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Vaccine hesitancy among people with multiple sclerosis

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ABSTRACT

Background: The current severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has raised awareness of vaccine hesitancy. Specific reasons for vaccine hesitancy among people with multiple sclerosis (pwMS) have not been fully described. Notably, pwMS may experience higher morbidity from vaccine-preventable diseases such as influenza, pneumococcal disease, and human papillomavirus (HPV)-associated warts and malignancies. Furthermore, screening for immunity against measles, mumps and rubella (MMR) is not standard practice, despite a resurgence of measles and mumps outbreaks in Europe and worldwide. We aimed to evaluate general vaccination status among pwMS to better inform vaccine practices in this cohort.

Methods: This was a prospective audit of pwMS attending an Irish tertiary referral MS centre. We designed a questionnaire that explored awareness, uptake, and hesitancy for the influenza, pneumococcal, SARS-CoV-2, HPV, and MMR vaccines. The clinician administered the questionnaire during the outpatient MS clinic.

Results: One-hundred-and-five pwMS participated in the audit, mean (SD) age 47.3 (12.8) years, mean MS disease duration 14.1 (9.5) years, median Expanded Disability Severity Scale (EDSS) score 2.0 (IQR 1.0-6.0), forty-nine (46.7%) were taking either maintenance immunosuppressive or immune reconstitution therapies. SARS-CoV-2 vaccine willingness among pwMS was higher (90.5 vs 60-80%) than that reported in other Western countries, and higher than that for the influenza and pneumococcal vaccines (~80%) for which perceived unnecessity and unfamiliarity respectively were the main limiting factors. The primary reason for SARS-CoV-2 vaccine hesitancy was safety concern. PwMS who were explicitly advised by a healthcare professional to obtain the influenza vaccine were more likely to do so than those who were not (odds ratio, 8.1, 95% CI 2.8 – 23.4, $p<0.001$). Of pwMS currently receiving B-cell therapy (ocrelizumab/rituximab, n=12), all but one (n=11, 91.7%) have never received the pneumococcal vaccine, and a quarter (n=3) were uncertain whether to obtain this in the future. Patient-reported uptake of HPV (1.0%) and MMR (51.4%) vaccines were suboptimal. Prevalence of vaccine promotion among healthcare professionals was low (influenza vaccine, 4.8 – 32.4%; pneumococcal vaccine, 0 – 18.1%).

Conclusions: Vaccine hesitancy is common (10-20%) in pwMS, consequent to insufficient knowledge and misconceptions about vaccination among pwMS and suboptimal vaccine promotion by healthcare professionals who manage pwMS. Conscientious and context-specific vaccination counselling is necessary to tackle vaccine hesitancy among pwMS, including (i) avoiding infection-associated disability accrual during MS relapses, (ii) reducing the potentially higher risk of life-threatening/treatment-refractory complications that may be observed in those who develop vaccine-preventable infections while receiving certain DMTs, and (iii) avoiding attenuated vaccine responses or delayed/interrupted DMT with early pre-treatment vaccine delivery where possible.

1. Introduction

Vaccine hesitancy is a threat to global public health (Health, 2019; Boekel et al., 2021; Schwarzinger et al., 2021; Ehde et al., 2021; Serrazina et al., 2021). The current severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has raised awareness of vaccine hesitancy (Boekel et al., 2021; Schwarzinger et al., 2021; Ehde et al., 2021; Serrazina et al., 2021). Specific reasons for vaccine

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hesitancy among people with multiple sclerosis (pwMS) have not been fully described. PwMS, particularly those on immunosuppressive disease-modifying therapies (DMTs) and/or with severe disability, have higher morbidity from vaccine-preventable infections, and MS relapses with superimposed infection may cause more severe and sustained disability than spontaneous ones (Reyes et al., 2020; Riva et al., 2021). Firstly, while it is routine to screen for varicella zoster immunity and cervical cytology/human papillomavirus (HPV) status before starting immunosuppressive therapies in pwMS (Riva et al., 2021), screening for immunity against measles, mumps and rubella (MMR) is not standard practice; this is concerning given the resurgence of measles and mumps outbreaks in Europe and worldwide, partly attributable to historical missed MMR vaccine doses and waning vaccinal immunity (Reyes et al., 2020; Yang et al., 2020). Secondly, pre-treatment HPV vaccination is not routine despite emerging reports of HPV-associated cutaneous/anogenital/oromucosal warts and malignancies, and cervical dysplasia, in pwMS on fingolimod (Mhanna et al., 2021). Finally, the propensity for respiratory tract infections in pwMS receiving B-cell-depleting therapies suggests that obligatory pre-treatment pneumococcal vaccination may well be warranted (Reyes et al., 2020).

The primary objective of this audit was to evaluate general vaccination status in pwMS, particularly the promotion, awareness, uptake, and hesitancy for the influenza, pneumococcal, SARS-CoV-2, HPV, and MMR vaccines, to identify the relevance of these vaccinations to pwMS to better inform vaccination practices for pwMS.

2. Methods

We performed a prospective audit of pwMS attending a tertiary referral MS centre. This audit was approved by the Clinical Audit Committee of the St. Vincent's Healthcare Group, Dublin. We designed a questionnaire that consisted of dichotomous (yes/no) and open-ended questions and explored promotion, awareness, uptake, and hesitancy for the influenza, pneumococcal, SARS-CoV-2, HPV, and MMR vaccines. The clinician administered the questionnaire during the outpatient clinic consultation.

At time of data collection (13th January to 31st March 2021), the Irish Department of Health was beginning the SARS-CoV-2 vaccine rollout during which the following groups were prioritised: frontline healthcare workers, people aged over 70 years, and residents and staff at long-term residential care facilities (Department of Health 2021). Meanwhile, the Irish national immunisation programme for the influenza, pneumococcal, HPV and MMR vaccines is as follows - (i) influenza vaccine: to be administered annually to at-risk groups, including and not limited to persons with chronic neurological disease (Health Service Executive 2021a); (ii) pneumococcal polysaccharide vaccine: to be administered at least once to those aged 65 years or older and those aged 2 years and over with long-term medical conditions including chronic neurological disease (Health Service Executive 2021b); (iii) HPV vaccine, first introduced in Ireland in 2010 to be administered to girls in first year of secondary school (roughly age 11-12 years), and since 2019 to be administered to both boys and girls in first year of secondary school (Health Service Executive 2021c); (iv) MMR vaccine, introduced in Ireland in 1988, to be administered to children at age 12 months and at 4-5 years (Health Service Executive 2021d).

Statistical analysis was performed using SPSS version 26. Normality of data was assessed using the Shapiro-Wilk test. We used the independent-samples t-test to assess differences in age and disease duration between vaccination groups, and similarly the Mann-Whitney-U test to assess differences in EDSS between these groups. We used the chi-square test to determine relationships between sex and vaccination categories, and vaccination categories with each other. A significance level of 0.05 was used.

3. Results

One-hundred-and-five pwMS participated in the audit; clinical and demographic characteristics of the cohort are shown in Table 1.

3.1. Influenza vaccine

Two-thirds (n=67, 63.8%) received the influenza vaccine within the past year; these pwMS had longer disease duration (mean 15.8 vs 11.2 years, p=0.009, 95% confidence interval, CI 1.1 – 8.0) and higher disability (median EDSS 2.0 vs 1.5, p=0.038) compared to those who did not receive the influenza vaccine. PwMS who were explicitly advised by a healthcare professional to obtain the influenza vaccine were more likely to do so than those who were not (odds ratio, OR 8.1, 95% CI 2.8 – 23.4, p<0.001). One-fifth (n=21, 20.0%) expressed hesitancy for the influenza vaccine. Of those who did not receive the influenza vaccine during the past year, the most common (n=19, 50.0%) reason was perceived lack of necessity (Table 2).

3.2. Pneumococcal vaccine

Promotion of the pneumococcal vaccine by healthcare professionals for pwMS was suboptimal (Table 2), and two-thirds (n=37, 63.8%) reported never having heard of the pneumococcal vaccine. Nineteen (18.1%) had obtained the pneumococcal vaccine – these pwMS were older (mean 55.4 vs 45.6 years, p=0.002, 95% CI 3.6 – 16.0) and more likely to be female (OR 4.6, 95% CI 1.0 – 21.1, p=0.037). PwMS who were explicitly advised by a healthcare professional to obtain the pneumococcal vaccine were more likely to do so than those who were not (OR 76.9, 95% CI 17.3 – 341.5, p<0.001). One-fifth (n=22, 21%) expressed hesitancy for the pneumococcal vaccine; the most common (n=12, 54.5%) reason was insufficient knowledge about the pneumococcal vaccine. Of pwMS currently receiving B-cell therapy (ocrelizumab/rituximab, n=12), all but one (n=11, 91.7%) have never received the pneumococcal vaccine, and a quarter (n=3) were unwilling/uncertain whether to obtain this in the future.

3.3. SARS-CoV-2 vaccine

At time of data collection (13th January to 31st March 2021), only one pwMS (also a healthcare worker) had received the SARS-CoV-2 vaccine (healthcare professionals were prioritised during the initial

Table 1
Clinical and demographic characteristics of the study population.

Age, years, mean (SD)	47.3 (12.8)	
Female, n (%)	73 (69.5)	
Type of MS		
Relapsing, n (%)	74 (70.5)	
Progressive, n (%)	31 (29.5)	
Time since MS diagnosis, years, mean (SD)	14.1 (9.5)	
EDSS score, median (IQR)	2.0 (1.0-6.0)	
Disease-modifying therapy use, n (%)		
Immune reconstitution therapies	8 (7.6)	
Cladribine	5 (4.8)	
Alemtuzumab	2 (1.9)	
Autologous stem cell transplantation	1 (1.0)	
Second-line therapies	41 (39.0)	
Fingolimod	15 (14.3)	
Natalizumab	14 (13.3)	
Rituximab	7 (6.7)	
Ocrelizumab	5 (4.8)	
First-line therapies	33 (31.4)	
First-line injectables	21 (20.0)	
Dimethyl fumarate	11 (10.5)	
	Teriflunomide	1 (1.0)
None	23 (21.9)	

SD, standard deviation; MS, multiple sclerosis; EDSS, expanded disability severity scale, IQR, interquartile range.

Table 2
Vaccine promotion, uptake and hesitancy reported by people with multiple sclerosis.

	Influenza	Pneumococcal	SARS-CoV-2	HPV	MMR
Vaccine uptake					
Received vaccine n (%)	67[a] (63.8)	19 (18.1)	1 (1.0)	1 (1.0)	55 (51.4)
Advised to get vaccine by:					
GP n (%)	34 (32.4)	19 (18.1)	nd	nd	nd
MS Nurse n (%)	4 (4.8)	0 (0)	nd	nd	nd
MS Doctor n (%)	7 (6.7)	0 (0)	nd	nd	nd
Vaccine promotion					
Heard of the vaccine n (%)	nd	38 (36.2)	nd	nd	nd
Felt vaccine was accessible n (%)	99 (94.3)	85 (81.0)	84 (80.0)	nd	nd
Vaccine hesitancy					
Unwilling/uncertain whether to get vaccine:					
of all pwMS n (%)	21 (20.0)	22 (21.0)	10 (9.5)	nd	nd
of those who have not received it n (%)	19[a] (50.0)	22 (25.6)	10 (9.6)	nd	nd
Uncertain about effectiveness n (%)	7 (6.7)	24 (22.9)	11 (10.5)	nd	nd
Uncertain about safety for pwMS n (%)	8 (7.6)	24 (22.9)	12 (11.4)	nd	nd
Uncertain about safety for general population n (%)	4 (3.8)	21 (20.0)	6 (5.7)	nd	nd
Uncertain about necessity n (%)	15 (14.3)	23 (21.9)	7 (6.7)	nd	nd
Verbatim reasons for vaccine hesitancy among pwMS unwilling/ uncertain whether to get vaccine n (%)	"Don't need it" 10 (47.6); "Personally/ know someone who suffered side effects" 6 (28.6); "Don't get sick often" 2 (9.5); "May worsen MS" 2 (9.5); "Vaccines cause problems" 1 (4.8).	"Don't know much about it" 12 (54.5); "Don't get sick often" 4 (18.2); "Don't need it" 2 (9.2); "May worsen MS" 1 (4.5); "May not be safe for pwMS" 1 (4.5); "Know someone who got sick despite vaccine" 1 (4.5); "Vaccines cause problems" 1 (4.5).	"May not be safe" 4 (40.0); "Not enough known about it" 2 (20.0); "Not tested in MS" 1 (10.0); "May cause MS relapse" 1 (10.0); "Will not work" 1 (10.0); "Currently pregnant" 1 (10.0).	nd	nd

[a] in the past year; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; HPV, human papillomavirus; MMR, measles mumps rubella; nd, not determined; GP, general practitioner; MS, multiple sclerosis; pwMS, people with MS; DMT, disease-modifying therapy.

phase of the vaccine rollout in Ireland). Hesitancy for the SARS-CoV-2 vaccine was reported by ten (9.5%) pwMS, approximately half that for the influenza and pneumococcal vaccines. The most common (n=4, 40.0%) reason for SARS-CoV-2 vaccine hesitancy was perceived safety concern (Table 2). PwMS willing to obtain the SARS-CoV-2 vaccine had higher disability (median EDSS 2.0 vs 1.5, p=0.035) compared to those hesitant, and no significant differences were observed in age, sex, MS disease duration, and DMT use, between the two groups. PwMS hesitant for the influenza vaccine were more likely to also be hesitant about receiving the SARS-CoV-2 vaccine (OR 20.5, CI 3.9 – 109.0, p<0.001).

3.4. HPV vaccine

Only one pwMS had obtained the HPV vaccine, albeit for a separate reason unrelated to MS (patient was administered the HPV vaccine in addition to colposcopy and cervical biopsy upon discovery of high-grade cervical dysplasia).

3.5. MMR vaccine

Around half (n=51, 48.6%) reported that they did not receive or were uncertain about having received the MMR vaccine during childhood. The proportion of pwMS who reported that they never had or were uncertain about having had prior measles, mumps, or rubella infection were 56.2% (n=59), 73.3% (n=77) and 91.4% (n=96) respectively.

4. Discussion

We showed that vaccine hesitancy is common (10-20%) among pwMS, consistent with previous findings (Health, 2019; Boekel et al., 2021; Schwarzinger et al., 2021; Ehde et al., 2021; Serrazina et al., 2021), and consequent to insufficient knowledge and misconceptions about vaccination (Table 2). Interestingly, SARS-CoV-2 vaccine willingness in our Irish cohort is notably higher (91.5%) than that reported elsewhere (60-80%) (Boekel et al., 2021; Schwarzinger et al., 2021; Ehde et al., 2021; Serrazina et al., 2021), and higher than that for the influenza and pneumococcal vaccines for which perceived unnecessity and unfamiliarity respectively were the main limiting factors. One possible explanation is the persistent reinforcement by public health messaging of its health, societal and economic benefits immediately and directly relevant to them (i.e., prevent severe SARS-CoV-2 illness and reduce viral transmission thereby enabling easing of social restrictions and a more rapid return to "normality"). Additionally, the SARS-CoV-2 pandemic may have been perceived by pwMS as a more acute and ubiquitous threat compared to influenza and pneumococcal disease. Taken together, these findings demonstrate the potentially large impact on vaccine uptake that may be had with dedicated patient education by healthcare professionals on the direct relevance of vaccination to pwMS (Health, 2019; Boekel et al., 2021; Ehde et al., 2021; Serrazina et al., 2021).

This audit revealed a low prevalence of vaccine promotion among healthcare professionals (influenza vaccine, 4.8 – 32.4%; pneumococcal vaccine, 0 – 18.1%). The clinical significance of promoting vaccinations for pwMS was likely under-appreciated among healthcare professionals and therefore under-performed, however, these findings may also be subject to patient recall bias. Nonetheless, training of healthcare professionals to promote vaccinations effectively and rigorously among pwMS is warranted. Moreover, we showed that uptake for the SARS-CoV-2, pneumococcal and HPV vaccines was particularly low (Table 2). Whilst the minimal uptake of the SARS-CoV-2 vaccine may be explained by the very early stage of vaccine rollout in Ireland at time of data collection (Department of Health 2021), the suboptimal uptake of the pneumococcal vaccine among pwMS likely resulted from healthcare professionals restricting promotion of this vaccine to older (e.g., ≥65

years) and/or more severely disabled individuals without recognising its relevance to all pwMS (i.e., increased morbidity with vaccine-preventable infections developed on immunosuppressive DMTs and increased disability accrual with infection-associated relapses) (Reyes et al., 2020). Meanwhile, HPV vaccine uptake was poor because this vaccine was introduced in Ireland merely a decade ago and largely recommended for 11 to 12-year-olds (Health Service Executive 2021c); this finding highlights the stark absence of adequate immunity against HPV (Mariani and Venuti, 2010) among the current generation of pwMS who may be at risk of vaccine-preventable HPV-associated warts and cancers that may develop with DMT use, especially with fingolimod, and raises the question of whether pwMS should undergo obligatory HPV vaccinations before commencing certain DMTs. Certainly, the efficacy and cost-effectiveness of obligatory HPV and pneumococcal vaccinations before commencing fingolimod and B-cell therapies respectively should be further explored in large-scale studies (Riva et al., 2021).

Importantly, we showed that pwMS who were advised by a healthcare professional to obtain the influenza or pneumococcal vaccines were more likely to do so than those who were not. Physician advice has been shown to be the most important predictor of vaccine acceptance (Health, 2019). We suggest context-specific vaccination counselling for pwMS, namely (i) avoiding infection-associated additional disability accrual during MS relapses (Reyes et al., 2020); (ii) reducing the potentially higher risk of life-threatening/treatment-refractory complications (e.g., measles encephalitis, mumps meningitis/orchitis/oophoritis, HPV-associated chronic warts and malignancies) (Yang et al., 2020; Mhanna et al., 2021) that may be observed in those who develop vaccine-preventable infections while receiving certain DMTs; and (iii) avoiding attenuated vaccine responses or delayed/interrupted DMT with early pre-treatment vaccine delivery where possible (Riva et al., 2021). Moreover, effective vaccine promotion messaging should be delivered simply without medical jargon, with misconceptions corrected in a timely manner and supported by scientific evidence (Volpp et al., 2021).

This audit has several limitations. Firstly, our results were confounded by patient recall bias and the inability to objectively confirm patient reports because documentation of immunisation was not readily available. This is especially relevant regarding childhood MMR vaccination: half of pwMS in our cohort did not receive or were uncertain of having received the MMR vaccine. Consequently, screening for anti-measles and anti-mumps antibodies at MS diagnosis with subsequent MMR vaccination where inadequate immunity is found (Reyes et al., 2020; Riva et al., 2021), may be considered. Additionally, an electronic immunisation registry is recommended, and artificial intelligence immunisation information systems (Atkinson et al., 2020) hold promising potential for tackling vaccine hesitancy. Secondly, the prospective nature of data collection may have led to a social desirability bias regarding selection of participants. Thirdly, we did not collect data about hesitancy for the HPV and MMR vaccines because administration of these vaccines prior to DMT commencement is currently not widely performed and enquiry about willingness to obtain these vaccines for MS-related reasons might have caused undue confusion among pwMS. Nevertheless, it would be useful to know whether pwMS will accept HPV and MMR vaccines for MS-related reasons – this data should be collected as part of recommendations for further work, including a re-audit of this patient cohort after 12 months of vaccination counselling in the outpatient MS clinic. Finally, we did not use a validated vaccine acceptance questionnaire because most of these established scales have focussed on parental attitudes towards childhood vaccination (Larson et al., 2015; de Figueiredo et al., 2020; Akel et al., 2021) and recent large-scale vaccine hesitancy studies have used modified versions of established scales to, firstly, reflect vaccination attitudes of adults; and secondly, to answer study-specific questions (de Figueiredo et al., 2020; Akel et al., 2021; Helmkamp et al., 2021; Kumari et al., 2021; Ogilvie et al., 2021; Lazarus et al., 2021). Moreover, our questionnaire items encompass the three main reasons for vaccine hesitancy: motivation about health and prevention; risk/benefit of vaccines, and communication environment (Larson et al., 2015).

In conclusion, this prospective audit of 105 pwMS revealed suboptimal levels of vaccine uptake and willingness among pwMS and inadequate vaccine promotion by healthcare professionals, although it was also found that vaccine willingness was higher in pwMS who were explicitly advised by a healthcare professional to obtain the vaccine compared to those who were not. Consistent and context-specific vaccination counselling is necessary to tackle vaccine hesitancy among pwMS. Meanwhile, the appropriateness of obligatory vaccine delivery at MS diagnosis/pre-treatment should be further elucidated.

Data availability statement

Anonymised data will be shared on request with any suitably qualified investigator.

CRediT authorship contribution statement

Siew Mei Yap: Conceptualization, Project administration, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Mahmood Al Hinai:** Investigation, Writing – review & editing. **Maria Gaughan:** Writing – review & editing. **Ian Callanan:** Resources, Supervision, Writing – review & editing. **Hugh Kearney:** Conceptualization, Supervision, Writing – review & editing. **Niall Tubridy:** Conceptualization, Writing – review & editing. **Christopher McGuigan:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

SMY received research support from Novartis. NT received research support from Novartis. CMG received research support from Biogen, Novartis, and Roche. MAH, MG, IC, and HK declare that there is no conflict of interest.

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