Transverse Myelitis Following SARS-CoV-2 Vaccination: A Pharmacoepidemiological Study in the World Health Organization's Database

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Background: Transverse myelitis (TM) has recently been associated by health authorities with Ad26.COV2.S (Janssen/Johnson & Johnson), one of the 5 US Food and Drug Administration (FDA) or European Medicines Agency (EMA) labeled severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) vaccines. It is unknown whether a similar association exists for the other FDA or EMA labeled SARS-CoV-2 vaccines (BNT162b2 [Pfizer/BioNTech], mRNA-1273 [Moderna], ChAdOx1nCov-19 [Oxford–AstraZeneca], and NVX-CoV2373 [Novavax]). This study aimed to evaluate the association between SARS-CoV-2 vaccine class and TM.

Methods: This observational, cross-sectional, pharmacovigilance cohort study examined individual case safety reports from VigiBase, the World Health Organization's pharmacovigilance database. We first conducted a disproportionality analysis with the information component (IC) using the reports of TM that occurred within 28 days following exposure to the FDA or EMA labeled SARS-CoV-2 vaccines, from December 1, 2020 (first adverse event related to a SARS-CoV-2 vaccine) to March 27, 2022. Second, we analyzed the clinical features of SARS-CoV-2 vaccine-associated TM cases reported in VigiBase.

Results: TM was significantly associated both with the messenger ribonucleic acid (mRNA)-based ($n = 364$; $IC_{025} = 0.62$) and vector-based ($n = 136$; $IC_{025} = 0.52$) SARS-CoV-2 vaccines that are authorized by the FDA or the EMA.

Conclusions: Findings from this observational, cross-sectional pharmacovigilance study showed that mRNA-based and vector-based FDA/EMA labeled SARS-CoV-2 vaccines can be associated with TM. However, because TM remains a rare event, with a previously reported rate of 0.28 cases per 1 million vaccine doses, the risk–benefit ratio in favor of vaccination against SARS-CoV-2 virus remains unchallenged. Rather, this study suggests that clinicians should consider the diagnosis of TM in patients presenting with early signs of spinal cord dysfunction after SARS-CoV-2 vaccination.

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Transverse myelitis (TM) is a focal neuro-inflammatory condition affecting the spinal cord and is characterized by acute demyelination, which leads to motor, sensory, and autonomic dysfunction.[1] Causes of TM include autoimmune diseases, infections (including severe acute respiratory syndrome-coronavirus 2 [SARS-CoV-2]),[2]

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paraneoplastic syndromes, and drugs. TM has been reported after exposure to attenuated (eg, measles, mumps, and rubella virus) and inactivated vaccines (eg, influenza virus).[3–7] The infectious antigen in the vaccine may trigger an auto-immune reaction in predisposed individuals, leading to TM.[8,9] However, vaccine-associated TM is rare, and the causal nature of this association as well as its potential mechanism are not well elucidated.[10]

Since the beginning of their use, several neurological adverse events (AEs) related to SARS-CoV-2 vaccines have been reported. In the 1 to 28-day period after vaccination, a significant association was found between the ChAdOxInCov-19 vaccine and Guillain-Barré syndrome (incidence rate ratio [IRR] = 2.04, 95% confidence interval [CI] = 1.60–2.60) as well as Bell's palsy (IRR = 1.29; 95% CI = 1.08–1.56).[11] On October 6, 2021, based on individual reports, the European Medicine Agency (EMA) recommended that TM should be added in the Summary of Products Characteristics (SmPC) as a side effect of Ad26.COV2.S (Janssen/Johnson & Johnson, New Brunswick, New Jersey, U.S.A.). Ten of these TM reports were considered to have a possible causal relationship with the vaccine, and one to have a probable causal relationship.[12] Several cases of TM have also been reported after vaccination with ChAdOx1nCov-19 (Oxford–AstraZeneca, University of Oxford/Cambridge, UK), BNT162b2 (Pfizer/BioNTech, New York City, U.S.A./Mainz, Germany), mRNA-1273 (Moderna, Cambridge, Massachusetts, U.S.A.), and Ad26.COV2.S (Janssen/Johnson & Johnson, New Brunswick, New Jersey, U.S.A.).[2,13–21]

To investigate a potential association among exposure to mRNA-, vector-, or recombinant protein-based SARS-CoV-2 vaccines and the occurrence of TM, we first conducted a disproportionality analysis in VigiBase, the World Health Organization's (WHO) pharmacovigilance database. Subsequently, we aimed to describe clinical features of SARS-CoV-2 vaccine-associated TM.

Methods

This observational and retrospective pharmacovigilance study was conducted in a de-duplicated dataset of VigiBase. VigiBase is the pharmacovigilance database developed by the WHO and is monitored by the Uppsala Monitoring Centre (UMC, Uppsala, Sweden). VigiBase is the largest database of de-identified individual case safety reports, with over 28 million reports of suspected drug AEs since 1968. Contributors come from more than 150 member countries of the Programme for International Drug Monitoring (WHO PIDM). Reports originate from health or non-health care professionals as well as patients or manufacturers.[22,23] Reports are mostly notified postmarketing and most national centers review case reports before they are sent to the UMC.[24] Because notifications are anonymous, no additional data can subsequently be obtained by the UMC or by investigators.

We queried TM reports in VigiBase. TM reports were identified with the preferred term "myelitis transverse" of the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 24.1) from December 1, 2020 (first report of an AE related to a SARS-CoV-2 vaccine) to March 27, 2022 (ClinicalTrials.gov identifier, NCT05178264). The 5 SARS-CoV-2 vaccines labeled by the US Food and Drug Administration (FDA) or the EMA were evaluated: BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), which are messenger ribonucleic acid (mRNA)-based vaccines, Ad26.COV2.S (Janssen/Johnson & Johnson) and ChAdOx1nCov-19 (Oxford–AstraZeneca), which are adenoviral vector-based vaccines, and NVX-CoV2373 (Novavax, Gaithersburg, Maryland, U.S.A.), which is a recombinant protein-based vaccine. No age limit was set. To ensure the ability of the database to detect previously established associations, we also queried VigiBase to identify TM reports associated with a positive control. Influenza vaccines (anatomic therapeutic chemical classification: J07BB) were chosen as a positive control due to the presence of TM in their SmPC and to previous reports of TM after exposure to influenza vaccines.[3–6] In our study, all suspected reports of SARS-CoV-2 vaccine-associated TM were considered cases and all other reports were considered non-cases. All cases were individually verified to avoid duplicated reports and chronological discrepancies (authors S.N. and P.-M.M.). Co-reported neurological AEs were gathered following the MedDRA classification in Supplementary Table 1 in Appendix S1.

The monthly count of TM cases was collected from VigiBase to identify a potential notoriety bias, in the event that notifications increased after the first EMA safety alert in October 2021.

Only TM cases occurring within 28 days following vaccination were included in the primary analysis. Cases occurring after 28 days were considered unlikely to be attributable to the vaccine, according to previous studies and expert opinions.[11]

Each report in VigiBase contains administrative data (date of reporting, qualification of the reporter, patient sex, country of reporting, and age at AE onset), clinical features of the AE (latency period, evolution, and co-reported AEs or investigations), and co-administrated drugs. The latency period was defined as the interval between the last administration of a SARS-CoV-2 vaccine and the onset of TM. Co-reported neurological AEs with a proportion over 1% were gathered using MedDRA (version 24.1).

Statistical Analysis

The association between SARS-CoV-2 vaccines and TM was assessed using disproportionality (also called case/non-case) analysis, which is the most commonly used method to assess a suspected association between a drug and an AE in VigiBase.[25,26] To perform the disproportionality analysis, we used the information component (IC), which is a flexible and automated Bayesian indicator developed by the UMC. The IC calculation is based on the number of cases observed for a drug-AE combination and the number of cases expected for the same pair. The IC reflects the strength of a drug-AE association.[27]

The IC is defined by the following equation: $IC = \log2\ (N_{observed} + 0.5)/(N_{expected} + 0.5)$ where $N_{expected} = (N_{drug} \times N_{effect})/N_{total}$.

$N_{observed}$ is the number of cases reported for the drug-AE combination (eg, SARS-CoV-2 vaccines-TM). $N_{expected}$ is defined as the number of case reports expected for a drug-AE combination. N_{drug} refers to the number of case reports for a drug of interest (eg, SARS-CoV-2 vaccine), regardless of AE. N_{effect} refers to the number of case reports for the AE of interest (eg, TM), regardless of the drug. Finally, N_{total} refers to the total number of case reports in VigiBase (since inception or during a specific study period). The IC is designed to detect new signals of an association between a drug and a specific AE.[27] It corresponds to the ratio of $N_{observed}$ compared to $N_{expected}$. The more the coefficient is positive and far from zero, the more the strength of the signal is important. However, without incidence data, the values of the ICs cannot be compared between different drugs or AEs.[28] IC_{025} and IC_{975} are the 95% lower- and upper-ends of the credibility interval for the IC, respectively. A positive IC_{025} value (IC_{025} >0) identifies an association between a drug and an AE.[26] Sensitivity analyses were performed regarding: (i) sex; age classes: (ii) 18 to 44 years old, (iii) 45 to 64 years old; (iv) time to TM onset ≤42 days; (v) only cases reported by healthcare professionals; (vi) only cases from reporters in Europe and the United States, and (vii) only cases after excluding patients with co-reported conditions known to induce TM (eg, multiple sclerosis, neuromyelitis optica spectrum disorder, paraneoplastic myelopathy, or neurosarcoidosis). These prespecified conditions were inferred from co-reported AEs and co-medications.

In a post hoc analysis, we measured whether the monthly count of TM cases after SARS-CoV-2 vaccination was correlated with the monthly count of all AEs reported after SARS-CoV-2 vaccination. Finally, a supplementary disproportionality analysis was performed, including cases without a reported latency period.

We reported medians and interquartile ranges (IQRs) for quantitative variables and percentages for qualitative variables. Descriptive analyses were performed using GraphPad (Prism version 8; GraphPad Software, San Diego, CA, USA). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. The use of pharmacovigilance confidential, electronically processed de-identified patient data was approved by the Caen University Hospital Research Ethics Committee (No. #2646). No individual patient consent was sought because this was a retrospective analysis of anonymized data. Institutional access was provided and approved by the UMC.

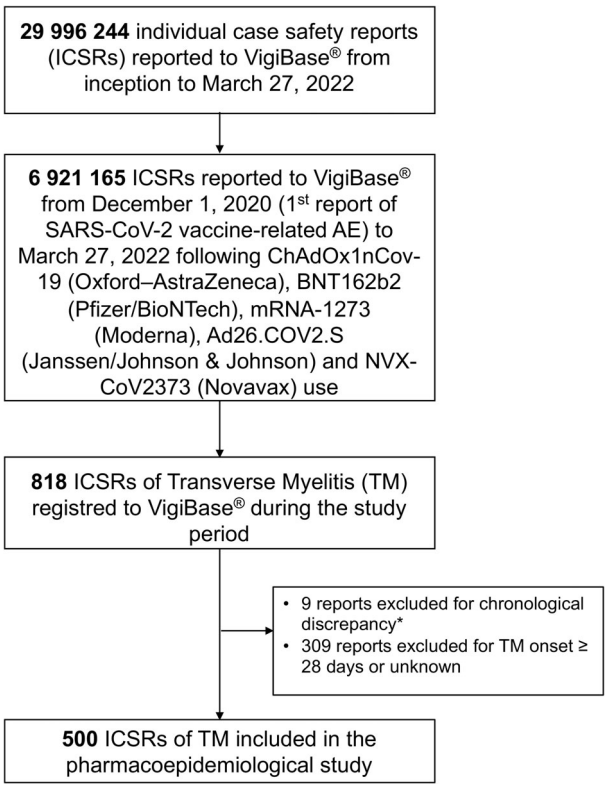

FIGURE 1: Study flow chart of the pharmacoepidemiological study. AE = adverse event; ICSRs = individual case safety reports; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; TM = transverse myelitis.

Results

From inception to March 27, 2022, a total of 29,996,244 reports of AEs were made to VigiBase. During the study period (December 1, 2020, to March 27, 2022), 6,921,165 reports of AEs were made, including 3,375,325 reports related to the 5 FDA or EMA labeled SARS-CoV-2 vaccines of interest.

Of 818 reports of TM associated with SARS-CoV-2 vaccines, 9 were excluded because TM symptoms occurred prior to vaccination and 309 were excluded because time to onset of TM was more than 28 days after vaccination or unknown (Fig 1). A total of 500 TM cases occurring

TABLE 1. Disproportionality Analysis Using VigiBase, the WHO's Pharmacovigilance Database

Vaccine type	N_{total}	N_{drug}	N_{effect}	$N_{observed}$	$N_{expected}$	IC	[IC_{025}; IC_{975}]
mRNA-based vaccines	6,921,165	2,471,747	586	364	209	0.80	**0.62**; 0.92
BNT162b2 (Pfizer/BioNTech)	6,921,165	1,783,189	586	280	150	0.89	**0.69**; 1.03
mRNA-1273 (Moderna)	6,921,165	688,558	586	84	58	0.52	**0.16**; 0.78
Vector-based vaccines	6,921,165	920,267	586	136	77	0.80	**0.52**; 1.00
ChAdOx1nCov-19 (Oxford–AstraZeneca)	6,921,165	765,411	586	95	64	0.55	**0.21**; 0.79
Ad26.COV2.S (Janssen/Johnson & Johnson)	6,921,165	154,856	586	41	13	1.61	**1.09**; 1.98
Influenza vaccines (positive control)	6,921,165	33,649	586	8	2	1.34	**0.13**; 2.15

The information component (IC) and its 95% credibility interval lower and upper end points (IC_{025} and IC_{975}) evaluate the observed-to-expected ratios of transverse myelitis cases associated with one of 4 US Food and Drug Administration or European Medicines Agency labeled SARS-CoV-2 vaccines in VigiBase (from December 1, 2020, to March 27, 2022). A positive IC_{025} value (>0; **in bold type**) denotes an association between a drug and an adverse event. No TM cases were reported following NVX-CoV2373 (Novavax) use.
SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; TM = transverse myelitis; WHO = World Health Organization.

within 28 days after vaccination were included in the study.

Throughout VigiBase, disproportionality analysis yielded significant associations between TM and both mRNA-based and vector-based SARS-CoV-2 vaccines (Table 1), with positive IC_{025} values of 0.62 and 0.52, respectively. Separately, the IC_{025} value was 0.69 for BNT162b2 (Pfizer/BioNTech), 0.16 for mRNA-1273 (Moderna), 0.21 for ChAdOx1nCov-19 (Oxford–AstraZeneca), and 1.09 for Ad26.COV2.S (Janssen/Johnson & Johnson). No TM cases were reported for NVX-CoV2373 (Novavax) during the study period. Influenza vaccines, used as positive control, were also significantly associated with TM (IC_{025} = 0.13; n = 8 of 586 TM cases reported during the study period).

For the 500 included TM cases, 280 (56%) were after vaccination with BNT162b2 (Pfizer/BioNTech), 84 (17%) after mRNA-1273 (Moderna), 95 (19%) after ChAdOx1nCov-19 (Oxford–AstraZeneca), and 41 (8%) after Ad26.COV2.S (Janssen/Johnson & Johnson; Table 2). Median age at onset of TM was 46 years (IQR = 37–60 years) for the mRNA-based vaccines and 49 years (IQR = 37–59 years) for the vector-based vaccines. Only 5 TM cases were reported in children, all of which were aged 13 to 17 and followed vaccination with BNT162b2 (Pfizer/BioNTech). A total of 222 of 363 (61%) and 62 of 136 (46%) of TM cases were reported in female patients following exposure to mRNA-based and vector-based vaccines, respectively. Cases were mainly reported in the Americas (mRNA-based: 277/364 [76%] and vector-based: 37/136 [27%]) and Europe (75/364 [21%] and 83/136 [61%]). The median number of TM cases after vaccination against SARS-CoV-2 was 33 per month (IQR = 27–41), ranging from 5 to 61. This number was correlated with the total number of AEs reported after exposure to SARS-CoV-2 vaccines (Pearson's value = 0.918; $p < 0.001$; Fig 2). The median latency period from first exposure to mRNA-based vaccines to TM was 6 days (IQR = 1.2–13 days). For vector-based vaccines, the median latency period was 8 days (IQR = 2–14 days).

Outcome was available in 206 cases, among which 78 (38%) were reported as recovered or recovering, 11 (5%) as recovered with sequelae, and 117 (57%) as not recovered. Other non-SARS-CoV-2 vaccine drugs were reported as co-suspected for 3 TM cases, without specifying which drug was suspected.

Among 500 cases of TM, 397 (79%) experienced at least one other additional AE (or investigation) following the SARS-CoV-2 vaccination. Among other neurological AEs, demyelinating conditions, such as Guillain-Barré syndrome, peripheral neuropathies, acute disseminated encephalomyelitis, multiple sclerosis, or neuromyelitis optica spectrum disorder were co-reported respectively in less than 10% of the cases (Table 3). Main co-reported biological and imaging investigations and considered of interest for the diagnosis of TM following SARS-CoV-2 vaccine are available in Supplementary Table 2 in Appendix S1.

Overall, sensitivity and supplementary analyses were consistent with the primary analysis and are available in Supplementary Tables 3 and 4 in Appendix S1.

TABLE 2. Characteristics of Patients Diagnosed with SARS-CoV-2 Vaccine-Associated Transverse Myelitis in VigiBase

	TM following mRNA-based vaccines (n = 364)		TM following BNT162b2 vaccine (n = 280)		TM following mRNA-1273 vaccine (n = 84)		TM following vector-based vaccines (n = 136)		TM following ChAdOx1n Cov-19 vaccine (n = 95)		TM following Ad26.COV2.S vaccine (n = 41)	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Reporters												
Available data	**88**		**76**		**12**		**102**		**92**		**10**	
Health care professional	47	53	39	51	8	67	50	49	44	47	6	60
Non health care professional	41	47	37	49	4	33	52	51	48	53	4	40
Sex												
Available data	**363**		**280**		**83**		**136**		**95**		**41**	
Female	222	61	182	65	40	48	62	46	53	55	9	22
Male	141	39	98	35	43	52	74	54	42	45	32	78
Location												
Available data	**364**		**280**		**84**		**136**		**95**		**41**	
Africa	0	0	0	0	0	0	2	1	1	1	1	2
Americas	277	76	205	73	72	86	37	27	5	5	32	78
Asia	3	1	3	1	0	0	3	2	3	3	0	0
Oceania	9	2	8	3	1	1	11	8	11	12	0	0
Europe	75	21	64	23	11	13	83	61	75	79	8	20
Age at onset, yr												
Available data	**252**		**187**		**65**		**111**		**77**		**34**	
Median (IQR)	46 (37–60)		45 (37–59)		50 (39–62)		49 (37–59)		49 (38–62)		47 (32–57)	
Range	13–90		13–90		18–79		18–79		21–79		18–64	
Outcomes												
Available data	**103**		**84**		**19**		**103**		**89**		**14**	
Recovered/ recovering	44	43	30	36	14	74	34	33	24	27	10	72
Recovered with sequelae	6	6	6	7	0	0	5	5	4	4	1	7
Not recovered	53	51	48	57	5	26	64	62	61	69	3	21

Data collection was made from December 1, 2020, to March 27, 2022. Available data (n) are shown in the first row for each characteristic and were used to compute percentages (%).
IQR = interquartile range; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; TM = transverse myelitis.

Discussion

To our knowledge, this is the first study highlighting an association between mRNA-based and vector-based FDA or EMA labeled SARS-CoV-2 vaccines and TM.

Since the first approval of BNT162b2 (Pfizer/BioNTech) by the EMA in December 2020, the efficacy and safety of SARS-CoV-2 vaccines were assessed in several randomized controlled trials (RCTs), of which some

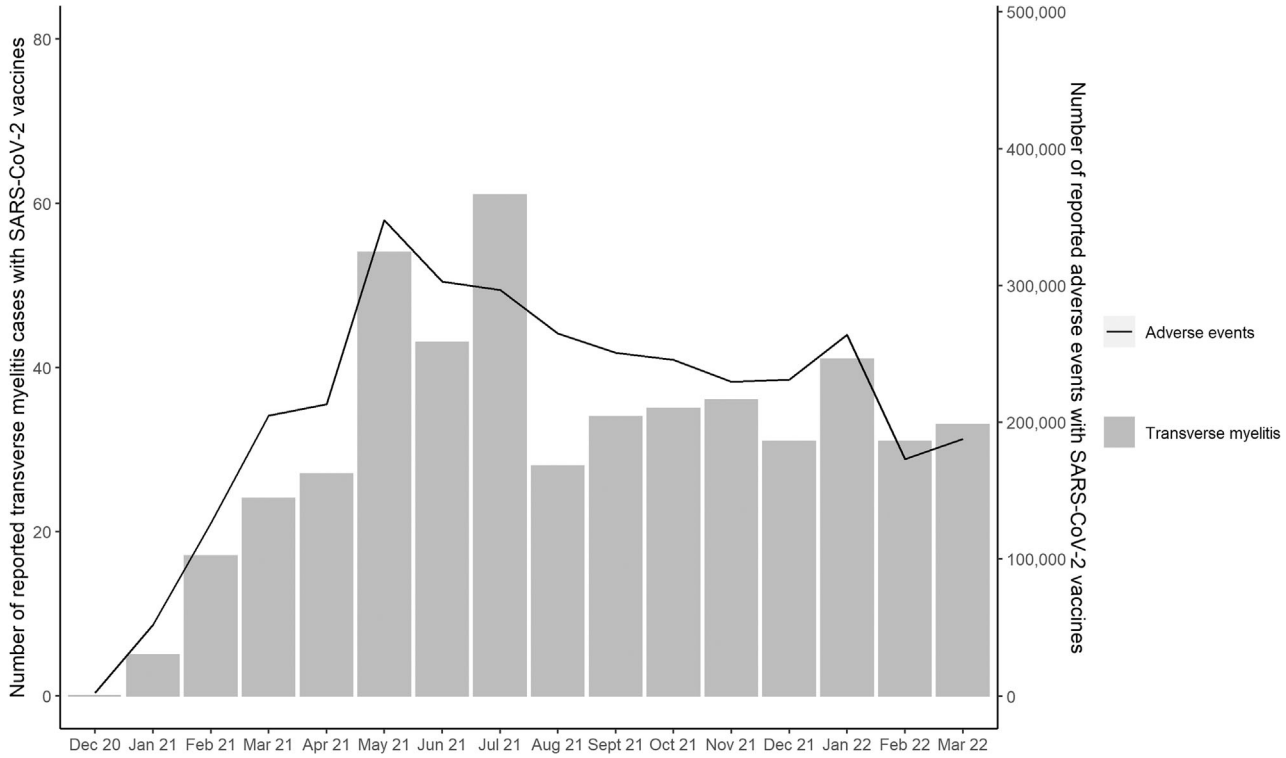

FIGURE 2: Monthly count of transverse myelitis (n = 500 cases) and all adverse events following administration of SARS-CoV-2 vaccines reported to VigiBase. Data collection was made on March 27, 2022. SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2.

TABLE 3. Co-Reported Neurological Adverse Events in SARS-CoV-2 Vaccine-Associated Transverse Myelitis in VigiBase

	TM following mRNA-based vaccines (n = 364)		TM following BNT162b2 vaccine (n = 280)		TM following mRNA-1273 vaccine (n = 84)		TM following vector-based vaccines (n = 136)		TM following ChAdOx1n Cov-19 vaccine (n = 95)		TM following Ad26.COV2.S vaccine (n = 41)	
Adverse Events	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Guillain-Barre Syndrome	12	3	5	2	7	10	9	6	5	8	4	11
Peripheral neuropathies	8	2	4	2	4	6	5	3	2	3	3	8
Multiple sclerosis	11	2	9	4	2	3	5	3	2	3	3	8
Cranial nerve disorders	5	1	2	1	3	4	4	3	2	3	2	5
Neuromyelitis optica spectrum disorder	10	2	8	4	2	3	3	2	2	3	1	3
CNS hemorrhages and cerebrovascular events	4	1	2	1	2	3	1	1	0	0	1	3
Encephalitis	1	0	0	0	1	1	4	3	2	3	2	5
ADEM	6	1	5	2	1	1	0	0	0	0	0	0

Data collection was made from December 1, 2020, to March 27, 2022.

ADEM = acute disseminated encephalomyelitis; AE(s) = adverse event(s); CNS = central nervous system; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; TM = transverse myelitis.

are still ongoing, including adult and pediatric patients. Vaccine-associated TM cases in RCTs are poorly described. A pooled interim analysis of 4 trials reported 2 cases of TM in the ChAdOx1nCov-19 (Oxford–AstraZeneca) vaccine group (n = 12,021). Among them, one case of TM occurred 14 days after the booster vaccination and the other was considered as unlikely to be related to vaccination by an independent committee of neurological experts. In the control group (n = 11,724), Voysey and colleagues reported a TM case diagnosed 68 days after injection and potentially related to a meningococcal vaccine.[29] In addition, no TM case has been diagnosed in the clinical trials that assessed Ad26.COV2.S (Janssen/Johnson & Johnson; n = 21,895 in the vaccine group),[30] mRNA-1273 (Moderna; n = 15,181 in the vaccine group), [31] and BNT162b2 (Pfizer/BioNTech; n = 18,860 in the vaccine group).[32] Although NVX-CoV2373 (Novavax) was marketed more than 1 year after the other SARS-CoV-2 vaccines, only 500 VigiBase reports were made following NVX-CoV2373 (Novavax) use and no TM was reported with this vaccine. Thus, we were not able to perform a disproportionality analysis and to assess a potential association between NVX-CoV2373 (Novavax) and TM.

Regarding postmarketing data, 10 case reports of SARS-CoV-2 vaccine-associated TM have been published.[2,13–21] TM following Ad26.COV2.S (Janssen/Johnson & Johnson), ChAdOx1nCov-19 (Oxford–AstraZeneca) and mRNA-1273 (Moderna) involved both men and women, with an age ranging from 36 to 76 years. The latency period from vaccination to onset of neurological symptoms ranged from 5 days to 3 weeks. These data are in line with our study, where cases appeared to be balanced between women and men. A 2009 review of 37 case reports of TM following non-SARS-CoV-2 vaccines showed that three-quarters of TM cases occurred during the first month following vaccination.[3] A more recent review found a male predominance and a mean age of 45 years.[17] Whereas the pathophysiology of vaccine-associated TM remains unknown, the theory of "molecular mimicry" suggests that the immune system may be activated by SARS-CoV-2 antigens, leading to spinal cord demyelination.[33,34] Although our study was not informative concerning the medical management of TM, according to the literature, the initial treatment used by physicians includes high dose intravenous methylprednisolone from 3 to 5 days, ± a relay to prednisolone 1 mg/kg per day. The duration of treatment with corticosteroids remains unclear. Recovery is reported to occur days to weeks following initiation of corticosteroids. In 3 cases, no recovery was observed, and second-line treatment with plasma exchanges was performed.[14,16,17]

A recent self-controlled case series evaluated the association between SARS-CoV-2 vaccines and neurological AEs. Overall, 32,552,534 patients who received a first dose of ChAdOx1nCov-19 (Oxford–AstraZeneca) or BNT162b2 (Pfizer/BioNTech) in England were included.[11] This study did not highlight an increased risk of the composite outcome "encephalitis, meningitis, and myelitis" after ChAdOx1nCoV-19 vaccination, with an IRR of 1.32 (95% CI = 0.99–1.76) in the 8 to 14 days after vaccination. However, the authors found an increased risk of "encephalitis, meningitis, and myelitis" in the 1 to 28 days following SARS-CoV-2 infection (IRR = 2.07, 95% CI = 1.78–4.11). The incidence of "encephalitis, meningitis, and myelitis" in the month following the first SARS-CoV-2 dose was 185 cases for 20,417,752 patients with ChAdOx1nCov-19 (Oxford–AstraZeneca) and 97 cases for 12,134,782 patients with BNT162b2 (Pfizer/BioNTech), respectively 9.25 per 1 million and 8.03 per 1 million. This was compared with the overall incidence of TM in the general population, which is between 1 and 4 per 100,000 persons per year in the most recent data.[35] A similar self-controlled case series method could be used on larger databases to identify enough TM cases after SARS-CoV-2 vaccination to clearly prove an association between SARS-CoV-2 vaccines and TM.

SARS-CoV-2 infection can also induce TM.[2] Using background incidence rates in the United States, incidence rates following acute SARS-CoV-2 infection, and the US national Vaccine Adverse Event Reporting System (VAERS), Frontera et al[36] highlighted that the rate of neurological events following SARS-CoV-2 vaccination is 132 to 617-fold lower than after SARS-CoV-2 infection. These data could suggest a protective effect of vaccination against the occurrence of neurological complications associated with SARS-CoV-2. Furthermore, the VAERS study did not find an association among the 3 SARS-CoV-2 vaccines (Ad26.COV2.S, BNT162b2, or mRNA-1273) and TM in the 1 to 42 days following vaccination. However, this study included 86 TM cases collected between January 1 and June 14, 2021, and may have lacked statistical power to demonstrate a potential association.[36] Using the US Vaccine Safety Datalink, Klein et al[37] did not show an association between TM and mRNA-based SARS-CoV-2 vaccines among 11,845,128 total doses administered to 6.2 million individuals (study period: December 14, 2020, to June 26, 2021). The small number of TM cases (n = 3 within 42 days following the most recent dose) and the interim nature of this analysis probably explains these results. Despite the large number of patients included, this study also failed

to show an association with myocarditis, which is now reported in the SmPC of mRNA vaccines.[38] This highlights the usefulness of pharmacovigilance data for the detection of rare AEs.

Up to December 10, 2021, 4.38 billion people were exposed to at least one dose of the SARS-CoV-2 vaccine. Manufacturers reported that 8.41 billion doses were administered, but these numbers are only available for some countries (including the United States and the European Union).[39] Using the estimated rate of 0.28 per 1,000,000 vaccine doses in the study by Frontera et al, we expected to observe at least 2,355 cases of TM following the SARS-CoV-2 vaccination during this period. Therefore, our study roughly included a quarter of all expected cases of TM.

Strengths and Limitations

Among the strengths of our study, we reported the largest and most extensive clinical characterization of TM associated with SARS-CoV-2 vaccines using reports from the WHO's pharmacovigilance database, providing more comprehensive data in real-life setting use. We focused on mRNA-based and vector-based FDA/EMA labeled SARS-CoV-2 vaccines during the study period, allowing us to conclude that TM is probably not only restricted to Ad26.COV2.S (Janssen/Johnson & Johnson) use. This reinforces the need for close monitoring of patients involved in ongoing RCTs and postmarketing studies. Furthermore, the use of influenza vaccines as positive control, known to be associated with TM, strengthens the internal validity of our results.

However, this study has many limitations, which are common to studies involving pharmacovigilance databases. First, and inherently to VigiBase's design, we could not re-ascertain the clinical examination, biological results (eg, SARS-CoV-2 test) and radiological findings (eg, magnetic resonance imaging) that lead to the diagnosis of TM. The available data on cerebrospinal fluid (CSF) and imaging results were not sufficient to further characterize the TM cases. We could not evaluate the likelihood of a causal association between the vaccination and TM on a case-by-case basis. As a result, TM cases could have included other neurological syndromes. For example, 5 of 500 reports had co-reported acute disseminated encephalomyelitis. However, the association remained unchanged after excluding patients with co-reported conditions known to induce TM. Data were missing for several variables, such as vaccination schedule, rechallenge, latency period, duration of TM, and outcomes. Second, we cannot exclude that TM cases may be linked to SARS-CoV-2 infection itself. Third, a potential increase of the IC_{025} may have resulted from a notoriety bias after the October 2021 to December 2021 EMA warnings. However, the number of TM cases reported per month did not increase after October 2021. The absence of over-notification may result from lack of mediatization in the press of EMA's safety updates. This is also consistent with a recent study that demonstrated that the strength of disproportionality signals does not increase in the FDA Adverse Event Reporting System after FDA warnings, for 31 drugs evaluated outside of the SARS-CoV-2 pandemic.[40] Fourth, considering the low number of TM cases reported in children during the study period, disproportionality analysis could not be performed in this specific population. Finally, the exact number of patients exposed to each of the labeled SARS-CoV-2 vaccines was not known, as VigiBase is not designed to estimate the incidence of AEs.

Conclusion

Findings from this observational, cross-sectional pharmacovigilance study showed that mRNA-based and vector-based FDA/EMA labeled SARS-CoV-2 vaccines can be associated with TM. However, TM remains rare and the risk of TM is likely higher after SARS-CoV-2 infection than SARS-CoV2 vaccination. The risk–benefit ratio in favor of vaccination against SARS-CoV-2 remains unchallenged. Clinicians should consider the diagnosis of TM in patients presenting with early signs of spinal cord dysfunction after SARS-CoV-2 vaccination.

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Author Contributions

P.M.M. contributed to conception and design of the study. S.N., E.B., B.C., A.N., and P.M.M. contributed to the acquisition and the analysis of the data. S.N., E.B., B.C., M.S., G.D., A.N., V.L.B., J.A., S.F., and P.M.M. contributed to the drafting of the text and preparing of the figures.

Potential Conflicts of Interest

J.A. reports honoraria for presentations and consulting fees from Bayer, BMS, Pfizer, Amgen, and Bioserenity, outside the submitted work.

Data Availability

At this time, data from VigiBase (the WHO pharmacovigilance database) are only available for national pharmacovigilance centers and the Uppsala Monitoring Centre. Public access to overview statistics from VigiBase can be gained through the VigiAccess website, http://www.vigiaccess.org/.

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