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Perspective

Waiting for Certainty on Covid-19 Antibody Tests — At What Cost?

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Governments around the world and throughout the United States are beginning to "reopen their economies" in stages. Some have been considering the use of serologic antibody testing to screen for possible immunity and to identify people who could return to the workplace with less severe mitigation measures[1] or be assigned to higher-exposure tasks. Although availability of antibody tests is lagging and successful mitigation has kept seroprevalence too low to rely fully on positive test results, at some point in the near future antibody testing will become a viable option. This idea is not without its critics. On April 24, for example, the World Health Organization (WHO) issued the following guidance: "At this point in the pandemic, there is not enough evidence about the effectiveness of antibody-mediated immunity to guarantee the accuracy of an 'immunity passport' or 'risk-free certificate.'"[2]

The WHO is right to note the many uncertainties. Do antibodies confer immunity and, if so, for how long? How accurate is the antibody test? What are the individual and collective harms that may be caused if persons with no actual immunity are certified for return to the workplace? How great is the danger that people desperate to return to work may seek intentional exposure to the virus in the hope of developing antibodies?

But we believe that the WHO is dead wrong to suggest that we cannot act until we "guarantee" the accuracy of the immunity-certification process. Demanding incontrovertible evidence may be appropriate in the rarefied world of scholarly scientific inquiry. But in the context of a raging pandemic, we simply do not have the luxury of holding decisions in abeyance until all the relevant evidence can be assembled. Failing to take action is itself an action that carries profound costs and health consequences.

For caregivers, acting on incomplete information is not a revolutionary idea. Practicing medicine means relying on imperfect evidence to balance harms against benefits on a daily basis. Physicians use tests offering less than 100% accuracy every day, knowing that there will always be false positives and false negatives. When we judge that the likely benefits of acting on a correct diagnosis outweigh the possible harms of mistakenly acting on an incorrect diagnosis, we act. We choose to perform appendectomies, for example, even though we rarely have irrefutable evidence that a patient's appendix is inflamed. Though we arrive at pub-

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lic health policies and clinical decisions by different avenues, in both domains we must often make choices with less-than-perfect evidence.

Many U.S. governors are opening up workplaces now without requiring evidence of immunity or prior infection. Is this policy better than a more nuanced policy of requiring less virologic testing and mitigation for people who obtain a positive result from a serologic test — even an imperfect one — based on the unproven but likely premise that there is some immunity conferred by the presence of antibodies? We don't give penicillin to everyone with a sore throat; a throat culture is usually a prerequisite. Even though throat cultures have false positives and false negatives, they are still useful.

Demands for guarantees are both particularly appealing and especially dangerous in times of crisis. The Covid-19 pandemic throws the risk–benefit trade-off into relief so stark that many of us would rather turn away than confront it. By soft-pedaling the less tangible, less emotionally salient considerations that figure into a decision, insisting on certainty permits policymakers to speak with persuasive, decisive clarity in the space of a tweet. No need for "on the other hand" equivocation. Those who believe that no economic benefit justifies the risk of spreading Covid-19 can find shelter in the solution of not reopening the economy until the entire population is covered by a completely effective vaccine or until a highly effective treatment is widely available. At the other extreme is the solution arrived at by those who would reopen the economy without regard for the risks that individual workers would incur and impose on others.

A more reasoned, humane position is to take explicit stock of the benefits and harms. Four independent pieces of information need to be weighed against one another in assessing serologic testing as a basis for returning people to work.

First is our understanding of the presence of SARS-CoV-2 antibodies in the population (prevalence). Second is our understanding of the performance of serologic testing — both its ability to detect the presence of antibodies (test sensitivity) and its ability to confirm the absence of SARS-CoV-2 antibodies when they are truly absent (test specificity). Third is our beliefs about whether and how antibodies confer immunity; if they do, what do we assume about the relationship between antibody level (titer) and the resultant degree and persistence of any immunity that is conferred? Fourth is our belief about the relative magnitude of the two different kinds of harm that we could cause: the net harm of mistakenly releasing a susceptible, and potentially infectious, person into the workforce with minimal mitigation (false positive cost) and the net cost of failing to certify a truly immune person to rejoin the workforce (false negative cost).

The delicate balance to be struck among these four considerations can be described mathematically, but the bottom line is this: we have enough evidence and expert opinion to make an informed decision today. And we can put the monitoring systems in place to learn from that decision so that we can make even better choices tomorrow.

In the world of randomized clinical trials, statisticians test scientific hypotheses by requiring a probability of less than 5% that the observed result could have occurred by chance. This so-called type I error — and the associated mistake of approving a truly ineffective (or even dangerous) drug — is the enemy of the truth. But reducing the risk of type I error places us unavoidably at greater risk of committing a type II error and failing to approve a truly effective drug. In times of crisis, when the consequences of both action and inaction are so serious, it makes sense to take into account the benefits and harms of all possible errors and to be prepared to commit some type I errors in exchange for fewer type II errors and the opportunity to learn something important.

To be sure, there are problems with serologic testing. Tests with poor quality control and unacceptably high error rates need to be culled out, as the Food and Drug Administration has begun to do.[3] Persons receiving false positive test results may be mistakenly reassured that they are safe and may pay less attention to basic prevention (e.g., social distancing). Tests with nontrivial false positive rates should not be used when the prevalence of the condition being tested for is too low, as it remains in most communities. First-generation antibody tests for HIV had specificities in the range we currently see for Covid-19 antibody tests, but today HIV antibody tests are 99.5% specific.[4] Soon, Covid-19 antibody tests could reach that level of accuracy.[5]

Important ethical questions need to be addressed regarding

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the implications of restricting work on the basis of health status. Any public policy that distinguishes among citizens according to their Covid-19 serologic status has the potential to threaten rights of equal access to paid employment, undermine freedom to socialize and to travel, violate expectations of privacy, and exacerbate enforcement practices that discriminate against vulnerable groups.

The risks of reopening workplaces and the economy to individuals and communities are real; steps in that direction should be taken cautiously. Antibody testing, made available to those in the workforce, will soon offer a scientifically valid way to better determine workplace access and mitigation strategies based on the risk that individuals may transmit the virus to or acquire the virus from coworkers. But the costs of delaying any reopening until we are certain that no one returning to work will transmit Covid-19 are also real. There is no such thing as a 100% safe bet. Let's not permit an unattainable ideal to be the enemy of a very good option that we currently have.

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