COVID-19 Q&A

about the body's immune response

with

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Amy Moore, PhD (GO2 Foundation for Lung Cancer) and Upal Basu Roy, PhD, MPH (LUNGevity Foundation) spoke with Nicolas Vabret, PhD, an assistant professor of Medicine, Hematology, and Oncology at the Icahn School of Medicine at Mount Sinai, who answered several questions about COVID-19 related to the body's immune response and testing for the presence of SARS-CoV-2, the coronavirus that leads to COVID-19. It is important to note that the conversation took place on May 13, as issues around the COVID-19 pandemic can change rapidly.

Notes:

1. PCR is short for "polymerase chain reaction," a laboratory method that can be used to detect fragments of genetic material (RNA) found in the SARS-CoV-2 virus.
2. The FDA recently authorized the first antigen test for rapid detection of the virus that causes COVID-19.

Below are the answers to the questions discussed in the accompanying video:

What happens when someone is infected by SARS-CoV-2, the coronavirus that leads to the disease COVID-19? What is the body's immune response?

When someone is infected by SARS-CoV-2 or any other virus, the body produces an immune response. Generally, we classify the immune response as two different waves.

The first wave consists of the innate immune response, which is specifically the ability of all of the cells of the body to detect whether they are infected by the virus. When the virus is going to penetrate the cell, there are proteins that are able to detect the presence of the virus and generate a signal that alerts the cells of the immune system that an infection is taking place, that a virus has penetrated the body.

This signal activates a second wave of immune response, which is called the adaptive immune response. It's called adaptive because it's going to be specific to the particular virus. During the adaptive immune response, other cells of the immune system are adapted and activated, and they produce weapons to fight the infection.

These weapons can be classified into two types. First, there is the production of molecules like proteins, typically antibodies, which are small proteins. These are produced by the cells from the adaptive immune response. They bind the virus to try to prevent its ability to infect new cells and to lead with the degradation, or destruction, of the virus.

The second weapon of the adaptive immune response is the production of a class of cells called T-cells, or cytotoxic T-cells, which are specifically going to kill the cells that are infected by the virus to prevent the production of new viral particles.

Can you elaborate on the timing of the innate versus the adaptive immune response?

The innate immune response is immediate. Whenever pathogens or a virus like SARS-CoV-2 go inside the body, an innate immune response is generated almost immediately—typically within hours. The adaptive immune response, because it requires the body to generate new weapons—new antibodies—takes much more time. The objective of the innate immune response is to contain the viral infection during the time it takes for the adaptive immune response to take place. Adaptive immune response, generally, is going to take between days and weeks to get to full capacity.

Patients hear the words antibody and antigen. Can you explain what the difference is between the two?

Antibodies are the molecules that recognize and bind the virus. The part of the virus that is going to be bound by the antibody is the antigen. Essentially, an antigen is a part of virus that is going to be targeted. The antigen is the viral part, and the antibody is the immune system part.

How can we find out whether a person is currently infected with the SARS-CoV-2 virus?

It's very straightforward. If you want to test whether someone is infected by the virus, you're going to look for a trace of the virus itself. Generally, we do a PCR test[1], which tries to detect the viral RNA. The RNA is a part of the virus that is going to contain all of its genetic information.

There is another test that is much less used but has been essentially approved by the FDA to look at another part of the virus, the antigen. Remember that the antigen is what is recognized by the antibody. The test looks at the presence of a piece of the viral particle. It looks directly at the protein that is produced by the virus rather than at the RNA. This test is meant to be a rapid diagnostic test.[2]

We just talked about how to determine whether somebody is actively infected with the SARS-CoV-2 virus. How can we test if somebody has previously been infected and may or may not have fully recovered?

When you want to test whether someone had been infected—and it's possible that this person recovered from the infection, so may not even have any trace of the virus itself in the body—you can look at the immune responses.

We assume that if someone was infected, at some point the body produced immune responses, and this is what we look for. Specifically, blood is drawn and we look for the presence of antibodies. This is a test for which it takes, depending on the test, a few hours or a few days to get the results.

What exactly is an antibody test? How is it done?

Blood is drawn from the patient. Serum is the liquid fraction of the blood, and that is purified. The test checks whether the antibody can be detected in that.

Can an antibody test look for actively infected patients? Or is it only used after a patient has gone through an infection?

Because of the dynamic of the immune response and the time that is required for the immune system to produce the antibody, antibodies cannot be detected in someone who just has been infected. The virus needs to

have infected the body for a certain amount of time. Depending on the test, generally what we consider to be a good time to start looking for antibodies is approximately three weeks after the onset of the symptoms because only after three weeks does a body start to produce enough antibodies to allow us to confidently test for their presence.

If you suspect that you are currently infected because you have symptoms, it's probable that the infection took place not a long time ago, so if you want to know whether you are infected, you can look for the virus itself with a PCR test.

How long does it take to get the results of the antibody test back?

There are many antibody tests on the market now, and they don't all work the same way. Depending on the test, some are going to give you a result very quickly, and some will need more blood processing and more sample processing; those could take a few days.

As states start to reopen, people going out want to know, "Am I immune to the virus? Am I somehow protected?" What do the antibody test results mean, and how accurate are they?

There are two things that determine the accuracy of an antibody test: the rate of false positives and the rate of false negatives.

A false positive is if the test says that you have the antibody, but you don't. This could be problematic because we don't want to tell someone, "Okay, you had the virus because we have detected the antibody," if it was not the case. A false negative is if the test failed to detect the presence of the antibody in your system when it is actually there.

There are many antibody tests on the market now, and they all have various false positive and false negative rates, and this is something that you need to take into account when you need to pick which antibody test you're going to take.

How is it determined what these rates are?

For example, there are banks of blood samples from patients that were collected last year, when there was no COVID-19. All of these samples should be negative when tested for the presence of antibodies. They may not be, and a false positive rate can then be determined. Tests are also evaluated against each other using the same sample, and we can see which tests are better.

Does the timing of the test matter? Does it matter when in the course of infection and recovery a patient goes and gets an antibody test?

Absolutely. What the physicians advise today is to wait at least three weeks after the onset of your symptoms because, sooner than that, the test might not detect the production of antibodies even if your body is in the process of producing them. You really want to make sure that you are at the peak of the ability of your immune system to produce antibodies to reduce the chances of having false negative results.

We know that SARS-CoV-2 belongs to a family of coronaviruses that includes four kinds of naturally circulating ones that cause more or less a common cold, as well as the original SARS and MERS. Is it possible that a prior infection with one of those other coronaviruses could give you a positive test on this antibody test?

We don't have a definite answer. The jury is still out, and it is probably very dependent on the kind of antibody test. There are some that are more specific in this sense than others.

How should we interpret these tests?

Producing antibodies is probably a good sign saying that you have developed some protection against possible reinfections, but we don't know yet what level of antibodies you need. We are not completely convinced that antibodies will be enough to ensure that you will be protected against reinfections. The pandemic is very recent, so we have only a few weeks to a few months of analysis and follow-up of patients to generate data on. Even if we trust positive test results, we cannot yet conclude that it means that you are immune to reinfections by SARS-CoV-2.

If a patient has antibodies, are they no longer infectious?

This is also a question for which we cannot have a definite answer yet. We do know that the large majority of people who recover from infection produce antibodies. However, a few recent studies from Mount Sinai Hospital show that even if you have antibodies and have recovered from the infection, some viral parts are still detectable in your body. We don't know yet if this virus is alive, if it's complete, and if it's able to infect a new person. We know that we can detect it, but we don't know if it's an infectious virus, and if there is a risk of someone who has recovered and has antibodies to transmit the virus. Unfortunately, we cannot give any advice except to be extremely cautious.

What about the severity of cases? Does the level of antibody response differ between mild and severe cases?

The few studies that we have are not completely in accord with each other on this. It seems, though, that the level of antibodies that you generate, what we call the antibody titers, is not really correlated to either the severity of infections or the length of time that the symptoms that you have persist.

People are working on it, trying to understand exactly what determines whether you're going to induce a very strong antibody response or a low antibody response.

Some tests show IgM and IgG. Some tests only show IgG. Can you tell us a little bit about what they are, and what IgA is?

IgG, IgM, and IgA are different classes of antibodies. Without going into details, they all have different functions, a different length of time they end up staying in the body, and a different part of the body in which they're going to circulate to survey any infection. They are just different classes of antibody, and we like to test the different classes to make sure that what we detect is actually an antibody response.

Is a test that looks at both igG and igM better than one that only looks at IgG?

At this point, it really depends on the test and the accuracy of each test, but, as a rule of thumb, testing two different kind of antibody is probably better than only one.

How long do the antibodies last?

At this point, we don't know because the pandemic just started at the beginning of the year. We do have some clues, though, because we can get some information from other coronaviruses.

As already mentioned, there are other coronaviruses that infect humans, cause a common cold, and circulate in the population. We have determined how long the antibodies stay in these infections. We also have data on other coronaviruses, the SARS and the MERS coronaviruses, that look more like SARS-CoV-2. The SARS coronavirus caused an outbreak in 2003, while the MERS coronavirus caused an outbreak in 2012. Both of these caused pathology more similar to that caused by SARS-CoV-2 than to the common cold viruses. We know for them approximately how long the antibody response was. For MERS, for example, we knew that the antibodies lasted at least two to three years.

However, this is absolutely not insurance that antibodies against SARS-CoV-2 are going to behave similarly. It's merely some kind of indication that provides a basis for researchers to study this COVID-19 disease and to compare. We can hope that we will see an antibody response in the data of COVID-19 that's going to last more than one year.

If you had to predict, do you think a one-time vaccination will be sufficient? Or do you foresee that we may be in a situation where we have to get annual or every-other-year vaccinations?

What I like to say is that when you design a vaccine, you aim at generating an immune response that is going to be better than the one that is induced by natural infection. Ideally, you would like to design a vaccine that is going to induce immunity for life. Some vaccines do. We only have one vaccine injection for some diseases when we are kids, for example, and after that we are immune for life.

There is one thing that is a source of hope in the case of SARS-CoV-2. That is, if you compare SARS-CoV-2 to other RNA viruses like HIV, or polio, or even influenza, SARS-CoV-2 and all the coronaviruses have this particularity that they are relatively stable.

We know that polioviruses, for example, mutate a lot. With HIV, it's one of the reasons why we are struggling so much to produce a vaccine. With influenza, every year we are infected by a different strain of influenza, and so we know that the vaccine that we have can only protect us for the year.

In the case of SARS-CoV-2, data so far show that it's relatively stable, and that we can hope that a vaccine would be able to protect for the moment against all the isolates of SARS-CoV-2 that circulate in the world because they are relatively similar to each other.

However, this is speculation. We need to look and survey the different vaccine candidates that are being produced right now to see the kind of immune responses that they generate. Are the immune responses going to be protective? If they are protective, how long are the protections going to last? All are questions that researchers are working hard on right now, and hopefully we will have an answer soon.

We know that the elderly population has been particularly hard hit by COVID-19. We also know that the immune system is not as robust in elderly patients. Can you speak about that and the added challenge of how we address that when we have dampening of the immune response in older patients?

In terms of vaccination, it's a very important point because ideally you want to have vaccines that will work particularly well in an elderly population; they are the ones who are at higher risk. It is the population that you want to protect first.

As you said, the aging of the immune system in older people makes it more challenging to elicit good, strong immune responses. This is one of the challenges of the vaccination, for sure.

In terms of linking the aging of the immune system to the higher pathogenicity of the virus, at this point it's really speculation. It's very tempting to consider that one of the reasons why older people have higher severity of disease is because their immune system is not as efficient as that of younger people. This is one of the main targets of immune research right now. However, for the moment, this is nothing more than a theory.

How should people get tested?

The first question is, “Should I get tested?” I think that so far, since we don't really know the link between the production of antibodies and protection, we are not really completely sure that production of antibodies means protection against reinfections. There is a real question whether it is worth it to get tested if you have the result of a test and you don't know what to do with it. Today we can say, "Yes, probably. Having antibodies is probably a good sign of a small level of protection." However, it's in no way a guarantee that you are protected. Once again, I really want to emphasize that. People need to be aware of that before getting tested.

The second question is, “I want to get tested, but there are so many tests available. I don't know which one to take, I don't know how to compare them, and I don't understand exactly what the results mean.” The best thing I would say here is that if you have access to your physician, ask your questions. The physician can order a test for you, and all of this will be explained to you: all the terms, the accuracy of the test, and what you can conclude from it. I know that in New York, you can just ask for a test and pay for it out of pocket. However, if you really want to get the most out of the test, it's probably better to go through your physician, who will order a test they can trust and be able to advise you on the results you get. In some places, you can also request the test through a testing laboratory.

You mentioned New York. Do you think that it's more sensible to get tested in New York City, where you know the infection is all around you, than somewhere in the Midwest, say, where there are fewer cases of COVID-19?

I think it really depends on the kind of test that you have access to in New York and in the Midwest. If it's the same test, I don't see why you should get tested more in New York than in the Midwest. At this point, the pandemic is really everywhere, even though there are many more cases in New York, so this would not be a reason why you should be less careful in the Midwest.