

News in focus

response might also contribute. Some people who were critically ill with COVID-19 had high blood levels of proteins called cytokines, which can ramp up immune responses. They include a small but potent signalling protein called interleukin-6 (IL-6). IL-6 is a call-to-arms for some components of the immune system, including cells called macrophages. Macrophages fuel inflammation and can damage normal lung cells. The release of those cytokines, known as a cytokine storm, can also occur with other viruses, such as HIV.

The ideal counter, then, would be a drug that blocks only IL-6 activity and so reduces the flow of macrophages into the lungs. Such drugs, known as IL-6 inhibitors, already exist for the treatment of rheumatoid arthritis and other disorders. One drug, called tocilizumab, has been approved in China to treat people with COVID-19, and researchers worldwide are working to test it and other drugs of this type.

Immune challenges

But globally there is not enough of the drug, and many clinicians are turning to steroids, says James Gulley, an immuno-oncologist at the National Cancer Institute in Bethesda, Maryland. IL-6 inhibitors might suppress only those immune responses that are governed by IL-6, allowing other immune responses that could help the body fight COVID-19 to continue. But steroids could reduce the body's ability to fight infection overall. These drugs will suppress not only macrophages, but also immune cells called CD4 T cells, which are crucial for initiating immune responses, and also CD8 T cells, which are the body's antiviral assassins, capable of destroying infected cells with more precision than macrophages. "When things get really bad, they'll throw on steroids," says Gulley. "I am a bit worried about where some people are going."

Steroids and other immune suppressants are already being tested against coronavirus in clinical trials. In March, UK researchers launched the RECOVERY study, a randomized clinical trial that will evaluate the steroid dexamethasone and other potential treatments for COVID-19. This worries rheumatologist Jessica Manson at University College Hospital in London. Evidence from previous outbreaks caused by related coronaviruses suggests that steroids deliver little benefit, and might even delay recovery, she says.

But Peter Horby, who studies infectious diseases at the University of Oxford, UK, and leads RECOVERY, notes that the trial will use relatively low steroid doses. "Higher doses are not routinely recommended, but the jury is out on lower doses," he says. "And many authorities, including the World Health Organization, recommend a trial."

A combination of damage from a virus and from an immune response is not uncommon, says Rafi Ahmed, a viral immunologist

at Emory University in Atlanta, Georgia. The effects of 'hit-and-run' viruses such as norovirus, which cause illness immediately, are more probably due to the virus itself, he says. By contrast, people infected with viruses such as the coronavirus do not show symptoms until several days after infection. By then, collateral damage from the immune response has often contributed to the illness. But it's hard

to work out the contribution of each, Ahmed says. "It's almost always a combination of the two."

Ahmed is hopeful that, in the absence of an answer, researchers will arrive at a combination therapy, such as an IL-6 inhibitor that does not completely suppress the immune system, combined with an antiviral drug that directly targets the virus.

CORONAVIRUS TESTS GO UNUSED IN THEIR THOUSANDS

US labs that underwent huge efforts to retool for COVID-19 testing are still facing major obstacles.

By Amy Maxmen

As the United States struggles to test people for the coronavirus, academic laboratories that are ready and able to run diagnostics are not operating at full capacity.

A *Nature* investigation of several university labs certified to test for the virus finds that they have been held up by regulatory, logistic and administrative obstacles, and stymied by the fragmented US health-care system. Even as testing backlogs mounted for hospitals in California, for example, clinics were turning away offers of testing from certified academic labs because they didn't use compatible health-record software or didn't have existing contracts with the hospital.

"Our capacity is 2,000 tests a day," says

Stacey Gabriel, a human geneticist at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, where testing facilities were approved in March. "But we aren't doing that many. Yesterday was around 1,000. What is holding us back?" she says.

The Broad Institute and several other leading US labs spent thousands of dollars to pivot their facilities – which usually focus on topics from genome engineering to stem-cell research – to testing people for coronavirus. They navigated complex federal regulations and tweaked their molecular-biology protocols. But despite this, some say they're performing at half capacity or less because of supply shortages or because hospitals won't send them samples.

"We can give results in 12 hours – 24 at the most," says David Pride, an infectious-disease



Academic labs face many hurdles in their push to help with coronavirus testing.

MAX & JULES PHOTOGRAPHY

specialist who is helping to lead a testing operation at the University of California, San Diego. But he's found that many hospitals continue to stick with the diagnostic companies they are accustomed to – even though turnaround times are reported to be three to seven days owing to demand.

To be able to report test results to people, the labs require a Clinical Laboratory Improvement Amendments (CLIA) certificate, showing that they meet stringent quality standards. Earning the certificate is cumbersome, so many labs have found partners at CLIA-certified clinics nearby.

“This was deeply non-trivial,” says Fyodor Urnov, a scientific director at the Innovative Genomics Institute at the University of California, Berkeley, which launched a testing operation on 30 March. His institute, led by Jennifer Doudna, co-discoverer of the CRISPR gene-editing tool, realized it could get into the game by partnering with the university's student health centre. Another step was working out the most reliable test to use, while ensuring that necessary reagents wouldn't run out. Urnov chose a test developed by the biomedical company Thermo Fisher Scientific, headquartered in Waltham, Massachusetts, chiefly because the company's scientific officer guaranteed that it would keep the institute supplied.

At Boston University School of Medicine in Massachusetts, stem-cell biologist George Murphy opted to use the World Health Organization's testing protocol, but asked researchers in his lab to find alternative ingredients in case shortages cropped up. “Every day, there is something running out, so we are always making and validating changes,” he says.

An odyssey

A new wave of challenges began when the labs contacted hospitals in need of tests. US hospitals use a range of software platforms for electronic health records. Many also have strict administrative procedures for setting up accounts with labs, exchanging samples and handling billing. For this reason, several hospitals chose to stick with the commercial labs they were already working with, despite huge backlogs.

Some groups are making progress, but only with partners who are willing to be flexible. “It took about 2,000 phone calls and many e-mails, but we're getting there,” says Gabriel. Still, she worries that the same hurdles faced by her team at the Broad Institute will slow down other labs.

Testing efforts will be especially important as the country relaxes social-distancing measures, says Patrick Ayscue, an epidemiologist involved in testing at the Chan Zuckerberg Biohub in San Francisco, California. “We need a national framework for states to make decisions on testing,” he says.

WHY POLLUTION IS FALLING IN SOME CITIES — BUT NOT OTHERS

Signs that coronavirus lockdowns are making air cleaner aren't as straightforward as they seem.

By Quirin Schiermeier

The lockdowns implemented worldwide to stem the spread of the coronavirus have caused an economic downturn, but also seem to have an upside – cleaner air in urban regions. Scientists are now rushing to analyse why the effect is larger in some places than in others. But they caution that the drop might not last long if the global economy ramps back up after the crisis.

Still, shutting off a large portion of the economy forms a natural experiment by cutting emissions, says Dan Westervelt, a climate and air-pollution researcher at Columbia University's Lamont–Doherty Earth Observatory in Palisades, New York.

Satellite observations have shown a marked drop in nitrogen dioxide (NO₂) concentrations over China and northern Italy since the coronavirus crisis began in January. These countries were the first to introduce broad lockdowns as their coronavirus infections soared. NO₂, an airborne pollutant created mainly by vehicles and power plants that burn fossil fuels, can cause respiratory diseases in humans. There are signs that atmospheric concentrations of other harmful pollutants, including particulate matter, have dropped.

But the data are still preliminary, caution

researchers, and thorough analysis of satellite observations of air pollution is lacking.

But in China and Italy, “the changes observed are so large that we feel confident they cannot be explained by weather-induced variability alone”, says Henk Eskes, an atmospheric scientist at the Royal Netherlands Meteorological Institute in De Bilt, who analyses observations by an instrument called TROPOMI on a European Space Agency satellite. Now, more research is needed to establish the causes and quantify the scale of any changes, he says.

The situation is fuzzier in the United States. Reports that air pollution has dropped in New York and other big cities because of COVID-19 precautions imposed in March are premature, says Dan Goldberg, an atmosphere researcher at Argonne National Laboratory in Lemont, Illinois. “I haven't seen any statistically significant changes in air pollution in most US cities, which is contrary to the claims in some media articles,” he says. According to TROPOMI data, the only US city with a statistically significant improvement in air quality is Los Angeles, California (see ‘Weather factor’). The caveat, he says, is that it has been unusually rainy there in the past few weeks, so it is unclear what fraction of the improvement is due to weather and what to COVID-19 precautions. “Probably both are simultaneously helping,” he says.

WEATHER FACTOR

Weather can substantially affect pollution. The only US city that shows a significant downward trend in nitrogen dioxide levels is Los Angeles, California, satellite data show.

