Protecting people with multiple sclerosis through vaccination

Saúl Reyes, Mary Ramsay, Shamez Ladhani, Gayatri Amirthalingam, Neena Singh, Carlos Cores, joela Mathews, Jonathan Lambourne, Monica Marta, Benjamin Turner, Sharmilee Gnanapavan, Ruth Dobson, Klaus Schmierer, G Giovannoni

ABSTRACT

Vaccination is one of the most effective and cost-efficient methods for protecting people with multiple sclerosis (MS) from infections. However, use of vaccines has often been problematic because of misguided concerns that they may exacerbate the disease and/or that some disease-modifying therapies may influence the immune response to immunisations and/or their safety. People with MS risk higher morbidity and mortality from vaccine-preventable infections. It is, therefore, important to address any patient’s reluctance to accept vaccination and to provide clear guidance for clinicians on which vaccinations to consider proactively. We have reviewed the current literature and provide recommendations regarding vaccines in adults with MS, including specific advice regarding vaccination safety in patients receiving—or going to receive—disease-modifying therapies, vaccination during pregnancy, pretravel counselling and patient education.

INTRODUCTION

Immunisation through vaccination is one of the most cost-effective tools for preventing potentially serious and life-threatening infectious diseases. Recent outbreaks of vaccine-preventable infections in countries where these infections had been considered eliminated have drawn attention to the implications of a declining vaccine coverage worldwide. Factors affecting vaccine uptake include parental or patient reluctance to vaccinate (‘vaccine hesitancy’), difficulty in accessing immunisation services and failure of healthcare professionals to offer and promote appropriate vaccination correctly. False contraindications to vaccination were a known cause of under-vaccination in the 1980s, but for the healthy population have been largely mitigated by the ready availability of authoritative advice, such as the UK’s Immunisation Against Infectious Disease (the ‘Green Book’).

Research into public confidence in vaccination concludes that it is currently high in the UK, and most people trust respective advice from healthcare professionals. Nevertheless, coverage in England has declined for all vaccinations routinely given to children in 2018–2019 compared to previous years. A report from National Health Service (NHS) Digital showed that coverage of the measles, mumps and rubella (MMR) vaccine for children reaching 2 years of age fell for the fifth successive year. Uptake was 90.3% in England in 2018–2019, down from 91.2% in 2017–2018 and the lowest level since 2010–2011. In 2018, there were 913 laboratory-confirmed cases of measles in England. Adults aged 15 years and over who missed their MMR vaccine in childhood have been particularly affected.

As adults are also at risk of acquiring vaccine-preventable infections, either because of incomplete immunisation or waning immunity, vaccination may be recommended throughout life and some vaccines may be specifically targeted to those with underlying medical conditions. However, immunisation coverage in at-risk adults remains low for most routinely recommended vaccines. Although influenza vaccination coverage for the UK population aged over 65 years remains above 70%, coverage in individuals aged less than 65 years in clinical risk groups remains suboptimal and is only 50.3% in those with neurological conditions. Similarly, vaccine coverage for shingles prevention in England has declined more than 15% since the programme began in 2013. Logistical
challenges that may have contributed to this trend include issues around eligibility criteria, attempting to give the vaccine at the same visit as the influenza vaccine, and difficulties identifying those in whom the live-attenuated vaccine is contraindicated. 8

Apart from the risks to unvaccinated individuals, declining vaccine coverage in the population has potentially serious implications for at-risk groups such as people with multiple sclerosis (MS). It is, therefore, very important that people with MS (and their relatives or contacts) undergo an appropriate vaccination programme.

VACCINATION AND MS

Historical observations of postvaccination encephalomyelitis or the onset/relapse of other demyelinating illnesses following vaccination have contributed to damaging controversies in vaccine safety 9; case reports of patients developing MS following hepatitis B vaccine caused concern in the 1990s. 10 However, in the past two decades, multiple studies have shown the absence of a causal link between vaccination and the onset or relapse of MS. The available evidence suggests that hepatitis B, human papillomavirus, influenza, tetanus, diphtheria, pertussis, polio, BCG, typhoid, tick-borne encephalitis or MMR vaccinations do not increase the risk of developing MS. 11–13 Similarly, several studies have found no increased risk of MS exacerbation following hepatitis B, tetanus, tick-borne encephalitis or influenza vaccinations. 11–13 16 17 One possible exception, despite relatively little evidence, is the live-attenuated vaccine against yellow fever, where a case series showed relapses in 5/7 people with MS soon after receiving this. 18 However, this report has been criticised for methodological issues. 19 More recently, a small retrospective study reported that yellow fever vaccination was associated with neither an increase in MS relapses nor emergence of brain and/or spinal cord lesions. 20 These contrasting results could relate to differences in the efficacy profile of disease-modifying therapies used soon after yellow fever vaccination and we need further research to establish or exclude any potential causal association. 20

Although there is no compelling evidence that vaccines increase the risk of relapse in MS, some experts remain concerned that vaccination may worsen relapse severity in people with MS who are actively experiencing a relapse. 17 Vaccination in routine MS clinical practice is typically non-urgent (ie, a delay of a few weeks would not significantly increase the risk of any vaccine-preventable disease), and so immunisation of people with MS experiencing a relapse should be deferred until clinical resolution or until the relapse is no longer active/progressive. 17

In people with MS not receiving immunotherapy, the benefits of most vaccines greatly outweigh any potential risks. These people should be capable of mounting an immune response to antigenic stimulation similar to those who do not have MS. 21 A disease-related influence on vaccination response is unlikely in the light of recent studies showing that interferon-treated patients have similar seroconversion rates to influenza vaccine compared to healthy controls. 22–25 People with MS should have their vaccination status reviewed and updated as soon as possible after establishing their diagnosis of MS to prevent future delays in starting immunotherapies. 17

High immunisation rates within a community protect not only the people who are vaccinated but also vulnerable individuals via herd (indirect or population) immunity, including immunocompromised adults who cannot be immunised with live vaccines and who may be less well protected by the other vaccines that they can receive. 26 Those with MS exposed to immunosuppressive therapies and those with worse disability are not only more susceptible to infection but also risk higher morbidity and mortality from many vaccine-preventable infections. 27 28 Additionally, MS exacerbations associated with infections may lead to more severe and sustained neurological deficit than spontaneous relapses. 29–31

Table 1 summarises some of the current vaccines available to adults (either privately or on the NHS) and our recommendations about their administration in people with MS. 3 32 These recommendations are in line with the national immunisation programme. 33 Additional information for each vaccine is available via the ‘electronic medicines compendium’ and should be consulted for specific information relating to these products. 32

Disease-modifying therapies for MS may influence the immune response against vaccines and their safety. Although there are no major concerns about vaccination in people with MS treated with interferon β preparations, this is not the case with newer disease-modifying therapies. 34 Everyone with MS who is immunocompromised or being considered for immunotherapy needs their vaccination history assessed carefully and to have a plan made for future vaccinations. The optimal timing for any vaccination should be based upon a judgement about the relative need for rapid protection and the likely response to vaccination. 3

Inactivated vaccines should ideally be given at least 2 weeks before starting maintenance immunosuppressive and immune reconstitution therapies (ie, short course therapies resulting in long-term qualitative changes in immune function, such as alemtuzumab and cladribine). 3 35 A recent study showed that people with MS treated with ocrelizumab had an attenuated humoral response to tetanus, pneumococcus and seasonal influenza vaccination, compared to those exposed to interferon β or no therapy. 36 Although this finding supports current recommendations that people with MS ideally receive inactivated vaccines before
starting immunosuppressive therapies, it also suggests that seasonal vaccinations such as the inactivated influenza vaccine have a favourable safety profile and will still provide some protection in patients already receiving these disease-modifying therapies.34 36 When immunisation with inactivated vaccines is not possible before starting treatment, inactivated vaccines can be given at any time, with re-immunisation considered after treatment is stopped/finished and the immune system has recovered/reconstituted (ie, resolution of lymphopenia, adequate antibody responses to vaccines and no increased risk of immunosuppression-related complications, such as opportunistic infections and secondary malignancies).3 35

Due to the risk of vaccine-transmitted disease, live-attenuated virus vaccines such as MMR, varicella-zoster virus (VZV) and yellow fever vaccines are generally not recommended in people with MS during and shortly (<4 weeks) before maintenance immunosuppressive and immune reconstitution therapies (even though the duration of vaccine-induced viremia is shorter for some live vaccines).3 37 However, they could be cautiously considered if the risk of infection is high (eg, endemic risks or local pandemics) and/or if there are no inactivated alternatives.17 Careful consideration of the benefits and risks should accompany the decision to administer live-attenuated virus vaccines in this situation. Patients on immune reconstitution therapies who are considered to have reconstituted their immune systems should be able to tolerate and respond to such live-attenuated virus vaccines.38 Extrapolating from the HIV literature, a CD4 count of 200 cells/μL may be a suitable cut off value below which vaccination with live vaccines should not be given.39

The effect of B cell-depleting agents and alemtuzumab on the level of protection provided by immunisations started before disease-modifying therapies remains largely unknown. In the case of B cell depleting therapy, some patients develop an exposure-dependent hypogammaglobulinemia, which might affect their levels of protection from prior immunisations.34 However, data from the OPERA I and OPERA II studies showed that ocrelizumab does not appear to affect pre-existing humoral immunity.40 Similarly, a small pilot study showed retained humoral immunological memory (against

### Table 1  Suggested vaccines for adult people with MS

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Schedule</th>
<th>Recommendation in MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boostrix-IPV</td>
<td>Diphtheria, tetanus, pertussis (acellular) and polio (inactivated)</td>
<td>Single intramuscular dose any time from 16 weeks up to 32 weeks of pregnancy</td>
<td>Pregnant women with MS</td>
</tr>
<tr>
<td>Gardasil</td>
<td>Human papillomavirus 6, 11, 16 and 18 (recombinant)</td>
<td>3 intramuscular doses at months 0, 2 and 6. All three doses should be given within a 1-year period</td>
<td>People with MS aged ≤25 years who are unimmunised or partially immunised against human papillomavirus</td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>Human papillomavirus 6, 11, 16, 18, 31, 33, 45, 52 and 58 (recombinant)</td>
<td>3 intramuscular doses at months 0, 2 and 6. All three doses should be given within a 1-year period</td>
<td>People with MS aged ≤25 years who are unimmunised or partially immunised against human papillomavirus</td>
</tr>
<tr>
<td>Trivalent influenza vaccine</td>
<td>Influenza virus (inactivated)</td>
<td>Single intramuscular dose every year</td>
<td>People with MS aged ≥65 years</td>
</tr>
<tr>
<td>Quadrivalent influenza vaccine</td>
<td>Influenza virus (inactivated)</td>
<td>Single intramuscular/SC dose every year</td>
<td>People with MS aged &lt;65 years (including pregnant women with MS)</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide vaccine</td>
<td>Pneumococcus (polysaccharide)</td>
<td>Single intramuscular/SC dose</td>
<td>People with MS aged ≥65 years. Also, regardless of age: patients who anticipate long-term immunosuppression and for those with compromised pulmonary function or high levels of disability (EDSS ≥7)</td>
</tr>
<tr>
<td>Priorix or M-M-RvaxPro</td>
<td>MMR vaccines (live-attenuated vaccine)*</td>
<td>2 intramuscular/SC doses given 4 weeks apart</td>
<td>People with MS who are susceptible to primary MMR infections</td>
</tr>
<tr>
<td>Varilrix</td>
<td>VZV (live-attenuated vaccine)*</td>
<td>2 SC doses given 6 weeks apart</td>
<td>People with MS who are susceptible to primary VZV infection</td>
</tr>
<tr>
<td>Varivax</td>
<td>VZV (live-attenuated vaccine)*</td>
<td>2 intramuscular/SC doses given 4–6 weeks apart</td>
<td>People with MS who are susceptible to primary VZV infection</td>
</tr>
<tr>
<td>Zostavax</td>
<td>VZV (live-attenuated vaccine)*</td>
<td>Single intramuscular/SC dose</td>
<td>Prevention of herpes zoster and postherpetic neuralgia in people with MS aged 70–79 years**</td>
</tr>
<tr>
<td>Shingrix</td>
<td>VZV (recombinant)</td>
<td>2 intramuscular doses separated by 2–6 months</td>
<td>Prevention of herpes zoster and postherpetic neuralgia in people with MS aged ≥50 years</td>
</tr>
</tbody>
</table>

*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.
antigens previously met) after alemtuzumab treatment. In contrast, most haematopoietic stem-cell transplant recipients lose specific humoral immunity 1 year after transplantation and should be considered as never vaccinated. Therefore, people with MS receiving a haematopoietic stem-cell transplant should be considered for a re-immunisation programme after transplantation. Table 2 summarises these and other vaccination recommendations for disease-modifying therapies.

Live vaccines should not be given to people with MS who for any reason are receiving or have received in the past 3 months high-dose corticosteroids (ie, >40 mg/day of prednisone or equivalent for ≥7 consecutive days OR >20 mg/day of prednisone or equivalent for ≥14 consecutive days). Although inactivated vaccines may be given to people taking high-dose corticosteroids, they may elicit a lower response than in immunocompetent individuals.

SPECIFIC ADVICE REGARDING INDIVIDUAL VACCINES

Influenza vaccine

In the UK, the influenza vaccine is available each year to protect against the strains of influenza that are expected to circulate in the coming season. The Public Health England routine immunisation schedule guideline states that adults with chronic neurological conditions, such as MS, and/or those who are immunosuppressed due to disease or treatment should receive the influenza vaccine (table 1). Influenza immunisation should also be recommended for household members and carers of people with MS, as well as healthcare professionals with face-to-face duties managing people with MS.

Every year, up to 650 000 people die from complications of seasonal influenza worldwide. We recently had a fatal case of influenza A pneumonia in a disabled person with MS who developed grade 4 lymphopenia after receiving off-label subcutaneous cladribine. Unfortunately, this patient had not had the influenza vaccine despite its wide availability on the NHS. Whether or not this patient would have been protected by this vaccine is unknown. Notably, there have not yet been any published formal vaccine trials in people with MS receiving cladribine. However, as the trivalent and quadrivalent inactivated influenza vaccines can generally be considered safe at any point of treatment and are likely to provide some protection, we recommend annual influenza vaccination with inactivated but not live vaccines, in immunocompromised people with MS.

The live-attenuated influenza vaccine is given as a nasal spray and is only licensed for children and young people aged <18 years. It is contraindicated in people with MS who are clinically severely immunocompromised and in those where close contact with very severely immunocompromised people with MS (ie, haematopoietic stem cell transplant recipients during the first months after transplantation or if they have graft-vs-host disease) is likely or unavoidable.

Pneumococcal vaccine

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia in adults, with case fatality rates ranging from 16% to 55%. Failure of natural immunity to Streptococcus pneumoniae may predispose to invasive pneumococcal disease. Therefore, the 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended in the UK for people at high risk of pneumococcal disease, including all adults aged ≥65 years and at-risk individuals aged 2 to <65 years, including those who are immunocompromised or have a neurological disease with a risk of aspiration. In particular, PPV23 should be offered to people with MS who are likely to require long-term immunosuppression and for those with compromised pulmonary function, such as people who are wheelchair users or bed-bound (table 1). Given that immunosuppressed people with MS may have impaired antibody responses, PPV23 is recommended to be given at least 2 weeks before starting maintenance immunosuppressive and immune reconstitution therapies. Patients who are likely to be severely immunocompromised, such as after haematopoietic stem cell transplantation, should also be offered the 13-valent pneumococcal conjugate vaccine (PCV13; Prevenar13) at least 8 weeks before PPV23. Giving PPV23 8 weeks after PCV13 will boost the immune response to PCV13 and help protect against the additional PPV23 serotypes that are currently responsible for the majority of pneumococcal cases in the UK. Although both pneumococcal vaccines can also be given to patients who are already on disease-modifying therapies, this decision should be considered on an individual basis. Immunocompromised people with MS may not be as well protected against pneumococcal disease as immunocompetent individuals after vaccination.

Varicella vaccines

A higher incidence and more severe herpes virus infection/reactivation occur in immunosuppressed patients. Patients without a history of chickenpox or vaccination against VZV should be tested for anti-VZV antibodies before initiating maintenance immunosuppressive or immune reconstitution therapies. A full course of VZV vaccination for people with MS who are susceptible to primary VZV infection is recommended, and starting such therapies should be postponed for 4 weeks after completion of the vaccination schedule to allow optimal immune response following vaccination (table 2).

In the UK, VZV vaccination is
For protection against herpes zoster (shingles) and related complications in older people in the UK, since September 2013, Zostavax (a live-attenuated vaccine) is routinely offered to currently offered using Varivax/Varilrix live-attenuated vaccines; adults should receive two doses at least 4 weeks apart.* For protection against herpes zoster

**Table 2 Vaccination and disease-modifying therapies**

<table>
<thead>
<tr>
<th>Class</th>
<th>Vaccination</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon β</td>
<td>Maintenance immunomodulatory</td>
<td>Safe and effective</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Maintenance immunomodulatory</td>
<td>Safe. Inactivated influenza vaccine may be less effective</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Maintenance immunomodulatory</td>
<td>Inactivated neoantigens (first vaccination) and recall antigens (re-exposure) have been found to be safe and effective. Live-attenuated vaccines should be avoided during treatment and for 6 months after stopping (SmPC recommendation) The long half-life of teriflunomide should be considered (unless an accelerated elimination protocol is used) when contemplating vaccination with live-attenuated vaccines after stopping teriflunomide.</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Maintenance immunosuppressive</td>
<td>Inactivated neoantigens and recall antigens have been found to be safe and effective. Live-attenuated vaccines should be avoided until lymphocyte counts have returned to above 800/mm³ after stopping treatment. MMR screening before starting treatment,* VZV screening is also advisable given the potential risk of persistent lymphopenia (&lt;800/mm³)**</td>
</tr>
<tr>
<td>Fingolimod (and other sphingosine-1-phosphate–receptor modulators)</td>
<td>Maintenance immunosuppressive</td>
<td>During—</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Maintenance immunosuppressive</td>
<td>Although immune responses to inactivated neoantigens and recall antigens have been found to be preserved, some studies have suggested that inactivated influenza vaccine may be less effective. Live-attenuated vaccines have not been studied and should, therefore, be avoided (in particular neurotropic viruses). MMR screening before starting treatment,* VZV screening is also advisable given the potential risk of VZV-associated CNS infections/vasculitis**</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Immune reconstitution therapy</td>
<td>Although immune responses to inactivated neoantigens and recall antigens are preserved after alemtuzumab, vaccination within 6 months of treatment may result in a smaller proportion of responders. Live-attenuated vaccines are not recommended until immune reconstitution has occurred. MMR* and VZV** screening before starting treatment. The SmPC recommends against the use of live-attenuated vaccines for at least 6 weeks before treatment, which differs from the 'Green Book' guidelines adopted in this manuscript.</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Immune reconstitution therapy</td>
<td>Not recommended until immune reconstitution has occurred. MMR* and VZV** screening before starting treatment</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Maintenance immunosuppressive</td>
<td>Non-live vaccines may be less effective. Live-attenuated vaccines have not been studied and should, therefore, be avoided during treatment and after discontinuation until B-cell repletion. MMR* and VZV** screening before starting treatment</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Immune reconstitution therapy</td>
<td>Inactivated influenza vaccine may be less effective. Live-attenuated vaccines are not recommended earlier than 3 months after the last dose of chemotherapy and/or until immune reconstitution has occurred. MMR* and VZV** screening before starting treatment</td>
</tr>
<tr>
<td>Haematopoietic stem cell transplant (HSCT)</td>
<td>Immune reconstitution therapy</td>
<td>Inactivated vaccines after haematopoietic stem cell transplant are safe and specific revaccination programmes have been recommended by the ECIL group. Live-attenuated vaccines are not recommended earlier than 24 months after the transplant and should only be considered in patients with no graft-versus-host disease and no ongoing immunosuppression. There is no evidence that inactivated vaccines trigger or worsen graft-versus-host disease. Donor immunisation with Live-attenuated vaccines is contraindicated 4 weeks before donation. Close contacts of haematopoietic stem cell transplant recipients should be immunised according to the national recommendations and special considerations apply when using live-attenuated vaccines†</td>
</tr>
</tbody>
</table>

*People with MS without a reliable history of appropriate immunisation (ie, having received two doses of MMR) should be tested for measles and rubella antibodies. **People with MS without a confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for VZV antibodies. †Close contacts who need VZV or MMR live-attenuated vaccines should be temporarily separated from the haematopoietic stem cell transplant recipient. People with MS who have received haematopoietic stem cell transplant should have no contact with the stools or diapers of infants who have received the rotavirus live-attenuated vaccines vaccine in the previous 4 weeks. CNS, central nervous system; ECIL, European Conference on Infections in Leukaemia; HPV, human papillomavirus; MMR, measles, mumps and rubella; MS, multiple sclerosis; SmPC, summary of product characteristics; VZV, varicella-zoster virus.
immunocompetent people aged 70 years. A catch-up programme has also been underway since 2013 for individuals aged 71–79 years, based on evidence of cost-effectiveness (table 1). In the USA, Shingrix (a recombinant vaccine) is recommended for adults aged 50 years and older. The UK Joint Committee on Vaccination and Immunisation has recommended that Shingrix should be offered to adults aged 60–70 years, immunocompromised people who are eligible in the current programme but contraindicated for immunisation with Zostavax and immunocompromised people aged 50 years and older. Shingrix, however, is not currently available under the NHS.

VZV vaccines can be given at the same time as polysaccharide pneumococcal and inactivated influenza vaccines. Responses to varicella and MMR vaccines are adequate when the vaccines are successfully co-administered on the same day. However, the interferon production stimulated by the replication of a first vaccine virus may prevent the replication of a second agent when these live vaccines are not administered simultaneously. Where any vaccine is required rapidly then they can be administered at any interval, but an additional dose of the vaccine given second should be considered at least 4 weeks later. Since this may delay starting disease-modifying therapy, the potential risks and benefits must be considered on a case-by-case basis.

Human papillomavirus vaccine
Human papillomavirus is responsible for 99.7% of cases of cervical cancer and is also strongly associated with the development of other anogenital and oropharyngeal cancers. A major reason to vaccinate people with MS is that immunosuppression is associated with an increased risk of these virus-associated malignancies. From 2019, routine vaccination will be offered to all girls and boys aged 12–13 years when they are in school year 8. The current vaccine offered is Gardasil, which protects against human papillomavirus types 6, 11, 16 and 18. These four types cover about 70% of cervical cancers in the UK. The newer polyvalent vaccine, Gardasil 9, protects against human papillomavirus 6, 11, 16, 18, 31, 33, 45, 52 and 58 and covers over 90% of cervical cancers but is not yet available through the national programme (table 1).

Human papillomavirus vaccines are highly effective in protecting against cervical cancer in adolescents and young women before they acquire natural human papillomavirus infection. Unvaccinated individuals currently remain eligible for vaccination on the NHS until they reach 25 years of age. Vaccinating men and women older than 25 years, and those who have already been infected, may also reduce their chances of developing precancerous lesions and can be offered outside of the national programme at the discretion of the clinician. A 3-dose schedule (0, 1–2 and 6 months) over a period of maximum 12 months should be used if immunisation is started at age 15, which will delay starting continuous immunosuppressive therapies for more than 6 months (at least 2 weeks after the last dose). In the case of some immune reconstitution therapies (cladribine and alemtuzumab), the initial two doses could be given (0 and 1–2 months) before starting such treatments and the third dose after the immune system reconstitution (months 9–11). A recent study in the US showed that just one dose of human papillomavirus vaccine is associated with a significant reduction in cervical disease. In clinical practice, physicians and people with MS must decide on whether the potential benefit of human papillomavirus vaccination outweighs the risks of delaying treatment at the individual patient level. Vaccination against human papillomavirus should be particularly considered before starting fingolimod, and other emerging sphingosine-1-phosphate–receptor modulators, which may result in impaired intrinsic cancer immunosurveillance. A link between fingolimod and human papillomavirus-driven conditions has been recently highlighted by a report of chronic and treatment-refractory cutaneous and genital warts in people with MS treated with fingolimod.

Although ideally the human papillomavirus vaccine should be given before people become immunocompromised, this vaccination is safe and likely also to benefit those with impaired immune responsiveness. Routine cervical/human papillomavirus screening according to national guidelines is critical for all women with MS, regardless of their human papillomavirus vaccination status. Women aged 25–49 years are invited every 3 years, whereas those aged 50–64 years are invited every 5 years.

MMR vaccine
Given the recent increase in measles virus circulation in England, we have started to screen our patients with MS for previous MMR vaccination, before starting maintenance immunosuppressive or immune reconstitution therapies (table 2). People with MS who missed one MMR vaccination when they were younger may not be immune. Patients without a reliable history of appropriate immunisation (ie, having received two doses of MMR) are tested for measles and rubella antibodies and, if not immune, we recommend MMR vaccination, which can be provided on the NHS (table 1). Our aim is to de-risk MS treatments because measles is a highly contagious virus and measles inclusion body encephalitis, for example, results in neurological deterioration and death in people with impaired cellular immunity within months of the acute illness. Although over 99% of persons who receive two doses of MMR vaccine develop measles antibodies, waning measles immunity occurs in approximately 5% of cases within 10–15 years after vaccination. However, measles infection in those with pre-existing immunity should be treated promptly with antimeasles immunoglobulin and intramuscular immunoglobulin and with ribavirin if infections are severe or immunosuppressive.
is generally less severe and less transmissible than infection in unimmunised individuals.70

VACCINES DURING PREGNANCY
As MS is more commonly diagnosed in women than men, and during their childbearing years, consideration needs to be given to pregnant women with MS taking disease-modifying treatments. Pregnant women in the UK are routinely offered the inactivated influenza and the inactivated diphtheria, tetanus and acellular pertussis (dTaP) vaccines, while other vaccines may be considered in cases of high risk or specific exposure.3 33 Due to changes in systemic immunity during pregnancy, morbidity and mortality rates associated with influenza are higher in pregnant women, particularly in the second and third trimesters.71 As such, women who are pregnant during the influenza season (from September to February) should be offered the inactivated influenza vaccine. It is safe to receive this vaccine at any stage of an uncomplicated pregnancy.72 The recommendations for the influenza vaccine in the context of disease-modifying treatments have been detailed in the previous section.

A pertussis-containing vaccine for pregnant women arose as a recommendation following the 2012 epidemic of pertussis in the UK, with 9300 cases reported in England.73 A programme involving the vaccination of pregnant women started in September to February) should be offered the inactivated influenza vaccine. It is safe to receive this vaccine any stage of an uncomplicated pregnancy. The recommendations for the influenza vaccine in the context of disease-modifying treatments have been detailed in the previous section.

A pertussis-containing vaccine for pregnant women arose as a recommendation following the 2012 epidemic of pertussis in the UK, with 9300 cases reported in England.73 A programme involving the vaccination of pregnant women started in October 2012; such programmes also exist in the US, Australia and some European countries.74 75 The vaccine should ideally be given at 20–32 weeks gestation to allow optimal maternal antibody transfer across the placenta to help protect the fetus and newborn against pertussis, but the vaccine can be given from as early as 16 weeks gestation.3 The vaccine currently offered in the UK is Boostrix-IPV, which is a combined dTaP and inactivated poliovirus vaccine (table 1). Pregnant women with MS should be vaccinated according to the national recommendations described earlier. The vaccine does not contain any live components and, as such, should be safe to administer to pregnant women with reduced immunocompetence, although the vaccine response may be attenuated.32

TRAVEL VACCINATIONS
International travellers may be at risk for various potentially severe and vaccine-preventable infections that are absent or uncommon in their home territories. People with MS who plan overseas travel should undergo a risk assessment (based on their itinerary, duration of stay and planned activities) and guidance on vaccination by a general practitioner or a travel clinic, ideally at least 6–8 weeks before travelling. Prevention should also focus on ensuring safe food and water, good personal hygiene, travel medications (such as malaria prophylaxis) and precautions about avoiding being bitten by insect vectors.76 In addition, a pretravel consultation provides an opportunity to discuss not only travel vaccines but also all routinely recommended vaccines.76 Figure 1 provides a simple guide to travel immunisations (if indicated) for adults with MS, focusing on vaccines available in the UK.3 77 The safety and immunogenicity of inactivated and live vaccines in people with MS receiving immunotherapy should be carefully considered before the administration of travel vaccines, and those with MS on such treatments should be advised to highlight these to their travel clinics. Travel vaccines other than those shown in figure 1 may be required in some specific situations. TRAVAX and the National Travel Health Network and Centre portal ‘TravelHealthPro’ provide more detailed information on travel vaccines.3 77

PATIENT EDUCATION
Vaccine hesitancy has been identified by the WHO as one of the top global threats in 2019.79 The WHO’s Strategic Advisory Group of Experts on Immunisation has defined vaccine hesitancy as ‘a delay in acceptance or refusal of vaccines despite availability of vaccination services’.80 The factors underlying hesitancy are variable and differ by areas, cultures, communities, socioeconomic status, political inclinations, parental age, beliefs about safety and effectiveness, and the availability of lay advice via online and social media resources.81 The claim linking the MMR vaccine with autism has been a widely publicised example of misinformation, which was difficult to rectify, not least due to its publication in a high-impact journal and despite overwhelming evidence refuting the claim.82

Addressing vaccine hesitancy is paramount in the age of administering immunosuppressive therapies because of the increased risk of significant morbidity and mortality associated with infection in a patient with reduced immunocompetence. We need strategies to manage vaccine hesitancy, particularly in those with MS, to prevent delays in starting disease-modifying treatments. Redirection of patients to trusted, clinically verified online information sites via the WHO’s ‘Vaccine safety net’ initiative should be encouraged. The UK has applied Tailoring Immunisation Programme methodologies created by the WHO/Europe, for example, to the Orthodox Jewish Charedi community of North London.83 The Tailoring Immunisation Programme is a framework that provides tools to identify low vaccine coverage groups, diagnose supply-side and demand-side immunisation barriers, identify motivators to vaccination and create evidence-based responses to sustain vaccination.84
The role of the general practitioner and other healthcare professionals is key, because they are the most trusted sources of information on vaccination. For people with chronic medical conditions, such as MS, recommendations for vaccinations at the appropriate time by their clinical specialist will facilitate the process and help support both the patient and the primary care team in ensuring that optimal protection is achieved against vaccine-preventable diseases. Routinely offering vaccinations during regular health checks, and providing information in local languages is also key to promoting vaccine uptake.

CONCLUSION

Although vaccinations are safe and effective for the vast majority of people with MS, some specific considerations should be kept in mind when planning vaccination strategies for them before, during and after receiving immunotherapy. People with MS may have an increased risk of morbidity and mortality from vaccine-preventable infections and, therefore, we must address their concerns with confidence. The aim has to be that we all, physicians and scientists, recognise the threat this poses and that, together with public health initiatives, we improve current vaccine uptake overall and in people with MS, within our practices and communities. As primary care physicians are among the most trusted advisors and influencers of vaccine decisions, we should support them in their mission to build confidence in the effectiveness and safety of vaccines. Community vaccination may be one of the most cost-effective methods for protecting people with MS.

Figure 1 Travel immunisations for adults with MS. *Combined hepatitis A/typhoid (ViATIM) and hepatitis A/hepatitis B (Twinrix Adult) vaccines are also available in the UK. **If more than 2 years have elapsed since the last vaccination, the primary course should be repeated. ***The list of countries considered by the WHO to be infected with polio or vulnerable to it has been recently reviewed and is in the public domain.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Route of administration</th>
<th>Number of doses</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Subcutaneous</td>
<td>1</td>
<td>1 dose</td>
</tr>
<tr>
<td>Typhoid Fever</td>
<td>Oral or subcutaneous</td>
<td>2</td>
<td>1 dose + 1 dose (2nd dose 6-12 months after 1st dose)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Intramuscular</td>
<td>1</td>
<td>1 dose</td>
</tr>
<tr>
<td>Polio</td>
<td>Oral</td>
<td>3</td>
<td>3 doses (at 2, 4, and 6 months of age)</td>
</tr>
<tr>
<td>Rabies</td>
<td>Intramuscular</td>
<td>3</td>
<td>1 dose + 2 doses (booster doses 6-12 months after 1st dose)</td>
</tr>
<tr>
<td>Cholera</td>
<td>Oral</td>
<td>1</td>
<td>1 dose</td>
</tr>
</tbody>
</table>

At-risk areas and countries include:

- While travelling in countries with higher rates of Typhoid Fever, a single dose of typhoid vaccine can prevent infection.
- At-risk areas for yellow fever include the Americas, Africa, Southeast Asia, and the Pacific Islands.
- At-risk areas for rabies include parts of Africa, Asia, and South America.
- At-risk areas for Cholera include parts of South America, Africa, and Asia.

The use of combination vaccines, such as hepatitis A/typhoid, can help reduce the number of doses needed.


[Figure 1: Travel immunisations for adults with MS. *Combined hepatitis A/typhoid (ViATIM) and hepatitis A/hepatitis B (Twinrix Adult) vaccines are also available in the UK. **If more than 2 years have elapsed since the last vaccination, the primary course should be repeated. ***The list of countries considered by the WHO to be infected with polio or vulnerable to it has been recently reviewed and is in the public domain.78

†Postexposure schedule depends on a risk assessment and the calculation of a composite rabies risk. A single dose of yellow fever vaccine appears to confer lifelong protective immunity against yellow fever disease. HAV, hepatitis A virus; IM, intramuscular; JEV, Japanese encephalitis virus; RV, rabies virus; SC, subcutaneous; TBEV, tick-borne encephalitis virus; Td, tetanus/diphtheria; YFV, yellow fever virus.]}
Key points

► Unvaccinated individuals are at risk and create a risk of infection to the whole community.
► The evidence shows no link between vaccination and development of multiple sclerosis (MS), and no association at a population level between vaccination and MS relapses.
► Poor vaccine uptake represents a serious threat to people with MS and other patient groups who are immunocompromised.
► People with MS may experience delays in starting disease-modifying therapies if they need to be vaccinated.
► Although having MS does not automatically make vaccination high risk, disease-modifying therapies may influence the immune response against immunisations and their safety.
► Reviewing and updating immunisations should be an integral part of routine MS care.
► Patient education is required proactively on the part of the primary, secondary and tertiary healthcare professionals to present correct information and to promote opportunities for people with MS to be vaccinated.

Twitter G Giovannoni @gavingiovannoni.

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ORCID iDs
Saul Reyes http://orcid.org/0000-0002-3230-3263
Monica Marta http://orcid.org/0000-0002-5464-9070
Benjamin Turner http://orcid.org/0000-0002-7537-2357
Ruth Dobson http://orcid.org/0000-0002-2993-385X
Klaus Schnierer http://orcid.org/0000-0002-9293-8893
G Giovannoni http://orcid.org/0000-0001-9995-1700

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