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### Title

Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19

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### Authors

Ibarrondo, F Javier  
Fulcher, Jennifer A  
Goodman-Meza, David  
[et al.](#)

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## CORRESPONDENCE

## Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19

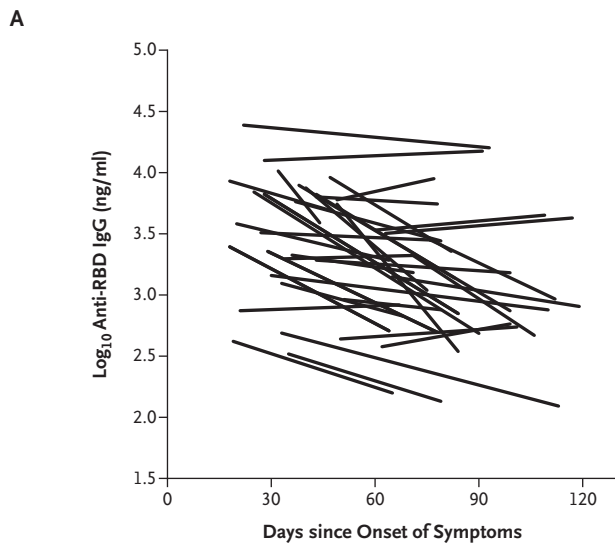
**TO THE EDITOR:** A recent article suggested the rapid decay of anti-SARS-CoV-2 IgG in early infection,<sup>1</sup> but the rate was not described in detail. We evaluated persons who had recovered from Covid-19 and referred themselves to our institution for observational research. Written informed consent was obtained from all the participants, with approval by the institutional review board. Blood samples were analyzed by enzyme-linked immunosorbent assay (ELISA) to detect anti-SARS-CoV-2 spike receptor-binding domain IgG.<sup>2</sup> The ELISA was further modified to precisely quantify serum anti-receptor-binding domain activity in terms of equivalence to the concentra-

tion of a control anti-receptor-binding domain monoclonal IgG (CR3022, Creative Biolabs).

Infection had been confirmed by polymerase-chain-reaction assay in 30 of the 34 participants. The other 4 participants had had symptoms compatible with Covid-19 and had cohabitated with persons who were known to have Covid-19 but were not tested because of mild illness and the limited availability of testing. Most of the participants had mild illness; 2 received low-flow supplemental oxygen and leronlimab (a CCR5 antagonist), but they did not receive remdesivir. There were 20 women and 14 men. The mean age was 43 years (range, 21 to 68) (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

**Figure 1. Longitudinal Assessment of Anti-SARS-CoV-2 Receptor-Binding Domain IgG in Persons Who Recovered from Covid-19.**

Approximately 80 persons who recovered from Covid-19 referred themselves to our institution to inquire about observational research. Of 68 persons who volunteered to provide initial blood samples, 41 returned to provide repeat samples. Of those persons, 3 were excluded from this analysis because of unclear timing of infection and 4 were excluded because of initial and repeat serum antibody measurements below the limit of reliable quantitative detection. For the 34 participants in our analysis, anti-SARS-CoV-2 receptor-binding domain (RBD) serum IgG concentrations were quantified by enzyme-linked immunosorbent assay as equivalent binding activity to a concentration of a control monoclonal IgG for at least two time points (31 of the 34 participants had two measurements, and the remaining 3 participants had three measurements). Panel A shows log-transformed IgG concentrations plotted against the time since the onset of symptoms in each participant. Panel B shows a linear regression model that was created to estimate the effects of the participants' age and sex, the days from symptom onset to the first measurement, and the first measured log<sub>10</sub> antibody level on the slope reflecting the change in anti-RBD antibody levels (in log<sub>10</sub> ng per milliliters per day). The values for age and antibody level were centered at the mean. The time since symptom onset was centered at day 18 and adjusted per 100 days. Thus, the intercept of the model can be interpreted as the average slope adjusted for age, sex, and time and value of the first measurement. CI denotes confidence interval.



**B**

Predictor	Slope		
	Estimate	Standard Error	95% CI
Intercept	-0.0083	0.0016	-0.0115 to -0.0050
Age (per 10-yr change)	0.0026	0.0012	-0.0001 to 0.0051
Sex (female reference)	0.0010	0.0034	-0.0059 to 0.0079
First antibody level (log <sub>10</sub> ng/ml)	-0.0049	0.0032	-0.0114 to 0.0016
Per 10 days since symptom onset	0.0016	0.0012	-0.0010 to 0.0041

A total of 31 of the 34 participants had two serial measurements of IgG levels, and the remaining 3 participants had three serial measurements. The first measurement was obtained at a mean of 37 days after the onset of symptoms (range, 18 to 65), and the last measurement was obtained at a mean of 86 days after the onset of symptoms (range, 44 to 119).

The initial mean IgG level was 3.48 log<sub>10</sub> ng per milliliter (range, 2.52 to 4.41). On the basis of a linear regression model that included the participants' age and sex, the days from symptom onset to the first measurement, and the first log<sub>10</sub> antibody level, the estimated mean change (slope) was -0.0083 log<sub>10</sub> ng per milliliter per day (range, -0.0352 to 0.0062), which corresponds to a half-life of approximately 36 days over the observation period (Fig. 1A). The 95% confidence interval for the slope was -0.0115 to -0.0050 log<sub>10</sub> ng per milliliter per day (half-life, 26 to 60 days) (Fig. 1B).

The protective role of antibodies against SARS-CoV-2 is unknown, but these antibodies are usually a reasonable correlate of antiviral immunity, and anti-receptor-binding domain antibody levels correspond to plasma viral neutralizing activity. Given that early antibody decay after acute viral antigenic exposure is approximately exponential,<sup>3</sup> we found antibody loss that was quicker than that reported for SARS-CoV-1,<sup>4,5</sup> and our findings were more consistent with those of Long et al.<sup>1</sup> Our findings raise concern that humoral immunity against SARS-CoV-2 may not be long lasting in persons with mild illness, who compose the majority of persons with Covid-19. It is difficult to extrapolate beyond our observation period of approximately 90 days because it is likely that the decay will decelerate.<sup>3</sup> Still, the results call for caution regarding antibody-based "immunity passports," herd immunity, and perhaps vaccine durability, especially in light of short-lived immunity against common human coronaviruses. Further studies will be

needed to define a quantitative protection threshold and rate of decline of antiviral antibodies beyond 90 days.

F. Javier Ibarondo, Ph.D.  
Jennifer A. Fulcher, M.D., Ph.D.  
David Goodman-Meza, M.D.  
Julie Elliott, M.S.  
Christian Hofmann, Ph.D.  
Mary A. Hausner, M.S.  
Kathie G. Ferbas, Ph.D.  
Nicole H. Tobin, M.D.  
Grace M. Aldrovandi, M.D.  
Otto O. Yang, M.D.

David Geffen School of Medicine at University of California,  
Los Angeles  
Los Angeles, CA  
oyang@mednet.ucla.edu

Drs. Ibarondo, Fulcher, Aldrovandi, and Yang contributed equally to this letter.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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