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Antibody response to SARS-CoV-2 booster vaccines

1. Introduction

The mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) vaccines have demonstrated high efficacy at preventing hospitalization and death due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Breakthrough infections due to new variants and possibly waning immunity led to the recommendation of booster vaccines in the general population.

Commercial assays that measure binding antibodies directed against the spike (S) protein of the virus, which are induced by the mRNA vaccines, are readily available in clinical laboratories. Importantly, these antibodies have been shown to correlate with neutralizing antibodies [1] which correlate with vaccine efficacy [2]. Here, we determined anti-SARS-CoV-2-S IgG (anti-S) response following administration of a homologous booster vaccine in a population of individuals employed in a healthcare setting.

2. Method

This study was conducted at the National Institutes of Health in November and December 2021. Two samples of blood were collected from 91 participants (49 women) with a median age of 45 (range 18–80) years old. Participants were not screened for health conditions prior to collection but were recruited from employees presenting for vaccination. All participants had received two doses of Moderna (N = 65) or Pfizer (N = 26) vaccines at a median of 280 (range 206–326) days before the first blood collection. The first blood sample preceded the booster shot by a median of 0 (range 0–24) days. The second blood sample was drawn at a median of 8 (range 5–29) days after the booster. Blood was processed and anti-S antibodies were measured by immunoassay on a Roche cobas-6000 analyzer as previously described [3]. In this study the analytical measurement range (AMR) for this assay was 0.4–250 U/mL with a reportable range up to 25,000 U/mL (on-board 1:100 dilution) and a positive/negative cutoff value of 0.8 U/mL. For statistical analysis and figures, a level > 25000 U/mL was assigned a value of 25,000 U/mL.

We used Wilcoxon test to compare anti-S levels pre- and post-booster and linear regression for the association between time since second shot and log pre-booster anti-S level. $P < .05$ was considered significant. Statistical analyses and figures were prepared in GraphPad Prism version 9.3.1 (GraphPad Software). Anti-S levels > 25000 U/mL (upper limit of reportable range) were assigned values of 25,000 U/Ml.

3. Results

Median anti-S levels pre-booster were 1047 U/mL. Anti-S levels increased significantly following booster (Fig. 1A), and the median difference was 22,804 U/mL (P <.0001). Interestingly, pre-booster anti-S levels among participants did not differ significantly over ~ 4 months since the second vaccine shot (Fig. 1B). Our dataset was not powered to investigate effects of vaccine type, sex, or age group. However, visual inspection revealed that anti-S levels did not appear to differ between vaccine types (Fig. 1C), between men and women (Fig. 1D), or among age groups (Fig. 1E). Two participants who endorsed chemotherapeutic (P1) and disease modifying drugs (P2) had negative and modestly increased anti-S levels post-booster with Moderna, respectively (Fig. 1F).

4. Discussion

Booster vaccines are associated with a lower incidence of infection, severe disease, or death from SARS-CoV-2 [4]. These measures of efficacy have also been positively correlated with binding antibodies [5]. In our study, there was a significant increase in anti-S levels following the booster vaccine that did not appear to be affected by age or gender [4]. Anti-S levels did not appreciably increase in two participants, which raises the question whether the decrease in anti-S levels will predict increased vulnerability to SARS-CoV-2 infection or disease. In a study of booster vaccine in healthcare workers in Israel, low levels of anti–S antibodies were associated with a greater incidence of SARS-CoV-2 infection[6]. By contrast, compelling evidence supports other immune responses that may offer protection even as antibodies decline [7].

Interestingly, while booster shots significantly increased anti-S levels, pre-booster levels were already above the AMR and required instrument on-board dilution. Furthermore, anti-S levels did not appear to decrease significantly over roughly a 4-month period reflecting the shortest (206 days) and the longest (326 days) intervals between the second vaccine dose and the first time point pre-booster. Our observation suggests that the waning of antibodies occurs most rapidly in the first few months following vaccination. This has been recently shown for neutralizing antibodies although binding IgG antibodies decreased at a more constant rate [8]. This is also consistent with findings of robust increases in anti-S levels following vaccination that then decrease rapidly over the initial couple of months and more slowly after that [7]. In our study, median anti-S levels pre-booster at 1047 U/mL were clearly higher than the suggested high/low titer cutoff level of 132 U/mL for this assay [9].This raises the question whether pre-booster anti-S levels in our study had been sufficient to prevent breakthrough infections and ultimately what and if anti-S cutoff levels would determine immunity or the need for additional booster shots.

Our study is limited by sample size which was not powered to identify subgroup differences in demographics or in the types of vaccine received. Another limitation is the lack of baseline anti-S levels shortly following the second dose of vaccination or more frequent sampling following the booster vaccine. While the finding of significantly

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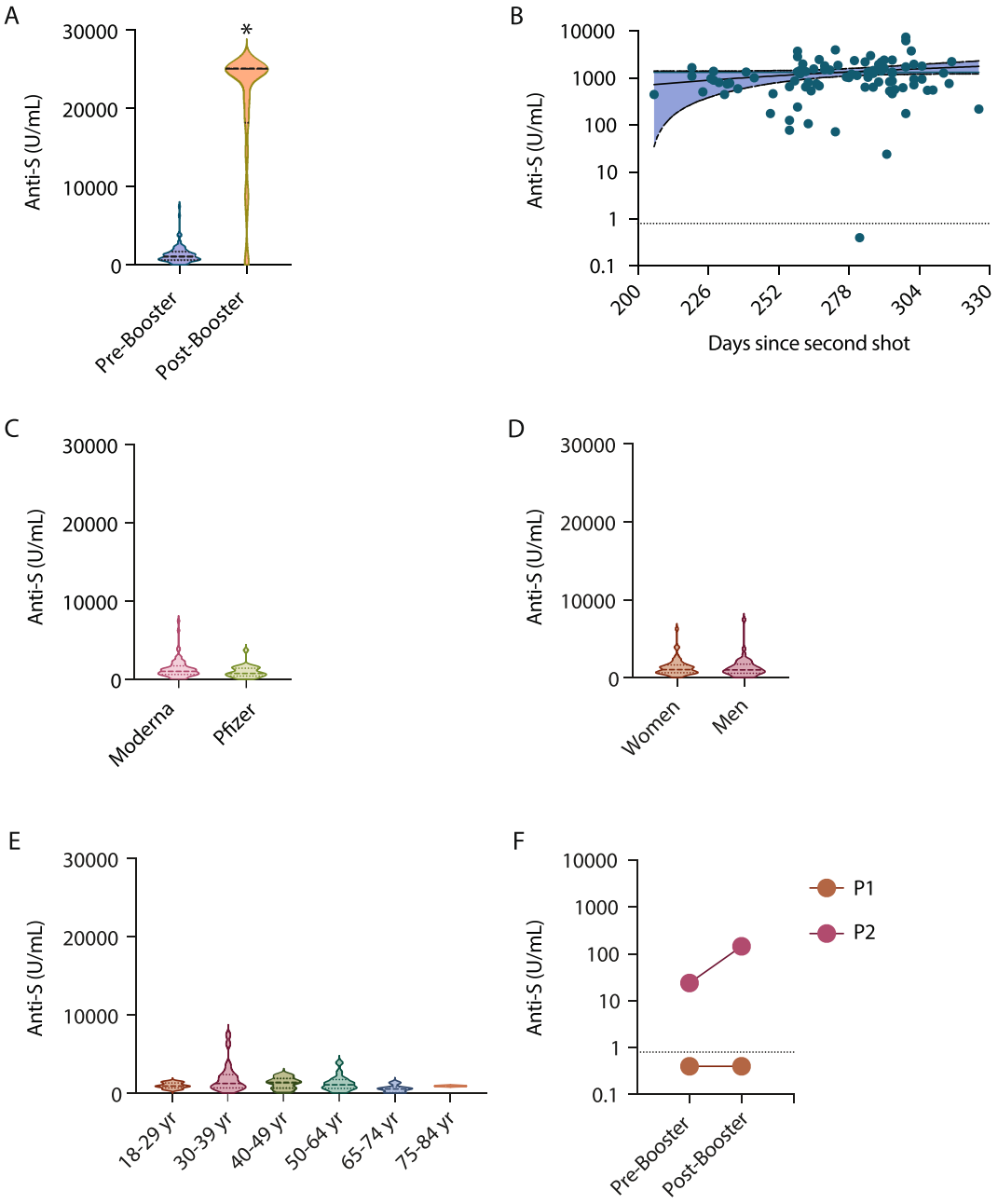

Fig. 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody levels following booster shots with Moderna or Pfizer vaccines. A, Anti-spike protein (anti-S) levels increased significantly post-booster (Wilcoxon test; N = 91, median difference = 22804 U/mL, 95% CI = 17305 – 20,516 U/mL, *P* <.0001). B, Pre-booster anti-S levels did not differ by months since vaccine second shot (0.38% increase [95% CI: –0.63 – 1.39%] per day, P =.50). Solid circles represent individual anti-S levels; shaded area represents linear regression with 95% confidence interval. C, Pre-booster anti-S levels by vaccine type (Moderna: N = 65, median = 1223 U/mL, 95% CI = 873 – 1365 U/mL; Pfizer: N = 26, median = 796 U/mL, 95% CI = 512 – 1399 U/mL). D, Pre-booster anti-S levels by gender (women: N = 49, median = 1056 U/mL, 95% CI = 782 – 1379 U/mL; men: N = 42, median = 1014 U/mL, 95% CI = 749 – 1353 U/mL). E, Pre-booster anti-S levels by age group (18–29 yr: N = 12, median = 930 U/mL, 95% CI = 630 – 1365 U/mL; 30–39 yr: N = 20, median = 1261 U/mL, 95% CI = 782 – 2215 U/mL; 40–49 yr: N = 21, median = 1280 U/mL, 95% CI = 654 – 1678 U/mL; 50–64 yr: N = 30, median = 1081 U/mL, 95% CI = 725 – 1399 U/mL; 65–74 yr: N = 6, median = 564 U/mL, 95% CI = 0.4 – 1353 U/mL; 75–84 yr: N = 2, median = 925 U/mL, 95% CI = 869 – 981 U/mL). C-E, Median post-booster levels for all datasets (vaccine type, gender, age group) except age groups 65–74 yr (N = 6, median = 21487 U/mL) and 75–84 yr (N = 2, median = 15813 U/mL) were > 25000 U/mL. F, Anti-S levels were negative (P1) or low (P2) in two participants who reported chemotherapeutic and disease modifying drugs, respectively. Data were plotted on linear (A, C, D, E) and logarithmic (B, F) scales. Asterisk denotes statistical significance. Dashed lines represent cutoff threshold at 0.8 U/mL. CI: confidence interval; P: participant; yr: Year.

increased anti-S levels following the booster shot is expected, the lack of appreciable decline of pre-booster anti-S levels over a relatively wide interval is noteworthy; however, the link to breakthrough infections and assessing the need for booster shots remains unclear.

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