Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Neurology and Neurosurgery 220 (2022) 107374

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Full length article

COVID-19 vaccination in people with multiple sclerosis, real-life experience

Raed Alroughani, MD [a,b], Jasem Al-Hashel, MD [c,d], Fathi Abokalawa [c], Malak AlMojel [d], Samar Farouk Ahmed, MD [c,e,*]

[a] Division of Neurology, Amiri Hospital, Arabian Gulf Street, Sharq 13041, Kuwait
[b] MS Clinic, Ibn Sina Hospital, P.O. Box 25427, Safat 13115, Kuwait
[c] Department of Neurology, Ibn Sina Hospital, P.O. Box 25427, Safat 13115, Kuwait
[d] Department of Medicine, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait
[e] Department of Neurology and Psychiatry, Minia University, P.O. Box 61519, Minia 61111, Egypt

ARTICLE INFO

Keywords:
COVID-19
Vaccination
Multiple sclerosis
Kuwait

ABSTRACT

Background: Vaccination against the severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) virus is recommended in multiple sclerosis (MS) to reduce the risk of complications from Coronavirus disease 2019 (COVID-19) infection. These vaccines were not investigated in people with MS (PWMS).
Objective: This study aimed to report the short-term safety of the COVID-19 vaccines among PWMS.
Methods: Pfizer-BioNTech mRNA (BNT162b2) vaccine and Oxford-Astra Zenecaa chimpanzee adenovirus-vectored (ChAdOx1 nCoV-19) vaccine have been approved to be used in Kuwait since December 2021. PWMS registered in Kuwait national registry were contacted by phone, WhatsApp, or through face-to-face interviews and were invited to complete our questionnaire. Demographic, clinical data, symptoms following the vaccine, worsening of pre-existing MS symptoms, and occurrence of relapse were recorded.
Results: Of the 820 PWMS, 647 completed the questionnaire. Between January 2021 and 31 August 2021, 383 (59.28%) PWMS received at least one dose of the approved vaccinations versus 63.4% of the general population on the same date. Their mean age was 36.82 + 8.80, and most of them, 247 (64.3%), were females. A total of 356 vaccinated cohorts (92.6%) were treated with disease-modifying therapies. Adverse events were reported by 261 (68.15%) subjects. One case of COVID-19 infection was encountered after the first dose of the BNT162b2 vaccine. Twenty-one (5.48%) cases reported worsening of pre-existing MS symptoms after the vaccine. Five patients (1.31%) reported relapse after the COVID-19 vaccine. The most common adverse events of the COVID-19 vaccine were pain at the injection site, fatigue, low-grade fever, and body ache; and resolved within one week. There was no significant association between use of disease modifying therapy (DMT) and COVID-19 vaccine adverse events.
Conclusion: BNT162b2 and ChAdOx1 nCoV-19 are safe for PWMS. No increased risk of relapse activity or worsening of pre-existing MS symptoms.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), is a global public health emergency with high rates of morbidity and mortality [1,2]. Safe and effective vaccines are highly indicated. COVID-19 vaccination directly protects immunized individuals and indirectly protects the whole community by slowing virus transmission.

Pfizer-BioNTech mRNA (BNT162b2) vaccine [3] is a COVID-19 mRNA vaccine that received emergency use authorization by the US food drug administration (FDA) in December 2020. It is a new type of lipid nanoparticle-formulated vaccine, based on nucleoside-modified mRNA vector vaccine encoding the prefusion spike glycoprotein of SARS-CoV-2. Two doses are given 21 days apart [3]. The other vaccine approved in Kuwait is ChAdOx1 nCoV-19. It is a replication-deficient chimpanzee adenovirus vector with the SARS-CoV-2 spike glycoprotein antigen gene [4]. Two intramuscular injections are given 4–12 weeks apart in various ongoing trials [5].

* Corresponding author at: Department of Neurology, Ibn Sina Hospital, P.O. Box 25427, Safat 13110, Kuwait.
E-mail addresses: alroughani@gmail.com (R. Alroughani), jasemkumsa@hotmail.com (J. Al-Hashel), dr_fathi2010@yahoo.com (F. Abokalawa), malak.almojel@gmail.com (M. AlMojel), samerelshayb@hotmail.com (S. Farouk Ahmed).

https://doi.org/10.1016/j.clineuro.2022.107374
Received 13 October 2021; Received in revised form 18 March 2022; Accepted 9 July 2022
Available online 19 July 2022

The BNT162b2 vaccine and the ChAdOx1 nCoV-19 vaccine are approved for use in Kuwait for people aged 16 or older [6]. Patients received two intramuscular injections, 21days apart, delivered in the deltoid muscle. Each injection contained 30 μg of BNT162b2 (0.3 mL volume per dose). Two intramuscular injections are given 4–12 weeks apart in various ongoing trials at a dose of 5×10^{10} viral particles [5,7].

PWMS may have a higher risk of severe COVID compared to the general population; if they are older and if they have comorbidities [8]. The factors related to MS that can increase the risk of severe COVID are increased disability, recent treatment with corticosteroids and the use of antiCD20 treatment [9]. The vaccines' safety and their association with MS worsening is still uncertain [10].

The approved vaccines have been investigated in large clinical trials that recruited healthy subjects and patients with chronic diseases. However, the COVID-19 vaccines have not been studied in PWMS [11–15].

The National MS Society (NMSS) published guidance on COVID-19 mRNA vaccines that encouraged vaccination and emphasized safety in PWMS. Specific guidelines for vaccine timing in relation to the dosing of individual DMTs were also included to maximize vaccine efficacy. NMSS strongly recommended that PWMS receive the COVID- 19 vaccine based on a low theoretical risk and the high potential benefit of vaccination [11,15].

Few studies reported information regarding the safety and efficacy of the vaccines in this group. Previous studies reported that COVID-19 vaccines are safe and do not increase the short-term risk of clinical relapses in PWMS [16]. Untreated COVID-19-vaccinated MS patients can develop protective SARS-CoV-2 humoral responses, similarly to healthy vaccinated. In MS patients treated with high-efficacy DMTs, the immune response to COVID-19 vaccination varied [17]. The efficacy of the COVID-19 vaccine may be low in PWMS treated with ocrelizumab, rituximab, and fingolimod [18].

Therefore, real-life studies on the safety of the COVID-19 vaccine among PWMS are essential. In this study, we aimed to evaluate the safety, and short-term risk for MS relapses in PWMS who received COVID-19 vaccination in Kuwait.

2. Methods

This is a cross-sectional, observational study to assess the safety of the COVID-19 vaccine among PWMS. The ministry of health in Kuwait follows guidelines of NMSS of COVID-19 vaccination for PWMS.

Subjects in Kuwait either received two intramuscular injections, 21 days apart, delivered in the deltoid muscle and injection contained 30 μg of BNT162b2 (0.3 mL volume per dose) or received two intramuscular injections given 4–12 weeks apart at a dose of 5×10^{10} viral particles of ChAdOx1 nCoV-19 vaccine [5,7].

Patients diagnosed with MS according to the 2017 McDonald criteria [19], who were recorded in the Kuwait National MS Registry (KNMSR), were invited to answer a questionnaire regarding their vaccination status. Since the dates for the first and second vaccine doses were pre-scheduled, data were collected within 21days after each vaccine dose by the treating neurologists during a face-to-face interview, contact using phone calls, or WhatsApp application with a link to the survey made by using Google Forms. The questionnaire was written in English, then translated into Arabic. It was reviewed by two independent neurologists and tested on 10 PWMS for validation. The questionnaire was designed to report demographic, clinical, and medications data. It also records the frequency, severity, and duration of the vaccine side effects among the PWMS and the impact of the vaccine on symptoms of MS.

The questionnaire queried demographics (age, gender, job, and social state), MS characteristics (disease course, disease duration, EDSS (Expanded Disability Status Scale) and DMT), and whether the patient received the vaccine or not yet. If the patient received the vaccine, they report in questionnaire symptoms following each vaccine dose as follow: no vaccine-associated symptoms; pain at the injection site tenderness/ swelling/ redness; fever/chills; fatigue and/or general weakness; headache; muscle and/or body ache; arthralgia; flu-like symptoms/sore throat; nausea/ vomiting: diarrhea; post-vaccination COVID-19 infection; MS relapse; and worsening of MS symptomatology. Grading of the side effects was done according to FDA's Toxicity Grading scale; grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (serious or life-threatening) [20].

Patients who reported relapse or worsening of MS symptoms underwent a neurological evaluation to confirm or exclude the event.

Patients with cognitive disabilities and patients unwilling to participate in the study were excluded from the study.

Ethical considerations.

All patients gave their informed consent and the study was approved by the Research Ethics Committee of the ministry of health in Kuwait, Number1670/2020.

2.1. Statistical analysis

The statistical analyses were performed using SPSS Statistics Software version 26.0 (IBM Corporation, Armonk, NY, USA). Descriptive data are shown as number (percentage) or mean ± standard deviation for continuous variables, whereas categorical ones were expressed as proportions and percentages. Paired sample *t*-test was used to compare between continuous variables and the chi-squared test(X^2) was used to compare between categorical variables. Pearson correlation coefficient test "r" was used to measure the association between COVID-19 vaccine adverse events and the use of DMT. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of the study cohort

Vaccination started in Kuwait on 24/12/2020. At the end of this study, there were about 2375,455 (63.4%) vaccinated persons in Kuwait [21]. Between first January 2021 and 31 August 2021, 646 out of 820 PWMS contacted completed the questionnaire (78.9% response rate).

Table 1 displays the demographic and clinical characteristics of all PWMS cohorts. The mean age was 36 years (range 16–74). The majority, 301 (65.2%), were female. Mean disease duration was 10 years (range 1–42), and median EDSS 3.0 (range 0–7.5). Most of the studied cohort was of relapsing-remitting MS 356 (73.9%), whereas 70 (10.8%) patients were untreated. A total of 383 participants (59.28% of the responders) had received at least one dose of the approved vaccinations versus 63.4% of the general population on the same date. 225 received BNT162b2 vaccine and 159 received ChAdOx1 nCoV-19. Few patients, 79 (12.2%), rescheduled/postponed their DMT doses because of vaccine, and 160 (24.8%) patients postponed vaccine administration because of DMT time of administration. 28 Patients on anti CD20 needed to postpone the vaccine or reschedule their medications.

Table 2 displays the demographic and clinical characteristics of the vaccinated PWMS cohort. Their mean age was 37 years, and most of them, 247 (64.3%), were females. Mean disease duration was nine years (range 1–42), and median EDSS 3.0 (range 0–7.5). Only 27 (7%) of vaccinated PWMS are untreated. 180 (46.99%) had received only one dose, and 203 (53.0%) had received both doses. The mean time from the second dose to data analysis was 63.2 ± 17.3 days.

3.2. The short term safety profile of the COVID vaccine among PWMS

Adverse events were reported by 261 (68.15%) participants. There was one case of COVID-19 infection encountered after the first dose of the BNT162b2 vaccine. She was a 32 years old female who had been treated with interferon Beta interferon-1a IM. COVID-19 diagnosis was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) technique from a sample of nasaoropharynx swab. She was in contact

Table 1
Demographic and clinical Characteristics of PWMS patients Number= 646.

Variables	Mean + SD/Number (%)
Mean Age	36.28 + 8.98
Range	16–74
Gende	225 (34.8)
	421 (65.2)
• Male	
• Female	
Job	• 337 (51.2)
	• 83 (12.9)
• Full time	• 40 (6.2)
• Part time	• 113 (17.5)
• Student	• 42 (6.5)
• Retired	• 31 (4.8)
• Jobless	
• Self employed	
Social state	• 188 (29.1)
	• 395 (61.1)
• Single	• 53 (8.2)
• Married	• 10 (1.5)
• Divorced	
• Widow	
Mean disease Duration	9.89 + 5.82
Range	1–42
Disease Type	• 16 (2.48)
	• 467 (72.30)
• CIS	• 97 (15.02)
• RRMS	• 66 (10.20)
• SPMS	
• PPMS	
Median EDSS	3
Range	0–7.5
DMT	• 56 (8.7)
	• 5 (0.8)
• Beta-interferons (1a and 1b)	• 45 (7.0)
• Teriflunomide	• 108 (16.7)
• Dimethyl fumarate	• 122 (18.9)
• Natalizumab	• 110 (17.0)
• Fingolimod	• 88 (13.6)
• Ocrelizumab	• 9 (1.4)
• Rituximab	• 33 (5.1)
• Cladribine	• 70 (10.8)
• Alemtuzumab	
• Untreated	
History of COVID-19 infection	101 (15.6)
State of COVID-19 infection	• 71 (11.0)
	• 27 (4.2)
• Mild	• 3 (0.3)
• Moderate	
• Severe	
State of COVID Vaccine	• 383 (59.28)
	• 263 (40.71)
• Yes	• 180 (28)
• No	• 203 (31.4)
• First dose	
• Two doses	
Type of COVID vaccine	• 225 (34.8)
	• 159 (24.6)
• BNT162b2	
• ChAdOx1 nCoV-19	
Reschedule/postpone DMT because of Vaccine	79(12.2)
Postpone Vaccine because of DMT	160 (24.8)

PWMS: people with multiple sclerosis; BNT162b2: the Pfizer-BioNTech mRNA vaccine; ChAdOx1 nCoV-19: the Oxford-AstraZenecaa chimpanzee adenovirus-vectored vaccine; clinically isolated syndrome: CIS; Relapsing-remitting MS: RRMS, secondary progressive MS: SPMS, primary progressive MS: PPMS; EDSS, Expanded Disability Status Scale' DMT: disease-modifying therapy.

Table 2
Demographic and clinical Characteristics of vaccinated PWMS patients.

Variables	Total N = 383	BNT162b2 N = 225 (58.6%)	ChAdOx1 nCoV-19 N = 158 (41.1%)	P
Mean Age	36.82 + 8.80	36.50 + 9.36	37.30 + 7.96	0.619
Gender	137 (35.7)	77 (20.1 148 (38.6)	60 (15.7) 99 (25.7)	0.451
• Male	247			
• Female	(64.3)			
Mean disease Duration	9.31 + 6.15	9.59 + 6.60	8.94 + 5.42	0.069
Job	• 217 (56.5)	• 119(31.01)	• 98 (25.3)	0.178
	• 34 (8.9)	• 16 (4.2)	• 18 (4.7)	
• Full time	• 16 (4.2)	• 11 (2.9)	• 5(1.3)	
• Part-time	• 86 (22.4)	• 58(15.1)	• 28(7.3)	
• Student	• 14 (3.6)	• 10 (2.6)	• 4 (1.0)	
• Retired	• 17 (4.5)	• 11 (2.9)	• 6 (1.6)	
• Jobless				
• Self-employed				
Social state	• 100 (26.1)	• 55(14.4)	• 45 (11.7)	0.102
	• 243 (63.3)	• 140(36.6)	• 103 (26.9)	
• Single	• 37 (9.6)	• 26 (6.8)	• 11 (2.8)	
• Married	• 4 (1)	• 4 (1)	• 0	
• Divorced				
• Widow				
DMT	• 33 (8.6)	• 16 (4.2)	• 17 (4.4)	0.293
	• 4 (1.0)	• 3 (0.8)	• 1 (0.2)	
• Beta Interferons (1a/1b)	• 33 (8.6)	• 17 (4.4)	• 16 (4.2)	
• Teriflunomide	• 80 (20.8)	• 49 12.8)	• 31(8.1)	
• Dimethyl fumarate	• 91 (23.7)	• 48 (12.5)	• 43 11.2	
• Natalizumab	• 53 (13.8)	• 35 (9.1)	• 18 (4.7)	
• Fingolimod	• 34 (8.9)	• 24(6.3)	• 10 2.6)	
• Ocrelizumab	• 23 (6)	• 16 (4.4)	• 6 (1.6)	
• Rituximab	• 6 (1.6)	• 2 (0.9)	• 4 (2.5)	
• Alemtuzumab	• 27 (7)	• 15(3.9)	• 12 (3.1)	
• Cladribine				
• Untreated				
History of SARS-CoV-2 infection prior vaccination	54 (14.1)	37 (9.7)	17 (4.4)	0.116
State of COVID Vaccine	• 181 (47.2)	• 64 (16.7)	• 117 (30.5)	0.001
	• 203 (52.9)	• 161 (42.2)	• 42 (10.7)	
• First dose				
• Two doses				

DMT: disease modifying therapy; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2;PWMS: people with multiple sclerosis; BNT162b2: the Pfizer-BioNTech mRNA vaccine; ChAdOx1 nCoV-19: the Oxford-AstraZenecaa chimpanzee adenovirus-vectored vaccine; N: number.

with a subject that was identified as COVID-19 positive. She had mild symptoms and was treated with symptomatic treatment at home. No SARS-CoV-2 infections were reported after the second vaccination dose of the BNT162b2 vaccine or the ChAdOx1 nCoV-19 vaccine.

Twenty-one (5.48%) cases reported worsening of pre-existing MS symptoms after the vaccine. These symptoms were transient and related to low-grade fever post relapse. Five patients (1.31%) reported relapse after the COVID-19 vaccine. Relapses were confirmed with a neurologist in absence of fever and evidence of infection. Three patients had a significant relapse that need treatment with steroids. The other two patients reported new sensory symptoms that do not need steroid treatment.

Many patients reported adverse events following the COVID-19 vaccine, as outlined in Table 3/Fig. 1. The most frequent adverse event was generalized body/muscle ache in 46% no significant difference among PWMS who received the ChAdOx1 nCoV-19 vaccine compared to those who received BNT162b2 vaccine. This was followed by fatigue, injection site reaction, and swelling and redness at the site of injection. Injection site pain/tenderness/ swelling/ redness was more significantly frequent among PWMS who received BNT162b2vaccine

Table 3
Stratification of adverse events by Vaccine N = 383.

Variables	Total vaccinated cohort N = 383	BNT162b2 N = 225	ChAdOx1 nCoV-19 N = 158	P
Adverse events Yes	261 (68.15%)	151 (39.43%)	110 (28.729%)	0.056
Worsening of MS symptoms	21(5.48%)	12(3.13%)	9 (2.35%)	0.956
MS relapse	5 (1.31%)	2 (0.52%)	3 (0.78)	0.145
Local side effects	141 (36.81%)	91 (23.76%)	50 (13.05%)	0.040
	170 (44.39%)	113 (29.50%)	57 (14.88%)	*
• Injection site pain/tenderness				0.004 *
• Swelling/ redness				
Systemic side effects	57 (26.6%)	22 (5.74%)	35 (9.14%)	0.019
	176(45.95%)	100 (26.11%)	76(19.84%)	*
	46 (12.01%)		10(2.62%)	0.396
• Fever/Chills	176 (45.95%)	36 (9.40%)	78 (20.37%)	0.002
• Fatigue	77 (20.10%)	98 (23.50%)	37 (9.66%)	*
• Headache	10 (2.61%)	40 (10.44%)	4 (1.04%)	0.274
• Body/muscle ache	12 (3.13%)	6 (1.57%)	8 (2.09%)	0.165
• Arthralgia	8(2.09%)	4 (1.04%)	5 (1.31%)	0.915
• Flu like symptoms/ Sore throat		3 (0.78%)		0.074
• Nausea/ Vomiting				0.175
• Diarrhea				
SARS-CoV-2 Infection after vaccination	1 (0.62%)	1 (0.39%)	0	0.380

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; BNT162b2: the Pfizer-BioNTech mRNA vaccine; ChAdOx1 nCoV-19: the Oxford-AstraZenecaa chimpanzee adenovirus-vectored vaccine; N: number; * significance level of < 0.05.

compared to those who received ChAdOx1 nCoV-19 vaccine. Fatigue showed no significant difference among both groups. Fever was reported in 27%, and it was significantly more frequent among PWMS who received the ChAdOx1 nCoV-19 vaccine compared to those who received the BNT162b2 vaccine. Headache was significantly prevalent among PWMS who received the BNT162b2 vaccine.

Most reported adverse events were mild (62.07%), while moderate adverse events were observed in (24.90%) subjects, as shown in Fig. 2.

The duration of adverse events was two days in 80/261 (30.65%) of subjects who experienced adverse events. Some patients have adverse events up to one week 116/261 (44.44) and only 13/261 (4.98%) reported adverse events for more than one week, Fig. 3.

There was no significant association between the use of DMT and adverse events of the COVID-19 vaccine or the severity of adverse events. Also, no significant association between the use of DMT and worsening of pre-existing MS symptoms or relapse (Table 4).

3.3. The attitude of non-vaccinated toward COVID-19 vaccine (N = 262)

127/262 (48.47|%) of PWMS reported that they would get the vaccine once it is available, 25/262 (9.54%) decided that they will not receive it, and 111/262 (42.37%) are still hesitant to decide.

4. Discussion

Vaccination against the SARS-CoV-2 pandemic is currently ongoing

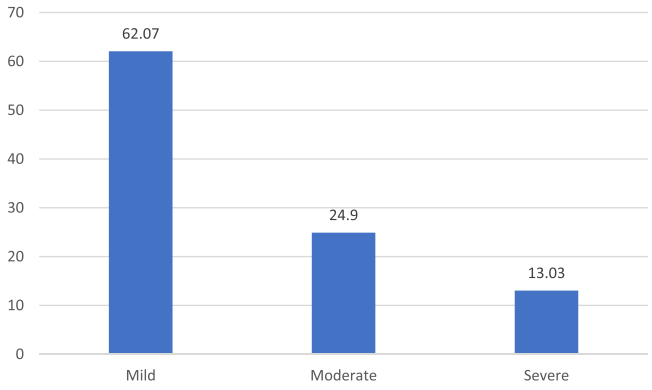

Fig. 2. Severity of adverse events.

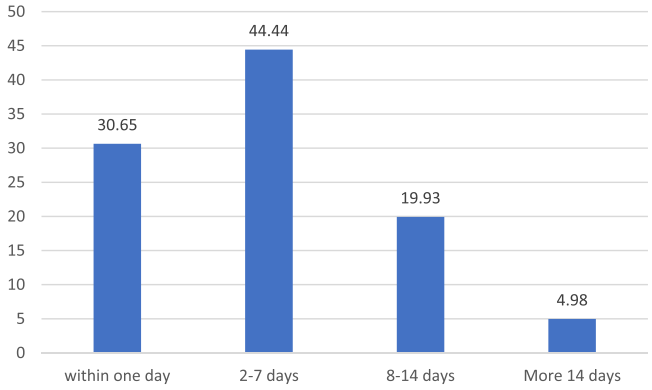

Fig. 3. Duration of adverse events.

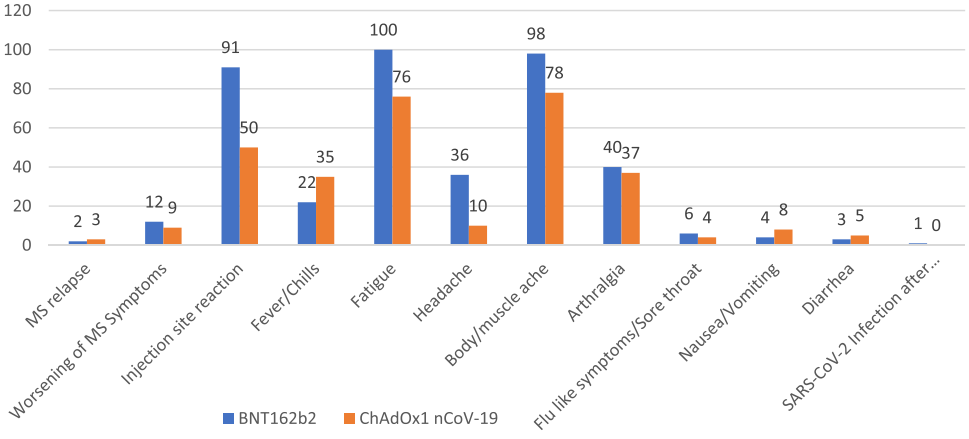

Fig. 1. Stratification of adverse events by Vaccine.

Table 4
Correlation between used of DMT and COVID-19 vaccine adverse events.

Variable	DMT
Occurrence of COVID-19 adverse events	R= 0.065 P = 0.341
Severity of COVID-19 adverse events	R= 0.115 P = 0.147
Worsening of preexisting MS symptoms	R= 0.011 P = 0.805
Occurrence of MS relapse	R= 0.149 P = 0.076

DMT: disease modifying therapy; MS: multiple sclerosis.

in large populations all worldwide, and among them, many PWMS are being vaccinated. [22]. There are uncertainties about the safety of the vaccines for both MS patients and neurologists. In this study, we reveal real-life experience regarding the safety of the COVID-19 vaccine among PWMS in Kuwait.

The overall rate of adverse events among our cohort is 68%. Our results showed that PWMS had a similar record of adverse events to that has been reported in the general population following BNT162b2 and ChAdOx1 nCoV-19 vaccination against SARS-CoV-2 infection [3–5,7, 22] and similar real-life studies [23–25].

Adverse events that were reported in our cohort matches the adverse events reported from both the normal population [3–5] and from the PWMS used other vaccinations [26]. Thus, these findings suggest that PWMS do not show a higher risk for vaccine-induced adverse events.

Similar to the clinical trials, local reactions such as pain, redness, and swelling at the injection site were the most common adverse events [3–5]. The frequency and characteristics of adverse events with the BNT162b1/BNT162b2 vaccines reported in our study are comparable to those reported during the phase 1 trial in the United States [27].

In our MS cohort, fatigue was reported in 46%, and headache in 12%. Our results are in partial agreement with Achiron et al. [24], who reported fatigue in 20% and headache in 9%. Fatigue is a common complaint in many PWMS and may be underestimated as an adverse event related to vaccination. Fever was reported in 27% in our BNT162b2 vaccinated cohort, which is nearly similar to the MS cohort of Achiron et al. who reported fever 15%. Non-MS subjects in a clinical trial showed the rate of fever was 16% [3].

In this study, most of the reported adverse events are mild and moderate (87%). Severe adverse events were infrequent in our cohort. The occurrence of adverse events following vaccination could be mediated by immunological responses, reflecting the activity of the immune system [28,29]. Most of our cohort were treated with DMT and many of which have an immunosuppressive effect. If the adverse events are related to the immune system's activity, PWMS treated with immunosuppressive medications may not develop severe adverse events following vaccination.

The adverse events resolved within two days in most of our cohort 80.5%, which is consistent with the results of Achiron study [24].

21 participants (5.5%) reported worsening pre-existing multiple sclerosis symptoms following the vaccination. This result is lower than the result of Lotan et al. who reported a 15% worsening of neurological symptoms [23]. The low rate of worsening pre-existing multiple sclerosis symptoms following the COVID-19 vaccine, in addition to its overall mild severity, is in agreement with previous studies on other non-live-attenuated vaccines that were not related to an increased risk of MS rsymptoms [30,31].

We reported MS relapse in 5 cases (1.3%). All cases were reported shortly after the first dose of the vaccine. Three cases were reported after the first dose of BNT162b2 and 2 cases after the first dose of ChAdOx1 nCoV-19. Similarly, Maniscalco reported a female MS patient presented with paraesthesia and weakness in her left arm and left leg 48 h after receiving the mRNA COVID-19 vaccination [32]. The early onset of relapse after the vaccination questioned the causal association with the vaccine. A previous study that included 555 MS patients showed that acute relapses were detected in 2.1% of patients after the first dose and 1.6% of patients after the second dose of the BNT162b2 vaccine. After vaccination, the relapse rate in our cohort was similar to the relapse rate in a comparative time period without vaccination and this finding is in agreement with Achiron study [24].

Our result is in disagreement with K. Allen-Philbey who did not observe any lasting neurological sequelae or MS relapse. The disagreement can be explained by the smaller number of Allen-Philbey K et al.; 33 PWMS compared to the number of our cohort 383 PWMS [33]. COVID-19 can worsen MS, so the vaccination can reduce the risk of relapses by dropping the risk of infections [24].

Previous studies show that COVID-19 vaccines seem to be not associated with an increased risk of acute relapses [16,24]. Data from an interim analysis of the efficacy and safety of the ChAdOx1 nCoV-19 vaccine from four blinded, randomized, controlled trials (COV001, COV002, COV003, and COV005) reported a case of transverse myelitis occurred 10 days after the first dose of ChAdOx1 nCoV- 19 in a patient with MS, that was determined to be unlikely to be related to vaccination by an independent committee of neurological experts [7].

We reported one case of COVID-19 infection encountered after the first dose of the BNT162b2 vaccine. However, mRNA vaccines do not contain live viruses, do not integrate with the human genome, and cannot cause COVID-19 infection [34].

There was no significant association between use of DMT and adverse events of the COVID-19 vaccine or worsening of pre-existing MS symptoms or relapse. Previous studies reported that COVID-19-vaccinated MS patients can develop protective SARS-CoV-2 humoral responses. PWMS treated with DMTs had variable immune responses to COVID-19 vaccination [17,18].

Our results showed 48.5% of PWMS would accept a COVID-19 vaccine. This is a lower rate compared to online surveys conducted for the United Kingdom general pub population (67%) [35], patients with autoimmune diseases from Netherland (61%) [36], PWMS from Portugal (80.9%) [37], and PWMS from the united state (66%) [38]. 42.4% are hesitant to decide, and 25% refused to receive the COVID-19 vaccine. Vaccine hesitancy regarding COVID-19 vaccines has been reported in a significant proportion of PWMS patients [38–40]. The vaccine hesitancy is due to lack of confidence in the safety and effectiveness of the vaccine [41]. The data reported in the present study help to address the safety concerns related to the vaccine among PWMS.

5. Conclusions

PWMS patients had similar rates of adverse events to the general population following COVID-19 vaccination. BNT162b2 and ChAdOx1 nCoV-19,COVID-19 vaccines are likely safe in PWMS on various DMTs. Worsening of MS is uncommon with these COVID-19 vaccines. BNT162b2 and ChAdOx1 nCoV-19 vaccinations do not exacerbate MS or provoke a relapse. We do not recommend discontinuing or modifying DMTs to improve vaccine efficacy, as the risk of disease reactivation and progression outweigh the potential benefit.

Our findings provide safety information related to COVID-19 vaccination in patients with MS and support recommendations to promote and not to delay vaccination during the still expanding SARS-CoV-2 pandemic.

6. Limitations of the study

The limitation of our study is the short follow-up period and relatively small size of the cohort. Self-reported side effects may cause bias in answer accuracy. Also, the nonresponding rate of approximately 21% may bias the results, as the rate of adverse events and new or worsening neurological symptoms among those who did not respond may be different from that reported by the responders. Another limitation of the study was that we did not compare the reported adverse events among

PWMS with the general population in our community. Another limitation that we did not assess immunoglobulins after vaccines.

7. Strength of the study

To our knowledge, we report the first experience with the COVID-19 vaccine in the middle east and Arabian Gulf among PWMS. This study represents the first comprehensive description of the safety of side effects of COVID-19 vaccines among PWMS.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

The Ethics Committee of Kuwait's ministry of health approved the study according to the Declaration of Helsinki.

CRediT authorship contribution statement

Raed Alroughani: Designed and conceptualized the study and wrote the initial draft. **Samar Ahmed**: Major role in methods creation, Statistical analysis, Interpretation of data. **Jasem Al-Hashel, Samar Ahmed, Fathi Abokalawa, Malak AlMojeld**: Major role in the acquisition of data. **Raed Alroughani**: Reviewed and criticized the manuscript. **Samar Ahmed**: Interpreted the data, Wrote the initial draft, Revised the manuscript for intellectual content. All authors who contributed to the article approved the submitted version.

Declaration of Competing Interest

RA is an Advisory Board member of Bayer, Biogen, Merck Serono, Novartis, Roche, Sanofi- Genzyme, and received honoraria for speaking or consultation fees from Bayer, Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme. He is also the principal investigator in clinical trials for Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme. SFA acted as Advisory Board members of Bayer, Merck Serono, Novartis, Sanofi-Genzyme, and received honoraria for speaking or consultation fees from, Bayer, Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme. She is also the co-investigator in clinical trials for Biogen, Merck Serono, Novartis, Roche, Sanofi-Genzyme. JA is an Advisory Board member and received honoraria for speaking from Bayer, Biogen, Merck Serono, Novartis, Roche, Sanofi- Genzyme. FA and MA declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments

The authors thank Nurse Enyaat Khairy and brother Osama Elazab for their outstanding help in communication with the patients. We extend our appreciation to Mai Ashraf Elshorbgy, at Dentistry, Biritish university of Egypt for her meticulous revision of the manuscript's language.

References

[1] World Health Organization, Novel coronavirus situation report: 99. 28 April 2020. ⟨https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200428-sitrep-99-covid-19. pdf?sfvrsn=119fc381_2⟩. Accessed 28 Apr 2020.
[2] E.S. Hosseini, N.R. Kashani, H. Nikzad, J. Azadbakht, H.H. Bafrani, H.H. Kashani, The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies, Virology 551 (2020) 1–9.
[3] F.P. Polack, S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J. L. Perez, G.P. Marc, E.D. Moreira, C. Zerbini, R. Bailey, Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine, N. Engl. J. Med. (2020).
[4] P.M. Folegatti, K.J. Ewer, P.K. Aley, B. Angus, S. Becker, S. Belij-Rammerstorfer, D. Bellamy, S. Bibi, M. Bittaye, E.A. Clutterbuck, C. Dold, Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial, Lancet 396 (10249) (2020) 467–478.
[5] AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis [WWW Document]. URL. ⟨https://www.astrazeneca.com/media-ce ntre/press releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html⟩. accessed 3.22.21.
[6] M. Kuwait, Kuwait COVID-19 Vaccine, 2021; Available from: ⟨https://ourworldindata.org/covid-vaccinations?country=OWID_WRL⟩.
[7] M. Voysey, S.A. Clemens, S.A. Madhi, L.Y. Weckx, P.M. Folegatti, P.K. Aley, B. Angus, V.L. Baillie, S.L. Barnabas, Q.E. Bhorat, S. Bibi, 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, Lancet 397 (10269) (2021) 99–111.
[8] A. Salter, R.J. Fox, S.D. Newsome, J. Halper, D.K. Li, P. Kanellis, K. Costello, B. Bebo, K. Rammohan, G.R. Cutter, A.H. Cross, Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis, JAMA Neurol. 78 (6) (2021) 699–708.
[9] D. Baker, C.A. Roberts, G. Pryce, A.S. Kang, M. Marta, S. Reyes, K. Schmierer, G. Giovannoni, S. Amor, COVID-19 vaccine-readiness for anti-CD20–depleting therapy in autoimmune diseases, Clin. Exp. Immunol. 202 (2) (2020) 149–161.
[10] H. Kelly, B. Sokola, H. Abboud, Safety and efficacy of COVID-19 vaccines in multiple sclerosis patients, J. Neuroimmunol. 356 (2021), 577599.
[11] COVID-19 Vaccine Guidance for People Living with MS. ⟨www.nationalmssociety.org/coronavirus-covid⟩- 19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance (accessed 18 January 2021).
[12] COVID-19 vaccination guidance for people with MS 2021 Available from: ⟨https://www.msaustralia.org.au/about-ms/covid-19-and-ms/⟩ covid-19-vaccination-guidance-people-ms.
[13] COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) and MS 2021 Available from: ⟨https://mssociety.org.il/en/covid⟩ -19-mrna-vaccines-pfizer-biontech-and-moderna-and-ms/.
[14] MS, the coronavirus and vaccines – updated global advice 2021 Available from: ⟨https://www.msif.org/news/2020/02/10/the⟩- coronavirus-and-ms-what-you-need-to-know/.
[15] MS Treatment Guidelines During the Coronavirus pandemic | National MS Society | National Multiple Sclerosis Society [WWW Document]. URL. ⟨https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coron⟩ avirus/ms-treatment-guidelines-during-coronavirus. accessed 3.21.21.
[16] M.P. Sormani, M. Inglese, I. Schiavetti, L. Carmisciano, A. Laroni, C. Lapucci, G. Da Rin, C. Serrati, I. Gandoglia, T. Tassinari, G. Perego, Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies, EBioMedicine 72 (2021), 103581.
[17] A. Achiron, M. Mandel, S. Dreyer-Alster, G. Harari, D. Magalashvili, P. Sonis, M. Dolev, S. Menascu, S. Flechter, R. Falb, M. Gurevich, 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 (2021).
[18] M. Di Filippo, C. Cordioli, S. Malucchi, P. Annovazzi, P. Cavalla, V.T. Clerici, P. Ragonese, V. Nociti, M. Radaelli, A. Laroni, F. Buttari, mRNA COVID-19 vaccines do not increase the short-term risk of clinical relapses in multiple sclerosis, J. Neurol., Neurosurg. Psychiatry (2021).
[19] A.J. Thompson, B.L. Banwell, F. Barkhof, W.M. Carroll, T. Coetzee, G. Comi, J. Correale, F. Fazekas, M. Filippi, M.S. Freedman, K. Fujihara, Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria, Lancet Neurol. 17 (2) (2018) 162–173.
[20] Food, U., et al., Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials, 2007.
[21] Covidvax.live : Live COVID-19 Vaccination Tracker - See vaccinations in real time! [Internet]. Covidvax.live. 2021 [cited 2021 Jun 29]. Available from: ⟨https://covidvax.live/location/kwt⟩.
[22] M.N. Ramasamy, A.M. Minassian, K.J. Ewer, A.L. Flaxman, P.M. Folegatti, D. R. Owens, M. Voysey, P.K. Aley, B. Angus, G. Babbage, S. Belij-Rammerstorfer, Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial, Lancet 396 (10267) (2020) 1979–1993.
[23] I. Lotan, A. Wilf-Yarkoni, Y. Friedman, H. Stiebel-Kalish, I. Steiner, M.A. Hellmann, Safety of the BNT162b2 COVID-19 vaccine in multiple sclerosis (MS): Early experience from a tertiary MS center in Israel, Eur. J. Neurol. (2021).
[24] A. Achiron, M. Dolev, S. Menascu, D.N. Zohar, S. Dreyer-Alster, S. Miron, E. Shirbint, D. Magalashvili, S. Flechter, U. Givon, D. Guber, Y. Stern, M. Polliack, R. Falb, M. Gurevich, COVID-19 vaccination in patients with multiple sclerosis: What we have learnt by February 2021, Mult. Scler. 27 (6) (2021) 864–870, https://doi.org/10.1177/13524585211003476.
[25] CDC, Possible Side Effects After Getting a COVID-19 Vaccine. Available online at: ⟨https://www.cdc.gov/coronavirus/2019-ncov/vaccines/expect/after⟩. html (accessed June 15, 2021).
[26] S. Reyes, M. Ramsay, S. Ladhani, G. Amirthalingam, N. Singh, C. Cores, J. Lambourne, M. Marta, B. Turner, S. Gnanapavan, R. Dobson, Protecting people with multiple sclerosis through vaccination, Pract. Neurol. 20 (6) (2020) 435–445.
[27] E.E. Walsh, R.W. Frenck Jr., A.R. Falsey, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, K. Neuzil, M.J. Mulligan, R. Bailey, K.A. Swanson, Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates, N. Engl. J. Med. 383 (25) (2020) 2439–2450.

[28] T. Nakayama, Causal relationship between immunological re- sponses and adverse reactions following vaccination, Vaccine 37 (2) (2019) 366–371.
[29] C.L. Zhuang, Z.J. Lin, Z.F. Bi, et al., Inflammation-related adverse reac- tions following vaccination potentially indicate a stronger immune response, Emerg. Microbes Infect. 10 (1) (2021) 365–375.
[30] M.T. Mailand, J.L. Frederiksen, Vaccines and multiple sclerosis: a sys- tematic review, J. Neurol. 264 (6) (2017) 1035–1050.
[31] M.F. Farez, J. Correale, Immunizations and risk of multi- ple sclerosis: systematic review and meta-analysis, J. Neurol. 258 (7) (2011) 1197–1206.
[32] G.T. Maniscalco, V. Manzo, M.E. Di Battista, S. Salvatore, O. Moreggia, C. Scavone, A. Capuano, Severe multiple sclerosis relapse after COVID-19 vaccination: a case report, Front. Neurol. (2021) 12.
[33] K. Allen-Philbey, A. Stennett, T. Begum, A.C. Johnson, R. Dobson, G. Giovannoni, S. Gnanapavan, M. Marta, I. Smets, B.P. Turner, D. Baker, Experience with the COVID-19 AstraZeneca vaccination in people with multiple sclerosis, Mult. Scler. Relat. Disord. 52 (2021), 103028.
[34] N. Pardi, M.J. Hogan, F.W. Porter, D. Weissman, mRNA vaccines—a new era in vaccinology, Nat. Rev. Drug Discov. 17 (4) (2018) 261–279.
[35] Web Page: YouGov, 2020, How many Britons are willing to take a coronavirus vaccine? Access date: 3 February 2021. ⟨https://yougov.co.uk/topics/health/articles-repor⟩ ts/2020/11/16/how-many-britons-are-willing-take-coronavirus-vacc.
[36] L. Boekel, F. Hooijberg, Z.L.E. van Kempen, E.H. Vogelzang, S.W. Tas, J. Killestein, et al., Perspective of patients with autoimmune diseases on COVID-19 vaccination, Lancet Rheuma 3 (4) (2021) e241–e243.
[37] F. Serrazina, A. Sobral Pinho, G. Cabral, M. Salavisa, A.S. Correia, Willingness to be vaccinated against COVID-19: An exploratory online survey in a Portuguese cohort of multiple sclerosis patients, Mult. Scler. Relat. Disord. 51 (2021), 102880.
[38] D.M. Ehde, M.K. Roberts, T.E. Herring, K.N. Alschuler, Willingness to obtain COVID- 19 vaccination in adults with multiple sclerosis in the United States, Mult. Scler. Relat. Disord. 49 (2021), 102788.
[39] L. Diem, C. Friedli, A. Chan, A. Salmen, R. Hoepner, Vaccine hesitancy in patients with multiple sclerosis: preparing for the SARS- CoV-2 vaccination challenge, Neurol. Neuroimmunol. Neuroinflam 8 (3) (2021).
[40] X.M. Xiang, C. Hollen, Q. Yang, B.H. Brumbach, R.I. Spain, L. Wooliscroft, COVID-19 vaccination willingness among people with multiple sclerosis, Mult. Scler. J. Exp. Transl. Clin. 7 (2) (2021).
[41] N.E. MacDonald, Vaccine hesitancy: definition, scope and determinants, Vaccine 33 (34) (2015) 4161–4164.