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Recommendations by the Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology (DCNI/ABN) and the Brazilian Committee for Treatment and Research in Multiple Sclerosis and Neuroimmunological Diseases (BCTRIMS) on vaccination in general and specifically against SARS-CoV-2 for patients with demyelinating diseases of the central nervous system

Recomendações do Departamento Científico de Neuroimunologia da Academia Brasileira de Neurologia (DCNI/ABN) e do Comitê Brasileiro de Tratamento e Pesquisa em Esclerose Múltipla e Doenças Neuroimunológicas (BCTRIMS) sobre vacinação em geral e contra a SARS-CoV-2 para pacientes com doenças desmielinizantes do sistema nervoso central

Jefferson BECKER[1], Lis CAMPOS FERREIRA[2,3], Alfredo DAMASCENO[4], Denis Bernardi BICHUETTI[5], Paulo Pereira CHRISTO[6], Dagoberto CALLEGARO[7], Marco Aurélio LANA PEIXOTO[6], Nise Alessandra de CARVALHO SOUSA[8], Sérgio Monteiro DE ALMEIDA[9], Tarso ADONI[10], Juliana SANTIAGO-AMARAL[6], Thiago JUNQUEIRA[11], Samira Luisa APÓSTOLOS PEREIRA[7], Ana Beatriz Ayroza Galvão RIBEIRO GOMES[7], Milena PITOMBEIRA[12], Renata Barbosa PAOLILO[7], Anderson KUNTZ GRZESIUK[13], Ana Claudia PICCOLO[14], José Arthur Costa D´ALMEIDA[12], Antonio Pereira GOMES NETO[15], Augusto Cesar PENALVA DE OLIVEIRA[16], Bianca Santos de OLIVEIRA[17], Carlos Bernardo TAUIL[18], Claudia FERREIRA VASCONCELOS[19], Damacio KAIMEN-MACIEL[20], Daniel VARELA[21], Denise SISTEROLLI DINIZ[22], Enedina Maria LOBATO DE OLIVEIRA[5], Fabiola RACHID MALFETANO[23], Fernando ELIAS BORGES[24], Fernando Faria ANDRADE FIGUEIRA[25], Francisco de Assis AQUINO GONDIM[26], Giordani Rodrigues dos PASSOS[1], Guilherme DIOGO SILVA[7], Guilherme SCIASCIA DO OLIVAL[27,28], Gutemberg Augusto CRUZ DOS SANTOS[23,29], Heloisa Helena RUOCCO[29,30], Henry Koiti SATO[31], Herval Ribeiro SOARES NETO[32], Leandro CORTONI CALIA[33], Marcus Vinícius MAGNO GONÇALVES[34], Maria Cecilia ARAGÓN DE VECINO[35], Maria Lucia VELLUTINI PIMENTEL[36], Marlise de CASTRO RIBEIRO[37], Mateus BOAVENTURA[7], Mônica Koncke FIUZA PAROLIN[38], Renata Brant de SOUZA MELO[15], Robson LÁZARO[39], Rodrigo Barbosa THOMAZ[40], Rodrigo KLEINPAUL[6], Ronaldo MACIEL DIAS[41], Sidney GOMES[42], Simone Abrante LUCATTO[43], Soniza Vieira ALVES-LEON[44], Thiago FUKUDA[45], Taysa Alexandrino Gonsalves JUBÉ RIBEIRO[22], Thereza Cristina D'ÁVILA WINCKLER[38], Yara Dadalti FRAGOSO[46], Osvaldo José Moreira do NASCIMENTO[23,29], Maria Lucia BRITO FERREIRA[47], Maria Fernanda MENDES[28], Doralina Guimarães BRUM[48], Felipe VON GLEHN[4,49], and the NEUROIMMUNOLOGY BRAZILIAN STUDY GROUP

[1]Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre RS, Brazil.

[2]Universidade Federal de Sergipe, Aracaju SE, Brazil.

[3]Universidade Tiradentes, Aracaju SE, Brazil.

[4]Universidade de Campinas, Faculdade de Ciências Médicas, Campinas SP, Brazil.

[5]Universidade Federal de São Paulo, Escola Paulista de Medicina, São Paulo SP, Brazil.

[6]Universidade Federal de Minas Gerais, Belo Horizonte MG, Brazil.

[7]Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil.

[8]Universidade Federal do Amazonas, Manaus AM, Brazil.

[9]Universidade Federal do Paraná, Curitiba PR, Brazil.
[10]Hospital Sírio Libanês, São Paulo SP, Brazil.
[11]Escola Bahiana de Medicina e Saúde Pública, Salvador BA, Brazil.
[12]Hospital Geral de Fortaleza, Fortaleza CE, Brazil.
[13]Clínica Nossa Senhora das Graças, Cuiabá MS, Brazil.
[14]Hospital Santa Marcelina, São Paulo SP, Brazil.
[15]Santa Casa, Belo Horizonte MG, Brazil.
[16]Instituto de Infectologia Emílio Ribas, São Paulo SP, Brazil.
[17]Fundação Centro Integrado de Apoio ao Portador de Deficiência, João Pessoa PB, Brazil.
[18]Secretaria de Estado da Saúde, Brasília DF, Brazil.
[19]Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil.
[20]Santa Casa, Londrina PR, Brazil.
[21]Hospital de Clínicas de Passo Fundo, Passo Fundo RS, Brazil.
[22]Universidade Federal de Goiás, Goiânia GO, Brazil.
[23]Universidade Estácio de Sá, Rio de Janeiro RJ, Brazil.
[24]Private Service, Goiânia GO, Brazil.
[25]Hospital São Francisco na Providência de Deus, Rio de Janeiro RJ, Brazil.
[26]Universidade Federal do Ceará, Fortaleza CE, Brazil.
[27]Associação Brasileira de Esclerose Múltipla, São Paulo SP, Brazil.
[28]Santa Casa, São Paulo SP, Brazil.
[29]Universidade Federal Fluminense, Niterói RJ, Brazil.
[30]Pontifícia Universidade Católica, Campina SP, Brazil.
[31]Instituto de Neurologia de Curitiba, Curitiba PR, Brazil.
[32]IAMSPE, São Paulo SP, Brazil.
[33]Private Service, São Paulo SP, Brazil.
[34]Universidade da Região de Joinville, Joinville SC, Brazil.
[35]Hospital Moinhos de Vento, Porto Alegre RS, Brazil.
[36]Santa Casa, Rio de Janeiro RJ, Brazil.
[37]Universidade Federal Ciências da Saúde de Porto Alegre, Porto Alegre RS, Brazil.
[38]Private Service, Curitiba PR, Brazil.
[39]Faculdade de Medicina de Jundiaí, Jundiaí SP, Brazil.
[40]Hospital Israelita Albert Einstein, São Paulo SP, Brazil.
[41]Hospital de Base do Distrito Federal, Brasília DF, Brazil.
[42]Hospital Beneficiência Portuguesa, São Paulo SP, Brazil.
[43]Hospital Regional de Vilhena, Vilhena RO, Brazil.
[44]Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro RJ, Brazil.
[45]Hospital Universitário Prof. Edgar Santos, Salvador BA, Brazil.
[46]Universidade Metropolitana de Santos, Santos SP, Brazil.
[47]Hospital da Restauração, Recife PE, Brazil.
[48]Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, Botucatu SP, Brazil.
[49]Universidade de Brasília, Faculdade de Medicina, Brasília DF, Brazil.

JB https://orcid.org/0000-0002-9981-3620; LCF https://orcid.org/0000-0002-4456-2684; AD https://orcid.org/0000-0002-7919-3989; DBB https://orcid.org/0000-0002-4011-3734; PPC https://orcid.org/0000-0003-1224-5243; DC https://orcid.org/0000-0003-0077-173X; MALP https://orcid.org/0000-0003-2454-681X; NACS https://orcid.org/0000-0003-3185-2903; SMA https://orcid.org/0000-0001-5690-105X; TA https://orcid.org/0000-0002-5008-2783; JSA https://orcid.org/0000-0003-1615-8008; TJ https://orcid.org/0000-0002-5679-1759; SLAP https://orcid.org/0000-0003-3493-1199; ABAGRG https://orcid.org/0000-0003-1657-6891; MP https://orcid.org/0000-0002-3298-0264; RP https://orcid.org/0000-0003-3548-8467; AKG https://orcid.org/0000-0002-7480-6782; ACP https://orcid.org/0000-0003-0834-1056; JADA https://orcid.org/0000-0002-6627-6515; APGN https://orcid.org/0000-0002-0755-9478; ACPO https://orcid.org/0000-0002-4084-7973; BSO https://orcid.org/0000-0001-7484-3586; CBT https://orcid.org/0000-0003-1137-2398; CFV https://orcid.org/0000-0003-0833-4024; DKM https://orcid.org/0000-0002-8699-0636; DV https://orcid.org/0000-0002-3043-1640; DSD https://orcid.org/0000-0002-3078-6804; EMLO https://orcid.org/0000-0002-4939-7200; FRM https://orcid.org/0000-0002-8275-3801; FEB https://orcid.org/0000-0001-7668-0434; FFAF https://orcid.org/0000-0003-3242-9007; FAAG https://orcid.org/0000-0002-8957-5796; GRP https://orcid.org/0000-0002-8949-6115; GDS https://orcid.org/0000-0001-9764-3763; GSO https://orcid.org/0000-0002-2717-7522; GACS https://orcid.org/0000-0002-7333-1420; HHR https://orcid.org/0000-0001-5394-648X; HKS https://orcid.org/0000-0002-5582-1792; HRSN https://orcid.org/0000-0002-1694-0457; LCC https://orcid.org/0000-0002-5758-5789; MVMG https://orcid.org/0000-0002-9127-7886; MCAV https://orcid.org/0000-0001-9393-6999; MLVP https://orcid.org/0000-0003-3515-4061; MCR https://orcid.org/0000-0002-4402-099X; MB https://orcid.org/0000-0002-5914-8099; MKFP https://orcid.org/0000-0003-2171-8241; RBSM https://orcid.org/0000-0002-6267-2940; RL https://orcid.org/0000-0001-7537-5729; RBT https://orcid.org/0000-0002-9287-6864; RK https://orcid.org/0000-0001-5750-6828; RMD https://orcid.org/0000-0003-3987-9596; SG https://orcid.org/0000-0002-9744-5916; SAL https://orcid.org/0000-0002-8856-0007; SVAL https://orcid.org/0000-0002-1538-6730; TF https://orcid.org/0000-0002-7718-4288; TAGJR https://orcid.org/0000-0001-8202-8856; TCDAW https://orcid.org/0000-0003-1438-2583; YDF https://orcid.org/0000-0001-8726-089X; OJMN https://orcid.org/0000-0003-3516-485X; MLBF https://orcid.org/0000-0002-6136-4612; MFM https://orcid.org/0000-0003-3983-6019; DGB https://orcid.org/0000-0002-9050-3319; FVG https://orcid.org/0000-0002-1004-7641

Correspondence: Felipe von Glehn; Email: felipeglehn@gmail.com.

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ABSTRACT

The Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology (DCNI/ABN) and Brazilian Committee for Treatment and Research in Multiple Sclerosis and Neuroimmunological Diseases (BCTRIMS) provide recommendations in this document for vaccination of the population with demyelinating diseases of the central nervous system (CNS) against infections in general and against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. We emphasize the seriousness of the current situation in view of the spread of COVID-19 in our country. Therefore, reference guides on vaccination for clinicians, patients, and public health authorities are particularly important to prevent some infectious diseases. The DCNI/ABN and BCTRIMS recommend that patients with CNS demyelinating diseases (e.g., MS and NMOSD) be continually monitored for updates to their vaccination schedule, especially at the beginning or before a change in treatment with a disease modifying drug (DMD). It is also important to note that vaccines are safe, and physicians should encourage their use in all patients. Clearly, special care should be taken when live attenuated viruses are involved. Finally, it is important for physicians to verify which DMD the patient is receiving and when the last dose was taken, as each drug may affect the induction of immune response differently.

Keywords: Demyelinating Autoimmune Diseases, CNS; Multiple Sclerosis; Neuromyelitis Optica; Vaccination; COVID-19; SARS-CoV-2.

RESUMO

O DC de Neuroimunologia da ABN e o BCTRIMS trazem, nesse documento, as recomendações sobre vacinação da população com doenças desmielinizantes do sistema nervoso central (SNC) contra infecções em geral e contra o coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), causador da COVID-19. Destaca-se a gravidade do atual momento frente ao avanço da COVID-19 em nosso País, o que torna mais evidente e importante a criação de guia de referência para orientação aos médicos, pacientes e autoridades de saúde pública quanto à vacinação, meio efetivo e seguro no controle de determinadas doenças infecciosa. O DCNI/ABN e o BCTRIMS recomendam que os pacientes com doenças desmielinizantes do SNC (ex., EM e NMOSD) sejam constantemente monitorados, quanto a atualização do seu calendário vacinal, especialmente, no início ou antes da mudança do tratamento com uma droga modificadora de doença (DMD). É importante também salientar que as vacinas são seguras e os médicos devem estimular o seu uso em todos os pacientes. Evidentemente, deve ser dada especial atenção às vacinas com vírus vivos atenuados. Por fim, é importante que os médicos verifiquem qual DMD o paciente está em uso e quando foi feita a sua última dose, pois cada fármaco pode interagir de forma diferente com a indução da resposta imune.

Palavras-chave: Doenças Autoimunes Desmielinizantes do Sistema Nervoso Central; Esclerose Múltipla; Neuromielite Óptica; Vacinação; COVID-19; SARS-CoV-2.

INTRODUCTION

The Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology (DCNI/ABN) and Brazilian Committee for Treatment and Research in Multiple Sclerosis and Neuroimmunological Diseases (BCTRIMS) provide recommendations in this document for vaccination of the population with demyelinating diseases against infections in general and against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. These are not absolute recommendations, as there is yet no published evidence on the safety and efficacy of vaccines, particularly against SARS-CoV-2 and its variants in this population, but it may serve as a guide to vaccination. The text is based on the limited scientific evidence available, mainly centered on other autoimmune diseases and on expert opinion. However, for some specific vaccines, there are already more robust clinical trials related to the use of some disease-modifying drugs (DMDs), which are discussed in more detail below.

We emphasize the seriousness of the current moment in view of the progression of COVID-19 in our country, and refer to new variants of SARS-CoV-2, especially the P1 variant identified throughout the country, with the possibility of coinfection events occurring[1]. The participation of the entire medical and health community is essential to raise awareness of the importance of non-pharmacological measures associated with vaccination.

The history of vaccination in humans began in 1796 in the United Kingdom with the development of the smallpox vaccine[2]. It is clear, therefore, that the experience and knowledge of the effects and safety of immunizations, especially in public health, are already scientifically consolidated[3]. Immunization should be understood as a way of exposing the immune system beforehand to a particular pathogen through its antigens, so that immune memory is developed and the body can respond more quickly in the case of infection, reducing the morbidity and mortality associated with the disease. Traditional forms of vaccination use live attenuated viruses, dead viruses or recombinant proteins, with or without polysaccharides[4]. Most of the existing vaccines available in the Brazilian National Immunization Program (NIP)[5] and in several other countries use these techniques[6]. Unvaccinated individuals are at increased risk of morbidity and mortality by a given infectious disease and of spreading the infection.

An ideal vaccine should contain antigens targeted by the immune system, produce effective immunity (antibodies and T cells) and protective immunity, provide a good level of protection, preferably without the need for booster doses, cause few or no side effects, not cause illness or death, and be inexpensive, easy to administer and biologically stable[4,7]. During the current COVID-19 pandemic, other types of vaccines have been introduced, such as those with a non-replicating viral vector and with DNA or RNA of the pathogen (Table 1). Due to

Table 1. Characteristics of the main vaccine types.

Type of vaccine	Live attenuated	Inactivated virus	Subunit	Toxoid	Nucleic acid	Recombinant vector
Mechanism	Made with whole pathogen, weakened under laboratory conditions	Uses the whole pathogen that has been inactivated in the laboratory	Uses the most immunogenic components of the pathogen	Uses inactivated bacterial toxins	Acts by encoding the RNA or DNA of the target antigen in order to produce antibodies	Employs an inactivated viral vector to introduce the pathogen's genetic material
Advantages	Provides strong humoral and cellular responses, conferring long-term immunity with one or two doses	Safe and stable as it contains no active virus	Safe and stable, as it contains no active pathogen	Safe and stable, as it contains no active pathogen	Stable and low-cost. Safe in principle, as it contains no active virus	More specific delivery of genes to target cells. Safe, in principle, as it contains no active virus
Disadvantages	Contraindicated in people with compromised immune systems, as it can induce reactivation of the pathogen and cause the disease	Provides a weaker immune response, which is why additional adjuvant or booster doses may be required	Increased cost, as the combination of antigens that will generate an effective response needs to be determined	Aims to protect against a specific toxin only. Does not provide collective protection and requires multiple doses to maintain protection	Induces limited response to antigen protein, thereby not being highly immunogenic	Can induce the formation of neutralizing antibodies that can reduce its effectiveness

the great current importance of this subject, issues related to SARS-CoV-2 infection will be discussed later as a separate topic.

Whenever the use of vaccines is addressed in the context of immune-mediated diseases, we must take into consideration two main issues. First, we must assess whether vaccines are safe in this population[8]. It is important to remember that after more than 200 years of use, there is no evidence that vaccination causes serious adverse events or deaths. Although there are reports of adverse effects, no causal link has been definitively established, and as such, the scientific community worldwide considers that the benefits of vaccination far outweigh the possible risks[9]. The second aspect concerns the individual's ability to generate or not generate an adequate protective immune response while using therapies that act on the immune system[10,11]. It is important to note that this response can be affected in a totally different way, depending on the treatment used and the time interval since the last dose was received. In Brazil, it is recommended that the vaccination of individuals with Central Nervous System (CNS) immunological diseases not only comply with the recommendations of the NIP according to age groups, but also include coverage for some pathogens that can infect patients using immunosuppressive drugs, such as varicella zoster virus and encapsulated bacteria (i.e., pneumococci and meningococci)[12]. It is important that the attending physician review the patient's vaccination record at the initial consultation and at any planed DMDs change. The vaccination history should specifically include seasonal influenza, pneumococcus, hepatitis A and B, tetanus/diphtheria, varicella (chickenpox) and measles vaccination. Pre-vaccination serology testing for hepatitis A, hepatitis B, measles, rubella, and varicella zoster may also be necessary. Another important aspect is to assess the vaccination status of household contacts and close contacts of patients, especially those who use immunosuppressants and vaccinate contacts if necessary.

Several medical specialty societies and the American agency Center for Disease Control (CDC, USA) consider immunocompromised patients to be at high risk for the development of serious infectious diseases compared to immunocompetent individuals, whether they present permanent or reversible immune dysfunction[6]. The risks of developing serious forms of infectious diseases are related to conditions such as cancer, bone marrow transplant, solid organ transplant, genetic immunological deficiencies, human immunodeficiency virus (HIV), chronic use of intravenous or oral corticosteroids, and use of immunosuppressive medications, among others. The effectiveness of vaccination depends on the person's intact immune response, especially concerning antigen function, activation of T and B lymphocytes, formation of plasma cells and antibodies production. Therefore, immunization may be less effective in immunocompromised patients compared to the general population[4]. Table 2 shows the main medications used for the treatment of demyelinating diseases of the CNS.

Regarding safety, vaccines containing inactivated virus, subunits, toxoid, nucleic acid and recombinant virus do not pose a risk in immunosuppressed patients, since they inoculate the inactivated pathogen or fragments of it. In transplant patients or patients with autoimmune diseases, there are no data indicating risk of transplant rejection or increased activity of the

Table 2. List of the main therapies available or in the process of approval in Brazil for the treatment of CNS autoimmune demyelinating diseases.

Oral immunosuppressants	immunomodulators	Immunobiological/ venous immunosuppressants	Others
Azathioprine	Glatiramer acetate	Alemtuzumab	Gene therapies
Cladribine	Beta interferons	Cyclophosphamide	Autologous stem cell transplant
Corticosteroids		Eculizumab	
Fingolimod		Human immunoglobulin	
Dimethyl fumarate		(intravenous)	
Methotrexate		Inebilizumab	
Mycophenolate mofetil		Mitoxantrone	
Siponimod		Natalizumab	
Teriflunomide		Ocrelizumab	
		Ofatumumab	
		Rituximab	
		Satralizumab	

underlying autoimmune disease associated with vaccination[6]. Additionally, data on vaccination for other diseases do not indicate increased risks. In the specific case of Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum Disorders (NMOSD), and other CNS demyelinating diseases, there is no causal association between any type of vaccine and risk of developing these autoimmune inflammatory conditions[10,11,13]. Most studies on vaccination and MS have been conducted with a seasonal influenza vaccine, including randomized placebo-controlled clinical trials that found no evidence of increased risk of MS after vaccine administration[14,15].

Regarding vaccines with live attenuated viruses, there are reports of induced relapses in isolated cases, such as the yellow fever vaccine in patients with MS[10,13,15]. For this reason, the recommendation of this type of vaccine is made after assessing the benefits against the risk of inducing an exacerbation of the disease. It is important to emphasize that there is no causal association and, in most cases, the benefits outweigh the risks. Table 3 shows all available vaccines, including those accessible through the NIP and recommendations for use in patients with CNS demyelinating diseases.

CONSIDERATIONS ON THE EFFICACY OF VACCINES DURING TREATMENT WITH IMMUNOMODULATORY/ IMMUNOSUPPRESSIVE DRUGS

An effective immune response that provides long-term immune memory is generated primarily by the adaptive immune system, including B lymphocytes (humoral or antibody-mediated response) and T lymphocytes (cellular response). The humoral response is usually measured using serum IgG antibody levels against a specific antigen. The cellular response, on the other hand, is less studied, more complex, and methods for its evaluation vary in the literature[4].

The immunomodulatory and immunosuppressive effects of different DMDs make assessment of vaccine efficacy more complex. The impact of these therapies on the adaptive immune system can decrease the response to vaccination by modifying the development of long-term immune memory[8,10,11,13]. Few studies have specifically addressed this issue and scientifically based recommendations do not yet exist for most existing therapies (Table 4).

In general, the use of interferons beta and glatiramer acetate probably do not imply a reduction in seroprotection in response to influenza, tetanus, and diphtheria vaccines. On the other hand, the use of anti-CD20 monoclonal antibodies or fingolimod, for example, may result in decreased seroprotection in response to the influenza vaccine[8]. Given the lack of knowledge regarding the real impact of different DMDs on the effectiveness of particular vaccines, it may be appropriate to evaluate the seroprotection after vaccine administration for those patients under treatment and to consider the administration of booster doses, if necessary, after case-by-case evaluation. Whenever possible, evaluation of the vaccine-induced immune memory should be performed four weeks after application of the last recommended dose (expert opinion, level VII evidence).

VACCINATION FOR SARS-COV-2

Since January 2020, the world has been facing one of the worst pandemics. The SARS-CoV-2 virus has already infected millions of people globally and caused more than 2.5 million deaths. The only measures that can contain the spread of the virus are social distancing and isolation, frequent hand washing, and the correct use of masks[39]. This new infectious disease caused by the coronavirus (COVID-19), which causes severe acute coronavirus 2 respiratory syndrome (SARS-CoV-2), is a complex clinical syndrome that most often produces systemic manifestations and represents an ongoing challenge for neurologists who care for people with MS or NMOSD[40]. According to the World Health Organization (www.who.int), on November 3, 2020, there were 47 vaccine candidates under clinical evaluation and 155 vaccine candidates under preclinical evaluation.

Table 3. Types of vaccines and recommendations for their use in patients with CNS demyelinating diseases.

Vaccine	Vaccine type	Timetable recommended by the Brazilian Immunization Society (SBIm)	Recommendation for patients with MS/NMOSD
Acellular triple bacterial vaccine for adults Diphtheria-Tetanus-Pertussis (DTaP or DTaP-IVP) Diphtheria-Tetanus (DT) for adults	Diphtheria and tetanus toxoids Inactivated components of the *Bordetella pertussis* capsule	Update the DTaP regardless of previous DT or TT intervals. With complete basic vaccination regimen: DTaP boost every 10 years. With incomplete basic vaccination regimen: one dose of DTaP at any time and complete the basic vaccination with DT (double adult vaccine) in a total of three doses of vaccine containing the tetanus component. Unvaccinated and/or unknown vaccination history: one dose of DTaP and two doses of DT in regimen of 0 - 2 - 4 to 8 months. For individuals who intend to travel to countries where poliomyelitis is endemic: DTaP vaccine combined with inactivated polio (DTaP-IVP) is recommended. The DTaP-IVP can replace the DTaP.	Considered safe
HPV	Recombinant vaccine Virus particles	For unvaccinated adolescents ≥ 15 years of age, the regimen is 3 doses (0, 1-2, 6 months.) Two vaccines are available in Brazil: quadrivalent HPV, licensed for women aged 9 to 45 years and men aged 9 to 26 years; and bivalent HPV, licensed for women from 9 years of age.	Probably safe
Triple viral MMR (measles, mumps, rubella)	Live attenuated virus	Two doses of vaccine above 1 year of age, with minimum interval of one month between the two. For fully vaccinated adults, there is no evidence to justify a routine third dose, which can be considered in situations of a mumps and/or measles outbreak and disease risk	Probably safe, consider immunosuppression used
Meningococcal ACWY	Inactivated vaccine	Administer 2 (two) doses, at 3 (three) and 5 (five) months of age, with interval of 60 days between doses, minimum 30 days. Adolescents aged 11 and 12 years, administer 1 (one) booster dose or a single dose, according to their vaccination status. For unvaccinated adults: one dose	Probably safe
Meningococcal B	Recombinant vaccine	3 and 5 months of age and between 12 and 15 months. For adolescents not previously vaccinated, 2 doses one month apart are recommended. For adults up to 50 years of age, when justified: two doses with an interval of one to two months. After 50 years: use is off-label. High-risk groups, such as people living with HIV, or anatomic or functional asplenia, who have a complement deficiency or are using eculizumab or other biological drugs that interfere with the complement pathway: booster dose given three years after completing the vaccination regime	Probably safe
10-valent pneumococcal conjugate vaccine (VPC10) 13-valent pneumococcal conjugate vaccine (VPC13)	Inactivated vaccine	Routine vaccination with VPC10 or VPC13 is recommended for children from 2 months to 6 years of age. For children over 6 years of age, adolescents and adults with certain chronic diseases, the VPC13 and VPP23 vaccines are recommended. For those aged over 50 years, and especially over 60 years, the VPC13 and VPP23 vaccines are recommended	Probably safe
23-valent pneumococcal polysaccharide	Polysaccharide vaccine	From the age of 60 years, administer 1 (one) single additional dose, respecting a 5-year minimum interval from the initial dose.	Insufficient data

Table 3. Cont.

Vaccine	Vaccine type	Timetable recommended by the Brazilian Immunization Society (SBIm)	Recommendation for patients with MS/NMOSD
Herpes zoster	Live attenuated virus	Vaccine is licensed for people aged 50 + years and is recommended as routine for those over 60 years of age. Generally contraindicated in immune suppressed individuals	Insufficient data, consider immunosuppression used
Hepatitis B	Recombinant vaccine	Administer 1 (one) dose at birth, as early as possible in the first 24 hours, preferably in the first 12 hours after birth, still in the maternity ward. This dose can be administered up to 30 days after birth. Children from 7 (seven) years of age: Without vaccination proof: administer 3 (three) doses of hepatitis B vaccine with an interval of 30 days between the first and second dose, and 6 (six) months between the first and third dose (0, 1 and 6 months). With incomplete vaccination regimen: do not restart vaccination schedule, simply complete it according to the situation encountered. For pregnant women, any age group and gestational age: administer 3 doses of hepatitis B vaccine, considering the previous vaccination history and recommended intervals between doses. If it is not possible to complete the vaccination schedule during pregnancy, it must be completed after delivery	Considered safe
Hepatitis A	Inactivated vaccine	One dose administered at 15 months of age. For those children up to 4 years, 11 months and 29 days, who missed vaccination, administer one dose of hepatitis A vaccine. Case-by-case evaluation should be made of children with immunosuppression and those susceptible who fall outside the age range recommended in the National Vaccination Calendar	Considered safe
Inactivated Polio	Inactivated vaccine	Administer 3 (three) doses, at 2 (two), 4 (four) and 6 (six) months of age, with an interval of 60 days between doses. The minimum interval is 30 days between doses. Individuals 5 years of age or older without proof of vaccination or with an incomplete vaccination schedule should receive the OPV as an exception if they are residing in Brazil and will travel to areas with a vaccine recommendation.	Considered safe
Haemophilus influenzae type B (Pentavalent vaccine)	Conjugate vaccine	Administer 3 (three) doses, at 2 (two), 4 (four) and 6 (six) months of age, with an interval of 60 days between doses, minimum of 30 days. The third dose should not be administered before 6 (six) months of age. The pentavalent vaccine is contraindicated for children from 7 (seven) years of age.	Insufficient data
Yellow Fever	Live attenuated virus	Children from 9 (nine) months and younger than 5 (five) years of age: Administer 1 (one) dose at age 9 (nine) months, and a booster dose at 4 (four) years. Individuals from 5 (five) years to 59 years of age: Administer 1 (one) single dose. Conduct a risk-benefit assessment from 60 years of age. Yellow fever vaccine is usually contraindicated in immune suppressed patients (rheumatological diseases, malignant neoplasms, solid organ transplant, hematopoietic stem cell transplant), but it may be considered in certain situations depending on the degree of immunosuppression and epidemiological risk, with careful medical evaluation being necessary in such cases.	Probably increases the risk of an outbreak; the immunosuppression drug used should be considered

Table 3. Cont.

Vaccine	Vaccine type	Timetable recommended by the Brazilian Immunization Society (SBIm)	Recommendation for patients with MS/NMOSD
Influenza	Inactivated vaccine	For individuals from 9 (nine) years of age: administer 1 (one) dose annually during campaigns. Where available, the quadrivalent influenza vaccine (4V) is preferable to the trivalent influenza vaccine (3V), as it provides greater coverage of circulating strains.	Considered safe
Varicella (component of tetraviral vaccine available in the public health system)	Live attenuated viruses	Routinely recommended for children from 12 months of age onwards (use from 9 months onwards in exceptional circumstances, for example in situations of outbreak). All susceptible children, adolescents and adults (who have not had chickenpox) should be vaccinated	Probably safe, consider immunosuppression used

Table 4. Effect of main disease-modifying drugs in response to vaccination.

Medicines	Comments
Interferons beta	No change in humoral response when compared to healthy individuals. Tested for influenza, meningococcal, pneumococcal and DT[8,11,16,17]. Level III evidence *American Academy of Neurology* (AAN); or 3 *Centre for Evidence-Based Medicine – University of Oxford* (CEBM)
Glatiramer	Possible slight reduction in seroprotection in response to influenza vaccinations, when compared to healthy individuals or those using beta-interferons[8,11,17]. Level III evidence (AAN); or 3 (CEBM)
Teriflunomide	Studies with small sample sizes have shown a slight reduction in immune response after vaccination against influenza and rabies[16,18]. Level III evidence (AAN); or 2 (CEBM) The AAN recommendation is to not use live attenuated virus during treatment, or immediately before and up to 6 months after stopping treatment. Screening for tuberculosis (TB) and Varicella. Vaccinate for varicella (immune susceptible).
Dimethyl fumarate	A small sample study showed no difference in humoral response to vaccination, when compared to individuals using beta-interferons (DT, meningococcal and pneumococcal)[19]. Level III evidence (AAN); or 3 (CEBM) Post-hoc analysis of a subgroup of patients showed no relationship between lymphocyte count and response to vaccination[19]. Level IV evidence (AAN); or 4 (CEBM)
Fingolimod	Reduced immune response against influenza (A and B) and tetanus vaccines, when compared to patients using beta-interferons or healthy individuals[17,20–22]. Level I/II evidence (AAN); or 2 (CEBM) Screening for hepatitis B. Vaccinate for varicella (immune susceptible). There may be a reduction in antibody titers produced by the vaccine after initiation of treatment with fingolimod[23]. Level III evidence (AAN); or 3 (CEBM).
Natalizumab	Some studies suggest a reduced immune response against influenza and tetanus vaccines in a percentage of patients using natalizumab, when compared to those using beta-interferons or healthy individuals[17,21,24,25]. Level III evidence (AAN); or 3 (CEBM)
Ocrelizumab	The VELOCE study showed a reduction in immune response and seroconversion rate in patients treated with ocrelizumab compared to patients using beta-interferons or without treatment (tetanus, pneumococcal, meningococcal and influenza vaccines were evaluated)[26]. Level II evidence (AAN); or 2 (CEBM). Vaccinate with live attenuated virus vaccine at least 4 weeks before starting treatment and 2 weeks before for other vaccines. If the patient is already using ocrelizumab, the vaccine should ideally be applied between the 3rd and 5th month after the last infusion, so that induction of immune memory is more effective. In the event that additional doses are required, it is recommended that both or at least one of them be performed in this time window (expert opinion). Level 5 evidence (CEBM). The AAN recommendation is not to use a live attenuated virus vaccine during treatment, or immediately before and up to 6 months after stopping treatment. Screening for hepatitis B.

Table 4. Cont.

Medicines	Comments
Ofatumumab	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated. In the absence of specific studies for ofatumumab, the authors recommend observing the same recommendations made for ocrelizumab (expert opinion).
Alemtuzumab	Insufficient data on medication interference in the humoral response after vaccination. A small study suggests that humoral responses to vaccination performed prior to treatment are maintained[27]. Level IV evidence (AAN); or 4 (CEBM) Prophylaxis for herpes at the start of treatment for up to 2 months or until lymphocyte > 200. Screening for TB and varicella, vaccination for varicella before starting treatment. Immunization should be performed at least 4 to 6 weeks before infusion of alemtuzumab. If the patient has already used the medication, wait at least 3 months, and if possible 6 months, to perform the vaccination (expert opinion). The AAN recommendation is to not use live attenuated virus vaccine during treatment or immediately before, and up to 6 months after stopping treatment
Cladribine	Insufficient data. A recent small study showed that MS patients treated with cladribine achieved seroprotection levels after influenza vaccination, but only 33% met seroconversion criteria[28]. Level IV evidence (AAN); or 4 (CEBM) Consider immunization schedule for immunocompromised patients (expert opinion). Live attenuated virus vaccines generally contraindicated. Immunization should be performed at least 4 to 6 weeks before administration of cladribine. If patient has already used the medication, wait a minimum of at least 3 months, and if possible 6 months from the last dose before carrying out vaccination (expert opinion). Level 5 evidence (CEBM)
Cyclophosphamide	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM).
Rituximab	The use of rituximab in studies of patients with rheumatoid arthritis has been associated with a reduction in humoral response and seroconversion rate to influenza and pneumococcal vaccines[29–31]. Level III evidence (AAN); or 3 (CEBM) A study of patients with NMOSD showed similar data to the influenza vaccine[32]. Level III evidence (AAN); or 3 (CEBM) Live attenuated virus vaccines are generally contraindicated. In the absence of specific studies for rituximab, the authors recommend observing the same recommendations made for ocrelizumab (expert opinion).
Azathioprine	Studies in patients with inflammatory bowel disease suggest that patients treated with azathioprine have a normal response to pneumococcal, tetanus and Haemophilus influenzae type B vaccines, but may have a reduced response to the hepatitis B vaccine[33,34]. Level III evidence (AAN); or 3 (CEBM) Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated.
Mycophenolate mofetil	Studies in kidney transplant patients with mycophenolate use suggest a reduction in humoral response and seroconversion rate for influenza vaccine (Mulley WR et al Kidney Int 2012; Tsujimura K et al Transplant Proc 2018). Level III evidence (AAN); or 3 (CEBM) Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated.
Methotrexate	Some articles show a reduction in humoral response and seroconversion to influenza and pneumococcal viruses in patients with rheumatoid arthritis[35–37]. Level III evidence (AAN); or 3 (CEBM) Discontinuation of treatment for 2 weeks can improve response to the influenza vaccine[38]. Level II evidence (AAN); or 2 (CEBM) Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated.

Table 4. Cont.

Medicines	Comments
Corticosteroids	Live attenuated virus vaccines are contraindicated within 3 months after treatment discontinuation for adults using 20mg/day or children using 2mg/kg/day for more than 2 weeks. If the patient has used corticosteroids in high doses, there should be a gap of at least 15 days before carrying out the vaccination (expert opinion). Level 5 evidence (CEBM).
Eculizumab	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated. Patients need to receive vaccines for meningococcus at least 2 weeks before starting treatment. If medication needs to be started sooner than this, prophylactic treatment should be given for 2 weeks
Inebilizumab	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated. In the absence of specific studies for inebilizumab, the authors recommend observing the same recommendations made for ocrelizumab (expert opinion)
Satralizumab	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated

Vaccines in development or already approved by regulatory agencies are formulated with nucleic acids (RNA or DNA), viral vector with adenovirus (non-replicating), inactivated virus or protein components of the virus – vaccine types that have no chance of viral replication – and consequently considered safe for use in immunosuppressed patients, without the need to suspend or modify the dosage of disease-modifying therapies cited below[8,41,42]. As previously discussed, the use of live attenuated virus-based vaccines is not recommended in patients taking immunosuppressive therapies, should vaccines of this type against SARS-CoV-2 be approved in the future by any regulatory agency.

The shorter than usual approval time for these new vaccines can be explained by a number of factors. First, research on RNA vaccines began years prior to the emergence of the COVID-19 pandemic and many resources have been allocated for this purpose in a short period of time. Second, in comparison with traditional clinical trials, the results obtained have been evaluated quickly by regulatory agencies. This evaluation was performed as the data was produced and not just after completion of the entire study, as usually occurs.

Some examples of vaccines against SARS-CoV-2 already released by different international regulatory agencies include:

mRNA-based vaccines (Moderna and Pfizer/BioNTech), which promote an immune response against viral spike proteins;

Vaccines based on non-replicating adenovirus vector (CanSino, Gamaleya, Johnson & Johnson, Oxford-AstraZeneca), which increase the immune response against the coronavirus through a genetically modified vector that produces the spike glycoprotein;

Protein-based vaccines (Vector, Novavax, others), which induce an immune response against various proteins present in the coronavirus;

Inactivated virus-based vaccines (Sinopharm-Beijing, Sinopharm-Wuhan, Sinovac), which induce response to the different components of the inactivated coronavirus.

If there is no contraindication, immunosuppressed patients should be vaccinated due to the potential risk of developing severe forms of COVID-19 when infected with SARS-CoV-2. It is important to highlight that as of the beginning of February 2021, no international or national epidemiological study, such as that of the Brazilian Academy of Neurology (ABN) Brazilian Register of Neurological diseases (REDONE), has demonstrated an increased risk of serious COVID-19 disease in patients with MS and NMOSD treated with different DMDs or increased susceptibility for relapsing or CNS demyelination progression[43].

There is currently no data on the effectiveness of the available vaccines in this group of individuals, as no clinical study with an adequate sample size of patients with these conditions has yet been conducted. Considering safety aspects, clinical studies of vaccines against SARS-CoV-2 do not indicate a relationship with the onset of CNS demyelinating inflammatory diseases in vaccinated individuals[44].

The main side effects that have been associated with approved vaccines for SARS-CoV-2 are low fever, myalgia, headache, nausea, fatigue, and pain/redness at the injection site. These effects are more frequent after the second dose (booster dose) of the vaccine and are self-limited[45,46]. Additional data will become available from time to time through existing vaccine monitoring programs in different countries. It is important to note that most vaccines have been tested on patients over 18 years of age, and none were tested on pregnant women.

Immunosuppressed patients vaccinated against COVID-19 should be advised about the potential for reduced effectiveness and, therefore, they should be advise to continue with protective measures, including social distancing, mask wearing, and hand washing and hygiene. People living with these patients should also be vaccinated to protect them.

Patients using DMDs who are known to have been infected with SARS-CoV-2, whether or not COVID-19 developed, should be vaccinated. Although some immune memory against the virus is to be expected, the immune response may be less efficient or even absent upon re-exposure to the virus.

Data on the efficacy of vaccination in patients with lymphopenia are limited, but there is evidence that it may reduce the effectiveness of the vaccine. Considering that the use of DMDs can lead to lymphopenia, physicians can make administration of the DMD more flexible, temporarily suspending or delaying the dose before beginning vaccination against COVID-19, resuming treatment after the vaccination schedule has been completed. Decisions must be made on individual basis, weighing the risks of suspending treatment against the underlying disease and the risk of severe COVID-19. Although there are no definitive recommendations for this group yet, and in the absence of a specific contraindication, vaccination should be considered rather than rejected, even in cases where the use of DMDs induces lymphopenia or more severe immunosuppression (less than 500 lymphocytes per ml of blood). Therefore, in the context of potential lymphopenia, it is recommended to request a complete blood count before immunization.

If there is no time to relax the administration of drugs, it is better to vaccinate and acquire a minimum degree of immunity against infection than otherwise. High vaccination rates in a community protect not only those who have been vaccinated, but also those who have not been vaccinated for some reason, whether or not they have developed immunity to the virus. This is the collective or 'herd' immunity that is so important in the fight against the SARS-CoV-2 pandemic.

In light of the above, the DCNI/ABN and BCTRIMS recommend that patients with MS or NMOSD be constantly monitored in terms of updating of their vaccination regimen, especially at the onset or before a change in DMD treatment. If the patient has vaccines pending, it is recommended that they be administered whenever possible before starting a DMD that may interfere with induction of immune memory. The safety of vaccines should be emphasized, and physicians should encourage their use in all patients. Clearly, special attention should be paid when live attenuated viruses are involved. Finally, it is important for physicians to verify which DMD the patient is taking and when the last dose was taken, as each drug may affect the induction of immune response differently.

SUPPLEMENTARY MATERIAL

Names in alphabetic order and afiliations.

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