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.

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Incidence of COVID-19 after vaccination in people with multiple sclerosis in Argentina: Data from the nationwide registry RelevarEM

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ABSTRACT

The objective of the study was to evaluate the incidence of COVID-19 after complete vaccination in people with multiple sclerosis (PwMS) included in the Argentinean MS and NMOSD registry (RelevarEM, NCT 03375177).
Methods: cohort study conducted between May 2021 and December 2021. The primary outcome was the appearance of infection during the follow-up time (at least three months after complete vaccination (second dose)). Data was collected through the contact between the treating physician and the patient. Specific information was requested (date, symptoms, need for hospitalization, ventilatory assistance, treatment, and evolution). The contact was made every 30 days during the period of 3 months after the full dose vaccination. A positive COVID-19 case was defined according to the definition established by the Ministry of Health in Argentina. Cumulative incidence was reported by Kaplan Meier survival curves as well as incidence density.
Results: A total of 576 PwMS were included, mean age 45.2 ± 13 years, 432 (75%) RRMS, 403 (70%) were female. The mean and median time of follow-up after the second dose was 91 ± 17 and 94 ± 21 days respectively. Most frequent first and second dose received was Astra-Zeneca vaccine, followed by Sputnik V vaccine. During follow-up a total of twenty COVID-19 cases were observed for a total exposure time of 39,557 days. The overall cumulative incidence for the observed period was 3.4% (SE 0.4%) with an overall incidence density of 5 × 10.000 patients/day (95%CI 0.7–12). We observed more cases in woman than men with an incidence density of 6 × 10.000 patients/day (95%CI 0.9–9) vs. 3 × 10.000 patients/day (95%CI 0.2–6) respectively, but not significantly different (IRR 1.7 95% CI 0.56–7.37 $p = 0.15$).
Conclusion: we found an incidence density of breakthrough COVID-19 infection of 5 × 10.000 patients/day (95% CI 0.7–12) after vaccination in Argentina.

1. Introduction

Different vaccines have been evaluated and implemented to achieve immunization against COVID-19 in the world (Achiron et al., 2021; Alonso et al., 2021a, 2021b; Belete, 2021)

In people with multiple sclerosis (PwMS), during the last months, several publications have demonstrated evidence about the effect of vaccination against COVID-19 mainly on serological responses and, to a minor extent, on T cell response (Achiron et al., 2021; Brill et al., 2021; Sahin et al., 2020; Salter et al., 2021). This was translated in a reduction in the frequency of PwMS infected post vaccination as well as a reduction in the severity of COVID-19 cases (Achiron et al., 2021; Brill et al., 2021; Sahin et al., 2020; Salter et al., 2021)(Belete, 2021; Reyes et al., 2021; Sormani et al., 2021; Tortorella et al., 2022) . However, much of the information comes from studies done in Europe or North America and scarce studies were done to evaluate technologies like Sputnik, Astra-Zeneca or inactivated vaccines for COVID-19 in PwMS like Sinopharm as well as heterologous schemes of those vaccines (Achiron et al., 2021; Belete, 2021; Brill et al., 2021; Reyes et al., 2021; Sahin et al., 2020; Salter et al., 2021; Sormani et al., 2021; Tortorella et al., 2022).

The objective of the study was to evaluate the incidence of COVID-19 infections after complete vaccination in PwMS in Argentina included in the Argentinean MS and NMOSD registry (RelevarEM, NCT 03375177).

2. Methods

This was an ambispective cohort study that started in May 2021 and finished in December 2021. The study was run on the current MS registry in Argentina, RelevarEM (Rojas et al., 2020, 2019). RelevarEM is a longitudinal, strictly observational MS and neuromyeltis optica spectrum disorders (NMOSD) registry in Argentina (Rojas et al., 2020, 2019). It is open to all practicing neurologists and MS specialists and their teams across the country. The registry tracks the outcomes of routine clinical practice of patients with MS and NMOSD in a web-based platform that allows researchers to register and follow up their patients. The primary objective of the registry was to create an MS physician network in Argentina that captures pragmatic and relevant information from MS patients in terms of clinical and demographic aspects (Rojas et al., 2020, 2019). Eligible subjects were contacted by their neurologist. Once the patient was included data was collected about demographic and clinical data of the disease (age at vaccination, EDSS at study entry, ongoing treatment, MS phenotype, and comorbidities); vaccine received at first dose, second dose, dose, and dates; adverse events of vaccination and follow up time. Patients were actively followed during at least three months since the second dose of COVID-19 vaccine (complete suggested vaccine scheme).

The primary outcome was the appearance of infection during the follow up time (at least three months after complete vaccination (second dose of vaccination)). This data was collected through the contact between the treating physician and the patient to assess whether they were infected in that period. If the answer was affirmative, specific information was requested from the treating physician regarding the infection (date, symptoms, need for hospitalization, ventilatory assistance, treatment, and evolution). The contact was made every 30 days during the period of 3 months after the full dose vaccination was done and the contact by the doctor was proactive, contacting the patient to obtain data on this result (Sormani et al., 2021). It was defined as a positive COVID-19 case according to the definition established by the Ministry of Health in Argentina. This implies performing a PCR or Antigen test at least as a microbiological confirmation, or in the absence of laboratory confirmation, a close contact with a COVID-19 case and compatible symptoms was considered a confirmed case.

A specific form was developed to collect the data of the research project. The form was added to the RelevarEM registry as a vaccination sub form to follow every patient.

3. Sample

All patients diagnosed with MS included in RelevarEM who received the vaccine were invited to participate in the study. To reduce the

possibility of selection bias, we seek to include all professionals in Argentina who oversee caring for patients with MS in Argentina and are active members of RelevarEM.

Each center submitted the project for approval following the competent local regulations.

An institutional ethics committee approved the registration or declare that it is exempt from the need for approval as well as its informed consent (IC).

4. Statistical analysis

Baseline characteristics of the cohort were reported in percentages for categorical data and in median and range or mean ± SD for continuous data. Only patients with a complete vaccination scheme (at least two doses) and at least three months follow up were included in the analysis. Cumulative incidence of COVID-19 infections was reported for the entire cohort by Kaplan Meier survival curves as well as incidence density. Sub-analysis of incidence of infection by gender, vaccine received and homologous or heterologous scheme during follow up was also done.

5. Results

A total of 576 PwMS were included during the study period that started in May 2021 and finished in December 2021. The mean age of included patients was 45.2 ± 13 years, mean disease duration 10.7 ± 6.4 years, 432 (75%) were RRMS, 403 (70%) were female, median EDSS 2.7 ± 2. The rest demographic and clinical variables are shown in Table 1.

The mean and median time of follow up after the second dose in included patients was 91 ± 17 and 94 ± 21 days and 55 (9.5%) patients reported to be infected by COVID-19 pre-vaccination (Table 2). Most frequent first and second dose received was Astra-Zeneca vaccine, followed by Sputnik vaccine (Table 2) and when homologous or heterologous scheme was described, 82.5% received a homologous scheme (Sputnik-Sputnik or Astra Zeneca-Astra Zeneca or Sinopharm-Sinopharm) vs. 17.5% that received and heterologous scheme of vaccination to complete the scheme (Table 2).

During follow up a total of twenty COVID-19 cases were observed for a total exposure time of 39,557 days (only one case of hospitalization due severe COVID-19 infection was reported in a patient treated with ocrelizumab) (Table 3). The overall cumulative incidence for the observed period was 3.4% (SE 0.4%) with an overall incidence density of 5 × 10.000 patients/day (95%CI 0.7–12) (Table 3). When we stratified the sample, we observed more cases in woman than men in the incidence density 6 × 10.000 patients/day (95%CI 0.9–9) vs. 3 × 10.000 patients/day (95%CI 0.2–6) respectively, but not significantly (IRR 1.7 95% CI 0.56–7.37 $p = 0.15$) as well as in the homologous scheme vs heterologous scheme (incidence density 5 × 10.000 patients per day (95%CI 0.8–8) vs. 1 × 10.000 patients per day (95%CI 0.02–3)

Table 1
Baseline characteristics of included patients.

	$N = 576$
Mean age at study entry, years (SD)	45.2 (13)
Mean disease duration, years (SD)	10.7 (6.4)
RRMS, n (%)	432 (75)
SPMS, n (%)	67 (11.6)
PPMS	77 (13.4)
Female gender, n (%)	403 (70)
Median EDSS, (SD)	2.7 (2.0)
Interferon beta, n (%)	84 (14.58)
Glatiramer acetate, n (%)	43 (7.47)
Teriflunomide, n (%)	50 (8.68)
Fingolimod, n (%)	102 (17.71)
Dimethylfumarate, n (%)	25 (4.34)
Natalizumab, n (%)	48 (8.33)
Alemtuzumab, n (%)	25 (4.34)
Ocrelizumab, n (%)	33 (5.73)
Rituximab, n (%)	9 (1.56)
Cladribine, n (%)	37 (6.42)
No treatment	120 (20.83)
Median Charlson score of comorbidities, (SD)	0.23 (0.52)

RRMS= relapsing remitting multiple sclerosis; SPMS= secondary progressive multiple sclerosis; PPMS= primary progressive multiple sclerosis; EDSS= expanded disability status scale; SD= standard deviation.

Table 2
Follow up time and vaccines received in included patients.

	$N = 576$
Median follow up time after second dose, days (SD)	**94 ± 21**
Mean follow up time after second dose, days	**91 ± 17**
Previous covid infection, n (%)	55 (9.54%)
First dose vaccine received	
Sputnik V, n (%)	172 (29.86%)
Astra Zeneca, n (%)	283(49.3%)
Sinopharm	106 (18.40%)
Jansens	15(2.6%)
Second dose vaccine received	
Sputnik V, n (%)	123(21.35%)
Astra Zeneca, n (%)	312(54.16%)
Sinopharm	94 (16.3%)
Moderna	26 (4.51)
Pfizer	21(3.64)
Median time between first and second vaccine dose, (SD)	55±18
Homologous vaccine scheme, n (%)	475 (82.5)
Heterologous vaccine scheme, n (%)	101 (17.5)

SD= standard deviation.

Table 3
Incidence of COVID-19 after vaccination.

Breakthrough COVID-19 infections during follow up (n)	20	
Hospitalizations cases of COVID-19 infections, n	1	
Total exposure time (days)	39,557	
Overall cumulative incidence of infection	3.4% (SE 0.4%)	
Overall incidence density of infection	5 × 10.000 patients/day (95% CI 0.7–12)	
Cumulative incidence in men (4 cases) /women (16 cases)	2.3% (SE 0.3%)	3.9% (SE 0.5%)
Incidence density in men (exposure time 12,364 days)/ women (exposure time 27,546 days)	3 × 10.000 patients/day (95% CI 0.2–6)	6 × 10.000 patients/day (95% CI 0.9–9)
Frequency of infections per vaccines used		
Sputnik-Sputnik n (%)	4 (20)	
Astra-Astra, n (%)	10 (50)	
Sinopharm-Sinopharm n (%)	5 (25)	
Heterologous vaccine scheme, n (%)	1 (5)	
Frequency of infections per treatment used		
Interferon beta, n (%)	2 (0.02)	
Glatiramer acetate, n (%)	1 (0.02)	
Teriflunomide, n (%)	2 (0.04)	
Fingolimod, n (%)	3 (0.02)	
Dimethylfumarate, n (%)	1 (0.04)	
Natalizumab, n (%)	2 (0.04)	
Alemtuzumab, n (%)	1 (0.04)	
Ocrelizumab, n (%)	5 (0.15)	
Rituximab, n (%)	1 (0.11)	
Cladribine, n (%)	1 (0.02)	
No treatment	1 (0.008)	
Cumulative incidence in homologous scheme (19 cases)	3.3% (SE 0.4%)	
Incidence density in homologous scheme (exposure time 33,300 days)/ and heterologous scheme (1 cases, exposure time 6610 days)	5 × 10.000 patients per day (95%CI 0.8–8)	1 × 10.000 patients per day (95%CI 0.02–3)

respectively, IRR 3.77, 95%CI 0.59- 26, $p = 0.15$) Table 3).

6. Discussion

This is the first study in the country and one of the first study in the region to evaluate the incidence of COVID-19 infection post vaccination in PwMS.

In our Study we observed a cumulative incidence of 3.4% (SE 0.4%) with an overall incidence density of COVID-19 infection post vaccination of 5 × 10.000 patients/day (95%CI 0.7–12). The frequency observed by vaccines used and schemes (homologous vs. heterologous scheme) was quite similar and only one patient required hospitalization (Table 3).

Our study is in line with previous studies performed in other regions. Sormani et al. in a long term clinical follow up of the CovaXiMS (Covid-19 vaccine in multiple sclerosis) evaluated the SARS-CoV-2 breakthrough infections incidence and the impact of DMTs on cumulative incidence of infections (Sormani et al., 2021). In that study, of a total of 1705 patients who had a full vaccination cycle (2 doses), 23 breakthrough infections were identified, displaying a cumulative incidence of 1.5% SE 0.3% after a mean 0f 108 days after the second dose (Sormani et al., 2021). Authors analyzed the role of treatments on the risk of infections and severity of infections and showed that the probability to be infected was associated with SARS-CoV2 antibody levels measured after the second vaccine dose (HR= 0.63, $p = 0.007$) and antibody levels of 660 U/mL as the cut-off (Sormani et al., 2021). In another study that followed 19,641 MS patients after complete vaccination for a median of 8 months, authors identified 137 breakthrough infections (cumulative incidence of 0.69%), and the sub analysis of risk between the incidences across DMTs showed an increased in patients treated with ocrelizumab and fingolimod ($p<0.001$) (Schiavetti et al., 2022). Rose et al. investigate breakthrough coronavirus disease 2019 (COVID-19) in vaccinated people with multiple sclerosis (PwMS) on DMT (Rose et al., 2021). A total of 13 patients of 344 fully vaccinated people with multiple sclerosis on disease modifying therapies were diagnosed with COVID-19 after vaccination (cumulative incidence of 3.77%). No incidence density was described in the study (Rose et al., 2021).

It is important to comment that many of the included patients in our cohort were not receiving a specific treatment for MS (20.83%). This was mainly because we included PPMS (13.4%) and SPMS (11.6%) and many of those patients were untreated for the disease. It is also important to mention that when we developed the study, for the Argentine health system, the complete vaccination schedule consisted of having two doses of the COVID-19 vaccines available in our country. That is why from the design we proposed that methodological parameter in each MS patient and we did not consider extra doses of COVID −19 vaccines.

Our study has many limitations that should be mentioned. First and probably the most relevant is that we were not able to perform a serological test to all the included patients, however, this was not the objective of the study. Second the observational design implemented and the possibility of information bias, however the strictest follow up possible was implemented to try to limit this possibility. Finally, we could not stratify the analysis by treatment received per patient to analyze the incidence risk by DMT. A future study is ongoing to answer this aspect with an increase sample.

In conclusion, we found an incidence density of breakthrough COVID-19 infection of 5 × 10.000 patients/day (95%CI 0.7–12) after vaccination in Argentina mainly with Sputnik or Astra Zeneca vaccines.

Despite increasing evidence is being collected and the gap of evidence is narrowing, still much is needed regarding the response to other vaccines and other factors like the ones we consider in our study.

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Credit author statement

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We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property

Declaration of Competing Interest

Authors declare no potential conflicts of interest regarding this research, authorship and/or publication of this article.

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