Clinical Characteristics of Healthcare Workers with SARS-CoV-2 Infection after Vaccination with BNT162b2 Vaccine

Andrea Lombardi (✉ andrea.lombardi@unimi.it)  
University of Milan

Giulia Renisi  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Dario Consonni  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Massimo Oggoni  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Patrizia Bono  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Sara Uceda Renteria  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Alessandra Piatti  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Angela Cecilia Pesatori  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Silvana Castaldi  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Antonio Muscatello  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Luciano Riboldi  
University of Milan

Ferruccio Ceriotti  
Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico

Andrea Gori  
University of Milan

Alessandra Bandera  
University of Milan

Research Article

Keywords: SARS-CoV-2, COVID-19, vaccination, symptoms, BNT162b2

Posted Date: August 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-778554/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Version of Record: A version of this preprint was published at BMC Infectious Diseases on January 28th, 2022. See the published version at https://doi.org/10.1186/s12879-022-07083-1.
Abstract

Background: The pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has hardly affected the entire world. Vaccines against COVID-19 appear as a tool able to curb out the mortality and to reduce the circulation of the virus. Little is known so far about the clinical characteristics of individuals who developed SARS-CoV-2 infection after having received the vaccination, as well as the temporal relationship between vaccine administration and symptoms onset.

Methods: Retrospective cohort study among the healthcare workers (HCWs) of the Fondazione IRCCS Ospedale Maggiore Policlinico of Milano, vaccinated with the BNT162b2 vaccine who developed SARS-CoV-2 infection (documented through positive RT-PCR on NPSs).

Results: Overall, we have identified 15 HCWs with SARS-CoV-2 infection after vaccination, 7 (46.7%) of them were male and the mean age was 38.4 years (SD 14). In 4 of them the presence of SARS-CoV-2 anti-nucleocapside (anti-N) antibodies was assessed before vaccination and resulted positive in 1 case. In all HCWs the presence of SARS-CoV-2 anti-spike (anti-S1) antibodies was assessed, in average 42.2 days after the completion of vaccination, with a mean value of 2,055 U/mL (SD 1,927.3). SARS-CoV-2 infection was ascertained in average 56.2 days after vaccination. The mean cycle threshold (Ct) of SARS-CoV-2 PCR was 26.4, the lineage was characterized in 9 HCWs. None of the HCWs reported a primary or secondary immunodeficiency. Regarding symptoms, they were reported only by 7 (46.7%) HCWs and appeared on average 55 days after the second dose of vaccination. Of those who reported symptoms, one (14.3%) had fever, 7 (100%) rhinitis/conjunctivitis, 4 (57.1%) taste and smell alterations, none had respiratory symptoms, 4 headache/arthralgia (57.1%) and 1 gastrointestinal symptoms (14.3%). All symptoms disappeared in a few days and no other unclassified symptoms were reported.

Conclusions: Infections occurring after vaccination with BNT162b2 vaccine are mostly asymptomatic and are not associated with the serum titre of anti-S1 antibodies. We did not find a predominance of a specific viral variants, with several lineages represented.

Background

The pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has hardly affected the entire world. Vaccines against COVID-19 appear as a tool able to curb out the mortality and to reduce the circulation of the virus. Consequently, mass vaccination campaigns are ongoing worldwide. Healthcare workers (HCWs) are a population who has been vaccinated early in the pandemic due to their high exposure to the virus, the corresponding elevated risk of infection and the possible role in spreading the disease. Little is known so far about the clinical characteristics of HCWs who developed SARS-CoV-2 infection after having received the vaccination, as well as the temporal relationship between vaccine administration and symptoms onset. To answer these questions, we conducted a retrospective study among the HCWs vaccinated with BNT162b2 who developed SARS-CoV-2 infection (documented through positive RT-PCR on NPSs) in a large university hospital, collecting their clinical characteristics.

Methods

All the HCWs of the IRCCS Ospedale Maggiore Policlinico, a university hospital in Milan, Italy, were offered the COVID-19 vaccination with BNT162b2 vaccine. Among the 3,622 HCWs, 3,219 (88.9%) received the full schedule, 170 (4.7%) received only the first shot and 233 (6.4%) were not vaccinated. The two prescribed shots were administered during the months of January and February 2021. The HCWs of our hospital who are working at direct contact with proven or possible COVID-19 patients are subject to mandatory surveillance NPS for SARS-CoV-2 every two weeks, irrespective of the presence of symptoms. We collected the demographic, clinical and virologic characteristics of those who had a positive NPSs in the period 01/03/2021-30/04/2021. For SARS-CoV-2 RNA detection was used the Alinity m SARS-CoV-2 assay on Alinity m (Abbott Molecular, IL, USA). The test is a rRT-PCR that allow simultaneous detection of RdRp and N genes. Serologic analyses were performed with two electrochemiluminescence immunoassay (ECLIA), Elecsys Anti-SARS-CoV-2 and Elecsys Anti-SARS-CoV-2 S on Cobas e801 (Roche Diagnostic, Mannheim, Germany) for the detection of total antibodies (including IgG) directed against SARS-CoV-2 nucleocapside (N) antigen and SARS-CoV-2 spike protein receptor-binding domain (RBD) respectively. Full genome sequences were obtained by amplifying using CleanPlex for SARS-CoV-2 Research and Surveillance NGS panel (Paragon Genomics, Hayward CA,USA). A library was prepared with the PCR products and sequencing was performed on Illumina MiSeq platform. The results were aligned to the reference genome NC_045512.2 by SOPHIA DDM software, v4 (SOPHIA GENETICS, USA). The software used to assign lineages to SARS CoV-2 sequences was Phylogenetic Assignment of Named Global Outbreak LiNeages (Pango COVID-19 Lineage Assigner). Descriptive statistics were obtained for all the variables collected, analyses were performed with Stata 17 (StataCorp. 2019). All the enrolled patients signed a written informed consent. The study protocol (#828_2021) was approved by the local (Milano Area 2) Ethics Committee.
Results

Overall, we have identified 15 HCWs with SARS-CoV-2 infection after vaccination, 7 (46.7%) of them were male and the mean age was 38.4 years (SD 14). In 4 of them the presence of SARS-CoV-2 anti-nucleocapside (anti-N) antibodies was assessed before vaccination and resulted positive in 1 case. In all HCWs the presence of SARS-CoV-2 anti-spike (anti-S1) antibodies was assessed, in average 42.2 days after the completion of vaccination, with a mean value of 2,055 U/mL (SD 1,927.3). SARS-CoV-2 infection was ascertained in average 56.2 days after vaccination. The mean cycle threshold (Ct) of SARS-CoV-2 PCR was 26.4, the lineage was characterized in 9 HCWs (Table 1).

None of the HCWs reported a primary or secondary immunodeficiency.

| ID | Age | Sex | Previous COVID-19 | Days between vaccination and serology | Anti-S1 antibodies (U/mL) | Days between vaccination and symptoms | Days between vaccination and positive swab | Ct | Lineage |
|----|-----|-----|-------------------|--------------------------------------|---------------------------|----------------------------------------|---------------------------------------------|----|---------|
| 1  | 29  | M   | unknown           | 24                                   | 2974                      | no symptoms                            | 36                           | 41  | unknown |
| 2  | 28  | F   | unknown           | 46                                   | 460                       | no symptoms                            | 29                           | 36.5| unknown |
| 3  | 29  | M   | no                | 82                                   | 866                       | 26                                     | 24                           | 21.8| B.1.351 |
| 4  | 28  | F   | unknown           | 63                                   | 3787                      | no symptoms                            | 29                           | 14.2| B.1.1.241|
| 5  | 60  | M   | unknown           | 36                                   | 353                       | 63                                     | 65                           | 16.5| C.36    |
| 6  | 28  | F   | unknown           | 35                                   | 3838                      | no symptoms                            | 72                           | 21.6| C.36    |
| 7  | 38  | F   | unknown           | 37                                   | 1902                      | 50                                     | 51                           | 17.8| P.1     |
| 8  | 22  | F   | unknown           | 65                                   | 1925                      | no symptoms                            | 66                           | 34.5| unknown |
| 9  | 46  | M   | no                | 34                                   | 637                       | 58                                     | 58                           | 16.6| B.1.1.7 |
| 10 | 31  | M   | unknown           | 36                                   | 1493                      | 34                                     | 35                           | 19.8| B.1.525 |
| 11 | 57  | M   | unknown           | 37                                   | 162                       | no symptoms                            | 70                           | 41.9| unknown |
| 12 | 39  | F   | yes               | 36                                   | >7500                     | 93                                     | 95                           | 39.6| unknown |
| 13 | 66  | M   | no                | 40                                   | 1115                      | no symptoms                            | 109                          | 20.4| C.11    |
| 14 | 48  | F   | unknown           | 28                                   | 2790                      | no symptoms                            | 49                           | 39.4| unknown |
| 15 | 26  | F   | unknown           | 34                                   | 1005                      | 55                                     | 55                           | 14.1| B.1.177.7|

CT: cycle threshold

Regarding symptoms, they were reported only by 7 (46.7%) HCWs and appeared on average 55 days after the second dose of vaccination. Of those who reported symptoms, one (14.3%) had fever, 7 (100%) rhinitis/conjunctivitis, 4 (57.1%) taste and smell alterations, none had respiratory symptoms, 4 headache/arthralgia (57.1%) and 1 gastrointestinal symptoms (14.3%). All symptoms disappeared in a few days and no other unclassified symptoms were reported (Table 2).
Table 2
Symptoms reported at time of positive nasopharyngeal swab in patients vaccinated with BNT162b2 with documented SARS-CoV-2 infection through positive RT-PCR.

| ID  | Symptoms | Fever | Rhinitis/Conjunctivitis | Taste/Smell alterations | Cough/dyspnoea | Headache/arthralgia | GI symptoms | Other |
|-----|----------|-------|-------------------------|-------------------------|---------------|---------------------|--------------|-------|
| 1   | no       | no    | no                      | no                      | no            | no                  | no           | no    |
| 2   | no       | no    | no                      | no                      | no            | no                  | no           | no    |
| 3   | yes      | no    | yes                     | yes                     | no            | yes                 | no           | no    |
| 4   | no       | no    | no                      | no                      | no            | yes                 | no           | no    |
| 5   | yes      | no    | yes                     | no                      | no            | yes                 | no           | no    |
| 6   | no       | no    | no                      | no                      | no            | yes                 | no           | no    |
| 7   | yes      | no    | yes                     | yes                     | no            | yes                 | no           | no    |
| 8   | no       | no    | no                      | no                      | no            | yes                 | no           | no    |
| 9   | yes      | no    | yes                     | no                      | no            | yes                 | yes          | no    |
| 10  | yes      | no    | yes                     | yes                     | no            | no                  | no           | no    |
| 11  | no       | no    | no                      | no                      | no            | no                  | no           | no    |
| 12  | yes      | no    | yes                     | no                      | no            | yes                 | no           | no    |
| 13  | no       | no    | no                      | no                      | no            | no                  | no           | no    |
| 14  | no       | no    | no                      | no                      | no            | no                  | no           | no    |
| 15  | yes      | yes   | yes                     | yes                     | yes          | no                  | no           | no    |

GI: gastrointestinal

Discussion

We have identified 15 HCWs who developed SARS-CoV-2 infection after complete vaccination schedule with BNT162b2 vaccine. Symptoms were reported by less than half of those included in the study, were mild, with only one case of fever, and disappeared quickly. The infections were detected through the mandatory surveillance system applied in our hospital, in average almost 2 months after the completion of the vaccination schedule.

The absence of important symptoms is a reassuring finding, which confirms the data about efficacy of the BNT162b2 vaccine in preventing the severe form of COVID-19 reported in the registration study. Intriguingly is the high incidence of rhinitis and conjunctivitis, which resulted the most frequently reported symptom. Conjunctivitis is usually reported in about 1% of COVID-19 patients, with a higher prevalence (3%) among severe cases. The expression on the conjunctiva of the entry receptor for SARS-CoV-2, ACE-2, is disputed, even though it has been shown how the inoculation in the ocular conjunctiva of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques. It is possible to speculate that the conjunctiva represents the site with the highest viral concentration in patients with the infection after vaccination, and this is reflected by the presence of a vigorous inflammatory response. Further studies are necessary to assess the concentration of immunoglobulins against SARS-CoV-2 in the ocular fluids after vaccination and their neutralizing activity.

Regarding the mean value of the serum anti-S1 antibodies, we observed in those who developed SARS-CoV-2 infection a value superior to the mean value of all the vaccinated HCWs of our hospital (1,577 U/mL) and also superior to the mean value of the vaccinated HCWs without a previous SARS-CoV-2 infection (1,374 U/mL). This suggest that the raw value of the anti-S1 antibodies cannot predict the future development of infection, the neutralizing activity of these antibodies could be a better tool to predict the efficacy of the humoral response.

Interestingly, we did not find a predominance of a specific viral variants, with several lineages represented. This is in accordance with published data, which highlighted a reduced but still efficacious immune response against viral variants in those vaccinated with BNT162b2, and suggest that the risk of infection after vaccination is not currently related to the viral genotype but to other variables yet to be uncovered.
A limitation of our study is the short observation time post-vaccination, restricted to two months, which led to the identification of 15 infections post-vaccination in a large cohort of HCWs. A longer observation time might have led to the identification of a higher number of cases, increasing the chance of also finding infections with severe clinical manifestations. Surveillance protocol is still ongoing in our hospital and further update on a longer observation time will be produced.

Conclusions

Infections occurring after vaccination with BNT162b2 vaccine are mostly asymptomatic and are not associated with the serum titre of anti-S1 antibodies.

Abbreviations

COVID-19: coronavirus disease 2019;
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2;
HCWs: Healthcare workers;
ECLIA: electrochemiluminescence immunoassay.

Declarations

Ethics approval and consent to participate

All the enrolled patients signed a written informed consent. The study protocol (#828_2021) was approved by the local (Milano Area 2) Ethics Committee.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

We declare that we have no conflicts of interest.

Funding

This study was partially supported by Ministry of Health RC 2021 and by Intesa San Paolo 2020 Fund. These funds covered the costs of laboratory consumables employed in the study.

Contributors

AL, DC and AG conceived the study. PB, SUR, DC, FC, MO collected the data. DC performed statistical analysis. AL and GR wrote the first draft of the manuscript. AL, DC, AG, PB, SURC, FC, MO, GR, AB, ACP, SC, AM, LR, AP reviewed the final version of the manuscript.

Acknowledgments

None.

References

1. Haas EJ, Angulo FJ, Mclaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel : an
observational study using national surveillance data. Lancet [Internet]. 2021;397(10287):1819–29. Available from: http://dx.doi.org/10.1016/S0140-6736(21)00947-8

2. Lombardi A, Bozzi G, Ungaro R, Villa S, Castelli V, Mangioni D, et al. Mini Review Immunological Consequences of Immunization With COVID-19 mRNA Vaccines: Preliminary Results. Front Immunol. 2021;

3. Lombardi A, Mangioni D, Consonni D, Cariani L, Bono P, Cantù AP, et al. Seroprevalence of anti-SARS-CoV-2 IgG among healthcare workers of a large university hospital in Milan, Lombardy, Italy: a cross-sectional study. BMJ Open [Internet]. 2021 Feb 22;11(2):e047216. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2020-047216

4. Rambaut A, Holmes EC, O’Toole Á, Hill V, McCrone JT, Ruis C, et al. Addendum: A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. Nat Microbiol [Internet]. 2021;6(3):415. Available from: http://dx.doi.org/10.1038/s41564-021-00872-5

5. Rambaut A, Holmes EC, O’Toole Á, Hill V, McCrone JT, Ruis C, et al. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. Nat Microbiol [Internet]. 2020;5(11):1403–7. Available from: http://dx.doi.org/10.1038/s41564-020-0770-5

6. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med [Internet]. 2020 Dec 31;383(27):2603–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33301246

7. Zhou L, Xu Z, Castiglione GM, Soiberman US, Eberhart CG, Duh EJ. ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection. Ocul Surf [Internet]. 2020;18(4):537–44. Available from: https://doi.org/10.1016/j.jtos.2020.06.007

8. Lange C, Wolf J, Auw-Haedrich C, Schlecht A, Boneva S, Lapp T, et al. Expression of the COVID-19 receptor ACE2 in the human conjunctiva. J Med Virol. 2020;92(10):2081–6.

9. Deng W, Bao L, Gao H, Xiang Z, Qu Y, Song Z, et al. Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques. Nat Commun. 2020;11(1):1–7.

10. Lombardi A, Consonni D, Oggioni M, Bono P, Renteria SU, Piatti A, et al. SARS-CoV-2 anti-spike antibody titres after vaccination with BNT162b2 in naive and previously infected individuals. J Infect Public Health [Internet]. 2021 Aug;14(8):1120–2. Available from: https://doi.org/10.1016/j.jiph.2021.07.005

11. Liu Y, Liu J, Xia H, Zhang X, Fontes-Garfias CR, Swanson KA, et al. Neutralizing Activity of BNT162b2-Elicited Serum. N Engl J Med [Internet]. 2021 Apr 15;384(15):1466–8. Available from: http://www.nejm.org/doi/10.1056/NEJMmc2102017