Open Forum Infectious Diseases

BRIEF REPORT

Impact of Previous Coronavirus Disease 2019 on Immune Response After a Single Dose of BNT162b2 Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine

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Immune response after a single dose of BNT162b2 vaccine was markedly increased in subjects with previous severe acute respiratory syndrome coronavirus 2 infection, reaching similar immunoglobulin titers to those elicited by the full 2 doses in naive cases, and increased modestly after the second dose. These data may inform the priority of the boosting dose.

Keywords. COVID-19; health care workers; immune response; SARS-CoV-2; vaccine.

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is proposed by the World Health Organization as the main option, at the present time, to control the coronavirus disease 2019 (COVID-19) pandemic. However, limited vaccine supply reduces the ability to reach a substantial proportion of individuals and delay the expectations of herd immunity [1]. The standard vaccination protocol for messenger RNA (mRNA) vaccines includes a 2-dose vaccine administration 3–4 weeks apart [2]. In this setting, a strategy to use a single dose of mRNA vaccines for some individuals could accelerate the achievement of this goal. Data on immune responses to single-dose vaccination with BNT162b2 are limited to a few observational studies with small numbers of patients [3–6]. Moreover, the impact of previous natural infection on vaccine response is not well known. We thus sought to evaluate the immune responses after the first and second mRNA vaccine doses according to different groups of previous SARS-CoV-2 infection and clinical COVID-19 presentation.

METHODS

A random sample of 642 health care workers (HCWs) enrolled in a previous hospital-wide seroprevalence study of 2590 HCWs (April 2020 and November 2020; [7]) were invited to participate in this study, based on stratification of 3 groups according to their seropositive status in both surveys: (1) naive SARS-CoV-2 patients (seronegative in both surveys); (2) transient seropositivity (seropositive in first survey and negative in second survey); and (3) persistent seropositivity (seropositive in both surveys). Seropositive HCWs were further classified according to the severity of their previous SARS-CoV-2 infection: asymptomatic; moderate COVID-19 (attended as outpatients); or severe COVID-19 (required hospital admission).

Blood samples from HCWs who had received the first dose of the mRNA BNT162b2 vaccine (Pfizer/BioNTech) were obtained just before the administration of the second dose of vaccine (21 days after the first dose) and 3 weeks after the second dose.

Previous SARS-CoV-2 infection was considered when SARS-CoV-2 reverse-transcription polymerase chain reaction or immunoglobulin G (IgG) was positive (regardless of symptoms) in the first seroprevalence survey.

The SARS-CoV-2 IgG assay used is a chemiluminescent immunoanalysis of microparticles used for the quantitative detection of IgG antibodies against the spike protein (receptor-binding domain) of SARS-CoV-2 (IgG-S) in the Architect system (ABBOTT Diagnostics) with a cutoff of <50 arbitrary units (AU)/mL.

Statistical Analysis

Demographics were compared by univariate analysis using χ^2 test and the Student *t* test. IgG-S titers were described as geometric mean (GM), median and interquartile range. We used univariate nonparametric test, Mann-Whitney *U* test, and Kruskal-Wallis test to compare IgG-S titers between groups. Multiple comparisons were adjusted by Bonferroni method. To compare change between first and second dose, we use the nonparametric related-sample test, Wilcoxon test.

To estimate the difference between subgroups, anti-spike IgG titer was log transformed and mixed linear regression models were performed (Supplementary Table 3). Data were evaluated with SPSS version 17 (IBM, Armonk, New York) and R 3.4.4 software (https://cran.r-project.org/bin/windows/base/old/3.4.4/).

Received 26 April 2021; editorial decision 1 June 2021; accepted 3 June 2021.

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Open Forum Infectious Diseases®2021

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DOI: 10.1093/ofid/ofab299

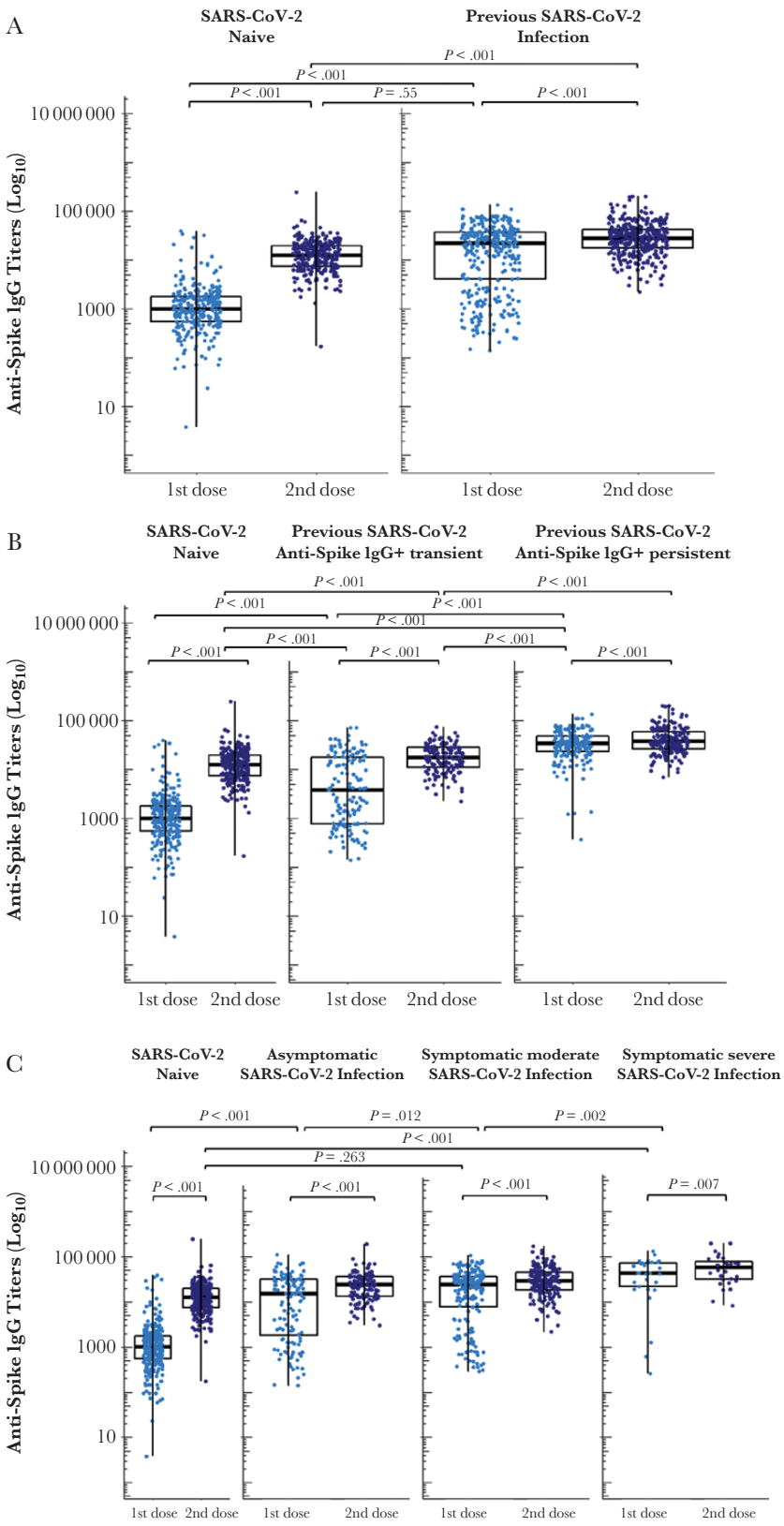

Figure 1. Serological response after 1 or 2 doses of the BNT162b2 messenger RNA coronavirus disease 2019 (COVID-19) vaccine in 641 health care workers. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin G anti-spike (IgG-S) were determined 3 weeks after the first dose (light blue dots; n = 641) and 3 weeks after the second dose (dark blue dots; n = 623) with chemiluminescent immunoanalysis (Architect, ABBOTT Diagnostics) with a cutoff of <50 arbitrary units (AU)/mL. IgG-S titers are represented in a logarithmic scale (y-axis). Individual data (dots) and median values and interquartile range (boxes) of different groups (x-axis) are depicted. Statistics: univariate nonparametric test, Mann-Whitney *U* test, and Kruskal-Wallis test were used, as appropriate, to compare IgG-S titers between groups. Multiple

All participants signed written consent. The protocol was approved by the independent review board of our hospital.

RESULTS

A total of 642 HCWs were invited to participate in the study; 641 accepted (99.8%), and follow-up was completed in 623 (97.0%). Mean age was 45.8 (standard deviation, 10.7) years and 77.3% were women. There were no significant differences among the groups except for a lower percentage of tobacco use (14.8 vs 21.5%, $P = .029$) and higher percentage of obesity (11.6 vs 6.2%, $P = .014$) in patients who developed COVID-19 (Supplementary Table 1).

IgG-S titers were about 12-fold higher after the first dose of the vaccine in HCWs with previous SARS-CoV-2 antibodies (GM, 11 701 AU/mL) than in naive individuals (GM, 992 AU/mL; $P < .001$) and of similar magnitude to those achieved after the second dose in naive cases (GM, 11 895 AU/mL; $P < .001$) Figure 1A, Supplementary Table 2. The boost dose in naive subjects induced about a 12-fold increase in median IgG-S titers, as compared to a modest 2-fold increase in nonnaive cases.

Naive SARS-CoV-2 individuals, transient seropositive subjects, and persistent seropositive subjects exhibited progressively higher IgG-S titers after the first dose of the vaccine (GM of 992, 3664, and 31 426 AU/mL, respectively; $P < .001$ for all comparisons) Figure 1B). In other words, as compared with naive SARS-CoV-2 subjects, transient seropositive patients showed about a 4-fold, and persistent seropositive patients about a 32-fold higher level of IgG-S after the first dose of the vaccine. Interestingly, the serologic response after the first dose in transient seropositive cases was lower than that obtained with 2 doses in naive subjects (Figure 1B). The boost dose induced about a 4.6-fold increase in median IgG-S titers in transient seropositive cases but a mere 1.2-fold increase in persistent seropositive subjects (Supplementary Table 2).

Previous COVID-19 clinical severity was also associated with increased titers of IgG-S 3 weeks after the first dose of the vaccine: asymptomatic (GM, 7752 AU/mL), mild to moderate (GM, 13 458 AU/mL), and severe (GM, 29 625 AU/mL) (Figure 1C). For all symptomatic patients, IgG-S titers after the first dose of the vaccine were higher than those achieved in naive cases after the full 2-dose vaccination. The boost effect of the second dose was inversely related to the severity of the clinical presentation (Supplementary Tables 2 and 3).

A total of 13 subjects developed symptomatic COVID-19 after the first dose of the vaccine, showing a GM IgG-S titer of 3039 AU/mL. Since it is impossible to discern the relative contribution of the vaccine and postvaccine SARS-CoV-2 infection to the IgG titer, no comparison was made between this group and others.

We further evaluated the different serological response in the groups mentioned above with a linear regression model after a logarithm transformation of IgG titers and adjusting for age, sex, and comorbidity. Qualitatively the results are essentially unchanged. Previous SARS-CoV-2 exposure and disease severity were associated with strong serologic response after the first dose of at least a similar magnitude as the full 2-dose vaccine in SARS-CoV-2–naive subjects (Supplementary Table 3). The boosting dose effect was lower for groups with a strong response to the first dose.

DISCUSSION

Our serological evaluation in HCWs shows a dramatic differential response 3 weeks after a single dose of the BNT162b2 mRNA vaccine according to previous SARS-CoV-2 infection and serological status. So far, this is one of the largest studies on immune response after the first and second doses of BNT162b2 vaccine. Of note, patients with previous history of SARS-CoV-2 infection reached at least 1 order of magnitude higher titers of anti-spike IgG. Interestingly, IgG-S titers achieved by a single dose in seropositive patients were of similar magnitude than those achieved by full vaccination in SARS-CoV-2–naive cases.

Although we have not assessed the presence of neutralizing antibodies, our results reinforce preliminary reports with a small number of cases [3–6]. This robust serologic response is highly correlated to the presence of neutralizing antibodies [8]. However, at present, we have no data regarding the duration of the serologic response nor the degree of protection against SARS-CoV-2 infection.

Our work provides some additional interesting data. First, HCWs who had lost their SARS-CoV-2 antibodies exhibited a lower response that might be insufficient to provide SARS-CoV-2 protection [3, 8]. Conversely, the combination of clinical COVID-19 and the presence of anti-spike IgG SARS-CoV-2 antibodies before vaccination are strong predictors of a robust serologic response to a single dose of the mRNA vaccine. This response is of similar magnitude or higher than that achieved by a 2-dose vaccination

comparisons were adjusted by the Bonferroni method. *A*, IgG-S titers in individuals who were SARS-CoV-2 naive or with previously documented infection. Of note, the strong serologic response in previously infected individuals after the first dose was of similar magnitude to that elicited by the 2-dose vaccine protocol in naive subjects. *B*, IgG-S titers in individuals according to their serologic SARS-CoV-2 status before vaccination. Seronegative: seronegative in both surveys. Transient seropositivity: seropositive in first survey and negative in second survey. Persistent seropositivity: seropositive in both surveys. Of note, the strong serologic response in infected individuals with persistent seropositivity after the first dose was even higher than that elicited by the 2-dose vaccine protocol in naive and transient seropositive patients ($P < .001$ for both comparisons); the response to the first dose of the vaccine in transient seropositive subjects was intermediate between seronegative subjects and persistent seropositive subjects. Boost effect was inversely related to the strength of the response to the first dose ($P < .001$; Supplementary Table 3). *C*, IgG-S titers in SARS-CoV-2–infected individuals according to their clinical COVID-19 presentation. Of note, the strong serologic response in subjects with previous SARS-CoV-2 infection after the first dose was even higher than that elicited by the 2-dose vaccine protocol in SARS-CoV-2–naive patients and increased progressively with the severity of the disease ($P < .001$). Boost effect was inversely related to the strength of the response to the first dose ($P < .001$; Supplementary Table 3).

in naive SARS-CoV-2 subjects. Our data suggest that the serologic response is close to saturation in seropositive patients after a single mRNA vaccine dose, as suggested by a limited boost response to a second dose of the vaccine.

There is current controversy about the most efficient strategy regarding the use of available vaccines in order to offer a wider population protection [9, 10]. In this regard, results from the United Kingdom suggest a decrease of COVID-19 following a program of single-dose vaccination [11]. In addition, this strategy may reduce the exacerbated clinical symptoms associated with the second dose in seropositive individuals [5]. Whether enhanced single-dose mRNA vaccine–induced serologic response among previously seropositive individuals will show a lasting response as compared to boosted vaccines is currently unknown. As no trial has evaluated the medium-term protective effects of a single-dose mRNA protocol, health policy makers rely on surrogate markers, such as SARS-CoV-2 seropositivity prior to vaccination, for this difficult decision [12]. Our results suggest that deferring the second dose of the vaccine for seropositive individuals with a predictable strong serologic response may not be a high-risk strategy for them, offering the option of vaccinating other individuals at risk until a wider vaccine availability allows for a standard 3- to 4-week interval between mRNA vaccine doses, as this is the protocol that has been tested in clinical trials. If SARS-CoV-2 serology is available, seropositive patients may be offered a deferred boost vaccination. Unfortunately, our serologic survey provided only qualitative information and we cannot provide estimation on vaccine response according to different levels of basal IgG titers. In circumstances where serology is unknown, previous COVID-19 severity may guide the selection of patients.

Supplementary Data

Supplementary materials are available at *Open Forum 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

Acknowledgments. We thank all workers of the Hospital Universitario Fundación Alcorcón for their everyday work and cooperation in this study and to the Alcorcón COVID-19 Working Group (Algora Weber, Alejandro; Alonso Punter, Juan Carlos; Bonilla Zafra, Gregorio; Bueno Campaña, Mª Mercedes; Carrión Pulido, Camilo; Diaz Cuasante, Ana Isabel; Fabero Jiménez, Aurora; Fariña García, Rosa María; González Anglada, María Isabel; Izquierdo Patrón, Mª Mercedes; Lorenzo Martínez, Susana; Mosquera González, Margarita; Pérez Encinas, Montserrat; Pérez Fernandez, Elia; Pérez Vega, Francisco José; Renilla Sánchez, Maria Esther and Mª José Goyanes Galán, Juan Emilio Losa-García, Gil Rodriguez-Caravaca.)

Potential conflicts of interest. All authors: No reported conflicts of interest.

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.

References

1. World Health Organization. Background document on the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19: background document to the WHO interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing, 14 January 2021. **2021**. Available at: https://apps.who.int/iris/handle/10665/338671. Accessed 8 May 2021.
2. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med **2020**; 383:2603–15.
3. Manisty C, Otter AD, Treibel TA, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. Lancet **2021**; 397:1057–8.
4. Prendecki M, Clarke C, Brown J, et al. Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine. Lancet **2021**; 397:1178–81.
5. Krammer F, Srivastava K, Alshammary H, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. N Engl J Med **2021**; 384:1372–4.
6. Saadat S, Rikhtegaran Tehrani Z, Logue J, et al. Binding and neutralization antibody titers after a single vaccine dose in health care workers previously infected with SARS-CoV-2. JAMA **2021**; 325:1467–9.
7. Galán MI, Velasco M, Casas ML, et al. Hospital-wide SARS-CoV-2 seroprevalence in health care workers in a Spanish teaching hospital [manuscript published online ahead of print 18 December 2020]. Enferm Infecc Microbiol Clin **2020**. doi:10.1016/j.eimc.2020.11.015.
8. Bartsch YC, Fischinger S, Siddiqui SM, et al. Discrete SARS-CoV-2 antibody titers track with functional humoral stability. Nat Commun **2021**; 12:1018.
9. Bieniasz P. The case against delaying SARS-CoV-2 mRNA vaccine boosting doses [manuscript published online ahead of print 27 January 2021]. Clin Infect Dis **2021**. doi:10.1093/cid/ciab070.
10. Kadire SR, Wachter RM, Lurie N. Delayed second dose versus standard regimen for Covid-19 vaccination. N Engl J Med **2021**; 384:e28.
11. Vasileiou E, Simpson CR, Robertson C, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. *SSRN* [Preprint]. Posted online 19 February **2021**. Available at: https://www.ssrn.com/abstract=3789264. Accessed 10 May 2021.
12. Bubar KM, Reinholt K, Kissler SM, et al. Model-informed COVID-19 vaccine prioritization strategies by age and serostatus. *Science* **2021**; 371:916–21.