

Are people previously infected with SARS-CoV-2 likely to experience COVID-19 symptoms again after vaccination? Results from an Italian COVID-19 referral center

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To the Editor,

Once approved by the US Food and Drug Administration and the European Medicines Agency, the first dose of the mRNA-based vaccine BNT162b2 (Pfizer-BioNTech) have been administered in Italy on December 27, 2020.

However, despite the excitement and anticipation positively affecting the health-working community and the population, questions on the safety of these much anticipated, fast-tracked vaccines have been raised.

On a brighter side, data from C4591001 Study have suggested a favorable safety profile for the BNT162b2, with mild-to-moderate and self-limited local reactions and systemic events.¹ Along with the beginning of vaccination programmes, *ad hoc* national pharmacovigilance systems have been implemented worldwide. In Italy, 1,550,019 doses of BNT162b2 have been administered during the first month of vaccination and the Adverse Event Following Immunization (AEFI) cumulative rate was 471 reports/100,000 doses, mostly mild. Overall, only 14 cases of anaphylaxis and 18 cases of Bell's palsy have been reported.² These findings match larger US and UK data sets which confirmed the rarity of the BNT162b2 vaccine-related anaphylaxis.^{3,4}

These data corroborate the absence of severe vaccine-induced allergic events. Nevertheless, there is initial evidence that the vaccine reactogenicity might be more pronounced in individuals who recovered from SARS-CoV-2 infection, who have reported a higher frequency of systemic COVID-19-like symptoms, such as fever, chills and diffuse polymyalgia.⁵ Hence, although the Advisory Committee on Immunization Practices recommended to offer vaccination regardless of the preexisting natural immunity,⁶ it is currently debated whether individuals who were previously infected with COVID-19 should receive the two scheduled doses of BNT162b2 vaccination, or only the first one, or none at all. In addition, the possibility that a single vaccine dose could elicit a robust antibody response in these individuals makes it even more unclear which approach should be adopted.⁷ This is especially true in European, suboptimal vaccine availability scenario.⁸

In an attempt to shed light on this timely and important topic, we here analyze the cohort of health-care workers (HCWs) who underwent two doses of BNT162b2 between

December 27, 2020 and February 9, 2021 in our Hospital, Fondazione IRCCS Policlinico San Matteo of Pavia, a national SARS-CoV-2 referral center in Northern Italy.

In November 2020, before the start of the national vaccination campaign, we conducted a seroprevalence study of SARS-CoV-2 antibodies in the HCWs of our Hospital on a voluntary basis. In order to identify those HCWs with SARS-CoV-2 previous infection, the Elecsys Anti-SARS-CoV-2 assay has been performed.

Four boxes in our Infectious Diseases outpatient clinic were each equipped with a doctor and a specialist nurse, who administered the vaccine to the entire HCWs, working unceasingly every day of the following week, 8 hours a day. Moreover, a specialist in anesthesiology and reanimation was recruited in specific days, as a precautionary measure for potential allergic reactions in poliallergic HCWs.

After the vaccine was administered, every HCW was kept in a waiting area for 15 minutes, in order to intercept eventual fast AEFI.

Moreover, every HCW was requested to report any adverse effect occurred in the following minutes, hours or days. For that purpose, a dedicated telephone number had been set up.

Finally, due to the lack of spontaneous reporting, which might have driven to an underestimation of the possible counter-effects of the vaccine, every HCW was interviewed right before their second vaccine dose injection was scheduled, in order to retrieve any AEFI which were potentially overlooked after their first dose.

Our first aim was to investigate whether a previous SARS-CoV-2 exposure might have an impact on the arising of vaccine-induced AEFI. Our second hypothesis was that SARS-CoV-2 antibody titer might be directly correlated to the higher frequency of COVID-like symptoms.

At the time of writing, a total of 4189 HCWs of our Hospital have completed the two BNT162b2 doses and, among these, 555 (13.1%) had previously infected by SARS-CoV-2.

A total of 224 AEFI was reported. The majority of HCWs who experienced AEFI were females, with a mean age of 46 years old.

Characteristics of our cohort of HCWs who experienced AEFI are shown in [Table 1](#).

We divided the reported AEFI in three main groups: local (such as pain in the injection site), COVID-like (such as fever,

Table 1. Characteristics of HCWs who experienced AR after the first, second and both doses of BNT162b2 vaccine and characteristics of the reported AEFI.

	n (%)	Number of BNT162b2 vaccine doses				p-value
		First (n = 75)	Second (n = 138)	Both (n = 11)	Total (n = 224)	
Gender	M	26 (34.7)	26 (18.8)	1 (9.1)	53 (23.7)	
	F	49 (65.3)	112 (81.2)	10 (90.9)	171 (76.3)	<.01
Age	Mean (SD)	47.1 (10.7)	44.9 (11.5)	49.4 (12.2)	45.9 (11.3)	.17
Previous COVID-19	No	28 (37.3)	110 (79.7)	4 (36.4)	142 (63.4)	
	Yes	47 (62.7)	28 (20.3)	7 (63.6)	82 (36.6)	<.01
Local reactions		23 (30.7)	32 (23.2)	4 (36.4)	59 (26.3)	.31
COVID-like symptoms		65 (86.7)	136 (98.6)	11 (100)	212 (94.6)	<.01
Fatigue		20 (26.7)	32 (23.2)	4 (36.4)	56 (25.0)	.69
Cephalgia		19 (25.3)	73 (52.9)	6 (54.5)	98 (43.8)	<.01
UA symptoms		4 (5.3)	4 (2.9)	3 (27.3)	11 (4.9)	.65
Chest pain		4 (5.3)	4 (2.9)	1 (9.1)	9 (4.0)	.61
GI symptoms		17 (22.7)	40 (29.0)	3 (27.3)	60 (26.8)	.43
Lymphomegaly		9 (12.0)	22 (15.9)	0 (0.0)	31 (13.8)	.56
Allergic reactions		24 (32.0)	38 (27.5)	2 (18.2)	64 (28.6)	.59
Skin rash		19 (25.3)	6 (4.3)	5 (45.5)	30 (13.4)	<.01
Respiratory symptoms		2 (2.7)	0 (0.0)	1 (9.1)	3 (1.3)	.22

UA = Upper airways; GI = Gastrointestinal. Reported AEFI were divided in three main groups (highlighted in bold font).

* p-value were obtained only from comparisons between the first and second dose.

fatigue, cephalgia, lymphomegaly, gastrointestinal and upper-airways symptoms) and allergic reactions (skin rash and respiratory symptoms).

Overall, 212 HCWs experienced COVID-like symptoms, 64 experienced allergic reactions and 59 had injection site symptoms after the first or the second vaccine dose, while only 11 HCWs had any AEFI both after the first and the second vaccine dose. Some of the HCWs experienced multiple AEFI at once. Specifically, 20 HCWs had both allergic and COVID-like symptoms after the first or the second vaccine doses.

Remarkably, COVID-like symptoms occurred more frequently after the second than after the first dose ($\chi^2_{2df} = 3.506, p < .01$).

To firstly explore the hypothesis that previous SARS-CoV-2 infection might have an impact on the rate of vaccine-induced reactions, a χ^2 analysis was performed. Interestingly, our results strongly confirmed the hypothesis: 75 out of 555 HCWs with a history of SARS-CoV-2 infection had COVID-like symptoms after the first or the second vaccine dose, whereas only 134 out of 3634 HCWs without history of SARS-CoV-2 infection had the same outcome ($\chi^2 = 3.456, p < .01$). Furthermore, in order to meet our second aim and verify the hypothesis that SARS-CoV-2 antibody titer would be directly correlated to COVID-like symptoms frequency, we selected HCWs with previous SARS-CoV-2 infection and we performed a t-test to assess if a higher antibody titer was associated with a higher likelihood of having COVID-like symptoms. The result of this analysis upheld our hypothesis ($t(df) = 1234, p = .025$).

To our knowledge, this is the first report of BNT162b2-induced AEFI in previously SARS-CoV-2 infected individuals in the European scenario.

We believe that it might be recommended to inform all the individuals to be vaccinated about the risk of suffering such reactions, especially if they have been previously infected with SARS-CoV-2. Furthermore, although we should not rush to conclusions, our results offer an interesting perspective in exploring the potentially, yet to be confirmed option of deferring vaccination in such individuals, also considering the slow progression of our vaccination campaign.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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