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Long-term serological SARS-CoV-2 IgG kinetics following mRNA COVID-19 vaccine: real-world data from a large cohort of healthcare workers

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ABSTRACT

Objectives: This study aimed to assess kinetics and predictive variables of humoral immune response to mRNA SARS-CoV-2 vaccine administration.
Methods: We collected blood samples before (T0) and 15, 90, and 180 days after vaccination (T1, T2, and T3, respectively). The Quant SARS-CoV-2 Immunoglobulin (IgG) II Chemiluminescent Microparticle Immunoassay was used to determine anti-spike IgG.
Results: In almost 3000 healthcare-collected blood samples at the three time points, we found the following: at 15 days postvaccination, 97.6% of subjects presented a robust IgG anti-spike response (>4160 AU/ml); then, at three and six months, it decreased in median 6.5-fold to 35.0% and 3.0-fold to 3.3%, respectively. A linear mixed-effects model supported that female gender, younger age groups, and being seropositive prevaccination maintained higher antibody titers. Curves became tighter with time progression, although titers from seropositive subjects decrease at a slower rate than seronegative ones.
Conclusion: These findings strengthen the case for a steep decrease of anti-SARS-CoV-2 antibodies up to six months, suggesting that serological evaluation might guide the need for periodic booster vaccinations in specific groups prone to lower antibody titers.

Introduction

In late 2019, SARS-CoV-2 triggered a new pandemic. Vaccines started to be urgently developed, and the United States Food and Drug Administration authorized their use in an emergency context on December 11, 2020, after demonstrating 95% efficacy (United States Food and Drug Administration, 2020). In Portugal, healthcare workers (HCWs) received the first doses of the BNT162b2 mRNA COVID-19 vaccine (Pfizer/BioNTech) by the end of December 2021. Vaccine efficacy against COVID-19 was 91.3% through six months of follow-up in subjects without evidence of previous SARS-CoV-2, thus reflecting a gradual decline in vaccine efficacy (Thomas et al., 2021).

By this time, numerous studies of Immunoglobulin G (IgG) humoral immunity were being carried out to understand the kinetics of antibodies (Lo Sasso et al., 2021; Oliveira-Silva et al., 2022; Salvagno et al., 2021; Tré-Hardy et al., 2021) better. Nevertheless, the long-term duration of humoral immunity from the SARS-CoV-2 vaccine remains unclear because of the lack of data from large, real-world studies. Bayart et al. (2021) observed a waning of IgG antibodies over time, although at 180 days after vaccination, subjects still had detectable anti-Spike antibodies. As reported elsewhere, after the first contact with the virus, B cells produce antibodies that decrease over months, particularly in older pa-

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tients, men, and immunosuppressed subjects (Chavarot et al., 2021; Geisen et al., 2021; Levin et al., 2021). Concordantly, previously infected individuals maintained higher IgG titers over three-month studies (Lau et al., 2021; Tré-Hardy et al., 2021).

Considering that antibody titers might be a good biomarker for the protective efficacy of antibodies and successful humoral immune responses after SARS-CoV-2 exposure or vaccination, it is considered that SARS-CoV-2 IgG kinetics concedes relevant information concerning the immune status and a proxy for immunization status (Bayart et al., 2021; Levin et al., 2021). In this study, we report humoral immunity data of the first six months of follow-up after vaccination from a large cohort, which emphasizes the decline of IgG antibodies.

Material and Methods

HCWs from the Centro Hospitalar e Universitário de Coimbra were vaccinated in late December 2020 with BNT162b2 mRNA and included in a prospective cohort to evaluate SARS-CoV-2 IgG serological kinetics. Subjects were tested for anti-spike IgG antibody before the first dose (T0) and then 15 days (T1), 3 months (T2), and 6 months (T3) after completion of the second dose. HCWs with a previous diagnosis of SARS-CoV-2 were excluded from the first phase of vaccination. Only subjects with complete serological data at all time points were included in analyses (n = 2968). In this population, most HCWs were naïve (seronegative for SARS-CoV-2 IgG before vaccination), whereas 63 were seropositive (because of eventual asymptomatic past contact with the virus). This study was approved by the hospital's Ethics Committee (OBS.SF.106-2021), and deferred consent was obtained under stringent application of ethical and legal procedures for data collection, such as protection of confidentiality of the personal data and mitigation of risks to privacy.

Blood was collected from each participant at every time point and processed to serum within four hours. A chemiluminescent microparticle immunoassay, SARS-CoV-2 IgG II Quant, was used to determine the IgG anti-spike, receptor-binding domain (RBD) S1 subunit of SARS-CoV-2 on Alinity *i* (Abbott Laboratories). The cutoff and upper detection limits of the Abbott S-RBD IgG test were 50 and 80 000 AU/ml, respectively, whereas sensitivity and specificity were 99.37% and 99.55%. As per manufacturer recommendations, antibody titers above 50 AU/ml were considered reactive. We used IgG antibody titers > 4160 AU/ml as an indicator of strong neutralizing activity, as previously reported (Ebinger et al., 2021). All measurements were undertaken following appropriate quality control procedures and performed daily for routine clinical assessment of SARS-CoV-2 IgG.

Statistical analysis

Departure from normality was tested using the Shapiro-Wilk test, and data were presented as median and interquartile range (IQR). For longitudinal comparison of SARS-CoV-2 IgG titers between time points (T0, T1, T2, and T3), the Friedman's followed by Wilcoxon tests were used, with Bonferroni correction for multicomparison. To assess differences among independent variables (gender, age groups, and reactive titers in T0) at each time point, the Mann-Whitney or Kruskal-Wallis tests were applied.

We modeled the decrease after vaccination (over T1, T2, and T3) using a linear regression model with mixed-effects. Our data were grouped by subject. This model is appropriate for longitudinal data and extends the linear model by adding random effects that can be seen in terms of additional error, accommodating correlation between observations from the same individual. Fixed effect covariates included gender, age group (18–30, 30–40, 40–50, 50–60, and >60 years), humoral status before vaccination (T0 above or below 50 AU/ml), and time (in months). Interactions with time were also included. After $\log_{10}$ transformation of IgG titers, models were fitted with population-level fixed effects and individual-level random effects (Worker ID) for intercept and slope. Models with random effects only for intercept were also fitted. We started by fitting the null model, only including the outcome variable and individual-level random effects. The model presented is the model that fits our data better. Model comparisons were conducted using the difference in Akaike information criterion (AIC) above 4 (Burnham et al., 2011) as significant and fitted using maximum likelihood. We estimated the marginalized R^2, the proportion of variance explained by the fixed effects (Nakagawa and Schielzeth, 2013), and the conditional R^2 of the model, that is, the proportion of variance explained by both the fixed and random factors (Nakagawa and Schielzeth, 2013). Statistical analyses were conducted using R Software version 4.0.05 (The R Foundation for Statistical Computing, Vienna, Austria), and a linear model with mixed-effects was fitted using the lmer function (lme4 package).

Results

Data were collected between December 2020 and August 2021. Close to 3000 subjects participated in this study, with median age of 45 years (IQR 36–55) (77.5% female). All had full data on IgG titers at the time points T0, T1, T2, and T3. Before vaccination, most participants were naïve (median = 6.8, IQR = 6.8–6.8 AU/ml), although 2.1% (n = 63) of the subjects had IgG anti-SARS-CoV-2 above cutoff (>50 AU/ml) but below 4160 AU/ml.

After vaccination, test reactivity (>50 AU/ml) was maintained throughout the study in 99.9%, 99.8%, and 99.7% of the population at T1, T2, and T3 time points, respectively. Fifteen days after vaccination (median IgG = 21.3×10^3, IQR = 13.3×10^3 – 33.0×10^3 AU/ml), 97.6% subjects presented a robust humoral response (>4160 AU/ml), whereas at three months (median = 3.2×10^3, IQR = 2.0×10^3 – 5.1×10^3 AU/ml) it decreased in median 6.5-fold × to 35.0% and then by 3.0-fold to 3.3% at six months (median = 1.0×10^3, IQR = 0.64×10^3 – 1.6×10^3 AU/ml). The Friedman's test [$c^2(3) = 8652.4$, $P < 0.0001$] revealed a statistically significant difference in SARS-CoV-2 IgG throughout the follow-up, further confirmed by Wilcoxon between time points ($P < 0.0001$) (Figure 1). The comparison between strata of the independent variables, gender, age group, and IgG reactivity before vaccination is listed in Table 1.

Regarding the mixed-effects model, the final model included random effects for the intercept and slope. The marginalized and the conditional R^2 were 0.71 and 0.91, respectively.

Figure 2 and 3.

Female gender, previous reactive titers, and younger age group each contributed to higher antibody levels at the first time point after vaccination (Table 2). We verified that every month, the log-transformed IgG levels decreased 0.230 times ($P < 0.001$). Interaction of gender and age with time was strongly correlated with the variate time and was excluded. (Table 3). The variable interaction of time and IgG titers for seropositive participants was significant ($P = 0.0002$). Therefore, antibody levels from participants seropositive at T0 showed higher values after vaccination and decreased at a slower rate (−0.23 vs −0.168, $P < 0.001$), suggesting that at six months after vaccination, the IgG levels remain divergent.

Discussion

This real-world study of COVID-19 humoral response after BNT162b2 vaccination demonstrated a significant decline in anti-spike IgG titers six months after vaccination. Despite an early increase at 15 days after completing the second dose, the IgG levels decreased significantly at both three-month and six-month

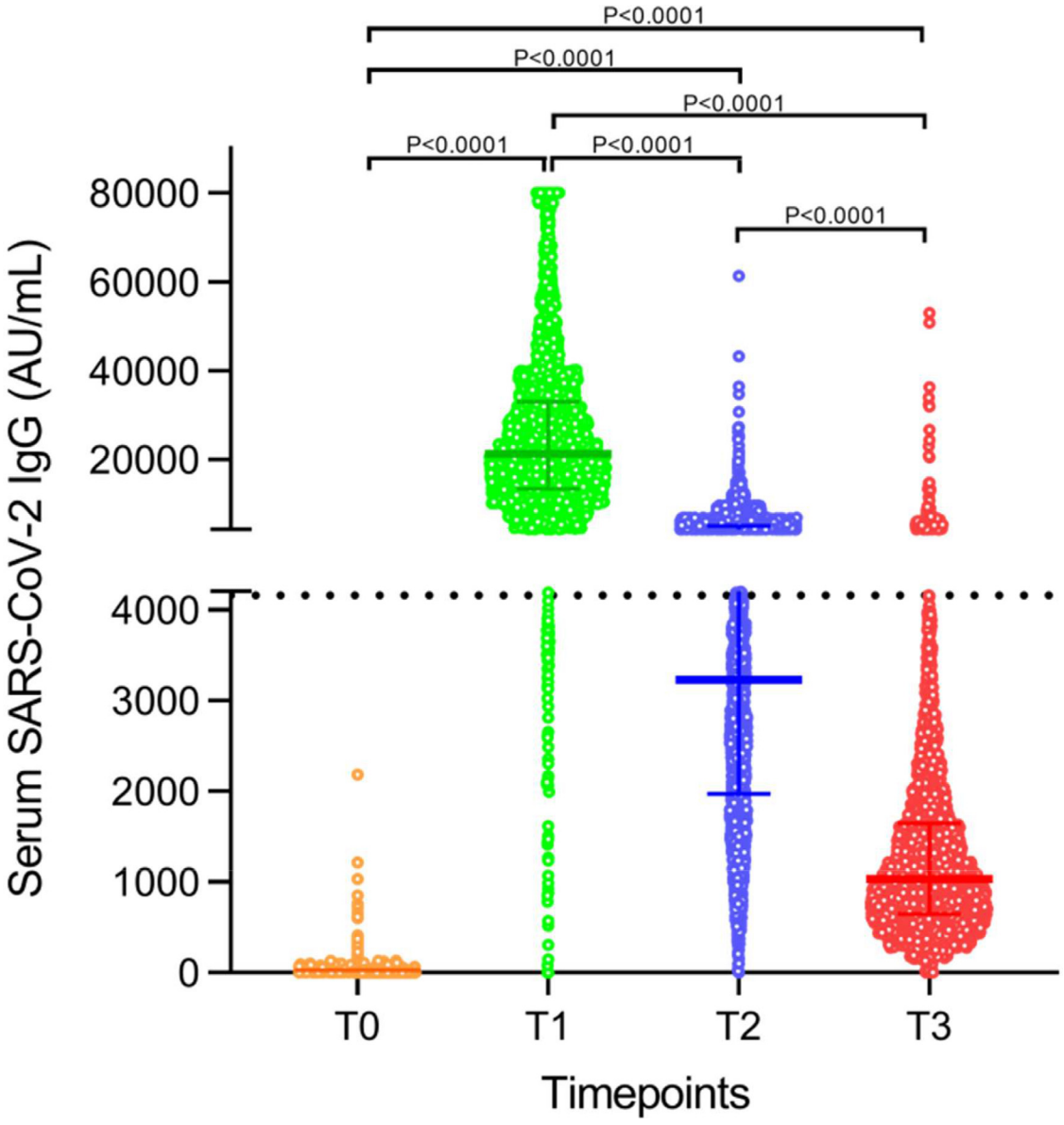

Figure 1. Serum SARS-CoV-2 IgG throughout the study follow-up, depicting the kinetics of antibodies. Data are presented as median and interquartile range. AU = arbitrary units.

time points. Our findings agree with data reported by others (Gaebler et al., 2021; Naaber et al., 2021; Salvagno et al., 2022; Bilich et al., 2021).

A recently published randomized placebo-controlled clinical trial, following up over 40,000 subjects vaccinated with BNT162b2 for COVID-19, described that effectiveness peaked at 96.2% during the first two months after the second dose and declined to 83.7% in the four to six months after immunization, marking an average decline of 6% every two months (Tartof et al., 2021; Thomas et al., 2021).

After vaccination with the BNT162b2 vaccine, anti-SARS-CoV-2 IgG kinetics peak around 4 to 30 days, followed by a substantial reduction over time, with significantly lower levels at six months (Levin et al., 2021; Naaber et al., 2021). Here, in a large cohort of HCWs, we observed that although postvaccination IgG titers were reactive (>50 AU/ml) for over 99.5% of the population at T1, T2, and T3 time points, when we used the cutoff indicating a robust humoral response (>4160 AU/ml), the frequency of participants declined by 6.5-fold from 97.6% after 15 days to 35.0% at 3 months, and then by 3.0-fold to 3.3% at 6 months. Similar studies with a reduced number of participants yielded common findings (Bayart et al., 2021; Levin et al., 2021). Seemingly, the decrease in IgG levels throughout postvaccination follow-up occurs in parallel with neutralization titers (Terpos et al., 2021). In our study, the significant decrease in titers was independent of gender, age, or IgG reactivity before vaccination, which agrees with previous data (Dan et al., 2021). The lack of proportionality between the decline in mRNA vaccine effectiveness and the decrease in humoral immune response kinetics over time suggests that, during postvaccination follow-up, the protection might have become dependent on immunological mechanisms other than humoral. Notably, declines in effectiveness of the COVID-19 vaccine have also been attributed to the widespread dissemination of the Delta variant (Bayart et al., 2021).

The efficacy of humoral immunity alone against SARS-CoV-2 has been questioned, and the relevance of T cell memory evaluated. Studies investigating antibody and T cell responses in matched samples of convalescent patients revealed decreasing

Table 1
Serological levels SARS-CoV-2 Immunoglobulin G (IgG), overall, and by strata of gender, age group, and IgG reactivity, before and after COVID-19 mRNA vaccination.

	N (%)	Prevaccination T0 ($\times 10^1$)	15 days postvaccination T1 ($\times 10^3$)	90 days postvaccination T2 ($\times 10^3$)	180 days postvaccination T3 ($\times 10^3$)
IgG titers, AU/ml*	2968 (100)	6.8 [6.8, 6.8]	21.3 [13.3, 33.0]	3.2 [2.0, 5.1]	1.0 [0.64, 1.6]
Gender					
Male	667 (22.5)	6.8 [6.8, 6.8]	18.7 [11.7, 29.3]	2.9 [1.7, 4.8]	0.97 [0.58, 1.6]
Female	2301 (77.5)	6.8 [6.8, 6.8]	22.1 [14.0, 34.0]	3.3 [2.0, 5.2]	1.1 [0.66, 1.7]
P-value ***		0.655	<0.0001	<0.0001	0.004
Age group, years					
20–30	416 (14.0)	6.8 [6.8, 6.8]	26.9 [17.9, 38.9]	4.3 [2.9, 6.3]	1.5 [0.96, 2.1]
30–40	694 (23.4)	6.8 [6.8, 6.8]	22.6 [16.0, 34.0]	3.4 [2.3, 5.3]	1.1 [0.73, 1.7]
40–50	802 (27.0)	6.8 [6.8, 6.8]	20.2 [12.5, 31.9]	2.8 [1.7, 4.5]	0.91 [0.56, 1.5]
50–60	787 (26.5)	6.8 [6.8, 6.8]	19.9 [11.8, 31.6]	3.0 [1.7, 5.0]	0.95 [0.58, 1.6]
>60	267 (9.0)	6.8 [6.8, 6.8]	16.8 [10.5, 28.8]	2.8 [1.7, 4.2]	0.89 [0.59, 1.6]
P-value **		0.529	<0.0001 [a]	<0.0001 [b]	<0.0001 [c]
IgG reactivity at T0, AU/ml	2905 (97.9)	6.8 [6.8, 6.8]	21.3 [13.3, 32.6]	3.2 [1.9, 5.0]	1.0 [0.64, 1.6]
<50	63 (2.1)	134.4 [90.4, 322.8]	32.5 [1.7, 4.2]	7.7 [3.4, 12.4]	3.1 [1.4, 5.4]
≥50					
P-value ***		<0.0001	<0.0001	<0.0001	<0.0001

Data are presented as median and interquartile range.
*P-value <0.0001 for all comparisons between time points (Wilcoxon test).
**Kruskal-Wallis test, followed by Mann-Whitney tests. [a]$P < 0.0001$ for all comparisons except 40–50 vs 50–60 ($P = 0.288$), 40–50 vs >60 ($P = 0.002$) and 50–60 vs >60 ($P = 0.027$) (Mann-Whitney tests). [b]$P < 0.0001$ for all comparisons except 40–50 vs 50–60 ($P = 0.238$), 40–50 vs >60 ($P = 0.745$) and 50–60 vs >60 ($P = 0.262$) (Mann-Whitney tests). [c]$P < 0.0001$ for all comparisons except 40–50 vs 50–60 ($P = 0.199$), 40–50 vs >60 ($P = 0.804$) and 50–60 vs >60 ($P = 0.535$) (Mann-Whitney tests).
***Mann-Whitney test.
AU = arbitrary units.

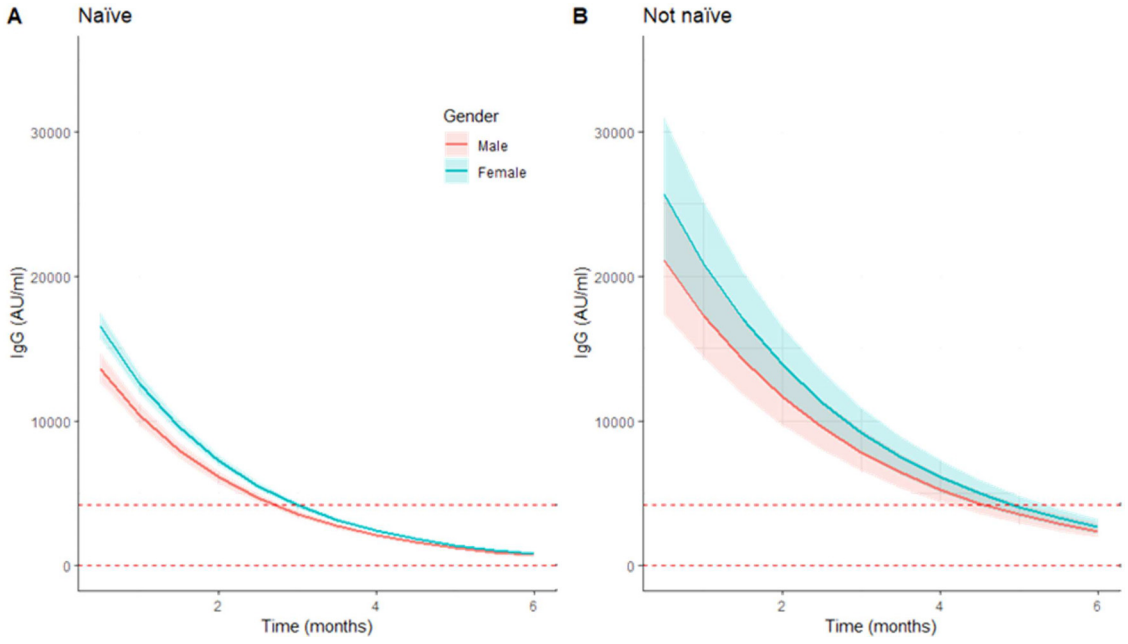

Figure 2. Predicted trajectories of immunoglobulin G (IgG) levels over six months by naïve status at T0 between gender. Predicted trajectories of IgG levels, after base 10 exponentiation of predicted values and 95% confidence interval limits. Figures represent the predictions for naïve HCWs (A) and for HCWs with previous titers >50 AU/ml (B). Median age was used on these estimates. The dotted horizontal lines represent 4160 AU/ml and 50 AU/ml levels. HCWs = healthcare workers; AU = arbitrary units.

spike-specific and stable nucleocapsid-specific antibody responses. In contrast, functional T cell responses remained robust, increasing in both frequency and intensity (Bilich et al., 2021). Circulating antibody titers were shown to be not predictive of T cell response to SARS-CoV-2 (Dan et al., 2021). Notably, whereas IgG antibodies decreased significantly over time, the number of RBD-specific memory B cells remained unchanged six months after infection (Gaebler et al., 2021). Despite a slight decrease in association with age, memory B cells seem to be efficiently primed by mRNA vaccination and detectable after the second vaccine dose, which concedes memory B cells a role in mounting recall responses to SARS-CoV-2 (Goel et al., 2021).

Taken together, our and others' findings suggest that serological tests for SARS-CoV-2 might not reflect the immune memory response in terms of robustness and durability, highlighting the need to determine cellular responses in addition to serologies (Cromer et al., 2021; Tretyn et al., 2021).

We found significant differences in antibody titers between naïve versus seropositive subjects before vaccination and in each of the subsequent time points. There was a trend to decrease in abso-

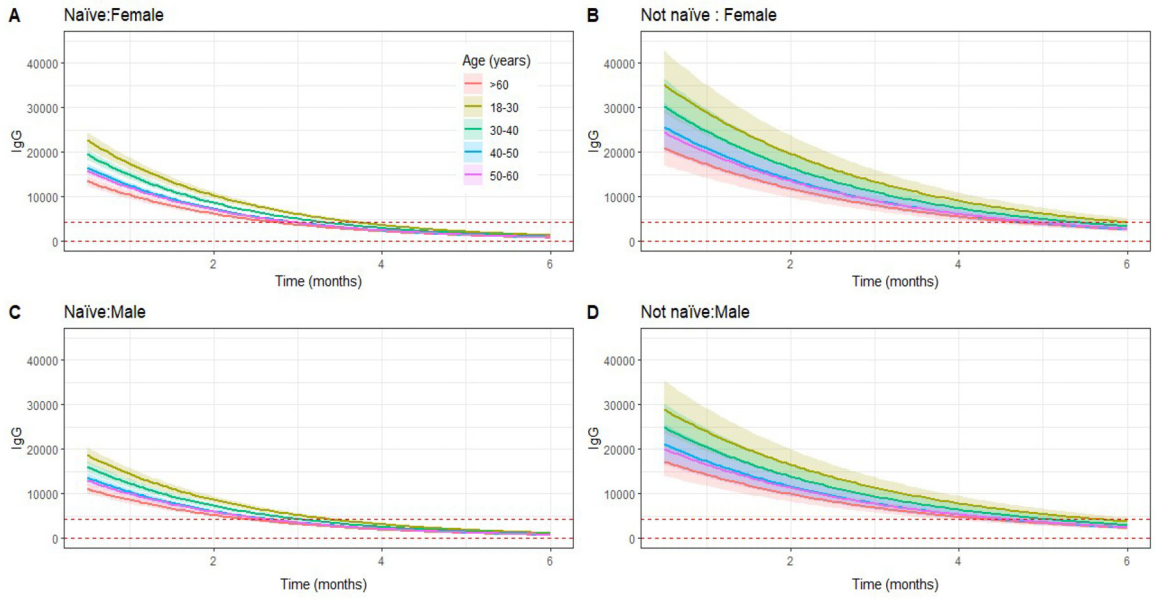

Figure 3. Predicted trajectories of immunoglobulin G (IgG) levels over six months by gender and naïve status at T0 between age groups. On the top (A and B) are represented the predictions for female gender and on the bottom (C and D) the ones for male HCWs. Also, on the left (A and C) are represented the predictions naïve HCWs and on the right (B and D) for HCWs with previous titers >50 AU/ml. The dotted horizontal lines represent 4160 AU/ml and 50 AU/ml levels. HCWs = healthcare workers; AU = arbitrary units.

Table 2
Results from linear mixed effects model for log_{10}-transformed Immunoglobulin gG (IgG) antibody titers. Reported are the estimated fixed effects along with their standard error and *P*-values.

Dependent variable: IgG levels (AU/ml) log_{10}-transformed			
Variables	Value	Std. Error	*P*-value
Intercept	4.51	0.0193	<0.001
Month	−0.233	0.0009	<0.001
Age (years, >60 as reference)			
18–30	0.219	0.0231	<0.001
30–40	0.136	0.0205	<0.001
40–50	0.056	0.0199	0.0053
50–60	0.050	0.0199	0.0120
Gender (female)	0.070	0.0135	<0.001
T0 (titers >50 AU/ml)	0.155	0.0422	0.0002
Interactions			
Months xT0 (titers >50 AU/ml)	0.062	0.0062	<0.001

AIC = 1849.178; Marginalized R^2 = 0.71; Conditional R^2 = 0.91.
AU = arbitrary units.

Table 3
Estimations of intercept and decrease rates based on the linear mixed effects model for log_{10}-transformed Immunoglobulin gG (IgG) antibody titers, for each group of covariates included.

	Intercept				
	Age group (years)				
Female	18–30	30–40	40–50	50–60	>60
Naïve	4.994	4.911	4.831	4.825	4.775
Not naïve	5.180	5.097	5.017	5.011	4.961
Male					
Naïve	4.194	4.211	4.131	4.125	4.075
Not naïve	4.480	4.397	4.316	4.311	4.261

lute difference as a time to depart from the antibody peak. Those with reactive titers before vaccination remained with higher levels at six-month follow-up. Indeed, the mixed-effects linear model revealed that being seropositive at T0 contributes to higher antibody levels, at the peak and during the observed period. These results agree with previous studies showing that baseline seropositives have a longer estimated half-life and less accentuated decline in SARS-CoV-2 IgG titers (Bayart et al., 2021; Salvagno et al., 2021; Zhong et al., 2021).

Age was inversely related to the immune response at all time points of the postvaccination follow-up. We observed that median IgG antibody levels decreased over six months in all age groups, although the difference among age groups decreased over time. Nonetheless, in the mixed-effects model, age remained a significant independent factor to predict antibody levels. These results align with other reports that observed a negative correlation between age and antibody levels (Naaber et al., 2021; Salvagno et al., 2021) and with neutralizing antibodies (Salvagno et al., 2021). Given that our study is from a working population, subjects aged over 68 years were not included. Nonetheless, evidence suggests there is a lower humoral response at six months after the vaccine for patients above 60 (Tretyn et al., 2021) and over 65 years old (Levin et al., 2021).

Gender remained a significant factor throughout all time points analyzed, with female HCWs presenting higher titers than their male counterparts after vaccination. The linear model with mixed-effects showed that the female gender contributed independently toward higher antibody levels, albeit this effect seems to decrease through time. These observations agree with previous reports (Levin et al., 2021; Salvagno et al., 2021).

This study included a cohort of HCWs, a professional group exposed to the occupational risk of COVID-19. Eligible participants were active workers, younger than 67 years of age, without substantial co-morbidities, with only limited generalizability to the older population and adults with serious co-morbidities. Although initially designed to include only naïve subjects, a small number of participants were found to be seropositive. Therefore, findings comparing titers from naïve versus seropositive participants should be interpreted cautiously, despite their being in line with other larger studies (Bayart et al., 2021; Ebinger et al., 2021). Here, we focused on the serological evaluation of immunological response to the COVID-19 mRNA vaccine, even though the immune response to the vaccine is multifaceted and involves neutralizing antibodies and T memory cells beyond IgG antibodies in postvaccination protection (Krause et al., 2021).

Notwithstanding those limitations, we present serological data from a cohort with large sample size and a longer follow-up period compared with others in the literature. Moreover, we used a mixed-effects model suitable for longitudinal datasets where multiple correlated measurements were taken from each subject, allowing more accurate and precise estimates of population heterogeneity (Bottino et al., 2021).

Data presented here provide further evidence for the eventual requirement of SARS-CoV-2 IgG serology-guided booster vaccinations. Despite being controversial, this strategy has been adopted by some countries for older subjects and immunocompromised patients with over six months of postvaccination follow-up time (Bar-On et al., 2021; Krause et al., 2021).

Although we present data of IgG antibodies decline over time, which could be expected, provided that not all vaccine-induced plasmablasts commit or are maintained as long-lived memory plasma cells (Naaber et al., 2021), it is also well established that vaccine efficacy remains high after six months (Thomas et al., 2021). Thus, even if humoral immunity appears to wane, it does not necessarily mean a reduction in efficacy (Krause et al., 2021).

Conclusion

The decline of specific anti-SARS-CoV-2 IgG antibodies over time through six months postvaccination suggests waning of humoral immunity and impaired capacity to fight the virus and supports the need to re-activate IgG production. This is a cohort study planned for a one-year follow-up, which will permit the sharpening of the antibodies' kinetics model. Accurately evaluated antibody response, together with cellular immunity status and other covariates, including age and gender, may add to clinical reasoning to support the individualization of the immunization plan. This work further contributes to delineating the pattern of the immune response to the COVID-19 mRNA vaccine, fostering additional research to determine the titers needed for protection.

Conflicts of interest

Authors disclose support from Abbott Laboratories to participate in meetings (TR, CL, RR, LA, FR). The remaining authors do not have any conflicts of interest to declare.

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Authors contributions

JOS, TReis, CL, and RB contributed to conceptualization, methodology, investigation, writing the original draft, and final review and editing of the manuscript. RR contributed to conceptualization, methodology, investigation, writing the original draft, supervision, and final review and editing of the manuscript. GM contributed to data curation and to final review and editing of the manuscript. VP, TRodrigues, AA, VP, contributed to resources, investigation, and final review and editing of the manuscript. LA, FR, and IA contributed to the conceptualization, supervision, and final review and editing of the manuscript.

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