Yale Medicine | Yale NewHaven Health

SARS-CoV-2 Antibody Testing and Covid-19 Disease

Recommendations:

The following recommendations are provided from the Yale Medicine/Yale New Haven Health Testing Stewardship Committee based on current information and CDC guidelines:

• https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html	Updated 9/21/21
• https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html	Updated 11/5/21

Clinical Decision Making and Infection Prevention

- Clinical decision making should not be influenced by antibody testing (i.e., serologic status) except in cases of MIS-C and MIS-A (multi-inflammatory syndrome in children / adults).
    - MIS-C / A are serious post-infectious complication of Covid-19 in children or adults. Covid-19 antibodies should be ordered in any patient where MIS-C / A is considered in the differential diagnosis.
- Antibody testing results **MUST NOT** be used to adjust infection prevention measures and behaviors (including use of PPE), determine whether vaccination is indicated in someone with prior Covid-19 infection, or inform return to work/school status after Covid-19 infections, travel, or exposures.
- Currently, the CDC, FDA, and several professional societies (see references) **DO NOT** recommend antibody testing to assess post-vaccine immunity or the need for initial or repeat vaccination including 3rd doses or boosters. Further, per CDC, those with a history of Covid-19 should still be vaccinated, regardless of serology status.
- In rare circumstances in which a recent infection is suspected on clinical grounds but viral RNA testing is negative or absent (such as RT-PCR), serology should not be sent within 2 weeks following symptom onset but can be considered three to four weeks after symptom onset to detect evidence of past SARS-CoV-2 infection.
- Currently there are no clinical indications for repeated antibody testing.

Situation:

Guidance is needed on 1) the potential role for SARS-CoV-2 antibody testing to identify immune response from previous Covid-19 infection and following vaccination, and 2) results interpretation.

Background and Definitions:

General Background

- Following infection with SARS-CoV-2, detectable antibodies are made against viral protein targets: spike (S) and nucleocapsid (N) proteins. Anti-S antibodies may occur after viral infection or after vaccination, and anti-N antibodies occur only in patients with prior infection.
- All currently authorized antibody tests provide a qualitative result (positive/negative). Some tests provide a numerical result and have undergone additional procedures to allow comparability among results. However, these tests are classified as semi-quantitative

rather than quantitative by the FDA so the utility of numerical values is not known at this time.

- The S protein contains the receptor binding domain (RBD) which can also induce measurable antibodies. Neutralizing antibodies that inhibit SARS-CoV-2 replication *in vitro,* and which may provide protective immunity, mainly target the RBD. Widely available commercial antibody assays, including those performed within YNHHS, **DO NOT** assess for the presence of neutralizing antibodies.
- Levels of protective immunity may differ among viral variants, and thresholds for immunity have not been established for antibody types, assays, variants, and patient populations.

Identifying Individuals with Prior Exposure to SARS-CoV-2

- Positive antibody testing may aid in identifying individuals with an adaptive immune response to prior SARS-CoV-2 infection or following vaccination though serologic testing is NOT routinely recommended for these purposes.
- In cases where a recent infection is suspected on clinical grounds but viral RNA testing is negative or absent, antibody testing should not be sent within 2 weeks following symptom onset but can be considered three to four weeks after symptom onset to detect evidence of past SARS-CoV-2 infection.
- If ordering, antibody testing should be performed at a high-quality laboratory using tests that have received Emergency Use Authorization from the FDA.
    - If testing for prior infection (regardless of vaccination status), both anti-S (Full-length Spike or S1-RBD) and anti-N antibody tests should be positive.
    - If testing after vaccination (without known prior infection), only anti-S (Full-length Spike or S1-RBD) should be positive; anti-N should be negative.

Antibody Tests Are Not Used to Diagnose Acute SARS-CoV-2 Infection

- Antibody testing should NOT be used to diagnose acute Covid-19. The gold standard for diagnosis of acute SARS-CoV-2 infection is the detection of SARS-CoV-2 RNA by amplified testing for viral RNA (such as RT-PCR).

Assessment:

1. In unvaccinated individuals, positive antibody testing with validated assays indicates prior infection and helps document prior infection in those who were not tested for viral RNA or tested negative for viral RNA. Positive antibody testing likely correlates with immune protective mechanisms, but reinfection and/or infection after vaccination is possible. Results of antibody testing should not be used to guide decisions around vaccination.
2. A proportion of persons infected with SARS-CoV-2 may not develop measurable antibodies. Therefore, negative antibody testing does not exclude previous infection. Also, false negative results may occur if tested sooner than 14-21 days post symptom onset, prior to antibody rise. Further, measurable antibodies may wane over time and those with mild infection may not produce detectable antibodies.
3. Post-vaccination antibody values that indicate protection from infection remain unknown and no assays are currently available that document vaccination efficacy. However, vaccine formulations and delivery regimens were designed based on antibody induction and this is an

area of on-going investigation. Even in immunocompromised populations, antibody response cannot be used to guide booster or concomitant dosing strategy. Vaccination decisions should be consistent with guidelines and regulatory authorizations independent of antibody test results.

4. The following table is provided as general guidance for test selection and interpretation:

Clinical Scenario	Spike* (IgG or Total)	Nucleocapsid (IgG or Total)
Evaluation of prior viral infection >11 days ago	Positive	Positive
Evidence of vaccination (after full course)**	Positive	Negative
Evaluation of possible MIS-C / MIS-A***	Positive	Positive
* Includes Spike Receptor Binding Domain (RBD) ** Immunocompromised patients may have negative serology post-vaccination *** Multisystem Inflammatory Syndrome in Children or Adults		

Recommendations: Recommendations are listed above in the box at the beginning of the document.

Other References:

Agency / Guideline	Date of Last Update	Link
CDC	September 21, 2021	https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
CDC	November 5, 2021	https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html
FDA	May 19, 2021	https://www.fda.gov/medical-devices/safety-communications/antibody-testing-not-currently-recommended-assess-immunity-after-covid-19-vaccination-fda-safety
IDSA	August 18, 2020	https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/
ACR	October 27, 2021	https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf
ASH - ASTCT	August 18, 2021	https://www.hematology.org/covid-19/ash-astct-covid-19-and-vaccines