A Landscape Analysis of Laboratory Technologies for Covid-19

Response in Low- and Middle-Income Countries: Equipment, Reagents, and Supplies for Diagnostic Molecular, Antigen, and Serological Testing

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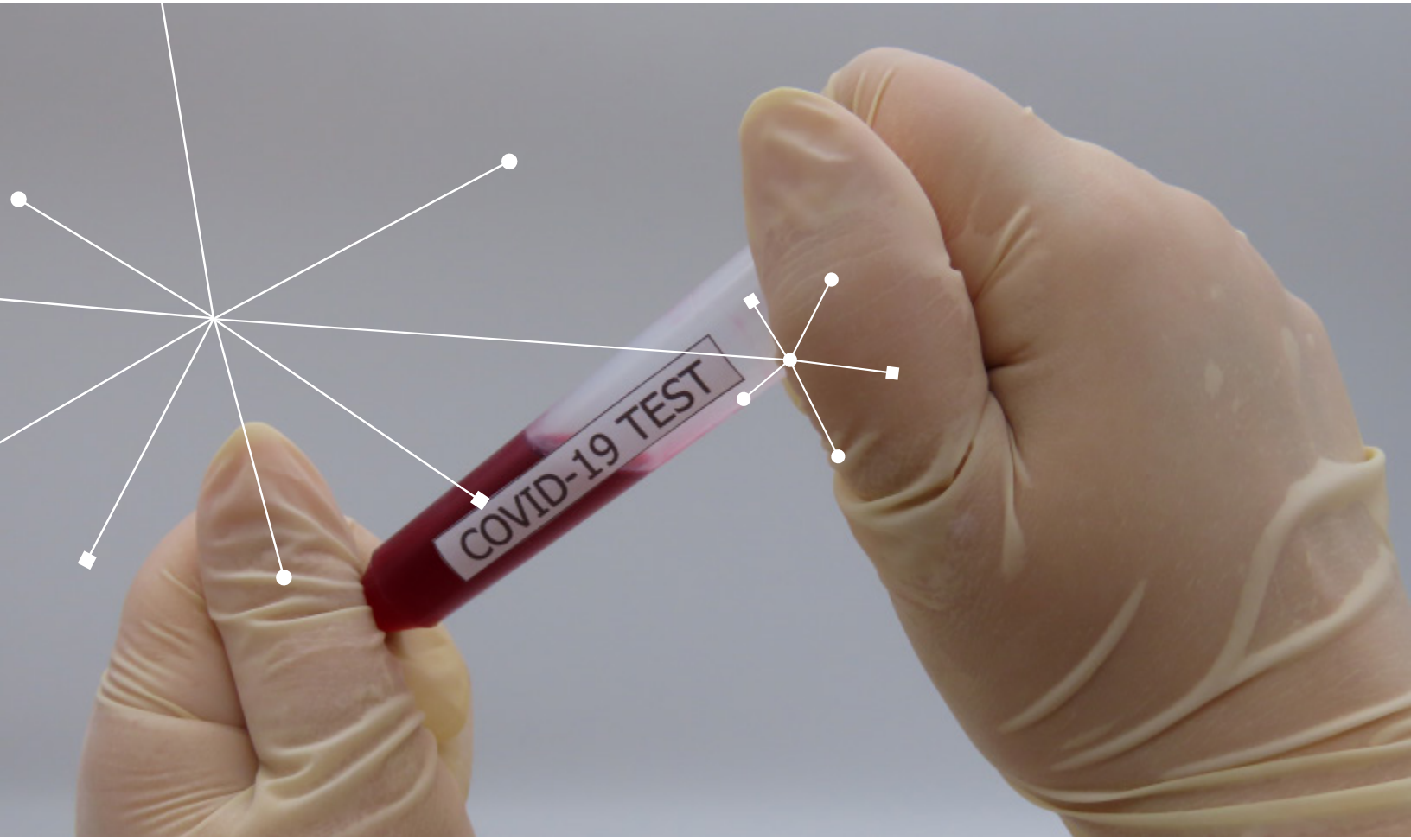
Abbreviations

Ab	antibody
ACT	Accelerator Covid-19 Tools initiative
Ag	antigen
AMDF	Africa Medical Devices Forum
ASLM	African Society for Laboratory Medicine
ATTC	American Tissue Culture Collection
BSL	biosafety level
CDC	US Centers for Disease Control and Prevention
CE	European Conformity (Conformité Européenne) certification
CE-IVD	European Conformity (Conformité Européenne)–in vitro diagnostic
CFDA	China Food and Drug Administration
CLIA	chemiluminescent immunoassay
Covid-19	coronavirus disease 2019
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EUA	emergency use authorization
EUL	Emergency Use Listing (WHO)
EVAg	European Virus Archive
FDA	Federal Drug Administration
FIND	Foundation for Innovative New Diagnostics
HAS	Health Science Authority of Singapore
HIC	high-income country
HIV	human immunodeficiency virus
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IVD	in vitro diagnostic
LAMP	loop-mediated amplification
LIS	laboratory information system
LMICs	low- and middle-income countries
MERS	Middle East respiratory syndrome
MiRNA	micro-ribonucleic acid
mL	milliliter
mm	millimeter
MSH	Management Sciences for Health
NAAT	nucleic acid amplification test
NAFDAC	Nigeria Agency for Food and Drug Administration
NCPV	National Collection of Pathogenic Viruses

QCMD	Quality Control for Molecular Diagnostics
PACT	Partnership to Accelerate Covid-19 Testing (PACT) in Africa
POC	point of care
PCR	polymerase chain reaction
PEPFAR	US President's Emergency Plan for AIDS Relief
RDT	rapid diagnostic test
RNA	ribonucleic acid
RT-qPCR	quantitative reverse transcriptase PCR
RT-PCR	reverse transcriptase polymerase chain reaction
SARS–CoV-2	severe acute respiratory syndrome coronavirus-2
TAT	turnaround time
TGA	Therapeutics Goods Association of Australia
USAID	US Agency for International Development
UVT	universal virus transport
WHO	World Health Organization



Key Definitions

Antibodies: Also known as immunoglobulin (Ig), proteins that help fight off new antigens to the body (such as pathogenic bacteria and viruses).

Antigen: A toxin or other foreign substance that induces an immune response in the body, especially the production of antibodies.

Biosafety level (BSL) of laboratory: Classification of a laboratory's capacity for bio-containment, ranging from basic, containment, and maximum containment based on risk assessment. It consists of four biosafety tiers: 1, 2, 3, and 4. Biosafety levels are determined based on the composite of the design features, construction, containment facilities, equipment, practices, and operational procedures required for working with agents from various risk group.

Covid-19: Also known as coronavirus disease, an infectious disease caused by the most recently discovered coronavirus, SARS-CoV-2. Coronaviruses are a large family of viruses, which may cause mild to severe respiratory infections in humans. Covid-19 has been declared a global pandemic by the World Health Organization (WHO).

Multi-disease platform: Diagnostic platform that can test for multiple types of infections, either simultaneously or sequentially.

POC: Refers to testing performed near where the patient is receiving care (point of care). Testing can be performed by professional or lay health workers, and results are typically available relatively quickly.

Near-POC: Refers to molecular testing that can be decentralized to a lower level but not yet to the community level.

Rapid diagnostic test: A medical diagnostic test that is quick and easy to perform. Rapid diagnostic tests (RDTs) provide quick results while the patient is at the health care facility or in the convenience of the patient's home.

Sensitivity: The proportion of patients with disease who have a positive test, or the true positive rate.

Specificity: The proportion of patients without disease who have a negative test, or the true negative rate.

Validation: Verification of the claimed analytical sensitivity (limit of detection) to determine the diagnostic accuracy of an in vitro diagnostic (IVD) test.

Acknowledgments

The Rockefeller Foundation would like to thank Management Sciences for Health (MSH) for their support in authoring this document. This work would not have been possible without their expertise and extensive experience in laboratory technologies.

This document outlines the methodology used to collect, collate, and validate publicly available data to create a dashboard aimed at listing globally available Covid-19 diagnostics and product features. The dashboard provides increased access to market information that will assist countries in the selection of high-quality Covid-19 diagnostics appropriate for their setting. The landscape analysis and dashboard have been developed to complement the different ongoing initiatives focused on increasing access to Covid-19 diagnostics in low- and middle-income countries (LMICs).

This document and the companion dashboard were developed by a multidisciplinary team at MSH. Alaine Umubyeyi Nyaruhirira led data collection, and analysis for the landscape analysis and dashboard. Randy Wilson created the open-source web-based dashboard. Ritu Kumar, Kwesi Eghan, and Meenakshi Mehra provided additional technical support for data collection and analysis. Julian Fritz Chaesar Pratma Salim assisted with the editing of the document. The project team was led by Dr. Hector Castro, who provided overall direction and design for the project.

The MSH team would like to thank the staff of the African Society for Laboratory Medicine (ASLM), Africa Centers for Disease Control (Africa CDC), Clinton Health Access Initiative (CHAI), Africa Medical Supplies Platform (AMSP) of the Africa CDC and Africa Union, the Foundation for Innovative New Diagnostics (FIND), and National Health Laboratory Service (NHLS) of South Africa for the valuable information and feedback shared during the development of the landscape and dashboard.

Executive Summary

Covid-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as one of the most significant humanitarian challenges in recent history. Accurate and rapid diagnostic tests (RDTs) will be critical to achieving control of the ongoing Covid-19 pandemic. Diagnostic tests for Covid-19 fall into three main categories: molecular, antigen, and antibodies detection.

From May 22 to August 8, 2020, MSH conducted a landscape analysis and developed a user-friendly, open-source dashboard using a two-pronged approach of desk research and key informant interviews. A rapid literature review of the diagnostic landscape for Covid-19 was completed during this period. The literature review focused on types of molecular and serology tests available in the market and in the pipeline; product features of available tests such as regulatory approvals, sensitivity, specificity, and time to results; quality assurance processes and status; testing guidelines and recommendations related to diagnostics from global and regional agencies such as WHO, the US Centers for Disease Control and Prevention (CDC), Africa CDC, ASLM, FIND, the Global Fund, and Unitaid; and trends in the Covid-19 diagnostic markets and testing strategies underway in LMICs.

To supplement the literature review and understand the future direction of the global Covid-19 diagnostic market, MSH experts conducted key informant interviews with 15 global experts. This included participants from WHO, FIND, Africa CDC, ASLM, AMSP, CHAI, and key laboratories stakeholders from selected countries (Afghanistan, Bangladesh, Brazil, Ivory Coast, Pakistan, Rwanda, South Africa, and Ukraine).

The scope of this landscape analysis is limited to molecular, antigen, and antibody diagnostic devices to detect Covid-19 infection. The information presented in the analysis and dashboard has been verified via triangulation between secondary data sources and supplemental key informant interviews. The dashboard can be accessed **here**. Demand for Covid-19 diagnostic tests increases as the pandemic grows globally. This initiative aims at improving decision-making processes in LMICs by reducing the asymmetry of information regarding the emerging laboratory technologies for Covid-19. The market for Covid-19 diagnostics is changing rapidly, and the landscape analysis will require regular updates to keep it relevant for the global community battling the pandemic.

Disclaimer

The scope of this landscape analysis is limited to molecular, antigen, and antibody diagnostic devices to detect Covid-19 infection. The information presented in the analysis and dashboard has been verified via triangulation between secondary data sources and supplemental key informant interviews. However, the analysis in the report is not exhaustive of all available tests in the market since it is focused on tests that are suitable for LMIC needs. This includes tests that leverage existing PCR platforms and tests that have been introduced through global pooled procurement initiatives. All efforts have been made to ensure that the report provides an accurate overview of the listed Covid-19 diagnostics. However, the landscape for Covid-19 diagnostics is rapidly changing and additional devices entering the market after the completion of the report may not be included, and information supplied concerning the identified tests may change rapidly or vary by geography.

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Introduction

Types of Tests

Covid-19, an infection caused by SARS-CoV-2, is one of the most significant humanitarian challenges in recent history. The ability to detect SARS-CoV-2 in respiratory secretions is essential for determining when an individual is infected and mitigate the impact of Covid-19. Accurate and rapid diagnostic tests will be critical to achieving control of Covid-19. Currently available diagnostic tests for Covid-19 fall into three main categories:

- **Molecular tests:** Molecular tests are used to detect viral RNA in patient samples from the upper and lower respiratory tract (e.g., using 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.
- **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 to 14 days after 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.
- **Antibody tests:** Antibody tests are used to detect antibodies produced in the blood of infected patients starting from 5 to 10 days after infection. A positive IgM (type of antibody) antibody test in patients who fulfill 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.

The goal of a testing strategy is to identify infected individuals with the goal of reducing onward transmission. Any strategy should include a choice of a test or tests, and how to use them. Key factors in test choice include accuracy of the test and the time it takes to get the results. While all types of tests are considered important in developing a successful Covid-19 response strategy, the reverse transcriptase polymerase chain reaction (RT-PCR) molecular test is widely used as the reference standard for diagnosis of Covid-19. However, RT-PCR tests also have limitations, including potential false-negative results, changes in diagnostic accuracy over the course of the disease, and precarious availability of test materials.

Market Characteristics

The rapid introduction of and ensuing widespread familiarity with diagnostic tests for SARS-CoV-2 in the market has been quite remarkable. FIND is leading several global efforts to accelerate access to innovative diagnostics in LMIC. FIND's publicly available database has listed over 750 diagnostics for Covid-19 that are available or under development. However, the performance and quality of most tests have yet to be independently validated. Tests have not been sufficiently validated for their accuracy in routine clinical settings or for a broad cross-section of population. A clear understanding of the tests' performance and the interpretation of their findings is important as countries dedicate limited resources to purchase them. While there are hundreds of tests in development, we still lack a simple, easy-to-use, affordable, and reliable test that can be made available to everyone, everywhere.

Health technologies such as therapeutics or diagnostics must undergo evaluation, and they require the approval of a well-established regulatory body for their use in any market. Approvals from the US Food and Drug Administration (US FDA), the European Medicines Agency (EMA), the WHO Emergency Use Listing Procedure (WHO-EUL), and or/other stringent regulatory bodies are often seen as an indicator for a high-quality, safe, and efficacious product. Given the urgency of the pandemic and the limited timeframe for validation of new products, regulatory authorities are choosing to grant emergency use authorization (EUA) for many products during the validation process. The US FDA, and other national regulatory agencies, have granted EUA for many tests. Many tests have also received EUA approvals from the EMA (i.e., meeting European conformity–in vitro diagnostic (CE-IVD marked). However, it is crucial to note that a conditional approval such as an EUA does not confirm diagnostic accuracy. Conditional market approvals are for a limited time period, and independent validation needs to be completed during this time.

Beyond 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 materials is immense. Many molecular tests require laboratory infrastructure and are difficult to implement at lower levels of the health system. Many tests and testing materials are in short supply, requiring alternative products to be used. Furthermore, the shortage of laboratory testing materials have led to the use of multi-disease platforms for Covid-19 testing, which has disrupted services across many national programs such as those for HIV and TB. Global and regional solidarity initiatives such us Accelerator Covid-19 Tools (ACT), Pandemic Action Network (PAN), and Partnership to Accelerate Covid-19 Testing (PACT) in Africa have emerged to support LMICs. Such initiatives have helped advocate for fund mobilization, streamline supply chains, and encouraged manufacturers to increase the production of laboratory supplies. However, given the global demand and the need for easy-to-use tests suitable for LMICs' context, monitoring the pipeline and performance of tests remains important.

A list of tests approved by US FDA can be found at
https://www.fda.gov/medical-devices/coronavirus-disease-2019-Covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas

List of commercially available tests and tests in the pipeline can be found at:
https://www.finddx.org/Covid-19/

https://chs.asu.edu/diagnostics-commons/testing-commons

Need for Access to Information on Covid-19 Diagnostics

LMICs are seeing surges in Covid-19 while they contend with the economic fallout of lockdowns imposed to control the pandemic's spread Many are gradually easing lockdowns to limit economic impact but need to match this with increased Covid-19 testing to quickly identify and control infections. Brazil, Chile, Colombia, India, Iran, Mexico, Peru, and South Africa are now among the top 10 countries by highest number of Covid-19 cases. Most cannot afford mass testing, given their limited resources. Therefore, there is a need to spend resources thoughtfully, and on tests that align with testing strategies in each country. Given the rapidly changing diagnostics market, disease epidemiology, and variable pandemic control/management strategies, it is important for countries to stay informed about the global testing landscape.

This landscape analysis and the companion open-source dashboard have been developed to address the critical need for reliable and up-to-date information related to Covid-19 diagnostics. With funding from the Rockefeller Foundation, MSH has developed a dashboard of the current pipeline of Covid-19 diagnostic tests. This tool provides a listing of available quality-assured diagnostic tests for LMICs along with key product features. The dashboard is intended to facilitate the selection of appropriate tests by development partners, country governments, laboratory professionals, other end users, donors, and implementers supporting the Covid-19 response in LMICs. The dashboard enables evidence-based decision making for selection of molecular and serological testing. The landscape analysis provides the methodology for creation of the dashboard so that it can be continued to be updated and enhanced with additional features by future users or developers. Both the landscape analysis and dashboard complement the work of FIND and other global stakeholders engaged in increasing access to Covid-19 diagnostics.

The dashboard of approved tests is available at the following webpage: **https://www.rockefellerfoundation.org/lmic-covid-19-diagnostic-resources/dashboards/**. The dashboard is as an open-source data visualization tool that is publicly accessible and uses an easy-to-interpret web-based format. The dashboard enables users to view tests available and approved by stringent regulatory authorities along with key product features relevant to selection of the appropriate molecular and serological testing. The dashboard also includes a list of basic equipment requirements, reagents, and supplies needed with the various tests

The landscape analysis and dashboard do not address the validation gaps observed for most of the tests. WHO is working in partnership with FIND, other international organizations, and country partners to accelerate the independent validation or evaluation process of promising molecular and serology tests. The dashboard will guide end users to the FIND Covid-19 diagnostics **resource** to access up-to-date information on validation of tests.

Methodology

The landscape analysis and the companion dashboard were developed using a two-pronged approach of desk research and key informant interviews.

Desk Research

MSH diagnostics and supply chain experts conducted a rapid literature review from May 22 to August 08, 2020, on the diagnostic landscape for Covid-19. Themes of focus included:

a) Types of molecular and serology tests available in the market and in the pipeline
b) Product features such as regulatory approvals, sensitivity, specificity, time to results, test setting and complexity, and others
c) Quality assurance processes and status
d) Testing guidelines and recommendations related to diagnostics from global and regional agencies such as WHO, CDC, Africa CDC, ASLM, FIND, Global Fund, and Unitaid
e) Trends in the Covid-19 diagnostic markets and testing strategies underway in LMIC

The literature review targeted peer-reviewed literature; published and unpublished reports from Covid-19 response partners, WHO, and Africa CDC; US CDC policies and systematic reviews; FIND technology updates; corporate prospectuses, press releases, diagnostic developer websites; and websites of regulatory authorities including (but not limited to) the US FDA, the EMA, WHO-EUL, the Australian Therapeutics Goods Association (TGA), and the Singapore Health Science Authority (HSA).

Key Informant Interviews

MSH experts conducted key informant interviews with global experts to supplement the literature review, with a focus on validating information obtained via desk research and understanding the future direction of the global Covid-19 diagnostic market. Experts interviewed were selected based on their involvement and leadership in the diagnostics space and the global response to Covid-19. MSH conducted ($N = 15$) interviews with experts from WHO, WHO Regional Office for Africa, FIND, Africa CDC, ASLM, AMSP, CHAI, and key laboratory stakeholders from selected LMICs (Afghanistan, Bangladesh, Brazil, Ivory Coast, Pakistan, Rwanda, South Africa, and Ukraine). Interview areas of focus included:

a) Current priorities for testing and types of diagnostics in LMICs
b) Priority product features important for selection of appropriate diagnostics in LMICs
c) Availability and funding trends in LMICs: challenges and donor support
d) Additional sources of information relevant to the landscape analysis and dashboard

Dashboard Design

Test Selection

Tests were selected for inclusion in the dashboard based on the literature review and discussions with global and country experts on parameters of importance to LMICs. Tests were selected based on the following:

a) *Quality assurance of the tests.* Tests included have been approved by regulatory authorities endorsed by WHO and approved under WHO's Emergency Use Diagnostics Prequalification program. Regulatory authorities included are the US FDA, EMA, TGA of Australia, the China Food and Drug Administration (CFDA), Health Canada, the HSA of Singapore, and other regulatory bodies that have WHO endorsement.

b) *Recommendations from global initiatives focused on equitable access to Covid-19 diagnostics* such as the Accelerator for Access to Covid-19 Tools (ACT), Partnership to Accelerate Covid-19 Testing (PACT) in Africa, reports of the Africa Medical Devices Forum (AMDF) Covid-19 Task Force, and a few LMIC key stakeholder interviews/feedback. This allowed for consideration of tests that were not being targeted by HICs; tests that were being donated to LMICs; and tests recommended for purchase using donor funds such as Global Fund, Unitaid, or USAID.

Product Features/Dashboard Categories

The product features of the tests relevant for the dashboard design were selected based on the literature review, discussions with global experts, and information availability. Product features included in the dashboard include manufacturer's name, name of the test, test type (molecular/antigen/serological), test system (stand-alone/proprietary vs. others), specimen type, platform type, platform name, throughput, turnaround time (TAT), testing setting, specimen collected by, quality assurance information (specificity/sensitivity and availability of independent validation data), regulatory approvals, and others. The full list of key features of selected technologies and their definitions are available in Appendix 1.

Target Audience

The landscape analysis and dashboard have been developed to provide accurate market information on Covid-19 diagnostics and support the rational selection of tests appropriate for LMIC settings. Targeted users include policy makers involved in Covid-19 response in LMICs, personnel from ministries of health, laboratory managers and technicians, other health professionals engaged in the Covid-19 response, not-for-profit organizations, donors, and international agencies. The landscape analysis and dashboard are focused on the public-sector response to Covid-19 and aimed at officials who make decisions about deployment and procurement of laboratory tests and equipment.

Limitations

The rapidly changing market of emerging technologies for Covid-19 response is perhaps the biggest challenge for work products such as this analysis and the open-source dashboard. Mapping all emerging technologies and their potential value is not feasible as new tests continue to enter the market. The pipeline of Covid-19 tests presented in this first landscape analysis is therefore not exhaustive. Tests selected are based on data gathered from May to early August 2020 and on publicly available information on test features, quality, and validation. The dashboard and landscape analysis will need to be updated

regularly as new information becomes available. Performance data for any product described in this landscape analysis are derived from literature reviews and interviews. Attempts have been made to validate the veracity of claims regarding test accuracy from multiple sources when available. Nonetheless, the methodology presented in this document may serve to expand or update our work in future iterations. Emerging data on the accuracy and performance of tests can be found at the FIND website here.

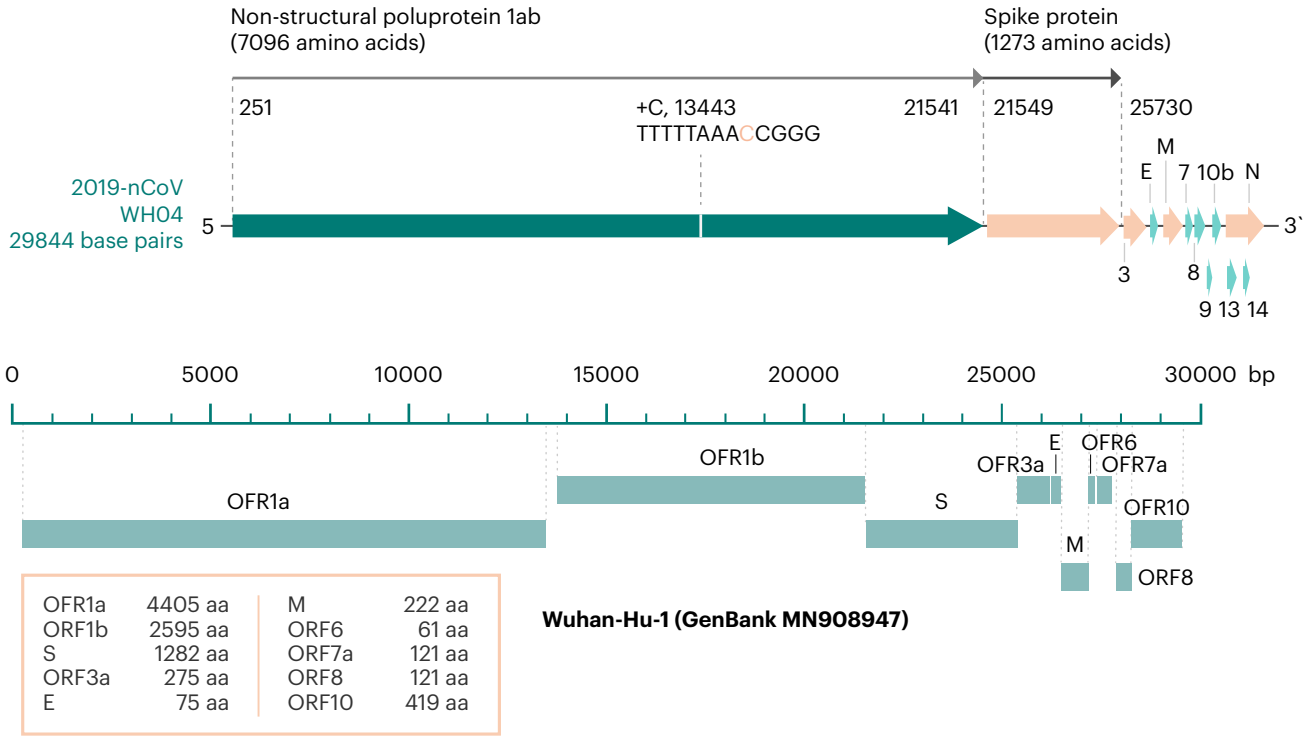
Mapping Types of Tests for COVID-19

A total of 177 molecular technologies have been investigated with high-level summaries provided for the most relevant technologies. These include (1) stand-alone PCR kits (*N* = 29) that require application on various laboratory instrumentation and (2) integrated high-throughput systems, which include PCR kits combined with existing instrumentation (extraction and amplification) (*N* =102). Antigen tests and systems (kits and instruments) are included (*N* = 2) and a number of serology tests (*N* = 22). The remainder of the tests do not have sufficient information available to be assigned any of these categories. The complete list of technologies, with product features, is accessible on the open-source dashboard.

Molecular Tests

Molecular tests are nucleic acid amplification tests (NAATs), which detect viral RNA in patient samples from the upper and lower respiratory tract (e.g., using nasal or oropharyngeal swabs, sputum, or bronchial lavage) to diagnose and/or confirm cases for clinical treatment or surveillance purposes. Molecular tests may also detect fragments of the pathogen before it is fully cleared from the body, even if the pathogen is no longer able to replicate or cause disease. The diagnostic tests rely on a technique called reverse transcription-polymerase chain reaction (RT-PCR) to detect the presence of SARS-CoV-2 virus. These tests can provide qualitative results (i.e., positive or negative reading) as well as quantitative information on the amount of circulating virus in a patient sample. These tests are sensitive and specific but their period of optimal use is limited to 1–7 days after the onset of symptoms.[4,14] A variety of RNA gene targets are used by different manufacturers, with most tests targeting one or more of these: the envelope (*env*), nucleocapsid (*N*), spike (*S*), RNA-dependent RNA polymerase (*RdRp*), and *ORF1* genes. The basic gene structure shown in Figure 1 outlines the targets amplified by molecular technologies.

Figure 1: Wuhan-Hu-1 structure and targeted genes.



Source: FIND. (2020). SARS-COV-2 DIAGNOSTIC PIPELINE

Other assay technologies, including a CRISPR-based nucleic acid detection system, may be used in POC formats in the future if appropriate sensitivity can be achieved.

Antigen (Ag) tests are used to detect viral proteins in samples from both the upper and lower respiratory tract. Ag tests can be used to detect active infection from 1 to 14 days after onset of symptoms, but they may not be as sensitive as molecular tests. However, they could serve as a rapid means of triaging suspected cases and/or screening contacts exposed to infected individuals in settings where access to molecular testing is limited. Many of these tests are RDTs, which serve as an alternative to NAATS and provide decentralized access to testing with a fast TAT (15–40 minutes). Negative results using this assay should be confirmed by a more sensitive method, such as RT-PCR.[6] Tests with the highest possible sensitivity must be prioritized to minimize false-negatives, as these may lead to missing cases.

Accuracy of Molecular Tests

Several commercial assays as well as laboratory-developed RT-PCR tests are now available to detect SARS-CoV-2 from clinical samples under emergency use authorizations from stringent regulatory authorities such as the US FDA. Studies conducted by the manufacturers of these assays describing their analytical accuracy are updated at the FDA's EUA webpage under "In Vitro Diagnostics." In general, these assays have high analytical sensitivity with an estimated limit of detection ranging from 100 to 1000 copies, and very high specificity. In other words, these tests are highly accurate, with the exception of the Abbott ID NOW point-of-care assay, which is reported to have lower sensitivity. However, a "positive" PCR result reflects only the detection of viral RNA and does not necessarily indicate the presence of viable virus.

A systematic review of the accuracy of Covid-19 tests reported false-negative rates between 2% and 29% (equating to a sensitivity of 71%–98%), based on negative RT-PCR tests that were positive on repeat testing. However, the certainty of the evidence was considered very low because of the heterogeneity of sensitivity estimates among the studies, lack of blinding to index test results in establishing diagnoses, and failure to report key RT-PCR characteristics. Taken as a whole, the evidence, while limited, raises concern about frequent false-negative RT-PCR results. Compiling data from peer reviewed papers shows that RT-PCR accuracy of viral RNA swabs in clinical practice varies depending on the site and quality of sampling, with the highest rate observed in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%), and pharyngeal swab (32%).

False-negative results occurred mainly due to inappropriate timing of sample collection in relation to illness onset and deficiency in sampling technique, especially of nasopharyngeal swabs. Specificity of most of the RT-PCR tests is 100% because the primer design is specific to the genome sequence of SARS-CoV-2. Additionally, it will be important to note occasional false-positive results that may occur due to technical errors and reagent contamination. No test gives a 100% accurate result; tests need to be evaluated to determine their sensitivity and specificity, ideally by comparison with a gold standard. The lack of such a clear-cut standard for Covid-19 testing makes evaluation of test accuracy challenging.

As previously mentioned, the antigen tests currently available are not as sensitive as RT-PCR. Sensitivity of these types of tests can vary between 34% and 80%. Additionally, they may also present false positives if they also detect other viruses. Until further validation information is available, WHO does not recommend the use of antigen tests for patient care. The CDC guidance shown in Figure 2 provides helpful tips on interpreting test results in light of patient symptoms.

Figure 2. US CDC guidance to keep in mind for Covid-19 molecular testing

What you need to know when introducing a test

- When interpreting the result of a test for Covid-19 depends on two things: accuracy of the test, and the pretest probability or estimated risk of disease before testing.
- A positive RT-PCR test for Covid-19 test has more weight than a negative test because of the test's high specificity but moderate sensitivity.
- A single negative Covid-19 test should not be used as a rule-out in patients with strongly suggestive symptoms.
- Laboratory and clinicians should share information with patients about the accuracy of the Covid-19 tests.

Source: Centers for Disease Control and Prevention. (2020). Information for Laboratories about Covid-19.

Antibody (Serological) Tests

Serological, or antibody, tests detect evidence of the body's immune response to an infection, which can provide information on both current and prior infection. Serological tests make it possible to detect infections after the immune system has successfully eliminated the pathogen. Antibodies (Ab), also known as immunoglobulins (Ig), are produced by B cells and are part of a highly specific defense against new antigens.

Two classes of antibodies, immunoglobulin M (IgM) and immunoglobulin G (IgG), are common targets for serological tests because of their roles in targeting and destroying new infections. The immune system typically produces IgM soon after infection as a frontline defense, and IgG is generated later. Additionally, IgG persists in the body longer than IgM and contributes to longer-term immune memory, which enables the immune system to rapidly identify and respond to future infections by the same pathogen. IgA is another type of antibody, typically found in mucous membranes, which can be produced in high quantities during infections. Diagnostic platforms used for the detection of specific antibodies to SARS-CoV-2 proteins include (1) rapid diagnostic tests, (2) enzyme-linked immunosorbent assays, and (3) naturalization assays and chemiluminescent immunoassay.

Rapid diagnostic tests rely on a lateral flow immunoassay (LFIA) that returns qualitative (positive or negative) results within minutes. A small blood sample is placed at one end of the test strip, and the antibodies of interest in the blood sample interact with tagged proteins embedded in the test. The test displays colored lines at the end of the strip corresponding to a positive, negative, or inconclusive result with respect to the presence of the desired antibodies. RDTs are not capable of providing quantitative results indicating the *amount* of the antibodies in the specimen. They are small, portable, and can be used at point-of-care. In the context of Covid-19, RDTs most frequently test for the presence of patient antibodies (IgM and IgG) specific to SARS-CoV-2.

Enzyme-linked immunosorbent assay (ELISA) relies on specific binding of patient antibodies to a fixed viral protein of interest, often in a 96-well plate. ELISAs can return qualitative or quantitative results and are generally performed in a laboratory setting. These tests use whole blood, plasma, or serum samples. Patient samples are incubated with the viral protein of interest to allow antibody-protein binding.

The resulting antibody-protein complexes are then exposed to a second antibody or a substrate that produces a color or fluorescent-based signal when bound to the complexes. The resulting signal reflects the presence and/or level of specific antibodies in the patient sample in the context of Covid-19. ELISAs most frequently test for patient antibodies (IgM and IgG).

Neutralization assays and *chemiluminescent immunoassay (CLIA)* provide quantitative information on the ability of patient Ab to confer protective immunity. Neutralization assays are the most time-consuming and skill-based of the three tests described. Using cell culture, live virus, and patient antibodies, researchers can visualize and quantify in a patient sample the level of antibodies capable of blocking viral replication. These tests require whole blood, serum, or plasma samples from the patient. Because these tests require live virus to challenge the antibodies, neutralization assays must be performed in the appropriate biosafety containment level (biosafety level 3 [BSL-3] or above) and require a week or longer to return results. Only neutralization assays can provide information regarding the ability of antibodies to inhibit viral growth. Diagrams demonstrating how these tests function can be found in Appendix 2.

Accuracy and Use of Serology Tests

Serological tests are important because many patients show asymptomatic progression of the disease. Asymptomatic patients are unlikely to receive a molecular test since patients without symptoms do not show up at clinics, and the PCR test is not suitable for later stages of the infection. However, the characterization of exposure to SARS-CoV-2 is valuable information about these patient. Ab tests are a must to determine seroprevalence in each population and to develop appropriate pandemic control strategies. Along with molecular testing, they can improve the rate of positive contact tracing. However, validated, accurate tests are currently in short supply. In this landscape analysis, we seek to draw attention to the major available approved serology tests, as options for expanding access. Drawing on research and public health knowledge, the following summarizes suggested uses for RDTs for detecting Ag and Ab:

- Ag RDTs should be prioritized for case management to enable decentralized testing, especially when access to PCR testing is limited.
- Ab RDTs should be prioritized for seroprevalence surveys to inform public health measures and testing of contacts to establish previous spread of the virus.

Table 1 provides an overview of the suggested uses of Ag versus Ab tests.

Table 1. Uses of rapid diagnostic tests for Covid-19

Suggested Use		Ag	Ab
Case management in high prevalence/ active outbreak settings	Triage suspect cases Positive: no confirmatory testing required Negative: confirmatory testing with PCR recommended, if available	✓	
	Aid diagnosis in symptomatic cases presenting late (≥ 10 days post–symptom onset) Used in addition to PCR/Ag, not as a replacement		✓
	Monitor active infection	✓	
Public health measures	Screen contacts for infection	✓	
	Screen contacts for previous exposure (≥ 10 days post-exposure)		✓
	Conduct seroprevalence surveys to define levels of population exposure, including vaccine trial support		✓

Source: www.finddx.org/Covid-19.

Rapid POC tests for detection of antibodies have been widely developed and marketed; they are of variable quality. In the United States only, it has been reported that dozens of serology tests being marketed are not providing accurate information and are not comparable to each other. These tests are purely qualitative in nature and can indicate only the presence or absence of SARS-CoV-2 antibodies. The long-term persistence and duration of protection conferred by the neutralizing antibodies remains unknown. Many serological tests for Covid-19 have become available in a short period, including some marketed for use as rapid, POC tests. The pace of development has, however, exceeded that of rigorous evaluation, and important uncertainty about test accuracy remains. Many manufacturers are not transparent about the nature of antigens used. However, the regulatory agencies such the US FDA stipulate, among other requirements, that manufacturers operating without EUA must state that they have clinically validated their tests using specimens from patients with PCR-confirmed infections. The test reports must note that the FDA has not reviewed the assays and that they should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform patients of infection status.

A systematic review and meta-analysis of 40 studies evaluated the quality of available evidence on the pooled sensitivities and specificities of different test methods; analyses showed the accuracy of serological tests for SARS-CoV-2 infection to be as follows: the pooled sensitivity of ELISAs measuring IgG or IgM was 84.3% (95% confidence interval, 75.6%–90.9%); that of LFIAs was 66.0% (49.3%–79.3%); and that of CLIAs was 97.8% (46.2%–100%). In all analyses, pooled sensitivity was lower for LFIAs, the potential POC method. Pooled specificities ranged from 96.6% to 99.7%. The review also looked at patient characteristics associated with test accuracy. Of the samples used for estimating specificity, 83% (10,465/12,547) were from populations tested before the epidemic or not suspected of having Covid-19. Among LFIAs, pooled sensitivity of commercial kits (65.0%, 49.0%–78.2%) was lower than that of noncommercial tests (88.2%, 83.6%–91.3%). Heterogeneity was seen in all analyses. Sensitivity was higher at least three weeks after symptom onset (ranging from 69.9% to 98.9%), compared with within the first week (13.4%–50.3%).

Currently, WHO and CDC do not recommend using antibody testing as the sole basis for diagnosis of infection. WHO only recommends using antibody tests for epidemiological research. Antibody tests are not authorized by the FDA for such diagnostic purposes under its EUA approval. In certain situations, serological assays may be used to support clinical assessment of persons who present late in their illnesses, when used in conjunction with viral detection tests.

Placement of molecular and serology tests

As countries are urged to employ WHO's "test, treat, trace" strategy, selection of tests to be deployed is extremely important. Key factors that influence choice of test include intended use, setting and availability of needed resources (personnel and infrastructure), quality assurance protocol, biosafety requirement for collection and testing process, and supply chain constrains. However, one of the bottlenecks in accessing diagnostic tests during this pandemic involves the supply of personal protective equipment and laboratory commodities. Countries are advised to select companies with positive track records in global supply and that meet international quality management standards (i.e., ISO 13485 or equivalent) for manufacturing. 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.

In addition to the equipment, internal controls, and reagents required for running RT-PCR tests, RDT antigen, or serology tests, countries should be prepared during the quantification process to assess all additional sample collection materials and consumables required to perform the test, or if these need to be purchased separately from the manufacturer or another distributor. The **dashboard** summarizes some of the key indicators that will assist during this process.

Before procuring a test, it is imperative to be aware of the requirements needed to support its rollout in addition to understanding the sensitivity and specificity of the test; peer review validation data must also be assessed. If selecting an antibody test for Covid-19, it is ideal to choose a kit that has sensitivity and specificity greater than 98% and to ensure that these calculations are based on large sample sizes, as validation results are not yet available globally.

POC tests are intended to supplement laboratory testing, making testing available to communities and populations unable to readily access laboratory testing, and bolstering testing to quickly address emerging outbreaks. Table 2 summarizes the suggested placement of Covid-19 diagnostic tests in a tiered laboratory system based on TAT infrastructure required, and target population.

Table 2. Placement of molecular and serology in the tiered laboratory network

	Type of test	Time to results	What it tells us	What it cannot tell us	Test analysis setting and expertise needed
Molecular test	RT-PCR test (system) or kit only	2–5 days	These tests can provide qualitative as well as quantitative information on the amount of circulating virus in a sample. Optimally taken 1–7 days after onset of symptoms.	These cannot provide a diagnostic result for someone who was infected previously and has already cleared the infection. These cannot confirm if the virus is live.	Lab space and BSL2/3 are required, as well as extensive training required (central/ referral laboratory at tertiary level).
Serology tests	Antigen RDT	15–40 minutes	The test detects viral proteins in samples and can be used 1–14 days after onset of symptoms.		Point-of-care or near-POC testing is possible but requires training and a laboratory or health worker professional.
	Rapid diagnostic test	10–30 minutes	The test detects the presence or absence (qualitative) of antibodies against the virus present in patient serum.	The test cannot indicate the amount of antibodies in the patient serum, or whether these antibodies are able to inhibit virus growth.	POC testing, usually handheld; minimal training needed.
	ELISA	2–5 hours	Test detects the presence or absence (quantitative) of antibodies against the virus present in patient serum.	Test cannot tell us whether the antibodies are able to inhibit virus growth.	Lab space is generally required (BSL1); some technical training is required.
	Neutralization assay	3–5 days	Test indicates the presence of active antibodies in patient serum that are able to inhibit virus growth ex vivo—in a cell culture system.	Test may miss antibodies that are specific for viral proteins not involved in replication.	Lab space is required, at least BSL-3 if using live SARS-CoV-2; extensive training is needed.

Source: Adapted from: Developing a National Strategy for Serology (Antibody Testing) in the United States (John Hopkins University, Center of Health security (April 2020).

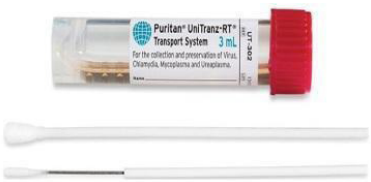
Overview on specimen collection devices and transport media

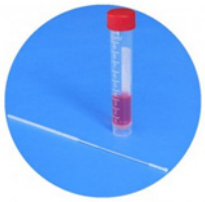
Proper collection of specimens is the most important step in the laboratory diagnosis of infectious diseases. A specimen that is not collected correctly may lead to false-negative test results. The following specimen collection guidelines from WHO and the CDC can be source material for developing standard operating procedures in LMICs:

- WHO (May 2020 version): https://www.who.int/publications/i/item/laboratory-biosafety-guidance-related-to-coronavirus-disease-(Covid-19)
- CDC: https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html

All available tests are not provided with collection devices and transport media. In table 3 we refer to few collection devices as well as transport media available from major suppliers, which can be accessed in the dashboard.

Table 3. Collection devices combined with transport media*

Name of Company and Products	Overall specifications	Quantity by kit
COPAN FLOQSwabs® 503CS01	Flexible minitip (nasopharyngeal) or FLOQSwabs 519CS01 regular (oropharyngeal). Swabs with 100 mm breakpoint are added to 3 mL of UTM® universal viral transport medium and transported at ambient temperature. Organism viability is maintained for 48 hours at ambient or refrigerated temperature. The swabs are compatible with PCR and the swabs have been tested with the cobas® SARS-CoV-2.	Packaging: 1,000 pieces (10 boxes of 100 pieces) per case unless otherwise noted
Puritan Medical Products Collection Devices and Swabs 	The company provides four swab types: • Sterile elongated flock swab with 100-mm molded breakpoint • Sterile elongated and ultrafine flock swabs • Sterile minitip and standard polyester swabs • Sterile standard polyester swab All are provided with a 3-mL vial of UniTranz-RT transport medium, which contains (1) antimicrobial agents to minimize bacterial and fungal contamination and (2) glass beads to release and disperse sample into the medium during vortexing. Specimens are transported at ambient temperature, remain viable and are compatible with PCR and viral antigen rapid tests.	10 boxes of 50 individually wrapped swabs = 500/cs

Name of Company and Products	Overall specifications	Quantity by kit
Huachenyang (Shenzhen) Technology Co., Ltd Swab Kit 	Specimen collection swab kit consisting of polyester-tipped swabs with a scored plastic shaft, a plastic polyester minitip swab and 3-mL universal virust transport (UVT). Specimens are transported at room temperature and viral viability is maintained. The UVT includes protein for stabilization, antibiotics to minimize bacterial and fungal contamination, and a buffer to maintain a neutral pH. The specimens are compatible with PCR	Pack of individual sterile swab (1,200 sets)
BD™ Universal Viral Transport System 	The BD swabs are provided in five formats, each in 3-mL UVT • Sterile nylon minitip flocked swab with a scored plastic • Sterile nylon regular flocked-tip swab with a scored plastic shaft • One sterile nylon flocked-tip regular swab and one sterile nylon flocked flexible swab, both with a scored plastic shaft • One sterile minitip swab with a scored plastic shaft • One sterile nylon flocked flexible flocked-tip swab with a scored plastic shaft The UVT, which should be transported at 2–8°C within 24 hours, contains proteins for stabilization, antibiotics to minimize bacterial and fungal contamination, and a buffer to maintain a neutral pH. The specimens are compatible with PCR and have been tested with both the cobas SARS-CoV-2 and the CerTest BioTec coronavirus assays.	50 per shelf pack

Name of Company and Products	Overall specifications	Quantity by kit
Thermo Scientific MicroTest™	Comprises two plastic shaft traditional-tipped polyester swabs and 3 mL of transport media. Four different transport media are available: • MicroTest M4 contains gelatin, vancomycin, amphotericin B and colistin, and is transported at **-25°C** or refrigerated. • MicroTest 4M-RT contains gelatin, gentamicin and amphotericin B, and can be transported at **2–30°C**. • MicroTest M5 contains vancomycin, amphotericin B, colistin, and protein stabilizers, and is transported at **-25°C** or **refrigerated.** • MicroTest M6 contains gelatin, vancomycin, amphotericin B, and colistin in a 1.5-mL tube and can be transported at **2–30°C**. Virus viability is maintained, and the specimens are compatible with PCR, ELISA, and DNA probe technology. The MicroTest M4-RT and M6 specimens have been used with the film array multiplex PCR assay.	72 drams/pack Packaged in partitioned boxes
Longhorn Vaccines and Diagnostics Media 	PrimeStore® molecular transport medium (MTM) Pathogens, proteins, and enzymes are inactived, with RNA, DNA, and mRNA are preserved for molecular testing. Specimens are transported at ambient temperature and are stable for extended periods. PrimeStore MTM is compatible with Thermo Fisher, Roche Molecular, Qiagen, and BioMerieux assays.	50 racks (tube) per pack

*Table developed based on data from manufacturers' websites

COVID-19 IVD validation process

Ensuring that tests are comparable and accurate requires a validation process with access to many patient samples, overseen by regulatory bodies and WHO prequalification program. 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-characterized samples is 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. Many serological tests for Covid-19 have become available in a short period, including some marketed for use as rapid, POC tests. The pace of development has, however, exceeded that of rigorous evaluation, and significant uncertainty about test accuracy remains.

Debate has focused on the accuracy of antibody tests, which identify prior infection, with less attention paid to diagnostic testing (molecular and or antigen), which identifies current infection. Diagnostic tests (typically involving a nasopharyngeal swab) can be inaccurate in two ways. A false-positive result erroneously labels a person as infected, with consequences including unnecessary quarantine and contact tracing. False-negative results are more consequential, because in infected persons who might be asymptomatic may not be isolated and can go on to infect others. As per quality management system in the laboratory two processes are needed to resolve these issues:

- Independent validation
- Uses of internal control

Independent Validation

Authorized regulatory bodies such us the US FDA, the EMA, the CFDA, the WHO Prequalification of In Vitro Diagnostics program, and other technical stakeholders such us FIND and research institutes have started to organize independent evaluations to assess the stated performance of molecular tests. Although a validation process is also underway for available serology tests, it is unclear when this will be completed. The first independent evaluation conducted by FIND with the University Hospital of Geneva to verify the limit of detection (LOD) has been released. The validation assessed the clinical performance of 21 manual molecular test kits in comparison to an in-house PCR protocol that was optimized based on the Tib Molbiol assay. Data for all the tests included in the first round of the evaluations are available **here** with detailed information. Tests were selected for evaluation according to scoring criteria that included LOD, regulatory status, type of organization, quality management system, and other products available in LMIC.

Internal Quality Control Panel Requirement

Not all RT-PCR kits approved and released for use are provided with internal control. Internal quality control (IQC) is a means of monitoring the reliability and accuracy of the test; a "control" sample that has been previously tested and verified for a range of results is used as a part of the IQC system. Currently, two options are available: isolates and nucleic acids. Various repositories housing isolates and nucleic acids are accessible through referral molecular laboratories and research institute repositories, including:

1. American Tissue Culture Collection (ATCC)
2. European Virus Archive—Global (EVAg)
3. Biodefense and Emerging Infections Research Resources Repository (BEI Resources)
4. Quality Control for Molecular Diagnostics (QCMD)
5. National Collection of Pathogenic Viruses (NCPV)

Maintenance of a quality management system is crucial to a laboratory for providing the correct test results every time. It aims to analyze the accuracy of the entire testing process from receipt of sample and testing to reporting of results *(*also known as *proficiency testing)*. The following elements of a quality management system in each laboratory carrying out testing as per WHO recommendations (shown at https://www.who.int/diagnostics_laboratory/quality/en/) are crucial:

- Documentation
- Standard operating procedures
- Quality control samples (procedures used in each assay to assure a test run is valid and results are reliable). It will need to have kit controls, including quality control samples.
- External quality assessment scheme

Table 4 shows available isolates and nucleic acids in order of repository of preference, according to availability and accessibility by provider or the ease of online ordering. The material type: isolate refers to infectious-cell culture supernatant containing virus, which will require cell culture.

Table 4. Various repositories housing isolates and nucleic acids*

Repository name	Item	Material type	Positive/ negative control	Culture required
ATCC	SARS-CoV-2 heat-inactivated Strain	Heat inactivated strain	Positive	No
	Betacoronavirus 1ATCC® VR-1558™	Isolate	Negative	Yes
	Human coronavirus 229EATCC® VR-740™	Isolate	Negative	Yes
	Synthetic SARS-CoV-2 RNA: ORF, E, N (ATCC® VR-3276T™)	RNA	Positive	No
	Quantitative Synthetic SARS-CoV-2 RNA: spike 5'ATCC® VR-3277SD™	RNA	Positive	No
	Quantitative synthetic SARS-CoV-2 RNA: spike 3'ATCC® VR-3278SD™	RNA	Positive	No
	SARS-CoV-2 genomic RNA	RNA	Positive	No
	RNA from human coronavirus 229E strain 229EATCC® VR-740D™	RNA	Negative	No
	Quantitative synthetic human coronavirus NL63 RNAATCC® VR-3263SD	RNA	Negative	No
	Quantitative genomic RNA from human coronavirus 229EATCC® VR-740DQ™	RNA	Negative	No
	RNA from betacoronavirus 1, strain OC43ATCC® VR-1558D™	RNA	Negative	No
	Quantitative synthetic human coronavirus HKU1 RNAATCC® VR-3262SD™	RNA	Negative	No
	Quantitative synthetic Middle East respiratory syndrome coronavirus (MERS-CoV) RNAATCC® VR-3248SD™	RNA	Negative	No

Table continued on the next page

Repository name	Item	Material type	Positive/ negative control	Culture required
EVAg	SARS-CoV-2 strain/NL/2020	Isolate	Positive	Yes
	Human 2019-nCoV strain 2019-nCoV/ Italy-INMI1	Isolate	Positive	Yes
	Human 2019-nCoV (France)	Isolate	Positive	Yes
	Human 2019-nCoV isolate (Germany)	Isolate	Positive	Yes
	MERS coronavirus strain IP/COV/MERS/ Hu/France/FRA2	Isolate	Negative	Yes
	MERS coronavirus (Netherlands)	Isolate	Negative	Yes
	Betacoronavirus 1/bovine coronavirus	Isolate	Negative	Yes
	Human 2019-nCoV strain 2019-nCoV/ Italy-INMI1 RNA	RNA	Positive	No
	Human 2019-nCoV RNA (Germany)	RNA	Positive	No
	2019-nCoV E gene-stabilized RNA as positive control; shipping at room temperature	RNA	Positive	No
	Coronavirus RNA specificity panel	RNA	Positive	No
	MERS-CoV (hCoV-EMC) 1A assay (confirmatory assay)	RNA	Negative	No
	MERS-CoV (hCoV-EMC) upstream E (upE) assay (screening)	RNA	Negative	No
	Wuhan coronavirus 2019 E gene control	Gene	Positive	No
	Wuhan coronavirus 2019 RdRP gene control	Gene	Positive	No
BEI Resources	SARS-related coronavirus 2 Isolate USA-WA1/2020 NR-52281	Isolate	Positive	Yes
	Quantitative synthetic RNA from SARS-related coronavirus 2 NR-52358	RNA	Positive	No
	Genomic RNA from SARS-related coronavirus 2, isolate USA-WA1/2020 NR-52285	RNA	Positive	No
	Heat-inactivated, SARS-related coronavirus 2, USA-WA1/2020 NR-52286	Heat-inactivated strain	Positive	No
QCMD	Coronavirus Outbreak Preparedness EQA Pilot Study: Panel	On request	Positive and negative	No
NCPV	0310051v human coronavirus *229E* HCoV-229E	Isolate	Positive	Yes

*Table developed based on country-level Interviews and data from manufacturers' websites.

Notes: ATCC collects, stores, and distributes standard reference microorganisms, cell lines, and other materials for research and development. BEI Resources have been managed under contract by ATCC since 2003. QCMD (Quality Control Molecular Diagnostic) external quality assessment programs support the clinical laboratory's regulatory requirements and are also educational in application. NCPV is one of four culture collections of Public Health England.

Conclusions and recommendations

Globally, the demand for Covid-19 diagnostic tests is increasing as the pandemic continues growing across the world. WHO is encouraging countries to "test, treat, and trace" to reach as many infected individuals and manage the spread of the outbreak. However, testing is one of the biggest challenges facing communities amid the coronavirus outbreak.

In response to the rapidly growing need and the shortage of laboratory-based molecular testing capacity and reagents, several diagnostic test manufacturers around the world are committed to developing and supplying rapid test kits to detect Covid-19. Currently, several hundreds of tests are available on the global market. However, only some of these have received EUA approval from stringent regulatory authorities (e.g., 203 had EUA approval from the FDA at the first week of August).

The pipeline of serology tests, which detect immunoglobulins, including IgG and IgM, is growing, with the aim of detecting individuals who have had previous infection and therefore theoretically have developed immunity. The time course and accuracy of serology tests, however, are still under investigation. From the landscape analysis exercises, a few observations can be made:

1. Inaccurate serology tests could lead to false reassurances, behavior change, and disease spread. If suitable levels of accuracy can be established in the future, the benefits of these antibody tests would include establishing when populations are immune, informing decisions about the lifting of lockdowns, and allowing the population to return to work.
2. Although at present a large number of coronavirus (Covid-19) test kits are available, external validation has been limited. Countries need to establish quality control measures and cross-checking against "gold standard" molecular tests until independent evaluation data are available. Additionally, countries need to stay updated on the external validations being undertaken by agencies such as WHO, the CDC, FIND, and collaborative research institutes.
3. The WHO message "test, treat, trace" is important from a population perspective. However, RT-PCR tests have limitations when used to guide decision making for individual patients. Positive tests can be useful to "rule in" Covid-19, but a negative swab test cannot be considered definitive for "ruling out."
4. Global effort and regional solidarity initiatives such us the Accelerator Covid-19 Tools, Pandemic Action Network and PACT have spurred the creation of demand, initiated streamlining of supply chains, and are working with manufacturers to maintain and even increase the production of laboratory supplies. These different initiatives have tried to decrease disparities across continents, but much still needs to be done.
5. Certain LMICs have been successful in their response to Covid-19 by building on existing laboratory infrastructure and equipment such as high-throughput platform technologies, where laboratory networks were already well structured. However, the RT-PCR remains expensive, with a long TAT, which undercuts quick action on isolation of positives cases. Lastly, many countries are struggling with the supply of reagents and disruption across their laboratory system. This is of concern because not only does it affect the Covid-19 response, but it also impacts other disease programs.[51]

There is no time to waste. An effective strategy of pandemic resilience will require additional efforts, including:

- Innovation in testing methodologies
- Strengthening validation processes from the start of the concept, with clear standardized validation protocol to allow easy introduction of technology at the country level
- Strengthening supply chains and infrastructure, particularly in LMICs
- Strengthening national regulatory authorities for ease of access and introduction of new IVD and laboratory tools

This landscape analysis, supported by an open-source dashboard, is a complementary tool for use by initiatives implemented by other global agencies such as FIND, ACT, PACT, and WHO. It provides updated information for end users and policy makers on the selection mix of centralized, high-volume platform, and POC diagnostics based on each country's unique needs. This landscape report is derived from an independent analysis, and the SARS-CoV-2 technologies pipeline is still evolving. There is a need for a continual technical review and maintenance support.

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Appendix 1. Checklist of Indicators Used for the Landscape Analysis and Dashboard Development

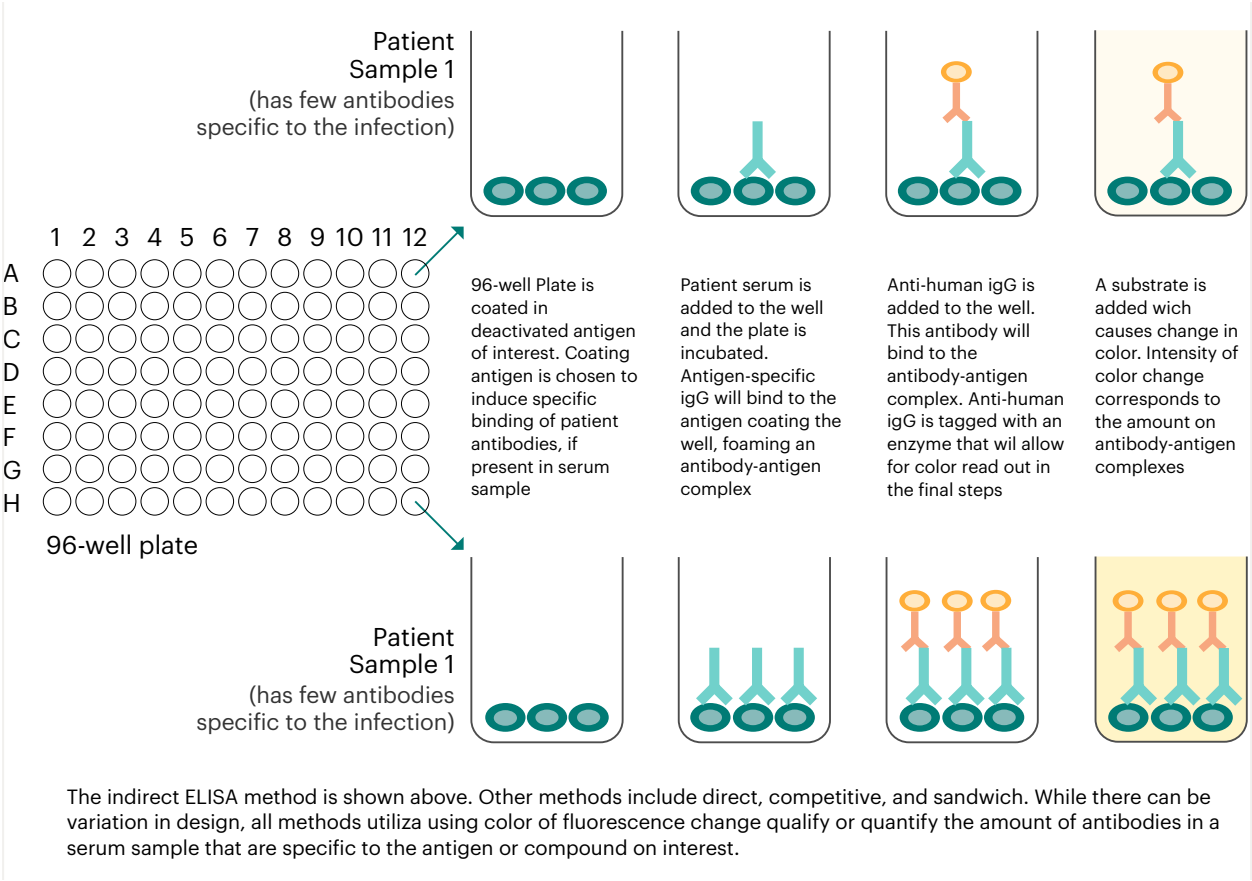
Serial no.	Indicator	Definition
1	Manufacturer name	Official name in the regulatory approval certificate
2	Test name	Brand name for test
3	Test category	Molecular, antigen, and serological
4	Diagnosis target	Viral antigen (VirAG), Viral RNA (VirRNA), next-generation sequencing, and antibody
5	Detection technology	Immunoassay, nucleic acid testing
6	Platform type	1. Loop-mediated isothermal amplification (isothermal LAMP) 2. Lateral flow immonoassay 3. Next-generation sequencing 4. Real-time reverse transcription PCR 5. ELISA
7	Throughput	Number of tests per kit/cartridge/run (or number of tests performed per day according to machine capacity)
8	Interpretation method	· Manual · Automated · Benchtop · Freestanding
9	FDA approval type	Type of approval given by the FDA, such as emergency use authorization or research use only
10	FDA approval date	Date of approval by the FDA
11	Other jurisdiction approvals	Approvals by other regulatory authorities (see complete list of stringent regulatory bodies of consideration after this table)
12	Specimen collected	Fingerstick, saliva, swab, venous
13	Specimen collected by	Self, health care professional, company-trained individual
14	Analysis location	Type of laboratory setting required for test based on WHO Covid-19 safety manual recommendation: 1. Laboratories under BSL3 category: These settings are at the tertiary level of the health system or could be referral labs. Staff usually require extensive technical training to conduct a RT-PCR complex test or neutralized serology test. 2. Laboratories under BSL2 category: These labs are can be at secondary- or tertiary-level health facilities. Staff require moderate technical training. 3. Laboratories under BSL1 category: These are basic labs which can be found at primary health facility levels. Staff require basic technical training. 4. Self-test or health worker provided testing, which may require a short orientation.

15	Time to result (turnaround time)	Minutes to run the test (not including communicating the results)
16	Claimed sensitivity	Ability of a test to correctly identify those with the disease (true positive rate). This is measured in percentages
17	Claimed specificity	Ability of a test to correctly identify those without the disease (true negative rate). This is measured in percentages
18	Country of manufacture	Location of manufacture as per approval certificate or location of production of the test when available
19	Manufacturer link	Link to commercial website where the manufacture or representative advertise the test approved

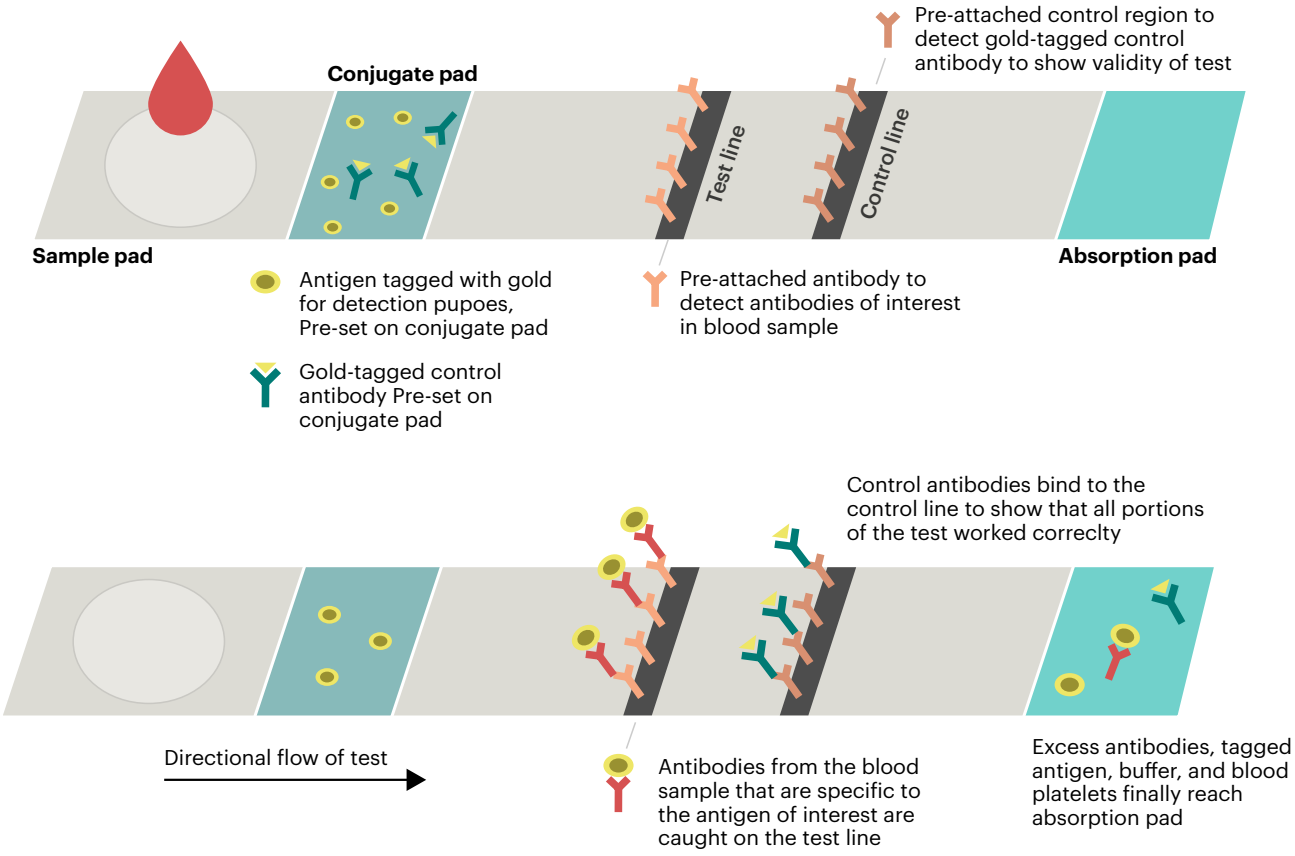
Tests included in the dashboard were selected based on the literature review and discussions with global experts as well as potential contextual needs in LMICs. Selection criteria for tests include:

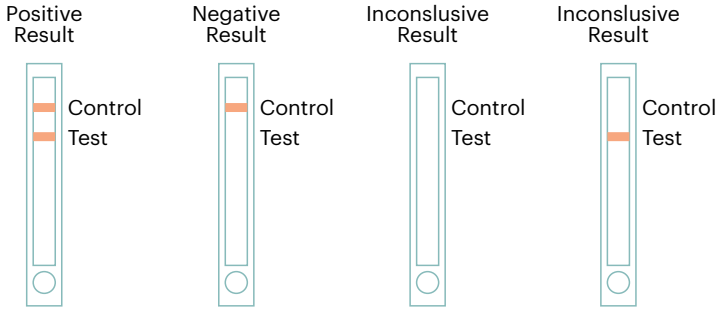
1. Quality assurance of the tests: The selection was rationally based on regulatory authorities endorsed by WHO under the Emergency Use Diagnostics Pre-qualification program such us the US FDA, the European Conformity IVD registration, the Therapeutic Goods Administration (Australia), the China Food and Drug Administration, Health Canada, the Health Science Authority of Singapore (HSA), and other regulatory bodies as stated in the FIND and WHO interim laboratory guidance.
2. Recommendations from global initiatives focused on equitable access to Covid-19 diagnostics: These include Accelerator for Access to Covid-19 Tools, the Partnership to Accelerate Covid-19 Testing in Africa, and the Reports of Africa Medical Devices Forum (AMDF) Covid-19 Task Force, as well as few LMIC key stakeholders interviews feedback. This allowed for consideration of tests that were not being targeted by high-income countries; tests that were being donated to LMICs; and tests recommended for purchase using donor funds such funding from Global Fund, Unitaid, and USAID.

Appendix 2. Diagrams Demonstrating How Serology Tests Function



The indirect ELISA method is shown above. Other methods include direct, competitive, and sandwich. While there can be variation in design, all methods utiliza using color of fluorescence change qualify or quantify the amount of antibodies in a serum sample that are specific to the antigen or compound on interest.


Pre-attached control region to detect gold-tagged control antibody to show validity of test
Conjugate pad
Test line
Control line
Sample pad
Absorption pad
Antigen tagged with gold for detection pupoes, Pre-set on conjugate pad
Pre-attached antibody to detect antibodies of interest in blood sample
Gold-tagged control antibody Pre-set on conjugate pad
Control antibodies bind to the control line to show that all portions of the test worked correclty
Directional flow of test
Antibodies from the blood sample that are specific to the antigen of interest are caught on the test line
Excess antibodies, tagged antigen, buffer, and blood platelets finally reach absorption pad


Positive Result
Control
Test
Negative Result
Control
Test
Inconslusive Result
Control
Test
Inconslusive Result
Control
Test