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Commentary

# Immunological response after mild COVID-19: How long will it last?

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In this issue of E Bio Medicine, Alexander Wunder wood and colleagues, reported neutralisation titers, IgG and IgA levels, at baseline and 6 months after COVID-19 in a cohort of 48 individuals. Participant were 18 years or older, diagnosed between March and July 2020 with mild COVID-19, confirmed by PCR assessment in all but 3 cases, who were assessed by serology. Findings were compared with 41 healthy controls [1].

This manuscript contributes to add a missing tile to the mosaic. The first key-message of this manuscript is that all subjects demonstrated neutralizing activity at baseline as well as 6 months after symptom onset [1].

The second key-message is that neutralizing titres were persistent but significantly lower at 6 months, with such a trend mainly due to the greater difference in titers detected in those patients tested at one month after symptoms initiation. There was an absence of significant differences between baseline samples drawn in the second or third month and the corresponding 6 month test. The significantly lower neutralization titres in samples collected at between 2 and 3 months after the symptom onset suggests that the peak occurs at one month [1].

The kinetics between the baseline and the six month time points showed a decreasing (44% of patients), unchanged (50%) or increasing (6%) pattern of the neutralizing antibodies. The timing of sampling at baseline, in terms of time elapsed after symptom onset, could at least partially explain the different kinetics between the decreasing and the stable pattern, with later baseline sampling having missed the highest peak occurring roughly at 1 month after the infection. Baseline blood tests were not performed homogeneously, but with a relatively wide range after symptom onset (median of 49 days, range 29–86), whereas 6 month tests were consistently drawn at a median of 186 days (range 182–192). The increasing pattern of neutralizing antibodies in 3 patients was likely due to a re-exposure [1].

A third message comes from the observed trend between the neutralization titres at 6 months and the number of symptoms reported, but not the duration of symptoms. Patients in this cohorts reported a median of 5 symptoms (interquartile range -IQR: 4–8), with the most common being fatigue (73%), fever (71%), and headache (67%), elapsing a median of 14 days (IQR: 8–16) [1].

A cohort of mild COVID-19 has been described here. For the purpose of this study, Underwood and co-authors defined “mild” as those COVID-19 cases who recovered with “no requirement of hospitalization or therapeutic intervention” [1]. The extent of the therapeutic intervention is not detailed, but, cases requiring a prescription for non-steroidal anti-inflammatory drugs might have been excluded.

The kinetics of viral persistence within these 48 patients was not determined. RNA positivity in patient nasal-pharyngeal swabs might have persisted or not. One would expect that those who had a persistent RNA positivity in their mucosae might have maintained immunological response for a longer time.

When spike-specific antibodies were measured by enzyme-linked immunosorbent assays (ELISA), 88% of the patients had detectable IgG levels at baseline and 79% at 6 months, whereas 83% had detectable IgA levels at baseline and 75% at 6 months. Differences between each baseline and 6 month sample pairs were detected only for IgA amounts, with, again, the largest decline occurring in patients with earliest baseline measurements, able to detect the peak. The IgA longitudinal decrease was associated with changing neutralising titres. IgA are indeed expected to wane after the viral shedding stopped [1,2].

Detecting neutralizing antibodies or IgG per se at 6 months is somewhat expected, at least in patients with sustained response at the onset, as antibody half-life is roughly 6 months [2–4]. What is of the utmost importance will be to detect their persistence overtime, beyond 6 months [3,4]. Moreover, the minimum protective titre against SARS-CoV-2 remains to be determined, as in other viral infections [2–6]. Are patients with lower antibody levels necessarily at higher risk of subsequent reinfection? [7] Will immunological response behave similarly after exposure to subsequent variants? [8] Or will some more aggressive variants elicit a stronger response, regardless of the clinical pattern? Shall we expect the acquired immunity to wane overtime and after how long? Or will it last up to an $n^{th}$ mutation which will lead to a resistant variant? Furthermore, addressing these issue in vaccinated individuals will be of the utmost importance, as the general health status of the humankind might rely on the persistence of neutralizing titres after the ongoing vaccination campaign [9–10].

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Hopefully it will not take long before we learn more about the efficacy of the vaccine in the long-term. Such knowledge might boost the capacity to provide vaccinations throughout the planet. As the inclusion of low-income countries within the immunization program is crucial.

## Contributors

Commentary was written solely by AB.

## Declaration of Competing Interest

No disclosures relevant to this topic.

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