Antibody Dynamics, Seroreversion, and Persistence After SARS-CoV-2: Another Answer

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COVID-19 has galvanized the attention of the world. In December of 2019, the canvas we call SARS-CoV-2 was blank. In a very short time, and reflective of what the scientific world can accomplish when focused and funded, large swaths of that canvas have been filled in—though much remains to be discovered. What is the duration of immunity after symptomatic versus asymptomatic infection? Can antibody measures tell us that answer? Do such measures vary by age, gender, race, or other parameters—such as, which variant one was infected with or whether subclinical wild virus (or vaccine-induced) boosting has occurred? What is the correlate(s) of protection? These issues surrounding antibody dynamics and persistence, as well as many other questions, rightly preoccupy scientists and clinicians.

In this issue of CID, den Hartog and colleagues report the result of a nationwide cross-sectional convenience seroepidemiology sample of 353 persons in the Netherlands with documented COVID-19 infection [1]. Their objective was to assess the persistence of IgM, IgA, and IgG antibodies to Spike S1 protein over time, as well as antibody avidity over time, and to relate antibody persistence to degree of symptoms at the time of infection.

The importance of such studies relates to advancing the science given the recent emergence of the SARS-CoV-2 virus, understanding the kinetics of antibody decay (seroreversion) over time, and to measure seroprevalence in populations of interest. In turn, such data may be useful in answering the questions raised above by determining potential correlates of protection, providing estimates of time to susceptibility after infection (perhaps based on disease symptomatology), and differences in antibody kinetics based on viral variant. In turn, these answers are important to informing public health policy in regard to changing population levels of immunity based on which variant(s) are

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circulating, optimal timing of COVID-19 vaccination after documented COVID-19 infection, and the potential need for booster immunizations.

The findings are interesting and helpful in furthering our understanding. As expected, IgM spike S1 antibodies rapidly (exponentially) declined over time, as did IgA antibodies. In contrast, anti-IgG spike S1 antibodies determined by a Luminex bead assay seven months after infection were maintained in 95% of subjects who had experienced symptomatic COVID-19 infection, versus 87% in subjects who had asymptomatic or mild infection. Higher IgA and IgG antibodies were observed in males and persons over age 50 years. Another finding, in a small random subsample of 73 subjects, was evidence of a 2-fold increase in antibody avidity to spike S1 over 7 months. Notable was the presence of IgM antibodies as long as six months later in 33% of the subjects. Does this represent re-infection after COVID-19 infection, subclinical wild virus boosting, a highly sensitive assay, or true kinetics of IgM after COVID-19 infection? Answers to these questions are important to understanding and interpreting the findings. Other explanations might include an element of prolonged or chronic infection; however, to date, that has not been observed in non-immunocompromised individuals.

Like all studies, this study presents some limitations worth noting. The sample size is small (n=353) and the avidity sub-study even smaller (n=73) in a country with a population of 17 million and a blood donation center that tests over 10,000 samples per week. Individuals in the study were selected from round one of the PIENTER-Coronavirus Study (n>3,200), and round two (n>7,300) took place during a time when the seroprevalence of infection in the Netherlands was 3% and 4%, respectively. Expanding this type of study across sex, age groups of interest, race, and major categories of co-morbidities would be extremely valuable, as would continuing the study as

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successive waves of infection occur with different SARS-CoV-2 variants over time. Ideally, the use of neutralizing antibody assays that included not just antibody against the S1 protein, but also the receptor-binding domain (RBD) could be done, as well as cellular markers of immunity such as has been done in other studies [2]. Protection against disease involves innate, adaptive humoral, and cellular arms of immunity and information on all three would be informative. Nasal washes to measure anti-S1 IgA antibody would also be of interest, given the portal of entry for this virus, as well as the potential role of antibody to other SARS-CoV-2 structural and non-structural proteins—including N, M, and perhaps E proteins.

So how does this study advance our understanding of COVID-19 immunology and its correlation with clinical symptoms? First, waning of anti-S1 IgA may be in part responsible for subsequent asymptomatic or mildly symptomatic nasal epithelial infections. Neither COVID-19 infection nor immunization produce sterilizing immunity, but both do induce disease-blocking immunity. The implication is that whether after infection or vaccination, it is possible to develop upper airway (nasal) infection (or reinfection) that may be transmissible to others. Second, studies such as this may allow us to compare and contrast immunology across parallel studies of naïve and previously COVID-19 infected persons after receipt of various SARS-CoV-2 vaccines. The immunological response after wild-type SARS-CoV-2 virus infection is different than after an S-only vaccine approach [3, 4], and understanding those differences is likely to be helpful. Third, the results reported by den Hartog et al. can be compared against other similar-in-intent studies with a view toward understanding the meaning of the heterologous findings across studies. The largest such study is the Icelandic study of 1,237 COVID-19 infected persons followed over four months with no appreciable change in anti-spike IgG antibodies measured by enzyme-immunoassay (EIA) [5]. Higher antibody levels were observed in those with increased body mass index (BMI), and lower antibody levels were seen in women (who had less severe infections), smokers, and those who took

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nonsteroidal anti-inflammatory drugs (NSAIDs). The UK study of 522 COVID-19-positive healthcare workers demonstrated that 94% of those with anti-spike IgG antibodies measured by EIA remained positive over a 180-day time period [6]. Wang et al. studied 173 COVID-19-positive patients over three months: IgG neutralizing antibodies gradually declined over three months, with a median decrease of 34% [7]. Twenty percent had a > 70% decline over 90 days. Iyer et al. demonstrated only very gradually declining anti-IgG RBD antibodies measured by EIA over 90 days [8]. On the other hand, a US study demonstrated an anti-spike IgG RBD measured by EIA half-life of 73 days [9]. Finally, a small study in the US demonstrated a four-fold decline in IgG neutralizing antibody level over a four-month time period [10]. The den Hartog study, like many others, observed higher anti-spike IgG antibody levels in symptomatic hospitalized patients, followed by symptomatic non-hospitalized patients, and the lowest levels in those with asymptomatic infections.

The authors of this study have usefully utilized existing biospecimens to carry out a study that offers clinically practical and useful results. I would encourage them to continue the study longitudinally, given the importance of what can be learned, and to consider adding additional antibody assays (including IgG subclass studies and neutralization assays—at least in a subset of samples) against other SARS-CoV-2 structural proteins, documenting any differential immune responses based on different viral variant infections, and intentionally recruiting subjects across age groups, race, sex, and major categories of co-morbidities, including subjects experiencing “long haul COVID-19.” Further efforts to match immunological measures over time with initial and ongoing clinical symptomatology would be useful. In addition, clinicians are confused over interpretations of differences in assays that measure NT_{50}, binding Ab, neutralizing Ab, Luminex, and EIA-based assays. In this regard, parallel studies of EIA, Luminex, and neutralizing antibody measures of anti-spike S1 and RBD, as well as antibodies to other structural proteins, would significantly deepen our knowledge base.

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Science tends toward reductionistic epistemology, even in the face of evidence that profound positively and negatively synergistic interactions occur in biological processes. The implication is that it is quite likely, as one example, that recommendations for potential booster doses of COVID-19 vaccines may differ between young and old, immunocompromised and healthy, one type of vaccine over another, and differential efficacy by circulating viral variant [11]. Collecting the data suggested above are highly likely to be informative of such public health and clinical guideline policies, including the optimal timing for the use of monoclonal antibodies in treatment, timing of the collection of convalescent plasma after COVID-19 infection (and the timing of its use) [12], booster immunization policies, the need and timing of immunization in previously infected persons [13] in the context of a limited vaccine supply in the midst of a pandemic, and serve as a model for future studies. Finally, similar immunological and clinical studies could be usefully carried out in vaccinated human challenge studies such as have been planned in the UK, and critical knowledge could be obtained. With emerging variants, new monoclonal antibody therapies, and an increasing time interval between initial COVID-19 infection or vaccination among the population, the need for additional knowledge of antibody dynamics and persistence is urgently needed.

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Disclosures

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland received personal fees for consulting from Eli Lilly and Company, AstraZeneca, and Moderna, and for serving as a scientific advisor for Janssen Global Services LLC/Johnson & Johnson, during the conduct of the study. Dr. Poland has received personal fees for consultative advice on vaccine development to Merck & Co., Merck Research Laboratories, Medicago, GlaxoSmithKline, Sanofi Pasteur, Emergent Biosolutions, Dynavax, Genentech, and Genevant Sciences Inc., Bavarian Nordic, Exelixis, Regeneron, Vyriad, Kentucky Bioprocessing, and Pfizer, outside the submitted work. Dr. Poland holds patents related to vaccinia and measles peptide vaccines (Vaccinia Virus Polypeptides, U.S. Patent Numbers 9,389,232; and 9,446,119; Naturally Processed Measles Virus Peptides from Class II HLA Molecules, U.S. Patent Number 8,221,762; Peptide Originating from Vaccinia Virus, U.S. Patent Number 7,622,120; Naturally Processed Measles Virus Peptides Eluted from Class II HLA Molecules, U.S. Patent Number 7,579,004). Dr. Poland has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine, during the conduct of the study. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

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