

# Vaccinations in patients with multiple sclerosis: review and recommendations

In a new MS diagnosis, immunisation status may be overlooked — careful planning from early in the treatment course is key

**M**ultiple sclerosis (MS) is an autoimmune disorder treated with immunomodulatory or immunosuppressive disease-modifying therapies (DMTs). Immunosuppression predisposes to infection risk, including opportunistic infections; a higher long term risk of some infection-related malignancies is also likely. Infections in patients with MS may result in increased relapses, functional decline and pregnancy complications.<sup>1</sup> Immunisations play a critical role in preventing viral and bacterial infections, and in the setting of DMTs, they require careful and individualised planning from early in the treatment course. Here we provide an Australian perspective on vaccine safety and efficacy when given with DMTs.

## General vaccination considerations in patients with MS

Cassie Nesbitt<sup>1,2</sup>



Louise Rath<sup>1</sup>



Michael Zhong<sup>1,2</sup>



Allen C Cheng<sup>1,2</sup>



Helmut Butzkueven<sup>1,2</sup>



Robb Wesselingh<sup>1,2</sup>

Olga Skibina<sup>1</sup>

Mastura Monif<sup>1,2</sup>

Wei Yeh<sup>1,2</sup>

Julia ML Brotherton<sup>3,4</sup>

Stephen Reddel<sup>5</sup>

Anneke Van Der Walt<sup>1,2</sup>

<sup>1</sup> Alfred Health, Melbourne, VIC.

<sup>2</sup> Monash University, Melbourne, VIC.

<sup>3</sup> University of Melbourne, Melbourne, VIC.

<sup>4</sup> VCS Foundation, Melbourne, VIC.

<sup>5</sup> Concord Repatriation General Hospital, Sydney, NSW.

[C.Nesbitt@alfred.org.au](mailto:C.Nesbitt@alfred.org.au)

The immunisation status of patients should be considered at the time of MS diagnosis. Standard investigations before DMT initiation are highlighted in **Box 1**. A full course of vaccinations should be considered for non-immune patients before commencing a DMT; this is sometimes forgotten in the urgency of managing a new MS diagnosis.

Inactivated (non-live) vaccines contain a killed/inactivated or subunit/conjugate of the pathogen and can be safely administered with DMTs. The immunogenicity of these vaccines when used with DMTs has not been conclusively established. Live vaccinations use an attenuated viral or bacterial strain and are contraindicated with most DMTs because of the risk of disseminated infection when used in immunocompromised states.<sup>3</sup> Administration of live

vaccines is recommended before DMT commencement (**Box 2**).

Routine vaccinations are not associated with increased MS relapse risk,<sup>10</sup> although the risk of relapse associated with yellow fever vaccination remains unclear.<sup>11</sup> Immunisations administered in accordance with local guidelines are considered the best strategy for minimising the risk of infections that could trigger MS relapses.<sup>9,12</sup> In patients experiencing clinically significant relapses, delaying vaccine administration has been suggested until patients have stabilised and show signs of improvement (typically 4–6 weeks).<sup>12</sup>

Additional consideration is required for women with MS who are planning a pregnancy. Women should receive live vaccinations before conception to prevent adverse pregnancy outcomes;<sup>13</sup> however, DMT cessation to allow vaccination before conception is often not feasible. Vaccination should therefore be explored as early as possible, preferably before commencement of DMT, as it may represent a one-off opportunity.

It is generally considered safe to vaccinate close immunocompetent contacts (eg, family members) of patients on DMTs without risk of disseminated infection.<sup>14</sup>

Due to the potential for disseminated infection, we recommend delaying recommencement of a DMT by at least 4–6 weeks following the final dose of a live vaccine. Should a patient on a DMT require live vaccines, treatment cessation should be followed by an appropriate washout period before immunisation. No evidence-based guidelines exist for washout periods between DMTs.<sup>15</sup> Patients receiving DMTs with long lasting biological effects (eg, ocrelizumab, alemtuzumab, cladribine) may require prolonged treatment interruption and monitoring to ensure a return to immunocompetency before vaccination (**Box 3**). The risk of delayed DMT recommencement, including risk of relapse and worsening neurological disability, should be carefully considered against the benefits of immunisation. Ultimately, the long term benefits of vaccination may outweigh the short term risk of relapses.

Confirming seroconversion after vaccination is sometimes advised to ensure those who do not generate adequate titres are informed about any possible risk associated with future exposure. An attenuated humoral response is seen with ocrelizumab therapy.<sup>27</sup> However, it should be noted that serological testing is insensitive to the contribution of vaccine-associated cellular immunity, which is likely to offer at least partial protection.<sup>29</sup>

### 1 Standard safety and immune status workup before commencing disease-modifying therapy

- Varicella zoster serology (IgG)
- Measles serology (IgG)
- Mumps serology (IgG)
- Rubella serology (IgG)
- Hepatitis B (surface antibody and antigen, and core antibody) and C serology
- Human immunodeficiency virus serology
- Syphilis serology
- *Mycobacterium tuberculosis* interferon- $\gamma$  release assay\* and/or chest x-ray
- Travel vaccine workup if clinically appropriate
- Additional considerations: vaccination and infection history; cervical screening

\* May be affected by immunosuppressive therapies taken at the time of testing; this has been established for patients on teriflunomide and may be the case for other drugs.<sup>2</sup> ♦

## 2 Summary of vaccines

Vaccine type	Recommendations and comments
Influenza*	<ul style="list-style-type: none"> <li>Safe and recommended annually for patients with MS, including those on DMTs<sup>4</sup></li> </ul>
Varicella zoster virus <sup>†</sup> primary infection (chickenpox)	<ul style="list-style-type: none"> <li>Give before DMT as two doses at least 1 month apart; consider reducing interval to 2 weeks if DMT commencement is urgent<sup>5</sup></li> <li>Avoid re-checking varicella zoster virus serology after vaccination, as failure to seroconvert may not preclude functional immunity<sup>6</sup></li> <li>Delaying DMT commencement to retest for seroconversion is also not recommended</li> <li>When DMT cannot be delayed or ceased, antiviral prophylaxis could be considered in high risk circumstances until a window for vaccination arises</li> <li>Prophylaxis could be similarly considered if a patient is inadvertently given live vaccine while receiving DMT<sup>5</sup></li> </ul>
Varicella zoster virus <sup>†</sup> reactivation (shingles)	<ul style="list-style-type: none"> <li>Give before DMT</li> <li>Prophylaxis could be considered if a patient is inadvertently given live vaccine while receiving DMT<sup>5</sup></li> <li>Non-live vaccine may prove useful to patients taking DMTs in future but is currently in global short supply<sup>7</sup></li> </ul>
Measles–mumps–rubella <sup>†</sup>	<ul style="list-style-type: none"> <li>Give before DMT in vaccine- and infection-naïve patients — recommended as two doses, at least 1 month apart<sup>5</sup></li> <li>Recommended for women considering future pregnancy, if no evidence of immunity before DMT commencement</li> <li>Patients who lose serological immunity despite exposure or single-dose vaccination may benefit from single-dose revaccination<sup>8</sup></li> <li>Patients unable to receive vaccine require education about post-exposure management</li> </ul>
Pneumococcus*	<ul style="list-style-type: none"> <li>Adults should be offered a single dose with a follow-up dose after 5 years</li> <li>The multidose schedule should be particularly applied to patients receiving B cell-depleting agents, or after immune-ablative therapies. In adults without a history of pneumococcal vaccination, the preferred order is one dose of 13vPCV followed by a dose of 23vPPV 8 weeks later; if 23vPPV is administered first, then 13vPCV should be administered 1 year later<sup>5</sup></li> </ul>
Hepatitis B virus*	<ul style="list-style-type: none"> <li>Recommended for patients with MS, who generally fit at-risk category owing to their chronic condition and immune status</li> <li>Three-dose schedule at months 0, 1 and 6; where possible, first dose should be given before commencement of any DMT</li> <li>Some flexibility between dosing is permissible: minimal interval between doses 1 and 2 is 1 month; minimum of 2 months between doses 2 and 3; and 4 months between doses 1 and 3<sup>5</sup></li> <li>Serological response should be measured and specialist advice sought for vaccine non-responders</li> <li>Specialist referral before DMT commencement is required for patients with serological evidence of prior or chronic infection</li> </ul>
Diphtheria–tetanus–pertussis*	<ul style="list-style-type: none"> <li>Vaccination recommended for patients with MS lacking immunity; consider booster before DMT commencement</li> <li>Adults who sustain deep and/or dirty wounds and have not received the vaccine within the previous 5 years should be revaccinated with either diphtheria–tetanus–pertussis or diphtheria–tetanus vaccine<sup>5</sup></li> <li>Vaccination should not be delayed even in patients experiencing an active relapse, as the benefits are thought to outweigh the risks<sup>9</sup></li> <li>In addition, tetanus immunoglobulin is recommended for patients with defective humoral immunity (eg, anti-CD20 therapy) who sustain such wounds</li> </ul>
Meningococcus*	<ul style="list-style-type: none"> <li>Patients with MS treated with DMTs are recommended to have both routine combination quadrivalent conjugate and non-routine meningococcal B vaccinations</li> <li>Also recommended if close contact with laboratories, health care and young children has occurred</li> <li>Close contacts of meningococcal cases should also be considered for post-exposure prophylaxis with vaccination<sup>5</sup></li> </ul>
Human papillomavirus*	<ul style="list-style-type: none"> <li>In Australia, vaccination at 12–13 years of age is routine for both females and males; those aged ≤ 19 years are eligible for a government-funded vaccine, while older patients may need to self-fund</li> <li>Three doses spaced at 0, 2, and 6 months for people &gt; 15 years (two-dose schedule for non-immunocompromised aged under 14 years)</li> <li>Vaccination should be considered in DMT-exposed, non-vaccinated adults and adolescents</li> </ul>
Additional considerations for special groups	<ul style="list-style-type: none"> <li>Travel vaccines: yellow fever<sup>†</sup>, hepatitis A virus*, typhoid (oral<sup>†</sup> and intramuscular* vaccines), Japanese encephalitis<sup>†</sup>, rabies*, cholera<sup>†</sup>, polio (oral<sup>†</sup> and intramuscular* vaccines), tuberculosis (bacille Calmette–Guérin vaccine)<sup>†</sup>, dengue* (not yet available)</li> <li>Q fever* vaccine for people working in abattoirs</li> </ul>

13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; DMT = disease-modifying therapy; MS = multiple sclerosis. \* Non-live vaccine: safe with DMTs but immunogenicity not conclusively established. <sup>†</sup> Live vaccine: contraindicated with DMTs. ♦

## Individual vaccinations and specific considerations

### Influenza (non-live)

The seasonal influenza vaccine is considered safe for patients with MS regardless of DMT exposure and is recommended annually.<sup>4</sup> Efficacy may be reduced

by some DMTs, and seroconversion is attenuated by anti-CD20 therapy.<sup>27</sup>

### Primary varicella (live)

The risks associated with varicella zoster virus infection in patients with MS receiving DMTs highlight the importance of vaccination in this

population.<sup>30</sup> Vaccination should be considered before DMT commencement in patients lacking demonstrable serological immunity who have an absent or unclear history of chickenpox, shingles or vaccination.<sup>31</sup>

## Varicella zoster reactivation (live)

Zostavax (Merck) reduces the risk of shingles and post herpetic neuralgia; it is a larger dose of the live attenuated primary varicella vaccine and is therefore

### 3 Vaccine safety and efficacy with disease-modifying therapies

Disease-modifying therapy	Recommendations	Vaccine use in clinical trials
Corticosteroids	<ul style="list-style-type: none"> <li>Generally used to accelerate recovery in the setting of a relapse (eg, 3–5 days). Guidelines suggest avoiding vaccinations during clinical multiple sclerosis relapses.<sup>9,12</sup></li> <li>Low dose corticosteroids (&lt; 20 mg/day): safe to give vaccinations.<sup>5</sup></li> <li>Higher dose steroids &gt; 20 mg/day used for &lt; 14 days: give live vaccines 1 month before or any time after treatment;<sup>5</sup> some experts recommend waiting 2 weeks after higher dose steroids before giving live vaccines.<sup>16</sup></li> <li>Higher dose steroids used for &gt; 14 days: wait 1 month before live vaccine use.</li> <li>Non-live vaccines are safe.</li> </ul>	
Teriflunomide	<ul style="list-style-type: none"> <li>Clinical trials and post marketing data suggest non-live vaccinations are safe and effective during treatment.<sup>17</sup></li> <li>Live vaccines should be avoided during therapy and be given after a washout period of at least 6 months due to prolonged effects on the immune system.</li> <li>Although accelerated washout can be achieved using cholestyramine or activated charcoal, there are no data regarding earlier use of live vaccinations following this.</li> </ul>	<ul style="list-style-type: none"> <li>Seasonal influenza vaccine was found to be safe and efficacious.<sup>18</sup></li> <li>A double-blind placebo-controlled study evaluated immune responses to a neoantigen (rabies) and recall antigens in healthy subjects treated with teriflunomide. The treatment group achieved seroprotective levels against rabies, albeit at reduced levels compared with the placebo group. Recall antigens were not affected, suggesting no adverse effect on cellular memory response.<sup>7</sup> Teriflunomide impairs tuberculosis interferon-<math>\gamma</math> release assay, which should be cautiously interpreted in this setting.<sup>2</sup></li> </ul>
Dimethyl fumarate	<ul style="list-style-type: none"> <li>Clinical trials and post marketing data suggest non-live vaccinations are safe and effective during treatment.<sup>19</sup></li> <li>Use of live vaccinations is not recommended during treatment. If required, the final live vaccine dose should be given 4–6 weeks before the commencement or recommencement of treatment.</li> </ul>	<ul style="list-style-type: none"> <li>An open label multicentre study evaluated immune response to tetanus, diphtheria, polyvalent pneumococcal vaccine, and meningococcal conjugate vaccines in patients receiving dimethyl fumarate or interferon. Serological evidence consistent with protection for all vaccines was comparable between the two groups, with no safety concerns raised.<sup>19</sup></li> </ul>
Fingolimod	<ul style="list-style-type: none"> <li>Clinical trials and post marketing surveillance data suggest that non-live vaccinations are safe with fingolimod, albeit with impaired efficacy.</li> <li>The use of live vaccinations is not recommended during treatment. A washout period of 2–3 months is recommended to enable immune reconstitution. There are no data to support the use of lymphocyte counts as a marker of immune reconstitution for vaccine safety.</li> <li>The commencement or recommencement of fingolimod should be delayed until 4–6 weeks after the final vaccine dose.</li> <li>Fingolimod has also been associated with infection-associated malignancies such as cervical cancer. Careful observance of screening programs is recommended.</li> </ul>	<ul style="list-style-type: none"> <li>A blinded randomised placebo-controlled study evaluated vaccination response in 138 fingolimod-treated patients. The response rates for novel antigen influenza vaccine (fingolimod v placebo) were 54% and 85%, respectively, at 3 weeks, and 43% and 75%, respectively, at 6 weeks after vaccination. For tetanus toxoid, response rates were 40% and 61%, respectively, at 3 weeks, and 38% and 49%, respectively, at 6 weeks after vaccination. The authors concluded that, despite reduced vaccine response, patients remained capable of producing antibody levels consistent with protection.<sup>20</sup></li> </ul>
Cladribine	<ul style="list-style-type: none"> <li>Use of live vaccinations is not recommended during treatment, and treatment should not be initiated within 4–6 weeks after live vaccinations. The manufacturer recommends against live vaccination during or after a treatment, until white blood cell counts have normalised.<sup>21</sup></li> <li>Data regarding safety or efficacy of vaccines following treatment are lacking.</li> </ul>	<ul style="list-style-type: none"> <li>Live vaccines were prohibited in the placebo-controlled CLARITY trial.<sup>22</sup></li> <li>Several patients were exposed to non-live vaccinations with no adverse events reported.</li> <li>The optimal timing of vaccination with regard to treatment, and the impact of cladribine therapy on vaccine efficacy, are not known.</li> </ul>

## 3 Continued

Disease-modifying therapy	Recommendations	Vaccine use in clinical trials
Natalizumab	<ul style="list-style-type: none"> <li>Clinical trials and post marketing surveillance data suggest that non-live vaccinations are safe and effective during treatment.</li> <li>The use of live vaccinations is not recommended during therapy.</li> </ul>	<ul style="list-style-type: none"> <li>A phase 4, open label, randomised study measured response to tetanus in natalizumab-treated patients, all of whom achieved protective levels of tetanus antibodies.<sup>23</sup></li> <li>A study found no statistically significant difference in mean influenza IgG levels between patients receiving natalizumab and healthy controls following vaccination, suggesting maintained humoral immune response.<sup>24</sup> A study observed reduced long term protection after H1N1 influenza vaccination in natalizumab-treated patients; the authors suggested the need for two vaccine doses in the setting of an influenza pandemic.<sup>4</sup></li> </ul>
Alemtuzumab	<ul style="list-style-type: none"> <li>Alemtuzumab treatment should be delayed for 6 weeks following the final dose of a live vaccine.</li> <li>The efficacy of non-live vaccines during or after alemtuzumab therapy for multiple sclerosis is unclear. One study suggests patients are able to maintain viral immunity following treatment. Data regarding the safety of live vaccines following immune reconstitution are also lacking; this may in theory be safe, especially if T and B cell subsets have normalised.</li> </ul>	<ul style="list-style-type: none"> <li>A case-control study observed preserved serological response to diphtheria, tetanus, polio, <i>Haemophilus influenzae</i>, meningococcal C and pneumococcus vaccines in alemtuzumab-treated patients.<sup>25</sup></li> <li>Pre and post alemtuzumab antibody levels to common viruses (measles-mumps-rubella, varicella zoster and Epstein-Barr) were comparable with historical controls, suggesting pre-existing immunity does not decline after treatment.<sup>25</sup></li> <li>Data from alemtuzumab used for rheumatoid arthritis suggests that vaccine response to both neoantigens and recall antigens returns to normal and remains normal up to 20 years.<sup>26</sup></li> </ul>
Ocrelizumab, rituximab	<ul style="list-style-type: none"> <li>Vaccine response in patients receiving anti-CD20 agents may be attenuated.<sup>27</sup> It is therefore recommended that all necessary vaccines be completed before anti-CD20 treatment.</li> <li>Anti-CD20 therapy should be delayed for 4–6 weeks following the final dose of a live vaccine. The safety of immunisation with live vaccines following ocrelizumab has not been studied and it is therefore not recommended during treatment and until B cell repletion (which may take up to 72 weeks).<sup>28</sup></li> <li>Ocrelizumab exposure during pregnancy may result in neonatal B cell depletion, which may impact the safety and efficacy of neonatal vaccinations. Monitoring of neonatal CD19 counts is recommended, and vaccines should be administered only after normalisation.<sup>28</sup></li> </ul>	<ul style="list-style-type: none"> <li>Following treatment for over 2 years, the proportion of patients with positive antibody titres against pneumococcus, measles-mumps-rubella and varicella zoster virus were similar to baseline, suggesting CD20 B cell depletion does not impact pre-existing protective viral antibodies.<sup>28</sup></li> <li>A randomised controlled trial investigated the impact of ocrelizumab therapy on response to tetanus, influenza and pneumococcus vaccines. An adequate vaccine response was mounted by all patients but was attenuated in the ocrelizumab group relative to the control group.<sup>27</sup></li> </ul>

also contraindicated with DMTs.<sup>5</sup> Vaccination should be considered 4–6 weeks before commencing any DMT; however, reimbursement in many countries is reserved for older age groups, in whom efficacy may be uncertain.<sup>7</sup>

### Measles-mumps-rubella (live)

The combined measles–mumps–rubella vaccine is part of childhood vaccination schemes in most high income countries. It should be administered to patients who lack immunity to any of these viruses before commencing DMT.<sup>5</sup> Women planning future pregnancy are advised to have immunity against rubella to prevent adverse outcomes such as miscarriage and congenital defects.<sup>5</sup>

### Pneumococcus (non-live)

Australian guidelines for pneumococcal vaccination are currently in flux; readers are encouraged to check

the *Australian immunisation handbook* for up-to-date recommendations.<sup>5</sup> Two non-live vaccines against *Streptococcus pneumoniae* are available in Australia: a 13-valent conjugate and a 23-valent polysaccharide vaccine. The benefits of pneumococcal immunity are potentially significant in the MS population, and the multidose schedule should be particularly applied to patients receiving B cell-depleting agents, or after immune-ablative therapies.<sup>5</sup>

### Hepatitis B virus (non-live)

Patients receiving DMTs enter a higher risk category for hepatitis B given their chronic condition, immunocompromise and potentially frequent health care contact.<sup>5</sup> Other risk factors to consider include frequent close contact with blood, compromised immunity, intercourse or residence with someone infected with hepatitis B virus, having more than one sexual partner, and frequent travel. To optimise the

immune response, the first of three doses should be given before DMT exposure where possible. To prevent treatment delays the remaining doses may be given after DMT commencement. Specialist referral before DMT commencement is required for patients with serological evidence of prior (core antibody positive and surface antigen negative) or chronic (surface antigen positive and/or DNA positive) hepatitis B virus infection, for surveillance and antiviral therapy to mitigate reactivation risk. This is a particular risk with fingolimod and lymphocyte-ablative therapies.

### Diphtheria–tetanus–pertussis (non-live)

Vaccination against the highly infectious *Bordetella pertussis* is routine in Australian children, with a booster recommended for special risk adults including those in close contact with health care, children and infants.<sup>5</sup> Vaccination with the diphtheria–tetanus–pertussis vaccine should be strongly considered for patients with MS who lack immunity or have not have a booster within the previous 5 years.

### Meningococcal disease (non-live)

Combination quadrivalent conjugate meningococcal vaccination is routine for Australian infants, children and adolescents.<sup>5</sup> Given their chronic medical condition and immunosuppression, patients with MS treated with DMTs are recommended to receive both combination quadrivalent conjugate and non-routine meningococcal B vaccinations.<sup>5</sup> Further risk factors include frequent travel, individuals living in close quarters, and smoking.

### Yellow fever (live)

Patients with MS planning travel to yellow fever endemic regions should be encouraged to think carefully about their itinerary. A small study of patients not on highly effective DMTs observed a significant increase in relapse rate following exposure to the yellow fever vaccine,<sup>11</sup> although this was not corroborated in a recent case series.<sup>32</sup> When yellow fever vaccination is essential, DMT cessation with a washout period is required. Given a single-dose vaccine is protective for life, yellow fever vaccination could be offered before DMT commencement, especially if DMT initiation is delayed for other vaccinations. Concerns regarding the elevated risk of vaccine-related adverse events in older patients should also be considered.<sup>33</sup> When the risk of vaccination outweighs the benefits and the itinerary cannot be

changed, a letter detailing why the vaccine cannot be administered should be provided. Patients should also be informed of the quarantine requirements and national policies of their destination.

### Human papillomavirus (non-live)

Substantial evidence suggests immunocompromise predisposes to persistent human papillomavirus (HPV) infection and related diseases, including cervical and anal cancer.<sup>34</sup> HPV vaccination is not routinely recommended for adults, except for immunocompromised patients, and men who have sex with men.<sup>35,36</sup> Although data on women with MS are lacking, the nonavalent HPV vaccine should be considered in non-vaccinated adults and adolescents preparing for, or already taking, DMTs. The use of cervical HPV DNA testing to determine potential benefit from vaccination is not recommended.<sup>35,36</sup> The Australian National Cervical Screening Program recommends immunocompromised women with a negative HPV result be re-screened every 3 years (rather than every 5 years in immunocompetent women).<sup>35,36</sup>

### Travel vaccines

Patients with MS should be counselled regarding their itinerary, need to travel, and risks of infections in the context of their travel plans and prescribed DMT. As with other vaccines, non-live vaccinations are considered safe, whereas live vaccines are contraindicated in those receiving DMTs and must be given after an appropriate washout period. Patients should be made aware that the immunogenicity of non-live vaccines in the context of DMTs is inadequately studied. Referral to a specialised travel medicine clinic is recommended.

### Summary

Determining immunisation status when commencing DMTs is key, as is an individualised approach to risk–benefit assessment when considering vaccinations. Live vaccinations are contraindicated in patients once they have commenced a DMT. Although we consider it safe to combine non-live vaccinations with DMTs, data are limited regarding their efficacy and durability.

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