Review 2: "Adverse effects and antibody titers in response to the BNT162b2 mRNA COVID-19 vaccine in a prospective study of healthcare workers"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

- This article is well-written and structured, but some fundamental information needs to be provided. For example, two important pieces of information regarding when, on average, participants received the two vaccine doses and when, after the vaccination, the determination of the antibody titers was performed should be clarified in the text. Is this period of time relatively homogeneous or are there large ranges of dates?
- The findings of the article are interesting even if their interpretation may be limited by the small sample size.
- The authors state that the study is prospective, which it is not. The study reported here is an observational study (retrospective for the data on vaccinations and perhaps for the data on antibody titers, and cross-sectional considering the symptoms' investigation).
- Seventy percent of the study's sample is made up of women and some symptoms are, not unexpectedly, more frequent in women.
- The study reports in the abstract and conclusions sections a result which is not supported by the study's findings: "This study also suggests that it may be possible to design future mRNA vaccines that confer robust antibody responses with lower frequencies of vaccine-associated symptoms. Indeed, emerging studies suggest the balance between vaccine immunogenicity and reactogenicity can be better tuned for COVID-19 mRNA-based vaccines as well (32)". I would suggest deleting this sentence.
- The results of the study are reliable and generally justified according to the methodology and data presented. Even considering the possible limitations, the data is in line with current scientific literature (i.e. a large variety of symptoms reported after COVID-19 vaccines are relatively frequent, there are no severe effects for the vast majority, and symptoms are more common after the second dose). I am not sure

about the finding related to a higher reporting of symptoms after vaccination in younger individuals, because, in this case, this result is a bit contradictory with the finding of no relations with antibody titers; we would expect a stronger immune response in younger adults compared to older subjects.

- Accordingly, the manuscript confirms previous work and contributes to the collection of evidence on COVID-19 mRNA vaccine-related adverse effects and antibody titers induced.
- Some recent and relevant papers already published on the topic are not considered; I suggest citing some of them and considering them in the discussion section of the results:

1) Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, Wellington E, Stowe J, Gillson N, Atti A, Islam J, Karagiannis I, Munro K, Khawam J, Chand MA, Brown CS, Ramsay M, Lopez-Bernal J, Hopkins S; SIREN Study Group. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet*. 2021 May 8;397(10286):1725-1735. doi: 10.1016/S0140-6736(21)00790-X.

2) Chapin-Bardales J, Gee J, Myers T. Reactogenicity Following Receipt of mRNA-Based COVID-19 Vaccines. *JAMA*. 2021 Jun 1;325(21):2201-2202. doi: 10.1001/jama.2021.5374.

3) Favresse J, Bayart JL, Mullier F, Dogné JM, Closset M, Douxflis J. Early antibody response in health-care professionals after two doses of SARS-CoV-2 mRNA vaccine (BNT162b2). *Clin Microbiol Infect*. 2021 May 8:S1198-743X(21)00224-X. doi: 10.1016/j.cmi.2021.05.004. Epub ahead of print.

4) Modenese, A.; Paduano, S.; Bargellini, A.; Bellucci, R.; Marchetti, S.; Bruno, F.; Grazioli, P.; Vivoli, R.; Gobba, F. Neutralizing Anti-SARS-CoV-2 Antibody Titer and Reported Adverse Effects, in a Sample of Italian Nursing Home Personnel after Two Doses of the BNT162b2 Vaccine Administered Four Weeks Apart. *Vaccines* 2021, 9, 652. <https://doi.org/10.3390/vaccines9060652>

5) Tré-Hardy M, Cupaiolo R, Papeux E, et al. Reactogenicity, safety and antibody response, after one and two doses of mRNA-1273 in seronegative and seropositive healthcare workers [published online ahead of print, 2021 Apr 1]. *J Infect*. 2021;S0163-4453(21)00158-4. doi:10.1016/j.jinf.2021.03.025

- 6) Padoan A, Dall'Olmo L, Rocca FD, Barbaro F, Cosma C, Basso D, Cattelan A, Cianci V, Plebani M. Antibody response to first and second dose of BNT162b2 in a cohort of characterized healthcare workers. *Clin Chim Acta*. 2021 Aug;519:60-63. doi: 10.1016/j.cca.2021.04.006.
- 7) Manisty C, Otter AD, Treibel TA, McKnight Á, Altmann DM, Brooks T, Noursadeghi M, Boyton RJ, Semper A, Moon JC. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. *Lancet*. 2021 Mar 20;397(10279):1057-1058. doi: 10.1016/S0140-6736(21)00501-8.
- 8) Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. *Eur Rev Med Pharmacol Sci*. 2021 Feb;25(3):1663-1669. doi: 10.26355/eurrev_202102_24877.