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To be or not to be vaccinated: The risk of MS or NMOSD relapse after COVID-19 vaccination and infection

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ABSTRACT

Background: COVID-19 vaccination and infection are speculated to increase the activity of immune-mediated diseases, including multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). The aim of this study was to evaluate a short-term risk of relapse after COVID-19 vaccination and COVID-19 infection in patients with these demyelinating disorders of the central nervous system and to determine disease exacerbation risk factors.

Methods: Data in this retrospective, observational cohort study was collected via the Czech nationwide registry ReMuS from March 1, 2020, to October 30, 2021. We compared the proportion of patients with at least one clinical relapse in the 90 days following vaccination or infection to the 90-day intervals during the year before. For the evaluation of the risk factors of relapse, a comparison between groups with and without relapses after COVID-19 vaccination or infection was made.

Results: We identified 1661 vaccinated (90.11% BNT162b2) patients with MS without a history of COVID-19 and 495 unvaccinated patients with MS who experienced COVID-19. A mild increase in the proportion of patients with at least one clinical relapse (-360 to -270 days: 4.46%; -270 to -180: 4.27%; -180 to -90: 3.85%; -90 to 0: 3.79% vs. 0 to +90 days: 5.30%) after vaccination in patients with MS was observed, as well as a rise in the proportion of patients with at least one clinical relapse after COVID-19. Lower age was associated with MS relapse after vaccination or infection. Although there were only 17 vaccinated and eight post-COVID-19 patients with NMOSD, the results were broadly consistent with those of patients with MS.

Conclusion: There is a mild increase in the relapse incidence after the COVID-19 vaccination. The risks, however, need to be balanced against the risks of COVID-19 itself, also leading to the rise in relapse rate and particularly to morbidity and mortality.

1. Introduction

Globally, there have been almost 300 million confirmed cases of coronavirus disease 19 (COVID-19), including nearly 3.5 million deaths, at the beginning of 2022 (World Health Organisation, 2022). The key element of strategies to reduce the severity of the disease and to suppress the spread of infection is vaccination. COVID-19 vaccines authorised by the European Medicines Agency (EMA) (European Medicines Agency, 2022) have been tested in randomised clinical trials (Baden et al., 2021; Polack et al., 2020; Sadoff et al., 2021; Voysey et al., 2021) which were designed to establish efficacy and safety in the general population. However, these clinical trials were not designed to evaluate safety
profile in patients with multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD).

MS and NMOSD are chronic autoimmune inflammatory diseases of the central nervous system. Generally, vaccines work by stimulating the immune system. Their immunogenicity is key to achieving protection against specific pathogens. Therefore, there is one more potential risk of vaccination in patients with MS and NMOSD in comparison with the healthy population: the risk of induction of disease exacerbation. The risks, however, need to be balanced against the risks of COVID-19 itself, leading to morbidity and death even in people without disabilities. Moreover, numerous data is demonstrating a higher risk of more severe COVID-19 course in patients with MS and NMOSD treated with high-dose glucocorticoids or anti-CD20 monoclonal antibodies (Barzegar et al., 2021a; Prosperini et al., 2022; Stastna et al., 2021) and there are also data showing an association between systemic infection and risk of MS or NMOSD relapse (Correale et al., 2006; Ma et al., 2020).

To our knowledge, data assessing the effect of COVID-19 infection and vaccination on the risks of relapse in MS and NMOSD are scarce, inconsistent, and mostly evaluated on relatively small cohorts (Achiron et al., 2021; Barzegar et al., 2021b; Cai et al., 2021; di Filippo et al., 2021; Dinoto et al., 2021; Etemadifar et al., 2021; Fragoso et al., 2021; Jovicic et al., 2021; Lotan et al., 2021b, 2021a). Thus, in the light of the ongoing global COVID-19 pandemic situation and the continuing need for vaccination, we aimed to evaluate the short-term risks of clinical relapse in the 90-day period after the first dose COVID-19 vaccine administration and COVID-19 infection as well as the safety profile of COVID-19 vaccines in patients with MS and NMOSD. Our goal was also to determine factors related to the potential increase of immediate disease activity.

2. Methods

2.1. Data collection

Two of the largest Czech MS centres representing almost one-third of the Czech MS population participated in this retrospective, observational cohort study. Data from the largest one (General University Hospital in Prague) were used for the main analysis, data from the second MS centre (Hospital Teplice) for the independent validation of results. The data was collected via the Czech nationwide registry ReMuS from March 1, 2020, to October 30, 2021. The guarantor of expertise of this registry is the Section for Neuroimmunology and Liquorology of the Czech Neurological Society. Data in register ReMuS are collected using standardized software iMed. Before the release of the coded patient-level data to investigators, there is a multiple-level quality control process (Horakova et al., 2019).

2.2. Standard protocol approvals, registrations, and patient consents

ReMuS was established by the Endowment Fund IMPULS (NF IMPULS, 2022) and approved by local ethics committees in each MS centre (The Ethics Committee of the General University Hospital in Prague and The Ethics Committee of The KZ a.s. - Hospital Teplice). ReMuS is based on informed consent, thus it is possible to use retrospective data for scientific and research purposes without requiring new approvals. An informed consent was obtained from all patients enrolled in ReMuS.

2.3. Population of interest

The inclusion criteria for participants of this study were (1) MS or NMOSD diagnosis, (2) administration of at least one dose of COVID-19 vaccine or a COVID-19 diagnosis based on a positive result of a SARS-CoV-2 polymerase chain reaction test (PCR) or positive antigen test or positive serological test, (3) together with a healthcare professional completed vaccine adverse events (AEs) questionnaire (containing questions about most common AEs (Baden et al., 2021; Meo et al., 2021; Polack et al., 2020; Sadoff et al., 2021; European Medicines Agency, 2022; Voysey et al., 2021), their severity and free text option) or known outcome of acute SARS-CoV-2 infection (return to normal activities or end of self-isolation in asymptomatic cases; or death), (4) minimum of 90-day follow up taking as baseline the day of the first vaccine dose administration or COVID-19 symptoms appearance or positive COVID-19 laboratory test (what earlier). Patients who experienced both COVID-19 vaccination and infection in the 90-day period after baseline were excluded.

2.4. Variables assessed and definitions

Data on demographics, MS or NMOSD, COVID-19 course, vaccination (together with AEs and their severity) were collected (Table 1, 2 and 3). MS exacerbation/relapse was defined as the development of a new neurological abnormality, or worsening of a pre-existing one, for more than 24 h. It must have been preceded by a stable or improving neurological state for at least 30 days, in the absence of concurrent fever, infection or steroid withdrawal. Severe relapse was defined by the increase of Expanded Disability Status Scale (EDSS) by 2.5 steps in total or by two steps in three and more functional systems (FS) or by hospitalisation due to MS or NMOSD relapse. Moderate relapse was defined by an increase of EDSS by one or two steps in total or increase by two steps in one or two FS or by one step in four or more FS. Mild relapse was defined by lower severity than a moderate one.

AEs were defined as medical occurrences temporally associated with the vaccine administration, but not necessarily causally related. They were classified as life-threatening, severe (requiring hospitalization or invasive intervention), moderate (lasting at least seven days or requiring interventional treatment) and mild (lasting less than seven days, not requiring intervention, hospitalisation, or treatment). All information was collected by healthcare professionals.

2.5. Statistical analyses

Vaccinated patients and patients who experienced COVID-19 were analysed separately. Also, patients with MS and NMOSD were analysed independently. For the assessment of the short-term risk of an acute exacerbation, we compared the proportion of patients with at least one clinical relapse (PPR) in the 90 days following the baseline to the 90-day intervals during the year before via McNemar paired test. As supportive evidence, we also compared annualised relapse rates (ARR) before and after baseline using paired t-test. The ARR after baseline was estimated by extrapolation of the first 90 days after baseline. To avoid bias caused by disease-modifying treatment (DMT) changes, we repeated the whole analysis excluding patients with DMT changes in the observation periods. For the evaluation of the risk factors of MS relapse, a comparison between groups with and without relapses after COVID-19 vaccination or infection was made using t-test and chi-squared test with continuity correction. We did not use any data imputations. Alpha was set to 0.05. Data analyses were performed in R version 4.0.4. For independent validation of results based on data from General University hospital in Prague, repeating all analyses were used on data from the Hospital Teplice.

2.6. Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.
3. Results

3.1. Effect of COVID-19 vaccination on relapsing activity in patients with MS

By October 30, 2021, we identified 1661 vaccinated patients with MS without a history of COVID-19 infection (details in Table 1). The majority (95.79%) of patients were vaccinated with mRNA vaccine (98.87%) of them got two doses. All patients got the same type of the vaccine.

A mild increase in ARR and PPR after vaccination was observed. Not all differences were statistically significant. However, after the exclusion of patients with DMT change in each 90-day period, the ARR and PPR increases were accentuated and became significant in all comparisons (Table 3). Results in the validation group of 394 vaccinated MS patients from Hospital Teplice were similar (Table 4).

Most relapses before as well as after vaccination were mild or moderate (Table 3, Fig. 1). The mean time from the first dose of vaccine to the first relapse was 41.08 days (SD 26.80). Relapses were reported more often in patients with younger age and shorter MS duration. DMT type was not shown as a significant risk factor of relapse after COVID-19 vaccination.

3.2. The safety profile of COVID-19 vaccination in patients with MS

Early AEs following at least one dose of vaccine were reported by 1221 (73.51%) patients. A total of 3002 (93.32%) AEs were mild, 214 (6.65%) moderate and one (0.03%) severe (anaphylaxis after the second dose of BNT162b2 vaccine in a 47-year-old female treated with fingolimod). There was also a report of death in a 57-year-old female, who died 73 days after the first dose of BNT162b2, and a 66-year-old female, who died 62 days after the first dose of BNT162b2. According to medical reports, the cause of death was not related to the vaccination in either patient. The number and seriousness of AEs after the first and second dose was quite similar. In general, AEs were reported less frequently in the BNT162b2 vaccine compared to the mRNA-1273 vaccine and vector vaccines. The spectrum and proportion of AEs are shown in Table 2.

3.3. Effect of COVID-19 infection on relapsing activity in patients with MS

A total of 495 patients with MS who experienced COVID-19 infection without previous vaccination were included in this analysis. COVID-19 diagnosis was based on a positive PCR in 435 (87.88%) patients, an antigen test in 38 (7.68%) patients and a serological test in 22 (4.44%) patients. Altogether, 99 (20.0%) patients had clinically suspected (dry cough, fever and shortness of breath) or radiologically confirmed pneumonia. One 69-year-old female treated with ocrelizumab died due to a new pneumonia. One 69-year-old female treated with ocrelizumab died due to a new pneumonia.
to COVID-19 pneumonia. For more characteristics see Table 1.

Statistically insignificant increases in ARR and PPR after COVID-19 infection were noticed. Nevertheless, after the exclusion of patients with DMT change in each followed period, the ARR and PPR increases were accentuated and became significant in all comparisons except for the comparison between the 90-day period before and after the COVID-19 onset (Table 3, Fig. 1). We found similar results in the validation group of 268 post-COVID-19 patients with MS from the Hospital Teplice (Table 4).

Most relapses before as well as after COVID-19 infection were mild or moderate. The mean time from the COVID-19 onset to the first relapse was 38.17 days (SD 25.10) (Table 3). Patients with relapses were younger and were treated more often with the first-line DMT than non-relapsing post-COVID-19 patients (Table 5).

### 3.4. Patients with NMOSD

Characteristics of 17 vaccinated patients with NMOSD without COVID-19 in their medical history and 8 patients with NMOSD who experienced COVID-19 infection without previous vaccination are presented in Table 6. Although there were only a few patients with NMOSD and the differences did not reach statistical significance, the results were broadly consistent with those of patients with MS.

### 4. Discussion

Vaccines work in principle by stimulating the immune system. Therefore, over and above classical AEs, there is an additional potential risk in patients with autoimmune diseases such as MS and NMOSD, the risk of disease exacerbation. This was confirmed in our analysis of 1661 vaccinated patients with MS, where a slight increase in the proportion of patients with at least one clinical relapse (PPR) and ARR in 90 days after vaccination against COVID-19 was found. After the exclusion of patients with DMT change in followed periods (less stable patients), the increase was even more pronounced.

Conversely, two previous cohort studies addressing this issue did not show an increase in relapse frequency after COVID-19 vaccination (Achiron et al., 2021; di Filippo et al., 2021). The Israeli observational study (Achiron et al., 2021) on 555 patients with MS compared the incidence of relapses after BNT162b2 vaccine administration with the incidence of relapses in non-vaccinated patients in the same period during the prepandemic era. This study, however, suffers from the limitation of a heterogenous follow-up period (about 20% of patients with relapses were followed for less than 14 days after vaccination) which might have lowered the number of recorded relapses. In addition, vaccinated and unvaccinated cohorts from this study (Achiron et al., 2021) might include patients with different MS activities. An Italian study (di Filippo et al., 2021) with 324 patients with MS compared the incidence of relapses 60 days before and after BNT162b2 vaccination. The main limits of this study were a relatively small size associated with the small number of clinical relapses, heterogeneity of the sample (8.6% of patients had experienced COVID-19 infection before vaccination) and a short reference period before vaccination. In addition, there was an international recommendation not to vaccinate patients shortly after relapse treated with high-dose glucocorticoids (Horakova, 2021; Multiple sclerosis international federation, 2022). Therefore, the comparison of PPR after with the period directly before the vaccine administration is at least problematic. Especially for this reason, we consider the main outcome of our study to be a PPR difference when comparing 90-day period after with the period between 90 and 180 days before vaccination (that mean 1.38 times increase, respectively two-fold increase when excluding patients with DMT change).

Another goal of our study was to identify patients at higher risk of relapse after vaccination. As we assumed, clinical relapses occurred more frequently in patients with younger age (<55 years) and shorter MS durations. This is probably due to a more vigorous immune response mounted by younger individuals, as the immune system tends to gradually deteriorate with age (Müller et al., 2015; Sadighi Akha, 2018; Uher et al., 2021). Regarding the vaccination-related AEs, corresponding to previous publications (Achiron et al., 2021; Lotan et al., 2021b), their spectrum was comparable to that reported in the general population (Baden et al., 2021; Meo et al., 2021; Polack et al., 2020; Sadoff et al., 2020).

### Table 2

| Type of adverse event          | Total | 1st Comirnaty | 2nd Comirnaty | 1st Spikevax | 2nd Spikevax | 1st Vaxzevria | 2nd Vaxzevria | Janssen |
|-------------------------------|-------|---------------|---------------|--------------|--------------|---------------|---------------|---------|
| Fatigue                       | 693   | 288           | 326           | 24           | 36           | 13            | 4             | 2       |
| Pain in the injected extremity| 626   | 342           | 234           | 22           | 20           | 2             | 4             | 2       |
| Injection site pain           | 569   | 295           | 216           | 26           | 18           | 8             | 6             | 0       |
| Headache                      | 226   | 90            | 108           | 9            | 10           | 5             | 3             | 1       |
| Worsening of neurological symptoms | 207  | 94            | 93            | 6            | 9            | 2             | 2             | 1       |
| Subfebrile temperature        | 181   | 64            | 89            | 8            | 12           | 6             | 2             | 0       |
| Chills                        | 164   | 54            | 85            | 5            | 10           | 5             | 2             | 3       |
| Arthralgia                    | 110   | 37            | 50            | 5            | 11           | 5             | 1             | 1       |
| Fever                         | 97    | 21            | 48            | 5            | 14           | 6             | 1             | 2       |
| Muscle ache                   | 91    | 37            | 45            | 3            | 3            | 2             | 3             | 0       |
| Injection site redness        | 28    | 8             | 13            | 3            | 2            | 1             | 1             | 0       |
| Lymphadenopathy               | 26    | 10            | 13            | 3            | 0            | 0             | 0             | 0       |
| Nausea                        | 25    | 7             | 16            | 1            | 1            | 0             | 0             | 0       |
| Infection                     | 23    | 12            | 9             | 0            | 0            | 1             | 1             | 0       |
| Fainting                      | 22    | 9             | 9             | 1            | 3            | 0             | 0             | 0       |
| Injection site oedema         | 21    | 3             | 14            | 3            | 1            | 0             | 0             | 0       |
| Anxiety                       | 18    | 7             | 9             | 0            | 1            | 1             | 0             | 0       |
| Local allergic reaction       | 16    | 4             | 5             | 2            | 4            | 1             | 0             | 0       |
| Hot flash                     | 13    | 2             | 8             | 0            | 2            | 1             | 0             | 0       |
| Insomnia                      | 9     | 2             | 6             | 1            | 0            | 0             | 0             | 0       |
| Diarrhoea                     | 8     | 4             | 4             | 0            | 0            | 0             | 0             | 0       |
| Sweating                      | 6     | 1             | 4             | 1            | 0            | 0             | 0             | 0       |
| Injection site haematoma      | 6     | 2             | 3             | 0            | 0            | 1             | 0             | 0       |
| Loss of appetite              | 5     | 1             | 2             | 0            | 2            | 0             | 0             | 0       |
| Vomiting                      | 5     | 1             | 3             | 0            | 1            | 0             | 0             | 0       |
| Menstrual changes             | 4     | 0             | 4             | 0            | 0            | 0             | 0             | 0       |
| Dizziness                     | 3     | 1             | 2             | 0            | 0            | 0             | 0             | 0       |
| Other                         | 15    | 6             | 9             | 0            | 0            | 0             | 0             | 0       |

1 Only 1 patient received Sputnik V, he did not refer any adverse events.
Table 3
Clinical relapses in patients from General University Hospital in Prague.1

| NO. OF PATIENTS WITH AT LEAST 1 CLINICAL RELAPSE (ALL) | p value |
|------------------------------------------------------|---------|
| In 90 days after vaccination                          |         |
| Time between 1st dose of vaccine and relapse (SD), d |         |
| Between 0–90 days before vaccination                  | (26.80) |
| Between 90–180 days before vaccination               | (4.83%) |
| Between 180–270 days before vaccination              | 0.039   |
| Between 270–360 days before vaccination              | 0.181   |
| Between 360–270 days before vaccination              | 0.279   |
| In 90 days after COVID-19                           | 38.17   |
| Time between COVID-19 onset and relapse (SD), d      | (25.10) |
| Between 0–90 days before COVID-19                    | (6.81%) |
| Between 90–180 days before COVID-19                  | (4.65%) |
| Between 180–270 days before COVID-19                 | 0.185   |
| Between 270–360 days before COVID-19                 | 0.077   |
| Annualised relapse rate after vaccination            | 0.22    |
| Annualised relapse rate before vaccination           | 0.17    |
| Annualised relapse rate after COVID-19               | 0.29    |
| Annualised relapse rate before COVID-19              | 0.22    |
| NO. OF PATIENTS WITH AT LEAST 1 CLINICAL RELAPSE (PATIENTS WITH DMT CHANGES EXCLUDED) |         |
| In 90 days after vaccination                          |         |
| Between 0–90 days before vaccination                  | (3.22%) |
| In 90 days after vaccination                          | <0.001  |
| Between 90–180 days before vaccination               | (2.43%) |
| In 90 days after vaccination                          | 0.003   |
| Between 180–270 days before vaccination              | (3.57%) |
| In 90 days after vaccination                          | <0.001  |
| Between 270–360 days before vaccination              | (6.88%) |
| In 90 days after COVID-19                            | 0.665   |
| Between 0–90 days before COVID-19                    | (6.02%) |
| In 90 days after COVID-19                            | 0.006   |
| Between 90–180 days before COVID-19                  | (2.67%) |
| In 90 days after COVID-19                            | 0.025   |
| Between 180–270 days before COVID-19                 | (2.97%) |
| In 90 days after COVID-19                            | 0.003   |
| Between 270–360 days before COVID-19                 | (2.15%) |
| Annualised relapse rate after vaccination            | 0.18    |
| Annualised relapse rate before vaccination           | 0.09    |
| Annualised relapse rate after COVID-19               | 0.26    |
| Annualised relapse rate before COVID-19              | 0.009   |
| Annualised relapse rate before COVID-19              | 0.13    |

DMT = disease modifying therapy; 1. 1661 patients with MS from General University Hospital in Prague were vaccinated, 495 experienced COVID-19; 2. 3 patients had 2 relapses, 29 (31.87%) relapses were mild, 56 (61.54%) moderate and 6 (6.59%) severe; 3. 1 patient had 2 relapses, 30 (46.88%) relapses were mild, 28 (43.75%) moderate and 6 (9.38%) severe; 4. 1 patient had 2 relapses, 16 (24.62%) relapses were mild, 47 (72.31%) moderate and 2 (3.08%) severe; 5. 3 patients had 2 relapses, 28 (37.84%) relapses were mild, 44 (59.46%) moderate and 2 (2.70%) severe; 6. 2 patients had 25 relapses, 32 (32.89%) relapses were mild, 46 (60.53%) moderate and 5 (6.58%) severe; 7. relapse was mild in 16 (44.44%), moderate in 18 (50.00%) and severe in 2 (5.56%) patients; 8. 1 patient had 2 relapses, 14 (40.00%) relapses were mild, 21 (60.00%) moderate and 0 severe; 9. relapse was mild in 6 (26.09%), moderate in 15 (65.22%) and severe in 2 (8.70%) patients; 10. 1 patient had 2 relapses, 13 (50.00%) relapses were mild, 12 (46.15%) moderate and 1 (3.85%) severe; 11. 1 patient had 2 relapses, 9 (39.13%) relapses were mild, 11 (47.83%) moderate and 3 (13.04%) severe.

Table 4
Clinical relapses in patients from Hospital Teplice.1

| NO. OF PATIENTS WITH AT LEAST 1 CLINICAL RELAPSE (ALL) | p value |
|------------------------------------------------------|---------|
| In 90 days after vaccination                          |         |
| Between 0–90 days before vaccination                  | (3.51%) |
| In 90 days after vaccination                          | 13      |
| Between 0–90 days before vaccination                  | (4.42%) |
| In 90 days after COVID-19                            | 11      |
| Between 0–90 days before COVID-19                    | (4.42%) |
| In 90 days after COVID-19                            | 11      |
| Between 0–90 days before COVID-19                    | (4.27%) |
| In 90 days after COVID-19                            | 6       |
| Between 0–90 days before COVID-19                    | (4.35%) |
| In 90 days after COVID-19                            | 11      |
| Between 0–90 days before COVID-19                    | (4.54%) |
| In 90 days after COVID-19                            | 2       |
| Between 0–90 days before COVID-19                    | (2.67%) |
| In 90 days after COVID-19                            | 11      |
| Between 0–90 days before COVID-19                    | (5.16%) |
| In 90 days after COVID-19                            | 2       |

DMT = disease modifying therapy; 1. 394 MS patients from Hospital Teplice were vaccinated, 268 experienced COVID-19.

For a comprehensive view of this issue, it is necessary to look at the risks associated with the COVID-19 infection itself, leading to morbidity or even death and a higher risk of relapse, according to our findings. After the exclusion of patients with DMT change during each followed period, the ARR and PPR increases became statistically significant, except for the comparison between the 90-day periods before and after COVID-19. We suggest the increase of PPR before COVID-19 could be caused by a higher risk of COVID-19 infection due to high-dose glucocorticoids indicated for the treatment of relapses.

Our findings are supported by the recent small sample size study (Barzegar et al., 2021b) comparing the incidence of relapses after COVID-19 infection in 41 patients with MS with an incidence in the previous two years. The second small sample size study (Etemadifar et al., 2021) (54 patients with MS) dealing with this issue did not show a higher incidence of relapses after COVID-19. However, in this study, they compared the period after infection to only six months preceding the vaccination. Thus, the bias caused by the relapse rate increase shortly before infection plays a bigger role here.

As for NMO, a few post-vaccination disease relapses have been reported via smaller studies (Dinoito et al., 2021; Fragoso et al., 2021; Jovicic et al., 2021; Lotan et al., 2021a). The frequency of relapses within one month of vaccination in the largest one was 4% (one out of 26
Fig. 1. No. of patients with at least 1 clinical relapse before and after COVID-19 vaccination or infection
1661 MS patients from General University Hospital in Prague were vaccinated; 495 experienced COVID-19.
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Table 5
Risk factors of an acute MS relapse after vaccination or COVID-19.1

| Study population | Without relapse after vaccination | With relapse after vaccination | p value2 | Without relapse after COVID-19 | With relapse after COVID-19 | p value2 |
|------------------|-----------------------------------|------------------------------|----------|-------------------------------|---------------------------|----------|
| Age, mean (SD), y | 48.70 (11.39)                     | 47.49 (11.57)                | 0.003    | 46.14 (11.00)                 | 41.93 (10.36)             | 0.024    |
| <55              | 1141 (70.82%)                     | 74 (84.09%)                  | 0.007    | 350 (76.25%)                 | 32 (88.89%)               | 0.082    |
| Female           | 459 (28.18%)                      | 14 (15.91%)                  | 0.367    | 109 (23.75%)                 | 4 (11.11%)                | 0.830    |
| MS duration (SD), y | 17.55 (10.16)                    | 13.37 (10.49)                | <0.001   | 15.57 (9.44)                 | 13.71 (9.63)              | 0.271    |
| EDSS             |                                   |                              |          |                               |                           |          |
| EDSS < 4         | 978 (63.42%)                      | 51 (63.75)                   | 0.953    | 317 (70.92%)                 | 25 (71.43%)               | 0.949    |
| EDSS > 4         | 564 (36.58%)                      | 29 (36.25)                   | 0.511    | 130 (28.32%)                 | 10 (28.57%)               | 0.911    |
| DMF              | 1195 (75.97%)                     | 64 (72.73%)                  |          | 364 (79.30%)                 | 32 (88.89%)               |          |
| Interferons      | 328 (20.85%)                      | 15 (17.05%)                  |          | 88 (19.17%)                  | 8 (22.22%)                |          |
| Teriflumide       | 86 (5.47%)                        | 6 (6.82%)                    |          | 30 (6.54%)                   | 0 (0%)                    |          |
| Glutamater acetate| 123 (7.92%)                      | 6 (6.82%)                    |          | 42 (9.15%)                   | 5 (13.89%)                |          |
| Dimethyl fumarate | 89 (5.66%)                       | 3 (3.41%)                    |          | 16 (3.49%)                   | 6 (16.67%)                |          |
| Anti-CD20         | 138 (8.77%)                       | 10 (11.36%)                  |          | 51 (11.11%)                  | 3 (8.33%)                 |          |
| Fingolimod       | 263 (16.72%)                      | 10 (11.36%)                  |          | 73 (15.90%)                  | 6 (16.67%)                |          |
| Other 2nd line DMF| 168 (10.68%)                      | 14 (15.91%)                  |          | 64 (13.94%)                  | 4 (11.11%)                |          |
| No DMT           | 378 (24.03%)                      | 24 (27.27%)                  |          | 95 (20.79%)                  | 4 (11.11%)                |          |
| COVID-19 vaccine  |                                   |                              |          |                               |                           |          |
| BNT162b2 (Comirnaty) | 1414 (88.89%)                   | 81 (92.05)                   |          |                               |                           |          |
| Time between doses | 36.80 (10.06)                    | 43.70 (19.16)                |          |                               |                           |          |
| (SD), d          |                                   |                              |          |                               |                           |          |
| mRNA-1273 (Spivelax)| 91 (5.79%)                      | 5 (5.68)                     |          |                               |                           |          |
| Time between doses | 36.13 (7.63)                     | 42.20 (15.75)                |          |                               |                           |          |
| (SD), d          |                                   |                              |          |                               |                           |          |
| Vector vaccines   | 68 (4.32%)                        | 2 (2.27%)                    |          |                               |                           |          |
| Time between doses | 77.75 (17.85)                    | 109.00                       |          |                               |                           |          |
| (SD), d          |                                   |                              |          |                               |                           |          |
| COVID-19 severity |                                   |                              |          |                               |                           |          |
| Mild COVID-19    | 375 (81.70%)                      | 27 (75%)                     | 0.322    |                               |                           |          |
| More severe COVID-19 | 84 (18.30%)                   | 9 (25%)                      |          |                               |                           |          |

MS = multiple sclerosis; EDSS = expanded disability status scale; DMF = disease modifying drug. Anti-CD20 = ocrelizumab + rituximab; Other 2nd line DMF = alemtuzumab + natalizumab + cladribine.

1. All patients got 2 doses of vaccine; 2. Data were missing for 9.09% of patients; 3. A comparison between groups with and without relapses after COVID-19 vaccination or infection; 4. MS duration is insufficient to generalize conclusions. We believe that characteristics of patients after COVID-19 vaccination and infection were different, it is impossible to directly compare these two cohorts. The adjustment or matching could be performed only on known and collected factors such as age or EDSS. However, the selection bias caused, for example, by the vaccination strategy in patients with MS is not removable by a statistical method - the risk of confounding would remain too great and could lead to misinterpretation.

5. Conclusion

To sum up, there was a mild increase in relapse risk after the COVID-19 vaccination in comparison to the previous year in MS patients, mainly in those younger than 55 years. The risks, however, need to be balanced against the risks of COVID-19 itself, also leading to the rise in relapse rate and particularly morbidity and mortality, especially in elderly patients (Stastna et al., 2021). Thus, based on our findings, patients who have the lowest risk of relapse after vaccination are at the greatest risk for a more severe COVID-19 course. However, further studies are needed to confirm our conclusion. Results in patients with NMOSD are broadly consistent, but the risks from COVID-19 infection are more pronounced. Unfortunately, the relatively low number of patients with NMOSD is insufficient to generalize conclusions. We believe these results can improve clinical practice by facilitating clinical decisions about vaccination and preventive measures during COVID-19 pandemic.
| Table 6 | Clinical and demographic characteristics of NMOSD patients at the date of the 1st dose of COVID-19 vaccine or COVID-9 onset. |
|---------------------------------|---------------------------------|
| Study population                | Vaccinated                      | Post-COVID-19                  |
| Age, mean (SD), y               | 17 (49.09 (14.50))              | 8 (53.33 (10.27))              |
| Female                          | 11 (64.71%)                     | 6 (75.00%)                     |
| NMOSD duration (SD), y          | 16 (94.12%)                     | 5 (62.50%)                     |
| EDSS                            | 17 (11.26)                      | 10.66 (5.04)                   |
| COVID-19 vaccine                | BNT162b2 (Comirnaty) – mRNA      | 17 (100%)                      |
| COVID-19 severity               |                                 | 28.82 (7.84)                   |
| Death                           | 2 (25%)                         |                               |
| Need of invasive ventilation or |                                 |                               |
| extracorporeal membrane        |                                 |                               |
| oxygenation                     |                                 |                               |
| Need of non-invasive            |                                 |                               |
| ventilation or high-flow        |                                 |                               |
| oxygen therapy                  |                                 |                               |
| Need of supplemental oxygen     |                                 |                               |
| Radiologically confirmed        |                                 |                               |
| pneumonia                       |                                 |                               |
| Suspected pneumonia (dry        |                                 |                               |
| cough, fever and shortness of   |                                 |                               |
| breath)                         |                                 |                               |
| Symptomatic                     |                                 |                               |
| Asymptomatic                    |                                 |                               |
| Patients with at least 1        |                                 |                               |
| clinical relapse                | 1 (5.88%)                       | 2 (25%)                       |
| Time between 1st dose of vaccine| 41 (Time between 1st dose of    |                               |
| and relapse (SD), d             | vaccine and relapse (SD), d      |                               |
|                                | 0 (Between 0–90 days before     |                               |
|                                | vaccination)                     |                               |
|                                | 0 (Between 90–180 days before   |                               |
|                                | vaccination)                     |                               |
|                                | 0 (Between 180–270 days before  |                               |
|                                | vaccination)                     |                               |
|                                | 2 (Between 360–370 days before  |                               |
|                                | vaccination)                     |                               |
| In 90 days after COVID-19       | 2 (25%)                         |                               |
| Time between COVID-19 onset and | 30 (7.07)                       |                               |
| acute relapse (SD), d           |                               |                               |
|                                | 0 (Between 0–90 days before     |                               |
|                                | COVID-19)                        |                               |
|                                | 0 (Between 90–180 days before   |                               |
|                                | COVID-19)                        |                               |
|                                | 1 (12.5%)                       |                               |
|                                | 1 (12.5%)                       |                               |

NMOSD = neuromyelitis optica spectrum disorder; EDSS = expanded disability status scale; DMT = disease modifying treatment.

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