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Short communication

Second dose of the BNT162b2 mRNA vaccine: Value of timely administration but questionable necessity among the seropositive

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ABSTRACT

This study monitored titers of neutralizing IgG against the receptor-binding domain of the SARS-CoV-2 S1 subunit 14 days post-injection of each dose of the BNT162b2 mRNA Covid-19 vaccine in 401 Greek healthcare workers aged 20–67. After the first dose, titers varied upon age and history of infection, being lower in the 50+ age group and significantly higher among the seropositive. After the second dose, immunogenicity was significantly boosted in the age 50+ and SARS-CoV-2-naïve individuals, indicating the effectuality of its timely administration, yet questioning its value among the seropositive.

1. Introduction

To address current deficits in vaccine supplies and dissemination, experts have contemplated novel vaccination regimens, such as delaying administration of the second dose [1] or even omitting it among previously-infected subjects [2]. Although the former practice has been abandoned due to compromised vaccine effectiveness [3] and increased risk of new variant emergence [4], the latter gains momentum [5]. We sought to assess the viability of these alternatives, conducting a phase IV immunogenicity study on the BNT162b2 mRNA Covid-19 vaccine. Launched by Pfizer-BioNTech, this vaccine was the first to receive FDA and EMA approval, displaying 95% efficacy in pre-marketing clinical trials [6]. Latest real-world evidence confirms its high effectiveness, reaching 94% for symptomatic Covid-19 [7] and attests to its robust immunogenicity in 92% of recipients [8,9]. Antibody generation was found significantly pronounced among previously-infected convalescent subjects in the aftermath of the first dose, questioning the necessity of a booster dose to those individuals [2,5]. The aim of the present study was to provide a comprehensive analysis of the humoral immune responses of 401 vaccinees to both doses of the BNT162b2, laying emphasis on certain subgroups of interest, including seniors and seropositive individuals.

2. Materials and methods

2.1. Enrolment and methods

In our study, we measured the generation of antibodies elicited 14 days post-injection of each dose of the BNT162b2 mRNA vaccine in Greek healthcare workers aged 20–67. In the first phase of our study, antibody levels were monitored in a total of 425 participants that received the first dose of the vaccine [9]. Our final sample consisted of 401 subjects that were immunized with both doses of the vaccine, since 24 vaccinees did not show up for the second antibody measurement 14 days after the second dose. Our study population included both uninfected (n = 342) and previously-infected convalescent subjects (n = 59) with PCR-confirmed SARS-CoV-2 infection occurring 1 to 4.5 months prior to immunization. We employed the SARS-CoV-2 IgG II Quant assay on the Architect System (Abbott, Sligo, Ireland) to monitor titers of neutralizing IgG against the receptor-binding domain (RBD) of the

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S1 subunit of the spike protein in participant-derived serum samples.

2.2. Ethics approval

The study protocol was reviewed and approved by the Scientific Committee of the "G. Gennimatas" General Hospital (protocol number:1/13.1.2021). All subjects agreed to voluntarily participate in the study.

2.3. Statistical analysis

Stata 16.1 (Stata Corp. LLC, College Station, TX) was used for data analysis. Descriptive statistics included proportions of immunogenic response and geometric means of concentration (GMC) of RBD-specific IgG (AU/ml) and the corresponding 95% confidence intervals (95% CI) of each studied group stratified by gender, age, and history of previous SARS-CoV-2 infection. Independent samples t-tests were used to assess differences in log10 IgG levels and fold changes among gender- and SARS-CoV-2 infection history groups. Paired samples t-tests were employed for the corresponding comparisons between first and second dose. One-way ANOVA with Sidak correction for multiplicity was employed for the comparison of age groups. P-values less than 0.05 were considered statistically significant.

3. Results

After the first dose, titers were found to fluctuate with age, marking a significant decline in the 50–60 age group, while dropping even further in participants aged over 60 ($p < 0.001$). This difference was surmounted following the second dose, as the titer fold-changes recorded were significantly higher in the 50–60 age group, while escalating in subjects aged over 60 ($p < 0.001$). Eventually, satisfactory levels of neutralizing antibodies were detected in all of our study participants in the aftermath of the second dose, regardless of age (Table 1, Fig. 1).

As demonstrated by our findings, the immunogenic effect of the first dose of the BNT162b2 was robust in the uninfected group, yet far more potent among previously-infected convalescent subjects ($p < 0.001$). Immunogenicity was boosted after the second dose in the uninfected group, this effect being much less pronounced among previously-infected subjects in consistency with latest small-scale data [5]. After the second dose, although the IgG GMC remained significantly higher in the previously-infected group compared to the uninfected ($p < 0.001$), the respective fold-change reached significance only among the uninfected ($p < 0.001$), while being marginal in the seropositive group ($p = 0.0543$). The humoral immune response of previously-infected subjects to the first dose was more intense than the respective response of the uninfected to the second dose, as inferred from the comparison of GMC relative changes ($p < 0.001$) (Fig. 2).

Concerning reactogenicity, data were not collected systematically since participants were encouraged to report any adverse event to the Greek National Organization for medicines (EOF) via the official reporting form (Yellow Card scheme). However, no serious adverse events were reported in this study.

Table 1
Geometric mean concentrations (GMC) of anti-SARS-CoV-2 RBD IgG 14 days post-immunization after the first and second dose of the BNT162b2 vaccine along with fold changes thereof. P values are based on log10 transformed values. *PCR-confirmed SARS-CoV-2 infection 1 to 4.5 months prior to immunization date.

		n	%	Post-1st dose IgG GMC (AU/ml)	95% CI	Post-2nd dose IgG GMC (AU/ml)	95% CI	GMC Fold-change	95% CI	*p-value*
Sex	Female	245	61	577.15	(459.30, 725.22)	17730.34	(16100.97, 19524.59)	30.72	(25.13, 37.55)	*<0.001*
	Male	156	39	503.06	(360.56, 701.89)	14478.86	(12543.01, 16713.49)	28.78	(21.92, 37.79)	*<0.001*
	p-value (F vs M)							*0.231*		
Age	20-	15	3.7	1832.56	(759.90, 4419.38)	22054.43	(14781.35, 32906.19)	12.03	(5.40, 26.82)	*<0.001*
	30-	65	16.2	1482.83	(989.84, 2221.35)	21004.94	(17783.16, 24810.42)	14.17	(9.77 20.54)	*<0.001*
	40-	117	29.1	725.79	(525.47, 1002.46)	18414.02	(16147.15 20999.13)	25.37	(18.81, 34.22)	*<0.001*
	50-	154	38.4	383.95	(281.88, 522.97)	14990.79	(13049.11, 17221.39)	39.04	(30.34, 50.25)	*<0.001*
	60-	50	12.4	160.02	(95.89, 267.04)	10868.03	(8250.02, 14316.81)	67.91	(43.74, 105.45)	*<0.001*
	p-value (age groups)			*<0.001*		*<0.001*		*<0.001*		
Prior infection*	Yes	59	14.7	21041.75	(16406.04, 26987.35)	28020.87	(23959.37, 32770.87)	1.33	(1.08, 1.65)	*0.0543*
	No	342	85.2	291.50	(255.67, 332.35)	14938.08	(13678.54 16313.6)	51.25	(45.86, 57.27)	*<0.001*
	p-value (Y vs N)							*<0.001*		
Post-1st dose IgG > 50AU/ml	Yes	374	93.27	695.39	(581.79, 831.18)	17554.11	(16233.59, 18982.04)	25.24	(21.58, 29.53)	*<0.001*
	No	27	7.76	19.74	(13.34, 29.20)	6316.34	(4197.00, 9505.87)	319.99	(207.41, 493.68)	*<0.001*
	p-value (Y vs N)							*<0.001*		
Post-2nd dose IgG > 50AU/ml	Yes	401	100	547.11	(452.59, 661.37)	16386.62	(15106.17, 17775.6)	29.95	(25.49, 35.20)	*<0.001*
	No	0	0							
Total		401		547.11	(452.59, 661.37)	16386.62	(15106.17, 17775.6)	29.95	(25.49, 35.20)	*<0.001*

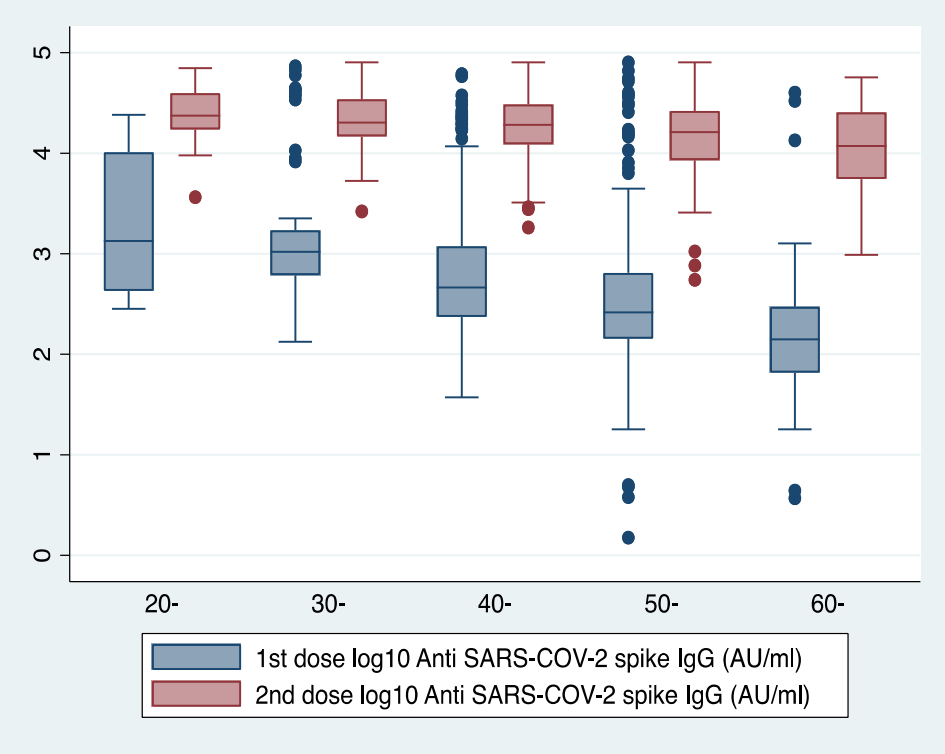

Fig. 1. Post-1st and post-2nd dose IgG titers in the different age groups.

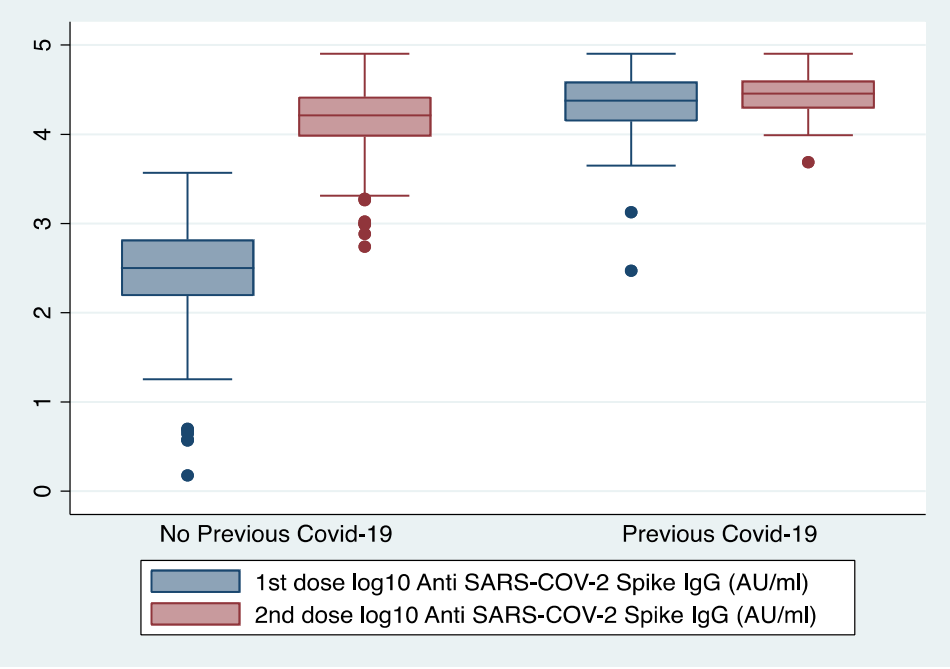

Fig. 2. Post-1st and post-2nd dose IgG titers in previously-infected and uninfected groups. Post-2nd dose titers significantly increased in the previously-uninfected group, while being marginal in the seropositive group (p = 0.0543).

4. Discussion

Overall, our findings attest to the potent immunogenicity elicited by the BNT162b2 in the wide age range included in this study (20–67), suggesting that timely administration of the booster-dose maximizes the immunogenic potential of the vaccine in the 50 + age group. These outcomes, along with congruent evidence [3], underline the value of the current immunization regimen involving two injections 3 weeks apart, firmly recommending its continuation.

The marginal titer fold-change detected in the seropositive group after the second dose supports the equivalence of previous infection to immune priming and questions the necessity of administering a second dose to seropositive individuals. These findings are well in line with those of other studies [2,5], while recent evidence also verified our observation that the antibody responses of the seropositive to the first dose exceeded those of uninfected vaccinees to the second dose [2,10].

A limitation of our study is that a neutralization assay was not employed, however, RBD-IgG titers obtained by the IgG assay used have been positively associated with neutralizing anti-SARS-CoV-2 IgG GMTs in a phase II randomized controlled trial [11] and 100% correlated with a plaque reduction neutralization test outcome of ID50 [12].

Concluding, our findings are consistent with those reported in literature [2,5,10] and unanimously suggest the need for timely administration of the second dose to SARS-CoV-2-naïve individuals, while questioning its necessity among previously-infected patients. Thus, we strongly urge thorough verification of these outcomes, as they are of decisive importance for the establishment of more prudent vaccine prioritization practices to accelerate the accomplishment of herd immunity.

CRediT authorship contribution statement

Konstantina Kontopoulou: Conceptualization, Data curation, Writing – original draft. **Alexandra Ainatzoglou:** Writing – original draft. **Georgios Papazisis:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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