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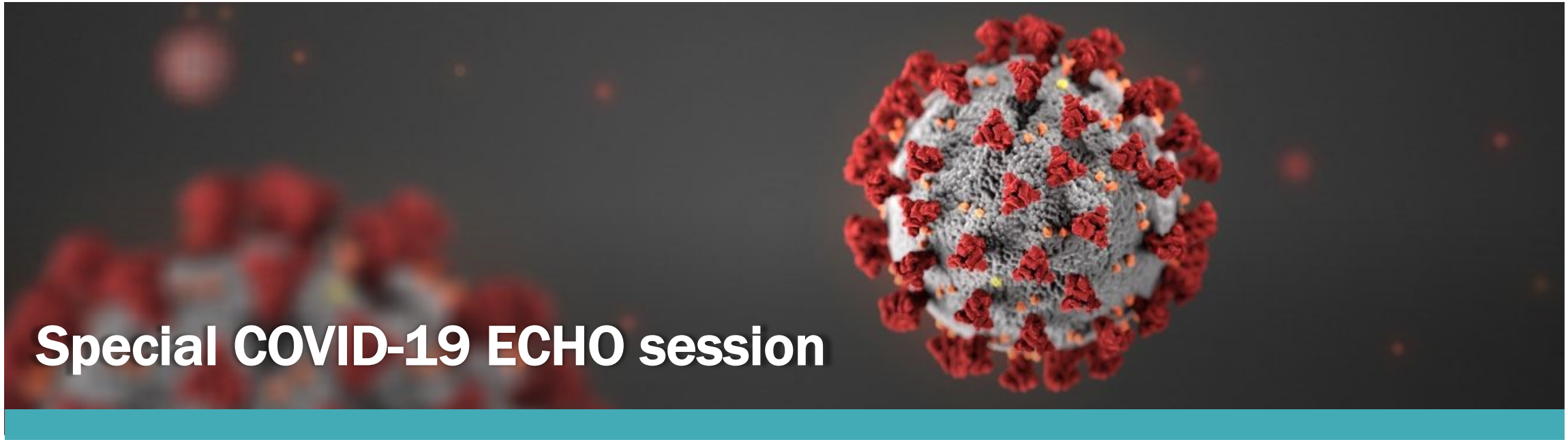
Because diagnosis matters



Special COVID-19 ECHO session

Cassandra Kelly-Cirino, Director of Emerging Threats, FIND

30 March 2020

FIND is a global non-profit driving diagnostic innovation to combat major diseases affecting the world's poorest populations

- WHO Collaborating Centre for Laboratory Strengthening & Diagnostic Technology Evaluation
- WHO SAGE-IVD member
- ISO-certified quality management system for IVD clinical trials

ANTIMICROBIAL RESISTANCE	HEPATITIS C & HIV	MALARIA & FEVER
NEGLECTED TROPICAL DISEASES	PANDEMIC PREPAREDNESS	TUBERCULOSIS

We address market failure by partnering to develop and deliver diagnostic solutions to LMICs

COVID-19: situation overview

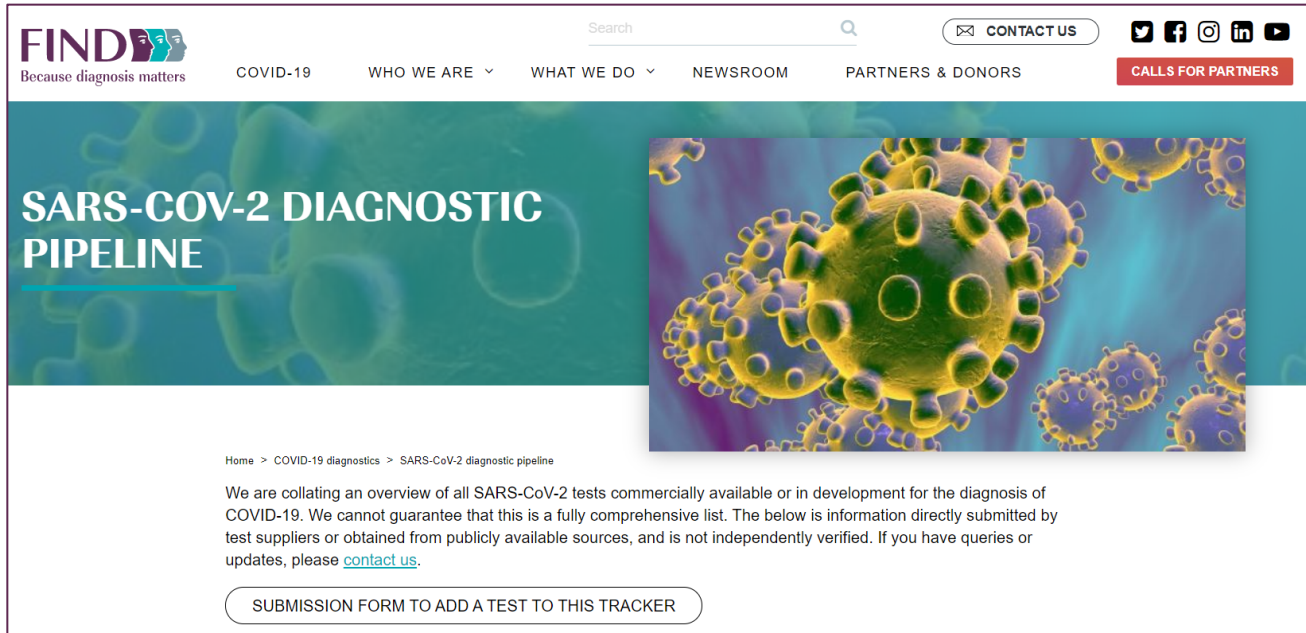
- As the world is struggling to contain the novel coronavirus (COVID-19) outbreak, **healthcare infrastructure and testing capacity** have emerged as major issues
- Adequate **testing capacity** for SARS-CoV-2 is lacking worldwide, preventing people from accessing care and impeding accurate tracking of COVID-19
- Emerging cases in Europe and the US have **overwhelmed the health systems** of high-income countries
- Resource-limited countries – in Africa and South-East Asia in particular – are **highly vulnerable** due to their already-fragile health systems

How is FIND supporting the global COVID-19 response?

- Rapid **evaluation of new/existing tests** for SARS-CoV-2, prioritized for use in LMICs, to enable procurement of quality supplies
- **Capacity development** in LMIC laboratories, for rapid scale-up of diagnostics
- Continued **monitoring of the R&D and supply pipeline** for fit-for-purpose tests for SARS-CoV-2, supporting countries and developers in bringing new diagnostic products rapidly to market
- Driving completion of development of new diagnostic assays for SARS-CoV-2 that can be used on **existing LMIC laboratory infrastructure** or do not require labs (RDTs)

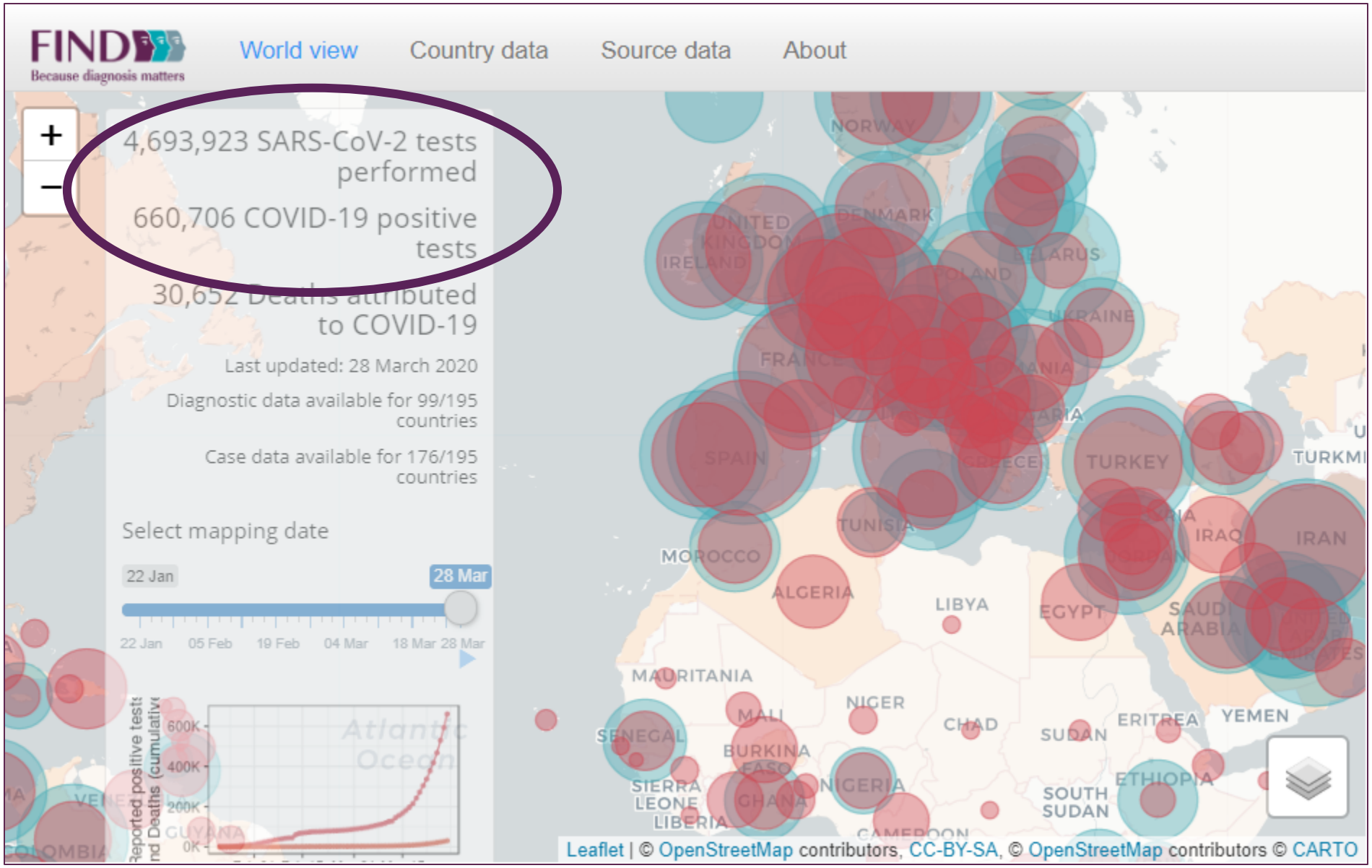
World Health Organization

AFRICA CDC
Centres for Disease Control and Prevention
Safeguarding Africa's Health



Over 4,6 million SARS-CoV-2 tests have been performed to date

(diagnostic data reported by 99/195 countries)



What is the goal of testing for COVID-19?

***Either*:**
Stop transmission and prevent spread

- Countries with **no cases**
- Countries with 1 or more cases, imported or locally detected (**sporadic cases**)
- Countries experiencing **clusters of cases** related in time, geographic location, or common exposure

***Or*:**
Slow transmission, reduce case numbers, end community outbreaks; reduce health, social, economic impact; minimize healthcare disruptions for non-COVID-19 illness

- Countries experiencing larger outbreaks or sustained and pervasive local transmission (**community transmission**)

https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf

Who should be tested?

- Use clinical (**symptoms**) and epidemiological factors (**exposure risk**) to ascertain likelihood of infection
  - **PCR testing of asymptomatic or mildly symptomatic** contacts can be considered in the assessment of individuals who have had contact with a COVID-19 case
  - Rapid collection and testing for patients meeting suspected case definition for COVID-19 is a priority for
    1. Clinical management
    2. Outbreak control

https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117

Case definitions to guide testing

Suspect	Probable	Confirmed
A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset **OR** B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset **OR** C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation	A. A suspect case for whom testing for the COVID-19 virus is inconclusive* **OR** B. A suspect case for whom testing could not be performed for any reason *Inconclusive being the result of the test reported by the laboratory	A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms See laboratory guidance for details: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance

https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)

Overview: COVID-19 diagnostics to detect SARS-CoV-2 infection

	Molecular test	Immunoassay		Non disease-specific tests
		Antibody based	Antigen based	
How does it work?	Detects the presence of viral genetic material in a sample	Detects the presence of anti-viral antibodies in a sample	Detects the presence of viral proteins (antigens) in a sample	Detects signs and symptoms of disease
What technique is used?	Usually based on a technique called polymerase chain reaction (PCR), which makes millions of copies of a specific section of the viral genome, amplifying small amounts to detectable levels	Usually based on a technique called enzyme linked immunosorbent assay (ELISA), in which molecules attach to the antibodies or antigen in the sample and produce a detectable signal		Techniques include thermal scanning to identify people with a fever (higher than normal temperature) and computed tomography (CT) chest scans to distinguish from other chest infections
Where does testing take place?	Usually performed in a laboratory due to equipment requirements	May be laboratory based or performed at point of care (depending on test design)		Usually performed outside of the laboratory, in clinic or at point of care, depending on equipment needs
What is the most common use?	Testing people suspected of having COVID-19	Assessing overall infection and immunity rates in a community	Testing people suspected of having COVID-19 or screening/ triage to identify candidates for further testing (depending on test design)	Screening/triage to identify candidates for further testing
A positive result…	Confirms a current SARS-CoV-2 infection	Indicates a recent or past infection, and could be used to screen for current infection (tests may not be reliable in early phase of infection)	Confirms a current SARS-CoV-2 infection or suggests a potential infection (depending on test design)	Suggests a potential infection and indicates that further testing is needed

Samples used for SARS-CoV-2 tests

- Nasopharyngeal swabs are commonly taken for SARS-CoV-2 diagnostics

- Other sample types that may be tested include
  - Sputum (if you are coughing it up)
  - Blood: used for serological (antibody) testing
  - Stool and/or urine
  - Bronchoalveolar lavage (fluid that has been used to wash the lungs)

- Samples may be taken
  - At home, by a visiting healthcare professional
  - At a drive-thru centre (where a nasal or throat swab is taken through your car window)
  - At a hospital or clinic

- Samples are then sent to a laboratory for testing or may be assessed directly at the point of care, depending on product availability and the design of your diagnostic network

Molecular tests for SARS-CoV-2

- Molecular tests for COVID-19 are based on genetic sequences from the SARS-CoV-2 viral genome
  - All require either an upper or lower respiratory sample
- Tests use sequences unique to SARS-CoV-2 to distinguish from other coronaviruses
  - Two known strains of SARS-CoV-2: different infection rates & disease severity
  - Tests can use sequences common to both strains
- A molecular test requires a number of basic ingredients
  - The enzymes and short DNA sequences (known as primers) that copy the genetic material
  - The building blocks of DNA (nucleotides)
  - A buffer solution
  - The viral genetic material (if present), extracted from the sample using a separate kit
  - The tests are run in a machine that uses repeated cycles of heating and cooling to drive the amplification of the viral genetic material until it reaches detectable levels

Molecular tests for SARS-CoV-2: open vs closed systems

There are three main categories of molecular test for SARS-CoV-2, all of which are performed in labs and therefore **rely on sample collection/transport/result return systems** to ensure decentralized access to testing

	Lab-developed tests (LDT)	Open, manual kits	Closed, proprietary tests & platforms
Test format and quality	• Lab develops their own testing protocol sourcing basic ingredients separately • Lab is responsible for verifying the accuracy of the test and ensuring consistent quality of testing	• Commercial company supplies a kit with all the basic ingredients and is responsible for ensuring their quality • Lab is responsible for ensuring consistent testing quality	• Commercial company supplies a test where all the basic ingredients are already combined, ensures accuracy and quality of the test and has built-in QC to enable monitoring of consistent test quality
Sample type & extraction	• Viral RNA has to be extracted separately then added to PCR test	• Viral RNA has to be extracted separately then added to PCR test	• Usually, extraction and PCR reaction are all integrated
Time to result	• Minimum 3–5 hours	• Minimum 3–5 hours	• Minimum 1 hour
Pros	• Usually the fastest to develop in a more experienced lab • Not reliant on a particular test supplier	• Compatible with a range of lab equipment • Can leverage existing personnel and infrastructure familiar with PCR	• Enables more automation ranging from high-throughput centralized testing to lower-throughput more decentralized testing; can leverage existing install-base and trained personnel, if available • More built-in QC, therefore higher confidence in quality of results
Cons	• Requires separate nucleic acid extraction • More prone to variability and requires QC and QA of test reagents and end-users	• Requires separate nucleic acid extraction • Requires well-trained staff and frequent proficiency testing to ensure quality	• Requires procurement of new machinery if no existing install-base or new space capacity

Molecular tests for SARS-CoV-2: product overview

Examples; list not exhaustive

LDTs	Manual/open kits	Closed/proprietary tests

• https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance
  ➢ China CDC
  ➢ Charité
  ➢ US CDC
• US FDA EUA labs: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd
	• altona Diagnostics, RealStar®
	• BGI Genomics Co. Co. Ltd, Real-time RT-PCR kit
	• DAAN Gene Co. Ltd, detection kit for 2019-nCOV RNA
	• Primerdesign Ltd. Genesig RT-PCR assay
	• Seegene Inc. Allplex 2019-nCoV assay S
		• Abbott RealTime SARS-CoV-2 assay(m2000 sp/rt)
		• Biofire COVID-19 Test
		• Cepheid Xpert Xpress SARS-CoV-2 test (GeneXpert)
		• CerTest, VIASURE SARS-CoV-2 (BD MAX™)
		• Roche cobas SARS-CoV-2 (68/8800)

Pipeline of tests that are commercially available & in development:
https://www.finddx.org/covid-19/pipeline/

Tests that have been approved for use by various national regulatory authorities:
https://www.who.int/diagnostics_laboratory/200326_imdrf_collated_table_26_march_2020.pdf?ua=1

Decentralized, wide-spread access to SARS-CoV-2 testing is needed

- POC tests which can be performed outside of the laboratory
  - A prime example of this are RDTs in which testing can occur outside of laboratories by trained personnel
  - RDTs are usually based on detecting viral Ag or Ab and thus are rarely as accurate as lab-based testing
- Widespread sample collection with transport to central labs with high-throughput PCR or to more mid-level laboratories with lower testing throughput
- Consideration of rapid setup of mobile laboratories

Unique features of SARS-CoV-2 that should be considered when using RDTs

- SARS-CoV-2 is a respiratory pathogen, unlike HIV, dengue, Zika, chikungunya
- Immune response may be atypical
  - HIV, flaviviruses, other viruses: IgM is detectable in the blood during active infection and then wanes after a few weeks; IgG levels rise after the acute phase
  - SARS-CoV-2: preliminary studies suggest that *both* IgM and IgG rise after the first few days of infection and may remain high for weeks (more data needed)
- There may be high levels of virus days before the onset of symptoms
- In a pandemic situation, where there are no specific treatments and the goal is to minimize spread of the infection, strive to select tests with the *highest possible sensitivity* to minimize the possibility of missing active cases
  - To reduce the burden on confirmatory testing, a positive result from a screening test (even with low specificity and thus a higher probably of false positivity) may not require confirmation
  - In this scenario, all individuals who screen positive should be directed to home-isolate or be admitted to a healthcare facility, if symptoms are indicative of hospitalization

RDTs can detect either ANTIGEN or ANTIBODY: different uses in the COVID-19 response

	Antigen (Ag)	Antibody (Ab) IgM or IgG; preferentially IgM & IgG
How does it work	• Directly detects the presence of the virus, indicating ACTIVE infection	• Detects the body's immune response to the virus, in the form of antibodies, which are present during ACTIVE infection and persist to indicate PREVIOUS infection
Most common uses	• Screen/triage patients who have ACTIVE infection and exclude individuals who are uninfected • May be considered to monitor active infection and recovery	• Identify people who have been exposed to the virus and have immunity* • Insufficient data on whether can be used to rule in or rule out ACTIVE infection ➢ A positive test in the presence of symptoms is likely consistent with COVID-19
Sample type	• Nasopharyngeal, nasal, or oropharyngeal swab; potentially, oral fluid and stool	• Finger stick blood, venous blood; potentially, oral fluid
Where & who performs	• Trained healthcare workers, wearing appropriate PPE in decentralized points of need	

** Insufficient data on whether immunity convers protection*

RDTs can detect either ANTIGEN or ANTIBODY: results interpretation

	Antigen (Ag)	Antibody (Ab) IgM or IgG; preferentially IgM & IgG
A positive result…	• If used as a SCREENING test, means the person is *likely infected*; follow with a CONFIRMATORY PCR • If used as a CONFIRMATORY test, means the person is *infected* and should home-isolate or be admitted to the healthcare facility	• Indicates a *current or past* infection ➢ To INCUDE/EXCLUDE active infection, need to follow with a test that directly detects virus (i.e. PCR or Ag)
A negative result…	• Means the person is *likely uninfected* (depending on the SENSITIVITY of the test) ➢ If low sensitivity in the presence of symptoms, need a CONFIRMATORY PCR test; if no symptoms, then should monitor and consider a CONFIRMATORY test	• May indicate the person has *not been exposed* to the virus • Could also mean the is *early* in the course of ACTIVE infection (window period) and antibodies are not yet detectable ➢ To INCLUDE/EXCLUDE active infection, need to follow with a test that directly detects virus (i.e. PCR or Ag)
A FALSE positive result…	• The person is uninfected but will unnecessarily be in home-isolation or be admitted to health facility to manage symptoms	• If used to screen for infection, the person is uninfected, but will unnecessarily be in home-isolation or be admitted to the heal • If used to screen for immunity, the person is actually not immune and could be put at risk and pose a risk to others
A FALSE negative result…	• The person is infected, but is missed. (S)he may not receive the care (s)he needs and *will contribute to community transmission* if not in isolation	• If used to screen for infection, the person is infected and likely in the window period, so is missed. (S)he may not receive the care (s)he needs and will contribute to community transmission if not in isolation • If used to screen for immunity, the person is actually immune, but no action is taken and represents a missed opportunity

- Selection of **HIGH sensitivity** tests decreases the risk of FALSE NEGATIVE results
- Selection of **HIGH specificity** tests decreases the risk of FALSE POSITIVE results

COVID-19 test types: summary of uses

Use case	Molecular (open/closed PCR)	Antigen RDT	Antibody (RDT or lab-based IA)
Confirmation of active infection	X	X	Depending on performance
Monitor disease progression	X	Depending on performance	
Previous exposure			X
Population surveillance			X

Once you set your testing algorithm, select specific products

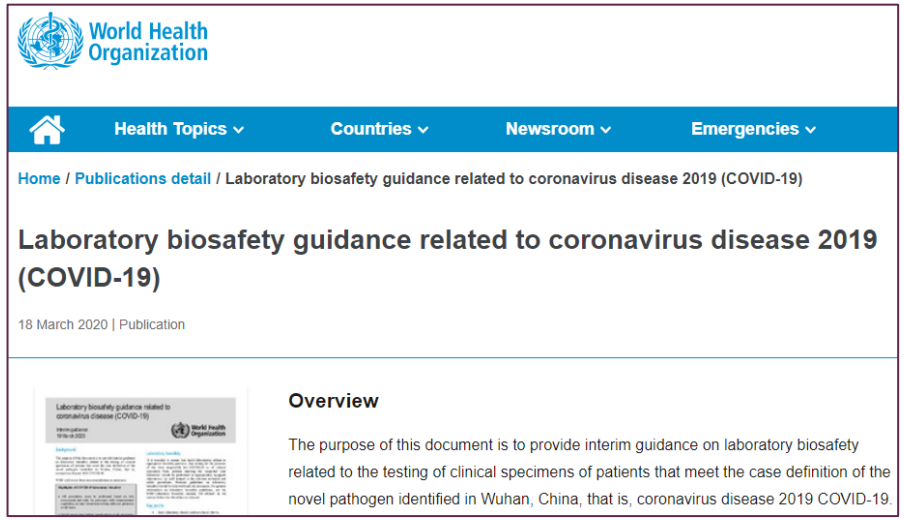
- Prioritize tests that have been assessed through a national emergency use authorization or WHO emergency use listing
  - *Note that requirements for emergency use may vary substantially between countries and generally are less rigorous than existing regulatory approval procedures*
- Select companies that meet international quality management systems, i.e. ISO13485 or equivalent
- Prioritize tests that already have an existing distributor/supply network in your country may enable more rapid and continual access to kits
- Understand what sample collection materials and other reagents/consumables are required to perform the test that are not supplied by the test manufacturer
- Ask suppliers for a copy of their instructions for use before implementing their test: be clear on requirements needed to support the roll out of the test and be clear on the supplier's performance data
  - Consult independently generated performance data where possible (e.g. FIND evaluations)

Biosafety is critical for every test

- Recommended biosafety level: **BSL-2**
- Risk assessment
  - Site- & activity-specific risk assessments to determine if enhanced biosafety precautions are warranted

Follow standard precautions for any potential COVID-19 specimens and use Class II biosafety cabinet in case of procedures with potential to generate aerosols or droplets (vortexing, centrifuging, pipetting)

- Disinfectants
  - EPA-registered hospital disinfectants with label claims as effective against other respiratory pathogens
- Waste disposal
  - Standard procedures for other respiratory pathogens, e.g. biohazardous waste containers should be leakproof & closed prior to removal from the laboratory
- Specimen handling, packaging & transport
  - Follow UN 3373 Biological Substances, Category B: leak-proof primary container, rigid, leak-proof, watertight secondary packaging with absorbent material, rigid outer packaging to protect the specimens during shipment



https://www.who.int/publications-detail/laboratory-biosafety-guidance-related-to-coronavirus-disease-2019-(covid-19)

Assuring quality of molecular SARS-CoV-2 testing: available EQA schemes

Provider	Number of samples	Applicability	Registration deadline	Evaluation period	Fee
QCMD	8	Global	1 Apr 2020	Spring 2020	€373
INSTAND	8	Global	Not mentioned	Spring 2020	€295
WHO Health Emergencies and Global Influenza programme	5	Influenza RL	31 Mar 2020	Spring 2020	None
ECDC/EVD-LabNet/ERLI-Net	Unknown	EU influenza RL	1 Apr 2020	Spring 2020	None

List not exhaustive – many other groups are beginning to offer EQA schemes.
Choose providers who are experienced in delivering EQAs within your region.

Assuring quality of molecular SARS-CoV-2 testing: available control materials

Provider	Material / product name	Targeted genes	Concentration	Price
ZeptoMetrix	NATtrol™ SARS-CoV-2 (recombinant) Stock	N	Ct range 22–25	US$550
	NATtrol™ SARS-CoV2 (E/ORF1ab recombinant) Stock	E/ORF1	Ct range 22–25	US$550
SeraCare	AccuPlex™ SARS-CoV-2 Reference Material Kit	N/E/ORF1/RdRp	5,000 copies/mL	US$485
EVA	2019-nCoV E gene stabilized RNA as positive control	E	100 rxn/vial	€200
	SARS-CoV-2 RdRp gene stabilized RNA as positive control	RdRp	100 rxn/vial	€50
BIO-RAD	SARS-CoV-2 Standard	N/E/ORF1/RdRp/S	200,000 copies/mL	Unknown

All are full process controls, i.e. require RNA extraction.
List not exhaustive & does not include control material provided in RT-PCR kits.

Overview of key considerations for diagnostic implementation

Country policy & planning

Diagnostic network

Infrastructure

Personnel

Lab–clinical interface

Biosafety & quality assurance

Supply chain

Implementation monitoring

Open-source digital solutions

Financing

COMING SOON: Online technical assistance and laboratory training

- FIND is partnering with ASLM and LSHTM to develop an online learning platform comprising learn-at-your-own-pace training modules
- Target launch: 20 April 2020

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ASLM
AFRICAN SOCIETY FOR LABORATORY MEDICINE

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

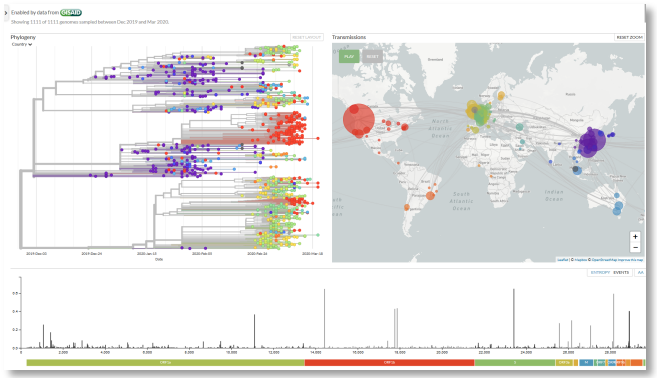
Future Learn

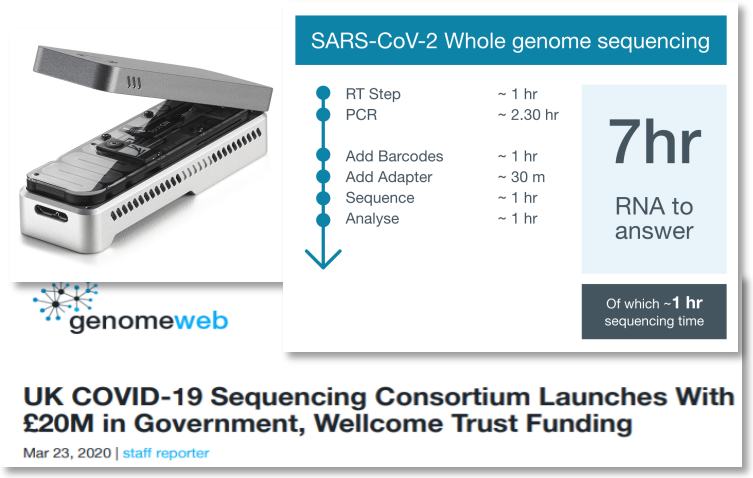
Outstanding questions

- The overall kinetics of expression of viral RNA, viral antigen and specific antibodies need to be better studied to more accurately inform the appropriate use of each biomarker in diagnosis, monitoring and surveillance for COVID-19 disease

- Despite the tremendous speed with which novel tests for SARS-CoV-2 have been developed, there is minimal independent data verifying the accuracy of tests

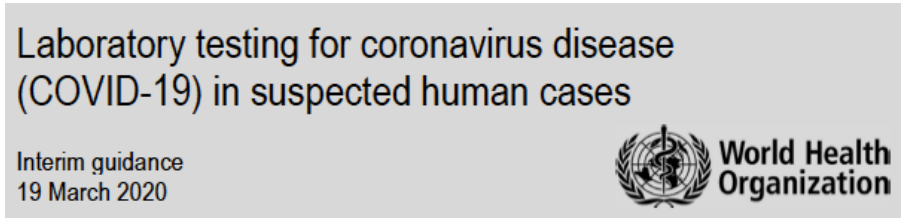
Next-generation sequencing for COVID-19 and beyond





- Can be used for outbreak tracing, transmission mapping and surveillance, critical for ‘genomic epidemiology’
- Characterises the virus to help public health authorities understand the identity of the virus, whether it is changing and how and where it is being transmitted
- Example: Oxford Nanopore, performed using the MinION platform
  - Whole genome sequencing protocol
  - Can also be used to sequence portions of viral RNA
  - Can be used to sequence other respiratory viruses in a sample
  - Already in use in multiple countries
- LMIC sequencing **capacity building needed** for broad and sustained use in COVID-19 and future outbreak management and surveillance
- Complex bioinformatics requires training and capacity building; data sovereignty issues must be addressed

Further reading



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https://www.cdc.gov/coronavirus/2019-ncov/lab/lab-biosafety-guidelines.html

https://www.finddx.org/covid-19

SARS-COV-2 DIAGNOSTIC PIPELINE

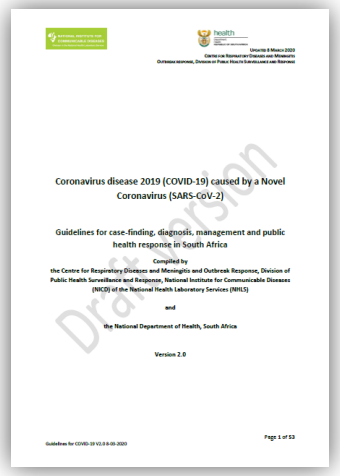
SARS-COV-2 DIAGNOSTICS: PERFORMANCE DATA

SARS-COV-2 TEST TRACKER (INTERACTIVE MAP)

SARS-COV-2 DIAGNOSTIC USE CASES

FIND EVALUATION UPDATE: SARS-COV-2 MOLECULAR TESTS

FIND EVALUATION UPDATE: SARS-COV-2 IMMUNOASSAYS



http://www.nicd.ac.za/wp-content/uploads/2020/03/NICD_DoH_COVID-19_Guidelines_8_March_2020_final.pdf

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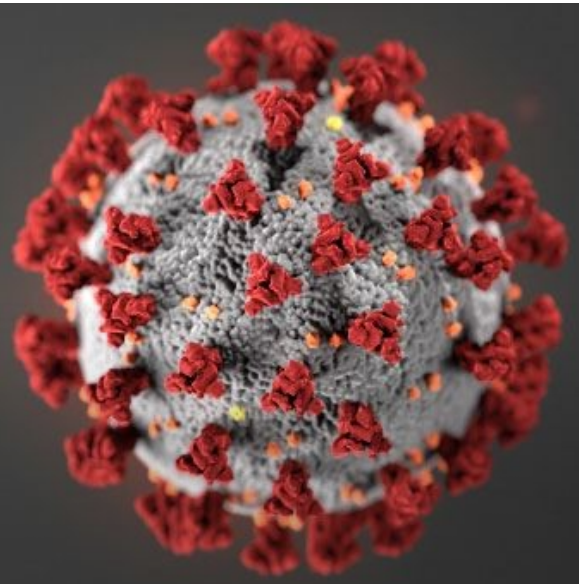
THANK YOU



For more information please contact the FIND Pandemic Preparedness team:
outbreaks@finddx.org

www.finddx.org/covid-19