Review Article

Updated Clinical Recommendations for Multiple Sclerosis by Saudi Neurology Experts

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Abstract

This study presents an update on clinical recommendations in the diagnosis and management of people with multiple sclerosis (pwMS). This has been accomplished through a systematic effort by a committee of leading neurology experts appointed by the Ministry of Health in Saudi Arabia to review the latest scientific literature on MS to enhance the care of MS patients. These recommendations encompass multifaceted aspects of MS care, facilitate an optimized approach for healthcare providers, and include diagnosis, management, and special considerations unique to pwMS.

Keywords: *Disease-modifying therapy, evidence-based care, multiple sclerosis, neuroimmunology, Saudi Arabia*

Background and Methodology

Multiple sclerosis (MS) is a chronic debilitating autoimmune neurological disease causing the inflammation and demyelination of the central nervous system (CNS). It affects more than two million people worldwide and has a significant impact on the quality of life and functionality of patients.[1] Although the worldwide incidence of MS is 35.9 per 100,000 population, we found that Saudi Arabia has a higher incidence of 40.40 per 100,000 population and an even higher incidence among Saudi nationals (61.95/100,000).[1,2] Given the significant progress in research and discovery in MS, it is essential to continuously update the Saudi consensus MS recommendations.[3-7] This ensures physicians make informed decisions and patients receive care based on the latest clinical practices.

Methods

To update MS clinical recommendations, the Ministry of Health in Saudi Arabia formed a committee of expert neurologists to oversee the national MS registry and the task of updating the recommendations. This study provides a concise version of the Saudi national consensus guidelines previously published in separate manuscripts—including diagnosis, treatment, symptomatic management, immunizations, and special considerations in pregnant and pediatric populations—with incorporated updates based on the latest international upgraded guidelines.

Diagnosis

The diagnosis of MS relies on applying the 2017 McDonald criteria in patients who present with typical demyelinating syndrome. Dissemination in space (DIS) and time (DIT) must be confirmed on a clinical or paraclinical basis, in addition to ruling out alternative etiology with better explanatory power. DIS is fulfilled with the presence of at least one T2-hyperintense lesions characteristic of MS in two or more of the following CNS locations; periventricular, cortex or juxtacortex, infratentorial, and the spinal cord.[8] It is noteworthy that the MAGNIMS consensus guidelines also included the optic nerve in the demonstration of DIS.[9] Regarding imaging, DIT is fulfilled on magnetic resonance imaging (MRI) with the simultaneous presence of gadolinium-enhancing and non-enhancing lesions on the same scan, or new/enlarging T2 lesions in a separate scan irrespective of the time interval.[8] Cerebrospinal fluid (CSF)-restricted bands

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can also fulfill DIT.[8] Clinically, DIS can be fulfilled by a polyfocal onset clinical event that can be anatomically correlated with previously mentioned locations. A relapse would not only fulfill DIT but also DIS if it affects a different location on the neuronal axis.[8] Erroneous application of McDonald's diagnostic criteria is a major contributor to misdiagnosis. Clinicians should exercise caution with patients who present with atypical clinical syndrome, radiological features, or demographics. As for the lack of a better explanation, a differential diagnosis must be made to rule out mimicking conditions by paying close attention to various clinical, radiological, and laboratory red flags as up to one in five patients with an established MS diagnosis may, in reality, have different clinical conditions.[10] For instance, many presentations misdiagnosed as MS can be cases of migraine, fibromyalgia, neuromyelitis optica spectrum disorder, psychogenic disorders, or just nonlocalizing/nonspecific symptoms mistakenly associated with abnormal imaging findings.[11] Clinicians must ensure appropriate use of the criteria and essentially apply them for typical MS presentations (e.g., one-sided optic neuritis, partial transverse myelitis, or brainstem syndromes) accompanied by at least a characteristic lesion as well as supporting evidence (abnormal neurological exam and/or paraclinical findings).[12] The clinician must vigilantly observe "red flags" that diverge from the typical manifestations while assessing the patient's presentation. As such, clinical "red flags" include extremes of age at presentation (<16 years or >50 years), complete transverse myelitis, hyperacute clinical course, and vague neurological symptoms. As for paraclinical "red flags," these may be atypical radiological signs (e.g., lesions < 3 mm, stable lesions over time, or large mass effect) or laboratory indicators (e.g., negative oligoclonal CSF bands, CSF white blood count >50, or elevated titers of autoimmune antibodies).[4,13] New concepts of progression independent of relapse activity (PIRA) or silent progression—where disability accumulates in the absence of relapses across all categories of MS—challenge the revised 2013 Lublin phenotype classification.[14,15] Nonetheless, we still advise clinicians to adhere to the latter classification due to its use in the medication regulatory approval process. As such, the disease shall be classified as follows; (1) clinically isolated syndrome (CIS), (2) relapsing-remitting MS (RRMS), and (3) progressive MS; active progressive, nonactive progressive, active nonprogressive, and nonactive nonprogressive.[15] It is important to note that progressive MS can also be primary or secondary (i.e., following a course of RRMS).

Acute Relapse Treatment

A relapse is defined as a "new or worsening neurological deficit lasting 24 h or more in the absence of fever or infection."[16] Once a relapse is diagnosed, the recommended treatment approach depends on the severity of the relapse and the clinician's assessment of the risks and benefits of using high doses of steroids.[16] As such, no relapse therapy may be needed—as per the judgment and decision of the attending physician in a patient-individualized fashion—for mild relapses, defined by a rise of 1.5–2 points in the Expanded Disability Status Scale (EDSS) score from the time directly preceding the flare-up to the time of peak worsening of its symptoms.[16,17] Moderate (identified by a rise of 2.5–3 EDSS score points) to severe relapses (identified by a rise of at least 3.5 EDSS score points) usually require treatment to be started as soon as possible; the treatment for relapse is high-dose intravenous (IV) methylprednisolone (1 g/day) for 3–5 days.[16,17] The oral formulation of methylprednisolone is also acceptable.[16] Alternatively, oral prednisone can also be used (1250 mg prednisone = 1000 mg IV methylprednisolone).[18] In patients with severe relapses and unsatisfactory recovery with steroid therapy, plasmapheresis (PLEX) should be considered after assessing risks and benefits.[19]

Radiologically Isolated Syndrome Treatment

Radiologically isolated syndrome (RIS) is characterized by typical demyelinating lesions in morphology and topography with a lack of historical account of typical demyelinating syndrome or progressive neurological deficits.[20] The DIS criteria have evolved, moving from the strict Barkhof criteria established in Okuda's foundational work to the more lenient revised 2023 RIS criteria.[21] The Swanton RIS criteria serve as an intermediary stage in this evolving landscape.[21-24] After a 10-year follow-up, half of the RISC cohort transitioned to a diagnosis of MS.[25] However, no distinct predictive factors could be identified to forecast the disease phenotype.[25]

Risk factors for a first clinical event after 10 years were gadolinium-enhancing lesions during follow-up, younger age at RIS diagnosis, positive CSF, and infratentorial or spinal cord lesions on MRI.[25] The likelihood of transitioning to MS was greater with a higher number of positive risk factors.[25] Two separate randomized controlled trials (RCT), ARISE and TERIS, have provided evidence for the effectiveness of dimethyl fumarate (DMF) and teriflunomide (TRF), respectively, in preventing the first clinical demyelinating event.[26,27] While these two drugs show only moderate effectiveness in clinically established RRMS, their impact is notably strong, likely due to the earlier stage at which intervention occurs. In a study using the highly effective treatment, ocrelizumab was discontinued due to a slow rate of participant enrolment.[28] Owing to the absence of biological predictors of phenotypes, selecting an appropriate disease-modifying therapy (DMT) becomes a challenge when deciding to treat such patients.

We recommend consulting a neuroimmunologist experienced in treating these cases, as general neurologists may not always be equipped to make therapeutic decisions for pre-RIS, RIS, and pre-symptomatic MS.

We advocate for the adoption of the Okuda criteria and strongly recommend that patients fitting these criteria be evaluated in specialized MS clinics. Such specialized settings are crucial for conducting comprehensive diagnostic procedures, considering alternative diagnoses, making prognostic assessments, and ultimately formulating appropriate management decisions.

CIS Treatment

Following their first neurologic demyelinating attack, and with the presence of at least two MS-typical brain lesions on MRI, patients with CIS should be offered DMT after a discussion weighing the risks and benefits of treatment.[29] It is recommended for the treating physician and the patient to decide together which DMT to choose from interferons (IFNs),[30,31] glatiramer acetate (GA) or TRF,[32,33] or DMF in a personalized approach.[34] The recommendation for these DMTs bears limitations as the trials investigating their efficacy were carried out before the modifications applied to the McDonald criteria in 2017. It is noteworthy that with these modifications, it is unlikely to find patients who fall into this category given that the majority will have positive oligoclonal bands. However, patients would fit this category in the presence of one clinical attack with no clear enhancing lesions, negative oligoclonal bands, or if they refuse to undergo lumbar puncture.

RRMS Treatment

As previously stated in the "Saudi Consensus Recommendations on the Management of Multiple Sclerosis," we still recommend no DMT use for inactive RRMS over 3 years.[3] In this case, the patient's status should be monitored with periodic serial imaging no more than once yearly for 5 years along with follow-up visits every 6 months.[29]

Similar to the ECTRIMS/EAN and MENACTRIMS guidelines and consistent with our previously published guidelines, we maintain our stance on the importance of individualizing the choice of DMT based on the patient's condition.[3,13,34] For naive inactive RRMS over 3 years, no DMT is required.[34] For naive active RRMS, we recommend IFN-β, GA, TRF, DMF, fingolimod, siponimod, cladribine, natalizumab (NTZ), ocrelizumab, ofatumumab, or rituximab.[34] As for naive highly active MS, it is recommended to choose from fingolimod, siponimod, cladribine, NTZ, ocrelizumab, ofatumumab, or rituximab.[34] The selection should be made based on the patient's specific characteristics, such as comorbidities, disease activity, drug safety, and accessibility to medication.[34] National Institute for Health and Care Excellence UK updated treatment recommendations concerning DMT that can be used for RRMS patients.[35] Nrf2 activators (diroximel fumarate), sphingosine 1-phosphate receptor modulators (ponesimod and siponimod), and anti-CD 20 monoclonal antibodies (mAbs; ofatumumab) have been approved for use in RRMS cases.[35] There is a recommendation of moderate strength to treat active RMS with ponesimod, ofatumumab, or diroximel fumarate, with the latter drug only being used if it is not a case of highly active/rapidly evolving severe RRMS.[35] The American Academy of Neurology recommends the use of alemtuzumab, fingolimod, or NTZ for highly active MS, and permits the use of cladribine or azathioprine in circumstances where there is no access to approved DMTs for relapsing MS.[29] We have listed the drugs we recommend for different types of RRMS in the treatment algorithm section [Figure 1]. It is noteworthy to mention that NTZ is now also available in subcutaneous form, for which healthcare professionals anticipate efficiency and cost benefits.[36] Biosimilar drugs also facilitate access to treatment by offering cost-effective therapy options while maintaining desirable treatment outcomes.[37] For instance, contemporary evidence from an RCT demonstrates a similar efficacy and safety profile of biosimilar IFN-1 βa to the reference product.[38] Additionally, the first biosimilar mAb of NTZ, biosimilar-NTZ matched the reference product in efficacy, immunogenicity, and safety in a phase 3, parallel-group RCT.[39] It is also important to note that the Institute for Clinical and Economic Review encouraged the AAN, the National MS Society, and physicians to support the use of rituximab and its biosimilar molecules to improve healthcare access and affordability for patients with relapsing MS.[40] Indeed, similar results in a small group of patients in terms of disease activity improvement were seen with both rituximab and its biosimilar, as evidenced by EDSS scores, imaging, and lymphocyte count.[41]

Regarding updates on drug safety, the French Multiple Sclerosis Society warned of a higher risk of urinary tract infections (UTI) with alemtuzumab, cyclophosphamide, and rituximab, but no increased risk with NTZ.[42]

Moreover, autologous hematopoietic cell transplantation (HSCT) has been proven to be effective among people with highly active or aggressive RRMS who are treatment-resistant and have a low EDSS score. We recommend that this be offered through shared decision-making at facilities with the capability to perform HSCT and MS experts.[43] Bearing the described updates of international recommendations in mind, the caring physician needs to make sure the selected therapy is aligned with the Saudi Food and Drug Administration (SFDA) indications.

Treatment algorithm

We devised the treatment algorithm below to facilitate the selection of the most suitable therapy for patients based on their disease activity.

Sub-Optimal Responders: Switching Due to Suboptimal Response

A suboptimal response is defined as "one clinical relapse and/or lesion activity on MRI."[44] In this case, medications

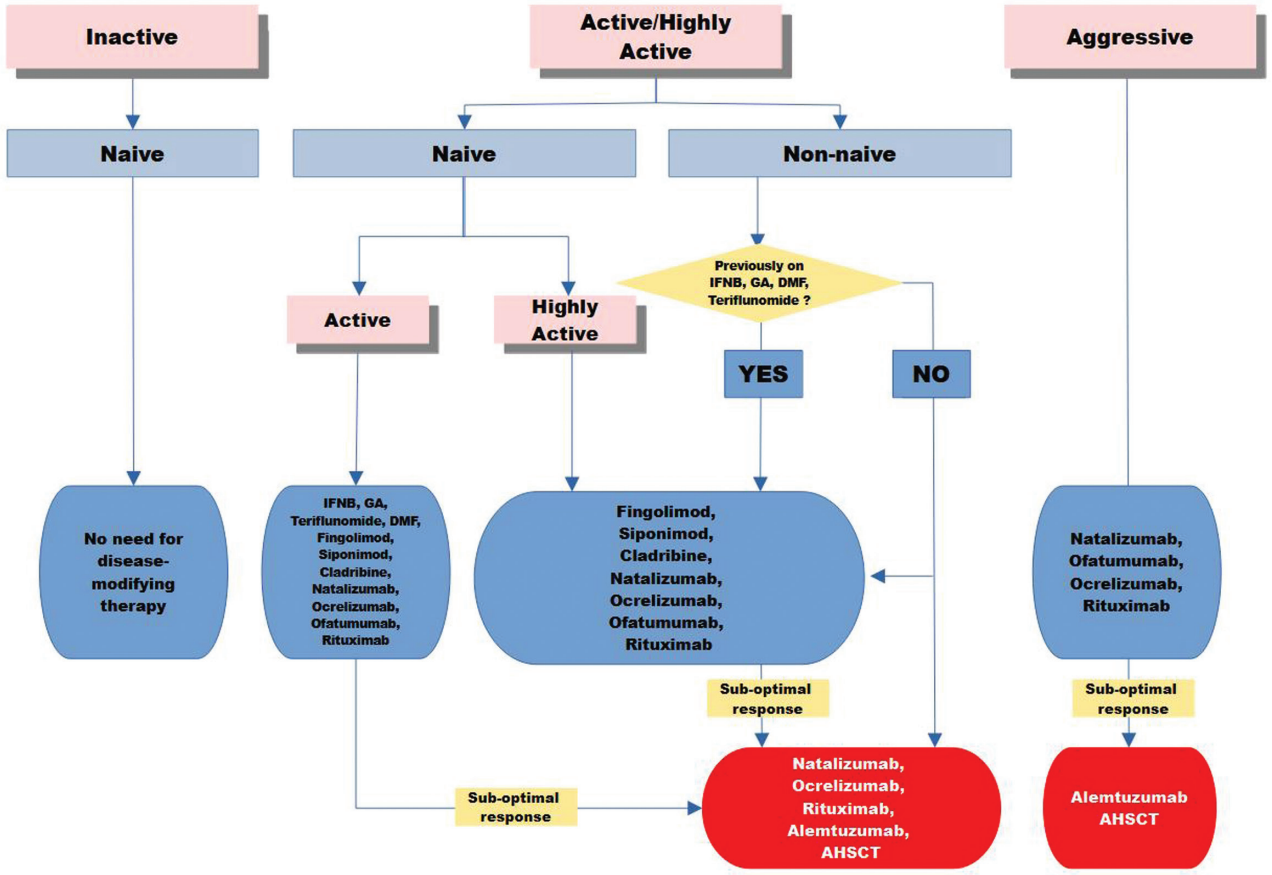

Figure 1: Therapeutic pathways for relapsing MS

are switched because therapeutic goals were not achieved. No evidence of disease activity (NEDA-3) encompasses therapeutic goals of MS disease stabilization characterized by the absence of clinical relapses, EDSS progression, or MRI with new T2 or enhancing lesions.[45,46] Some researchers also use NEDA-4, which adds brain volume loss to the prior-mentioned criteria.[47] However, contemporary scientific evidence shows that NEDA is often difficult to achieve.[48] Aiming for minimal evidence of disease activity (MEDA)—defined as "early marginal MRI activity of one to two new T2 lesions, in the absence of both relapses and contrast-enhancing lesions"—may be more achievable.[49] Therefore, the decision-making process for switching DMTs relies on the clinician's judgment of the patient's clinical evolution since disease onset with an assessment of MRI disease activity and other variables.[34] This is due to the absence of international standards defining treatment failure or the specific timing by which switching should occur.[34]

It is appropriate to discuss a possible treatment switch in patients who have been adherent to treatment for a period sufficient enough to demonstrate a full therapeutic effect and still experience any of the following features over 1 year on the same DMT: (1) at least one clinical relapse, (2) at least two newly detected MRI lesions, and (3) worsening disability.[29] As such, we recommend a switch to fingolimod, siponimod, cladribine, NTZ, ocrelizumab, ofatumumab, or rituximab if the patient displays sub-optimal response and has nonnaive/highly active RRMS previously treated with IFN, DMF, or TRF.[50]

Due to therapeutic latency/lag, a 6-month new baseline scan would serve as a new reference point for future comparison.[29,34]

Discontinuation of Treatment

Guidelines have not been developed on when to consider or recommend DMT discontinuation in people with MS (pwMS). Reasons for discontinuation of immunotherapy include side effects, stable disease, and disease activity or progression. For instance, with B-cell depletion, vigilant monitoring is imperative for potential adverse effects, such as an early decline in absolute lymphocyte count, hypogammaglobulinemia, and heightened susceptibility to infections, possibly necessitating hospitalization.[51] Reasons relating to family planning and pregnancy are considered separately in the respective section. In a long-term study of 2477 participants with MS, the relapse rate decreased by 17% every 5 years with accelerated rates of decline in relapse frequency as age increased.[52] Yet, studies on discontinuation have been observational and retrospective and mostly include small cohorts. Separating the reason for discontinuation is

important to help clinicians counsel pwMS and their families to enable shared decision-making.[52]

The main questions are whether immunotherapy can be safely discontinued and, if so, what are the circumstances for that.

Jakimovski *et al*.[53] studied a cohort of 216 MS patients who discontinued therapy extracted from a multi-site MS disease registry. The authors found that discontinuation of DMTs is associated with disability progression regardless of prior stable disease and age.[53] One-third of the previously stable MS patients had nonrelapse-related disability worsening and progression.[53] This finding was not different among people younger than 55 years old compared to those 55 years or older.[53] People with a higher EDSS score were found to be at a greater risk of disability worsening and progression than others.[53] Hua *et al*.[54] specifically looked at people aged 60 years and older exploring a specific question of whether they stayed off DMT or not. Out of 600 participants, the cohort included 178 (with relapsing or progressive disease) who discontinued therapy.[54] Most discontinuers stayed off DMT and up to two-thirds of the discontinuations were initiated by the treating physician, these patients exhibited lower levels of disability based on their performance scores, wherein reduced scores corresponded to less disability. In contrast, this was not the case when DMT discontinuation was initiated by the patients themselves.[54] Additional analysis of patient-reported outcomes demonstrated that DMT discontinuation in MS patients older than 60 years old did not result in a significant negative impact on the quality of life.[54] It is important to mention that most discontinuations included IFN-β 1b and GA, which may reflect negative experiences associated with routine injection therapy.[54] Kaminsky *et al*.[55] also looked at people aged 50 years and older who had relapsing MS at the onset of their disease and no less than 3 years of stable disease before discontinuation of immunotherapy. The authors found no difference between the two groups (132 compared with 366); however, discontinuation of immunotherapy was associated with a higher risk of disability progression.[55]

Pasca *et al*.[56] studied a cohort of 60 people with relapsing MS who discontinued immunotherapy (azathioprine, INF-β, azathioprine with INF-β, GA, and DMF) and argue that achieving NEDA-3 for a duration of >5.5 years is a predictor of remission after discontinuation of immunotherapy among people with relapsing MS irrespective of age. The treating physician should also take into consideration whether the patient was previously on highly effective therapy or an old platform therapy.

A recent study by Bsteh *et al*.[57] devised a 6-point scoring system for the risk of disease activity recurrence called the VIAADISC score (Vienna Innsbruck DMT discontinuation score based on age, activity on MRI, and duration in stable course); the multivariable analysis in the generation sample revealed three factors independently predictive of disease reactivation after DMT discontinuation:

1. Age at discontinuation (4× risk below 45 years and 2× between 45 and 55 years).
2. MRI activity at discontinuation [4× risk; defined as three or more new/enlarged T2 lesions or one or more gadolinium-enhancing (Gd+) lesions].
3. Duration of clinical stability before discontinuation (4× increased risk below 4 years and 2× between 4 and 8 years).

The score was highly predictive of disease reactivation ($R^2 = 0.811$; $P < 0.001$) with higher scores correlated with increased probability of disease reactivation.[57] Furthermore, studies on the use of this scoring tool are needed.

Thus, there is still very little evidence-based guidance for providers counseling patients regarding DMT discontinuation. In addition to discontinuation, de-escalation, reducing the dose, or increasing the inter-dose interval, is not systematically studied. The decision to discontinue or de-escalate should be individualized depending on multiple factors, such as age at discontinuation, MRI activity, and duration of clinical stability, after discussion with the patient. Moreover, it is important to note that to better answer the question of treatment discontinuation, we encourage involved physicians to participate in the national registry resulting in a complete database describing the characteristics of the Saudi MS populations.

Progressive MS

The classification system was refined in 2013 by Lublin *et al*.[15] serves more as a descriptive framework rather than a categorization grounded in underlying biological mechanisms. The authors underscore their awareness of the lack of precision in the term "disease progression" as used in observational cohort studies and registries, usually referring to "worsening from multiple attacks, poor recovery from a severe attack, or onset of a progressive phase of the illness."[15] To facilitate conceptual simplification and to draft easy-to-implement regulatory guidelines, we adopt a reductionist approach by differentiating between cases that progress following an initial inflammatory phase, termed "secondary progressive," and those that do not exhibit this initial phase, known as "primary progressive." Understanding secondary progressive disease is challenging, especially with the introduction of new concepts like PIRA and silent progression. The shift from relapsing-remitting to secondary progressive disease lacks a distinct temporal boundary and is not readily discernible through available biomarkers. Another layer of complexity is introduced by regulatory bodies' divergent definitions of disease

activity.[58] In line with our mission, the aim is to craft definitions that may differ from evolving norms, ensuring clarity and consistency until the next revision.

Secondary progressive MS

For the definition of secondary progressive MS, we are guided by the criteria established by Lorscheider *et al*.[59] This involves a three-strata progression magnitude, confirmed after 3 months within the dominant functional system, and mandates an EDSS step of not <4 along with a pyramidal score of a minimum of 2.[59] Moreover, it is important to note that progression may not always be in the form of mobility problems but rather other deficits, such as those related to cognition.

Primary progressive MS

For diagnosing primary progressive MS, we recommend adhering to the criteria outlined in the 2017 version of the McDonald criteria.[8] In the setting of progressive disease over 1 year, patients should exhibit at least two out of three criteria: evidence of brain involvement, spinal cord involvement, and positive oligoclonal bands. The diagnosis of primary progressive MS should not be made in the absence of MRI spinal cord and CSF analysis results.[8]

Disease activity

We have adopted Lublin *et al.*'s[15] definitions for what constitutes an active disease. Clinically, active disease is described as "relapses, acute or subacute episodes of new or increasing neurologic dysfunction followed by full or partial recovery, in the absence of fever or infection." Radiologically, it is defined by "Imaging (MRI): occurrence of contrast-enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions."[15]

Drug effectiveness on disease progression hinges on the presence of inflammatory activity.[60] For patients with secondary progressive MS, treatment initiation or switch is advised if they meet the following criteria: clinical events within the last 2 years or radiological activity on scans taken 6–12 months before decision, a disease duration less than 15 years, and an EDSS score <7. Siponimod is the sole medication backed by evidence from a randomized controlled clinical trial for treating active secondary progressive MS.[61]

In primary progressive MS patients with a disease duration of less than 15 years, we advise using ocrelizumab if they meet one of the following criteria: an EDSS score of less than 6.5 and age under 55 years, or an EDSS score of <8 accompanied by CELs in scans conducted 6–12 months before treatment, irrespective of age. Counseling would be useful to help navigate the intricacies involved in assessing treatment response among pwMS. It is also important to provide the appropriate rehabilitation and symptomatic treatment for people with progressive MS.

Symptomatic Management

The priority in managing MS symptoms is to ensure that the primary disease is well-controlled. Addressing symptoms (e.g., headache or fatigue) without prioritizing disease activity, especially when patients are on an old platform DMT regimen without recent brain MRI scans for at least 1 year, is inefficient in terms of time and patient effort. Thus, successful symptomatic therapy only comes after optimal control of the underlying primary disease process.

Fatigue

Given that up to 80% of MS patients may suffer from fatigue,[62] we still recommend considering any potential contributing factors, such as depression, anxiety, and sleep disorders, as well as ordering the laboratory tests outlined in our previous recommendations.[5]

After addressing the above-mentioned factors, it is advised to manage fatigue symptoms using behavioral modifications first (e.g., rehabilitation interventions), given that these often surpass pharmacological interventions in reducing tiredness.[63,64] It is important to encourage the patient to exercise regularly, to adopt an "energy conservation" strategy in daily activities (e.g., setting priorities, comfortably organizing the workspace, and planning breaks for rest), and to adopt a healthy diet.[65] Pharmacological options, such as amantadine, modafinil, or methylphenidate, can also be considered, although we still need stronger evidence to establish their efficacy.[65,66]

Depression and cognitive impairment

To screen for depression, it is important to use internationally validated questionnaires to screen or diagnose depression in MS patients, such as the Patient Health Questionnaire or the Beck Depression Inventory.[67,68] We encourage adopting psychoeducational interventions to alleviate mild-to-moderate depressive symptoms. Severe and/or prolonged depression may require pharmacologic intervention with antidepressant medications.[5] The most commonly affected cognitive functions in patients with MS are episodic memory, executive function, processing speed, and attention. It is also important to rule out contributing factors to cognitive impairment, such as psychiatric disorders, fatigue, sleep disorders, or side effects of medications (e.g., neuropathic pain medications, opioids, and antispastics).[69] To alleviate cognitive symptoms, it is recommended to use conservative nonpharmacologic interventions (e.g., encouraging regular exercise and social interaction) in the patient's daily life.[70] Diaries and calendars are also helpful with memory and attention problems.[70]

Lower urinary tract symptoms

Urinary symptoms in MS patients are the result of failure/difficulty to store or void urine. Generally, conservative management with fluid restriction at night, scheduled voiding, and avoidance of bladder irritants (e.g., caffeine,

tobacco, and vitamin C) can be used to alleviate symptoms caused by storage problems. Pelvic muscle floor training is also an important intervention. However, one ought to monitor the patient for any potential red flags necessitating a referral to urology, such as hydronephrosis, renal function compromise, hematuria, recurrent UTIs, or stress incontinence. If conservative strategies are not successful, the treating physician may opt to treat an overactive bladder with post-void residual volume <100 cc with anticholinergic agents (e.g., oxybutynin and tolterodine).[71] Nevertheless, it is important to use these agents with caution in the elderly due to possible contraindications (e.g., dementia and glaucoma).[72] Other strategies, such as the use of intermittent self-catheterization, in addition to alpha-blockers, may be used for voiding failure problems.[71] Posterior tibial nerve neurostimulation may be beneficial in reducing nighttime frequency, urgency, and urgency incontinence.[73] Sacral nerve stimulation and repetitive transcranial magnetic stimulation can also help with voiding symptoms.[74-76]

Spasticity, gait difficulties, paroxysmal symptoms, and pain

Patients with MS often complain of neurologic disturbances, such as spasticity, gait impairment, and dysphagia.[77] For spasticity, first-line pharmacologic agents (e.g., baclofen, gabapentin, and tizanidine) may be needed as determined by the treating physician.[77,78] Second-line pharmacologic agents include diazepam, dantrolene, or nabiximols.[78] Patients with localized spasticity may benefit from botulinum toxin injections or intrathecal baclofen pumps.[77] Intrathecal baclofen pumps aid patients with lower limb spasticity in maintaining ambulation.[79] Patients with gait difficulties may also benefit from physical and occupational therapy and dalfampridine. It is important to perform the 25-foot walk test before and after administering dalfampridine and consider stopping it if the patient shows no improvement within 4 weeks.[80] For paroxysmal symptoms and neuropathic pain, we recommend using carbamazepine for trigeminal neuralgia and tonic spasms.[81,82] Other medications, such as oxcarbazepine, gabapentin, and lacosamide, may also be beneficial.[81,82] Patients complaining of Lhermitte's sign or neuropathic pain may experience relief with the use of any of the following agents; amitriptyline, pregabalin, gabapentin, and duloxetine.[82]

Sexual dysfunction

As for complaints of sexual dysfunction, we continue to recommend taking detailed sexual history and considering potential contributing factors, such as MS-related fatigue and mood disorders.[83] Sildenafil may be beneficial for men with sexual dysfunction,[84] whereas women with reduced lubrication may benefit from water-soluble lubricants, pelvic muscle floor training, and topical estrogen combined with methyltestosterone to manage issues related to sexual desire.[85,86] It is noteworthy that these currently available options need stronger evidence for further validation.

Gastrointestinal problems

Studies have shown that up to 73% of patients with MS suffer from bowel dysfunction with constipation being more commonly reported than diarrhea or fecal incontinence.[87] Conservative measures for constipation usually consist of the implementation of lifestyle modification, which includes encouraging the patient to exercise, increase hydration, and add fiber to their diet.[87] When conservative measures fail, laxatives may be used; bulking agents (e.g., *Psyllium*), osmotic agents (e.g., lactulose and polyethylene glycol), or stimulants (e.g., bisacodyl) are available choices.[87] For diarrhea complaints, treatment plans involving diet modification, biofeedback, and loperamide may be adopted.[87] Another problem reported by 30%–40% of patients is dysphagia.[88] The presence of swallowing difficulties is usually elicited during history-taking and diagnosis is confirmed through video fluoroscopy or fibreoptic endoscopy.[89] Once the diagnosis is established, a management plan to alleviate dysphagia symptoms set by a multidisciplinary team of specialists (from neurology, ear, nose, and throat, nursing, dietetics, speech, and occupational therapy) needs to be put forward.[89]

Pregnancy and Breastfeeding

For (pwMS, fertility is not affected by the disease or the DMT.[90,91] MS should not discourage patients from making families of their own. With no additional risk factors for adverse pregnancy outcomes, pregnant women with MS should receive routine medical care and adherence to general recommendations.[92] With the plethora of available therapeutics, it is now easier than ever to plan for a safer pregnancy for both the patient and the child alike. A counseling discussion on this matter should take place at the time of diagnosis and on routine follow-up visits.

Generally, DMTs can be classified into two groups; in the first group, drugs can be given leading into or during pregnancy, whereas the second group of treatments cannot be given to pregnant women and need adherence to stringent washout periods. The first group includes IFNs, NTZ, rituximab, ocrelizumab, ofatumumab, ublixtumab, and DMF. It is noteworthy that recent evidence has shown no increased risk of unfavorable pregnancy outcomes with DMF.[93] The following drugs belong to group two: fingolimod, TRF, cladribine, alemtuzumab, and siponimod. Overall, all mentioned drugs can be given in specific clinical contexts during pregnancy when the benefits outweigh the risks.

Risks to the fetus are teratogenicity, impaired immune system development, infection, impaired vaccine response, as well as hepatic and hematological abnormalities. The risk of rebound disease activity is a major concern for the

mother in the post-partum period.[7] Other risks include disease progression, pregnancy-related complications, and infection.[7] This information makes it easier for the prescribing physician to make therapeutic decisions once the pregnancy is planned. Unfortunately, almost 41% of pregnancies are not planned,[94] and 72% would be aware of the pregnancy before 6 weeks.[95,96] This presents a challenge that must be navigated collaboratively by the patient and their doctor. The risk of accidental exposure in the first trimester to DMTs and/or rebound disease activity can be reduced by carefully selecting and managing treatments for women of childbearing age.

Ideally, women with MS should be well under control for 1 year before conception. Physicians should exercise extreme caution when facing a patient on lymphocyte trafficking blockers. We recommend a referral to an MS specialist for assessment and management. If the patient is treated with fingolimod, which has consistent data on rebound disease activity risk,[97] we recommend a switch to a single dose of an enduring therapeutic agent, such as B-cell depletors (rituximab), or NTZ infusion, every 6 weeks till gestational week 30–32. Although NTZ is another lymphocyte trafficking blocker with data on rebound disease activity, this medication can be continued during pregnancy every 6 weeks till gestational age 30–32 years to ameliorate the risk.[98,99]

The same rules apply to women with MS who might undergo assisted reproductive therapies. Bove *et al*.[100] reported a case series and meta-analysis (with 220 cycles) showing an increased risk of relapse in patients who underwent assisted reproductive technology on their pooled analysis. These findings stand in contrast to the results of a French cohort [with 334 in vitro fertilization (IVF) cycles], in which there was no increased risk of relapse after IVF.[101] Although both publications suffer from methodological limitations, we sensed that the French cohort had a higher number of patients, treatment cycles, and no major risk of selection bias: data drawn from The French National Health Insurance database (Système National des Données de Santé). All disabling relapses can be treated with oral or intravenous steroids, and severe or steroid-unresponsive relapses can be treated with plasma exchange. Imaging with MRI should be restricted to nonroutine use, without gadolinium.

The choice of delivery method and anesthesia can usually be determined without significant concern or intervention from MS or its specialists.[102-104] However, it is noteworthy that the treating neurologist may recommend cesarean delivery in a minority of cases in a shared decision-making process with the obstetrician. Education on labor onset signs is needed as decreased sensation secondary to thoracic spine lesions can affect the patient's perception of labor pain.[90] In case of postpartum hemorrhage or other indication of blood transfusion, irradiated blood products should be used for patients who have been treated with Alemtuzumab or Cladribine.[90]

Newborns should undergo necessary examinations to check for potential side effects stemming from their mothers' exposure to certain DMTs.[105,106] Their immunization schedule needs modification for two key reasons: the condition of their B-cell population due to late exposure to B-cell therapy during gestation, and the potential infection risk to their mothers.[107] Thus, if a newborn is exposed to anti-CD20 mAbs, we recommend delaying live vaccines until B-cells recover.

We encourage all women to breastfeed their neonates. Oral agents are directly excluded from this advice except for Cladribine, as breastfeeding can be started after 10 days. INFs and glatiramer can be administered to lactating women. We believe that aside from alemtuzumab and NTZ, B-cell mAbs can be given. Although alemtuzumab—IgG_1—mAbs do not get easily to milk, the potential for adverse reactions—including reduced lymphocyte counts—in a breastfed child calls for a recommendation against breastfeeding for 3 months after the last dose. Data that pertain to Natalizumab—IgG_4—are concerning for increased secretion over time with subsequent injection; especially in an exclusively breastfed child.[108] Until more data are available, we do not recommend breastfeeding while the patient is on NTZ. Breastfeeding should be delayed for 3–4 h after administration of methylprednisolone or prednisolone.[109] A pump and dump method should be applied for 24 h after administration of an old-generation gadolinium-based contrast agent.[109,110]

MS in Children and Adolescents

Pediatric MS occurs at a rate of 14.33/100,000 among Saudi pediatric patients and has a more inflammatory and polyfocal clinical presentation in comparison with adult MS and thus requires special attention.[111-114] It is important to note that our recommendations regarding diagnosis and treatment remain the same given that substantial developments in pediatric MS remain unchanged. We continue to recommend the utilization of the 2012 IPMSSG criteria in diagnosing pediatric patients.[115,116] Additionally, we advocate for the utilization of the key diagnostic criteria and workup detailed in our earlier recommendations to differentiate other inflammatory demyelinating diseases.[6] We continue to endorse the use of INF-β, GA,[117] fingolimod,[118] and DMF[119] with an emphasis on the importance of prompt initiation following diagnosis and rigorous follow-up and monitoring thereafter.[120] For patients who do not respond to the previously mentioned therapies, there is some real-world evidence that using Rituximab and NTZ is acceptable.[121,122] Moreover, our preferred approach for relapse management continues to involve high-dose intravenous steroid pulse therapy followed by PLEX.[123,124]

Infections and Immunizations

General aspects of vaccination

Vaccines are designed with the primary goal of safeguarding individuals from harmful infectious diseases. It is important to emphasize that immunizations yield a supplementary advantage within the context of MS given their capability to reduce the risk of infections that may exacerbate symptoms or trigger a relapse.[125] pwMS often express concerns that vaccines may trigger or worsen their symptoms. These concerns necessitate comprehensive reassurance through evidence-based guidance from healthcare professionals. Current scientific evidence does not conclusively substantiate that vaccines increase the risk or severity of MS or other demyelinating syndromes of the CNS.[126-128]

For individuals with MS, adhering to standard vaccination schedules including the annual inactivated influenza vaccine is crucial. While most vaccinations, such as those for influenza, do not generally increase the risk of MS exacerbations, caution is advised when considering live vaccines. This caution primarily relates to potential risks and specific health considerations of individuals with MS, especially those receiving immunosuppressive therapies.[128-131]

Vaccination varieties and considerations

Different types of vaccines are available for use in individuals with MS. The choice of vaccine should be influenced by the individual's treatment regimen, particularly the use of DMTs that have immunosuppressive effects. All vaccines can be given to untreated patients with MS as well as those on INF-β and GA. Inactivated vaccines are preferred over live-attenuated vaccines for MS patients, especially those receiving immunosuppressive DMTs, due to the potential risks associated with live vaccines in such cases. Nonlive vaccines are generally considered safer for MS patients and can be administered to ensure protection against vaccine-preventable diseases. Inactivated vaccines, such as the seasonal influenza vaccine, are strongly recommended for all MS patients, including those on immunosuppressants, although these patients may have a reduced antibody response. The timing and choice of vaccination should be tailored to the individual's clinical situation and type of DMT, considering both the need for rapid protection and the potential risk of vaccine-induced side effects.[126,130]

Tailoring vaccination strategies: DMTs and immunosuppression

Customization of vaccination strategies is important due to the diverse range of DMTs used in managing MS and their varying impacts on the immune system. Individuals undergoing treatment with immunosuppressive DMTs, such as DMF, TRF, sphingosine-1-phosphate modulators, NTZ, cladribine, and anti-CD20 mAbs, might experience altered immune responses that make the benefits of vaccination particularly vital for them. On the other hand, DMTs, such as INF-β and GA, do not significantly impair vaccine efficacy and immune responses. Therefore, while nonlive vaccines can be given to all MS patients, those on certain immunosuppressive therapies may need a more strategic approach to vaccination scheduling to optimize the immune response and maintain vaccine efficacy [Figure 2].[126,128,132] Released vaccines by the SFDA are outlined in Table 1.

Special focus on influenza and COVID-19 vaccines

Influenza vaccine

It is recommended that individuals with MS receive an annual influenza vaccination, excluding live vaccines (e.g., FluMist). Inactivated influenza vaccines provide substantial protection against flu infections and their potential complications for the MS population. The benefits of influenza vaccination in reducing the risk of infection and potentially mitigating the exacerbation of MS symptoms are significant.[126]

COVID-19 vaccine

Various coronavirus disease 2019 (COVID-19) vaccines, including mRNA vaccines, have been authorized for emergency use. The current consensus emphasizes the safety and benefits of COVID-19 vaccination for individuals with MS, suggesting that the advantages of vaccination greatly outweigh the potential risks. Adaptation of COVID-19 vaccination strategies might be necessary, considering the specific DMTs that individuals with MS are receiving, to ensure optimal vaccine benefits and immune responses. While the efficacy of vaccination may be impacted by some DMTs, significant protection is still afforded.[125,132]

Timing considerations

Strategic timing of vaccine administration is crucial, particularly when considering MS relapses and the use of high-dose steroids. It is generally recommended to delay live attenuated vaccines for at least 4 weeks after high-dose steroid treatment. In cases of MS relapses, vaccination should ideally be postponed until the relapse has clinically resolved or stabilized. While MS relapses and short-term steroid use do not significantly disrupt inactivated vaccine schedules, prolonged or high-dose steroid administration might require a re-evaluation of vaccination timing. This re-evaluation ensures that the vaccine's effectiveness is not compromised and a robust immune response is elicited. Inactivated vaccines should ideally be administered at least 2 weeks before the introduction of immunosuppressive DMTs due to concerns about vaccine efficacy.[126,130,131]

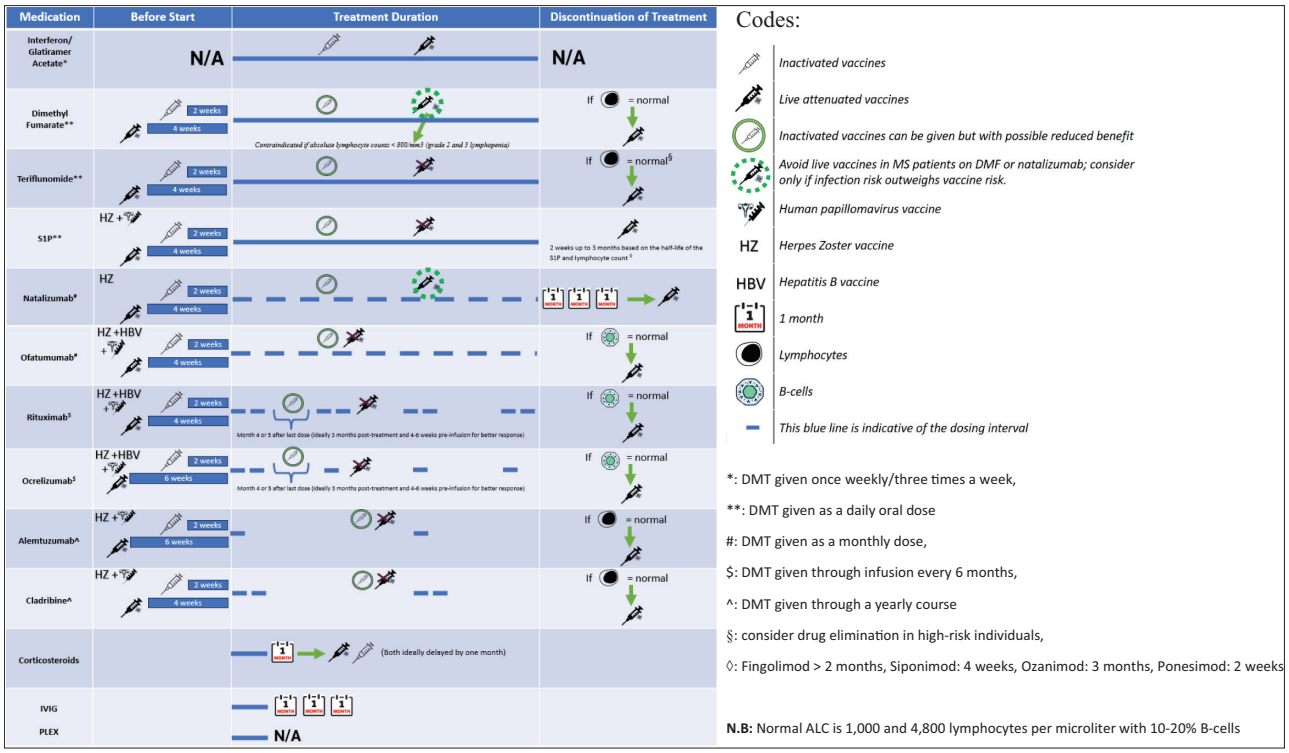

Figure 2: Recommended vaccination strategies across therapies—pre-, during, and post-treatment

For pregnant patients with MS, we advise completing live vaccines at least 1 month before pregnancy and considering the increased fetal infection risk with this type of vaccine. As for other vaccines, it is noteworthy that inactivated vaccines are generally safe to administer during the second and third trimesters, whereas the inactivated influenza vaccine can be given any time during pregnancy and would be, especially beneficial when given at the beginning of the influenza season. Post-partum, the attending physician can complete the administration of live vaccines following delivery except for the yellow fever vaccine, and on the condition of completing them 4–6 weeks before reintroducing the patient to immunosuppressive DMT. Inactivated vaccines can be given anytime post-delivery, but ideally 2 weeks pre-DMT. Vaccines are generally safe for breastfeeding, except for the yellow fever vaccine.

Concerning elderly patients or those with significant disability, it is important to ensure that the patient is receiving yearly influenza and pneumococcal vaccines. Elderly patients should also receive inactivated herpes zoster vaccine. Contacts of MS patients on immunosuppressive therapies, such as household members and healthcare, should be advised to take influenza vaccines and measles, mumps, and rubella (MMR) and/or varicella vaccines if nonimmune and if the MS patient lacks adequate protection. Patients planning to travel internationally can get inactivated vaccines regardless of therapy. However, it is important to avoid live vaccines in those on immunosuppressive drugs. Patients planning to undertake Hajj or Umrah should receive the meningitis vaccine, adhering to the vaccination considerations per DMT outlined in Figure 2.

Vaccination plays a crucial role in the comprehensive care and management of individuals with MS, aiding in the prevention of infections that could adversely affect their condition. It is important to bear in mind that the vaccination considerations mentioned for adults can also be applied to pediatric patients [Figure 2]. A nuanced and individualized approach, taking into consideration the nature of the vaccines and the specific treatments and therapies that individuals with MS are receiving, is essential in formulating and implementing effective vaccination strategies. We summarized our vaccination recommendations for specific groups with MS in Box 1.

Conclusion

These guidelines demonstrate the need for continuous review and update of recommendations about MS and its management every 2 years or as needed. We have provided here a summary of updated recommended clinical practices based on the latest available scientific evidence as well as our experts' opinions.

Declaration of generative AI in scientific writing

During the preparation of this work, the authors used ChatGPT to improve word choice and sentence structure. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Table 1: Released vaccines by the SFDA

	Vaccine	Brand	Dose (mL)	Mode		Vaccine	Brand	Dose (mL)	Mode
Live attenuated	MMR	M.M.R II	0.5	IM or SC	SRP and C*	*Haemophilus influenzae* type B	Act-HIB (pediatric)	0.5	IM
		PRIORIX	0.5	IM or SC		Hepatitis B	Engerix	1	IM
	Rotavirus	ROTARIX (pediatric)	1	Oral			Euvax (pediatric)	0.5	IM
		ROTATEQ	2	Oral		HPV (6, 11, 16, 18)	GARDASIL	0.5	IM
	Chickenpox	VARILRIX	0.5	IM or SC		Pneumococcal 13-valent conjugate—diphtheria CRM 197 protein	Prevenar 13 pre-filled syringe	0.5	IM
		VARIVAX	0.5	IM or SC		Pneumococcal 23-valent	Pneumovax 23	0.5	IM or SC
	Yellow fever	STAMARIL	0.5	IM or SC		Meningococcal	MENVEO	0.5	IM
	Tuberculosis	BCG vaccine (AJV)	0.1	Intradermal		(serogroups A, C, Y, and W-135)	MENACTRA	0.5	IM
Inactivated	Hepatitis A	HAVRIX	1	IM			NIMENRIX	0.5	IM
		AVAXIM	0.5	IM		Meningitis (B)	BEXSERO	0.5	IM
	Influenza	INFLUVAC	0.5	IM or SC		Varicella	SHINGRIX	0.5	IM
		Vaxigrip tetra	0.5	IM or SC		Typhoid fever	TYPHIM	0.5	IM
	Poliomyelitis	IPOL	0.5	IM or SC	Covid-19	mRNA	Pfizer-BioNTech (Pfizer Inc., NY, USA) COVID-19 vaccine	0.3	IM
	Rabies	VERORAB	0.5	IM			Spikevax (mRNA-1273 COVID-19 vaccine Moderna, Moderna Tx Inc. Cambridge, MA, USA)	0.5	IM
Toxoid	Diphtheria toxoid, tetanus toxoid, pertussis toxoid, hepatitis B virus HbsAg surface antigen, and *Haemophilus influenzae* type B	ARAPENTA	0.5	IM		Viral vector vaccine	Vaxzevria (COVID-19 vaccine AstraZeneca, Cambridge, UK)	0.5	IM
	Diphtheria, tetanus, pertussis, poliomyelitis, and invasive infections caused by *Haemophilus influenzae* type B	PENTAXIM (pediatric)	0.5	IM			Covishield	0.5	IM
	Diphtheria, tetanus, pertussis, hepatitis B (rDNA), poliomyelitis (inactivated), and *Haemophilus influenzae* type B conjugate vaccine	HEXAXIM (pediatric)	0.5	IM			COVID-19 vaccine ChAdOX1-S (R-COVI) [Recombinant] (R-PHARM)	—	IM
	Tetanus, diphtheria, and pertussis	BOOSTRIX	0.5	IM					
	Tetanus	STABLIX	0.5	IM					

*SRP and C: subunit, recombinant, polysaccharide, and conjugate vaccines

Box 1:Vaccination recommendations for special populations with MS

- **MS relapse:** Vaccination should ideally be delayed until clinical resolution or stabilization.
- **Patients with MS who are not on DMT:** Inactivated and live attenuated vaccination can be used as per the general population.
- **Pregnant patients with MS:** Vaccination protocol mirrors that of the general population with the following considerations:
  - Live vaccination should be completed at least 1 month before pregnancy.
  - Inactivated vaccines are safe in the second and third trimesters.
  - Influenza vaccine can be given anytime, especially at the beginning of the influenza season.
  - Live vaccines should be avoided during pregnancy due to fetal infection risk.
- Post-partum patients with MS:
  - Live vaccines can be completed post-delivery, excluding yellow fever, and 4–6 weeks before initiation of immunosuppressive DMT.
  - Inactivated vaccines can be administered at any point post-delivery, ideally 2 weeks pre-DMT.
  - Vaccines are safe for breastfeeding mothers, except for yellow fever.
  - Live vaccines should be avoided in newborns exposed to anti-CD20 until B-cell recovery.
- Patients with MS who are elderly or have significant disability:
  - Yearly influenza vaccination and pneumococcal vaccination is recommended.
  - The inactivated herpes zoster vaccine for the elderly is recommended.
- Household and healthcare professional contacts of patients with MS:
  - In the case of patients with MS on immunosuppressive therapies, we recommend completing:
  - Influenza vaccines for all contacts.
  - MMR and/or varicella vaccines if nonimmune, and if the patient lacks adequate protection.
- **MS patients traveling internationally:** Patients can get travel-inactivated vaccines regardless of therapy. We recommend avoiding live vaccines in those on immunosuppressive drugs.
- **Children with MS:** We recommend following the same precautions as in the adult population with MS.

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