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Covid-19 Antibody Tests **for Healthcare Professionals**

Introduction

SARS-CoV-2 antibody (serological) tests are available through Public Health laboratories and commercially in Canada.

Physicians and scientists developed this reference document for healthcare professionals in Canada. It summarizes current knowledge about Covid-19 serological tests, the significant limitations of these tests, and the narrow indications for their use.

We used information from the World Health Organization, the U.S. Centers for Disease Control and Prevention, the Public Health Agency of Canada, Public Health Ontario, and scientific journals.

What do we know about the immune system response to SARS-CoV-2 infection?

SARS-CoV-2 infection elicits a multifaceted and variable immune system response, involving antibodies from B cells, CD4 T helper cells, and CD8 killer T cells. Antibodies to viral antigens, including components of the SARS-CoV-2 spike (S) protein and nucleocapsid (N), are produced.

Immunoglobulin (Ig) G, IgM, and IgA antibodies against S and its subunits can generally be detected within 1 to 3 weeks of infection. IgM and IgA antibodies decline more rapidly after infection than IgG antibodies. Notably, between 5% and 10% of people infected with SARS-CoV-2 do not develop IgG antibodies. After acute infection, memory B and T cells provide protection against reinfection for at least 8 months. Any link between detected antibodies, antibody levels, and virus neutralization isn't known. In other words, it is not known whether antibody presence or specific antibody levels correspond to protection against re-infection.

What do we know about the immune system response to Covid-19 vaccination?

The S protein is the antigen responsible for triggering the immune system response in a person who receives an mRNA or viral vector Covid-19 vaccine. As with SARS-CoV-2 infection, immune system responses to vaccination are multifaceted and variable. Generally, helper T cells stimulate B cells to make binding and neutralizing antibodies.

What SARS-CoV-2 antibody tests are available?

The majority of currently available serological tests are antibody-binding tests. Test antigens bind and detect antibodies present in a collected specimen. Most commonly, the antigens used are parts of the SARS-CoV-2 S protein or N protein. Antibody tests have been developed that measure IgA, IgM, IgG, and total antibody levels. Antibody levels can be reported in qualitative (reactive, non-reactive) or quantitative (antibody concentration) terms.

Tests vary in their characteristics, with sensitivities and specificities ranging from 0% to 100%. The ability of antibody binding tests to detect antibodies depends on the antigens used. Test timing relative to infection influences results, as these tests perform poorly when collected before antibodies develop, and as antibody levels wane. Commercial and public laboratories may test for different antibodies, and the tests used may perform differently. In general, point-of-care tests are less sensitive than laboratory tests.

Neutralizing antibody tests are investigational at this time.

What are the limitations of SARS-CoV-2 antibody tests?

- There is a lack of test standardization.
- The role of antibodies in conferring immunity to SARS-CoV-2 infection is unclear, so the utility of these tests in confirming immunity is unknown. These tests should not be used to guide individual-level decisions about risk of infection or the use of mitigation measures.
- It is unclear how durable antibody responses are to SARS-CoV-2 infection, so the utility of these tests in confirming prior infection is unknown.
- The sensitivity of antibody testing in older persons and immunocompromised persons is not known, so their role in these populations is unknown.
- Serological tests have not been validated as a means of confirming immune status after vaccination. This is in contrast to antibody tests for other viral illnesses, like measles or varicella, for which antibody levels corresponding with protective immunity have been established.

When should SARS-CoV-2 antibody tests be considered?

Antibody tests have a very limited role in routine clinical care.

Antibody testing can be considered for patients suspected of having multisystem inflammatory syndrome (MIS-C, or MIS-A) who did not have a SARS-CoV-2 polymerase chain reaction (PCR) diagnostic test, or whose SARS-CoV-2 PCR test result was negative, indeterminate, or inconclusive.

At the population level, these tests may have utility in research and in informing Public Health responses.

Can SARS-CoV-2 antibody tests confirm prior infection?

A positive result may indicate prior infection with SARS-CoV-2. In low SARS-CoV-2 prevalence populations, where the pre-test probability of prior infection is low, clinicians should be mindful of the potential for false positive results. Importantly, a negative test does not rule out prior infection.

Can SARS-CoV-2 antibody tests confirm an adequate immune system response to vaccination?

No. Antibody tests have not been validated for this purpose. Several different tests are available, and tests are not standardized. As a result, binding antibody tests may be negative in vaccinated persons if the antigen in the test is not the antigenic component of vaccines. Even if the antigen in the test matches the antigenic component of vaccines, antibody production is only one element of the immune system response to vaccine. It is not clear that the presence or absence of antibodies corresponds fully or meaningfully with protection against SARS-CoV-2 infection after vaccination. While antibody reference ranges that correspond with clinical immunity exist for other viral infections, analogous reference ranges have not been established for SARS-CoV-2 antibodies. Antibody test results should not guide clinical decisions.

Bottom line:

SARS-CoV-2 antibody tests are variable in their performance, and have significant limitations that severely limit their utility in clinical practice.

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Contributors: Andrea Chittle, MD; Department of Family Medicine, McMaster University. Noah Ivers, MD, PhD; Women's College Hospital-University of Toronto. Samira Jeimy, MD, PhD, FRCP; Division of Clinical Immunology and Allergy, Department of Medicine, Western University. Sabina Vohra-Miller, MSc; Unambiguous Science.

Designed by Adrian Poon, BA; University of Waterloo.

Reviewed by Theresa Liu, MD, FRCP; Infectious Diseases, Grand River Hospital & St. Mary's General Hospital; Assistant Clinical Professor, Department of Medicine, Faculty of Health Sciences, McMaster University. Rosemary Killeen, BScPhm, PGCert, RPh; School of Pharmacy, University of Waterloo.



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