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Review article

Immunogenicity of The Influenza Vaccine in Multiple Sclerosis Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Multiple sclerosis is a neurodegenerative disease thought to be of autoimmune origin. It can lead to development of neurological symptoms and increase the risk of infection from communicable diseases. Thus, vaccines are endorsed to mitigate this risk. However, it has not yet been confirmed whether the dysfunctional immune system of these patients combined with taking immunosuppressants can lead to a dampened immunity in response to the influenza vaccine. Infection with the influenza virus is a concern for multiple sclerosis patients. Previous research on multiple sclerosis patients who have received the influenza vaccine focuses on safety and relapse rates. Studies that focus on the immune response mounted against the vaccine in this patient cohort are scant. This study serves to provide a comprehensive picture of the immunogenicity of the influenza vaccine in MS patients.

Methods: A systematic review of compiled research was conducted. Data obtained from the research was used in a meta-analysis using risk differences with a 95% confidence interval.

Results: Across the various strains incorporated into the influenza vaccine analyzed in this paper, there was no statistical difference in immune response mounted against the influenza vaccine between healthy controls and multiple sclerosis patients.

Conclusion: The results of this study suggest that multiple sclerosis patients can mount an adequate immune response to the influenza vaccine when compared to healthy controls. Most of the immunotherapies these patients are on do not appear to affect this immune response. Therefore, the influenza vaccine should continue to be recommended to multiple sclerosis patients.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system (Dendrou et al., 2015, Ghasemi et al., 2017). It is characterized by progressive demyelination and axonal degeneration. Two key factors are thought to contribute to the pathogenesis of this disease – genetic predisposition and environmental triggers. Certain major histocompatibility complexes (MHC) show a strong association with increasing the risk of developing MS, especially HLA-DRB1. In addition, multiple environmental factors have been identified such as decreased vitamin D levels and sunlight exposure, geographic latitudes, and viral infections including EBV and HHV-6.

Although various susceptibility factors have been implicated, the exact underlying mechanism of MS initiation has yet to be elucidated. However, the overall mechanism appears to be autoimmune in origin (Dendrou et al., 2015, Ghasemi et al., 2017). One of the first major events to occur is the breakdown of the blood-brain-barrier (BBB). Leukocytes then penetrate the more permeable BBB, possibly through increased adhesion molecule expression (Al-Badri and Castorina, 2018). CD4+ and CD8+ T lymphocytes, specifically, are indicated as being the primary instigators of the auto-reactive immune response seen in this disease. These T cells have been shown to recognize myelin as foreign and initiate an attack, with consequent release of cytokines and reactive oxygen species (Dendrou et al., 2015, Ghasemi et al., 2017, Al-Badri and Castorina, 2018). Other immune cells such as macrophages and B lymphocytes are also recruited at this time. Moreover, the neuroglial cells,

Abbreviations: MS, Multiple sclerosis; MHC, Major histocompatibility complex; BBB, Blood-brain-barrier – BBB.

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particularly the oligodendrocytes, are injured in this process. The subsequent inflammatory response produces much of the damage to the axons seen in MS. The body appears to attempt remyelinating the damaged axons (Dendrou et al., 2015, Ghasemi et al., 2017, Al-Badri and Castorina, 2018) .However, the continuous process of demyelination and remyelination causes scarring and formation of plaques which are characteristic of MS (Dendrou et al., 2015, Ghasemi et al., 2017).

Although there is no current cure, current treatment options slow the progression of the disease and provide symptomatic relief. Among these therapies are corticosteroids and disease-modifying agents including biologics and interferons (Dargahi et al., 2017). These medications have a common mechanism of action which is to suppress the abhorrent autoreactive immune system prevent ing further immune-mediated damage and destruction (Dargahi et al., 2017). Although these medications can improve the quality of life, they can dampen the immune system of these individuals against other infections. This is best exemplified with the higher infection rate of MS patients and increased severity of infections when compared to the general population (Celius). Infections are one of the chief causes of death among MS patients (Smestad et al., 2009).

One particular infection of concern is the influenza virus. Five to ten percent of adults and 20-30% of children are infected with the influenza virus annually (World Health Organization, 2019). In the United States (US), one out of every five individuals contracts influenza A or B and becomes ill every year. The infection with the virus accounts for over 200,000 hospital admissions per year (Centers for Disease Control and Prevention. Disease Burden of Influenza, 2019). Each year between 3, 000 to 49,000 individuals die as a result of this infection making it the most common cause of vaccine-preventable deaths. It has been estimated that the direct medical expenditures of a seasonal influenza outbreak costs the US about $10 billion (Centers for Disease Control and Prevention. Disease Burden of Influenza, 2019). As this virus is easily transmissible and can lead to serious illness, prevention has become a major initiative by the National Institute of Health in the US as well as the World Health Organization globally (World Health Organization, 2019). Compared to the general population, MS patients have a higher rate of influenza-related hospital admissions (Montgomery et al., 2013, Wijnands et al., 2017). They also have increased rates of relapse after contracting the virus (Correale et al., 2006). Most importantly, influenza infection has been linked to increased mortality in MS patients (Sumelahti et al., 2010).

As this is an area of concern for these patients, the influenza vaccine is recommended annually to help mitigate this risk (Farez et al., 2019). The influenza vaccine is one of the most widely received vaccines annually. The vaccine is available via injection or intranasal routes (Centers for Disease Control and Prevention, 2019). The effectiveness of the vaccines regardless of the type is determined by how well matched the strains contained are to the ones circulating within the community (Centers for Disease Control and Prevention, 2019). The vaccine is modified yearly as the virus is capable of genetically assorting its segmented genome (Centers for Disease Control and Prevention, 2019). There are three types – an inactivated influenza vaccine, live attenuated influenza vaccine, and recombinant influenza vaccine available in a trivalent or quadrivalent form (Centers for Disease Control and Prevention, 2019). The trivalent form is composed of two strains of influenza A and one lineage of influenza B while the quadrivalent form is composed of two strains of influenza A and two lineages of influenza B (Centers for Disease Control and Prevention, 2019). The influenza genera is comprised of four subsets with three being able to infect humans and cause disease – influenza type A, influenza type B, and influenza type C. Influenza A and B are responsible for the seasonal epidemic in the fall and winter, peaking between the months of December and February (World Health Organization, 2019). Influenza A viruses are the more complex of the three. It can be separated into subtypes based on the type of neuraminidase (N) and hemagglutinin (H) glycoproteins found on the envelope of the virus (Centers for Disease Control and Prevention, 2019). This allows for multiple strains of influenza A to be formed with the most common being H1N1 and H3N2. There are also two lineages of influenza B viruses – B/Victoria and B/Yamagata (Centers for Disease Control and Prevention, 2019).

Vaccination is the most popular and most effective means of prevention against the influenza virus with regard to the general healthy population (World Health Organization, 2019, Centers for Disease, 2019). However, there are limited studies looking at the immunogenicity of the vaccine once it has been administered in MS patients. The purpose of this study is to provide a systematic review and meta-analysis comparing the humoral immunogenicity of the influenza vaccines in patients with multiple sclerosis to that of healthy controls.

2. Methods

A literature search was conducted to find relevant studies. The studies all reported MS patients and healthy controls receiving the influenza vaccine. The search was conducted on February 14th, 2019 using the following electronic databases: PubMed (1809 to present), Google Scholar (1900 to present), MEDLINE (1946 to present), CINAHL (1937 to present), and Embase (1980 to present). There was no time frame applied to the search. Several keywords used include, "multiple sclerosis," "influenza," "vaccine," "vaccination," "influenza vaccine," "immunogenicity," and "seroconversion." No language restriction was placed on the search. Reference lists were manually scanned as well for additional studies.

For a study to be selected, it was required to have MS patients as the population of interest compared against healthy controls. This was irrespective of the patients' duration of the disease, age, activity level, treatment regime, or severity of the disease. A study must have also quantitatively examined the immunogenicity of vaccination. The accepted immunogenicity measurements included the following: seroconversion (SC), defined as the $\geq$4-fold increase in antibody titers after vaccination, or seroprotection (SP), defined as antibody titers $\geq$1:40 using the hemagglutination inhibition assay after vaccination. The full inclusion and exclusion criteria are presented in Table 1. The articles were first deemed adequate based on their titles and abstracts. Once the initial screening was complete, the articles were rescreened based on their full text. Articles that did not meet the aforementioned criteria were then removed. Duplicates were also removed. The selection process is displayed as a flowchart in Fig. 1.

Once the articles were compiled, a meta-analysis was conducted. The data extracted from each study included the following: definition of groups, size of the experimental group, size of the healthy control group, patient demographic, medications, type of influenza strain, vaccination type and route of administration, and SP and SC rates. The risk

Table 1
Inclusion and exclusion criteria of studies selected for this systematic review and meta-analysis

Inclusion criteria	Exclusion criteria
• Published in English • Adults (no age limit) • MS patients as the study population, irrespective of disease duration, severity, or treatment • Healthy control group • Vaccination against influenza (regardless of vaccine type or method of administration) • Description of treatments for multiple sclerosis, irrespective of regime, dose, duration or route of administration, or frequency • Results demonstrating seroprotection rates, seroconversion rates, or antibody titers or geometric mean titers post-vaccination.	• No healthy control group· • No quantitative results on the immunogenicity of the vaccination • No results specifically pertaining to patients with multiple sclerosis • Articles not available in the English language • Not peer-reviewed • Research protocols, letters, commentary, case reports, review article, or duplicated publications

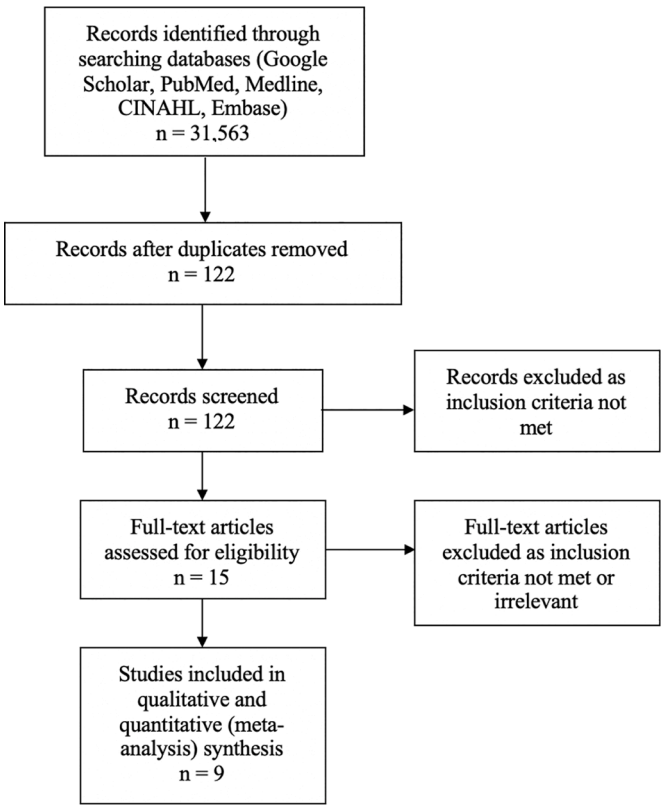

Fig. 1. PRISMA flow diagram of study selection

differences were calculated with 95% confidence intervals. A random-effects model was also performed. The use of a random-effects model is appropriate for this meta-analysis because the implementation of the different studies is heterogeneous. The results were displayed on forest plots. To evaluate the studies for heterogeneity, chi-square tests, and I^2 statistics were utilized. A value of 0.05 was the level of significance for the chi-square tests and I^2 values $\geq$ 75% was indicative of high heterogeneity.

3. Results

The safety of the influenza vaccine has been studied both in the general and MS patient population. However, research on its immunogenicity in individuals with MS is still scant. This study serves to fill this gap by compiling the current literature to provide a more comprehensive picture of the immunogenicity of the influenza vaccine in MS patients. From the initial literature search conducted, 122 articles were selected based on titles or abstracts alone. After manual reference list searches and full-articles reviews, eight articles with nine total studies were selected to be included (two studies reported in one article) (Olberg et al., 2014). Duplicates were removed. This study includes eight studies comprised of 789 subjects (332 MS patients and 457 healthy controls). Six hundred and eighty-six (72.1%) participants were women.

To determine whether the H1N1 strain of the influenza A virus was efficacious, five studies (631 participants) were used (Fig. 2) (Olberg et al., 2014, Olberg et al.,2018, Mokhtarian et al.,1997, Kim et al.,2013). Three studies indicated that MS patients receiving IFN-ß therapy were able to mount an adequate immune response after administration of the H1N1 vaccine in comparison to healthy controls (Olberg et al., 2014, Olberg et al., 2018, Kim et al., 2013). One study did note the use of glatiramer acetate, natalizumab, and mitoxantrone seems to reduce the long-term protection provided by this vaccine (Salvetti et al., 1995). However, this was contradicted in another study in which the protection rate at 12 months post-vaccination for patients taking interferon, natalizumab, or glatiramer acetate was not statistically different from those found in the healthy controls (Olberg et al., 2018). The same study also noted MS patients taking fingolimod expressed reduced protection rates. Overall, when the data were pooled, there was no significant effect of treatment on the immune response of MS patients when compared to healthy controls after receiving the H1N1 vaccine.

To investigate the immunogenicity of the H3N2 strain of the influenza A vaccine, four studies (326 participants) were used (Fig. 3) (Olberg et al., 2014, Olberg et al., 2018, Mokhtarian et al., 1997, Moriabadi et al., 2001). All four studies indicated an overall significant increase in antibody titers post-vaccination in the MS and healthy control groups. One study also indicated protection rates for H3N2 was lower for glatiramer acetate, natalizumab, and mitoxantrone groups than in the IFN-ß group (Olberg et al., 2014). This was supported by a study that noted that although there was a significant increase in titers post-vaccination in all MS patients across medication groups, they were significantly less likely to be protected when compared to healthy controls (Olberg et al., 2018). Three studies (Vagberg et al., 2012, Mehling et al., 2013, Mehling et al., 2011) (118 participants) and three studies (Mokhtarian et al., 1997, Mehling et al., 2013, Mehling et al., 2011) (111 participants) provided information on vaccine immunogenicity for influenza A and B strains, respectively (Figs. 4 and 5). All of these studies indicated similar results to that of the H1N1 vaccine. When the data were pooled, there was no significant effect of treatment on the immune response of MS patients when compared to healthy controls after receiving the H3N2, influenza A, or influenza B vaccine.

Moderate heterogeneity as measured by an I^2 close to 75% for the influenza B results (73%) was noted. The random-effects model was employed on the assumption that any primary study result is influenced by myriad unsystematic influences (therefore "random effects" model). In case of the existence of true heterogeneity in this study, it may be that there are omitted systematic moderators of the effect of interest or as aforementioned unsystematic influences. Nevertheless, a publication-

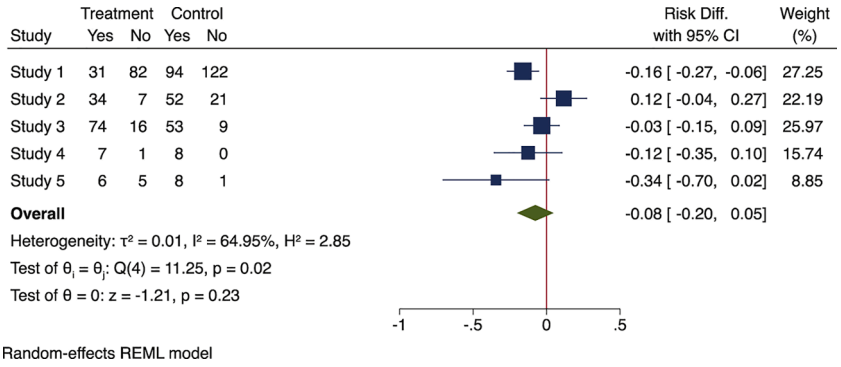

Fig. 2. Forest plot for the risk difference of response rate for influenza H1N1 between MS patients and healthy controls

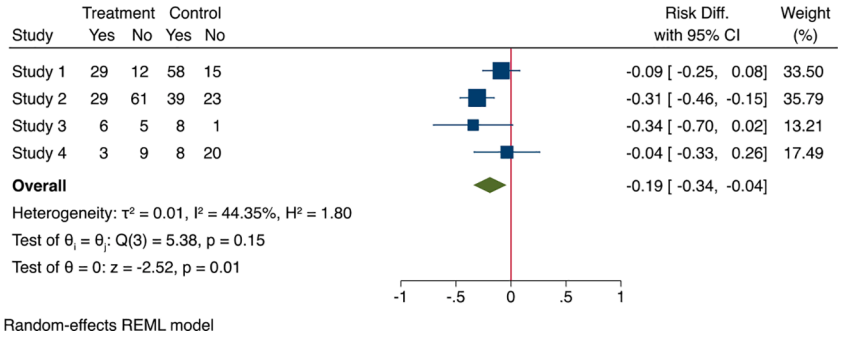

Fig. 3. Forest plot for the risk difference of response rate for influenza H3N2 between MS patients and healthy controls

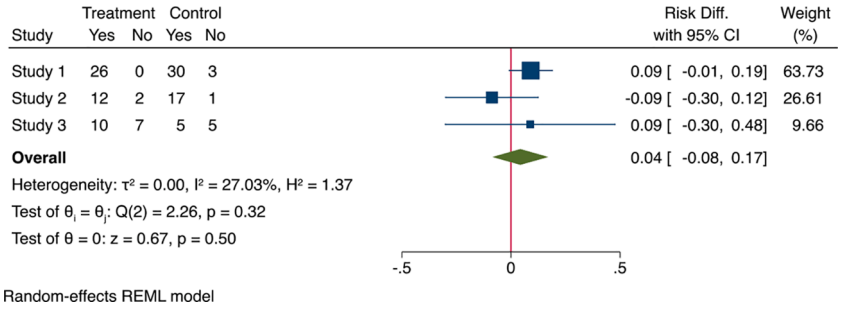

Fig. 4. Forest plot for the risk difference of response rate for influenza A between MS patients and healthy controls

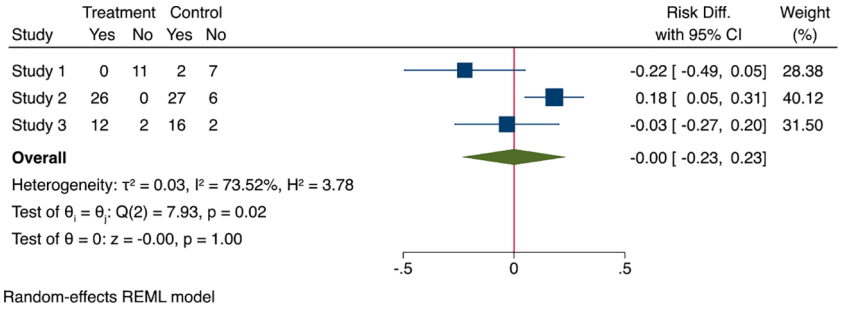

Fig. 5. Forest plot for the risk difference of response rate for influenza B between MS patients and healthy controls

bias review using a funnel plot was run. No asymmetry was found, so it was concluded that this heterogeneity is due to the few numbers of studies available for the influenza B analysis.

4. Discussion

In this systematic review and meta-analysis, the humoral immune response to influenza vaccines were evaluated in 332 MS patients and 457 healthy controls. From the aforementioned results of the nine studies, there appears to be no difference in immune response mounted by MS patients against the influenza vaccine when compared to healthy controls. This is consistent with previous literature. Our approach of pooling the patient data from various studies with the inclusion of more recent studies was performed in hopes of increasing weight via a meta-analysis of the previous research. Although, it appears certain therapeutics of MS patients may have some effect on this immune response , especially for the H1N1 and H3N2 strains. MS patients taking IFN-ß consistently showed similar humoral responses to the healthy controls across studies, while those taking biologics showed a decreased long-term protective response. When the data were pooled, this effect appeared to be not significant. The MS patients were still able to mount an immune response that showed significant increases from their baseline antibody titer levels that indicated seroconversion or seroprotection. This response was similar to that seen in the healthy controls. These results suggest that the vaccine is immunogenic in MS patients.

Several limitations should be mentioned. The research in this area is sparse and therefore, the sample size was small, potentially weakening the statistical significance of this study. To increase the power of future studies, larger randomized control trials, and meta-analyses should be conducted measuring the immunogenicity of the influenza vaccine in MS patients. Confounding factors such as disease duration, sex, or age were also not corrected during data analysis. The former limitation could lead to possible systemic error and for future studies should be corrected. Additionally, general keywords that produced a large volume of results such as "autoimmune diseases" were not utilized for the literature search, however, this may have limited the number of articles potentially relevant to this study. Lastly, due to missing or incomplete data, study sizes varied by analysis.

Although various studies have looked into the safety of receiving the influenza vaccine in MS patients, there is little evidence evaluating the humoral response produced by these patients (Salvetti et al., 1995, Farez et al., 2012, Miller et al., 1997, Auriel et al., 2012, Confavreux et al., 2001). Our study found that MS patients appear to be able to mount an adequate immune response against the influenza vaccine.

Thus, the influenza vaccine should continue to be recommended to MS patients annually in line with the American Academy of Neurology guidelines (Farez et al., 2019). This could be beneficial to these patients as they are immunocompromised and could help MS patients to decrease the mortality and morbidity associated with contracting this infection. Future studies should be conducted to further strengthen the data and additional research is warranted to investigate the effect of specific therapeutics on the immunogenicity of the influenza vaccine in patients with MS.

CRediT authorship contribution statement

Jackie Nguyen: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Patrick Hardigan:** Validation, Formal analysis, Data curation, Writing - review & editing, Visualization. **Marc M. Kesselman:** Writing - review & editing. **Michelle Demory Beckler:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision.

Declaration of Competing Interest

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