Evidence Summary on the Use of Rapid Antigen Test Kits for the Diagnosis of COVID-19

Service Line	Evidence Summary
Publication Date	30 April 2020
Adopted Report	Rapid Review on the Use of Rapid Antigen Test Kits for the Diagnosis of COVID-19 (published on 24 September 2020)
Summary Length	33 Pages
Prepared by	Health Technology Assessment Council Health Technology Assessment Unit
Contact details	hta@doh.gov.ph | 8-875-7734 loc. 260 or 258

Acronyms Used in the Evidence Summary	
Acronym	**Definition**
Australia PHLN	Australia Public Health Laboratory Network
Australia TGA	Australian Therapeutic Goods Administration
Ct	Cycle threshold
DOH	Department of Health (Philippines)
ECDC	European Center for Disease Prevention and Control
FIND	Foundation for Innovative New Diagnostics
Japan MHLW	Ministry of Health, Labor, and Welfare of Japan
NPS	Nasopharyngeal Swab
OPS	Oropharyngeal Swab
PHAC	Public Health Agency of Canada
PhilHealth	Philippine Health Insurance Corporation
RITM	Research Institute for Tropical Medicine
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UK MHRA	United Kingdom Medicines and Health Products Regulatory Agency
US CDC	United States of America Center for Disease Control and Prevention
US FDA	United States of America Food and Drug Administration
WHO	World Health Organization

Table of Contents

I. Background

The World Health Organization (WHO) declared the novel coronavirus disease (COVID-19), caused by severe acute coronavirus 2 (SARS-COV-2), a global pandemic affecting hundreds of countries and millions of people around the world.

In response to this public health emergency, the Philippine Department of Health (DOH) issued testing guideline policies which currently sets the real time reverse transcriptase polymerase chain reaction (RT-PCR) as the standard confirmatory test to diagnose COVID-19. Due to the nationwide limited capacity to perform laboratory-based tests and the proliferation of other COVID-19 diagnostic technologies in the market, the use of point-of-care tests have been explored and the Health Technology Assessment Council (HTAC) has already evaluated rapid antigen tests last October 2020. In its interim recommendation, the HTAC has approved the use of rapid antigen tests only for these very specific purposes:

- For targeted screening and diagnosis of suspect and probable cases of COVID-19 meeting the clinical and/or epidemiologic criteria as currently defined by the WHO (i.e., with high index of suspicion) in the hospital or community settings (e.g., for testing of first-degree contacts);
- For testing of patients in the hospital setting, where the turnaround time is critical, to guide patient cohort management in order to minimize transmission of COVID 19 among healthcare workers and other patients. (Hospitals are high-risk settings among healthcare workers and patients.) Otherwise, use RT-PCR in case of elective procedures.

Further, the HTAC has set at least 80% and 97% specifications for clinical sensitivity and clinical specificity, respectively, along with other technical requirements such as turnaround time, reference standard, among others.

This evaluation has led to the integration of rapid antigen test kits in the Omnibus Interim Guidelines on Prevention, Detection, Isolation, Treatment, and Reintegration Strategies for COVID-19 (DM 2020-0439).

This evidence summary was developed to update evidence on regulatory data on gene targets, country guidelines on use of RAgT as well as repeated testing, as well as the diagnostic performance of these tests for COVID-19 detection.

II. Policy Question

Should the Philippine Department of Health consider the use of rapid antigen test kits (RAgTs) for the diagnosis of COVID-19?

III. Research Questions

1. Regulatory Approval

1.1. What are the gene targets recommended by regulatory agencies for the antigen test kits?

2. Performance Characteristics

2.1. What is the value (diagnostic performance) of repeated antigen testing compared to confirmatory RT-PCR and to symptom-based screening?

2.2. What is the value (diagnostic performance) of rapid antigen tests in screening and diagnosing COVID-19?

3. Global guidelines and position on use of RAgTs

3.1. What are the current use cases of rapid antigen tests (COVID-19 diagnosis) based on country guidelines?

3.2. What is the role (use case) of repeat antigen testing vs. RT-PCR?

3.3. For repeat testing or serial testing, what are the recommended duration/intervals?

IV. Evidence Considered

A. Responsiveness to Disease Magnitude, Severity, and Equity

The World Health Organization (WHO) declared the novel coronavirus disease (COVID-19), caused by severe acute coronavirus 2 (SARS-COV-2), a global pandemic. The most common symptoms are fever, sore throat, malaise and dry cough. The symptoms are usually mild and begin gradually. It can spread from person-to-person through small droplets when coughing or sneezing. As of 23 March 2021, it has affected more than 192 countries and regions with at least 123,623,396 cases and 2,722,167 deaths worldwide (Johns Hopkins CoronaVirus Resource Center, 2021). In the Philippines, COVID-19 affected over 671,792 cases with 12,972 deaths as of 22 March 2021 (DOH, 2021).

B. Safety and Effectiveness

1. Regulatory Standards

Of the 11 regulatory agencies reviewed for any regulatory guidelines for recommended gene targets of COVID-19 RAgTs, no agency has explicitly provided a recommendation on the preferred gene target for rapid antigen tests, to date. However, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) briefly mentioned in their target product profile that the desired target analyte be two or more RNA or antigen targets. Likewise, Paul-Ehrlich-Institut in Germany mentions that manufacturers must specify the antigens that will be identified by the test. Furthermore, they mention that evidence must be provided that mutations of SARS-CoV-2, which lead to a variation in the spike antigen (e.g. the "UK variant") are still reliably detected when the target antigen being detected by the test is the surface (spike) protein.

2. Guideline Recommendations

Thirteen countries (US, Japan, South Korea, Vietnam, United Kingdom (UK), Australia, Malaysia, China, Philippines, Canada, Singapore, Indonesia and Thailand) as well as the European Union (EU) and the WHO were checked regarding their current recommendations on antigen testing. Of these:

- *Recommended use cases for antigen testing* Nine countries (US, Philippines, Vietnam, Canada, Japan, UK, Australia, and Malaysia) as well as the EU and WHO recommend the use of antigen testing for COVID-19.
    - Currently, the US, Philippines, Canada, Japan, Malaysia, Vietnam, EU, and WHO recommends the use of RAgTs in the diagnosis of COVID-19. In particular, the Philippines, US, EU, and Canada recommend its use among symptomatic patients particularly those with high pretest probability. The Philippine DOH also allows the use of antigen testing for the diagnosis of close contacts in communities and closed or semi-closed institutions with confirmed outbreaks and in remote settings where RT-PCR is not immediately available. The EU also recommends the use of the test for contacts of confirmed cases and outbreak clusters. On the other hand, Japan mentions that this test can be used for patients suspected of COVID-19, while Vietnam notes that these tests must reach the standards set by WHO or US CDC before being used as a confirmatory test. In Malaysia, antigen testing is considered as a confirmatory test but only in certain circumstances where there are confirmed COVID-19 clusters or outbreaks or areas identified by Malaysian Ministry of Health. The WHO also recommends the use of antigen tests as a diagnostic test in a range of settings such as in responding to suspected outbreaks of COVID-19 in remote settings, institutions and semi-closed communities where nucleic acid amplification test (NAAT) is not immediately available, in monitoring trends in disease incidence in

communities, in areas with widespread community transmission, and in testing asymptomatic contacts of cases.

- As a diagnostic test, Japan MHLW, US CDC, Philippines, and WHO consider a positive antigen test to be reliable given the high specificity of approved tests; while a negative test must be considered presumptive and a confirmatory test must be conducted when applicable. The US CDC, Philippines, and the WHO guidelines highlighted that confirmatory testing following a negative antigen test should be done subject to the use case, pretest probability, and clinical context of the patient while the guidelines released by MHLW in Japan states that the physician will decide on the need to conduct PCR test for a negative antigen test. In general, the decision on conducting confirmatory testing for a negative antigen result should be based on the clinical characteristics and history of the patient.
- In terms of screening, the Philippines, US, EU, Singapore, Malaysia, and WHO recommend the use of RAgT for screening purposes in specific settings.
    - The US, EU, and the Philippines recommend its use for testing in high-risk congregate settings while Singapore allows the use of the test in pre-event testing. In addition, the EU recommends the use of the test for this use case at the population-wide level in epidemiological situations or areas where proportion of test positivity is high or very high. In any case, the EU includes in their recommendation the need for strategies to be put in place to clarify when confirmatory testing by RT-PCR or a second rapid-antigen test is needed. In Malaysia, antigen tests are used as screening tests in the following scenarios: emergency and semi-emergency procedures or surgical cases with high probability of COVID-19 infection, brought in dead (BID) in low probability cases when indicated, symptomatic person in a confirmed cluster/outbreak management, for close contact in a confirmed cluster/outbreak management, screening for Acute Respiratory Infection (ARI), and other screening identified by the Malaysian Ministry of Health. Lastly, the WHO mentions that RAgT can be used to screen at-risk individuals in confirmed COVID-19 outbreaks and rapidly isolate positive cases and prioritize sample collection from RDT-negative individuals for NAAT.
    - In terms of result interpretation, the US guidelines for the screening of populations with high pre-test probability using RAgT follow the same recommendation as that for the diagnostic testing among populations with high pre-test probability using RAgT. However, for the screening of patients with low pretest probability, the US guidelines require patients with positive antigen test to isolate until confirmed by RT-PCR, while a negative antigen test can be considered negative and may not anymore require an RT-PCR confirmatory test. In Malaysia, a positive antigen test result is regarded as probable COVID-19 and shall be followed by RT-PCR to confirm as COVID-19 case, similar to the guidelines for use in Singapore.

    - A separate section is presented for the review of guidelines mentioning the use of antigen testing for border control policies.

  - In the UK, no specific use case was mentioned for the use of antigen tests. However, they note that a positive antigen result interpretation depends on where the antigen test is conducted. If conducted at a testing site, a PCR test *may* be asked to confirm the result; otherwise, if conducted at home, a PCR test is necessary to confirm the result. A negative antigen result suggests the test did not find signs of coronavirus. On the other hand, Australia did not have guidelines on the use of antigen tests but its Public Health Laboratory Network (PHLN) noted that these are currently being evaluated to determine clinical utility in various settings.

- *Use cases where antigen testing is not recommended* According to the WHO guidelines, there are instances in which RAgTs are not recommended for use:
  - settings or populations with low prevalence of disease;
  - in individual without symptoms, unless that person is a contact of a confirmed case;
  - in areas where there are zero or only sporadic cases;
  - in areas where appropriate biosafety and infection prevention and control measures are lacking;
  - in situations in which the management of patient does not change based on the result of the test;
  - in airport or border screening at points of entry; and,
  - in screening prior to blood donation.

- South Korea, and China do not mention the use of antigen testing in their current national testing guidelines and recommend the use of RT-PCR as the standard test in diagnosing COVID-19. Indonesia and Thailand do not have publicly accessible national testing guidelines.

Repeated antigen testing Of the guidelines reviewed for use of rapid antigen tests, we note the following countries that mention the use of repeated antigen testing:

- The US CDC and Public Health Agency of Canada (PHAC) suggests the use of repeated rapid antigen tests in congregate settings where highly sensitive tests are not feasible, or if turnaround times are prolonged. They note that negative results be considered as presumptive negative and that health care providers should consider them in the context of clinical observations, patient history, and epidemiological information. There was no information on the timing of repeated testing for both agencies. Only the US CDC mentioned regarding the recommended interval for repeat testing but only for institutions of higher education (IHEs). They recommended that screening should be done on all

students, including those who live off campus, and should also consider implementing entry screening testing for faculty and staff. In the context of low community transmission, entry screening alone prior to the beginning of each term may be sufficient. In the context of moderate community transmission, the US CDC recommends IHEs to implement both universal entry screening and expanded serial screening testing at least weekly if sufficient testing capacity is available. Lastly, in the context of substantial or high community transmission, the US CDC recommends universal entry screening and expanded serial screening testing at least *twice* weekly if sufficient testing capacity is available.

- In settings where there is widespread community transmission (e.g. health facilities, care homes, prisons, schools) and in COVID-19 testing centres sites, contact tracing, or for front-line and healthcare workers, the WHO cautions that a negative antigen test cannot completely exclude active COVID-19 infection; hence, suggests repeat testing using antigen test or preferably confirmatory testing by nucleic-acid amplification tests be performed when possible especially among symptomatic patients. This is similar to the guidance of the EU Commission stating that strategies must be put in place to clarify when a second antigen test or confirmatory testing via RT-PCR is required. The WHO, however, does not mention a recommended interval for conducting repeat testing given a negative initial result but the European CDC advises that the test be repeated two to four days later for screening asymptomatic patients in high prevalence areas and testing symptomatics, excluding symptomatic patients in hospitals, long-term care facilities, or other social care settings. In addition, EU CDC also mentions that RAgTs can be used for screening and serial testing every two to three days for residents and staff of healthcare, home care, long-term care facilities, closed setting and occupational settings with community transmission. In the latest omnibus testing guidelines of the Philippines (DM 2020-0512) only RT-PCR test is mentioned for the recommended confirmatory test for those with negative antigen results. It is noted, however, that in the previous omnibus testing guidelines (DM 2020-0468), both confirmatory RT-PCR test and repeat antigen test are recommended for negative antigen results.
- The UK, Japan, South Korea, Singapore, Indonesia, Vietnam, Australia, Malaysia, and China did not mention repeated antigen testing in its current guidelines.

Use of Antigen testing for Border Control Of the guidelines reviewed for use of rapid antigen tests, we note the following countries that mention the use of rapid antigen testing for border control:

- **Six** countries (US CDC, Malaysia, UK, Japan, Indonesia, **Germany**) recommend the use of antigen tests for border control. Of these, three countries (US, Malaysia, UK) recommend its use for local and international border control; two countries (Japan and Germany) for international control only; and, one country for local border control only (Indonesia). Details are presented in Table 1.
- Meanwhile, one country guideline (Philippines) was noted to have an unclear recommendation on its use for border control. In the current testing guidelines, it mentions that RAgT is included as part of the additional measures and requirements for

asymptomatic interzonal domestic travelers (with no established exposure/contact to a probable or confirmed case). However, this is not explicitly stated as one of the recommended use cases for antigen testing.

- The recommendations of the US CDC is similar to that of the findings from the modelling study of Wells et al. (2021) which mentions that the optimal testing time is at day five or six for quarantine durations of up to 7 days. Furthermore, the study mentions that testing upon entry to quarantine carries risk of false negatives as the virus may not be immediately detected among individuals due to low viral loads at the early stage of disease. This is aligned with the recommendations of the US, Malaysia, UK, Japan, and Germany which still requires antigen testing beyond entry to quarantine.
- Three countries (South Korea, Canada, ECDC) do not recommend the use of rapid antigen testing for border control. The ECDC noted that RAgTs are not ideal for low-prevalence populations such as screening incoming travellers. Further, they note that a positive RAgT for low-prevalence populations should still be confirmed with an RT-PCR test. This is also similar to the WHO guidelines which state that rapid antigen tests should not be used in healthy traveller populations with low expected prevalence of disease.
- Five countries (China, Thailand, Australia, Vietnam, Singapore) did not mention the use of rapid antigen tests for border control in their guidance documents. All inbound travellers to Singapore are required to undergo RT-PCR, and those with previous infection are also required to undergo serology testing for surveillance. Australia requires RT-PCR tests done at most 72 hours prior to entering the country. On the other hand, Vietnam requires a negative RT-PCR test three to seven days prior arrival. Similarly, travellers to Thailand are required to present a negative PCR test issued no more than 72 hours before departure.

Table 1. Summary of Border control policies mentioning the use of Antigen Testing

Country	Recommendation on antigen testing for international border control	Recommendation on antigen testing for local border control	Timing of Test	Post Arrival Measures
US CDC	Recommended the use of antigen tests including RAgTs		Within 3 days prior to departure *Fully vaccinated domestic travelers* do not need to get tested before travel unless their destination requires it. Vaccinated people are also required to be asymptomatic in some states.	Nucleic acid amplification test or antigen testing 3-5 days after arrival, combined with self-monitoring, and a 7-day home quarantine. If not tested, a 10 day quarantine is required. *Fully vaccinated domestic travelers* do not need to get tested after travel unless their destination requires it. Self monitoring for symptoms, isolation, and testing if symptoms develop are still recommended.
UK	Recommended the use of antigen tests such as lateral flow devices from test providers for pre-departure testing as long as they oblige the requirement of ≥97% specificity and ≥80% sensitivity at viral loads above 100,000 copies/ml.		Within 72 hours prior to departure	10 full days of quarantine with repeat testing done on Day 2 and at least Day 8 of quarantine
Japan	Recommends quantitative antigen testing (e.g. Chemiluminescence enzyme immunoassay, CLEIA) but not qualitative antigen tests such as some RAgT (e.g. immunochromatographic assay) Quantitative antigen tests are also utilized in airport inspection measures		Within 72 hours prior to departure	Regardless of a negative pre-departure test result, a 14-day home or facility quarantine is still mandatory for all international travelers. *For travelers coming from or traveled within 14 days to countries endemic to mutant strains,* facility quarantine for 3-14 days and additional viral testing (e.g. quantitative antigen test) at day 3 and day 6 from their arrival are required.

Indonesia		Local travel guidelines require travelers to present a negative RT-PCR or RAgT result for domestic travel to and from the islands of the country	In the island of Bali, travellers via air transportation are required to present a negative RT-PCR result taken within a maximum period of 48 hours or a negative RAgT result taken within a maximum of 24 hours pre-departure while travellers via land or sea transportation are required to present a negative RT-PCR or RAgT result within a maximum period of 72 hours. Travellers to other islands of Indonesia, including Java, via land private transportation, train commute, and sea transportation, are encouraged to carry out a negative RT-PCR or RAgT result within 72 hours pre-departure. Air travellers to these islands are required to show their negative results from an RT-PCR test within a maximum period of 72 hours or from a RAgT within a maximum period of 48 hours.	
Malaysia	Recommended the use of RAgTs for symptomatic travelers with mild symptoms, and for asymptomatic individuals who acquired symptoms during their quarantine period	Recommended the use of RAgTs for travellers transiting from Kuala Lumpur International Airport to Sabah, Sarawak, and Labuan without a valid COVID certificate	RT-PCR is required within 3 days or 72 hours prior to departure	RAgTs are used in screening individuals *(with or without a valid COVID-19 certificate)* with mild symptoms. In asymptomatic individuals under quarantine, they require an RT-PCR or RAgT at Day 5 (with COVID certificate) or Day 8 (without COVID certificate). The asymptomatic traveler with a negative test result shall be released on Day 7 (with COVID certificate) or Day 10 (without COVID certificate).
Germany	Recommended the use of RAgTs for all persons		Time of swab should be within 48 hours prior to entering Germany	The individual Länder [federal state] are responsible for quarantine regulations. The

	travelling to Germany, except for persons under six years of age and aircraft crews.			Länder have put in place their own regulations on the basis of a specimen regulation. Travelers coming from a risk area should undergo home (or other place of accomodation) quarantine upon arrival and remain isolated there for a period of ten days. Home quarantine can be lifted earlier with a negative result, at the earliest after 5 days, depending on the quarantine rules of the Federal Land. Travelers who have spent time in an area of variants of concern should undergo quarantine for 14 days.

3. Diagnostic Performance

a. Evidence from Local Diagnostic/Evaluation Studies

The Research Institute for Tropical Medicine (RITM) has conducted an evaluation of rapid antigen tests using a prospective evaluation of freshly collected respiratory swab samples from symptomatic and asymptomatic patients. For symptomatic patients, participants must be at least 18 years of age and with specimen **collection** to be done at most 5 days from symptom onset. On the other hand, asymptomatic participants must be healthy and of the same age without any symptoms of COVID-19. A minimum of 30 SARS-CoV-2 PCR positive and PCR negative samples were used. Seven rapid antigen test kits were evaluated by RITM. Below are their key findings:

- For the symptomatic cohort, sensitivity estimates were varied ranging from 27.78% to 91.43%. On the other hand, specificity estimates were high and more consistent at 95.08% to 100%. For the asymptomatic cohort, only specificity was reported. Point estimates likewise were high ranging from 97 to 100%.
    - Symptomatic population: Among the brands tested, the *Lansion Biotech Dry Fluorescence Immunoassay* had the highest overall sensitivity at 91.43%. Meanwhile, the *Lumiquick Quick Profile* had the lowest sensitivity at 27.78%. In terms of specificity, three brands *(SD Biosensor Standard Q Rapid Antigen Test, Abbott Panbio Antigen RDT, and Rapigen Biocredit COVID-19 Ag)* had a point estimate of 100%. The *Lansion Biotech Dry Fluorescence Immunoassay and Quidel Sofia SARS Antigen Fluorescence Immunoassay* had the lowest specificity at 95.08% and 95.65% respectively.
    - Asymptomatic population: Six *(SD Biosensor Standard Q Rapid Antigen Test, Abbott Panbio Antigen RDT, Quidel Sofia SARS Antigen Fluorescence Immunoassay, Rapigen Biocredit COVID-19 Ag, Lansion Biotech Dry Fluorescence Immunoassay, and Assure Tech (Hangzhou) Fa Step)* of the seven brands had specificity of 100% while the *Lumiquick QuickProfile* had a sensitivity of 97% for this population group.
- A subgroup analysis at a cycle threshold value of less than 30 was also conducted by RITM. Based on this analysis, sensitivities of the rapid antigen test kits were found to be higher for all brands tested and less varied, with point estimates ranging from 86.36% to 100%. Of the seven, two brands *(Lansion Biotech Dry Fluorescence Immunoassay and Lumiquick Quick Profile)* had sensitivities of 100% at the <30 Ct value.

b. Evidence from International Diagnostic Studies

- Based on the systematic review conducted by Burog et al. (2021), the overall pooled sensitivity of RAgTs was 72% (95% CI: 64-78; I^2: 95.77), while the specificity was 99% (95% CI: 99-100; I^2: 93.16) based on 30 studies and 10 evaluation reports. The range of point estimates of included studies for sensitivity was from 0% to 100% while the range for specificity was more consistent from 90% to 100%.
- Given the expected heterogeneity for pooled estimates, subgroup analysis was pre-determined according to test brand, presence of symptoms, timing of testing, and type of specimen used.

- Based on 11 studies (n = 16060) with moderate to high methodological quality, the *BinaxNOQ COVID-19 Card (Abbott Diagnostics)* test kit showed the highest pooled sensitivity at 90% (95% CI: 0.66 to 0.93). Other test brands that had 80% sensitivity or higher were the following: *NowCheck COVID-19 Ag Test (Bionote Inc)* at 89% (95% CI: 81 to 95), *VITROS Immunodiagnostic Products SARS-CoV-2 Antigen Test* at 80% (95% CI: 74 to 90), and *Bioeasy 2019-nCoV Ag Fluorescence Rapid Test Kit* at 80% (95% CI: 62 to 91; I2=0%).
- In terms of presence of symptoms, pooled sensitivity of RAgTs was higher among symptomatic patients (78%; 95% CI: 69-86; 30 studies) than in asymptomatic patients (51%; 95% CI: 39-63 7 studies).
- When the test was used for testing patients in the early phase (0-7 days) of the disease, pooled sensitivity estimate was found to be 71% (95% CI 44-89; 12 studies) compared to 65% (95% CI: 57-71; 2 studies) when used in patients in the late phase (8-14) of the disease. The reviewers also noted that this needs further validation studies as the number of participants and studies included in the late phase was small (n=831).
- In terms of the specimen used, anterior nares swab specimens alone showed the highest pooled sensitivity of 84% (95% CI: 66-93; 15 studies) followed by nasopharyngeal swabs with sensitivity of 72% (95% CI: 65-78; 36 studies). Saliva specimens had the lowest pooled sensitivity at 17% (95% CI: 13-23; 2 studies).

- The methodological quality of included studies was rated to be moderate by the review authors. Four studies were found to have high quality while 16 studies and 10 evaluation reports were found to have moderate quality and 10 studies were found to have a low quality.

C. Household Financial Impact

While the HTAC has recommended the use of RAgTs for specific use cases since October 2020, the Philippine Insurance Corporation (PhilHealth) does not have yet an existing coverage mechanism for the cost of rapid antigen testing. As far as COVID-19 testing is concerned, they are only covering the cost of RT-PCR testing, to date.

In addition, there is no price ceiling for rapid antigen testing yet, although the DOH and the Department of Trade and Industry (DTI) are currently forming a technical working group to set the price ceiling. Based on their initial survey, the median costs of rapid antigen testing (based on charge) are PhP 700 and PhP 1,000 for non-hospital-based and hospital-based government facilities, respectively. Among the private institutions, the median costs (based on charge) recorded are PhP 1,500 and PhP 1,800 for non-hospital-based and hospital-based facilities, respectively.

D. Cost-effectiveness

The evidence was not reviewed. A full-blown cost-effectiveness analysis is currently not done for rapid reviews under a pandemic situation due to its emergency nature. A full blown cost-effectiveness analysis that takes on a societal perspective (i.e., including the economic and

social impacts) will be performed once sufficient evidence is available and when full market authorization has been granted.

E. Affordability and viability

As mentioned, the initial survey of DOH and DTI on the cost of rapid antigen in the Philippines shows that the median costs of rapid antigen testing (based on charge) are PhP 700 and PhP 1,000 for non-hospital-based and hospital-based government facilities, respectively. Among the private institutions, the median costs recorded (based on charge) are PhP 1,500 and PhP 1,800 for non-hospital-based and hospital-based facilities, respectively.

V. Recommendations *(as 30 April 2021)*

A. The HTAC **maintains that RT-PCR remains the standard diagnostic test for COVID-19**, and would like to emphasize that the following *interim recommendations on rapid antigen testing are subject to change* pending new evidence.

B. We reiterate the previous HTAC recommendation that rapid antigen tests when positive are most useful in immediately identifying COVID-19 cases and therefore can be used to initiate contact tracing, epidemiological surveillance and clinical management. In *Table 2*, HTAC recommends the **use cases, intended population, sample specimen, interpretation of results, repeat antigen testing and contact tracing**.

Table 2. HTAC Recommendations for Rapid Antigen Testing

Recommended Use Cases *[UPDATED]*	The HTAC **does not recommend the use of rapid antigen tests** for indiscriminate use in mass screening, for return-to-work clearance and for COVID-19 diagnosis in individuals with low index of suspicion (i.e., asymptomatic and no history of exposure). Rapid antigen tests are currently recommended **by HTAC only for very specific purposes:** ● For **targeted screening and diagnosis of suspected and probable cases of COVID-19** (i.e., with a high index of suspicion), meeting the clinical and/or epidemiologic criteria in the hospital or community settings as defined below: ● *Suspected cases of COVID-19* are individuals: ○ with acute onset of the following signs and symptoms adopted on the WHO clinical criteria, (Fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered

	mental status, anosmia (loss of smell) or ageusia (loss of taste)) **OR** ○ satisfying the following epidemiology criteria): ■ Residence or work in an area with high risk of transmission of virus (e.g. congregate settings) ■ Residence or travel to an area with community transmission ■ Work in any healthcare setting ● *Probable cases of COVID-19* are: ○ Individuals meeting the above clinical criteria AND is a contact of a probable or confirmed case or linked to a cluster of COVID-19 cases ○ Suspect cases with chest imaging suggestive of COVID-19 ○ Individuals with sudden onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause. ● For testing of patients in the hospital setting, where the turnaround time is critical, to guide patient cohort management in order to minimize transmission of COVID 19 among healthcare workers and other patients. (Hospitals are high-risk settings among healthcare workers and patients.) Otherwise, use RT-PCR in case of elective procedures; ● For targeted screening and diagnosis of suspect and probable cases of COVID-19 (as defined above) in presumptive outbreaks where the result of the RT-PCR test of a one suspect has not yet been released and in settings where RT-PCR is not immediately available or when delayed release of result or prolonged turnaround time is expected (i.e., more than 48 hours). ● For local border screening at points of entry **for individuals travelling from areas with a high daily positivity rate averaged over a seven-day period (i.e., >10%) or as reported by the DOH-Epidemiology Bureau** based on its periodic updates of prevalence rate/positivity rate; and, ● For **international border screening** at points of entry, always assume a high prevalence/positivity rate. A periodic update every month of prevalence rate/positivity rate per country is also suggested. It is recommended that RT-PCR or RAgT test be used for screening of all incoming individuals in accordance with existing protocol and testing guidelines. Facility- or home-based

<table>
<tr><td></td><td>quarantine shall also be implemented together with RT-PCR or Rapid Antigen testing.</td></tr>
<tr><td>Intended Population
[UPDATED]</td><td>

In general, the RAgT can be used for individuals with a high index of suspicion:

Symptomatic individuals with or without known exposure (For symptomatic individuals, RAgT is recommended to be performed within the first 5-7 days after the onset of symptoms for best results.)
Asymptomatic individuals with exposure (For asymptomatic individuals with exposure, the RAgT is recommended to be performed from 4 to 11 days after exposure, even before symptoms develop.)

The RAgT is not recommended for use by individuals with a low index of suspicion (i.e., asymptomatic individuals without history of exposure)

<table>
<tr><th></th><th>WITH history of exposure</th><th>WITHOUT history of exposure</th></tr>
<tr><td>WITH symptoms</td><td>HIGH index of suspicion:
Recommended for rapid antigen testing</td><td>HIGH index of suspicion:
Recommended for rapid antigen testing</td></tr>
<tr><td>WITHOUT symptoms</td><td>HIGH index of suspicion:
Recommended for rapid antigen testing

Applicable to guide patient cohort management to minimize transmission of COVID 19 to healthcare workers and other patients</td><td>LOW index of suspicion:
NOT recommended for rapid antigen testing</td></tr>
</table>

The intended population for RAgT includes individuals with the following exposure:

People in close contact with a suspected, probable or confirmed case (e.g., household members, workmates). Examples would be:

Face-to face contact with a suspected, probable or confirmed case within 1 meter and for at least 15 minutes;

</td></tr>
</table>

	- Direct physical contact with a suspected, probable or confirmed case; - Direct care for a patient with probable or confirmed COVID-19 disease without using recommended personal protective equipment; - Other situations as indicated by local risk assessments - Note: Window of exposure to suspected, probable or confirmed case is anywhere between 2 days before or within 14 days of onset of symptoms. ○ People **coming from an area with a high positivity rate averaged over a seven-day period** (i.e., >10%) or as reported by the DOH-Epidemiology Bureau based on its periodic updates of prevalence rate/positivity rate ○ People residing in **closed or semi-closed institutions** (as defined in DM 2020-0468), **crowded area**s (i.e., more than one person per three square meter circular area or those sharing common facilities) **with presumptive outbreak** (as defined above**) or confirmed outbreaks** (per DM 2020-0397) ○ People **working in areas with presumptive outbreak** (as defined above**) or confirmed outbreaks** (per DM 2020-0397) ● If sufficient testing capacity is available, serial rapid antigen testing *at least weekly* in congregate settings (e.g., workplaces, prisons, nursing homes) with **moderate transmission** and *at least twice weekly* for areas with substantial or **high community transmission** is recommended (*US CDC Interim Guidance for SARS-CoV-2 Testing and Screening at Institutions of Higher Education, 2021*). ● Finally, the HTAC **does not recommend the use of RAgTs to issue clearances for return to work or for earlier release from quarantine** because of the likelihood of false negatives.
Sample Specimen *[NEW]*	The specimens to be collected for RAgT must be nasal, nasopharyngeal and/or oropharyngeal swabs.
Interpretation of Results *[UPDATED]*	● It is recommended that **individuals with positive rapid antigen test results (positive for COVID-19)** be isolated and managed as COVID-19 cases.

	• For **individuals with a high index of suspicion and who tested negative using rapid antigen tests should be isolated until they can be confirmed negative by RT-PCR or repeat antigen results (DM 2021-0169).** ○ The confirmatory RT-PCR test for those who tested with negative rapid antigen test result should be done at least within 48-72 hours from the initial antigen test. **It is important to always correlate the test results with the overall clinical and epidemiological context (e.g., history of exposure).** The previous recommendation was for a confirmatory RT-PCR test for those who test negative. However, this was found impractical in community settings where RT-PCR laboratories may not be accessible.
Other recommendations *[UPDATED]*	Other overarching recommendations of the HTAC are as follows: • Publicize standards on diagnostic performance to address the observed wide variability of performance in all COVID-19 testing kits in the market • Strengthen system for monitoring and evaluation of compliance of manufacturers to regulatory standards and post-marketing requirements. Departmental constraints must be addressed to enable strict compliance and to add teeth to implementation. • Testing (using RAgTs or NAATS) should be used in addition to other health measures such as minimum public health standards (including the use of face masks/face shields), physical distancing, ventilation, quarantining/isolation, symptom-based screening and contact tracing • The HTAC is actively on the watch for evidence as it is rapidly evolving, and shall update its recommendation when new information becomes available.

C. The HTAC likewise maintains its **previously recommended minimum sensitivity and specificity which are 80% and 97% for Rapid Antigen Tests,** respectively. These were adapted from the UK Medicines & Healthcare products Regulatory Agency and the World Health Organization Interim Guidance. Further to this, **RAgT must also satisfy the following 2021 recommended minimum regulatory, technical and operational specifications set by the HTAC** found in Table 3**.**

Table 3. Recommended specifications for RT-PCR kits using NPS/OPS and saliva specimens

Parameter	Requirement (HTAC recommendation 2020)	Requirement (updated as of 19 April 2021)
Regulatory Requirement	Must have a certificate of product registration (CPR) or emergency	Must have a certificate of product registration (CPR) or emergency

	authorization (EA) from the FDA Philippines	authorization (EA) from the FDA Philippines
Test kit package content	It is desirable that rapid antigen test kits contain all materials and accessories necessary for the procedure.	It is desirable that rapid antigen test kits contain all materials and accessories necessary for the procedure.
Result output	Qualitative, result must be read visually or with a reader but must be operable using batteries	Qualitative, result must be read visually or with a reader but must be operable using batteries
Human resource training ***[Updated]***	Less than half a day to no additional training needed for healthcare professionals to be able to optimize performance	***Minimum of 4-hour long training needed for healthcare professionals to be able to optimize performance Training module available at WHO (https://extranet.who.int/hslp/content/sars-cov-2-antigen-rapid-diagnostic-test-training-package)***
Biosafety concerns	Can be done without the need for BSL 2 or 3 facilities, provided that there is evidence that the live virus was deactivated early in the process	Can be done without the need for BSL 2 or 3 facilities, provided that there is evidence that the live virus was deactivated early in the process
Clinical Sensitivity	At least 80% sensitivity A useful assessment is the sensitivity of the test in patients with a rRT-PCR cycle threshold (Ct) below a specific value (e.g., 28 or 30)	At least 80% sensitivity A useful assessment is the sensitivity of the test in patients with a rRT-PCR cycle threshold (Ct) below a specific value (e.g., 28 or 30)
Clinical Specificity	At least 97% specificity	At least 97% specificity
Processing Time	Less than 2 hours from sample collection to result	Less than 2 hours from sample collection to result
Reference Standard	In-house laboratory RT-PCR test or if commercial RT-PCR test, must adhere to the specification stipulated in the HTAC Guidance Document on RT-PCR test kits	In-house laboratory RT-PCR test or if commercial RT-PCR test, must adhere to the specification stipulated in the HTAC Guidance Document on RT-PCR test kits
Sample Requirement in Validation Studies	Positive samples: minimum of 30 positive specimens Negative samples: 30 negative specimens Include details such as: • specimen type • specimen collection date • date of onset of symptoms (if present) • date of PCR testing	Positive samples: minimum of 30 positive specimens Negative samples: 30 negative specimens Include details such as: • specimen type • specimen collection date • date of onset of symptoms (if present) • date of PCR testing • severity of symptoms (if known)

	● severity of symptoms (if known) ● tests used to identify COVID19 patients, etc.	● tests used to identify COVID19 patients, etc.
Requirement for Independent Validation ***[Updated]***	Must have been validated by an independent or a third-party reputable government or private research institution including but not limited to the following: ● Research Institute for Tropical Medicine (RITM) ● UP National Institutes of Health (NIH) ● US Food and Drug Administration (US-FDA) ● World Health Organization, Foundation for Innovative New Diagnostics (WHO-FIND) ● Therapeutic Goods Administration (TGA, Australia) ● Medicines and Healthcare products Regulatory Agency (MHRA, UK) ● Japan Pharmaceuticals and Medical Devices Agency	RAgTs must be authorized by the Philippine Food and Drug Administration, and validated by any of the following: ● Research Institute for Tropical Medicine (RITM) ● US Food and Drug Administration (US-FDA) ● World Health Organization, Foundation for Innovative New Diagnostics (WHO-FIND) ● Therapeutic Goods Administration (TGA, Australia) ● Medicines and Healthcare products Regulatory Agency (MHRA, UK) ● Japan Pharmaceuticals and Medical Devices Agency ● ***Other DOH-designated institutions for test kit validation recognized by RITM in its letter to the Secretary of Health dated 01 April 2021 (Annex A) unless these laboratories are developing their own test kits***
Transport and Storage Requirements	The storage and working temperature can be 18 to 30 °C. It should be used in a controlled environment.	The storage and working temperature can be 18 to 30 °C. It should be used in a controlled environment.
Shelf-Life	Shelf-life should not be shorter than twelve (12) months at the time of delivery	Shelf-life should not be shorter than twelve (12) months at the time of delivery
Calibration Requirement	If calibration is required, it can be done onsite	If calibration is required, it can be done onsite
Cost of test kit ***[Updated]***	The cost of the RAgT kit should be significantly less than the cost of the RT-PCR test kit	The total cost of the initial and possible repeat testing using the RAgT kit should be significantly less than the cost of the ***government price cap for RT-PCR test kit.***

VI. References

1. ACE Singapore (2020, April 25). PCR Testing for COVID-19: Where to Swab? Retrieved from https://www.ace-hta.gov.sg/public-data/covid-19-resources/PCR%20testing%20for%20COVID-19%20-%20where%20to%20swab%20(24%20April%202020).pdf
2. Australia Department of Health (2020). *Coronavirus (COVID-19) domestic travel restrictions and remote area access.* Retrieved on 21 April 2021 from https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-restrictions/coronavirus-covid-19-domestic-travel-restrictions-and-remote-area-access#state-and-territory-travel-restrictions
3. Australia Department of Health (2021). *Coronavirus (COVID-19) advice for international travellers.* Retrieved on 21 April 2021 from https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-restrictions/coronavirus-covid-19-advice-for-international-travellers#travel-into-australia
4. Australia Therapeutic Goods Authority. (2021). *COVID-19 test kits included in the ARTG for legal supply in Australia.* Retrieved February 5, 2021, from https://www.tga.gov.au/covid-19-test-kits-included-artg-legal-supply-australia
5. Burog, Bayona, Cabaluna & Maglente. (2021). Should rapid antigen tests be used in the diagnosis of COVID-19 in clinically suspected patients? Philippine COVID-19 Living Clinical Practice Guidelines.
6. Center for Disease Control (2020). *Interim Guidance for Rapid Antigen Testing for SARSCoV-2*. Retrieved March 23, 2021, from https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html
7. Centers for Disease Control and Prevention- USA. (2020c, February 11). *Information for Laboratories about Coronavirus (COVID-19)*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html#anchor_1590264293982
8. Communicable Diseases Network Australia. (2021). *Coronavirus Disease 2019 (COVID-19) CDNA National Guidelines for Public Health Units.* Retrieved March 23, 2021, from https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-novel-coronavirus.htm
9. Department of Health and Social Care. (2021). *Types and uses of coronavirus (COVID-19) tests.* Retrieved March 23, 2021, from https://www.gov.uk/government/publications/types-and-uses-of-coronavirus-covid-19-tests/types-and-uses-of-coronavirus-covid-19-tests
10. Department of Health- Philippines (2020, April 9). Department Memorandum 2020-0184: Clarification on the Financing and Reimbursement of COVID-19 Antibody Test Kits by the

Department of Health (DOH) and Philippine Health Insurance Corporation (PhilHealth), respectively

11. Department of Health- Philippines (2020, May 1). Department Memorandum 2020-0200: Omnibus Interim Guidelines for the Quarantine and Testing Procedures for All Arriving Overseas Filipinos (OFs) and Foreign Nationals During the Coronavirus Disease 2019 (COVID-19) Pandemic.
12. Department of Health- Philippines (2020, May 11). Department Memorandum 2020-0220: Interim Guidelines on the Return-to-Work
13. Department of Health- Philippines (2020, May 29). Department Memorandum 2020-0258: Updated Interim Guidelines on Expanded Testing for COVID-19
14. Department of Health Philippines. (2020). *Department Memorandum 2020-0512: Revised Omnibus Interim Guidelines on Prevention, Detection. Isolation Treatment, and Reintegration Strategies for COVID-19.* Retrieved February 8 2021, from https://doh.gov.ph/sites/default/files/health-update/dm2020-0439.pdf
15. Directorate General of Immigration of the Republic of Indonesia (2021). Retrieved April 21, 2021, from https://www.imigrasi.go.id/covid19/detail/1b645389/penutupan-perbatasan-dan-pengecualian
16. DOH (2021). UPDATES ON NOVEL CORONAVIRUS DISEASE (COVID-19). Retrieved March 23, 2021, from https://doh.gov.ph/2019-nCoV
17. European Center for Disease Prevention and Control (2020). Options for the use of rapid antigen tests for COVID-19 in the EU/EEA and the UK. Retrieved March 23, 2021 from https://www.ecdc.europa.eu/sites/default/files/documents/Options-use-of-rapid-antigen-tests-for-COVID-19.pdf
18. European Union. 2020. Coronavirus: Commission puts forward rules on rapid antigen tests and secures 20 million tests for Member States. Retrieved February 8, 2021 from https://ec.europa.eu/commission/presscorner/detail/en/IP_20_2483
19. Food and Drug Administration of the Philippines. (2020, March 20). *COVID-19 FDA UPDATES*. https://www.fda.gov.ph/covid-19-fda-updates/
20. Germany Federal Foreign Office (2021). *Information on entry restrictions and quarantine regulations in Germany*. Retrieved April 28, 2021, from https://www.auswaertiges-amt.de/en/einreiseundaufenthalt/coronavirus#content_0
21. Johns Hopkins Coronavirus Resource Center. (2021). *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)*. Retrieved March 23, 2021, from https://coronavirus.jhu.edu/map.html
22. Kang, H., Kwon, S., and Kim, E. (2021) COVID-19 Health System Response Monitor, updated February 2021.WHO. Retrieved April 21, 2021 from: https://apps.who.int/iris/bitstream/handle/10665/337371/9789290228219-eng.pdf?sequence=1&isAllowed=y
23. Kontou, P. I., Braliou, G. G., Dimou, N. L., Nikolopoulos, G., & Bagos, P. G. (2020). Antibody Tests in Detecting SARS-CoV-2 Infection: A Meta-Analysis. *Diagnostics*, *10*(5), 319. https://doi.org/10.3390/diagnostics10050319

24. Lachenbruch, P. A. (1988). Multiple reading procedures: The performance of diagnostic tests. Statistics in Medicine, 7(5), 549-557.
25. McGill University. (2021). *COVID-19 vaccines tracker.* Retrieved March 23, 2021, from https://covid19.trackvaccines.org/vaccines/
26. Medicines and Healthcare Products Regulatory Agency- United Kingdom. (2020). *Target Product Profile: Antibody tests to help determine if people have immunity to SARS-CoV-2*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/883897/Target_Product_Profile_antibody_tests_to_help_determine_if_people_have_immunity_to_SARS-CoV-2_Version_2.pdf
27. Ministry of Foreign Affairs Japan (2021) Border enforcement measures to prevent the spread of novel coronavirus (COVID-19), updated April 20, 2021. Retrieved April 21, 2020 from: https://www.mofa.go.jp/ca/fna/page4e_001053.html
28. Ministry of Foreign Affairs Korea (2021) Entry Restriction and Visa Restriction due to COVID-19, updated on 11 February 2021. Retrieved April 21, 2021 from: https://overseas.mofa.go.kr/au-en/brd/m_3306/view.do?seq=760568
29. Ministry of Foreign Affairs of the Republic of Indonesia (2021). *INTERNATIONAL TRAVEL HEALTH PROTOCOL DURING THE CORONA VIRUS DISEASE PANDEMIC 2019 (COVID-19)*. Retrieved April 21, 2021, from https://kemlu.go.id/portal/id/page/73/covid-19
30. Ministry of Health for Malaysia (25 February 2021). *COVID-19 Management Guidelines in Malaysia No.5 / 2020. Annex 9*. Retrieved February 21, 2021, from http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_9_Management_of_COVID-19_PoE_25022021.pdf
31. Ministry of Health Malaysia. (2021). *ANNEX 4c: GUIDELINE ON COVID-19 TESTING USING ANTIGEN RAPID TEST KIT (RTK-Ag) FOR THE HEALTH FACILITIES IN MINISTRY OF HEALTH VERSION 5.0.* Retrieved March 23, 2021, from http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/ANNEX_4c_GUIDELINE_ON_COVID-19_TESTING_USING_ANTIGEN_RAPID_TEST_KIT_(RTK-Ag)_FOR_THE_HEALTH_FACILITIES_IN_MINISTRY_OF_HEALTH.pdf
32. Ministry of Health, Labor and Welfare (2020). Clinical Management of Patients with COVID-19. Retrieved March 23, 2021, from https://www.mhlw.go.jp/content/000646531.pdf
33. Ministry of Health, Labour, and Welfare (2021) About New Measures related to Border Measures, Retrieved April 21, 2021 from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00209.html
34. Ministry of Health, Labour, and Welfare (2021) About presentation of inspection certificate, updated April 16, 2021. Retrieved April 21, 2021 from https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00248.html
35. National Institute of Health (2021). Covid-19 treatment guidelines. Retrieved March 23, 2021, from https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf
36. Paul-Ehrlich-Institut. (2021). Minimum Criteria for Rapid SARS-CoV-2 Antigen Tests

Pursuant to Section 1 para 1 Sentence 1 TestVO (Statutory Test Regulation): Rapid Antigen Tests. Retrieved February 8, 2021 from https://www.pei.de/SharedDocs/Downloads/EN/newsroom-en/dossiers/minimum-criteria-for-rapid-sars-cov2-antigen-tests-01-12-2020.pdf?__blob=publicationFile&v=5

37. Premkumar, L., Segovia-Chumbez, B., Jadi, R., Martinez, D. R., Raut, R., Markmann, A., Cornaby, C., Bartelt, L., Weiss, S., Park, Y., Edwards, C. E., Weimer, E., Scherer, E. M., Rouphael, N., Edupuganti, S., Weiskopf, D., Tse, L. V., Hou, Y. J., Margolis, D., … de Silva, A. M. (2020). The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. *Science Immunology*, *5*(48), eabc8413. https://doi.org/10.1126/sciimmunol.abc8413
38. Public Health Laboratory Network. (2020). *PHLN guidance on laboratory testing for SARS-CoV-2 (the virus that causes COVID-19), v1.16*. Retrieved March 23, 2021, from https://www.health.gov.au/resources/publications/phln-guidance-on-laboratory-testing-for-sars-cov-2-the-virus-that-causes-covid-19
39. Republic of the Philippines. Proclamation No 922. Declaring a State of Public Health Emergency Throughout the Philippines. Accessed 14 May 2020 at: https://www.officialgazette.gov.ph/downloads/2020/02feb/20200308-PROC-922-RRD-1.pdf
40. Robert Koch Institute (2020). *Digital registration on entry.* Retrieved April 28, 2021, from https://www.einreiseanmeldung.de/#/
41. Royal Thai Embassy (2021). *Updated regulations to enter Thailand and procedures of the quarantine*. Retrieved 21 April, 2021 from https://thaiembdc.org/2021/03/31/updated-regulations-to-enter-thailand-and-procedures-of-the-quarantine-effective-from-1-april-2021/
42. Senthuraman, N., Jeremiah, S. S., & Ryo, A. (2020). Interpreting Diagnostic Tests for SARS-CoV-2. JAMA, 323(22), 2249. https://doi.org/10.1001/jama.2020.8259
43. Singapore Ministry of Foreign Affairs (n.d.). *Vietnam.* Retrieved on 21 April 2021 from https://www.mfa.gov.sg/countries-regions/v/viet-nam/travel-page
44. South Korea Ministry of Health and Welfare (2020). *Guideline for the operation of COVID-19 screening clinic*. Retrieved March 23, 2021, from http://ncov.mohw.go.kr/en/guidelineView.do?brdId=18&brdGubun=181&dataGubun=&ncvContSeq=2937&contSeq=2937&board_id=&gubun=#
45. UK Department of Health and Social Care. (2021). *Guidance: How to quarantine when you arrive in England. Retrieved on 21 April 2021 from* https://www.gov.uk/guidance/how-to-quarantine-when-you-arrive-in-england#testing-in-quarantine
46. UK Department of Transport (2021). *Guidance: Coronavirus (COVID-19) testing before you travel to England.* Retrieved on 21 April 2021 from https://www.gov.uk/guidance/coronavirus-covid-19-testing-for-people-travelling-to-england#test-providers-and-type-of-test
47. UK NHS. (2021). *Your coronavirus test result.* Retrieved March 23, 2021, from https://www.nhs.uk/conditions/coronavirus-covid-19/testing-and-tracing/what-your-test-result-means/

48. US CDC (2021) Domestic Travel During COVID-19, updated 02 April 2021.Retrieved April 21, 2021 from: https://www.cdc.gov/coronavirus/2019-ncov/travelers/travel-during-covid19.html#travel-restrictions
49. US CDC (2021) Requirement for Proof of Negative COVID-19 Test or Recovery from COVID-19 for all Air Passengers Arriving in the United States, updated 08 April 2021.Retrieved April 21, 2021 from: https://www.cdc.gov/coronavirus/2019-ncov/travelers/testing-international-air-travelers.html
50. US CDC (2021) Test for Current Infection, updated 08 March 2021. Retrieved April 21, 2021 from: https://www.cdc.gov/coronavirus/2019-ncov/testing/diagnostic-testing.html
51. US Embassy & Consulates in Mexco (2021) COVID-19 Information for US Citizens in Mexico, update April 19, 2021. Retrieved April 21, 2021 from: https://mx.usembassy.gov/u-s-citizen-services/covid-19-information/
52. US FDA. (2020). *FDA Approves First Treatment for COVID-19.* Retrieved March 23, 2021, from https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19
53. US Food and Drug Administration. (2021). *In Vitro Diagnostics EUAs.* Retrieved February 5, 2021, from https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas
54. Vietnam Prime Minister. *Directive No. 01/CT-TTg dated January 05, 2021 of the Prime Minister on strengthening the provision and control of COVID-19 pandemic.* Retrieved on 21 April 2021 from https://english.luatvietnam.vn/irective-no-01-ct-ttg-dated-january-05-2021-of-the-prime-minister-on-strengthening-the-prevention-and-control-of-covid-19-pandemic-196690-Doc1.html
55. Vietnam Tourism (2021). *New COVID-19 Policies in Vietnam.* Retrieved on 21 April 2021 from https://vietnam.travel/things-to-do/covid-19-travel-policies-vietnam
56. WHO-FIND. (2020, June 24). *Evaluation update: SARS-CoV-2 immunoassays*. FIND. https://www.finddx.org/covid-19/sarscov2-eval-immuno/
57. WHO-FIND. (2020a, April 7). *SARS-CoV-2 diagnostic use cases*. FIND. https://www.finddx.org/covid-19/dx-use-cases/
58. World Health Organization (2020). *Viet Nam COVID-19 Situation Report #14*. Retrieved March 23, 2021, from https://www.who.int/docs/default-source/wpro---documents/countries/viet-nam/covid-19/vnm-moh-who-covid-19-sitrep14.pdf?sfvrsn=95e5ea23_2&download=true
59. World Health Organization (WHO). (2020). Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays: Interim guidance. Retrieved September 14, 2020 from:

https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

60. World Nomads (2021). *Coronavirus (COVID-19) travel restrictions in Thailand*. Retrieved April 21, 2021 from https://www.worldnomads.com/travel-safety/southeast-asia/thailand/latest-thailand-travel-warnings-alerts
61. Yokota, I., et al. (2020) Performance of qualitative and quantitative antigen tests for SARS-CoV-2 in early symptomatic patients using saliva. Retrieved April 22, 2021 from: https://www.medrxiv.org/content/10.1101/2020.11.06.20227363v1.full.pdf

VI. Annexes

Table 4. Comparison of Target Product Profiles for RAgTs

Parameter	***US FDA***	***UK MHRA***		***WHO***	
		Acceptable	***Desirable***	***Acceptable***	***Desirable***
Intended Use	No specific requirement	Aid in triage of current SARS-CoV2 infection by detection of SARSCoV-2 nucleic acids or antigens in samples from people of all ages during the acute phase of infection.	Aid in triage of current SARS-CoV-2 infection by detection of SARS-CoV-2 nucleic acids or antigens in samples from people of all ages at any point during active infection.	In areas with confirmed SARS-CoV-2 community wide transmission or confirmed outbreaks in closed or semi-closed communities and in high risk groups: Early detection of SARS-CoV-2 cases where molecular/ reference assays are not available or services are overloaded, leading to turnaround times that are not useful for guiding clinical case management and infection control measures. In suspected SARS-CoV-2 outbreak situations: multiple positive cases highly suggestive of SARS-CoV-2 Monitor trends in disease incidence	
Target Population	No specific requirement	People with clinical signs and symptoms associated with SARS-CoV-2 infection.	People with or without clinical signs and symptoms associated with SARS-CoV-2 infection, if testing is appropriate.	Patients with acute or subacute respiratory symptoms or fever or other suspicious symptoms (diarrhoea, anosmia) and either a known contact with a confirmed or probable COVID-19 patient or living in an area of cluster or community transmission, and close contacts (with or without symptoms) of index patients (confirmed COVID-19 patients).	
Turnaround time	No specific requirement	Less than 2 hours from sample to result	Less than 30 minutes from sample to result	≤ 40 minutes	≤20 minutes
Number of antigens to be detected	No specific requirement	Single SARS-Cov-2 RNA or antigen target	Dual (or more) SARS-CoV-2 RNA or antigen targets	SARS-CoV biomarker (e.g. RNA, protein/antigen(s) specific for acute e.g. first week after onset of symptoms /current infection (assumption that SARS-CoV-1 is not	SARS-CoV-2 only biomarker (e.g. RNA, protein/antigen) specific for acute and subacute e.g. first two weeks after onset of symptoms/current infection

				circulating)	
Specimen	No specific requirement	Nasopharyngeal or oropharyngeal swabs, lower respiratory tract aspirates, bronchoalveolar lavage, nasopharyngeal wash/aspirate or nasal aspirate	Sputum, saliva or other method not using invasive swab	Nasopharyngeal, oropharyngeal swab (or wash) nasal swab (anterior nares or mid-turbinate), nasal wash, sputum	Anterior nares, saliva/oral fluid, sputum
Clinical Sensitivity	If you intend to seek a claim for saliva, oral fluid, blood, or other specimen types, you should test at least 30 positive specimens with paired polymerase chain reaction (PCR) results from an NP swab.	Greater than 80% (within 95% confidence intervals of 70-100%)	Greater than 97% (within confidence intervals of 93-100%)	≥ 80% The targets are for the estimated true sensitivity and specificity; therefore, the lower bound of confidence intervals should ideally equal or exceed the target.	≥90% The targets are for the estimated true sensitivity and specificity; therefore, the lower bound of confidence intervals should ideally equal or exceed the target.
Clinical Specificity		Greater than 95% (within 95% confidence intervals of 90-100%)	Greater than 99% (within confidence intervals of 97-100%)	≥ 97% The targets are for the estimated true sensitivity and specificity; therefore, the lower bound of confidence intervals should ideally equal or exceed the target.	>99% The targets are for the estimated true sensitivity and specificity; therefore, the lower bound of confidence intervals should ideally equal or exceed the target.
Sample size	You should confirm the performance of your assay by testing a minimum of 30 positive specimens and 30 negative specimens in a randomized blinded fashion	**Clinical sensitivity:** At least 150 positive clinical samples. The samples should cover a clinically meaningful range of viral loads (i.e. should be from people with high, medium and low viral load) that represents the population the test is intended to be used in. For tests with lower sensitivity, it is envisaged that when used in practice people with negative results will need confirmatory checking by an additional test. **Clinical specificity:** At least 250 negative clinical		None mentioned	None mentioned

		samples. For tests with lower specificity, it is envisaged that when used in practice people with positive results will need confirmatory checking by an additional test.			
Comparator test	We recommend only using an EUA test with high sensitivity and reverse transcription polymerase chain reaction (RT-PCR), which uses a chemical lysis step followed by solid phase extraction of nucleic acid (e.g., silica bead extraction) as the comparator method. The comparator method should be one of the more sensitive RT-PCR assays authorized by FDA. We encourage you to review the results from the FDA SARS-CoV-2 Reference Panel available here when selecting your comparator method; we strongly recommend you contact us to discuss your choice of comparator assay.	A validated CE marked laboratory method in current clinical use, against which the Negative/Positive Percent Agreement is calculated	A composite clinical reference standard or dPCR reference method.	Determination of sensitivity and specificity should be against an approved/authorised by a stringent regulatory authority (SRA), molecular-based COVID-19 assay7.Product assessment of clinical specificity must include patients/samples with other human coronaviruses and pathogens in differential diagnosis for presenting signs/symptoms.	
Storage temperature	• FDA considers 15-30°C to represent room temperature conditions. Ideally, you should evaluate stability at both 15°C and 30°C; however, for the	Storage of kit and reagents at 2-8° C for at least 12 months. Stable for 12 hours once removed from cold storage.	No cold chain (15 to 30° C).	12 months4 at 4-30°C; tolerates brief periods > 40°C; humidity 75%+ 5% any associated equipment must meet or exceed these requirements.	18-24 months at 4-40°C; tolerates freezing and brief periods > 45°C; humidity 75%+ 5%.; any associated equipment must meet or exceed these requirements.
Operating		15 to 30° C	15 to 30° C	15-35°C; 25-80% relative	10-40°C; 25-90% relative

conditions (temperature, humidity, etc.)	purposes of the EUA evaluation, we believe 30°C is acceptable as it represents the worse-case scenario. ● Unopened kit Shelf-Life Stability: a. You should evaluate real-time kit stability studies with unopened kits stored at the claimed storage temperature for your test. b. Accelerated stability evaluations for unopened kits can be included for EUA submissions while the real-time studies are on-going. ● Unopened kit Shipping Stability: Study should evaluate the anticipated handling and shipping times and temperatures expected for unopened kits. ● In-use/Opened Kit Stability: Depending on your device, your stability study design should also support in-use stability of the kit			humidity up to 1500m.	humidity up to 3000m.

	reagents once the kit has been opened, e.g., storage at 2-8°C for 7 days. This includes on board stability once reagents have been placed on the instrument (if applicable).				
Biosafety	No specific requirement	Standard PPE and safety procedures need to be followed. No need for BSL 2 or 3 laboratory facilities. Evidence that live virus is deactivated early in the process.	Standard PPE and safety procedures need to be followed. No need for BSL 2 or 3 laboratory facilities. Evidence that live virus is deactivated early in the process.	Standard respiratory sample collection safety precautions recommended, and all materials are free of components with a GHS classification H (particularly H350, H340, H360)8	Tests that minimize the need for biosafety requirement are strongly preferred e.g. with a self-sample collection device with virus inactivation