

TESTING FOR THE PATHOGEN DURING THE COVID-19 PANDEMIC AND FUTURE ONES

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Introduction

The United States has failed to deploy adequate testing for the presence of the coronavirus SARS-CoV-2 during the Covid-19 pandemic and has been unable to avoid continued spread of the virus. In this report, we explain why such testing is an essential factor in efforts to control the pandemic, why adequate testing has been difficult to achieve, and why the United States has not met the challenge. We conclude by recommending ways to provide more extensive testing in this and future epidemics.

Why testing in the Covid-19 pandemic is both essential and difficult.

The United States has now been in the midst of the Covid-19 pandemic for about half a year. The effects on the nation have been appalling, with dramatic losses of life, health, social well-being, and economic stability.

Some of this disaster can be attributed to the inherent characteristics of the infectious agent, the coronavirus SARS-CoV-2. Because it is novel, there is no vaccine to block infection, there are no therapies to significantly reduce the morbidity of the disease it causes, and no segment of the population has been rendered naturally immune because of prior exposures. Because the virus spreads efficiently from one infected person to another, apparently by multiple routes, and can do so even when an infected person has no symptoms of the disease¹, it is difficult to slow transmission sufficiently to avoid epidemic growth of the disease.

These traits are innate to the virus, wherever it appears. Yet the United States has fared among the worst of all nations---large and small, rich and poor---that have faced the pandemic², despite the country's wealth and scientific prowess and despite its traditional standing as a nation well-prepared to combat disease³.

¹ S Lee; T Kim, E. Lee et al. Clinical Course and Molecular Viral Shedding Among Asymptomatic and Symptomatic Patients With SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea, JAMA August 6, 2020

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2769235>

² E. Yong, How the Pandemic Defeated America - The Atlantic, Sept.2020

<https://www.theatlantic.com/magazine/archive/2020/09/coronavirus-american-failure/614191/>; The Unique U.S.

Failure to Control the Virus, [https://www.nytimes.com/2020/08/06/us/united-states-failure-](https://www.nytimes.com/2020/08/06/us/united-states-failure-coronavirus.html?smid=nytcore-ios-share)

[coronavirus.html?smid=nytcore-ios-share](https://www.nytimes.com/2020/08/06/us/united-states-failure-coronavirus.html?smid=nytcore-ios-share); How the Virus Won

<https://www.nytimes.com/interactive/2020/us/coronavirus-spread.html?smid=nytcore-ios-share>

³ Global Health Security Index, 2019 <https://www.ghsindex.org/?smid=nytcore-ios-share>

Why has this happened? And how can the country change its course in this pandemic and act more effectively in future ones? These are questions that our Subgroup, composed of former members of President Obama’s Council of Advisors on Science and Technology (PCAST), has been asking over the course of the past few months. We have previously examined the federal stockpiles of medical equipment⁴, methods for tracing contacts of infected individuals⁵, and management of pandemic-relevant public health data⁶. In all three settings, we have found systemic deficiencies and proposed remedies.

Here we explore the role of testing---mainly for the virus, but also for the host responses to it---and offer additional explanations for why the United States has done so poorly during the Covid-19 pandemic. These include confused messages from political leaders about the significance of testing, shortcomings in test design and certification, inadequate financing of tests, deficiencies in the availability of tests, and failures to test as broadly, frequently, and equitably as possible. Of course, the problems with testing do not, by themselves, complete the list of explanations for the U.S. failures.

The issues we raise here cannot be viewed solely as matters that concern the technology of testing; they must be considered in the light of the other elements of a public health response and in the context of a complex society. It is widely recognized that a test revealing the coronavirus in an ailing patient allows accurate diagnosis and guides the therapeutic strategy for that person⁷. But, with respect to control of an epidemic in a community, a test will be of little value if not linked to rigorous practices of public health, so that contacts are identified, interviewed, tested themselves, and, if found to be infected, properly isolated to prevent further spread of the virus⁸. Careful management and interpretation of test data are also required to design strategies for effective control of the pandemic⁹.

The tests must be accurate, widely accessible, rapidly performed, efficiently reported, and used extensively for surveillance as well as diagnosis. And, generally, they should be subsidized. Achieving all this can be especially difficult in this country’s heterogeneous society, with its many ethnicities, religions, and social classes; its diverse climates, geographies, and population densities; its uneven distribution and quality of health care, delivered in so many different ways; the premium that many of its citizens place on individualism and resistance to behavioral directives; and its complicated systems of governance at the federal, state, and local levels.

Methods to test for the presence or past history of infection are especially important in situations like the current pandemic, in which the infection may not produce symptoms,

⁴http://adhocresponsegroup.org/OPCAST_Ad_Hoc_Subgroup_Stockpile_Recommendations_05-20-20.pdf

⁵http://adhocresponsegroup.org/OPCAST_On_Contact_Tracing_06-18-20.pdf

⁶http://adhocresponsegroup.org/OPCAST_Public_Health_Data_Report_07-28-20.pdf

⁷ Testing in the U.S. | CDC <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/testing-in-us.html>; Test for Current Infection | CDC <https://www.cdc.gov/coronavirus/2019-ncov/testing/diagnostic-testing.html>

⁸http://adhocresponsegroup.org/OPCAST_On_Contact_Tracing_06-18-20.pdf

⁹http://adhocresponsegroup.org/OPCAST_Public_Health_Data_Report_07-28-20.pdf

the disease is difficult to diagnose even when symptoms appear, and no preventive vaccines or highly effective therapies are yet available.

There are three broad categories of tests. **Viral tests** are designed to identify the microbe directly for three main purposes: to make a definitive diagnosis of the disease that the virus causes (**diagnostic tests**), to ascertain whether those known to have been exposed to infected people are infected (**contact-based tests**), and to monitor the distribution of the infectious agent in populations of asymptomatic people (**surveillance tests**). **Serological tests** are designed to document and characterize host immune responses to the infectious agent. **Prognostic tests** appraise the severity of individual cases. An expanded account of the nature, purpose, and status of these tests in the context of Covid-19 is provided in the **Appendix**.

As we argue below, to curb the spread of the coronavirus in the current pandemic, surveillance testing will need to be massively increased, achieving a far greater scale than the diagnostic and contact testing that have accounted for the majority of viral tests administered in the United States to date. Serological testing will likely play an important role at a later stage in the course of the pandemic and its aftermath, but for now emphasis must be placed on widespread viral testing to detect those currently infected, so that they may be isolated and their contacts traced, tested, and isolated when appropriate.

How to bring a pandemic to an end without treatments or vaccines.

Without an effective vaccine, without pre-existing herd immunity, and without effective anti-viral drugs, public health measures to control a viral outbreak must be focused on methods that restrain spread of the virus---impeding further progress of the pandemic and ultimately ending it. The most effective means to block further transmission of a virus in this situation is to identify all people who are infected so that they can isolate themselves, for as long as they remain infected, from those who are not infected. This extreme method can rarely be implemented perfectly, but it can be supplemented by using equipment (face masks, shields, gloves, and other protective gear) and virus disinfectants (to wash hands and contaminated surfaces) to further constrain spread of the virus.

If there were no tests to determine who is and is not infected, the physical separation strategy could be implemented successfully only by separating everyone from everyone else---an approach that is socially, economically, and emotionally unacceptable. But if it were possible to know at all times who is and who is not infected, any pandemic could be ended by using that information to limit isolation only to those who are infected and to limit its duration only to the period of infection. The availability of tests to detect the presence of the virus is thus critical for management of the pandemic, and the speed, cost, accuracy, extent, and frequency of use of those tests will determine how effectively transmission can be controlled by isolation methods alone¹⁰.

¹⁰ DB Larremore, B Wilder, E Lester, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. <https://doi.org/10.1101/2020.06.22.20136309>

Hypothetically then, if every person in a given region were tested for virus *every day*--- currently a logistically untenable proposition, but perhaps achievable in the future---we could know who should remain completely isolated until their infection disappears, while others could interact with other uninfected people at work or at school, in social or commercial activities. In theory, if done accurately and efficiently, this approach would rapidly eliminate the virus from that region---at least until an infected person appeared from elsewhere.

Less far-reaching but more realistic strategies for ending the Covid-19 pandemic can be measured against this rigorous but currently infeasible standard. The impracticality of testing every person can be at least partially offset by the other methods designed to protect against virus spread. These strategies include several already in use: the identification and quarantining of people who have been in contact with others known to be infected (“contact tracing”) and the practices of mask-wearing, hand-washing, and social distancing.

The scale of surveillance testing can also be reduced by focusing on those most likely to be exposed to infected people. Currently, the tests most often used to detect SARS-CoV-2 are diagnostic tests of symptomatic people or contact-based tests of asymptomatic people known to have been exposed to infected individuals. Testing more broadly and strategically---especially by surveying those who are at higher than average risk because they encounter large numbers of people in daily life or at unusual events---should reduce dependence on the other transmission-blunting measures, which have their own costs, difficulties of enforcement, and limited efficacies. But any effort to expand surveillance testing depends on a commitment to lower barriers, such as cost, inconvenience, and slow return of results, and to provide appropriate contact-tracing and other public health measures quickly and effectively when a test is positive for the virus.

The dilemmas of testing for virus during COVID-19

Because of their central role in efforts to control the pandemic in the absence of an effective vaccine, tests for the virus have been the subject of extended, vociferous public debate about their availability, turn-around time, accuracy, appropriate use, cost, and reimbursement. Indeed, the nation’s inadequacies in controlling Covid-19 can be attributed in large measure to deficiencies in testing in all of the aspects of testing described below.

The first cases of Covid-19 in Wuhan, China, in December 2019, were followed by the rapid isolation and identification of the causative coronavirus, SARS-CoV-2, and by the swift determination and dissemination of the sequence of the viral RNA genome in January, 2020. Once that information became available, only a few days were required to develop a relatively simple PCR-based test that could detect the coronavirus RNA in a matter of hours¹¹. (It is instructive to recall that tests for the causative agent of AIDS, the retrovirus HIV, were not available until a few years, rather than a few weeks, after the first report of the disease in 1981, which highlights the power of new technologies that allow the rapid identification and characterization of novel viral pathogens and the development of specific molecular tests to detect them.)

¹¹ PCR-based tests are explained in the Appendix

As has been widely reported, the swift identification of SARS-CoV-2 and the rapid design of molecular tests to detect it were followed by a multiplicity of problems that have impaired the ability of many countries, including the United States, to make testing widely, easily, and cheaply accessible for the diagnosis of individuals and for monitoring the spread of infection in broad populations.

Why has this happened? According to multiple reports, soon after the first case of Covid-19 was reported in Seattle WA, on January 20th, the agency responsible for providing materials for and guidance about microbial tests, the Centers for Disease Control and Prevention (CDC), began distributing small numbers of test kits, some of which were flawed because they included inappropriate control samples¹². In addition, the agency did not endorse the use of tests for virus detection available from other countries. As a result, U.S. national testing capacity was initially woefully small.

Over the ensuing months, testing capacity in the United States has gradually grown, using a variety of sampling kits and laboratory-based methods, supplied mostly by private companies, but also by academic institutions and government agencies, and approved by the Food and Drug Administration (FDA) under Emergency Use Authorizations (EUAs). As this is written, about 730,000 tests are performed in the US per day (about 20 million per month)¹³. It appears that the vast majority of these tests are diagnostic, with a smaller number being contact-based; the number of surveillance tests is not known, but they are likely to be relatively uncommon. Further, officials in many states and cities continue to bemoan the difficulties of obtaining tests for SARS-CoV-2 for any purpose and the efficacy of much of the surveillance testing is undermined by the slow return of results¹⁴.

As a result, the number of people who have been infected with SARS-CoV-2, with or without symptoms, remains uncertain, but probably ranges from 2- to 10-fold more than the number of documented cases¹⁵, a number that can only be determined more accurately by widespread deployment of serological tests to identify those who have been infected in the past¹⁶.

Although it is not known how many people are tested repeatedly or how many tests are performed for surveillance rather than diagnosis, about 1.5 percent of the US population is tested per week for all purposes (about 0.2 percent per day), with the frequency of

¹² The Unique U.S. Failure to Control the Virus, <https://www.nytimes.com/2020/08/06/us/united-states-failure-coronavirus.html?smid=nytcore-ios-share>; Lessons unlearned: Four years before the CDC fumbled coronavirus testing, the agency made some of the same mistakes with Zika https://www.washingtonpost.com/investigations/lessons-unlearned-four-years-before-the-cdc-fumbled-coronavirus-testing-the-agency-made-some-of-the-same-mistakes-with-zika/2020/07/03/c32ca530-a8af-11ea-94d2-d7bc43b26bf9_story.html?utm_campaign=wp_post_most

¹³ The COVID Tracking Project. <https://covidtracking.com>

¹⁴ Coronavirus Live Updates: Testing Results Take Too Long, U.S. Official Concedes <https://www.nytimes.com/2020/07/26/world/coronavirus-live-updates.html?smid=nytcore-ios-share>

¹⁵ C.D.C. Says Cases Could Be 2 to 13 Times Higher Than Reported in Parts of U.S. <https://www.nytimes.com/2020/07/21/world/coronavirus-covid-19.html?smid=nytcore-ios-share>

¹⁶ Presuming that the serological tests are accurate and that detectable amounts of anti-viral antibodies remain.

surveillance testing being probably 5- to 10-fold lower. If it is assumed that about 10 percent of the population is at a relatively high risk of exposure to the virus---because of work, school, or other factors---and that they should be tested on at least a weekly or bi-weekly basis, then the country is underusing surveillance testing by a factor of about 10- to 100-fold. Or put another way: if as much as 10% of the US population is at relatively high risk of exposure and should be tested at least weekly, such surveillance testing would require nearly five million tests per day, an order of magnitude more than the number of all people currently being tested, who are mainly symptomatic patients and identified contacts. These estimates inform our recommendations for expanded surveillance testing.

Many reasons have been advanced to explain the deficiency in the use of virus testing. The prices of the tests, although controlled by Congressional legislation and the Center for Medicare and Medicaid Services (CMS), are significant (generally about \$100 per test) and reimbursable by Medicare, Medicaid, or private insurers only when used for established indications (symptoms or contacts), not for surveillance. Access to testing sites appears to be limited in many places, especially for some of the most severely affected populations (including underserved minorities, and uninsured, poor, and rural populations). The methods of obtaining samples from the upper respiratory tract are not standardized, are often uncomfortable (discouraging some from seeking tests), and do not always provide material from infected regions of the mucosa, discouraging some from seeking testing.

The value and attraction of the tests are further reduced by slow return of results---which often take as long as five to ten days from sampling to reporting in the case of some commercial vendors¹⁷ meaning that infected subjects are unaware of their status and capable of transmitting the virus to others for several days before they are quarantined and interviewed by contact tracers. Such lags make contact tracing nearly useless. And, despite extensive efforts to improve the efficiency of testing through research on the underlying technologies, nearly all tests for the three primary purposes, including surveillance testing, are still performed individually in central laboratories, using standard PCR-based methods, rather than newer, potentially faster, cheaper, and more convenient technologies, including protein- rather than RNA-based tests, as described further below.

Without sufficient surveillance testing to identify a large fraction of infected asymptomatic individuals, most of the country has had to resorted to other methods that are less specific, more costly, and less effective. The most extreme has been the shutting down of all but the most essential activities in our society, which has brought economic disaster for many, made life difficult for all, and failed to protect essential workers, who must remain at their jobs, from high risk of infection. The most acceptable and simplest methods, but still not uniformly adopted, reduce virus transmission with masks, gloves, disinfection, and safe distancing. Other methods include inherently inaccurate diagnostic surrogates for viral testing (temperature-sensing devices and symptom-reporting, often used at workplaces, meeting centers, and airports) and prompts to get tested (e.g., via contact-tracing that informs people that they have been exposed to an infected person).

¹⁷ Testing Results Take Too Long, U.S. Official Concedes
<https://www.nytimes.com/2020/07/26/world/coronavirus-live-updates.html?smid=nytcore-ios-share>

Clearly, though, the totality of measures that have been used in this country has fallen short of controlling Covid-19. The tsunami of new cases occurring in most states several months after the pandemic began offers grim testimony for the need to expand testing so that a much larger fraction of infected people will know that they are virus carriers and can be separated from others. The case for much wider testing and a more precise plan to find and isolate infected individuals has become especially compelling at a time when restrictions on commercial and social life are being lifted, schools and colleges are trying to reopen, and people are tiring of the emotionally draining isolation strategies justifiably imposed by state and city governments during the first months of the pandemic.

A closer look at the challenge of widespread surveillance testing for the virus

Why has it been difficult to provide an inexpensive, accurate test with a rapid return of results so that many more people might be monitored for the presence of virus on a regular basis, perhaps even daily, weekly, or bi-weekly? To understand the difficulties and to consider means to overcome them, especially as this country attempts to reopen in this country, it is useful to analyze the testing process step-by-step, revealing its complexities, costs, recent failures, and opportunities for improvement.

Deciding to be tested

Testing begins with a decision to have a test done. That decision is now made in a variety of ways that reflect the unevenness of U.S. testing practices. The primary reasons for obtaining a test fall into three categories: (i) an individual has symptoms suggestive of Covid-19 and decides (often after a recommendation from health care personnel) to have a diagnostic test for SARS-CoV-2; (ii) an asymptomatic person learns about a recent contact with an infected individual and is requested (or volunteers) to have a contact-based test; and (iii) a presumably healthy person undergoes surveillance testing as part of an effort to reduce the number of carriers present in a workplace, school, or large event or in response to a request to participate in a survey designed to determine the prevalence of virus carriers.

Unfortunately, these three sets of circumstances are often not considered separately when considering how much testing should be done, what testing methods should be used, how they should be financed, or even where and how they should be performed. Moreover, the results are not usually tracked separately when public health information is compiled. As a result, the total number of tests performed over time in any location and the fraction of tests that yield positive results may be misinterpreted. (For example, a higher percentage of positive tests is expected from diagnostic tests of symptomatic people than from surveillance tests of well people, but it is typically not possible to disaggregate these different circumstances.)

The frequency at which people decide to obtain tests that are not mandated (e.g. by an employer, school administrator, or event organizer) will depend on a number of factors: the location of sampling sites, the mode of sampling, the way in which the significance of the test has been communicated, the time required for return of results, and the cost and the likelihood of reimbursement. At present, public and private health insurance will

reimburse virus tests for diagnosis (when a patient has symptoms of Covid-19) or for evaluation of contacts with an infected person. Virus surveillance requires additional financial support since the tests are not generally eligible for reimbursement. The problems of cost are magnified by the need for repeated surveillance: those with a negative test today may become virus-positive tomorrow.

Taking the sample

The second steps are physical: getting to a sampling site and having a sample taken for viral testing. With few exceptions, samples for viral testing of all three types are obtained by trained personnel at sites outside homes and workplaces. Although the number of such sites has grown, they are still inequitably distributed, sometimes depleted of necessary personal protective equipment (PPE), swabs, or tubes, and often inconvenient because they are far away or require long wait-times. Since the motivation is greater for a symptomatic person to obtain a diagnostic test than for an asymptomatic person to obtain a surveillance or contact-tracing test, inconvenient testing sites will disproportionately discourage the latter. Expansion of viral testing would be facilitated by greater attention to the distribution and efficiency of sampling sites or by greater use of test kits that allow self-sampling at home or work.

Although the coronavirus grows in many cell types and can be found at many sites in the body, the conventional approach is to sample the upper respiratory tract where the virus appears to be most abundant and transmissible. There is, however, still no consensus about the best method for procuring the sample. Initially, nearly all sampling was performed by inserting long swabs through the nose to obtain material from the posterior pharynx. For several reasons---the discomfort of this procedure, early shortages of the swabs, and the apparent ability of some laboratories to obtain reliable results from samples taken with less invasive approaches ---sampling is now often performed in other ways: by swabbing the anterior nose or the oral cavity or by collecting saliva. These alternative sampling methods have obvious advantages; they are less uncomfortable, can be self-administered, and can obviate the requirement to travel to a sampling site. But it is distressing that, several months into the pandemic, there have been no large-scale, systematic studies and no consensus about which sampling procedure should be followed under which circumstances to achieve the most accurate results.

Transporting the sample

As most viral tests are currently performed at dedicated central laboratories, the samples need to be safely, securely, and swiftly brought from the sampling site (at home, workplace, or sampling facility) to the testing location. This step would be eliminated, of course, if tests could be performed at the site of sampling (see below), but currently most tests are performed in large laboratories using expensive equipment managed by trained technical staff. The reliability and speed of transit to the testing site are important variables in the process, requiring careful tracking, but no regulations currently mandate such tracking.

Detecting the virus

The molecular methods used to detect SARS-CoV-2 are at the heart of the testing process. Although the PCR-based test used from the start of the pandemic is now standard (see **Appendix**) and many versions have received FDA approval for emergency use, it is still inefficient, relatively expensive, and performed nearly exclusively at centralized laboratories. (The variable cost per test is estimated to be about \$20, but the price per test is generally at or near the Medicare rate of \$100 per sample and occasionally much more¹⁸.) Other potentially cheaper, faster, and simpler testing methods are under development in commercial, governmental, and academic laboratories, as discussed below.

Of special interest are tests for surveillance that can be conducted rapidly at the site of sample collection, since such tests could then be performed at the entry points at work places, schools, large meetings, or social or cultural events; in such settings, identification of even one infected asymptomatic person could prevent transmission to many susceptible people. Testing in those settings could be made cheaper and faster with methods that detect viral proteins (antigens) rather than viral RNA, in the manner used for existing tests (e.g. for pregnancy) that take only a few minutes to perform. This antigen testing may sacrifice sensitivity of detection for convenience and economy; but, importantly, the advantages of much wider and more frequent use could offset the loss of sensitivity and be as effective in suppressing viral spread.¹⁹

Returning results

Regardless of the reason for testing, rapid return of results, especially positive results, is essential to ensure that the best course of treatment is pursued and that any infectious persons and all contacts are informed and appropriately counseled to minimize further spread of the virus. Tests performed at centralized laboratories typically require several hours to process. But the actual time from sample collection to delivery of results is often much longer, sometimes as long as 5 to 10 days, especially from commercial providers that are well compensated²⁰. During the delays, infected people can spread infection to many others and may themselves develop life-threatening symptoms of Covid-19.

The timely return of results is heavily dependent on the technical methods used for testing and the number of samples waiting to be tested, but also on the efficiency with which a testing pipeline operates and the administrative competence of the entity that performs the test. Moreover, the results must be sent to health care personnel and public health agencies with suitable speed (at least within 24 hours). Patients and health care providers should also receive appropriate statements about the documented frequency of false-negative and false-positive results and about the indications for repeated testing. Some of

¹⁸ Most Coronavirus Tests Cost About \$100. Why Did One Cost \$2,315?

<https://www.nytimes.com/2020/06/16/upshot/coronavirus-test-cost-varies-widely.html?smid=nytcore-ios-share>

¹⁹ The Rockefeller Foundation, Covid-19 National Testing & Tracing Action Plan -

<https://www.rockefellerfoundation.org/national-covid-19-testing-and-tracing-action-plan/> ;

DB Larremore, B Wilder, E Lester, et al Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance <https://doi.org/10.1101/2020.06.22.20136309>

²⁰ Testing Results Take Too Long, U.S. Official Concedes

<https://www.nytimes.com/2020/07/26/world/coronavirus-live-updates.html?smid=nytcore-ios-share>

these issues will, of course, be obviated if very rapid tests (such as tests for viral protein) that can be performed at the site of sampling, including the home, come into common use.

Acting on the results: tracing contacts and isolating infected individuals

After a positive result has been transmitted to and received by the subject and public health authorities, efforts must be made to identify, inform, and guide as many people as possible who are known or suspected to have been in contact with the infected person, as outlined in our Subgroup's report on contact tracing²¹. In addition, appropriate guidance about quarantining and medical care needs to be provided by someone with adequate time and knowledge to address a patient's concerns. The CDC offers recommendations about such matters²², but it is not known whether and how often the recommendations are followed.

As the foregoing discussion of these components of the testing process reveals, the process is complex, even when the molecular test for viral RNA is relatively simple in design and execution. Moreover, the path towards much more widespread use of surveillance tests---on a scale that would dramatically improve population-based strategies to control the pandemic, not simply diagnose and treat symptomatic individuals---is uncertain and not yet pursued with the urgency, attention, and rigor that would be expected for responses during other kinds of national emergencies, such as a military attack.

Strategies for improved testing: Medical Research, Technical Platforms, and Data Repositories

As noted above, numerous explanations have been proposed for the U.S. failure to test adequate numbers of people, including surveillance of asymptomatic people, for SARS-CoV-2 during the current pandemic: lack of political commitment and leadership, high costs and inadequate reimbursement, poor public communication about the purposes of testing, and a weak public health system for following up on positive results. These are barriers that other countries have been able to overcome with consistent, informed direction by governments and with support from well-organized public health systems. Still, if the tests were faster and cheaper, if they had greater capacity and accuracy, and if they could be performed on saliva in the home or workplace, the United States would likely be in much better shape at this time.

Opportunities for improved testing

Several commentators have noted ways in which testing for virus might be improved:

- *Viral level.* Although viral tests are almost always reported as simply being positive or negative, the quantitative level of virus present at a given time varies across individuals by 100 million-fold. Some of the variation is due to the stage of infection, with levels being

²¹ http://adhocresponsegroup.org/OPCAST_On_Contact_Tracing_06-18-20.pdf

²² Case Investigation and Contact Tracing: Part of a Multipronged Approach to Fight the COVID 19
<https://www.cdc.gov/coronavirus/2019-ncov/php/principles-contact-tracing.html>

higher soon after infection and declining thereafter, but much may be due to inter-individual differences. While it is reasonable to guess that an individual's viral level would be related to their infectiousness, with the highest levels perhaps being more likely to give rise to super-spreading events, there is little empirical evidence on this point. Systematic collection, analysis, and understanding of the role of viral levels might inform both regulatory and public health strategies, including trade-offs between test cost and sensitivity and how to deploy resources to limit spread.

- *Pooling.* One obvious possibility is to increase testing capacity by pooling multiple samples in a single test reaction, especially for surveillance testing when the prevalence of virus carriers is low²³. If the pooled test reveals no virus, the individual samples need not be tested. Some institutions (including intramural NIH and Stanford University) have used such pools of tens or hundreds of samples to survey employees for virus, and the FDA recently granted Emergency Use Authorization (EUA) to a commercial vendor (Quest Diagnostics) to pool samples for virus tests, but only four per tube. Of course, whenever a pool includes at least one positive sample, substantial extra work and time is required to identify the infected person.
- *Barcoding.* Another approach to enlarging testing capacity involves equipping each sample with a unique molecular barcode so that thousands or tens of thousands of samples could be evaluated at once²⁴. Such technology is widely employed in DNA and RNA sequencing experiments but has not yet been fully validated for viral testing. To enhance sensitivity, the tests would be performed with rapid DNA sequencing methods after DNA amplification with PCR. The wide variation of viral levels across infected individuals may offset the efficiency of barcoding, because it will be necessary to perform very deep sequencing to reliably detect barcodes present at levels differing by 100 million-fold.
- *Testing for viral protein.* There is widespread interest in developing viral tests, especially for surveillance, that detect viral proteins (which can be specifically identified as antigens, using well-characterized antibodies) as a cheaper, faster, and simpler substitute for current tests that detect the coronavirus by measuring its RNA. Such tests are already in use in other countries and the FDA is beginning to grant them EUAs. They have the potential to lower costs to well under \$10 per test, can be performed at the place of sampling (even as self-administered tests at home), and could identify more infected individuals than RNA-based tests, despite their lower sensitivity, simply by more frequent and more widespread use²⁵. Large-scale systematic studies are still needed to compare the time course and levels

²³ How to Test More People for Coronavirus Without Actually Needing More Tests
<https://www.nytimes.com/interactive/2020/07/27/upshot/coronavirus-pooled-testing.html?smid=nytcore-ios-share>

²⁴ H Varmus, The Lack of Testing Is Holding Science

Back. <https://www.theatlantic.com/ideas/archive/2020/05/lack-testing-holding-science-back/611422/>

²⁵ The Rockefeller Foundation, Covid-19 National Testing & Tracing Action Plan

<https://www.rockefellerfoundation.org/national-covid-19-testing-and-tracing-action-plan/>;

DB Larremore, B Wilder, E Lester, et al Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. <https://doi.org/10.1101/2020.06.22.20136309>

of viral protein and viral RNA, as well as the sensitivity and specificity of different antigen tests.

- *Testing at sampling sites.* Options other than antigen-based tests are under development to make molecular tests suitable for use at the site of sampling, even at home or in a workplace. These methods include DNA amplification that does not require cumbersome thermocycling machines²⁶ and detection techniques based on properties of certain gene-editing systems²⁷.
- *Testing entire communities.* Other approaches to population-based evaluation of virus prevalence are currently being used to detect virus particles in sewage or other pooled community effluvia as a means to sense the presence of non-infectious remnants of pathogenic viruses like SARS-CoV-2 in entire neighborhoods.

Research on testing

The federal government has a number of tools at its disposal that might accelerate such improvements. The first and most obvious is to expand traditional mechanisms for supporting goal-oriented programs through grants and the use of government laboratories staffed by agency scientists. Some programs of this type have recently been launched. Funds provided to the National Cancer Institute (NCI) by the CURES Act in April, 2020, are being used to establish a Serological Sciences Network (SSN), based at the NCI's Frederick National Laboratory, to improve serological and related testing and to address underlying features of the host response to infection with SARS-CoV-2²⁸. In addition, the NIH has used funds appropriated under the CURES Act to establish an important initiative (called Rapid Acceleration of Diagnostics or RADx) to improve testing methods for SARS-CoV-2²⁹. Although it is moving as swiftly as possible with traditional program planning, calls for proposals, and expedited peer review, RADx has just begun select grantees, several months after the enacting legislation.

These programs---and related scientific work that may be in even earlier phases, when the applicability of basic science to testing may not yet be apparent---are essential means to improve national testing capacity over the long term. But part of the problem has been a failure to use the technology that already exists in an effective manner. Many companies are working diligently and competitively to improve virus and serological testing, and they

²⁶ J Kashir & A. Yaquinnuddin, Loop mediated isothermal amplification (LAMP) assays as a rapid diagnostic for COVID-19, *Med. Hypotheses*, 2020. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7182526/>

²⁷ The US already has the technology to test millions of people a day <https://www.technologyreview.com/2020/04/28/1000671/covid-tests-millions-per-day-crispr-biotechnology-advances/>

²⁸ National Cancer Institute: Serological Sciences Network for COVID-19 (SeroNet). <https://www.cancer.gov/research/key-initiatives/covid-19/coronavirus-research-initiatives/serological-sciences-network>

²⁹ NIH: Rapid Acceleration of Diagnostics: <https://www.nih.gov/research-training/medical-research-initiatives/radx>; BJ Tromberg, TA Schwetz, EJ Perez-Stable, et al. Rapid Scaling Up of Covid-19 Diagnostic Testing in the United States: The NIH RADx Initiative, *New Engl. J. Med.* Aug 13, 2020, <https://www.nejm.org/doi/full/10.1056/NEJMSr2022263>

could be further encouraged during the pandemic by administrative incentives, such as fast action on patent applications and tax incentives.

Technical Platforms

The government could take advantage of developments in academic and commercial science: the recognition that certain kinds of investigation can be markedly accelerated by the organization of “**technical platforms**”---units with specialized machines and highly trained staff that expedite experiments in which large numbers of samples are swiftly processed, often with the help of robotics and sophisticated data analysis, to approach a specific goal³⁰. In the usual conduct of medical research, such goals include the identification of small molecules that block a disease-promoting factor or the discovery of genes that have roles in the development of a disease. The critical concept is that the methodology is generic and can be rapidly adapted to study a novel problem when enough is learned to apply the platform specifically to that problem. For instance, the discovery of a novel agent responsible for a pandemic and determination of the sequence of the agent’s genome would allow the swift use of existing platforms to produce diagnostic tests, optimize serological assays, and develop vaccine candidates.

Data repositories

During the Covid-19 pandemic, the public has been most effectively informed about the dynamics of the pandemic through efforts to compile and analyze public data by academic institutions, like Johns Hopkins University, and by major news outlets ³¹. Also illustrative of the poor performance in informing the public, some government-held data have been released for public viewing only after challenges under the Freedom of Information Act. More recently, case reporting to the federal government has recently been redirected exclusively to HHS (which has hired a private contractor to handle the flow of information), rather than to the CDC, as in the past. This shift has created uncertainty about the use, reliability, and accessibility of the data, as reviewed in an earlier report from our Subgroup³².

An improved, government-supported, national public registry of available tests, accompanied by a comprehensive presentation of the results in accord with the purpose of the tests, would enhance the ability of state and city public health departments and other non-governmental entities to analyze the data and to adjust plans for the control of the current outbreak and any future ones. Key components of the relevant data sets, especially the number of ascertained infections, should be based on reliable tests for the virus and for serological responses to it. A database of this scope and quality would also encourage the sharing of research results and reagents and the formation of research collaborations.

³⁰ E. Mardis, Next-Generation Sequencing Platforms, Ann. Rev. Anchem, June 2013.

<https://www.annualreviews.org/doi/abs/10.1146/annurev-anchem-062012-092628>;

<https://www.bmh.manchester.ac.uk/research/domains/platform-sciences-technologies/>

³¹ The COVID Tracking Project. <https://covidtracking.com>

³² http://adhocresponsegroup.org/OPCAST_Public_Health_Data_Report_07-28-20.pdf

Recommendations

Although a comprehensive history of the Covid-19 pandemic cannot yet be written, it is apparent that the United States has fared poorly by many criteria, in significant part because the nation has lacked effective, centralized, scientifically based oversight of the response, including testing³³. A full accounting will require more time and a deeper evaluation---the kind of study that can be done only by a suitably staffed and financed “national commission” on Covid-19 established after the pandemic has run its course. A commission of this type should be directed to identify the causes of failure during the pandemic and to propose the functional and structural changes that would allow a more effective response to pandemics (and perhaps other health emergencies) in the future³⁴.

But, even now, it is possible to recommend some changes that could improve control of the current pandemic and better prepare us for the next one. With the country experiencing the extensive economic, social, and medical consequences of a severe pandemic, Congress and the public should be convinced by now of the need to pay the costs of effective testing and many other aspects of pandemic control---no less a commitment than the public would demand to confront an invasion by foreign troops.

Recommendation #1: Congress should expand Federal financial support for viral testing immediately, mandate wider surveillance testing, and enhance reimbursement for appropriate use of viral and serological tests during epidemics. As a first step, Congress should pass and the President should sign legislation that provides at least \$60 billion for viral testing over the next eight months, with an additional \$15 billion provided to support contact tracing. The legislation should also require a nation-wide plan for expanded testing.

According to our calculations, the amount we recommend would allow an approximately 10- to 20-fold increase in surveillance and contact-based testing, focused on individuals at high risk of exposure, and would also support contact tracing itself, an obligatory accompaniment to achieve the goals of testing. These sums align with the \$75 billion designated for testing and contact tracing in the version of the HEROES Act recently passed by the House of Representatives and awaiting consideration by the Senate. The amount is also consistent with the recommendations by others³⁵ and with a recommendation in our Subgroup’s recent report on contact tracing³⁶. Since continued improvements in testing technologies and costs are likely, and since the course of the pandemic has been difficult to predict, the situation should be reevaluated in about six months.

³³ E. Yong, How the Pandemic Defeated America - The Atlantic, Sept.2020

<https://www.theatlantic.com/magazine/archive/2020/09/coronavirus-american-failure/614191/>

³⁴ How a review of the U.S. response to Covid-19 could get started.

https://www.statnews.com/2020/06/29/us-needs-federal-commission-investigate-covid19-response-where-it-should-start/?utm_source=STAT+Newsletters

³⁵ W. A. Galston, Test Every American for Covid-19, The Wall Street Journal, August 4,

2020 <https://apple.news/A6MIWDInlSceAywh8DYBECw> ;The Rockefeller Foundation, Covid-19 National Testing & Tracing Action Plan - <https://www.rockefellerfoundation.org/national-covid-19-testing-and-tracing-action-plan/>

³⁶ http://adhocresponsegroup.org/OPCAST_On_Contact_Tracing_06-18-20.pdf

Decisions about allocation of funds to states and localities for testing and contact tracing should be administered by the Office of the Secretary (OS) at the DHHS, with guidance primarily from the Centers for Disease Control and Prevention (CDC) and also the Office of the Assistant Secretary for Preparedness and Response (OPR), the Biomedical Advanced Research and Development Authority (BARDA), and the Center for Medicare and Medicaid Services (CMS). These decisions should be presented to Congress within 30 days of the signing of the legislation, in the context of a national plan, developed in conjunction with states and localities, to detect SARS-CoV-2, especially in populations at high risk of infection; to quarantine all those found to be infectious; and to recognize variations in the prevalence of infection in different locations and among those with different occupations and behavioral patterns.

Recommendation #2: CDC should establish a national testing website and registry to ensure effective communication about the appropriate use, value, and results of laboratory tests.

The CDC has traditionally been assigned the responsibility for informing states, localities, and the general public about the availability, uses, interpretations, and outcomes of tests designed to detect microbial pathogens, to assess host responses, and to monitor spread of infection in the population. For reasons that have yet to be fully investigated, the agency was widely judged not to have fulfilled that critical role successfully during the current pandemic³⁷, and its role as recipient of healthcare data has recently been reassigned to DHHS by the White House, sowing significant confusion³⁸.

To rectify matters, the DHHS should work with the CDC and other departmental components to improve the public information that the CDC provides about tests relevant to the current and future pandemics and to accelerate the delivery of such information. That information should include the nature and number of tests performed in the context of the pandemic, and the CDC should work with the Office of the National Coordinator at DHHS to improve electronic data collection and presentation. The informatics infrastructure at the CDC should also be enhanced, in accord with our recently released report on data management³⁹. In our view, it will be faster and more efficient to identify and repair the weaknesses in the CDC, rather than to empower a different or new institution with some of the CDC's responsibilities.

³⁷ The CDC and States Are Misreporting COVID-19 Test Data
<https://www.theatlantic.com/health/archive/2020/05/cdc-and-states-are-misreporting-covid-19-test-data-pennsylvania-georgia-texas/611935/>; Lessons unlearned: Four years before the CDC fumbled coronavirus testing, the agency made some of the same mistakes with Zika
https://www.washingtonpost.com/investigations/lessons-unlearned-four-years-before-the-cdc-fumbled-coronavirus-testing-the-agency-made-some-of-the-same-mistakes-with-zika/2020/07/03/c32ca530-a8af-11ea-94d2-d7bc43b26bf9_story.html?utm_campaign=wp_post_most

³⁸ Trump Administration Strips C.D.C. of Control of Coronavirus Data, The New York Times, July 14, 2020.
<https://www.nytimes.com/2020/07/14/us/politics/trump-cdc-coronavirus.html>

³⁹ http://adhocresponsegroup.org/OPCAST_Public_Health_Data_Report_07-28-20.pdf

Recommendation #3: As part of its authorization and appropriations processes, Congress should re-examine the roles assigned to three major Public Health Service (PHS) agencies for the development, approval, implementation, and analysis of testing during public health emergencies⁴⁰.

Historically, the NIH has been expected to perform the basic and applied research required to produce improved tests for diseases, the FDA has had responsibility for evaluating and approving new tests, and the CDC has been assigned the tasks of guiding the use of the tests and reporting and analyzing the results, in conjunction with state and local public health authorities. In view of the country's failure to control the Covid-19 pandemic, Congress should determine whether the powers and budgetary resources provided by the Federal government are sufficient for them to carry out their responsibilities in national public health emergencies. If it concludes that they are not, the Congress should augment them.

Special consideration should be given to the CDC, in view of the widespread perception that it was unable to provide strong Federal leadership of the nation's response to the Covid-19 pandemic⁴¹. The standards by which the FDA accords EUAs for tests should also be re-examined to determine whether such authorization is being allocated too readily or too slowly^{42,43}.

Recommendation #4: The agencies of the PHS should use current authorities to strengthen the nation's preparedness for testing during this and future epidemics. These measures should include: building versatile, efficient, and low-cost technical platforms and point-of-care devices that can be used in routine healthcare and rapidly adapted for specific situations, such as national or global infectious disease emergencies; providing clear criteria for swift approval of novel tests; and creating an informatics infrastructure for nation-wide deployment of tests and interpretation of the results.

By many accounts, the United States has failed to adapt existing technologies and to provide tests at the speed and scale required to diagnose and control the spread of SARS-CoV-2 at many stages of the current pandemic, despite the widely acknowledged strengths of U.S. biomedical science.

The NIH should build upon its new programs in viral and serological testing to create and maintain advanced technical platforms that promote the provision of reliable testing

⁴⁰ The U.S. Public Health Service is comprised of eight of the eleven divisions of the DHHS; three of the largest are relevant to several aspects of this report: the NIH, the FDA, and the CDC.

⁴¹ E. Yong, How the Pandemic Defeated America - The Atlantic, Sept.2020

<https://www.theatlantic.com/magazine/archive/2020/09/coronavirus-american-failure/614191/>;

How the Virus Won <https://www.nytimes.com/interactive/2020/us/coronavirus-spread.html?smid=nytcore-ios-share>; The CDC and States Are Misreporting COVID-19 Test Data- The Atlantic, May 2020

<https://www.theatlantic.com/health/archive/2020/05/cdc-and-states-are-misreporting-covid-19-test-data-pennsylvania-georgia-texas/611935/>

⁴² <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>

⁴³ <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-posts-new-template-home-and-over-counter-diagnostic-tests-use-non>

programs during public health emergencies, while also continuing to support basic science programs with their inherent potential to improve methods used for testing. As mentioned under Recommendation 3, the FDA should examine its criteria for issuance of EUAs, especially to ensure that appropriate criteria are provided for evaluation of novel low-cost viral tests that can be performed at sampling sites. And the CDC should guarantee that its recommendations to (and communications with) public health authorities are responsive to the varied status of the current pandemic in different states and localities and aligned with our prescriptions for better management of relevant data, including data concerning the results of testing, as described under Recommendation 2.

APPENDIX 1: TYPES OF TESTS AND THEIR FUNCTIONS

1. Viral Tests

Tests that detect the causative agent of any infectious disease are based either on the growth of the organism (requiring that the agent retain biological activity) or on some chemical or physical attributes, regardless of viability. Tests for infectious SARS-CoV-2 are available---performed mostly with cultured cells, sometimes with experimental animals---and are often used for research purposes, especially in studies of host immune responses and viral disease-causing mechanisms. But virtually all tests used in clinical practice to diagnose Covid-19 and to track epidemiological patterns for public health purposes measure an essential chemical component of the virus---the SARS-CoV-2 RNA genome or one or more of the proteins present in virus particles.

Such molecular tests are generally cheaper, safer, faster, and often more sensitive than tests for infectious virus. Nearly all FDA-approved tests currently in use⁴⁴ measure viral RNA and depend upon a common two-step process: copying the coronavirus RNA into DNA, with the enzyme called reverse transcriptase, then amplification of parts of the resulting viral DNA many times over, using the polymerase chain reaction (PCR). Other methods for measuring viral RNA are available for research purposes or under development for surveying larger numbers of healthy individuals, as discussed in the text and elsewhere⁴⁵.

Tests that detect virus by measuring viral proteins, using antibodies specific for known proteins, are potentially faster and cheaper than most tests for viral RNA and may prove amenable to self-administered use. Such tests are being pursued commercially, as well as in the public sector, but only two have been granted an EUA by the FDA⁴⁶.

As described in the text, virus tests may be **diagnostic** (used to establish the cause of disease), **contact-based** (used to seek evidence of infection in persons believed to have

⁴⁴ [https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas'](https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas)

⁴⁵ <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-posts-new-template-home-and-over-counter-diagnostic-tests-use-non>

⁴⁶ [https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas'](https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas)

been in contact with an infected person), or a means of **surveillance** (for infected, asymptomatic people in populations without known contacts with infected people). Identification of the causative agent is essential for a specific diagnosis of any infectious disease in an individual patient; in its absence, diagnosis is presumptive⁴⁷. Surveillance tests must be available in large quantities and to all sectors of the population; relatively simple, rapid, and inexpensive. They can achieve their purpose of infection control even if not as accurate as tests used for diagnostic purposes or for contact-tracing.

The reliability of tests for SARS-CoV-2 depends on the timing and mode of sampling, as well as the sensitivity and specificity of the method. False-positive tests are generally rare, but sometimes occur due to poor test design or contamination of samples with viral RNA or DNA⁴⁸. (Since a false-positive result can lead to unnecessary quarantine, contact tracing, or treatment, even a low error rate is problematic.) Negative results for persons who have been infected most commonly occur if the sample is taken before the virus has multiplied to produce amounts that allow detection or if the sampling of material from the upper respiratory tract has been ineffective. The sensitivity of PCR-based tests for viral RNA is generally great enough to detect even very low concentrations of virus. Antibody-based tests for viral proteins, however, are inherently less sensitive and may fail to detect a significant minority of virus-positive subjects---a trade-off for simplicity, speed, and lower costs. A report by the JASON group explores the significance of false-negative findings in greater detail⁴⁹, and others have argued that the simplicity, speed, and low cost of antigen-based tests for virus can outweigh the virtues of the high sensitivity of RNA-based tests, when tests are used for surveillance⁵⁰.

2. Serological tests

Tests that ascertain the host's immune response to the infectious agent depend largely on immunological methods to detect antibodies that bind proteins found in virus particles. Immune responses to SARS CoV-2 are most commonly sought with tests for either of two viral proteins: the spike (S) protein, which is on the surface of the virus particle, composes its predominant halo (or "corona"), and mediates entry of virus into cells by binding to a specific host receptor protein (called ACE2); or the nucleocapsid (N) protein, which is an essential component of the internal core of the virus.

⁴⁷ This issue has been dramatically illustrated in the current epidemic. Although over 99% of Covid-19 patients in whom coronavirus RNA was detected were later shown to have made virus-specific antibodies, validating the diagnosis, less than 40% of patients with a presumptive diagnosis of Covid-19, without testing for viral RNA, produced antibodies against SARS-CoV-2. Thus, in over 60%, the symptoms were likely produced by another condition. F Wajnberg, F Amanat, A Firpo et al SARS-CoV-2 infection induces robust, neutralizing antibody responses that are stable for at least three months.

medRxiv 2020.07.14.20151126; doi: <https://doi.org/10.1101/2020.07.14.20151126>

⁴⁸ False positives in reverse transcription PCR testing for SARS-CoV-2 | medRxiv
<https://www.medrxiv.org/content/10.1101/2020.04.26.20080911v2>

⁴⁹ JASON, Managing the Risk From COVID-19 During a Return to On-Site University Research
<https://fas.org/irp/agency/dod/jason/covid-19.pdf>; S. Woloshin, N. Patel, & A. S. Kesselheim, False Negative Tests for SARS-CoV-2 Infection — Challenges and Implications. *New Engl. J. Med.*, June 5, 2020.
<https://www.nejm.org/doi/full/10.1056/NEJMp2015897>

⁵⁰ The Rockefeller Foundation, Covid-19 National Testing & Tracing Action Plan -
<https://www.rockefellerfoundation.org/national-covid-19-testing-and-tracing-action-plan/>

When properly designed and performed, these tests can provide definitive evidence that the individual has been infected by the relevant microbe at some time in the past---at least several days or a few weeks before a sample (usually blood) is taken for testing---since the relevant cells in the immune system require time to produce sufficient antibody for detection. Many versions of such tests for antibodies against the S and N proteins have been designed, approved by the FDA under Emergency Use Authorization (EUA), and deployed in epidemiological studies to determine the fraction of a population that has been infected by SARS-CoV-2 or in medical practice to ascertain whether an individual patient has been infected in the past.

The general utility, regulation, demand for, and pricing of such tests are unresolved issues. Although detection of antibodies ascertains that the subject was once infected, it does not reveal whether virus is still present⁵¹. Whether naturally infected persons acquire truly protective immunity can be established only by ascertaining resistance to subsequent infection; this can be difficult to document unless a cohort of individuals who have been naturally infected is closely followed for re-infection while infection rates remain high in the general population. But the detection of neutralizing antibodies, especially at high levels, offers presumptive evidence for immunity and suggests that development of a successful vaccine is possible. The persistence of the state of immunity after natural infection, however, remains uncertain and that too will have important implications for the success of vaccination programs.

The presence of neutralizing antibodies in sera from patients convalescing from Covid-19 also signifies the potential utility of such sera for treatment of severely ill patients, and it provides motivation for the generation of neutralizing monoclonal antibodies as therapeutic agents. Clinical trials of these immunologically-based therapies are in progress. Finally, other more specialized tests of immune cell function, including tests for the reactivity of T cells against virus-infected cells, can provide additional information about the host immune response, but they are still generally confined to research settings.

3. Prognostic tests

Tests that indicate the severity of the clinical course of the disease and predict its outcome measure various kinds of host responses, such as immune cell factors implicated in tissue inflammation or in signaling between cell types in the immune system. (One FDA-approved example is a test for the cytokine, IL-6.) Such tests are being developed during the Covid-19 pandemic to predict which patients are likely to manifest the severe syndromes (profound respiratory distress, renal disease, vascular disorders, and a Kawasaki-like syndrome in children) that arise in a subset of infected individuals and require specialized treatment. Identification of such “biomarkers” may prove to be important to devise new therapies, use them appropriately, and reduce the case mortality rate; tests to do so will require an extensive research effort; fortunately, such work is currently underway in government, academic, and commercial laboratories throughout the world.

⁵¹ Equally important, more specialized tests---for antibodies that inactivate (“neutralize”) the infectivity of the virus---are required to gauge whether the individual is likely to be resistant to infection (immune).