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

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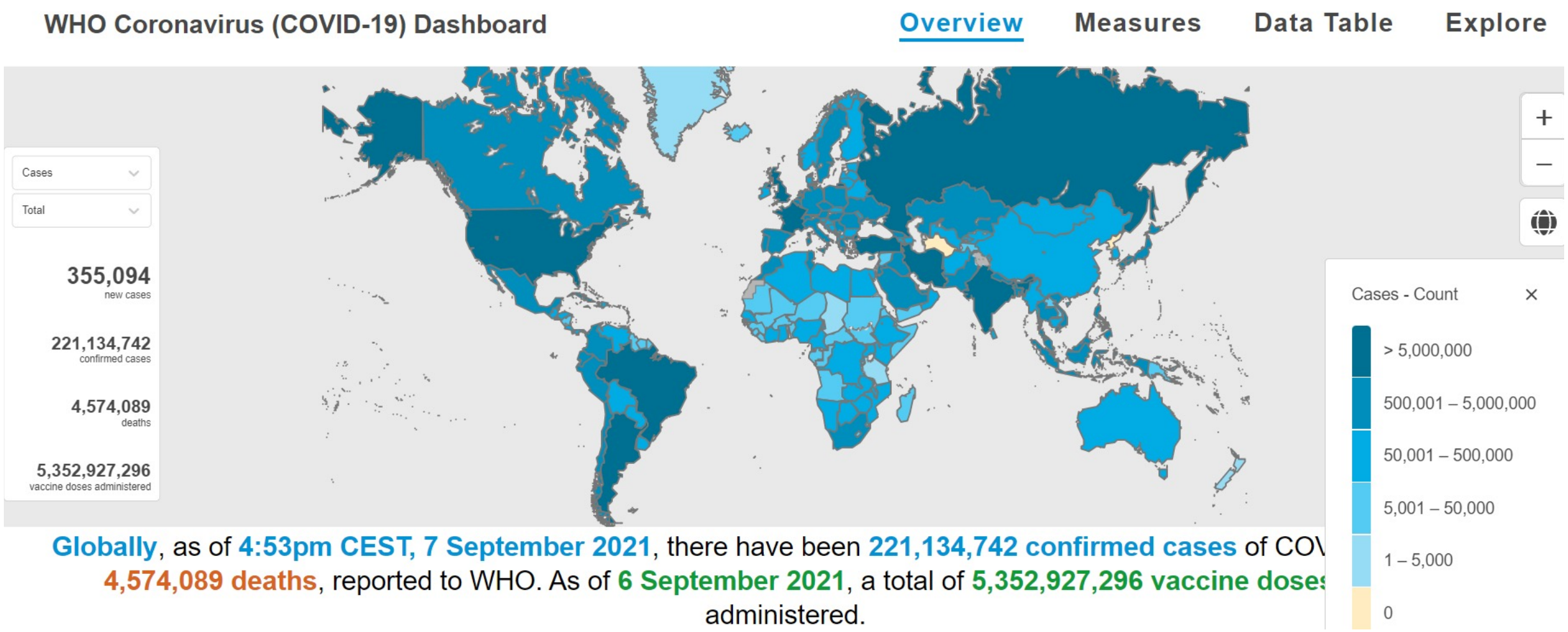
Plan of Presentation

- 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

The COVID-19 Pandemic Today



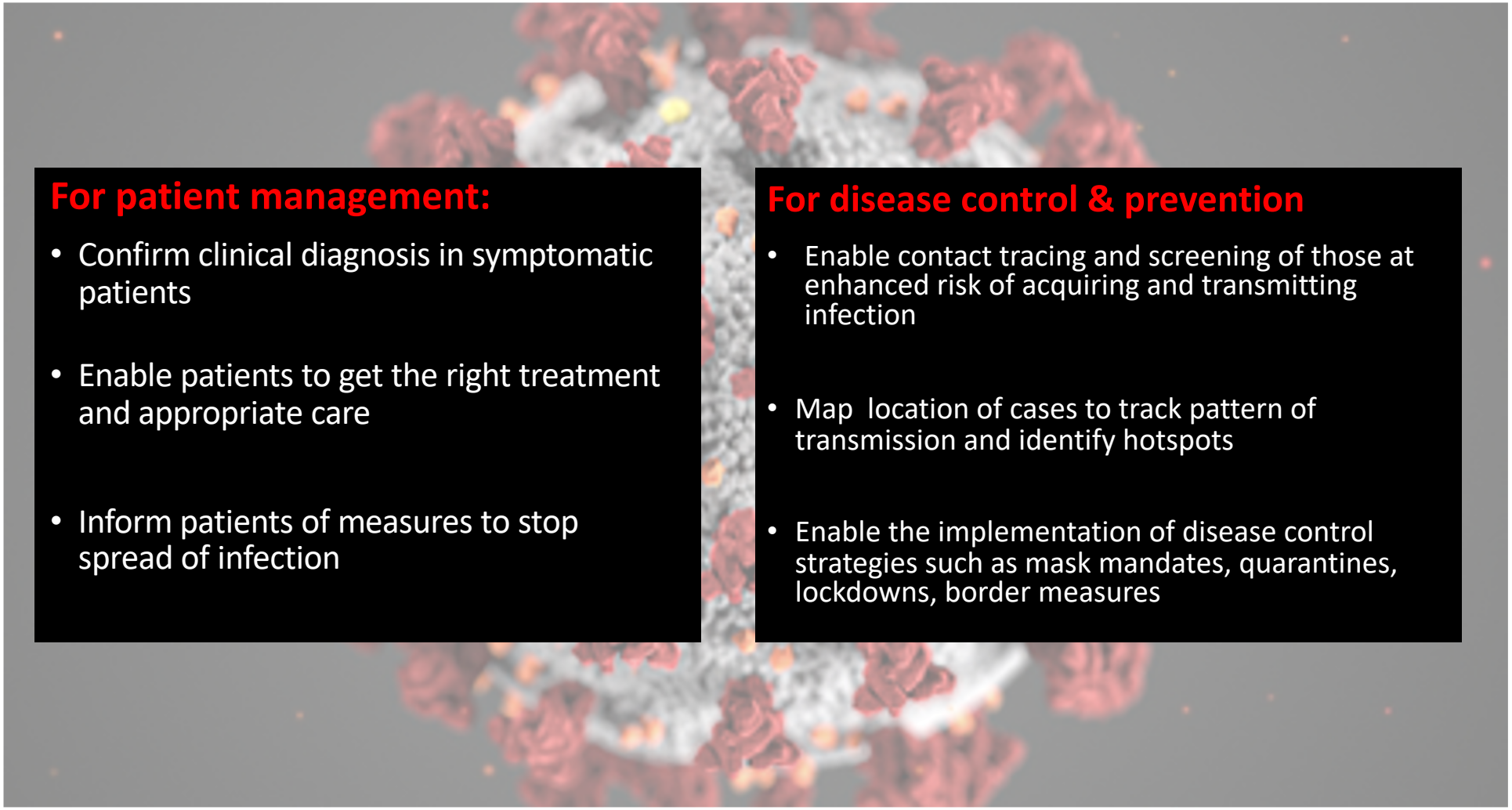
COVID-19 Pandemic: Test, Test, Test

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.

World Health Organization. Director general’s opening remarks at the March 16 2020 media briefing. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---16-march-2020

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

Diagnostic Tests	Target	Optimal time for use post onset symptoms	Use Case	Accuracy		Access-ibility	Affordability
				Sens	Spec		
Molecular: Lab POC	Viral RNA	day 0-7	confirm infection	****	****	√ √√	$$$
Antigens: Lab POC	Viral Proteins	day 0-7	confirm infection	**	***	√√ √√√	$$
Serology: Lab POC	Host Antibodies	day 7-40	exposure, surveillance	***	***	√√ √√√	$

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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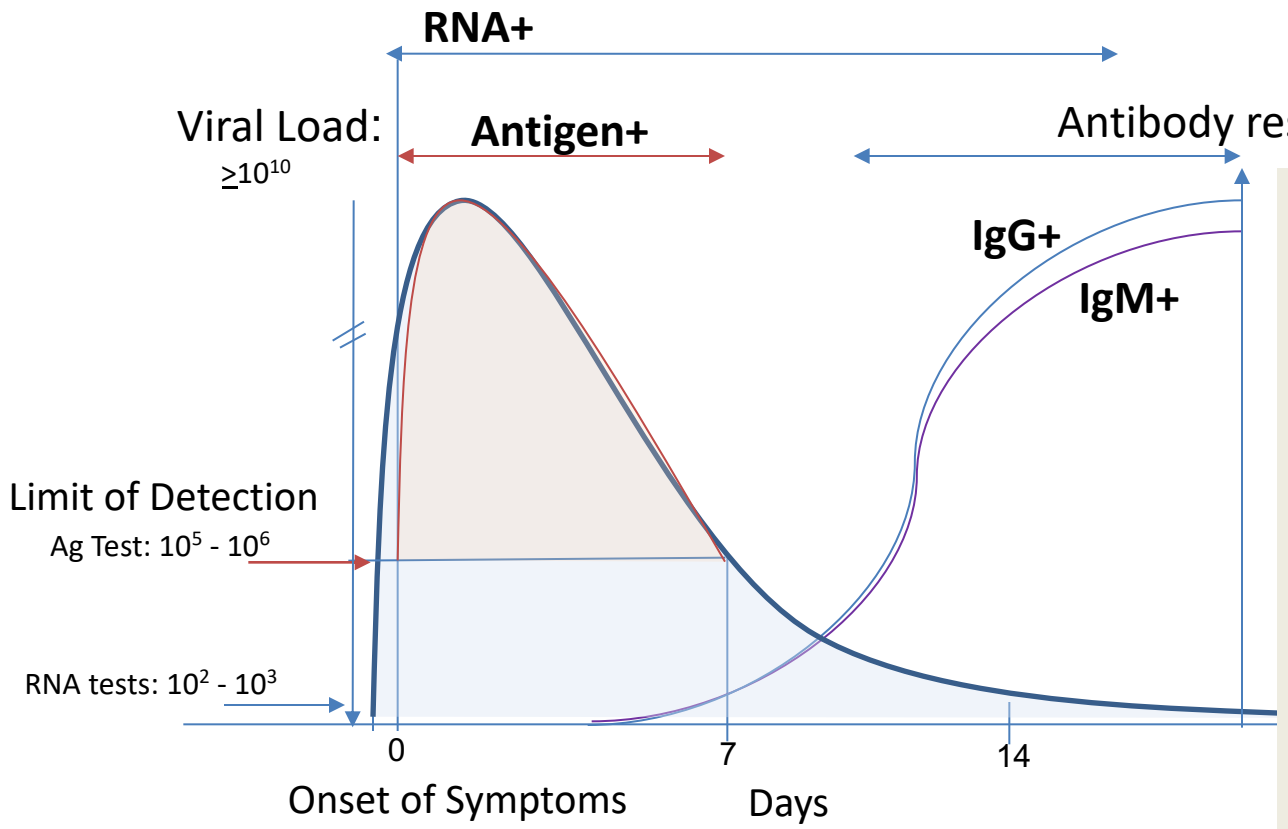
COVID-19: using the right test at the right time



Unique features of COVID-19:

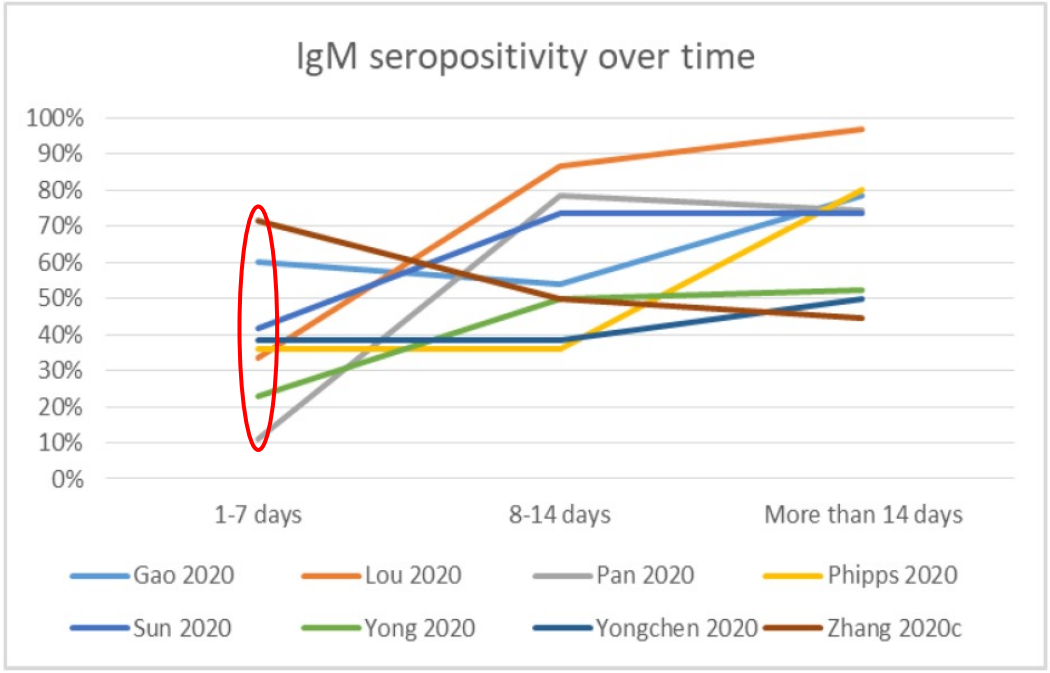
- Infected individuals can shed virus 2-3 days before onset of symptoms

- Infectivity period: 8-9 days post onset of symptoms

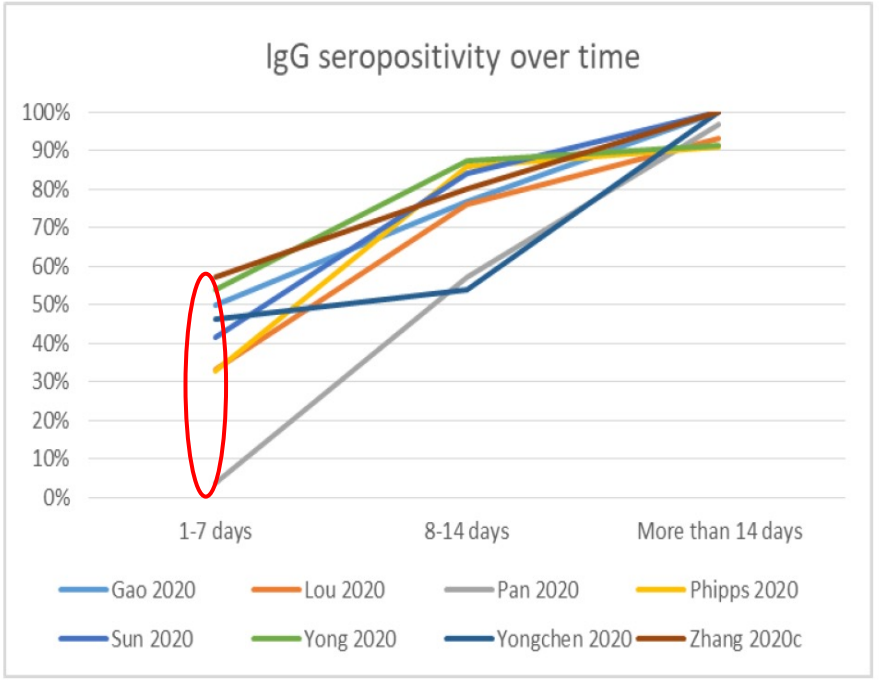
- By day 7 post onset of symptoms, 10-70% of patients already have detectable IgM and IgG antibodies

- RNA+ can persist for weeks

IgM and IgG Responses in Symptomatic COVID-19 Patients



Note – Zhang 2020 collected data at following time points: <10 days, 10-20 days and 20-30 days.



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Source: Health Information and Quality Authority, Ireland, 2020

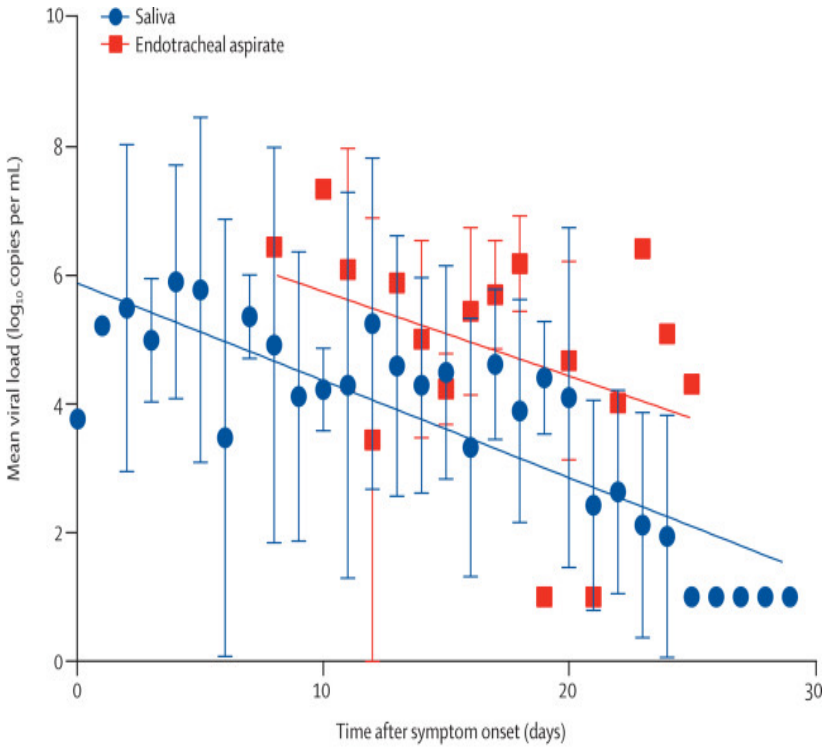
Use of Tests in Combination: RNA/Antigen + Serology Tests

- 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

Days post onset of symptoms	# patients	RNA+ (%)	AB+ (%)	RNA +Ab (%)
1-7	94	66.7	38.3	78.7
8-14	135	54.0	89.6	97.0
15-39	90	45.5	100	100

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

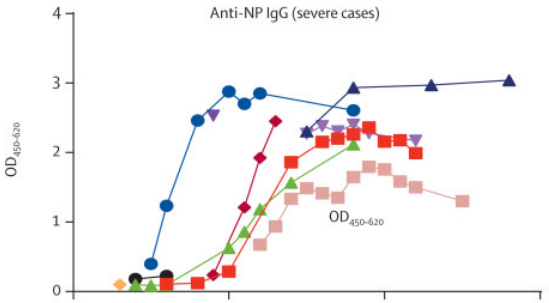


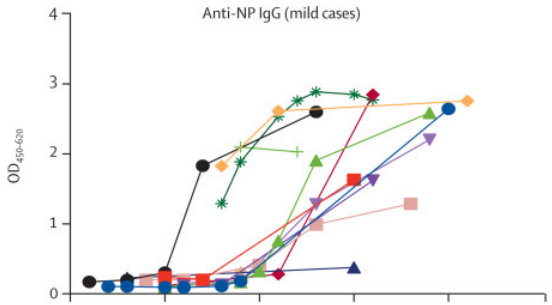
To et al. Lancet Infect Dis Mar 2020

Severe cases, N=10

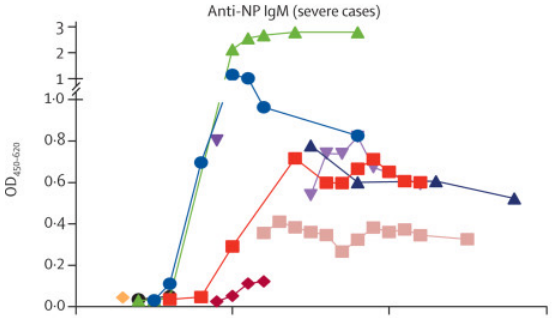
Mild cases, N=13

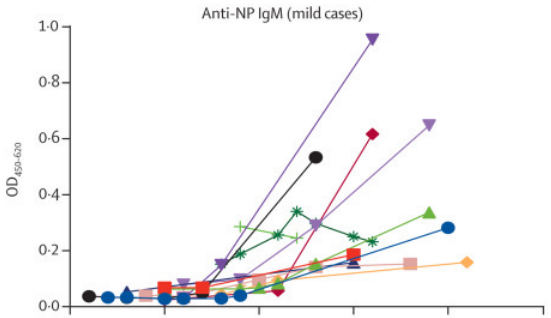
Anti-NP IgG



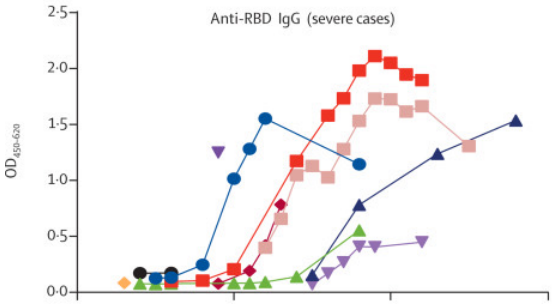


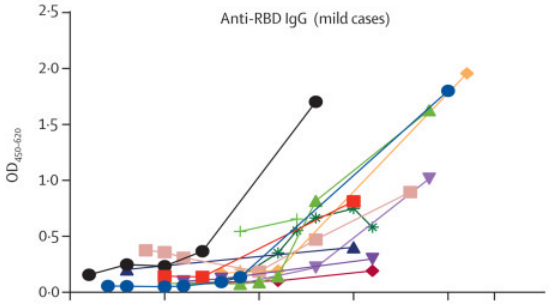
Anti-NP IgM



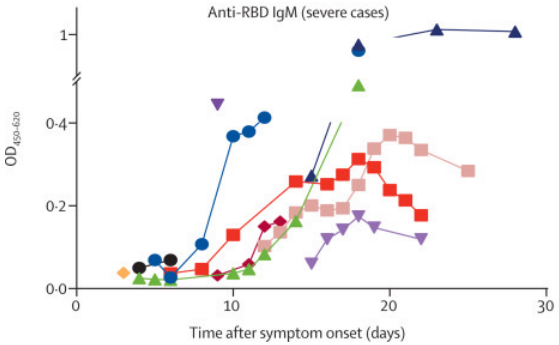


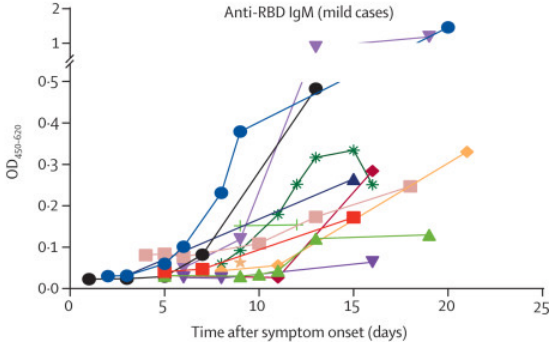
Anti-RBD IgG





Anti-RBD IgM





RBD = Receptor Binding Domain (RBD) of the Spike protein

NP = nucleocapsid protein (NP)

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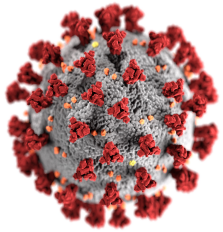
Covid-19 Diagnostic Algorithm



Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities

Interim guidance
25 June 2021

World Health Organization

https://apps.who.int/iris/handle/10665/342002
https://iris.paho.org/handle/10665.2/54449

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

Challenges with PCR Testing

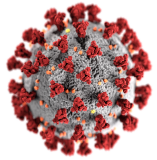
- High per test cost

- 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

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

*Performance data from companies

NuP = nucleocapsid protein; sym= symptomatic; A=asymptomatic; N=nasal; NP= nasopharyngeal

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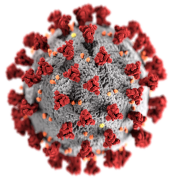

Patient with COVID-like symptoms

Antigen Test

Positive

SARS-CoV-2 detected

Negative

Molecular or 2nd antigen test

Positive

Negative

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

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25 June 2021

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Evolving Role of Diagnostics: from Pandemic Response to Control

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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

Rapid Molecular/Antigen Tests

- Testing of symptomatic individuals
- Testing contacts of cases
- Screening of health care workers, care home workers, first responders

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Mass Gatherings

Online

Border Crossings

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

Company/test	Home test	Asym/ Sym	Nasal/ NPswab	Sensitivity	Specificity	Limit of detection
FDA EUA: (performance data from companies)						
Abbott BinaxNOW	-	A+S	N	93.3%	99.9%	-
Abbott BinaxNOW home test (app)	√	A+S	N	91.7%	100%	-
Abbott BinaxNOW self-test (app)	√	A+S	N	84.6%	98.5%	-
Access Bio/CareStart	√	A+S	N, NP	88.4%	100%	-
Ellume/Ellume home test (app)	√	A+S	N	96.0%	100%	-
Princeton BioMedtech/Status	-	Sym	NP	93.9%	100%	-
Quidel/Quikvue home test	√	A+S	N	84%	99%	-
WHO EUAL: (performance data from FIND)						
Abbott PanBio	-	A+S	NP N	90.9%; 86.4% CT<25: 96.8%	99.2% 99.2%	6.88 x 10^5 Viral copy/mL
SD Biosensor/Standard Q	-	sym	NP	89%; CT≤25: 97%	99.7%	1.15x 10^6 Viral copy/mL
Premier Sure Status	-	Sym	NP	74-91%	99.6%	5.97x105 Viral copy/mL

Time to result: 10-15 min

Most Ag-RDTs use the SARS-CoV-2 Nucleocapsid Protein of as 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

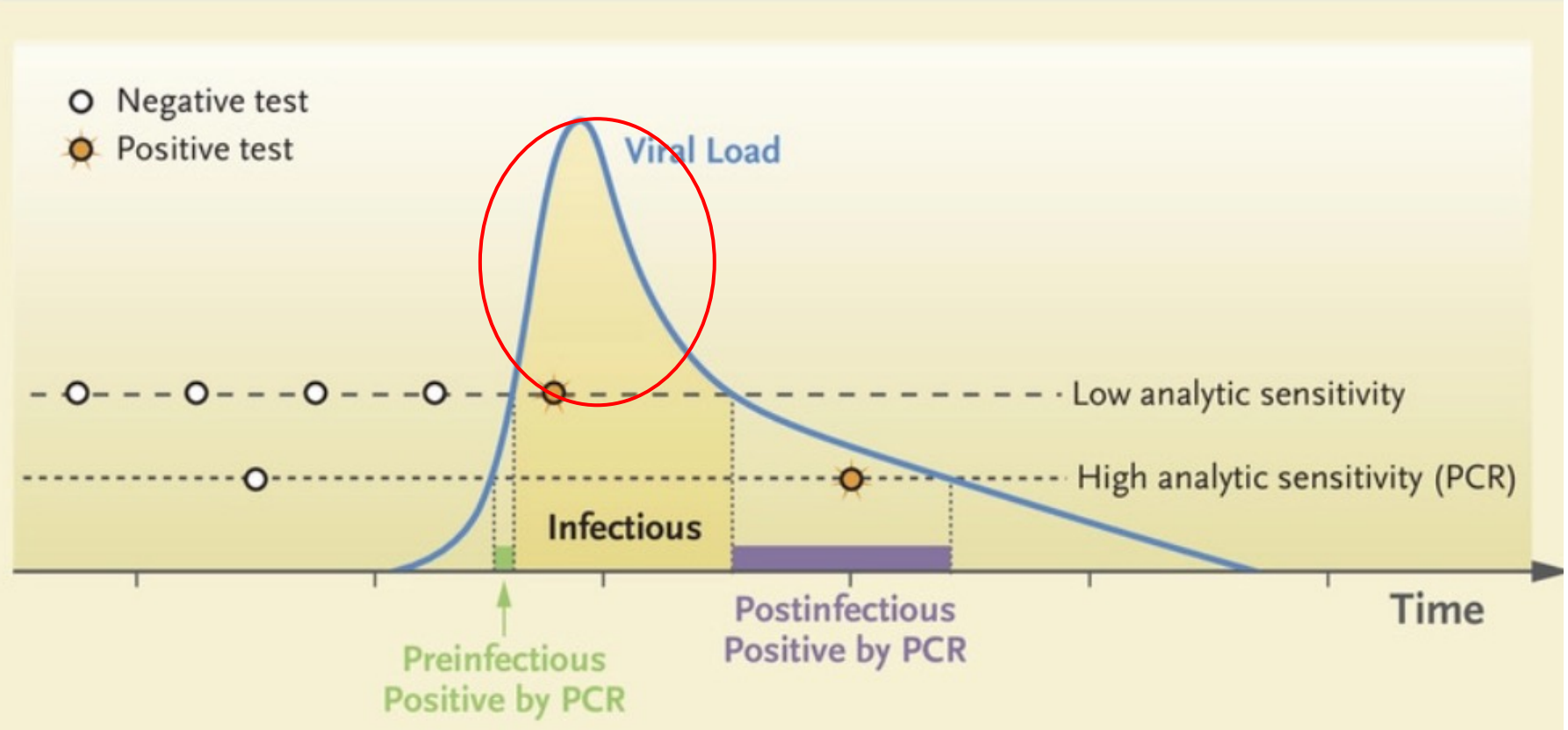
Home tests available over the counter for 2.5- 5 USD

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

- https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-antigen-diagnostic-tests-sars-cov-2

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

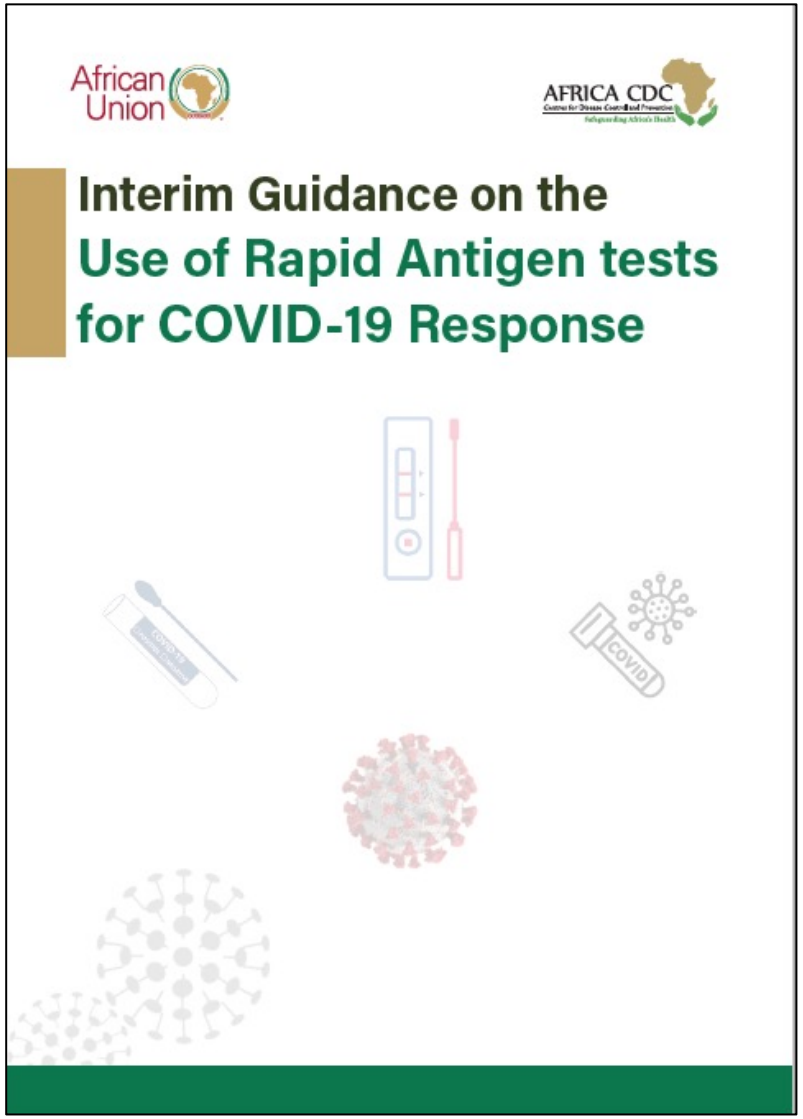
Period of infectiousness ~8 days post onset of symptoms

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

Mina MJ et al. Rethinking strategy for containment. N Engl J Med 2020; 383:e120

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

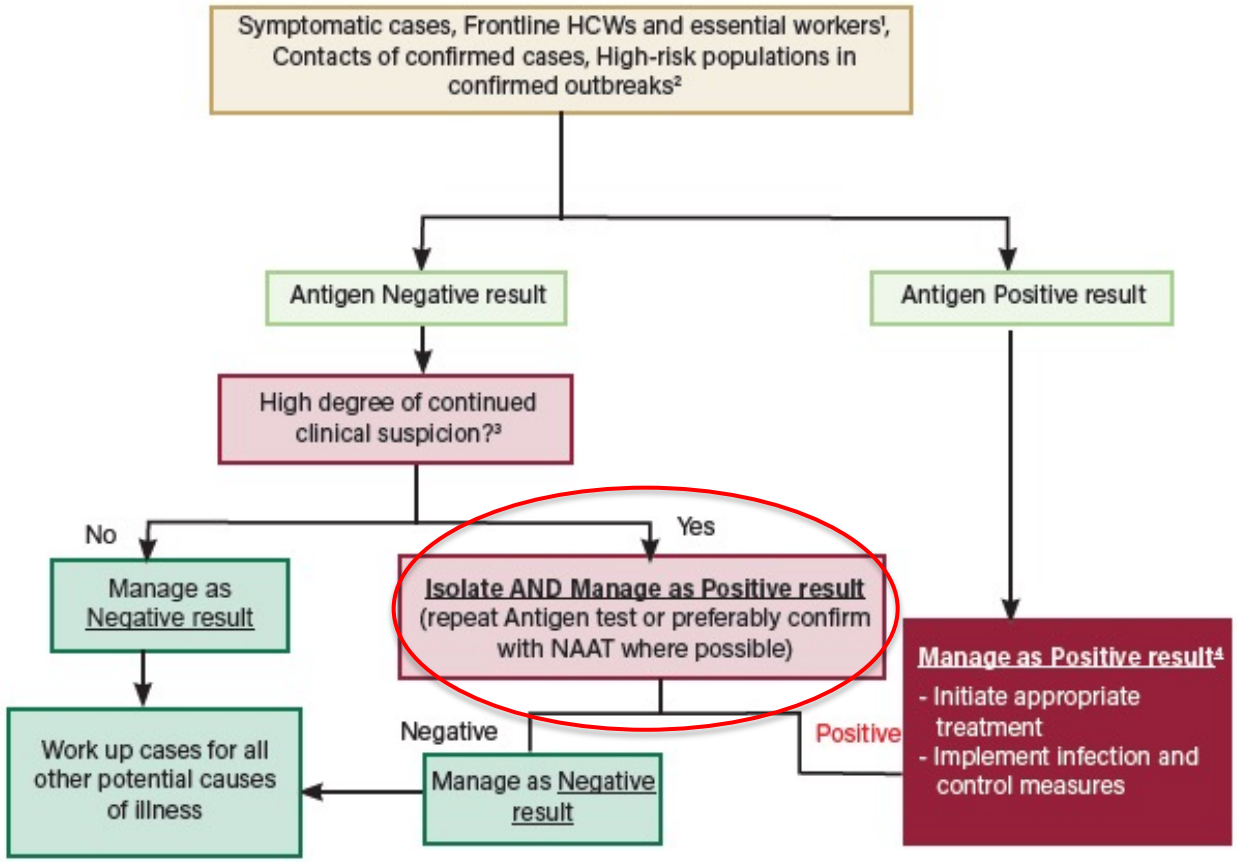


Figure 1: ***Algorithm when testing populations with higher suspicion of positivity, including: (1) individuals with symptoms, (2) frontline healthcare workers and/or essential workers, (3) contacts of confirmed cases, (4) high-risk populations in confirmed outbreaks***

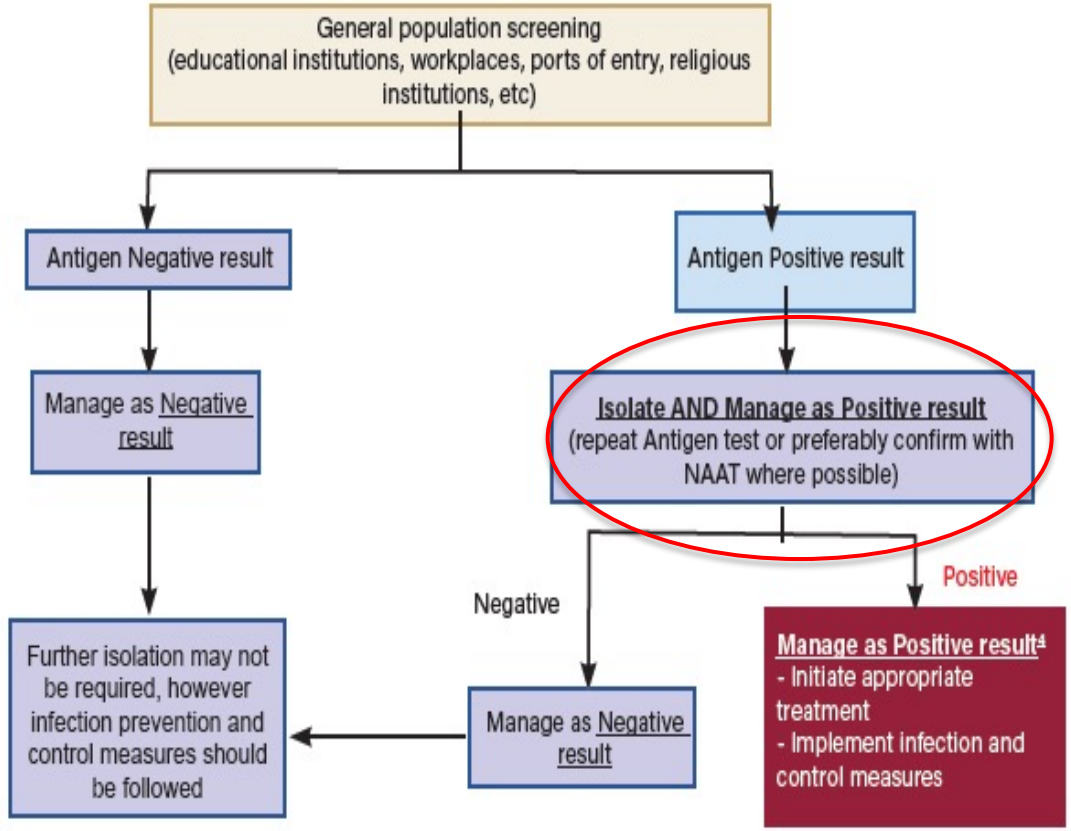


Figure 2: ***Algorithm for general screening of persons (irrespective of symptoms) in settings with unknown or low community transmission, including in schools, workplaces, ports of entry or houses of worship, etc.***

COVID-19 in Cameroon

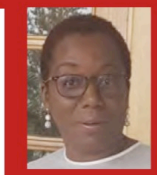
COVID-19 Response: Track Test and Treat

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 engagment**

FEATURED TOPIC

Scaling up laboratory testing for COVID-19 in Cameroon

Challenges, lessons learnt and perspectives



Sara Eyangoh, PhD, HDR

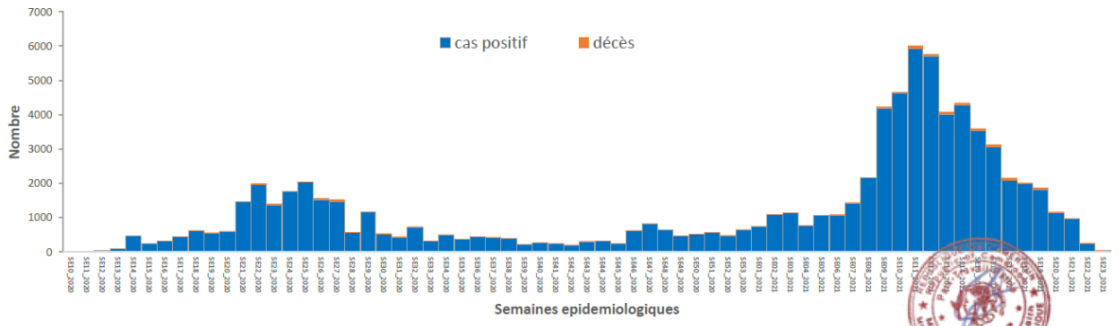


Figure 2 : *Evolution nationale des cas confirmés de COVID-19 par semaine épidémiologique, 04 mars 2020 au 09 Juin 2021*

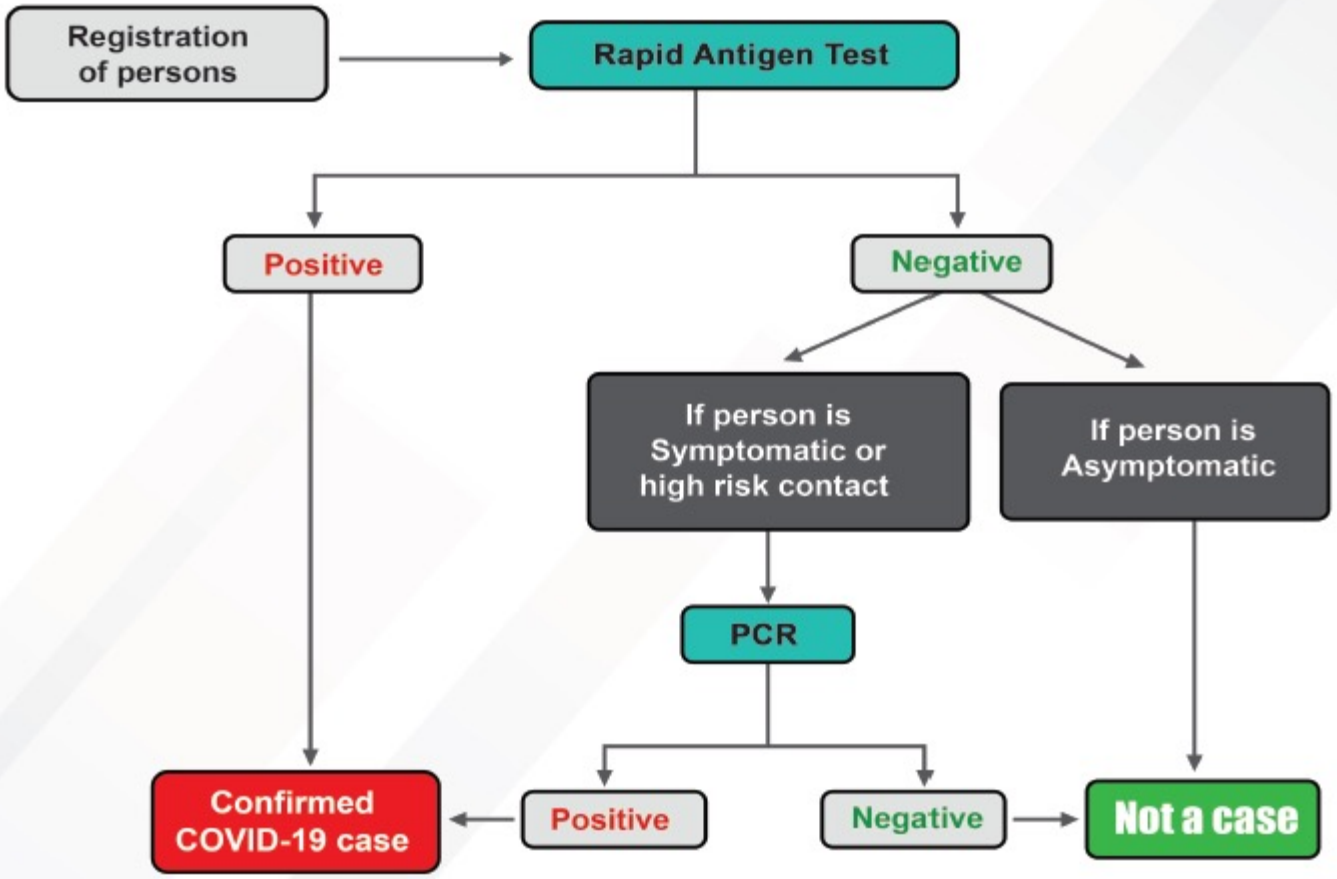
Evolution of COVID-19 Detection among Symptomatic patients

MINSANTE

REPUBLIC DU CAMEROON
MINISTRY OF PUBLIC HEALTH

PHEOC

NATIONAL ALGORITHM FOR COVID-19 TESTING



Use of Antigenic RDTs

- 80,000 Reported cases
- 60% Detected with Antigenic RDTs

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

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

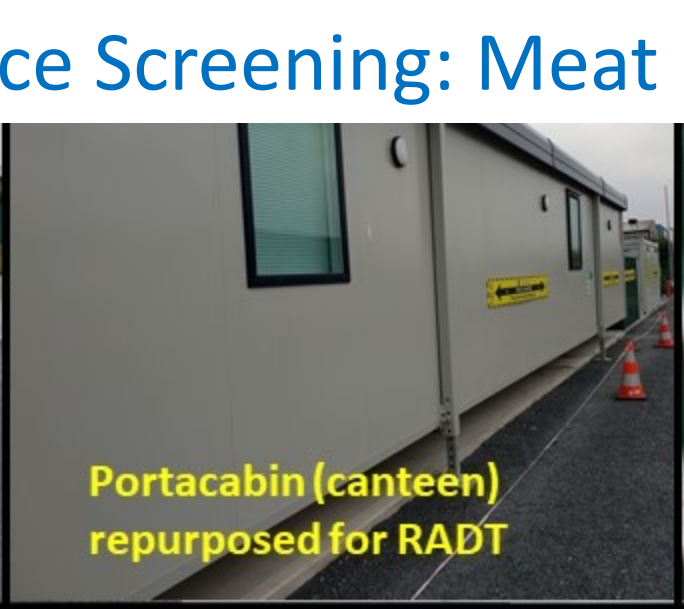
- Much of Africa's multibillion-dollar cross-border trade has been halted because of the COVID-19 pandemic
- Trucks at the port carry cargo destined for Uganda, Rwanda, Burundi, South Sudan and the Democratic Republic of the Congo are stuck at the port of Mombasa, Kenya
- Truck drivers identified as 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



Mass Gathering: Amir Cup Football Final, Qatar

Participants: 20,000, outdoor event

Ref: Dergaa et al. Organising football matches with spectators during the COVID-19 pandemic: What can we learn from the Amir Cup Football Final of Qatar 2020? A call for action. Biol Sport. 2021;38(4):677–681.

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

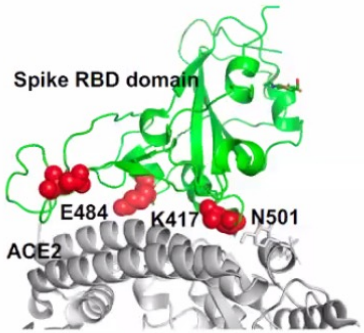
Mass Gathering: Music Event, Barcelona

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	Concert	Post-event
Checks: • temperature **Preventive measures**: • Wearing masks **Testing**: • Who: all • What test: antigen tests • When: 9 hours before entry	**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	**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

SARS-CoV-2 Variants of Concern

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



Modelling Strategies for Reducing Importation Risk of COVID-19 Cases

Dickens BL et al. J Travel Med Aug 2020

	Reduction in case rates relative to S1
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%**

Evolving Role of Diagnostics: from Pandemic Response to Control

Pathogen identified and genome sequence known

- Dx 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**

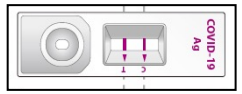
Asymptomatic and pre-symptomatic transmission confirmed

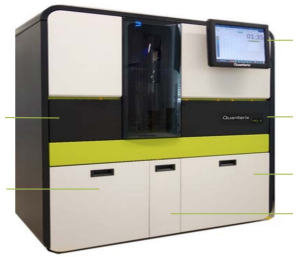
- Testing of **symptomatic individuals** and **contacts** continues
- Screening of **populations at high risk of acquisition and transmission** e.g. health and elder home care workers
- Testing for **travel and occupational groups** in non-health care settings

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**

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

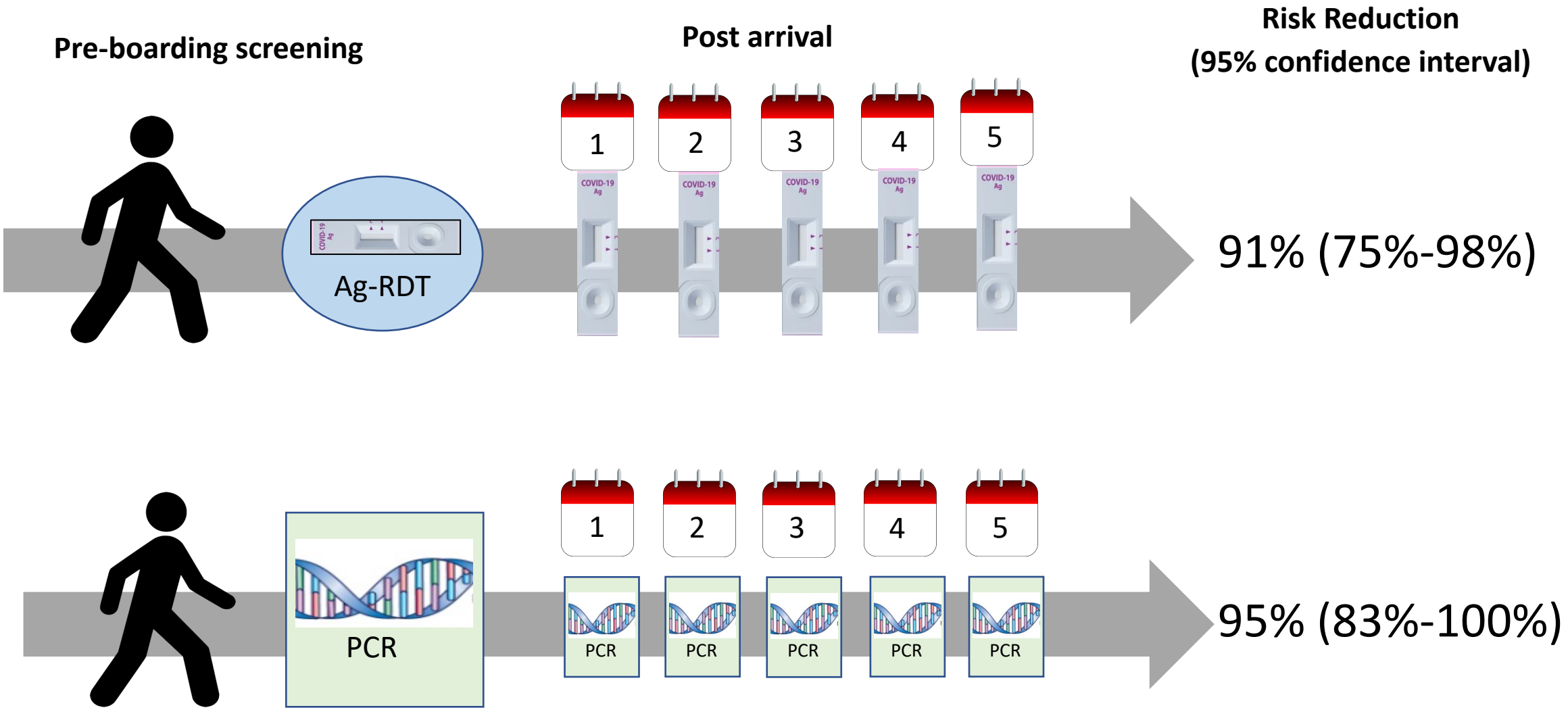
As a public health tool:

- 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

Testing on Arrival + No Quarantine



Quilty BJ, et al. Quarantine and testing strategies to reduce transmission risk from imported SARS-CoV-2 infections: a global modelling study. medRxiv preprint doi: https://doi.org/10.1101/2021.06.11.21258735; posted June 14, 2021.

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 …

After the pandemic: perspectives on the future trajectory of COVID-19

https://doi.org/10.1038/s41586-021-03792-w

Received: 12 May 2021

Accepted: 1 July 2021

Amalio Telenti[1,2], Ann Arvin[1], Lawrence Corey[3], Davide Corti[4], Michael S. Diamond[5,6,7], Adolfo García-Sastre[8,9,10,11], Robert F. Garry[12], Edward C. Holmes[13], Phil Pang[1] & Herbert W. Virgin[1,14,15]

Globally accessible diagnostics and deep-sequencing tools to establish continuous and sustained global surveillance of disease and variants.

What are the current key gaps in developing an effective global response?

Research questions

Epidemiology

- What are the effects of geographical and socioeconomic variations in vaccine coverage and disease on the ability to convert the pandemic to an endemic or epidemic disease?
- What is the contribution of immunosuppressed populations to the rapid evolution of SARS-CoV-2?

Virology

- What are the mechanisms by which viruses adapt to different hosts, thereby crossing species barriers?
- Is viral sequence evolution effectively reduced by vaccination?

Immunology

- What are the correlates of protection for vaccines and natural immunity? The assessment of protection will require the coherent application of reproducible immunologic assays in populations to follow disease incidence and severity.
- What is the impact of antigenic drift?
- What are the criteria for the renewal or boosting of vaccines?
- What is the role of mucosal immunity in limiting viral shedding and preventing severe disease?

Tools and technologies

Surveillance

- Globally accessible diagnostics and deep-sequencing tools to establish continuous and sustained global surveillance of disease and variants.

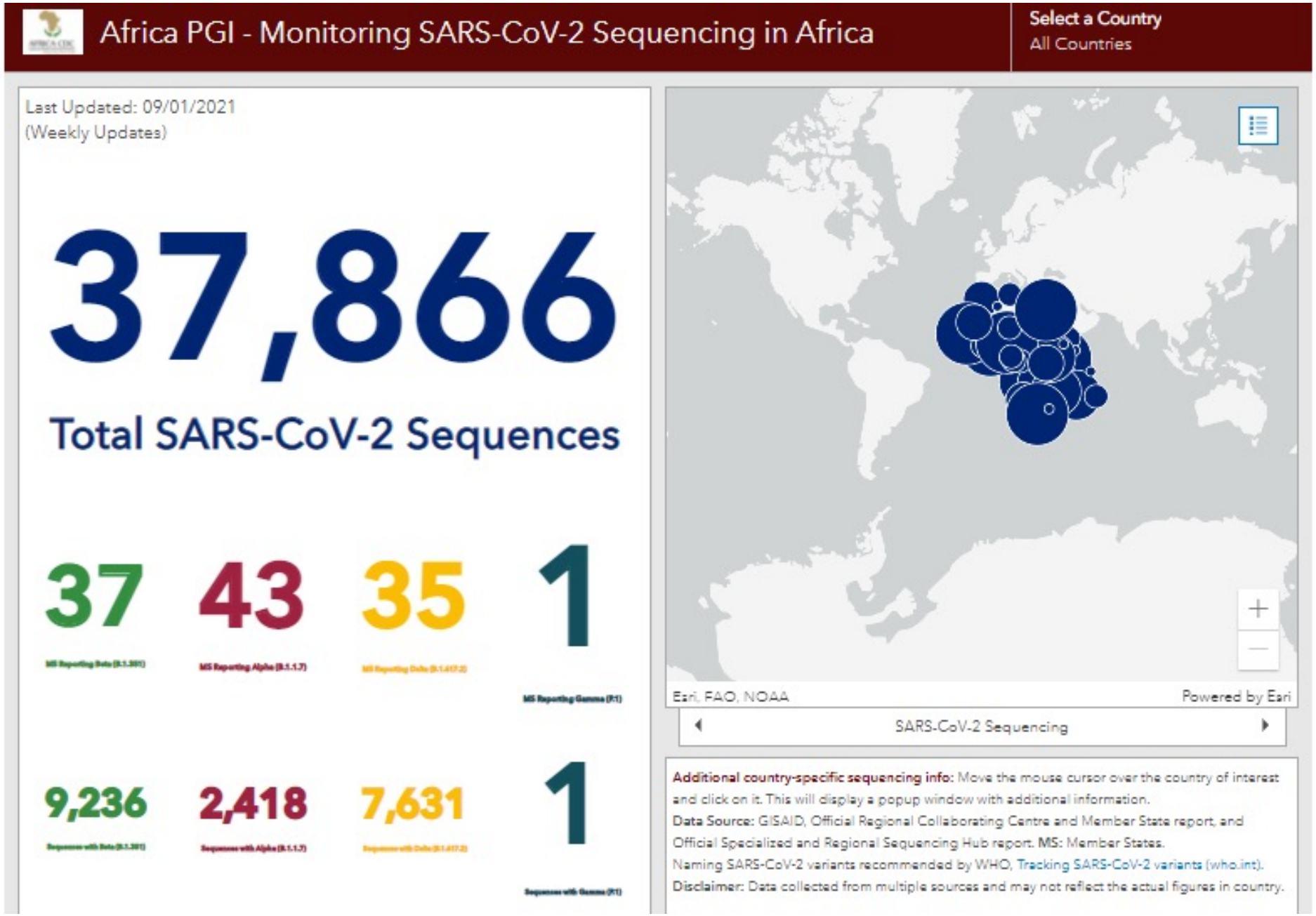
Vaccines

- Pan-sarbecovirus vaccines and monoclonal antibodies that will address both SARS-CoV-2 variants and the future introduction of pandemic coronaviruses into the human population.

Therapeutics

- Next-generation therapeutics in the form of cheap oral antiviral agents.
- Long-acting monoclonal antibody prophylaxis for persons not likely to achieve effective vaccination.
- Addressing inequalities in pandemic healthcare and access worldwide to the most effective vaccines and therapeutics.

Telenti A, et al.*Nature* (2021). https://doi.org/10.1038/s41586-021-03792-w



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