Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients

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We measured plasma and/or serum antibody responses to the receptor binding domain (RBD) of the spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 343 North American patients infected with SARS-CoV-2 (of which 93% required hospitalization) up to 122 days after symptom onset and compared them with responses in 1548 individuals whose blood samples were obtained before the pandemic. After setting seropositivity thresholds for perfect specificity (100%), we estimated sensitivities of 95% for immunoglobulin G (IgG), 90% for IgA, and 81% for IgM for detecting infected individuals between 15 and 28 days after symptom onset. Although the median time to seroconversion was nearly 12 days across all three isotypes tested, IgA and IgM antibodies against RBD were short-lived, with median times to seroreversion of 71 and 49 days after symptom onset. In contrast, anti-RBD IgG responses decayed slowly through 90 days, with only three seropositive individuals seroreverting within this time period. IgG antibodies to SARS-CoV-2 RBD were strongly correlated with anti-S neutralizing antibody titers, which demonstrated little to no decrease over 75 days since symptom onset. We observed no cross-reactivity of the SARS-CoV-2 RBD-targeted antibodies with other widely circulating coronaviruses (HKU1, 229E, OC43, and NL63). These data suggest that RBD-targeted antibodies are excellent markers of previous and recent infection, that differential isotype measurements can help distinguish between recent and older infections, and that IgG responses persist over the first few months after infection and are highly correlated with neutralizing antibodies.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has spread rapidly around the world since first identified in Wuhan, China, in December 2019 (1). On 11 March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, which surpassed 1 million reported global deaths on 28 September 2020 (2).

Currently, our understanding of antibody responses after infection with SARS-CoV-2 is limited (3–5). Specifically, we lack detailed descriptions and precise estimates concerning the magnitude and duration of responses, cross-reactivity with other coronaviruses and viral respiratory pathogens, and correlates of protective immunity after infection. A detailed characterization of antibody responses is needed to determine whether antibody-based tests can augment viral detection–based assays in the diagnosis of active or recent infection and to inform the design and interpretation of seroepidemiologic studies.

In this study, we characterize the kinetics and antibody isotype profile to the receptor binding domain (RBD) of the spike (S) protein of SARS-CoV-2 in a longitudinal cohort of North American patients infected with SARS-CoV-2, most of whom were hospitalized for COVID-19, and in prepandemic controls. We also examined how well these responses correlated with neutralizing antibody (NAb) activity directed at the S protein. In addition, we evaluated the cross-reactivity of these responses with other coronavirus RDVs and characterize assay performance using dried blood spots (DBSs) as an alternative to serum or plasma.

RESULTS

Study cohorts

Using an in-house enzyme-linked immunosorbent assay (ELISA), we measured anti-RBD antibody responses in two cohorts: (i) symptomatic patients who tested positive for SARS-CoV-2 by polymerase chain reaction (PCR) ($n = 343$) and (ii) healthy ($n = 1515$) and febrile controls ($n = 33$) collected before the SARS-CoV-2 pandemic.
Kinetics of anti–SARS-CoV-2 RBD antibody responses
If followed for more than 14 days since symptom onset, most cases (92%) had at least one immunoglobulin G (IgG) measurement higher than seen among any prepandemic control (Fig. 1). From days 5 to 14, there was a sharp rise in RBD-specific antibodies of all isotypes, and IgG measurements continued to rise until day 25 after the onset of symptoms (fig. S2A). The population average IgA and IgM responses peaked less than a week earlier than IgG and then declined toward concentrations measured in prepandemic samples (figs. S2 and S3). IgG antibody responses also began to wane, but at a slower rate. Among 117 cases with ≥4 measurements, the individual peak IgM measurement often occurred before that of IgG (before: 55%, simultaneous: 38%) and with that of IgA (before: 28%, simultaneous: 53%). Among hospitalized patients, the population average trajectory differed little between severity levels; the average IgG concentrations among hospitalized cases admitted to the ICU were higher than hospitalized cases not admitted to the ICU (fig. S2B). Concentrations of all isotypes were lower among immunosuppressed individuals (fig. S2C).

Accuracy of RBD antibodies for identifying recent SARS-CoV-2 infection
Each antibody isotype was indicative of infection, and the area under the receiver operating curve (AUC) for each antibody isotype increased to above 98% during the period of 15 to 28 days after symptom onset (Table 2). The AUC remained high for IgG (99%) and IgA (98%) after 28 days but began to fall for IgM (93%). Using test cutoffs set to ensure no false positives within the prepandemic samples (i.e., 100% within sample specificity), we found that the sensitivity of IgG antibodies rose from 7% (≤7 days) to 95% after 14 days of symptoms. The sensitivity of IgA and IgM rose to 90 and 81% 2 to 4 weeks after symptom onset but dropped after 4 weeks to 66 and 44%, respectively. Through 10-fold cross-validation, we found that the mean specificity for each isotype was 99.9% (fold-specific range: 99.4 to 100%).

Combining multiple isotype measurements to improve accuracy
We found that the accuracy of serologic identification of recent infections could be slightly improved by adding measurements of IgM and/or IgA to IgG at the earlier phases of infection (table S2 and fig. S4). Using random forest models to combine measurements of different isotypes, we estimated a cross-validated AUC (cvAUC) of 92% for IgG and IgM and 91% for IgG and IgA at 8 to 14 days after symptom onset. These models provide an estimate of the contribution of each antibody isotype as well as an approximation of the maximum predictive value of combined measures of anti-RBD IgG, IgA, and IgM responses. Although all isotypes contributed nearly equally to identifying recent infection antibody profiles in the early phase of illness, IgG responses were the most indicative of infection 8 or more days after the onset of symptoms (fig. S5). Using the predetermined thresholds for seropositivity for each antibody isotype, out of the 357 samples collected during early infection (<14 days after symptom onset), we were able to correctly identify an additional 19 (5%) cases among the IgG-negative samples by adding IgM, 21 (6%) by adding IgA, and 33 (9%) by adding both IgM and IgA. When accounting for class imbalance in the random forest procedure, similar results were obtained (figs. S6 and S7).
Estimation of time to seroconversion and seroreversion for each isotype

Using the cutoffs defined earlier, we estimated the distribution of the time required to become seropositive (seroconversion) and return to becoming seronegative (seroreversion). Overall, 324 (94%) individuals had more than one measurement for every 28 days of follow-up. Of the 159 cases with samples after 20 days post-symptoms, most had evidence of seroconversion for all isotypes (IgG: 96%, IgM: 88%, IgA: 89%). The estimated median time to seroconversion from symptom onset was comparable across antibody isotype: 10.7 days [95% confidence interval (CI): 9.6 to 11.9] for IgG, 11.7 days (10.4 to 13.0) for IgA, and 11.9 days (10.5 to 13.4) for IgM (Fig. 2). On average, we estimated the median time to seroconversion among hospitalized patients to be over 4 days earlier as compared with nonhospitalized patients for all isotypes; men and those aged <65 years also seroconverted more quickly on average (table S3).

Of seroconverted cases with samples 46 days post-symptoms or after, most eventually had IgM (45 of 61) and IgA (30 of 64) seronegative measurements. The median time to seroreversion for IgM was 48.9 days (95% CI: 43.8 to 55.6), with the first 5% seroreverting by 23.7 days (95% CI: 21.6 to 26.0). We estimated a slightly later median seroreversion time for IgA of 70.5 days (95% CI: 58.5 to 87.5), with the first 5% seroreverting by 27.7 days (95% CI: 22.8 to 32.9; Fig. 2). Only 3 of 70 cases had evidence of seroreversion for IgG. All three patients who seroreverted for IgG required ICU-level care; however, two of the three did not have robust IgG responses (peak IgG measurement <2 µg/ml, one of whom was immunosuppressed).

Association between RBD responses and the development of NAbs targeting the S protein

We measured pseudo-NAbs targeting the SARS-CoV-2 S protein in 88 samples from 15 individuals collected between 0 and 75 days post-symptoms (Fig. 3). Over the course of infection, all individuals tested developed detectable NAbs. NAb titers were correlated with the concentration of anti-RBD IgG ($r = 0.87$). Similar to anti-RBD IgG responses, NAb titers plateaued and remained detectable at later time points despite the more rapid decline of IgA and IgM responses.

Evaluation of cross-reactivity with other coronaviruses

We evaluated antibody responses to RBDs derived from S proteins of endemic human coronaviruses (i.e., HKU1, 229E, OC43, and NL63), SARS-CoV-1, and Middle East respiratory syndrome coronavirus (MERS-CoV) (fig. S8). Antibody responses to the endemic coronaviruses were comparable between prepandemic controls and individuals with COVID-19 at all phases of infection, demonstrating a lack of cross-reactivity. Although a few individuals with SARS-CoV-2 infection had increasing levels of antibodies to endemic coronaviruses over time, which could be explained by cross-reactive anamnestic responses/immunologic memory, the majority stayed the same. Thus, overall, we did not observe a detectable cross-reactive response to the RBDs of the endemic human coronaviruses across the population of individuals infected with SARS-CoV-2. In contrast, we did observe substantial cross-reactivity to SARS-CoV-1 RBD in individuals with COVID-19, but no notable cross-reactive responses to the MERS-CoV RBD. There were three prepandemic controls (samples collected before October 2019) with IgA cross-reactivity to SARS-CoV-1.
Comparison of plasma responses with DBS

Because DBS could be used in large serosurveys where venous blood may be logistically challenging to collect and process, we also evaluated the assay with simulated DBS eluates in a subset of patients (n = 20 at two time points; 40 samples) and prepandemic controls (n = 20). The anti-RBD IgG DBS measurements had a high degree of linear correlation in both cases and control plasma (r = 0.99; fig. S9). Although the classification of all samples was the same between DBS and plasma samples (100% classification concordance), values between the two sample types diverged more at low titer values.

DISCUSSION

In this study, we found that antibodies against the RBD region of the S protein were accurate indicators of recent severe SARS-CoV-2 infection. The presence of IgG antibodies targeting SARS-CoV-2 RBD was a highly sensitive (95%) marker of infection after 14 days from onset of illness. This is consistent with a growing body of data, which demonstrate that measurement of anti-RBD antibodies can accurately classify individuals recently infected with SARS-CoV-2 (6–9). Because this study was conducted in a large cohort of individuals with known SARS-CoV-2 infection (N = 343) and controls (N = 1548), it provides a robust measure of the accuracy of anti-RBD antibodies.

These findings also add to emerging evidence on the persistence and decay of antibody responses after SARS-CoV-2 infection. IgM and IgA responses to RBD were short-lived, and most individuals seroreverted within 2.5 months after the onset of illness. However, IgG antibodies persisted at detectable levels in patients beyond 90 days after symptom onset, and seroreversion was
Antibody responses to SARS-CoV-2 infection have led to widespread misperception that antibody testing may be inaccurate (16, 17). In contrast, our study, based on a very large sample of cases and controls, should provide significant confidence in the contribution of serologic measures in public health efforts to improve epidemiological investigations (18) and to provide high-resolution estimates of infection incidence across geographies and populations. In addition, the lack of cross-reactivity of antibodies to SARS-CoV-2 RBD with common cold coronaviruses provides additional data supporting the specificity of the assay.

One limitation of our study was that our cohort of individuals with SARS-CoV-2 infection was skewed toward adults with severe disease or with risk factors for disease progression. It is important to study the kinetics and, in particular, the decay of antibody responses in individuals with severe infection for several reasons. First, the magnitude and duration of the responses in individuals with severe infection likely provide an estimate of the upper bounds of the achievable immune response and the development of B cell memory. Second, these findings are expected to have significant implications for protective immunity in a population, which is vulnerable to poor outcomes when exposed. However, caution is required in generalizing these results to those with less severe infection. Individuals with mild or asymptomatic infection have been shown to develop less robust antibody responses (12), which may lead to false negatives if our proposed assay thresholds are applied in serosurveillance settings. In addition, the lack of cross-reactivity of antibodies to SARS-CoV-2 RBD with common cold coronaviruses also suggests that the detection of antibodies against SARS-CoV-2 RBD in individuals with mild or asymptomatic SARS-CoV-2 infection (11, 12).

Reverse transcription PCR (RT-PCR)–based detection of SARS-CoV-2 is sensitive early in the first week after the onset of symptoms (13), and our results suggest that the detection of antibodies against the SARS-CoV-2 RBD by ELISA, even when using all isotypes, is not likely to contribute significantly to the early diagnosis of COVID-19. However, beyond 2 weeks after symptom onset, supplementing viral detection assays with antibody-based testing methods increases sensitivity in diagnosing recent infection (14, 15), particularly as the sensitivity of RT-PCR for SARS-CoV-2 infection wanes (12). In particular, our results demonstrate that the earlier seroreversion of IgA and IgM responses will be helpful in distinguishing older infections from recent ones. Thus, the measurement of multiple isotypes, taking into account the early decay of IgA and IgM, is likely to be critical in interpreting the results of serosurveys and epidemiologic studies to estimate the time from infection. All considered, these findings suggest clearly defined applications for serologic testing of RBD responses in both clinical and public health surveillance settings.

Testing for anti–SARS-CoV-2 RBD antibodies can also be applied in seroepidemiologic studies, even in areas of low prevalence, given their excellent specificity and defined kinetics. Variation in the performance of commercial serologic tests and confusion about the role of antibodies as biomarkers of past infection versus protective immunity has led to widespread misperception that antibody

Fig. 3. SARS-CoV-2 pseudovirus neutralization antibody titers in symptomatic PCR-positive cases and correlation with anti-RBD IgG responses. (A) Each point represents a measurement of 50% neutralizing titer (NT₅₀). Lines connect measurements from the same individual, and a loess smooth function is shown in blue. (B) Overall repeated measures correlation coefficient (r). Lines represent simple linear models for each time period.
protection against symptomatic infection and decreased viral shedding (5). In addition, in vaccinated rhesus macaques challenged with SARS-CoV-2 infection, NABs directed at the S protein were also a strong correlate of protective immunity (20). Thus, neutralization titers, in the absence of other known markers, have become a de facto immunologic marker of protection pending further investigation. In this context, note that anti-RBD IgG antibodies were strongly correlated with the same NABs that were associated with protection in vaccinated macaques (20). This correlation with neutralizing titers was stronger than observed for other previously tested commercial serologic assays (21), and both anti-RBD and NABs persisted over a 2.5-month follow-up period.

Our results, therefore, provide strong support for the application of anti-RBD antibodies as a marker of recent SARS-CoV-2 infection as well as new and detailed information related to the specificity and decay kinetics of the anti-RBD responses. The testing approach used meets the Centers for Disease Control and Prevention’s guidelines for serologic testing (22) and has the potential to facilitate accurate diagnosis in clinical settings and the implementation of population-based studies of previous infection globally. Although the association between anti-RBD–IgG and neutralizing titers and the persistence of these antibodies at late time points is encouraging, further work is needed to define the optimal antibody-mediated correlates of protective immunity.

MATERIALS AND METHODS

Study design

We evaluated the magnitude and kinetics of the early human antibody response to the RBD of SARS-CoV-2 S protein, with the additional objective of evaluating the specificity and sensitivity of these antibody responses for identifying individuals with recent infection. Thus, we measured antibody concentration in blood samples obtained from confirmed patients with symptomatic SARS-CoV-2 infection and from control individuals whose samples were collected before the pandemic. IgG, IgA, and IgM antibody concentrations were measured by ELISA using recombinant SARS-CoV-2 RBD in all samples. In a subset of samples, NAB responses directed against the S protein were also measured using a lentivirus pseudoneutralization model. From these data, we modeled the classification accuracy for each individual isotype and combinations of isotypes at different time points and the temporal dynamics of seroconversion and seroreversion after the onset of symptoms.

Sample collection

We obtained plasma and/or serum samples, collected for routine clinical care, from individuals with PCR-confirmed SARS-CoV-2 infection presenting, with fever and/or viral respiratory symptoms from March to April 2020 and who met criteria for RT-PCR testing. Testing criteria for SARS-CoV-2 changed over time but primarily included patients with severe symptoms requiring hospital admission, those who had other risk factors for disease progression (e.g., were age 60 or older, had diabetes, or were immunocompromised), or those who worked or lived in a setting where infection control requirements dictated a need for testing. Additional serum/plasma samples collected from September 2015 to December 2019 before the SARS-CoV-2 pandemic included healthy adults seen at the Massachusetts General Hospital (MGH) Immunization and Travel Clinic before travel, patients undergoing routine serology, and patients presenting with other known febrile illnesses. Plasma samples, except for the routine serology samples, were heat-inactivated at 56°C for 1 hour before analysis. Patient demographic information, laboratory results, and clinical outcomes were extracted from the electronic medical record. Patients were considered immunosuppressed if they had underlying immunosuppressive condition (e.g., HIV with CD4 count less than 200) or were on an immunosuppressive/immunomodulating agent at the time of their admission (e.g., methotrexate and rituximab). All research was approved by the Institutional Review Board for Human Subjects Research at MGH.

Dried blood spots

Seventy-two microliters of single-donor, seronegative whole blood collected from sodium heparin tubes (Becton, Dickinson, NJ) was spiked with 8 μl of heat-inactivated plasma (10% of the whole blood volume) to maintain the relative whole blood composition. Assuming that plasma is 50% of the whole blood volume, the spiked plasma was 18.18% of the final plasma volume. Whole blood (40 μl) was spotted onto Whatman 903 Protein Saver cards (GE Healthcare, Cardiff, UK) in replicate and allowed to dry overnight at room temperature. Two 6-mm² punches from the DBS card (5 μl of plasma per punch) were placed in 133 μl of phosphate buffered saline-0.05% Tween 20 (pH 7.4) (Sigma-Aldrich, St. Louis, MO) and incubated overnight at 4°C with gentle agitation eluates that were then recovered after centrifugation. The total dilution of the spiked plasma in DBS eluate was assumed to be 1:73.15, which accounts for the initial dilution from spiking (1:5.5) and the further dilution during DBS elution (1:13.3).

Enzyme-linked immunosorbent assay

We measured IgG, IgA, and IgM responses to the RBD of the S protein from SARS-CoV-2 (GenBank: MN975262, MERS virus (GenBank: AFY13307.1), SARS-CoV-1 (GenBank: AAP13441.1), and common cold coronaviruses HKU1 (GenBank: AAT98580.1), OC229E (GenBank: AAK32191), OC43 (GenBank: AAT84362), and NL63 (GenBank: AKT07952). RBD sequences were cloned into pVRC vector followed by expression in mammalian Expi293 cells (Thermo Fisher Scientific, Waltham, MA) with a C-terminal streptavidin-binding peptide (SBP)–His8X tag and purified over TALON resin (Takara, Mountain View, CA) followed by size exclusion chromatography and cleavage of the His tag. RBD-specific antibody concentrations (in micrometers per milliliter) were quantified using isotype-specific anti-RBD monoclonal antibodies. The RBDS were expressed in Expi293F suspension cells with a C-terminal SBP-His8X tag and purified using affinity chromatography and then size exclusion chromatography before removal of the His tag as described previously (23). Briefly, 384-well Nunc MaxiSorp plates (Invitrogen, Carlsbad, CA) were coated by adding 50 μl of RBD in carbonate buffer (1 μg/ml) and incubating for 1 hour at room temperature. Plates were then blocked for 30 min at room temperature with 5% nonfat milk in tris-buffered saline (TBS). Diluted samples (1:100 in TBS with 5% milk, 0.05% Tween 20) were added to the plate (25 μl per well) and incubated for 1 hour at 37°C with shaking. Serial fourfold dilutions to 1:6400 were also included for individuals with high titers. At the end of incubation, samples were washed five times with 1× high-salt TBS with 0.05% Tween 20. Subsequently, goat anti-human IgA, IgG, and IgM horseradish peroxidase–conjugated secondary antibodies diluted (Jackson ImmunoResearch) at 1:10,000 (IgG, IgM) or 1:5000 (IgA) in 5% milk in TBS–TWEEN 20 were added.
to plates (25 μl per well) and incubated at room temperature with shaking for 30 min followed by five washes of 1× high-salt TBS with 0.05% Tween 20 and a last wash with 1× TBS. Bound secondaries were detected using 1-step Ultra TMB (tetramethylbenzidine; 25 μl per well; Thermo Fisher Scientific, Waltham, MA). Plates were incubated at room temperature for 5 min in the dark before addition of 2 N sulfuric acid stop solution (25 μl per well). The optical density (OD) was read at 450 and 570 nm on a plate reader. OD values were adjusted by subtracting the 570-nm OD from the 450-nm OD. We used a standard curve of the anti-SARS-CoV-2 monoclonal, CR3022 (24), to calculate the concentration of anti-RBD IgG, IgA, and IgM expressed in micrograms per milliliter. Note that for the DBS and plasma comparisons, the starting concentration was 1:200.

Pseudovirus neutralization assay

To determine the SARS-CoV-2 neutralization activity of our plasma samples, we used a lentivirus pseudoparticle neutralization model as previously described (20), which is a strong correlate of protective immunity in challenged rhesus macaques (25). We expressed results from this assay as the antibody titer required to neutralize 50% of the SARS-CoV-2 pseudovirus (NT50).

Statistical analysis

Single isotype thresholds

We first explored how cutoffs of individual isotypes (IgM, IgG, and IgA) performed in identifying previously infected individuals. We compared measurements from prepandemic controls with those taken at any time, ≤7 days, 8 to 14 days, 15 to 28 days, and >28 days after the onset of symptoms. We estimated the AUC for each isotype and time period combination and calculated bootstrap 95% CIs. Using the isotype cutoffs defined by the maximum concentration found among the full set of prepandemic controls (IgG: 0.57 μg/ml, IgM: 2.63 μg/ml, IgA: 2.02 μg/ml), we estimated sensitivity and bootstrap 95% CIs. We also evaluated how setting a cutoff defined by maximum concentration would affect specificity through 10-fold cross-validation.

Random forest classification models

We explored how combining multiple isotype-specific responses with random forest classification models, which allows for complex non-linear interactions between isotypes, performed identifying previously infected individuals. Using a previously described cross-validation procedure (26), we allocated both cases and controls into 10 equally sized groups (i.e., folds) and calculated a pooled cvAUC. We also assessed variable importance within these different models using a permutation test–based metric, mean decrease in accuracy. To investigate the impact of class imbalance (i.e., the fact that we had many more negative controls than positives) on our model performance metrics, we investigated the effect of downsampling controls to have the same number as cases on model performance.

Analysis of time to seroconversion and seroreversion

We limited our analysis to individuals who had at least one measurement for every 28 days of follow-up (i.e., between symptom onset and their last measurement). For individuals with fluctuations around the predefined cutoff (N = 6), the time to the first event was used in the analysis. Using individual-level interval-censored data, we fitted nonparametric (i.e., Turnbull’s estimator) and parametric accelerated failure time models using the icenReg R package (27). All time-to-event data were assumed to be log-normal distributed. Bootstrapped 95% CIs were estimated by sampling individuals with replacement. All analyses were completed using R (version 3.6.1) within RStudio (version 1.2.5019).

SUPPLEMENTARY MATERIALS

immunology.sciencemag.org/cgi/content/full/5/52/eabe0367/DC1

Figs. S1 to S9

Tables S1 to S4

View/request a protocol for this paper from Bio-protocol.

REFERENCES AND NOTES


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