NEURO-COVAX: An Italian Population-Based Study of Neurological Complications After COVID-19 Vaccines

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Article

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Abstract

Objective

In this Italian population-based study, we aimed to evaluate neurological complications after first and/or second dose of COVID-19 vaccines and factors potentially associated with adverse effects.

Methods

Our study included adults aged-18 years and older, receiving two vaccine doses in vaccination Hub Novegro (Lombardy) between July 7–16 2021. NEURO-COVAX questionnaire was able to capture neurological events, onset and duration. Data digitized centrally by Lombardy-Region were used to match demographic/clinical characteristics and identify a vulnerable profile. Associations between vaccine-lines and development of complications were assessed.

Results

NEURO-COVAX-cohort included 19.108 vaccinated-people: 15.368 mRNA BNT162b2, 2077 mRNA-1273, 1651 ChAdOx1nCov-19 and 12 Ad26.COV2, subsequently excluded. About 31.3% of sample developed post-vaccination neurological complications, particularly ChAdOx1nCov-19. Vulnerable clinical profile emerged, over 40% of symptomatic people showed comorbidities in clinical history. Defining neurological risk profile, we found increased risk for ChAdOx1nCov-19 of tremor (OR:5.12, 95% CI:3.51–7.48), insomnia (OR:1.87, 95% CI:1.02–3.39); muscle spasms (OR:1.62, 95% CI:1.08–2.46) and headache (OR:1.49, 95% CI:0.96–1.57); for mRNA-1273 of parethesias (OR:2.37, 95% CI:1.48–3.79), vertigo (OR:1.68, 95% CI:1.20–2.35), diplopia (OR:1.55, 95% CI:0.67–3.57), daytime sleepiness (OR:1.28, 95% CI:0.98–1.67).

Discussion

This study estimates prevalence and risk of neurological complications associated to COVID-19 vaccines, improving vaccination guidelines and loading in future to personalized preventive medicine.

1. Introduction

The mass vaccination campaigns against COVID-19 posed to the clinicians across the world emerging questions on risks, benefits and the timing of the vaccination for a correct stimulation of the immune system. Although the randomized clinical trials[1–3] have been confirmed by observational[4,] and nationwide mass vaccination setting studies[5], they have been questioned because of their lack of power to identify less common adverse event. This represents a limitation of clinical trials and this is why

surveillance continues after trials using observational data. An important scientific effort is now focused on identifying the specific safety profile for each vaccine. Thus, a recent nationwide mass vaccination setting study,[6] demonstrated that BNT162b2 was associated with an excess risk of myocarditis. When we put under a magnifying glass the potential neurological complications post-vaccination, the first concern is dated in September 2020, when AstraZeneca/Oxford University reported a severe inflammation of the spinal cord.[7] In May 2021, the American Neurology Academy provided the first report on the common neurological complications after COVID-19 vaccines.[8] In December 2021, a large population-based study identified rare neurological adverse events after the first dose of ChAdOx1nCoV-19 and BNT162b2 vaccines.[9] However, little is yet known about the common neurological complications after both doses of COVID-19 vaccines.

In this large population-based study, we aimed to evaluate the neurological complications after the first and second doses of COVID-19 vaccines approved in Italy (mRNA BNT162b2, mRNA-1273, and ChAdOx1nCoV-19) and used in the massive vaccination Novegro Hub (Lombardy) in July 7–16 2021. We tested the hypothesis that age, sex and vaccines can be useful to stratify the risk to develop adverse reactions in a large cohort of Italian people. Additionally, in a subpopulation of people developing neurological complications, we investigated the associations between vaccines and the development of specific adverse events. Finally, we evaluated whether the presence of comorbidities, as well as, previous SARS-COV-2 infection, can be useful to identify a clinical profile more vulnerable to develop neurological adverse effects.

2. Methods

2.1 Design, Setting and Participants

NEURO-COVAX is an observational study to identify acute and subacute neurological complications after the administration of first and second dose of COVID-19 vaccines used in Novegro Hub (Milan) during the period from July 7 to 16, 2021. We defined acute as the neurological complications within the first 15–30 minutes and subacute as those within the first two weeks after vaccination. Firstly, we collected the NEURO-COVAX questionnaires (details below), in the total group of participants at the second dose (acute) of vaccines, with the possibility to retrospectively investigate the first dose-related effects (acute and subacute), and to prospectively evaluate the second dose (subacute-related effects). Secondly, we identified the symptomatic subgroup (subjects manifesting of at least one neurological symptom in at least one dose) to describe neurological manifestations, onset and duration, and the vaccine safety profile. To corroborate the association between vaccines and adverse events, we calculated the risk measures (Odds Ratio and Relative Risks). Thirdly, we characterized the symptomatic subgroup from a clinical point of view identifying comorbidities: non-neurological disorders (heart, lung, kidney asthma, diabetes), neurological disorders, previous SARS-COV2 infection, history of anticoagulants drugs, pregnancy. An accurate evaluation on the immune system activity, hyperactivity (allergies) and hyporeactivity (immunosuppressive conditions) has been performed. With this in mind, 20.445 persons

vaccinated in the Novegro Hub during the period previously indicated have been recruited in this population-based study. Eligibility criteria were: i) an age of 18 years or older; ii) being afferent to Hub Novegro; iii) a written informed consent to the participation to study. Hub of Novegro, managed by the Gruppo Ospedaliero San Donato, opened in April 2021 and closed in August 2021, is an excellence of the mass vaccination sites in the Lombardy Region (Italy). It represents a "immunization islands" model useful to improve quality, efficiency and safety of COVID-19 mass vaccination site.[10] In July 2021, four vaccine lines were available: mRNA BNT162b2 (80%), ChAdOx1nCov-19 (10%), mRNA-1273 (9%) and Janssen Ad26.COV2.S (1%). Data regarding the demographic data, anamnesis, and COVID-19 infection were digitized centrally by Lombardy Region. The study was approved by the National Ethical Committee Spallanzani, National Institute for Infectious Diseases Lazzaro Spallanzani, Rome, Italy under the project ID number 362 of the Trial Register 2020/2021 and by the local Ethical Committee of “Vita-Salute” San Raffaele University, Milan, Italy. Finally, all our methods and experiments were performed in accordance with the relevant guidelines and regulations.

2.2 NEURO-COVAX Questionnaire

NEURO-COVAX questionnaire consists of four simple sections: **Section I-Vaccine Information**: vaccine center, date of administration and vaccine type; **Section II-Personal Data**: surname and name; date of birth; telephone number/e-mail address and residence; **Section III-Neurological complications list**: a grid listing the main adverse symptoms of our interest; **Section IV-Neurological complications characterization**: a box (symptom box) dedicated to each neurological manifestation in which the participants could point the onset and duration of their symptoms. Combining the different timepoints of our evaluation and the number of doses planned for the vaccines, we have designed 4 potential questionnaires for double dose-vaccines and 2 for single dose-vaccine as following: NEURO-COVAX First Dose Acute, NEURO-COVAX First Dose Subacute; NEURO-COVAX Second Dose Acute; NEURO-COVAX Second Dose Subacute, NEURO-COVAX (Single) Dose Acute, NEURO-COVAX (Single) Dose subacute. Thus, for each participant, we could potentially have more doses and more questionnaires (events), 1 person:2 doses:4 events and we potentially expected to collect about 76.432 questionnaires (19.108 partipiatnts x 4 events). Of interest, under the section “other” of the questionnaire, the subject could note: i) neurological reactions not included in the questionnaire such as sudden loss of strength in the limbs, progressive difficulty walking and facial paralysis; ii) access to emergency room; iii) hospitalizations in neurological setting; iv) a non-neurological reactions. A model of the NEURO-COVAX questionnaire is reported in the supplentary material.

Regarding the procedures of the NEURO-COVAX administration, our protocol provided three steps. Firstly, the questionnaire was given by the medical staff pre-vaccination during the anamnesis; Secondly, during the waiting time post-vaccination, participants were asked to fill out the questionnaire on a voluntary basis. A highly trained and qualified medical staff (NEURO-COVAX staff, 9–10 persons) explained how to fill in the questionnaire in the Italian language. A support in the English language was also provided for foreign people. Thirdly, after filling in the questionnaire, the sections concerning the acute and subacute complications after first dose and acute second dose was committed to the staff, while the section

focused on the subacute complications of the second dose (or subacute single dose) was required participants to send to a dedicated hospital address via e-mail after the two vaccinations (neuro.covax@hsr.it). Participants could also be contacted via phone/e-mail by NEURO-COVAX staff.

2.3 Statistical Analysis

Descriptive statistical analysis was conducted in each group, stratified according to the vaccine lines. We described the characteristics of each group in terms of sex and age including mean, standard deviation and median. Additionally, pre-established ranges were considered to investigate clinical variability across the age. Frequency analyses have been implemented to assess neurological complications and describe these in terms of onset and duration. In the total group, we constructed a multivariable logistic regression model to quantify the association between potential factors and neurological adverse effects. In this multivariable model, the candidate factors were age, sex (female or all others) and vaccine lines. We used the presence of neurological complications as the dependent variable, vaccine lines as factors and age as covariate (continuous variable). A separate bivariate logistic regression model was constructed in the symptomatic group, to identify neurological adverse reactions associated to vaccine lines. The grater odds ratio (OR) for each vaccine have been presented. Relative risks (RR) and confidence intervals (CI) at 95% were calculated to evaluate the associations between dose/onset and the development of neurological reactions. The first RR model has been constructed considering the people exposed to the first dose compared to those exposed to the second dose. The second RR model has been constructed considering as the people exposed that developing neurological complications with acute onset compared to those with subacute onset. RR greater than 1 indicated an increased risk to develop neurological symptoms at first dose and with an acute onset. A value of $p < 0.05$ was considered statistical significance, and all tests were 2-tailed. Analyses were performed with the use of JASP (version 0.15.0) and Jamovi (version 1.6.23) and re-tested with RStudio software, (version 2021.09.02).

3. Results

3.1 Study population

A total of 20.465 persons were considered for the NEURO-COVAX study. Of these, 19.108 participants (total group) were eligible for the inclusion in the vaccination cohort. The remaining 1357 people were excluded because of the incorrect compilation of the questionnaire (656 incomplete, 397 lacked the personal data, and 304 were not filled) (Supplementary Fig. 1). The adherence to filling in the questionnaire was greater than 99% in the nine days of enrollment. Of note, we collected 67.324 (88.1%) questionnaires, as follows: 19.108 first dose acute 19.108 second dose subacute, 19.108 second dose acute and 10.016 (52.4%) second dose subacute. Table 1 summaries the salient characteristics of all participants. We divided the outcomes experienced following vaccination/suspected adverse events into two categories: non-neurological and neurological complications. Non-neurological side effects including arm pain, fever, gastroenteric disorders and other have been found only in a lower percentage of our

vaccinated cohort (3.5–10%). This was probably due to the different investigation (spontaneously reported by the partecipants under the voice “other” of the questionnaire).

Table 1
Demographic and clinical characteristics of the Total Group of people receiving COVID-19 vaccines in the massive Hub Novegro (Lombardy) between 7 July 2021 and 16 July 2021.

	mRNA BNT162b2 **n(%)**	***VACCINE LINES*** **mRNA-1273** **n(%)**	**ChAdOx1nCov-19** **n(%)**
Total number of people	15.368(80.4)	2077 (10.8)	1651(8.6)
Sex			
Female	7497(48.7)	988(47.5)	867(52.5)
Male	7869 (51.2)	1089(52.4)	784(47.4)
Not-Determined	2(0.01)	-	-
Age Groups (years)			
Mean (s.d.)	45.9±11.1	43.7±10.8	66.1±5.49
18–29	747(4.86)	133(6.40)	4(0.24)
30–39	3834(24.94)	764(36.78)	12(0.72)
40–49	4007(26.07)	335(16.12)	9(0.54)
50–59	5736(37.32)	799(38.46)	23(1.39)
60–69	684(4.45)	31(1.49)	1352(81.88)
70–79	213(1.38)	10(0.48)	242(14.65)
≥80	56(0.36)	2(0.09)	8(0.48)
Not-Determined	91(0.59)	3(0.14)	1(0.06)
Non-Neurological complications post-vaccination			
-Total number	553 (3.5)	131(6.3)	171(10.3)
Neurological complications post-vaccination			
-Total number	4650 (30.2)	729 (35.0)	583 (35.3)

It is noteworthy that about a third of our sample developed neurological manifestations after COVID-19 vaccines (so-called symptomatic group). Demographic and clinical characteristics of this group are

reported in Table 2. When we characterized symptomatic group from a clinical point of view, some intriguing evidence emerged. Firstly, a positive SARS-COV2 test (before vaccination) was small but different for vaccines (Table 2). We did not exclude, however, that patients reporting no related SARS-COV2 symptoms may be positive to PCR test. Indeed, only 5% of the participnts performed SARS-COV2 test, having a negative result. In addition, this data could reflect the availability and utilization of the COVID-testing at the time. Secondly, about 40% of the symptomatic group had specific comorbidities: allergies represented the largest share in all three vaccines. (Table 2). Finally, neurological diseases were less commonly found (3–6%) in the symptomatic people developing neurological complications. These findings corroborates our hypothesis as the neurological adverse symptoms may be associated to COVID-19 vaccine rather than to the previous neurological disorders.

Table 2

Demographic and clinical characteristics of the people receiving the COVID-19 vaccines in the massive Hub Novegro, (Lombardy) between 7 July 2021 and 16 July 2021, developing neurological complications in at least one dose (Symptomatic Group)

	mRNA BNT162b2 (N = 4650)	***VACCINE LINES*** **mRNA-1273 (N = 729)**	**ChAdOx1nCov-19 (N = 583)**
Sex n,(%)			
Female	2788 (59.9)	439(60)	380(65)
Male	1862(40)	290(40)	203(35)
Age Groups (years)			
Mean (s.d.)	46.0±11.2	39.0±11.2	66.0±5.88
18–29	282(6.06)	56(7.68)	1(0.17)
30–39	1340(28.8)	315(43.2)	4(0.68)
40–49	1252(26.9)	107(14.6)	4(0.68)
50–59	1495(32.1)	232(3.18)	9(1.54)
60–69	192(4.12)	16(2.19)	487(83.5)
70–79	44(0.94)	2(0.27)	78(13.3)
≥80	15(0.32)	1(0.13)	-
Not-Determined	30(0.64)	-	-
Positive SARS-COV2 test (before vaccination)	34(0.73)	22(3.0)	8(1.37)
Comorbidities			
Total Number n,(%)	1933(41.5)	283(38.8)	278(47.6)
-Allergies[x]	1310 (67.7)	184(65.01)	140 (50.35)
-Seasonal (pollen)	406	60	30
-Food	389	67	38
-Materials (Latex)	55	6	4
-Drugs	668	82	82

[x]Data were calculated in the symptomatic group with comorbidities distinguished in accordance to the vaccine-lines.

	mRNA BNT162b2 (N = 4650)	*VACCINE LINES* mRNA-1273 (N = 729)	ChAdOx1nCov-19 (N = 583)
Antibiotics	282	41	36
Anti-inflammatory	271	28	28
Other	115	3	18
- Cardiovascular, lung, kidney, asthma, diabetes and blood diseases	600(31.0)	98(34.6)	138(49.6)
-Immunodepressive disorders (leukaemia, lymphoma, HIV and transplantation)	130(6.72)	13(4.59)	14(5.03)
-Antitumoral Drugs	106(5.48)	16(5.65)	19(6.83)
-Neurological comorbidities (central and peripheral nervous system disorders) (n,%)	114(5.89)	17(6)	9(3.23)
-Transfusions	35(1.81)	6(2.12)	4(1.43)
-Pregnancy	36(1.86)	7(2.47)	-
-Breastfeeding	33(1.7)	5(1.76)	.
-History of anticoagulants drugs	19(0.98)	2(0.70)	18(6.47)
-History Adverse Reactions to previous vaccination	13(0.67)	1(0.35)	5(1.79)

[x]Data were calculated in the symptomatic group with comorbidities distinguished in accordance to the vaccine-lines.

3.2 Neurological complications post-vaccination

The frequency distribution of the neurological complications after COVID-19 vaccines is detailed in Table 3 and schematically represented in Fig. 1. Headache had higher prevalence, especially for INN-Covid 19 mRNA vaccine. Sleep disorders including excessive daytime sleepiness (EDS) and insomnia were frequent: EDS was the second most common neurological complication (36.0%) prevalently associated to INN-Covid 19 mRNA(45.1%) while insomnia was (5.1%) less common, and was more frequently associated to ChAdOx1nCov-19 vaccine (5.8%). Cognitive fog was reported in less than 10%, of our cohort and mainly after mRNA-vaccine especially, BNT162b2. Of note, we found 132 cases of diplopia (2.2%) and 115 tinnitus (1.9%). While diplopia was slightly more frequent after the administration of the mRNA-vaccine especially mRNA-1273 (2.2% vs 1.88%), tinnitus was more typically

presented after adenovirus vaccine. Smell and taste alterations were mainly reported in people reporting mRNA-1273. Supplementary Table 1 summarizes the characteristics of onset and duration for each neurological complication. Table 4 riaasumes most frequently onset and duration of neurological complications. It is also needed to underline that: 1 participant (woman, BNT162b2), has had access to the emergency room for sudden difficulty walking, 1 participant (man, BNT162b2) reported sudden memory loss (lasting 1 day) and 1 participant with facial paresis (young man, BNT162b2). Of note, no other severe neurological complication has been reported in our vaccinated cohort.

Table 3
Frequency distribution of the neurological complications in the symptomatic group and distinguished according to the vaccine lines

NEUROLOGICAL COMPLICATIONS	**Symptomatic Group[x] (N = 5985)**	**mRNA BNT162b2 (N = 4650)**	***VACCINE LINES*[x] mRNA-1273 (N = 729)**	**ChAdOx1nCov-19 (N = 583)**
Headache	3067(51.2)	2348(50.5)	409(56.1)	310(53.2)
Excessive daytime sleepiness	2256(37.7)	1805(38.8)	290(39.7)	161(27.6)
Vertigo	800(13.4)	625(13.4)	116(15.9)	59(10.1)
Paresthesias	620 (10.3)	486(10.4)	106(14.5)	28(4.8)
Cognitive Fog	362(6.04)	300(6.4)	44(6.0)	18(3.08)
Insomnia	306(5.1)	249(5.3)	23(3.2)	34(5.8)
Tremor	282(4.7)	149(3.2)	56(7.7)	77(13.2)
Muscle spasms	288(4.81)	201(4.3)	43(5.9)	44(7.5)
Diplopia	132(2.2)	101(2.2)	20(2.7)	11(1.9)
Tinnitus	115(1.9)	85(1.8)	14(1.9)	16(2.7)
Taste alterations	51(0.8)	35(0.7)	12(1.6)	4(0.7)
Dysphonia	50 (0.8)	42(0.9)	5(0.7)	3(0.5)
Smell alterations	30(0.5)	20(0.4)	6(0.8)	4(0.7)

[x] Data were expressed as number and percentage.

Table 4
Clinical onset and duration of neurological complications more frequently reported after COVID-19 vaccines

NEUROLOGICAL COMPLICATION	First Dose		Second Dose	
	Clinical Onset (Minutes/Days)	Duration (Day/Week)	Clinical Onset (Minutes/Days)	Duration (Day/Week)
Headache	Within first 15 minutes	1 day	Within first 3 days	1 day
Excessive daytime sleepiness	From 15-to 30 minutes	up a week	Within first 3 days	up a week
Vertigo	From15-to 30 minutes	1 day	Within 30 minutes	1 day
Paresthesias	From15-to 30 minutes	1 day	From 15-to 30 minutes	1 day
Cognitive Fog	Within first 3 days	up a week	Within first 3 days	up a week
Insomnia	Within first 3 days	up a week	Within first 3 days	up a week
Tremor	Within first 15 minutes	1 day	Within first 3 days	1 day
Muscle spasms	Within first 15 minutes	< 1 day	Within first 3 days	< 1 day
Diplopia	From 15-to 30 minutes	1 day	Within first 15 minutes	1 day
Tinnitus	From 15-to 30 minutes	1 day	From 15-within 30 minutes	1 day
Taste alterations	Within 3 days	up a week	Within 3 days	up a week
Dysphonia	Within first 3 days	< 1 day	Within first 3 days	< 1 day
Smell alterations	Within 3 days	>a week	Within 3 days	>a week

3.3 Neurological Risk Profile

Concerning the risk profile, we observed an increased risk of neurological complications for ChAdOx1nCov-19 (OR:1.67, 95% CI:1.34–2.06), and rend for mRNA-1273 (OR:1.12, 95% CI:-0.96-1.31) and BNT162b2 vaccine (OR:0.91, 95% CI:0.82–1.07). We also found an increased risk of neurological complications in females (OR:1.97, 95% CI:1.80–2.09) whereas there was no risk association with the age (OR:0.98, 95% CI:0.98–0.99).

We defined a neurological risk profile for each vaccine line. We found an increased risk for ChAdOx1nCov-19 vaccine of: tremor (vs BNT162b2 OR:5.12, 95% CI:3.51–7.48) insomnia (vs INN-Covid 19, OR:1.87, 95% CI:1.02–3.39); tinnitus (vs BNT162b2 OR:1.75, 95% CI:0.90–3.40); muscle spasms (vs BNT162b2 OR:1.62, 95% CI:1.08–2.46) and headache (vs BNT162b2, OR:1.49, 95% CI:0.96–1.57). There was an increased risk for INN-Covid 19 mRNA vaccine of: taste alterations (vs ChAdOx1nCov-19: OR:3.03, 95% CI:0.83–10.7;) parethesias (vs ChAdOx1nCov-19: OR:2.37, 95% CI:1.48–3.79), smell alterations (vs BNT162b2 OR:1.96, 95% CI:0.78–4.92;), vertigo (vs ChAdOx1nCov-19: OR:1.68, 95% CI:1-20-2.35) diplopia (vs ChAdOx1nCov-19: OR:1.55, 95% CI:0.67–3.57); EDS (vs ChAdOx1nCov-19 OR:1.28, 95% CI:0.98–1.67). An increased risk of cognitive fog has been reported for BNT162b2 (vs ChAdOx1nCov-19 OR:1.54, 95% CI:0.90–2.61).

We also observed an increased RR to develop almost all the neurological complications at the first dose and with an acute onset. Increased RR to develop almost all neurological complications at first dose: EDS (RR = 2.20; 95% CI = 1.99–2.43), muscle spasms (RR = 1.67; 95% CI = 1.24–2.21), tremor (RR = 1.57; 95% CI = 1.19–2.08), taste alterations (RR = 1.51; 95% CI = 0.71–3.21), headache (RR = 1.50; 95% CI = 1.41–1.59), smell alterations (RR = 1.45; 95% CI = 0.56–3.77), cognitive fog (RR = 1.42; 95% CI = 1.08–1.86), insomnia (RR = 1.25; 95% CI = 0.94–1.67), vertigo (RR = 1.22; 95% CI = 1.05–1.40) and tinnitus (RR = 1.14; 95% CI = 0.76–1.73), whereas a reverse trend has been observed diplopia (RR = 0.84; 95% CI = 0.60–1.17), dysphonia (RR = 0.84; 95% CI = 0.47–1.50) and paresthesias (RR = 0.80; 95% CI = 0.69–0.92). Figure 2 shows the risks to have specific adverse events at the first dose in comparison to the second. Finally, we calculated the RR to develop neurological complications with acute onset according to the specific vaccine. Interestingly, we observed an increased risk to develop with acute onset for almost all the neurological cimplications: diplopia with INN-Covid 19 (RR = 2.55; 95% CI = 1.27–5.09), paresthesias with INN-Covid 19 (RR = 1.30; 95% CI = 0.57–2.08), tinnitus with INN-Covid 19 (RR = 1.46; 95% CI = 0.58–3.68), EDS with ChAdOx1nCov-19 (RR = 1.21; 95% CI = 0.91–1.56), a trend for muscle spasms with ChAdOx1nCov-19 (RR = 1.10; 95% CI = 0.68-1,76), tremor with ChAdOx1nCov-19 (RR = 1.10; 95% CI = 0.80–1.58). Of note, the clinical onset of cognitive fog, taste and smell alterations; and insomnia was subacute for each vaccine and both doses. Figure 3 shows RR for single adverse neurological events stratified for each vaccine.

4. Discussion

This large population-based study in Italy investigated the neurological complications associated with first and second dose of three COVID-19 vaccines in use in Hub Novegro (Milan). We identified several crucial findings, of clinical relevance to public health and scientific interest for clinicians and researchers across the world. Firstly, we observed an increased risk of neurological adverse events in females, and for adenovirus ChAdOx1nCov-19 vaccine, a trend for mRNA vaccine as mRNA-1273 and BNT162b2. Secondly, in the symptomatic vaccinated group, we identified a neurological risk profile specific for each vaccine. There was an increased risk for ChAdOx1nCov-19 vaccine of tremor, insomnia, tinnitus, muscle spasms and headache; an increased risk for mRNA-1273 vaccine of taste and smell alterations, vertigo, diplopia, excessive daytime sleepiness, parethesias and dysfonia; then, an increased risk mRNA

BNT162b2 vaccine of cognitive fog. Finally, defining the symptomatic group, we found that over 40% showed comorbidities in the clinical history.

Neurological risk profile of AstraZeneca vaccine included: headache, tremor, muscle spasms, insomnia, and tinnitus. Of note, 53.2% (310/583) of people receiving AstraZeneca developed headache, with an increased risk at the first dose and subacute onset. Headaches had a short-term duration, being more frequently reversible within a day. Headaches were expected following AstraZeneca vaccine. A clinical trial[11] recently found headaches as the most common adverse events, probably related to the nature of this vaccine, a modified adenovirus vector vaccine thus miming not only the immunogenicity but also the side effects.[12–15] A fascinating hypothesis proposed the activation of the trigemino-vascular system mediated by the pathogen itself on trigeminal branches present at this level or through olfactory-trigeminal interactions, as the pathophysiological mechanism underlying headache.[16] About 13.2% (77/583) of people receiving AstraZeneca developed tremor, with an increased risk at the first dose, and it commonly reverted within one day. Acute onset and short-term duration, however, seems to direct towards psychogenic rather than organic form. Psychogenic movement disorders especially tremor have been described in adolescents precipitating with H1N1 influenza vaccination.[17] New-onset movement disorders including psychogenic disorders have been found in COVID-19 cases.[18] Sleep disorders, in particular insomnia has been reported in 5.8% (34/583) persons receiving AstraZeneca, with an increased risk at the first dose, subacute onset and more frequently reversible within one week. Insomnia has been found in COVID-19 cases.[19] Some questions, however, still remain unresolved. Firstly, we do not know whether our symptomatic people suffered of insomnia before vaccination; this could be of great interest, since insomnia is a risk factor decreasing the vaccine response.[20,21] Secondly, we do not know whether our symptomatic people had developed an initial, intermediate or final insomnia rather than a misperception of their sleep quality due to the vaccination-stress. Future studies assessing sleep profile before and after COVID-19 vaccination are need. Tinnitus is reported in 2.7% (16/583) of people receiving AstraZeneca, with increased risk at the first dose, subacute onset and short-term duration, features suggestive of a transient phenomenon. Despite the incidence of tinnitus post-vaccination is infrequent, several cases have been described after COVID-19 vacines.[22–23] A hypersensitivity reaction with an abnormal autoimmune response as cross-reactivity between anti-spike SARS-CoV-2 antibodies and otologic antigens or vasculitic event have been hypnotized as pathogenetic mechanisms.[22,23]

The neurological risk profile of the Moderna vaccine included: EDS, vertigo, diplopia, parethesias, taste and smell alterations, and dysphonia. EDS was present in 39.7% (290/729) of people receiving Moderna, with an increased risk at the first dose and acute onset. Its duration in most of the cases was within one week. EDS in core adverse vaccination events is not unexpected. Firstly, an increased incidence of narcolepsy was observed in Europe following administration of Pandemrix, a vaccine against H1N1 virus.[24] Secondly, a case of hypersomnia relapse after receiving the COVID-19 vaccine has been also reported: a case of female with previous history of hypersomnia secondary presented EDS after CoronaVac injection.[25] Finally, about 33.01% of the people affected by COVID-19 infection may experience EDS.[26] Taken together, this evidence suggest that there could be a strict relationship between

the development of EDS and immune responses to vaccine/infection. A fascinating hypothesis suggests that influenza vaccines might lead to selective immune-mediated destruction of orexin-producing neurons, a T-cell-mediated neuronal damage, thus triggering narcolepsy.[27,28] Considering that the same can occur for COVID-19 vaccines, future investigations monitoring the new-onset hypersomnia in vulnerable individuals are urgently need. About 15.9% (116/729) of people receiving Moderna showed vertigo, with an increased risk at I dose and an acute onset. Its duration was more commonly within one day, suggesting a sudden but reversible complication. “Acute vertigo” post COVID-19 vaccination has been reported.[29] An abnormal autoimmune response or a vasculitic event with subsequent localized damage to the cochlea, have been proposed as potential mecchanisms.[30] Parethesias were reported in 14.5% (106/729) of people receiving Moderna, with an increased risk at the second dose and acute onset. These were more reversible after one day. A recent study[31] found non-specific sensory symptoms following BNT162b2 first-dose immunization probably mediated by stress-related responses. On the other hand, cases of new-onset central nervous system demyelination, severe relapse in Multiple Sclerosis patients, as well as and GBS have been reported.[32–34] These conditions, however, are not reversible in a short-time period. Interestingly diplopia has been reported in 2.7% (20/729) of people receiving Moderna, with an increased risk to the second dose and acute onset. However, its short duration (within one day) was suggestive of a transient event. Binocular diplopia associated to a transient oculomotor nerve palsy occurred after the first dose of Moderna.[35] Isolated abducens nerve palsy may be present days after COVID-19 onset.[36] Immune response activated by a vaccine, however, may have an individual variability. A reactivation of immune response and diabetes mellitus may be precipitants factors for oculomotor nerve palsy.[35] Our symptomatic people showed increased risk to develop diplopia at the second dose, as if a reactivation of the immune response was necessary to trigger diplopia. Finally, taste/smell alterations may occur after Moderna with an increased risk at the first dose, subacute onset and a longer duration. Otolaryngology-specific symptoms are described post-vaccination, especially in subjects with a previous COVID-19 infection.[37]

Despite the neurological profile of Pfizer vaccine included several neurological symptoms, we found an increased risk for cognitive fog. About 6.4% (300/4650) of people received Pfizer developed cognitive fog, with an increased risk to present at the first dose, onset subacute and it was reversible within one week. Brain fog is a type of cognitive impairment presenting as a "foggy brain state" including a lack of intellectual clarity, difficulty with concentration, mental fatigue and anxiety.[38] Hypotheses including systemic inflammation crossing the blood–brain barrier, neuroinflammation after viral infection leads and microglial activation are emerging to explain this phenomnen in COVID-19 patients.[39]An alternative speculation is that the symptomatic people may have a subclinical cognitive dysfunction before vaccination and that this was a trigger. Prospective studies are required to investigate the relationship between development of brain fog and vaccines.

Interestingly, we identified baseline factors potentially associated to adverse events. There is an increased risk of developing neurological complications in females. We are in line with a recent study revealing that several factors including the female sex were associated with greater odds of adverse effects.[40] Why this

occurs is a fascinating question. Biologically, differences between females and males can affect COVID19 infection as well as contribute to sex-specific vaccine outcomes.[41,42] The mechanism is probably related to genetic and hormonal factors. A genetic profile characterizes the female sex, since X chromosome contains the most prominent immune-related genes in the human genome[43] thus causing a stronger inflammatory immune responses.[44] In addition, estradiol, a primary female sex steroid, binding to the cytoplasmic estrogenic receptors on T cells and B cells, triggers the humoral immunity to produce antibodies against infections.[45] Furthermore, the evidence that immune system dysfunctions (allergies/immunodepressive disorders) are frequently reported in our symptomatic group is more than a chance. Indeed, concerning the clinical profile more vulnerable to develop post-vaccination complications, we reported: i) 47.6% of AstraZeneca symptomatic people showed comorbidities; allergies and non-neurological diseases has been similarly reported; an history of antitumoral and anticoagulants drugs was more frequent in this population; ii) 38.8% of Moderna symptomatic people showed comorbidities; allergies are more frequently represented (especially drugs). A history of neurological diseases and transfusions and previous SARS-COV 2 was more frequently observed in this population; iii) 41.5% of Pfizer symptomatic people showed comorbidities. Allergies are more frequently reported (especially drugs). An history of immunodepressive disorders was more commonly observed in this population.

This study has limitations. Firstly, we evaluated the risks associated with the first and second dose of the vaccine, although the data concerning the second dose were limited. A possible misunderstanding of the study, and/or an inability to send the questionnaire may occur. Secondly, we required to report neurological complications within first 14 days following the first and second doses. Nerveless, we can exclude that people may develop neurological complications in a longer time. Third, the different composition of eligible population regarding race, ethnicity, social status, education level, could impact on the development of adverse events with different estimates risks. This study has several strengths. Firstly, this was a single-center population-based study investigating neurological complications associated with the first and second doses of COVID-19 vaccines used in Italy in July 2021. Secondly, the study design allowed a serial neurological investigation at different time-points, thus collecting prospectively recorded medical data. Thirdly, the large sample size provided sufficient power to quantify the risk of neurological complications according to female sex, age, vaccine lines, dose and clinical onset, that did not assess through clinical trials.

This study identifies, for the first time, a neurological risk profile for each vaccine and a clinical profile more vulnerable to develop neurological complications after COVID-19 vaccines. Clinicians should be aware that several neurological complications may commonly occur after COVID-19 vaccines, but in most cases these have a benign nature. On the other hand, caution should be placed when administering COVID-19 vaccines in vulnerable people, such as that suffering of allergies. We strongly believe that our findings might be of relevance for the public health regarding safety vaccine in a large cohort.

Declarations

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Author Contributions

MS, CS and LFS contributed to the conception and design of the study; AO, MP, VFA, VC, SM, MM, contributed to the acquisition and analysis of data; MS, and LFS contributed to drafting the text or preparing the figures

Potential Conflicts of Interest: nothing to report

Data Accessibility: The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figures

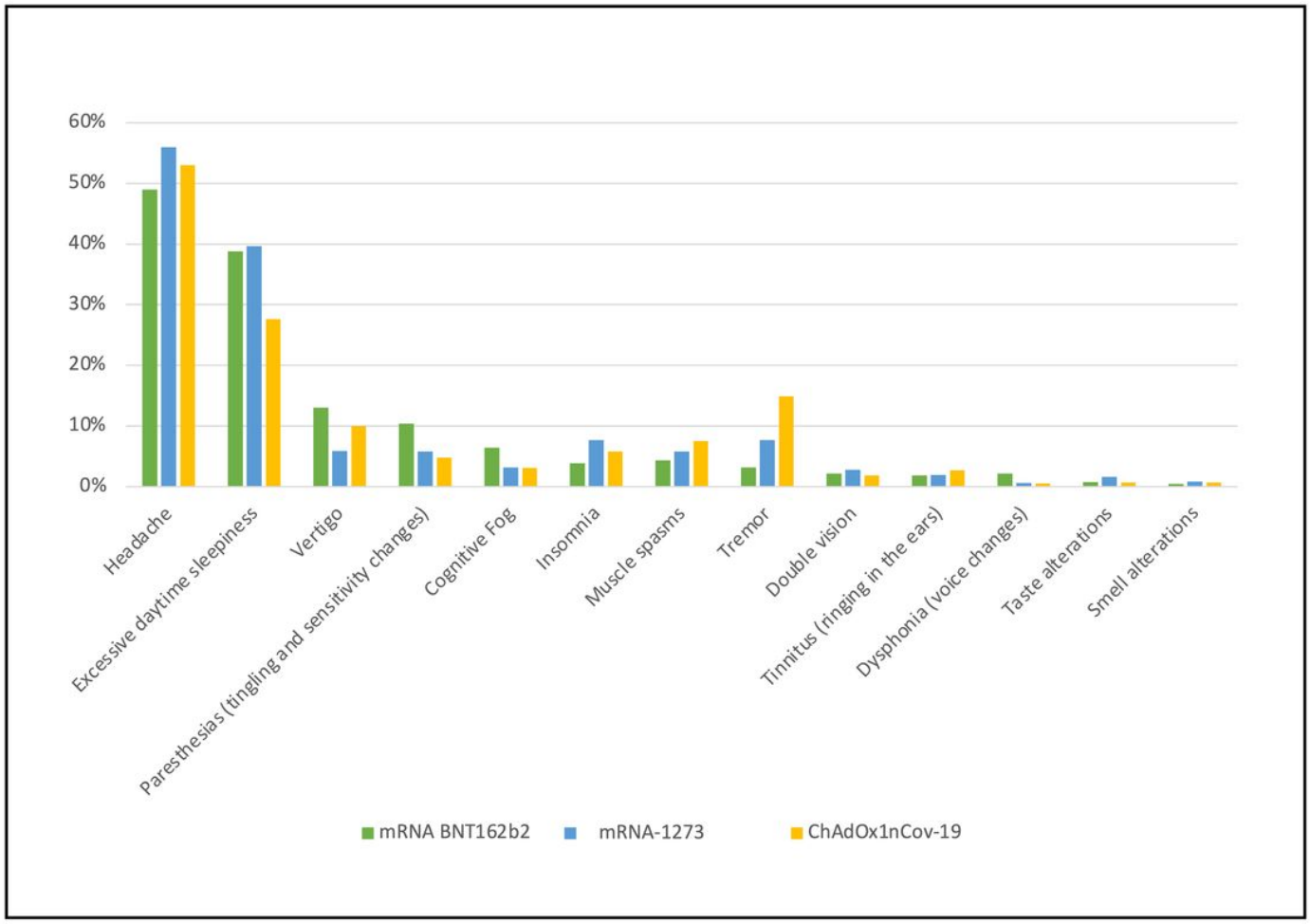

Figure 1

Title Neurological Complications following COVID-19 Vaccines. *Legend:* Percentage distribution of neurological adverse events, distinguished for specific symptom and stratified for each vaccine. The color green, yellow and blue are representative of mRNA BNT162b2, mRNA-1273 and ChAdOx1nCov-19 vaccine, respectively.

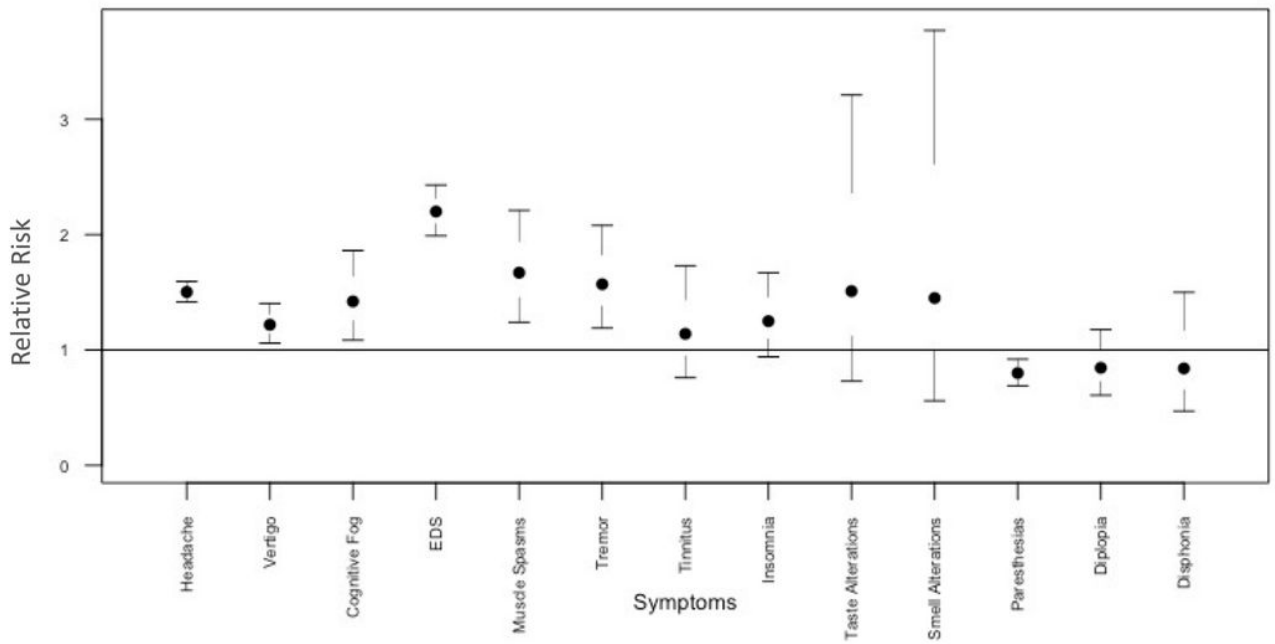

Figure 2

Title Relative risks (RR) to develop neurological complications at first dose of COVID-19 vaccines. *Legend* Increased RR (>1) has been observed for excessive daytime sleepiness (RR=2.20; 95% CI=1.99-2.43), muscle spasms (RR=1.67; 95% CI=1.24-2.21), tremor (RR=1.57; 95% CI=1.19-2.08), taste alterations (RR=1.51; 95% CI=0.71-3.21), headache (RR=1.50; 95% CI=1.41-1.59), smell alterations (RR=1.45; 95% CI=0.56-3.77), cognitive fog (RR=1.42; 95% CI=1.08-1.86), insomnia (RR=1.25; 95% CI=0.94-1.67), vertigo (RR=1.22; 95% CI=1.05-1.40) and tinnitus (RR=1.14; 95% CI=0.76-1.73). Diplopia (RR=0.84; 95% CI=0.60-1.17), dysphonia (RR=0.84; 95% CI=0.47-1.50) and paresthesias (RR=0.80; 95% CI=0.69-0.92) showed a reverse trend (RR<1).

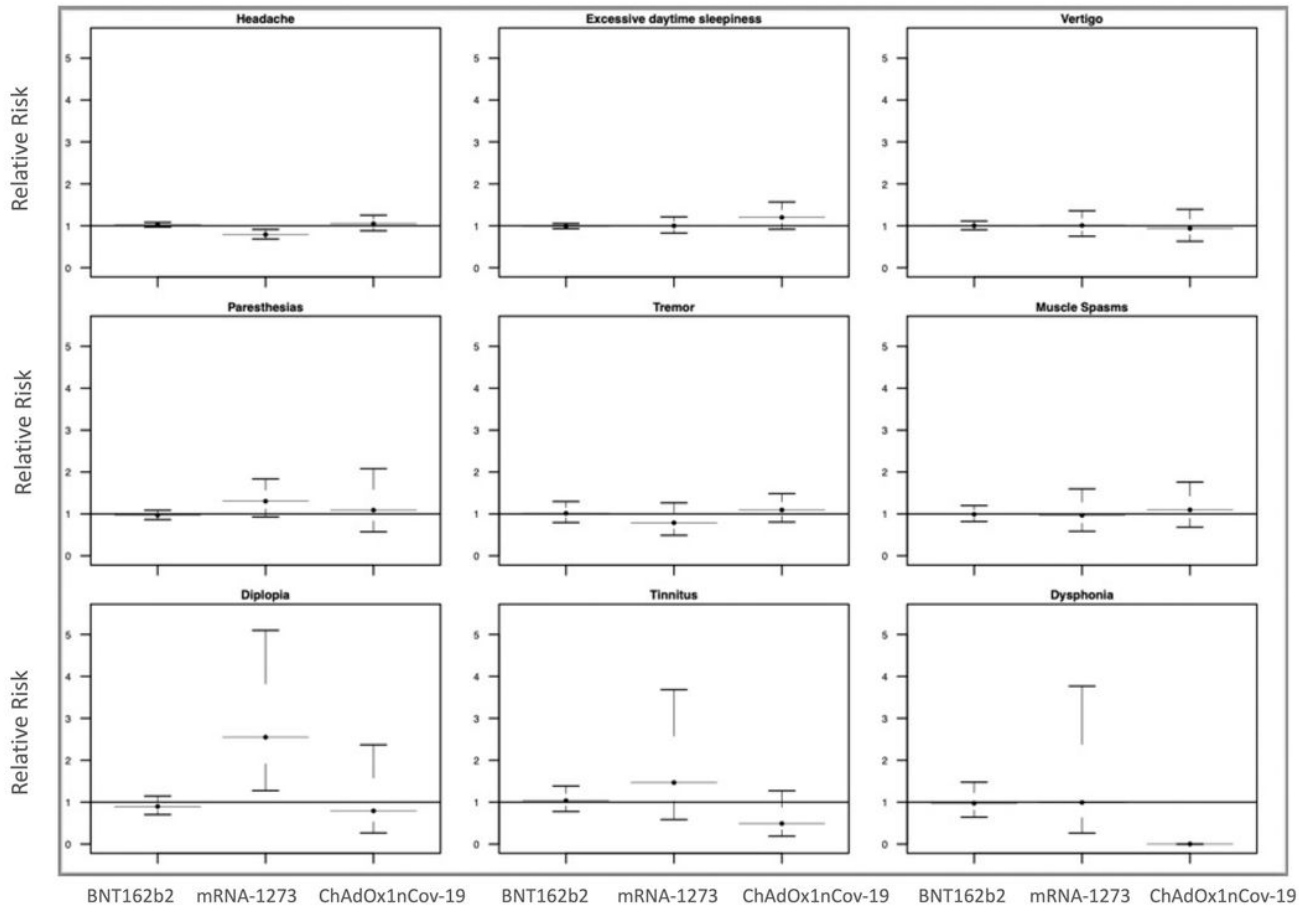

Figure 3

Title Relative risks (RR) to develop neurological complications with an acute onset of COVID-19 vaccines. *Legend* RR were calculated for each symptom and stratified according to specific vaccine. Increased RR (>1) has been observed for diplopia with mRNA-1273 (RR=2.55; 95% CI=1.27-5.09), paresthesias with INN-Covid 19 and ChAdOx1nCov-19 (RR=1.30; 95% CI=0.57-2.08; RR=1.10; 95% CI=0.93-1.83 respectively), tinnitus with INN-Covid 19 (RR=1.46; 95% CI=0.58-3.68), EDS with ChAdOx1nCov-19 (RR=1.21; 95% CI=0.91-1.56), muscle spasms with ChAdOx1nCov-19 (RR=1.10; 95% CI=0.68-1,76), tremor with ChAdOx1nCov-19 (RR=1.10; 95% CI=0.80-1.58). For all symptoms associated to specific vaccine we observed a RR≤1.

Supplementary Files

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