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Screening the General Population for SARS-CoV-2 Virus and COVID-19 Antibodies: A Counterargument

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A major effort to contain the coronavirus disease 2019 (COVID-19) pandemic in the United States is the "shelter-in-place" mandate issued by the federal government and individual states. Although these actions have been successful in "flattening" the curve of infections, they have led to an economic recession. After weeks of sheltering, the nation's workforce is anxious to return to work. The White House has indicated that more virus and antibody testing is needed to determine who is infected and who is immune. For PCR viral testing, there continue to be shortages in the availability of nasopharyngeal swabs, reagents, and personal protective equipment. Testing for the presence of serum antibodies was more scarce because test kits become available later in the United States, but testing supplies are not longer a limitation *(1)*. Manufacturers from our in vitro diagnostics industry are working overtime to provide the necessary supplies, and I am confident that these shortages will be temporary. Once fully supplied, the principal question is, should there be a massive antigen and antibody screening program across the United States?

Viral nucleic acid testing for the presence of COVID-19 among asymptomatic individuals is more invasive and expensive than serum antibody testing. Nasopharyngeal sampling requires more skill and training to produce a good sample and to minimize false-negative results. Healthcare workers are at high risk of contracting the virus from an infected person. Transportation of samples from the point of collection to testing laboratories presents additional infection-control challenges. Point-of-care testing devices are available for reverse transcription PCR (RT-PCR) that can detect the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 5 minutes *(2)*. More studies are needed to compare the sensitivity of these platforms against central laboratory tests. Work is also underway for development of an immunoassay for a relevant SARS-CoV-2 protein (antigen test). Although this test will still require nasopharyngeal sampling, as the SARS-CoV-2 virus content in blood is low, immunoassay testing is easier and less expensive than RT-PCR.

The prevalence of disease is an important issue for mass screening. The number of acute SARS-CoV-2 infections is currently unknown in the United States because not all individuals who are asymptomatic have access to virus testing. If it turns out that the prevalence is low, the clinical sensitivity of current virus tests will be inadequate for mass screening. Although the clinical specificity

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of the RT-PCR test for SARS-CoV-2 is high, one study conducted in China reported clinical sensitivity of only 59% in 1014 patients *(3)*. False-negative results could be caused by inadequate sampling or timing relative to the onset of the infection and symptoms. Sampling a cross-section of asymptomatic individuals for the virus will likely find very few cases unless screening takes place in highly pandemic areas.

Detecting antibodies to SARS-CoV-2 is a better approach toward mass screening of asymptomatic individuals because the window for detection will be much broader. Collecting and testing blood for the presence of COVID-19 antibodies in serum on a mass screening is easier than molecular testing for the virus. Moreover, point-of-care antibody testing devices are available that can produce results within 15 minutes from a fingerstick blood sample. However, the sensitivity of antibody tests will need to be high for this approach to be successful. Whitman et al. evaluated 10 lateral flow assays for COVID antibodies—testing devices likely to be used for screening *(4)*. On blood collected ≥21 days after disease onset, these investigators showed that for detecting either IgM or IgG antibodies, 9 of 10 kits had clinical sensitivity ≤90%. Use of these tests will also be inadequate for mass screening of a population with a low infection rate. For example, if only 10% of the general population has antibodies, use of a test with a 90% sensitivity and 90% specificity will produce an equal number of true-positive and false-positive results (see Table 1). More accurate tests and/or a higher prevalence of past infection will improve the utility of screening. Central laboratory assays for SARS-CoV-2 antibodies have been cleared and approved by the US Food and Drug Administration (FDA), have higher clinical sensitivity and specificity, and would produce more favorable results for mass screening *(5)*. However, there may be a preference by agencies conducting screening to use point-of-care tests because results can be made available immediately without sending samples to a clinical laboratory.

Another testing issue will challenge the value of a mass screening program using antibody detection. An effective infection control program requires demonstration that antibodies produced in blood are neutralizing against the virus. In general, antibodies can be produced to any of the SARS-CoV-2 proteins, including the spike, nucleocapsid, and membrane proteins. Most of these proteins do not participate in the replication of the virus within the host. One study suggested that some individuals produce anti-COVID-19 antibodies that are not neutralizing against the virus *(6)*. Most virologists believe that it is the receptor binding domain of the spike protein that binds to the ACE2 receptor to gain entry to the cell *(7)*. Moreover, the spike protein must be "primed" by extracellular serine proteases so that the viral membrane protein can fuse with the host cell, enabling virus entry *(8)*. The gold standard for determining whether a serum antibody is neutralizing is the plaque-reduction neutralization test *(9)*. Experimental cells are treated with serum containing antivirus antibodies from patient sera, and then live virus is added. If these antibodies can inhibit transfection, they are considered neutralizing. One recent study correlated antibody results from COVID-infected patients against the plaque-reduction neutralization test *(6)*. The authors reported correlation coefficients ranging from $r = 0.42$ to $r = 0.51$ when the capture antibody used in the immunoassay was the S1 and S2 subunits and the receptor binding domain of the spike protein. These results suggest that some patients produce neutralizing antibodies that do not result in a positive COVID-19 antibody response (false negative). In this situation, the immunoassay is detecting the wrong antibody. Other patients have COVID-19 antibodies but they cannot neutralize a viral infection (false positive). It is possible that the antibodies produced in these patients were directed toward a viral protein that

Table 1. Bayesian statistics for COVID-19 antibody screening.

	Antibody test result Not infected	COVID-19 disease status Infected
Negative	810 (true negative)	90 (true positive)
Positive	90 (false positive)	10 (false negative)

Assumptions: Prevalence of 10% among 1000 subjects tested. Test clinical sensitivity and specificity of 90% each.

is not essential for its replication. In the haste to produce a COVID-19 antibody test and the relaxing of FDA approval through the emergency use authorization, the quality and reliability of these assays may be substandard. A next-generation antibody test is required that has higher correlation to virus neutralization. More recent papers have demonstrated a higher degree of correlation against plaque reduction tests (r=0.86) [*10*].

I am not in favor of mass screening of the general population using the current virus and antibody assays. The COVID-19 pandemic has eased in many parts of the world where the pandemic started, with a return of citizens to their prepandemic activity levels. Some of these countries have experienced a second wave of infections *(11)*. How many lives are we prepared to sacrifice to stimulate a nation's economy? If I lost my job because of COVID-19, I probably would take risks needed to provide for my family, as would most others. Fortunately, as healthcare workers, our occupation is secure, and we are not faced with making these difficult decisions. However, promoting dangerous medical practices is against the fabric of our occupational existence. If we are going to release COVID antibody testing on a continental or even global scale, let us at least educate the public regarding the information they are receiving.

Nonstandard Abbreviations: COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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