

Interim Guidance on the **Use of Rapid Antibody Tests for COVID-19 Response**

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in partnership with



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Purpose

The purpose of this document is to provide guidance for Ministries of Health (MOHs) in the African Union Member States in the selection and application of rapid antibody tests to respond to the COVID-19 pandemic. This interim guidance will serve as a reference for the national laboratory leads and experts when selecting and prioritizing laboratory diagnostics for testing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This document has elaborated the use case scenarios for antibody tests and emphasized the importance of choosing test kits with high-performance characteristics confirmed by independent evaluation using a large sample size. This interim guidance will be reviewed and updated as more evidence becomes available regarding the use of rapid antigen and antibody-based tests for SARS-CoV-2 from global studies and evaluation efforts.



1. Background

The speed of developing diagnostics for SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), has been quite remarkable. Diagnostics have focused on nucleic acid amplification testing (NAAT) to identify infected individuals in acute-phase disease for timely implementation of mitigation strategies and case management. More and more immunodiagnosics, mostly rapid diagnostic tests, are being made available as an alternative to NAATs. This type of test can be used out-of-laboratory conditions at large scale.

The United States Federal Drug Agency (US FDA), and other national regulatory agencies, have granted the Emergency Use Authorization (EUA) for many of these tests; most are also CE-IVD marked. However, one major hurdle to selecting specific assays for use is obtaining the validation data needed to assess the quality or performance of each test. Current EUA review procedures do not include any independent assessment of test performance and therefore such authorizations alone **do not** confirm diagnostic accuracy. Additionally, many rapid antibody-based assays are being developed and sold without any independent evaluation, validation, or verification.

In addition to test quality and performance, the availability of diagnostics is another major hurdle. COVID-19 is a global problem and the demand for all assays and associated laboratory requirements is immense. Many molecular tests require laboratory infrastructure and are difficult to implement at lower levels of the health system and some tests are in short supply requiring alternative products to be used. This makes validation of the available assays, even more important.

2. Assessing Test Quality and Performance

The performance of an assay is measured by sensitivity and specificity, which indicate the ability of a test to correctly identify positive and negative samples, respectively. However, as COVID-19 is a newly emerging virus, access to well-characterised samples are limited. Manufacturer evaluations may have been performed on very small sample sizes, which result in wide confidence intervals around the point estimates of sensitivity and specificity. Reliable and accurate data can only be gathered after an appropriate sample size is used for evaluations (as discussed by Banoo et al). Until a sufficient number of samples have been tested, preliminary data should be considered with caution.

Test quality is dependent on whether quality management systems are used in the manufacturing process of a diagnostic test. Companies that have been certified by the International Standards Organization (ISO) for quality manufacturing (ISO 13485) are more likely to be able to produce high-quality products consistently. This can be verified through inspections and lot to lot testing.



3. Diagnostic Tests for COVID-19

Diagnostic tests are critically needed in any outbreak response:

- For rapid identification and confirmation of clinically suspected cases **to guide patient management**
- For conducting a **rapid situation analysis** to inform public health measures and control strategies
- For **surveillance** to monitor trends and effectiveness of control interventions and strategies

There are 3 major types of diagnostic tests for COVID-19, each with its own attributes and limitations. Hence it is important that the right test is used for the right patient in the right place and at the right time considering the resources available.

3.1 Molecular tests

Molecular tests are used to detect viral RNA in patient samples from the upper and lower respiratory tract (e.g. nasal or oropharyngeal swabs, sputum, or bronchial lavage). These tests are highly sensitive and specific but can only be used optimally from 1-7 days post-onset of symptoms.

3.2 Antigen detection tests

Antigen detection tests are used to detect viral proteins in samples from both the upper and lower respiratory tract and can be used from 1-14 days post-onset of symptoms; they may not be as sensitive as molecular tests but could likely serve as a rapid means of triaging suspected cases in settings where access to molecular testing is limited.

3.3 Antibody tests

Antibody tests are used to detect antibodies produced in the blood of infected patients starting from 5-10 days post-onset of symptoms. A positive IgM or total antibody test in patients who fulfil the clinical case definition for COVID-19 is strongly suggestive of recent infection. IgG antibodies can persist for a long period and usually provide evidence of past infection.

All the above tests are available as laboratory-based assays or as point of care tests. The performance of these tests is being evaluated as an ongoing effort to ensure the necessary sensitivity and specificity for quality testing. Member States should consider the availability of independent evaluation data on the assays before they select diagnostics for COVID-19. Collaboration among the Member States is encouraged to sharing findings that will speed the process for independent evaluation.

4. Selection of Diagnostics for COVID-19 Pandemic Response

Countries should carefully choose the appropriate test depending on intended use and setting. Tests that have been assessed through a national EUA and/or WHO Emergency Use Listing (EUL) should be prioritized for the COVID-19 testing. The list of tests that have been given EUA in the USA can be found here: <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd> and information on the WHO EUL procedure, including lists of tests that have been authorized by many national regulatory agencies, can be found here: https://www.who.int/diagnostics_laboratory/EUL/en/). The requirements for EUA may vary substantially among countries and are less rigorous than the regulatory approval procedures in normal scenarios.

Selection of companies that have substantial and positive track records and that meet international quality management systems (i.e. ISO 13485 or equivalent) for manufacturing is important. Prioritizing companies that already have an existing distributor/supply network in-country may enable more rapid and continual access to kits if they have access to an authorized test.

Additional Equipment/Reagents Required: When selecting a product, it is important to know if additional sample collection materials and reagents/consumables are required to perform the test or if these need to be purchased separately from the manufacturer or another distributor. Ask suppliers for a copy of their instructions for use, before purchasing a test to understand the requirements needed to support the roll-out of the test.

Sensitivity/specificity of the assay: Additionally, these inserts will also include limited data on the performance of the test that has been generated by the supplier, which may be helpful to understand how sensitive or specific the assay is. If selecting an antibody test for SARS-CoV-2, it is ideal to choose a kit that has sensitivity and specificity of more than 98% and that these calculations are based on large sample sizes.

It is essential to have independently verified data on the performance of the test (i.e. analytical sensitivity, cross-reactivity, clinical sensitivity, and specificity) before procuring.

List of available assays as compiled by FIND can be found at <https://www.finddx.org/covid-19/pipeline/>

5. Role of Antibody Testing in the COVID-19 Response

In settings where there is limited access to laboratories or challenges with supplies for molecular testing, rapid antibody tests offer an option to guide patient management and inform disease control strategies. This approach can only be used in individuals 5–10 days post-onset of symptoms when antibodies start to become detectable. In some patients, seroconversion is typically achieved by 10–12 days post-symptoms for Immunoglobulin M (IgM) and by 12–14 days for Immunoglobulin G (IgG). Rapid antibody test kits often include all materials needed to perform the test (tests, reagents, lancets for finger pricks, alcohol swabs, and disposable pipets) and can be performed by healthcare providers with minimal training. However, the interpretation of results needs to be contextualized based on the clinical findings, inherent characteristics of test kit chosen, and other factors. For example, antibody assays may not have been validated in the context of prevalent illnesses in Africa, such as HIV infection. It is known that COVID-19 is more severe in immune-compromised individuals but there are no data on the accuracy of assays that detect antibodies in immunocompromised individuals, so caution is warranted. Use of only rapid antibody tests with high sensitivity and specificity is critically important to avoid missing true cases of COVID-19 as well as unnecessary quarantine of people with false-positive results due to cross-reactivity with seasonal coronaviruses.

At present, the use of antibody-based rapid tests can be considered in the following situations:

a. Triage of symptomatic individuals in healthcare or community settings

Where there is limited or no access to molecular tests, rapid antibody tests provide a means to quickly triage suspect cases of COVID-19 provided the test is highly sensitive and specific for COVID-19. A positive IgM or total antibody test results in symptomatic patients fulfilling the COVID-19 case definition is strongly suggestive of a recent infection with SARS-CoV-2. This approach has allowed a large number of symptomatic individuals to be rapidly tested in the community or healthcare setting, relieving the backlog and waiting time for molecular testing and preventing the healthcare system from being overwhelmed. This approach is relevant specifically if there is evidence of community transmission for which timely laboratory diagnostic is essential. Negative antibody test in individuals with signs and symptoms suggestive of COVID-19 **does not** exclude the disease and a swab should be taken for molecular testing.

b. Testing of contacts of confirmed COVID-19 cases

Testing all close contacts of a confirmed case, who are symptomatic, is critical in interrupting the chain of transmission in the community. Those who test positive by a total antibody test should self-isolate or seek treatment, if warranted. If testing is done within 7–10 days post the exposure event, those who test negative should be swabbed for molecular testing. Additionally unless daily testing is available, contacts who are found to be negative on antibody or molecular tests should be advised to continue to quarantine as they may still become infectious and/or symptomatic.

c. Informing situation analysis and serosurveillance

In countries that have set up syndromic surveillance, such as surveillance for influenza-like illness (ILI) or severe acute respiratory infections (SARI), that collects blood and throat swabs routinely at sentinel sites, these surveillance samples can be tested for COVID-19 using molecular, antigen or antibody tests, either alone or in combination. If any of these samples are positive, it means COVID-19 has been circulating in the community. If serial samples are available, it may be possible to date when COVID-19 established itself in a community or country. For conducting prospective surveys, it may be useful to consider the use of dried blood spot (DBS) for antibody testing and deep saliva samples for molecular or antigen testing. These sample types are less cumbersome and hazardous to collect in the field. Collection of DBS samples followed by testing on a high-volume immunoassay will both enable the use of better performing tests (some laboratory-based immunoassays have high sensitivity and specificity) as well as reduce costs.

In general, antibody tests can be used to determine the true extent of an outbreak, map its geographic distribution, and identify at-risk populations. These could be especially helpful to monitor prevalence in healthcare or other high-risk essential workers and could further inform public health measures and control strategies.

At this point, use of antibody tests are not recommended for the following situations:

- As criteria to discharge patients from hospitals**
- As criteria for workers, including health care workers, to return to work**

The optimal criteria for hospital discharge are two negative molecular tests. Studies show that in general, viral RNA levels decline slowly despite rising antibody levels. Tests that detect neutralizing antibodies (such as antibodies against the receptor-binding domain (RBD) of the Spike protein or the nucleocapsid protein) are commercially available but studies have shown that some patients remain RNA positive despite having rising levels of IgM and IgG antibodies. Some studies have also reported that high IgG levels are associated with severe disease. Hence it is not clear that the concept of “Immunity Passport” is a safe means of allowing workers to return to work or for lifting social distancing and other public health and social measures.



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