Problems with COVID-19 antibody testing – Expanded Explanation **By Daniel Van Durme, MD, MPH**

This week there was a major roll-out at both LabCorp and Quest to directly market to patients their ability to get antibody testing for COVID-19. This included "QuestDirect" where patients can order their own testing (for $119) **without** a doctor's order. Patients will be requesting and may get the testing themselves and ask for an interpretation from their physician. The following will hopefully help clinicians to help patients navigate the complexities of these tests and the results.

CORE CONCEPTS - REMINDERS

--We still do not know WHAT LEVEL of antibodies will provide protection from re-infection.
--We also do not know HOW LONG any protection will last.
--Some of these tests show CROSS REACTIVITY (or positive results) from other benign coronaviruses that cause mild upper respiratory illnesses.

Bottom line – we risk causing very real harm to our patients and the population if we simply order the test and then tell patients they are or are not immune. We need to proceed thoughtfully and communicate clearly. If a patient presents with results, we MUST learn more about their specific scenario (and pre-test likelihood or probability) before we attempt to explain and interpret the results for them.

TEST ACCURACY – KEEP READING FOR DETAILS ON HOW TO INTERPRET RESULTS

--Neither LabCorp nor Quest have been willing/able to provide information on the sensitivity and specificity of their tests. (Not available on their website and phone calls to lab managers have yielded a response of "we do not have that information".)

Exception – Quest reports using EUROIMM & Abbott tests with 98.5 – 99.4% specificity but no info on sensitivity

--According to information from Johns Hopkins, the tests that have been given Emergency Use Authorization by the FDA (NOT the same as "FDA Approval") have reported sensitivity ranging from 87.5% to 99% and specificity values that range from 95.6% to 100%.

Critical concept when considering test ordering and interpretation of results – Epidemiology can get tricky.
Tests have sensitivity (how often they show as positive in those who REALLY have the condition) and specificity (how often they show as negative in those who do NOT have the condition). When we say a test has 97% sensitivity, it means that it will "miss" 3% of those with the disease – this is called the false negative rate. Similarly, if a test has 97% specificity, it will incorrectly label 3% of the people as a having a disease (a false positive rate). HOWEVER – MOST IMPORTANTLY – when we use a test and interpret results in a given population, we do not know whether the person REALLY has the disease or condition. We simply get a positive (or negative) result and we are left trying to figure out whether to believe it as "truly positive" or "falsely positive" (or negative). AND we must interpret results differently based on the characteristics (or pre-test probability) of the populations being tested.

For example, a rapid strep test is generally considered 90-95% sensitive and 99% specific. When testing a child with sore throat, fever, red-purulent posterior pharynx and enlarged lymph nodes – and the test is negative – we would be more likely to think the test "missed" it (or was falsely negative). If we tested an adult with only a sore throat and no other symptoms, and test was negative, we would believe it. (Epidemiologically speaking, we would say there is a lower pre-test probability for the adult and thus a higher "negative predictive value"). Or in "layman's terms" you could say there is a lower rate of false negatives in populations like the adult, than for populations like the child with multiple symptoms. Similarly, for a positive result, in populations like the child we would have a higher pre-test probability and higher positive predictive value, than for populations like the adult; or a lower rate of false positives in those kids.

Without reasonably accurate baseline numbers or prevalence of the condition, interpreting test results is virtually impossible. Here are three potential scenarios that may provide help.

COVID antibody testing

We will give tests the benefit of the doubt and say they have 98% sensitivity and 98% specificity. As a test itself, there would be 2% false positives and 2% false negatives **but we must interpret and explain to patients differently based on different scenarios**.

Scenario #1 – Testing 1000 random patients – never had significant COVID symptoms but get tested "just to see if they have antibodies (or are immune)" – estimates from a variety of sources suggest that 10% (or more) of some populations may have been infected (with many being asymptomatic).

Let's estimate that 10% of these folks (or 100 of the 1000) REALLY have antibodies. 98% sensitive → test will show positive in 98 people (and miss it in 2). 98% specific means that test is negative in 98% of the 900 WITHOUT antibodies. Negative in 882 people, but (falsely) positive in 18. This gives us a total of 116 positive tests (98+18) and only 98 are true positive. 18 of 116 (or 15.5%) are false positive. We risk telling ~16% of the people (or 1 in 6 people) that they have COVID-19 antibodies when they actually do NOT. They may think they are immune when they could actually contract and spread the disease.

CALCULATOR	COVID antibody REALLY present	COVID Antibody REALLY Absent	Total	Pos and Neg Pred Values		
Test will be Positive	98	18	116	84.5%	False Pos rate or % of all positive tests that are false positives =	15.5%
Test will be Negative	2	882	884	99.8%	False Neg rate or % of all negative tests that are false negatives =	0.2%
Totals	100	900	1,000			
Sensitivity and Specificity	98.0%	98.0%		10.0%		
	Sensitivity	Specificity		Prevalence		

In NYC they are estimating that 20% of the population there is COVID positive. In that scenario, there would be positives in 196 of the 200 with COVID and positive results in 16 of the 800 without COVID. When interpreting results, 16 of the total 212 (196+16) positive results would be falsely positive. We need to know that 7.5% (or 1 in 13) of the people who get a positive result do not have the antibodies.

Correction from earlier example.

Scenario #2 – Testing 1000 patients who actually had COVID-19 – they were tested positive. Assuming a fully functional immune system, we might expect nearly all of them to develop appropriate antibodies a few weeks after the infection. Let's estimate that 99% REALLY have antibodies. Test is 98% sensitive and 98% specific.

CALCULATOR	COVID antibody REALLY present	COVID Antibody REALLY Absent	Total	Pos and Neg Pred Values		
Test will be Positive	970	0	970	100.0%	False Pos rate or % of all positive tests that are false positives =	0.0%
Test will be Negative	20	10	30	33.1%	False Neg rate or % of all negative tests that are false negatives =	66.9%
Totals	990	10	1,000			
Sensitivity and Specificity	98.0%	98.0%		99.0%		
	Sensitivity	Specificity		Prevalence		

- Total of 30 negative test results, with 20 false negative and 10 true negative
- This 67% "false negative rate" in this specific group of previously infected people requires careful explanation to these patients. We risk telling 2/3 of these post-infected people who REALLY DO have the antibodies that they do not have them. They cannot return to work, they live in unnecessary fear, etc.

Scenario #3 – Testing 1000 patients who had some symptoms that were suspicious for possible COVID-19 but were never tested (or were tested for virus very early when viral load was low, and may have had false negative test). This is tricky and requires the most clinical judgement, but if the clinician thinks there is about a 50:50 chance they had COVID-19, then this is where the testing has its greatest utility (but still has risks).

CALCULATOR	COVID antibody REALLY present	COVID Antibody REALLY Absent	Total	Pos and Neg Pred Values		
Test will be Positive	490	10	500	98.0%	False Pos rate or % of all positive tests that are false positives =	2.0%
Test will be Negative	10	490	500	98.0%	False Neg rate or % of all negative tests that are false negatives =	2.0%
Totals	500	500	1,000			
Sensitivity and Specificity	98.0%	98.0%		50.0%		
	Sensitivity	Specificity		Prevalence		

- Only 2% of all positive results are falsely positive & only 2% of negative tests are falsely negative.
- In this scenario we might tell the patient that the test is not perfect, but it is HIGHLY likely that they really do (or do not) have the antibodies.
- They STILL need to be cautioned that we do not know how much protection that provides (if any) or for how long.

If you are comfortable with Excel spreadsheets, these numbers are easily demonstrated in a 2x2 table. Email Daniel.vandurme@med.fsu.edu and I will be happy to send the spreadsheet to you. The numbers can also be seen and adjusted with medical calculator apps such as MedCalX and EBMStatsCalc.