Review Article

Update on the management of multiple sclerosis during the COVID-19 pandemic and post pandemic: An international consensus statement

Saúl Reyes [a,b,c], Anthony L. Cunningham [d], Tomas Kalincik [e,f], Eva Kubala Havrdová [g], Noriko Isobe [h], Julia Pakpoor [i], Laura Airas [j], Reem F. Bunyan [k], Anneke van der Walt [l], Jiwon Oh [m,n], Joela Mathews [o], Farrah J. Mateen [p,q], Gavin Giovannoni [a,r,*]

[a] Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[b] Fundación Santa Fe de Bogotá, Bogotá, Colombia
[c] School of Medicine, Universidad de los Andes, Bogotá, Colombia
[d] The Westmead Institute, University of Sydney, Sydney, Australia
[e] CORe, Department of Medicine, University of Melbourne, Melbourne, Australia
[f] Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia
[g] Department of Neurology and Center for Clinical Neuroscience, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic
[h] Department of Neurology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[i] Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[j] Department of Clinical Neurosciences, Turku University Hospital and University of Turku, Turku, Finland
[k] Department of Neurology, Neurosciences Center, King Fahd Specialist Hospital (KFSH)-Dammam, Dammam, Saudi Arabia
[l] Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Australia
[m] Division of Neurology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada
[n] Department of Neurology, Johns Hopkins University, Baltimore, MD, USA
[o] Department of Pharmacy, Royal London Hospital, Barts Health NHS Trust, London, UK
[p] Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
[q] Harvard Medical School, Boston, MA, USA
[r] Department of Neurology, Royal London Hospital, Barts Health NHS Trust, London, UK

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ABSTRACT

In this consensus statement, we provide updated recommendations on multiple sclerosis (MS) management during the COVID-19 crisis and the post-pandemic period applicable to neurology services around the world.

Statements/recommendations were generated based on available literature and the experience of 13 MS expert panelists using a modified Delphi approach online.

The statements/recommendations give advice regarding implementation of telemedicine; use of disease-modifying therapies and management of MS relapses; management of people with MS at highest risk from COVID-19; management of radiological monitoring; use of remote pharmacovigilance; impact on MS research; implications for lowest income settings, and other key issues.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has put an enormous strain on medical resources and, in most countries, healthcare systems have had to reconfigure to manage the surge of cases of severe COVID-19 and to reduce the risk to vulnerable patients of being exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Berlin et al., 2020). We need to acknowledge that COVID-19 surges will continue until vaccination efforts expand across the world and massive vaccination programs produce adequate immunity in the general population. It is essential that the management of people with multiple sclerosis (pwMS) is adapted, but not compromised, to deal effectively with the challenges posed by COVID-19.

The COVID-19 spectrum ranges from asymptomatic cases, uncomplicated upper respiratory tract (URT) infections to severe pneumonia. About 80% of symptomatic cases are mild with URT symptoms, while pneumonitis occurs in approximately 20%, of which about 5% require intensive care unit (ICU) admission and artificial ventilation (Williamson et al., 2020; Wu and McGoogan, 2020). The global mean mortality of clinical COVID-19 is 3% but varies widely and is increased by pressure on ICU facilities. The mortality and ICU admission rate increases markedly with age, especially those aged 70 years or older, and for those with severe immunosuppression (e.g. organ transplantation and hematopoietic stem cell transplantation) and chronic cardiac and respiratory diseases, diabetes and hypertension (Williamson et al., 2020; Wu and McGoogan, 2020). For pwMS who are immunosuppressed owing to disease-modifying therapies (DMTs), there is still concern among neurologists regarding their morbidity and mortality with COVID-19.

In this consensus statement, we aim to provide updated recommendations on the management of MS during the COVID-19 crisis and the post-pandemic period that are applicable to MS services around the globe, and how to prioritize MS services as the pandemic evolves and the post-pandemic landscape begins to unfold. This guidance may not completely capture global practice patterns during COVID-19 times especially because the epidemiology of COVID-19 varies widely across the globe as many nations ramp up their vaccination drives. These recommendations are likely to change depending on the rapid evolution of the COVID-19 situation worldwide.

2. Methods

We assembled a multidisciplinary expert panel of 13 MS specialists to provide recommendations related to MS management during the COVID-19 pandemic and the post-pandemic period. The panel comprised members of the Treatment and Research in Multiple Sclerosis online (*triMS.online*) Scientific Steering Committee and other expert leaders in MS from across the world (who all spoke at the *triMSx.online* educational virtual meeting on the management of MS during the COVID-19 pandemic) ("triMSx: Managing MS during the COVID-19 pandemic (2020) – triMS.online – Treatment and Research in Multiple Sclerosis online," n.d.). The primary mode of communication was email. Initially, the panel members identified and articulated key questions and concerns about MS management during COVID-19 times. These were separated into specific topics and assigned to panel members according to their area of expertise. Statements/recommendations were drawn out of the available literature and based on the experience of the assigned members. In round 1, the statements/recommendations were circulated to all members, who individually scored each of them using a modified Delphi scoring system (strongly agree, agree, neutral, disagree or strongly disagree). Statements/recommendations for which consensus (i.e. ≥ 75% of the panel scored that they strongly agreed or agreed with the statement/recommendation) was not reached in round 1 were revised according to feedback received from the panelists. The revised statements/recommendations were submitted for ranking of agreement in further rounds of voting. Modifications were made iteratively until consensus was reached on all statements/recommendations.

2.1. Data availability statement

All data analyzed in this manuscript will be shared as anonymized data via request from any qualified investigator.

3. Results and discussion

In total, 39 recommendations/statements were drafted by the expert panel and voted on. All members voted on all recommendations/statements. After five rounds of voting, consensus was reached on all statements/recommendations. A summary of the available evidence and panel discussion for each topic is provided in the following, and the final statements/recommendations for each topic provided in Table 1. Complete results of all five Delphi rounds are shown in eTable 1.

3.1. Advice for health professionals to share with pwMS

PwMS exposed to immunosuppressive therapies and those with worse disability are more susceptible to infection and also risk higher morbidity and mortality from many infections (Epstein et al., 2018; Reyes et al., 2020). However, MS alone is not a risk factor for symptomatic infection with SARS-CoV-2 or for critical COVID-19 (Korsukewitz et al., 2020; Zabalza et al., 2020). Data from populations in ongoing studies suggest that most COVID-19 cases in pwMS are mild and in line with observations in the general population (Bowen et al., 2020; Bsteh et al., 2020; Loonstra et al., 2020; Sormani, 2020). These reports are even more reassuring considering that a considerable proportion of pwMS who have asymptomatic or mild COVID-19 who self-isolate and recover spontaneously may not be enrolled in these studies. Nevertheless, these findings should not be generalized to all pwMS as the risk of COVID-19 and COVID-19-related complications may vary widely depending on multiple circumstances including, but not limited to, age, sex, race, comorbidities and the local epidemiology of COVID-19 (Korsukewitz et al., 2020). Therefore, long-term data acquisition remains crucial to gain more knowledge about the course of COVID-19 in pwMS. In the meantime, clinicians' advice should be comprehensive and should follow national and local guidelines for reducing the risk of infection with SARS-CoV-2. These can include social distancing, frequent hand washing and/or disinfecting, avoiding public transport, practicing good respiratory hygiene and wearing facemasks in public (MS International Federation, 2020; World Health Organization (WHO), 2020). As the population of pwMS recovering from COVID-19 grows, it is paramount to establish an understanding of the persistent and prolonged effects after acute COVID-19 (i.e. subacute or ongoing symptomatic COVID-19, and chronic or post-COVID-19 syndrome) (Nalbandian et al., 2021). Cognitive impairment, fatigue, anxiety and depression, which are also common in MS, have been found to be important components of post-acute COVID-19 (Nalbandian et al., 2021). It is clear that the care for patients with COVID-19 extends beyond the acute phase of infection and the aim has to be to encourage the early recognition, careful documentation, investigation and management of any sequelae of COVID-19 that may pose an additional burden on pwMS.

3.2. Specific DMTs and COVID-19

Most DMTs used to control autoimmunity in MS are targeted against CD4 and Th17 T cells, and memory (CD19+ CD27+) and naive (CD19+ CD27-) B cells (Berger et al., 2020; Kunkl et al., 2020). Although it is reasonable to assume that such immunotherapies would not substantially reduce the capacity to counter the SARS-CoV-2 infection, one should remember that some MS therapies are associated with broad and profound immunosuppression (such as alemtuzumab or chemotherapy with autologous hematopoietic stem cells salvage therapy) (Baker et al., 2020a). Furthermore, minor collateral effects of therapies on the

Table 1

Recommendations for the management and treatment of MS during COVID-19 times.

Advice for health professionals to share with pwMS

- All pwMS should be advised to follow national or local guidelines for reducing the risk of infection with SARS-CoV-2.
- PwMS should be encouraged to report any ongoing or new symptoms following acute COVID-19 so that a competent assessment to identify and manage post-acute COVID-19 syndrome can take place.

Specific DMTs and COVID-19

- Any decision to start or re-dose a DMT during COVID-19 times will need to be taken carefully and will depend on the local epidemiology of COVID-19, as well as patient's individual factors such as MS severity, disease activity and comorbidities.
- Interferons, glatiramer acetate andteriflunomide can be prescribed as usual during COVID-19 times.
- An extended interval dosing of natalizumab (every 5–6 weeks) is recommended to allow patients to make fewer trips to the hospital and minimize their risk of exposure to SARS-CoV-2.
- Dimethyl fumarate, fingolimod and cladribrine can be prescribed as usual during COVID-19 times. For pwMS who are severely lymphopenic owing to these drugs, it is recommended to be extra-vigilant about precautions aimed to reduce the risk of SARS-CoV-2 infection.
- Anti-CD20 monoclonal antibodies such as ocrelizumab or rituximab can be offered to pwMS with highly active MS under strict sanitary rules and social distancing restrictions. However, an alternative highly effective DMT with a more favorable profile in terms of COVID-19 outcomes may be considered.
- Alemtuzumab can be offered to patients with highly active MS and strict rules should be considered for the protection of patients with lymphopenia. However, an alternative highly effective DMT with a more established safety profile in terms of COVID-19 outcomes could be considered.
- Immune reconstitution therapies such as mitoxantrone or HSCT are not recommended when the risk of COVID-19 is high.

COVID-19 vaccine guidance

- There is no reason to avoid the COVID-19 vaccine based on the hypothesis that these vaccines may trigger MS relapses or demyelinating disease.
- Vaccination and DMTs can be timed to maintain disease control and also allow effective vaccination against SARS-CoV-2 (Table 2).

Management of MS exacerbations

- PwMS experiencing relapses or pseudorelapses should be actively screened for symptoms of COVID-19.
- When high-dose corticosteroids are needed, their administration (oral or intravenous) at home is recommended to avoid high-risk travel and unnecessary contacts. Also, steroid tapering should be avoided.
- Pseudorelapses must be excluded to avoid unnecessary treatment with corticosteroids or to add appropriate therapy in the case of co-infections.

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pwMS at highest risk from COVID-19

- All pwMS need to be risk assessed by adopting an individualized case-by-case approach, considering their age, comorbidity and ethnicity, in addition to MS-specific factors such as disability or immunosuppressive treatment.
- Those at heightened risk should be advised to be particularly stringent when applying infection control recommendations and social distancing measures.
- Where possible, neurology appointments for pwMS at heightened risk should be prioritized and facilitated through a virtual telemedicine platform to avoid unnecessary hospital exposure.
- Where possible, supply of medication (distribution of DMTs and long-term medications) for pwMS at heightened risk should be prioritized to facilitate isolation/shielding if required.

COVID-19 and pregnancy in pwMS

- Pregnant women may be more susceptible to severe illness associated with COVID-19 or its complications; pregnant pwMS should be counseled and monitored accordingly.
- Pregnancies of pwMS infected with SARS-CoV-2 should be handled similarly to pregnancies of other individuals with the infection.

Management of MS in pediatric patients

- There is no evidence that children with MS are more susceptible to COVID-19 or its complications.
- Children with MS should continue effective immunotherapy during COVID-19 times unless there are major safety concerns or a clinical rationale to stop.
- Particular attention should be paid to the mental health of children with MS during COVID-19 times.

Remote management

- Telemedicine represents a feasible option for the remote assessment and management of MS during the COVID-19 pandemic and the post-pandemic period.
- Patient-reported outcome measures should be used as an aid in the remote assessment of pwMS.
- Timely proactive measures should be taken in COVID-19 high-risk areas to reduce non-essential hospital visits for pwMS.

Radiological monitoring

- The risks of contact with a healthcare facility and COVID-19 need to be weighed against the risk of subclinical MS disease activity on a case-by-case basis.
- All imaging facilities should follow local public health guidelines to decrease the risk of SARS-CoV-2 transmission in patients attending the facility.
- As imaging facilities may face capacity constraints amid recurrent COVID-19 waves and outbreaks, neurologists should appropriately designate which pwMS need an MRI more urgently, and which patients can have their MRI safely deferred.

Remote pharmacovigilance

- Abbreviated blood monitoring for patients receiving DMT is desirable to mitigate the potential risk of SARS-CoV-2 exposure associated with frequent traveling to clinical sites.
- Reduced blood monitoring schedules should be established locally, taking into account local patient numbers on each drug, site risks of how phlebotomy is undertaken, and staffing capacity to monitor the results.

Implications for lowest income settings

- Guidelines for pwMS in low-income populations with country-specific recommendations should be established and updated as the COVID-19 situation evolves.
- PwMS in low-income populations would benefit from broader access to affordable telemedicine services.
- Professional society recommendations should be translated into multiple languages and formats to improve accessibility to low-income groups.
- Support should be provided for neurologists in lowest income populations who may be at risk of professional burnout and becoming unable to provide routine MS care.
- Registries and networks of pwMS in lower income populations should be created to provide support and information as the COVID-19 situation evolves.

Impact on MS research

- Additional research efforts are needed to improve the knowledge of the biology and pharmacokinetics of MS DMTs in the setting of COVID-19.
- New approaches to MS trials and cohort studies, including online platforms, wearable devices, and patient-reported outcome measures should be used in tandem with traditional outcomes measures.
- Multi-stakeholder collaboratives across heterogeneous populations and settings are recommended to share data rapidly and efficiently.

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying treatment; HSCT = hematopoietic stem cell transplantation; MS = multiple sclerosis; pwMS = people with multiple sclerosis; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

immune mechanisms implicated in the response to SARS-CoV-2 have been described (such as reduction in CD8+ memory T cells against certain myelin epitopes) (Sabatino et al., 2019). Evidence from international registries of COVID-19 among pwMS and the known pharmacology of DMTs enable us to draw some conclusions about the effect of MS therapies on COVID-19.

3.2.1. First-generation DMTs and teriflunomide

Interferons are not considered to be immunosuppressive. Type I interferons have potent in vivo antiviral effects (e.g. decreased viral replication) that may even contribute to their efficacy in MS (Hong et al., 2002). A virus-infected cell releases viral particles that can infect nearby cells, however, the infected cell can also protect neighboring cells against a potential infection by releasing interferons. In line with this view, both interferon alfa and interferon beta have been tested as potential treatments in coronavirus infection (El-Lababidi et al., 2020; Shalhoub, 2020). Glatiramer acetate also does not have systemic immunosuppressive properties and does not increase the risk of viral infections in pwMS (Giovannoni, 2018). Interferons and glatiramer acetate have been associated with a lower risk of SARS-CoV-2 infection in PwMS (Reder et al., 2021). Teriflunomide promotes cytostasis in T and B cells via selective inhibition of dihydro-orotate dehydrogenase, which is a key mitochondrial enzyme in de novo pyrimidine synthesis required by rapidly dividing lymphocytes (Giovannoni, 2018). Viral replication requires host resources to make viral protein and replicate the viral DNA/RNA genome. Teriflunomide promotes G1/S phase arrest, thus impeding viral replication (Bilger et al., 2017). When tested in animals it leads to a decrease in viral load (herpes simplex virus type 1, BK virus and cytomegalovirus) (Bilger et al., 2017). It is therefore not surprising that teriflunomide could play a potential therapeutic role in COVID-19 through dual antiviral and immunomodulatory actions (Maghzi et al., 2020). Teriflunomide has not been shown to increase the risk of severe COVID-19 (Reder et al., 2021; Simpson-Yap et al., 2021; Sormani et al., 2020). There is no need to stop treatment or wait to start treatment with interferons, glatiramer acetate or teriflunomide in pwMS during COVID-19 times.

3.2.2. Drugs with lymphopenic effects

Dimethyl fumarate (DMF) can cause severe prolonged lymphopenia in a small proportion of patients. However, there is only a slightly increased rate of infections in pwMS treated with DMF (Giovannoni, 2018). DMF does not increase the risk of patients developing severe COVID-19 and stopping or delaying treatment with DMF during COVID-19 times is not recommended (Reder et al., 2021; Simpson-Yap et al., 2021; Sormani et al., 2020). Fingolimod and sphingosine 1-phosphate receptor (S1PR) modulators cause reversible sequestration of lymphocytes in lymphoid tissues, which may increase the risk of infections (Giovannoni, 2018). Infections that are observed during fingolimod treatment include herpetic infections, lower respiratory tract infections and very rarely ones leading to progressive multifocal leukoencephalopathy (PML) (Giovannoni, 2018). In animal models, S1PR modulators were shown to limit cytokine storm, which is one of the mechanisms leading to severe COVID-19. In the light of this, fingolimod is under investigation as a potential treatment for COVID-19-associated acute respiratory distress syndrome. Although some case studies suggest that fingolimod may increase the risk of severe COVID-19 (Barzegar et al., 2020), this finding was not seen in larger cohorts (Reder et al., 2021; Simpson-Yap et al., 2021; Sormani et al., 2020). Postponing treatment with fingolimod during COVID-19 times is not recommended. Similarly, stopping treatment with fingolimod should be discouraged because of the possibility of severe rebound disease activity and worsen disability (Giovannoni, 2018). Lymphopenia has been associated with poor outcomes in patients with COVID-19 (Huang and Pranata, 2020). For pwMS

who are severely lymphopenic owing to DMF or fingolimod, it is recommended to be extra-vigilant about precautions aimed to reduce the risk of SARS-CoV-2 infection.

3.2.3. Natalizumab

Natalizumab inhibits lymphocyte trafficking across the blood–brain barrier and does not cause lymphopenia or systemic immunosuppression (Giovannoni, 2018). Natalizumab has been associated with a slightly higher rate of URT infections (Polman et al., 2006; Rudick et al., 2006), but whether this is significant in relation to SARS-CoV-2 infection is unknown. Patients should be warned that there is a risk of rebound (i. e. severe increase in relapse relate) associated with stopping or delaying treatment with natalizumab by longer than 8 weeks (Giovannoni, 2018). Natalizumab does not increase the risk of severe COVID-19 (Reder et al., 2021; Simpson-Yap et al., 2021; Sormani et al., 2020) and stopping treatment with natalizumab or delaying its initiation during COVID-19 times is not recommended. Extended interval dosing of natalizumab (every 5–6 weeks) is recommended to allow patients to make fewer trips to the hospital and minimize their exposure risk as much as possible.

3.2.4. Anti-CD20 drugs

The anti-CD20 monoclonal antibodies rituximab and its more humanized successors ocrelizumab and ofatumumab selectively deplete circulating CD20+ B cells via complement- and antibody-dependent cytotoxicity, antibody-dependent cellular phagocytosis and direct apoptosis (Giovannoni, 2018). Repeated 6-monthly CD20 depletion is associated with hypogammaglobulinemia in some individuals, and also a small but increased risk of severe infections (Baker et al., 2020b). Anti-CD20 therapies have been associated with an increased risk of SARS-CoV-2 infection in PwMS (Reder et al., 2021; Zabalza et al., 2020). In addition, data from the Multiple Sclerosis and COVID-19 (MuSC-19) Italian cohort ($n = 844$ pwMS) suggested an increased frequency of a severe COVID-19 course in pwMS treated with anti-CD20 agents (ocrelizumab or rituximab) compared with those receiving other DMTs (Sormani et al., 2020). More recently, results of the COVID-19 in MS Global Data Sharing Initiative and a large cohort of North American pwMS showed that anti-CD20 DMTs were associated with worse COVID-19 outcomes (Salter et al., 2021; Simpson-Yap et al., 2021). Although anti-CD20 monoclonal antibodies can be offered to pwMS with highly active or severe disease, an alternative highly effective DMT with a more favorable profile in terms of COVID-19 outcomes may be considered in the COVID-19 era. Reducing the frequency of dosing, or adjusting it according to the monitoring of B-cell repopulation kinetics in individual patients, may maintain efficacy while limiting the risk of infection and associated morbidity (Sormani et al., 2020). Neutralizing antibodies such as bamlanivimab/etesevimab or casirivimab/imdevimab may have a prophylactic role in individuals deemed to be at high risk of severe COVID-19 (Taylor et al., 2021). It remains to be determined whether these neutralizing antibodies could mitigate the risk of poor outcomes in anti-CD20-treated pwMS before or after exposure to SARS-CoV-2.

3.2.5. Immune reconstitution therapies

Some pwMS on immune reconstitution therapies (IRTs) may be at risk for various potentially severe infections (Giovannoni, 2018). However, differentiation between the depletion phase and the immune reconstitution phase is important. Although lymphopenia during the depletion phase is associated with an increased risk of infection and infection-related complications, once the total lymphocyte counts have returned to normal or near normal (i.e. post immune reconstitution) the risk of severe infection is probably no higher than expected for the background population (Giovannoni, 2018). Cladribine is a purine nucleoside analog that selectively depletes peripheral lymphocytes without a major impact on cells of the innate immune system

(Giovannoni, 2018). Transient and typically mild to moderate lymphopenia after each course of treatment with cladribine may be accompanied with an increased risk of infection. However, available data have shown that there is no increased risk of severe COVID-19 in pwMS treated with cladribine (De Angelis et al., 2020; Jack et al., 2020, 2021; Sormani et al., 2020). Treatment with cladribine can be considered during COVID-19 times in patients with highly active disease and in those for whom first-line DMTs have failed. Lymphopenia has been associated with poor outcomes in patients with COVID-19 (Huang and Pranata, 2020). For pwMS who are severely lymphopenic following a course of cladribrine, it is recommended to be extra-vigilant about hygiene and social distancing, and avoid high-risk travel (Giovannoni et al., 2020). Alemtuzumab is a CD52-specific monoclonal antibody that markedly depletes T and B lymphocytes (Giovannoni, 2018). Alemtuzumab may be an appropriate treatment choice across a broad range of pwMS, especially those with highly active disease. However, the use of alemtuzumab has been associated with an increased risk of infectious events, including opportunistic infections (Giovannoni, 2018). Although alemtuzumab may not lead to a severe COVID-19 course (Iovino et al., 2021; Matías-Guiu et al., 2020; Simpson-Yap et al., 2021; Sormani et al., 2020), the number of pwMS treated with alemtuzumab who have been included in COVID-19 series/registries has been deemed to be too low to draw meaningful conclusions. DMTs with a more established profile in terms of COVID-19 outcomes could be considered during COVID-19 times and temporarily delaying (between 6 and 12 months) re-dosing of alemtuzumab could be considered based on the local epidemiology of COVID-19. Hematopoietic stem cell transplantation (HSCT) is an off-label treatment used for highly active MS (Sharrack et al., 2020). HSCT causes profound immunosuppression that predisposes some individuals to severe infectious complications (Sharrack et al., 2020). However, the actual risks of COVID-19 in pwMS treated with HSCT are not known. Given the experience with other respiratory viruses, it has been suggested that HSCT recipients may develop severe clinical disease (Waghmare et al., 2020). Moreover, recent data from a multicenter study of 318 patients with hematologic malignancies or related disorders showed that HSCT recipients were at increased risk of death from COVID-19 compared with the general population (Sharma et al., 2021). HSCT is therefore seen as a high-risk strategy to initiate during COVID-19 times. Treatment alternatives with a more favorable profile in terms of COVID-19 outcomes should be considered for treating MS when the risk of COVID-19 is high. A similar recommendation has been made for mitoxantrone, which is a cytotoxic agent capable of broad immunosuppression.

Table 2 summarizes our recommendations about the use of DMTs in pwMS during COVID-19 times.

3.3. COVID-19 vaccine guidance

Vaccination is the most important strategy to end the pandemic. Although vaccines are widely understood as safe and effective public health interventions, their use in pwMS has long been a controversial subject, partly because of misguided concerns that they may cause or exacerbate the disease. However, strong evidence supports that no association exists between vaccination and the onset or relapse of MS (Kalincik, 2015; Reyes et al., 2020). The only vaccine that has been reported to potentially trigger disease activity in MS is the live yellow fever vaccine and this is based on 1 report, which subsequently has not been replicated (Farez and Correale, 2011; Huttner et al., 2020). The two cases of transverse myelitis that occurred with the Oxford–AstraZeneca COVID-19 vaccine raised controversies regarding COVID-19 vaccine safety. However, they were deemed unrelated to the vaccine and all participants have recovered or are recovering (Knoll and Wonodi, 2021; Kolber et al., 2021). More recently, the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine was found to be safe in pwMS and the rate and types of reported adverse events following immunization is not expected to be different when compared to the general population

(Achiron et al., 2021a). There is no current evidence that COVID-19 vaccines trigger MS relapses or demyelinating disease.

The use of DMTs that may influence the immune response to immunizations is also a matter of discussion (Reyes et al., 2020). No efficacy concerns have been reported for interferon, fumarates and teriflunomide in relation to vaccinations in general. For glatiramer acetate and natalizumab the available evidence is less conclusive, with some studies showing the inactivated influenza vaccine may be less effective in pwMS taking these DMTs (Reyes et al., 2020). Reduced immune response to some vaccines in patients treated with S1PR modulators has been described (Kappos et al., 2015; Ufer et al., 2017). A blunted, but not absent, humoral response to vaccines has also been documented in pwMS treated with ocrelizumab (Bar-Or et al., 2020).

Finally, pwMS on immune reconstitution therapies (eg, alemtuzumab, cladribine, or HSCT) who have reconstituted their immune systems should be able to respond to vaccines with some considerations: (1) vaccination within 6 months of treatment with alemtuzumab may result in a smaller proportion of responders (McCarthy et al., 2013), (2) data from MAGNIFY-MS and CLOCK-MS suggests that pwMS receiving cladribine are able to mount responses to influenza and varicella-zoster vaccines irrespective of lymphocyte count (Achiron et al., 2021b), and (3) vaccines have been found to induce a response in a substantial proportion of the patients as early as 3 months after HSCT (Cordonnier et al., 2019). In terms of the COVID-19 vaccine, a recent study from Israel showed that cladribine did not impair the humoral response to COVID-19 vaccination in pwMS (being vaccinated as early as 4.4 months after the last treatment dose), while most pwMS treated with fingolimod or ocrelizumab had blunted antibody responses to the vaccine (Achiron et al., 2021b). However, a blunted antibody response does not necessarily translate into a lack of long-lasting immunity to the infection, and the role of vaccine-induced cellular immunity to SARS-CoV-2 is yet to be defined. Although some DMTs may be associated with attenuated vaccine responses in pwMS, even a blunt vaccine response is likely to protect them against infection or at least severe COVID-19. Vaccination and DMTs can be timed to maintain disease control and also allow effective vaccination against SARS-CoV-2 (Table 2).

3.4. Management of MS exacerbations

It has been established that MS exacerbations associated with infections may lead to more severe and sustained neurological deficit than spontaneous relapses, but whether COVID-19 can aggravate existing MS is unknown (Buljevac et al., 2002; Correale et al., 2006; Marrodan et al., 2019). As there is a theoretical potential for worsening of MS symptoms during systemic infections, pwMS experiencing relapses or pseudorelapses should be actively screened for symptoms of COVID-19 (Brownlee et al., 2020).

The use of corticosteroids has been largely discouraged in patients with COVID-19 given concern that corticosteroid-induced immunosuppression could lead to worse outcomes and increase viral shedding (Gibson et al., 2020). However, as inflammation plays an important role in more severe manifestations of COVID-19, the anti-inflammatory properties of corticosteroids might potentially be useful. Data from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial of dexamethasone showed that the benefits of steroid treatment outweigh any potential harm in hospitalized patients with COVID-19 who are receiving respiratory support (RECOVERY Collaborative Group, 2021). The impact of receiving steroids during COVID-19 times for other underlying diseases (i.e. recent MS exacerbations) is just beginning to be elucidated.

Moderate- to high-dose glucocorticoids have been associated with a higher risk of hospitalization for COVID-19 in patients with rheumatic disease (Gianfrancesco et al., 2020). Similarly, data from the MuSC-19 study group showed that methylprednisolone in the month preceding the first symptoms of COVID-19 was significantly associated with a worse outcome (Sormani et al., 2020). More recently, data from a large

Table 2
Main attributes of licensed MS DMTs in relation to COVID-19.

DMT	Mode of action	Class	Safe to start treatment?	Advice regarding treatment	In the event of COVID-19?	COVID-19 vaccination	Attributes and caveats
Interferon beta	Immunomodulatory (not immunosuppressive), pleiotropic immune effects	Maintenance immunomodulatory	Yes	Continue	Continue	Likely to be effective. Stopping or delaying treatment for vaccination is not recommended.	Has antiviral properties that may be beneficial in the case of COVID-19
Glatiramer acetate	Immunomodulatory (not immunosuppressive), pleiotropic immune effects	Maintenance immunomodulatory	Yes	Continue	Continue	Some non-live vaccines may be less effective. COVID-19 vaccination is nevertheless strongly encouraged. Stopping or delaying treatment for vaccination is not recommended.	–
Teriflunomide	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis), anti-proliferative	Maintenance immunomodulatory	Yes	Continue	Continue	Likely to be effective. Stopping or delaying treatment for vaccination is not recommended.	Has antiviral properties that may be beneficial in the case of COVID-19
Dimethyl fumarate	Pleotropic, NRF2 activation, downregulation of NF-κB	Maintenance immunosuppressive	Yes	Continue.	Continue	Likely to be effective. Stopping or delaying treatment for vaccination is not recommended.	The risk can only be considered low in patients who do not develop persistent lymphopenia
S1P modulators (fingolimod, siponimod or ozanimod)	Selective S1P receptor modulator, prevents egress of lymphocytes from lymph nodes	Maintenance immunosuppressive	Yes	Continue.	Continue	Likely to be blunted. COVID-19 vaccination is nevertheless strongly encouraged. PwMS should ideally be fully vaccinated at least 2–4 weeks before starting S1P modulators. Stopping treatment for vaccination is not recommended.	Theoretical risk that S1P modulators may result in prolonged viral shedding. Paradoxically S1PR modulators may reduce the severity of COVID-19; fingolimod is being trialed.
Natalizumab	Anti-VLA4, selective adhesion molecule inhibitor	Maintenance immunosuppressive	Yes	Continue, but consider EID	Continue or delay the next infusion depending on timing	Some non-live vaccines may be less effective. COVID-19 vaccination is nevertheless strongly encouraged. Stopping or delaying treatment for vaccination is not recommended.	As COVID-19/SARS-CoV-2 is neurotropic, natalizumab could theoretically prevent viral clearance from the CNS. Lower theoretical risk on EID. There are still concerns about creating an environment in mucosal surfaces and the gut that may promote prolonged viral shedding. There is a risk of rebound (i.e. severe increase in relapse relate) associated with delaying treatment with by longer than 8 weeks.
Cladribine	Deoxyadenosine (purine) analog, adenosine deaminase inhibitor, selective T- and B-cell depletion	IRT (semi-selective)	Yes	Continue. Temporary suspension of dosing if lymphopenic	Temporary suspension of dosing depending on timing	Likely to be effective. Stopping or delaying treatment for vaccination is not recommended.	Only reduces the T-cell compartment by ~50% and has less of an impact on the CD8+ population. Provided total lymphocyte counts are above 500/mm^3 appropriate antiviral responses should be maintained. Theoretical risk that in the immune depletion phase cladribine may result in prolonged viral shedding
Anti-CD20 therapies	Anti-CD20, B-cell depleter	Maintenance immunosuppressive	Probably	Risk assessment –	Temporary suspension of	Likely to be blunted within 9 months of the	Drops both the CD4+ and CD8+ T-cell

(continued on next page)

Table 2 (*continued*)

DMT	Mode of action	Class	Safe to start treatment?	Advice regarding treatment	In the event of COVID-19?	COVID-19 vaccination	Attributes and caveats
(ocrelizumab, ofatumumab, rituximab or ublituximab)				continue or suspend dosing	dosing depending on timing	last infusion. COVID-19 vaccination is nevertheless strongly encouraged. PwMS should ideally be fully vaccinated at least 2–4 weeks before starting or redosing anti-CD20 therapies.	populations by up to 20% and this may interact with other factors to affect antiviral responses. Theoretical risk that ocrelizumab and other anti-CD20 therapies may result in prolonged viral shedding.
Alemtuzumab	Anti-CD52, non-selective immune depleter	IRT (non-selective)	Probably	Risk assessment – continue or suspend dosing	Temporary suspension of dosing depending on timing	Vaccination with non-live vaccines within 6 months of treatment may result in a smaller proportion of responders. COVID-19 vaccination is nevertheless strongly encouraged. PwMS should ideally be fully vaccinated at least 2–4 weeks before starting or redosing Alemtuzumab.	Theoretical risk that in the immune depletion phase alemtuzumab may result in prolonged viral shedding
Mitoxantrone	Immune depleter (topoisomerase inhibitor)	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Likely to be blunted.	Theoretical risk that in the immune depletion phase mitoxantrone may result in prolonged viral shedding
HSCT	Immune depletion and hemopoietic stem cell reconstitution	IRT (non-selective)	No	Suspend dosing	Suspend dosing	Likely to be blunted. COVID-19 vaccination is nevertheless strongly encouraged. Crucial vaccinations are recommended from 3 months after transplant.	Theoretical risk that in the immune depletion phase HSCT may result in prolonged viral shedding

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; EID = extended interval dosing; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit; IR = immune reconstitution; IRT = immune reconstitution therapy; MS = multiple sclerosis; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; NRF2 = nuclear factor-E2-related factor 2; S1P = sphingosine-1-phosphate; TLC = total lymphocyte count; VLA4 = very late antigen-4.

cohort of North American pwMS also suggested a negative effect of corticosteroids on COVID-19 outcomes (Salter et al., 2021).

As most MS relapses are followed by some degree of spontaneous recovery, in some cases it is acceptable to monitor rather than immediately treat very mild relapses (Repovic, 2019). However, corticosteroids should be administered if deemed clinically indicated. There is good evidence that high-dose oral methylprednisolone is as effective as high-dose intravenous methylprednisolone when treating a relapse (Lattanzi et al., 2017; Liu et al., 2017). Therefore, in pwMS experiencing a relapse who require acute treatment during COVID-19 times, the use of oral corticosteroids is recommended over intravenous corticosteroids to prevent patients having to travel to clinical sites. Home administration of intravenous corticosteroids (Chataway et al., 2006), when feasible, could also be a good alternative to minimize potential risk of exposure and further spread of the virus. Steroid tapering does not contribute to recovery and should be avoided. Lastly, it is imperative to distinguish true relapses from pseudorelapses to avoid unnecessary treatment with corticosteroids among those whose symptoms are brought on by concurrent illness, fever or infection.

3.5. PwMS at highest risk from COVID-19

The increased risk of becoming symptomatic or developing a relatively severe clinical phenotype with COVID-19 among those of old age and those with significant comorbidities has been documented in several characterizations of disease hospitalizations and mortality globally (Livingston and Bucher, 2020; Yang et al., 2020; Zhou et al., 2020). Early data from Italy identified that among more than 1600 deaths, 87.88% occurred among those aged 70 years or older, and the case-fatality rate increased with age (Livingston and Bucher, 2020). In a systematic review and meta-analysis incorporating 1567 patients with COVID-19, the most common comorbidities were hypertension (21.1%), diabetes (9.7%), cardiovascular diseases (8.4%), and respiratory diseases (1.5%) (Yang et al., 2020). The explanation underlying any relationship between ethnicity and COVID-19 is unclear but available data, particularly from Western countries, show that individuals from black, Asian or minority ethnic groups have a higher risk of developing COVID-19 and of having poorer clinical outcomes (Williamson et al., 2020). These risk factors will inevitably co-exist in many pwMS. In an Italian study of 232 pwMS with confirmed or suspected COVID-19, the 5 patients who died among 10 patients identified as having severe/critical COVID-19 tended to be older, and 4 out of 5 had significant comorbidities including diabetes and/or cardiovascular disease (Sormani, 2020). More recent data from the MuSC-19 cohort not only showed that age was a risk factor for severe COVID-19 in pwMS, but also that mortality was higher for those with progressive disease than for the general Italian population (Sormani et al., 2020). In line with these findings, the Covisep investigators identified age, disability and obesity as the main risk factors for COVID-19 severity (Louapre et al., 2020). Also, data from the COVID-19 in MS Global Data Sharing Initiative showed that older age,

progressive MS, higher disability and comorbidities were associated with worse outcomes (Simpson-Yap et al., 2021). Similar results have been reported by others (Chaudhry et al., 2020; Salter et al., 2021; Zabalza et al., 2020), highlighting the need to establish infection control strategies to protect this vulnerable population.

3.6. COVID-19 and pregnancy in pwMS

MS disease activity is suppressed in late pregnancy, but after the delivery there is often re-activation of the disease. There is similarly frequent post-partum activation in other Th1-type autoimmune diseases (Förger and Villiger, 2020). The pregnancy-associated modulation of autoimmunity is a consequence of the physiological modulation of the mother's immune system during pregnancy, which is necessary to ensure well-being and normal development of the fetus. Related to this, T-cell-mediated adaptive immune responses are suppressed in mid-pregnancy, which results in amelioration of Th1-type autoimmune diseases. Although the altered T-cell function might render the mother more susceptible to certain infections, pregnant women do not appear to be at greater risk of COVID-19 infection (Yam et al., 2020).

Experiences from pregnancies of mothers infected with the SARS-CoV-2 are growing. A review of 10,966 cases reported that pregnant women were not more affected by the respiratory complications of COVID-19, when compared to the outcomes described in the general population (Figueiro-Filho et al., 2020). In contrast, an analysis of approximately 400,000 women of reproductive age with symptomatic COVID-19 showed that intensive care unit admission, invasive ventilation, extracorporeal membrane oxygenation, and death were more likely in pregnant women than in nonpregnant women (Zambrano et al., 2020). A living systematic review of the literature and meta-analysis also found that pregnant and recently pregnant women are potentially more likely to need intensive care treatment for COVID-19 than nonpregnant women of reproductive age (Allotey et al., 2020).

There are as yet no published data on pregnancies of pwMS affected by COVID-19. As pregnant women may be more susceptible to severe COVID-19 (Wastnedge et al., 2021), pregnant pwMS should be counseled and monitored accordingly. There is no reason to believe that pregnant pwMS affected by COVID-19 should be treated any differently from individuals without MS. Principles for management of pregnant women with confirmed or suspected COVID-19 can be found in a recent publication by Rasmussen et al. (Rasmussen et al., 2020). One consideration is that some immunosuppressive DMTs may impair the immune defense system against pathogens during pregnancy, including COVID-19.

3.7. Management of MS in pediatric patients

Reported infection rates with SARS-CoV-2 are lower in children than adults, and children are often asymptomatic (Badal et al., 2021; Mehta et al., 2020; Zimmermann and Curtis, 2020). However, severe COVID-19 and death due to the infection have been reported in children with comorbidities (Mehta et al., 2020). MS is a disease of young adults and a small proportion of pwMS are children. In a study on COVID-19 outcomes in pwMS that included a cohort aged 13–71 years, severe COVID-19 requiring invasive ventilation was only described among adults (Parrotta et al., 2020). Although there is limited evidence on how COVID-19 affects children with MS, the consensus is to follow local COVID-19 prevention and control guidelines. Similar to recommendations for adult pwMS, an individualized risk assessment is needed when making immunotherapy decisions in children with MS during COVID-19 surges. As pediatric MS follows a relapsing–remitting course with a high relapse frequency (Waubant et al., 2019), children with MS taking DMTs should continue with their treatment unless there are major safety concerns or a clinical rationale to stop.

Children with MS frequently experience cognitive and mood disturbance. The evolving global crisis and recurrent waves of the pandemic have a significant impact on mental health (Kwong et al., 2020), which may be more prominent among children with MS. The accelerated global application of telehealth offered people with chronic disease easier access to their care teams. However, how this type of remote care is perceived by children with MS is not yet known. Further information on this special subgroup of pwMS is needed through establishing region-specific disease registries.

3.8. Remote management

During recurrent waves of the pandemic, most health services have redeployed services to urgent COVID-19 care and implemented guidelines to restrict non-essential hospital visits. In addition, fears around contracting the virus have led to many patients avoiding healthcare settings (Mateen et al., 2020; Vogel et al., 2020), even where outpatient services remained uninterrupted. Consultations for chronic diseases, including MS, have been diverted to telemedicine, via direct videolink or telephone (Portaccio et al., 2021). Telemedicine is established as a valid and acceptable tool to assess aspects of MS care and its implementation supported by the American Academy of Neurology (Hatcher-Martin et al., 2021; Yeroushalmi et al., 2019). Many software options are available and may be guided by the preference of the local institution. It is essential that clinicians are aware of local privacy guidelines and the requirement for patient consent prior to engaging in telemedicine visits (Australian Health Practitioner Regulation Agency, 2020).

The main drawback of telemedicine in MS care is the inability to perform a comprehensive neurological examination. The use of patient-reported outcome measures such as the Patient Determined Disease Steps (PDDS) could potentially overcome this limitation (Learmonth et al., 2013). The PDDS has been validated in MS and is strongly correlated with the Expanded Disability Status Scale (Learmonth et al., 2013). Completion of the PDDS prior to telehealth visits can give clinicians a better indication of a patient's physical health. Pre-appointment completion of a quality of life measure such as the Multiple Sclerosis Impact Scale (MSIS-29) may provide an evaluation of psychological health and could be used to complement the PDDS (Hobart et al., 2001; Moccia et al., 2020). Assessment of relapses and acute changes may however still require face-to-face evaluation, especially when treatment changes are being considered.

3.9. Radiological monitoring

In the early days of the COVID-19 pandemic, most healthcare facilities recommended that diagnostic tests take place for only urgent and emergent medical issues. Accordingly, routine magnetic resonance imaging (MRI) appointments for general disease monitoring and safety surveillance were postponed, so that pwMS could minimize potential exposure to COVID-19. As COVID-19-related restrictions eased around the world after the initial waves of the pandemic, many MS clinics partially resumed most routine MRI appointments for disease monitoring and safety surveillance. The risk of COVID-19 in pwMS must now be balanced with the risk of subclinical disease activity in MS, which can certainly cause disability progression over time (Bermel et al., 2013).

As the risk of COVID-19 is dynamic and differs significantly by region (Mishra et al., 2020), all imaging facilities should follow local public health and infection control guidelines regarding minimizing SARS-CoV-2 exposure and transmission. Specifically, patients should be screened for symptoms, recent travel to high-risk areas or close contact with a confirmed case of COVID-19 prior to entering the facility. In addition, hand sanitization should be mandated upon entering the facility, and masks should be worn if deemed necessary. Policies should be in place to ensure adequate social distancing in waiting areas, and thorough cleaning of MRI equipment should take place in between patients.

Imaging facilities may face capacity constraints amid recurrent COVID-19 waves and outbreaks, of greater or lesser magnitude.

Therefore, neurologists should underscore the importance of attending scheduled MRI appointments to patients, as the MRI has been deemed clinically necessary, and re-scheduling will be a challenge. Finally, neurologists should appropriately designate which pwMS need an MRI more urgently, and which patients can have their MRI deferred. Factors that may necessitate a more urgent MRI include moderate to highly active disease and safety monitoring for PML. In patients who have had stable disease for a number of years and depending on the local circumstances, it may be reasonable to defer their MRI until a later date. Neurologists should also consider patient-related factors that may potentially increase the risk of COVID-19 and COVID-19-related complications such as older age, higher disability and comorbidities.

3.10. Remote pharmacovigilance

Good pharmacovigilance aims to identify the risks and risk factors in the shortest possible time so that harm can be avoided or minimized (World Health Organization WHO, 2013). For DMTs in MS this was undertaken by routine blood and MRI monitoring to check for adverse events caused by the mechanism of action of the therapies (Giovannoni, 2018). These activities require the patient to attend a healthcare facility, most commonly a hospital. During COVID-19 surges, visiting healthcare facilities for non-urgent/essential activities has been discouraged to avoid further transmission of SARS-CoV-2. Some additional considerations have, therefore, been added to the risk–benefit analysis for each therapy: the risk of exposure to COVID-19 by undertaking the routine monitoring and the workload on stretched healthcare teams to monitor the blood test results and MRI reporting (Association of British Neurologists, 2020). A population-level risk assessment was undertaken for each DMT to reduce the routine monitoring, taking into account the risk of adverse events with the medication and new risks associated with COVID-19.

Table 3 shows recommended monitoring guidelines as per Prescribing Information/Summary of Product Characteristics and a reduced set of minimum monitoring guidelines taking into account the risk of

Table 3
Pharmacovigilance of DMTs based on the local epidemiology of COVID-19.

DMT	Standard blood test monitoring frequency[a]	Minimum level of monitoring during COVID-19 surges
Interferon beta	3 months, 6 months then every 6 months	3 months after initiation
Glatiramer acetate	No monitoring required	No monitoring required
Teriflunomide	Every 2 weeks for 6 months then every 2 months if stable	Every month for first 6 months, then every 4 months if stable
Dimethyl fumarate	Every 3 months	3 months after initiation then every 6 months if stable and lymphocytes above 500/mm^3
Fingolimod	At month 1, 3, 6, 12 then every 6–12 months	Every 6 months for 1 year then every 12 months
Natalizumab	Every 3 months	Every 6 months (but note if infusion is given in healthcare environment then routine monitoring should continue, if there are no capacity issues)
Cladribine	2 months and 6 months after each course, with monitoring every 2 months if lymphocytes count <0.5 × 10^9/L	2 months after each course, but can delay the 6-month blood test if the 2-month blood test results are stable and the lymphocytes are >0.5 × 10^9/L
Ocrelizumab	Every 6 months	Prior to dosing (which may be an extended dosing interval)
Alemtuzumab	Every month	Every 3 months

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy.

[a] Summary of product characteristics recommendations available at https://www.medicines.org.uk/emc

traveling to clinical areas during COVID-19 surges (Association of British Neurologists, 2020). If reduced monitoring is undertaken, it is important that patients remain vigilant to symptoms and report any concerns to a person with expertise in DMTs for MS promptly.

3.11. Implications for lowest income settings

The COVID-19 pandemic has affected countries of all income levels and had a disproportionately negative impact on poorer populations of many high-income countries (Sundaram et al., 2021). Data on COVID-19 in pwMS in low-income countries are still scant. This may relate to limited testing capacity for both COVID-19 and MS in these settings. The use of immunosuppressive drugs in lowest income settings is also likely weighted more toward lower efficacy DMTs, and at times, off-label agents (Mateen, 2019). Poorer populations may be at higher risk of exposure to SARS-CoV-2, due to social and economic circumstances, including work in service and public-facing industries, crowding, need for public transport, and less access to technologies such as online newsfeeds and telemedicine appointments. Access to information on COVID-19 has been inconsistent to low-income populations, possibly increasing risk to people with limited access to real-time updates (Mansoor et al., 2020). Middle-income countries have reported their experiences, including China (Fan et al., 2020), Iran (Safavi et al., 2020), Chile and other Latin American countries (Alonso et al., 2021; Ciampi et al., 2020; Guevara et al., 2020). However, national registries for pwMS in most lower income regions are absent, limiting any inferences that can be drawn. Where global experiences are gathered, lower income countries are not generally represented (Hughes et al., 2020). DMT access and visits for routine MS care are especially at risk in low-income settings, as attention gets diverted to infectious disease and supply chain and human resources become more scarce. Healthcare workers in low-income settings may be more at risk of getting COVID-19 due to limited personal protective equipment and redeployment to general medical care.

Special attention has been paid to the psychosocial issues of pwMS in low-income populations, including the increased rate of anxiety and fear that people may experience, even if they do not have COVID-19 (Haji Akhoundi et al., 2020). In India, recommendations by a professional society specific to pwMS have been made, which may be applicable more broadly to settings with similar situations and high-risk patient groups (Rohit et al., 2020).

3.12. Impact on MS research

The COVID-19 pandemic abruptly halted all non-COVID-19-related research activities, including MS studies. MS physician investigators were at times redeployed into frontline care of COVID-19 clinical work as existing personnel became over-stretched (Waldman et al., 2020). Many MS studies were put on hold and had to discontinue participant enrollment owing to the need to minimize interpersonal exposures. Clinical trials that were anticipated to begin had ethics board approvals revoked and recruitment was not permitted by institutions. Hiring freezes for research staff and advanced personnel were implemented. Stakeholders who prioritize MS funding were also profoundly affected. National societies, which depend on support from donations, charitable events and advocacy were unable to perform their usual operations (Research Grants|National Multiple Sclerosis Society, 2021). In response, the MS research community quickly learned how to implement alternative models to conduct clinical studies while mitigating the risks to the patients. Several clinical trials have incorporated online platforms to enable remote assessment of patients. Some studies began to utilize self-monitoring applications, of which there is now a broad range of choices (Lai et al., 2020). Also, patient-reported outcomes now play a more central role (Moccia et al., 2020).

During the evolution of the COVID-19 pandemic, new research needs for COVID-19 and MS knowledge, and new opportunities for

international collaborations have emerged. Research of the biology of response to SARS-CoV-2 has been progressing at a rapid pace and in combination with accumulating evidence on the use of DMTs during the pandemic, is leading to new recommendations (Baker et al., 2020a; Cao et al., 2020; Simpson-Yap et al., 2021; Sormani et al., 2020). National and international initiatives to address evolving research needs have formed promptly and new research streams have emerged, combining data acquisition across heterogeneous clinical and geographic settings, and appropriate analytical approaches (Peeters et al., 2020). A renewed recognition of strengthening health systems and the importance of data sharing have become evident. In the current climate, it is indeed the most adaptive of the research that will thrive the best.

4. Conclusion

The arrival of the COVID-19 pandemic disrupted MS services globally. The balance between ensuring that patients receive the best possible care while minimizing their risk for exposure to SARS-CoV-2 has framed our daily practice during the pandemic and the post-pandemic long-wave with recurrent infection outbreaks. As local risk levels may increase or decrease, healthcare providers should remain vigilant and counsel pwMS accordingly. Our recommendations, which represent an expert consensus based on current knowledge and best available evidence, can be used to guide management decisions in MS during the COVID-19 pandemic and the post-pandemic period. These guidelines will be periodically updated and should only be considered in the context of local circumstances.

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