Clinical Microbiology and Infection 28 (2022) 305–307

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

SARS-CoV-2 infection despite high levels of vaccine-induced anti-Receptor-Binding-Domain antibodies: a study on 1110 health-care professionals from a northern Italian university hospital

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ARTICLE INFO

Article history:
Received 14 September 2021
Received in revised form
22 October 2021
Accepted 23 October 2021
Available online 29 October 2021

Editor: L. Leibovici

To the Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination campaigns are at an advanced stage in many countries, but few concerns have been raised about cases of post-vaccination infection [1]. Real-world data are needed to guide health-policy-makers, especially now that the implementation of a third-dose administration protocol is being discussed.

Thanks to a longitudinal study (Covidiagnostix), funded by the Italian Ministry of Health, we investigated the antibody response, over a 6-month period, in 1110 health-care professionals (HCPs) injected with both doses of the BNT162b2 vaccine (January–February 2021) at the San Raffaele Hospital in Milan, Italy.

Health-care professionals previously infected by SARS-CoV-2 were identified by testing their sera, a few minutes before the first vaccination dose (T_0), for the presence of antibodies against the viral nucleocapsid-protein (N) (Roche Anti-SARS-CoV-2 electrochemiluminescence immunoassay (ECLIA); Roche, Basel, Switzerland). They were further tested after 21 (T_1) (immediately before the second vaccination dose), 42 (T_2) and 180 (T_3) days for the presence of antibodies against the receptor-binding domain (RBD) of the viral spike (S) protein (Roche Anti-SARS-CoV-2-S ECLIA). As part of a follow-up programme, HCPs were also sporadically subjected to RT-PCR amplification tests of nasopharyngeal swabs as well as to serological tests at time-points different from those of the Covidiagnostix.

At T_0, 90 HCPs (8.2%) were anti-N seropositive and showed the previously observed exceptional anti-RBD titre increase at T_1 upon receiving the first dose [2]. The remaining 1020 seronegative HCPs showed the production of anti-RBD antibodies upon receiving the first dose (T_1), which was boosted by administration of the second dose (T_2) [2] and was followed by a decrease of approximately 70%, at T_3, in the majority of the HCPs ($n = 929$, 91.1%). The remaining group ($n = 91$, 8.9%) showing T_3 minus T_2 anti-RBD titres ≥ 0 was tested (T_3) for the presence of anti-N antibodies. Ten of them resulted positive, indicating post-vaccination infections. As a control group, 410 HCPs showing T_3 minus T_2 titres ≤ 0 were also tested for the presence of anti-N antibodies; all of them were negative and none showed a positive RT-PCR swab test. Two more HCPs who were infected after vaccination, showing T_3 minus T_2 titres <0 (Table 1, participants 11 and 12), were identified through post-vaccination RT-PCR swab tests. Their infections were confirmed by the detection of anti-N serum antibodies at T_3.

Eight HCPs infected after vaccination were female, aged 49.8 ± 6.8 years, and four were male, aged 55.5 ± 15.3 years (Table 1). One individual was infected between the first and second vaccine doses, nine were infected between 7 and 99 days after the second dose and two were oblivious to having being infected (Table 1). All the individuals were asymptomatic, except for four

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https://doi.org/10.1016/j.cmi.2021.10.010

Table 1
Demographic characteristics, serological results and COVID-19 related information of the 12 HCPs post-vaccination infected by SARS-CoV-2

Subject	Sex	Age (years)	Anti-RBD (BAU/mL)			PCR cycles[a]		Type of variant	2nd dose to infection interval (days)[b]	Symptoms	Close contacts[f]	Time length of negativization[c] (days)	HCP position
			T_1	T_2	T_3	RdRp gene	E Gene						
1	M	76	2.93	2122	>2500	22.9	20.9	B.1.1.7	64	Asymptomatic	Yes	21	Institutional Review Board
2	F	42	142	>2500	>2500	34.1	N/A	N/A	59	Asymptomatic	Yes	13	Psychologist
3	M	54	<0.4	196	897	25.6	24.2	N/A	69	Partial anosmia/ageusia	Yes	13	Nurse (Pediatric)
4	M	39	1019	1866	>2500	N/A	N/A	N/A	N/A [d]	Asymptomatic	No	?	Administrative
5	F	57	<0.4	2047	>2500	N/A	N/A	N/A	N/A [d]	Asymptomatic	No	?	Administrative
6	F	55	208	>2500	>2500	N/A	N/A	N/A	<0[e]	Asymptomatic	No	?	Nurse (Infectious Diseases)
7	F	49	77.5	>2500	>2500	22.3	22.1	B.1.1.7	67	Partial anosmia/ageusia, cold, generalized pain	Yes	13	Nurse (Psychiatry)
8	M	53	0.79	339	>2500	223.1	23.5	B.1.1.7	84	Asymptomatic	No	16	Technician (Echography)
9	F	42	18.5	1131	>2500	30.8	31.8	N/A	42	Asymptomatic	Yes	14	Nurse (Psychiatry)
10	F	55	76.3	2046	>2500	30.1	30.3	N/A	99	Partial anosmia/ageusia, cold	Yes	22	Technician (Pathological Anatomy)
11	F	42	50.1	>2500	2495	21.4	20.8	N/A	14	Partial anosmia/ageusia, cold	Yes	14	Nurse (General medicine)
12	F	56	5.7	1066	714	28.1	27.8	N/A	7	Asymptomatic	Yes	17	Nurse (Cardiology Department)

[a] Values refers to the first positive swab test. Values were considered: positive (between 14 and 34) slightly positive (between 34 and 40), negative (>40).
[b] Intervals are calculated from the day of the 2nd dose to the day of the first positive RT-PCR test.
[c] Time length of negativization was calculated from the day of the first positive RT-PCR test to the day of the first negative RT-PCR test.
[d] COVID-19 was asymptomatic and the HCPs found out about the infection only through the serological test at T_3.
[e] Positivity was discovered by an occasional anti-N test performed at T_1.
[f] "Close contacts" refers to the presence of a SARS-CoV-2 positive unvaccinated household at the time of infection.

who reported partial anosmia and ageusia accompanied, in three cases, by a mild cold and, in one of those three cases, by a generalized pain (Table 1). The possibility of an in-hospital outbreak was ruled out because the 12 HCPs perform, within the hospital, different tasks (Table 1) with the exception of two nurses from the Psychiatric Department, but they were infected 1 month apart. Notably, 8 out of 12 HCPs infected after vaccination reported the presence of a SARS-CoV-2-positive family member (not vaccinated) as the potential source of infection (Table 1).

Reduced vaccination efficiency has been observed in older individuals (>60 years old) [2], but the 12 HCPs were between 39 and 57 years old, except for one who was 76 years old. Seven of the individuals had anti-RBD titres at T_2 above 2000 binding antibody units (BAU)/mL, three were between 1000 and 2000 BAU/mL and only two had titres below 400 BAU/mL (Table 1). An anti-RBD titre threshold of approximately 1300 BAU/mL was associated with neutralizing activity as previously described by Ferrari et al. [3]. Although the latter is not the only correlate for vaccine efficacy, with memory B and T cells possibly playing a key role in protection, we would have expected a better consistency between high anti-RBD antibody serum levels and protection from infection. These data further highlight the difficulty of finding a reliable and unique correlate of protection by assessing only the serum neutralizing antibody titres. It must be noted that two HCPs (individuals 3 and 5) did not respond to the first vaccine dose and showed T_1 anti-RBD titres <0.4 U/mL (Table 1).

In conclusion, 6 months after the vaccination of 1110 HCPs, 12 of them were infected despite receiving the proper BNT162b2 administration protocol (except for one, who was infected between the two doses). However, because some of the HCPs did not undergo anti-N serological testing, the number of infections might be underestimated. Post-vaccination infections, distributed throughout the whole observation period, were often associated with the presence of unvaccinated SARS-CoV-2-infected households. Importantly, no in-hospital (or related public areas) secondary cases were observed among colleagues (>95% of the San Raffaele Hospital employees were vaccinated). Our study showed that, in the observed cohort of HCPs, no severe clinical manifestations of coronavirus disease 2019 occurred. We might speculate that the latter is the consequence of the efficacy of the BNT162b2 vaccine, but infection and symptomatology were not related to a low anti-RBD antibody response. In the light of these data, we think that implementation/modification of current vaccine protocols should focus on further studies evaluating clinical outcomes in individuals who are infected after vaccination, their anti-RBD antibody titre and, importantly, the possible key role of memory immunity in the protection from severe coronavirus disease 2019.

Transparency declaration

The authors declare that they have no conflicts of interest.

Author contributions

DF designed the study, performed the data analysis and interpretation and wrote the article; NC, NM and ML wrote the article and supervised the study.

Funding

This project was supported by the Ministry of Health of Italy, '*Bando Ricerca COVID-19*'; project number: COVID-2020-12371619; project title: COVIDIAGNOSTIX—Health Technology Assessment in Covid serological diagnostics.

Statement on research ethics

The COVIDIAGNOSTIX study was approved by the San Raffaele Hospital Institutional Ethical Review Board (CE:199/INT/2020).ht.

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