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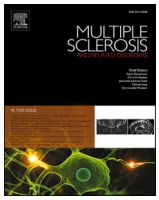

COVID-19 infection after two doses of SARS-CoV-2 mRNA vaccine in multiple sclerosis, AQP4-antibody NMOSD and MOGAD

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ABSTRACT

Background: In pre-vaccinated people with multiple sclerosis (MS), certain disease-modifying therapies (DMTs), particularly the anti-CD20 treatments, appear to be associated with an increased risk of COVID-19 infection and indeed with severe infection. It is still not known if such observations extend to vaccinated individuals and there have been considerably fewer studies in aquaporin-4-antibody neuromyelitis optica spectrum disorder (AQP4-NMOSD) and myelin oligodendrocyte glycoprotein-antibody associated disease (MOGAD) patients. In this study, we investigated the rates of symptomatic COVID-19 infection in adult patients with MS, AQP4-NMOSD and MOGAD who had received 2 doses of SARS-CoV-2 mRNA vaccine.

Methods: This was a prospective observational study conducted at the 2 main neuroimmunology referral centres in Singapore. Only patients on active follow-up were recruited to ensure robust data collection. Data on demographics, disease history, DMTs and SARS-CoV-2 mRNA vaccinations were recorded, and for those infected with COVID-19, data on COVID-19 infection was collected.

Results: Nineteen (13 MS, 5 AQP4-NMOSD, 1 MOGAD) out of 365 (231 MS, 106 AQP4-NMOSD, 28 MOGAD) patients had COVID-19 infection despite 2 doses of SARS-CoV-2 mRNA vaccine. Amongst the infected patients, 11 patients were on DMTs (3 rituximab, 2 interferons, 1 azathioprine, 1 mycophenolate, 1 prednisolone, 1 cladribine, 1 alemtuzumab, 1 fingolimod), while 8 patients were untreated. The crude infection rate was calculated using time-at-risk analysis, revealing that rituximab had the highest infection rate amongst all the DMTs. A lower crude infection rate was observed in patients who received a third vaccination. The majority of infections were mild and no patients required oxygen supplementation.

Conclusion: Our findings suggest that patients on rituximab are still at risk of COVID-19 infection after 2 vaccinations and the receipt of a third vaccination may help to prevent infection. Future large scale studies will be required to better delineate the infection risk of different DMTs after the second and subsequent vaccinations.

1. Introduction

The COVID-19 pandemic has raised concerns in people living with CNS inflammatory diseases, including the potential for infection particularly in those receiving disease-modifying therapies (DMTs). A meta-analysis (literature search done up till April 2021) estimated that the pooled prevalence of COVID-19 infection in multiple sclerosis (MS) patients to be 4% (Moghadasi et al., 2021), although this is likely to be heavily influenced by local infection rates. Whilst most infections are generally mild, several factors have now been identified to be associated with a higher risk of infection and indeed of severe infection in MS patients. These include older age, higher disability, as well as the use of anti-CD20 therapies (Sormani et al., 2021; Simpson-Yap et al., 2021; Louapre et al., 2020; Luna et al., 2020; Salter et al., 2021). These studies, however, were performed in unvaccinated patients, thus it is still not known if such associations are also present in vaccinated individuals, given that SARS-CoV-2 mRNA vaccines that are highly effective in preventing symptomatic infections have since been introduced (Self

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et al., 2021). Furthermore, most reports have only investigated MS patients with considerably fewer studies in aquaporin-4-antibody neuromyelitis optica spectrum disorder (AQP4-NMOSD) and myelin oligodendrocyte glycoprotein-antibody associated disease (MOGAD) patients (Louapre et al., 2021; Fan et al., 2020; Louapre et al., 2022). In this study, we investigated the rates of symptomatic COVID-19 infection in adult patients with MS, AQP4-NMOSD and MOGAD who had received at least 2 doses of SARS-CoV-2 mRNA vaccine.

2. Methods

This was a prospective observational study conducted at the Departments of Neurology at the National Neuroscience Institute and the National University Hospital, the 2 main neuroimmunology referral centres in Singapore, under local ethics approval (CIRB 2020/2410). We only included patients who were on active follow-up as this represented a closely monitored patient cohort that would allow for the collection of detailed information regarding COVID-19 infection, vaccination and DMT use. All MS patients fulfilled the 2017 McDonald criteria, and all AQP4-NMOSD and MOGAD patients were diagnosed using cell-based assays. Data on demographics, disease history, DMTs and SARS-CoV-2 mRNA vaccinations were recorded; for those infected with COVID-19, data on COVID-19 infection were collected. As DMT use at the time of vaccination is one of the main determinants of immune responses to vaccination in MS patients (Achiron et al., 2021), we analyzed the data by the type of DMT at first vaccination rather than at COVID-19 infection. DMT at first vaccination must be commenced at least 3 months prior to vaccination and maintained till the administration of the second vaccination. Patients who had received immune reconstitution therapies are ascribed to these treatments regardless of the duration between treatment and first vaccination. Patients on B cell depleting therapies are classified under these treatments if they have received treatment within 6 months prior to first vaccination. Untreated patients are classified as such if they had not been on DMTs for at least 3 months prior to their first vaccination. A pre-determined study cut-off date of 31st December 2021 was established.

Statistical analysis and graphical representation were performed using GraphPad Prism (version 6) and STATA (release 14). Comparative analyses between patient groups were performed using Mann-Whitney U test or 2-sample t-test as appropriate for continuous variables. Chi-square or Fisher exact tests were used for categorical variables as appropriate. Multivariable logistic regression was performed to identify potential factors associated with an increased risk of COVID-19 infection. Odds ratios (OR) were calculated with 95% confidence intervals (CI). Two-tailed p values of <0.05 were considered statistically significant.

3. Results

Three hundred and sixty-five patients who completed at least 2 doses of SARS-CoV-2 mRNA vaccination met the inclusion criteria – 231 (63.3%) MS, 106 (29.0%) AQP4-NMOSD and 28 (7.7%) MOGAD, with

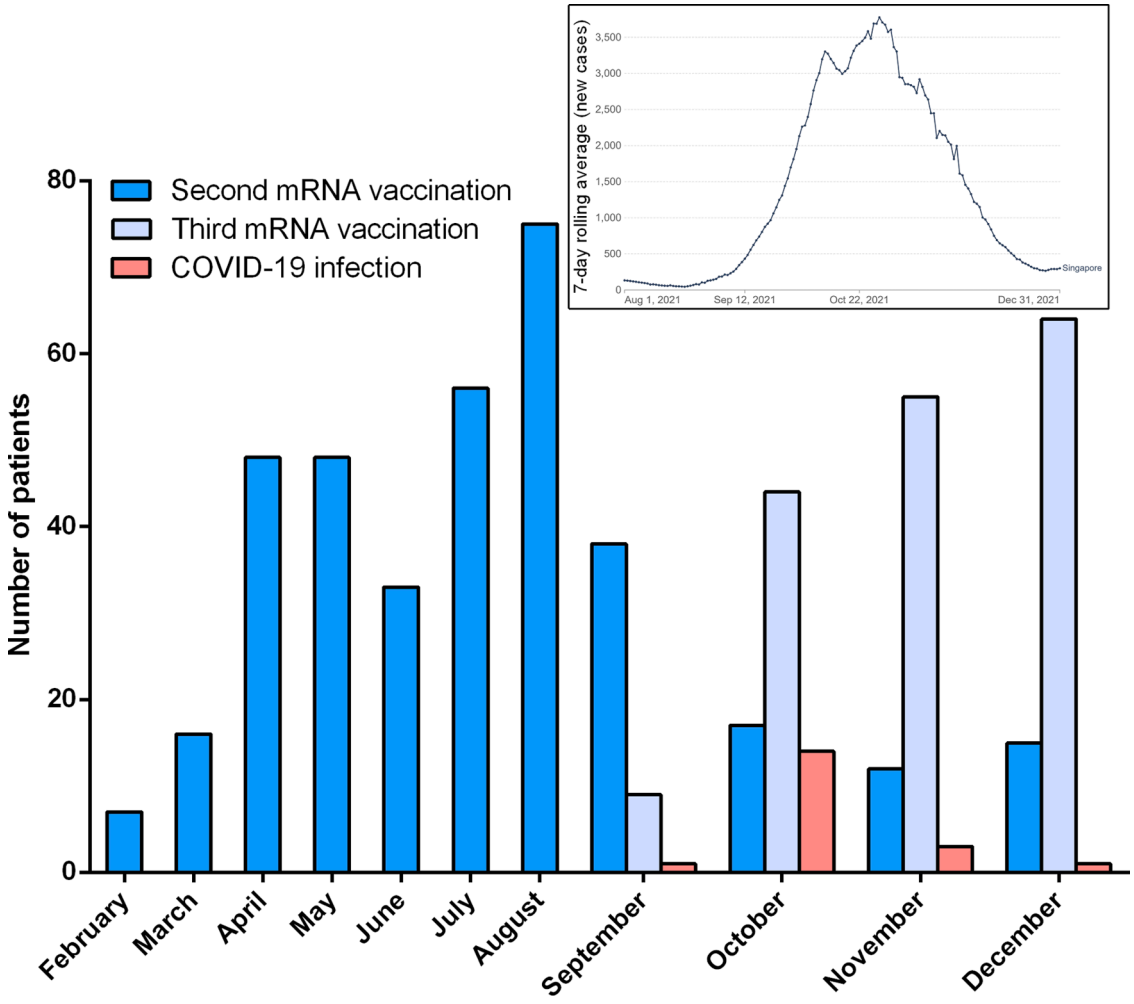

Fig. 1. Bar charts showing the number of SARS-CoV-2 mRNA vaccinations and COVID-19 infections in the study cohort by month in 2021. The boxed inset shows the 7-day rolling average of new infections in Singapore from 1st August 2021 to 31st December 2021 (data obtained from references 13 and 14 with permissions).

the proportion of each disease reflecting recent local epidemiological data (Tan et al., 2021). Three hundred and twenty-seven patients (89.6%) received the Pfizer-BioNTech vaccine and 38 (10.4%) received the Moderna vaccine. The earliest completed vaccination (i.e. 2 doses) was on 9th February 2021 and the latest on 28th December 2021. One hundred and seventy-two patients received a third dose of mRNA vaccine – 141 (82.0%) received the Pfizer-BioNTech vaccine and 31 (18.0%) received the Moderna vaccine, with the earliest third vaccination on 15th September 2021 and the latest on 31st December 2021. The bar chart representing the number of vaccinations by month is shown in Fig. 1.

Two hundred and fifty-eight patients were on DMTs while 107 were untreated. Rituximab ($n = 47$) was the most commonly used treatment, followed by mycophenolate ($n = 46$), azathioprine ($n = 34$), interferons ($n = 27$), cladribine ($n = 25$), dimethyl fumarate ($n = 17$) and fingolimod ($n = 17$); other DMTs had less than 10 patients ascribed to them. Details of DMTs stratified by diagnosis are shown in Table 1. Five patients on either azathioprine or mycophenolate were also on concomitant prednisolone, albeit at low doses of 5 mg or less, hence they were classified according to their steroid-sparing DMTs.

Nineteen patients (19/365, 5.2%) had COVID-19 infection – 13 MS, 5 AQP4-NMOSD and 1 MOGAD. The number of infections stratified by month is shown in Fig. 1 – 1 infection occurred in September, 14 infections in October, 3 infections in November, and 1 infection in December. This mirrored the infection rates in the Singaporean population with a rise in cases beginning in September, peaking in October with a 7-day rolling average of over 3000 new cases, declining in November, and then stabilizing in December (Dong et al., 2020; Coronavirus Pandemic (COVID-19), 2022). This represented the last wave of the Delta variant in Singapore, prior to the first Omicron variant wave which began in January 2022 and peaked in February 2022. The clinical details of these infected patients are tabulated in Table 2. Median age was 45.4 years (interquartile range [IQR) 34.2–58.1), median disease duration was 6.6 years (IQR 4.4–11.6) and median expanded disability status scale (EDSS) score was 2.0 (IQR 0.0–6.0). All infections were confirmed on polymerase chain reaction (PCR) testing except for 2 which were established with antigen rapid tests (ART). Infection was detected at a median interval of 21.0 weeks (IQR 12.4–24.7) from second vaccination. All except 1 patient received the Pfizer-BioNTech vaccine. Only 1 patient received a third mRNA vaccination; infection occurred at just over a week after receiving the third dose. The majority (16/19, 84.2%) of infections were mild while 3 were moderate (National Institutes of Health severity classification) (National Institutes of Health COVID-19 Treatment Guidelines, 2021); none required oxygen supplementation. Eight patients were hospitalized with 1 requiring high-dependency monitoring. All patients recovered from their infections. Of note, 4 patients had neutralizing antibodies measured (Genscript® cPass™ assay) after their second vaccination, prior to COVID-19 infection – 2 untreated patients showed robust humoral response (~97% inhibition), 1 rituximab-treated patient had attenuated but present response (57.5% inhibition) and another rituximab-treated patient had absent neutralizing antibodies (i.e. less than 30% inhibition).

Amongst the 19 infected patients, 11 were on DMTs (rituximab, $n = 3$; interferons, $n = 2$; azathioprine, $n = 1$; mycophenolate, $n = 1$; prednisolone, $n = 1$; cladribine, $n = 1$, alemtuzumab, $n = 1$; fingolimod, $n = 1$), while 8 patients were untreated. For the most commonly used DMTs, the proportion of patients infected was calculated (i.e. number of infected patients on that DMT ÷ total number of patients on that DMT). Interferons had the highest proportion of infected patients (2/27, 7.4%), followed by rituximab (3/47, 6.4%), fingolimod (1/17, 5.8%), cladribine (1/25, 4%), azathioprine (1/34, 2.9%) and mycophenolate (1/46, 2.2%; Fig. 2). To better delineate the infection risk solely after 2 vaccination doses (i.e. without the effect of third vaccination), the crude infection rate was calculated considering time-at-risk (i.e. number of infected patients on that DMT ÷ total time-at-risk contributed by all patients on that DMT). For uninfected patients, the time-at-risk was the interval between the second and third vaccination in those who had already received the third vaccination; for those yet to receive the third vaccination, the exposure time was the interval between the second vaccination and the study cut-off date, i.e. 31st December 2021. For infected patients, the time-at-risk contributed was defined as the interval between the second vaccination to COVID-19 infection. Rituximab demonstrated the highest crude infection rate (3.9 per 1000 person-weeks), followed by interferons (3.2 per 1000 person-weeks), fingolimod (3.0 per 1000 person-weeks), cladribine (2.1 per 1000 person-weeks), azathioprine (1.4 per 1000 person-weeks) and mycophenolate (1.0 per 1000 person-weeks).

A case (infected), control (uninfected) analysis was performed to identify potential factors associated with COVID-19 infection (Table 3). Univariate analysis revealed there were no significant differences between the 2 groups with regards to age, gender, diagnosis, disease duration, proportion of patients with EDSS ≥6, DMT use and vaccine brand. A higher proportion of infected patients (18/19, 94.7%) had not received a third vaccination, compared to uninfected individuals (175/346, 50.6%) ($p < 0.001$). This remained a significant independent factor for COVID-19 infection (OR = 19.7, 95% CI 2.5 – 152.9, p = 0.004) on multivariable logistic regression, adjusted for age, disability (i.e. EDSS ≥6 versus <6), disease duration and DMT use (i.e. on DMTs versus untreated).

To better delineate the risk of COVID-19 infection associated with the non-receipt of a third vaccination, a retrospective cohort analysis was performed. Exposure was defined as the non-receipt of a third vaccination and the outcome was COVID-19 infection. One of 172 patients (0.6%) who had received a third vaccination was infected, compared to 18 of 193 (9.3%) patients who received only 2 vaccinations ($p < 0.001$). For rituximab patients, there were no infections in 16 patients who had received 3 vaccinations, compared to 3 of 31 (9.7%) patients who received only 2 vaccinations. To account for the differing time of exposure to potential infection between patients who received 3 vaccinations and in those who had only 2 (and to minimize the potential bias that patients who had received 3 vaccinations had done so as a result of not being infected), time-at-risk was calculated to obtain the crude infection rate (i.e. number of infected patients who received that

Table 1
DMTs use in patients grouped by diagnosis.

	Total (n = 365)	MS (n = 231)	AQP4-NMOSD (n = 106)	MOGAD (n = 28)
Nil	107	90	6	11
Rituximab	47	20	25	2
Mycophenolate	46	-	41	5
Azathioprine	34	2	26	6
Interferons	27	27	-	-
Cladribine	25	25	-	-
Dimethyl fumarate	17	17	-	-
Fingolimod	17	17	-	-
Alemtuzumab	7	7	-	-
Ocrelizumab	7	7	-	-
Prednisolone	6	-	2	4
Methotrexate	4	-	4	-
Natalizumab	4	4	-	-
Teriflunomide	4	4	-	-
AHSCT	3	3	-	-
Glatiramer	3	3	-	-
Leflunomide	3	3	-	-
Clinical trial	1	1	-	-
Cyclosporin	1	-	1	-
Siponimod	1	1	-	-
Sulfasalazine	1	-	1	-

Abbreviations: AHSCT, autologous hemopoietic stem cell transplantation; AQP4-NMOSD, aquaporin-4-antibody neuromyelitis optica spectrum disorder; MOGAD, myelin oligodendrocyte glycoprotein-antibody associated disease; MS, multiple sclerosis.

Table 2
Clinical details of the 19 patients who had COVID-19 infections. None required oxygen supplementation and all recovered. Date is represented in DD/MM/YYYY format.

Patient	Age (years)	Gender, ethnicity	Co-morbidities	Diagnosis	Disease duration (years)	EDSS	Date of V2	Vaccine	Post-V2 neutralizing antibodies (inhibition %)	Date of V3	Date of COVID-19 infection	Duration of V2 to infection (weeks)	COVID-19 infection severity	Hospitalized	DMT at V1	DMT at COVID-19 infection
1	67.7	Male, Chinese	Osteoporosis	AQP4-NMOSD	8.4	2	11/04/2021	Pfizer-BioNTech	57.5% (21/07/2021)	-	01/10/2021 (PCR)	24.7	Moderate	Yes	Rituximab	Rituximab
2	76.6	Female, Chinese	Osteoporosis	AQP4-NMOSD	5.2	7	06/06/2021	Moderna	-	-	31/10/2021 (PCR)	21.0	Moderate	Yes	Rituximab	Rituximab
3	59.2	Female, Chinese	Nil	AQP4-NMOSD	9.7	6	13/09/2021	Pfizer-BioNTech	14.0% (13/10/2021)	-	15/11/2021 (PCR)	9.0	Mild	Yes	Rituximab	Rituximab
4	56.6	Female, Chinese	Osteoporosis, hyperthyroidism	MS	16.6	7	07/06/2021	Pfizer-BioNTech	-	-	26/10/2021 (PCR)	20.1	Mild	Yes	Interferon (Rebif)	Rituximab
5	23.2	Female, Malay	Nil	MS	8.8	0	02/08/2021	Pfizer-BioNTech	-	-	27/12/2021 (PCR)	21	Mild	No	Interferon (Rebif)	Interferon (Rebif)
6	46.0	Female, Chinese	Nil	MS	5.5	1	21/05/2021	Pfizer-BioNTech	-	-	31/10/2021 (ART)	23.3	Mild	No	Alemtuzumab	Alemtuzumab
7	50.9	Male, Indian	Hypertension	MS	20.4	7	11/06/2021	Pfizer-BioNTech	-	-	08/11/2021 (PCR)	21.4	Mild	Yes	Azathioprine	Azathioprine
8	45.4	Male, Indian	Hypertension	MS	6.6	1.5	19/07/2021	Pfizer-BioNTech	-	-	12/10/2021 (PCR)	12.1	Mild	Yes	Cladribine	Cladribine
9	36.8	Female, Indian	Nil	MS	5.2	0	05/06/2021	Pfizer-BioNTech	-	-	15/10/2021 (PCR)	18.9	Mild	No	Fingolimod	Fingolimod
10	58.0	Female, Others	Nil	AQP4-NMOSD	4.7	1	27/05/2021	Pfizer-BioNTech	-	-	06/11/2021 (PCR	23.3	Mild	No	Mycophenolate	Mycophenolate
11	60.9	Male, Chinese	COPD, spinal stenosis, stroke, prostatic hypertrophy	AQP4-NMOSD	3.6	7	19/04/2021	Pfizer-BioNTech	-	18/10/2021	27/10/2021 (PCR)	27.3	Mild	Yes	Prednisolone (5 mg)	Prednisolone (2 mg)
12	34.4	Female, Malay	Liver fibrosis	MS	2.1	0	23/04/2021	Pfizer-BioNTech	-	-	24/09/2021 (PCR)	22	Mild	No	Nil	Nil
13	29.5	Female, Chinese	Hypothyroidism	MS	4.4	0	15/08/2021	Pfizer-BioNTech	-	-	01/10/2021 (PCR)	6.7	Mild	No	Nil	Nil
14	42.5	Male, Malay	Nil	MS	11.6	2	20/03/2021	Pfizer-BioNTech	-	-	06/10/2021 (PCR)	28.6	Mild	No	Nil	Nil
15	29.3	Male, Others	Ulnar neuropathy	MOGAD	3.7	2.5	23/04/2021	Pfizer-BioNTech	-	-	17/10/2021 (ART)	25.3	Mild	No	Nil	Nil
16	43.5	Female, Others	Hypertension, impaired glucose tolerance, OSA	MS	13.4	0	07/07/2021	Pfizer-BioNTech	97.0% (21/07/2021)	-	19/10/2021 (PCR)	14.9	Moderate	Yes (required HD monitoring)	Nil	Nil

(*continued on next page*)

Table 2 (*continued*)

Patient	Age (years)	Gender, ethnicity	Co-morbidities	Diagnosis	Disease duration (years)	EDSS	Date of V2	Vaccine	Post-V2 neutralizing antibodies (inhibition %)	Date of V3	Date of COVID-19 infection	Duration of V2 to infection (weeks)	COVID-19 infection severity	Hospitalized	DMT at V1	DMT at COVID-19 infection
17	55.8	Female, Indian	Osteoarthritis knee	MS	31.2	6	21/03/2021	Pfizer-BioNTech	-	-	20/10/2021 (PCR)	30.4	Mild	No	Nil	Rituximab
18	29.1	Female, Malay	Nil	MS	2.5	1	05/08/2021	Pfizer-BioNTech	-	-	24/10/2021 (PCR)	11.4	Mild	No	Nil	Nil
19	34.2	Female, Indian	Nil	MS	8.6	2	01/08/2021	Pfizer-BioNTech	97.6% (30/08/2021)	-	27/10/2021 (PCR)	12.4	Mild	No	Nil	Nil

Abbreviations: AHSCT, autologous haemopoietic stem cell transplantation; AQP4-NMOSD, aquaporin-4-antibody neuromyelitis optica spectrum disorder; ART, antigen rapid test; COPD, chronic obstructive pulmonary disease; DMT, disease-modifying therapy; EDSS, expanded disability status scale; HD, high-dependency; MOGAD, myelin oligodendrocyte glycoprotein-antibody associated disease; MS, multiple sclerosis; OSA, obstructive sleep apnea; PCR, polymerase chain reaction; V2, second vaccination; V3, third vaccination.

specified number of vaccinations ÷ total time-at-risk contributed by patients who had received that specified number of vaccinations). In infected patients, the time-at-risk was defined as the interval to COVID-19 infection after the second (in those who had only 2 vaccinations) or third vaccination (in those with a third vaccination). In uninfected patients, the time-at-risk was the time to study end date (i.e. 31st December 2021) after the second (in those with only 2 vaccinations) or third vaccination (in those with 3 vaccinations). This revealed a crude infection rate of 0.9 per 1000 person-weeks for patients who had 3 vaccinations, compared to 5.2 per 1000 person-weeks for those who only had 2 vaccinations. If the crude infection rate after the third vaccination was assumed to be similar to that after the second vaccination, an estimated 5.7 infections (for the entire cohort) would have occurred during the at-risk period after the third vaccination, however only 1 infection occurred. For rituximab patients who had only 2 vaccinations, the crude infection rate was 7.2 per 1000 person-weeks and an estimated 0.7 infections would have occurred during the at-risk period after 3 vaccinations. No infections were observed in rituximab patients who had 3 vaccinations.

4. Discussion

Current evidence suggests that pre-vaccinated MS patients on anti-CD20 therapies are at a higher risk of COVID-19 infection (Luna et al., 2020), and show attenuated humoral responses postinfection (Louapre et al., 2022). Importantly, it is also now clear that anti-CD20 therapies as well as fingolimod result in lower humoral immunity (compared to other DMTs) after SARS-CoV-2 vaccinations (Achiron et al., 2021; Tallantyre et al., 2022). While it is not certain whether this observation translates to an increased risk of infection, especially when post-vaccination cellular responses appear to be robust (for anti-CD20 therapies) (Apostolidis et al., 2021; Pompsch et al., 2021), several studies have emerged to shed light on this matter.

In a UK population-based study using merged DMT prescription and COVID-19 infection datasets, Garjani et al showed that the incidence rate ratio of infection for patients on ocrelizumab and fingolimod increased (as compared to the general population) in the post-vaccination period, whereas there were no significant changes for other DMTs (Garjani et al., 2021). However, individual-level data on COVID-19 vaccination was not available to accurately determine if MS patients were indeed vaccinated, and by using inferential data, only ~56% of the UK adult population had received their second vaccination at the time of the study. Other studies have since provided individual-level data, albeit with small sample sizes of infected cases, which is not unexpected given the efficacy of the SARS-CoV-2 mRNA vaccines. Rose et al reported 13 infections amongst 344 fully vaccinated MS patients (94.5% received mRNA-based vaccines) from the Cleveland MS Clinic (Rose et al., 2021). Of the 13 infected patients, 10 were on anti-CD20 therapies and 3 on fingolimod. Two patients (both on anti-CD20 therapies) were hospitalized but only 1 required supplemental oxygen. In the French COVISEP registry, Januel et al reported 18 cases of COVID-19 infection (17 MS and 1 AQP4-NMOSD) after 2 doses of Pfizer-BioNTech vaccination (Januel et al., 2021). However, COVID-19 diagnosis in the majority of cases (17/18) was based on typical COVID-19 symptoms without microbiological confirmation. Thirteen patients were treated with anti-CD20 therapies, 4 with fingolimod, 1 with interferon, and the authors found that anti-CD20 therapies were significantly associated with post-vaccine infection. COVID-19 infections were generally mild with only 2 patients requiring hospitalizations. In the Italian CovaXiMS cohort comprising 1705 MS patients who all received mRNA vaccines, 23 COVID-19 infections were reported – 9 on ocrelizumab, 1 on rituximab, 4 on fingolimod, 6 on dimethyl fumarate, 1 on teriflunomide and 2 untreated (Sormani et al., 2021). This corresponded to a higher infection incidence in ocrelizumab, fingolimod, rituximab and dimethyl fumarate as compared to teriflunomide and untreated patients. Only 2 patients required

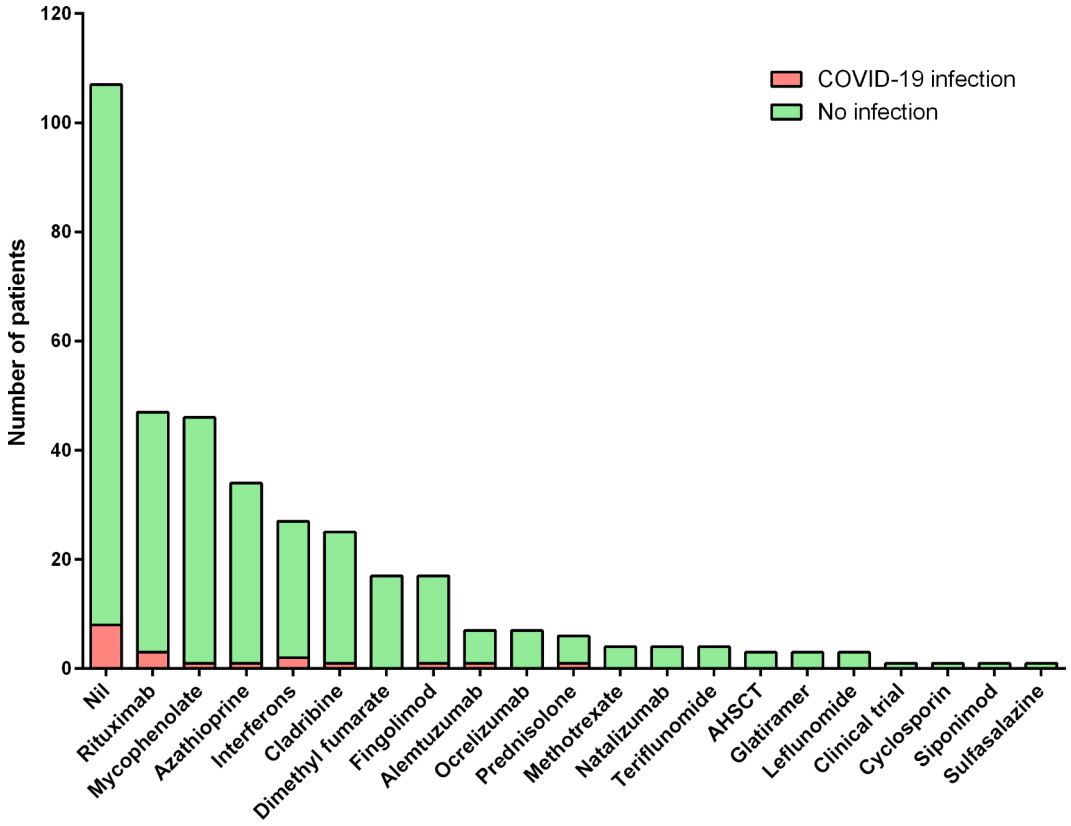

Fig. 2. Stacked bar charts showing the number of patients with and without COVID-19 infections stratified by DMTs. Abbreviations: AHSCT, autologous hemopoietic stem cell transplantation; DMTs, disease-modifying therapies.

Table 3
Comparison of COVID-19 infected with non-infected patients.

	Infected (n = 19)	Uninfected (n = 346)	*p* value
Age, years (median [IQR])	45.4 (34.2–58.1)	43.4 (33.3–54.8)	0.682
Female, no. (%)	13 (68.4)	280 (80.9)	0.231
Diagnosis			0.868
MS, no. (%)	13 (68.4)	218 (63.0)	0.808
AQP4-NMOSD, no. (%)	5 (26.3)	101 (29.2)	1.000
MOGAD, no. (%)	1 (5.3)	27 (7.8)	1.000
Disease duration, years (median [IQR])	6.6 (4.4 – 11.6)	7.6 (3.3 – 12.8)	0.831
EDSS ≥6, no. (%)	6 (31.6)	68 (19.7)	0.240
DMT use, no. (%)	11 (57.9)	247 (71.4)	0.208
Rituximab, no. (%)	3 (15.8)	44 (12.7)	0.722
Interferons, no. (%)	2 (10.5)	25 (7.2)	0.642
Fingolimod, no. (%)	1 (5.3)	16 (4.6)	0.605
Cladribine, no. (%)	1 (5.3)	24 (6.9)	1.000
Alemtuzumab, no. (%)	1 (5.3)	6 (1.7)	0.314
Azathioprine, no. (%)	1 (5.3)	33 (9.5)	1.000
Mycophenolate, no. (%)	1 (5.3)	45 (13.0)	0.488
Prednisolone, no. (%)	1 (5.3)	5 (1.4)	0.276
Received Pfizer vaccine for first two doses, no. (%)	18 (94.7)	309 (89.3)	0.706
Not received third mRNA vaccine, no. (%)	18 (94.7)	175 (50.6)	<0.001

Abbreviations: AQP4-NMOSD, aquaporin-4-antibody neuromyelitis optica spectrum disorder; DMT, disease-modifying therapy; EDSS, expanded disability status scale; IQR, interquartile range; MOGAD, myelin oligodendrocyte glycoprotein-antibody associated disease; MS, multiple sclerosis.

hospitalizations. Given that the non-mRNA vaccines appear to have relatively lower efficacies (Fan et al., 2021; Rotshild et al., 2021), the infection risk post-vaccination could conceivably be higher in patients who had received these vaccines. In Iran, using patient-volunteered information, Ghadiri et al reported 102 infected patients after vaccination (more than 99% of vaccines were non-mRNA-based), although it was not clear if all infections were PCR/ART confirmed (Ghadiri et al., 2021). Ninety-three percent of infections were managed as outpatients suggesting that they were mild and the authors found no association of anti-CD20 therapies with COVID-19 infection.

The main finding from our study is consistent with prior reports in that we observed a higher post-vaccination (i.e. 2 doses of mRNA vaccine) COVID-19 infection rate in patients treated with rituximab. Several findings from our study, however, differed from previous reports. Amongst all infected patients, untreated patients (8/19, 42.1%) comprised the majority whereas they were a minority in prior reports. We also noted a higher infection rate in interferon-treated patients as compared to fingolimod; post-vaccination infection has only been reported in 1 patient on interferon to date (i.e. end date of current study) (Januel et al., 2021). These findings have to be interpreted with caution due to the small number of cases within each DMT subgroup. It is notable that 2 infected patients in our cohort, i.e. patients 4 and 17 (Table 2) who were on interferon and untreated respectively at the time of vaccination, developed COVID-19 infection after they switched to rituximab post-vaccination. This raises concern that rituximab initiation could predispose patients to infection even after 'appropriate' vaccination especially in the presence of waning immunity over time. Although 2 of the 3 patients on rituximab had infections of moderate severity, it is reassuring that most infections in our cohort were generally mild. Further longitudinal studies to determine the relative infection risk of DMTs, especially newly initiated DMTs in the post-vaccination period, will need to be conducted.

Our study also revealed that the non-receipt of a third vaccination was associated with COVID-19 infection after correcting for clinically-relevant factors. This finding was further supported by longitudinal

time-at-risk analysis which factored in the different exposure times for potential infection in those who had received only 2 vaccinations from those who had 3 vaccinations. This highlights the importance of a third vaccination in patients with CNS inflammatory diseases to prevent COVID-19 infection. Additionally, we observed that having a robust humoral immune response after the second vaccination did not prevent subsequent COVID-19 infection, suggesting that other immune components, in particular cellular immunity, are involved in determining susceptibility to infection.

We acknowledge that by including only patients on active follow-up, data capture for patients not on DMTs may not be complete, particularly for progressive MS and monophasic MOGAD patients who have either been lost to follow-up or treated and discharged. This may have overestimated the high infection rate in untreated patients in our cohort. However, our study was designed to ensure robust data capture with regards to COVID-19 infection detection, vaccination status and DMT use. Other notable strengths of our study include the analysis of AQP4-NMOSD and MOGAD patients, having defined criteria for patients to be ascribed to a particular DMT, a pre-determined study stop date which allowed for time-at-risk analysis and molecular confirmation of COVID-19 infection.

As the COVID-19 pandemic continues and eventually transits into an endemic state, future large scale studies are required to better define the infection risk of patients on different DMTs after 'full' vaccination. A third vaccine dose (as part of the primary series) is now recommended in several countries, including Singapore, for patients who are on immunosuppressive therapies. Our finding of a protective effect from a third mRNA vaccine and the fact that to date, we and others have observed no cases of severe infections after at least 2 vaccinations in patients with CNS inflammatory diseases, provide empirical evidence to support such an immunization strategy. More studies will be required to determine whether this approach will be effective in inducing robust long-term protective immunity and more importantly, whether this can prevent or mitigate COVID-19 infections especially in light of the emergence of new variants.

5. CRediT author contributions

T Yeo: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Roles/Writing - original draft. AML Quek: Investigation; Resources; Writing - review & editing. KP Yong: Investigation; Resources; Writing - review & editing. JSN Tye: Investigation; Resources; Writing - review & editing. P Ratnagopal: Investigation; Resources; Writing - review & editing. DTL Soon: Investigation; Resources; Writing - review & editing. K Tan: Conceptualization; Investigation; Resources; Supervision; Writing - review & editing.

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Declaration of Competing Interest

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References

Achiron, A, Mandel, M, Dreyer-Alster, S, et al., 2021. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther. Adv. Neurol. Disord. 14, 17562864211012835.

Apostolidis, SA, Kakara, M, Painter, MM, et al., 2021. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. Nat. Med. 27 (11), 1990–2001.

Coronavirus Pandemic (COVID-19). https://ourworldindata.org/coronavirus/country/singapore (accessed 11th April 2022).

Dong, E, Du, H, Gardner, L., 2020. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect. Dis. 20 (5), 533–534.

Fan, M, Qiu, W, Bu, B, et al., 2020. Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. Neurol. Neuroimmunol. Neuroinflamm. 7 (5).

Fan, YJ, Chan, KH, Hung, IF., 2021. Safety and Efficacy of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Different Vaccines at Phase 3. Vaccines (Basel) 9 (9).

Garjani, A, Patel, S, Bharkhada, D, et al., 2021. Impact of mass vaccination on SARS-CoV-2 infections among multiple sclerosis patients taking immunomodulatory disease-modifying therapies in England. Mult. Scler. Relat. Disord. 57, 103458.

Ghadiri, F, Sahraian, MA, Azimi, A, Moghadasi, AN., 2021. The study of COVID-19 infection following vaccination in patients with multiple sclerosis. Mult. Scler. Relat. Disord., 103363

Januel, E, De Seze, J, Vermersch, P, et al., 2021. Post-vaccine COVID-19 in patients with multiple sclerosis or neuromyelitis optica. Mult. Scler., 13524585211049737

Louapre, C, Collongues, N, Stankoff, B, et al., 2020. Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis. JAMA Neurol.. 77 (9), 1079–1088.

Louapre, C, Ibrahim, M, Maillart, E, et al., 2022. Anti-CD20 therapies decrease humoral immune response to SARS-CoV-2 in patients with multiple sclerosis or neuromyelitis optica spectrum disorders. J. Neurol. Neurosurg. Psychiatry 93 (1), 24–31.

Louapre, C, Maillart, E, Papeix, C, et al., 2021. Outcomes of coronavirus disease 2019 in patients with neuromyelitis optica and associated disorders. Eur. J. Neurol. 28 (10), 3461–3466.

Luna, G, Alping, P, Burman, J, et al., 2020. Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. JAMA Neurol. 77 (2), 184–191.

Moghadasi, AN, Mirmosayyeb, O, Barzegar, M, Sahraian, MA, Ghajarzadeh, M., 2021. The prevalence of COVID-19 infection in patients with multiple sclerosis (MS): a systematic review and meta-analysis. Neurol. Sci. 42 (8), 3093–3099.

National Institutes of Health COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (accessed 11th November 2021).

Pompsch, M, Fisenkci, N, Horn, PA, Kraemer, M, Lindemann, M., 2021. Evidence of extensive cellular immune response after SARS-CoV-2 vaccination in ocrelizumab-treated patients with multiple sclerosis. Neurol. Res. Pract. 3 (1), 60.

Rose, DR, Mahadeen, AZ, Carlson, AK, et al., 2021. Clinical features and outcomes of COVID-19 despite SARS-CoV-2 vaccination in people with multiple sclerosis. Mult. Scler. J. Exp. Transl. Clin. 7 (4), 20552173211057110.

Rotshild, V, Hirsh-Raccah, B, Miskin, I, Muszkat, M, Matok, I., 2021. Comparing the clinical efficacy of COVID-19 vaccines: a systematic review and network meta-analysis. Sci. Rep. 11 (1), 22777.

Salter, A, Fox, RJ, Newsome, SD, et al., 2021. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American Registry of patients with multiple sclerosis. JAMA Neurol. 78 (6), 699–708.

Self, WH, Tenforde, MW, Rhoads, JP, et al., 2021. Comparative effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) vaccines in preventing COVID-19 hospitalizations among adults without immunocompromising conditions - United States, March-August 2021. MMWR Morb. Mortal. Wkly. Rep. 70 (38), 1337–1343.

Simpson-Yap, S, De Brouwer, E, Kalincik, T, et al., 2021. Associations of Disease-Modifying Therapies With COVID-19 Severity in Multiple Sclerosis. Neurology 97 (19), e1870–e1885.

Sormani, MP, De Rossi, N, Schiavetti, I, et al., 2021. Disease-modifying therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis. Ann. Neurol. 89 (4), 780–789.

Sormani, MP, Schiavetti, I, Inglese, M, et al., 2021. Breakthrough SARS-CoV-2 infections after COVID-19 mRNA vaccination in MS patients on disease modifying therapies. medRxiv, 2021.2012.2023.21268177.

Tallantyre, EC, Vickaryous, N, Anderson, V, et al., 2022. COVID-19 vaccine response in people with multiple sclerosis. Ann. Neurol. 91 (1), 89–100.

Tan, K, Yeo, T, Yong, KP, et al., 2021. Central nervous system inflammatory demyelinating diseases and neuroimmunology in Singapore—epidemiology and evolution of an emerging subspecialty. Neurol. Clin. Neurosci. 9 (4), 259–265.