Position Statement in the Age of COVID-19
Real Time Information to Support Policy Decisions

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Immunity Passports Based on COVID-19
Antibody Testing: A Flawed Concept?

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Immunity passport concept
Social distancing, quarantine, and isolation measures have effectively reduced COVID-19 spread. Now, the disease’s devastating economic impact has led policymakers to propose using technology to enable opening up the economy and recreation. However, few proposals appear to have sound evidence-based approaches.

One idea that has gained traction is extending “immunity passports” to people who have recovered from COVID-19. The underlying assumption behind immunity passports is that those who recovered from COVID-19 are immune and unlikely to become sick and infectious if re-exposed. However, important questions remain unanswered about this assumption. In some proposals, even people who tested positive for SARS-CoV-2 infection, but experienced no symptoms, would be identified by testing for serum antibodies against the virus and eligible for such a passport.

WHO weighs in: Antibody response provides some protection
On April 24, 2020, the World Health Organization (WHO) issued a Scientific Brief to caution against immunity passports based on antibody testing, but the statement’s wording inadvertently caused confusion and anxiety among the public. WHO initially stated that “[t]here is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection,” which seems to contradict a widely held assumption that convalescence grants COVID-19 immunity. Despite WHO’s later clarification stating, “We expect that most people who are infected with #COVID19 will develop an antibody response that will provide some level of protection,” debate and confusion continue around the use of antibody tests to justify loosening or lifting social restrictions for people with positive results.

Use science to frame debate
Accurate information is critical to frame the public debate on health policy and determine which interventions work best. Setting aside the adverse societal ramifications that immunity passports may introduce, we briefly discuss here the scientific principles that make test-based immunity passports a risky proposition.

Undeniably, testing plays a central role in informing evidence-based decisions regarding COVID-19, but testing must be a component of broader strategies for relaxing restrictions while ensuring public safety. In the absence of an effective vaccine, relaxing social restrictions has to be a dynamic process that accepts the risk that new outbreaks will occur as restrictions are relaxed and that ongoing reassessment of social distancing practices will be needed.

Testing is critical to understand how lifting social restrictions or implementing other measures, such as immunity passports, will affect COVID-19 transmission rates. A prudent testing policy or guidance could allow decision makers to take action to contain hotspot outbreaks before they become widespread. However, having accurate information also entails
a thorough understanding of the limitations, evidence gaps, and unanswered questions pertaining to antibody testing. Some of these, as WHO points out, concern the biologic relationship between antibodies and immunity.

**Immune response to viruses affects utility of antibody testing**

A brief overview of the immune response to viruses is important to understand the limitations of COVID-19 antibody testing. As for many other viruses, recovery from COVID-19 happens when the patient’s immune response clears the infection. Without an effective response, viruses keep replicating until the process is incompatible with life. Nonspecific (“innate”) immune responses are typically insufficient to clear a widespread viral infection. Recovery usually involves a targeted response mediated by immunoglobulins secreted by B cells and T-cell receptors bound to T cells. Both B and T cells can become “memory” cells that confer immunity to disease, though some patients with immunity may still become asymptomatic carriers. Depending on the virus, convalescent immunity may not last more than a few months and may not protect against emerging viral strains.

**Why antibody tests may not reflect immunity level**

COVID-19 antibody tests are immunochemical assays that detect immunoglobulins based on their binding to COVID-19 surface proteins. Several types of laboratory tests and point-of-care tests are available. Tests in both categories have different readouts: some detect total antibodies, and some are specific for type G or type M immunoglobulins (IgG and IgM, respectively), which may differentiate active (IgM+) from chronic or past (IgM-) infections. Laboratory tests can quantify immunoglobulin levels and are typically more accurate, but they also take longer than point-of-care tests in cassette format.

Further complexity arises because how the immune system responds specifically to COVID-19 is still not completely understood. Antibody testing may not fully reflect immunity if COVID-19 responses are mediated primarily by T cells or by immunoglobulins that do not bind to SARS-CoV-2 particles but, for instance, bind to membrane proteins that the virus uses to infect cells. Preliminary studies have reported robust T-cell and B-cell responses in most COVID-19 survivors, which is also consistent with reports of successful convalescent serum therapy. However, many more studies are needed to confirm that IgG tests can detect immunity specific to COVID-19 (and not to other coronaviruses), in which patients, and for how long.

**Immunity passports require high test accuracy or risk potentially catastrophic decisions**

Even with a sound biological basis, no diagnostic test is 100% accurate. False test results can occur for many reasons. False positives, in particular, are critical barriers to using antibody tests to extend immunity passports. People cleared by a false-positive test result may become infected and spread the disease. If, as far as we know, the vast majority of the population has not yet been exposed or infected, false-positive tests may facilitate additional infection waves. Thus, immunity passports could contribute to reinstituting social restrictions rather than shortening them.

**Test accuracy** is typically expressed as sensitivity and specificity, which represent the rates of patients with and without the condition that a test classifies accurately. As of June 1, 2020, FDA has granted Emergency Use Authorization (EUA) to 15 serum COVID-19 antibody tests. FDA requires only bench validation (i.e., analytic validity) of tests to grant EUA; therefore, the performance (i.e., clinical validity) of these tests in real-world settings is unknown. However, positive predictive value estimates (i.e., proportion of positive tests that are correct) for FDA-approved tests are low for many of these tests even with an assumed 5% prevalence (10 times that of identified COVID-19 cases in the United States as of May 2020). Thus, some tests may be less reliable than others. In the absence of additional epidemiologic data and independent clinical validation of tests, caution is warranted when relying on test results for policy making.

**Antibody testing may have a place, but evidence bar must be high**

These limitations are not absolute barriers to the idea of immunity passports, but considerable evidence is needed to overcome them. Large, multinational epidemiologic and diagnostic cohort studies are needed to confirm that the tests reliably reflect COVID-19 immunity, are accurate enough to award immunity passports, and measure the epidemiologic impact of immunity passports. Also, if immunity passports are implemented, testing volume needs to be sufficient and accessible by the entire population, a practical consideration.
that may not be feasible. Thus, the bar is set very high for using immunity passports as a safe and effective intervention to prevent COVID-19 transmission.

Still, antibody tests may inform on population-wide immunity and guide government agencies on when it is reasonable to loosen social restrictions. Sufficient testing can also provide information on the level of background immunity, transmission rates, and at-risk individuals. This information can be used for data-driven decision making on lifting social restrictions in a dynamic manner, especially if most infected individuals are asymptomatic or exhibit only mild symptoms. Antibody testing may also let physicians, scientists, and decision makers monitor the epidemiologic impact of lifting measures to react in real time. Because the implications of false-negative test results pose little risk to the community (albeit a large burden on the individual), antibody testing may also help identify and isolate asymptomatic disease carriers.

Policymakers and healthcare organizations should engage with manufacturers to plan clinical studies to address evidence gaps on COVID-19 antibody testing. Until these data are available, using tests to guide social policies to prevent transmission should be accompanied by safeguards (e.g., active infection surveillance, contact tracing) that consider testing’s potential pitfalls.

Please also see the Position Paper “The Role of Diagnostic Testing in Combating COVID-19: Accuracy Matters.”

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