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.

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Letter to the Editor

Post-SARS-CoV-2 vaccination specific antibody decrease : Let's get the half-full glass perspective

Dear editors,

We read with great interest the papers recently published in the Journal of Infection tackling the issue of post-vaccination antibody levels to SARS-CoV-2 spike protein.[1,2] Our attention was caught by the report from Favresse and Douxfils[1] showing that high dilution of the tested samples provided a more accurate appreciation of post-vaccination antibody levels. The same authors just published a related study where anti-SARS-CoV-2 serology was followed-up for up to 3 months.[3] Because they found a significant decrease in day 56 and day 90 antibody levels, they conveyed this notion in the title of their publication. This certainly catchy label can however, in this touchy context, be interpreted as bad news. Here we would like to re-interpret these data in a more positive way by emphasizing the high antibody titers detected in this study.

Indeed, numerous reports to date have used the Roche Elecsys® assay (Anti-SARS-CoV-2 S, Roche GMBH) and can be compared. Of note, the manufacturers' recommendations to use 12 or 20 µL of undiluted serum (depending on the analysis instrument) yield an upper positive threshold of 250 U/mL. This already shows an about 300-fold increase compared to the 0.8 U/mL detection threshold. This range allowed for instance to positively compare post-vaccination anti-SARS-CoV-2 antibody levels between allogeneic hematopoietic stem cells recipients and healthcare workers, some reaching this upper threshold after just one injection of BNT612b2 (Pfizer BioNTech, Mainz, Germany).[4] Other studies have however previously indicated that anti-spike antibody levels could be high above this upper threshold of 250 U/mL. Indeed, in a comparative study of antibody responses of convalescents, vaccinated healthcare personnel and control samples, Suhandynata et al.[5] used a 1:10 dilution and thus raised the upper threshold to 2 500 U/mL. These authors reported a median value above 2500 U/mL for 100% of vaccinated individuals after a booster shot (range 1 009 -> 2 500), thus much above the 250 U/mL threshold of the undiluted serum assay. Similar results were reported by Mueller in assay comparisons,[6] with levels increasing in the course of a 5-week follow-up of vaccinated individuals.

Longer follow-up studies so far have mostly reported sustained antibody levels to the spike protein of SARS-CoV-2. In previously seropositive vaccinated healthcare workers, Tré-Hardy et al.[2] described stable levels over 400 U/mL at 3 months. A comparable result was observed in convalescent patients by Gerhards et al.[7] showing sustained levels up to 1 000 U/mL with little variation over 3 months. What Favresse and Douxfils.[1,2] tell us is that antibody levels in the range of 25 ,000 or above are reached after vaccination, i.e. a 30 ,000-fold increase compared to the negativity threshold < 0.8 U/mL. Close examination of their results discloses that, at three months, these titers still exceeded most previously reported upper thresholds. They ranged between 500 and 25 ,000 U/mL in individuals seropositive before the two doses of vaccines administered and between 500 and ~5000 U/mL in subjects seronegative before vaccination. The respective means at day 90 were around 10 ,000 and 1 250 U/mL respectively, thus 40 times and 5 times above the 250 maximal positive threshold of the standard assay and 4 and 3 logs above the detection level. The authors also report wisely on estimated times of possible seronegativation of respectively 1 184 and 554 days for these two groups of patients, pending no other antigenic stimulation has occurred.

The observation by Favresse et al.[2] is typically that of the normal kinetics of a strong post-vaccination humoral response. From a fundamental point of view, it has long been demonstrated that immune responses rely on consecutive cycles of clonal proliferation followed by clonal contraction leaving a progressively increasing pool of memory cells.[8] The latter are then liable to provide a quicker and more important anamnestic or secondary response.

The higher and more sustained response of previously seropositive individuals in the study by Tré-Hardy et al.[2] indicates that the vaccination indeed amplified an already settled immune response. These results can be compared to the smaller study of Doria Rose et al.[9] with different vaccine and assays, yet following patients for 6 months. In this cohort of 35 subjects, individual antibody kinetics clearly showed the booster effect of the second dose of vaccine. Indeed, an initial increase of antibody levels at day 15 was followed by a decrease of the primary immune response by day 29, just before the second injection, especially in neutralizing antibodies. Antibody titers then shot up.

Tré-Hardy et al.[2] pointedly mention that cellular responses of the T-cell compartment were not measured in their study but are likely to follow the same kinetics after infection and/or vaccination. Since cellular responses are even more efficient at eradicating viral infections than humoral responses, the results of this team are in fact quite encouraging.

It should also be mentioned that seropositive individuals are liable to even increase their protection level as long as the virus is still circulating. Indeed, a recent study by Turner et al.[10] has shown that at least 12 weeks after a boost injection of BNT612b2, S protein-binding germinal center B cells were still identified in draining axillary lymph nodes. These results also offer optimism that humoral responses to vaccination will be long-lasting. Close follow-up should thus be continued to assess the ongoing kinetics of immune responses to SARS-CoV-2 in the now well-immunized vaccinated population.

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