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Review article

Immunization and multiple sclerosis: Recommendations from the French multiple sclerosis society☆

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ABSTRACT

Objectives: To establish recommendations on immunization for patients with multiple sclerosis (MS)
Background: Vaccines have been suspected in the past to trigger MS and relapses. With the extension of the immunoactive treatment arsenal, other concerns have been raised more recently about an increased risk of infection or a decreased effectiveness of immunization in immunosuppressed patients.
Methods: The French Group for Recommendations into Multiple Sclerosis (France4MS) performed a systematic search of papers in Medline and other university databases (January 1975-June 2018). The RAND/UCLA appropriateness method was chosen to review the scientific literature and to formalize the degree of agreement among experts on 5 clinical questions related to immunization and MS. Readers from the steering committee conducted a systematic analysis, wrote a critical synthesis and prepared a list of proposals that were evaluated by a rating group of 28 MS experts. The final version of the recommendations was finally reviewed by a reading group of 110 health care professionals and classified as appropriate, inappropriate or uncertain.
Results: Neurologists should verify the vaccination status as soon as MS is diagnosed and before disease-modifying treatments (DMTs) are introduced. The French vaccination schedule applies to MS patients and seasonal influenza vaccination is recommended. In the case of treatment-induced immunosuppression, MS patients should be informed about the risk of infection and the vaccination standards of the French High Council of Health should be applied. Live attenuated vaccines are contra-indicated in patients recently treated with immunosuppressive drugs, including corticosteroids; other vaccines can be proposed whatever the treatment, but their effectiveness may be partly reduced with some drugs.
Conclusion: Physicians and patients should be aware of the updated recommendations for immunizations of patients with MS.

Introduction

Multiple sclerosis (MS) is an auto-immune disease in which all players in the inflammatory repertory react against myelin antigens. Autoreactive T cells, monocytes, and the more recently demonstrated B cells contribute to the pathophysiology. The suggestion that vaccines might be a generator of MS or a triggering factor of relapse has given rise to passionate debate. In France, the controversy over the link between vaccination against hepatitis B (HBV) and the occurrence of MS was particularly strong in the 1990s. Several formal consensus agreements and expert auditions were organized by the French health authorities between 2001 and 2011, leading to the conclusion of the absence of evidence of a causal association between HBV vaccine and MS or central nervous system (CNS) demyelinating events (Conférence de consensus 2001 sur la sclérose en plaques, 2018; Conférence de consensus 2003 sur la vaccination contre l'hépatite B, 2018; Audition

List of investigators in the Appendix.

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publique 'Vaccination contre le virus de l'hépatite B et sclérose en plaques: état des lieux', 2018; Bilan de pharmacovigilance et profil de sécurité d'emploi des vaccins contre l'hépatite B, 2018). In parallel, experts pointed out an 'ambivalence' perceived by the general public in the legal analysis of post-vaccination events: on one hand, a clearly identified framework for compulsory vaccination of health professionals allowed recognition of a presumption of accountability, that can lead to compensation; on the other hand, in all other cases, the absence of scientific evidence in favor of a causal relation results in an impossibility of satisfying a claim for compensation. The confusion and uncertainty around this debate have reached the general public as well as many health professionals and is an obstacle to vaccinating subjects who should be vaccinated.

In 2017, the French Multiple Sclerosis Society (Société Francophone de la Sclérose en Plaques, SFSEP) decided to initiate a task force to establish recommendations on immunization of MS patients, considering that:

- Reluctance to vaccinate persists, both for patients and health professionals, decreasing vaccination coverage in the general population, but especially in the family members of patients suffering from MS.
- The therapeutic arsenal for MS has been considerably enriched and many new DMTs are now available. In this context, questions arose on the effectiveness of vaccines in patients exposed to these new drugs, as well as on the most adapted application of the vaccination schedule and on the prevention of potential infectious risks induced by these treatments (Waubant et al., 2018).
- Important data on vaccination have been acquired in the last decade from patients with other auto-immune disorders, allowing extrapolation to MS.
- Data from the literature have also been enriched, which in itself justifies an update.

The objective of this work was to provide evidence-based and up-to-date recommendations on whether, how and when vaccines should be proposed to MS patients.

Methods

The methodology of studies into the relationship between vaccines and specific disease risk rarely provides a high level of evidence. Randomized trials are only feasible in practice to answer questions such as the risk of triggering a relapse after vaccination or the evaluation of the biological efficacy of a vaccine while on DMT. In contrast, evaluation of the risk of MS after vaccination would require a prospective follow-up of cohorts of dozens or even hundreds of thousands of exposed and unexposed individuals, because of a weak to moderate association, for a low prevalence disease (1 per 1000). There are numerous other methodological limitations in the current literature, including heterogeneous case definition, questionable quality of data collection and validation and variable exposure intervals.

The abundance of scientific literature containing methodological limitations that do not allow a conclusion to be reached justifies the methodological choice to formulate recommendations by formalized consensus (RAND) according to the recommendations of the French High Authority of Health (Haute Autorité de Santé, HAS) (Development of Good Practice Guidelines, 2018).

The "Formal consensus" method is both a method for development of good practice guidelines and a consensus method, derived from the RAND/UCLA Appropriateness method (Rand Corporation, 2001). Its main objective is to formalize the degree of agreement among experts by identifying and selecting, through iterative ratings with feedback, the points on which experts agree and on which the recommendations are secondarily based, and the points on which experts disagree or are undecided, to provide professionals and patients with assistance in deciding on the most appropriate care in given clinical circumstances.

The Steering Committee defined 5 clinical questions within the scope of the recommendations:

1 Are vaccines associated with an increased risk of MS?
2 Are vaccines associated with an increased risk of relapse in MS or a worsening of disability?
3 Are vaccines as effective in people with MS as in the general population (regardless of treatment)?
4 Are vaccines as effective in people with MS exposed to disease-modifying treatments?
5 What methods of prevention should be offered to patients with MS?

The literature search for publications in English and French was performed with the help of professional librarians, using the Medline database (http://www.ncbi.nlm.nih.gov/pubmed), the main websites referencing publications on recommendations and consensus conferences, and grey literature. An initial search was made with the following keywords: multiple sclerosis, central nervous system demyelination, clinically isolated syndrome, optic neuritis, vaccination, vaccine, relapse, infection, immunomodulators, immunosuppressants, interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, cyclophosphamide, methotrexate, cladribine, ocrelizumab, rituximab, alemtuzumab, campath, azathioprine, mycophenolate. A subsequent search was done by analyzing the references of each selected paper.

Readers from the steering committee then conducted a systematic analysis of the literature using reading grids and wrote a critical and hierarchical synthesis of the literature, including a referenced text and summary tables with mention of the levels of evidence of the studies. Members of the steering committee met to discuss the evidence reported and to prepare the list of proposals to be submitted to the rating group. Proposals were classified into levels A, B or C according to the HAS guidelines (Table 1). In the absence of sufficient data, the proposed recommendations corresponded to an expert agreement only. In the absence of expert agreement, the alternatives were exposed without any recommendations in favor of one or the other.

Thereafter, proposals were submitted to a rating group that did not participate in the initial drafting. Each rater had to decide on his/her level of agreement with each proposal, giving a score between 1 (total disagreement) and 9 (totally agree). All members of the steering

Table 1
Level of scientific evidence and grading of the recommendations.

Grading of recommendations	Level of scientific evidence provided by the literature
A **Established scientific evidence**	Level 1 - High-power randomized comparative studies - Meta-analysis of randomized comparative studies - Decision analysis based on well-conducted studies
B **Scientific presumption**	Level 2 - Low-power randomized comparative studies - Well-conducted non-randomized comparative studies - Cohort studies
C **Low level of evidence**	Level 3 - Case-control studies Level 4 - Comparative studies with a major bias - Retrospective studies - Case series

https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-03/good_practice_guidelines_fc_method.pdf.

Table 2
Conditions for expert agreement and judgment, according to the median value and the distribution of the ratings.

Proposal judged	Degree of agreement of the group	Conditions for obtaining Median value	Distribution of ratings in the interval
Appropriate	Strong agreement	≥7	[7–9]
	Relative agreement	≥7	[5–9]
Inappropriate	Strong agreement	≤3	[1–3]
	Relative agreement	≤3.5	[1.5]
Uncertain	Undecided	4 ≤ median ≤6.5	[1–9]
	Lack of consensus	All other situations	

Adapted from reference #6 Development of Good Practice Guidelines. "Formal Consensus" Method. December 2010, updated March 2015. https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-03/good_practice_guidelines_fc_method.pdf, (accessed 28.12.2018.).

committee and rating group collaborated in the drafting of the final recommendations during a face-to-face meeting.

A reading group made of neurologists and other health care professionals was asked to review the final version of the recommendations, giving a score between 1 (total disagreement) and 9 (total agreement) and making comments. Proposals were then classified as appropriate (median value ≥7), inappropriate (median value ≤3.5) or uncertain (median value 4–6.5), with a different degree of agreement (Table 2).

After analysis and discussion of ratings and comments made by the reading group, initial recommendations were modified according to the following rules:

- Recommendations based on a high level of evidence (level A or B): consideration of relevant comments to improve the form, changes to the content, if any, based on data provided, changing the level of the recommendation if necessary;
- Recommendations based on a low level of evidence (level C) or on agreement within the rating group: when the reading group confirmed the appropriate nature of the recommendation (≥90% of responses from the reading group within the range [5–9]), the recommendation was retained and relevant comments were considered to improve the form, when the reading group was more widely undecided or disagrees with the initial recommendation (<90% of responses from the reading group within the range [5–9]), the steering group, after debate with the rating group, proposed possible modifications based on comments or the rejection of the recommendation.

Results

An extensive French version of the summary of evidence, including tables with mention of the levels of evidence of the studies, is available on the website of the SFSEP (www.sfsep.org) or upon request to the authors. A summary of the recommendations is presented in Table 3. Detailed results of the final ratings are provided in Table 4.

Question 1: Are vaccines associated with an increased risk of MS?

Recommendation 1. Vaccines, in general, are not associated with an increased risk of MS or occurrence of a first demyelinating episode of the central nervous system, including hepatitis B and human papillomavirus vaccines (level B).

Rating: **Appropriate** (number of available scores: 71; 100% [5–9]); **Relative agreement** (median 8, min–max 5–9, 30th–70th percentile: 8–9)

The question of vaccinations as a risk factor for the occurrence of MS was first studied in a general way and then vaccine-by-vaccine. Available studies generally evaluate the association between one or more vaccination and the risk of a first episode of demyelination in the CNS rather than MS. This definition of cases may cover first episodes of MS, not fulfilling, at the time of the study, the diagnostic criteria for MS, but also other clinical situations that may not evolve later into MS (idiopathic inflammatory optic neuritis, disseminated acute encephalomyelitis).

All vaccines

Two class 3 studies found an odds ratio (OR) of 1.4 [95% confidence interval (CI) 0.5–4.3], respectively for any vaccination in the last 60 days (2.1 [0.7–6.0] between 61 and 180 days) and 1.03 [0.86–1.22] for any vaccination in the last 3 years. [8–9]

No study provided evidence for an increased risk of MS after any vaccination.

Hepatitis B (HBV)

Twelve studies, all class 3, published between 1999 and 2014, studied the risk of developing MS after HBV vaccination; two cohorts, and ten case-control studies, some nested within pre-existing cohorts. Four studies were conducted in France (Rand Corporation 2001; Langer-Gould et al., 2014; Touzé et al., 2002; Mikaeloff et al., 2007), four in the USA (Touzé et al., 2000; Mikaeloff et al., 2009; Zipp et al., 1999; Ascherio et al., 2001), two in Canada (DeStefano et al., 2003; Sadovnick and Scheifele, 2000), one in Iran (Ramagopalan et al., 2009) and one in the United Kingdom (Eftekharian et al., 2014). Three studies (Touzé et al., 2002; Mikaeloff et al., 2007; DeStefano et al., 2003) (two in France and one in Canada) focused specifically on the risk in children and adolescents.

One study only found a significant association between HBV vaccination and the occurrence of MS within 3 years, among 163 cases and 1604 matched controls, with an OR of 3.1 [1.5–6.3] (Eftekharian et al., 2014). However, strong methodological limitations questioned this result, in the context of a large number of other studies with negative results that appeared to be more robust. Therefore, it can be concluded that there is currently no evidence for an association between vaccination against HBV and the occurrence of MS, regardless of the time interval studied. This result is reinforced by a meta-analysis published in 2018, that confirmed the absence of an association between HBV vaccination and the occurrence of MS (OR = 1.19 [0.93–1.52]) or the first episode of CNS demyelination (OR = 1.25 [0.97–1.62]) (Hernán et al., 2004).

Human papilloma virus (HPV)

There are seven reported studies, all class 2 to 3, 3 cohorts (Mouchet et al., 2018; Chao et al., 2012; Madrid-Scheller et al., 2015), 3 case-control studies (Touzé et al., 2000; Willame et al., 2016; Grimaldi-Bensouda et al., 2014) and 1 pooled analysis of clinical trials (Grimaldi-Bensouda et al., 2017), studying the association between vaccination against HPV and the occurrence of MS or the first episode of CNS demyelination.

Overall, these studies did not find any association, and two French studies even reported significant protection.

Influenza

Four case-control studies (class 3) assessed the association between seasonal influenza vaccination and the occurrence of MS or a first CNS demyelinating episode (Ascherio et al., 2001; Sadovnick and Scheifele, 2000; Eftekharian et al., 2014; Angelo et al., 2014). Data on seasonal influenza vaccination were secondary analyses in all cases; the studies were designed to evaluate the risk associated with all vaccines or HBV only.

None of these studies provided evidence for an association.

Two additional studies focused specifically on H1N1 vaccination during the 2009–2010 pandemic and did not find any association (Zorzon et al., 2003; Lee et al., 2011).

There is no argument for an increased risk of developing MS after

Table 3
Summary of the recommendations of the French Multiple Sclerosis Society (SFSEP) on immunization and multiple sclerosis (MS).

Question 1: Are vaccines associated with an increased risk of MS?	
1. Vaccines, in general, are not associated with an increased risk of MS or occurrence of a first demyelinating episode of the central nervous system, including hepatitis B and human papillomavirus vaccines.	Level B
Question 2: Are vaccines associated with an increased risk of relapse or worsening of disability in MS?	
2a. Vaccines, in general, are not associated with an increased risk of relapse in patients with MS. An increased risk of relapse after vaccination against yellow fever cannot be excluded.	Level B Level C
2b. Influenza and BCG vaccines have no impact on the short-term accumulation of disability. Impact of other vaccines on disability has not been studied yet.	Level C
Question 3: Are vaccines as effective in people with MS as in the general population (regardless of treatment)?	
3. Available data on the efficacy of inactivated vaccines, in patients with MS and without disease-modifying treatment suggest that it is similar to the general population, particularly for mono-and trivalent influenza vaccines. No studies are available for live attenuated vaccines.	Level C
Question 4: Are vaccines as effective in people with MS exposed to disease-modifying treatments?	
4a. Interferon bêta The vaccine response to influenza of patients treated with interferon beta is not decreased compared to healthy controls and untreated MS. The vaccine response to Meningococcus, Pneumococcus, and Diphtheria-Tetanus, in patients treated with interferon beta, is not decreased compared to healthy controls and untreated MS. The other vaccines were not studied.	Level B Level C
4b. Glatiramer acetate The vaccine response to influenza in patients with MS treated with glatiramer acetate may be reduced compared to healthy controls and untreated MS. The other vaccines were not studied.	Level C
4c. Dimethylfumarate The vaccine response to Meningococcus, Pneumococcus and diphtheria-tetanus vaccines in patients with MS treated with dimethylfumarate appears to be comparable to that of MS treated with interferon beta. Due to the risk of lymphopenia it is advised to apply immunization recommendations for immunocompromised patients.	Level C Expert recommendation
4d Teriflunomide The vaccine response to influenza in patients treated with teriflunomide is decreased compared to MS treated with interferon beta. The other vaccines were not studied. It is advised to apply immunization recommendations for immunocompromised patients.	Level B Expert recommendation
4e. Mitoxantrone The vaccine response to influenza in patients treated with mitoxantrone is insufficient compared to healthy controls. The other vaccines were not studied. It is advised to apply immunization recommendations for immunocompromised patients.	Level C Expert recommendation
4f. Natalizumab The vaccine response in patients treated with natalizumab is reduced for influenza, but not for tetanus, compared to healthy controls. The other vaccines were not studied. It is advised to apply immunization recommendations for immunocompromised patients.	Level B Expert recommendation
4g**. Fingolimod** The vaccine response in patients treated with fingolimod is reduced compared to healthy controls, untreated MS and interferon beta-treated patients. It is advised to apply immunization recommendations for immunocompromised patients.	Level B Expert recommendation
4h**. Alemtuzumab** The data are insufficient to evaluate the vaccine response in patients treated with alemtuzumab. It is advised to apply immunization recommendations for immunocompromised patients.	Expert recommendation
4i. Ocrelizumab The vaccine response in patients treated with ocrelizumab is effective but decreased after 12 weeks for tetanus, Pneumococcus and influenza compared with non-treated and interferon beta-treated MS. It is advised to apply immunization recommendations for immunocompromised patients.	Level B Expert recommendation
4j. Cladribine	Expert recommendation

(*continued on next page*)

Table 3 (*continued*)

No vaccine has been studied in patients with MS treated with cladribine. It is advised to apply immunization recommendations for immunocompromised patients.	
4k. Cyclophosphamide (off-label) No vaccine has been studied in patients with MS treated with cyclophosphamide. It is advised to apply immunization recommendations for immunocompromised patients.	Expert recommendation
4l Methotrexate (off-label) No vaccine has been studied in patients with MS treated with methotrexate. The vaccine response in patients with rheumatoid arthritis treated with methotrexate is satisfactory. It is advised to apply immunization recommendations for immunocompromised patients.	Expert recommendation
4m**. Azathioprine/mycophenolate mofetil (off-label)** No vaccine has been studied in patients with MS treated with azathioprine or mycophenolate mofetil. It is advised to apply immunization recommendations for immunocompromised patients.	Expert recommendation
4n. Rituximab and other anti-CD20 (off-label) No vaccine has been studied in patients with MS treated with rituximab and other anti-CD20 (except ocrelizumab). It is advised to apply immunization recommendations for immunocompromised patients.	Expert recommendation
Question 5: What prevention methods should be offered to patients with MS?	
5a. The vaccination schedule of the general population should be applied to any patient with MS unless there is a specific contraindication.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique
5b. It is recommended to update the vaccination schedule as soon as possible after the diagnosis of MS and before any disease-modifying treatment is introduced.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique
5c. Seasonal flu vaccination is recommended for patients with MS who are treated with immunosuppressive drugs or with a significant disability (or any other reason recommended for influenza vaccination) unless there is a specific contraindication. For the other MS patients, seasonal flu vaccination can be proposed annually.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique Expert recommendation
5d. There is no restriction for vaccines associated with immunomodulators (interferon beta and glatiramer acetate).	Level B
5e. During treatment with immunosuppressants and in any other case of immunosuppression, live attenuated vaccines are contraindicated. Recommended vaccines are those of the vaccination schedule for the general population and vaccines specifically recommended in immunocompromised patients (influenza and Pneumococcus in particular). It is not recommended to vaccinate during relapse requiring high dose steroid therapy (expert recommendation).	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique Expert recommendation
5f. It is recommended to provide the immediate entourage of an immunocompromised person with the vaccination schedule, seasonal influenza vaccination and varicella vaccination in case of negative serology.	Recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique

vaccination with the H1N1 strain of the influenza virus.

Measles-Mumps-Rubella (MMR)

Several studies (all class 3) evaluated measles, mumps and rubella vaccines, alone or in combination, together with other risk factors and/or other vaccines (Ascherio et al., 2001; Sadovnick and Scheifele, 2000; Angelo et al., 2014; Bardage et al., 2011; Bansil et al., 1997; Pekmezovic et al., 2004).

Only the study by Zorzon et al. (Angelo et al., 2014) found a significant association, especially for measles vaccination anytime in the past, with a very unusually high crude OR of 50.4 [6.8–373.3] and adjusted OR 92.2 [12.1–700.2]. The crude ORs were also very high for all the other vaccines studied (51.4 [6.9–381.2] for mumps, 6.2 [2.3–15.3] for rubella), but the adjusted OR, not provided in the publication, were not significant for these two vaccines. These unusual and discordant results compared to those of the other available studies suggest potential methodological bias. In particular, the percentages of exposure to vaccines were much higher in cases than in controls, suggesting reporting bias with over-reporting in cases and under-reporting in controls, especially since the vaccination was not verified, neither for presence nor for absence of vaccines.

In conclusion, an increased risk of MS after vaccination against combined MMR or against each of the 3 viruses seems unlikely.

Diphtheria-tetanus-pertussis-poliomyelitis

No study has specifically evaluated the association between these vaccinations, used alone or in combination, and the occurrence of MS or a first CNS demyelinating episode.

Six case-control studies (class 3) are available (Ascherio et al., 2001; Eftekharian et al., 2014; Angelo et al., 2014; Bardage et al., 2011; Bansil et al., 1997; Ahlgren et al., 2009).

There are no arguments to support the hypothesis of an increased risk associated with any of the vaccinations against diphtheria, tetanus, pertussis or poliomyelitis.

Other vaccinations

There is insufficient data in the literature to conclude on the potential risks related to other vaccines; studies are either lacking or insufficiently powered. However, there is no signal described for vaccines against meningococcus, pneumococcus, varicella/zoster virus, yellow fever, typhoid, and BCG.

Question 2: Are vaccines associated with an increased risk of relapse in MS or of worsening of disability?

Recommendation 2a. Vaccines, in general are not associated

Table 4
Detailed results of the rating for each proposal, according to the RAND/UCLA methodology.

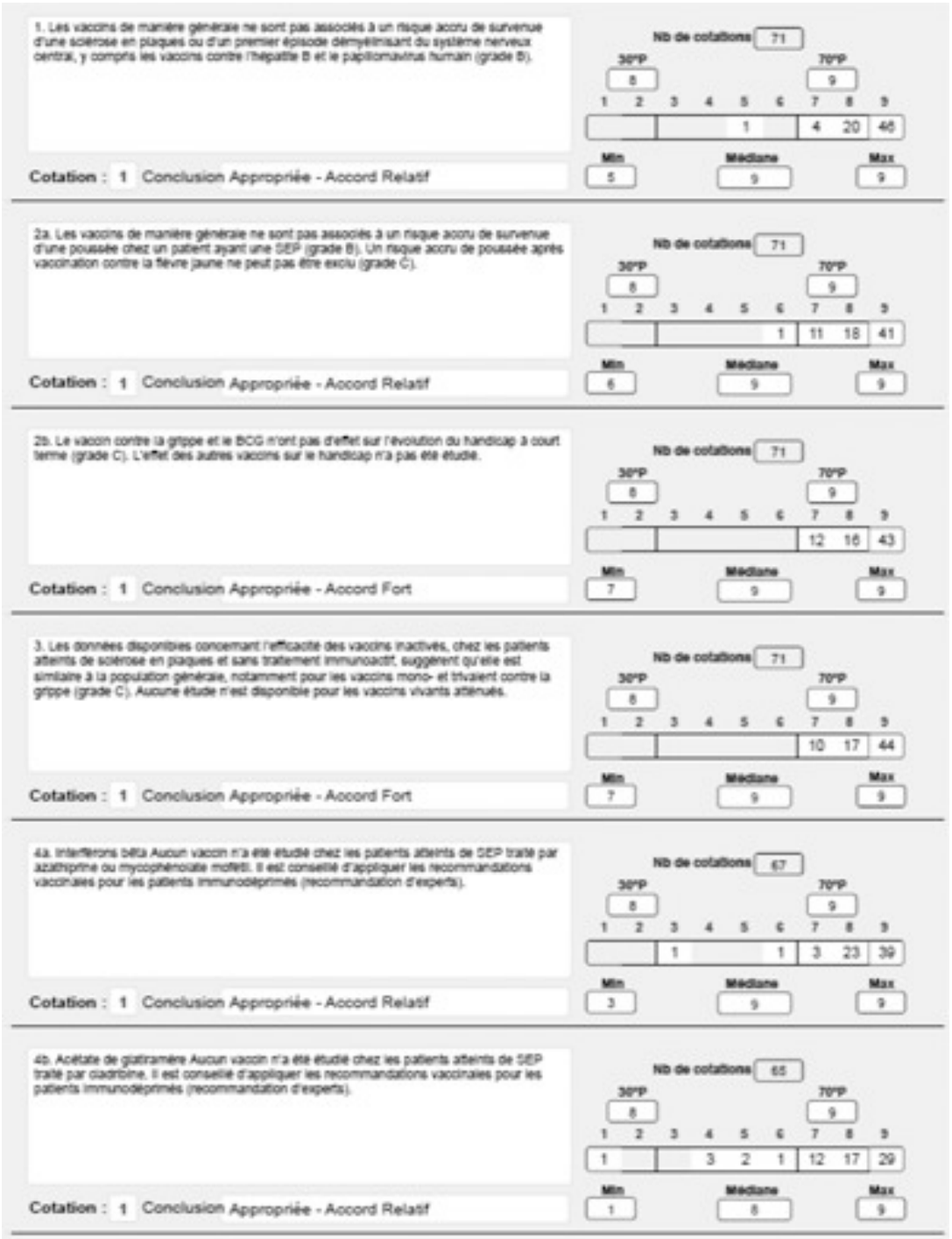

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Table 4 (*continued*)

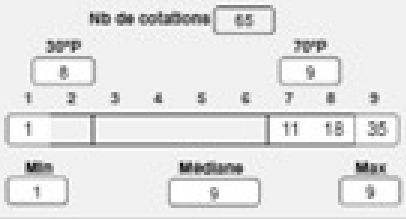
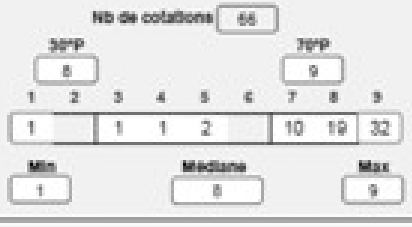
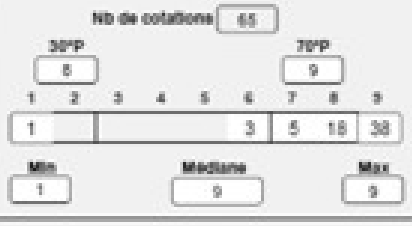
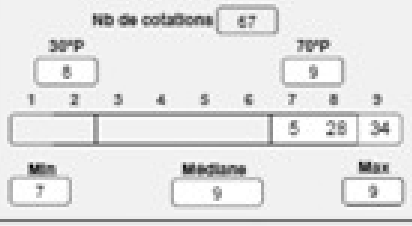
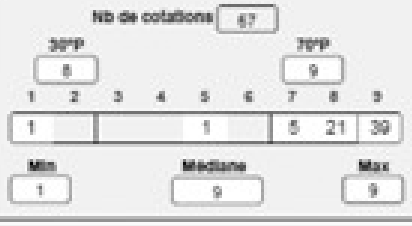
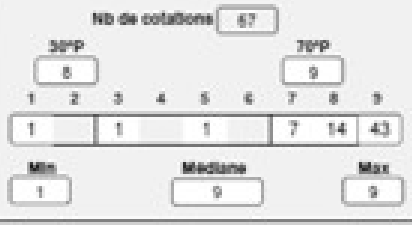
4c. Diméthylfumarate Aucun vaccin n'a été étudié chez les patients atteints de SEP traité par cyclophosphamide. Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4d. Tériflunomide Aucun vaccin n'a été étudié chez les patients atteints de SEP traité par methotrexate. La réponse vaccinale des patients ayant une polyarthrite rhumatoïde traités par méthotrexate est satisfaisante. Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4e. Mitoxantrone La réponse vaccinale contre la grippe des patients traités par acétate de glatiramère est diminuée en comparaison aux sujets sains et aux SEP non traitées (grade B). Les autres vaccins n'ont pas été étudiés. **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4f. Natalizumab La réponse vaccinale contre la grippe des patients traités par interferon bêta n'est pas diminuée en comparaison aux sujets sains et aux SEP non traitées (grade B). Les autres vaccins n'ont pas été étudiés. **Cotation :** 1 Conclusion Appropriée - Accord Fort	
4g. Fingolimod La réponse vaccinale contre la grippe des patients traités par mitoxantrone est insuffisante en comparaison aux contrôles sains (grade C). Les autres vaccins n'ont pas été étudiés. Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4h. Alemtuzumab La réponse vaccinale contre la grippe des patients traités par tériflunomide est diminuée en comparaison aux SEP traitées par interferon bêta (grade B). Les autres vaccins n'ont pas été étudiés. Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	

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Table 4 (*continued*)

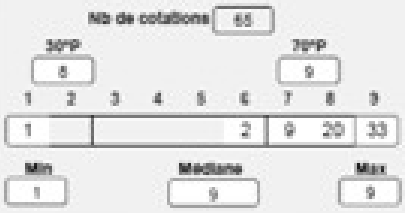
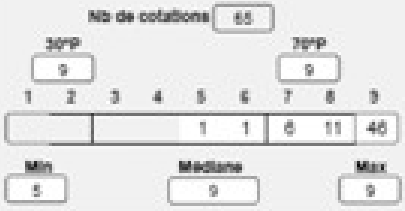
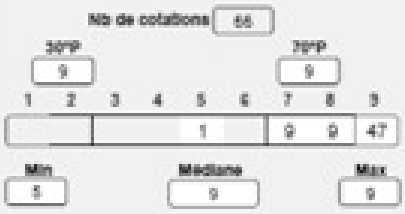
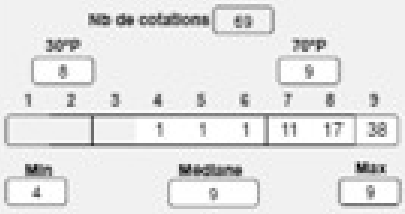
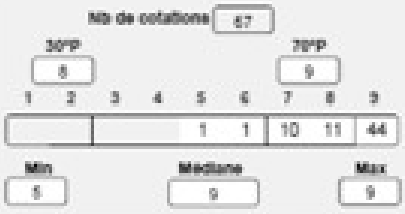
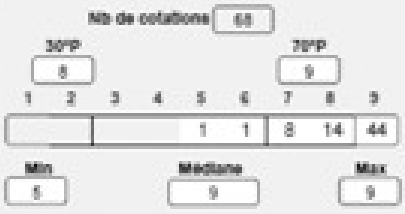
4i. Ocrelizumab La réponse vaccinale des patients traités par alemtuzumab est diminuée à 2 mois mais satisfaisante à 6 mois de la perfusion en comparaison à des contrôles sains historiques (grade C). Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4j. Cladribine La réponse vaccinale des patients traités par diméthylfumarate est comparable à celle des SEP traitées par interférons bêta (grade C). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4k : Cyclophosphamide La réponse vaccinale des patients traités par fingolimod est diminuée en comparaison aux contrôles sains, aux SEP non traitées et traitées par interféron bêta (niveau B). Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4l : Methotrexate La réponse vaccinale des patients traités par natalizumab semble diminuée pour la grippe, mais pas pour le tétanos, en comparaison aux contrôles sains (grade B). Les autres vaccins n'ont pas été étudiés. Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4m : Azathioprine-mycophénolate mofetil : Aucun vaccin n'a été étudié chez les patients atteints de SEP traité par azathioprine ou mycophénolate mofetil. Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	
4n : Rituximab et autres anti CD20 : Il est conseillé d'appliquer les recommandations vaccinales pour les patients immunodéprimés (recommandation d'experts). **Cotation :** 1 Conclusion Appropriée - Accord Relatif	

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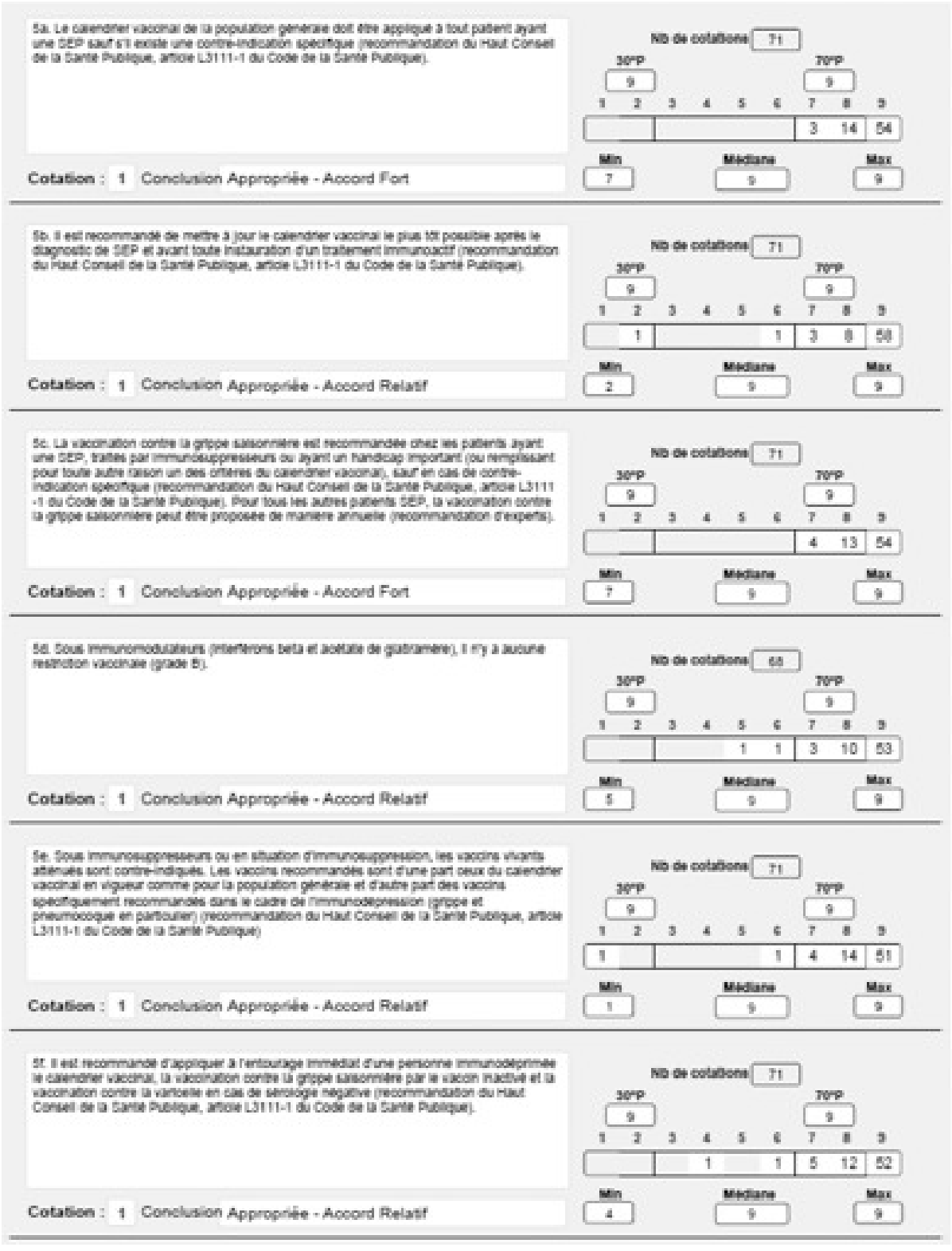
Table 4 (*continued*)



with an increased risk of relapse in a patient with MS (level B). An increased risk of relapse after vaccination against yellow fever cannot be excluded (level C).

Rating: **Appropriate** (number of available scores: 71; 100% [5–9]); **Relative agreement** (median 9, min–max 6–9, 30th–70th percentile:8–9).

Recommendation 2b. Influenza and BCG vaccines have no impact on the short-term accumulation of disability (level C). The impact of other vaccines on disability has not been studied yet.

Rating: **Appropriate** (number of available scores: 71; 100% [5–9]);

Strong agreement (median 9, min–max 7–9, 30th–70th percentile:8–9).

All vaccines

One study only focused specifically on the risk of relapse after any vaccination in MS patients (Zilber and Kahana, 1996). This was a case-crossover study (the patient was his own control, a period of two months followed by a relapse being compared to 4 control periods of the same duration, not followed by relapse, taken during the previous year) (class 2 or 3). The relative risk (RR) of exposure to any vaccination was 0.71 [0.40–1.26]. Sensitivity analyses for different periods (1 and 3 months) and according to the confirmation or not of the vaccine also found non-significant RRs. It can be concluded that there is no evidence for an association between vaccination and MS relapse.

Influenza

The literature on seasonal influenza and H1N1 vaccination is the richest, with a placebo-controlled randomized clinical trial (Confavreux et al., 2001) (class 1 or 2) and a series of cases with close MRI follow-up after vaccination (Miller et al., 1997).

In conclusion, available data on seasonal influenza vaccination does not support an increased risk of relapse and disability in MS patients, and the level of evidence for relapse is relatively high, with a randomized trial and little, but confirmatory MRI data. For the H1N1 strain, the positive results of one isolated small study (Mokhtarian et al., 1997) do not seem enough to counterbalance the negative results of all the other studies.

Hepatitis B

The only available data is a subgroup analysis of the VACCIMUS study, with an RR of 0.67 [0.20–2.17] (Zilber and Kahana, 1996). There is no information on the evolution of disability.

Measles-Mumps-Rubella (MMR)

No study has analyzed the risk of relapse and/or progression of disability following MMR vaccination.

Diphtheria-tetanus-pertussis-poliomyelitis

The only available data is a subgroup analysis of the VACCIMUS study, with a RR of 0.22 [0.05–0.99] for the combined vaccine and 0.75 [0.23–2.46] for tetanus alone (Zilber and Kahana, 1996). There is no information on the evolution of disability.

BCG

Two studies by the same group (McNicholas and Chataway, 2011; Ristori et al., 1999), including one randomized class 1 trial, found a significant decrease in MRI activity (RR for new gadolinium-enhancing T1 lesions = 0.54 [0.31–0.96], new or enlarging T2 lesions = 0.36 [0.21–0.64] and new T1 lesions = 0.15 [0.05–0.42] in BCG vaccinated compared to controls). Clinical results were confirmative, with a reduction in the risk of conversion to definite MS at 60 months (RR = 0.52 [0.27–0.99]). The change in disability measured by EDSS was similar in both groups at 6 months.

Overall, there is strong evidence for the absence of risk of relapse associated with BCG vaccination, with even a decrease in this risk. In addition, BCG does not seem to change the evolution of disability in the short-term.

Yellow fever

A single study on yellow fever vaccination is available (Ristori et al., 2014) (class 4 because of the small number of patients), including 7 relapsing-remitting MS (RRMS) patients followed clinically prospectively every 3 months with MRI, and matched with 7 healthy controls and 7 RRMS patients vaccinated for influenza over the same period of time. The RR was found significantly increased over the 1 to 5 weeks at-risk period (12.78 [4.28–38.13]) with an increase in the mean number of new or enlarging T2 lesions and gadolinium-enhancing T1 lesions.

It is difficult to draw firm conclusions from a single, small study, even though the clinical results were confirmed by radiological data and the evolution of a control group that received the influenza vaccine. An increase in the risk of relapse after vaccination against yellow fever cannot be ruled out.

Other vaccines

No conclusions can be drawn for other vaccinations because of the small amount or total absence of data.

In conclusion, vaccines, in general, do not appear to increase the risk of relapse in patients with MS. This has been particularly well studied for influenza and BCG. Only an isolated, well-documented, but small-sized study, reported an increased risk of relapse with the yellow fever vaccine.

There is no worsening of disability after vaccination against influenza or BCG, the only two vaccines for which data are available.

It should be underlined that in the reported studies, vaccines were not administered close to relapse.

Question 3: Are vaccines as effective in people with MS as in the general population (regardless of treatment)?

Recommendation 3. Available data on the efficacy of inactivated vaccines, in patients with MS and without disease-modifying treatment, suggest that it is similar to the general population, particularly for mono- and trivalent influenza vaccines (level C). No studies are available for live attenuated vaccines.

Rating: **Appropriate** (number of available scores: 71; 100% [5–9]); **Strong agreement** (median 9, min–max 7–9, 30th–70th percentile:8–9)

There are limited means to detect the biological effect of vaccines. Most assays are humoral based, but some of the protection provided by vaccines is also conveyed by T cells, which typically cannot be studied with commercially available assays. Therefore, the efficacy of a vaccine can be evaluated either biologically by measuring the titres of specific antibodies in the blood, suggestive of appropriate protection, or clinically by the incidence of the infectious disease. Only 6 studies have analyzed the efficacy of vaccination in untreated MS patients (Miller et al., 1997; Farez and Correale, 2011; Ross et al., 1996; Baumhackl et al., 2003; Moriabadi et al., 2001; Olberg et al., 2014). These were small-sized studies that primarily analyzed the change in antibody levels against the target pathogen. Two of these studies showed a significant increase in the level of antibodies against the varicella virus and the virus responsible for tick-borne encephalitis (Farez and Correale, 2011; Ross et al., 1996), although it was not clear whether protective titres were reached. Two other studies showed an increase in antibody titres after trivalent vaccination for seasonal influenza and a similar or even higher T-cell response in patients with MS than in the control population. (Miller et al., 1997; Baumhackl et al., 2003) Two cohort studies also showed that antibody titres were as high as in healthy controls after one injection of the H1N1 strain (Moriabadi et al., 2001) (percentage of protected patients at 3 months, 92.9% vs. 94.0%) (Olberg et al., 2014).

No study was found regarding the response to live attenuated vaccines in MS patients.

Question 4: Are vaccines as effective in people with MS exposed to disease-modifying treatments?

Recommendation 4a. Interferon beta

The response to influenza vaccines of patients treated with interferon beta was not decreased compared to healthy controls and untreated MS patients (level B). The response to the vaccines against Meningococcus, Pneumococcus, and Diphtheria-Tetanus, in patients treated with interferon beta, was not decreased compared to healthy controls and untreated MS patients (level C). The other vaccines were not studied.

Rating: **Appropriate** (number of available scores: 67; 99% [5–9]); **Relative agreement** (median 9, min-max 3–9, 30th–70th percentile:8–9)

The effectiveness of the influenza vaccine in interferon beta (IFNβ)-treated MS patients was evaluated in 5 studies, two of which compared the response to the H1N1 vaccine in healthy controls (Olberg et al., 2014; Olberg et al., 2018). Seroprotection titers were reached in 88.0 and 97.7% of IFNβ-treated MS patients. [45–46] In another study, the proportion of patients with protective titers was not statistically different between treated and untreated patients after one dose of the trivalent influenza vaccine but varied among the strains of the vaccine (Bar-Or et al., 2013). The pooled analysis found an OR of 1.6 [1.03–2.48], indicating greater protection in patients treated with IFNβ. The fourth study compared patients on IFNβ with healthy controls (Schwid et al., 2005). At 4 weeks, the percentage of patients fulfilling seroprotection criteria was respectively in IFNβ patients and controls, 100% vs. 78% for strain A (OR = 14 [0.76–259]); 100% vs. 82% for strain B (OR = 26 [1.4–468]). Finally, in a study conducted during the 2009–2010 vaccination campaign against the H1N1 influenza pandemic, 44% of the 36 IFNβ-treated patients had protective titers compared to 43.5% of healthy controls (OR = 1.03 [0.5–2.1] after 10 months (Moriabadi et al., 2001).

The response to Meningococcus, Pneumococcus, and Diphtheria-Tetanus has been evaluated in a study designed for another treatment, but with patients treated with interferon beta as one control group, beside healthy controls and untreated MS patients (Mehling et al., 2013). The response to other vaccines has not been studied with IFNβ-treated patients.

Recommendation 4b. Glatiramer acetate

The vaccine response to influenza in patients with MS treated with glatiramer acetate may be reduced compared to healthy controls and untreated MS patients (level C). The other vaccines were not studied.

Rating: **Appropriate** (number of available scores: 65; 94% [5–9]); **Relative agreement** (median 8, min–max 3–9, 30th-70th percentile: 8–9)

Two studies from the same team reported conflicting results. The first compared the effectiveness of vaccination against the influenza A virus in MS patients receiving different treatments, including 37 with glatiramer acetate (GA), versus 216 healthy controls (Moriabadi et al., 2001). The number of patients with persistent protective hemagglutination titers (≥40) was lower in patients on GA than in controls for H1N1 vaccination in 2009 (21.6% vs. 43.5%), H1N1 in 2010 (58.3% vs. 71.2%) and H3N2 in 2010 (41.7% vs. 79.5%). In a second similar study, conducted after the injection of a trivalent influenza vaccine (H1N1 and H3N2 strains) in 2012, 53 healthy subjects and MS patients treated with different DMTs including 23 on GA were compared (Olberg et al., 2014). There was no significant difference in the level of protection from H1N1 in patients treated with GA compared to controls at 3, 6 and 12 months, but a decreased level of protection was found for the H3N2 strain at 3 months in GA patients compared to untreated patients and healthy controls (21.6, 42.9 and 69.6% respectively).

These data indicate that for MS patients treated with GA the trivalent influenza vaccine was effective but may provide a lower level of protection than for healthy subjects.

The response to other vaccines has not been studied under GA.

Recommendation 4c. Dimethylfumarate

The vaccine response to Meningococcus, Pneumococcus and Diphtheria-Tetanus vaccines in patients with MS treated with dimethylfumarate appears to be comparable to that of MS patients treated with interferon beta (level C). Due to the risk of chronic lymphopenia, it is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 65; 98% [5–9]); **Relative agreement** (median 9, min–max 1–9, 30th–70th percentile:8–9)

A single open-label, multicenter study compared the responses to different vaccines in MS patients treated with dimethylfumarate (DMF) (38 patients) or IFNβ (33 patients)(class 2) (Mehling et al., 2013). They received successively 3 types of vaccines: a diphtheria-tetanus vaccine to test the T-cell dependent memory response; a 23-valent pneumococcal vaccine to test the T-independent humoral response; an antimeningococcal vaccine (group A, C, W135 and Y) CRM 197 oligosaccharide to test the T-cell response to a neoantigen. The primary endpoint was the proportion of patients showing a greater than 2-fold increase the tetanus IgG level in serum between the pre-vaccine period and 4 weeks post-vaccination. The proportion of responders was comparable on DMF and IFNβ (68% vs. 73%). Responder rates were also comparable for all serotypes studied: diphtheria (58% vs. 61%), pneumococcal serotype 3 (66% vs. 79%) and serotype 8 (95% vs. 88%), and meningococcal serogroup C (53% vs. 53%). Patients were considered to have achieved adequate seroprotection according to the thresholds defined by the American Academy of Allergy, Asthma and Immunology (Von Hehn et al., 2017).

Recommendation 4d Teriflunomide

The vaccine response to influenza in patients treated with teriflunomide was decreased compared to MS patients treated with interferon beta (level B). The other vaccines were not studied. It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 66; 95% [5–9]); **Relative agreement** (median 8, min–max 1–9, 30th–70th percentile:8–9)

Data are based on 2 studies. The TERIVA (teriflunomide and vaccination) study (Olberg et al., 2018) was a multicenter, multinational, parallel group study involving 128 patients in 3 arms, treated with teriflunomide 7 mg, 14 mg or IFNβ, receiving a single trivalent seasonal influenza vaccine injection (class 2 to 3). The vaccinal response in all 3 groups and for all strains was protective, but it was slightly lower in the 14 mg arm. In 2015, Bar-Or et al. performed a randomized, double-blind, placebo-controlled study (class 2). Twenty-three healthy subjects received teriflunomide (70 mg/day for 5 days then 14 mg/day for 25 days) and 23 received placebo for 30 days (Orange et al., 2012). Anti-rabies antibody levels at D31 and D38 were lower than placebo-treated patients, but all subjects achieved a sufficient level of seroprotection. The study was not conducted on MS patients

Recommendation 4e. Mitoxantrone

The vaccine response to influenza in patients treated with mitoxantrone was inadequate compared to that of healthy controls (level C). The other vaccines were not studied.

It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendation).

Rating: **Appropriate** (number of available scores: 65; 98% [5–9]); **Relative agreement** (median 9, min–max 1–9, 30th–70th percentile: 8–9)

In a Swedish cohort (Moriabadi et al., 2001), none of the 11 MS patients on mitoxantrone were protected after vaccination against the influenza A H1N1 2009 strain (0/11 vs. 94/216 healthy controls) and only one patient had detectable antibody titers against the 2010 H1N1 and H3N2 strains (1/4 vs. 58/73 healthy controls). These results indicate that influenza vaccination while on mitoxantrone does not provide adequate protection.

Recommendation 4f. Natalizumab

The vaccine response in patients treated with natalizumab was reduced for influenza, but not for tetanus, compared to healthy controls (level B). The other vaccines were not studied.

It is advised to apply the recommendations for immunization of immunocompromised patients. (expert recommendations).

Rating: **Appropriate** (number of available scores: 67; 100% [5–9]); **Strong agreement** (median 9, min–max 7–9, 30th–70th percentile: 8–9)

Three small studies have compared the efficacy of vaccines of different influenza strains in MS patients treated with natalizumab, compared to healthy controls (Moriabadi et al., 2001; Olberg et al., 2014; Bar-Or et al., 2015). All showed a decrease in the vaccinal response. Kaufman et al. evaluated the efficacy of a tetanus booster in 30 patients treated with natalizumab compared to 30 patients without treatment (Vagberg et al., 2012). After one month, 100% of controls and 94% of patients receiving natalizumab were adequately immunized against tetanus.

Recommendation 4g. Fingolimod

The vaccine response in patients treated with fingolimod was reduced compared to healthy controls, untreated MS and interferon beta-treated patients (level B). It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 67; 99% [5–9]); **Relative agreement** (median 9, min–max 1–9, 30th–70th percentile:8–9)

In a randomized clinical trial (class 1), Kappos et al. compared the vaccine responses to a trivalent influenza vaccine and to a tetanus booster in 93 fingolimod-treated MS patients and 43 placebo-treated patients (Kaufman et al., 2014). The rate of responders to vaccination was lower in patients taking fingolimod at 3 and 6 weeks for influenza (54% vs. 85% and 43% vs. 75% respectively) and for tetanus (40% vs. 61% and 38% vs. 49%, respectively). Similar results were found in smaller and non-randomized studies for influenza (Olberg et al., 2014; Schwid et al., 2005; Kappos et al., 2015; Mehling et al., 2011).

Overall, these studies demonstrate a qualitative and quantitative decrease in the vaccine response in patients treated with fingolimod.

Recommendation 4h. Alemtuzumab

The data are insufficient to evaluate the vaccine response in patients treated with alemtuzumab. It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 67; 97% [5–9]); **Relative agreement** (median 9, min–max 1–9, 30th–70th percentile:8–9)

A single case-control pilot study (Boulton et al., 2012) explored the immune competence in 24 patients after treatment with alemtuzumab (including 5 patients who had been vaccinated within 6 months of the last alemtuzumab infusions) by measuring the humoral response to 3 vaccines (the diphtheria-tetanus-poliomyelitis trivalent compound, the conjugated Haemophilus influenza type B and meningococcus type C vaccine, and the polysaccharidic pneumococcal vaccine). For meningococcus, 83% of MS patients were immunized at 4 weeks compared to 100% of historical healthy controls. For Haemophilus influenza type B, 95% of the patients were immunized compared to 90% of the historical healthy controls. For the pneumococcal vaccine, the level of immunization was correct, except in a patient vaccinated within 2 months after treatment despite a weak vaccine response, suggesting a lack of effective immunization at this time.

Recommendation 4i. Ocrelizumab

The vaccine response in patients treated with ocrelizumab was effective but decreased after 12 weeks for tetanus, Pneumococcus and influenza compared with non-treated and interferon beta-treated MS (level B). It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 65; 98% [5–9]); **Relative agreement** (median 9, min–max 1–9, 30th–70th percentile:8–9)

There is only one study, the results of which were only presented orally at the American Academy of Neurology in April 2018 (VELOCE study) (Mc Carthy et al., 2013). This was a phase IIIb clinical trial evaluating the vaccine response of MS patients exposed to ocrelizumab (class 1). Responses to 5 vaccines or neoantigens were evaluated, each selected because of the different mechanisms of the immunological response. Two-thirds of the patients were randomized to the ocrelizumab group, one-third to placebo or the IFNβ group. The vaccines were administered from the 12th week of the 1st cycle of treatment with ocrelizumab. The IgG response to a tetanus antigen was decreased in ocrelizumab compared to the control group (subjects without treatment or IFNβ treatment) but remained on average above the protective threshold. The percentage of patients who achieved a positive response was decreased at 4 and 8 weeks compared to controls, respectively 24.2% vs. 60.6% at 4 weeks and 23.9% vs. 54.5% at 8 weeks. For the pneumococcal IgG response, the percentage of patients who achieved a positive response was decreased for all serotypes studied at 4 weeks, but with 86.6% having a positive response to at least 2 serotypes, 77.6% to 4 serotypes and 37.3% to at least 12 serotypes. Seroprotection against influenza was also decreased but varied between 55.6 and 80.0% of subjects protected with ocrelizumab, depending on the strain. The neoantigen response was decreased for both IgM and IgG compared to untreated and IFNβ-treated patients. No vaccine safety issues were reported during the study. One of the limitations of the study was the lack of data on vaccine responses in patients with longer exposure, which can be assumed, at least for the B-cell response, to decrease with an increased duration of treatment exposure.

In conclusion, this study showed a decreased humoral response to vaccines during treatment with ocrelizumab, but with protective thresholds reached, particularly for the influenza vaccine, in a significant percentage of patients.

Recommendation 4j. Cladribine

No vaccine has been studied in patients with MS treated with cladribine.

It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 65; 100% [5–9]); **Relative agreement** (median 9, min–max 5–9, 30th–70th percentile: 9–9)

There is no data in the literature for patients with MS or other conditions.

Recommendation 4k. Cyclophosphamide (off-label)

No vaccine has been studied in patients with MS treated with cyclophosphamide.

It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 66; 100% [5–9]); **Relative agreement** (median 9, min–max 5–9, 30th-70th percentile: 9–9)

There is no data in the literature concerning MS patients. A study on ovarian cancer showed a decrease in vaccine efficiency (Stokmaier et al., 2018).

Recommendation 4l Methotrexate (off-label)

No vaccine has been studied in patients with MS treated with methotrexate. The vaccine response in patients with rheumatoid arthritis treated with methotrexate was satisfactory. It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 69; 99% [5–9]); **Relative agreement** (median 9, min–max 4–9, 30th–70th percentile: 8–9)

There is no data in the literature concerning MS patients.

Available data come from studies of patients treated for other autoimmune diseases (Chu et al., 2013; Loebermann et al., 2012). For patients with rheumatological autoimmune diseases, infections have been shown to be more frequent while on methotrexate, but results are confounded also by the older age of patients and the history of corticosteroid or immunosuppressive therapy (Club Rhumatismes et inflammations (CRI), 2019).

Recommendation 4m. Azathioprine/mycophenolate mofetil (off-label)

No vaccine has been studied in patients with MS treated with azathioprine or mycophenolate mofetil. It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 67; 100% [5–9]); **Relative agreement** (median 9, min–max 5–9, 30th-70th percentile: 8–9)

There is no data in the literature concerning MS patients.

Recommendation 4n. Rituximab and other anti-CD20 (off-label)

No vaccine has been studied in patients with MS treated with rituximab and other anti-CD20 (except ocrelizumab). It is advised to apply the recommendations for immunization of immunocompromised patients (expert recommendations).

Rating: **Appropriate** (number of available scores: 68; 100% [5–9]); **Relative agreement** (median 9, min–max 5–9, 30th–70th percentile: 8–9)

There is no data in the literature concerning MS patients.

Question 5: What prevention methods should be offered to patients with MS?

Recommendation 5a. The vaccination schedule of the general population should be applied to any patient with MS unless there is a specific contraindication (recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique, Table 5) (Morel et al., 2016).

Rating: **Appropriate** (number of available scores: 71; 100% [5–9]); **Strong agreement** (median 9, min–max 7–9, 30th–70th percentile: 9–9)

Recommendation 5b. It is recommended to update the vaccination schedule as soon as possible after the diagnosis of MS and before any disease-modifying treatment is introduced (recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique) (Morel et al., 2016).

Rating: **Appropriate** (number of available scores: 71; 99% [5–9]); **Relative agreement** (median 9, min–max 2–9, 30th–70th percentile: 9–9)

Recommendation 5c. Seasonal flu vaccination is recommended for patients with MS who are treated with immunosuppressive drugs or who have a significant disability (or any other reason recommended for influenza vaccination) unless there is a specific contraindication (recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique) (Morel et al., 2016; Calendrier des vaccinations et recommandations vaccinales, 2018). **For the other MS patients, seasonal flu vaccination can be proposed annually (expert recommendations).**

Rating: **Appropriate** (number of available scores: 71; 100% [5–9]); **Strong agreement** (median 9, min–max 7–9, 30th–70th percentile: 9–9)

Recommendation 5d There is no restriction for vaccines associated with immunomodulators (interferon beta and glatiramer acetate) (level B).

Rating: **Appropriate** (number of available scores: 68; 100% [5–9]); **Relative agreement** (median 9, min–max 5–9, 30th–70th percentile: 9–9)

Recommendation 5e. During treatment with immunosuppressants and in any other case of immunosuppression, live attenuated vaccines are contraindicated. Recommended vaccines are those of the vaccination schedule for the general population and vaccines specifically recommended for immunocompromised patients (influenza and Pneumococcus in particular) (recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique) (Morel et al., 2016; Calendrier des vaccinations et recommandations vaccinales, 2018).

It is not recommended to vaccinate during a relapse requiring high dose steroid therapy (expert recommendation).

Rating: **Appropriate** (number of available scores: 71; 99% [5–9]); **Relative agreement** (median 9, min–max 1–9, 30th–70th percentile: 9–9)

Recommendation 5f. It is recommended to provide the immediate entourage of an immunocompromised person with the vaccination schedule, seasonal influenza vaccination and varicella vaccination in case of negative serology (recommendation of the Haut Conseil de la Santé Publique, article L3111-1, Code de la Santé Publique) (Morel et al., 2016; Calendrier des vaccinations et recommandations vaccinales, 2018).

Rating: **Appropriate** (number of available scores: 71; 99% [5–9]); **Relative agreement** (median 9, min–max 4–9, 30th–70th percentile: 9–9)

In 2002 the first recommendations into the vaccination program for MS patients were issued (Rutschmann and McCrory, 2002). The recommendations highlighted the safety of vaccines in this disease, thus encouraging compliance with the same immunization schedule as that of the general population, whether patients were treated or not (mainly injectable immunomodulators at that time). However, these first recommendations did not address the interaction with the most recent DMTs: immunosuppressants or biotherapies. One paper only addressed the question of the need for specific vaccination for MS patients (Vinogradova et al., 2009). This case-control study showed that MS is a risk factor for pneumococcal pneumonia with an OR of 3.63 [2.70–4.88], in association with immunosuppressive treatment and significant physical disability.

Table 5
French 2018 vaccination schedule

	1 month	2 months	4 months	5 months	11 months	12 months	16-18 months	6 years	11-13 years	14 years	25 years	45 years	65 years and more
BCG													
Diphteria-Tetanus-Poliomyelitis													Every 10 years
Pertussis													
Haemophilus influenza type B													
Hepatitis B													
Pneumococcus													
Meningococcus type C													
Measles-Mumps-Rubella													
Human papillomavirus									2 doses at 0 and 6 months				
Seasonal influenza													Every year
Shingles													

Mandatory Recommended

Adapted from Calendrier des vaccinations et recommandations vaccinales 2018. Ministère de la Santé http://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinations_2018.pdf.

Due to the use of biotherapies and immunosuppressants in other inflammatory and auto-immune diseases, some elements of response can come from recommendations made for patients with rheumatic diseases in particular. Nevertheless, these auto-immune diseases can themselves contribute to immunosuppression, which is not the case in MS. It is therefore difficult to fully extrapolate these data to patients with MS on DMTs. However, immunosuppression induced by new MS treatments requires evaluation of the risk of infection that can be more serious because of the occurrence in the context of a debilitating and weakened condition, and to consider the possibility of prevention.

In France, official recommendations of the Haut Conseil pour la Santé Publique (High Council for Public Health) are updated and published every year (Morel et al., 2016). They describe the vaccination schedule for the general population, but since 2014 they also include a specific section for immunocompromised and asplenic patients, targeting all autoimmune and inflammatory diseases (Calendrier des vaccinations et recommandations vaccinales 2018). Therefore they apply also to MS patients, especially when treated with DMTs.

Beside all the other important and very practical points described in these recommendations one is of particular interest in MS: *"During steroid therapy, the administration of a live vaccine is contraindicated beyond the following doses and durations (immunosuppressive corticosteroid therapy):*

o In adults: 10 mg of prednisone equivalent per day, for more than two weeks.

o In children: 2 mg/kg of prednisone equivalent per day (and more than 20 mg per day in children over 10 kg), for more than two weeks.

o "Boluses" of corticosteroids contraindicate the administration of a live vaccine for the next three months."

Study funding

None

Author contribution

Dr. Lebrun – Study concept and design, acquisition of data, analysis and interpretation, writing

Dr. Vukusic – Study concept and design, acquisition of data, analysis and interpretation, writing

Potential conflict of interests

Dr. Lebrun has received lecturing fees, travel grants and research support from Sanofi-Genzyme, the manufacturer of the vaccines that are described in this study.

Dr. Vukusic has received lecturing fees, travel grants and research support from Sanofi-Genzyme, the manufacturer of the vaccines that are described in this study.

Endorsement

The 2019 recommendations on immunization and multiple sclerosis have been organized by the French Multiple Sclerosis Society (Société Francophone de la Sclérose en Plaques, SFSEP).

They are also endorsed by the French Neurological Society (Société Française de Neurologie, SFN), the French Federation of Neurology (Fédération Française de Neurologie, FFN) and the Vaccines and Prevention group of the French Society for Infectious Diseases (Société de Pathologies Infectieuses de Langue Française, SPILF).

An extensive French version including tables describing all contributing studies is available on sfsep.org/vaccination.

A tutorial iOS application SFSEP is available on AppStore.

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Appendix. France4MS group (List of investigators, alphabetical order)

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