AC Health
An Ayala Company

COVID-19 Antibody Testing

DISCUSSION DOCUMENT
Framework for analysis for corporate re-entry

April 2020

Rapid Testing has generated much interest - we recommend a selective testing approach, contingent on ensuring access to confirmatory tests

Executive Summary:

- Some **private sector players** are beginning to use Rapid Testing to screen employees
- We have reviewed **scientific literature** and available **guidelines** on the utility of Rapid Tests for screening – overall, it is used for surveillance and monitoring, but not for diagnosis
- We recommend pursuing a **selective approach to Rapid Testing**:
  - Prioritize testing **confirmed COVID cases or PUIs in recovery** to help in decision-making on when to return to work
  - Consider testing of asymptomatic front liners **only with the capacity to do confirmatory testing**

There is a clear demand to ramp up local testing capabilities; however, validation, accreditation, and training requirements have slowed progress

How is COVID-19 disease diagnosed?

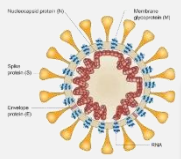
COVID-19 disease is confirmed by detecting the SARS-CoV-2 genetic material in a patient's sample through RT-qPCR testing.

Sampling

2 minutes

- Respiratory tract samples taken from patient (**nasal swab, oral swab, sputum sample**)

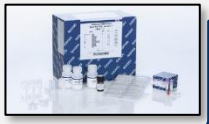
Virus Inactivation



1 hour

- SARS-CoV-2 must be inactivated by **qualified personnel**

Nucleic Acid (RNA) Extraction / Isolation



2-3 hours

- **Trace amounts** of the virus' genetic material are **isolated**

RNA Extraction Kit Required
- *Int'l: Php 25000/250 samples (Php100/sample)*

*Testing Kit Required
- *UP: Php 1500*
- *Int'l: Php 6000-8000*

PCR Amplification

Php 2.8-3.5M

2 hours

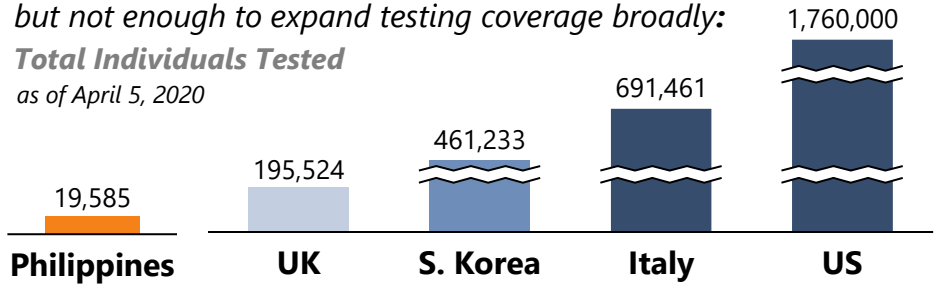
- Genetic material is **copied for confirmation**

***Locally available kits today:**
- *RITM kits (Japan)*
- *UP-NIH kits (Philippines)*
- *21 FDA-approved kits from other countries (China, Korea, Singapore, UK, Germany, Spain, US)*

On Testing Kits

- *With the **availability of over 100,000 testing kits** from various donations, we may have enough supply for the next few months, but not enough to expand testing coverage broadly:*

Total Individuals Tested
as of April 5, 2020



On Testing Centers

- ***Currently, RITM has a capacity to process ~1000 samples/day.** While **subnational labs have started mobilization** to process more samples, DOH aims to take up capacity to 10,000 tests/day (equivalent to additional 4-8 labs) :*

Designated Subnational Laboratories:
- Baguio General Hospital and Medical Center
- San Lazaro Hospital
- Lung Center of the Philippines
- Vicente Sotto Memorial Medical Center
- Southern Philippines Medical Center

Regulatory Aspect

- ***Requirements on accreditation and training** also require additional investments on capex, facilities, and personnel*

In contrast to PCR tests which measure viral RNA, Rapid Testing is a diagnostic tool that measures antibodies from a blood sample

Methodology for Nucleic Acid Testing (Molecular Detection) and Serology (Immunoassay)

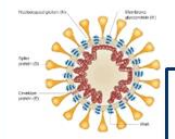
1 Detection of SARS-CoV-2 Genetic Material

Example: RT-qPCR (~6h)

Sampling — *2 minutes*

- Respiratory tract samples taken from patient (nasal swab, oral swab, sputum sample)

Virus Inactivation — *1 hour*



- SARS-CoV-2 must be safely inactivated (disables ability to infect cells without eliminating it) by qualified personnel

Nucleic Acid (RNA) Extraction / Isolation — *2-3 hours*

- Trace amounts of the virus' genetic material is isolated

PCR Amplification — *2 hours*

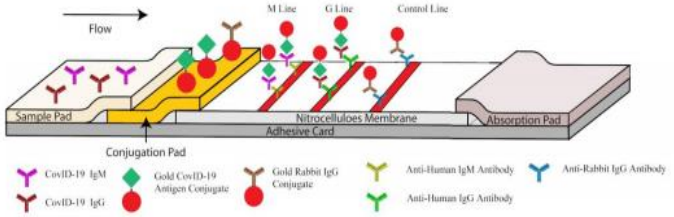
- Genetic material is processed and amplified for confirmation

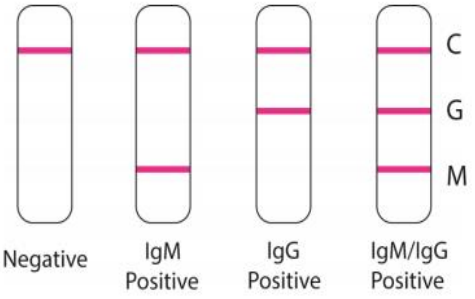
Use	Time	Cost	Resources	Personnel
Gold Standard	6 hours run-time	~P2,000-P8,000	BSL 2 Lab PCR	Special Training

2 Detection of Immune Response to Virus

Example: Rapid Test Kits / Point-of-Care (<30 minutes)

Rapid Test Kit Diagram





SOURCE: Li et. al. (2020). Development and Clinical Application of A Rapid IgM-IgG Combined Antibody Test for SARS-CoV-2 Infection Diagnosis. *Journal of Medical Virology,* Pre-Print. doi: 10.1002/jmv.25727

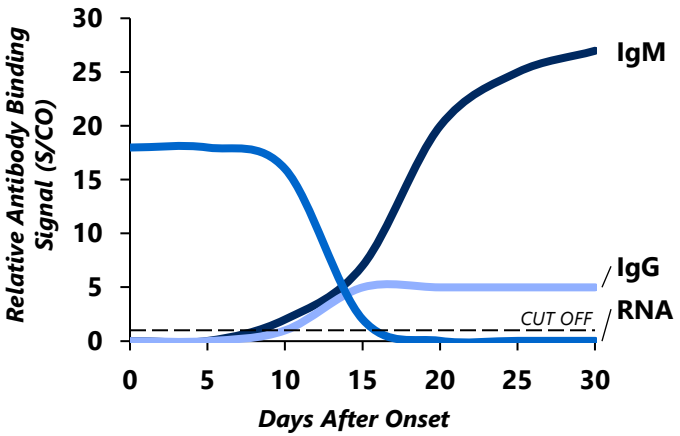
~10-15 minutes

Use	Time	Cost	Resources	Personnel
Adjunct	10 mins	~P750	None	None

Rapid Testing for COVID is an emerging science; it works on the premise that antibodies can potentially be markers of past and active infections

Principles of COVID-19 Antibody Testing

*Presence of Viral RNA, IgG, IgM vs Time**



IgM	IgG	Indication
-	+	Past infection
+	-	Ongoing infection
+	+	Ongoing or past infection
-	-	No antibodies detected

- As the **viral load (RNA) decreases**, **the antibodies increase**
- In current studies, at about 10-12 days after symptom onset, **IgM and IgG are both present** at the same level

Sensitivity and Specificity of COVID-19 Antibody Tests

	Sensitivity	Specificity
Definition	Ability to correctly identify those with the disease (**true positive rate**)	Ability to correctly identify those without the disease (**true negative rate**)
Range	**87.30% to 100%**	**93.65% to 97.92%**

COVID-19 Antibody Testing Applied

Antibody testing to complement confirmatory tests

- While the FDA approved antibody tests, the **CDC recommends RT-PCR testing as initial screening**
- **Health Sciences Authority (HSA)** provided Provisional Authorization for antibody tests

Antibody testing for issuing "immunity certificates"

- There is **ongoing research** to study use of RDTs to assess community immunity to SARS-CoV-2; basis for **"immunity certificates"**
- The UK is exploring **testing via RDTs and issuing "immunity passports"**

Antibody testing in the Philippines

- COVID-19 RDT can only be used in **symptomatic people**; if **IgM positive, RT-PCR test should be done to confirm**
- The **IgG antibody can be used as adjunct test** to clear patients who have recovered post-discharge
- RDTs strictly for **medical professional use**
- **Confirmatory testing** is required

*Lou et. al. (2020). Serology characteristics of SARS-CoV-2 infection since the exposure and post symptoms onset. PrePrint. doi: https://doi.org/10.1101/2020.03.23.20041707

Antibody testing is recommended for surveillance and monitoring – there is no evidence to support use in diagnosis or mass testing

WHAT WE KNOW

WHAT WE DON'T KNOW

Key Issues around Understanding Immune Response against COVID-19:

1. Immune response in a viral infection **typically occurs in progression** such that high **IgM is indicative of active** infection, and high **IgG is indicative of past infection**

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1. The **immune response against COVID-19 is not well-known** yet:
   - Timeline of appearance of antibodies still a topic of research
   - The same studies also show an overlap in the time period when viral RNA, IgG, and IgM are positive
2. It is **unclear how long immune response lasts** – estimates range from 3 months – lifetime but it is too early to tell
   - Could depend on rate of mutation
   - Could depend on how stable antibody protein targets are
3. It is unclear if **asymptomatic** patients that test positive are infectious

Key Issues around Rapid Testing:

1. Rapid test kits are **faster, cheaper, and easier to administer** – no need for special labs or personnel
2. Not all tests created equal: **Specificity and sensitivity varies** from test to test

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1. Sensitivity and specificity **evidence considered limited** – tested in labs, but not yet widely tested on people
2. **Cross-reaction** not ruled out yet – reacting antibodies could be antibodies for other viruses
3. **Detection limit** of kits not declared or established – different methods are used

We recommend adopting a selective approach to testing to be done only in conjunction with confirmatory testing

Scenarios and recommendations for rapid antibody testing

	Scenario	Recommendation	Interpretation*	IgM	IgG	Next Step
1	Previously Confirmed COVID-19 Cases, Now in Recovery		Previous Infection	-	+	*Cleared for work If symptomatic, should be sent for confirmatory testing*
2	Mild Symptoms, Never Tested (i.e. Mild PUIs)		Possible Active Infection	+	+	*For confirmatory testing; Continue or put in quarantine*
3	No Symptoms, High-risk for exposure (i.e. Frontliners)		Possible Active Infection	+	-	*For confirmatory testing; Continue or put in quarantine*
4	No Symptoms, Low-risk exposure (i.e. Work-from-Home employees)		No Trace of Active/Previous Infection	-	-	*Cleared for work*

Interpretation of results should be done **in consultation with doctors*

While there is still no cure, some drugs in trial are showing promising results – vaccines development could take another 18 months

1 *There is no treatment for COVID-19 to date, but medicines used for other diseases are under investigation*

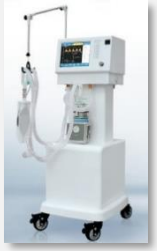
Medication	Authors / Manufacturer	Overview of the Study
Hydroxychloroquine (Plaquenil) Chloroquine *Malaria* *Rheumatoid arthritis*	Gao, et al. (China)	- Preliminary study on 100 patients showing decreased viral load, shorter symptom duration, and less severe cases - Support from medical community is split because of adverse effects - Several ongoing clinical trials to check safety and efficacy
with **Azithromycin** (Zithromax) *Atypical Pneumonia*	Gautret et al. (France)	- A total of 26 patients were given hydroxychloroquine +/- azithromycin which showed significant viral load reduction
Ritonavir – Lopinavir (Kaletra) *HIV*	Cao, et al. (China)	- Tested on 199 patients, no benefit observed for severe patients
	Qin Ning, et al (China)	- Ongoing Phase 4 randomized trial on 400 patients, to be completed by July 2020
Remdesivir *Ebola*	Gilead	- 6 ongoing clinical trials for mild, moderate and severe COVID cases, 2 of which are Phase III clinical trials to be tested on about 1,000 patients - Test improvement on 5-day and 10-day dosing regimen
Favilavir (Avigan) *Influenza*	Hisun Pharmaceuticals	- First medicine approved by National Medical Products Administration of China for treatment; effective in reducing duration of mild sickness

2 *Treatment is focused on supportive therapy. Empiric antimicrobials are given to target the most common causes of pneumonia*

Supportive	Antibiotics	Antivirals	Immune Modulators
▪ Paracetamol ▪ Oxygenation ▪ Ventilation ▪ Fluids	▪ Ceftriaxone IV/ Cefuroxime tab ▪ Azithromycin tab ▪ **Hydroxychloroquine tab** ▪ **Chloroquine tab**	▪ Ritonavir + Lopinavir tab ▪ Oseltamivir (influenza)	▪ IV Immunoglobulin

3 *Locally, there is a foreseen supply issue on ventilators nationwide*

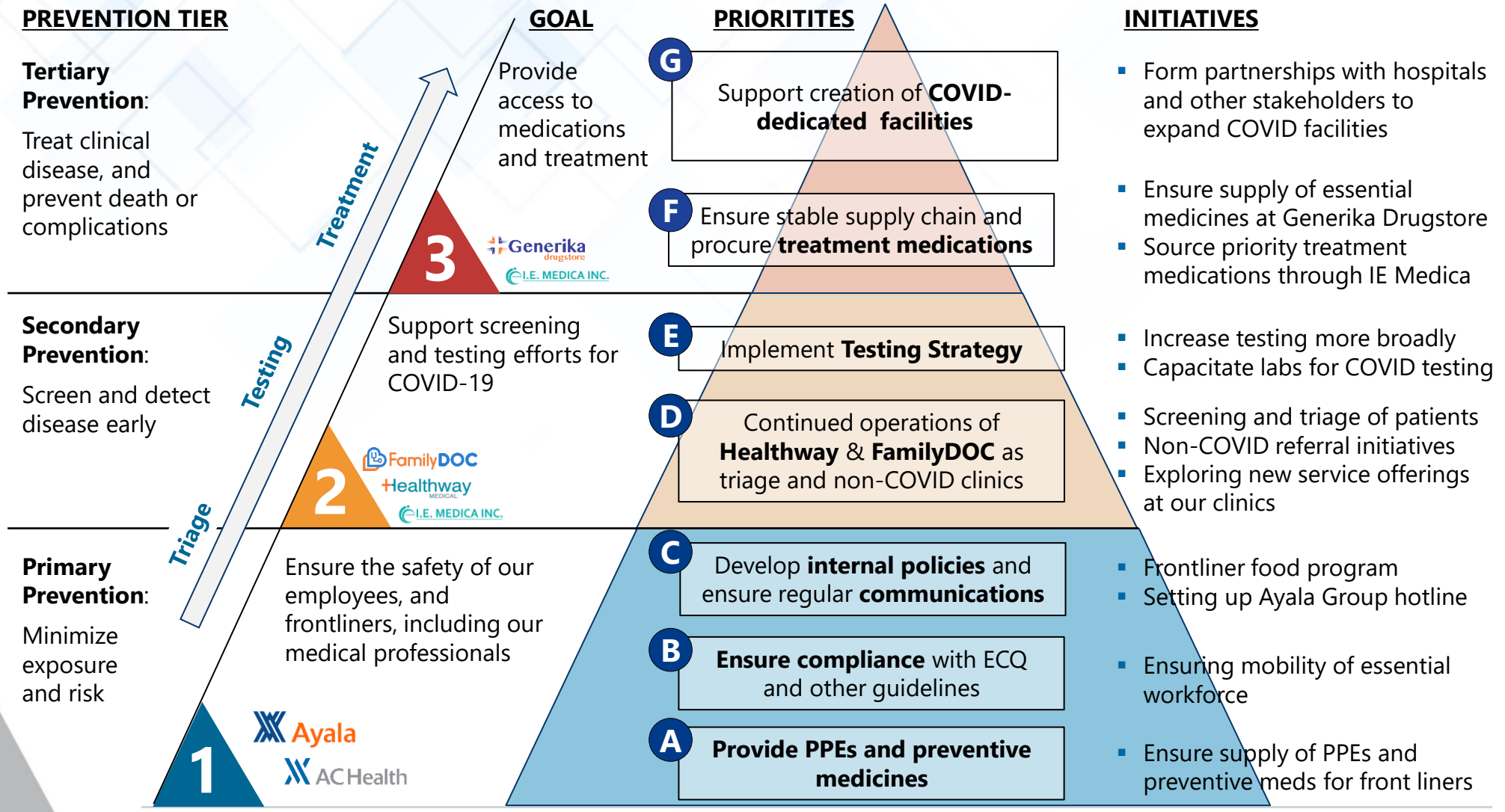
- Estimated ICU beds: 1,300 in Metro Manila (5% of total hospital beds)
- DOH estimates that there are ~1,500 ventilators nationwide
- Assuming a peak of 1,000 active critical cases and that half of ventilators will be allocated for COVID patients, we need 250 more ventilators



Cost: Php 750K – 1.8Mn

We are working on different initiatives to respond to COVID-19, prioritizing extending the frontline through our clinics

COVID-19 Response Framework



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