HealthManagement.org
The Journal
LEADERSHIP • CROSS-COLLABORATION • WINNING PRACTICES
VOLUME 20 • ISSUE 5 • 2020 • € 22
ISSN = 1377-7629

Cover Story:

COVID-19 Superheroes

COVID-19 Antibody Testing – Why it Matters and Factors to Consider

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As we move into the next phase of the COVID-19 pandemic, there will be a need to test a broad strata of population, much more than what molecular tests can handle. The solution lies with serological tests.

As the world continues the fight against COVID-19, healthcare executives are in an uncomfortable position – having to make critical decisions without answers they would typically obtain to guide their reasoning. There is a lot to be learned about SARS-CoV-2, its transmission rates and the immune response it generates, among other open questions, with a lot of attention in the diagnostic industry and the various solutions it provides.[1-2]

Earlier this year the primary focus was diagnosing the disease, and molecular tests which directly detect viral nucleic material are ideal for this clinical use. But these tests have complex sample handling requirements, high cost and limited availability, all of which caused testing deficiencies even when deployed exclusively for targeted populations, ie symptomatic individuals and close contacts.[3]

As we move to the next phases of the pandemic, new questions arise which will require testing even broader strata of the population – much more than what molecular tests can handle. The solution lies with serological tests which detect the antibodies against the virus.[1]

Public health and policy decisions need to be made based on the dynamics of the pandemic, such as extent of past and current transmission in specific geographical regions, strategies to target future vaccination programmes, and estimations of population-level immunity.

Targeted monitoring is also needed for populations with high infection risk or in whom infection has wider consequences, such as healthcare workers or households of case-patients. And finally, employers and private individuals may rely on antibody tests to assess how to best resume their normal activities.

Among all uncertainties in this pandemic, one thing is certain – antibody tests will be a key factor impacting our lives in the near future.

In this scenario, there are two critical questions we need to address:

Do antibodies to SARS-CoV-2 provide immunity against COVID-19?

Most likely yes, but not all detectable antibodies confer immunity. While data to fully establish immunity as scientifically documented evidence is not yet available, there are several reasons and indirect evidence pointing in this direction, such as the history of other viral diseases including closely related coronaviruses,[4-8] the clinical improvement in patients who receive plasma from previously infected individuals,[9-10] plus animal and in-vitro studies performed during vaccine and therapeutic antibody development.[11-15] These would indicate that individuals who are exposed to SARS-CoV-2 and develop antibodies with neutralising activity will enjoy at least some degree of protection.

Protection by neutralising antibodies is mainly mediated through blocking the interaction between virus and host cells, inhibiting viral entry and progression of disease. Therefore, most neutralising antibodies are against viral surface proteins.[16] The spike protein (S), which protrudes from the viral surface, connects with receptors on the human cell. Antibodies expressing neutralising activity are predominantly against S protein.[17-18]

Several recent publications highlight the impact of different antibodies detected by serological assays. Many individuals exposed to SARS-CoV-2 did not develop neutralising antibodies, with some studies showing over 50% of asymptomatic individuals had no detectable neutralising antibodies.[19-21] Simply knowing that you were exposed does not guarantee protection. Studies have also shown significant proportions of individuals testing positive for antibodies against nuclear protein (N) but not having detectable

anti-S antibodies potentially capable of neutralising viral activity.[19] These individuals may have a false sense of security based on the positive test for anti-N antibodies. Even more concerning, a study by the New York Blood Center showed that 14% of convalescent plasma donors only had antibodies against N, raising questions if plasma from these individuals should be used to treat severely ill COVID-19 patients.[21] Finally, a clinical study in hospitalised patients showed an association between lower disease severity and higher titers of anti-S antibodies, indicating potential benefit in improving clinical course. The same study showed the opposite pattern for N antibodies, which were present in higher titers in more severe, ICU patients.[22]

To truly understand antibody-mediated protection to COVID-19, we need to measure the activities of neutralising antibodies. There are biological tests which directly measure neutralising activity by mimicking viral infection in cultured cells. They are time-consuming, labour-intensive, low throughput, and require viral particles and live cells. These operational complexities preclude them from scaled up routine testing in large populations.[23] All these challenges highlight the need for easier to use, surrogate markers of viral neutralisation, and studies have shown that levels of anti-S or anti-S1 antibodies have the best correlation to neutralising titers.[21]

Are serological tests available today reliable enough to help assess COVID-19 immunity?

Yes, but not all serological tests. A recent study by a group at New York Blood Center evaluated six different serological tests for their correlation with neutralisation. The tests evaluated represent a variety of technology platforms, both commercially available rapid tests and laboratory-based technologies, with different antibody targets. The study showed that laboratory assays had better correlation with neutralising titers than rapid tests, and assays targeting the S1 protein exhibited better correlation than assays targeting the N protein. The authors concluded that serological tests showing strong correlation with neutralising titers might serve to predict antiviral activity against SARS-CoV-2.[21]

In addition to correlation with neutralising titers, the performance of these tests, measured by their diagnostic sensitivity and specificity, is also important. All healthcare professionals who rely on serological tests for critical decisions need to be educated about the exact performance of the assay they plan to use.[24-25] If serological tests are used to help assess protection via correlation to neutralising activity, the biggest risk, for individuals and society alike, is the reporting of a false positive result which conveys a false sense of security. For this reason, while sensitivity is still very important, we need to pay special attention to specificity – the percentage of true negative results in individuals who do not have antibodies.

Unfortunately, this critical marker of test performance varies significantly among different assays, from specificity levels as low as 90%, to outstanding specificity levels with assays offering 100% specificity.[25] It is critical to note that even apparently small differences in specificity (ie 100% to 98%) actually represent a major difference in the clinical value of the test in real life, due to the low prevalence of SARS-CoV-2 exposure in the general population. Even in Spain, one of the nation's hardest hit by the pandemic, only about 5% of the population has been exposed to the virus.[26] It is therefore reasonable to expect that current global levels of exposure are significantly lower. If we assume a global population currently with 2% prevalence of exposure and we test 100 individuals with an assay having only 98% specificity (thus an assay which reports 2% false positives), we would end up with 2 out of 4 positive tests reported (50%) being a false positive. This rate of erroneous results can be catastrophic as individuals may consider themselves protected when they were not.

In conclusion, we are learning more every day about COVID-19 and many important open questions remain.[27] Still, healthcare executives must make decisions now, without all the answers they would usually seek for their reasoning. But a few important factors are already well-established and can guide these decisions in a time of uncertainty, including:

- Public health policy decisions will require antibody testing for seroepidemiological studies.
- Not all previously infected individuals develop detectable neutralising antibodies.
- Antibodies which provide neutralising activity are predominantly targeting the Spike protein.
- The performance of antibody tests in the market vary tremendously, and the selection of tests with the highest specificity (close to or at 100%) is critical for adequate management decisions to be made. ■

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