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Has COVID-19 Testing Made the Problem Worse? Confusion Regarding "The True Health Impacts"

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Concerns about the virus SARS-COV-2 that causes the disease called COVID-19 have centered around reported mortality rates. However, errors in reporting those rates have led to confusion regarding the true health impacts. Because estimated rates are dependent on the test used to identify infected patients, understanding that test and its history could lead to much needed clarity.

Errors in reported mortality rates have come from mistakes in calculation. An example has been equating the measured case fatality rate (deaths divided by patients actively infected) with the actual mortality rate (deaths divided by patients who were ever infected). The latter number is unknown and will not be known until antibody titers can be performed to see who has previously been infected. But that actual mortality rate is expected to be much lower, perhaps around 0.3% as estimated by an epidemiologist from Stanford University.

Another common error has been attributing the deaths of all infected people to COVID-19, regardless of other pre-existing illnesses. This error has been magnified by governments mandating that all deaths of presumptive patients be listed as death from COVID-19, even if the patient was never tested for SARS-COV-2 at all.

The mortality rate errors would be further worsened if there were errors in testing for presence of the virus. What is becoming increasingly clear is that there have been serious questions regarding the reliability of that testing.

The test in question uses a technique called reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) to identify the presence of RNA from SARS-COV-2. Testing follows different protocols in different countries and the first problem was seen in China, the reported origin of the virus.

The Chinese Mystery

A scientific study was performed in China that targeted subjects who had been in close contact with SARS-COV-2 infected patients. The results were peer-reviewed and published in the *Chinese Journal of Epidemiology* on March 5th, 2020. The data-driven conclusion of the study was that "nearly half or even more" of patients testing positive for SARS-COV-2 did not actually have the virus. In other words, half of the results were false positives.

For perspective, this study was peer-reviewed and published in a Chinese state journal a month after COVID-19 was said to have surpassed the 2003 SARS epidemic and just as the World Health Organization (WHO) declared the outbreak to be a pandemic. This was a full month after China had ordered a lockdown affecting over 36 million people.

Mysteriously, this peer-reviewed study was withdrawn a few days after publication and is no longer available for review. In response, one investigative team asked a Chinese graduate student to contact the lead author of the study, Dr. GH Zhuang, for explanation. Dr. Zhuang responded by email but did not cite a reason for withdrawal of the paper, only saying that it was "a sensitive matter." Others then made the false assumption that the author had identified a mistake in the science despite the fact that no such mistake was ever identified.

As reported by the investigative team that contacted Dr, Zhuang,

> "Without access to the paper, nobody can assess the value of the work or determine whether it suffers from a scientific flaw. It's also unknown if the paper was retracted for political reasons."

To understand the concept of a false positive one should realize that analytical test methods need to be balanced with respect to quality considerations like sensitivity and specificity. If a test is not sensitive enough, the analyte of interest will not be found when it is there, giving a false negative. If a test is not specific enough, something else in the test sample will be identified as being the target analyte when it is not, giving a false positive.

In this case, a false positive could mean that the test is reacting to another virus or genetic source. Alternatively, the test could be detecting the presence of SARS-COV-2 residues after a previously infected individual is no longer sick. Lastly, even very small amounts of contamination in the laboratory can cause a false positive. No matter the cause, false positives mean higher reported mortality rates, more confusion, more fear, and more bad decisions.

The RT-qPCR test for SARS-COV-2 is being used as a qualitative test, despite the technique name including the word quantitative. This means that the actual amount of virus in a sample is not considered important, only the presence of even a small amount of virus. This concern would be lessened if the actual test results showing levels of virus detected were available. Unfortunately, all the public sees are numbers of positive or negative determinations.

WHO Guidance and the Test

The World Health Organization (WHO) originally based testing on a kit developed in Germany, not on the Chinese protocol. WHO has since developed general guidance for testing SARS-COV-2. This guidance requires some understanding of terminology so it's helpful to understand the virus and the principle of testing.

RT-qPCR involves multiple steps. The sample is first lysed (i.e. the cells are cut) to release any viral material. Then the target RNA is converted into complementary DNA (cDNA) using an enzyme called reverse transcriptase. This is sometimes called the "extraction" step. After this, the cDNA is used as a template for amplification using qPCR, allowing the original quantity of target RNA to be determined.

The amplification is not done on the entire cDNA sequence but on segments that are expected to be representative of the specific genome of interest and, correspondingly, not representative of other genetic materials that could be present. Segments of the SARS-COV-2 genetic code that are usually targeted correspond to sections of the original RNA named ORF1a, ORF1ab, S, M, E, and N.

Synthetic primers and fluorescent probes are identified to match up with the target genetic segments to facilitate amplification and detection. The primers are small nucleotide sequences that bind to the target segments of the cDNA genetic sequence. The primers used are critical and issues with primer design can lead to variation in results.

As described in an article in *The Scientist*, the WHO-recommended primers first target the E gene of SARS-COV-2. The E gene is considered highly divergent and therefore more specific to the different coronaviruses. If a lab following WHO guidance obtains a positive screening test, it will do confirmatory testing targeting other areas of the virus genome. To avoid false positives, "every positive test has been confirmed with whole genome sequencing, viral culture, or electron microscopy."

The U.S. Test

Unfortunately, the U.S. decided to follow its own rules for testing of SARS-COV-2. In fact, WHO and CDC never discussed the U.S. using the same test as being done internationally. Investigators from *The Scientist* found that it was "not clear why the CDC chose to develop a different assay to that selected by the WHO and taken up by other countries. The CDC declined to respond to questions."

The CDC was criticized for its decision and problems were later found with its test kits. Although CDC has been secretive about the details, the concerns with its test appear to have included both test design issues and contamination.

CDC began manufacturing its test kit in January and shipped it on February 5th to state labs and to 30 other countries including 191 international labs. A week later, in a February 12th briefing at the CDC, problems with the test were reported. Although the statements made were unclear, it appeared that states were complaining the test was "inconclusive" and therefore CDC was going to focus on "redoing the manufacturing."

It was reported that, "the CDC added to the confusion by providing limited information to labs in the weeks that followed. There was a period of time after the tests were recalled where there was near silence. It was about two weeks." It was only after an open letter to Congress on February 28th, from more than 100 virologists and other specialists, that the CDC responded by allowing independent labs that had validated their own tests to begin testing.

The CDC test originally included three primers, all targeting one gene—the N gene of SARS-

COV-2 that encodes for the nucleocapsid. The primers were denoted N1, N2, and N3. Nucleocapsids of RNA viruses "are fairly simple structures that contain only one major structural protein…This protein is usually basic or has a basic domain."

Although the CDC test might have provided good sensitivity, it appears that it did not provide high specificity as it targeted only one basic gene of the coronavirus. CDC admitted the lack of certainty in a disclaimer noted in the method, saying, positive results "do not rule out bacterial infection or co-infection with other viruses. The agent detected may not be the definite cause of disease."

At first, due to CDC secrecy, problems with the test kit were difficult to understand. As the *Washington Post* reported, "The trouble with the CDC test arose because the third attempt at a match, known as the N3 component, produced an inconclusive result even on known samples of the coronavirus."

But that was not the whole story.

On February 28th, as the open letter to Congress was being recognized, it was reported that the N3 primer of the CDC kit was contaminated. The contamination caused the negative control within the kit, containing DNA that was unrelated to SARS-COV-2, to react as if it was a positive hit for SARS-COV-2. In other words, the kits were generating false positives for negative controls.

How much contamination was present was not clear because, again, the actual test results giving amounts of virus found are not available to the public. And CDC has not been open with communications about the problems found. Oddly enough, in April, test kits in the UK were also found to be "contaminated with COVID-19."

What did CDC do to correct the problems with the kit? Instead of re-manufacturing the N3 primer as originally planned, on March 15th the CDC simply told everyone who had the kit to remove the N3 primer and use the kits without it. Additionally, CDC changed its method requirements to eliminate the need to confirm positive results. This made the test kit that was based on detection of only one basic gene in SARS-COV-2 even less specific and told users that results didn't need to be confirmed. These changes made the test less reliable in terms of identifying SARS-COV-2 and therefore made any subsequent estimates of mortality rates less reliable as well.

Summary

The history of testing for SARS-COV-2 infection has involved problems that have led to delays in testing and reporting of rates of infection than are falsely higher than actual. Complicating these issues are government mandates for medical professionals to list COVID-19 as cause of death for patients who have inconclusive causes of death and, in some cases, were never tested for SARS-COV-2 at all.

Understanding problems with the test performed for identification of infected patients can lead to much needed clarity and less panic. There are many questions that still need answers. For example: Are reported rates for other diseases like influenza dropping in proportion to the rise in reported infection by SARS-COV-2? What were the details of the Chinese study that was mysteriously retracted? What has investigation into the CDC kit contamination revealed? What other countries have based their mortality figures on test kits

that provided unreliable results?

Citizens can help by calling on authorities and test facilities to publicly share the details of testing including the actual results of the RT-qPCR tests showing levels of virus present. In addition to information sharing, an international investigation into the problems seen with testing, starting with Chinese results and U.S. test kits, should be conducted. Such an investigation could lead to preventing the reporting of false positives and the ensuing panic and bad decision making that come from artificially high estimated mortality rates.

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