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Review

COVID-19 Antibody Tests: A Valuable Public Health Tool with Limited Relevance to Individuals

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Antibody tests for detecting past infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have many uses for public health decision making, but demand has largely come from individual consumers. This review focuses on the individual relevance of antibody tests: their accuracy in detecting prior infection, what past SARS-CoV-2 infection can currently infer about future immunity or possible medical sequelae, and the potential future importance of antibody tests for vaccine selection and medical screening. Given uncertainty about the antibody tests (quality, accuracy level, positive predictive value) and what those tests might indicate immunologically (durability of antibodies and necessity for protection from reinfection), seropositive test results should not be used to inform individual decision making, and antibody testing should remain a tool of public health at this time.

Advent of the Coronavirus Disease 2019 Antibody Testing Market

Serology testing (or equivalently, serological, or antibody testing) for coronavirus disease 2019 (COVID-19) is useful to determine whether people were previously infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This capability contrasts with diagnostic tests, which are used to determine if someone is currently infected and presumably capable of infecting others. Diagnostic tests either amplify viral genomic material or detect viral antigens present in a patient sample. Although patients can simultaneously have a positive test result for diagnostic and serologic tests, seropositivity is typically later in the course of disease. Serology tests also require a blood sample, as opposed to the upper respiratory specimens typically needed for molecular diagnostics. Given rampant problems in diagnostic testing accessibility and the high incidence of asymptomatic infections, not everyone who is infected has the opportunity to be tested before clearing the virus [1,2]. Antibody tests for SARS-CoV-2 can therefore provide important information about a person's medical history.

The presence of antibodies to SARS-CoV-2 was originally hoped to be sufficient for release from physical distancing early in the pandemic, particularly in March 2020 [3]. Various nations, including the UK, Germany, and Italy, considered using antibody testing for 'immunity passports,' or official documentation designating an individual immune to SARS-CoV-2 reinfection, and this cohort of already-recovered people was considered to be critical to opening the economy [4–6]. Only a few months into the pandemic, it was too soon to determine if the presence of antibodies truly indicated protective immunity. Although serology tests have an international scope, this discussion focuses primarily on the United States. On 31 March 2020, a bipartisan group of 113 members of the US Congress urged the US Department of Health and Human Services to rapidly deploy antibody tests to help individuals determine if they had already had the disease [7]. 'It will be an unnecessary economic tragedy if our citizens remain cowering at home because

Highlights

There is high consumer demand for antibody tests to detect past infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but there is a great deal of uncertainty about what a positive test means immunologically.

Uneven test accuracy and statistical challenges, especially in areas of low disease prevalence, further complicate use of antibody tests for individual decision making.

Antibody tests are important for convalescent plasma donation and may have future utility to identify coronavirus disease 2019 medical sequelae and for vaccine selection and prioritization.

At the population level, tests are needed to support serosurveillance studies, to determine the case fatality rate, and to track increases or decreases in incidence and prevalence, but currently they are of limited utility for individuals.

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we failed to provide them with the simple, inexpensive means of proving their immunity,' they wrote [7]. The FDA issued guidance indicating that they would not object to use of unreviewed serology tests, as long as they were not used as the sole method for diagnosis [8].

High consumer demand and light regulation led to a deluge of antibody tests – more than 200 [9]. Most insurance companies do not cover antibody testing, so individuals paid between \$300 and \$600 per test, including specimen collection [10]. Independent validation studies indicated many tests were of poor quality, which led to media attention and Congressional hearings [11–13]. On 4 May 2020, the FDA announced a validation process conducted by the National Cancer Institute to determine test accuracy, in addition to required data submissions to the FDA, and a higher accuracy threshold for tests to be marketed [14]. Hopes for instituting an immunity passport faded due to the challenges in getting accurate tests, questions about how long immunity may last, and pragmatic considerations due to low disease prevalence: If only 5% of the population had COVID-19 and were presumed to be immune from further infection, that would be insufficient to 'open' the economy [15]. The ethical ramifications of serology testing and use of test results include potential discriminatory practices based on serostatus, profiling based on high-risk populations, and violations of workers' rights [16–18]. Also, if only the previously infected could be employed, it would create perverse incentives, driving people to try to become infected.

Inaccurate tests are still in use; yet, there have been no recalls. Though some major biotechnology companies have stopped selling tests following poor independent validation studies, the FDA issued guidance revoking Emergency Use Authorization (EUA) for just two tests [19–21]. Some test manufacturers fraudulently claimed FDA approval for their tests [22]. Independent research groups have led the way in monitoring evaluations of antibody tests [23–26]. The FDA now maintains a list of tests that have not received EUA and that should not be distributed, now including 155 serology tests, but this information is not prominently displayed [27]. The lack of clear messaging on FDA EUA status has led to the use of potentially inaccurate tests [28].

Antibody tests should not be used for individual decision making at this time. This paper describes why this is the case: (i) antibody test results may be inaccurate without multiple sequential testing due to low disease prevalence and statistical limitations; (ii) many tests on the market are not of good quality, leading to inaccurate results; (iii) it is unknown whether past exposure to SARS-CoV-2 leads to durable immunity or if reinfection is possible; and (iv) it is unknown whether transmission is possible even if reinfection does not lead to clinical symptoms. Antibody tests are valuable at the population level to support serosurveillance studies, to determine the case fatality rate, to track increases or decreases in incidence and prevalence, and to grow the body of scientific knowledge about medical sequelae following recovery [29]. For example, in the latest Centers for Disease Control and Prevention–led seroprevalence survey, antibody tests indicated that there was much higher COVID-19 prevalence than molecular tests showed [30]. Many people wish to be tested because a seropositive result may theoretically release them from the constraints of physical distancing measures [31]. Although reinfection with SARS-CoV-2 has been very rare, it is possible, and the presence of antibodies cannot serve as proof of immunity to reinfection [32]. Consequently, individuals who have had past SARS-CoV-2 infection could potentially be reinfected and then contribute to viral transmission. Given current uncertainties about immunity and SARS-CoV-2, individual use of antibody tests could lead to a false sense of security.

Accuracy of the Tests

There are several different tests to measure the presence of antibodies to SARS-CoV-2. For the remainder of this discussion, an accurate test would have over 90% sensitivity and 95%

specificity, as defined by FDA templates for EUA applications [33]. Briefly, ‘sensitivity’ refers to the ability of a test to capture all true-positive results while minimizing false-negative findings. ‘Specificity’ refers to the ability of a test to define all truly negative samples while minimizing false-positive results. No currently available test can tell an individual that they are immune to re-infection by SARS-CoV-2, and no commercially available test can detect neutralizing antibodies. Quantitative tests, such as ELISAs and chemiluminescent immunoassays, provide richer data, such as levels of antibodies in a patient sample. Importantly, even quantitative tests such as ELISAs often have stipulated within the EUA that the test is for qualitative use only in patients; quantification of antibody levels may be used for research only. Rapid diagnostic tests, typically lateral flow assays, are qualitative and provide a positive/negative readout of serostatus. The accuracy and performance of SARS-CoV-2 serology tests vary; quantitative tests are generally more accurate than qualitative tests, partially due to the detailed data generated [34]. Antibody test accuracy also increases with time since symptom onset, with greater than 14 days after symptom onset being the optimal time for testing. Antibody levels after SARS-CoV-2 infection wane, especially after mild or asymptomatic infections, which may result in a negative test result if levels dip below the detection threshold [35]. Independent evaluations of test performance are essential in understanding the accuracy of a test. Such evaluations have revealed sensitivities as low as 66%, whereas the FDA currently maintains a threshold of 90% sensitivity to even apply for an EUA [33,36].

Due to statistical realities, test results are less accurate for an individual than for a population, if the test is less than 100% accurate, and if the disease is of low prevalence. This has to do with the predictive value, also referred to as the ‘base rate fallacy,’ which takes into account both test performance and the background population prevalence of disease. In other words, the more prevalent a disease, the higher the predictive value for a positive test [37]. Performance statistics for tests with EUA are available [34]. For example, the Cellex test has 93.8% sensitivity and 95.8% specificity, so 6.2% of tests will yield false-negative results, and 4.2% of tests will yield false-positive results [38]. If disease prevalence is 5%, the positive predictive value is low: The probability that a positive test is truly positive would only be 53%. The positive predictive value climbs with disease prevalence; for 15% disease prevalence, the probability that a positive test result is accurate is 80%. There are online calculators to determine these probabilities [26,39]. For diseases in which accuracy is medically important even in low-prevalence settings, such as HIV/AIDS, the standard is to administer up to three sequential tests [40].

Serostatus and Immunity

While knowledge of the presence (and levels) of antibodies is important in understanding past infections within a population, this section explores the significant knowledge gaps that exist in our understanding of protective immunity to SARS-CoV-2.

Durability of Immunity

While the role of antibodies in protection against reinfection remains under investigation, the presence of antibodies to SARS-CoV-2 does indicate previous infection. The ability of the immune system to prevent reinfections differs with each pathogen; some pathogens elicit long-lasting, specific immunity, whereas others do not. Immunity also differs among individuals, from the magnitude of the response to the specificity of the response [41,42]. Antibody levels, or titers, may change rapidly over the course of infection and afterward [43].

Past infection with SARS-CoV-2 is thought to lead to immunity from reinfection, but this remains an open research question. Studies in nonhuman primates show that recovered animals have detectable immune responses and are protected from advanced disease upon reinfection [44,45].

Past studies of patients infected with SARS-CoV-1 or Middle East respiratory syndrome show that patients have persistent immune cells, including memory T cells, for years after exposure to the virus [46,47].

Correlates of Immunity

It is unclear which components of the immune system are most important in fighting SARS-CoV-2 and what levels of antibodies are required to maintain immunity. Most patients seroconvert, or become antibody positive, after 2 weeks of infection [48]. Antibodies are detected as early as 6 days after symptom onset and increase steadily over the first 3–4 weeks after symptom onset [35]. Overall, antibodies appear to peak 14–30 days after symptom onset and then slowly decline for 2–3 months [43,49].

Antibody levels vary with isotype and disease severity; patients with severe disease have higher antibody levels that may persist longer. IgA and IgM levels decline after 60 days post-symptom onset, though IgG levels remain significant [42,50]. IgG antibodies have been shown to persist up to 90 days, even in mild cases [51,52]. Patients with severe COVID-19 appear to have higher levels of antibodies than those with mild/asymptomatic cases, but the kinetics of antibody levels are similar across all cases [53]. In a study in Wuhan, China, researchers found that spike receptor binding domain (RBD)-specific IgG levels in asymptomatic patients were lower than in symptomatic patients, though prevalence was similar between the two groups (IgG prevalence of over 80% of all cases 3–4 weeks after exposure) [35]. Importantly, antibodies are only one element of the immune response. The cellular immune response, which involves T cells, cannot be measured through an antibody test.

Neutralizing Antibodies

Many studies analyzing antibody levels over time do not indicate if these antibodies are neutralizing and protect against infection in laboratory tests. In blood donors who recovered from COVID-19 and were eligible to donate convalescent plasma, neutralizing antibody levels were highly variable [54,55]. Therefore, neutralizing antibodies must be quantified on a case-by-case basis. Although neutralizing antibodies can be difficult to quantify outside of a laboratory setting, recent work shows that IgG levels correlate well with neutralizing antibody levels [56]. Levels of antibodies are measured using dilution factors; convalescent plasma should have a titer higher than 1:160, but the range of neutralizing antibody concentrations in convalescent plasma can be from 1:60 to 1:2650 [56,57]. Neutralizing antibody levels could offer a method to screen potential donors through quantification of levels of IgG. Researchers have also identified that neutralizing IgG antibodies can emerge as early as 9 days after symptom onset, appearing to peak at 31–35 days [58,59]. These levels also appear to correlate with the severity of disease [60]. Titers of neutralizing antibodies in patients with severe COVID-19 are up to seven times higher than in those with mild disease [54,60–62]. Neutralizing antibodies may decline below detection thresholds by 2–3 months after symptom onset [48,63]. Importantly, it should be noted that some neutralization studies use pseudoviruses (nonpathogenic viruses that have been genetically modified to present SARS-CoV-2-specific proteins) that are manipulated at lower biosafety containment levels, but these are not standard neutralization assays.

Role of T Cells and Innate Immunity

‘Cell-mediated immunity’ refers to the adaptive immune response that is independent of antibodies but involves immune cells that specifically recognize, target, and clear infected host cells. Cell-mediated immunity and how it correlates to antibody levels should be further investigated in the context of SARS-CoV-2. T cells (both CD4⁺ and CD8⁺) are important mediators of infection in other coronavirus diseases. CD8⁺ cells, or ‘killer’ cells, are capable of destroying virus-infected

cells, whereas CD4⁺ cells, or ‘helper’ T cells, act indirectly to control or direct other components of the immune system to control the infection, including directing CD8⁺ cells to kill infected cells. Other T cells called ‘memory T cells’ circulate in small numbers after an infection and can activate the immune system quickly in response to the same pathogen. Recent work in convalescent patients demonstrated that SARS-CoV-2–specific CD4⁺ T cells were present in all patients and that CD8⁺ T cells were present in 90%, indicating a potential role for cell-mediated immunity for SARS-CoV-2 infections [64].

In both severe and mild COVID-19 patients, patients have SARS-CoV-2–specific T cell responses [65,66]. In recovered patients, CD4⁺ and CD8⁺ T cell responses were more robust in patients with severe COVID-19 [65]. Importantly, mild and asymptomatic cases of COVID-19 also appear to have SARS-CoV-2–specific T cell responses [67]. These responsive T cell titers appeared to correlate with antispike, anti-RBD, and anti-nucleoprotein (NP) antibody levels. Although mild cases had lower specific memory T cell responses, they did have active, mature membrane protein (M)- and NP-specific CD8⁺ T cells. A smaller study of index patients diagnosed with mild COVID-19 and their familial contacts showed persistent SARS-CoV-2–specific T cells up to 80 days after symptom onset [68]. Importantly, even without seroconversion, contact cases still had active T cell responses. The presence of reactive T cells in all patient populations holds promise for a multipronged immune defense. While more accessible tests are being created to study neutralizing antibodies in lower biocontainment settings, T cell screening is more difficult to scale up because most T cell assays rely on flow cytometry methods, which require a laboratory.

Current and Potential Uses for Antibody Tests for Individuals

Identifying and Managing Patient Care after Recovery from COVID-19

COVID-19 infection history could be important for future medical management. There is a growing body of evidence for medical sequelae following SARS-CoV-2 infection, even in mild cases. Serology testing to identify past SARS-CoV-2 infection could be particularly helpful in pediatric patients with multisystem inflammatory syndrome in children (MIS-C), as recommended by the Infectious Diseases Society of America [69]. Recent increases of cases of MIS-C alerted healthcare professionals to the possible link to SARS-CoV-2 infection; indeed, there is high seroprevalence in children presenting with MIS-C, accompanied by neutralizing antibodies to the virus [70–72]. In adults, multiple sequelae have been associated with long-term health impacts. Cardiovascular impacts, for instance, are seen in 20–35% of patients, and long-term cardiovascular impacts such as myocarditis have been observed in young adults recovered from COVID-19 [73–75]. As this understanding evolves, the use of antibody tests to determine past infection may become more important [76]. In resource-limited settings, serologic testing may offer a method for screening symptomatic patients and following their contacts. The Africa Centers for Disease Control and Prevention has provided interim guidance for the use of rapid serology tests, and this could better inform patient care and community surveillance [77].

Cytokine Storm and Sequelae in COVID-19 Patients

Inflammation is a major part of the body’s defense against infection and other assaults, but a hallmark of many SARS-CoV-2 infections is the loss of regulation of the inflammatory response. Severe cases of COVID-19 (i.e., those with acute respiratory distress syndrome) are characterized by systemic hyperinflammation, or ‘cytokine storm.’ The hyperexpression of proinflammatory cytokines and chemokines leads to increased infiltration of immune cells (e.g., macrophages and neutrophils) to the lungs, damaging other immune cells and the lung’s architectural components. Subsequently, the virus can leak out of the lungs and spread to other organs by moving through the vascular system and infecting other cells that express the ACE2 receptor; the virus can also

spread between adjacent cells [106,107]. Coagulation defects lead to microvascular COVID-19 lung vessel obstructive thromboinflammatory syndrome, or ‘microCLOTS’: thousands of tiny clots throughout the entire vasculature. Blood clotting, strokes, embolism, and heart, kidney, and neurological damage have been observed in these severe cases [78]. Such impacts of hyper-immune activation may lead to long-term COVID-19 sequelae in patients, who are now described as ‘long haulers.’ Long haulers can be any age and of any health status, with children and adults alike experiencing these impacts [79–81]. Serology testing for such individuals, especially if they have had asymptomatic infections, could provide causation for their symptoms [82].

Of particular concern is long-lasting neurologic damage: in recovered SARS patients, persistent neurocognitive deficits lasted up to 18 months after discharge [83]. Early reports from Wuhan and Italy suggested similar effects will be associated with SARS-CoV-2 infections as well; reports of anxiety, depression, malaise, and muscle weakness (demyelination and other neuromuscular complications) are accumulating [84,85]. It is already clear that recovery from COVID-19 can take months and, as the pandemic progresses, perhaps years.

Donating Convalescent Plasma

Serology testing is often necessary to determine eligibility to donate convalescent plasma, a therapy for COVID-19 that is currently being investigated in several clinical trials and has been given EUA from the FDA [86]. Convalescent plasma therapy is also known as ‘passive immunization’; in theory, giving plasma from recovered COVID-19 patients who have SARS-CoV-2–specific antibodies to patients with active infections bolsters the recipients’ immune response [87]. The FDA now requires a confirmatory laboratory-based test (molecular or serology) for COVID-19 infection before plasma donation, with resolution of symptoms at least 14 days prior to donation [88]. Convalescent plasma appears to have limited clinical benefit but appears most effective if administered early and with high antibody titers [89–93]. Levels of overall antibodies appear to vary greatly among convalescent plasma donors [54,55]. Blood donation centers, including the American Red Cross, are now offering serology tests to all blood donors, providing data that could be used to identify potential donors [94–96]. Additionally, serology testing of all donors could identify asymptomatic individuals who may have sufficient levels of antibody to donate plasma.

Vaccine Selection

Another important use of individual testing is determining the risk of antibody status before immunization. Phases I and II clinical trials testing the safety and efficacy of a new vaccine measure the immune response to the immunization; hence, individuals with previous exposure should be differentiated in evaluating the response to vaccination.

In addition, vaccine manufacturers are watching carefully for any signs of antibody-dependent enhancement (ADE). Briefly, ADE occurs when antibody levels specific to a virus are low enough to allow increased reinfection by the same virus. There are multiple mechanisms described, but generally ADE occurs when the binding of non-neutralizing antibodies enhances viral entry into cells. There is evidence for ADE in SARS-CoV-1–infected nonhuman primates, but currently there is no evidence of ADE associated with SARS-CoV-2 infection [97,98]. If evidence of ADE in SARS-CoV-2 infections does emerge, it may be important to assess antibody levels in individuals before and after vaccination. This could ensure that levels are sufficiently high to neutralize the virus and not contribute to ADE. Variable levels could in fact dictate vaccination schedules.

As vaccine candidates advance worldwide, with several entering Phase III trials, serostatus could be relevant to the patient and the healthcare provider [99,100]. If it is determined that a single

SARS-CoV-2 exposure induces long-lasting protective immunity, a positive serology test could indicate that an individual does not require vaccination or should not receive priority for vaccination. This ‘triage’ of individuals eligible for vaccination could be useful if vaccine doses are limited. However, antibody levels have been shown to wane over time. Therefore, an individual who was exposed several months before taking a serology test may have a negative test result.

A Tool for Public Health, Not Individuals

Recent public discussion has given many the false impression that a seropositive antibody test result indicates a return to ‘normal’ and release from physical distancing public health measures [101,102]. However, given uncertainty about the antibody tests (quality, accuracy level, positive predictive value) and what those tests might indicate immunologically (durability of antibodies and necessity for protection from reinfection), seropositive test results should not be used to avoid appropriate physical distancing or mask wearing.

Individual antibody test results should also be used with caution by employers or other institutions because they may be inaccurate or have performance discrepancies from those reported by the manufacturer. The US Equal Employment Opportunity Commission clarified that it is unlawful for employers to require antibody testing as a prerequisite for their employees to return to work under the Americans with Disabilities Act [18]. However, there are reports of some universities considering allowing only those with seropositive test results to participate in certain group activities, which creates perverse incentives [103]. The US Department of Defense considered a proposal to bar seropositive recruits, presumably because COVID-19 may lead to medical sequelae in the future; it will be important to monitor these efforts to protect individuals from ethical hazards and from discrimination [104,105].

Concluding Remarks

Validated and highly accurate antibody tests have an important role in the ongoing response to the COVID-19 pandemic at the population level. With the current limited understanding of correlates of immunity, prevalence of disease, and durability of immunity, antibody testing should remain a tool of public health until more is understood about long-term impacts of SARS-CoV-2 on the immune system. When more is understood about how antibodies reflect protective immunity and how serostatus correlates with medical sequelae, the value of antibody testing at the individual level can be re-evaluated (see [Outstanding Questions](#)).

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Outstanding Questions

Which components of the immune system are most important in fighting SARS-CoV-2, and, if antibodies, what titers are required to maintain immunity?

Will past infection by SARS-CoV-2 have future importance for medical screening, vaccine selection, or vaccine prioritization?

How long do neutralizing antibodies last?

Is a single infection sufficient to induce memory B and T cell development?

Will changes in disease prevalence substantially affect performance and utility of serology tests?

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