The Evolving Role of Diagnostics in the COVID-19 Pandemic Response

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Director, International Diagnostics Centre

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Plan of Presentation

• Value of diagnostics in epidemic preparedness and response

• Special features of SARS-CoV-2 relevant to diagnostic testing

• Changes in use of diagnostics over the course of the pandemic
  – Diagnostics for clinical medicine
  – Diagnostics for public health

• Summary
Globally, as of 4:53pm CEST, 7 September 2021, there have been 221,134,742 confirmed cases of COVID-19 and 4,574,089 deaths, reported to WHO. As of 6 September 2021, a total of 5,352,927,296 vaccine doses were administered.
The Director-General of the World Health Organization urged countries to “test, test, test.”

He said testing, isolation, and contact tracing should be the backbone of the global pandemic response.

The Value of Diagnostics for Infectious Diseases of Epidemic Potential

For patient management:
• Confirm clinical diagnosis in symptomatic patients
• Enable patients to get the right treatment and appropriate care
• Inform patients of measures to stop spread of infection

For disease control & prevention
• Enable contact tracing and screening of those at enhanced risk of acquiring and transmitting infection
• Map location of cases to track pattern of transmission and identify hotspots
• Enable the implementation of disease control strategies such as mask mandates, quarantines, lockdowns, border measures
The **Right Test** for the **Right Patient** at the **Right Time** in the **Right Setting**

<table>
<thead>
<tr>
<th>Diagnostic Tests</th>
<th>Target</th>
<th>Optimal time for use post onset symptoms</th>
<th>Use Case</th>
<th>Accuracy</th>
<th>Access-ibility</th>
<th>Affordability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular: Lab</td>
<td>Viral RNA</td>
<td>day 0-7</td>
<td>confirm infection</td>
<td>****</td>
<td><strong>√</strong></td>
<td>$$$$</td>
</tr>
<tr>
<td>POC</td>
<td>Viral Proteins</td>
<td>day 0-7</td>
<td>confirm infection</td>
<td>**</td>
<td><strong>√√</strong></td>
<td>$$$$</td>
</tr>
<tr>
<td>Serology: Lab</td>
<td>Host Antibodies</td>
<td>day 7-40</td>
<td>exposure, surveillance</td>
<td>***</td>
<td><strong>√√</strong></td>
<td>$</td>
</tr>
<tr>
<td>POC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Sens**: Sensitivity
- **Spec**: Specificity
- **√**: High
- **√√**: Moderate
- **√√√**: Low
- **$$\$$**: High Cost
- **$$**: Moderate Cost
- **$**: Low Cost
Evolving Role of Diagnostics: from Pandemic Response to Control

Pathogen identified and genome sequence known
- Diagnostics to refine COVID19 case definition
- Testing all symptomatic individuals to enable public health measures, determine extent and speed of transmission & conduct studies to understand the modes of transmission
- Testing contacts of confirmed cases to interrupt the chain of transmission

Asymptomatic and pre-symptomatic transmission confirmed
- Testing of symptomatic individuals and contacts continues
- Screening of populations at enhanced risk of acquisition and transmission e.g. health and elder home care workers
- Testing for travel and occupational groups in non-health care settings

Vaccination and variants of concern (VOCs)
- Demand for testing of symptomatics, contacts and screening in high risk environments in health and non-health care settings may decrease with vaccination roll out but testing is now important for surveillance, esp to track VOCs
- Testing for travel to include pre-boarding and on-arrival testing
- Pilot use of rapid tests to return to schools, work and mass gatherings to save livelihoods
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COVID-19: using the right test at the right time

Unique features of COVID-19:
- Infected individuals can shed virus 2-3 days before onset of symptoms
- Infectivity period: 8-9 days post onset of symptoms
- By day 7 post onset of symptoms, 10-70% of patients already have detectable IgM and IgG antibodies
- RNA+ can persist for weeks
IgM and IgG Responses in Symptomatic COVID-19 Patients

Source: Health Information and Quality Authority, Ireland, 2020
Use of Tests in Combination: RNA/Antigen + Serology Tests

- Patients typically present late as symptoms for a variety of reasons
- A combination of molecular/antigen + serology tests may be useful for delayed case finding and contact tracing

<table>
<thead>
<tr>
<th>Days post onset of symptoms</th>
<th># patients</th>
<th>RNA+ (%)</th>
<th>AB+ (%)</th>
<th>RNA +Ab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>94</td>
<td>66.7</td>
<td>38.3</td>
<td>78.7</td>
</tr>
<tr>
<td>8-14</td>
<td>135</td>
<td>54.0</td>
<td>89.6</td>
<td>97.0</td>
</tr>
<tr>
<td>15-39</td>
<td>90</td>
<td>45.5</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Zhao et al. Antibody responses to SARS-CoV-2 in patients of novel corona virus disease. CID 2020
Neutralising antibody responses and viral load in hospitalised COVID-19 patients

To et al. Lancet Infect Dis Mar 2020

RBD = Receptor Binding Domain (RBD) of the Spike protein
NP = nucleocapsid protein (NP)
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Covid-19 Diagnostic Algorithm

Patient with COVID-like symptoms

Molecular Test

Positive

SARS-CoV-2 confirmed

Negative

Repeat molecular test if high index of suspicion

Positive

Negative*

No evidence of COVID-19, but should continue to adhere to public health measures

*Still high index of suspicion: Do Antibody test – not part of WHO recommendation

https://apps.who.int/iris/handle/10665/342002
https://iris.paho.org/handle/10665.2/54449
Challenges with PCR Testing

- High per test cost
- Requires laboratory and expensive equipment
- Requires skilled personnel
- Results take hours or even days
- Global competition led to inequities of access
- POC tests but supply limited by speed of manufacturing
## FDA EUA approved COVID-19 Antigen Instrument-based Assays

WHO has **recommended Ag Test sensitivity of 80% and Specificity of 97% vs Molecular test e.g. PCR**

<table>
<thead>
<tr>
<th>Company/test</th>
<th>Assay Technology</th>
<th>Ag</th>
<th>Sym/Asym</th>
<th>Nasal/NP swab</th>
<th>Time to result</th>
<th>Sensitivity (95% CI)*</th>
<th>Specificity (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becton-Dickinson/Veritor</td>
<td>Chromatographic Digital Immunoassay + flu A and B</td>
<td>NuP</td>
<td>A+Sym</td>
<td>N</td>
<td>15 min</td>
<td>84% (67-93)</td>
<td>100% (98-100)</td>
</tr>
<tr>
<td>Luminostic/ClipCOVID</td>
<td>Lateral flow immunoluminescent assay</td>
<td>NuP</td>
<td>Sym d.1-5</td>
<td>N</td>
<td>30 min</td>
<td>97% (84-99.9)</td>
<td>100% (97-100)</td>
</tr>
<tr>
<td>Lumira</td>
<td>Microfluidic Immunofluorescence assay</td>
<td>NuP</td>
<td>Sym d.1-12</td>
<td>N, NP</td>
<td>12 min</td>
<td>97.5% (87-99.6)</td>
<td>97.7% (94.7-99)</td>
</tr>
<tr>
<td>Quidel Sofia</td>
<td>Lateral Flow, Fluorescence + flu</td>
<td>NuP</td>
<td>A+Sym</td>
<td>N, NP</td>
<td>15 min</td>
<td>96.7% (83-99)</td>
<td>100% (98-100)</td>
</tr>
</tbody>
</table>

*Performance data from companies

NuP = nucleocapsid protein; sym= symptomatic; A=asymptomatic; N=nasal; NP= nasopharyngeal
Covid-19 Diagnostic Algorithm

Patient with COVID-like symptoms

Antigen Test

Positive

SARS-CoV-2 detected

Negative

Molecular or 2nd antigen test

Positive

No evidence of COVID-19, but should continue to adhere to public health measures

Negative
Evolving Role of Diagnostics: from Pandemic Response to Control

Pathogen identified and genome sequence known

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COVID-19 Pandemic: Policy decisions on scaling up testing

Access options:

Health Facilities

Community Venues

Diagnostic options:

Lab based Molecular Tests
- Testing of symptomatic individuals
- Testing contacts of cases
- Screening of health care workers, care home workers, first responders

Rapid Molecular/Antigen Tests

Screening of asymptomatic individuals:
- in schools
- in workplaces
- Mass gatherings
- for travel

Coverage? Frequency? What test? Where?
# Examples of Single-use Disposable COVID-19 Ag-RDTs

<table>
<thead>
<tr>
<th>Company/test</th>
<th>Home test</th>
<th>Asym/Sym</th>
<th>Nasal/NPswab</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Limit of detection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA EUA:</strong> (performance data from companies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott BinaxNOW</td>
<td>-</td>
<td>A+S</td>
<td>N</td>
<td>93.3%</td>
<td>99.9%</td>
<td>-</td>
</tr>
<tr>
<td>Abbott BinaxNOW home test (app)</td>
<td>✓</td>
<td>A+S</td>
<td>N</td>
<td>91.7%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Abbott BinaxNOW self-test (app)</td>
<td>✓</td>
<td>A+S</td>
<td>N</td>
<td>84.6%</td>
<td>98.5%</td>
<td>-</td>
</tr>
<tr>
<td>Access Bio/CareStart</td>
<td>✓</td>
<td>A+S</td>
<td>N, NP</td>
<td>88.4%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Ellume/Ellume home test (app)</td>
<td>✓</td>
<td>A+S</td>
<td>N</td>
<td>96.0%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Princeton BioMedtech/Status</td>
<td>-</td>
<td>Sym</td>
<td>NP</td>
<td>93.9%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Quidel/Quikvue home test</td>
<td>✓</td>
<td>A+S</td>
<td>N</td>
<td>84%</td>
<td>99%</td>
<td>-</td>
</tr>
<tr>
<td><strong>WHO EUAL:</strong> (performance data from FIND)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott PanBio</td>
<td>-</td>
<td>A+S</td>
<td>NP</td>
<td>90.9%; 86.4%</td>
<td>99.2%</td>
<td>6.88 x 10^5 Viral copy/mL CT&lt;25: 96.8%</td>
</tr>
<tr>
<td>SD Biosensor/Standard Q</td>
<td>-</td>
<td>sym</td>
<td>NP</td>
<td>89%; CT&lt;25: 97%</td>
<td>99.7%</td>
<td>1.15 x 10^6 Viral copy/mL</td>
</tr>
<tr>
<td>Premier Sure Status</td>
<td>-</td>
<td>Sym</td>
<td>NP</td>
<td>74-91%; CT&lt;25: 97%</td>
<td>99.6%</td>
<td>5.97 x 10^5 Viral copy/mL</td>
</tr>
</tbody>
</table>

Time to result: 10-15 min

Most Ag-RDTs use the SARS-CoV-2 Nucleocapsid Protein as a target – performance unlikely to be affected by variants of concern

Performance varies depending on reference standard used and the viral load of specimens used for their evaluation

Home tests available over the counter for 2.5-5 USD

sym = symptomatic; A = asymptomatic; N = nasal; NP = nasopharyngeal; CT = cycle threshold


[https://www.finddx.org/sarscov2-eval-antigen/](https://www.finddx.org/sarscov2-eval-antigen/)
For COVID-19 Screening, Test Sensitivity is Secondary to Frequency and Turnaround time

RNA tests can be positive for weeks after onset of symptoms

Period of infectiousness ~8 days post onset of symptoms

Although less sensitive most antigen Test should be able to detect individuals who are at risk of transmission (viral loads equivalent to PCR Cycle Thresholds (CT) of <25)

Larremore et a. Test Sensitivity is Secondary to Frequency and Turnaround time for COVID-19 Screening. Sci Adv 2020

Testing strategy for the COVID-19 pandemic: Need for a broader framework for policy consultations

- Establishing clear roles for both COVID-19 Ag RDTs and RT-PCR within the new testing strategy

- Support systems are critical to maximize the impact of COVID-19 Ag-RDT implementation by providing:
  - comprehensive training* and supervision
  - Supply chain management
  - quality assurance

- Capturing and integrating testing data to inform evidence-based decisions

- continuously learning and updating testing strategies based on information gained domestically and across the broader African Union region

*ASLM e-Learning platform for Ag-RDTs: https://www.youtube.com/watch?v=N-32qAqZhCw
Africa CDC Recommendations for Ag-RDTs

Figure 1: Algorithm when testing populations with higher suspicion of positivity, including: (1) individuals with symptoms, (2) frontline healthcare workers and/or essential workers, (3) contacts of confirmed cases, (4) high-risk populations in confirmed outbreaks.

Figure 2: Algorithm for general screening of persons (irrespective of symptoms) in settings with unknown or low community transmission, including in schools, workplaces, ports of entry or houses of worship, etc.
COVID-19 Response: Track Test and Treat

1. Control the spread of the SARS-CoV-2
   - Detection

2. Limit the mortality due to COVID-19
   - Patient management

3. Limit the socio-economic impact of COVID-19
   - Continuity of activities
   - Community engagement
Evolution of COVID-19 Detection among Symptomatic patients

Use of Antigenic RDTs
- 80,000 Reported cases
- 60% Detected with Antigenic RDTs
Scaling up testing – policy decision-making needs to be:

- **Science-based**
- **Inclusive** – not limited to:
  - Public health, health professionals
  - Education
  - Civil societies e.g. indigenous groups, disabled persons
  - Finance
  - Trade
  - Tourism
  - Border security
- **Context specific**: political, cultural, social, and economic
- **Agile** – evolve with pandemic trends and new issues:
  - Variants of concern
  - Vaccination
- **Conveyed in clear and compelling messages to the public**

Testing in healthcare settings to save lives:
- Hospitals
- Care homes for the elderly
- Clinics/doctor’s offices
- Nursing stations in remote settings

Testing in non-healthcare settings to save livelihoods:
- Pharmacies
- Schools
- Workplaces
- Mass gatherings
- Border crossings
Testing Truck Drivers in Kenya

- Much of Africa’s multibillion-dollar cross-border trade has been halted because of the COVID-19 pandemic
- Trucks at the port carry cargo destined for Uganda, Rwanda, Burundi, South Sudan and the Democratic Republic of the Congo are stuck at the port of Mombasa, Kenya
- Truck drivers identified as a high-risk group for spreading the virus have to be tested for coronavirus before they leave the port but results can take up to 2 weeks

The International Organization for Migration (IOM) provided rapid COVID-19 PCR tests to truck drivers across Kenya as part of an effort to reinvigorate regional economies in Eastern and Central Africa.

Test results were available within 24-36 hours. IOM staff had tested >17,000 drivers from July to Oct 2020 and ~2% came back positive.

Where once one had 90-kilometer traffic jams at a border, now there is a relatively freer flow of goods out of the port of Mombasa to countries in the region.
Workplace Screening: Meat Processing Plant in Ireland

Main entrance & thermal imaging
Portacabin (canteen) repurposed for RADT
Point of entry to sampling/testing area
View from entrance

“Registration” on entry
Self-sampling booth behind screens
Makeshift “Laboratory”
Test devices labelled with worker ID & time
Mass Gathering: Amir Cup Football Final, Qatar

# Participants: 20,000, outdoor event

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**Entry**

Checks:
- temperature

Preventive measures:
- Wearing masks

Testing:
- Who: all
- What test: antigen tests
- When: 72 hours before entry

---

**Stadium**

Contact time: several hours

Physical distance:
every other seat empty

Preventive measures:
Wearing masks

On site medical personnel

---

**Post-event**

Monitoring of safe environment:
Not done – call for action
Mass Gathering: Music Event, Barcelona

Venue: indoor centre
# Participants: 465 (RCT, control group of 495 did not enter the venue)
Ref: Revello et al. Lancet Inf Dis May 2021

Entry

**Checks:**
- temperature

**Preventive measures:**
- Wearing masks

**Testing:**
- Who: all
- What test: antigen tests
- When: 9 hours before entry

Concert

**Contact time:** mean 2.5 hours, max. 5 hours
**Ventilation:** standard + windows and doors open
**Preventive measures:**
- Wearing masks

**Physical distance:**
- None – all can sing/dance

On site medical and security personnel

Post-event

**Monitoring of safe environment:**
- All participants, including control group, tested 8 days post event.
- None tested positive among case group vs 2 in control group

Ref: Revello et al. Lancet Inf Dis May 2021
# SARS-CoV-2 Variants of Concern

<table>
<thead>
<tr>
<th>Variant of Concern</th>
<th>First identified</th>
<th>Mutations of concern</th>
<th>#countries Reporting</th>
<th>Increased Transmission*</th>
<th>Impact on vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha B.1.1.7</td>
<td>United Kingdom Sept 2020</td>
<td>H69/V70 deletion; Y144 deletion; <strong>N501Y</strong>; A570D; P681H</td>
<td>118</td>
<td>59-74%</td>
<td>Minimal reduction in neutralization by convalescent and post-vaccination sera</td>
</tr>
<tr>
<td>Beta B.1.351</td>
<td>South Africa May 2020</td>
<td>L242/A243/L244 deletion; K417N; E484K; <strong>N501Y</strong></td>
<td>64</td>
<td>~50%</td>
<td>Reduced neutralization by convalescent and post-vaccination sera</td>
</tr>
<tr>
<td>Gamma P.1</td>
<td>Brazil Nov 2020</td>
<td>L242/A243/L244 deletion; K417N; E484K; <strong>N501Y</strong></td>
<td>38</td>
<td>not clear</td>
<td>Significant reduction in neutralization by convalescent and post-vaccination sera</td>
</tr>
<tr>
<td>Delta B.1.672.2</td>
<td>India Oct 2020</td>
<td>L452R, T478K, D614G, P681R</td>
<td>&gt;100</td>
<td>&gt;50% compared to Alpha variant</td>
<td>Reduction in neutralization by convalescent and post-vaccination sera</td>
</tr>
</tbody>
</table>
Modelling Strategies for Reducing Importation Risk of COVID-19 Cases

Dickens BL et al. J Travel Med Aug 2020

No controls

Testing on arrival; +ve quarantine 7 days 90.2%

Testing on arrival; +ve quarantine 14 days 91.7%

Quarantine 7 days 55.4%

Quarantine 14 days 91.2%

Testing on arrival; denied entry if positive 77.2%
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Use of COVID-19 Antigen Tests

As a diagnostic tool:

- Confirm clinical diagnosis in symptomatic patients:
  - hospitals
  - clinics, doctors’ offices
  - testing centres
- Contact tracing
- Case finding in individuals at risk of acquiring and transmitting infection:
  - health care workers
  - first responders
  - essential workers

As a public health tool:

- Test to protect: vulnerable populations
- Time to release: quarantine
- Test to enable: re-opening of schools, return to work; mass gatherings; travel

Home testing:

- Over-the-counter self testing
- Prescription use with telehealth proctor
Limit the Socio-economic Impact of COVID-19 in Cameroon

**Bold Response to COVID-19**

1. No lockdown
2. Schools and Universities opened
3. Organization of major gathering
   - CHAN Football
   - Regional Elections
   - CAN Handball
   - AFCON 2022
4. Burial ...
Globally accessible diagnostics and deep-sequencing tools to establish continuous and sustained global surveillance of disease and variants.

Africa PGI - Monitoring SARS-CoV-2 Sequencing in Africa

Last Updated: 09/01/2021
(Weekly Updates)

37,866
Total SARS-CoV-2 Sequences

37 43 35 1

9,236 2,418 7,631 1

https://africacdc.org/institutes/ipg/
Summary

• We need to use all the diagnostic tests available to end the pandemic

• COVID-19 tests are critical for case detection and to guide patient management

• COVID-19 tests are being used as public health tools to protect public safety, to release from quarantine and to enable economic recovery, re-opening of schools and workplaces, in combination with other preventive measures such as mask wearing, quarantine, hand hygiene and distancing

• Choice of test need to balance risk and benefits of test accuracy, accessibility (ease of use), affordability and time to result

• Testing for surveillance and genomic sequencing are important means of monitoring COVID-19 case rates and the emergence and spread of variants of concern

• Border measures to reduce importation risk will likely become simpler with vaccine rollout and as countries transition from a COVID-19 pandemic response to living with the virus