To the Editor

We read with interest the editorial regarding the use of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologic tests as a screening tool in populations with low prevalence.1 We agree that use of antibody tests for the novel coronavirus have the potential to be useful for clinical and population health applications. This is particularly true when the prevalence of antibodies in the tested population is at least 10% or greater. As the authors show, lower prevalence results in suboptimal positive predictive values even for serologic tests that have 99% specificity.

Of concern to us is how the authors chose to represent the clinical sensitivity of the 10 serologic tests that had been granted emergency use authorization (not approval) by the Food and Drug Administration (FDA) as of April 30, 2020. The sensitivities shown in Table 1 of their article are acknowledged as being derived from information on the FDA website. However, rather than reporting sensitivity (positive percent agreement) relative to the day of coronavirus disease 2019 (COVID-19) symptom onset or diagnosis, the authors chose to calculate sensitivity using the total of all specimens tested, without regard to the timing of sample collection (personal communication from authors). In our opinion, reporting sensitivity in this way is misleading, as it understates the optimal sensitivity, defined as the ability of a test to detect SARS-CoV-2 antibodies when they are present. No test is able to detect antibodies that are not present because they have not yet been produced or are at a concentration that is well below analytical sensitivity, as will happen in very early infection. The authors justified their calculation of sensitivity by stating that the tested population may not always be several days to weeks away from diagnosis. While this is true, the same could be said for any serologic test that is used as a screening test. As an example, the sensitivities of HIV antibody tests are calculated from individuals known to contain antibodies or from seroconversion panels. It is well known that tests for infectious disease antibodies will have lower sensitivities if used in very recently infected patients. The same is true for the novel coronavirus. Calculating and reporting antibody test sensitivity without regard to onset of infection is a practice to be avoided.

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Reference

1. Mathur G, Mathur S. Antibody testing for COVID-19: can it be used as a screening tool in areas with low prevalence? Am J Clin Pathol. 2020;154:1-3.

The Authors’ Reply

We would like to stress that our editorial intends to point out limitations of using antibody (serologic) tests as a screening tool mainly due to the low prevalence of COVID-19 in most parts of the United States and not specifically due to the limitations of test performance (sensitivity and specificity) of any individual test in the market. Test performance, mainly specificity, does contribute to low positive predictive value (PPV) of antibody tests. However, low prevalence is the main contributing factor, as shown in Table 2 of the editorial. We understand the concerns regarding presenting clinical sensitivity of the serologic tests as an average in Table 1 of the editorial instead of separating it by the timing of collection. We decided to present test performance data as an average of all specimens tested for the following reasons: (1) there is no uniformity in the data submitted to the FDA by test manufactures; (2) the table would have been too lengthy if we had split out sensitivity and specificity
for each cohort tested for each manufacturer; and (3) clinically the patients most likely will be tested irrespective of days post infection or start of the symptoms. To our knowledge, the manufacturers that have been granted emergency use authorization by the FDA do not specify in their instructions for use that the tests are intended to be used for patients only after certain days post infection or start of symptoms.

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