

# Out of the Darkness, Into the Light: Value of SARS-CoV-2 Antibody Testing in Populations to Benefit Public Health and in Individuals for Peace of Mind

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The coronavirus disease 2019 (COVID-19) pandemic has been nothing short of horrible and so terribly disruptive to an estimated 3 billion lives worldwide from health, economic, and social perspectives. No event in my nearly 40-year laboratory medicine career has had such a tragic impact. This event has been global; the WHO declared COVID-19 a pandemic with millions of people infected (1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is capable of human-to-human transmission and spreads via respiratory droplets, causing a respiratory illness that closely resembles severe acute respiratory syndrome (SARS) infection from about 20 years ago (2). The disease occurs from an infection by SARS-CoV-2, which is a member of the *Betacoronavirus* genus. The immune system's fulminant inflammatory response to SARS-CoV-2 can result in airway damage, respiratory failure, cardiac injury, and multiorgan failure, which can lead to death in vulnerable patients (3, 4). No other occurrence in the past 40 years has more clearly underscored the value and central importance of laboratory testing. Real-time reverse transcription

PCR (RT-PCR) testing is key to acute detection of SARS-CoV-2 virus infection and diagnosis of COVID-19. The recognized need and critical importance of greater access to RT-PCR testing in most areas of the United States and the world is abundantly clear from daily media reports. However, although RT-PCR assesses whether the patient currently has the SARS-CoV-2 virus, it is not able to inform about the disease's true prevalence in populations or assist in determining if the patient had COVID-19 previously and recovered. In this article, I address questions regarding reported and unreported COVID-19 and the prevalence of previous exposure to SARS-CoV-2 infection. The value of anti-SARS-CoV-2 testing will be the focus as a population surveillance tool of SARS-CoV-2 exposure and as a way of informing individuals about whether they had past exposure to, and infection by the SARS-CoV-2 virus.

The task now facing governments and national regulators is to balance urgency against the everyday sensitivity and specificity concerns that apply to any novel medical diagnostic test (5). We must also keep in mind the powerful influence that

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prevalence has on both negative predictive value and, predominately, positive predictive value. An example of this impact is demonstrated in [Table 1](#) for a test with 89% sensitivity and 96% specificity.

For any laboratory measurement to be optimally informative, the assay's design must target the best measurand available, and this is particularly true regarding the diagnostic specificity of anti-SARS-CoV-2 testing. One potential candidate for targeting is the virus's nucleocapsid protein, which is SARS-CoV-2's most abundant viral protein; therefore, the immune response to this antigen is likely to be most robust and easiest to detect (5). However, cross-reactivity must be a fundamental concern and depends on whether the results of the new test are distinct from related coronaviruses (5). SARS-CoV-2 is but one of several coronaviruses, and any proposed assay must offer the best specificity for minimizing cross-reactivity and false-positive results from other coronaviruses that are common in virtually all populations. The SARS-CoV-2 spike protein has been championed as the best target because among the coronaviruses, it offers a great number of unique epitopes to optimize specificity. Evidence indicates that the primary structure of the SARS-CoV-2 spike protein is more specific than and has only 75% identity with the amino acid structure of the earlier SARS virus (5, 6). Furthermore, the homology of amino acids between the SARS-CoV-2 spike protein and those of the common cold-causing coronaviruses is in the range of about 50%–60% (5). Although the nucleocapsid protein is abundant,

assays targeting key regions of the spike protein are distinct across coronaviruses; therefore, the spike protein of SARS-CoV-2 has been the focus for assessing exposure to the virus (5).

Early data indicate that the spike protein is the main antigen that elicits neutralizing antibodies, likely because this protein is the sole protein on the viral surface that is responsible for entry into the host cell (5). For this same reason, the SARS-CoV-2 spike protein is a viable candidate for vaccine development because the antibody response against the spike protein attacks the sole protein on the viral surface that contacts the host cell (5). Extending this rationale, another assay target could be the “the business end” of the spike protein, which is termed the receptor binding domain (RBD). The RBD has been identified as residues 331–524 of the SARS-CoV-2 spike protein. The RBD of the spike protein binds to the ACE2 cell receptor (7), which is nearly identical mechanistically to the SARS virus from 20 years ago (7, 8). However, reactivity of COVID-19 sera was documented as, in general, more avid against the full-length spike protein than against the RBD, likely reflecting the higher number of unique epitopes found on the larger spike protein (9). Regarding specificity of the spike protein, an early clinical study demonstrated that all patients but 3 out of 1343 (0.25%) with confirmed SARS-CoV-2 seroconverted to having anti-SARS-CoV-2 spike protein (10). Thus, practically all infected patients showed a robust anti-SARS-CoV-2 response to the spike protein. Of interest, the levels of antibodies produced did not vary between those with minimal or severe symptoms, but the neutralizing effect of these antibodies is incompletely understood (11).

**Table 1. Influence of prevalence on predictive value in a test with 89% sensitivity and 96% specificity.**

Predictive value	Prevalence					
	1%	2.5%	5%	10%	15%	20%
Positive, %	16.8	33.9	51.3	69.0	77.9	83.3
Negative, %	92.3	92.4	92.7	93.3	93.8	94.4

## IMPORTANCE TO PUBLIC HEALTH

Is determining the prevalence of exposure to the SARS-CoV-2 virus important to public health? The answer is a resounding yes, and quality

laboratory measurements of anti-SARS-CoV-2 assays represent the most effective and objective strategy to obtain this valuable information. As stated in a thoughtful editorial by Kenyon, serological testing is essential for estimating the prevalence of infections, including those that are asymptomatic (12). Reportedly, at least 30% of infected persons will not develop any symptoms at all (13). A small study of pregnant women admitted for delivery found that 13.5% were infected with SARS-CoV-2 but asymptomatic (14). Furthermore, approximately 80% of symptomatic individuals infected with SARS-CoV-2 experience signs and symptoms that are mild (15), so they may not seek care or be tested by RT-PCR for acute COVID-19.

Dealing with COVID-19 policy is not a “one size fits all” proposition. For example, the state of New York had overall prevalence of 14.9% based on 7500 anti-SARS-CoV-2 measurements (16). However, testing in New York City found a much higher rate of 24.7% positivity for antibodies to SARS-CoV-2. Prevalence of SARS-CoV-2 antibodies in the Westchester/Rockland area of New York was 15.1%, which was about the same as in the Long Island area at 14.4%. The rest of the state had relatively low prevalence of 3.2% antibody positivity (16). This information is valuable for determining hotspots, allocating resources, and making decisions about implementing policies that are more or less stringent. The assay for this study was developed by the New York State Department of Health and is coined the Wadsworth Center SARS-CoV-2 IgG test. Initially, data on the characteristics of this test were unavailable. More recently, however, this test has been reported to be 93%–100% specific, and literature states that significant cross-reactivity to other known respiratory viruses is not expected (17). However, 93% specificity can be characterized as moderate depending on the design and extent of the cross-reactivity studies conducted.

Inadequate knowledge about the extent of the COVID-19 epidemic poses a risk that public health response and planning will not be adequate or accurate. Because of the large number of asymptomatic individuals with COVID-19, medical and scientific surveyors may not be aware of the true disease prevalence because infections would likely go uncounted without broad population surveillance. Another example of the importance of anti-SARS-CoV-2 testing can be gleaned from the experience in Los Angeles, California (18), which caused 2 Stanford University faculty to opine in a *Wall Street Journal* article that the WHO’s estimate of the fatality rate from COVID-19 at between 2% and 4% may be far too high (19). At this point, much of the information is based on expert opinion, but Dr. Jay Bhattacharya of Stanford University strongly supports the need for anti-SARS-CoV-2 testing because “the facts to date are consistent with a wide range of uncertainty regarding the fatality rate from COVID-19.” His colleague Dr. Eran Bendavid also strongly supports population testing with anti-SARS-CoV-2 tools because “we desperately need a population-representative estimate of the seroprevalence of the disease so we can reduce that uncertainty and make better policy on the basis of our improved knowledge” (20). One must interpret the findings of this study with caution, however, because the anti-SARS-CoV-2 assay used in this study (i.e., Premier Biotech) was one of 12 tests with reliability that was openly called into question by the Congressional Committee on Oversight and Reform (21) based on data from a study conducted at the University of California, San Francisco (22).

Here in the state of Maryland, there is also a paucity of information. This is problematic, as illustrated by the fact that, to date, 44 424 individuals have been diagnosed with COVID-19, of which 2207 have died, for a mortality rate of 5%. Although these numbers change each day, the mortality is about 2-fold higher than the

presumably inflated WHO number of 2%–4% (19). One possible reason for a disparity between the Maryland and other regions is that 60% of the deaths in the Old Line State were residents in long-term care facilities. Broader anti-SARS-CoV-2 testing in Maryland will provide greater knowledge about the actual prevalence of past SARS-CoV-2 infection and a better estimate of the overall mortality rate.

### VALUE OF TESTING INDIVIDUALS

A second question concerns the value of testing and informing individuals regarding past infection with the SARS-CoV-2 virus. Like many people, almost everyone I speak with seems to have an anecdote about being ill with headache, respiratory symptoms with or without a fever, sore throat, gastrointestinal illnesses, and so forth in the weeks and months before the SARS-CoV-2 pandemic was known to have hit US shores. Although many people believe there is a good chance that they had COVID-19, as far as we know the probability is likely very low. A question such as “Do individuals consider such a test valuable for them?” is being “voted on” currently. In the Baltimore, Maryland, area, anti-SARS-CoV-2 testing is being offered to the public by commercial laboratories at a price of approximately \$120. It is uncertain at this point how many people will find it valuable to have the test run, whether or not it is free. I would opine, judging in part from the >26 million Americans who have paid between \$100 and \$200 for 23andMe-type ancestry services, that people will find the information valuable. Based on my personal interactions and reports from others who have offered this testing as an “occupational benefit,” I believe many will indeed consider anti-SARS-CoV-2 testing valuable.

One area of particular importance is the unprecedented risk of exposure to SARS-CoV-2 posed to healthcare workers on the front lines

(22). In an environment with high risk of SARS-CoV-2 infection, good estimates of past infection prevalence, rate of subsequent infection, and possible development of immunity are unknown and a serious knowledge gap during such a pandemic. We are offering anti-SARS-CoV-2 testing to approximately 30 000 individuals who are employees of, or associates at, our university medical system, using an orthogonal testing strategy given the suspected low prevalence. These measurements are offered as a free service to our medical system’s occupational community. We are learning how valuable our colleagues find this knowledge; however, care must be taken to caution individuals that because of the knowledge gap mentioned above, the presence of antibodies to SARS-CoV-2 in their blood is not known definitively to confer immunity. For this reason, we include an interpretation with reports of employee results that are positive or reactive for anti-SARS-CoV-2 testing: *“we strongly encourage you to follow all hospital and infection control practices including personal protective equipment.”*

In conclusion, there needs to be movement out of the “darkness” of inadequate information and knowledge into the “light” of insights provided by population science and individual preference, guided by quality information. Like any other laboratory test, anti-SARS-CoV-2 measurements must target the correct measurand, be well validated, and be conducted in an appropriately licensed laboratory. An accurate assessment of prevalence of SARS-CoV-2 exposure and infection, both past and present, is necessary to guide public health efforts. Furthermore, the scientific literature, lay media, and expert opinion can more accurately tailor their messages if informed by a better estimate of overall disease prevalence. The value of individuals knowing their exposure to the virus is unknown currently and needs to be determined. Wouldn’t you like to know? Stay tuned.

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

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