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ORIGINAL ARTICLE

Risk of disease relapse, safety and tolerability of SARS-CoV-2 vaccination in patients with chronic inflammatory neuropathies

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Abstract

Background and purpose: The aim was to evaluate the risk of relapse after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, and its safety and tolerability, in patients with chronic inflammatory neuropathies.

Methods: In this multicenter, cohort and case-crossover study, the risk of relapse associated with SARS-CoV-2 vaccination was assessed by comparing the frequency of relapse in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN) patients who underwent or did not undergo vaccination. Frequency of relapse in the 3 months prior to and after vaccination, and safety and tolerability of SARS-CoV-2 vaccination, were also assessed.

Results: In all, 336 patients were included (278 CIDP, 58 MMN). Three hundred and seven (91%) patients underwent SARS-CoV-2 vaccination. Twenty-nine patients (9%) did not undergo vaccination. Mild and transient relapses were observed in 16 (5%) patients (13 CIDP, 3 MMN) after SARS-CoV-2 vaccination and in none of the patients who did not undergo vaccination (relative risk [RR] 3.21, 95% confidence interval [CI] 0.19–52.25). There was no increase in the specific risk of relapse associated with type of vaccine or diagnosis. Comparison with the 3-month control period preceding vaccination revealed an increased risk of relapse after vaccination (RR 4.00, 95% CI 1.35–11.82), which was restricted to CIDP patients (RR 3.25, 95% CI 1.07–9.84). The safety profile of SARS-CoV-2 vaccination was characterized by short-term, mild-to-moderate local and systemic adverse events.

Conclusions: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in CIDP and MMN patients does not seem to be associated with an increased risk of relapse at the primary end-point, although a slightly increased risk in CIDP patients was found compared to the 3 months before vaccination.

KEYWORDS
chronic inflammatory demyelinating polyneuropathy, COVID-19, multifocal motor neuropathy, SARS-CoV-2, vaccination

INTRODUCTION

The safety of vaccination in patients with inflammatory neuropathies has been a matter of debate for decades [1–11]. Our current knowledge on the risk of relapse after vaccination and the safety and tolerability of vaccines in patients with inflammatory neuropathies is quite limited and this partially explains why vaccination coverage is slow in these patients [10–12].

Since December 2019 a pandemic illness (coronavirus disease 2019, COVID-19) has spread to millions of persons worldwide. In response, a vaccination campaign is under way. In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination phase III trials, subjects with a history of Guillain–Barré syndrome (GBS) or receiving immunomodulating agents within months prior to studying vaccine administration were excluded from participation [13–16]. Therefore, data from these trials do not provide reliable information regarding the safety of SARS-CoV-2 vaccinations in patients with chronic inflammatory neuropathies. During the post authorization safety surveillance, potential safety concern for GBS following receipt of the Ad26.COV2.S (Janssen/Johnson & Johnson) and the

ChAdOx1nCoV-19 (AstraZeneca) SARS-CoV-2 vaccines has been identified [17–19]. Together, these points support the need to investigate the safety of SARS-COV-2 vaccination in chronic inflammatory neuropathies.

The data of the INCLUSIVE (covId chroNiC infLammatory neUropathies Safety tolerabIlity VaccinEs) study that evaluated the risk of relapse after SARS-CoV-2 vaccination in patients with chronic inflammatory neuropathies and the safety and tolerability of SARS-CoV-2 vaccines in these patients are presented.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

Primary and secondary end-points

The relative risk of disease relapse associated with SARS-CoV-2 vaccination was prospectively assessed by comparing chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN) patients who underwent SARS-CoV-2 vaccination with CIDP and MMN patients who did not undergo vaccination (primary end-point). As secondary end-points, (1) the frequency of disease relapse in CIDP and MMN patients undergoing SARS-CoV-2 vaccination in the 3 months prior to (assessed retrospectively but confirmed by the records of the patients that were regularly followed at our centers) and after vaccination (assessed prospectively) was compared; (2) the duration and severity of relapses were evaluated, as well as the timing and completeness of recoveries in CIDP and MMN patients who had worsened after vaccination; (3) the presence of risk factors for relapse after vaccination was evaluated; and (4) the safety and tolerability of the SARS-CoV-2 vaccines in CIDP and MMN patients were evaluated by assessing the frequency of specific local and systemic adverse events.

Study design

In this multicenter, cohort, prospective and case-crossover study, patients with CIDP and MMN regularly followed by 27 Italian centers were enrolled from 1 January 2021 to 30 December 2021. Patients undergoing SARS-CoV-2 vaccination were assessed at baseline (within 1 month prior to the first dose of vaccine) and 3 months after receiving the first dose of vaccine (risk period) using the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale, the Medical Research Council (MRC) sum score, and the Rasch Overall Disability Scale (I-RODS for CIDP patients and MMN-RODS for MMN patients; Figure S1a). In the case of relapse within 3 months from the first dose of vaccine, these scales were also administered at the time of clinical worsening and then repeated once recovery was achieved. In patients undergoing vaccination with ChAdOx1 (AstraZeneca), for whom an interval of 8–12 weeks between the two doses of the vaccine is recommended [13, 14], the risk period was extended to 2 months after the second dose. Statistical analyses were repeated excluding patients who received vaccination with ChAdOx1 (AstraZeneca). Patients unwilling to be vaccinated underwent the same assessments at the time of study inclusion (baseline) and 3 months later (control period; Figure S1b). In the case of relapse during the control period, these scales were also administered at the time of clinical worsening and then repeated once recovery was achieved. Based on the literature, analyses were performed under the assumption that a relapse due to vaccination would occur within 2 months after vaccination [1, 20–24].

Clinical relapse was defined as (1) a change of ≥2 points on the MRC sum score [25] or (2) a change of ≥1 point on the INCAT disability score [25], (3) a change of ≥6 centile points on the I-RODS score for CIDP [25] and ≥4 raw points on the MMN-RODS for MMN (as the centile transformation is not published), or (4) the necessity of increasing dose or frequency of maintenance treatment or changing of neuropathy treatment related to clinical worsening. The same criteria for relapse definition were used in the retrospective analysis of the frequency of relapse in the 3 months preceding vaccination.

Safety and tolerability of SARS-CoV-2 vaccines were evaluated using a specific questionnaire that patients were asked to complete after the first and second doses of vaccine.

Inclusion criteria

All patients with a diagnosis of CIDP or MMN fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for probable/definite diagnosis [26, 27], regularly followed in day hospital or outpatient clinic, whose dose and frequency of maintenance therapy had not been reduced in the previous 3 months or who were in remission without ongoing active treatment were invited to participate in the study. Study subjects were selected amongst patients included in the Italian CIDP and MMN databases [20]. Patients with exclusion criteria (SARS-CoV-2 vaccination before study entry, recent COVID-19 infection) or unwilling to participate were excluded from the study. All the patients decided autonomously whether to undergo vaccination for SARS-CoV-2, as allowed by Italian law.

Assessment tools/scales

Muscle strength was tested bilaterally using the MRC sum score performed on 12 muscles (range 0–60) [28], including upper arm abductors, elbow flexors, wrist extensors, hip flexors, leg extensors and foot dorsiflexion. The INCAT disability scale (score 0–10) [29] and I-RODS for CIDP patients (score 0–48) [30] and MMN-RODS for MMN patients (score 0–50) were used to assess disability [31].

To evaluate safety and tolerability of vaccination for SARS-CoV-2 a self-reported specific questionnaire was used. The questionnaire included questions about type of vaccine performed, presence of pain at the injection site, fever (defined as temperature ≥38°C), fatigue, headache, appearance or worsening of sensory symptoms including pain in the upper and/or lower limbs (assessed according to the following scale: *mild*, does not interfere with activity; *moderate*, interferes with activity; *severe*, prevents daily activity; *extreme*, requires emergency department visit or hospitalization), redness and swelling (measured according to the following scale: *mild*, 2.0–5.0 cm in diameter, approximately; *moderate*, >5.0–10.0 cm in diameter, approximately; *severe*, >10.0 cm in diameter, approximately; and *extreme*, necrosis or exfoliative dermatitis) and use of antipyretic medication (not graded). The questionnaire also evaluated the occurrence of any medical event potentially related to the vaccination during the study period.

Standard protocol approvals, registration and patient consents

The study was approved by the Ethical Committee of the Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani IRCCS, Italy (ID 290; 2020–2021) and by the ethical committee of each participating center. Written informed consent was obtained from all participants in the study.

Statistical analysis

Vaccinated and unvaccinated patients were compared using the chi-squared test for categorical variables and the Wilcoxon–Mann–Whitney test for continuous variables. The risk of relapse was assessed amongst vaccinated and unvaccinated patients and compared between the two groups calculating relative risk (RR) with 95% confidence interval (95% CI). In the presence of zero cells in the 2×2 tables describing exposure (vaccine) versus outcome (relapse), a quantity of 0.5 was added to all cells to calculate the RR [32]. Risk factors for relapse in vaccinated patients were evaluated using univariable and multivariable logistic regression models, with relapse occurrence as dependent variable. Risk factors included as independent variables were sex, age, disease (CIDP or MMN), treatment with intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg), steroids, past or current use of immunosuppressant agents, disease severity (as measured by the INCAT, RODS and MRC scales) and type of vaccine. Results were presented as odds ratio (OR) and adjusted OR with 95% CI. The significance level was set at 5%. Analyses were performed using SAS 9.4 (SAS Institute).

RESULTS

In all, 278 patients with CIDP (233 patients with typical CIDP, 28 with multifocal CIDP, six with motor CIDP, five with distal CIDP, four with sensory CIDP, two patients with antibody anti-neurofascin-155) and 58 patients with MMN, fulfilling the EFNS/PNS criteria for a probable/definite diagnosis, were included in the study. None of the included patients had reduced or stopped a maintenance dose of therapy during the 3 months prior to the study. A total of 440 patients were excluded or refused participation (Figure 1).

Of the 336 patients included, 307 (91%; 260 with CIDP, 47 with MMN) underwent SARS-CoV-2 vaccination, including 269 (88%) patients with BNT-162b2 (Pfizer/BioNTech) [15], 28 (9%) patients with mRNA-1273 (Moderna) [16] and 10 (3%) patients with ChAdOx1 (AstraZeneca) [14]. Twenty-nine patients (9%; 18 with CIDP, 11 with MMN) did not undergo SARS-CoV-2 vaccination.

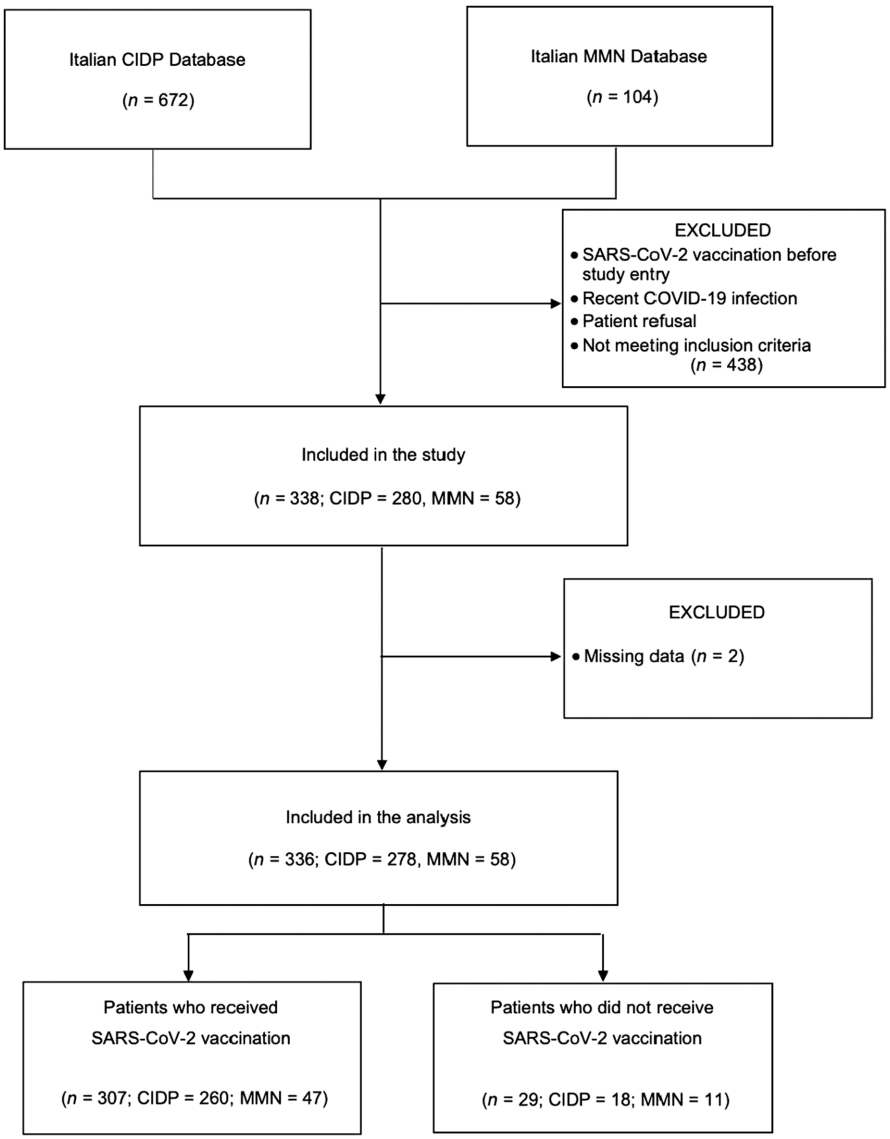
The baseline characteristics of the patients who did or did not undergo SARS-CoV-2 vaccination are shown in Table 1. Compared to the vaccinated group, the non-vaccinated group had a lower proportion of CIDP (62% vs. 85%; $p<0.001$), a higher proportion of multifocal CIDP (28% vs. 9%; $p=0.0244$), younger age (mean 54 vs. 60 years; $p=0.0287$), higher frequency of maintenance treatment (97% vs. 80%; $p=0.0243$), with more frequent treatment with IVIg (76% vs. 43%; $p<0.001$) and less frequent with SCIg (7% vs. 26%; $p=0.0224$).

Risk of relapse in patients with CIDP and MMN after SARS-CoV-2 vaccination

Clinical relapse was observed in 16 (5%) patients (13 CIDP; three MMN) who underwent SARS-CoV-2 vaccination and in none of the patients who did not undergo vaccination (RR 3.21, 95% CI 0.19–52.25; Table 2, Figure 2). One patient experienced transitory subjective gait deterioration that was not confirmed by outcome measures. When also this patient was considered in the analysis, the relative risk was 3.40 (95% CI 0.21–55.28). The specific relative risk for BNT-162b2 (Pfizer/BioNTech) was 2.77 (95% CI 0.16–45.74) and for mRNA-1273 (Moderna) was 9.31 (95% CI 0.52–165.33; Table 2). None of the 10 patients who received the ChAdOx1 (AstraZeneca) vaccine had a relapse. When the 10 patients who received the ChAdOx1 (AstraZeneca) vaccine were excluded from the analysis, for whom, per protocol, the risk period was 1–2 months longer, the relative risk was 3.32 (95% CI 0.20–54.00). The specific relative risk of relapse associated with SARS-CoV-2 vaccination in CIDP patients was 1.96 (95% CI 0.12–31.81), whilst in MMN patients it was 1.75 (95% CI 0.09–31.64; Table 2). When the patients in remission without ongoing treatment were excluded from the analysis, the relative risk did not change (RR 3.65, 95% CI 0.22–59.48).

During the 3-month control period preceding baseline, four (1%) of the 307 vaccinated patients had had a disease relapse confirmed by INCAT that in all had required treatment adjustment. All the four patients had CIDP and, during the study, received BNT-162b2 (Pfizer/BioNTech) vaccine. None of the four patients with disease relapse during the 3-month control period preceding baseline had a relapse after vaccination. Comparing the frequency of relapse in the 3-month period following vaccination (risk period) with that in

FIGURE 1 Flow diagram.



the 3-month control period that preceded baseline, the overall relative risk of relapse associated with SARS-CoV-2 vaccination was 4.00 (95% CI 1.35–11.82; Table 2, Figure 2). The specific relative risk for BNT-162b2 (Pfizer/BioNTech) was 2.77 (95% CI 0.90–8.49) and for mRNA-1273 (Moderna) was 9.00 (95% CI 0.48–166.45; Table 2). Patients with CIDP had an increased frequency of relapse after vaccination compared to the control period (RR 3.25, 95% CI 1.07–9.83), whereas MMN patients did not (RR 7.00, 95% CI 0.37–131.89; Table 2).

Table 3 shows the demographic and clinical features of the patients with and without disease relapse after SARS-CoV-2 vaccination. Of the 16 patients with disease relapse, 10 (62%) were men, mean age at study inclusion was 60 years (30–85 years) and mean disease duration was 13 years (1–36 years). Seven (44%) of them were on ongoing maintenance treatment with IVIg, three (19%) with SCIg, four (25%) with steroids and one (0.5%) with azathioprine. One patient was in remission, without treatment. Four (25%) patients relapsed after the first dose of vaccine (mean 20 days, range 0–36), and 12 (75%) after the second dose (mean 35 days, range 2–60). Five (31%) patients relapsed within 1 week after the first or second dose of vaccine. Mean relapse duration was 82 days (29–373 days) with 15 (94%) patients returning to their baseline level. A 77-year-old man with CIDP under treatment with intravenous steroids, who received BNT-162b2 (Pfizer/BioNTech), only partially improved after disease relapse, without returning to his baseline level after 1-year follow-up. Clinical worsening was confirmed by INCAT plus RODS and MRC in eight patients (50%), by RODS in three (18.5%) patients, by INCAT in two (12.5%) patients, by INCAT plus MRC in two (12.5%) patients, and by RODS plus MRC in one (6.5%) patient. Twelve (75%) patients received treatment adjustment after disease relapse, which in all consisted of a temporary treatment dose increase. In the remaining four patients, relapse was considered minor by the treating neurologist (two patients) or followed by a rapid recovery (two patients).

Univariate and multivariate analysis of possible risk factors for relapse after SARS-CoV-2 vaccination revealed that treatment with steroids was an independent factor significantly associated with an increased risk (Table S1; adjusted OR 5.98; 95% CI 1.46–24.5, $p = 0.0129$). A higher risk of relapse after vaccination with

TABLE 1 Baseline characteristics of the patients with CIDP and MMN who did or did not undergo SARS-CoV-2 vaccination.

Characteristic	Patients who received SARS-CoV-2 vaccination ($n=307$)	Patients who did not receive SARS-CoV-2 vaccination ($n=29$)	*p* value
CIDP:MMN	260:47	18:11	<0.001
Men:women	201:106	20:9	NS
Age at study inclusion, years; mean (range)	60 (12–88)	54 (16–90)	0.0287
Disease duration, years; mean (range)	11 (1–56)	12 (1–36)	NS
Clinical forms			
Typical CIDP, *n* (%)	221 (85%)	12 (67%)	NS
Multifocal/focal CIDP, *n* (%)	23 (9%)	5 (28%)	0.0244
Distal CIDP, *n* (%)	4 (1.5%)	1 (5%)	NS
Sensory/sensory-predominant CIDP, *n* (%)	4 (1.5%)		NS
Motor/motor-predominant CIDP, *n* (%)	6 (2%)		NS
Nodo-paranodopathy, *n* (%)	2 (1%)		NS
Type of treatment at study entry			
IVIg, *n* (%)	133 (43%)	22 (76%)	<0.001
SCIg, *n* (%)	79 (26%)	2 (7%)	0.0224
Steroids, *n* (%)	33 (11%)	4 (13%)	NS
PLEx, *n* (%)	4 (1%)		NS
Immunosuppressive agents, *n* (%)	17 (6%)	1 (3%)	NS
No treatment	62 (20%)	1 (3%)	0.0243
Disease severity at study entry			
INCAT score, mean (range)	2.3 (0–9)	2.6 (0–5)	NS
RODS score, mean (range)	I-RODS, 34.5 (0–48); MMN-RODS, 39 (16–50)	I-RODS, 29.4 (0–48); MMN-RODS, 35 (16–50)	NS
MRC sum score, mean (range)	56 (32–60)	54 (39–60)	NS
SARS-CoV-2 vaccine type			
BNT-162b2-Pfizer/BioNTech, *n* (%)	269 (88%)		
mRNA-1273-Moderna, *n* (%)	28 (9%)		
ChAdOx1-AstraZeneca, *n* (%)	10 (3%)		

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, inflammatory neuropathy cause and treatment disability scale; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; MRC, Medical Research Council; *n*, number; NS, not significant; PLEx, plasma exchange therapy; RODS, Rasch-built Overall Disability Scale; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCIg, subcutaneous immunoglobulin.

mRNA-1273 (Moderna) compared to BNT-162b2 (Pfizer/BioNTech) vaccine was also found, although it was not statistically significant (adjusted OR 4.47; 95% CI 1.17–17.1, $p=0.0912$; Table S1).

Safety and tolerability of SARS-CoV-2 vaccines

The questionnaire on the safety and tolerability of SARS-CoV-2 vaccination was completed after the first dose of vaccine by 250 patients and after the second dose by 231 patients. Mild-to-moderate pain at the injection site was the most reported local reaction (64% after the first dose and 34.5% after the second dose of vaccine), with 2% of participants reporting severe pain after the first dose and 0.5% after the second dose of vaccine (Figure 3a,b, Table 2). A noticeably lower percentage of participants reported injection-site redness or swelling (Figure 3a,b, Table 2). In general, local reactions were mostly mild to moderate in severity, and no patients reported a grade 4 local reaction. The most frequently reported systemic reactions were fatigue (35.5% after the first dose and 33% after the second dose) and headache (21.5% after the first dose and 14% after the second dose). Severe systemic events were reported in 1% or less of the patients after both doses, except for fatigue (in 4%) after the second dose. No patients reported a grade 4 systemic event. The proportion of patients reporting local and systemic reactions decreased after the second dose (Figure 3b, Table 2). Antipyretic medications were used by 15% of the patients after the first dose and 12.5% of the patients after the second dose of vaccine. Only two CIDP patients reported a transient medical event potentially related to vaccination, which in both occurred after the first dose of BNT-162b2 (Pfizer/BioNTech) (bilateral hand tremor, mild confusion). Neither of the two patients required hospitalization. When safety and tolerability of the

TABLE 2 Risk of disease relapse associated with SARS-CoV-2 vaccination.

	No. of patients with disease relapse (%)		
Type of vaccine	**Vaccinated (*n* = 307)**	**Not vaccinated (*n* = 29)**	**Relative risk (95% CI)**
Any	16 (5%)	0	3.21 (0.19–52.25)
BNT-162b2-Pfizer/BioNTech, *n* = 269	12 (4%)	0	2.77 (0.16–45.74)
mRNA-1273-Moderna, *n* = 28	4 (14%)	0	9.31 (0.52–165.33)
ChAdOx1-AstraZeneca, *n* = 10	0	0	
Disease group	**No. of patients with disease relapse (%)**		**Relative risk (95% CI)**
	Vaccinated (*n* = 260 CIDP; *n* = 47 MMN)	**Not vaccinated (*n* = 18 CIDP; *n* = 11 MMN)**	
CIDP, *n* = 278	13 (5%)	0	1.96 (0.12–31.81)
MMN, *n* = 59	3 (6%)	0	1.75 (0.09–31.64)
Case-crossover design	**No. of patients with disease relapse (%)**		**Relative risk (95% CI)**
	Risk period (*n* = 307)	**Control period (*n* = 307)**	
Any	16 (5%)	4 (1%)	4.00 (1.35–11.82)
BNT-162b2-Pfizer/BioNTech, *n* = 269	12 (4.5%)	4 (1.5%)	2.77 (0.90–8.49)
mRNA-1273-Moderna, *n* = 28	4 (14%)	0	9.00 (0.48–166.45)
ChAdOx1-AstraZeneca, *n* = 10	0	0	
CIDP, *n* = 260	13 (5%)	4 (1.5%)	3.25 (1.07–9.83)
MMN, *n* = 47	3 (6%)	0	7.00 (0.37–131.89)

Abbreviations: CI, confidence interval; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; *n*, number; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

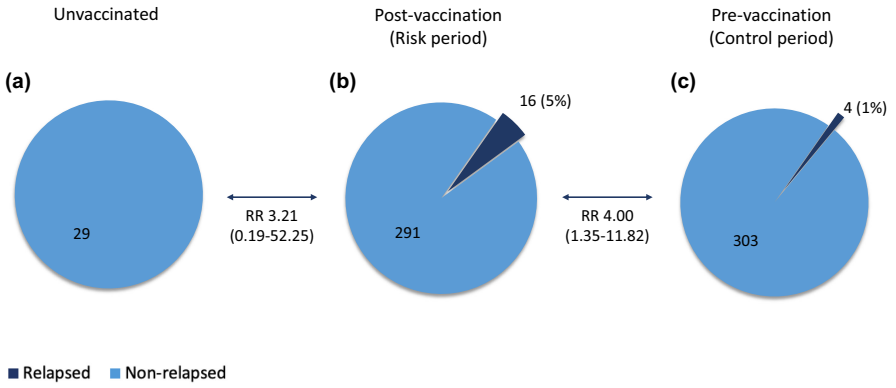


FIGURE 2 Frequency of disease relapse. (a) Frequency of disease relapse in non-vaccinated patients. (b) Frequency of disease relapse in the 3-month risk period following vaccination. (c) Frequency of disease relapse in patients vaccinated for SARS-CoV-2 in the 3-month control period preceding vaccination. Figure shows the risk of disease relapse in vaccinated (b) versus non-vaccinated patients (a) and in the 3-month following vaccination (b) versus the 3-month preceding vaccination (c).

different types of vaccines were compared, pain at the injection site after the first dose was less frequent in patients who received ChAdOx1 (AstraZeneca) vaccine compared to those who received BNT-162b2 (Pfizer/BioNTech) vaccine (25% vs. 66.5%, $p = 0.0161$) whilst redness after the second dose was less frequent in patients who received BNT-162b2 (Pfizer/BioNTech) vaccine compared to those who received ChAdOx1 (AstraZeneca) vaccine (12% vs. 25%, $p = 0.0434$). Redness and fever after the second dose were less frequent in patients who received BNT-162b2 (Pfizer/BioNTech) vaccine compared to those who received mRNA-1273

TABLE 3 Demographic and clinical features of patients with and without disease relapse after SARS-CoV-2 vaccination.

Characteristics	Patients with relapse after SARS-CoV-2 vaccination (*n* = 16)	Patients without relapse after SARS-CoV-2 vaccination (*n* = 291)
Age, years; mean (range)	60 (30–85)	60 (12–88)
Sex; men (%)	10 (62%)	191 (66%)
Diagnosis	13 (81%) CIDP; 3 (19%) MMN	247 CIDP (85%); 44 (15%) MMN
Disease duration, years; mean (range)	13 (1–36)	11 (1–56)
Neuropathy treatment		
IVIg, *n* (%)	7 (44%)	125 (43%)
SCIg, *n* (%)	3 (19%)	77 (26%)
Steroids, *n* (%)	4 (25%)	28 (10%)
PLEx, *n* (%)		4 (1.5%)
Immunosuppressant agent, *n* (%)	1 (0.5%)	15 (5%)
Disease severity at study inclusion		
INCAT; mean (range)	1 (0–6)	2 (0–9)
RODS; mean (range)	I-RODS 32 (3–48); MMN-RODS 30 (16–43)	I-RODS 35 (0–48); MMN-RODS 40 (16–50)
MRC sum score; mean (range)	55 (36–60)	56 (32–60)
Disease relapse		
No. of patients with relapse after the first dose of vaccine (%)	4 (25%)	
Time interval between the first dose of vaccine and relapse; days, mean (range)	20 (0–36)	
No. of patients with disease relapse after the second dose of vaccine (%)	12 (75%)	
Time interval between the second dose of vaccine and relapse; days, mean (range)	35 (2–60)	
No. of patients who received treatment adjustment (%)	12 (75%)	
Relapse duration; days, mean (range)	82 (29–373)	
Remission of disease, *n* (%)	15 (94%)	
Outcome measure revealing clinical relapse		
INCAT + RODS + MRC, *n* (%)	8 (50%)	
RODS, *n* (%)	3 (18.5%)	
INCAT, *n* (%)	2 (12.5%)	
INCAT + MRC, *n* (%)	2 (12.5%)	
RODS + MRC, *n* (%)	1 (6.5%)	

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, inflammatory neuropathy cause and treatment disability scale; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; MRC, Medical Research Council; *n*, number; PLEx, plasma exchange therapy; RODS, Rasch-built Overall Disability Scale; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCIg, subcutaneous immunoglobulin.

(Moderna) (12% vs. 19%, $p = 0.0365$, and 6.5% vs. 35%, $p < 0.001$, respectively). Use of antipyretic medications after the second dose was less frequent after BNT-162b2 (Pfizer/BioNTech) compared to the other two types of vaccine (4% vs. 38% and 37.5%, $p < 0.001$; Figure 3a,b). There was no significant difference in the other local and systemic side effect frequency amongst the three types of vaccine (Figure 3a,b). Tolerability of the SARS-CoV-2 vaccines was similar in CIDP and MMN patients (Figure 4a,b, Table 3).

DISCUSSION

The results of the present study show that the risk of relapse after SARS-CoV-2 vaccination is low in patients with CIDP and MMN, in line with previous studies performed in other autoimmune diseases [10, 11, 21, 33–39] and with a recent Dutch multicenter cohort study which observed worsening of symptoms after SARS-CoV-2 vaccination in 5% of 188 CIDP patients and 4% of 53 MMN patients [40].

Comparison with the control group did not show a statistically significant increased overall risk of relapse after vaccination, neither an increased relapse rate associated with a specific type of vaccine or with a specific disease, although this should be considered cautiously due to the small number of unvaccinated control group. Of note, in the 16 patients who relapsed, clinical worsening occurred at short intervals following SARS-CoV-2 vaccination, making a causal association likely. The higher number of patients on maintenance treatment in the unvaccinated control group suggests the presence of a higher proportion of patients with active disease in this group. However, when the analysis was repeated excluding patients in remission, the relative risk did not substantially change.

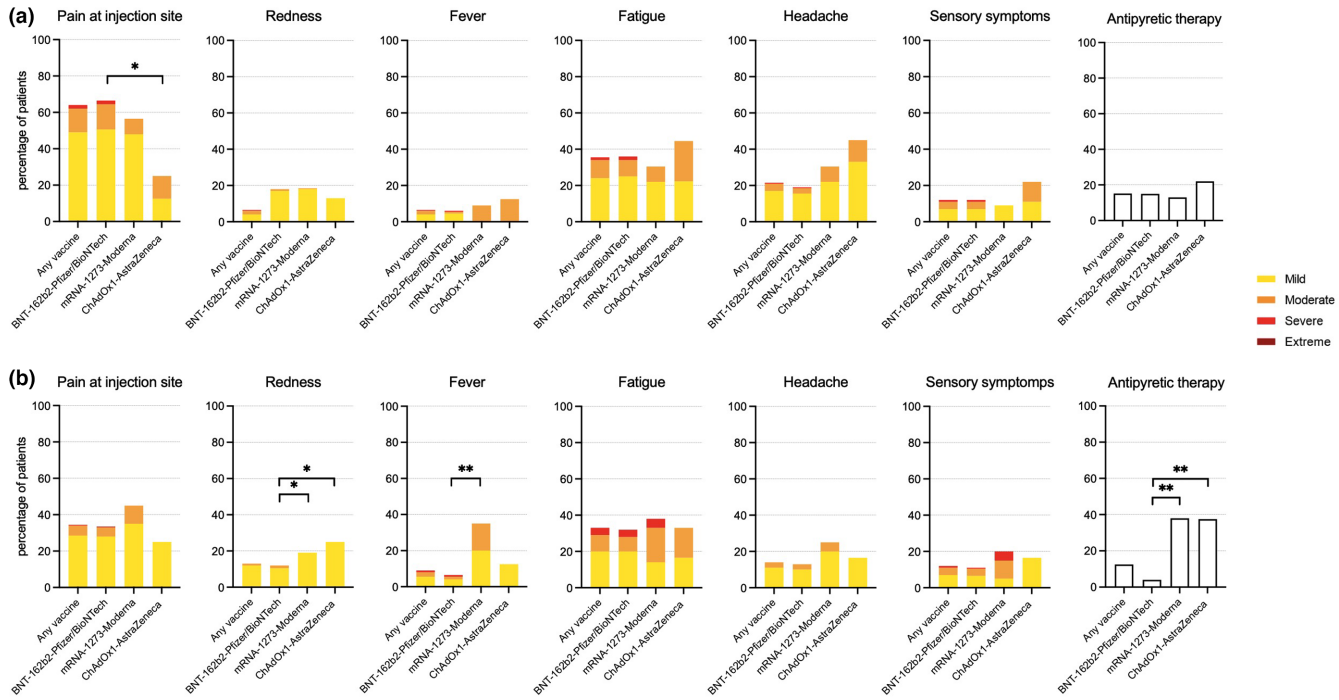


FIGURE 3 Local and systemic adverse events reported after SARS-CoV-2 vaccination by vaccine type. (a) Local and systemic adverse events reported after the first dose of SARS-CoV-2 vaccine by vaccine type. (b) Local and systemic adverse events reported after the second dose of SARS-CoV-2 vaccine by vaccine type. Figures show comparison of the frequency of local and systemic adverse events after the three types of SARS-CoV-2 vaccine. *Significant at 0.05 level. **Significant at 0.01 level.

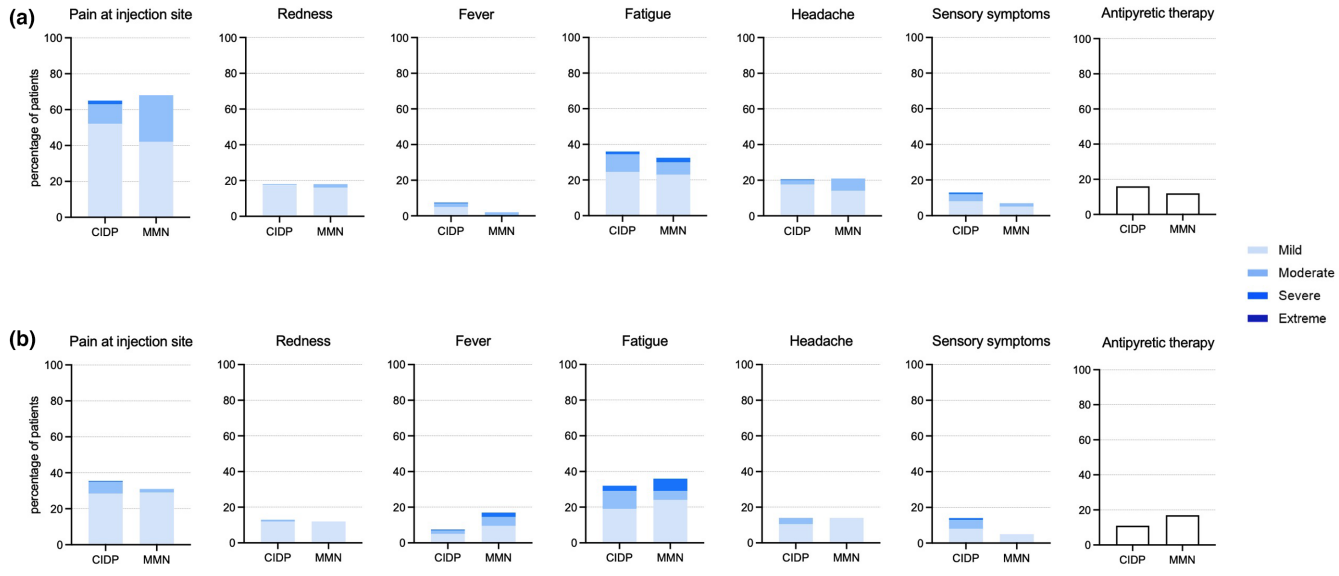


FIGURE 4 Local and systemic adverse events reported after SARS-CoV-2 vaccination by disease. (a) Local and systemic adverse events reported after the first dose of SARS-CoV-2 vaccine in CIDP and MMN patients. (b) Local and systemic adverse events reported after the second dose of SARS-CoV-2 vaccine in CIDP and MMN patients. Figures show comparison of the frequency of local and systemic adverse events between patients with CIDP and MMN.

When the frequency of relapse in the 3 months after vaccination was compared with that in the 3 months before vaccination, an increased risk following vaccination was found, specifically in CIDP patients. Although the case-crossover design might be associated with a risk of recall bias and lower accuracy of data collection, the short duration and proximity of the retrospective control period, the confirmation of the data using medical records, and the inclusion in the study of patients regularly followed by the participating centers make this risk low. The reason why the increased risk of relapse rate after vaccination was restricted to patients with CIDP remains to be

elucidated, although it may depend on the small number of MMN included patients. The exact mechanisms through which autoimmune reactions may be triggered by vaccination are not fully understood [41–44].

Treatment with steroids was associated with an increased risk of relapse occurrence in the univariate and multivariate analysis. To our knowledge there have not been similar observations in other autoimmune diseases. It can be hypothesized that patients on steroid treatment had a more active disease or that steroids somehow favor the immune reactivation triggered by vaccination. Further studies are needed to confirm this finding. A higher, albeit not statistically significant, risk of relapse was found after vaccination with mRNA-1273 (Moderna). Our study did not show an increased risk of relapse after ChAdOx1 (AstraZeneca), which was associated with an elevated incidence of GBS in some studies [45–49]. This might, however, be related to the small number of patients in our cohort who underwent vaccination with this specific type of vaccine.

The need of treatment adjustment in 12 of the 16 patients with disease relapse after vaccination can be used as a proxy of relapse severity. However, the short duration and the transience of relapses, with the majority of patients returning to their baseline levels, and the fact that no patient needed hospitalization suggests that relapses possibly related to SARS-CoV-2 vaccination were generally self-limited and mild to moderate in severity. It cannot be excluded that, in the patient with only partial improvement after 1-year follow-up, vaccination has accelerated an already undergoing clinical worsening of the disease.

This study also shows that SARS-CoV-2 vaccination in patients with CIDP and MMN is safe and tolerable in the short term. Most of the side effects were mild and moderately frequent. No patients reported grade 4 systemic events and only two CIDP patients reported a transient medical event potentially related to vaccination that did not require hospitalization. The incidence of local and systemic side effects in our study population was similar or lower than those reported in the clinical trials of the three vaccines [13–16]. Safety and tolerability of the three types of vaccines were similar, except for pain at the injection site and use of antipyretic medications. Tolerability of the SARS-CoV-2 vaccines was also similar in CIDP and MMN patients.

Limitations of our study include the small number of unvaccinated patients and the heterogeneity of the two groups (vaccinated and unvaccinated) in some factors including the proportion of patients on maintenance therapy. In Italy, the proportion of persons who joined the SARS-CoV-2 vaccination campaign was very high (80.5%) and this may explain the small number of unvaccinated patients in our study. The analysis of the risk was repeated excluding patients in remission, without ongoing treatment, and the risk was unchanged.

In conclusion, SARS-CoV-2 vaccination in CIDP and MMN patients was not associated with an increased risk of relapse in comparison with unvaccinated patients, even if this conclusion is limited by the quite small number of unvaccinated patients. Patients with CIDP, however, had a slightly increased risk of disease relapse after vaccination in comparison with the 3 months before vaccination. Worsening of neurological symptoms was not frequent and mostly self-limited, and vaccination was associated with an acceptable short-term safety profile. Given the high frequency of COVID-19 infection (almost 30% of the population in Italy) [50] and of its reported lethality (almost 1% of the population in Italy) [50], it appears that the benefits of SARS-CoV-2 vaccination in CIDP and MMN patients outweigh the risk of disease relapse.

AUTHOR CONTRIBUTIONS

PED designed and conceptualized the study, drafted the manuscript and figures, analyzed and interpreted the data. EB performed the statistical analysis, interpreted the data, revised the manuscript for intellectual content. CB, DC, FM, GMF, SM, AM, RF, LB, ML, MI, ER, GS, GC, GAM, MC, MF, GA, FN, SS, LC, CDA, TR, AG, MF, MC, EP, ES, MT, MS, LG, CS, FG, MR, FM, IRZ, DVV, EV, GM, SCP, LL, AC interpreted the data and revised the manuscript for intellectual content. ENO designed, conceptualized and supervised the study, analyzed and interpreted the data, revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

PED has received travel grants to attend scientific meetings from CSL Behring and Kedrion. CB has served on scientific advisory boards for Pfizer, Alnylam and Ionis, and has received travel grants from Kedrion and CSL Behring to attend scientific meetings. DC has received honoraria for lecturing from Shire, CSL Behring and Kedrion and travel grants to attend scientific meetings from Shire, Kedrion and CSL Behring. FM reports personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. AM has

received travel grants from Kedrion and CSL Behring to attend scientific meetings. RF has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion and CSL Behring to attend scientific meetings. ML has received travel grants to attend scientific meetings from Kedrion. GC has received travel grants to attend scientific meetings from CSL Behring and Kedrion. MC has received travel grants to attend scientific meetings from Kedrion. MF has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion, Baxter and CSL Behring to attend scientific meetings. EP has received travel grants to attend scientific meetings from CSL Behring. Eduardo Nobile Orazio reports personal fees for Advisory or Scientific Boards from Kedrion, Italy, Baxter, Italy, Novartis, Switzerland, CSL-Behring, Italy, Astellas, the Netherlands, outside the submitted work and travel grants to attend scientific meetings from Baxter, Grifols, Kedrion and Novartis, Italy. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Anonymized data used for this study are available upon reasonable request from the corresponding author.

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REFERENCES

1. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain–Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol*. 1979;110:105-123.
2. Tay SY, Chan WP. A 9-year-old female with bilateral leg weakness after influenza vaccination. *Pediatr Ann*. 2014;43:440-441.
3. Remiche G, Abramowicz M, Mavroudakis N. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) associated to hereditary neuropathy with liability to pressure palsies (HNPP) and revealed after influenza AH1N1 vaccination. *Acta Neurol Belg*. 2013;113:519-522.
4. Gable KL, Afshari Z, Sufit RL, Allen JA. Distal acquired demyelinating symmetric neuropathy after vaccination. *J Clin Neuromuscul Dis*. 2013;14:117-122.
5. Brostoff JM, Beitverda Y, Birns J. Post-influenza vaccine chronic inflammatory demyelinating polyneuropathy. *Age Ageing*. 2008;37:229-230.
6. Martín Arias LH, Sanz R, Sáinz M, Treceño C, Carvajal A. Guillain–Barré syndrome and influenza vaccines: a meta-analysis. *Vaccine*. 2015;33:3773-3778.
7. Watanabe T. Vasculitis following influenza vaccination: a review of the literature. *Curr Rheumatol Rev*. 2017;13:188-196.
8. Stassen PM, Sanders JS, Kallenberg CG, Stegeman CA. Influenza vaccination does not result in an increase in relapses in patients with ANCA-associated vasculitis. *Nephrol Dial Transplant*. 2008;23:654-658.
9. Bonetto C, Trotta F, Felicetti P, et al. Vasculitis as an adverse event following immunization—systematic literature review. *Vaccine*. 2016;34:6641-6651.
10. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, van Doorn PA. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *J Peripher Nerv Syst*. 2009;14:310-315.
11. Pritchard J, Mukherjee R, Hughes RA. Risk of relapse of Guillain–Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation. *J Neurol Neurosurg Psychiatry*. 2002;73:348-349.
12. Doneddu PE, Spina E, Briani C, et al. Acute and chronic inflammatory neuropathies and COVID-19 vaccines: practical recommendations from the task force of the Italian Peripheral Nervous System Association (ASNP). *J Peripher Nerv Syst*. 2021;26:148-154.
13. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK [published correction appears in Lancet. 2021 Jan 9;397(10269):98]. *Lancet*. 2021;397:99-111.
14. Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) COVID-19 vaccine. *N Engl J Med*. 2021;385:2348-2360.
15. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med*. 2020;383:2603-2615.
16. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.
17. Patone M, Handunnetthi L, Saatci D, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection [published correction appears in Nat Med. 2021 Nov 29]. *Nat Med*. 2021;27:2144-2153.
18. EMA. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5–8 July 2021. Updated July 5, 2021. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-5-8-july-2021. Accessed March 30, 2022.
19. Woo EJ, Mba-Jonas A, Dimova RB, Alimchandani M, Zinderman CE, Nair N. Association of Receipt of the Ad26.COV2.S COVID-19 vaccine with presumptive Guillain–Barré syndrome, February–July 2021. *JAMA*. 2021;326:1606-1613.
20. Doneddu PE, Bianchi E, Cocito D, et al. Risk factors for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): antecedent events, lifestyle and dietary habits. Data from the Italian CIDP database. *Eur J Neurol*. 2020;27:136-143.
21. Confavreux C, Suissa S, Saddier P, Bourdès V, Vukusic S, Vaccines in Multiple Sclerosis Study Group. Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. *N Engl J Med*. 2001;344:319-326.
22. Shaw FE Jr, Graham DJ, Guess HA, et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years. *Am J Epidemiol*. 1988;127:337-352.
23. Quast U, Herder C, Zwisler O. Vaccination of patients with encephalomyelitis disseminata. *Vaccine*. 1991;9(4):228-230.

24. Miller AE, Morgante LA, Buchwald LY, et al. A multicenter, randomized, double-blind, placebo-controlled trial of influenza immunization in multiple sclerosis. *Neurology*. 1997;48:312-314.
25. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint Task Force—Second revision. [published correction appears in J Peripher Nerv Syst 2022 Mar;27(1):94] [published correction appears in Eur J Neurol. 2022 Apr;29(4):1288]. *J Peripher Nerv Syst*. 2021;26:242-268.
26. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. *J Peripher Nerv Syst*. 2010;15:295-301.
27. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst*. 2005;10:220-228.
28. Aids to the investigation of peripheral nerve injuries. *J Neurol Psychiatry*. 1943;6:81.
29. Merkies IS, Schmitz PI, van der Meché FG, Samijn JP, van Doorn PA, Inflammatory Neuropathy Cause and Treatment (INCAT) group. Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry*. 2002;72:596-601.
30. van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology*. 2011;76:337-345.
31. Vanhoutte EK, Faber CG, van Nes SI, et al. Rasch-built Overall Disability Scale for Multifocal Motor Neuropathy (MMN-RODS(©)) [published correction appears in J Peripher Nerv Syst 2016 Mar;21(1):55]. *J Peripher Nerv Syst*. 2015;20:296-305.
32. Gart JJ. Alternative analyses of contingency tables. *J Roy Stat Soc*. 1966;28:164-179.
33. Dinoto A, Sechi E, Ferrari S, et al. Risk of disease relapse following COVID-19 vaccination in patients with AQP4-IgG-positive NMOSD and MOGAD. *Mult Scler Relat Disord*. 2022;58:103424.
34. Cannatelli R, Ferretti F, Carmagnola S, et al. Risk of adverse events and reported clinical relapse after COVID-19 vaccination in patients with IBD. *Gut*. 2022;71:1926-1928.
35. Di Filippo M, Cordioli C, Malucchi S, et al. mRNA COVID-19 vaccines do not increase the short-term risk of clinical relapses in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2022;93:448-450.
36. Elkharsawi A, Arnim UV, Schmelz R, et al. SARS-CoV-2 vaccination does not induce relapses of patients with inflammatory bowel disease. Eine SARS-CoV-2 Impfung ist nicht mit einer erhöhten Frequenz an CED-Schüben assoziiert. *Z Gastroenterol*. 2022;60:77-80.
37. Shapiro Ben David S, Potasman I, Rahamim-Cohen D. Rate of recurrent Guillain–Barré syndrome after mRNA COVID-19 vaccine BNT162b2. *JAMA Neurol*. 2021;78:1409-1411.
38. Ishizuchi K, Takizawa T, Sekiguchi K, et al. Flare of myasthenia gravis induced by COVID-19 vaccines. *J Neurol Sci*. 2022;436:120225.
39. Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? *Int Rev Immunol*. 2010;29:247-269.
40. Baars AE, Kuitwaard K, de Koning LC, et al. SARS-CoV-2 vaccination safety in guillain-barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy. *Neurology*. 2023;100:e182-e191. doi: 10.1212/WNL.0000000000201376
41. Chen RT, Pless R, Destefano F. Epidemiology of autoimmune reactions induced by vaccination. *J Autoimmun*. 2001;16:309-318.
42. Wraith DC, Goldman M, Lambert PH. Vaccination and autoimmune disease: what is the evidence? *Lancet*. 2003;362:1659-1666.
43. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. *Cell Mol Immunol*. 2018;15:586-594.
44. Chen Y, Xu Z, Wang P, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. *Immunology*. 2022;165:386-401.
45. Keh RYS, Scanlon S, Datta-Nemdharry P, et al. COVID-19 vaccination and Guillain–Barré syndrome: analyses using the National Immunoglobulin Database. *Brain*. 2023;146:739-748.
46. Kim JE, Park J, Min YG, Hong YH, Song TJ. Associations of Guillain–Barré syndrome with coronavirus disease 2019 vaccination: disproportionality analysis using the World Health Organization pharmacovigilance database. *J Peripher Nerv Syst*. 2022;27:206-214.
47. https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-8-september-2021_en.pdf
48. Tamborska AA, Singh B, Leonhard SE, et al. Guillain–Barré syndrome following SARS-CoV-2 vaccination in the UK: a prospective surveillance study. *BMJ Neurol Open*. 2022;4(2):e000309. doi:10.1136/bmjno-2022-000309
49. de Souza A, Oo WM, Giri P. Inflammatory demyelinating polyneuropathy after the ChAdOx1 nCoV-19 vaccine may follow a chronic course. *J Neurol Sci*. 2022;436:120231. doi:10.1016/j.jns.2022.120231
50. https://covid19.who.int/region/euro/country/it

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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