

Safety of COVID-19 vaccines and factors influencing the vaccine take-up rate in Polish adults with epilepsy: a single-center study

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Introduction The safety and efficacy of COVID-19 vaccines have been demonstrated in the general population; however, specific evidence in patients with epilepsy (PWE) is still scarce. According to recently published studies,¹⁻⁵ the risk of seizure exacerbation after COVID-19 vaccination in PWE appears to be low. However, seizures have been reported among the neurological manifestations of COVID-19.⁶ Therefore, many PWE and their caregivers express their concerns about the reliability, necessity, and safety of COVID-19 vaccines.

Our objective was to determine the safety and tolerability of COVID-19 vaccines in PWE and to identify variables associated with vaccine hesitancy among unvaccinated individuals.

Patients and methods This was a retrospective, cross-sectional study conducted at the University Hospital in Kraków, Poland. The participants were recruited from among consecutive PWE aged 18 years or older who attended an epilepsy clinic between January and April 2022.

Data were extracted from the patients' medical records and collected during structured face-to-face interviews. The following information was gathered: age, sex, age at the onset of epilepsy, epilepsy characteristics and its treatment, frequency of seizures, presence of physical or intellectual disability, comorbidities, and previous SARS-CoV-2 infection. We also collected data on the level of education, employment status, and place of residence.

The vaccinated individuals were also asked to provide information about the vaccine type, number of doses, and vaccine-related adverse events. The latter were classified as local, systemic, and epilepsy-related.

The unvaccinated patients were asked about the intention to vaccinate and the reasons for vaccine hesitancy.

The study protocol followed the principles of the Declaration of Helsinki and received approval from the university bioethical committee (122.621.191.2915). All patients gave their informed consent to participate.

Statistical analysis Qualitative data were presented as number (percentage) and compared using the χ^2 test (the Fisher exact test was used because of the small expected number of cases). Continuous variables were presented as medians and interquartile ranges (IQRs) due to their skewed distribution, and the differences between them were tested with the Mann-Whitney test. A *P* value below 0.05 was considered significant.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 27 (IBM Corp., Armonk, New York, United States).

Results Study population Our cohort consisted of 276 patients (women, *n* = 156 [56.5%]) at a median age of 33.5 years (IQR, 26–42). Most of the participants had focal epilepsy (*n* = 195 [70.7%]), and the majority of patients in this group (*n* = 188 [68.1%]) had drug-resistant epilepsy. Approximately half of the patients (*n* = 137 [49.6%]) were on antiseizure polytherapy. The most commonly prescribed antiseizure medications (ASMs) in monotherapy or polytherapy were levetiracetam (*n* = 118 [42.8%]), valproate (*n* = 95 [34.4%]), and lamotrigine (*n* = 89 [32.2%]). Physical and/or intellectual disabilities were present in 74 patients (26.8%), and 106 individuals (38.4%) had at least

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TABLE 1 Characteristics of vaccinated and unvaccinated patients with epilepsy

Variable		All patients (n = 276)	Vaccinated (n = 167)	Unvaccinated (n = 109)	P value ^a
Female sex		156 (56.5)	95 (56.9)	61 (56)	0.9
Age, y		33.5 (26–42)	36 (29–42)	30 (25–39)	<0.001
Age at the onset of epilepsy, y		16 (8–22)	16 (8–23)	16 (8–21)	0.39
Epilepsy type	Generalized	66 (23.9)	41 (24.6)	25 (22.9)	0.77
	Focal	195 (70.7)	117 (70.1)	78 (71.6)	
	Combined	10 (3.6)	5 (3)	5 (4.6)	
	Unknown	5 (1.8)	4 (2.4)	1 (0.9)	
Seizure freedom		88 (31.9)	57 (34.1)	31 (28.4)	0.36
Polytherapy		137 (49.6)	79 (47.9)	58 (52.3)	0.54
Level of education	None/primary school	55 (19.9)	34 (20.4)	21 (19.3)	0.62
	Secondary/vocational	155 (56.2)	90 (53.9)	65 (59.6)	
	Bachelor/master degree	66 (23.9)	43 (25.7)	23 (21.1)	
Place of residence	City >100 000 inhabitants	120 (43.5)	82 (49.4)	37 (33.9)	0.04
	City <100 000 inhabitants	60 (21.8)	31 (18.7)	29 (26.6)	
	Village	96 (34.9)	53 (31.9)	43 (39.4)	
Employed		123 (44.6)	83 (50)	40 (36.7)	0.04
Comorbidities		106 (38.4)	67 (40.1)	39 (36.1)	0.53
Physical disability		49 (17.8)	28 (16.8)	21 (19.3)	0.63
Intellectual disability		52 (18.9)	33 (19.8)	19 (17.6)	0.75

Data are shown as number (percentage) of patients or median (interquartile range).

a χ^2 test (or the Fisher exact test where appropriate) except for age (the Mann–Whitney test). Differences were considered significant at $P < 0.05$.

1 comorbid condition. A total of 66 participants (23.9%) reported previous infection with SARS-CoV-2. The demographic and clinical characteristics of the study group are presented in **TABLE 1**.

Vaccination status A total of 167 patients (60.5%) received at least 1 dose of a COVID-19 vaccine. Among them, 125 (74.8% of the vaccinated group) received 2 doses of the Pfizer/BioNTech vaccine, 16 (9.6%) received 2 doses of the Oxford/AstraZeneca vaccine, 12 (7.2%) received 2 doses of the Moderna vaccine, and 9 (5.4%) received 1 dose of the Janssen vaccine. Thirty-four patients (20.4% of the vaccinated group) received a booster dose.

We compared the vaccinated and unvaccinated patients in terms of demographics, epilepsy characteristics, comorbidities, and social background (**TABLE 1**). The vaccinated individuals were older ($P < 0.001$), more frequently employed ($P = 0.04$), and more likely to live in cities with over 100 000 inhabitants ($P = 0.04$).

Vaccine side effects Overall, 130 patients (77.8%) reported at least 1 adverse event after any dose of the vaccine. A total of 109 participants (65.3%) experienced at least 1 side effect after the first dose of the vaccine, and 93 individuals (60.4% of those who received the second dose) experienced at least 1 side effect after the second dose. In total, 100 patients (59.8%) experienced local side effects and 64 (38.3%) systemic side effects. The most commonly reported adverse events were injection site redness, swelling, pain, and fatigue. In

all patients, the side effects were mild or moderate and transient. Only 2 patients (1.2% of the vaccinated group) reported seizure worsening.

The frequency and types of adverse events are shown in Supplementary material, *Figure S1*.

We compared the patients with and without side effects in terms of demographics, epilepsy characteristics, comorbidities, and physical and intellectual disability (Supplementary material, *Table S1*). Adverse events were reported more frequently by women ($P = 0.03$) and less frequently by patients with physical disabilities ($P = 0.02$).

Reasons for vaccine hesitancy At the time of the study, 109 patients (39.5%) had not received a COVID-19 vaccination. Of these, 13 (11.9%) expressed their willingness to vaccinate.

The main reasons for vaccine hesitancy were as follows (multiple responses were possible): fear of epilepsy aggravation ($n = 35$ [32.1%]), fear of other side effects ($n = 27$ [24.8%]), disbelief in the safety and efficacy of the vaccine ($n = 15$ [13.8%]), and pregnancy/breastfeeding ($n = 9$ [14.8% of the unvaccinated women]). Other reasons were reported by 39 participants (36.1%), including a wish to consult a neurologists before vaccination ($n = 8$), comorbidities ($n = 7$), disbelief in the COVID-19 pandemic ($n = 6$), adverse events after a previous non-COVID-19 vaccination ($n = 5$), recent COVID-19 ($n = 3$), epilepsy as a contraindication to vaccination in childhood ($n = 3$), fear of multiple medical procedures ($n = 1$), and fear of interactions with ASMs ($n = 1$). Five patients had a vaccination appointment scheduled in the near future.

Discussion Our cross-sectional study aimed to explore the safety and tolerability of COVID-19 vaccines among PWE and to identify factors associated with vaccine hesitancy among the unvaccinated participants.

The rate of fully vaccinated patients in our cohort (58.8%) was similar to that in the general population of Poland. On April 30, 2022, 59.2% of the general Polish population was fully vaccinated.⁷ Much lower vaccination rates among PWE were found in Chinese, Kuwaiti, and German studies; however, one of the main reasons for low vaccination coverage was limited vaccine availability.³⁻⁵ In contrast, 90% of PWE analyzed by Romozzi et al² were vaccinated, which may reflect a very high vaccine take-up rate in the general population of Italy.⁸

Acceptance of the COVID-19 vaccine in our cohort was significantly associated with age, place of residence, and employment status. The vaccinated patients were older ($P < 0.001$), more frequently employed ($P = 0.04$), and more often lived in cities with over 100 000 inhabitants ($P = 0.04$). These results are in line with the overall data regarding vaccination acceptance in Poland—vaccination coverage is higher among older people and those living in large cities.⁷ Furthermore, according to a survey conducted among the general public, people with a higher level of education and older individuals were more willing to receive a COVID-19 vaccine.⁹ No associations were found between epilepsy characteristics and the decision to vaccinate.

The incidence of local vaccine-related adverse events (59.8%) was higher than reported in the previous studies among PWE¹⁻⁵ but lower than that obtained in the clinical trial on the Pfizer / BioNTech vaccine,¹⁰ which was the most commonly administered vaccine type in our cohort. The incidence of systemic side effects (38.3%) was consistent with the results of clinical trials and studies conducted among PWE.^{1-5,10} Adverse events were reported more frequently by women ($P = 0.03$). This finding corroborates the results of the study carried out in the general population.¹¹ We cannot explain the lower incidence of adverse events in patients with physical disabilities.

Only 1.2% of the vaccinated individuals reported an increased frequency/intensity of seizures after the COVID-19 vaccination. Similarly, a low risk of seizure exacerbation was found in the studies by Wrede et al¹ and Özdemir et al.⁵ A slightly higher percentage of PWE with worsening of seizures was observed in Kuwaiti and Italian studies.^{2,3} Lu et al⁴ reported an increase in seizure frequency in 10% of vaccinated PWE; however, one-third of those reporting the increase had stopped or reduced the dose of their ASMs.

The primary reasons for vaccination reluctance in our cohort were fear of epilepsy aggravation or other serious side effects. These findings corroborate the results of previously published studies, which consistently reported fear of disease exacerbation and concerns about vaccine safety

as the 2 main causes of vaccine hesitancy among PWE.^{2-5,12,13}

Our study has some limitations. First, the increase in the frequency/intensity of seizures after vaccination was estimated based on the participants' self-assessment. However, patients tend to overestimate the negative effects of COVID-19 vaccines. A recent meta-analysis showed that nocebo responses accounted for more than half of systemic adverse events after COVID-19 vaccination.¹⁴ Thus, we believe that the low percentage of seizure exacerbation in our cohort is a reliable result. Second, we studied a population of patients attending a university epilepsy clinic, which may differ substantially from the general population of PWE in terms of the frequency of seizures or the use of polytherapy. Third, our study had a retrospective design, which may have resulted in a recall bias in terms of adverse event reporting. Furthermore, caregivers answered questions on behalf of the intellectually disabled PWE and some adverse events may have been overlooked.

Conclusions The results of our cross-sectional study indicate that COVID-19 vaccines have a good safety and tolerability profile in PWE. The risk of seizure exacerbation after COVID-19 vaccination is low. However, the level of vaccine hesitancy among PWE remains high. The lack of willingness to vaccinate is driven by social factors and not epilepsy characteristics. The main reason for vaccine hesitancy is fear of epilepsy exacerbation and other side effects.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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