BRIEF REPORT

Effect of Previous SARS-CoV-2 Infection on Antibody Response to a Single Immunization with the Pfizer BNT162b mRNA Vaccine Among Healthcare Workers in Foggia, Italy

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ABSTRACT

Introduction: Data have suggested that SARS-CoV-2 infection causes an antibody response at least as strong as one BNT162b2 vaccine dose. Nevertheless, some aspects require further investigation to better understand the immunogenicity of one vaccine dose among infected individuals. Thus, we evaluated how

previous SARS-CoV-2 infection may influence the humoral immunity after a single Pfizer BNT162b mRNA vaccine dose in a sample of healthcare workers (HCWs).

Methods: As part of the routine surveillance activity conducted among HCWs of the Policlinico Riuniti Foggia Hospital (Apulia region, Italy), we conducted a retrospective serosurvey in the period January–March 2021. We compared specific antibody titres (anti-spike IgGs measured by enzyme-linked immunoassay, ELISA) after SARS-CoV-2 infection and after the first dose of the BNT162b2 vaccine, analysing the impact of sex, age, time since infection, and presence of symptoms on the humoral response.

Results: We included in the study 58 HCWs (mean age 44.1 years, 48.2% male) with anti-spike IgG titres available before and after the first BNT162b2 vaccine dose. Among these, we observed higher titres in previously infected cases ($N = 21$) than in COVID-19-naïve subjects ($N = 37$) (medians 1510 vs. 0.68; $p < 0.001$). A statistically significant difference in anti-spike IgG titres was also observed among previously infected HCWs before vaccine dose in comparison with post-dose infection-naïve HCWs (medians 18.37 vs. 0.68, $p < 0.001$). Among infected individuals, no differences by sex, age, or time since infection were reported ($p > 0.05$). Post-dose titres of symptomatic and asymptomatic infected HCWs slightly differed (medians = 1900 vs. 1090; $p = 0.048$).

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Conclusion: Our data support the viable hypothesis of a single-dose vaccine regimen in individuals with a history of COVID-19, but no conclusion on duration of protection in this group can be drawn from our study.

Keywords: SARS-CoV-2; COVID-19; Serological testing; Vaccination; Immune response

Key Summary Points

The choice to prioritize administering vaccines to those who have not been infected before remains a challenging public health decision.

COVID-19 infection causes an antibody response that is as strong as one BNT162b2 vaccine dose.

Among infected individuals, vaccine humoral response does not depend on the time since infection but is stronger in symptomatic individuals.

A single-dose vaccine regimen may be a viable hypothesis in individuals with a history of COVID-19, but no conclusion on duration of protection in this group can be drawn from our study.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first confirmed in December 2019 in Wuhan, China. As of June 2021, over 200 million people were recorded to have contracted COVID-19, and over 4 million died from the disease [1]. The first year of the COVID-19 pandemic was characterized by multiple waves and a patchwork of containment measures. Lockdowns controlled the pandemic to some extent, but at a high societal cost [2]. In such a context, anti-COVID-19 vaccinations have been crucial to limit COVID-19-related deaths and morbidity [3]. The administration of the first dose of the BNT162b2 mRNA

COVID-19 vaccine (Pfizer-BioNTech, Mainz, Germany) started in late 2020, and the first results of effectiveness in preventing COVID-19 infection, severe disease, and death [4] are in line with the efficacy trials [5].

The immune protection against COVID-19 after vaccination depends on multiple factors [6]. Although the level of antibodies in the blood does not directly translate into known correlates of protection, some early data suggested that COVID-19 infection causes an antibody response that is at least as strong as a single vaccine dose [7–11]. However, findings on COVID-19-induced protective immunity are not consistent across studies [12]. If natural immunization achieved after SARS-CoV-2 infection was comparable to the protection induced by one vaccine dose, postponing vaccination or delaying the second vaccine could have important implications for the optimization of vaccination programs worldwide [13].

Although the impacts of age, gender and ethnicity on the immune response of naïve and infected individuals before and after the first vaccine dose have already been investigated [6], the potential implications of disease severity [12, 14] and the time between infection and the first dose remain unclear [15]. Thus, several aspects require further investigation to better understand the level of protection of one vaccine dose among infected individuals. We evaluated the effect of previous SARS-CoV-2 infection on the humoral immunity acquired after a single Pfizer BNT162b mRNA vaccine dose in healthcare workers (HCWs). We also emphasize the impact of time since infection alongside infection severity.

METHODS

We describe a retrospective serosurvey study conducted in the Policlinico Riuniti Foggia Hospital (District of Foggia, Apulia region, Italy) after the start of the COVID-19 vaccination campaign (January–March 2021). We reported pre- and post-first dose antibody levels in a sample of HCWs stratified by SARS-CoV-2 infection. Furthermore, among the subgroup of infected individuals, antibody levels are

reported by sex, age, days between infection and first dose, and the presence of symptoms.

The BNT162b2 mRNA vaccine from Pfizer-BioNTech has been the main COVID-19 vaccine dispensed in Italy. As of 28 March 2021, 2.98 million vaccine doses were administered to HCWs, 93.3% of which BioNTech-Pfizer, 4.4% Oxford–AstraZeneca and 2.2% Moderna vaccines [16]. Policlinico Riuniti is the main hospital in the Foggia District; it serves over 600,000 inhabitants and has a capacity of 880 beds, of which 75 were allocated to the intensive care unit. Over 3700 HCWs of the hospital were offered BNT162b2 since 27 December 2020, and as of 31 March 2021, at least 90% of them had received at least one dose (hospital data).

Before the anti-COVID-19 vaccines became available, all HCWs were routinely invited by the hospital to undergo testing rounds of serological screening (about one round every 1.5 months). Enzyme-linked immunoassay (ELISA) was used for the analysis of blood samples to detect the presence of SARS-CoV-2 IgG antibodies. Anti-spike IgGs were obtained using chemiluminescence immunoassay DiaSorin LIAISON® SARS-CoV-2 S1/S2 IgG. Individuals with a positive serological test or suspected exposure to the SARS-CoV-2 virus were tested by polymerase chain reaction (PCR) on nasopharyngeal swabs.

As part of this surveillance activity, post-first dose IgG anti-spike antibody levels were measured in a sample of previously confirmed cases and COVID-19-naïve subjects. Measurements were performed at least 21 days after receiving the first BNT162b2 vaccine dose, before receiving the second vaccine dose. These screening data were used for the investigation, and infected or naïve HCWs were included in the study if both pre- and post-dose serological tests were available. For pre-dose evaluation, antibody levels measured at least 21 days after infection were used for COVID-19-positive subjects, whereas the most recent sample was used for naïve subjects (Fig. 1).

For descriptive tables, figures and analyses, R-studio software was used. We reported IgG medians and the Q1 and Q3 values by COVID-19 status and further stratified positive subjects by age, sex, time between infection and

vaccination, and presence/absence of symptoms during infection. In this study, symptoms were pooled regardless of their severity [17].

We compared antibody titres post-first dose between previously confirmed cases and COVID-19-naïve subjects. We also compared titres between SARS-CoV-2-infected HCWs before the first vaccine dose (pre-dose) and naïve HCWs after the first dose (post-dose). Additionally, among infected HCWs, post-dose titres were compared by sex and age subgroups (female vs. male and < 50 vs. ≥ 50 years of age, respectively), by the time between infection and first dose (< 6 months vs. ≥ 6 months) and by presence/absence of symptoms. The 6-month limit to categorize the time between infection and first dose was adopted in accordance with the initial Italian Ministry of Health recommendation of a single dose within 6 months if there was PCR evidence of a previous infection, regardless of symptom manifestation [17]. Finally, we compared post-dose titres between asymptomatic and naïve HCWs. For comparisons, a normality test was performed (Shapiro–Wilk test of normality < 0.05) to determine the appropriate statistical test. We tested differences between groups using the Mann–Whitney U test. We also visualized groups by violin-boxplots with medians, Q1 and Q3 on a $\log_{10}$ scale.

Compliance with Ethics Guidelines

As this study was conducted within the public health surveillance program established by the Ministry of Health, ethical approval was not required. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Moreover, according to the Italian regulation (DETERMINAZIONE AIFA-20 marzo 2008, GU n. 76 del 31-3-2008), this retrospective epidemiological study had only to be notified to the Regional Public Health Authority for the nature of the study itself. Informed consent was not obtained from participants because

Fig. 1 Schematic chart displaying the timeline of sample collection from COVID-19 positive and negative HCWs of Policlinico Riuniti Foggia Hospital

surveillance data and molecular and antibody testing were retrieved and analysed anonymously.

RESULTS

Titres before the administration of the first dose of BNT162b2 (pre-dose titres) were available for 3211/3733 (86%) HCWs. Titres after receiving the first vaccine dose (post-dose titres) were available for 58 HCWs (Fig. 2) that were included in the study. Of these, 37 were naïve and 21 had a previous PCR-confirmed SARS-CoV-2 infection (Fig. 2). The average age was 44.1 years (range 24–68); 48.2% of the participants were male. Results of the paired IgG titre samples of HCWs pre- and post-dose are summarized in Table 1.

Post-first dose antibody titres were higher in previously confirmed cases than in COVID-19-naïve subjects (medians 1510 vs. 0.68; $p < 0.001$). A statistically significant difference between IgG titres of infected HCWs pre-dose and naïve HCWs post-dose (medians 18.37 vs. 0.68; $p < 0.001$) was also found (Table 1 and Fig. S1). Post-dose titres among infected HCWs did not vary by sex (medians 1510 in men vs. 1115 in women; $p = 0.7$) or age (medians 1650

in < 50 years vs. 1320 ≥ 50 years; $p = 0.855$) (Table 1 and Figs. S2, S3). Post-dose titres among infected HCWs with an infection more or less than 6 months before the first dose were similar (medians 2005 vs. 1250; $p = 0.154$) (Table 1 and Fig. S4). In this study, COVID-19 symptoms were pooled, and the majority were mild or moderate, such as headache, fatigue and muscle pain with few HCWs reporting low grade fever. Post-dose titres of symptomatic and asymptomatic infected HCWs differed (medians = 1900 vs. 1090; $p = 0.048$) (Table 1 and Fig. S5). The titres in asymptomatic HCWs remained two log-scale magnitudes higher than in those who were naïve (median = 1090 vs. 0.68; $p < 0.001$).

DISCUSSION

In this retrospective study we describe how a previous COVID-19 infection may elicit strong antibody responses after the first dose of BNT162b2 vaccine, with no apparent relation to age, sex, time since infection, and presence of symptoms. More specifically, we found that, after a single dose, previously infected individuals showed IgG titres substantially higher than the naïve ones. Other studies have found that

Fig. 2 Study flowchart displaying the inclusion of COVID-19-positive and COVID-19-negative HCWs in the study. Policlinico Riuniti Foggia Hospital (District of Foggia, Apulia region, Italy), January–March 2021

after a single dose of mRNA vaccine, individuals with a history of COVID-19 had high levels of the receptor-binding domain (RBD) IgG and a higher neutralizing activity of the spike–ACE2 interaction than naïve subjects [7–11, 18, 19]. A very recent large national cohort study showed that prior SARS-CoV-2 infection is associated with a lower risk for breakthrough infection among individuals receiving the full schedule of mRNA vaccines [20]. Furthermore, we found that previously infected individuals showed pre-vaccine IgG titres substantially higher than the naïve ones after a single dose. These findings may suggest that their naturally acquired immunity might provide some degree of

protection, confirming that a single dose [21] could be a viable hypothesis in previously SARS-CoV-2-infected individuals.

However, several key questions remain unanswered as the duration and mechanism of the protection have not been fully clarified yet. Some of the main uncertainties concern whether the severity of the past infection is a decisive factor or not, and how long the natural immunity may last. It has been reported that levels of anti-SARS-CoV-2 serum antibodies decrease rapidly in the first few months after infection, raising concerns that long-lived bone marrow plasma cells may not be generated [22, 23]. Therefore, specific humoral immunity

Table 1 Median antibody titres in Italian healthcare workers before and after the first dose of the BNT162b2 anti COVID-19 vaccine

COVID-19	N	Pre-dose			Post-dose			Comparison	p value
		Median titre	Q1	Q3	Median titre	Q1	Q3		
Negative	37	0.47	0.21	3.8	0.68	0.23	30	COVID positive post-dose vs. COVID negative post-dose	< 0.001
Positive ^a	21	18.37	12.3	62.91	1510	384	2200	COVID positive pre-dose vs. COVID positive post-dose	< 0.001
<i>Total</i>	<i>58</i>	<i>3.8</i>	<i>0.3</i>	<i>12.7</i>	<i>48.2</i>	<i>0.4</i>	<i>1090</i>		
Sex (COVID-19 positive ^a)									
Female	10	39.8	13.82	63.35	1515	386.5	2100	Positive post-dose	0.7
Male	11	14.33	12.49	50.38	1510	736	2130	Male vs. female	
Age (COVID-19 positive ^a)									
< 50 years	12	26.04	13.55	55.55	1650	383.8	2075	Positive post-dose	0.855
≥ 50 years	9	14.33	12.3	62.91	1320	394	2200	< 50 vs. ≥ 50 years	
COVID-19 positive ^a , months between infection and first dose									
< 6 months ^b	15	33.7	12.05	58.2	1250	383.5	1910	Positive post-dose	0.154
≥ 6 months ^c	6	14.1	13	50.77	2005	1435	2237.5	< 6 vs. ≥ 6 months	
COVID-19 positive ^a , symptoms									
No	15	18.37	12.49	50.4	1090	362	2000	Positive post-dose	0.048
Yes	6	38.62	12.81	2,200	1900	1585	2177.5	Yes vs. no	

Policlinico Riuniti Foggia Hospital (District of Foggia, Apulia region, Italy), January–March 2021

^aCases were confirmed by PCR

^bMedian time between infection and first dose 96 days (range 39–89 days)

^cMedian time between infection and first dose 291 days (range 258–301)

may be short-lived, especially in people recovered from asymptomatic or mild disease [12, 23–25]. In our study, the post-dose titres of symptomatic vs. asymptomatic infected HCWs were slightly higher, confirming that asymptomatic recovered individuals might have a lower degree of protection. However, in our small population, not only the HCWs with mild-to-moderate symptoms but also the infected asymptomatic HCWs showed two log-scale magnitude higher IgG levels than in those who were naïve.

Interestingly, we also found that previously infected HCWs attained high IgG antibody

titres after one dose regardless of whether they were infected in the previous 6 months or earlier. This finding, consistent with the observation that immune response is maintained even 6 months after the infection and rapidly enhanced after just one dose of mRNA vaccine [26–29], is strongly suggestive that individuals who are infected with SARS-CoV-2 could mount a rapid and effective response to the virus upon re-exposure [23]. In this sense, observational studies have described low rates of reinfection among previously infected individuals [30].

However, our results should be cautiously transferred to the general population because of

the small sample of HCWs included in the study, mostly under the age of 65, that did not allow for adjusted analyses. Of note, information on comorbidities was not available for the analysis. Furthermore, since this is an observational study, we did not have precise control over the vaccination protocol and timing of blood sampling. Even though we can confirm that no reinfection was observed among positive individuals vaccinated with one dose, a longer-term formal follow-up could have provided additional information regarding the duration of immunity acquired from receiving a single dose versus a double dose of vaccine [7]. Limitations also include the lack of neutralization assays, and the lack of T cell response studies, especially considering the hypothesis that the neutralizing antibody after vaccination might be a marker of overall immune response [31].

CONCLUSIONS

If the choice to prioritize administering vaccines to those who have not been infected before remains a challenging public health decision, our findings seem to support the viable hypothesis of a single-dose vaccine regimen in individuals with a history of COVID-19. However, in the absence of known correlates of protection, further studies are needed to transfer these results to the wider population, especially regarding the time since infection and the presence of symptoms.

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Disclosures. Tobias Homan, Francesca Fortunato, Gaetano Corso, Pierluigi Lopalco, Rosa Prato and Domenico Martinelli all have nothing to disclose.

Compliance with Ethics Guidelines. As this study was conducted within the public health surveillance program established by the Ministry of Health, ethical approval was not required. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Moreover, according to the Italian regulation (DETERMINAZIONE AIFA-20 marzo 2008, GU n. 76 del 31-3-2008), this retrospective epidemiological study had only to be notified to

the Regional Public Health Authority for the nature of the study itself. Informed consent was not obtained from participants because surveillance data and molecular and antibody testing were retrieved and analysed anonymously.

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

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