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BRIEF REPORT

The Association Between Prebooster Vaccination Antibody Levels and the Risk of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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The correlation between anti–severe acute respiratory syndrome coronavirus 2 antibody levels and infection was reported. Here, we estimated the role of pre–fourth dose levels using data from 1098 healthcare workers. The risk of infection was reduced by 46% (95% confidence interval, 29%–59%) for each 10-fold increase in prebooster levels. Prebooster antibody levels could be used to optimally time boosters.

Keywords. SARS-CoV-2; mRNA vaccines; boosters; IgG levels; infection risk.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been instrumental in reducing the burden of coronavirus disease 2019 (COVID-19), including infections, symptomatic disease, severe disease, hospitalizations, and mortality [1–4]. Yet, several months following primary or boost dosing, waning of antibody titers led to decreased vaccine effectiveness [5, 6]. In particular, SARS-CoV-2 Omicron variants of concern were shown to largely reduce this protection [7]. Following vaccination, serum antibody levels strongly correlated with the risk of infection [8], and a large interpersonal variance in postbooster vaccination levels was reported [9].

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Hence, we hypothesize that individuals with low prebooster antibody levels will have a higher risk of infection even post-boosting. If correct, this would suggest that antibody levels could be used to optimally time the receipt of boosters. Accordingly, we aim to estimate the association between pre–fourth dose anti–SARS-CoV-2 antibodies and SARS-CoV-2 infections in the 6 months following vaccination.

METHODS

Study Setting

This is a prospective cohort study conducted among healthcare workers (HCWs) from Sheba Medical Center (SMC), the largest tertiary medical center in Israel. The cohort was originally formed before the initial rollout of SARS-CoV-2 vaccination and was previously described in detail [10]. All cohort members are required to undergo antigen rapid diagnostic testing (Ag-RDT) or quantitative real-time polymerase chain reaction (qRT-PCR) for SARS-CoV-2 detection in the event of exposure to an infected person or if they exhibited any COVID-19–related symptoms. Additionally, during the Omicron variant-of-concern surge, HCWs were encouraged to test weekly and received reminders through emails, text messages, or phone calls. All cohort members were asked to perform serology testing monthly. Detailed descriptions of the laboratory methods used are shown in Supplementary Methods 1.

The study was conducted during the dominancy of Omicron (transitioning from BA.1 to BA.2 and to BA.5 subvariants).

Study Design

The aim of this study was to estimate the association between anti–SARS-CoV-2 receptor-binding domain (RBD) immunoglobulin G (IgG) levels prior to receipt of a fourth-dose BNT162b2 vaccine and the risk of SARS-CoV-2 infection over a 6-month period following vaccination. The study period was from 27 December 2021 to 10 July 2022. Individuals from the cohort were eligible to participate if they were not previously infected with SARS-CoV-2 and had at least 1 anti–RBD-IgG measurement in the 3 months prior to receipt of the fourth-dose booster. Individuals were included in the analysis starting 7 days postvaccination.

The exposure of interest was the last anti–RBD-IgG level measurement taken prior to receipt of the fourth dose. The outcome was SARS-CoV-2 infection, defined as either a positive SARS-CoV Ag-RDT or qRT-PCR test, or seroresponse, that is, an increase in IgG levels that could not be attributed to vaccine receipt (Supplementary Methods 2). Covariates adjusted for the analysis included age, sex, and professional role (physician, nurse, paramedical personnel, or administrative staff). In

addition, we further adjusted for the time period postvaccination (categorized as 7–35, 36–102, and 103–181 days).

Definitions of the variables used in the study are included in Supplementary Table 1.

Statistical Analysis

The study population was described using appropriate statistics. Using a previously reported cutoff of 700 binding antibody units (BAU) [11], cumulative incidence curves were drawn using the Kaplan-Meier method for individuals with prevaccination IgG levels above and below the cutoff.

A Cox proportional hazards model was used to estimate the association between preinfection serology and the risk of infection, adjusted for age, sex, and professional role. The exposure was modeled both as categorical (using the above-mentioned threshold) and as continuous (transformed using the $base_{10}$ logarithm), assuming a linear relationship with the log-hazard. An additional model was fit modeling the exposure using a smoothing spline [12] to observe the shape of the association and to test for a nonlinear relationship. In all these analyses, calendar time was used as the timescale to adjust for the differing pandemic activity over time.

There were no missing data in the variables used for analysis. Analysis was performed with the R statistical programming language, version 4.1.2.

Additional Analysis

To account for the different time lengths, prior to receipt of the fourth dose, in which the serology tests were done, we performed an additional analysis in which the exposure was defined based on imputed IgG values on the day the fourth dose was given. This analysis used third-dose serology data from the entire cohort. More details are included in Supplementary Methods 3.

Ethical Considerations

The protocol was approved by the Institutional Review Board of the SMC and written informed consent was obtained from all study participants.

Table 1. Association Between Prevaccination Immunoglobulin G Level and the Risk of Infection

Term	Hazard Ratio (95% CI)
Categorical	
Prevaccination IgG <700 BAU	Reference
Prevaccination IgG >700 BAU	0.65 (.52–.80)
Continuous	
Prevaccination IgG ($base_{10}$ logarithm)	0.54 (.41–.71)

The association between prevaccination IgG levels and the risk of infection. The association was as estimated using a Cox proportional hazards model adjusted for age, sex, professional role, and time following vaccination, and using calendar time as the timescale. The coefficient for the prevaccination IgG level was exponentiated to derive the hazard ratio. Two models were fit, 1 in which the exposure was categorized to above and below 700 BAU, and 1 in which the exposure was kept continuous.

Abbreviations: BAU, binding antibody units; CI, confidence interval; IgG, immunoglobulin G.

RESULTS

Of the 15 263 healthcare workers taking part in the HCW cohort, 1098 were eligible and were included in this study (Supplementary Figure 1). A description of the population is included in Supplementary Table 2. Individuals with prevaccination IgG levels above and below the threshold of 700 BAU were similar in respect to their age, sex, body mass index, number of comorbidities, and professional role. The median time difference between the serology test used to define the exposure and receipt of the booster was 8 days, with an interquartile range of 0–22 days.

Cumulative incidence curves show higher infection rates among individuals with prebooster vaccination IgG levels <700 BAU (Supplementary Figure 2). Using a smoothing spline, the relative infection rate is shown to decrease linearly on the log-hazard scale as prevaccination IgG levels increase, with the nonlinear component nonsignificant ($P = .55$, Supplementary Figure 3).

Using an adjusted model and modeling the exposure as categorical, we estimate that a prevaccination IgG level >700 BAU is associated with a 35% (95% confidence interval [CI]: 20%–48%) reduced risk of infection in the 6 months following vaccination. Modeling the exposure as continuous, we estimate that for each 10-fold increase in IgG level, the risk of infection is reduced by 46% (95% CI: 29%–59%) (Table 1 and Supplementary Table 3).

The model imputing IgG values on the day the fourth dose was given showed good fit (Supplementary Figure 4). Repeating the analysis with these values yields similar results to the main analysis (Supplementary Table 4).

DISCUSSION

In this study, we estimated that pre–fourth dose IgG levels are strongly predictive of subsequent risk of infection. We estimated that those with preboosting levels >700 BAU have a 35% reduced risk of infection over a 6-month period compared to those with preboosting levels <700 BAU. Moreover, for each 10-fold increase in IgG levels, the risk of infection over a 6-month period is reduced by 46%.

Previous publications have demonstrated that there is a strong correlation between antibody levels and the risk of infection with SARS-CoV-2 [10, 13–15]. Here we show that this correlation persists for the Omicron variant, for a second booster (fourth dose overall), and even when the antibody levels are measured before receipt of the booster.

These findings have 2 potential uses. At the population level, the proper time for boosting can be decided by tracking serology levels in sentinel cohorts. At the individual level, as individuals show different rates of waning immunity [9], baseline serology could potentially be useful for creating individually tailored vaccination schedules. These schedules would be timed

to maintain the individual's antibody levels above a certain threshold, deemed sufficiently protective.

However, this causal conclusion is only suggested by our findings. While we do find that prevaccination IgG levels are strongly predictive of subsequent risk, this does not necessarily mean that increasing IgG levels (ie, by more frequent vaccination) would reduce that risk. Such a conclusion would require a randomized trial or an observational study capable of emulating such a trial.

This study has several limitations. First, we only estimated the association of IgG levels with SARS-CoV-2 infection, and not with severe outcomes, which did not occur in our study population. Second, only individuals who had undergone serologic testing 3 months prior to vaccination were eligible for the study. This selected population might not fully represent the general population. Third, the dominant Omicron subvariant changed over the course of the study, and it is possible that the association between prebooster IgG levels and the risk of infection is different for each subvariant, making the reported estimate an average of these distinct associations. Fourth, it is important to note that humoral immunity likely only explains part of the protection against infection. Last, it is possible that certain SARS-CoV-2 infections were not detected (affecting both eligibility and outcome). However, surveillance in the study population was intensive and included serologic testing, which is not often employed in other contexts and studies.

In conclusion, in this study we estimated that the prebooster anti–SARS-CoV-2 IgG levels are strong predictors of subsequent risk of infection, suggesting that individuals' antibody levels could be used to optimally time future vaccinations. Such a policy should be explored in future studies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Data availability. Due to data privacy regulations, the raw data of this study cannot be shared.

Potential conflicts of interest. G. R.-Y. reports institutional grant funding of studies not related to the current study from Pfizer and Moderna; and consulting fees/honoraria from Teva, MSD, AstraZeneca, Pfizer, Moderna, and Medison. N. B. and Y. L. report institutional grants from Pfizer and Moderna. Y. L. reports an investigator-initiated grant from Pfizer, unrelated to this work. Y. K. reports other financial or nonfinancial interests as a lecturer in Tel Aviv University—as a faculty and as guest lecturer in Reichman University. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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