Castorina, 2018). T lymphocytes are considered the main effector cells primarily responsible for mediating the auto-reactive immune responses characteristic of this condition. Myelin is perceived as foreign by these immune cells, and as a direct consequence, is damaged by the resulting cytokines and reactive oxygen species released by activated lymphocytes (Al-Badri and Castorina, 2018; Dendrou and Friese, 2015; Ghasemi et al., 2017). Among other functions, $CD4^+$ T cells are also known to recruit other immune cells such as macrophages and B cells during this process, while $CD8^+$ T cells are believed to attack the MHC class I-expressing oligodendrocytes and neurons (Hemmer et al., 2006). What ultimately follows is widespread CNS inflammation, axonal loss and damage, and a cyclical pattern of demyelination and

Abbreviations: MS, multiple sclerosis; CNS, central nervous system; DMTs, disease modifying therapies; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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remyelination, all of which contribute to the plaque formation and clinical manifestations of MS (Dendrou and Friese, 2015; Ghasemi et al., 2017; Dargahi et al., 2017).

Despite its incurable nature, multiple sclerosis can be treated and managed effectively with corticosteroids and disease modifying therapies (DMTs), an immunomodulatory class of drugs that include interferons and monoclonal antibody biologics like natalizumab (Dargahi et al., 2017). DMTs not only improve the quality of life for MS patients through symptomatic relief but also reduce the frequency, severity, and duration of relapses (Cree, 2007). Inherent to these drugs, however, is their ability to suppress the elements of the immune system chiefly responsible for the symptoms and complications associated with this debilitating disease. Thus, infections are a common concern for patients suffering from MS and unfortunately, the primary cause of death in this population (Smestad et al., 2009). In fact, MS patients are more likely to contract serious infections, experience more severe symptoms, and succumb to their infections relative to the general population (Montgomery et al., 2013; Celius, 2017; Nelson et al., 2015). As such, vaccination of this population is crucial, both as a means to prevent infections preemptively and to reduce the severity of disease should they arise.

The emergence of the deadly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, aptly named coronavirus disease 2019 (COVID-19), has only highlighted the need for vaccination of individuals living with MS. Considering a greater proportion of MS patients possess established risk-factors for COVID-19 infection including heart disease and hypertension, experts have strongly encouraged MS patients to undergo COVID-19 vaccination (Palladino et al., 2020). Three vaccines against SARS-CoV-2 are currently available in the United States: the Moderna (mRNA-1273), Pfizer/BioNTech (BNT162b2) and Johnson & Johnson (JNJ 78436735) vaccines. The Moderna and Pfizer/BioNTech vaccines are FDA-approved messenger RNA (mRNA) vaccines while the Johnson & Johnson vaccine is based on a non-replicating adenoviral vector (FDA Approves First COVID-19 Vaccine 2022; Coronavirus (COVID-19) update 2022). All three vaccines deliver RNA or DNA encoding for the spike protein of SARS-CoV-2 into host cells, thereby inducing a humoral immune response that ultimately affords patients vital protection from future infection.

The safety of vaccinations in the MS population has been investigated comprehensively in recent years. However, the literature regarding the immunogenicity of various vaccinations in this population, especially with the advent of new vaccine advancements such as those utilized in the COVID-19 vaccines, remains scant. The goal of this review is to summarize currently available data and ongoing research on the safety and immunogenicity of various vaccines in MS patients, particularly in the context of DMTs and the ongoing COVID-19 pandemic.

2. COVID-19 and multiple sclerosis

Most concerning for millions of MS patients is the ongoing COVID-19 pandemic. Concerns have been raised not only about the increased risk of contracting COVID-19 but also the potentially greater severity of disease and higher rate of mortality in infected MS patients. Preliminary studies conducted in France, Spain, and Iran found that MS patients with COVID-19 are at greater risk for hospitalization and adverse health outcomes (Louapre et al., 2020; F et al., 2020; Sahraian et al., 2020).

However, these findings demonstrating increased risk have not been met with consensus confirmation. An earlier Chinese study and a recent cohort study involving MS patients from the United Kingdom, United States, and Canada determined overall health outcomes and risk of severe COVID-19 infection to be comparable to that of the general population (Fan et al., 2020; Salter et al., 2021). Most notably, a systematic review encompassing 87 studies and involving 4310 MS patients with COVID-19 infection determined that hospitalization and mortality rates in this population are within the published ranges of the general population (Barzegar et al., 2021). Though encouraging, these data should be interpreted with caution. Given that this study's participants were predominantly young and female, and therefore less likely to require hospitalization, studies conducted on more diverse patient groups will be needed to confirm these findings.

Furthermore, there may be a subset of this MS patient population that is more at risk. Namely, individuals relying on DMTs for symptom management and relapse prevention are thought to be more susceptible to COVID-19 infection. Two Iranian studies observed that the use of B-cell depleting therapies, like rituximab and ocrelizumab, by MS patients can heighten their risk for developing COVID-19 (Sahraian et al., 2020; Safavi et al., 2020). Considering these therapeutic agents target and eliminate circulating B-cells and therefore blunt humoral immune responses to infections, the use of these monoclonal antibodies is expected to increase the susceptibility of MS patients to infections of any kind which was previously confirmed in a Swedish study (Luna et al., 2020).

Along with a heightened susceptibility to COVID-19 infection, a higher risk of severe infection has also been noted in MS patients treated with anti-CD20 monoclonal antibodies. Specifically, a Swedish cohort study determined that MS patients on rituximab or ocrelizumab were 3 times more likely to require hospitalization relative to those treated by any other DMT (Spelman et al., 2021). A 2021 study analyzing data collected from 2300 COVID-19-infected MS patients in 28 countries including Sweden came to a similar conclusion; rituximab use was associated with significantly higher hospitalization, intubation, and intensive care unit admission rates than treatment with any other DMT (Simpson-Yap et al., 2021). Compared to those not receiving DMTs, MS patients on B-cell depleting therapy have also been documented to be at a 4-fold higher risk of severe COVID-19 and 4.5 times more likely to be hospitalized as determined by Italian and North American multicenter studies (Salter et al., 2021; Sormani et al., 2021). Altogether, rituximab and ocrelizumab appear to not only heighten susceptibility to infection but confer risk for more severe COVID-19 in MS patients.

In contrast, the use of interferons and glatiramer acetate by MS patients does not appear to be linked to higher COVID-19 incidence or greater disease severity according to recently published data (Louapre et al., 2020; Sahraian et al., 2020; Salter et al., 2021; Chaudhry et al., 2020). In fact, two studies noted that rates of severe COVID-19 infection were higher in MS patients not receiving DMTs, suggesting that these therapeutics may impart some degree of protection to MS patients (Louapre et al., 2020; Chaudhry et al., 2020). These findings are largely consistent with early speculations that DMTs can mitigate the severity of the cytokine-storms characteristic of COVID-19 infections; a recent study even observed interferon-β treatment was associated with significantly shorter hospital stays, reduced mortality, and decreased likelihood of mechanical ventilation (Berger and Brandstadter, 2020; Sosa et al., 2021). As such, experts agree that continued interferon and glatiramer acetate use is likely safe in MS patients, but many still caution that certain high-efficacy DMTs, such as natalizumab and fingolimod, can impair MS patient immune responses to COVID-19 (Berger and Brandstadter, 2020; Kappos et al., 2015; Giovannoni et al., 2020; Korsukewitz et al., 2020).

3. COVID-19 vaccine

Of current concern are also the adverse effects, relapse potential, and reduced immunogenicity of the newly developed COVID-19 vaccines in MS patients. Indeed, when assessing MS patients' attitudes towards vaccination, many reported reluctance and even fear about the adverse effects and potential complications of COVID-19 vaccines, particularly in the context of DMTs (Ehde et al., 2021; Serrazina et al., 2021). According to recently published data from two major studies, adverse effects associated with the Oxford-AstraZeneca and Pfizer/BioNTech vaccines appear to occur in MS patients at a frequency and severity similar to the general population (Table 1) (FBS and Schmidt, 2021; A Achiron et al., 2021; Polack et al., 2020). In these cohorts, both first and second doses of either vaccine led to transient reactions typical of

Table 1
Landmark Studies Evaluating Safety and Immunogenicity of COVID-19 Vaccines in Individuals Living with MS.

Year	Location	Study Population	DMT	Vaccine	Notable Findings
2020	United States, Argentina, Brazil, South Africa, Germany, and Turkey	43,448 patients (21,720 with BNT162b2; 21,728 with placebo)	N/A	BNT162b2 or placebo	Two-dose regimen of the BNT162b2 vaccine is both safe and effective against COVID-19 (Polack et al., 2020)
2021	Israel	555 MS patients (1st dose); 435 MS patients (2nd dose)	Interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab, fingolimod, ocrelizumab, alemtuzumab, cladribine, or rituximab	BNT162b2	No evidence of heightened relapse activity following vaccination (A Achiron et al., 2021)
2021	United States	719 MS patients (1st dose); 442 MS patients (2nd dose)	B-cell depleting therapies, fumarates, S1P receptor modulators, glatiramer acetate, natalizumab, interferons, alemtuzumab, or cladribine	BNT162b2, mRNA-1273, Ad26.COV2.S, or ChAdOx1 nCoV-1	Vaccination side effects occur in patients with MS at a similar frequency and severity as the general population (FBS and Schmidt, 2021)
2021	Israel	172 patients (125 MS patients; 47 healthy control patients)	Cladribine, ocrelizumab, or fingolimod	BNT162b2	Most fingolimod-treated patients did not develop SARS-CoV-2 antibodies, unlike a vast majority of cladribine-treated patients (A Achiron et al., 2021). Ocrelizumab treatment was also noted to impair humoral responses to vaccination (A Achiron et al., 2021).
2021	United States and Denmark	60 MS patients	Ocrelizumab	BNT162b2 or mRNA-1273	Markedly reduced humoral responses to SARS-CoV-2 vaccines is evident with ocrelizumab treatment (Apostolidis et al., 2021)
2021	Switzerland	49 MS patients	Ocrelizumab or rituximab	BNT162b2 or mRNA-1273	Of 16 patients treated with B-cell depleting therapy, only one developed humoral immunity to SARS-CoV-2 after 3rd vaccine dose (Achtnichts et al., 2021)
2021	Switzerland	120 MS patients	B-cell depleting therapies, S1P receptor modulators, cladribine, or teriflunomide	BNT162b2 or mRNA-1273	While cladribine or teriflunomide treatment was not associated with reduced humoral responses to vaccination, B-cell depleting therapies and S1P receptor modulator treatment led to significantly impaired immune responses (Disanto et al., 2021)
2022	United Kingdom	473 MS patients	B-cell depleting therapies, natalizumab, alemtuzumab, dimethyl fumarate, cladribine, glatiramer acetate, fingolimod, interferon beta, or teriflunomide	ChAdOx1 nCoV-1, BNT162b2, or Ad26.COV2.S	Treatment with fingolimod or B-cell depleting therapies is associated with low seroconversion rates (Tallantyre et al., 2022)
2022	United States	80 study participants (13 health controls; 67 DMT-treated MS patients)	Rituximab, ocrelizumab, glatiramer acetate, dimethyl fumarate, natalizumab, or S1P receptor modulators	BNT162b2, Ad26.COV2.S, or mRNA-1273	Significantly reduced immune responses were noted in cladribine- or S1P receptor modulator-treated MS patients following vaccination (Sabatino et al., 2022)
2022	Israel	73 study participants (40 health controls; 33 MS patients)	Ocrelizumab	BNT162b2	Cytokine production by MS patients rivaled that of healthy controls shortly after vaccination (Brill et al., 2022). Waning SARS-CoV-2-specific T-cell and humoral responses were noted in MS patients 6 months after 2nd dose (Brill et al., 2022).
2022	Israel	211 MS patients	Interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab, fingolimod, ocrelizumab, alemtuzumab, cladribine, or rituximab	BNT162b2	Third vaccine dose is safe and effective for DMT-treated MS patients with no increased risk of disease relapse (Dreyer-Alster et al., 2022)
2022	United States and Denmark	64 MS patients	Ocrelizumab	BNT162b2	A 3rd vaccine dose did not lead to significantly greater humoral or cellular responses in ocrelizumab-treated MS patients (Bajwa et al., 2022)
2022	Switzerland	27 MS patients	Fingolimod	BNT162b2 or mRNA-1273	4 of 8 patients treated with fingolimod demonstrated sufficient humoral immunity after 3rd vaccine dose (Achtnichts et al., 2022)

COVID-19: coronavirus disease 2019; MS: multiple sclerosis; S1P: sphingosine-1-phosphate.

healthy individuals, such as fatigue, headache, and fever (FBS and Schmidt, 2021; A Achiron et al., 2021). Though noted in several case reports, disease relapse is also believed to be a rare occurrence in MS patients following vaccination (Etemadifar et al., 2021; Fujimori et al., 2021; Havla et al., 2022). An Israeli observational study independently confirmed these suspicions, demonstrating through its findings that relapse rates between vaccinated and unvaccinated MS patients are virtually indistinguishable (A Achiron et al., 2021).

On the other hand, concerns of reduced COVID-19 vaccine immunogenicity in MS patients may be warranted given currently available data. A study involving 125 MS patients found that while both untreated and cladribine-treated MS patients exhibited humoral immune responses that rivaled those of healthy controls, ocrelizumab and fingolimod treatment was associated with markedly reduced rates of antibody development following BNT162b2 vaccination (Table 1) (A Achiron et al., 2021). Two more recent studies reported similar findings; patients treated with fingolimod or anti-CD20 monoclonal antibody drugs were noted to exhibit significantly decreased rates of seroconversion after receiving an mRNA or adenovirus COVID-19 vaccine (Table 1) (Tallantyre et al., 2022; Sabatino et al., 2022). Both studies also observed that COVID-19 vaccines were similarly effective in untreated MS patients and those using glatiramer acetate, dimethyl fumarate, and natalizumab (Tallantyre et al., 2022; Sabatino et al., 2022). Altogether, these studies suggest that with the exception of fingolimod and B-cell depleting therapies, DMTs do not significantly impair humoral immune responses to the first and second doses of the Pfizer or Oxford-AstraZeneca vaccines. Additional studies will likely be needed to confirm the applicability of these findings to other COVID-19 vaccines.

Despite the growing body of evidence that B-cell depleting therapies significantly reduce COVID-19 vaccine immunogenicity, vaccines may still prove useful in this patient population. Researchers have observed these individuals producing robust, antigen-specific $CD4^+$ and $CD8^+$ T cell responses after mRNA vaccination against SARS-CoV-2; in one study, cytokine production by stimulated SARS-CoV-2-specific $CD8^+$ T cells was significantly greater in patients treated with rituximab or ocrelizumab than untreated patients (Table 1) (Sabatino et al., 2022; Apostolidis et al., 2021; Brill et al., 2022). Considering that better health outcomes have been associated with intact $CD8^+$ T cell immunity in B-cell depleted COVID-19 patients, vaccinated patients using rituximab or ocrelizumab may still be capable of mounting sufficient T cell responses to SARS-CoV-2 and consequently less likely to experience severe COVID-19 infection (Bange et al., 2021). Further research is needed to characterize the precise role of T cells in COVID-19 infection, but given currently available data, MS patients treated with rituximab or ocrelizumab may benefit from vaccination via cell-mediated immunity.

To promote long-term humoral immunity to SARS-CoV-2 and maintain antibody levels in patients months after initial vaccination, the administration of an additional (i.e. booster) dose of the COVID-19 vaccine has also been recommended. Preliminary data have revealed untreated MS patients and those receiving cladribine, dimethyl fumarate, natalizumab, teriflunomide, and glatiramer acetate infusions respond robustly to a third dose of the BNT162b2 vaccine (Table 1) (Dreyer-Alster et al., 2022). There was also no notable increase in their rates of relapse (Dreyer-Alster et al., 2022).

Vaccination of patients relying on high-efficacy DMTs like ocrelizumab have not been nearly as successful. Studies conducted on B-cell depleted MS patients have noted minimal changes in seroconversion rates following a third mRNA vaccine dose and have rarely observed patients who were initially seronegative after two vaccine doses become seropositive (Table 1) (Brill et al., 2022; Bajwa et al., 2022; Achtnichts et al., 2021). Patients on fingolimod have not fared much better; following a third mRNA vaccination, only 50% of MS patients on the sphingosine-1-phosphate receptor modulator achieved clinically significant IgG levels according to a Swiss study (Table 1) (Achtnichts et al., 2022). Altogether, these findings suggest that a third COVID-19 dose may be helpful in maintaining immunity in an already responsive minority of B-cell deficient patients but likely will not benefit most seronegative MS patients treated with ocrelizumab or fingolimod.

Moreover, modifications to a patient's COVID-19 immunization schedule and DMT regimen have been suggested as means to optimize vaccine efficacy. Specifically, the Swiss Multiple Sclerosis Society has recommended that a third COVID-19 vaccine be given to MS patients ahead of schedule to enhance seroconversion rates, a recommendation that likely arose from recent reports of diminishing vaccine-induced immunity over time and clinical benefits of a third dose (Swiss Multiple Sclerosis Society 2022; Levin et al., 2021; Bar-On et al., 2021; Patalon et al., 2022). Delaying the infusion of anti-CD20 therapy before vaccination is also believed to maximize humoral immune response (Cabreira et al., 2021). Levels of SARS-CoV-2-specific antibodies have been observed to progressively rise with longer spans of time between last infusion and vaccine dose, with significant differences emerging after 6 months according to a systematic review (Table 1) (Sormani et al., 2021; Schietzel et al., 2022; Disanto et al., 2021). This approach may be feasible and safe as recent studies have shown lengthening time between ocrelizumab or rituximab infusions by more than 7 months does not lead to significantly higher relapse rates or greater disease activity (Rolfes et al., 2021; Maarouf et al., 2020). With these findings in mind, physicians could help enhance vaccine efficacy in MS patients by making individualized modifications to a patient's vaccine schedule and DMT regimen.

Vaccination guidelines for MS patients and physicians have also been published by various organizations and societies. The American Academy of Neurology, Multiple Sclerosis International Federation (MSIF), National Multiple Sclerosis Society (NMSS), and European Committee for Treatment and Research in Multiple Sclerosis have all strongly recommended that patients with MS receive vaccination against SARS-CoV-2 (Marsh et al., 2021; Covid-19 Vaccine Guidance for People Living with MS 2022; Disease Modifying Therapy Guidelines During COVID-19 2022; Lee, 2022; The Coronavirus and MS 2021). Most, if not all, patients are encouraged to receive any of the available COVID-19 vaccines, continue their DMTs, and regardless of vaccination status, engage in additional precautionary measures such as social distancing, masking, and frequent handwashing (Marsh et al., 2021; Covid-19 Vaccine Guidance for People Living with MS 2022; Disease Modifying Therapy Guidelines During COVID-19 2022; Lee, 2022; The Coronavirus and MS 2021). The findings of the studies reviewed above largely support these recommendations, particularly in the case of patients relying on high-efficacy DMTs who may mount suboptimal humoral immune responses after vaccination and therefore should exercise extreme caution (A Achiron et al., 2021; Tallantyre et al., 2022; Sabatino et al., 2022). The MSIF and NMSS have even mentioned the possibility of altering the timing of DMT infusions as a means of optimizing vaccine efficacy, a strategy that has been demonstrated to be feasible, safe, and effective in previously mentioned studies (Sormani et al., 2021; Schietzel et al., 2022; Disanto et al., 2021; Rolfes et al., 2021; Maarouf et al., 2020; Covid-19 Vaccine Guidance for People Living with MS 2022; The Coronavirus and MS 2021).

4. Influenza vaccine

Although the safety of the influenza vaccine in MS patients has been extensively studied and its potential adverse effects thoroughly characterized, there have been a limited number of studies investigating the immunogenic responses of MS patients to these vaccines. We recently published a systematic review and meta-analysis providing insight into the immunogenicity of influenza vaccines in MS patients. Our study evaluated the immunogenicity of vaccinated MS patients via measured seroconversion and seroprotection in comparison to those of healthy controls (Nguyen et al., 2021). Of the nine total studies, five measured the immune responses of MS patients to vaccines for the H1N1 strain of influenza A (Olberg et al., Jul 2014; Olberg et al., Mar 2018; Mokhtarian et al., Aug 1997; Kim et al., Jun 2013). Most notably, rates of protection imparted by this vaccine were not observed to be significantly different between MS patients and their healthy counterparts (Nguyen et al., 2021).

In three of the five studies, interferon-β use in MS patients was not associated with significantly decreased immune responses, a finding that is largely consistent with an earlier, independently conducted study involving a smaller cohort (Nguyen et al., 2021; Metze et al., 2019). MS patients relying on DMTs including glatiramer acetate, natalizumab, and mitoxantrone were noted by one study to exhibit reduced long-term protection from influenza infection, while another study determined the rates of protection in vaccinated MS patients receiving interferon, natalizumab, or glatiramer acetate treatment to be statistically indistinguishable from those of healthy controls (Olberg et al., Jul 2014; Olberg et al., Mar 2018). Altogether, pooling of the data from both studies as well as several others revealed an absence of treatment effects on the immunogenicity of the H1N1 vaccine in MS patients (Nguyen et al., 2021).

Four of the nine studies measured immune responses of MS patients to vaccines for the H3N2 strain of influenza A (Olberg et al., Jul 2014; Olberg et al., Mar 2018; Mokhtarian et al., Aug 1997; Moriabadi et al., Apr 10 2001). In all four studies, antibody titers in these patients were found to be significantly higher following vaccination and comparable to those of their healthy, vaccinated counterparts (Nguyen et al., 2021). However, one study observed that vaccinated MS patients using glatiramer acetate, natalizumab, and mitoxantrone exhibited lower rates of protection than those relying solely upon interferon-β for disease management at six months post-vaccination (Olberg et al., Jul 2014). Another study led by the same researcher reported similar findings; all

vaccinated MS patients receiving any DMTs were determined to be protected at significantly lower levels than healthy controls (Olberg et al., Mar 2018).

In addition, we found adequate immune responses were elicited in MS patients after receiving vaccines for influenza A strains using data from three studies (Nguyen et al., 2021; Vagberg et al., Sep 2012; Mehling et al., 2013; Mehling et al., Feb 2011). Another three studies confirmed comparable humoral immune responses were achieved in MS patients vaccinated for influenza B strains (Mokhtarian et al., Aug 1997; Mehling et al., 2013; Mehling et al., Feb 2011). After pooling all the data, significant effects of treatment on the immune responses of MS patients to H3N2, influenza A, and influenza B vaccines were ultimately not found (Nguyen et al., 2021).

Though several studies have observed treatment effects on the immunogenicity of influenza vaccines in MS patients, our study and others suggest that the observed differences are not statistically significant (Kappos et al., 2015; Nguyen et al., 2021; Olberg et al., Mar 2018; Metze et al., 2019). Based on these most recent findings, it appears vaccinated MS patients can mount adequate immune responses and demonstrate similar rates of protection from influenza as compared to the general population, regardless of DMT use. Future studies that rely on larger sample sizes and control for confounding variables such as sex, age, ethnicity, and comorbidities will likely lend further support to these findings and provide invaluable insight into the potential effects of DMTs on the immunogenicity of influenza vaccines in MS patients.

5. Hepatitis B virus (HBV) vaccine

HBV poses a pressing health risk to populations worldwide, affecting over 2 billion individuals and causing chronic infection in an estimated 360 million patients (Lavanchy, 2004; Shepard et al., 2006). With the advent of HBV surface antigen-containing vaccines, rates of chronic infection and HBV-related complications, like hepatocellular carcinoma, have dropped significantly; the Centers for Disease Control and Prevention currently recommends infants, adolescents, and adults to undergo vaccination unless patients have a history of allergic reactions to any vaccine components (Shouval, 2003; Hepatitis, 2022). Though exceedingly safe in the general population, vaccination against HBV has raised concerns regarding its potential to cause MS and exacerbate its symptoms. These concerns were largely driven by early reports of patients with MS and otherwise healthy adults developing demyelinating lesions after vaccination (Herroelen et al., 1991; Tourbah et al., 1999). However, subsequent case-control studies failed to establish a link between HBV vaccination and elevated MS risk in adolescents and adults (DeStefano et al., 2003; Mikaeloff et al., 2007; Ascherio et al., 2001). A prospective study also observed an increased MS risk following live vaccination against HBV, but their findings have been inconsistent with the existing literature (Hernán et al., 2004). Namely, a case-crossover study found no association between HBV vaccination and risk of MS development or exacerbation (Confavreux et al., 2001). Recent systematic reviews have supported these findings, confirming that there is little to no evidence that HBV vaccination increases MS risk or causes relapse (Sestili et al., 2021; Mailand and Frederiksen, 2017). Like influenza vaccines, those against HBV are likely both effective and safe in MS patients and the general population.

The use of DMTs in MS patients with chronic HBV infections, however, is not without risks. Reports of HBV reactivation in patients using alemtuzumab, fingolimod, natalizumab, and ocrelizumab suggest that HBV screening is essential in this patient population prior to DMT administration (Lu et al., 2020; Hillen et al., 2015; Ciardi et al., 2018; Iannitto et al., 2005). As such, prudent management, and screening of DMT-dependent MS patients with latent HBV infections are necessary to prevent complications and promote long-term health.

6. Measles, mumps, and rubella vaccine

Measles, mumps, and rubella are viral infections that can be prevented by the highly efficacious MMR vaccine (Bankamp et al., 2019). Measles, a member of the *Paramyxoviridae* family, is typically spread by inhalation of respiratory droplets and causes fever, a maculopapular rash, cough, coryza, and conjunctivitis (Bankamp et al., 2019). Mumps, another member of the *Paramyxovirdae* family, typically causes orchitis, encephalitis, and meningitis, as well as fever, swelling, and tenderness of the salivary glands (Bankamp et al., 2019). Finally, rubella, a member of the *Togaviridae* family, is spread through sneezing or coughing, and causes a generalized maculopapular rash, fever, arthritis, lymphadenopathy, and conjunctivitis. If acquired in-utero, cataracts, cardiac abnormalities, and deafness can result (Bankamp et al., 2019).

To prevent these childhood viral illnesses, the live-attenuated MMR vaccine was first introduced in 1971[94]. The vaccine is typically given in two doses to children but may also be administered to adults (Bailey and Sapra, 2021). Between 2010 and 2015, global measles vaccination is estimated to have prevented more than 20 million deaths and decreased the measles incidence from 146 to 36 cases per million populations (Kowalzik et al., 2018). The MMR vaccine is typically regarded as immunogenic and safe (Bailey and Sapra, 2021).

Interestingly, an association between childhood illnesses and the development of MS has been identified. Childhood viral infections may play a role in MS development, as they may increase the risk of developing MS substantially (Eftekharian et al., 2016). Therefore, MMR vaccine administration is imperative. However, several cases of optic neuritis were observed following the MMR vaccine, thought to be associated with the toxic reactivation of the non-viral component of the vaccine (De Giacinto et al., 2016; Riikonen, 1989). All but one case subsequently developed MS (Riikonen, 1989). There were also several cases of transverse myelitis following MMR vaccine (Joyce and Rees, 1995; Lim et al., 2004). Of note, MS can develop 7–10 years after an acute demyelinating attack and thus, there may be limited use of the aforementioned studies. (De Giacinto et al., 2016; Riikonen, 1989; Joyce and Rees, 1995; Lim et al., 2004) Nonetheless, several studies have since aimed to understand if there is an association with the MMR vaccine and the development of MS and all but one have returned negative (DeStefano et al., 2003; Zorzon et al., 2003; Ramagopalan et al., 2009; C Ahlgren et al., 2009; C Ahlgren et al., 2009; MF Farez and Correale, 2011) The singular study that did find an association had a relatively small sample size, however (Zorzon et al., 2003).

It is largely recommended that individuals with MS be tested for immunity to measles, mumps, and rubella prior to starting immunosuppressive therapies (Reyes et al., 2020). If the individual is not currently immune, MMR vaccine administration is recommended (Reyes et al., 2020). However, because the MMR vaccine is a live-attenuated vaccine, administration should be avoided for those who are currently taking disease modifying, immunosuppressive therapy (Lebrun, 2019).

7. Human papillomavirus (HPV) vaccine

HPV is one of the most common sexually transmitted diseases worldwide, affecting more than 42.5 million people in America alone (Wang et al., 2020; Sexually Transmitted Infections Prevalence, Incidence, and Cost Estimates in the United States 2021). HPV typically infects squamous cell epithelium and is thereby largely associated with cutaneous and anogenital warts as well as various neoplastic illnesses, such as cervical, vulvar and vaginal cancer in women; penile cancer in men; and anal and mucosal cancers in both sexes (Wang et al., 2020; Pagliusi and Garland, 2007). While there are hundreds of HPV subtypes, less than a dozen are referred to as high risk - most common of which are HPV 16 and 18 (Wang et al., 2020).

Currently, there are 3 types of HPV vaccines, quadrivalent, bivalent, and nonavalent, that prevent around 90% of cancers caused by HPV

(Wang et al., 2020; Petrosky et al., 2015). Each vaccine is a noninfectious, virus-like particle (VLP) vaccine (HPV 2021). As of 2015, the World Health Organization (WHO) recommends two doses of the nonavalent HPV vaccine in individuals under the age of 15, and three doses for those 15 and older (Harper and DeMars, 2017). It is believed that the vaccine can provide prevention for HPV and HPV-related cancers until the individual enters the age of routine preventative screening (Harper and DeMars, 2017).

While the HPV vaccine's efficacy has largely been elucidated, the utility of the vaccine in the MS population is still controversial (Meggiolaro et al., 2018). A 2014 nested control study found an increased risk of CNS acquired demyelinating syndrome (ADS) within the first 30 days after HPV vaccination in individuals under 50 years old, thought to be attributed to a vaccine induced acceleration from subclinical to autoimmunity (Langer-Gould et al., 2014). No long-term effect was determined, however (Langer-Gould et al., 2014). Sutton and his team reported of five patients who presented with demyelinating syndromes 21 days after receiving the quadrivalent HPV vaccine (Sutton et al., 2009). Nonetheless, countless studies have since concluded against an association between the HPV vaccine and the development of MS and other ADS. A 2018 systematic review found no association between the quadrivalent HPV vaccine and the risk for MS and other ADS (Meggiolaro et al., 2018). Further studies have largely agreed (Langer-Gould et al., 2014; Scheller et al., 2015; Grimaldi-Bensouda et al., 2017; Pellegrino et al., 2013).

Fingolimod is a strong immunosuppressive and immunomodulating agent frequently prescribed to individuals with relapsing remitting MS (RR-MS) (Triplett et al., 2019; Lorvik et al., 2012). Its relationship to HPV and the HPV vaccine is a recent field of research (Triplett et al., 2019; Lorvik et al., 2012). Associations have been made between fingolimod and chronic treatment resistant HPV and HPV-related malignancies in a case series of 5 patients (Triplett et al., 2019). Improvement in those patients was observed following reduction or cessation of the medication (Triplett et al., 2019). It has been speculated that the risk of HPV-related malignancies in MS patients treated with DMTs increases due to decreased T-cell immunity (Benedetti et al., 2018). Nevertheless, considering the anecdotal nature of these studies, no change in current vaccination policy is warranted (Vaccinations 2022). Use of the HPV vaccine should be preceded with a conversation about the risks and benefits of vaccination (Vaccinations 2022). It is also currently advised to take a thorough medical history of HPV, HPV-related malignancies, and HPV vaccination status prior to starting fingolimod in patients with MS (Triplett et al., 2019).

8. *Streptococcus pneumoniae* vaccine

Streptococcus pneumoniae, the most common cause of both overall pneumonia and fatal pneumonia, is most common in children under the age of 2 and adults older than 65 years old (Ortqvist et al., 2005). Antibiotic resistance has developed over time and is most common in serotypes 6, 15, 19, 23, all of which are extremely common in children (Ortqvist et al., 2005).

There are currently two types of pneumococcal vaccines available in the United: conjugate vaccines and polysaccharide vaccines. The 23-valent capsular polysaccharide vaccine (PPSV23) was the first pneumococcal vaccine developed and is now primarily used as single dose after a 13-valent pneumococcal conjugate vaccine (PCV13) series in children ages 2–18 with certain medical conditions like sickle cell disease (Daniels et al., 2016). The PCV13 is available for children younger than 2 years old, and children between the ages of 2 and 18 with certain medical conditions (Pneumococcal vaccination 2022). Finally, the PCV15 and PCV20 are other approved conjugate pneumococcal vaccines recommended for adults 65 years old as well as adults ages 19–64 with certain medical conditions or risk factors (Pneumococcal vaccination 2022).

Individuals with MS on DMTs may have varied immune responses to pneumococcal vaccines. One study found that individuals on ocrelizumab had an attenuated reaction to non-live vaccines, including the pneumococcal vaccine, at 4 weeks, compared to those on interferon-β or untreated patients (Bar-Or et al., 2020). Conversely, a small historically controlled pilot study concluded that immunocompetence was maintained after use of alemtuzumab, a humanized monoclonal antibody used to treat active RR-MS by targeting CD52 and causing depletion of T and B lymphocytes (McCarthy et al., 2013; Havrdova et al., 2015). However, poor responses were observed when various vaccines were given within 2 months of alemtuzumab treatment, suggesting that immunization very early after alemtuzumab treatment may not be effective (McCarthy et al., 2013). Based on these data, current guidelines put forth by the United Kingdom recommend that people with MS ideally receive PPV23 at least 2 weeks before starting maintenance immunosuppressive and immune reconstitution therapies (Reyes et al., 2020). Additionally, those that are extremely immunocompromised should be offered the PCV13 at least 8 weeks before PPV23 (Reyes et al., 2020).

9. Yellow fever vaccine

Yellow fever, a potentially fatal vector-borne disease caused by the yellow fever virus (YFV), affects approximately 200,000 people annually (Staples et al., 2010). Part of the genus *flavivirus,* YFV is a small enveloped positive sense single-stranded RNA virus that is endemic to Sub-Saharan Africa and tropical South America. YFV is typically transmitted by a bite of a YFV-infected mosquito (Staples et al., 2010; Monath, 2005). Though it commonly causes fever, chills, severe headache, and back pain, in severe cases, it may progress to a hemorrhagic fever that is fatal in 20–50% of cases (Staples et al., 2010). At the present time, there is no curative treatment (Staples et al., 2010). Accordingly, prevention is key.

Current recommendations for the YFV vaccine in the general population is a single dose of a live-attenuated vaccine for individuals 9 months or older who are traveling to or living in high risk areas (Staples et al., 2010; Yellow Fever Vaccine 2021). Recommendations for those with MS remain controversial due to findings of recent studies. A 2011 study found a significant increase in exacerbation rates within 3 months following the YFV vaccine compared to pre-vaccination exacerbation rates (MF Farez and Correale, 2011). Of note, since its publication, the methodology of the aforementioned study has been called into question (Pool et al., 2012). On the other hand, a case series found no association between MS relapses and YFV vaccination (Huttner et al., 2020). Subsequent studies have found no change in first relapse between individuals with RR-MS who were "exposed" to the YFV vaccine when compared to individuals with RR-MS who were "non-exposed (Papeix et al., 2021)." Additionally, the time to first relapse did not differ between the two groups (Papeix et al., 2021). Importantly, all related studies have relatively limited sample sizes.

The utility of the YFV vaccine in the setting of individuals with MS on DMTs has also been an area of recent study. A 2018 study found that recurrent MS relapses were associated with the YFV vaccine when given within 2 months of fingolimod withdrawal (Barnett, 2007). Study researchers extrapolate that in the setting of fingolimod withdrawal, MS can be potentially triggered by live-attenuated vaccines, such as the YFV vaccine (Barnett, 2007). A later 2019 case study found a similar triggering effect of the YFV vaccine in the setting of fingolimod withdrawal (Rolfes et al., 2019).

Current guidelines per the French MS society articulate that live-attenuated vaccines are relatively contraindicated in patients recently treated with immunosuppressive drugs (Reyes et al., 2020). Individuals with MS and their healthcare providers must therefore consider the possible risk of an MS exacerbation following YFV vaccine administration as well as the risk of contracting the YFV (Huttner et al., 2020). Altogether, further research is needed to ascertain any causal association between the YFV and MS exacerbations.

10. Conclusion

Vaccination of patients living with MS remains an indispensable tool to prevent future infections, minimize risk of relapse, and above all, maintain the health of this exceedingly vulnerable population. There is only a growing body of evidence that supports the safety, immunogenicity, and efficacy of this preventive health measure. According to the most recent studies discussed above, a majority of MS patients will likely benefit from vaccination against COVID-19, influenza, HBV, MMR, HPV, *Streptococcus pneumoniae*, and YFV while those treated with DMTs may need to carefully weigh the risks and benefits of pursuing or forgoing vaccination. Without a doubt, future studies will be instrumental in shaping current guidelines and recommendations. Of the studies reviewed in this article, several were limited by restricted sample sizes and homogenous patient groups. As such, further research will likely be needed to confirm their respective findings in broader, more diverse patient populations and explore novel strategies through which the health of MS patients can be more effectively safeguarded.

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