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TITLE

Multiple Sclerosis and the risk of infection: Association of British Neurologists consensus guideline

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Multiple Sclerosis and the risk of infection: Association of British Neurologists consensus guideline

Abstract

Infection in the Multiple Sclerosis (MS) population is of major concern., particularly those receiving disease modifying therapies. This article explores the risk of infection in people with MS and provides guidance, developed by Delphi consensus by specialists involved in their management, on how to screen for, prevent, and manage infection in this population.

Summary of the Evidence

Introduction

Multiple sclerosis (MS) is an inflammatory condition affecting the central nervous system. Infection is a major consideration in the MS population due to its relevance to several stages of the disease process. Firstly infective processes, such as the Epstein–Barr virus, may ‘trigger’ or be causative factors for MS.^{1,2} Secondly, concurrent infection exacerbates symptoms in MS by causing pseudo-relapses or relapses. Thirdly, people with MS have a higher risk of infection than the general population, independent of concurrent treatment, but this risk is exaggerated in those receiving disease-modifying therapies (DMTs). In this guidance we focus on specific risks that predispose people with MS to infection and provide consensus recommendations, developed using a Delphi approach (Appendix 1 and 2) by specialists in the field of MS, immunology, infectious diseases and pharmacy on how to screen for, prevent, and manage infection in this population.

Infections in the MS population

Numerous studies have investigated patterns of infection within MS populations.^{3–6} Compared with age-matched controls, people with MS have more infections, including opportunistic infections, when compared with those without MS.⁵ The overall rate of infections, including serious and fatal infections, in MS populations is at least 50% higher compared with those without MS.^{4,7} The most common infections in people with MS include urinary tract infections (UTI), respiratory, skin and herpes infections.^{3,6}

Infection is a leading cause of death in people with MS (2.90-fold increase in mortality due to infection and respiratory diseases)⁸ when compared to the general population^{3,8,9} and is associated with a two- to four-fold higher incidence of hospitalisation.^{4,5,10} Infection-related use of healthcare, including physician consults and

antimicrobial drug prescriptions, is also 40–60% higher.⁶ The incidence of infections and hospitalisations appears to be increased in people with greater disability, and also (in some cohorts) in those receiving DMTs.⁷ UTIs are more common in people with MS⁵ with higher infection rates in those with longer disease duration and greater disability.^{11,12} Patients with recurrent UTIs, defined as ≥ 3 episodes of culture-positive UTI in the preceding 12 months or two UTIs in the preceding 6 months,¹³ are more likely to be older, male, with a progressive disease course and using a urinary catheter.¹⁴

When considering treatment, it is important that UTIs in people with MS should be considered as ‘complicated’ because of their association with structural and functional abnormalities of the genitourinary tract.¹⁵ Initial management should be aimed at treating lower urinary tract dysfunction, including measurement of post-void residual volume and appropriate catheterisation if >100 mL.¹⁶ When a UTI is suspected, broad-spectrum antibiotics should be started initially, based on local guidelines and any available previous culture results. The antibiotic choice may then necessarily have to change based on subsequent bacterial sensitivities. Asymptomatic bacteriuria should not generally be treated but may be considered in the context of an MS relapse when planning corticosteroid treatment.¹⁵ A 5–7 day course of antibiotics is generally advised, but extended to 14 days according to the severity of infection.¹⁷ Antibiotic prophylaxis is not routinely recommended, although can be considered for certain people.¹⁶ Although there is little evidence in people with MS, future interventions that may prove to be effective include weekly oral cyclic antibiotic (WOCA) regimens,¹⁸ antimicrobial-coated urinary catheters¹⁹ and D-mannose.²⁰ However, we need further clinical trials to assess these treatments further.

In addition to UTIs, respiratory tract infections are also more common in people with MS.⁵ Although they can occur at any disease stage, respiratory dysfunction and associated with respiratory infections are more frequent in people with advanced disability.²¹ There are few studies specifically looking at treatment of respiratory tract infections in people with MS but the UK National Institute of Health and Care Excellence

(NICE) guideline for community-acquired pneumonia provides robust advice for assessment, treatment, and antimicrobial practice.²²

Relapses and infections

Clinicians assessing people with MS often find it difficult to distinguish relapses from pseudo-exacerbations. It is well known that infective processes may worsen underlying MS symptoms – often manifesting as the return of previous symptoms. But several studies have also found more genuine relapses around the time of infection,^{23–26} or shown that even pseudo-exacerbations may be followed by incomplete recovery.²⁷ It is therefore important to exclude underlying infections when assessing patients with new symptoms. Clinicians should ideally treat concurrent infections first, as this may alleviate the symptoms, and avoid using corticosteroids if there are systemic symptoms.²⁸ However, corticosteroids and antibiotics may perhaps be given concurrently, if there are no systemic symptoms, especially when antibiotic sensitivity is available.^{29,30}

Individual risk factors for infection in people with MS

Certain factors may increase the risk of infections in the general population as well as those with MS, e.g. ageing, lifestyle, comorbid chronic lung disease or diabetes, history of immunosuppression, or exposure to infections,^{31,32}; some of these risk factors are modifiable. Modifiable risk factors for infections include cigarette smoking, use of alcohol and drugs of abuse, low or high body–mass index (BMI), nutritional deficiencies including vitamin D, poor dental hygiene and low levels of physical exercise (moderate exercise reduces upper respiratory tract infections, while conversely periods of intense exercise may be associated with an increased infection risk).^{33–38} There are also risk factors for infections more specific to MS, e.g. DMTs, increased disability and immobilisation, impaired breathing or swallowing, and structural or functional abnormalities of the urinary tract.

Specific DMTs and the risk of infection

Several immune-modulating DMTs used in MS carry an increased risk of infections (Table 1 and Table 2).

Relevant complications can include: (i) reactivation of latent pathogens e.g. tuberculosis (TB), hepatitis B (HBV) or herpes group viruses such as varicella zoster virus, (ii) novel opportunistic infections, e.g. listeria or cryptococcus, (iii) an increased burden of common infections, e.g. respiratory tract viral and bacterial infections in secondary antibody deficiency. The mechanism of action of some DMTs may explain a susceptibility towards certain infections.

Rituximab, an anti-CD20 monoclonal antibody used off-label for MS in several countries, is associated with a higher risk of infections, including serious infections, than other DMTs.⁷ Ocrelizumab, another CD20 drug, increases the frequency of mucosal, in particular sino-pulmonary, infections.⁷ Drugs targeting cell-mediated immunity, such as the anti-CD52 monoclonal antibody, alemtuzumab, tend to increase the risk of reactivation of latent herpetic viruses.³⁹ Natalizumab, a monoclonal antibody against the adhesion molecule very late antigen-4, reduces leukocyte migration into brain parenchyma resulting in depletion of the usual CNS immune surveillance, and a risk of reactivation of John Cunningham (JC) virus, causing progressive multifocal leukoencephalopathy (PML).⁴⁰ Fingolimod and natalizumab are associated with a 70% higher rate of herpetic infections (when compared to rituximab, interferons or glatiramer acetate), likely due to their effect on T-cell responses.⁷ Beta-interferons and glatiramer acetate are associated with fewer infection complications than newer DMTs,⁷ but their mode of administration may lead to skin site infections.^{41–43}

It is worth reflecting on some general points about DMTs and infection. Several DMTs induce lymphopenia, and sometimes its degree or duration may partly predict the infection risk (e.g. herpetic infections post-cladribine, and PML risk in people on dimethyl fumarate). However, while lymphopenia commonly accompanies several MS DMTs, the degree of lymphopenia is usually a poor surrogate for infection risk.^{39,44–47}

The timing of peak infection risk also differs according to the DMT. For example, with alemtuzumab or cladribine the infection risk is weighted towards the period immediately after starting, with the risk reducing with time from treatment. In contrast the infection risk during maintenance anti-CD20 therapy appears to be cumulative over time. These features must be considered when evaluating data on infection risk from short-term clinical trials.

Tuberculosis

Several DMTs induce lymphopenia, which in theory could predispose to reactivation of latent TB infection.

This has led to advice to pre-screen for latent TB before starting treatment with certain DMTs (Table 3).

However, the incidence of TB reactivation in the context of MS DMTs is very low. Alemtuzumab was associated with TB reactivation in ~0.3% of cases in CARE MS I and II clinical trials despite screening for latent TB infection^{48,49}, and long term data found no other cases. Similarly, cladribine, a nucleoside analogue of deoxyadenosine, has been associated with rare cases of TB reactivation (crude incidence rate in post-approval data 0.0004).^{50,51} Teriflunomide, another DMT with an effect on lymphocytes, was also associated with a small number of TB reactivations in clinical trials (although there was no mandatory screening for latent TB infection).⁵²

MS drugs targeting humoral immunity appear less likely to cause latent TB infection reactivation. For instance, there have been no reported cases of TB in phase 3 and extension trials of ocrelizumab, even though latent TB infection screening was not mandated. There were no reported cases during phase 3 ofatumumab trials, although participants were screened for latent TB infection.⁵³ No TB cases occur during phase 3 clinical trials of natalizumab and only three cases were reported in post marketing surveillance data.^{54,55} Similarly, fingolimod and dimethyl fumarate, despite inducing lymphopenia in many cases, have not been associated with an

increased risk of TB infection in clinical trials^{56–60}. There is some evidence that concomitant use of corticosteroids alongside DMT could increase the risk of tuberculosis.⁶¹

Despite the low absolute risk of TB with MS DMTs, current guidance around TB screening (Table 3) relates to the theoretical risk of severe morbidity in rare cases where TB reactivation occurs in those with suppressed cell-mediated immunity. Aside from checking for a history of untreated or partially treated TB, interferon-gamma release assays are typically used to screen for latent TB infection. Interferon-γ release assays (IGRAs: T-SPOT.TB, QuantiFERON TB Gold Plus) testing is recommended as a more reliable alternative to tuberculin skin testing (positive predictive value of IGRAs for TB-reactivation in high-risk populations is 4.5%; negative predictive value is 99.7%).⁶² However, users should be aware of the pitfalls of using IGRAs in populations with low background prevalence of TB (risk of frequent, cumulative, sporadic, and irreproducible positive results),⁶³ and also the finding that certain treatments (e.g. fingolimod, dimethyl fumarate, methylprednisolone) can cause false-negative or indeterminate results.⁶⁴ Further data on the risk–benefit analysis of TB screening for people commencing DMTs would help in future given the modest utility and high cost of existing TB screening approaches in populations with a low pre-test probability, and the risk that false positive tests result in unnecessary exposure to anti-TB therapy, which carries its own risks of morbidity. Other approaches to TB screening could include risk-stratification for exposure to cases of active TB and searching for evidence of residual changes on a chest X-ray that might indicate untreated prior TB infection.

Herpetic infections

Herpetic infection is a common complication of immunosuppressive medication, particularly those affecting cellular immunity (Figure 1). Infections with herpes simplex viruses 1 and 2 and varicella-zoster virus can occur de novo or because of viral reactivation. Incidence rates of herpes infection of 2–6% occurred in people with

MS receiving teriflunomide, fingolimod, siponimod, cladribine, ocrelizumab and ofatumumab in phase 3 clinical and extension trials.^{65–70} There were similar rates during early trials of alemtuzumab, but the introduction of antiviral prophylaxis for the first month of every cycle in subsequent trials was associated with a significant reduction in incidence of herpetic infections (Course 1, 4.9% without prophylaxis vs 0.5% with prophylaxis; Course 2, 2.4% without prophylaxis vs 0.8% with prophylaxis).³⁹ Likewise, the risk of herpes infection with cladribine was significantly higher than with placebo (observation-adjusted incidence rates per 100 patient-years (Adj-AE) of 4.15 versus 0.64 per 100 patient years). This was clustered around periods of grade 3 and 4 lymphopenia, (absolute lymphocyte count $<0.2 \times 10^9$ /L), which are fairly uncommon,⁷¹ but should prompt consideration of antiviral prophylaxis.^{72,73} Most herpes infections associated with MS DMTs have mild to moderate severity, but there are a few case reports of severe or fatal infection.^{65,74–77}

Dimethyl fumarate and natalizumab have not been associated with an excess of herpetic infections in clinical trials.^{55–59} However, long-term post-marketing data have reported rates of 9 cases per 1000 patient years for dimethyl fumarate and 11 cases per 1000 patient years for natalizumab.⁶⁹

Progressive Multifocal Leukoencephalopathy (PML) infection

PML is a rare but usually serious CNS infection caused by reactivation of the JC virus (Figure 1). More than 55% of the general population and people with MS have serological evidence of prior exposure to JC virus,⁸³ often with a mild or asymptomatic exposure. Seroconversion occurs at a rate of approximately 1–2% per year in the general population⁸⁴ (including people with MS), and this appears to be even higher in people treated with natalizumab (~10%/year).^{85,86} Following initial exposure, the JC virus remains latent within the body. Impaired CNS cell-mediated immunity increases the risk of JC virus reactivation and PML. This is particularly relevant to natalizumab, which reduces lymphocyte trafficking into the CNS.⁸⁷ Recognition of the causal association between natalizumab and PML during post-marketing surveillance led to a relicensing of natalizumab for use

within a framework of risk mitigation. A quantitative anti-JC virus antibody index is used to calculate the risk of PML in patients on natalizumab therapy, taking into account prior immunosuppression and duration of natalizumab treatment.^{88–91} In people with MS without previous immunosuppressant use, the estimated annual PML risk ranges from 0.01 per 1,000 during months 0–12 for those with a JC virus index <0.9, to 10 per 1,000 (1%) during months 60–72 for those with a JC virus index > 1.5.⁸² MR brain scanning is used every 4–6 months in those at highest risk, on the basis that pre-symptomatic PML has a more favourable clinical outcome.⁹² However, overall the mortality rate of natalizumab-related PML is ~20% but with substantial morbidity in survivors.⁹³ The risk of PML is lower in people who receive natalizumab with extended interval dosing (usually 6-weekly) versus standard interval dosing (300mg IV every 4 weeks), whilst maintaining efficacy.^{94–96}

Fortunately PML appears far less common with other DMTs, but low incidence means that it remains challenging to quantify and stratify risks for other DMTs.⁹⁷ The overall risk of PML with fingolimod therapy is estimated to be ~0.04 per 1,000 patient years,⁹⁸ although this may be increased with longer duration of treatment and higher age.⁹⁹ The risk of PML with dimethyl fumarate treatment is estimated to be ~0.01 per 1,000 patient years;¹⁰⁰ with the highest risk in those with severe and/or prolonged lymphopenia.¹⁰⁰ Changes in specific lymphocyte subsets and/or cerebrospinal fluid (CSF) immune profile in those receiving dimethyl fumarate may prove important in refining PML risk in the future, but we need more data.¹⁰¹ There have also been cases recorded with normal lymphocyte counts.¹⁰² While ocrelizumab is a relatively new drug in MS, there have been few reported PML cases so far, most of which (8 out of 10) were suspected to be carry-over cases related to exposure to prior DMTs (natalizumab and fingolimod).^{103–105} There have been no reported cases of PML with ofatumumab used for MS at the time of writing. The risk of PML with rituximab in the context of rheumatological is ~2.56/100,000 patients treated, but in rheumatoid arthritis rituximab is combined with other immunosuppressants,¹⁰⁶ and it remains challenging to quantify absolute risk in MS.^{106,107} There have been no cases of PML reported for siponimod thus far.

Immune-reconstituting therapies such as alemtuzumab and cladribine have also been associated with a low risk of PML. At the time of writing, to our knowledge, there has been only one case of PML reported in MS patients treated with alemtuzumab.¹⁰⁸ Of note, this patient had been treated with other immunosuppressive medications before receiving alemtuzumab. While cases of PML have occurred in patients treated with alemtuzumab for chronic lymphocytic leukaemia or in transplant-recipients,^{109–111} it is difficult to separate out the effects of the drug and the disease in that context. Similarly, although there have been reports of PML in people treated with parenteral cladribine for haematological malignancy, there have been no PML cases reported in MS patients treated with cladribine.

It is important to note that the use of anti-JC virus antibody index monitoring has not been validated for use in people with MS treated with DMTs other than natalizumab. In particular, DMTs expected to induce lymphopenia or affect antibody production might be expected to give unreliable results.

Hepatitis B infection

People infected with hepatitis B virus (HBV) can maintain a persistent carrier state, indicated by the presence of HBV core antibody. An immunosuppressed state may allow reactivation of HBV, leading to hepatitis and even liver failure. Prophylaxis can decrease the chance of reactivation.¹¹² In particular, anti-CD20 drugs such as ocrelizumab and rituximab have been associated with a high risk of HBV reactivation.^{113–115} Ocrelizumab trials included patients with a positive HBV core antibody and negative hepatitis B surface antigen and HBV DNA, who were re-tested every 12 weeks.^{65,116} On the other hand, phase 3 trials of alemtuzumab excluded patients with hepatitis B or C virus infection before starting treatment. This decision was likely influenced by the high reactivation rate of HBV in patients treated with alemtuzumab for haematological malignancies, accepting the likely confounding effect of haematological disease in these cases.¹¹⁷ Ofatumumab trials also excluded

patients at risk of HBV; and the summary of product characteristics recommends consulting a liver disease expert in those with positive HBV serology before starting treatment.⁵³ Fingolimod, dimethyl fumarate and teriflunomide probably carry a relatively lower risk of HBV reactivation,^{52,60,76,79} although trials varied with respect to screening practices. No HBV cases have been detected during natalizumab clinical trials, but one case has been reported in the post marketing setting.¹¹⁸

HPV infection

Cervical cancer can result from persistent infection by high-risk human papillomavirus (HPV) types leading to the pre-malignant stages of cervical intraepithelial neoplasia. Immunosuppression by DMTs could lead to an exacerbation of pre-existing HPV colonisation and failure to spontaneously clear HPV infection. HPV infection is also associated with cutaneous warts, non-melanoma skin cancers and oromucosal malignancies.¹¹⁹

Although there are few data on its incidence, there have been reported several cases of HPV-associated cervical dysplasia with natalizumab^{120,121}, fingolimod¹¹⁹ and alemtuzumab¹²². HPV vaccinations are routinely scheduled for teenage boys and girls in most European countries. The benefit of HPV vaccination for sexually active adults is less clear,¹²³ as some will have already contracted vaccine-type HPV strains. However, HPV vaccination is recommended for consideration before fingolimod use,¹²⁴ and may be worth considering before other lymphocyte depleting DMTs in adults who have not been previously vaccinated, particularly those known to be HPV negative.

Serious infections

People with MS are likely to be most interested in the rates and types of serious infections seen with MS DMTs. Serious infections (often defined according to the Medical Dictionary for Regulatory Activities) are overall uncommon with MS DMTs, with an overall incidence of ~1 to 2 per 100 patient years.⁷ The incidence of serious infections was 1.26 per 100 patient years in people receiving alemtuzumab during 6 years of follow-

up.^{39,125} There have been reported cases of sepsis with autoimmune pancytopenia in people with MS post-alemtuzumab.³⁹ The incidence of serious infections with cladribine was also low (0.76 per 100 patient years) in ~4-year extension data from clinical trials,⁵⁰ with herpes zoster being the most common serious infection.¹²⁶ Trial extension data of up to 7 years for ocrelizumab showed an incidence of serious infections of ~2 per 100 patient years, mostly UTIs, pneumonia and cellulitis. Serious herpes virus infections were uncommon. Serious infections were associated with low serum IgG but not low lymphocyte or neutrophil counts.¹²⁷ The rate of serious infections with rituximab was 1.97 per 100 patient years in a real-world cohort, with an infection profile of mainly UTIs and bacterial /viral respiratory tract infections.⁷ Rituximab, but not fingolimod or natalizumab, had a significantly higher risk of serious infection than interferon-B or glatiramer acetate.⁷ The most common serious infections during long-term follow-up with fingolimod are pneumonia and UTI.¹²⁸ Natalizumab is well-known for its association with PML, but has also been associated with higher risk of serious pneumonia, UTI, and herpetic infections.⁸² Interferon-B, teriflunomide and glatiramer acetate show overall low rates of serious infections.⁷

Other infections

Opportunistic Infections

Case reports of less common opportunistic infections have been associated with MS DMTs. Cryptococcal meningitis is rarely reported with long-term treatment with fingolimod, siponimod and natalizumab.^{129–131} Cases of human herpes virus associated Kaposi sarcoma and cerebral toxoplasmosis have also occurred with fingolimod.^{132,133} Alemtuzumab has been associated with cases of cytomegalovirus,¹³⁴ *Pneumocystis jirovecii* and legionella pneumonias,¹³⁵ nocardia,¹³⁶ pulmonary aspergillosis,¹³⁷ and candidiasis.^{48,96} There have been very rare reports of JC virus granule cell neuronopathy in patients receiving natalizumab.^{138,139} Clinical trials of ocrelizumab in MS reported cases of atypical pneumonia including *Pneumocystis jirovecii*, and fungal infections such as histoplasmosis. Cladribine was associated with a higher rate of opportunistic infections vs

placebo, (Adj-AE of 0.31 per 100 patient years for cladribine vs 0.17 per 100 patient years for placebo), primarily with fungal infections.⁵⁰

Listeria monocytogenes, a facultative intracellular Gram-positive bacillus, was the most common opportunistic infection in alemtuzumab-treated patients in post-marketing surveillance reporting.^{140,141} Severe and fatal cases of rhomboencephalitis, meningitis, meningoencephalitis, brain abscess formation, as well as septicaemia have been reported (Figure 1).^{142,143} The risk is estimated to be 0.25% in the first month after each cycle of alemtuzumab treatment without prophylaxis.¹⁴⁴ Patients starting on alemtuzumab are told to avoid ingestion of food associated with an increased risk of listeria infection, such as unpasteurised milk products, soft cheeses, and undercooked or raw meat.¹⁴⁵ However, cases have also been reported even in those avoiding these,¹⁴⁶ which may relate to reactivation of latent infection from persistent bacteria in body 'reservoirs' such as the gall bladder or bone marrow,¹⁴² so supplemental prophylactic antibiotics are also recommended. There have also been rare case reports of listeriosis in people with MS on other DMTs such as fingolimod and dimethyl fumarate.^{147,148} A history of recurrent or unusual infections associated with atypical CNS inflammation should prompt consideration of an underlying immunodeficiency disorder.¹⁴⁹

Autologous hematopoietic stem cell transplantation and Infection

Autologous hematopoietic stem cell transplantation is a highly effective option for long-term control of inflammatory disease activity. So far, it has been performed on 1500 patients with MS, although it is still not a standard treatment in many MS centres.¹⁵⁰ Infections are a common complication of the conditioning regimen used for the procedure, and so use of anti-viral, anti-bacterial, and anti-fungal prophylaxis is standard. Early UTIs and late post-transplantation viral infections including varicella zoster and human herpesvirus-6 (HHV6) have been reported.¹⁵¹ Available guidelines for patients following transplant recommend monitoring (e.g. cytomegalovirus, Epstein–Barr virus), infection prophylaxis, and vaccination.¹⁵² Better patient selection and

growing experience in autologous hematopoietic stem cell transplantation has lowered transplant-related mortality and infection rates.¹⁵²

Anti-CD20 therapy and hypogammaglobulinaemia

Hypogammaglobulinaemia is a well-recognised side effect of long-term treatment with anti-CD20 monoclonal antibodies.^{153,154} Long-term follow-up data from ocrelizumab clinical trials in RRMS (OPERA I and II) showed that ~30% of participants had at least one immunoglobulin subclass (IgG, IgM, IgA) below the lower limit of normal at Year 5 (versus 1–2% at baseline).⁷⁷ During the ASCLEPIOS trials, ofatumumab was associated with IgM reduced below the normal range in 14%, although there no decline in IgG.¹⁵⁵ Low serum immunoglobulin in the context of anti-CD20 treatment appears to predispose to higher rates of infection, especially bacterial and sinopulmonary infections.^{153,156} Most infections are self-limiting and the DMT does not need to be stopped, but there is some evidence that the increased burden of recurrent infections can be a precursor to severe infection; there have been cases of opportunistic viral or fungal infections in those with secondary antibody deficiency in other contexts.¹⁵³

Because of the risk of secondary antibody deficiency, patients taking anti-CD20 therapy should undergo a risk assessment at baseline and at every 6 months, including (i) an assessment of the amount and duration of any previous immunosuppressive therapy; (ii) serum immunoglobulins +/- disease-specific antibody titres; (iii) infection burden since last visit (e.g. number of sick days due to infection, number of antibiotic courses); (iv) additional risk factors known to increase the likelihood of antibody deficiency (e.g. chronic lung disease, urinary catheter use).¹⁵³ A serum IgG below 4 g/L may add more weight to the consideration of switching the DMT. These metrics can guide management but further research may help to develop more bespoke risk stratification algorithms.

COVID-19 Infection

The risk of severe COVID-19 in people with MS is increased by use of certain immunomodulating therapies,^{5,7,157–159} as well as by the presence of factors associated with an increased risk in the general population, such as increasing age, male sex, comorbidities, and having Black/African, Asian or minority ethnic ancestry.^{157,158,168,160–167} Progressive disease course of MS and increased levels of disability are also associated with more severe COVID-19 infection.^{157–162,164,165,167,169} Several studies have found associations between exposure to anti-CD20 DMTs and COVID-19 frequency and/or COVID-19 severity.^{157,158,163–165,170,171} The relative risk of COVID-19 in people taking anti-CD20s and fingolimod appears to have increased compared to the background population since the roll out of vaccines,^{159,166} which are known to be less effective in this group (see below). Less certain is the risk from COVID-19 in people recently exposed to corticosteroids or fingolimod, which have been subject to only a handful of studies.^{163,164,166} Likewise, there is some limited evidence that people with MS receiving interferons,^{163,165} glatiramer acetate,¹⁶³ fumarates¹⁶³ or natalizumab¹⁶⁴ may have improved clinical outcomes from COVID-19 infection. COVID-19 infection may also be associated with MS exacerbations (new and worsening pre-existing symptoms).¹⁷² One study found that those taking DMTs had a reduced risk of new MS symptoms during COVID-19 infection but the numbers involved were too small to comment on the effect of individual treatments.¹⁷²

Managing infection on treatment

Infections occurring during DMT treatment are mostly managed along generic treatment guidelines. There is no published guidance specifically for the treatment of tuberculosis, listeria or herpes virus infections occurring in people with MS taking DMTs. However, in people with clinical or radiological suspicion of PML, the DMT should be suspended. However, in cases of natalizumab-associated PML there is probably no longer a

role for plasma exchange to accelerate natalizumab clearance¹⁷³, as recent evidence showed less favourable outcomes, due to immune reconstitution inflammatory syndrome with plasma exchange.^{173–175}

Vaccinations

The role and response to vaccinations in people with MS has been reviewed in detail recently.¹⁷⁶ Reyes *et al.* highlighted the need for healthcare professionals to be aware of public health vaccine programmes, and to incorporate consideration of relevant vaccinations into the routine care of MS (Box 1). This should occur at the time of diagnosis and when considering DMTs.

In general, inactivated vaccines should be given at least 2 weeks before starting maintenance immunosuppressive and immune reconstitution therapies in order to ensure the recipient can mount a sufficient response.¹⁷⁷ If the vaccination schedule requires two doses, it may be appropriate to wait until after the second dose before starting DMTs. When immunisation with inactivated vaccines is not possible before starting treatment, they can safely be given at any time afterwards, but the timing of the vaccine may be chosen to coincide with anticipated or proven repopulation of lymphocytes in cell-depleting therapies. Re-vaccination may be considered after has been stopped or completed treatment and the immune system has recovered to cover for the possibility of insufficient earlier response.¹⁷⁷ Measuring responses to individual vaccines may help to guide management in this setting.¹⁷⁸

Live attenuated vaccines - such as MMR, varicella zoster and yellow fever (Table 4) - are not recommended in people with MS during and shortly (<4 weeks) before maintenance immunosuppressive and immune reconstitution therapies.^{138–139,141} However, they can be cautiously considered if there is a high risk of infection and/or if there are no inactivated alternatives.¹⁸⁰ Of note, for treatment with alemtuzumab, the Summary of Product Characteristics advises against using live-attenuated vaccines for at least 6 weeks before treatment.¹⁷⁶

Patients on immune-reconstitution therapies who have shown a return of their circulating lymphocytes should be able to tolerate and respond to live-attenuated virus vaccines¹⁸¹. Live vaccinations should also not be given to people with MS who are taking high dose corticosteroids, (>40 mg/day of prednisolone or equivalent for ≥ 7 consecutive days or >20 mg/day of prednisolone or equivalent for ≥ 14 consecutive days) or have received them in the past 3 months - inactivated vaccines can be given but may elicit a lower response than in immunocompetent individuals¹⁷⁷. During an MS relapse, vaccination should be deferred until clinical resolution or until the relapse is no longer active progressing.¹⁸⁰

There is no evidence that the MS itself causes any difference in vaccine response in untreated people with MS compared with healthy controls.¹⁸² Relatively little is known about the magnitude and duration of immune memory for infections and vaccines in people with MS in relation to DMT.¹⁷⁶ Several small, heterogeneous studies have studied a total of ~1,000 people with MS for immune responses following vaccines, with some conflicting results.^{183,184,193–196,185–192} Immune responses following exposure to novel antigens (to which the individual has not been previously exposed) have been studied using IgG serology to seasonal influenza and meningococcal conjugate vaccines, while recall (memory) immune responses can be tested by giving a vaccine that has been experienced before.

Novel vaccine responses appear unaffected in people with MS taking beta interferon^{183,197} or dimethyl fumarate.¹⁹⁷ Glatiramer acetate-treated patients showed reduced responses to inactivated influenza vaccines compared with healthy controls or those treated with beta-interferons.¹⁸⁵ Teriflunomide treated patients had a reduced response to inactivated influenza and rabies vaccinations, although responses were still expected to be protective.^{187,198} Fingolimod and siponimod have both been associated with a lower vaccine response to the inactivated influenza vaccine in people with MS.^{188,189} People receiving B-cell depleting therapies, including

ocrelizumab, showed significantly impaired responses to the inactivated influenza vaccine.¹⁹⁰ In a small study of people receiving alemtuzumab, seroconversion to meningococcal group C was over 80% overall in those with a mean interval of 18 months since last treatment.¹⁹¹ Less expected was the finding that some people with MS receiving natalizumab responded inadequately to the inactivated influenza vaccine.^{183,192} The vaccine responses in those patients who may have received many different sequential DMTs in a real-world setting is unknown.

With regard to recall (memory) humoral responses, people taking beta-interferon, dimethyl fumarate and teriflunomide have preserved responses.^{197,198} Fingolimod treatment results in a lower response rate to the tetanus toxoid booster¹⁸⁸ and recall responses in ocrelizumab-treated patients were also lower to tetanus toxoid and pneumococcal polysaccharide vaccines.¹⁹⁰ One isolated study of alemtuzumab showed maintained responses to recall antigens (tetanus-diphtheria toxoid vaccine, inactivated poliomyelitis vaccine, pneumococcal polysaccharide vaccine).¹⁹¹ Some patients receiving natalizumab have an inadequate response to the tetanus toxoid vaccine.¹⁹³ There have been no studies on recall responses for glatiramer acetate. Alemtuzumab¹⁹¹ does not appear to have a detrimental effect on pre-existing humoral immunity. Recently presented data suggest that people with MS taking cladribine show a maintained or increased antibody levels against varicella zoster and seasonal influenza.^{195,196}

Data on cellular (e.g. T-cell) responses to vaccines in people with MS on DMTs are scarce, as are directly comparative data on vaccine effectiveness across different DMTs. The relationship between DMT duration and vaccine response is unknown, as is the relationship between peripheral blood lymphocyte levels and vaccine response. These data have the potential to inform optimum timing of vaccines in relation to lymphocyte depleting therapies, and/or whether to halt the DMT temporarily to facilitate vaccine response. People with

MS undergoing autologous hematopoietic stem cell transplantation should be considered for re-immunisation after transplantation because of the loss of humoral immunity.¹⁵²

MS and COVID-19 vaccination

At the time of writing, several studies have shown that people with MS and on anti-CD20 and sphingosine-1-phosphate (S1P) DMTs, such as fingolimod and siponimod, have an attenuated humoral response to COVID-19 vaccination.^{199,200,209,201–208} T-cell responses to COVID-19 vaccination appear relatively preserved in people with MS on anti-CD20s,^{205,206,208,210–212} whereas several studies have shown fingolimod to be associated with lower magnitude T-cell response to SARS-CoV-2 antigens.^{207,208,213}

While the clinical correlate of these laboratory findings remains uncertain, it appears likely that people with MS exposed to anti-CD20 and S1P DMTs will be relatively more vulnerable to COVID-19. More recent data suggest that booster vaccination results in seroconversion in around a quarter of people with MS on anti-CD20 who were previously seronegative,²¹⁴ and may also enhance cellular responses in this group,²¹¹; thus booster vaccines may have a role in increasing protection in this group. Immune responses to COVID-19 vaccination appear relatively preserved in people on other DMTs and those on no DMT.^{202,204,207,208,215} Available data also indicate that COVID-19 vaccines appear to be safe and well tolerated in people with MS.^{204,216}

Conclusion

An increasing number of DMTs are available for MS, and early use of higher-efficacy DMTs is being encouraged. Clinicians must be familiar with the mechanism of action and risk-benefit profile of these drugs, whilst considering an individual's risk factors or infection, and must be able to manage emergent infections effectively. The lack of evidence in this field resulted in several recommendations based on expert consensus. Differences in trial methods pose challenges in quantifying and comparing infection risk in different DMTs, especially for rare infections such as tuberculosis, as some trials incorporate pre-screening, whilst others do

not. There is consensus around some rare but serious infections such as listeriosis associated with alemtuzumab, but this is more difficult to achieve for common infections such as HPV. The rare occurrence of PML with medications such as dimethyl fumarate and fingolimod makes it difficult to quantify risk and to communicate this to people with MS; there is little evidence on how monitoring should proceed for these drugs, unlike in natalizumab where a higher rate of PML and a large body of evidence enables modelling of risk. The COVID-19 pandemic has raised awareness of an increased susceptibility to infection and possible suboptimal response to vaccination in people with MS on DMTs.

Key Points

- 1. Infections may occur in association with disease modifying therapies (DMTs) and with advanced disability in MS; clinicians should be familiar with the mode of action of MS DMTs and their differing risks of infection.**
- 2. Infective complications of MS DMTs can include an increased frequency or severity of community-acquired infections e.g. respiratory or urinary tract infections, reactivation of latent pathogens as such herpes viruses infections, and occasionally rarer opportunistic infections such as listeria.**
- 3. These consensus guidelines aim to facilitate evidence-based management of infections in MS, and to develop a systematic approach to the screening, prevention, surveillance, and prophylaxis of infections in those receiving DMTs.**

Further Reading:

- Luna 2020: Luna, G., Alping, P., Burman, J., Fink, K., Fogdell-Hahn, A., Gunnarsson, M., Hillert, J., Langer-Gould, A., Lycke, J., Nilsson, P., Salzer, J., Svenningsson, A., Vrethem, M., Olsson, T., Piehl, F., & Frisell, T. (2020). Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. *JAMA neurology*, 77(2), 184–191. <https://doi.org/10.1001/jamaneurol.2019.3365>
- Epstein 2018: Epstein, D. J., Dunn, J., & Deresinski, S. (2018). Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management. *Open forum infectious diseases*, 5(8), ofy174. <https://doi.org/10.1093/ofid/ofy174>

Consensus guidelines

Management of relapse with infection

1. All people with MS in relapse should be evaluated for the presence of concurrent infection. (Category D)
2. Corticosteroids should be avoided in most cases of relapse associated with systemic infection as in theory they can exacerbate infection. (Category D)
3. Corticosteroid treatment can be considered for relapses associated with infection in the absence of systemic symptoms. Co-prescribing of antibiotics should be considered in these cases. (Category D)

Prevention of infection with MS DMTs

4. We recommend that clinicians assess for the presence of the following intrinsic and extrinsic risk factors for infection at diagnosis and when starting DMT, to facilitate discussion with the patient and encourage modification of any behaviours that may increase risk: (Category D)
 - a. Personal history of infectious disease
 - b. Nutritional deficiency
 - c. Travel history / future travel plans
 - d. Occupational history
 - e. Place of birth
 - f. TB exposure / risk
 - g. Vaccination status (ensure up to date as per UK schedule)
 - h. Smoking status
 - i. Alcohol intake
 - j. Drug abuse
 - k. Body-mass index
 - l. Primary or acquired immunodeficiency (e.g. HIV)
 - m. Chronic disease predisposing to infection
 - n. Exercise
5. The following should be assessed before starting any DMT expected to be associated with lymphopenia: (Category B-D)
 - a. Hepatitis B and C virus (HBsAg, HBcAb, HBsAb, HCVAb)
 - b. HIV Ag/Ab
 - c. Varicella zoster virus (VZV) IgG
6. Re-evaluation of infection risk (as per 5a-b) is recommended before the second or subsequent courses of alemtuzumab or cladribine. (Category D)
7. All patients starting DMT should be counselled about potential modifiable risk factors for infection e.g. smoking, alcohol. (Category D)

8. Before starting lymphocyte-depleting DMTs, individuals should be counselled about future travel. Relevant travel vaccinations should be considered ahead of starting DMT if future travel is planned. (Category D)
9. People starting alemtuzumab, cladribine, fingolimod or anti CD-20 drugs who are VZV-negative should be vaccinated for VZV. (Category B)
10. If in exceptional circumstances there is inadequate opportunity to complete full VZV vaccination in a person with negative VZV serology before starting alemtuzumab, cladribine, fingolimod or anti CD-20 DMT: (Category C – D)
 - a. Patients should be advised to seek medical advice if they are exposed to any person with chickenpox or shingles until such time as they are vaccinated or lymphocyte count has returned to normal.
 - b. A vaccination should be considered at a future time point according to clinician judgement about vaccine safety and expected efficacy (see recommendations 40-41).
 - c. Household contacts of the patient who have never had chickenpox should be offered VZV vaccination.
 - d. In the case of exposure to VZV, consider treatment such as varicella zoster immunoglobulin prophylaxis (VZIG), and referral to an Infectious Diseases expert.
 - e. Antiviral treatment (e.g. aciclovir) is an option for post-exposure prophylaxis in people who cannot receive varicella immune globulin (e.g., due to lack of availability, timing, or contraindications), but should be discussed on a case-by-case basis with local virology/ infectious diseases specialists.
 - f. Severe or fatal varicella can occur despite VZV immunoglobulin prophylaxis. Immunocompromised contacts given VZV immunoglobulin should still be monitored and aciclovir should be used at the first signs of illness.
11. Patients receiving immunomodulatory therapies should be educated to identify signs and symptoms of primary and recurrent infections with VZV and asked to report them promptly. (Category D)
12. If evidence of past/ active infection with HBV is identified, referral to an infectious disease/liver specialist is recommended before starting on DMT. (Category D)
13. If evidence of active infection with HCV is identified (both antibody and PCR positive) referral to an infectious disease/liver specialist is recommended before starting on DMT. (Category D)
14. Baseline screening for latent TB is justified for people with MS who will receive alemtuzumab/cladribine. Baseline screening for latent TB may also be considered in people with MS who have spent time in TB endemic areas AND are due to start any other DMT expected to cause lymphopenia. Risk assessment may vary according to local policy. (Category B)
15. Interferon- γ release assay is the recommended method for latent TB testing in high-risk cases e.g. T-SPOT® or QuantiFERON®-TB tests. (Category C)
16. If TB screening test is positive, patients should have a symptom screen and chest X-ray, and in parallel, be referred to the local infectious diseases/respiratory teams for further guidance.

17. If being treated for latent TB, the timing of starting DMT should be discussed with an infectious disease specialist. (Category D)
18. In patients who develop active TB when on DMT, a full course of TB therapy should be initiated and the decision to stop DMT should be evaluated with input from a TB specialist. (Category D)
19. When TB occurs and DMT stopped, in people with no evidence of ongoing MS disease activity, DMTs expected to cause lymphopenia should be postponed until ≥ 6 months of TB treatment has been given (which usually corresponds with treatment completion). (Category D)
20. Where there is TB infection before starting DMT, or this has prompted DMT discontinuation, AND concurrent evidence of ongoing MS disease activity, clinicians may consider (re)starting DMTs after at least 2 months of anti-TB treatment. (Category D)
21. Aciclovir prophylaxis (200-400mg BD) should be used for 4 weeks after each alemtuzumab treatment and considered during periods of grade IV lymphopenia (lymphocyte count < 200 cells/ μ L) following cladribine. (Category A)
22. Aciclovir rescue or suppressive therapy should be considered for patients with a history of recurrent oral or genital ulcers who are prescribed lymphocyte depleting DMT. (Category A)
23. Patients scheduled to receive alemtuzumab should follow a Listeria-free diet. (Category D)
 - a. The Listeria-free diet should be followed for at least 1 month (ideally 90 days) before and 1 month after treatment
 - b. In addition to a Listeria-free diet, antibiotic prophylaxis should be considered for 1 month after each alemtuzumab cycle (960mg three times a week)
 - c. For patients who are expected to be fully compliant with the Listeria-free diet an alternative is: eight days of amoxicillin 1g TDS or co-trimoxazole 960mg BD to eliminate Listeria colonisation (starting four days before alemtuzumab treatment) followed by the Listeria-free diet for one month after alemtuzumab.
24. All women starting DMTs should be asked to ensure cervical screening is up to date. (Category D)
25. Men and women not previously vaccinated for HPV could be considered for HPV vaccination outside of national schedule if they will receive DMTs that may induce lymphopenia. (Category D)
26. An annual cervical screening programme should be performed in women exposed to alemtuzumab. (Category D)
27. Recurrent urinary tract infections should prompt review of previous antibiotic sensitivities to check for resistance, and consideration of urinary tract imaging. (Category D)

Progressive multifocal leukoencephalopathy

28. Discussion of potential risk of PML infection is recommended in patients starting natalizumab, fingolimod or dimethyl fumarate, with regular re-evaluation and discussion of infection risk. (Category B)

29. Screening for PML in patients treated with natalizumab should be performed as per existing guidelines. (Category B)
30. A baseline MR scan of brain should be performed within 3 months before starting natalizumab, and also before switching from natalizumab to another drug to assess for PML carry over risk. (Category B)
31. As per updated recommendations on dimethyl fumarate (issued October 2020), increased vigilance is recommended in patients on dimethyl fumarate treatment with moderate ($<0.8 \times 10^9$) and severe ($<0.5 \times 10^9$) lymphopenia. (Category D) We recommend that this includes:
- Dimethyl fumarate should be stopped in patients with severe lymphopenia ($<0.5 \times 10^9$) persisting for >6 months.
 - Local guidance should be developed for how to detect and approach persistent ($>6m$) moderate lymphopenia e.g. discussion at multidisciplinary team meeting.
32. Testing for JCV index/ JCV serology should not routinely be performed before starting fingolimod or dimethyl fumarate (as there no risk mitigation algorithm for JCV index for dimethyl fumarate or fingolimod and validity of subsequent JCV index testing on these drugs has not been established). (Category D)
33. Suspected PML occurring during treatment should prompt immediate stopping of the DMT pending further work-up with contrast enhanced MR brain scan and CSF examination. If there is ongoing uncertainty about the presence of PML, interim treatment with lower risk DMTs should be considered. (Category D)

Monitoring patients taking anti-CD-20 drugs

34. Serum immunoglobulins should be measured before anti-CD20 therapy and 6-monthly thereafter for the duration of treatment. (Category B)
35. People receiving anti-CD20 DMTs should be monitored at least 12-monthly for infection burden e.g. sick days / number of courses of antibiotics since last visit. (Category D)
36. If secondary antibody deficiency (IgG) occurs during DMT, consider switching to a DMT with different mode of action or altering dosing schedule, in consultation with an immunology specialist. (Category D)

Vaccinations

37. Ideally, live vaccines should be given at least 4–6 weeks before starting alemtuzumab, cladribine, natalizumab, fingolimod, siponimod and anti-CD-20 drugs. (Category C)
38. Live vaccines should be delayed for alemtuzumab, cladribine, fingolimod and anti-CD-20 drugs, until total lymphocyte count or B-cell reconstitution has occurred. (Category B)
39. Ideally inactivated vaccines should be given at least 2 weeks before starting any lymphocyte-depleting DMTs to optimise immune response. (Category C)
40. In the context of B-cell depleting therapies, where there is evidence of secondary antibody deficiency and/or increased burden of infection, consider measurement of disease-specific antibody titres where

available (e.g. pneumococcus, haemophilus, and tetanus) to gauge immune memory, define the degree of functional impairment, and/or to inform consideration for future revaccination. Abnormal results should be discussed with an Immunology specialist where available. (Category D)

41. Pneumococcal polysaccharide vaccine should be offered to all people with MS aged ≥ 65 years. Pneumococcal vaccine may also be considered on an individual basis in those younger than 65 who have high levels of disability (e.g. EDSS >7.0 , impaired pulmonary function or high risk of aspiration) or show evidence of antibody deficiency on a DMT. (Category D)

42. Seasonal influenza vaccine and COVID-19 vaccines should be offered to all people with MS but may be less effective on certain DMTs. (Category C)

Table 1. Risk of serious infections.

DMT	VZV/HSV	TB	PML	Hepatitis B reactivation risk	Rates of serious infections vs. comparator in Phase 3 trials.^c
Teriflunomide	Low	Moderate ^a	Low	Low	No excess
Dimethyl Fumarate	Low	Low	Moderate	Low	No excess
Fingolimod	Moderate	Low	Moderate	Low	No excess
Cladribine	Moderate	Moderate ^a	Low ^b	High	Small excess
Alemtuzumab	Moderate(Low with prophylaxis)	Moderate ^a	Low ^b	High	Small excess ^{39,48,49,217}
Natalizumab	Low	Low	High	Moderate	No excess
Ocrelizumab	Moderate	Low	Low	Very high	No excess
Ofatumumab	Low	Low	Low	High	No excess

Notes:

a-Moderate risk implies that some cases of TB have been associated with treatment during clinical trials or post-marketing surveillance. Risk is likely to be highest in endemic areas and in high-risk patients such as patients with chronic renal impairment.

b-PML has been reported in the context of cladribine and alemtuzumab use for haematological malignancy

c-Serious infection is defined as requiring IV antibiotics/hospitalization or leading to death.

VZV, Varicella Zoster Virus; HSV, Herpes Simplex Virus; TB, Tuberculosis; PML, Progressive Multifocal Leukoencephalopathy

Table 2. Infection Risk by DMT

DMT	Very Common / Common ($\geq 1/100$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Very Rare	Frequency Unknown
Interferon - β				Injection site abscess
Glatiramer acetate	Influenza Bronchitis, Gastroenteritis, Herpes Simplex, Otitis media rhinitis Tooth abscess, vaginal candidiasis	Abscess Cellulitis Furuncle Herpes Zoster Pyelonephritis		
Teriflunomide	Influenza, URTI, UTI, Gastroenteritis, Oral herpes, Tooth infection, Tinea pedis			
Dimethyl Fumarate	Gastroenteritis, nasopharyngitis, UTI, bronchitis, influenza			Progressive multifocal leukoencephalopathy, Herpes zoster
Fingolimod	Influenza, UTI, Sinusitis Herpes virus infections, Bronchitis, LRTI ⁵⁶ , URTI, Tinea versicolor	Pneumonia		Progressive multifocal leukoencephalopathy, Cryptococcal infections
Cladribine	Oral herpes virus, herpes zoster		Tuberculosis	Pneumonia Urinary tract infection
Alemtuzumab	URTI, UTI, oral herpes virus infections, Herpes zoster infections, LRTI, gastroenteritis, oral candidiasis, vulvovaginal candidiasis, influenza, tooth infection	Onychomycosis, gingivitis, fungal skin infection, tonsillitis, acute sinusitis, cellulitis, pneumonitis, tuberculosis, cytomegalovirus infection		Listeriosis/listeria meningitis, Epstein-Barr virus (EBV) reactivation
Natalizumab	UTI, nasopharyngitis	Progressive multifocal leukoencephalopathy		
Ocrelizumab	URTI (nasopharyngitis), LRTI, influenza bronchitis, UTI, oral herpes, gastroenteritis, viral infection, herpes zoster, conjunctivitis, cellulitis			Progressive multifocal leukoencephalopathy
Ofatumumab	URTI, UTI, oral herpes			Progressive multifocal leukoencephalopathy

URTI, Upper Respiratory Tract Infection; UTI, Urinary Tract Infection; LRTI, Lower Respiratory Tract Infection

Drug	Tuberculosis screening ^a	Varicella zoster screening	Aciclovir (herpes) prophylaxis	HIV/HBV/HCV screening ⁱ	PML	Vaccinations ^f
Teriflunomide	Yes	No	No	No	Nil specific	Nil specific
Dimethyl Fumarate	Consider ^b	No	No	No	Baseline MRI. Stop if lymphs <0.5x10 ⁹ /L for > 6m	Consider VZV vaccination ^f
Fingolimod	Consider ^b	Yes	Consider during corticosteroid use (>5 days) ^g	No	Baseline MRI. Discontinue if lymphs < 0.2 x 10 ⁹ /L	-VZV vaccination ^f -Consider HPV vaccination
Siponimod	Consider ^b	Yes	No	No	Discontinue if lymphs < 0.2 x 10 ⁹ /L	VZV vaccination ^f
Cladribine ^e	Yes	Yes	Yes (during episodes of grade 4 lymphopenia) ^c	Yes	Baseline MRI as per SMPC	-VZV vaccination ^f -No live vaccinations within 2 weeks before starting treatment or if WCC not within range.
Ocrelizumab	No	Yes	No	Yes	Nil specific	Complete local vaccination 4 weeks pre-treatment.
Ofatumumab	No	Yes	No	Yes	Nil specific	-VZV vaccination ^f - Complete vaccination schedule prior to initiation; inactivated 2 weeks before starting -No live vaccinations until 2 weeks before starting
Natalizumab	Consider ^b	Consider	No ^d	No	Baseline MRI. Monitor PML risk profile as per guidance. ²¹⁸ 4 monthly MRI if high risk of PML. Continued vigilance for 6m after discontinuation.	Nil specific
Alemtuzumab	Yes	Yes	Yes (x1 month post treatment)	Yes	Nil specific	-VZV vaccination. ^h -Complete local vaccination 4 weeks pre-treatment.

Table 3. Screening and vaccination recommendations. (Red: caution required, or action mandated by SMPC, Amber: consideration required, Green: no specific need for caution.)

Notes:

a- Initiation of treatment should be delayed if possible latent or active TB infection is identified on pre-screening checks; discussion with an Infectious Diseases specialist is recommended. It is recommended to interrupt DMT treatment, where possible, if TB infection occurs.

b- Consider in people with recent habitation/ travel to endemic regions or at high risk e.g. chronic kidney disease

c -Grade 4 lymphopenia is defined as absolute lymphocyte count < 0.2 x10⁶

d- Consider aciclovir prophylaxis if patient has a history of prior immunosuppression or frequent oral/genital HSV recurrences

e-Re-evaluation of infection risk is recommended prior to the second course of treatment

f -Live attenuated vaccines, though not expressly contraindicated in several DMTs, would in general not be recommended during active immunosuppressive treatment. If possible, it is recommended to delay treatment with Alemtuzumab or Cladribine by 6 weeks and 4-6 weeks respectively.

g- VZV vaccination is recommended if serology is negative.

h- Co-trimoxazole 3x/week for 1m after alemtuzumab infusion (or amoxicillin 1g TDS/co-trimoxazole 960mg BD 4 days before and 4 days after infusion).¹⁴⁴

i – As a minimum, screening should include hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing

HCV, Hepatitis C Virus; HSV, HBV, Hepatitis B Virus; HIV, Human Immunodeficiency Virus; PML, Progressive Multifocal Leukoencephalopathy; SMPC, Summary of product characteristics; HPV, Human Papilloma Virus; VZV, Varicella Zoster Virus; MRI, Magnetic Resonance Imaging; CMV, Cytomegalovirus.

Table 4. Suggested vaccines for adult people with MS (Table adapted from Reyes S, Ramsay M, Ladhani S, et al. 2020)¹⁷⁶

Vaccine	Type	Schedule	Recommendation in MS
Boostrix-IPV	Diphtheria, tetanus, pertussis (acellular) and polio (inactivated)	Single intramuscular dose any time from 16 weeks up to 32 weeks of pregnancy	Pregnant women with MS
Gardasil	Human papillomavirus 6, 11, 16 and 18 (recombinant)	3 intramuscular doses at months 0, 2 and 6. All three doses should be given within a 1-year period	People with MS aged ≤25 years who are unimmunised or partially immunised against human papillomavirus
Gardasil 9	Human papillomavirus 6, 11, 16, 18, 31, 33, 45, 52 and 58 (recombinant)	3 intramuscular doses at months 0, 2 and 6. All three doses should be given within a 1-year period	People with MS aged ≤25 years who are unimmunised or partially immunised against human papillomavirus
Trivalent influenza vaccine	Influenza virus (inactivated)	Single intramuscular dose every year	People with MS aged ≥65 years
Quadrivalent influenza vaccine	Influenza virus (inactivated)	Single intramuscular/SC dose every year	People with MS aged <65 years (including pregnant women with MS)
Pneumococcal polysaccharide vaccine	Pneumococcus (polysaccharide)	Single intramuscular/SC dose	People with MS aged ≥65 years. Also, regardless of age: patients who (i) anticipate long-term immunosuppression, (ii) have compromised pulmonary function or high levels of disability (EDSS ≥7, (iii) have been shown to have low levels of pneumococcal antibodies.

Vaccine	Type	Schedule	Recommendation in MS
Priorix or M-M-RvaxPro	MMR vaccines (live-attenuated vaccine)*	2 intramuscular/SC doses given 4 weeks apart	People with MS who are susceptible to primary MMR infections
Varilrix	VZV (live-attenuated vaccine)*	2 SC doses given 6 weeks apart	People with MS who are susceptible to primary VZV infection
Varivax	VZV (live-attenuated vaccine)*	2 intramuscular/SC doses given 4–8 weeks apart	People with MS who are susceptible to primary VZV infection
Zostavax	VZV (live-attenuated vaccine)*	Single intramuscular/SC dose	Prevention of herpes zoster and postherpetic neuralgia in people with MS aged 70–79 years**
Shingrix	VZV (recombinant)	2 intramuscular doses separated by 2–6 months	Prevention of herpes zoster and postherpetic neuralgia in people with MS aged ≥50 years

*This vaccine should not be given to people who are already on an immunosuppressive disease-modifying therapy.

**Zostavax is licensed for immunisation of people aged ≥50 years and can be used outside of the national immunisation programme based on clinical discretion.

EDSS, Expanded Disability Status Scale; MMR, measles, mumps and rubella; MS, multiple sclerosis; SC: subcutaneous; VZV, varicella-zoster virus.

Box 1. List of live vaccinations available in the UK (Adapted from The Green Book) ¹⁷⁷

Live vaccines currently available in the UK are:

- Live influenza vaccine (Fluenz Tetra)
- Measles, Mumps and Rubella vaccine (Priorix, MMRVaxPro)
- Rotavirus vaccine (Rotarix)
- Shingles vaccine (Zostavax)
- BCG vaccine
- Oral typhoid vaccine (Ty21a)*
- Varicella vaccine (Varilrix, Varilvax)
- Yellow Fever vaccine

*Non-live alternative vaccine available

Figure 1. Infections associated with disease modifying treatments in MS.

- A. *Listeria rhombencephalitis*. Sagittal T1-weighted MR brain scan. Image from: Abbs A, Nandakumar T, Bose P, et al. *Listeria rhomboencephalitis* Practical Neurology 2012;12:131-132. <http://dx.doi.org/10.1136/practneurol-2011-000085>
- B. Herpes zoster rash in a dermatomal distribution. Image from: Le P, Rothberg M. Herpes zoster infection BMJ 2019; 364 :k5095. <https://doi.org/10.1136/bmj.k5095>
- C., D. Progressive Multifocal Leukoencephalopathy with patchy white matter T2 fluid-attenuated inversion recovery signal change. Image from: Itoh CY, Lee HS, Yee AH. Grey matter abnormality in progressive multifocal leukoencephalopathy Practical Neurology 2021;21:225-227. <http://dx.doi.org/10.1136/practneurol-2020-002852>

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