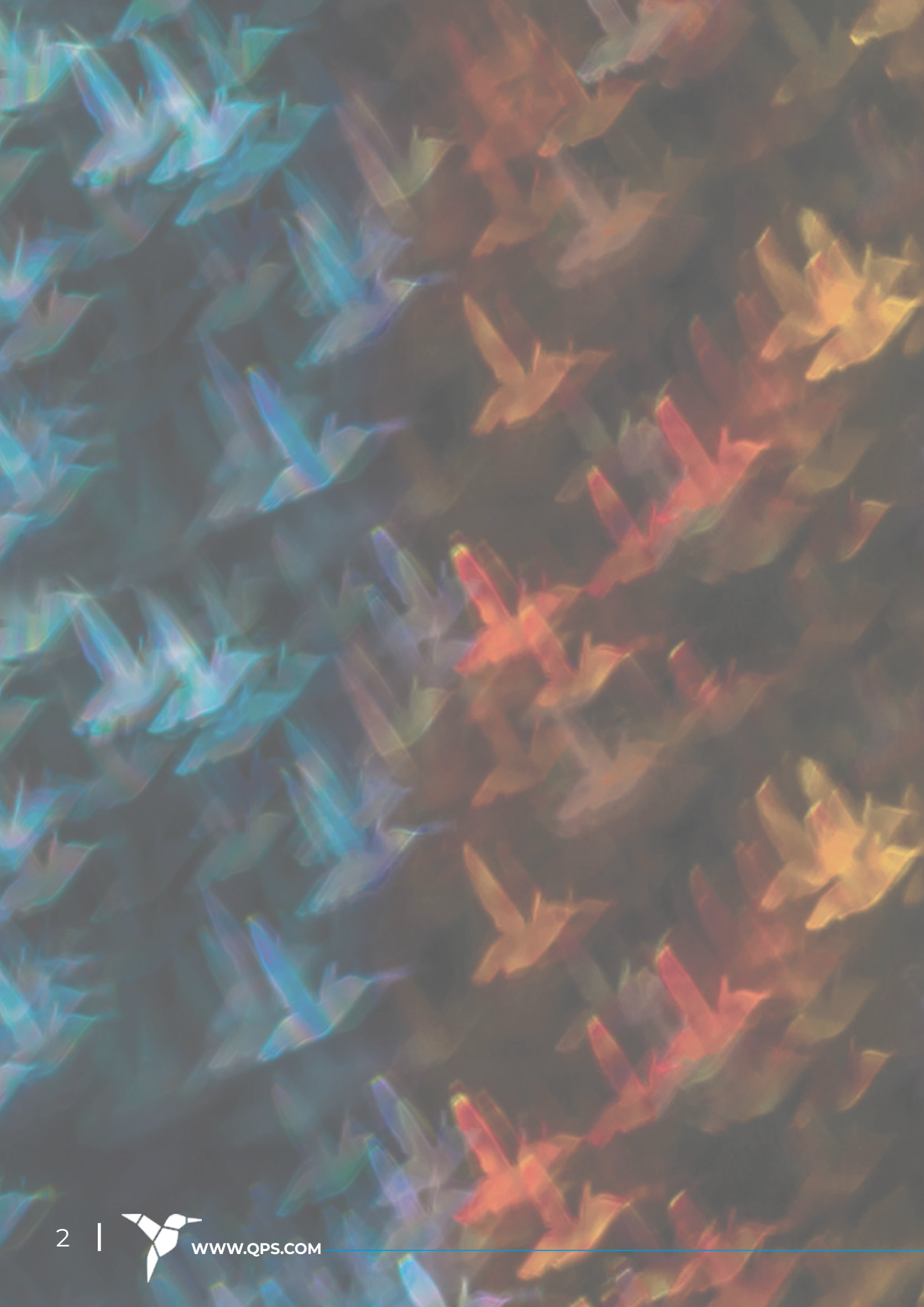




# COVID-19 PANDEMIC BLOG POSTS

*January 2020 - July 2020*

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# Aerosolized Droplet Study

April 29, 2020

## Can the Novel Coronavirus Spread through Speaking?

There are conflicting opinions on whether the novel coronavirus, the virus that causes COVID-19, can be spread via aerosol. Past studies have pointed to the possibility that the virus may remain suspended in the air under special circumstances, such as during medical procedures like intubation. In one study, the novel coronavirus stayed viable in airborne aerosols throughout the duration of the 3-hour experiment.

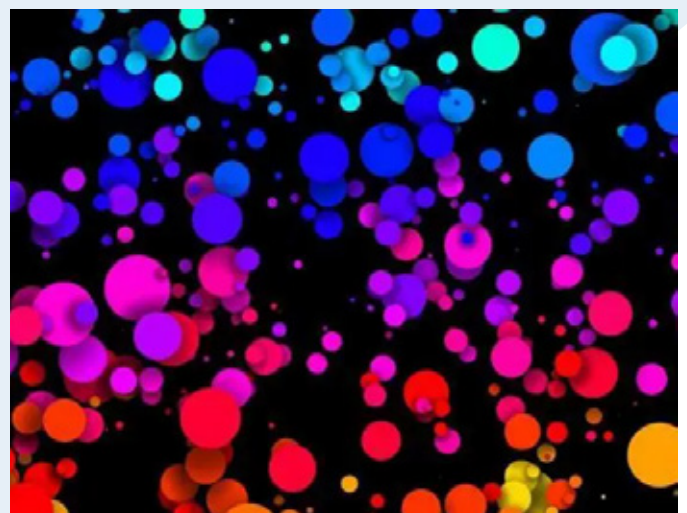
A laser light scattering experiment conducted by scientists from the University of Pennsylvania Perelman School of Medicine and the National Institutes of Health (NIH) concluded that speaking at a normal volume can produce small, aerosol-like droplets that hang in the air long enough to enter the airways of other people.

“Aerosols from infected persons may therefore pose an inhalation threat even at considerable distances and in enclosed spaces, particularly if there is poor ventilation,” says Harvard University biologist Matthew Meselson, commenting on the study.

## The Experiment

The experiment, published in the *New England Journal of Medicine*, generated droplets and visualized their trajectories using laser light scattering.

The scientists used a cardboard box with a black interior, slits along the side, and a HEPA filter on top to eliminate ambient dust. A 532-nanometer green laser operating at 2.5W optical power and transformed into a sheet of light 1 millimeter thick and 150 millimeters tall was directed through the slit and into the box’s interior.



An iPhone 11 Pro camera was aimed at the light sheet through a hole on the opposite side of the box. It recorded sound and video of light-scattering events at 60 frames per second. The scientists recorded ultrahigh-resolution video clips of the experiment while a participant spoke.

The volunteer subject first spoke into the box at a normal volume, saying “stay healthy.” Droplets (20–50 microns in size) generated while speak-

ing this short phrase traveled 50 to 75 millimeters before they hit the light sheet.

Flashes were produced when the droplets passed through the sheet of light. The brightness of the flashes reflected the size of the particles and the fraction of time they were present in a 16.7 millisecond frame of the video. The number of flashes in a single frame of video was highest with the “th” sound in “stay healthy.”



# Aerosolized Droplet Study (continued)

The participant repeated the phrase three times at various volumes, with pauses in between. The number of flashes was highest with the loudest speech. Additionally, the flash count during the pauses between the phrases was above the background level, indicating that aerosolized droplets lingered in the air.

The experiment was repeated with the participant's mouth covered with a damp cloth. The flash count remained similar to the background level observed before the start of the first trial, indicating a decreased number of forward-moving droplets.

Thus, this study provides evidence of speech-generated droplets and qualitatively describes the effect of a barrier over the mouth to curb droplet emission.

## The Implications

Sneezes can emit large infectious particles, which remain airborne for a short time before quickly settling to the ground. Infection through these larger particles occurs when people touch the surface where they have settled, then touch their eyes, mouth or nose. The virus can then enter their body through their upper respiratory tract, where it might be flushed by nasal secretions or swallowed before an infection can begin.

The infectious particles produced by talking, however, behave differently. Since they are much smaller, they can evaporate into droplet nuclei.

Droplet nuclei behave like an aerosol; in still air, a 10-micron particle can remain aloft for nine minutes. The tiny droplets can be carried by mild air currents caused by people moving thorough a room or natural or artificial ventilation. Inhaled viral particles can settle in the lungs after being inhaled, beginning the infection deeper in the body.

The UPenn and NIH study provides evidence that person-to-person transmission of the novel coronavirus, and other similar viruses, can occur through aerosolized droplets produced while speaking. “Aerosols from infected persons may therefore pose an inhalation threat even at considerable distances and in enclosed spaces, particularly if there is poor ventilation,” said Harvard University geneticist and molecular biologist Matthew Meselson, in a review of the study.

This study also qualitatively describes the effect of a mouth covering in curbing droplet emission. According to Meselson, it is advisable to wear “a suitable mask whenever it is thought that infected persons may be nearby” as well as to provide “adequate ventilation of enclosed spaces where such persons are known to be or may recently have been.”



# Airborne Coronavirus Discovered in China – Could It Transmit the Virus?

May 6, 2020

Earlier this week, we discussed an aerosolized droplet study conducted by the University of Pennsylvania Perelman School of Medicine and the National Institutes of Health (NIH). That research provided evidence that the novel coronavirus could be transmitted from person to person through the aerosolized droplets that people produce when speaking. Unlike the larger particles produced by sneezing or coughing, the particles produced when speaking are too small to quickly settle and remain suspended in the air long enough to enter the airways of other people. Therefore, especially in enclosed spaces with poor ventilation, aerosols produced by people infected with COVID-19 may pose a risk – even if those people are speaking at a normal volume and keeping their distance.

Now, the New York Times has reported evidence of airborne coronavirus in real-world conditions (source). In February and March 2020, scientists identified genetic markers of the SARS-

CoV-2 virus, which is responsible for the disease COVID-19, in different areas of two hospitals in Wuhan, China, where the virus was first identified in December 2019.

The aerodynamic analysis, published in the journal *Nature* on April 27, 2020, revealed that levels of airborne SARS-CoV-2 RNA were very low in isolation wards, ventilated patient rooms, and the majority of public areas. Areas with higher levels of airborne coronavirus included the patients' toilet areas, two public areas susceptible to crowds (in which there may have been people infected with COVID-19 present), and some medical staff areas. According to Dr. Linsey Marr, an expert interviewed by the *New York Times*, airborne droplets will remain afloat for at least two hours. In addition, "Dr. Marr said she calculated it would take about 15 minutes for a person to breathe in one virus particle."



The scientists have not yet established the airborne virus's infectivity (i.e., the ability of the pathogen to establish an infection), but they did propose that "SARS-CoV-2 may have the potential to be transmitted via aerosols." More research is needed to determine if coronavirus RNA aerosols are infectious or harmless. However, based on their research, the scientists recommended that the following measures be taken to limit the concentration of viral RNA in aerosols:

- ▶ Increase room ventilation
- ▶ Avoid small, confined spaces
- ▶ Regularly sanitize protective apparel
- ▶ Properly use and disinfect toilet areas

Thus far, the World Health Organization (WHO) has emphasized that COVID-19 is spread primarily through droplets of saliva or nose discharge that are emitted when an infected person coughs or sneezes and briefly remain airborne.

The WHO has also acknowledged that people can become infected by touching contaminated surfaces or objects and then touching their faces. But with evidence mounting that coronavirus can be spread through aerosols, the public should remain alert in case the WHO decides to update its public health recommendations based on this new information.



# COVID-19 Testing Challenges and Solutions

July 13, 2020

During the ongoing pandemic, all COVID-19-related testing used for the diagnosis, prevention, or treatment of disease, or for a health assessment, must adhere to the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Through the CLIA law, the Centers for Medicare & Medicaid Services (CMS) regulates all human diagnostic laboratory testing in the United States, except research, to ensure high-quality laboratory testing. The program aims to ensure that all test results are accurate, reliable, and completed in a timely manner. To clarify these requirements in regard to COVID-19 and help clinical laboratories respond to the current coronavirus health crisis, the CMS issued an important CLIA guidance and a set of frequently asked questions (FAQs) on March 26, 2020.

Covering approximately 260,000 laboratories, the CLIA regulations establish quality standards for laboratory testing and covers all aspects of testing, from general laboratory requirements and quality monitors to analytic performance, pre-analytics, post-analytics, and personnel requirements. In addition, the CLIA regulations require that clinical laboratories be certified

by their state as well as the CMS before accepting human specimens for laboratory testing for the diagnosis, prevention, or treatment of disease or for a health assessment.

Although these requirements have not been lifted during the COVID-19 pandemic and the agency does not have the authority to approve waivers (which would allow for program modifications), the CMS has relaxed some CLIA requirements due to the pandemic. The laboratory guidance that outlines these changes provides information regarding the remote viewing of pathology slides, proficiency testing, alternate collection devices, requirements for obtaining a CLIA certificate during the coronavirus pandemic, and more. The policy will enable the following relaxed regulations, amongst others:

- ▶ **Remote Slide Review:** Pathologists may review pathology slides remotely if specific criteria defined by the CMS are met. Typically, CLIA regulations require that both the slide preparation and the professional analysis occur on the laboratory premises.

- ▶ **No Penalty for Lack of Proficiency Testing:** The CMS won't penalize laboratories for a lack of proficiency testing (PT) results if the PT is postponed, suspended, or canceled with the approval of the CMS. In these situations, however, the laboratories should consider self-assessing the results to ensure reliability.
- ▶ **Expedited Review of CLIA Applications:** Laboratories need CLIA certification to perform any services, including COVID-19 testing that is used for the diagnosis, prevention, or treatment of disease, or for a health assessment. To ensure that U.S. laboratories applying for CLIA certification can begin COVID-19 testing as soon as possible, the CMS will assign each of these laboratories a CLIA number as soon as it identifies a qualified laboratory director and provides all information required on the CMS-116 application. Then, once applicable CLIA requirements have been met, the laboratory can begin testing.
- ▶ **Testing in Designated Overflow Locations:** If a facility has the appropriate CLIA certificates and follows applicable CLIA regulations (as well as state regulations), it may perform COVID-19 testing in a parking lot or any other designated overflow location.
- ▶ **Contiguous Buildings with a Single CLIA Certificate:** Normally each laboratory location must have its own CLIA certificate. Under the more relaxed guidance, laboratories located in contiguous buildings on a hospital or university hospital campus may hold a single CLIA certificate for all laboratory sites within the same physical location or street address. This adjustment will benefit large hospitals and medical centers that wish to temporarily expand their laboratory services during the COVID-19 pandemic.

With these updates, the CMS hopes to help ensure the availability of widespread, reliable COVID-19 laboratory testing in the United States. The guidance will only be applicable during the COVID-19 public health emergency.



# Coronavirus Testing Part I: Real-Time Reverse Transcriptase Polymerase Chain Reaction

April 20, 2020

Testing is the crucial first step to identifying and treating COVID-19. In the past few months, uncertainty has surrounded testing: how and if it works, who needs it, where to get one, and when there will be enough. Globally, testing availability, variability and approval by governing bodies varies by country. In the United States, while testing for coronavirus is technically available in every state, there remains a seemingly intractable lack of access to widespread testing.

As of March 31, 2020, 92 U.S. public health laboratories had undergone the Center for Disease Control's (CDC) verification process for approving coronavirus tests under the Emergency Use Authorization (EUA). The EUA stipulates that as long as tests meet the Food and Drug Administration's (FDA) standards for safety and efficacy, the test can be made available to the public without going through the normally lengthy approval process.

The World Health Organization (WHO) has encouraged health agencies to make testing top priority in their pandemic response; but the internation-

al response has been uneven. Widespread availability and use of testing has been key in reducing the spread of coronavirus in some countries, such as South Korea. However, Iceland has taken an even broader approach with a goal of testing its entire population, thus far achieving one of the highest proportion of tests performed by any country for the coronavirus.

This article is the first in a two-part series taking a closer look into the different types of testing available for COVID-19 infections and residual antibodies. There are two types of testing: real-time reverse transcriptase polymerase chain reaction tests (rRT-PCR) and serology tests. rRT-PCR testing is used to detect the presence of the coronavirus, diagnosing an active infection; serology tests look for the existence of antibodies, which indicate a previous infection and possible immunity. Since the novel coronavirus is still a very new public health challenge, the scientific community is still learning when, where and how to use each of these tests. The first part of this series will address rRT-PCR testing.

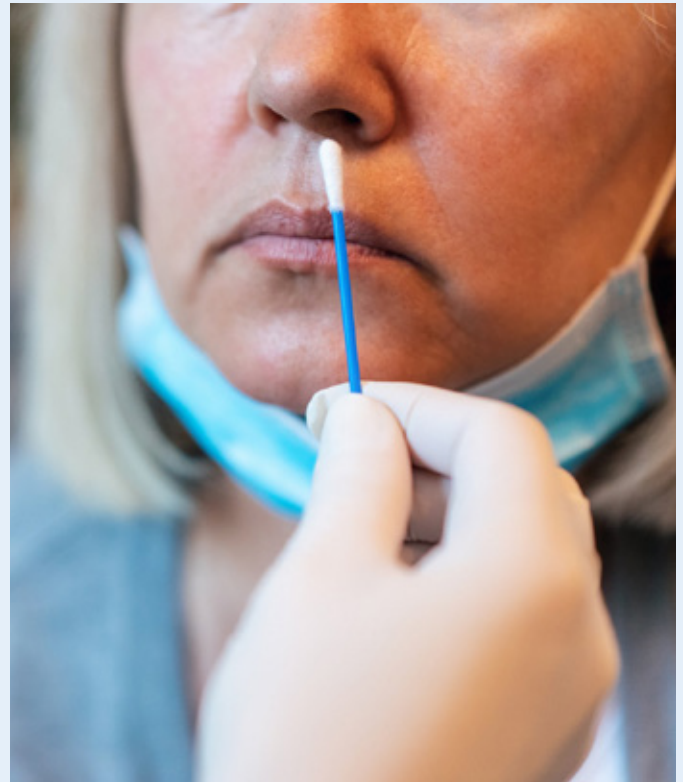
## Sample Collection

The rRT-PCR test is performed with a swab and diagnoses active infections by detecting viral RNA in clinical samples. The test is done either by or in consultation with a healthcare provider on both symptomatic and asymptomatic patients. A nasopharyngeal (NP) swab is introduced into either the anterior nares or the midturbinate region. Oropharyngeal swabs are also acceptable, and the CDC suggests collecting lower respiratory tract specimens if they are available. For patients who are intubated, a lower respiratory tract aspirate or bronchoalveolar lavage sample is recommended.

## How the PCR Test Works

Some viruses, such as the novel coronavirus, have ribonucleic acid (RNA) as the carrier for their genetic material. Once the sample or samples have been collected, the lab adds a series of chemicals to remove everything except the RNA. Scientists add enzymes to transcribe the RNA into DNA, then put that DNA into testing apparatus. One such machine, the Roche Cobas

8800, can run 376 samples at once; each cycle takes between three and four hours. The machine heats and cools the samples, copying the DNA thousands of times; those copied fragments bind to viral genetic material. The chemical markers attached to the DNA emit fluorescence when the DNA binding occurs, and these flashes indicate whether the virus is present. The primary difference between different PCR test kits involves which coronavirus genes each test targets.



# Coronavirus Testing Part I: Real-Time Reverse Transcriptase Polymerase Chain Reaction (continued)

## Challenges with PCR Testing

The PCR test has been difficult to obtain in the United States, and availability varies in other countries. In the US, problems began with technical difficulties in the test that the CDC created, which responded to non-novel coronavirus genetic material, yielding false positives. Supply chain issues, including shortages of nasal swabs, testing reagents, and other essential test kit components, have hampered the ability to conduct widespread testing and persist to this day.

Although the test only takes a few hours to run, other steps of the process are painstaking. Transportation to a centralized laboratory takes time, as does preparing the samples and loading them into the testing apparatus. Those factors, combined with the volume of tests being run, mean that rRT-PCR tests can take up to a week to return results. When trying to diagnose active infections that may result in a person being quarantined, that can prove problematic.

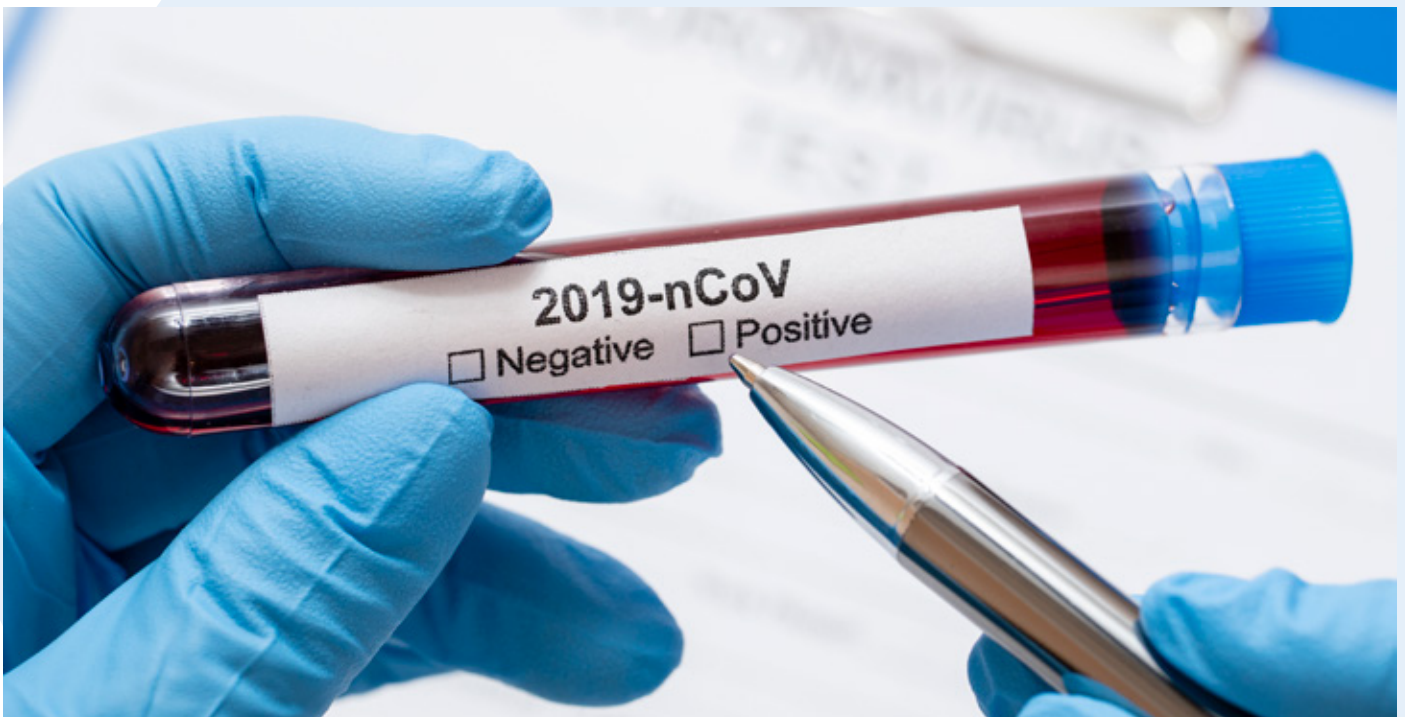
There are also challenges regarding the administration of PCR testing. Accurate results depend on the experience and expertise of the person performing the test; it is important to ensure the tip of the nasal swab reaches the deep anterior nares region. The condition of the sample collected is also a factor, since many samples are gathered at mobile testing sites and shipped to labs around the country.

## Point-of-Care PCR Testing

Point-of-care (POC) tests, which are done in the doctor's office or hospital, are in development and show promise for advantages in convenience and speed. These tests, however, require proprietary equipment and one-time use cartridges, which manufacturers are having trouble producing in sufficient quantities to meet demand. Additionally, POC tests can only run one sample at a time, while a traditional PCR test uses standard multi-well sample trays and can therefore more quickly provide a clearer picture of the infection rate in a population.

Abbott Labs is producing rapid POC tests that take five minutes for a positive result and 13 minutes for a rule-out. The test does not use the heating and cooling of samples that some other PCR tests need, and it is already in use at 18,000 locations across the USA. Abbott aims to distribute 50,000 of these tests a day.

These quick tests save hospital space and PPE, and they can let a sick health-care worker know that they must self-quarantine immediately. As the availability of POC tests increases, hospitals stand to benefit immeasurably.



# Coronavirus Testing Part II: Serology Testing

April 27, 2020

“Test, test, test,” was the singular message from the World Health Organization’s Director-General Tedros Adhanom Ghebreyesus during remarks on the coronavirus pandemic in mid-March.

In Part I of this blog series on testing for the novel coronavirus, we covered the real-time reverse transcription polymerase chain reaction (RT-PCR) assay, which is administered via nasal swab and can diagnose an active infection. The other primary type of testing for coronavirus is serology testing (also referred to as antibody testing).

From an epidemiological standpoint, positive PCR tests and hospitalizations for COVID-19 are only “the tip of the iceberg,” according to Robert Garry, a virologist at Tulane University School of Medicine. The scale of mild or completely asymptomatic infection is not yet known — and this data about the infection rate for the population is something serology tests can help provide.

## The Serology Test Process

A serology test requires a blood sam-

ple, which is transported to a central laboratory and spun down to separate the plasma. Technicians are not looking for the virus itself in the plasma, but for the presence of antibodies, that would have been formed while the body fought an active infection.

Although serology testing cannot diagnose active infection, the detection of antibodies indicates a previous novel coronavirus infection and the subsequent immune response. Antibodies, which are an important part of the human body’s response to any infection or illness, occur in three types:

- ▶ Immunoglobulin M (IgM) antibodies are the generic fighters. IgM levels spike within a few days of infection.
- ▶ As the infection proceeds, IgM is refined into immunoglobulin G (IgG), which can recognize and fight a specific virus. IgG peaks around 28 days after initial infection and can signal long-term immunity.
- ▶ A third type, immunoglobulin A (IgA), is present in mucosal tissues and is known to fight viruses such as influenza — and thus possibly the novel coronavirus as well.



## How Serology Tests Work

A serology test for coronavirus uses an enzyme-linked immunosorbent assay (ELISA), which is a screening test to detect the presence and concentration of specific antibodies that bind to viral protein. This assay targets either the spike protein (the crown-like structure from which coronaviruses get their name) or the nucleocapsid protein.

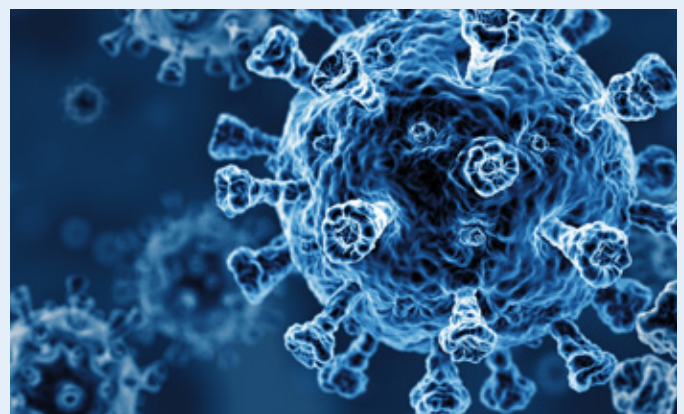
Serological tests are difficult to develop and each serology test is different; some look for all three types of antibodies, some for just one. A perfect assay would involve an entire inactivated virus batch; however, providing this amount of inactivated virus at scale is challenging due to time concerns as well as batch consistency.

## U.S. Serological Testing Status

Both the Centers for Disease Control (CDC) and several private labs are rolling out serological tests. Cellex Laboratories and Abbott Labs are two of the first companies to provide these

tests to hospitals and governmental organizations. Abbott has said it will distribute more than four million serological tests by late April 2020, and has pledged to make twenty million tests available per month starting in June. The Abbott assay, which identifies IgG, is run in a centralized lab using Abbott's instruments and can provide 100 to 200 results per hour.

Point-of-care (POC) serological tests are also in development. These function similarly to a pregnancy test, producing a paper readout and a colored indicator. POC tests could provide a way to overcome shortages of testing materials such as reagents and test swabs. POC serology tests cannot detect coronavirus antibodies early on; it takes the body about eight days to mount a detectable IgG response, with an IgG peak at 28 days.



# Coronavirus Testing Part II: Serology Testing (continued)

## Challenges with Serological Testing

There is still much to be learned about the potential uses and challenges of serological assays. Aside from the difficulty of developing accurate serological tests, there are instances of test failures, or false positives. Some of the serological tests in development have not been specific enough to target the novel coronavirus antibodies. These assays can also provide positive results when detecting antibodies specific to other coronaviruses, such as those that cause common colds and flu.

The serological tests deployed widely in the United Kingdom were plagued by both false negatives (not alerting to antibodies when they were present) and false positives (alerting to antibodies from other coronaviruses). The false positives are particularly concerning, as that result demonstrates that an individual has had an immune response to the virus when they have not. Since one plan is for these tests to be used to determine which individuals can go about more normal activities without causing the risk of a novel coronavirus infection to themselves or others, false

positives must be minimized as much as possible.

The WHO has issued a warning against assuming that a person who tests positive for coronavirus antibodies is immune. “Right now, we have no evidence that the use of a serological test can show that an individual is immune or protected from reinfection,” said Dr. Maria Van Kerkhove, head of WHO’s emerging diseases and zoonosis unit. There have been reports of individuals, who have had COVID-19 and recovered, being re-infected and falling ill again.

## Serology Test Use Cases

One promising use for serology tests is identifying antibody-rich plasma, or convalescent plasma, and using it to treat critically ill COVID-19 patients. This convalescent plasma treatment works on the premise that active antibodies in a plasma transplant can kick-start a patient’s own immune system. With the Food and Drug Administration’s Emergency Use Authorization in place, the Icahn School of Medicine at Mount Sinai is currently running serological assays to find plasma donors, and the Red Cross has set up a website to help identify donors.

In recent days, there have been a number of organizations shifting focus to this potential treatment.

Serology tests can also be used to determine population infection rates; this public health data is invaluable for tracking and estimating herd immunity, understanding community spread of the virus, assessing risk to specific populations, and all this data can be used for fighting future pandemics. The National Institutes of Health will be testing 10,000 healthy volunteers around the United States for the presence of antibodies in order to get a clearer picture of the virus's spread. Potential participants will be screened by telephone and finger prick kits will be sent to their homes to facilitate collection of micro samples of blood.

Some scientists have postulated that serology testing could create a type of "immunity passport" that would allow previously infected people to rejoin society. Theoretically, people who possess antibodies may have immunity against the virus, and therefore, not be able to contract the virus again. For example, healthcare workers who have antibodies to COVID-19 may be able to work without the fear of contracting

it again. As discussed in the previous section, however, there is no guarantee of immunity with a positive serology test.

Additionally, these antibody tests could work as a screening tool for potential study subjects. This testing may become standard practice for all clinical trials and could provide a degree of security that a study cohort will not be affected by coronavirus, preventing clinical trial results from being skewed. RT-PCR tests are currently being considered as screening tools for entry into clinical trials, as they can screen out individuals who are infected but not symptomatic.

Both Singapore and South Korea have implemented widespread serological testing and enabled contact tracing. Contact tracing identifies a positive case, then alerts every person who was exposed to that case, directing them to self-isolate and thus disrupting the transmission pathway. This combined approach has allowed both countries to contain the virus and relax social distancing measures with relative speed, although there are reports of a second wave of virus transmission that has come with the relaxation of social distancing in Singapore.

# Coronavirus Testing Part III: Antigen Testing

May 6, 2020

Part I of this series on testing for the novel coronavirus covered the real-time reverse transcription polymerase chain reaction (rRT-PCR) assay, which is administered via nasal swab and can diagnose an active infection. Part II covered serology testing, which scans blood samples for antibodies to the virus and can indicate a previous infection — and potential immunity.

Our third installment in this series focuses on antigen testing. This type of testing detects antigens via a nasal swab, indicating an active coronavirus infection. It does not require any special training or equipment (except for the nasal swabs, which currently have supply chain issues), can give a result in 30 minutes, can be manufactured at scale and will cost only about USD\$10. It is not, however, without its own set of challenges.

## Antigen Testing: The Process

An antigen is a part of a pathogen that elicits an immune response, causing the immune system to create antibodies. Antigens can be part of any sub-

stance that comes from outside the body, including viruses or bacteria.

An antigen test searches for fragments of viral surface proteins as a marker for active infection. In the case of the novel coronavirus, these proteins are from the virus's surface spikes and are large enough to study on their own. This makes the antigen test easier to administer than rRT-PCR tests, in which the tiny RNA fragments must be copied thousands of times in order to be detectable.

An antigen test begins with a nasal swab, similar to the PCR test. The swab is then put into a solution, and the solution is exposed to one end of a paper strip. The strip contains artificial antibodies that are designed to bind to the coronavirus antigens. As the solution moves up the paper strip, the antigens present will bind to the artificial antibodies and give a visual readout.



The coronavirus antigen test was created from the same basic platform that was used for the Zika virus and dengue fever virus antigen tests — both of which are 90%–95% accurate. Researchers predict that the same level of accuracy can be reached for the coronavirus antigen test.

Companies such as OraSure and E25Bio both have antigen tests in development and expect to eventually be able to produce millions of tests. They are also working on accompanying apps that will securely collect anonymous data, helping epidemiologists track the size and spread of the pandemic.

## **Challenges with Antigen Testing**

One of the major challenges with coronavirus antigen tests is that they are not easy to develop. Four months into the pandemic, scientists are finally beginning to understand the biology and structure of the coronavirus well enough to create a reliable antigen test. The key to success is discovering which proteins to look for.

But even more problematic is the possibility that an antigen test will not work for the coronavirus. Antigen tests work very well for bacterial diseases—such as streptococcal pharyngitis—and some viral diseases, but respiratory viruses behave much differently. For example, the influenza virus antigen test has about 70%–80% detection sensitivity — but only in children. This is because children carry a much higher viral load; with adults, the influenza test is about 50% accurate. This lack of test sensitivity is typical for respiratory viruses.

Additionally, the presence of the virus in the nasal cavity varies from person to person. Self-swabbing, although it does not require any special training, is invasive and uncomfortable, which may present a barrier to test accuracy.

Both E25Bio and OraSure have manufactured antigen tests for other diseases, but not for respiratory viruses. Antigen testing developers' estimates of 90% accuracy are based on lab-generated samples; they have not yet tested patient samples, which could be less accurate.

# Coronavirus Testing Part III: Antigen Testing (continued)

## RT-PCR and Serology Testing versus Antigen Testing

Some scientists posit that we will need to be testing upwards of 20 million people per day in order to safely relax stay-at-home orders; the United States is currently performing about 200,000 tests per day. According to Deborah Birx, the response coordinator for the White House Coronavirus Task Force, “There will never be the ability on a [PCR] test to do 300 million tests a day or to test everybody before they go to work or to school. But there might be with the antigen test.”

Both PCR and serology testing have been plagued by a lack of nasal swabs, testing reagents, and other supplies. Lee Gehrke, a professor at MIT and Harvard Medical School, says that the nature of COVID-19 is such that a patient could be negative one day and positive the next, which makes follow-up testing imperative; but a PCR test can take hours to run and as long as a week to come back, making effective follow-up

testing nearly impossible.

Antigen testing can identify the presence of coronavirus antigens in just a few minutes — with no specialized equipment or trained personnel. Thus, antigen testing would be easy to scale up, both in the home and at the point of care. This type of test could function well for the necessary frequent follow-up testing that guarantees a patient is virus-free. The fact that antigen testing can give quick yes-or-no results is especially valuable for settings such as hospitals and nursing homes, as well as in determining whether a healthcare worker can return to work.

Clinicians, researchers, and public health officials recognize that antigen testing will not replace rRT-PCR testing as the gold standard for active infection detection. But the potential for antigen testing to work alongside both PCR and serology testing is promising — potentially breaking up testing bottlenecks and helping the United States get to the 20 million tests per day that it needs to safely return to everyday life.

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# Coronavirus Testing Part IV: Saliva Testing

May 18, 2020

Accurate, rapid testing for the novel coronavirus (SARS-CoV-2) is crucial to controlling the COVID-19 pandemic. In previous installments of this blog series, we cover the real-time reverse transcription polymerase chain reaction (rRT-PCR) test, the serology test and the antigen test for the novel coronavirus.

The rRT-PCR assay sample is gathered by nasal swab, run on a QPCR machine and can diagnose an active infection. Serology testing, which scans blood samples for antibodies to the virus, can indicate a previous infection — and potential immunity. Antigen testing detects antigens in samples collected via nasal swab, indicating an active coronavirus infection. Each test has its own advantages and limitations.

rRT-PCR tests are the gold standard, but they have poor sensitivity for early infection detection and are inconsistent in serial testing throughout the course of the infection. The nasopharyngeal swab used in PCR and antigen testing (which is experiencing a global supply chain crisis) can be invasive and uncomfortable, thus limiting compli-

ance for repeat testing. The swab can also trigger coughing and sneezing, which puts healthcare workers at increased risk. The key limiting factor in accurate testing using nasal swab collection is the necessity of sample collection by a trained professional. These challenges are magnified in lower-income locations where the population lacks reliable access to testing components or healthcare.

The ideal SARS-CoV-2 test must be sensitive to mild and asymptomatic infections, so that it can be used to identify the need for self-isolation and reduce viral transmission. It must also be consistent and have a high level of accuracy, which will help to monitor disease progression and aid in clinical decisions. The ideal test must be scalable to large numbers of people so that it can shape public health policies. Finally, a more reliable and less resource-intensive sample collection method is needed — ideally one that could be self-administered. These qualities would enable the safest possible path forward to large-scale testing.



## Saliva Testing for SARS-CoV-2

According to a study from Yale School of Public Health called “Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs,” saliva-based testing could be a solution. Saliva has shown comparable sensitivity to nasal swabs in the detection of respiratory pathogens — including other coronaviruses — in past studies, and saliva sample collection is minimally invasive and can be reliably self-administered. Saliva samples are then sent to the lab to undergo the rRT-PCR assay.

The study tested nasopharyngeal and saliva samples from two cohorts: confirmed COVID-19 patients and self-collected samples from asymptomatic (but high- or medium-risk) healthcare workers on COVID-19 wards. Prior to the study, no rigorous evaluation had been performed comparing the two testing methods on inpatients. The researchers found that SARS-CoV-2 detection sensitivity was greater with saliva samples than with patient-matched na-

sopharyngeal samples. Saliva yielded both greater detection sensitivity and greater consistency in test results throughout the course of the infection.

## The Experiment

The team of 50 Yale researchers collected samples from 44 inpatient study participants with a range of disease severity. Of those 44 patients, 43 percent were in the ICU, 23 percent were intubated and 10 percent eventually died from the disease. Over the course of the study, 121 self-collected saliva samples or healthcare-administered nasopharyngeal swabs were collected from the cohort.



## Coronavirus Testing Part IV: Saliva Testing (continued)

From all of the positive samples tested, the researchers found that virus titers from saliva were about five times higher than those of nasopharyngeal swabs. In eight matched samples, the virus was detected in the saliva but not in the nasopharyngeal swabs.

Overall, temporal diagnostic testing from nasal swabs is reported to be variable. Thus, the team tested longitudinal nasopharyngeal samples and saliva samples to see which sample type provided more consistent results. Virus titers generally increased in both nasal and saliva samples following the reported date of symptom onset. There were five instances in this study in which the nasal swab was negative at the first test and positive at the next test — but no instances where this change in test results occurred when measuring by saliva. This is important because two consecutive negative tests are needed to make discharge decisions. The results suggest that saliva is more consistent for monitoring temporal changes in infection.

Saliva was also more consistent as a self-sampling method among 98 asymptomatic healthcare workers included in the study's second cohort. During the experimental period, the team collected saliva samples or nasal swabs an average of once every three days. Titers from asymptomatic healthcare workers' saliva were lower than for symptomatic patients. The data collected supports the fact that saliva would be more sensitive for detecting presymptomatic and asymptomatic infections, but a larger sample is needed to be certain.



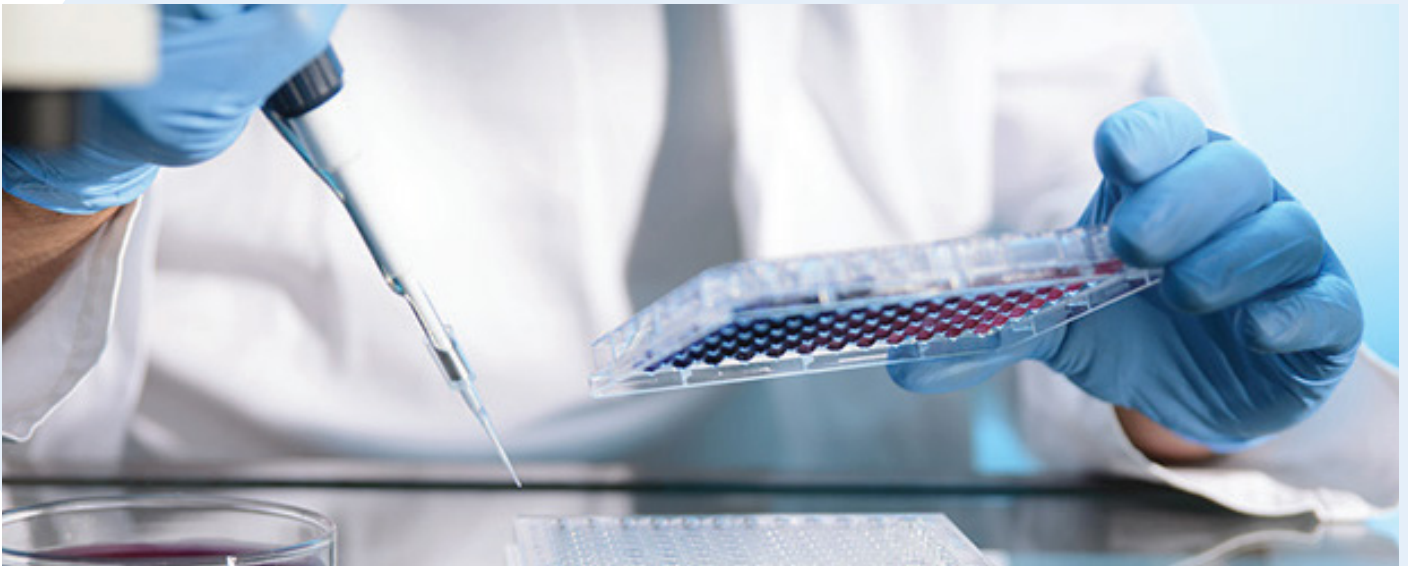
## Study Implications

Saliva testing provides more consistent results during extended hospitalization and recovery, and it can be more sensitive than testing nasopharyngeal swabs. Using saliva for diagnostic tests also negates the need for direct healthcare worker–patient interaction, as self-sampling is simple.

If saliva were validated for detection of subclinical infections, it would be

a game-changer for remote patient sample collection as well as surveillance of healthcare workers.

The authors of the study have called for immediate validation of the results and implementation of saliva diagnostics in clinical labs, and a saliva assay has already been granted emergency use authorization.



# COVID-19 Vaccine Developments

Published on bioanalysis-zone.com, April 2, 2020

Much of the science and healthcare news during these dire times has been disheartening. But there's been at least one encouraging development: new COVID-19 vaccines are on track to be the fastest ever to market. And that accelerated pace might become the new normal.

## Vaccine Development: The Process

New vaccines are approved through the Food and Drug Administration's Center for Biologics Evaluation and Research during a process that typically follows the same clinical pathway as that of drugs and other biologics. Developers must submit an Investigational New Drug application to the FDA that describes the vaccine's purpose, manufacturing process and quality control testing. Evidence for immunogenicity in animal testing and proposed clinical protocols for human testing are also included in the application.

The clinical development of the vaccine occurs in three phases:

▶ Phase 1 includes safety and immu-

nogenicity studies performed on a small number of closely monitored human subjects.

- ▶ In Phase 2, the vaccine undergoes dose-ranging studies on hundreds of participants.
- ▶ Phase 3 trials are typically run on thousands of test subjects, providing critical documentation of effectiveness and the safety data needed for licensing.

After the phased clinical trials, vaccine developers submit a Biologics Licensing Application, which provides the reviewing team (comprised of biostatisticians, chemists, microbiologists and medical officers at the FDA) with the information they need to make a risk/benefit assessment. This team then either recommends the vaccine for approval or denies the application.

The entire process typically takes about 10 years, according to the History of Vaccines information provided by the College of Physicians of Philadelphia (PA, USA).

But that may be about to change.

## COVID-19 Vaccine Development

Whether due to the global, catastrophic reach of this pandemic, or to new scientific breakthroughs in genomics and structural biology, the development of a vaccine is proceeding at a record-breaking pace. The National Institutes of Health (NIH; MA, USA) originally predicted a new vaccine would take about 100 days from genetic sequencing to clinical trial. But the first clinical trial began on March 16, 2020 — just 66 days after scientists first received the virus's genetic sequence. This demonstrates the very real possibility of significantly shortening the industry standard timeframe, not just for the coronavirus vaccine, but for others. The National Institute of Allergy and Infectious Diseases (NIAID; MA, USA) head Dr Anthony Fauci estimated that a COVID-19 vaccine could be ready in 12–18 months.

This accelerated timeline may have been achieved sooner if the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks had been a

more significant threat and thus received more attention. It took about 20 months to develop a SARS vaccine in 2002, but research and funding dried up after those outbreaks subsided. According to many infectious disease experts — such as Vincent Racaniello, a Columbia University professor (NY, USA) — if work had continued on these vaccines between pandemics, the scientific community would be closer to a solution for today's pandemic.



# COVID-19 Vaccine Developments (continued)

## The New Normal

The rapid turnaround time from initial genetic sequencing to clinical trials beginning may be the new normal for vaccine development. According to Kizzmekia S. Corbett, scientific lead for coronavirus vaccines at NIAID, a few factors contributed to this feat, including pre-established trial networks with academics nationwide and collaborations with companies that could proceed immediately, eliminating lengthy contract negotiations.

Another key to speeding up development of the COVID-19 vaccine involved using genetic sequencing instead of batches of attenuated virus. This method includes coding a piece of RNA with lipid nanoparticles to stabilize it, after which it can be directly injected. This type of novel vaccine technology will become an invaluable part of responding to emerging viruses.

One of the most promising vaccines relies on mRNA, a set of instructions that tells cells to make proteins that combat diseases. Developing vaccines in this way is almost a 'plug-and-play' technique, taking knowledge about

antigens from cousin viruses, such as SARS, to develop new ways of fighting novel viruses.

## Frontrunners in the COVID-19 Vaccine Race

Moderna (MA, USA), working in concert with the NIAID for Phase 1 clinical trials, has already dosed 45 healthy people with a new COVID-19 vaccine. Results from the trials are expected in about 2 months. Their record-setting timeline plots a vaccine release to healthcare workers and other designated individuals by fall 2020.

In early 2020, J&J (NJ, USA) began working through a series of vaccine options, eventually selecting the one that caused the most promising immune response during preclinical trials. The vaccine candidate was created in collaboration with Beth Israel Deaconess Medical Center (MA, USA) using an adenovirus vector-based platform. The company hopes to begin clinical trials by September 2020, with the vaccine ready for emergency use in early 2021. They are ramping up their manufacturing capabilities in order to supply 1 billion doses of the vaccine, available on a not-for-profit basis.

## The Future of Vaccines

This new model puts the cart before the horse in the most advantageous possible way. Scientists and infectious disease specialists can begin designing vaccines before viruses are even known to infect humans — for example, NIAID is leading an initiative to support vaccine development and testing against prototype pathogens.

The Coalition for Epidemic Preparedness Innovation (CEPI) is supporting

the development of vaccines against 5 epidemic pathogens on the World Health Organization's priority list. The organization is also developing platform technologies for "Disease X," which moves from viral sequencing to clinical trials in 16 weeks.

As difficult as it is to think about the next pandemic, establishing novel development and manufacturing platforms that can be adapted to new pathogens is the best way to protect against future outbreaks.



# COVID-19 Testing: Potential Challenges and Solutions

Published on bioanalysis-zone.com, March 23, 2020

As the COVID-19 pandemic extends its reach worldwide, the demand for available, accurate testing will grow exponentially. Science News reports that COVID-19 testing has been available in limited quantities from the Centers for Disease Control (CDC), but production has not been able to keep up with demand. The CDC plans to make millions of tests available as soon as possible; in the meantime, private labs have ramped up their capabilities to create and analyze tests as well as to develop potential vaccines.

## Testing Process

Administered by healthcare professionals — some in a drive-up capacity, in order to limit person-to-person exposure — tests for COVID-19 use respiratory samples obtained via nasopharyngeal (NP) or oropharyngeal (OP) aspirates or washes, NP or OP swabs, or bronchoalveolar lavage (BAL).

Scientists then purify the virus's genetic material from the sample, a time- and labor-intensive step that has the potential to create testing bottlenecks.

All tests for COVID-19 use a technique called a polymerase chain reaction (PCR), which can detect tiny amounts of viral genetic material. SARS-CoV-2, the virus that causes COVID-19, has single-strand RNA as its genetic material. This RNA must be copied into double-strand DNA in order to be tested via PCR, a process that can take up to 30 minutes. The CDC's test scans for two of the virus's genes, and the World Health Organization's (WHO) test scans for three of the genes. The entire testing protocol can take up to 3 hours, which poses challenges in terms of volume as demand grows.

## Private Labs

Most private labs are pursuing testing validation under the FDA's Emergency Use Authorization process (EUA). This means that new tests can be used with patients as soon as they are validated to the FDA's standards, after which the lab must file for EUA within 15 days. Additionally, the FDA will allow private companies to market tests to the public without prior approval, according to the Wall Street Journal.



There are numerous challenges for private labs as they work to develop testing capabilities — including staffing shortages, instrument access and supply shortages — as reported in Modern Health. For clinical workflow validation, labs need access to reagents, extraction kits and instruments, PCR systems and control materials. Currently, the supply of materials is not meeting demand — in particular, there is a shortage of attenuated virus and viral genome. Additionally, real-time PCR instrumentation and automated RNA extraction equipment are on back-order from manufacturers.

## Vaccine Development

According to the World Health Organization, there are currently more

than 20 vaccines in development around the globe for the treatment of COVID-19 and multiple therapeutics in clinical trials.

QPS is equipped with an access-restricted bioanalysis lab prepared to analyze COVID-19 clinical trial samples at their campus in Newark, DE, USA. This dedicated lab provides space for drug companies to quickly process samples and deliver results to evaluate the safety and effectiveness of potential vaccines and drug therapies. QPS has decades of experience helping drug companies slow the progress of viral outbreaks and is committed to supporting the life sciences community in fighting COVID-19.



# Clinical Trials: Coronavirus Impact and FDA Guidelines

April 13, 2020

The spread of the coronavirus is affecting every facet of the pharmaceutical industry — including clinical trials that currently underway or scheduled for the near future. Approximately 40,000 clinical trials are operating at any given time; these trials take place at thousands of sites, with tens of thousands of investigators and hundreds of thousands of trial participants.

## Possible COVID-19-related Challenges

Challenges to planned or ongoing clinical trials may include the following:

- ▶ Travel limitations due to quarantine or other safety concerns
- ▶ Testing site closures
- ▶ Quarantines and infections of site personnel
- ▶ Disruptions to the investigational product supply chain

These factors may create difficulties in meeting protocol-specified procedures laid out at the time of the study design and approval. The Food and Drug Administration (FDA) recognizes

that unavoidable circumstances will require deviations from these procedures.

## Considerations for Clinical Trials

The Department of Health and Human Services (HHS) aims to take every precaution to avoid impacts from the current global health emergency on clinical trials. But since many trials will unavoidably be interrupted — or, at the least, will require their protocols to be amended — the FDA has published a set of guidelines on the conduct of clinical trials during this time.

This advice is targeted toward Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), trial sponsors and investigators. These guidelines are nonbinding recommendations, going into implementation immediately without the customary comment period. They will be subject to comment going forward.

The FDA's aim is to protect the safety of human trial participants, minimize risks to the integrity of ongoing trials

during the pandemic and encourage the maintenance of good clinical practice (GCP). GCP ensures that a trial is conducted with a high standard of ethics and quality data collection, leading to scientifically sound outcomes and observations.

## FDA Guidelines

- ▶ Ensuring the safety of trial participants is paramount. All sponsors and investigators should take the circumstances into consideration and act accordingly. Decisions may include the discontinuation of recruitment, changes to patient monitoring or the use of investigational products.
- ▶ Trial sponsors may consult with investigators and IRBs on a case-by-case basis as to whether each participant's safety, welfare and rights are served by continuing the study.
- ▶ In cases where participants are not able to visit the regular clinic, safety assessments should be modified to include virtual visits, phone calls or alternative locations.
- ▶ In cases where the trial participant no longer has access to the investigational product or site, additional safety monitoring may be required; sponsors may consider withdrawing that participant from active treatment.
- ▶ Existing processes may need to be modified or new processes put in place. It may be appropriate to delay some assessments or consider the possibility that the study cannot be conducted at this time.
- ▶ If a COVID-19 screening is mandated for any person involved in the trial, it does not need to be reported as a change in protocol.
- ▶ IRBs and IECs should be engaged and consulted early and often by trial sponsors. If there are any recommended changes to protect the health of trial participants, they do not need to be preapproved — but must be reported after the change is made.
- ▶ To the extent possible, alternative processes in the trial should be consistent with protocol. All contingency measures, and the reasons for those measures, should be documented. How COVID-19 led to those changes, the duration of the changes and the impact on participants should be documented and reported.

# Clinical Trials: Coronavirus Impact and FDA Guidelines (continued)

- ▶ Missed visits or changes in study visits may lead to missing information. Case report forms should explain the basis of that lack of information, including its relation to COVID-19.
- ▶ Self-administered investigational products are amenable if scheduled clinic visits prove problematic.
- ▶ Protocol changes related to collecting efficacy endpoints (e.g., delays in assessments, virtual assessments, and alternative collections of specimens) should be done in consultation with the appropriate FDA review board. In cases where efficacy endpoint data cannot be collected at all, documentation should be provided, and the appropriate FDA review division should be consulted if protocol changes mean changing data management or statistical analysis plans.
- ▶ Remote monitoring programs are acceptable in cases where on-site monitoring visits become impossible.

## Clinical Trials Impacted by COVID-19

Clinical study reports for trials impacted by COVID-19 should include specific details and actions, including those outlined below.

- ▶ Any contingency measures taken to manage study conduct during disruptions.
- ▶ A list of participants affected by the COVID-related disruption. Each participant should be identified in documentation by their unique subject number identifier, the site, and the description of how their participation was impacted.
- ▶ Analysis and discussions that address the effect of the contingency measures, such as patient discontinuation or alternative procedures, on the safety and efficacy results.

## Impacts for Today and Tomorrow

The FDA is relying heavily on significant efforts by sponsors, clinical sites and IRBs/IECs to protect the data integrity and participant safety of trials in keeping with GCP. All efforts should be documented to clearly delineate how the pandemic has affected clinical trials.

COVID-19 will likely have lasting effects on how clinical trials are planned and executed. Pivoting to telemedicine and minimizing touchpoints during clinical trials may be a sustainable solution, especially for trial participants with health vulnerabilities.



# FDA Guidance Documents Overview

June 10, 2020

COVID-19 was declared a global pandemic on March 11, 2020. As the novel coronavirus continues to dominate headlines and impact communities around the globe, many life-sciences and pharmaceutical companies are working hard to develop tests, treatments, and vaccines to combat the virus. To help steer these companies in the right direction, the United States Food and Drug Administration (FDA) has developed and issued several rulings and guidances regarding SARS-CoV-2 and COVID-19. To keep our partners and other industry professionals up to date on the latest news, we have been adding links to these FDA guidance documents to the QPS website.

According to the FDA, the agency is “committed to providing timely recommendations, regulatory information, guidance, and technical assistance necessary to support rapid coronavirus disease 2019 (COVID-19) response efforts.” The FDA’s process for publishing COVID-19 related documents complies with their good guidance practices and allows the agency to publish items quickly. When it is not feasible or appropriate to do so, the FDA is not seeking out public comments prior to

publication. However, all guidances remain subject to comment and the FDA will revise its documents when necessary.

Let’s take a look at a few of the communications and guidance documents issued:

- ▶ **Coronavirus (COVID-19) Update: Serological Test Validation and Education Efforts:** This statement explains the FDA’s thoughts on serological tests, including expanding access to accurate and reliable serology tests and protecting Americans from fraudulent tests.
- ▶ **Important Information on the Use of Serological (Antibody) Tests for COVID-19 – Letter to Health Care Providers:** This resource for healthcare providers discusses information regarding serological (antibody) tests. While it recommends serological tests in hospitals, it also recognizes the limitations of these tests.
- ▶ **Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised):** This guidance document is designed to help labs and commercial manufacturers accelerate the availability of COVID-19 tests during this public health emergency.

- ▶ **FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency:** This guidance document reflects on how clinical trials might proceed during the pandemic. For example, it discusses changes such as using alternate laboratories or imaging centers and video conferencing with trial participants. It also discusses alterations to ongoing trials.
- ▶ **COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products:** This guidance document recommends a process designed to increase efficiency for drug and biological product developers seeking feedback on their supporting data, in the hope that these developers will be able to start clinical trials for their COVID-19-related drugs as soon as possible. It also clarifies the type of data that sponsors must provide before submitting an application to initiate studies.
- ▶ **COVID-19: Developing Drugs and Biological Products for Treatment or Prevention:** This guidance document offers recommendations for later-stage clinical trials and summarizes critical sponsor considerations,

with the goal of increasing the safety and effectiveness of COVID-19 products.

“Accelerating the investigation of safe and effective therapies that could benefit people affected by the COVID-19 pandemic is one of the FDA’s highest priorities,” said FDA Commissioner Stephen Hahn. “We are committed to maximizing our regulatory flexibility and using every tool at our disposal to speed the development and availability of these medical products and believe these new guidances will help innovators and researchers do just that.”

QPS will continue posting links to these helpful guidances for your convenience. For links to all of these FDA guidance documents, please visit QPS’s Guidance Documents page. This page also contains guidance documents related to a variety of important topics – biomarkers, drug development, drug interaction, drug metabolites, elemental impurities, generics, labeling, method validation, product quality assessments, toxicokinetics, and more – issued by the FDA and other global regulatory agencies.

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