News / Canada

When is a case of COVID still COVID? Critics suggest the gold-standard of testing could be too sensitive

Experts are concerned some people are being ordered to isolate who are no longer infectious or a threat to public health

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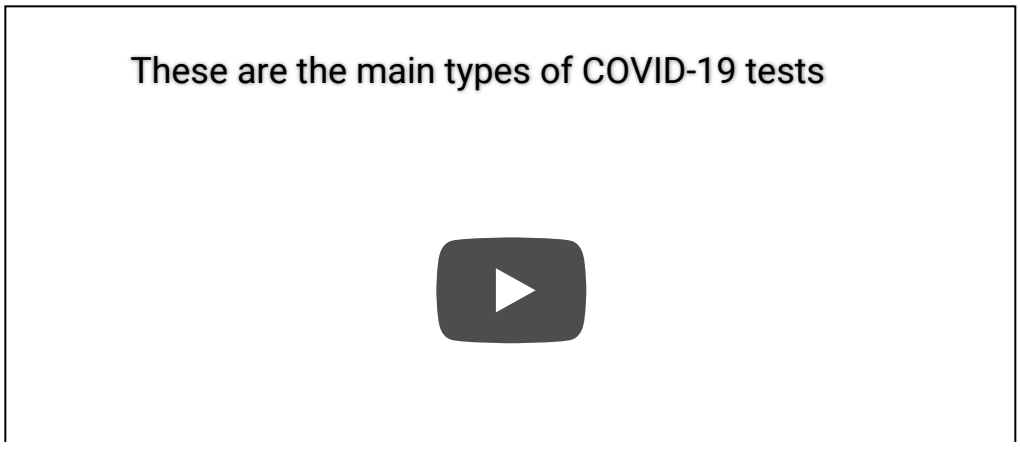
Oct 02, 2020 • October 3, 2020 • 7 minute read

A firefighter collects a test sample at a walk-through coronavirus testing center in Marseille, southeastern France, on October 2, 2020. PHOTO BY NICOLAS TUCAT/AFP VIA GETTY IMAGES

To understand the latest wrangle over COVID-19 testing, think of trying to identify a single person from a photo of a stadium packed with tens of thousands — a kind of Where's Waldo hunt.

The gold standard test used to detect the wily virus that causes COVID-19 works much the same way, by searching for miniscule pieces of viral genes from cells and mucus swabbed from someone's nose. If a trace amount of the virus' genetic material is detected, it's amplified, or copied, over and over again, cycle after cycle, each cycle doubling the amount of material and making millions of copies of what you're looking for — your Waldo.



It's like zooming in on your computer screen, says Harvard University's Dr. Michael Mina. "If you have to zoom a lot, then the thing was small to start with," he recently Tweeted, the "thing" being the starting amount of virus. If you only need to zoom a little, it was a big "thing" to begin with.

Now, some critics are asking, how many rounds, or cycles, are too many? When should you stop hitting "zoom in" and looking for proof of the virus? The likelihood of the person still being infectious can decrease with more cycles, because the test — reverse transcription polymerase chain reaction, or RT-PCR — is so sensitive it can pick up debris from an old infection. It's detecting genetic material and not live virus, meaning it can be positive after the person has cleared the live organism.

But RT-PCR is a binary yes/no test. No, negative. Yes, positive. Mina and others say it's not so neat. "We have to stop thinking of people as positive or negative," he said in an interview published in Science magazine this week, "and ask how positive?"

The concern is that some people are being ordered to isolate who are no longer infectious or a threat to public health, and that provinces are encouraging mass testing using a hyper-sensitive test that's churning out daily cases numbers, the implication being that a case always equals an active infection equals a person capable of spreading to others.

"We do know that PCR picks up dead organism that is not infectious," says Dr. Vanessa Allen, chief of medical microbiology at Public Health Ontario. "I think a lot of the discussion is, do we in fact need a test that's so sensitive, and what is the meaning of those tests at the very end threshold? Are they actually the people we need to isolate?"

In Canada, most labs set the limit of cycles to detect the virus' genetic material, or RNA, to between 35 and 40 cycles, though some Ontario labs have "positivity" cut-offs as high as 45 cycles, according to a study first flagged by Westphalian Times. Mina, a physician and epidemiologist, thinks the cut-off should be closer to 30. (The number of cycles to detect RNA is known as the cycle threshold, or CT value.)

These people may have had the disease for two

weeks or more, in which case, well, are we overcalling it?

Some researchers have reported that people may not be contagious if it takes more than 25 cycles to find the virus. Science magazine this week pointed to a study in Clinical Infectious Diseases,where researchers examined 3,790 samples that tested positive for the SARS-CoV-2 virus that causes COVID. They found 70 per cent of samples with a cycle threshold of 25 or lower could be cultured, meaning grown in a lab, meaning they were live, viable viruses, and the people were likely infectious. Only three per cent of cases with cycle thresholds above 35 could be cultured. While the authors cautioned it should not change public health policy, the work seems to confirm that high cycle thresholds — the more "enhancing" needed — the lower the viral loads.

In a Canadian collaboration between the University of Manitoba and Canada's national microbiology laboratory,researchers took samples from 90 Manitobans who tested positive for COVID-19 in the spring wave. The researchers were unable to grow live virus from samples taken from people more than eight days after they started showing symptoms, and that took more than 24 cycles to detect.

"We were able to grow the virus at higher than 25 when they were earlier in their disease course, and that's a good representation of someone who has a low viral load early in disease, and we're just catching him or her very early," says Dr. Guillaume Poliquin, acting head of the national microbiology lab.

A recent investigation by the New York Times found that in Massachusetts and New York, more than half of infections identified by PCR testing had cycle threshold values in the mid-to-upper 30s, indicating low viral counts. "Although such low counts could imply either an early- or a late-stage infection, the long duration of the RNA-positive tail suggests that most infected people are being identified after the infectious period has passed," Mina and colleagues write this week in the New England Journal of Medicine. (People usually have a higher amount of virus in their bodies at the beginning of an infection, and it tails off).

"Crucially for the economy, it also means that thousands of people are being sent into 10-day quarantines after positive RNA tests despite having already passed the transmissible stage of infection," they write.

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According to Public Health Ontario data provided to the National Post, of 866 positive tests from Sept. 1

According to Public Health Ontario data provided to the National Post, of 300 positive tests from Sept. 1 to Sept. 28, 65 per cent required 30 or fewer cycles to detect viral genes in the sample, while 35 per cent required 30 to 40 cycles. Roughly 16 per cent needed 35 to 40. The data doesn't account for all positive tests, and only involves tests conducted by Public Health Ontario.

"Please note that there is no evidence to date to conclusively conclude that all people with COVID-19 PCR results associated with CT values of greater than 35 are non-infectious," the agency says.

Still, people are very much interested in cycle threshold values, and whether or not testing centres should put them out with test results, says Dr. Jared Bullard, an associate director at Cadham Provincial Laboratories in Winnipeg, where scientists are conducting COVID tests.

But it can depend on the test — different brands have different cycle thresholds — and the sample. Some swabbers are rather aggressive — "they get right to the back of the throat and they get a whole bunch of material to start with," Bullard said. That means fewer cycles to pick it up. Others just get inside the nose, and not really back to where they need to be.

"Is it accurate to say that if you have somebody who has a CT value higher than 25 that they are less likely to be infectious? Yeah, that is accurate," Bullard says. It's also possible they *could* be infectious, though the probability decreases the higher the numbers of cycles you go.

Dr. Jared Bullard, associate medical director of Cadham Provincial Laboratory in Winnipeg. PHOTO BY RENEE SIMCOE

Any virus that's being picked up beyond 25 cycles is probably left over genetic material from dead virus, Bullard says. "But that doesn't mean it's a false positive, or that it's not important to find people, still."

Regardless of the number of cycles, RT-PCR has a 99.8 per cent specificity, meaning it is hugely unlikely to show a false positive, or tag someone without the virus as having the virus.

"These people may have had the disease for two weeks or more, in which case, well, are we overcalling it? No, because they still were a case — we still have to track down all of their contacts from when they earlier had the disease," Bullard says.

It's also possible that, if it takes 30 or more cycles to detect virus that the person is in day one or two of the infection. Give them another two or three days "and they're actually going to be highly infectious," Bullard says.

There is no controversy when testing people with symptoms of COVID. And, when faced with a global disaster, it's important every rock is uncovered, says Allen, of Public Health Ontario. The COVID virus can be hard to grow, so lab cultures may not be a great proxy for infectiousness in humans.

"If there is a signal of genetic material of the virus, we can't ignore that," Allen says. The majority of positive cases are detected after very reasonably low cycles, she says.

I think a lot of the discussion is, do we need a test that is so sensitive

But borderline cases do happen, and there's debate over whether COVID tests should come back with the cycle threshold value, instead of simply negative, or positive. Allen's network of labs has begun to report a cycle threshold above 35 as "low level positivity."

It won't change the public health response. There would be no recommendation that those people *shouldn't* isolate, "unless, let's say, they go back and find out their symptoms started three weeks ago," Allen says. According to current guidelines people no longer have to isolate if at least 10 days have passed since the start of symptoms.

Allen agrees with Harvard's Mina that we need more blunt instruments like antigen tests that work like pregnancy tests — tests that are cheaper, allow people to test multiple times a week and with fast turnaround times, to capture people when they're more likely to be infectious.

In Ontario, fewer than 50 per cent of PCR tests results are being delivered within two days. Does that worry Allen? “Absolutely, absolutely.” The provincial COVID-19 testing network led by Ontario Health received more than 47,000 tests Wednesday alone. “The volumes are much higher than what we currently have capacity for, but we are seriously building. This is basically, all hands on deck.”

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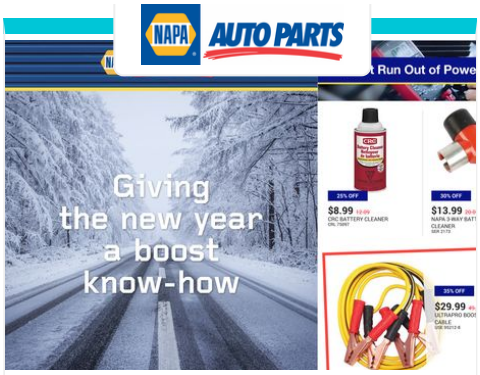

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