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Commentary

Waning antibodies to SARS-CoV-2 – Don't panic

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Most European countries were taken by surprise by the rapid spread of SARS-CoV-2 in spring 2020 resulting in a large first wave of COVID-19 cases that was finally controlled through harsh public health measures. Due to the lack of testing capacities and awareness in the population at the time, most SARS-CoV-2 infections were not detected, leading to a up to 10-fold underreporting of COVID-19 cases [1]. However, to inform public health decision makers and predict the future course of the pandemic, the actual number of people infected with SARS-CoV-2 needed to be estimated. Seroprevalence studies were initiated on national and regional level, e.g. Spain or the canton of Geneva [1,2], either targeting whole populations (random sampling) or specific highly exposed groups such as health care workers. In line with other nation-wide seroprevalence estimates in countries that had been similarly affected, like Spain [2], Ward et al. found an overall seroprevalence of 6% (95%CI: 5.8-6.1) in England 3 months after the peak of the first wave with higher seroprevalences detected in high density urban centres [3]. These estimates are based on the test results of an impressive number of nearly 100.000 randomly selected individuals, representative for the population of England, using a self-administered lateral flow immunoassay (LFIA). However, when the seroprevalence was estimated again at 4.5 and 6 months after the peak of the first wave, it declined by 19.0% (95%CI: 16.1-21.8) and 26.5% (95%CI: 23.8-29.0), respectively, leading to worried reports in some news outlets.

In general, a decline of seroprevalence (or seroreversion) always reflects the number of individuals that fall below the sensitivity threshold of the serological assay used in the particular study and does not represent the true number of individuals that completely have lost their antibodies or immunity [4]. Nevertheless, a decline of seroprevalence using a binary classification assay like the LFIA, is indicative of waning antibody levels assuming that the sensitivity of the assay did not change between different sampling time points. Recently, several studies assessed anti-SARS-CoV-2 antibody levels up to 6-8 months after SARS-CoV-2 infection [5,6]. In these cohort studies antibody levels only slightly decreased with binding or neutralizing geometric mean titres declining by 2-3-fold over the course of 6 months and the vast majority of patients remained seropositive. However, in contrast to the study by Ward et al. [3] these studies used more sensitive laboratory based serological assays and patients showed at least mild symptoms (i.e. no asymptomatic patients) [5,6], providing potential explanations for the observed differences. Another study that included asymptomatic patients reported lower levels of antibodies for asymptomatic patients compared to mild and severe patients [7], indicating that asymptomatic patients will serorevert earlier than symptomatic patients. In accordance with Ward et al, who reported the largest decline in seropositivity in the group that did not report COVID-19 symptoms (64% decline), the study by den Hartong et al. also found a higher rate of seroreversions at 6 months in asymptomatic/mildly symptomatic compared to symptomatic patients albeit at a considerably lower frequency (13% and 5% decline of seropositivity in asymptomatic vs symptomatic patients) [7]. Interestingly, Ward et al found the largest decline in seropositivity in people older than 75 years, while a recent study estimating the rate of protection from reinfection in the population of Denmark found a lower protection rate of individuals above 65 years (47.1% protection) compared to younger people (around 80% protection) [8]. Currently, it remains to be investigated whether there is a direct link between these observations. However, a recent analysis showed that binding and neutralizing antibodies correlate well with vaccine efficacy indicating that they will likely serve as a good correlate of protection from either reinfection or symptomatic COVID-19 [9].

It is widely accepted that neutralizing antibodies will likely play an important part in the prevention of reinfection [4]. However, there are several other compartments of the immune system that likely contribute to the prevention of clinical disease, especially in its more severe forms. Interestingly, the efficacy trials for mRNA vaccines have shown that protection from symptomatic COVID-19 disease starts around 10-12 days after administration of the first dose, i.e. at a time when there are very few neutralizing antibodies present indicating that the induction of T-cell responses likely play a role in prevention of symptomatic COVID-19 [10]. In line with this observation several studies found a strong and lasting induction of memory B and T-cell in SARS-CoV-2 infected patients at 6 months post onset even in asymptomatic individuals (summarized in [4]).

In conclusion, while waning (neutralizing) antibody levels in patients previously infected with SARS-CoV-2 might render them

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susceptible to reinfection again, the induction of a robust memory immune response makes it entirely plausible that the majority of these patients are still protected from severe COVID-19 disease.

Contribution

Benjamin Meyer is the sole author of this work and contributed to all aspects of this comment.

Declaration of interests

I have no conflict of interest to disclose.

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