Vaccines (Basel) 2023 Oct 21;11(10):1621.doi: 10.3390/vaccines11101621.

NEURO-COVAX: An Italian Population-Based Study of Neurological Complications after COVID-19 Vaccinations

Maria Salsone[1,2], Carlo Signorelli[3], Alessandro Oldani[2], Valerio Fabio Alberti[4], Vincenza Castronovo[2], Salvatore Mazzitelli[5], Massimo Minerva[3], Luigi Ferini-Strambi[2,6]
Affiliations expand

- PMID: 37897023
- PMCID: PMC10610846
- DOI: 10.3390/vaccines11101621

Abstract

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

Methods: Our study included adults aged 18 years and older who received two vaccine doses in the vaccination hub of Novegro (Milan, Lombardy) between 7 and 16 July 2021. The NEURO-COVAX questionnaire was able to capture the neurological events, onset and duration. That data that were digitized centrally by the Lombardy region were used to match the demographic/clinical characteristics and identify a vulnerability profile. Associations between vaccine lines and the development of complications were assessed. Digital healthcare system matching was also performed to evaluate severe neurological complications (Guillain-Barrè syndrome, Bell's palsy, transverse myelitis, encephalitis) and the incidence of hospital admissions and/or the mortality rate after two doses of the vaccines.

Results: The NEURO-COVAX-cohort included 19.108 vaccinated people: 15.368 with BNT162b2, 2077 with mRNA-1273, 1651 with ChAdOx1nCov-19, and 12 with Ad26.COV2.S who were subsequently excluded. Approximately 31.2% of our sample developed post-vaccination neurological complications, particularly with ChAdOx1nCov-19. A vulnerable clinical profile emerged, where over 40% of the symptomatic people showed comorbidities in their clinical histories. Defining the neurological risk profile, we found an increased risk for ChAdOx1nCov-19 of tremors (vs. BNT162b2, OR: 5.12, 95% CI: 3.51-7.48); insomnia (vs. mRNA-1273, OR: 1.87, 95% CI: 1.02-3.39); muscle spasms (vs. BNT162b2, OR: 1.62, 95% CI: 1.08-2.46); and headaches (vs. BNT162b2, OR: 1.49, 95% CI: 0.96-1.57). For mRNA-1273, there were increased risks of parethesia (vs. ChAdOx1nCov-19, OR: 2.37, 95% CI: 1.48-3.79);

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); and sleepiness (vs. ChAdOx1nCov-19, OR: 1.28, 95% CI: 0.98-1.67). In the period that ranged from March to August 2021, no one was hospitalized and/or died of severe complications related to COVID-19 vaccinations.

Discussion: This study estimates the prevalence and risk for neurological complications potentially associated with COVID-19 vaccines, thus improving the vaccination guidelines and loading in future personalized preventive medicine.

Keywords: Ad26.COV2.S vaccine; BNT162b2 vaccine; COVID-19 infection; ChAdOx1nCoV-19 vaccine; mRNA-1273 vaccine; neurological adverse events.

Conflict of interest statement

The authors declare no conflict of interest.

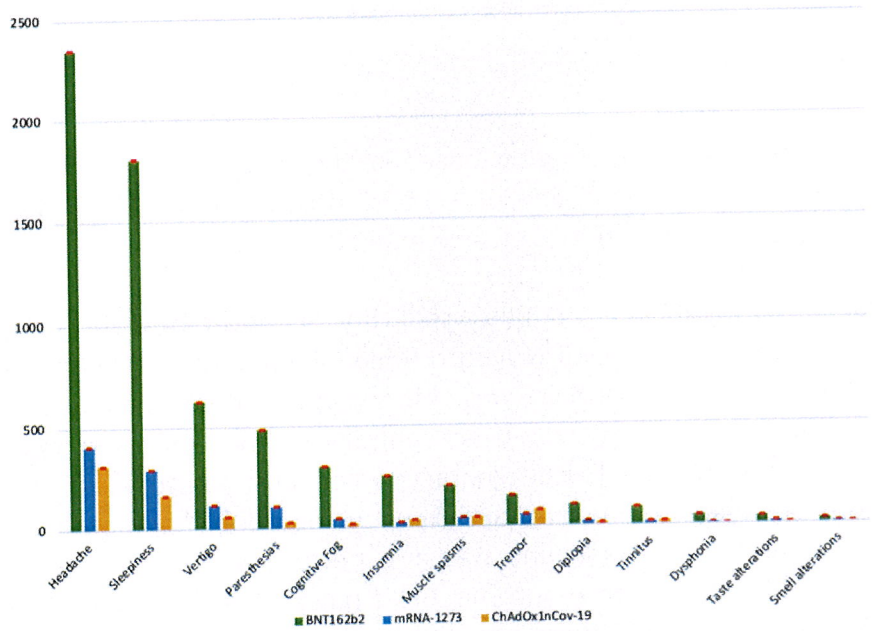

Figure 1
Neurological complications following COVID-19 vaccines. Distribution of adverse events, distinguished for specific symptom and stratified for each vaccine. Data are presented as total number of subjects presenting the specific neurological complication and standard error. The colors green, yellow and blue are representative of the BNT162b2, mRNA-1273 and ChAdOx1nCov-19 vaccines, respectively. The color red is representative of the standard error (SE). In detail, SEs for BNT162b2 vaccine are as follows: headache 0.50; sleepiness 0.49; vertigo 0.34; paresthesia 0.31; cognitive fog 0.25; insomnia 0.23; muscle spasms 0.20; tremor 0.18; diplopia 0.15; tinnitus 0.13; dysphonia 0.09; taste alterations 0.09; smell alterations 0.07. SEs for mRNA-1273 vaccine are as follows: headache 0.50; sleepiness 0.49; vertigo 0.37; paresthesia 0.35; cognitive fog 0.24; insomnia 0.17; muscle spasms 0.24; tremor 0.27; diplopia 0.16; tinnitus 0.14; dysphonia 0.08; taste alterations 0.13; smell alterations 0.09. SEs for ChAdOx1nCov-19vaccine were the following: headache 0.50; sleepiness 0.45; vertigo 0.30; paresthesia 0.21; cognitive fog 0.17; insomnia 0.23; muscle spasms 0.26; tremor 0.34; diplopia 0.14; tinnitus 0.16; dysphonia 0.07; taste alterations 0.08; smell alterations 0.08.

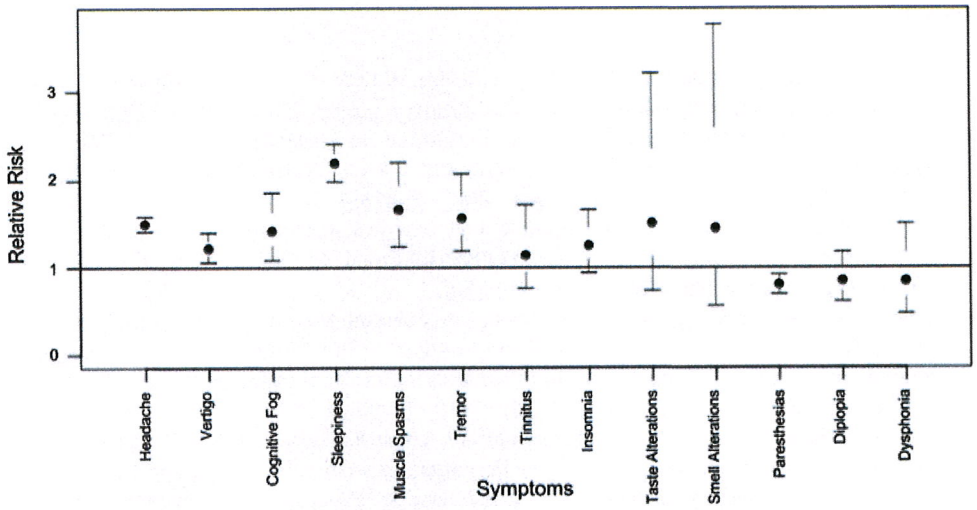

Figure 2

Relative risks (RRs) to develop neurological complications after first dose of COVID-19 vaccines. Increased RRs (>1) were observed for sleepiness (RR = 2.20; 95% CI = 1.99–2.43); muscle spasms (RR = 1.67; 95% CI = 1.24–2.21); tremors (RR = 1.57; 95% CI = 1.19–2.08); taste alterations (RR = 1.51; 95% CI = 0.71–3.21); headaches (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 paresthesia (RR = 0.80; 95% CI = 0.69–0.92) showed a reverse trend (RR < 1).

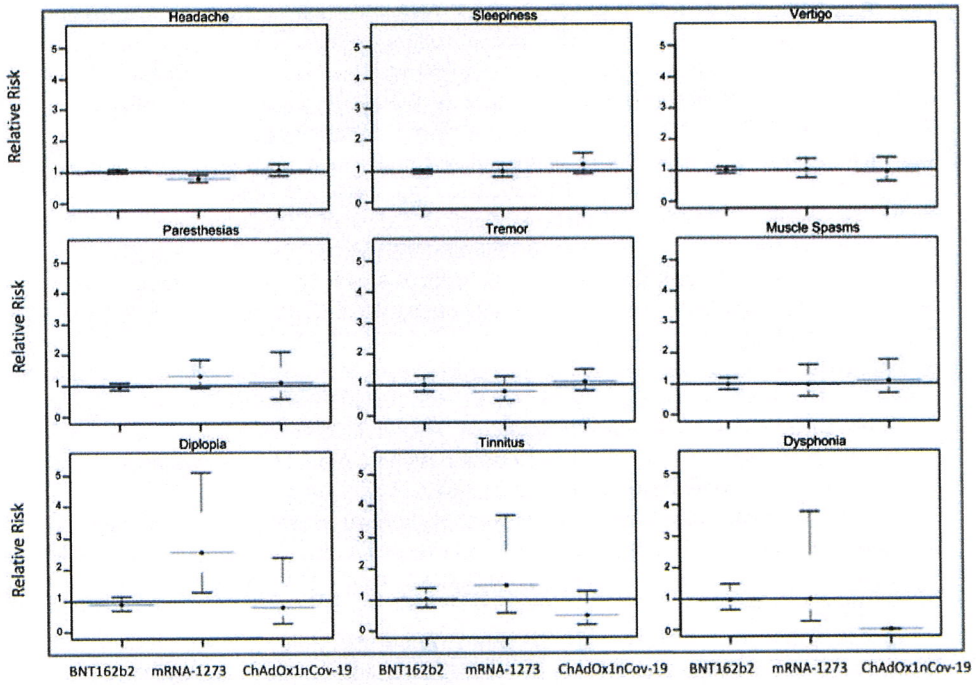

Figure 3

Relative risks (RRs) to develop neurological complications with an acute onset of COVID-19 vaccines. RRs were calculated for each symptom and stratified according to specific vaccine. Increased RR (>1) was observed for headaches with ChAdOx1nCov-19 (RR = 1.05; 95% CI = 0.88–1.25); diplopia with mRNA-1273 (RR = 2.55; 95% CI = 1.27–5.09); paresthesia with mRNA-1273; and ChAdOx1nCov-19 (RR = 1.30; 95% CI = 0.93–1.83; RR = 1.10; 95% CI = 0.57–2.08, respectively); tinnitus with mRNA-1273 (RR = 1.46; 95% CI = 0.58–3.68); sleepiness 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); and tremors with ChAdOx1nCov-19 (RR = 1.10; 95% CI = 0.80–1.58). For all symptoms associated with a specific vaccine we observed an RR ≤ 1.

References

1. Francis A.I., Ghany S., Gilkes T., Umakathan S. Review of COVID-19 vaccine subtypes, efficacy and geographical. Postgrad. Med. J. 2022;98:389–394. doi: 10.1136/postgradmedj-2021-140654. - DOI - PubMed
2. Polack F.P., Thomas S.J., Kitchin N., Absalon J., Gurtman A., Lockhart S., Perez J.L., Pérez Marc G., Moreira E.D., Zerbini C., et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N. Engl. J. Med. 2020;383:2603–2615. doi: 10.1056/NEJMoa2034577. - DOI - PMC - PubMed
3. Baden L.R., El Sahly H.M., Essink B., Kotloff K., Frey S., Novak R., Diemert D., Spector S.A., Rouphael N., Creech B., et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N. Engl. J. Med. 2020;384:403–416. doi: 10.1056/NEJMoa2035389. - DOI - PMC - PubMed
4. Voysey M., Clemens S.A.C., Madhi S.A., Weckx L.Y., Folegatti P.M., Aley P.K., Angus B., Baillie V.L., Barnabas S.L., Bhorat Q.E., et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397:99–111. doi: 10.1016/S0140-6736(20)32661-1. - DOI - PMC - PubMed
5. Menni C., Klaser K., May A., Polidori L., Capdevila J., Louca P., Sudre C.H., Nguyen L.H., Drew D.A., Merino J., et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: A prospective observational study. Lancet Infect. Dis. 2021;21:939–949. doi: 10.1016/S1473-3099(21)00224-3. - DOI - PMC - PubMed
6. Dagan N., Barda N., Kepten E., Miron O., Perchik S., Katz M.A., Hernán M.A., Lipsitch M., Reis B., Balicer R.D. BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Mass Vaccination Setting. N. Engl. J. Med. 2021;384:1412–1423. doi: 10.1056/NEJMoa2101765. - DOI - PMC - PubMed
7. Barda N., Dagan N., Ben-Shlomo Y., Kepten E., Waxman J., Ohana R., Hernán M.A., Lipsitch M., Kohane I., Netzer D., et al. Safety of the BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Setting. N. Engl. J. Med. 2021;385:1078–1090. doi: 10.1056/NEJMoa2110475. - DOI - PMC - PubMed
8. Allen A., Szabo L. Kaiser Health News. NIH Very Concerned about Serious Side Effect in Coronavirus Vaccine Trial. Scientific American 2020. [(accessed on 27 February 2021)]. Available online: https://www.scientificamerican.com/article/nih-very-concerned-about-seri...
9. Goss A.L., Samudralwar R.D., Das R.R., Nath A. ANA Investigates: Neurological Complications of COVID-19 Vaccines. Ann. Neurol. 2021;89:856–857. doi: 10.1002/ana.26065. - DOI - PMC - PubMed
10. Patone M., Handunnetthi L., Saatci D., Pan J., Katikireddi S.V., Razvi S., Hunt D., Mei X.W., Dixon S., Zaccardi F., et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat. Med. 2021;27:2144–2153. doi: 10.1038/s41591-021-01556-7. - DOI - PMC - PubMed
11. Garg R.K., Paliwal V.K. Spectrum of neurological complications following COVID-19 vaccination. Neurol. Sci. 2022;43:3–40. doi: 10.1007/s10072-021-05662-9. - DOI - PMC - PubMed
12. Tondo G., Virgilio E., Naldi A., Bianchi A., Comi C. Safety of COVID-19 Vaccines: Spotlight on Neurological Complications. Life. 2022;12:1338. doi: 10.3390/life12091338. - DOI - PMC - PubMed
13. Tana C., Bentivegna E., Cho S.J., Harriott A.M., García-Azorín D., Labastida-Ramirez A., Ornello R., Raffaelli B., Beltrán E.R., Ruscheweyh R., et al. Long COVID headache. J. Headache Pain. 2022;23:93. doi: 10.1186/s10194-022-01450-8. - DOI - PMC - PubMed
14. Straburzyński M., Kuca-Warnawin E., Waliszewska-Prosół M. COVID-19-related headache and innate immune response. Neurol. Neurochir. Pol. 2023;57:43–52. doi: 10.5603/PJNNS.a2022.0049. - DOI - PubMed
15. Signorelli C., Odone A., Gianfredi V., Capraro M., Kacerik E., Chiecca G., Scardoni A., Minerva M., Mantecca R., Musarò P., et al. Application of the "immunization islands" model to improve quality, efficiency and safety of a COVID-19 mass vaccination site. Ann. Ig. 2021;33:499–512. - PubMed
16. Castaldo M., Waliszewska-Prosół M., Koutsokera M., Robotti M., Straburzyński M., Apostolakopoulou L., Capizzi M., Çibuku O., Ambat F.D.F., Frattale I., et al. Headache onset after vaccination against SARS-CoV-2: A systematic literature review and meta-analysis. J. Headache Pain. 2022;23:41. doi: 10.1186/s10194-022-01400-4. - DOI - PMC - PubMed
17. Falsey A.R., Sobieszczyk M.E., Hirsch I., Sproule S., Robb M.L., Corey L., Neuzil K.M., Hahn W., Hunt J., Mulligan M.J., et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) COVID-19 Vaccine. N. Engl. J. Med. 2021;385:2348–2360. doi: 10.1056/NEJMoa2105290. - DOI - PMC - PubMed
18. Caronna E., Pozo-Rosich P. Headache as a Symptom of COVID-19: Narrative Review of 1-Year Research. Curr. Pain Headache Rep. 2021;25:73. doi: 10.1007/s11916-021-00987-8. - DOI - PMC - PubMed
19. Caronna E., Ballvé A., Llauradó A., Gallardo V.J., Ariton D.M., Lallana S., López Maza S., Olivé Gadea M., Quibus L., Restrepo J.L., et al. Headache: A striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. Cephalalgia. 2020;40:1410–1421. doi: 10.1177/0333102420965157. - DOI - PMC - PubMed
20. Magdy R., Hussein M., Ragaie C., Abdel-Hamid H.M., Khallaf A., Rizk H.I., Dahshan A. Characteristics of headache attributed to COVID-19 infection and predictors of its frequency and intensity: A cross sectional study. Cephalalgia. 2020;40:1422–1431. doi: 10.1177/0333102420965140. - DOI - PMC - PubMed

21. Rocha-Filho P.A.S., Magalhães J.E. Headache associated with COVID-19: Frequency, characteristics and association with anosmia and ageusia. Cephalalgia. 2020;40:1443–1451. doi: 10.1177/0333102420966770. - DOI - PMC - PubMed
22. Meinhardt J., Radke J., Dittmayer C., Franz J., Thomas C., Mothes R., Laue M., Schneider J., Brünink S., Greuel S., et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat. Neurosci. 2021;24:168–175. doi: 10.1038/s41593-020-00758-5. - DOI - PubMed
23. Harris S.R. Psychogenic movement disorders in children and adolescents: An update. Eur. J. Pediatr. 2019;178:581–585. doi: 10.1007/s00431-019-03317-8. - DOI - PubMed
24. Brandão R.P.P., Grippe T.C., Pereira A.D., Munhoz R.P., Cardoso F. New-Onset Movement Disorders Associated with COVID-19. Tremor Other Hyperkinet. Mov. 2021;11:26. doi: 10.5334/tohm.595. - DOI - PMC - PubMed
25. Wallbridge Bourmistrova N., Solomon T., Braude P., Strawbridge R. Long-term effects of COVID-19 on mental health: A systematic review. J. Affect. Disord. 2022;299:118–125. doi: 10.1016/j.jad.2021.11.031. - DOI - PMC - PubMed
26. De Mello M.T., Silva A., Guerreiro R.C., da-Silva F.R., Esteves A.M., Poyares D., Piovezan R., Treptow E., Starling M., Rosa D.S., et al. Sleep and COVID-19: Considerations about immunity, pathophysiology, and treatment. Sleep Sci. 2020;13:199–209. - PMC - PubMed
27. Spiegel K., Sheridan J.F., Van Cauter E. Effect of sleep deprivation on response to immunization. JAMA. 2002;288:1471–1472. doi: 10.1001/jama.288.12.1469. - DOI - PubMed
28. Ahmed S.H., Waseem S., Shaikh T.G., Qadir N.A., Siddiqui S.A., Ullah I., Waris A., Yousaf Z. SARS-CoV-2 Vaccine-Associated Tinnitus: A Review. Ann. Med. Surg. 2022;75:103293. doi: 10.1016/j.amsu.2022.103293. - DOI - PMC - PubMed
29. Tseng P.T., Chen T.Y., Sun Y.S., Chen Y.W., Chen J.J. The reversible tinnitus and cochleopathy followed first-dose AstraZeneca COVID-19 vaccination. QJM. 2021;114:663–664. doi: 10.1093/qjmed/hcab210. - DOI - PMC - PubMed
30. Feltelius N., Persson I., Ahlqvist-Rastad J., Andersson M., Arnheim-Dahlström L., Bergman P., Granath F., Adori C., Hökfelt T., Kühlmann-Berenzon S., et al. A coordinated cross-disciplinary research initiative to address an increased incidence of narcolepsy following the 2009–2010 Pandemrix vaccination programme in Sweden. J. Intern. Med. 2015;278:335–353. doi: 10.1111/joim.12391. - DOI - PubMed
31. Wu M., Li S.X., Pei Xue P., Zhou J., Tang X. COVID-19 Vaccine Could Trigger the Relapse of Secondary Hypersomnia. Nat. Sci. Sleep. 2021;13:2267–2271. doi: 10.2147/NSS.S345801. - DOI - PMC - PubMed
32. Liguori C., Pierantozzi M., Spanetta M., Sarmati L., Cesta N., Iannetta M., Ora J., Mina G.G., Puxeddu E., Balbi O., et al. Subjective neurological symptoms frequently occur in patients with SARS-CoV-2 infection. Brain Behav. Immun. 2020;88:11–16. doi: 10.1016/j.bbi.2020.05.037. - DOI - PMC - PubMed
33. Bassetti C.L.A., Adamantidis A., Burdakov D., Han F., Gay S., Kallweit U., Khatami R., Koning F., Kornum B.R., Lammers G.J., et al. Narcolepsy—Clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nat. Rev. Neurol. 2019;15:519–539. doi: 10.1038/s41582-019-0226-9. - DOI - PubMed
34. Lippert J., Young P., Gross C., Meuth S.G., Dräger B., Schirmacher A., Heidbreder A. Specific T-cell activation in peripheral blood and cerebrospinal fluid in central disorders of hypersomnolence. Sleep. 2019;42:zsy223. doi: 10.1093/sleep/zsy223. - DOI - PubMed
35. Di Mauro P., La Mantia I., Cocuzza S., Sciancalepore P.I., Rasà D., Maniaci A., Ferlito S., Tundo I., Anzivino R. Acute Vertigo After COVID-19 Vaccination: Case Series and Literature Review. Front. Med. 2022;8:790931. doi: 10.3389/fmed.2021.790931. - DOI - PMC - PubMed
36. Ciorba A., Corazzi V., Bianchini C., Aimoni C., Pelucchi S., Skarżyński P.H., Hatzopoulos S. Autoimmune inner ear disease (AIED): A diagnostic challenge. Int. J. Immunopathol. Pharmacol. 2018;32:2058738418808680. doi: 10.1177/2058738418808680. - DOI - PMC - PubMed
37. García-Grimshaw M., Ceballos-Liceaga S.E., Michel-Chávez A., García-Alanis M., Cadena-Fernández A., Galnares-Olalde J.A., Carbajal-Sandoval G., Carrillo-García D.A., Hernández-Valdivia N., Hernández-Vanegas L.E., et al. Transient sensory symptoms among first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine: A case-control study. Vaccine. 2021;39:6975–6979. doi: 10.1016/j.vaccine.2021.10.058. - DOI - PMC - PubMed
38. Khayat-Khoei M., Bhattacharyya S., Katz J., Harrison D., Tauhid S., Bruso P., Houtchens M.K., Edwards K.R., Bakshi R. COVID-19 mRNA vaccination leading to CNS inflammation: A case series. J. Neurol. 2022;269:1006–1093. doi: 10.1007/s00415-021-10780-7. - DOI - PMC - PubMed
39. Etemadifar M., Sigari A.A., Sedaghat N., Salari M., Nouri H. Acute relapse and poor immunization following COVID-19 vaccination in a rituximab-treated multiple sclerosis patient. Hum. Vaccin. Immunother. 2021;17:348–383. doi: 10.1080/21645515.2021.1928463. - DOI - PMC - PubMed
40. Rao S.J., Sahiba Khurana S., Murthy G., Dawson E.T., Jazebi N., Haas C.J. A case of Guillain-Barre syndrome following Pfizer COVID-19 vaccine. J. Community Hosp. Intern. Med. Perspect. 2021;11:597–600. doi: 10.1080/20009666.2021.1954284. - DOI - PMC - PubMed
41. Pappaterra M.C., Rivera E.J., Oliver A.L. Transient Oculomotor Palsy Following the Administration of the Messenger RNA-1273 Vaccine for SARS-CoV-2 Diplopia Following the COVID-19 Vaccine. J. Neurophthalmol. 2021 doi: 10.1097/WNO.0000000000001369. ahead of print . - DOI - PMC - PubMed

42. de Medeiros A.L., Martins T., Kattah M., Soares A.K.A., Ventura L.O., Ventura C.V., Barros E. Isolated abducens nerve palsy associated with coronavirus disease: An 8-month follow-up. Arq. Bras. Oftalmol. 2021 doi: 10.5935/0004-2749.20220063. ahead of print . - DOI - PubMed
43. Avcı H., Karabulut B., Eken H.D., Faraşoğlu A., Çakil T., Çoruk S., Özel H., Kaya N.K., Özbalta S. Otolaryngology-Specific Symptoms May Be Highly Observed in Patients with a History of COVID-19 Infection After Inactivated Coronavirus Vaccination. Ear Nose Throat J. 2021 doi: 10.1177/01455613211028493. ahead of print . - DOI - PubMed
44. Shimohata T. Neuro-COVID-19. Clin. Exp. Neuroimmunol. 2021;13:17–23. doi: 10.1111/cen3.12676. - DOI - PMC - PubMed
45. Writing Committee for the COMEBAC Study Group. Morin L., Savale L., Pham T., Colle R., Figueiredo S., Harrois A., Gasnier M., Lecoq A.-L., Meyrignac O., et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA. 2021;325:1525–1534. - PMC - PubMed
46. García-Grimshaw M., Ceballos-Liceaga S.E., Hernández-Vanegas L.E., Núñez I., Hernández-Valdivia N., Carrillo-García D.A., Michel-Chávez A., Galnares-Olalde J.A., Carbajal-Sandoval G., Del Mar Saniger-Alba M., et al. Neurologic adverse events among 704,003 first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine in Mexico: A nationwide descriptive study. Clin. Immunol. 2021;229:108786. doi: 10.1016/j.clim.2021.108786. - DOI - PMC - PubMed
47. Walker J.L., Schultze A., Tazare J., Tamborska A., Singh B., Donegan K., Stowe J., Morton C.E., Hulme W.J., Curtis H.J., et al. Safety of COVID-19 vaccination and acute neurological events: A self-controlled case series in England using the OpenSAFELY platform. Vaccine. 2022;40:4479–4487. doi: 10.1016/j.vaccine.2022.06.010. - DOI - PMC - PubMed
48. Botton J., Jabagi M.J., Bertrand M., Baricault B., Drouin J., Le Vu S., Weill A., Farrington P., Zureik M., Dray-Spira R. Risk for Myocardial Infarction, Stroke, and Pulmonary Embolism Following COVID-19 Vaccines in Adults Younger Than 75 Years in France. Ann. Intern. Med. 2022;175:1250–1257. doi: 10.7326/M22-0988. - DOI - PMC - PubMed
49. Kelly J.D., Leonard S., Hoggatt K.J., Boscardin W.J., Lum E.N., Moss-Vazquez T.A., Andino R., Wong J.K., Byers A., Bravata D.M., et al. Incidence of Severe COVID-19 Illness Following Vaccination and Booster With BNT162b2, mRNA-1273, and Ad26.COV2.S Vaccines. JAMA. 2022;328:1427–1437. doi: 10.1001/jama.2022.17985. - DOI - PMC - PubMed
50. Beatty A.L., Peyser N.D., Butcher X.E., Cocohoba J.M., Lin F., Olgin J.E., Pletcher M.J., Marcus G.M. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. JAMA Netw. Open. 2021;4:e2140364. doi: 10.1001/jamanetworkopen.2021.40364. - DOI - PMC - PubMed
51. Aksoyalp Z.S., Nemutlu-Samur D. Sex-related susceptibility in coronavirus disease 2019 (COVID-19): Proposed mechanisms. Eur. J. Pharmacol. 2021;912:174548. doi: 10.1016/j.ejphar.2021.174548. - DOI - PMC - PubMed
52. Klein S.L., Marriott I., Fish E.N. Sex-based differences in immune function and responses to vaccination. Trans. R. Soc. Trop. Med. Hyg. 2015;109:9–15. doi: 10.1093/trstmh/tru167. - DOI - PMC - PubMed
53. Bianchi I., Lleo A., Gershwin M.E., Invernizzi P. The X chromosome and immune associated genes. J. Autoimmun. 2012;38:J187–J192. doi: 10.1016/j.jaut.2011.11.012. - DOI - PubMed
54. Gebhard C., Regitz-Zagrosek V., Neuhauser H.K., Morgan R., Klein S.L. Impact of sex and gender on COVID-19 outcomes in Europe. Biol. Sex Differ. 2020;11:29. doi: 10.1186/s13293-020-00304-9. - DOI - PMC - PubMed
55. Al-kuraishy H.M., Al-Gareeb A.I., Faidah H., Al-Maiahy T.J., Cruz-Martins N., Batiha G.E.-S. The looming effects of estrogen in COVID-19: A rocky rollout. Front. Nutr. 2021;8:649128. doi: 10.3389/fnut.2021.649128. - DOI - PMC - PubMed