January 25, 2021

TO: Honorable Board of Supervisors

FROM: Nancy Williams, MD, MPH
El Dorado County Public Health Officer

SUBJECT: COVID TESTING — CYCLE THRESHOLD VALUES

In recent Board of Supervisors meetings, during discussions of the effects of the coronavirus pandemic and the County's response to it, members of the public have called in with questions or submitted comments about the "amplification cycles" or "cycle thresholds" associated with polymerase chain reaction (PCR) testing for the virus SARS-CoV-2. Both of these terms relate to the detection of the virus in specimen material. But before examining the details of PCR tests specifically, it is important to review why we perform this testing in the first place.

Although most COVID cases are minor, we of course want to know who is sick with COVID disease so those individuals can receive the appropriate treatment as soon as possible. And we must take actions as soon as we learn about people who test positive to limit additional infection transmission by them or by those whom they may already have infected. If we were only to track the more serious outcomes of infection (hospitalizations, severe illness, or deaths), we would be late in detecting trends and would miss important opportunities to prevent them. Also critical is that testing—along with tracking results and counting cases—is the earliest and easiest way to:

- Identify locations, populations, or other characteristics associated with infection and its spread
- Enable better, targeted interventions to prevent illness in the entire community
- Help determine when to implement which interventions
- Determine whether the interventions are having an effect

Some people have wondered if case counts continue to matter even during a surge such as we are experiencing now, and the answer is yes. Aggregate numbers continue to be useful in characterizing the pandemic's broad effects on our County. They continue to inform our approaches to intervention measures, and to what extent those measures have or haven't been effective, as well as how they should be applied to suppress the surge. Continuing to track case counts will help us identify when we've turned the corner.

We know that case counts and rates also matter because they determine, in part, the County's placement in the State's Blueprint Tiers system and whether Regional Stay-at-Home orders are applied.

What is a Cycle Threshold?

The most important coronavirus tests are called polyamerase chain reaction (PCR) tests. They determine with high certainty whether the person tested is infected with the virus. In the laboratory, several steps occur to turn a sample into a result that is useful for both treatment of sick patients and the collection of pertinent data:

- A specimen collected from a patient by swabbing the nose or collecting saliva is transferred to a machine where it is amplified, or grown, in a process that is repeated multiple times. This is what is meant by "amplification cycle."
- Each amplification cycle increases the amount of virus by some amount.
- If virus is present in the specimen, with enough repetition of the amplification cycle it will eventually be detectible by the testing equipment.. The number of cycles required before that detection occurs determines whether the specimen is deemed to be "positive" or "negative".

It is important to note that each lab is responsible for developing its own process for amplification and detection of virus, including setting its own 'threshold' number of cycles below which it is confident that the person tested is truly infected. The more was present in the specimen, the fewer cycles it takes for the virus to be detectible. The more virus present, the more likely the person is, on average, to be ill and to transmit it to other people. If people have less virus, does that mean they and the people around them will be safe from COVID? Not necessarily. That will be explained below, but first…

Are we overcounting?

A question we hear is whether cycle thresholds ("Ct" for short) are being set too high by labs and therefore detecting virus particles at levels so low as to be inconsequential. The presumption by some people that the answer to this question is 'yes' leads to the implication that we are distorting case counts artificially high.

But very simply, this is not the case. Amplifying test material will only produce a positive result if the virus was present in it in the first place.

Our Public Health Department (following California Department of Public Health guidelines) counts each person from whom a test specimen results in what the laboratory that performed the test determined to be a positive PCR test as having a case of COVID-19. For COVID-19 PCR tests, labs only report qualitative results ("positive", "negative", or sometimes "indeterminate"), not quantitative results.

Counting every positive result as a case is important because ample evidence has shown that asymptomatic, presymptomatic, and mildly symptomatic people carrying the virus can transmit illness to others, and interventions (isolation and quarantine) are effective in reducing further transmission. Public Health's role is to prevent additional people from become infected and ill, and accurate counting is a vital part of that effort.

Every lab's assay is different

El Dorado County has received qualitative results from over 100 labs. And the fine-tuning of laboratory processes, including setting maximum cycle threshold values, is done through collaboration between labs and the providers caring for patients who can clinically correlate patient's conditions with test results. (Public Health cannot do this because we do not see patients.)

It is important to note that labs have been instructed by the Association of Public Health Laboratories not to include Ct values with their lab results because of the difficulty in interpreting them. The APHL emphasizes that the tests are qualitative in nature.

The Director of Clinical Virology at Mayo Clinic in Rochester, Minn., expressed concerns about the reporting of Ct values on positive lab results: "Unfortunately, PCR Ct values may vary significantly between assays, even those using the same gene target. During the COVID-19 pandemic, it has become common for clinical laboratories to perform multiple real-time PCR assays to detect SARS-CoV-2. Therefore, including the Ct value on all positive results may be confusing and misleading to ordering providers." He recommended labs only report Ct values on a case-by-case basis so the physicians wishing more information about laboratory results can also have discussions with the laboratories about the limitations associated with Ct values while interpreting results.

Are case counts perfect? No. Do they need to be? No.

Given the scope of the pandemic and the challenges presented in wide-scale testing, both undercounts and overcounts are likely to occur. So tracking reported case counts, even if less than perfectly, continues to provide useful information about trends.

From the patient perspective, detection of the virus represents only a point-in-time snapshot that indicates infection at that time. The person tested could have mild or severe symptoms, or none at all, and the person's viral load could be either increasing or decreasing. Daily testing would be necessary to learn in which direction viral load was changing.

From the public health standpoint, it would be risky to assume that people with no or low symptoms are not infective to others. They could become more infectious to others after the test was performed. An abundance of evidence has shown that both presymptomatic and asymptomatic transmission occurs. Therefore, all people with positive results must isolate and their close contacts should quarantine.

More about Cycle Threshold Values

There is little if any dispute that low Ct values (that produce positive test results) are more likely to be associated with severe disease than high Ct values. However, there does not appear to be a specific number of cycles above which one can say that the viral load is not relevant. Based on multiple studies, however, higher cycle thresholds can also be associated with serious illness, and this is a reason for not using cycle thresholds to assess the validity of case counts.

The College of American Pathologists Microbiology Committee expressed that Ct values from viral RNA can vary depending on method of specimen collection, specimen source, transport, and the time from infection to collection to analysis, and that not all diagnostic assays or

platforms can produce a Ct value. Finally, no standard exists to validate quantitative assays that produce comparable results from labs and manufacturers. In other words, there is no apples-to-apples way to compare the various tests. And no quantitative COVID-19 test yet has an emergency use authorization from the FDA.

Survival rates and causes of death

Two additional COVID-related topics garner considerable public interest, and while they are not directly connected to cycle thresholds, they are nevertheless germane and it makes sense to address them here.

About survival rates, a quote we sometimes hear repeated is, “99.98% of people survive COVID-19.” The statement has sometimes been attributed to the U.S. Centers for Disease Control (CDC), but that assertion is false. A CDC spokesperson said, "Survival analysis is highly complex. CDC does not have the data to calculate survivability for COVID-19. Unclear as to where social media users are getting this information."

Johns Hopkins University puts the observed case fatality ratio—calculated as the number of known deaths divided by the number of confirmed cases—at about 1.7% for the U.S. CDC also estimates the percentage as 1.7%, i.e., 98.3% survival based on that formula.

For those not inclined not to believe Johns Hopkins or CDC statistics, there are other ways to show clearly that the 99.98% survival rate claim is incorrect. Even if, to hypothesize to an extreme, *everyone* in the U.S. were to be infected with COVID (and in reality we know only a fraction of people have been):

> US population (approx. 331,000,000) X 0.02% = 66,200. To date, however, there have been more than 400,000 deaths in the US attributed to COVID-19, which again disproves the 99.98% survival claim.

Finally, I will address the claim that only a few people with COVID-19 on their death certificates actually died from the virus.

This claim is untrue and has been since it was first made as a misrepresentation of data published by CDC months ago. At the time, Dr. Anthony Fauci explained, "The point that the CDC was trying to make was that a certain percentage of them had nothing else but just COVID. That does not mean that someone who has hypertension or diabetes who dies of COVID didn’t die of COVID-19 — they did."

Many chronic conditions put people at greater risk of dying from COVID. But just because someone has a chronic condition does not mean that person is about to die. Most people with chronic conditions live with them for many years. If COVID contributes to a person’s earlier than expected demise, it belongs on the death certificate and the death should be counted as a COVID death. Physicians are instructed only to indicate conditions on death certificates that caused or contributed to the deaths. Therefore, if it says “COVID” on the death certificate, it is correctly counted as a COVID death.

The bottom line is that not only are physicians trained on proper completion of death certificates, Public Health gives them a second look. Finally, the California Department of Public Health has guidelines, which El Dorado County also follows, for the recording of deaths that are based on

test results and death certificate documentation. We are confident that the counts of COVID deaths in our county are no less than what is being reported.

I hope you find this information helpful and that it provides you with additional information in which to respond to some of the questions being raised.

Attachments:

Association of Public Health Laboratories, Ct Values: What They Are and How They Can be Used, Version 1 • November 9, 2020

List of laboratories from which El Dorado County Public Health has received PCR COVID-19 test results, though January 13, 2021

cc: Don Ashton, Chief Administrative Officer
Don Semon, Director, HHSA
Kim Dawson, Clerk of the Board
Olivia Byron-Cooper, Acting Director of Public Health