Uptake and Attitudes About Immunizations in People With Multiple Sclerosis

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Abstract

Objective

By surveying a multiple sclerosis (MS) population, we tested the hypothesis that influenza vaccine uptake would not meet public health targets and that vaccine misconceptions would contribute to lower than desired uptake.

Methods

In spring 2020, we surveyed participants in the North American Research Committee on Multiple Sclerosis Registry regarding vaccinations. Participants reported whether they had received hepatitis A, hepatitis B, pneumococcal, shingles, varicella, measles/mumps/rubella, tetanus, or influenza vaccines. Participants who had not received influenza vaccine last year reported the reasons. We summarized responses descriptively. Using multivariable logistic regression, we assessed participant characteristics associated with uptake of seasonal influenza vaccine.

Results

Of 5,244 eligible respondents, 80.8% were female, with a mean (SD) age of 61.8 (10.1) years. Overall, 43.0% (2,161/5,032) of participants reported that their neurologist had ever asked about their immunization history. The percentage of participants who received the seasonal influenza vaccine last year ranged from 59.1% among those aged 18–24 years to 79.9% for persons aged ≥65 years. Among those who did not get the influenza vaccination, the most common reasons were personal preference (29.6%), concerns about possible adverse effects in general (29.3%), and concerns that the vaccine would worsen their MS (23.7%).

Conclusion

Vaccination uptake is lower than desired in the MS population compared with existing recommendations, including for seasonal influenza. Misconceptions about the safety of vaccination in the context of MS and personal preference appear to play important roles in vaccination choices, highlighting the importance of education about these issues.

Individuals with multiple sclerosis (MS) have an elevated risk for infection compared with individuals without MS1,2 and an elevated risk for postinfectious complications. For example, individuals with multiple sclerosis (MS) have an elevated risk for infection compared with individuals without MS1,2 and an elevated risk for postinfectious complications.
with MS are more likely to be hospitalized and die of influenza than individuals without MS. Influenza infection also increases relapse risk. Several potentially serious infections, including influenza, can be prevented by vaccination. Vaccinations are of increasing concern as stronger immunomodulating therapies are used more widely for MS management, as these therapies may influence the need for and safety of vaccinations. Recent guidelines from the American Academy of Neurology focused on vaccinations, and the COVID-19 pandemic has heightened interest in vaccines in people living with MS.

Few studies have evaluated vaccination uptake in the MS population, and most have focused on influenza. In Israel, only one-third of respondents reported receiving seasonal flu vaccine in 2009–2010. In Manitoba, Canada, fewer than 40% of persons with MS received the influenza vaccine in 2015. In other populations with immune-mediated diseases, general and disease-specific barriers to vaccination have been reported, but relevant barriers in the MS population have not been reported. We aimed to determine uptake of seasonal influenza vaccine in a large sociodemographically diverse MS population, to investigate reasons for not obtaining the vaccine, and to determine lifetime uptake of other common vaccinations. We hypothesized that influenza vaccine uptake would not meet public health targets and that vaccine misconceptions would contribute to lower than desired uptake.

Methods
Study Population
The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is a self-report registry for persons with MS. At enrollment, participants report sociodemographic and clinical information, which is updated semiannually via survey. Surveys are completed either on paper or online.

Standard Protocols, Approvals, and Participant Consents
Participants permit use of their deidentified information for research purposes. At the time of the spring 2020 survey, the NARCOMS Registry was approved by the Institutional Review Board of Washington University at St. Louis.

Participant Characteristics
For this study, we used information from the enrollment and spring 2020 questionnaires. The information obtained from the enrollment questionnaire included birth date, sex, race, education level, region of residence, and age at MS symptom onset and diagnosis. We categorized race as White or non-White. We categorized education level as high school/General Educational Development certificate and postsecondary (associate’s degree, bachelor’s degree, postgraduate education, and technical degree).

We obtained all the remaining information from the spring 2020 questionnaire, including annual household income, marital status, health behaviors, and disability status. Annual household income was reported as ≤$50,000, $50,001–$100,000, >$100,000, and “I do not wish to answer.” We categorized marital status as single (never married, divorced, widowed, or separated) and married (married or cohabiting). Health behaviors captured included smoking status, physical activity, and alcohol intake. Participants reported their current smoking status as no, yes some days, or yes every day, using a question from the Behavioral Risk Factor Surveillance Survey; we aggregated these responses to yes/no. They reported whether they had participated in any physical activity or exercise during the past month (yes/no). Participants also reported alcohol intake using 1 question from the Alcohol Use Disorders Identification Test. We modified the question to ask about alcohol intake over the past 6 months instead of the past 12 months. Response options were never, monthly or less, 2 to 4 times a month, 2 to 3 times a week, or 4 or more times a week.

Disease duration from symptom onset was categorized (<10, 10–19, and ≥20 years). Participants reported disability status using Patient Determined Disease Steps (PDDS), a single-item measure with response options ranging from 0 (normal) to 8 (bedridden). The PDDS correlates strongly with a physician-scored Expanded Disability Status Scale score. For this analysis, we categorized PDDS as mild (0–1), moderate (2–4), and severe (5–8). Based on the relevant items from SymptoMScreen, we classified participants as having any depression (yes/no) or anxiety (yes/no) symptoms. Participants reported use of disease-modifying therapies (DMTs) in the last 6 months. We grouped these as none or any.

Immunization
Participants reported whether their neurologist had ever asked about their immunization/vaccination history (yes, no, or don’t know) and who they thought was responsible for determining which vaccinations they should receive (neurologist, primary care physician, participant, and other; multiple options were allowed). Participants were asked to report whether they had ever received vaccines for any of the following: hepatitis A, hepatitis B, pneumococcal, shingles, varicella, measles/mumps/rubella, and tetanus, where reasons were yes, no, or don’t know. For all vaccines except influenza, the time frame was ever receipt of the vaccine. We did not distinguish types of pneumococcal or zoster vaccines to avoid potential confusion by participants.

For influenza, we focused on the most recent influenza season to better assess current behaviors and attitudes. We adapted a questionnaire previously used in persons with inflammatory bowel disease (IBD). Participants who indicated that they had not received an influenza vaccine were asked to mention the reason, with potential responses being (1) never offered; (2) did not think I needed it; (3) allergy to eggs/vaccine; (4) concerned about side effects from the vaccine; (5) too expensive; (6) too busy/forgot; (7) my doctor advised against a flu shot; (8) concerned that the vaccine would worsen my MS; (9) vaccine not available; and (10) other (specify). Finally, participants were asked whether their neurologist had advised them to avoid certain vaccines and, if yes, to indicate which ones—the choices were the same as described earlier.
We excluded individuals who did not report a confirmed diagnosis of MS, sex, or date of birth; those who did not live in the United States to reduce heterogeneity due to differences in health system delivery in other countries; and those with an age at symptom onset <16 years. Missing responses were not imputed.

First, we used descriptive statistics to summarize the characteristics of the respondents using means (SD), median (interquartile range), and frequency (percent) and their responses to the vaccination questions. Second, we summarized uptake of each vaccine queried overall and stratified by sex, age (18–34, 35–49, 50–64, and ≥65 years), disability status (mild, moderate, and severe), and DMT use (no as reference). Third, we summarized the reasons for not receiving influenza vaccine.

Finally, we examined factors associated with the uptake or nonuptake of the influenza vaccination using binary logistic regression. The models included sex (female as the reference group), age (≥65 years as the reference group), disease duration (<10 years as reference), race (White as reference), education level (high school as reference), income (<$50,000 as reference), current smoking status (no as reference), alcohol intake (never as reference), physical activity (inactive as reference), disability status (mild as reference), DMT use, depression (no as reference), and anxiety (no as reference). We used standard methods to assess model assumptions and assessed model fit using the Hosmer-Lemeshow goodness of fit statistic.\(^{16}\) We report the C-statistic for each model. Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc., Cary, NC).

### Data Availability

The data sets generated and analyzed during this study are held by the NARCOMS Registry (narcoms.org).

### Results

The spring 2020 survey was distributed to 10,210 participants, of whom 6,385 (62.5%) responded. Compared with nonresponders, responders were more likely to be White (86.7% vs 82.6%, \(p < 0.001\)), female (80.9% vs 78.7%, \(p = 0.009\)), older (62.0 vs 59.0 years), and with a higher level of education (postsecondary 72.7% vs 68.9%, \(p < 0.001\)). However, most of these differences were statistically different but not clinically meaningful. After applying exclusion criteria, 5,244 participants constituted the final sample (figure e1, links.lww.com/CPJ/A292). Most participants were aged ≥51 years, White, and female, with moderate or severe disability (table 1).

### Vaccination Uptake

Of the vaccinations queried, the most commonly received was tetanus, followed by measles, mumps, rubella (MMR),
and the flu shot (table 2). Vaccination uptake varied by age, and these age-related patterns differed by vaccine (figure 1).

The percentage of participants who received the seasonal flu vaccine last year increased with age, reaching 79.9% for persons aged ≥65 years. Uptake of zoster (59.1%) and pneumonia (84.7%) vaccines was also highest among the oldest age group, consistent with the indications for those vaccines. However, the reverse pattern was observed for hepatitis A and B vaccinations, where the highest uptake was among those aged 18–45 years (hepatitis A: 93.9%, hepatitis B: 100%). We observed less variation in vaccination uptake among those aged 18–64 years.

Factors Associated With Receiving Influenza Vaccination

On univariate logistic regression, several demographic factors and health behaviors were associated with the likelihood of influenza vaccination. Compared with persons aged ≥65 years, those younger than 65 years had lower odds of being vaccinated (table 3). Postsecondary rather than high school education, a higher level of annual household income, a higher level of alcohol intake, being physically active, and using any DMT were also associated with increased odds of being vaccinated. In contrast, being male, symptoms of depression or anxiety, and currently smoking were associated with reduced odds of being vaccinated. Race, disability status, and disease duration were not associated with being vaccinated.

On multivariable analysis, postsecondary education, household income >$100,000 vs <$50,000 remained associated with increased odds of being vaccinated. Compared with no alcohol intake, alcohol intake 2–4 times per month was associated with increased odds of being vaccinated, as was physical activity.

Younger age and currently smoking continued to be associated with reduced odds of being vaccinated. Sex and symptoms of depression or anxiety were no longer associated with the odds of being vaccinated. Of MS characteristics, only use of a DMT was associated with vaccination. Participants reporting any use of a DMT had 41% increased odds of receiving influenza vaccination.

Attitudes Regarding Influenza Vaccination

Of the 1,303 participants who did not get the influenza vaccination in the last flu season and who reported their reasons for not doing so, the most common reasons were related to personal preference (29.6%) and concerns about possible adverse effects in general (29.3%), followed closely by concerns that the vaccine would worsen their MS (23.7%) (table 4). The personal preference category was dominated by the perception that the individual did not need it (339/391, 86.7%). However, misconceptions that the influenza vaccine (by injection) was contraindicated with several disease-modifying therapies were also reported.

When asked who is responsible for determining what vaccinations you should receive, two-thirds of participants responded themselves (2,659, 66.9%), followed by their primary care providers (2,302, 57.9%) and their neurologists (1,636, 41.2%). A very small percentage of participants indicated that someone other than these 3 choices was responsible (88, 2.2%). Advice to avoid particular vaccines was infrequent, being reported most often for Zoster (362, 6.9%), followed by influenza nasal mist (287, 5.5%), other (273, 5.2%), influenza shot (132, 2.5%), pneumonia (76, 1.5%), varicella (48, 0.9%), MMR (39, 0.7%), hepatitis (24, 0.5%), and tetanus (14, 0.3%).

Discussion

In this large cross-sectional study, we found that in the most recent fall/winter season, multiple demographic factors and health behaviors were associated with the likelihood of receiving an influenza vaccination, including age, higher level of education, higher level of income, smoking, and physical activity. Only one of the MS characteristics we examined, use of a disease-modifying therapy, was associated with receiving an influenza vaccination. Among those who did not receive a vaccination, half had concerns regarding adverse effects and misconceptions about the possible impact of the vaccine on their MS. Although these were infrequent, access issues were also reported. Uptake of the other vaccinations queried varied substantially with age.

The most recent American Academy of Neurology guidelines recommend that people with MS follow all local vaccine standards unless there is a specific contraindication and receive the influenza vaccination annually unless there is a specific contraindication.9 In the United States, tetanus vaccination is recommended for all adults every 10 years. Vaccination to prevent shingles is recommended for all adults aged ≥50 years; and pneumococcal vaccine is recommended for all adults aged...
≥65 years, and for immunocompromised adults aged ≥19 years. These targets were not met among our study participants even when we considered the age-specific nature of some of these recommendations.

In the 2018-19 season, 39.0% of US adults aged 18–64 years received the influenza vaccine, whereas 68.1% of adults aged 65 years and older received the vaccine. This appears lower than among our participants. However, uptake was higher among adults with high-risk conditions than among adults without high-risk conditions, possibly due to more frequent health system contacts. In other immune-mediated diseases such as IBD, uptake reportedly ranges from 6% to 80%7 and in rheumatoid arthritis varies from 26.6% to 85%.18,19 Comparable prior work regarding uptake of immunizations in people with MS is limited, focusing mainly on influenza vaccination. A Norwegian immunization register-based study reported that of 6,755 persons with MS, 60.7% received the pandemic (H1N1) vaccine in 2009–2010.20 A study of 101 persons with MS followed in Tel Aviv, Israel, found that 37.6% of participants received the seasonal flu vaccine in 2009/10, and 34.7% received the H1N1 flu vaccine, whereas 23.7% received both vaccines.5 A recent population-based study in Manitoba, Canada, found that approximately 40% of persons with MS received an influenza vaccination in 2015. Similar to our findings in the NARCOMS cohort, the uptake of the influenza vaccine was highest among those aged ≥65 years at 60%.6

We found that several factors were associated with uptake of the influenza vaccine. In the Manitoba, Canada, study, older age, higher socioeconomic status, and use of disease-modifying therapies were associated with increased uptake of the vaccine by people with MS, consistent with our findings.6 In contrast to our findings showing that sex was not associated with uptake, that study also found that female sex was associated with increased uptake. Another study showed that a postsecondary education and being female are associated with greater awareness of vaccine-preventable diseases.21

About 1 in 2 participants who did not get seasonal influenza vaccine reported a fear of general adverse effects or of adverse effects on their MS as the reason. One in 10 was advised against getting a flu shot by their physicians. Multiple factors may contribute to the decision not to get a vaccine, but these findings highlight important misconceptions about influenza vaccination and MS among patients and physicians. In the aforementioned Israeli study, the influenza vaccines were well tolerated. Only 5/49 participants who received at least 1 vaccine reported fever or flu-like symptoms, and no neurologic symptoms occurred after receiving vaccine.5 There is no convincing evidence that influenza vaccination causes exacerbations of MS.9 The inactivated influenza shot is not contraindicated, even in persons with MS who receive immunosuppressive therapies. Although the response to vaccination may be attenuated in individuals taking some therapies,22-25 some benefit may still be achieved. Our findings are generally concordant with those in other populations. In a 2015/2016 survey of the Canadian general population, commonly reported reasons for not getting the influenza vaccine included a lack of perceived susceptibility to influenza, lack of perceived severity of infection, and not believing in the vaccine’s effectiveness.26 In populations with immune-mediated diseases other than MS, additional factors cited include not receiving information about vaccination from a physician, concerns about adverse effects, lack of...
awareness about indications for vaccination, and misconceptions about the effects on their disease.15,27 For example, in 1 study, 18% of persons with IBD who did not get vaccinated reported not doing so because it could be harmful for their IBD.7 In the previously mentioned Israeli study, cited reasons for not getting these vaccinations included fear of non-neurologic adverse effects (72.7%) or that their treating physician had recommended against it because of their MS (11.7%). This latter observation highlights the potential role of physician barriers to vaccination,28,29 including gaps in knowledge about safety of and recommendations for vaccinations in specific populations.

Studies in other immune-mediated disease populations have highlighted interventions that can improve vaccination rates. For example, in an IBD clinic, a vaccine questionnaire was distributed to patients during the influenza season, and any outstanding vaccinations were offered at the visit.30 This increased uptake of the influenza vaccination from 54% in the prior year to 81% and uptake of pneumococcal vaccine in the prior 5 years from 31% to 54%. This approach is potentially feasible for improving vaccinations in people with MS, too. Provider recommendation is strongly associated with uptake of the seasonal influenza vaccine31; thus, recommendations at the time of routine clinic visits may be helpful.

Study limitations should be considered. The response rate was 62%, similar to the mean response rate of 60% in the medical literature.32 Responders differed with respect to

Table 3 ORs (95% CIs) for the Association Between Participant Characteristics and Receipt of the Influenza Vaccination (n = 4,697)

| Characteristic                        | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---------------------------------------|------------------------|----------------------|
| Sex                                   |                        |                      |
| Male                                  | 1.0                    | 1.0                  |
| Female                                | 0.81 (0.68–0.95)        | 0.88 (0.73–1.05)     |
| Age group (y), n (%)                  |                        |                      |
| 18–34                                 | 0.36 (0.20–0.67)        | 0.29 (0.14–0.60)     |
| 35–49                                 | 0.47 (0.38–0.57)        | 0.35 (0.27–0.45)     |
| 50–64                                 | 0.64 (0.56–0.74)        | 0.57 (0.49–0.66)     |
| 65+                                   | 1.0                    | 1.0                  |
| Race                                  |                        |                      |
| Non-White                             | 1.0                    | 1.0                  |
| White                                 | 1.00 (0.82–1.20)        | 1.12 (0.92–1.38)     |
| Education                             |                        |                      |
| High school/GED                       | 1.0                    | 1.0                  |
| Postsecondary education               | 1.43 (1.24–1.64)        | 1.26 (1.08–1.47)     |
| Annual household income               |                        |                      |
| Less than $50,000                     | 1.0                    | 1.0                  |
| $50,001–$100,000                      | 1.23 (1.04–1.45)        | 1.07 (0.89–1.28)     |
| Over $100,000                         | 1.58 (1.31–1.90)        | 1.44 (1.16–1.79)     |
| I do not wish to answer               | 1.27 (1.06–1.51)        | 1.11 (0.92–1.34)     |
| Current smoking status                |                        |                      |
| No                                    | 1.0                    | 1.0                  |
| Yes                                   | 0.51 (0.41–0.64)        | 0.60 (0.47–0.77)     |
| Alcohol intake                        |                        |                      |
| Never                                 | 1.0                    | 1.0                  |
| Monthly or less                       | 1.17 (0.99–1.38)        | 1.16 (0.97–1.37)     |
| 2–4 times a month                     | 1.36 (1.12–1.66)        | 1.26 (1.02–1.56)     |
| 2–3 times a week                      | 1.36 (1.08–1.71)        | 1.19 (0.93–1.52)     |
| ≥4 times a week                       | 1.32 (1.07–1.62)        | 1.23 (0.98–1.54)     |
| Physical activity                     |                        |                      |
| Inactive                              | 1.0                    | 1.0                  |
| Active                                | 1.30 (1.14–1.47)        | 1.22 (1.05–1.42)     |
| Depression                            |                        |                      |
| No                                    | 1.0                    | 1.0                  |
| Yes                                   | 0.86 (0.76–0.99)        | 1.04 (0.87–1.24)     |
| Anxiety                               |                        |                      |
| No                                    | 1.0                    | 1.0                  |

Abbreviations: CI = confidence interval; OR = odds ratio.
C-statistic = 0.63, Hosmer-Lemeshow goodness of fit $\chi^2 = 12.9, p = 0.15$. Bold indicates statistical significance.
Table 4 Reasons for Not Receiving Seasonal Influenza Vaccination (n = 1,303 Participants)

| Reason                              | N (%)          | 95% CI       |
|-------------------------------------|----------------|-------------|
| Personal preference                 | 391 (30.0)     | 27.6, 32.6  |
| Did not think I needed it           | 339 (26.0)     | 23.7, 28.5  |
| Personal choice                     | 24 (1.84)      | 0.01, 0.03  |
| Concerns about flu efficacy         | 19 (1.46)      | 0.94, 2.27  |
| Misperceptions about the flu shot*  | 9 (0.69)       | 0.36, 1.31  |
| Side effects or illness from the vaccine | 3 (29.3)    | 26.9, 31.8  |
| Concerned about side effects        | 3 (28.4)       | 26.0, 30.9  |
| Previous illness following flu shot | 12 (0.92)      | 0.53, 1.60  |
| Access/availability                 | 27 (2.07)      | 1.43, 3.00  |
| Too expensive                       | 6 (0.46)       | 0.21, 1.00  |
| Difficulty accessing clinic         | 9 (0.69)       | 0.36, 1.31  |
| Vaccine not available               | 12 (0.92)      | 0.53, 1.60  |
| Contextual factors                  | 121 (9.29)     | 7.83, 11.0  |
| Too busy/forgot                     | 83 (6.37)      | 5.17, 7.83  |
| COVID-19                            | 5 (0.38)       | 0.16, 0.90  |
| Sick when flu shot available        | 4 (0.31)       | 0.12, 0.79  |
| Never offered flu shot              | 38 (2.92)      | 2.13, 3.98  |
| My doctor advised against a flu shot| 157 (12.1)     | 10.4, 13.9  |
| Concerned that the vaccine would worsen my MS | 308 (23.6) | 21.4, 26.0 |
| Allergy to eggs/vaccines            | 66 (5.07)      | 4.00, 6.39  |
| Don’t know                          | 52 (3.99)      | 3.06, 5.20  |
| Other                               | 73 (5.60)      | 4.48, 6.99  |

Abbreviations: CI = confidence interval; MS = multiple sclerosis.
*Example reported reasons: “Any live vaccine because on Gilenya”, “IVIG”, “Ocrevus contraindicated/concerned about interaction”, “No live viruses”, “Told long ago never to do with MS”, and “on other meds conflicted”.

Race, sex, age, and educational status compared with nonresponders, although some of these differences were quite small. NARCOMS participants are volunteers, creating a potential selection bias, which may limit the generalizability of our findings to the entire MS population. We relied on self-reported vaccination status; however, in a cohort with IBD, the positive predicted value of self-reported influenza vaccination was 96.7% and that of pneumococcal vaccination was 96.4%. The positive predictive value of other vaccinations is lower. Our questionnaire asked about multiple reasons for not getting the influenza vaccination but did not explicitly ask about lack of efficacy; thus, we may have underestimated the frequency of this concern. Although we asked participants to report reasons for not obtaining the influenza vaccination, we did not capture reasons for not obtaining other optional vaccinations such as those for hepatitis or Zoster, and these would also be important to guide policy. Study strengths included the large sample size and evaluation of a broad range of demographic factors, health behaviors, and clinical characteristics with vaccination uptake.

Vaccination uptake is lower than desired in the MS population compared with public health recommended targets, including for seasonal influenza vaccination. This places people with MS at risk for preventable infections and related hospitalizations and complications. Misconceptions about the safety of vaccination in the context of MS highlight the importance of education about these issues and consistent recommendations by health care providers.

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