VIEWPOINT: COVID-19

COVID-19 testing: One size does not fit all

To control the pandemic, testing should be considered a public health tool

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Tests for detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were developed within days of the release of the virus genome (*1*). Multiple countries have been successful at controlling SARS-CoV-2 transmission by investing in large-scale testing capacity (*2*). Most testing has focused on quantitative polymerase chain reaction (qPCR) assays, which are capable of detecting minute amounts of viral RNA. Although powerful, these molecular tools cannot be scaled to meet demands for more extensive public health testing. To combat COVID-19, the "one-size-fits-all" approach that has dominated and confused decision-making with regard to testing and the evaluation of tests is unsuitable: Diagnostics, screening, and surveillance serve different purposes, demand distinct strategies, and require separate approval mechanisms. By supporting the innovation, approval, manufacturing, and distribution of simpler and cheaper screening and surveillance tools, it will be possible to more effectively limit the spread of COVID-19 and respond to future pandemics.

Many types of tests are available for COVID-19 for clinical and public health use (see the figure). Testing can be performed in a central laboratory, at the point of care (POC), or in the community at the workplace, school, or home. COVID-19 testing begins with specimen collection. For medical use, a nasopharyngeal swab collected by a health care professional has been used for detection of virus infections. Demands on testing throughput for COVID-19, however, have driven new collection approaches, including saliva and less invasive nasal swabs. COVID-19 tests include molecular tests such as qPCR, isothermal amplification, and CRISPR, as well as antigen tests that detect SARS-CoV-2 proteins directly. Although rapid antigen tests have lower analytical sensitivity (i.e., require greater amounts of virus material to turn positive) than qPCR-based tests, their ability to detect infectious individuals with culturable virus is as high as for qPCR (*3*). Specificity (i.e., correctly identifying those not infected with SARS-CoV-2) of antigen tests achieves comparable results to molecular tests (*4*).

Diagnostic testing for COVID-19 focuses on accurately identifying patients who are infected with SARS-CoV-2 to establish the presence or absence of disease and is performed on symptomatic patients or asymptomatic individuals who are at high risk of infection. This type of testing requires assays that are highly sensitive, so as to not miss COVID-19 patients (false negatives), and specific, so as to not wrongly diagnose SARS-CoV-2–negative individuals as having COVID-19 (false positives). These tests are typically performed by centralized high-complexity laboratories with specialized equipment using qPCR assays, with results that can be reported within 12 to 48 hours. Major bottlenecks in testing, however, have led to turnaround times exceeding 5 to 10 days in some regions, making such tests useless to prevent transmission.

POC diagnostic testing at medical facilities can be qPCR assays, isothermal amplification, or antigen-based (*4*). These POC tests often require instruments that run a limited number of tests and can return results in under an hour. The need for an instrument limits the number of tests that can be performed and where they can be used. However, newer antigen tests are becoming available that do not require instruments or skilled operators, potentially allowing for much more distributed POC testing.

Surveillance testing of populations can be used both as a tool for understanding historical exposures and as a measure of ongoing community transmission. For the former, serological testing of individuals for the presence of SARS-CoV-2–specific antibodies is used to identify those previously infected. For the latter, surveillance testing can be an effective way to monitor real-time SARS-CoV-2 spread in communities. One promising method is wastewater surveillance, which has been used to assess community transmission of poliovirus (*5*) and has shown potential for COVID-19 (*6*). qPCR testing of wastewater is used to detect SARS-CoV-2, and frequency dynamics of viral genetic material indicate COVID-19 infections in a community. Surveillance can also be performed from swab or saliva samples taken directly from individuals, and, in populations with low COVID-19 prevalence, pooling can be used to increase capacity and lower cost.

For surveillance testing, the goal is not identification of every case but rather the collection of data from representative samples that accurately measure prevalence and serve to inform public health policy and resource allocation. Because the focus is on extrapolations to the population and not the individual, tests with known deviations from 100% sensitivity and specificity are still appropriate when the variance can be statistically corrected (*7*). To be most effective, results should include reported qPCR cycle thresholds, which is an estimate of viral load (*7*), to model epidemic trajectory and allow for real-time evaluation of mitigation programs (*8*), including once vaccination programs have begun.

Screening testing of asymptomatic individuals to detect people who are likely infectious has been critically underused yet is one of the most promising tools to combat the COVID-19 pandemic (*9*). Infection with SARS-CoV-2 does not lead to symptoms in ~20 to 40% of cases, and symptomatic disease is preceded by a presymptomatic incubation period (*10*). However, asymptomatic and presymptomatic cases are key contributors to virus spread, complicating our ability to break transmission chains (*10*).

Entry screening to detect infectious individuals before accessing facilities (e.g., nursing homes, restaurants, and airports), along with symptom screening and temperature checks, can be beneficial, particularly in high-risk facilities such as skilled nursing facilities. When used strategically, entry-screening measures can be effective at suppressing transmission. Entry screening requires testing that provides rapid results—ideally within 15 min—to be most effective. The required sensitivity and specificity of entry-screening tests are, like all tests, context dependent. Entry-screening tests for a nursing home, for example, must be highly sensitive because the consequences of bringing SARS-CoV-2 into a nursing home can be devastating. Such tests must also be highly specific because the consequences of grouping a false-positive person with COVID-19–positive individuals could be deadly. Conversely,

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because children have substantially reduced mortality from COVID-19, entry screening into schools might require greater compromise that balances resources and sensitivity to test as many individuals as possible with a need to minimize disruptive false positives. Key to use of tests for entrance screening is that a negative test alone should not be considered sufficient to enter—that should be based on satisfying other requirements, including masks and physical distancing. Conversely, a positive test should be sufficient to bar entry in most settings.

Public health screening is potentially the most powerful form of COVID-19 testing, aimed at outbreak suppression through maximizing detection of infectious individuals. This type of screening entails frequent serial testing of large fractions of the population, through self-administered at-home rapid tests, or in the community at high-contact settings, such as schools and workplaces (*9*). Public health screening can achieve herd effects by stopping onward spread through detection of asymptomatic or presymptomatic cases (fig. S1).

Notably, not every transmission chain needs to be severed to achieve herd effects. Mathematical models that incorporate relevant variation in viral loads and test accuracy suggest that with frequent testing of a large fraction of a population, a sufficient number of cases could be detected to create herd effects (*11*). For example, Slovakia undertook public health screening to address COVID-19 (*12*): During a 2-week period, ~80% of the population was screened using rapid antigen tests. With 50,000 cases identified, combined with other public health measures, it reduced incidence by 82% within 2 weeks (*12*). An important feature of large-scale public health screening is that centrally controlled reporting and contact tracing programs are not essential to induce herd effects as they are for surveillance testing. In a robust public health screening program, sufficient numbers of people are routinely testing themselves, such that contact tracing is subsumed by the screening program (*11*).

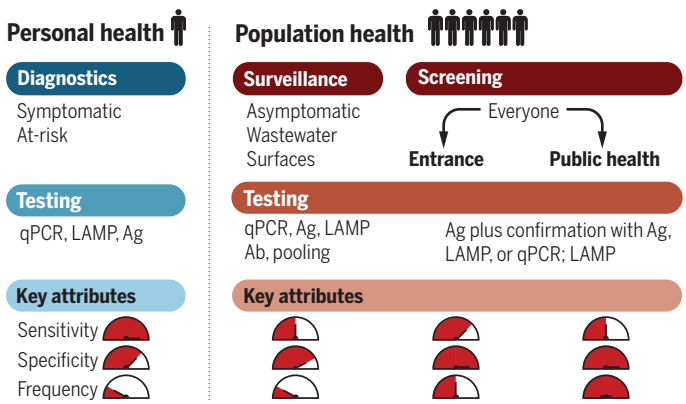
Similar to home pregnancy tests, screening tests should be easy to obtain and administer, fast, and cheap. Like diagnostic tests, these tests must produce very low false-positive rates. If a screening test does not achieve high-enough specificity (e.g., >99.9%), screening programs can be paired with secondary confirmatory testing. Unlike diagnostic tests, however, the sensitivity of screening tests should not be determined based on their ability to diagnose patients but rather by their ability to accurately identify people who are most at risk of transmitting SARS-CoV-2. Such individuals tend to have higher viral loads (*13*), which makes the virus easier to detect (*14*). A focus on identifying infectious people means that frequency and abundance of tests should be prioritized above achieving high analytical sensitivity (*11*). Indeed, loss in sensitivity of individual tests, within reason, can be compensated for by frequency of testing and wider dissemination of tests (*9*). In addition, public health messaging should ensure appropriate expectations of screening, particularly around sensitivity and specificity so that false negatives and false positives do not erode public trust.

Tests for public health screening require rapid, decentralized solutions that can be scaled for frequent screening of large numbers of asymptomatic individuals. Lateral-flow antigen tests and upcoming paper-based synthetic biology and CRISPR-based assays fit these needs and could be scaled to tens of millions of daily tests (*9*). These tests are simple and cheap, can be self-administered, and do not require machines to run and return results. The Abbott BinaxNOW rapid antigen test, which recently received an Emergency Use Authorization (EUA) in the United States as a diagnostic device, also comes with a smartphone app, allowing self-reporting of COVID-19 status that could be used instead of centralized reporting by public health agencies. Critically, despite being shown to be highly effective at detecting infectious individuals (*14*), very few of these tests are currently approved for screening of asymptomatic individuals, substantially limiting their utility. If such tests were made available direct to consumer (priced to allow equitable access) or produced and provided free of charge by governments, individuals could obtain their COVID-19 status at their own choosing and without complex medical decisions.

Testing is a central pillar of clinical and public health response to global health emergencies, including the COVID-19 pandemic. Nearly all testing modalities have a role, and the one-size-fits-all approach to testing by many Western countries has failed. Many lower- and middle-income countries—including Senegal, Vietnam, and Ghana—have fared far better in their COVID-19 response, often using strong testing programs. The focus on diagnostic tests and the use of preexisting authorization pathways focused on qPCR-based clinical diagnostics not only slows the development and deployment of new surveillance and screening tests but also confuses the picture of what metrics effective public health tools should achieve. Testing to diagnose a patient with COVID-19 is fundamentally different from testing a person to prevent onward transmission. Regulatory pathways should be modified to incorporate these differences so that public health and screening tests are appropriately evaluated. It is necessary to be innovative and produce, distribute, and continuously improve the tests that exist to save lives and gain control of the COVID-19 pandemic.

COVID-19 testing strategies

Testing for SARS-CoV-2 can be for personal or population health. Collection can be from symptomatic or asymptomatic individuals, as well as from wastewater and swabs of surfaces. The tests may be performed in central laboratories, at the POC, or using rapid tests. Attributes of tests differ according to application.



Ab, antibody; Ag, antigen; LAMP, loop-mediated isothermal amplification; POC, point of care; qPCR, quantitative polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

GRAPHIC: KELLIE HOLOSKI/*SCIENCE*

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SUPPLEMENTARY MATERIALS

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