Helping keep your people safe:

A guide to asymptomatic population testing options for SARS-CoV-2

If you're responsible for COVID-19 safety at a university, school, or workplace, asymptomatic testing of students or employees can be a key strategy to reduce the spread of the virus—while also helping you return to something closer to normal.

This guide can help you understand and evaluate the asymptomatic testing options available to your organization.

What is asymptomatic/serial population testing?

Asymptomatic testing means testing the broad population of students or employees in your organization, rather than just testing those that exhibit COVID-19 symptoms. Asymptomatic testing is carried out widely and frequently, so that infected people with or without symptoms can be identified and quarantined. The FDA and CDC also use the term "serial testing," emphasizing that individuals are tested multiple times at varying intervals as part of asymptomatic testing. You may also hear asymptomatic testing referred to as "mitigation testing," or just an "expanded COVID-19 testing program".

Why is asymptomatic/serial testing so important?

The CDC estimates that roughly 40% of people infected with the SARS-CoV-2 virus are asymptomatic, meaning they don't show any symptoms of COVID-19.[1] But they can still spread the virus to others in their community, who can become seriously ill. Finding and quarantining them is critically important in reducing transmission.[2]

SARS-CoV-2 infections can increase exponentially. But according to the *Journal of the American Medical Association*, regular, broad testing can "flatten the curve." In one projection, when only people with symptoms are tested, hundreds of additional people become infected in 80 days, compared to a projection in which the entire population is tested every 1 or 2 days.[3]

Frequent, broad testing has helped some college campuses achieve a lower COVID-19 incidence rate than their surrounding communities. In Wisconsin in Fall of 2020, the average virus positivity rate was around 14%, but multiple colleges and universities within the state had positivity rates as low as 1%. This difference has been attributed to frequent testing and robust contact tracing,[4] which is allowing students and faculty to return to campus for in-class learning.

What asymptomatic/serial testing technologies are available?

First, it's important to understand the difference between testing for an active infection and testing for previous infections. Serology tests or antibody tests show whether a person has had a SARS-CoV-2 infection in the past by detecting the presence of antibodies for the virus. These types of tests do not identify an active infection. However, we'll be discussing tests for active infections, which are the type used in asymptomatic testing to help prevent virus spread.

PCR (polymerase chain reaction) tests work by detecting the genetic material of the virus in samples collected from individuals. They are the most sensitive and accurate COVID-19 tests available. PCR tests can be designed to identify multiple targets of the same virus (multiplexing) therefore safeguarding these types of tests against new variants, also known as virus mutations. These tests also include a built-in control to assess sample integrity. There are two types:

- **Real-time PCR tests** are the gold standard for SARS-Cov-2 detection. Saliva, nasal, or nasopharyngeal (deep nasal) samples have their RNA extracted and amplified to detect even small amounts of virus genetic material.[5]

- **Fast PCR tests** (also known as Direct PCR) use the same technology, but with a different workflow bypassing the RNA extraction step, and other modified conditions. Saliva samples are used. Fast PCR runs faster, uses fewer materials and plastics, and has proven to be more cost effective.

RADTs (Rapid antigen detection tests) work by detecting specific viral antigens (proteins) on the surface of the virus. They are also called point of care (POC) antigen tests, because they can be run in a doctor's office or in a laboratory. RADTs use nasal and deep-nasal samples.

RADTs are not as sensitive as PCR tests because there is no amplification, which means they are less likely to detect an infection if the amount of virus is low.[6] This makes RADTs more relevant for diagnostic testing within 5-7 days of symptom onset, when viral loads are high, than for testing asymptomatic people or those at the beginning stage of the disease when the viral loads are lower.

LAMP (loop-mediated isothermal amplification) tests detect virus genetic material in saliva and nasal samples using a different kind of amplification than PCR tests.[7] Like RADTs, they can be run at point of care or in a lab, and are comparable in sensitivity to Fast PCR. However, they require specialized workflow expertise, because the unconstrained amplification process poses a risk of long-term lab contamination.

Unlike PCR tests, most LAMP-based tests detect one target at a time, meaning they can't check for multiple variants of a virus at once. (There is a newer design and technique for LAMP that checks for multiple variants, but it requires additional specialized expertise.)

What criteria should I take into account when evaluating asymptomatic testing options?

Sample type, sample collection method, and sample receiving

You will need to understand and evaluate the sample types required for each test method, the sample collection methods that are options for your organization, and how samples will be received by the testing facility. Examining these factors will help determine the ease of implementation and testing compliance you can expect in your population. For the tests we've discussed, there are three sample types:

- **Saliva** is the least-invasive sample type and relatively simple to obtain by the person being tested or an HCP.
- **Nasal swab samples** are collected in the nostrils using swabsticks. They can be collected by the person being tested or by an HCP.
- **Nasopharyngeal swab samples** are collected only by HCPs. A long swabstick is inserted deep in the nasal passages. This is the most invasive sample type, and the least comfortable.

Note that less-invasive sample types can lead to higher compliance among people being tested, since they are more comfortable or easier to obtain. Here are the sample types required for each testing method:

Test Type	Sample Type Required
Real-time PCR	Saliva, Nasal, Nasopharyngeal swab
Fast PCR	Saliva
LAMP	Nasal swab or Saliva
RADT	Nasal swab or Nasopharyngeal swab

Here are the sample collection methods, the sample types for which they are appropriate, and considerations for each:

Collection Method	Sample Type	Considerations
HCP Collection: Trained medical personnel collect samples from people being tested	Nasal, Nasophary-ngeal, or Saliva	Assures sample integrity HCPs are trained in collection safety
Supervised Collection: HCP supervises the person collecting their own sample, in-person or via telemedicine	Nasal or Saliva	Reduces staffing requirements Safer for HCPs since contact with infected people is reduced HCP can still verify that sample is collected correctly
Self-Collection: Individuals collect their own samples and return them to a collection center	Nasal or Saliva	Reduces staffing requirements Provides operational/ cost efficiencies Reduces exposure to infection during collection

Lastly, you'll need to think about how samples will be received so that they can be sent to the testing facility. There are two options:

- Samples can be collected at a walk-in or drive-through COVID-19 testing center. This is required for HCP collection but can also be used for supervised collection and self-collection.
- Collection materials can be provided to individuals for self-collection, and the samples can be mailed in or dropped off at a pickup point or collection center. For this approach, you'd want to make sure that the test includes an assessment for a "human control", which will help ensure that the sample is valid.

Test accuracy

Testing methods differ in how accurately they identify people who do or do not carry the virus. A test's ability to detect the virus in a sample is called its **sensitivity.** A high-sensitivity test can detect low levels of the virus, while a low-sensitivity test cannot.

Sensitivity is important because a low-sensitivity test could miss individuals with low levels of the virus and incorrectly identify them as virus-free, which is called a **false-negative.** A person with a false negative would be free to transmit the virus in the community without being appropriately quarantined.

Here's how the different testing methods compare in terms of sensitivity:

Test Type	Accuracy/Sensitivity Considerations
Real-time PCR	Most sensitive—the gold standard for COVID testing
Fast PCR and LAMP	Highly sensitive, but less sensitive than Real-time PCR
RADT	Considerably less sensitive than other options Produces more false negatives More appropriate for testing people with symptoms due to their higher viral levels

The pooled sample testing option

In certain situations, pooled testing is an option that makes it possible to increase the number of people who can be tested using a fixed amount of resources. In pooled testing, samples from multiple people are combined into one pooled sample for one lab test. If the pooled test result is negative, all the constituent samples are presumed to be negative, and individual sample tests aren't needed. If the pooled test result is positive, the people whose samples were included need to be retested to determine whose samples are positive.[8,9]

Samples can be pooled together in two ways:

- **Pod pooling means that samples from a group of people are combined when the samples are collected, then sent to the testing laboratory as one combined sample.** With pod pooling, if there is a positive result from the combined sample, new samples will need to be drawn from the people in the pod and tested individually to determine who has been infected.[10]
- **Lab pooling means that individual samples are sent to the testing laboratory, where portions of the samples are combined for a single test.** Because the individual samples are retained, if the pooled test has a positive result, the lab already has the individual samples needed for testing to determine exactly who is infected.

Real-time PCR and Fast PCR tests are ideal for pooling. Their high sensitivity can detect the virus even with samples that have been diluted by pooling, thanks to the amplification process. RADT and LAMP tests don't work well for pooling because of their limited point-of-care logistics.

The CDC recommends that pooled testing should only be used in situations and areas where there is a low prevalence of SARS-CoV-2 infections.[9] When widespread infections are not anticipated in the population, the time- and cost-savings make pooled testing a sensible alternative to individual sample testing. Only the pooled tests with a positive result require further testing of individual samples, which lowers the total number of tests given in that population.

Time to results: speed, throughput, and scalability

How quickly can an individual result be obtained, from start to finish? This is important because the longer it takes, the longer an infectious person could be transmitting the virus to others before taking precautions, such as quarantining. Time to results includes the total time for:

- Sample collection
- Gathering samples for the testing lab (if lab-based)
- Performing the test
- Communicating the result to the individual
- If using pooled testing, the time needed to collect and/or retest individual samples to identify people with infections

The timing for all of these steps must be considered, but you also must know how the timing is affected by the number of people being screened at the scale of your organization's population. You'll need to look at throughput, meaning the total number of tests that can be processed in a given period of time, and scalability, meaning how easily a testing method can handle a large number of samples. Looking only at the testing step, point-of-care tests (LAMP and RADT) are fast, delivering results from a single sample for a single individual in 15-30 minutes. Real-time PCR, Fast PCR, and Lab-based LAMP will take an hour or longer and are often performed at a centralized location/lab. POC tests are much faster than lab-based tests. However, speed is not the only factor in testing.

- **POC tests can only be run one sample at a time, so they are ideally suited to testing small numbers of people.** If you need to test hundreds or even thousands of people per day, POC tests would require dozens to hundreds of instruments and a large staff to operate them. As such, the total time to results would be hours and not minutes simply due to the queuing required for people standing in line for their 15–30-minute tests.

- **PCR-based tests are scalable. They can process up to 382 samples at a time while still providing individual results, making them ideal for processing large volumes of samples.** Depending on your population size, even when adding in the waiting time needed to collect samples for batch processing in a PCR run, the total time to results could be less than the time required for the same number of samples with POC testing.

The bottom line: Testing large numbers of people per day can make RADT or POC LAMP slow, operationally difficult, expensive, and a poor experience for the people being tested.

Footprint and required materials

How much physical space and consumable inventory would it take to implement a particular type of testing program at your organization? Here are the factors that affect the practicality and affordability of an on-site testing program.

- Will you be sending samples to a partner lab for testing, or does your organization have an on-site laboratory to perform testing?

- How much laboratory bench space, equipment and consumables would be required for your population with an on-site laboratory?

- If an on-site laboratory is preferred, have you considered your supply chain? Suppliers with mature and established supply chains can help avoid shortages in the required test components or reagents.

- Can a third-party laboratory bring their services to you, either in a permanent space or mobile laboratory?

- If considering point-of-care RADT or LAMP testing, what is the size of the population you need to test? For a large daily test volume, the footprint needed for POC testing could be much larger than a PCR lab footprint.

Total cost

Determining the total cost involves adding up individual line items, looking at the size of the population to be tested, and considering the throughput and scalability of the testing method. You'll need to account for:

- Consumables
- Equipment costs
- Space costs and utilities
- Employees required

PCR tests are the most accurate, but they're more expensive than the other test types because of the instrumentation needed. Point-of-care tests are less expensive in terms of instrumentation and reagents on a per test basis. However, the size of your population could make PCR tests more cost efficient than less-scalable test types, resulting in a lower overall cost or cost-per-test. If you're looking for a balance between cost and test sensitivity/accuracy, Fast PCR might be the sweet spot: the high accuracy of PCR at a lower cost than Real-time PCR.

Test regulatory status

Whichever testing method you use for your testing program, it's important to understand the regulatory requirements and how they affect your testing program.

- In the U.S., the FDA approves test kits with an **Emergency Use Authorization or EUA** for individual diagnostic and testing use.

    - Some tests which have not received EUA status are capable of returning individual results, but can't be usedfor that purpose without an EUA. They can only be used for **surveillance testing**, meaning that they can be used to assess the prevalence of infections in a community, but not to inform individuals of an infection.

    - However, there is a workflow for some universities that has been sanctioned by the U.S. Centers for Medicare and Medicaid Services (CMS) that allows surveillance tests to yield a "presumptive positive" result to an individual. Confirmatory testing would then require an EUA diagnostic test.

- In Europe and the U.K., a test kit is approved with a CE-IVD (In Vitro Diagnostic) marking.

- There are many commercially available COVID-19 test kits of all types that have received EUA and/or CE-IVD status, and many more are going through the approval process. Tests that haven't yet received an EUA or CE-IVD designation are marked as Research Use Only (RUO).

What else is required for a successful asymptomatic/serial testing program?

High testing frequency

Testing should be done frequently, but how frequently? The answer for your organization depends on:

- Population size
- How frequently they interact with people outside your organization
- Current virus prevalence in the community
- Population's typical behaviors

For example, a population of people who socialize frequently, such as college students, might require more frequent testing than other populations. But keep in mind what research has demonstrated:

- *The Journal of the American Medical Association* projects that testing the entire population every 1 or 2 days, as opposed to only testing individuals who are symptomatic, can reduce COVID-19 spread significantly.[3]

- Many U.S. universities have demonstrated successful programs by testing their students and faculty one to two times per week.

- Testing people only once at entry (i.e., at the beginning of a university semester) is projected to not be as effective in preventing virus transmission as frequent, regular testing.[3]

Fast reporting

There are multiple ways to inform people of their COVID-19 test results:

- Email for negative tests
- Email and phone call for positive tests
- Text
- Online test result look-up through smartphone app or website

Quarantine

If a person in your population receives a positive test result, or if they are experiencing symptoms, they should quarantine immediately to lessen the chance that they could pass the virus on to anyone else. They should not leave home except to receive medical care.[11] Certain organizations, such as universities, might consider setting aside an "isolation dormitory" for infected students. Refer to your local health authorities for guidance on quarantine protocols.

Thorough contact tracing

Contact tracing can help curb the spread of COVID-19 within a community by determining who else has been in contact with a person confirmed as infected via testing.

Contract tracing can happen in many ways, but some organizations have made use of smartphone technology in particular to facilitate it. For example, the State of California has implemented a system (CA Notify) that allows smartphone users to become notified of possible exposure to COVID-19 if they enable Bluetooth™ wireless technology. Similar smartphone apps are making this technology more broadly available.

A checklist for developing your asymptomatic/serial population testing program

We've covered a lot of important information in this guide, but this short checklist puts all of the things you need to consider in a digestible form. Refer back to the details in this guide as needed to keep your planning on track.

1. Evaluate the testing technologies that are available for your testing program by considering…

- [ ] Test accuracy/sensitivity
- [ ] Sample types, sample collection methods, and sample receiving
- [ ] Suitability of pooled testing for your population
- [ ] Time to results: speed, throughput and scalability
- [ ] Footprint and required materials
- [ ] Total cost

2. Consider the additional steps needed to "flatten the curve" of infections with a testing program:

- [ ] High testing frequency
- [ ] Fast reporting
- [ ] Quarantine planning
- [ ] Thorough contact tracing

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