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Vaccination strategies in multiple sclerosis patients with Delphi methodology: A Turkish consensus

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Abstract

Background: Both the presence of multiple sclerosis (MS) and the use of immunomodulatory therapy for this disease can change the vaccine response in individuals with MS. In this study, due to the lack of guidelines for vaccination of MS patients in our country, the aim was to create a Delphi consensus on vaccination practices and vaccine types in MS patients. *Methods:* The Real-time Delphi technique, a more structured and predefined version of the traditional Delphi study was used to ensure

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a comprehensive research process. The stages of the structured online Delphi application process, which includes repeated rounds, (three rounds) are applied. Fifteen participants are sufficient to achieve homogeneous outcomes according to expertise criteria and in this study, the group comprised 31 experts who met these criteria and participated in all stages. *Results:* The assessment of the level of consensus among panelists revealed that there was "almost perfect consensus" on 16 items and "significant consensus" on 12 items. When examining the items in which the panelists did not reach a consensus, it was found that there was "minor consensus (slight-1)" on 1 item, and there was "no consensus (indicate poor-0)" on 2 items.
Conclusion: We wanted to share a "country" practice and our current recommendations on vaccination strategies, by making use of articles containing country-based recommendations and working-group recommendations, as well as our national experiences.

Keywords: multiple sclerosis, Delphi technique, vaccination, practical approach

INTRODUCTION

Multiple sclerosis (MS) is an immune mediated neuroinlammatory-neurodegenerative disease that has the potential to affect individuals of almost all ages, including childhood. Both the presence of MS and the use of immunomodulatory therapy for this disease can change the vaccine response in individuals with MS. The relationship between MS and vaccination has been discussed on many grounds for years.[1-3]

The fundamental questions in these discussions could be elaborated as the possible role of vaccination in the development of MS, which can be detailed as follows: the association between vaccination and relapse in MS patients, the vaccine response in naïve patients, interaction between disease-modifying treatments (DMTs), aging and vaccination response.

METHODS

All procedures adhered to the ethical standards of the responsible committee on human experimentation (institutional and national) and conformed to the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from Samsun University on May 5, 2024, with protocol number GOKAEK 2024/8/4.

Research model

This study aimed to obtain and evaluate expert opinions on vaccination strategies for individuals with MS on a national basis. To ensure the reliability and validity of our findings, we used the structured online Delphi technique, which combines qualitative and quantitative research skills. This technique, also known as the consensus method, involves obtaining a reliable survey by providing controlled feedback with the opinion of a group of experts.[4] Since the participants in the Delphi technique process should consist of knowledgeable and interested individuals, a purposeful sampling approach was adopted to determine the study group.[5] The purpose of this sampling approach is to collect in-depth information about the person, event or situation that constitutes the subject of the research and for a specific purpose.[6-8]

Our study used the Real-time Delphi technique, a more structured and predefined version of the traditional Delphi study, ensuring a comprehensive research process.[7] As the second part of this article, which provides Delphi consensus on general vaccination, the 2nd Delphi consensus study on vaccine-specific approach to MS is being carried out and is being prepared for publication as a follow-up.

Study group

Studies employing the Delphi technique have reported that 10–15 participants are sufficient to achieve homogeneous outcomes according to expertise criteria.[4] In this study, the group comprised 31 experts who met these criteria and participated in all stages. MS experts with a minimum of 5 years of active clinical experience and research in the field were selected from various regions and cities to ensure nationwide representation. Additionally, two experts in infectious diseases and clinical microbiology were included. Data were recorded in real-time to ensure the reliability of the online Delphi study. The Delphi process collects expert opinions through multiple rounds of surveys conducted anonymously, thus enhancing individual judgment through the power of collective intelligence and obtaining a collective view on a topic.[9] In this context, the effective use of online environment during data collection process has significantly contributed to creating a setting where experts were not influenced by each other's responses.[9]

Data collection

An intramethod mixing approach was adopted in the online Delphi method and utilised in the study design. This approach was a mixed methods strategy used to collect data simultaneously in a single questionnaire.[10] In line with this strategy, the stages of the structured online Delphi application process, which includes repeated rounds, are outlined below.

1. In the Delphi technique, creating the first session (survey) to start the process was the most important and difficult part, forming the basis of the next rounds.[11] In this context, a structured initial survey form was created to provide a rich data set and to help experts generate ideas. The first survey form was created by conducting face-to-face focus group interviews with five experts (core team) in three consecutive sessions. In the Delphi technique, the "core team" consists of experts who initiate the process and create the first survey form, evaluate the data received during the process, and conduct focus group interviews, which play a critical role in ensuring the success of the Delphi method. They create the initial survey design, which determines the structure and content of subsequent rounds. They are responsible for analysing the data collected throughout the process. They enrich the content of the survey with insights gained through focus group discussions.

2. The first survey form, created by a consensus of experts, was sent simultaneously online to 31 experts who agreed to participate as Delphi panelists and the first Delphi round was started. A free text area was also created where experts could express their opinions and suggestions regarding the item determined in the first survey form sent to the panellists.

3. The core team examined the data obtained from the first Delphi round, which lasted approximately two weeks with the participation of all panellists. It was observed that no regulation or new article suggestions came from the panellists. Only a few items were edited in line with suggestions to improve their clarity. After the items were finalised, the second survey form was prepared. Unlike the first survey form, a graduated Likert-type measurement tool (very weak =1 to very strong =9) was used to determine the recommendation level of each item, and the second survey form was designed so that the panellists could freely share any ideas, was sent with explanatory instructions.

4. As a result of the second Delphi round, the evaluation results from the panellists were examined by the core team. In the second round, it was observed that there were no regulations or suggestions for new articles from the panellists. The panellists only determined the recommended difficulty level for the relevant item. They stated their reasons if there were items, they found weak or not strong enough (score of 6 or less). Based on the data obtained, the consensus levels of the experts for each item (percentage agreement, mean, quarterly coefficient of variation), agreement between raters for all items (Fleiss' Kappa) and rater reliability (ICC) were calculated. After this stage, the form, which included the experts' average consensus levels for each item and the panellist's score for each item in the previous round, was rearranged, and the third Delphi round was initiated.

5. As a result of examining the third Delphi round data from the experts, it was seen that no new ideas were produced anymore, all the strengths and weaknesses of the items were determined and there was no change in the recommendation levels of the experts. After it was determined that the experts had reached a consensus on the 28 items, they were thanked for their participation. The principles created in line with the latest data were sent along with their instructions (Figure 1).

Data analysis

In many consensus-based Delphi studies, binary decisions (agree/reject; include/exclude) were constructed from a nine-point scale.[12] In this regard, a nine-point Likert-type measurement tool (very weak = 1 to very strong = 9) was used to determine the recommendation levels of the Delphi panellists. An equal number of rating categories is needed to allow qualitative comparison and adjust reliability measures (Lange *et al*., 2020).[12] Therefore, the values on the nine-point scale are categorized as high/important (9-8-7), medium/important but not critical (6-5-4), and weak/not important (3-2-1) recommendations.

In determining the agreement levels of the panellists for the obtained items, analysis was made by applying the statistical procedure accepted in the literature, and the results were aimed to confirm each other. For this purpose, the most commonly used descriptive statistics (percentage agreement, mean, quarter coefficient of variation) and inferential (Intraclass Correlation Coefficient-ICC, Fleiss' kappa) statistics were

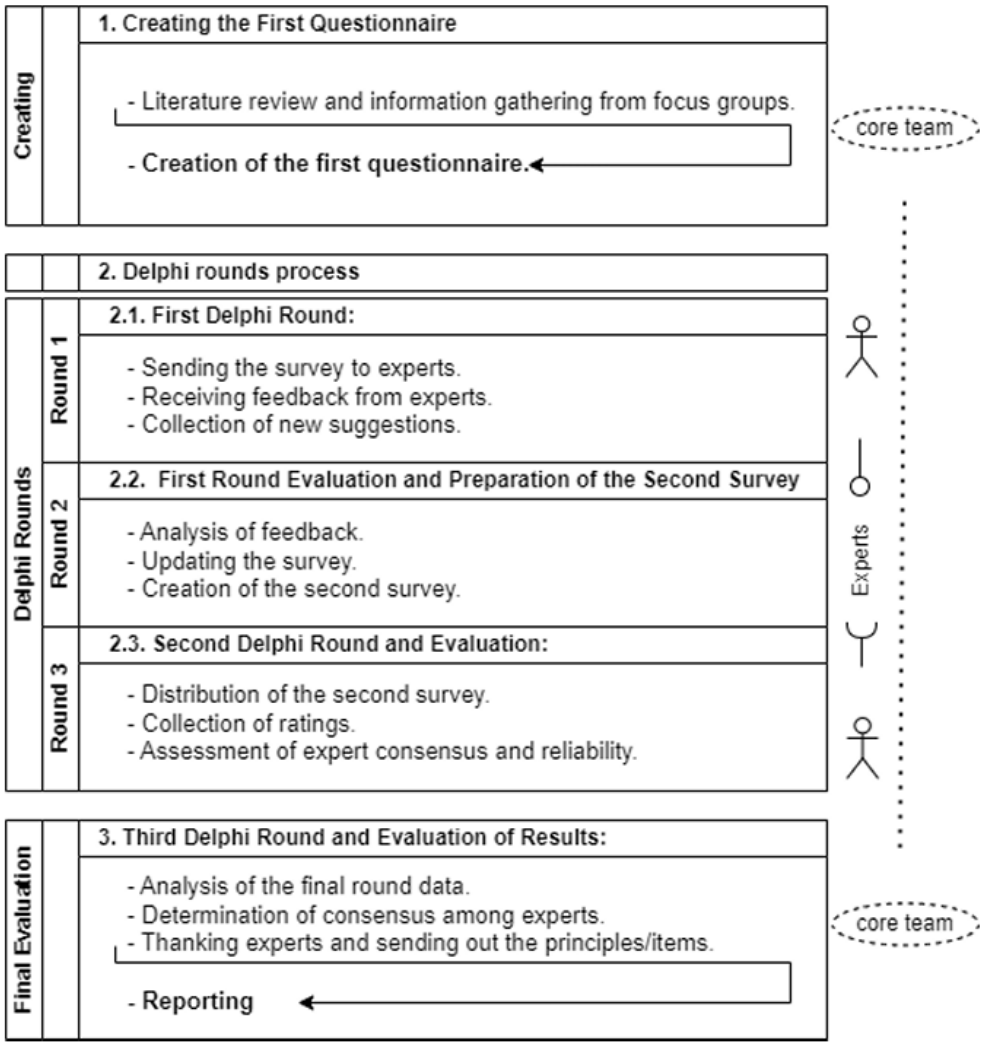

Figure 1: Study design

used to determine the consensus on the items. At this point, there was a high difficulty (9-8-7) consensus regarding the relevant article; Stability was sought in the panellist consensus rate (≥75%), mean value (≥7) and quartile coefficient of variation - CQV (≤.015). The reliability of the rating attribute for the obtained items was determined by Intra-Class Correlation Coefficient (ICC≥.75), and Fleiss' kappa coefficient (k>.40) values were used to determine the level of agreement between experts.

RESULTS

In comparing the evaluation scores between the first and second rounds of the Delphi study, no statistically significant difference was found between the mean scores calculated for the participants' responses (second-round mean = 8.069, SD = 1.062; third-round mean = 8.134, SD = 1.148) ($t(30) = -1.814$, $p>0.05$). These results were supported by the high correlation ($r=.987$, $p<0.001$) and denoted significant consistency between the two rounds. With the results of Cohen's kappa analysis (⩽.001, range [.636-1.00]), which was conducted to determine the consistency of the raters over time, it was determined that the panellists showed consistency between the two rounds for each item. These results indicated that the high consistency levels were not due to chance and that no significant change existed between the participants' scores. A high level of agreement among the panellists elaborated that the Delphi process can be completed without further data collection. In this context, the Delphi rounds were terminated,

and the data from the panellists were evaluated using descriptive and inferential statistics. As a result of the analysis, it was determined that 31 Delphi panellists reached consensus on 28 of 31 items (Table 1).

The limit values of the most accepted descriptive statistics (consensus pct. ≥75%, Mean ≥7, CQV≤.15) and the results of the categorical evaluation for consensus (K>.04) confirmed each other. As a result of evaluating the agreement levels of the panellists, a consensus was reached. There was "almost perfect agreement – 5" on 9 items (m2, m6, m8, m10, m11, m13, m15, m16, m17, m18, m20, m21, m22, m23, m25, m26, m27, m28, m29, m30). and "substantial agreement – 4" on 8 items (m1, m4, m7, m9, m14a, m14b, m19, m24). When the items on which the panellists were not in agreement were examined, it was determined that there was "slight – 1" agreement on 3 items (m3, m5, m12).

Table 1: General approach recommendations regarding vaccination in MS patients

	Items (I)	Mean	Consensus (%)	CQV	K (95 % CI)	Comment (K)
i1.	Vaccines are not expected to cause MS disease.	8.45	93.10	0.06	.80	4*
i2.	Inactivated vaccines are not expected to trigger an MS attack.	8.55	96.55	0.03	.90	5*
i3.	Live vaccines are not expected to trigger an MS attack.	4.41	17.24	0.50	.02	1
i4.	Since yellow fever *(live vaccine)* may trigger an MS attack, it should be decided on a patient-by-patient basis whether it should be administered to people travelling to endemic areas.	7.86	93.10	0.09	.80	4*
i5.	There is no harm in individuals with MS who are not under treatment receiving live vaccines.	5.34	44.83	0.43	.00	1
i6.	There is no harm in individuals with MS who are not under treatment receiving inactivated vaccines.	8.41	96.55	0.06	.90	5*
i7.	Vaccines are not expected to affect the course of MS disease and the disability that may develop.	8.14	93.10	0.06	.80	4*
i8.	The vaccination response of individuals with MS who have never received immunomodulatory/immunosuppressant treatment is expected to be the same as that of the normal population of similar age and gender.	8.38	96.55	0.06	.90	5*
i9.	It is expected that the vaccination response of individuals with MS who have not received immunosuppressive treatment for the last year will be the same as the normal population of the same age and gender.	8.14	93.10	0.06	.80	4*
i10.	Regardless of treatment, ageing may affect the immune response to vaccination in individuals with MS.	8.28	96.55	0.09	.90	5*
i11.	Regardless of treatment, the presence of comorbidities *(diabetes and other autoimmune diseases)* may affect the immune response that vaccination may create in individuals with MS.	8.48	100.0	0.06	1.00	5*
i12.	Regardless of treatment, the clinical phenotype of MS (relapsing or progressive) may influence the immune response to vaccination.	4.62	17.24	0.41	.04	1
i13.	In newly diagnosed MS patients who will be planned for immunosuppressive treatment, especially if Hepatitis B, Varicella Zoster, COVID-19, and HPV antibodies are negative, the vaccination program should be applied in accordance with national vaccination guidelines and with a one-month interval between vaccines. Accelerated and strengthened vaccination programs may be applied depending on the situation.	8.48	96.55	0.06	.90	5*
i14.a.	Individuals with MS who have received corticosteroid *(IVMP)* treatment for attacks or any other reason should not receive any vaccination within 1 month after the last dose.	8.17	89.66	0.06	.71	4*
i14.b.	Whether or not a person with MS who has an attack has received corticosteroid *(IVMP)* treatment, any vaccination should not be given until 1 month has passed since significant improvement in attack symptoms or stabilisation of the clinical picture has been achieved.	8.10	89.66	0.06	.70	4*

i15.	In individuals with MS who are under immune treatment, the vaccination and timing of the vaccination program should be decided by considering the treatment received.	8.83	100.0	0.00	1.00	5*
i16.	Vaccination can be performed at any time in individuals with MS who are under interferon-beta therapy.	8.76	100.0	0.00	1.00	5*
i17.	Vaccination response in individuals with MS under interferon beta therapy is expected to be the same as in the normal population.	8.69	100.0	0.03	1.00	5*
i18.	Individuals with MS who are under first-line treatment with glatiramer acetate and teriflunomide can be vaccinated at any time without discontinuing treatment, even if a partial decrease in the vaccination response is expected with some vaccines.	8.69	100.0	0.03	1.00	5*
i19.	A complete vaccination response is expected in MS individuals under dimethyl fumarate treatment.	8.14	89.66	0.06	.71	4*
i20.	Vaccination response is expected to be adequate in individuals with MS under dimethyl fumarate treatment unless there is significant lymphopenia.	8.52	100.0	0.06	1.00	5*
i21.	Live vaccines should not be administered to individuals with MS who are receiving immunosuppressive treatment.	8.72	100.0	0.00	1.00	5*
i22.	In individuals with MS receiving immunosuppressive treatment, the vaccination response is expected to decrease depending on the treatment used.	8.76	100.0	0.00	1.00	5*
i23.	Although vaccinations in individuals with MS under fingolimod treatment are expected to reduce the vaccine antibody response, vaccination should be done without discontinuing treatment.	8.72	100.0	0.00	1.00	5*
i24.	Although vaccinations in individuals with MS under natalizumab treatment may cause a limited decrease in the vaccine antibody response, vaccination should be done without discontinuing treatment.	8.62	93.10	0.00	.80	4*
i25.	Completing vaccination applications before starting treatment is appropriate in individuals with MS who are planned to use one of the treatments with potent immunosuppressive effects, such as ocrelizumab and other B-cell suppressive treatments or alemtuzumab and cladribine.	8.97	100.0	0.00	1.00	5*
i26.	Suppose vaccination is required in individuals with MS receiving ocrelizumab and other B-cell suppressor treatments. In that case, this vaccine should be administered at the earliest 3 months after the last treatment, preferably before the next administration, and the MS treatment in question should be scheduled to be administered 1 month after the last dose vaccination. should be done.	8.79	100.0	0.00	1.00	5*
i27.	In individuals with MS receiving treatments with potent immunosuppressive effects, such as ocrelizumab and other B-cell suppressive treatments, as well as alemtuzumab and cladribine, mRNA or inactive vaccines can be administered in special cases where vaccination is required *(temporary availability of the vaccine, etc.)*.	8.72	100.0	0.00	1.00	5*
i28.	Inactivated and mRNA-based vaccines can be safely administered to pregnant women with MS during the second and third trimesters of pregnancy if indicated.	8.31	96.55	0.06	.90	5*
i29.	Pregnant women with MS should not receive live vaccines during pregnancy.	8.66	100.0	0.03	1.00	5*
i30.	It is appropriate for pregnant women with MS to be vaccinated against diphtheria, tetanus, and pertussis *(Tdap)* in the third trimester of pregnancy.	8.41	100.0	0.06	1.00	5*

*High difficulty in reaching consensus (9-8-7); consensus pct. (≥75%), mean (≥7), CQV (≤.15), Felis' Kappa -K (>.40), Comment K (5- almost perfect agreement, 4- substantial agreement, 3- moderate agreement, 2- fair agreement, 1-slight agreement, 0- indicate poor agreement)

DISCUSSION

Although there are some international and regional recommendations or guidelines such as the European or AAN and others on vaccination practices in MS due to national recommendations and/or guidelines in many countries there is no a clear cut global consensus.[15-17] Due to different implementation strategies, different epidemiological characteristics, availability of MS treatments in each country and risks, it is very important for countries to create their consensus statements based on scientific publications. Thus, a global approach to MS and vaccination strategies can be created, where regions are evaluated separately.

In addition to the difficulties of vaccination in MS, such as timing, effectiveness, and safety, the occasional reluctance of individuals with MS to vaccinate may also cause some difficulties in daily practice.[13,14] This situation can be considered a result of individuals with MS having insufficient knowledge about vaccination and the lack of optimal vaccination promotion by MS specialists.

A consensus study on MS and vaccines stated that the most important problem was related to live vaccines and immunosuppressed patients.[15] In all consensus studies, issues such as vaccine effectiveness, safety, immunization strategies, and application in special populations were focused on, and recommendations were sought.[18-20]

Consensus on immunisation in MS was sought in this study, based on questions developed for topics such as the immune system may be affected by vaccines in MS, the interaction between immunomodulatory/immunosuppressant drugs and vaccines, the possible effects of vaccines on the immune system of the individual with MS, and immunisation in special cases. The core team examined all the data and grouped all the questions blindly. After reaching an agreement on the question groups in a final meeting, The propositions were discussed under separate headings in line with the responses given to the propositions regarding immunisation strategies in MS.

Effect of vaccination on MS development/disease course

There are some non-evidence-based concerns that vaccination may reveal MS or trigger an attack. After several case reports indicating an increased risk of central nervous system (CNS) demyelination following Hepatitis B vaccination in adults, all studies showed that hepatitis B vaccine did not increase the risk of developing MS or cause exacerbations.[21,22] In a study conducted with a few cohorts claiming a relationship between the Yellow Fever vaccine (YFV) and the development of demyelinating disease, cases of both CNS and peripheral nervous system involvement were reported.[23] However, later studies did not show a significant relationship between the YFV vaccine and MS development.[24] In additon, no significant relationship also could be established between the Bacillus Calmette-Guerin (BCG) vaccine and MS development or attack risk.[25]

In our study, while it is generally agreed that vaccines do not affect MS development or attacks *(i1,i2,i6)*, no consensus has been reached regarding the relationship between live vaccines and attacks *(i3,i5)* (Table 2). This may be related to the different results of studies on live vaccines and MS.[26,27] The primary cause of the discrepancy between these two articles appears to be a paucity of data regarding live vaccines, compounded by limited experience. This results in MS experts having difficulty making decisions on this issue. In this study, a consensus was reached on a patient-specific basis on whether YFV, one of the live vaccines, should be administered to people travelling to an endemic region *(i4)*.

In the VACCIMUS study, one of the most comprehensive studies on MS and vaccines, the risk between vaccination and attack was evaluated in 643 patients with MS, and no increase in risk was found with influenza, hepatitis B or combined diphtheria-tetanus vaccine.[28] Commonly administered vaccines, such as BCG, influenza, tetanus or hepatitis B vaccines, have not been shown to increase the risk of relapse and/or progression of disability in MS. Inactivated vaccines can be used safely in MS patients who are naive or are receiving DMDs. In a retrospective study. Rabies vaccination and MS relapse risk were evaluated, and no increase in the annual attack risk was observed.[29] Given the fatal progression of rabies infection, strict adherence to the national vaccination program is highly recommended when vaccination is indicated. In the ECTRIMS/EAN consensus held in 2023, a consensus was reached that inactive vaccines do not trigger MS attacks or MS development, in line with our recommendations.[16]

Effect of MS on immunization-general approach

Various immunomodulatory and immunosuppressive effects of different DMTs increase the complexity of vaccination.[30] However, since

Table 2: The effect of vaccines on the development of MS/disease course

ii1	Vaccines are not expected to cause MS disease.
ii2	Inactivated vaccines are not expected to trigger an MS attack.
ii3	Live vaccines are not expected to trigger an MS attack.
ii4	Since the yellow fever vaccine *(live vaccine)* is likely to trigger an MS attack, it should be decided on a patient-by-patient basis whether it should be given to people travelling to the endemic region.
ii5	There is no harm in individuals with MS who are not under treatment to be vaccinated live.
ii6	There is no harm in individuals with MS who are not under treatment to receive an inactivated vaccine.
ii7	Vaccines are not expected to affect the course of MS disease and possible disability.

these changes are not expected in people without any immunomodulatory/immunosuppressant treatment, a consensus has been reached that the vaccine response should be similar to the healthy population *(i8)*. Similarly, the effect of previous treatment on the immune response is thought to wane over time. Therefore, individuals with MS who have not received immunomodulatory or immunosuppressive therapy in the past year are expected to have a similar vaccine response to individuals with MS who have not received treatment or immunosuppressive therapy and to a healthy population of the same age and gender *(i9)*. Previously published vaccine consensus reports did not specify that comparable vaccine responses could be anticipated in a healthy population of similar age and gender. Conducting controlled studies on this issue may yield further evidence to support vaccination recommendations.

Infectious diseases are very important, especially in immune mediated neuroinlammatory-neurodegenerative disease such as MS. In these diseases, infections can affect both the attack and the severity of the disease. Furthermore, certain immunotherapies are known to elevate the risk of infectious complications.[31,32] Infection prevention in individuals with multiple sclerosis is a critical component of treatment and has a substantial impact on disease progression. For these reasons, an individualised approach should be adopted before and during MS treatment. This approach should include patient-specific treatment strategies and cover issues related to infection and vaccination.

The immunogenicity induced by the vaccine can be influenced by several factors, with age being a primary determinant. Many studies show that vaccination effectiveness in the elderly is significantly reduced compared to young adults.[33-35] Immunobiography refers to each individual's comprehensive immunological, clinical, socio-economic and geographical history. This concept describes the wide heterogeneity observed among older individuals, accounting for large individual variations in health conditions and the effectiveness of vaccines. Thus, it has been agreed that irrespective of treatment, aging can influence the immune response elicited by vaccination in individuals with MS *(i10)*. Immune responses are influenced by age, comorbidities, infections, and the use immunosuppressive therapies. The presence of diabetes and other autoimmune diseases as comorbidities may complicate the post-vaccination immune response in individuals with MS. Diabetes may reduce vaccine response by weakening immune function through chronic inflammation and microvascular damage. Other autoimmune diseases may cause the immune system to respond excessively or inadequately, which may negatively affect the effectiveness of vaccines. Additionally, immunomodulatory drugs used to treat these diseases may directly affect the post-vaccination immune response. Such comorbidities may lead to variability and unpredictability in the immune response among individuals with multiple sclerosis. Therefore, when determining vaccination strategies in individuals with MS, comorbidities should be considered, and each patient's immune status should be evaluated individually.[36-38] Considering this information, a consensus has been reached that the presence of comorbidities (diabetes and other autoimmune diseases), regardless of treatment, may affect the immune response that vaccination may create in individuals with MS *(i11)*. This recommendation is significant as it underscores the potential impact of comorbidities on vaccination outcomes and response assessment in the aging multiple sclerosis population. The consensus statement also emphasizes the need for further research into this previously underexplored factor.

The literature presents varying opinions on whether the clinical phenotype of multiple sclerosis influences the immune response triggered by vaccination. According to the first view, the natural history of RRMS and progressive MS is different. While the disease in RRMS patients progresses with periods of attacks and remissions, the disease progresses continuously in progressive MS patients. Relapsing-remitting MS (RRMS) patients may mount a stronger response to vaccines because their immune systems become more active during attack periods. Intensive work of the immune system during these attack periods may trigger a stronger immune response after vaccination. On the other hand, patients with progressive MS have persistent chronic inflammation and immune fatigue. This may cause the immune system to remain constantly underactive, leading to a weaker vaccine response. The ever-advancing disease process in progressive MS can cause the immune response to become slower and weaker. Therefore, differences in the natural history of RRMS and progressive MS may influence how the immune system responds to vaccines.[39]

Alternatively, it is argued that the clinical phenotype of multiple sclerosis may have little impact on the immune response to vaccination, as the response is more closely associated with the individual's overall immune status and medical history. The overall functioning of the immune system is determined more by the immunomodulatory or immunosuppressant treatments rather than the disease phenotype. These treatments, used in patients with both RRMS and progressive MS, may suppress the immune response, weakening the response to the vaccine regardless of phenotype. Therefore, the main factors determining vaccination response are the type of treatment and the individual's general health status, rather than the phenotype of the disease.[40] The lack of consensus in this study on whether the multiple sclerosis clinical phenotype influences the immune response to vaccination, independent of treatment, may stem from the diverse perspectives present in the literature *(i12)*. Although consensus was not achieved, this article is considered valuable for highlighting the need to investigate potential differences in vaccination effects between progressive and relapsing multiple sclerosis groups.

In patients diagnosed with MS and considering immunosuppressive treatment, especially if Hepatitis B, Varicella Zoster, Covid-19, and HPV antibodies are negative, a vaccination program should be applied under national vaccination guidelines. Vaccination strategies in these individuals should be carefully planned to optimise the immune response and reduce the risk of infection. For example, Sormani and Messina noted that Hepatitis B vaccination before immunosuppressive therapy may help protect patients from this infection. Additionally, they concluded that the COVID-19 vaccine is safe and effective in individuals with MS.[41] Therefore, vaccination programs before immunosuppressive treatment in individuals with MS should be planned and implemented in accordance with national guidelines. In some cases, accelerated or strengthened vaccination programs may also be considered depending on the patient's condition. This approach may increase patients' protection against infections and response to treatment. In our study, participants with MS who are newly diagnosed will be planned for immunosuppressive treatment, especially if Hepatitis B, Varicella Zoster, COVID-19, and HPV antibodies are negative; the vaccination program should be applied in accordance with national vaccination guidelines and with one month between vaccines, in line with the literature. A consensus was reached *(i13)*. Previous EAN/ECTRIMS and AAN consensus reports similarly recommended assessing immune status during the initial evaluation of individuals with multiple sclerosis and implementing appropriate planning accordingly. This Delphi consensus has reaffirmed that guidance.[16,42] (Table 3).

Relapse treatment and immunization in MS

The approach to MS treatment includes both controlling attacks and using appropriate DMD. Both live vaccines, inactivated and recombinant vaccines, are not recommended during attack periods.[42] This is because it is thought that vaccine responses may change, and side effects may increase during the attack period. In addition, the widespread use of corticosteroids during attack periods should also be considered. No increased risk has been detected in the use of corticosteroids with inactivated vaccines, and no increased risk is expected in the use of viral vector vaccines that do not replicate with mRNA. However, when there is no need for immediate immunity during high doses of corticosteroids, there may be situations where vaccination can be postponed, and it is more appropriate to vaccinate at the end of treatment and during the remission period. An interval of one month between live vaccines

Table 3: The effect of MS on immunization and general approach

i8	Individuals with MS who have never received immunomodulatory therapy/immunosuppressant therapy are expected to have the same vaccination response as the normal population of similar age and sex.
i9	The vaccination response of individuals with MS who have not received immunosuppressive therapy for the last 1 year is expected to be the same as the normal population of the same age and gender.
i10	Regardless of treatment, ageing may affect the immune response that vaccination may produce in individuals with MS.
i11	The presence of comorbidities *(diabetes and other autoimmune diseases)* independent of treatment may affect the immune response that vaccination may generate in individuals with MS.
i12	Regardless of treatment, the MS clinical phenotype may affect the immune response that vaccination *(relapsing or progressive)* may generate.
i13	In individuals with MS who are newly diagnosed and will be scheduled for immunosuppressive therapy, especially if Hepatitis B, Varicella Zoster, Covid-19 and HPV antibodies are negative, the vaccination program should be applied in accordance with national vaccination guidelines and one month between vaccinations. Depending on the situation, accelerated and strengthened vaccination programs can be implemented.

and the last administration of corticosteroids is recommended to prevent a vaccine-related reaction. In cases where local, short-term (<14 days) and low doses (prednisone equivalent <20 mg/day) corticosteroids are used, there is no need to discontinue corticosteroids even if live vaccines are administered.[43] In our study, a consensus was reached on two items regarding not administering the vaccine before both the clinical findings of the attack period have fully resolved and before one month has passed since the use of IVMP *(i14a, i14b)* (Table 4). Unlike previously reported articles that included recommendations, detailed recommendations were obtained with a strong recommendation level by asking the panelists in detail about the response to steroid treatment and vaccination.[16,42,43]

Relationship between vaccine response and DMD in MS:

What is more accepted than the view that the immune response may change due to the nature of MS is the risk that DMTs used in MS may change the vaccine response. For this reason, the timing of immunisation before starting some DMTs in individuals with MS becomes important. According to the suggestion made to the panellists in this study, It has been accepted by consensus that the timing of the vaccination program in individuals with MS who are under immune treatment should be decided by taking into account the treatment received *(i15)*.

Considering all DMDs, there are more studies on the relationship between injection treatments and immunisation, which are the first treatment options, than other drugs due to long experience. Immunisation studies in individuals with MS treated with interferon-β (IFN-β) have shown significant seroprotection against influenza vaccine.[44,45] Additionally, when IFN-β and teriflunomide treatments were compared regarding immunisation against influenza vaccine. Significant seroprotection was noted in both groups.[46] In studies conducted with Glatiramer acetate (GA), another injection treatment, different strains of influenza and seroprotection rates were evaluated, and it was observed that GA did not

Table 4: Relapse treatment and immunization in MS (i14a-i14b)

i14a	Individuals with MS who have received corticosteroid *(IVMP)* treatment for an attack or any other reason should not receive any vaccine until 1 month after the last dose.
i14b	Whether or not a person with MS has received corticosteroid (IVMP) therapy, no vaccine should be given until 1 month has passed after significant improvement in attack symptoms or stabilisation of the clinical picture.

cause any significant change in the vaccine response and seroprotection rates were similar to the healthy group.[44,47]

Dimethyl fumarate (DMF) and vaccine response have been studied more extensively. A diphtheria-tetanus vaccine to test the T-cell-dependent memory response, a pneumococcal vaccine to test the humoral response, and a meningococcal vaccine to test a neoantigen-specific T-cell response have been evaluated. Adequate seroprotection rates have been obtained against all vaccines, and it has been shown that the lymphocyte count does not affect vaccine response.[48] Our Delphi consensus on first-line DMTs and vaccination, regardless of timing, was reached in line with the literature *(i16,i17,i18,i19)* (Table 5). However, DMF is slightly more likely to cause lymphopenia than other first-line DMTs, but this does not require any additional precautions or applications in terms of both side effects and vaccine response data. In this Delphi consensus, MS experts agreed that the vaccination response was sufficient in individuals with MS using DMF unless there is severe lymphopenia *(i20)*. In the EAN/ECTRIMS consensus published in 2023, a lymphocyte count of grade 2/3 was stated as a risk in DMF, and in the consensus we reached, it was reported that severe lymphopenia could pose a risk.[16]

For the risk of VZV and HSV reactivation/infection, cryptococcal meningitis, and other opportunistic fungal or bacterial CNS infections,

Table 5: Relationship between vaccine response and DMD in MS (i15-i27)

ii15	The timing of vaccination and vaccination program in individuals with MS under immune therapy should be decided by considering the treatment received.
ii16	Vaccination can be done at any time in individuals with MS who are on interferon beta therapy.
ii17	Individuals with MS who are on interferon beta therapy are expected to have the same vaccination response as the normal population.
ii18	Individuals with MS under glatiramer acetate and teriflunomide 1st-line treatment can be vaccinated at any time without discontinuing treatment with some vaccines, even if a partial decrease in vaccination response is expected.
ii19	Individuals with MS treated with dimethyl fumarate are expected to have a complete vaccination response.
ii20	Individuals with MS who are treated with dimethyl fumarate are expected to have an adequate vaccination response unless there is significant lymphopenia.
ii21	Live vaccines should not be given to individuals with MS who are receiving immunosuppressive therapy.
ii22	Individuals with MS receiving immunosuppressive therapy are expected to have a lower response to vaccination compared to the treatment used.
ii23	Although vaccines in individuals with MS who are under fingolimod treatment are expected to reduce the vaccine antibody response, vaccination should be done before treatment is discontinued.
ii24	Vaccination should be done without discontinuing treatment, although vaccinations in individuals with MS who are on natalizumab treatment may lead to a limited decrease in the vaccine antibody response.
ii25	It is appropriate to complete vaccination before starting treatment in individuals with MS who are planning to use ocrelizumab and other B-cell suppressive therapies and one of the therapies with potent immunosuppressive effects, such as alemtuzumab and cladribine.
ii26	If vaccination is required in individuals with MS receiving ocrelizumab and other B-cell suppressive therapy, this vaccine should be administered no earlier than 3 months after the last treatment, preferably before the next administration. The MS treatment in question should be scheduled to be administered 1 month after the last dose of vaccination.
ii27	In individuals with MS who receive ocrelizumab and other B-cell suppressive therapies and treatments with potent immunosuppressive effects such as alemtuzumab and cladribine, mRNA or inactivated vaccines can be administered in special cases where vaccination will be required *(temporary availability of the vaccine, etc.)*.

similar or slightly higher incidence rates have been reported in MS patients treated with sphingosine 1 phosphate receptor (S1PR) modulators compared to placebo.[49] These data have led to the recommendation to check for VZV antibodies and, if necessary, to vaccinate before starting treatment with S1PR modulators. A study reported that sufficient seroprotection with influenza and tetanus vaccination occurs in most individuals with MS treated with fingolimod. Still, response rates are reduced compared to the placebo group.[50] Another study observed a significant increase in influenza-specific IgG avidity in individuals with MS treated with IFN-β and healthy controls. In contrast, a similar response was not observed in MS patients treated with fingolimod. In another study, the rate of responders to influenza and tetanus reminder doses in individuals with MS treated with fingolimod was significantly reduced compared to placebo.[51,52] In conclusion, there was no relationship between antibody levels and clinical results in individuals with MS treated with fingolimod. In general, when all the data are evaluated together; A qualitative and quantitative decrease in vaccine response may be observed in patients treated with fingolimod, and it should be kept in mind that antibody levels may be low when inactive vaccination is performed under fingolimod treatment.

Studies evaluating the immunogenicity of influenza vaccines in individuals with MS treated with natalizumab Have shown an attenuated humoral response to influenza vaccination.[41,42] Contrary to previous results, another study observed normal vaccine responses in the natalizumab-treated group.[53] Normal seroprotection rates were observed in another study conducted with the tetanus vaccine.[54] In this Delphi consensus, it was accepted that fingolimod and natalizumab may reduce the vaccine response, and a consensus was reached on the necessity of vaccination when necessary *(i23, i24)*. Fingolimod and natalizumab are two frequently used agents with moderate immunosuppressive effects. Literature knowledge reflected in clinical practice regarding immunisation under these treatments is considered very important. Another suggestion made with this consensus is that the vaccination response is expected to decrease depending on the treatment used in individuals with MS who receive immunosuppressive treatment. DMTs have immunosuppressive effects; S1PR modulators are anti-CD20s and anti-CD52s. While immunisation with a live vaccine is contraindicated with these treatments, the response to immunization with other vaccines varies depending on the treatment and timing. This consensus statement reached consensus on both propositions regarding this issue *(i21, i22)* (Table 5).

The ideal approach to immunisation in MS is to complete the vaccination schedule as much as possible before treatments. A consensus has been reached among MS experts on the proposition made in this direction *(i25)*. However, this may not always be possible in a highly dynamic disease such as MS. There is no timing relationship between first-line DMTs and vaccination. However, the same does not apply to immunosuppressive treatments. The VELOCE study evaluated the effects of ocrelizumab on the immune response to various vaccines in individuals with MS, confirmed that patients treated with ocrelizumab were able to develop humoral responses, albeit attenuated, against inactivated vaccines (tetanus, pneumococcal, and influenza vaccine).[55] However, it should be remembered that many patients (37–53%) still developed a humoral response under ocrelizumab treatment, and the T cell response appeared unaffected under B cell depletion.[55] Data on alemtuzumab treatment and vaccine immunisation are very limited. A study involving 24 patients using alemtuzumab and evaluating diphtheria, tetanus, polio, Haemophilus influenzae type b, meningococcal group C conjugate vaccine and pneumococcal vaccine responses. The patient group was exposed to alemtuzumab before vaccination (5 patients within the first 6 months after treatment). Significant seroprotection rates against tetanus, diphtheria, polio, Haemophilus influenzae type b and meningococcal group C were observed in all patients. Significant antibody levels were also observed when pneumococcal vaccination was administered after alemtuzumab, albeit with a reduced response. Although immune responses to commonly used vaccines were preserved after alemtuzumab, the proportion of responders to vaccination within 6 months after treatment was smaller.[56] However, a small, retrospective study of patients treated with cladribine tablets in the MAGNIFY-MS study reported that antibodies to seasonal influenza and VZV vaccines remained sufficient to provide protective immunity.[57] A substudy of CLOCK-MS evaluated the potential effect of prior treatment with cladribine tablets on the development of antibody titers to the influenza vaccine, and preliminary results showed significantly increased influenza titers.[58] Consistent with the data of this study, where significant seroprotection was

shown to be independent of lymphocyte count, the MAGNIFY-MS *study* also showed that patients using cladribine were able to mount and maintain effective humoral responses to influenza and varicella vaccines, regardless of the timing or total lymphocyte count after treatment administration.

Most information about the timing of vaccination after B cell-reducing treatments has been obtained during the COVID-19 period. In a study, it was understood that the most appropriate interval for vaccination time was between 90–180 days after treatment.[59] This consensus statement agreed that vaccination should be administered at the earliest 3 months after the last treatment application, preferably before the next application *(i26)*.

When the panellists were asked about the suggestion that mRNA or inactive vaccines can be administered in special cases where vaccination is required in individuals with MS receiving treatments with potent immunosuppressive effects such as ocrelizumab and other B-cell suppressive treatments and alemtuzumab and cladribine, a consensus was reached that vaccination should be done regardless of the measurable vaccine response *(i27)*. This situation was evaluated considering the accumulated data on hepatitis B and COVID-19 vaccines. Although it is quite reasonable to target the ideal immune system for ideal immunisation, the fact that this patient population is small cannot be denied in studies examining vaccination timing. It has been shown clinically and laboratoryly that the measurable B response changes and T cell responses are important in immunization.[60] For this reason, in cases where vaccination is necessary, such as a pandemic, it seems practical to administer non-live vaccines, regardless of timing.

Pregnancy and vaccination in MS

For MS, which is more common in women during the reproductive period, the pregnancy period constitutes a special period in terms of disease activity and treatment management, as well as infection risk and risk management. All inactive vaccines, which should be administered routinely during pregnancy, are considered safe for pregnant women with MS. Maternal influenza vaccination has been shown to reduce the risk of influenza and its complications among pregnant women and their infants younger than 6 months.[61] Additionally, pertussis, a respiratory infection caused by Bordetella pertussis, remains a significant cause of infant morbidity and mortality. Pertussis vaccination during pregnancy can protect infants through passive and active transfer of maternal antibodies until they receive their primary vaccination series.[62] The whooping cough vaccine is inactive and can be used between 20-36 weeks of pregnancy. It should be done during pregnancy weeks. In this Delphi consensus study, a high level of consensus was reached that there is no harm in administering inactivated vaccines to pregnant women and especially the Tdap vaccine should be administered *(i28, i30)* (Table 6). As a result, inactivated vaccines are generally considered safe during pregnancy and can be given during the second and third trimesters of pregnancy. Even in healthy individuals, live attenuated vaccines are contraindicated during pregnancy due to the risk of perinatal infection. This consensus study reached a consensus, with a high agreement that live vaccines should not be administered to pregnant women *(i29)*. However, when necessary, it is recommended that immunisation with live attenuated vaccine (except yellow fever vaccine) be completed after birth and 4-6 weeks before starting immunosuppressive DMT.[61]

Consequently, within the scope of this research, we aimed to elucidate a Delphi consensus on vaccination in MS patients. This step is crucial due to the absence of certain guidelines for vaccination in the MS treatment process and the potential challenges that may arise. Our findings could significantly impact the vaccination strategies for individuals with MS, underscoring the importance of this research in terms of its potential impact. We wanted to share a "country" practice and our current recommendations on vaccination strategies, by making use of articles containing country-based recommendations and working-group recommendations, as well as our national experiences.

Table 6: Pregnancy and immunization (i28-i30)

i28	Inactivated and mRNA-based vaccines can be safely given to pregnant women with MS during the second and third trimesters of pregnancy if indicated.
i29	Pregnant women with MS should not receive live vaccines during pregnancy.
i30	It is appropriate for women with MS *(every)* pregnant woman with MS to be vaccinated against diphtheria, tetanus, and pertussis *(Tdap)* in the third trimester of pregnancy.

DISCLOSURE

Data availability: The data supporting this study's findings are available on request from the corresponding author.

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