

CENTERING ON CORONAVIRUS

DIAGNOSTIC AND ANTIBODY TESTING

SARS-COV-2
RT-qPCR kit

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Centering on Coronavirus: Diagnostic and Antibody Testing

There is widespread bipartisan agreement that more and better COVID-19 testing will be essential to achieve a complete reopening of our economy. But today, the United States is conducting about 200,000 COVID-19 tests for active infection each day, compared to the minimum of 500,000 daily tests many experts believe will be required. In addition to testing for active COVID-19 infections, we will very soon need reliable antibody tests to identify who has already been exposed to the disease and more research to determine what, if any, immunity people acquire from these antibodies. Here, again, we're falling short.

Widespread testing for active infection is a crucial first component of an effective pandemic response plan. Testing helps to inform treatment for those infected, and when infected individuals are identified and isolated quickly, they can avoid spreading the virus to others. Comprehensive diagnostic testing also provides public health officials with useful information about the virus, such as its prevalence rate and modes of transmission. This in turn allows them to make predictions and formulate next steps in a response plan. As disease transmission progresses, antibody testing becomes an increasingly important tool in informing the reopening of society and the economy.

Both active and antibody testing for COVID-19 have posed significant problems, but for different reasons. Swab testing for active COVID-19—while dependent on various technologies—is becoming more reliable, with many lab-administered tests detecting over 95% of all positive samples. A new study from the Cleveland Clinic found that, while not all tests were as successful, the diagnostic test developed by the U.S. Centers for Disease Control and Prevention (CDC) correctly identified 100% of all positive samples. However, testing is too often unavailable due to shortages of testing materials and supply chain problems. Widespread COVID-19 antibody testing is also being held back by similar material and supply chain challenges, as well as even harder scientific questions about whether tests are screening for the right antibodies and what level of antibodies might confer immunity.

U.S. diagnostic testing capacity has increased exponentially since the beginning of the outbreak, but we still have a long way to go. And delays in reaching this point have proven to be costly. Bureaucratic hurdles, mixed messages from the federal government, and a faulty initial test from the CDC led to months of lost time during which new cases grew exponentially and testing was unable to reach those who needed it. As late as mid-February, the U.S. was only conducting about 100 tests per day.

In this paper, The New Center explores how the United States got behind the testing curve and how we might still be able to correct our course and start reopening the economy safely if we take steps to improve and expand testing now.

Diagnostic testing missteps

On January 17, the CDC announced its development of a diagnostic test for COVID-19. Due to limited testing capacity, they strictly limited who was eligible to receive a test. On January 21, the same day South Korea reported its first positive test, the first U.S. case of COVID-19 was confirmed in Washington state with the CDC's newly developed test. On January 31, Health and Human Services Secretary Alex Azar declared a public health emergency. This declaration initiated several new regulatory requirements for the development of testing. While intended to perfect diagnostic testing, these requirements amounted to a significant burden for private labs that had hoped to distribute their newly developed tests to the public as quickly as possible.



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Just days after the CDC distributed its tests to public health labs across the country, several of these labs reported that they were producing inconclusive results. The CDC acknowledged this and assured labs and the public that they were working on a solution. But while the CDC worked to resolve their error, the U.S. lost crucial days of testing. Public health labs that had received the faulty tests considered most of them to be unusable, and over the course of nearly three weeks in February, these labs conducted fewer than 300 total tests across the U.S. During this time, the CDC Lab in Atlanta took on the majority of all testing, but still tested fewer than 1,500 total samples collected from around the country. It was not until February 28 that the CDC announced a workaround for the test kit problem. The next day, the U.S. Food and Drug Administration (FDA) loosened testing development regulations to facilitate the development of new tests by public and private labs.

South Korea, a country with a population of 51.5 million, had tested about 100,000 people for the virus by March 1. By this time, the U.S. had tested fewer than 5,000 of its 329 million people. It was not until March 27 that the 24-hour total for tests conducted in the U.S. exceeded 100,000 for the first time. Significant hurdles for labs wishing to develop their own tests, a critical mistake at the CDC, and strict limitations on who was eligible to receive a test all contributed to costly delays and the persistent testing shortage.



WHO IS ELIGIBLE FOR TESTING? A TIMELINE OF CDC GUIDELINES

- January 17: Testing limited to those with fever, coughing, or difficulty breathing who had traveled to Wuhan—the site of the initial virus outbreak—within the preceding two weeks or who had close contact with someone already confirmed or under investigation for having the virus.
- February 1: Expanded to include any individual hospitalized with a fever who had traveled anywhere in China, rather than just Wuhan.
- February 28: Expanded to include anyone with symptoms severe enough to require hospitalization, regardless of prior travel.
- March 4: Above guidelines lifted and individual testing decisions deferred to physicians.

Antibody testing: more questions than answers

A critical step toward opening the economy in the short term—and keeping it open in the medium to long term—is widespread antibody testing, also known as serologic testing, to confirm who has been exposed to the virus and subsequently recovered. The presence of antibodies in the blood indicating exposure to a virus often confers at least some level of immunity to future infection from that same virus. However, there are still many unanswered questions relating to antibodies and immunity for COVID-19. It has yet to be proven that COVID-19 antibodies confer immunity, and at this point, estimates of the duration of a potential immunity are only speculations based on studies involving other coronavirus strains. Further, it is unlikely that immunity will manifest in the same way for everyone. The degree to which an individual is immune will largely depend on the strength of that individual's immune response.

In the wake of the diagnostic testing debacle, the FDA might have overcorrected in setting approval standards for newly developed serology tests, which has enabled many tests of questionable accuracy to hit the market. On March 16, the FDA issued a statement addressing the regulation of serologic tests. It allows for any serologic test to be sold and used without obtaining FDA approval, as long as the test “has been validated, notification is provided to the FDA, and warning statements are included with the tests, for example, noting the test has not been reviewed by the FDA and results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform infection status.” The FDA also offers a more rigorous route for those who wish for their tests to undergo formal review, but an overwhelming majority of test makers have chosen to bypass regulatory oversight, creating a market that Michael T. Osterholm, an infectious disease expert at the University of Minnesota, described as the “Wild West” of antibody testing. As of April 24, 166 unregulated serologic tests are on the market in the U.S., while only eight tests have been reviewed by the FDA.

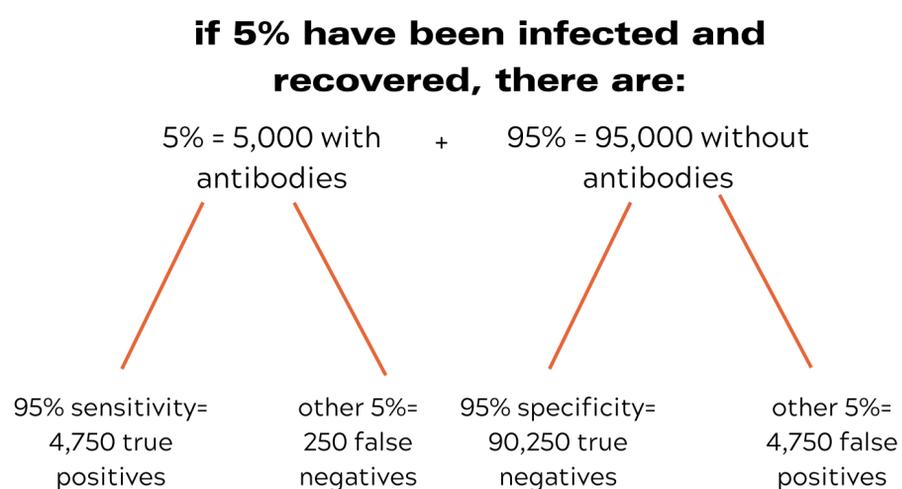
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Why might all these unregulated tests be a concern? To begin with, serologic tests in general are less accurate than molecular tests like the ones used to detect COVID-19. These tests are more prone to delivering inaccurate results for two reasons. First, a test might not be able to detect antibodies that are present. Given that individual immune responses vary, it is possible that a mild immune response could go undetected with a less sensitive test. Second, and most worrisome, is the possibility that some serologic tests could be too sensitive. They might detect antibodies from a different infection, such as a common cold caused by a different coronavirus, producing false positive results and incorrectly leading individuals to assume they are immune to COVID-19 infection in the future.

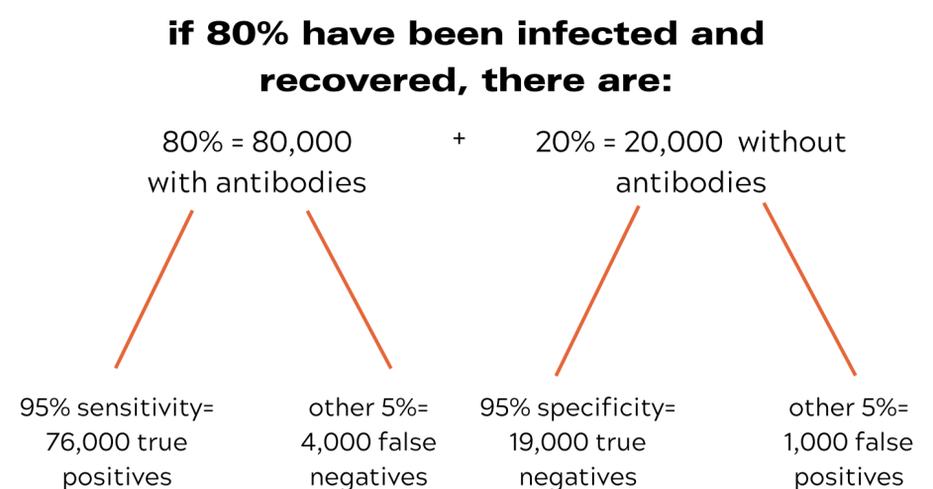
Test manufacturers often publicize these accuracy metrics—known as sensitivity and specificity rates—for their tests. Sensitivity describes the rate of detecting the presence of antibodies in individuals who have had the disease, thereby avoiding false negatives, while specificity describes the rate of not detecting antibodies in individuals who have not had the disease, thereby avoiding false positives. White House coronavirus task force coordinator Dr. Deborah Birx has set 90% sensitivity and specificity as the standard expectation for test manufacturers. While many manufacturers claim to have exceeded this expectation, much of the internal testing has relied on small sample sizes, and even the most accurate tests can lead to unsettling rates of incorrect results.

Additionally, statistical modeling shows that the prevalence of COVID-19 antibodies among the tested population also affects the validity of the results. The example below demonstrates how a test with 95% sensitivity and specificity performs in two hypothetical populations of 100,000. The first population is a group of individuals tested at random, in which it would be expected that the vast majority had not been exposed and therefore would not have antibodies. The second population is a group of individuals involved in the targeted testing of people who might have previously tested positive for the virus or been in close contact with someone who was infected. In this curated sample, you would expect to have a much higher proportion of positive serology tests than you would see if testing were conducted at random.

Random testing of 100,000 people



Targeted testing of 100,000 people



In the randomly tested population with a true antibody prevalence rate of 5 percent— a rate consistent with public health experts' estimates of the true prevalence of the virus nationwide—the test produces a total of 9,500 positive results. 4,750 of those are correct detections of antibodies in individuals who have recovered from the virus, but the other 4,750 are false positives in individuals who were never infected. In this case, the test gives half of those who tested positive for antibodies a false sense of immunity. Outcomes are even worse in populations where the virus is less widespread. The second example shows more promising results. If testing is targeted to those most likely to have antibodies, the true prevalence rate could be something like 80%. Overall, this group generates 77,000 positive results, with only 1,000 of them false positives. A positive result in this group is much more likely than in the first group to be a correct one.

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How should we use antibody testing?

In an ideal world with perfect testing and proven information about COVID-19 immunity, serologic testing could allow individuals with known immunity to return to work and resume their normal lifestyles. If the U.S. experienced a second wave outbreak in the fall or winter as some have predicted, a large contingent of people with known immunity would be crucial in treating the infected, keeping the economy running, and containing the spread.

Unfortunately, this is not yet the reality. Yet some countries, including the U.S., have discussed plans to rely heavily on serologic testing in determining immunity at the individual level. In the U.S., [Senator Bill Cassidy](#) (R-LA) has been especially vocal in his support of allowing those who test positive for antibodies to preferentially return to the workforce and the community. This would require the creation of an immunity registry—modeled on the registries that currently exist for childhood vaccinations—or the distribution of physical immunity certificates. Although it might be a very useful tool once public health officials are confident in the accuracy of antibody test results, a COVID-19 registry or immunity certification program would raise some ethical questions, especially when vaccination is not yet an option.

Some argue that those who have been the most careful in avoiding infection would be unfairly punished if immunity were required to return to work. Henry T. Greely, Stanford law professor and director of the Stanford Center for Law and the Biosciences, believes the concept of an immunity certificate would raise complicated discrimination concerns. [He writes](#), “These certificates have appeal—unless you are one of the many people who end up locked out of the world due to no fault of your own. For you, it is discrimination: some people can work, play, or travel while you cannot.”

“Like the ‘chickenpox parties’ of old, some workers will want to get infected,” I. Glenn Cohen, a bioethics expert at Harvard Law School, [told Bloomberg Law](#). “That sounds crazy, but if having the antibodies becomes the cost of entering the job market and thus feeding your family, there may be workers who feel pressured into it.”

Serologic testing has the potential to be valuable in guiding the next stage of the government’s pandemic response and helping officials determine when certain communities can start to relax social restrictions. Additionally, it will be critical in helping previously exposed individuals determine whether their illness has run its course and whether they could be immune. But we are still in the early stages of the outbreak, and not enough is known about the implications of antibodies on immunity to the virus.



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Fixing the problem

Given the shortages and concerns surrounding both diagnostic and serologic testing, what could Washington do to start alleviating the problems? A few ideas stand out:

The U.S. is still seeing new COVID-19 infections each day. At this point, we should not let the promise of immunity testing distract us from the urgent need to scale up diagnostic testing for new, active infections. In a recent op-ed in *The Atlantic*, University of Pennsylvania bioethicist Dr. Ezekiel Emanuel and Nobel Prize-winning economist Paul Romer offer several ideas that could help the U.S. reach its testing goals. To incentivize test development and use, they suggest the inclusion of “\$150 million in unrestricted research funds to the first five universities that can process 10 million tests in a week or less” in the next congressional stimulus bill as well as subsidies for businesses that agree to test all employees before they return to work. To minimize the effects of the testing supply shortage, they also suggest that the FDA prioritize the approval of new tests that can be administered with fewer reagents and by fewer staff members. Ashish Jha, director of the Harvard Global Health Institute, suggests coordination and distribution between states to combat shortages of some supplies in certain areas. The federal government would pinpoint the states in need of supplies and facilitate the exchange of these supplies from states where they were fully stocked.

Many of the same strategies for expanding diagnostic testing could also be useful for expanding serologic testing. To promote high quality testing, the National Institutes of Health (NIH) and the FDA are currently working to validate some of the serologic tests on the market using known positive samples to compare each test’s performance. More of these studies will be crucial in determining which tests offer the most reliable results. Additionally, more research will be necessary to gain a better sense of how immunity manifests. Congress could include funding for these types of studies in the next stimulus bill. For now, those who test positive for the presence of antibodies should be hopeful, but they should not consider their results a free pass to re-enter society.



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ABOUT CENTERING ON CORONAVIRUS

Centering on Coronavirus is a new policy series from The New Center that provides insights and analyses of how coronavirus is progressing, how it is impacting our health system, economy and workers, and the extraordinary human, policy, and technological resources that are being mobilized to fight it.

ABOUT THE NEW CENTER

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