Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

rare events. Only when the limit of quantification is achieved can the frequency be considered reliable.[4] The numbers of relevant events (RBD-specific B cells in this case) should be a defined percentage of the total acquired events.

RBD^+ cells are a fraction of the MBCs generated by vaccination. B cells acquire increased specificity and affinity thanks to the mechanisms of somatic mutation and selection in the germinal centers. These mechanisms are severely impaired in patients with CVID.[5]

Beyond the technicalities, an inaccurate evaluation of the number of specific MBCs may lead to the conclusion that patients are protected and will be able to react to a SARS-CoV-2 encounter thanks to their MBCs. In contrast, when serum titers decline, patients with CVID will be unable to produce new specific antibodies because they lack the right MBCs. Administration of mAbs may prevent severe disease and emergence of new viral variants in these cases.

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Reply

To the Editor:

We would like to thank Salinas et al[1] for reading our article[2] and for their comments. However, they interpreted our conclusions completely incorrectly. Our study did not suggest that vaccinated patients with inborn errors of immunity (IEI) are able to generate a *protective* immune response; rather, it described an early post-vaccine T-cell and B-cell immunogenicity in patients with IEI. This point is clearly emphasized in the Discussion section of our article.[2]

The recently reported "breakthrough" COVID-19 cases in vaccinated individuals, which are the result of both the emergence of new viral variants and waning immunity over time, are a challenge in healthy vaccinated individuals, let alone in vaccinated patients with IEI. That said, we are standing behind the presented data and believe that patients with IEI should be encouraged to get vaccinated.

As for the comments on our flow cytometry data that were expressed by Salinas et al,[1] we appreciate their concern regarding correct identification of rare events; however, it is absolutely unnecessary. As correctly noted by Salinas et al,[1] RBD-specific memory B cells are generated by vaccination. However, they should note that our analysis in Fig E2 of our article[2] identified RBD^+, $CD19^+$ IgG^+/IgA^+ B cells (ie, all IgG/IgA B cells that are specific to RBD) and not only memory B cells. Therefore, our analysis also includes activated B cells that may not be yet $CD27^+$, as well as plasmablasts that are on their developmental route to becoming antibody-secreting plasma cells. This strategy is completely different, and it is by no means disputed by the results that Salinas et al[1] present in their Fig 1. The reasons why we chose this population are the early time point at which the samples were collected (2 weeks after vaccination) and the fact that the frequency of RBD-specific B cells, and not only RBD-specific memory B cells, is highly correlated with humoral activation and B-cell responses to SARS-CoV-2.

Regarding the suggestion by Salinas et al[1] that the number of RBD-specific B cells be defined in a way similar to the number of paroxysmal nocturnal hemoglobinuria cells, in their article on consensus guidelines to detect glycosylphosphatidylinositol-deficient cells, Illingworth et al[3] specifically suggest that limit of detection and limit of quantification should be calculated out of the *gated* events acquired, and not the total number of events. Therefore, in our case, these events should be calculated out of the B-cell population. This approach would make sense, as patients with CVID can have B-cell lymphopenia, and calculating the number of RBD^+ cells out of the total number of events could result in underestimation of the frequency of antigen-specific B cells within the B-cell population.

In addition, our Fig E2[2] shows representative plot figures of RBD^+ B cells, and the percentage of RBD^+ cells correlated well with the donor anti-S IgG levels. We used several methods to evaluate our patients' humoral response, including commercial anti-S antibody detection assay, in-house ELISA assay, and inhibition assay. All 3 methods showed similar results. It is therefore reasonable to assume that these antibodies were produced by RBD-specific B cells.

Salinas et al[1] detected humoral vaccine response in only 23.5% of their patients with CVID, and they explain this finding by impaired mechanisms of somatic hypermutation and selection in the germinal center. In that regard, the term *CVID* probably includes a group of mechanistically distinct pathologies, mostly affecting cell maturation and differentiation.[4] Our study showed that patients with CVID exhibit a wide range of anti–SARS-CoV-2 antibody titers following vaccination, with a significantly better responses seen in younger patients (younger than 50 years), as opposed to older patients with CVID. In accordance with our

findings, 2 preliminary studies showed that most patients with CVID were able to mount an anti–SARS-CoV-2 / antivaccine humoral response. Kinoshita et al recently described a robust immune response after COVID-19, with 4 of 5 patients generating a humoral immune response despite their underlying antibody deficiency.[5] Similarly, Squire and Joshi[6] evaluated the humoral immune response to mRNA COVID-19 vaccine in 10 patients with underlying primary immune deficiency. Their cohort included 6 patients with CVID, 1 patient with hypogammaglobulinemia, 1 patient with Wiskott-Aldrich syndrome, 1 patient with 22q11.2 deletion syndrome, and 1 patient with X-linked agammaglobulinemia. All but the patient with X-linked agammaglobulinemia were able to produce specific anti–SARS-CoV-2 spike protein antibodies, suggesting that patients with antibody deficiency are able to respond to the vaccine.[6] That said, we agree that further data with larger-scale studies and longer duration of follow-up are required.

Obviously, we all want the best for our patients, and although concern for false reassurance is in place, at this point, vaccination is still our only way to try and prevent infection and should therefore be encouraged.

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