Safety and efficacy of vaccinations in patients with multiple sclerosis: a systematic review

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ABSTRACT. – OBJECTIVE: The study aims to show the efficacy/effectiveness and safety of vaccinations in patients with multiple sclerosis.
MATERIALS AND METHODS: This systematic review was conducted following the guidelines of the Cochrane Collaboration and the meta-analysis of observational studies in epidemiology (MOOSE).
RESULTS: At the end of the review process, 133 studies were included; the bibliographic search was conducted on PubMed/Medline and Scopus, combining free text and words.
CONCLUSIONS: In general, vaccinations do not seem to aggravate multiple sclerosis (MS) or increase the probability of relapse, particularly for inactivated vaccines and, in general, for the rest of the vaccines. However, it is advisable, especially for vaccines with a live attenuated virus, to carefully evaluate the risks and benefits of these vaccinations; as regards the effectiveness in relation to the drug taken, there is great variability in response. In particular, vaccinations are less effective in patients undergoing therapy with anti-CD20 and S1P modulators. At the same time, a small response is likely to be better than none. Whenever possible, vaccinations should be offered and recommended to patients with multiple sclerosis.

Key Words:
Multiple sclerosis, Vaccine, Vaccine-preventable diseases, Efficacy, Safety, COVID-19.

Introduction

Multiple sclerosis (MS) is the most common neurological disease of the central nervous system (CNS) of young adults. The etiology and pathogenesis remain poorly understood due to their complex and multifactorial nature. MS is marked by chronic inflammation and demyelination, axonal damage, and loss of neurons that causes motor, sensory, and cognitive disabilities; characterized by a complex array of symptoms that vary both over time and among individuals[1]. About 1 million individuals in the United States and 2.8 million individuals worldwide have multiple sclerosis, and the relapsing-remitting MS (RRMS) type accounts for most cases. This neurological disease is more common in females than in males (with a ratio of 3:1)[2]. The disease can present at any age, and about 10% of the cases occur before the age of 18[3]. Symptom onset generally occurs between 20-40 years old. The incidence of pediatric MS is relatively rare, with 2.7 to 10.5% of all MS cases in children <18 years of age, with a strong female preponderance[4]. Studies[3,4] confirm that modifiable environmental factors are strongly associated with MS risk, with higher prevalence in northern Europe and North America due to increasing latitude gradient. These findings confirm the importance of early life environmental exposures in the risk of MS, strongly indicating that exposures as early as *in utero* and at birth drive the latitudinal gradient[5]. Though classically considered an autoimmune disorder, MS may be better characterized as a disease of immune dysregulation marked by chronic inflammation and demyelination, and loss of neurons that causes

motor, sensory, and cognitive disabilities. Among the pathogenesis causes, although the role of nutritional factors remains to be established, the existence of a two-way connection between the gut microbiome, the intestinal barrier, and the immune system (known as the gut-brain axis) might have significant implications for the development of inflammatory demyelinating diseases like MS. A recent review[6] presents the evidence supporting the involvement of the gut-brain axis in MS pathogenesis and investigates the impact of interventions targeting the gut in MS treatment. The introduction of a series of novel pharmacological molecules has impressively improved the therapy of multiple sclerosis over the last 20 years[7]. In MS, the dysregulated immune system, in collaboration with the wide variety of immunomodulatory effects of MS disease-modifying therapies (DMTs), could affect the response to infections for their immune-suppressive and modulating mechanism of action[8]. DMTs are the mainstay for MS; they include fingolimod, interferons, dimethyl fumarate, and others. This type of treatment has been the subject of scientific research in MS patients and in clinical outcomes. For example, a recent research study[9] showed the association between DMTs and the severity of depression, anxiety, and insomnia symptoms among a cohort of MS patients without the known psychiatric disease (but at risk for these conditions due to stress symptoms). Results show that DMTs, including fingolimod, may impact mental health outcomes in stressed RRMS patients, although follow-up studies are required to fully understand the direction and mechanisms behind this association.

DMTs may, in a modality-dependent manner, affect the immune response to infection and vaccination. While immune system integrity is typically assessed clinically, vaccine response is a well-established method of objective assessment. Guidelines[10] continue to advise routine vaccination schedules. Scientific research[11] has evaluated a variety of vaccine responses in individuals with MS, although this data has been limited to adults and those who were already on DMTs. Vaccination represents, therefore, a fundamental weapon in the prevention of infectious diseases among patients with MS. However, it raises concerns about safety and efficacy. The objective of this systematic review is to comprehensively demonstrate the efficacy/effectiveness and safety of vaccinations in patients diagnosed with multiple sclerosis. Through rigorous analysis and evaluation, we seek to provide a thorough understanding of the effectiveness of vaccination protocols in this patient population, considering potential impacts on disease progression, immune response, and overall health outcomes.

Materials and Methods

Data Sources and Search Strategy

This systematic review was carried out following the guidelines of the Cochrane Collaboration[12] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[13]. To report the process and the results, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[14] were used. The literature search was carried out using the Pubmed/MEDLINE and Scopus databases on 30 October 2023. To see the search strategy, see **Supplementary Table I**. There were no time limits, and all published articles have been taken into consideration.

Exclusion and Inclusion Criteria

We considered the following inclusion criteria: (1) language: English; (2) population: patients with multiple sclerosis; (3) interventions: vaccination; (4) comparators/control: healthy subjects or subpopulations of patients affected by multiple sclerosis (not mandatory); (5) outcomes: efficacy/effectiveness and/or safety of vaccinations in patients with multiple sclerosis; (6) type of study: cohort, case-control, cross-sectional studies. Exclusion criteria: (1) articles not in English; (2) population: patients without multiple sclerosis; (3) full text not available; (4) interventions: not on vaccination; (5) comparators/control: patients with diseases other than multiple sclerosis; (6) outcomes: the study does not show results on the effectiveness/efficacy and/or safety of vaccinations in patients with multiple sclerosis; (7) type of study: editorials, case reports, trials, book chapters, review article, letters to the editor, meta-analysis, expert opinion, trials, commentaries. The exclusion/inclusion criteria are detailed in **Supplementary Table II**.

Data Extraction and Selection Process

Two reviewers (S.P. and C.V.) independently assessed the titles and abstracts of the manuscripts that were extracted using the search strategy. Afterward, they assessed whether the articles were eligible and then, again independently, after downloading the full text, they reviewed the articles. In cases where there was a disagreement

between the two authors, a third reviewer (O.E.S.) intervened and assessed the suitability of the articles after discussing the various cases. The full text was downloaded only for potentially eligible studies.

Those articles that conformed to the inclusion criteria were entered into a pre-defined, pre-piloted spreadsheet in Microsoft Excel®. The final table with extracted data included: Author, Publication Year, Country of study, Study Period, Study design, Population of patients with multiple sclerosis, Control group, Aim, Vaccine(s), Efficacy of vaccination, Safety of vaccination, Monoclonal antibodies/drugs taken, Funds, Conflicts of Interest.

Strategy for Data Synthesis

Supplementary Figure 1 shows the flow diagram created according to the PRISMA 2020 guidelines[15], this diagram shows the number of references in each phase of the review process. To show the qualitative results in a simpler and more adequate way, summary tables were created.

Critical Appraisal

The Newcastle-Ottawa scale (NOS)[16] was used for a critical evaluation of the articles and was carried out independently by two authors (F.C. and O.E.S.). This is a risk-of-bias assessment tool for observational studies in relation to three areas: (1) study group selection, (2) comparability, and (3) exposure and outcome assessment for case-control and cohort studies, respectively. Up to nine points can be assigned; the higher the score, the lower the risk of bias.

An adapted version of the NOS[17] was used to assess cross-sectional studies. Based on the standard cut-off used in the literature[18,19], if the score is ≥7, the study is considered of high quality; if between 4-6, the study is of moderate quality; if ≤3 the studies are classified as low quality.

Results

Literature Search

The total number of studies found was 5949. On Scopus, 3823 studies were found, and 2,126 on PubMed/MEDLINE. A total of 1,713 documents were eliminated because they were duplicates. Finally, 4,236 documents remained. After evaluating the title and abstract, 4,090 records were removed because, in 3,672 articles, the topic was unrelated, 330 articles were not original, 85 were not written in English, and 3 were not per-

formed on humans. Of the 146 final records, 13 were discarded, 9 studies were trials, and 4 full texts were not retrieved. Based on pre-assessments, 133 articles were ultimately included in our review[20-152] (see **Supplementary Figure 1**). After the first screening, the disagreement between the authors was 1.53%. In alphabetical order by author, the characteristics of the included studies are listed in **Supplementary Table III**.

Characteristics of Included Studies

Supplementary Table III shows the characteristics of the included studies. The studies included in the systematic review are reported below[20-152]. 89% of the studies have been carried out starting from 2021. Further, 27 studies were carried out in Italy, 22 studies in the United States of America; 12 in Germany, 11 in Israel, 5 in United Kingdom, 5 in Switzerland, 5 in Spain, 4 in Poland, 4 in Norway, 4 in France, the other studies in Argentina, Austria, Canada, Chile, Serbia, Croatia, Cyprus, Egypt, Kuwait, Iran, Netherlands, Sweden and Turkey. Other studies were multicentric.

Over 80% of the studies involved COVID-19 vaccination (n=110) and influenza (n=13 (see **Supplementary Table III** for other details). 48 studies received no funding, while in 20 studies whether the authors received funding for the study was not reported. On the other hand, funds were reported in the other studies (n=65). In 68 studies, the authors declared the conflicts of interest, and in 13, conflict of interest was not reported.

Quality Assessment

The scores of the studies ranged between 6 and 9; the level is medium-high overall for all studies. Complete in-depth assessments based on the NOS checklist are shown in **Supplementary Table IV**.

Excluded Studies After Screening

After the screening phase, 13 other studies were excluded: 9 because they were trials, and 4 because the full text was not available[153-165] (see **Supplementary Table V**).

Discussion

To make this systematic review easier to understand, Table I shows the characteristics of the main Disease-Modifying Therapies (DMT), and Table II shows the main characteristics of the vaccines present in this systematic review.

In general, vaccinations were found to be safe[30,37,62,69,71], although, with regards to vaccination against yellow fever, it is advisable to carefully evaluate the risks and benefits of vaccination[71,127], even if this indication must be considered for all live virus vaccinations.

From the point of view of vaccination efficacy, although subjects receiving therapy with monoclonal antibodies generally have a lower immune response than healthy subjects after vaccination, antibody protection is quite good in patients with multiple sclerosis (pwMS) except for those taking anti-CD20 or S1P modulators where the response is not very effective or even absent[35,36,92,124,141]. In these cases, it is not recommended to interrupt or modify the DMTs[168] to improve the effectiveness of the vaccine if the risk of reactivation and progression of the disease exceeds the potential benefit. However, in the choice between not taking action and getting the vaccination, it is better to get the vaccination.

Following is a more in-depth discussion regarding the safety and efficacy of the vaccines considered in this systematic review.

COVID-19

Efficacy/effectiveness

Regarding the vaccine efficacy of COVID-19 vaccination, 95 articles were found[21-29,34-36,38-40, 42-46,48-50,52-55,57-60,64-68,70,76-78,80-85,88-99,101,103-109,111-113,117,118,120-122,124-126,128-133,136,138,139,141-144,146,147,150-152].

In general, after vaccination, pwMS show lower antibody conversion compared to healthy subjects, with much variability depending on the monoclonal antibody or drug taken[38,99,147,150]. The protective response was demonstrated in about 100% of MS patients treated with cladribine, dimethyl fumarate, natalizumab, and teriflunomide, similarly to healthy subjects; however, the response was decreased in patients treated with fingolimod, ocrelizumab and alemtuzumab[21,22,106,109,112,122,128]. PwMS that received glatiramer acetate, interferon-ß, dimethyl fumarate, cladribine or natalizumab had intact humoral and cellular immune responses following vaccination against SARS-CoV-2. B-cell-depleting therapies reduced B-cell responses but did not affect T-cell responses. Sphingosin-1-Phospate (S1P) inhibitors strongly reduced humoral and cellular immune respon-

Table I. Characteristics of the main disease-modifying therapies (DMT).

DMT Class	Mode of action
IFN-β (Interferon-β)	Immunomodulatoy, pleitropic immune effects
Glatiramer acetate	Immunomodulatoy, pleitropic immune effects
Teriflunomide	Dihydro-orotate dehydrogenase inhibitor, antiproliferative
Dimethyl fumarate	Pleotropic, nuclear factor erythroid 2-related factor 2 (NRF2) activation, downregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ)
Natalizumab	anti-α4-integrin (anti-VLA-4), selective adhesion molecule inhibitor
Sphingosine-1-phosphate receptor modulator (S1P modulators): siponimod, fingolimod ponesimod, ozanimod)	Selective S1P modulator, prevents egress of lymphocytes from lymphnodes
Anti-CD20 monoclonal antibodies (Anti-CD20 mAb)	Anti-CD20 mAb: B-cell deplete (ofatumumab, ublituximab, rituximab, ocrelizumab)
Cladribine	Deoxyadenosine (purine) analogue, adenosine deaminase inhibitor, blocks T- and B-cell proliferation
Alemtuzumab	Anti-CD52 monoclonal antibodies (Anti-CD52 mAb): B- and T-cell depleter
Mitoxantrone	Immune depleter, blocks IFN-γ (Interferon-γ), Tumor necrosis factor (TNF)-α and Interleukin 2
Corticosteroids	Immune depleter

Table created using bibliographic source[166].

Table II. Characteristics of the vaccines considered in this systematic review.

Vaccine type	Preventable disease	Vaccines name (manufacturer)
Live-attenuated	Yellow fever	Yellow Fever 17D-204 vaccine (Stamaril)
	Measles-Mumps-Rubella (MMR)	MMR (Priorix GSK)
	Varicella Zoster	Varivax (MSD) or Varilrix (GSK)
Inactivated	COVID-19	(Sinopharm), Coronovac (SinoVac)
	Typhoid-paratyphus	Combined tetanus and enteric prophylactic (T.A.B.T.)
	Tick-borne encephalitis	Not specified
	Pneumococcal	13-valent conjugate pneumococcal vaccine (Prevnar). 23-valent pneumococcal polysaccharide vaccine (23-PPV, Pneumovax)
	Meningococcal ACWY	Various vaccines (not specified)
	Meningococcal B	Various vaccines (not specified)
	Rabies	Not specified
	Haemophilus i.B	Various vaccines (not specified)
Inactivated, fractioned or subunits Influenza		Various vaccines (not specified)
Inactivated, anatoxin vaccines	Tetanus, diphtheria, acellular pertussis	Various vaccines (not specified)
Recombinant DNA	Hepatitis B	Not specified
DNA	COVID-19	ChAdOx1nCoV-19 (AstraZeneca), Ad26.COV2.S (Johnson & Johnson's Janssen), Ad5nCoV (CanSino)
mRNA	COVID-19	COVID-19 BNT162b2 (Pfizer/BioNTech), Moderna mRNA-1273 (Moderna)
Virus-like particle (VLP)	COVID-19	NVX-CoV2373 (Novavax)

Table created using bibliographic source[167].

ses[45,49,58-60,64,65,130,131,136,138,139]. According to Achiron et al[23], after vaccination in untreated, teriflunomide-treated and alemtuzumab-treated MS patients, specific memory B-cells were detected in 41.9%, 40.0% and 41.7% of subjects at one month, in 32.3%, 43.3% and 25% at three months and 32.3%, 40.0%, 33.3% at six months. In the same patients, however, specific memory T-cells were detected in 48.4%, 46.7% and 41.7 at one month, in 41.9%, 56.7% and 41.7% at three months, and in 38.7%, 50.0%, and 41.7% at six months. As underlined before, the antibody and T-cell response is very varied, and for the majority of pwMS, it appears to be comparable to healthy subjects[34]. For pwMS taking anti-CD20 or S1P modulators, the response is often weak or attenuated. In anti-CD20-MS patients, the seroconversion rate was *circa* 30-50%[27,29,40,151]. S1P modulator-treated subjects exhibited both severely attenuated humoral responses and absent spike-specific T cell receptor (TCR) depth and breadth[28]. Compared to 97% in healthy controls, seroconversion occurred in 96% of untreated pwMS, 97% of patients on immunomodulatory DMTs, and 61% on immunosuppressive DMTs. Seroconversion was lower in patients on anti-CD20 monoclonal antibodies, followed by S1P modulators[52]. In patients treated with ocrelizumab and fingolimod, the IgG level was significantly lower, but only some patients failed to develop a measurable humoral response[53,70,76,90-93,98,99,101,103,113,136]. By contrast, all pwMS treated with anti-CD20 generated antigen-specific CD4 and CD8 T-cell responses after vaccination[35,36,88,118,120,124,126]. For example, about 90 patients treated with ocrelizumab and 100% of healthy controls had SARS-CoV-2-specific T-cells following vaccination[50,88], only about 50% of pwMS on ocrelizumab and 40% on fingolimod had a positive humoral response at four weeks after the first dose, with only 30-40% and 20-30% maintaining a positive response at sixth months (100% for healthy controls)[39,48,55,58,76-78,82-85,90,95,104,144,146].

As regards booster doses, the results of the studies are not always unequivocal. In some studies[24,43,66,81,89,105,107,141,143], the antibody titer did not always increase significantly. Achtnichts et al[25], in their study, showed that only in 50% of individuals treated with S1P modulators was there a clinically relevant antibody titer. Other studies[26,44,54,60,64,90-93,96,97,111,117,152], however, showed that the booster dose increased anti-Receptor-Binding-Domain-IgG (anti-RBD-IgG) titers in patients treated with fingolimod, cladribine, and IFN-β but not in patients treated with ocrelizumab. Another important factor is that fingolimod and anti-CD20 therapy were independently associated with a more severe COVID-19 course even if vaccinated, compared to those taking other types of DMTs[68]. Of note, MS patients had significantly higher humoral responses to the vaccine compared to uninfected patients if they were previously infected with SARS-CoV-2[129].

Regarding the risk of being hospitalized, two studies[42,94] conducted on the inactivated Sinopharm vaccine, BBIBP-CorV, have shown that pwMS who had had two doses of this vaccine had a lower risk of contracting the infection and being hospitalized; however, pwMS treated with rituximab and elderly subjects still showed a higher risk of hospitalization after receiving two doses of this vaccine. The SARS-CoV-2 messenger RNA (mRNA) vaccine (aOR: 0.36) and receiving a booster vaccination (aOR: 0.31) were independently associated with a reduced risk of hospitalization for COVID-19. Even among pwMS treated with rituximab, the risk of hospitalization for COVID-19 was reduced if more than six months had passed after the last rituximab infusion, regardless of the dose of vaccine administered (aOR: 0.22)[142].

As regards COVID-19 vaccines, on average in 66.9% of pwMS, a humoral response emerged after vaccination with differences in relation to the type of vaccine and the therapy taken. For example, for inactivated vaccines, the humoral response emerged in 62.6% of cases *vs.* 78.4% for mRNA vaccines[57,67]. Furthermore, positivity to anti-S1 antibodies was found in 100% of pwMS who did not receive therapy, in 100% of those taking natalizumab or alemtuzumab, 90% of those taking cladribines, 88% if they took fingolimod, 43% if the patient was treated with anti-CD20. In the latter case, positivity for anti-S1 antibodies was 38% if the patient had received an inactivated vaccine and 59% if he had received an mRNA vaccine[57,62]. Of note, vaccination with two doses of NVX-CoV2373 was able to elicit a specific response in people with MS who had not had an adequate immune response to the previously administered dose of mRNA or DNA vaccine[121].

In general, COVID-19 vaccination is still the best option, even if the response may not be like that of healthy subjects, as it tends to limit and reduce the risk of hospitalization and serious illness.

Safety

Regarding the safety of anti-COVID-19 vaccines, 35 studies were found[20,30-33,40,43,44,46,47,51-54,57,61-63,66,73-75,80,90,94,96,97,102,106,109,121,131,132,141,145].

As regards adverse events, they were generally mild, comparable to those of the healthy population. The most common symptoms were pain at the injection site (approximately 70%), flu-like symptoms (approximately 60%), fever (approximately 20%), fatigue (about 25%), and headache (about 20%); symptoms typically lasted up to 48 hours[30,46,53,61,62,66,74,75,94,97,106,109,121,132]. There were no serious adverse reactions[30,51,52,74,141]. A lower frequency of adverse events was found with inactivated vaccines (BBIBP-CorV, Coronovac) compared to DNA and mRNA vaccines[32]. None of the DMTs seems to predispose to particular side effects[61,62], although in one study[61], an adverse event classified as "Red-Flag" occurred: thrombosis in a 42-year-old patient two weeks after the first dose of the AstraZeneca vaccine.

Infrequent events with mRNA vaccines were herpes zoster infection and streptococcal pharyngitis in 3.8%[40]. Symptoms post-vaccination were similar to the non-MS population and were mostly temporary[31]. With mRNA vaccines, no increased risk of relapse activity was noted[20,33,44,54]. There were no statistically significant differences in MS relapse between vaccinated and non-vaccinated individuals[43,69]. Specifically for Sinopharm (BBIBP-CorV), a reference cohort of vaccinated pwMS showed no indication of increased post-vaccination relapse activity compared to pre-vaccination[73].

Younger age[94], female, previous SARS-CoV-2 infection, and administration of the AstraZeneca *vs.* BNT162b2 vaccine were associated with a more important reaction after the first dose of vaccine[46]. In general, women reported[74] reactions to vaccination more frequently than men.

Regarding monoclonal antibodies, in a study[90], pwMS taking ocrelizumab had a higher risk of vaccine-related side effects, even though the study included only a small cohort of 45 pwMS. With regards to ocrelizumab, 18.5% of patients reported mild adverse events[131]. Generally, in the-

se studies[30,46,53,61,62,66,106,109], mRNA vaccines were predominantly administered.

Regarding the COVID-19 vaccine BNT162b2 and antiCD-20 monoclonal antibodies and S1P inhibitors, a study[146] showed that the risk of vaccine-related acute phase adverse events (APAEs) in pwMS was generally lower than in the general population.

According to König et al[96], adverse effects were observed in 63% of pwMS treated with anti-CD20 therapy and in 38% treated with fingolimod; the most common symptoms were transient local pain and fatigue. No patient experienced serious adverse effects after revaccination[96]. According to Brunn et al[51], neither disease-modifying therapy nor B-cell therapies were associated with vaccine side effects or neurological symptoms[51], both for mRNA and DNA vaccines.

Haemophilus Influenzae B

Efficacy/effectiveness and safety

No studies have been found on the efficacy of this vaccine in patients with multiple sclerosis.

The study by Sbragia et al[137] shows that no increase in clinical/radiological activity 3/6 months after immunization was noted. This confirms the feasibility and safety of vaccinations in patients with MS.

Hepatitis B

Efficacy/effectiveness and safety

In the study by Landi et al[100], 13 pwMS treated with one cycle of cladribine (3.5 mg/kg) and previously vaccinated against the hepatitis B virus (HBV) were enrolled. Anti-HB titers were compared before and 12 months after treatment with cladribine. Among the 13 pwMS, all had anti-HB titers >10 mg/dl at baseline. In only one case did the anti-HBs titer fall below the reference value 12 months after cladribine. Cladribine mean anti-HBs pre-post values were not significantly different considering the entire cohort. Cladribine did not appear to reduce the humoral immune response in subjects previously vaccinated against HBV, as it has a low impact on plasma cells.

No studies were found on the safety of this vaccine in patients with multiple sclerosis.

Influenza

Efficacy/effectiveness

Regarding the effectiveness of influenza vaccination, eight studies were found[41,79,115,116,119,123,134,140].

The studies show that in pwMS, influenza infection was associated with an increased risk of acute hospitalization, while no increase in risk was observed after vaccination. Therefore, influenza vaccination could prevent the worsening of MS-related symptoms and the risk of hospitalization[79,119].

90% of pwMS reached a protective antibody titer after seasonal flu vaccination for the H1N1 and H3N2 strains[41] and approximately 70% of patients for B strains[116].

Taking into consideration the drugs taken, however, a fair variability in seroprotection rates was recorded. For example, fingolimod always provided reduced protection following vaccination, while natalizumab showed reduced protection at 3 and 6 months. Patients without immunomodulation did not show significantly different protection rates from controls at 3 and 12 months[123]. Seroprotection in pwMS treated with daclizumab beta was detected in 92% of patients for A/H1N1 strain, 91% (83%-96%) for A/H3N2 strain and 67% (56-76%) for B strain[115]. Patients treated with interferon achieved high seroprotection rates (>84%). Good seroprotection rates were observed in patients treated with glatiramer acetate[116]. However, comparing pwMS taking interferon beta-1a/1b and glatiramer acetate with a population of healthy subjects, no significant difference emerged between the rates of protection against the H1N1 strain at 3, 6 and 12 months after vaccination[123]. To conclude, according to Rolfes et al[134], MS patients treated with cladribine can develop an adequate immune response to influenza regardless of the duration of treatment and the time interval until the last administration of cladribine.

These studies[79,119,123] confirm that, albeit with some exceptions, it is important to vaccinate pwMS because they can have an adequate immune response[123] and because the risk of hospitalization is reduced[79,119].

Safety

Regarding the safety of influenza vaccination, eight studies were found[37,41,63,110,115,116,134,149]. Data regarding the safety of influenza vaccination are positive: the vaccination is safe and well tolerated[37,41], commonly side effects are local symptoms (pain, redness, swelling of the injection site) or flu-like symptoms, in a percentage that does not differ significantly from that of the general population[110,149]. No serious adverse events were reported[116,149]. Measuring the annualized relapse rate, disease activity decreased significantly; in fact, the year before carrying out the vaccination, the

rate was 0.64, and the year after carrying out the vaccination, the rate dropped to 0.38[149]. It should be noted that within six months of vaccination, the extended disability status scale remained stable compared to pre-vaccination values[116,149]. In one study[110], no statistically significant differences were found in terms of MS infections or relapses between the vaccinated and non-vaccinated groups. Furthermore, an exacerbation occurred within the following six weeks in 33% of pwMS after the influenza illness, while it occurred only in 5% pwMS after vaccination[63]. Therefore, this data shows that vaccination is in some way also indicated to prevent exacerbations caused by the stress of the flu illness.

Measles-Mumps-Rubella

Efficacy/effectiveness and Safety

Two studies on Measles-Mumps-Rubella were retrieved from the literature search. One study[56] was about vaccination against Measles-Mumps-Rubella and the other one[114] was about vaccination against Measles-Mumps. In the study by Carvajal et al[56], the objective was to evaluate the immunogenicity of a single dose attempt (SDA) compared to the standard immunization scheme (SIS) with varicella zoster. In the 67 pwMS vaccinated against measles, those who had been vaccinated with a single dose developed antibodies in 70% of cases compared to 96.3% of those who had received two doses.

The study by McFarland and McFarlin[114] shows that the cellular response was consistently lower for the measles virus than for the mumps virus, as measured by the lymphocyte proliferation test used in this study. No studies were found on the safety of this vaccine in patients with multiple sclerosis.

Meningococcal ACWY

Efficacy/effectiveness and safety

No studies have been found on the efficacy of this vaccine in patients with multiple sclerosis.

However, the study by Sbragia et al[137] shows that no increase in clinical/radiological activity 3/6 months after immunization was noted. This confirms the feasibility and safety of vaccinations in patients with MS.

Meningococcal B

Efficacy/effectiveness and safety

No studies have been found on the efficacy of this vaccine in patients with multiple sclerosis.

However, the study by Sbragia et al[137] shows that no increase in clinical/radiological activity 3/6 months after immunization was noted. This confirms the feasibility and safety of vaccinations in patients with MS.

Pneumococcal Conjugate Vaccination

Efficacy/effectiveness and safety

No studies have been found on the efficacy of this vaccine in patients with multiple sclerosis.

However, the study by Sbragia et al[137] shows that no increase in clinical/radiological activity 3/6 months after immunization was noted. This confirms the feasibility and safety of vaccinations in patients with MS.

Rabies

Efficacy/effectiveness and safety

No studies have been found on the efficacy of this vaccine in patients with multiple sclerosis. Only one safety study[87] for the rabies vaccine was found. In this study of 55 pwMS, the authors report that 21 patients had 24 relapses in the year before vaccination, whereas only 3 had one relapse each in the post-vaccination risk exposure period; another 3 had a total of 4 relapses in the subsequent post-risk period. The annualized relapse rates (ratio between the exposure risk rate and the pre-exposure periods) were 0.44, 0.22, and 0.10 in the pre-exposure, risk exposure, and post-risk periods, respectively. From this point of view, the vaccine analyzed can be considered reasonably safe.

Tetanus, Diphtheria, Acellular Pertussis

Efficacy/effectiveness and safety

No studies have been found on the efficacy of this vaccine in patients with multiple sclerosis.

As regards tetanus-based vaccines, side effects have been reported[149] in approximately 20% of vaccinated pwMS; pain, redness, and swelling at the injection site were the most reported reactions. The results suggest that the vaccines are safe and well tolerated in pwMS and do not have a negative impact on disease activity. Measuring the annualized relapse rate, disease activity went from 0.64 the year before vaccination to 0.38 the year after. Furthermore, the extended disability status scale remained stable within six months of vaccination compared to pre-vaccination values[149]. No increase in clinical-/radiological-activity 3/6 months after immunization was noted. This confirmed

the feasibility and safety of vaccinations in patients with MS[137].

Tick-Borne Encephalitis

Efficacy/effectiveness

The study by Winkelmann et al[148] shows that the geometric mean titer (GMT) increased four weeks after vaccination [from 169 to 719 Vienna units per milliliter (VIEU/mL)], with 78% of subjects who showed protective antibody titers after vaccination. Even in patients treated with beta interferons, GMT increased (from 181 to 690 VIEU/mL). The same goes for subjects treated with glatiramer acetate; they also developed an increase of 2 to 10 times. Among all, those who showed a reduced increase were pwMS taking fingolimod. The study included a population of 20 pwMS taking the following therapies: interferon beta, glatiramer acetate, fingolimod, and natalizumab.

Safety

The same study[148] also explored the safety of the vaccine showing that in these 20 vaccinated subjects the annualized relapse rate decreased from 0.65 in the year before vaccination to 0.21 in the following year. Considering the period of 2 years before vaccination and one year after vaccination, the extended disability status scale remained stable. The vaccination demonstrated a good degree of tolerability.

Typhoid and Paratyphus

Efficacy/effectiveness and safety

Unfortunately, it is appropriate to clarify that only one old study[72] from 1961 was found. It used a vaccine used in the past and is therefore difficult to compare with current vaccines. The study included a population of 21 pwMS against 23 healthy individuals. The study did not specify the type of therapy received by the study population. The data shows that subjects with MS produced fewer antibodies than healthy subjects after vaccination. No studies have been found on the safety of this vaccine in patients with multiple sclerosis.

Varicella Zoster

Efficacy/effectiveness

Two studies[56,135] about vaccination against Varicella were retrieved. In the study by Carvajal et al[56], the objective was to evaluate the immunoge-

nicity of a single dose attempt (SDA) compared to the standard immunization scheme (SIS) with Varicella Zoster. In the 31 pwMS vaccinated against chickenpox, those who had been vaccinated with a single dose developed antibodies in 57.2% of cases compared to 100% of those who had received two doses; in non-immunized subjects, an additional dose increased seroprotection to 95%. The second study, that of Ross et al. 135, planned to evaluate the antibody increase in subjects who were already positive for Varicella after vaccination. In this study, it emerged that all subjects showed an increase in antibody titer after vaccination.

Safety

As regards safety, we found only one study[135]. The vaccine showed an excellent degree of tolerability, and no one was harmed by it. However, the study population was only 50 pwMS, and the drugs taken were not reported. Therefore, this represents an important limitation of the study.

Yellow Fever

Efficacy/effectiveness and safety

No studies have been found on the efficacy of this vaccine in patients with multiple sclerosis.

However, two studies[71,127] discussed the safety of vaccination against yellow fever (YF): that of Farez and Correale[71], with a population of 7 pwMS, and that of Papeix et al[127], with a population of 128 pwMS.

According to Farez and Correale[71], vaccination should be recommended for MS patients traveling to yellow fever endemic areas based on a careful assessment of the risk of flare-up *vs.* the likelihood of exposure to the yellow fever virus. In fact, in this study, the annual rate of exacerbation was 8.5 after vaccination during the risk periods, whereas the relapse rate was 0.7 outside the risk period. Considering neuroradiological images, pwMS three months after vaccination showed a significant increase in new or enlarging T2-weighted lesions and gadolinium-enhancing lesions compared to 12 months before vaccination.

Papeix et al's study[127] instead evaluated the risk of relapsing-remitting multiple sclerosis (RR-MS) worsening after the yellow fever vaccine, taking into consideration vaccinated and unvaccinated subjects. The results show that one year after the yellow fever vaccine, the annualized relapse rate (ARR) did not differ between exposed and non-exposed subjects, 0.219 (0.420) *vs.* 0.208

(0.521), and the time to first relapse was not different between groups. The vaccine does not appear to worsen the course of relapsing-remitting multiple sclerosis (RRMS).

The authors suggest administering this vaccination carefully and after carefully evaluating the risks and benefits, as safety studies are conflicting. Furthermore, vaccination with live attenuated virus vaccines could be contraindicated in immunosuppressed subjects.

Limitations and Strengths

Although English is currently the most used language in the scientific community, as we only included articles published in English in our search, this may have reduced the total number of potentially eligible studies. The search string was very sensitive but not very specific; in fact, the authors decided to retrieve as many articles as possible and then possibly eliminate them after the screening. This led to a large number of articles that were not related to the topic. However, we believe that this approach allowed us to include as many articles as possible without omitting any. Second, this study only examined published articles indexed in PubMed and Scopus; rigorous scientific studies are normally disseminated through articles in scientific journals and not through editorials or comments and are indexed, at least those in the medical area, in the databases mentioned above.

Another limitation is that this systematic review is mainly composed of studies on COVID-19 vaccination. Unfortunately, there has been an "surge" of research and publications regarding this vaccination but little in the literature regarding the rest of the existing vaccinations.

Our manuscript also has some important strengths. It is a systematic literature review conducted in accordance with international guidelines and, to date, is the most up-to-date and comprehensive systematic review on the topic.

Conclusions

The effectiveness and safety of vaccinations in pwMS is a topic that must be explored and evaluated with further studies, better diversifying by the type of drug taken. In general, vaccinations do not seem to exacerbate MS or increase the probability of relapse, in particular for inactivated vaccines and, in general, for the rest of vaccines. However, administering a live virus vaccine to a pwMS may not be recommended or even contraindicated because some drugs taken by these patients can compromise the immunocompetence of the individual. Therefore, it is necessary to carefully evaluate the risks and benefits in these cases[169].

It may not be recommended to stop or modify DMTs to improve vaccine efficacy, as the risk of disease reactivation and progression outweighs the potential benefit[168]. At the same time, a small response is likely to be better than none. If possible, vaccinations should clearly be recommended and administered to pwMS.

Authors' Contributions

O.E.S. conceptualized the study, O.E.S. designed the study, and O.E.S. performed the literature search. O.E.S. performed resource analysis and data extraction. O.E.S., C.V., S.F., L.F., S.P., F.B., M.R., A.F., and F.C. wrote the first draft. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Informed Consent

Not applicable due to the design of the study.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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