



# Use of Rapid Antigen Test Kits for the Diagnosis of COVID-19

 **Evidence Summary**

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## *Evidence Summary*

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## 1. General information of the proposed health technology

<b>Generic Name</b>	Rapid Antigen Tests Kits
<b>Product Name</b>	Not applicable
<b>Food and Drug Administration approved indication</b>	Not applicable
<b>Proposed Indication/s</b>	Not applicable
<b>Dosage Formulation/Strength</b>	Not applicable
<b>Route of Administration</b>	Not applicable
<b>Dosage Regimen</b>	Not applicable
<b>Therapeutic Class</b>	Not applicable

## 2. 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 appraisal of the Health Technology Assessment Council (HTAC) was requested. An updated rapid review and recommendation on rapid antibody tests (RATs) was recently completed and issued. This review on the other hand focused on the role of another point-of-care test, the rapid antigen test for diagnosing COVID-19.

## Policy Question

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

## Research Questions

### 1. Regulatory Approval

- 1.1. *What are the performance standards used by selected regulatory agencies for the approval of COVID-19 RAgTs for market entry?*
- 1.2. *What are the validation testing requirements of selected regulatory agencies for COVID-19 RAgTs?*

### 2. Performance Characteristics

*What is the accuracy of RAgTs either alone or as an adjunct to RT-PCR in the diagnosis of COVID-19 as compared to RT-PCR alone?*

### 3. Global guidelines and position on use of RAgTs

- 3.1. *Which countries have implemented testing strategies using RAgTs for diagnosing COVID-19?*
- 3.2. *What is the current position of HTA agencies regarding the use of RAgTs for diagnosing COVID-19?*

### 4. Resource requirements

*What are the resource requirements needed to use RAgTs?*

## 3. Responsiveness to disease magnitude, severity, and equity

### 3.1. Responsiveness to disease magnitude and severity

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 15 September 2020, it has affected more than 188 countries and regions with at least 29, 279, 316 cases and 928, 403 deaths worldwide as of 15 Sept 2020 (Dong, Du & Gardner, 2020). In the Philippines, COVID-19 affected over 269, 407 cases with 4,663 deaths as of 15 September, 2020 (DOH, 2020). To date, treatment remains unknown.

Currently, there are no known treatments for COVID-19.

### 3.2. Regulatory Standards

Of the eleven regulatory agencies reviewed for any regulatory guidelines for the approval and validation testing of COVID-19 RAgTs, we found relevant information from five regulatory agencies namely Health Canada, Pharmaceutical and Medical Devices Agency (PMDA) of Japan, UK Medicines and Healthcare Products Regulatory Agency (MHRA), US Food and Drug Administration (US FDA), and the PH FDA. Among these five regulatory agencies, only the US FDA, PH FDA and Japan PMDA have issued authorizations for COVID-19 RAgTs and allowed them to be marketed in their respective

countries (PH FDA, 2020b; US FDA, 2020b; PMDA, 2020a). To date, the number of registered brands of RAgTs are four by the US FDA, eleven by the PH FDA, and two by the Japan PMDA. Both Health Canada and UK MHRA have not registered yet RAgTs in their markets. Health Canada, as of writing, still adopts the April 8, 2020 scientific brief of WHO on *Advice on the use of point-of-care immunodiagnostic tests for COVID-19* which does not recommend the use of antigen testing, but recommends research into their performance and potential diagnostic utility (Health Canada, 2020). The UK MHRA, on the other hand, has only provided a target product profile for point-of-care SARS-CoV-2 detection tests (MHRA, 2020a).

Among the three agencies which have authorized use of RAgTs in their markets, the US and the PH FDA issued emergency use authorizations (EUA) or special certification to the antigen tests while the approved antigen test in Japan has undergone the regular review scheme (PMDA, 2020b; PH FDA, 2020a). As for the standards used for regulatory approval, the US FDA recommends validation studies on analytical sensitivity, analytical specificity, microbial interference, and clinical agreement be conducted (US FDA, 2020c). For the Philippines, the PH FDA only requires the product registration of the COVID-19 test kit by a regulatory agency or accredited third party from countries with established regulations (PH FDA, 2020a). For Japan, no specific standards or requirements were presented for antigen tests, but the review summary for one of the approved antigen tests by the regulatory agency can provide information on the basis of approval which includes the evaluation of the clinical performance, cross-reactivity, stability, and precautions required for using the product (PMDA, 2020c).

Only the US FDA has published details on the validation requirements. For the clinical agreement study, the use of natural clinical specimens for the evaluation, collected either prospectively or retrospectively (minimum of 30 positive specimens and 30 negative specimens), with the testing done in a randomized and blinded fashion, is recommended. The recommended comparator is a high sensitivity EUA RT-PCR test. Furthermore, the test should be able to demonstrate a minimum sensitivity of greater than or equal to 80% for all sample types. No information on the minimum specificity required was mentioned in the document. In addition, the US FDA suggests providing studies supporting point-of-care claim such as data to demonstrate that non-laboratory personnel can perform the test in the intended use environment claimed by the manufacturer. (US FDA, 2020a)

For the UK MHRA target product profile for RAgTs, it is desirable that the test has a sensitivity of greater than 97% (within 93-100% C.I.) and specificity of greater than 99% (within 97-100% C.I.) while it is acceptable to have a sensitivity of greater than 80% (within 95% C.I. of 70-100) and specificity of greater than 95% (within 95% C.I. of 90-100). (MHRA, 2020b)

### 3.3. Guideline Recommendations

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

- US, Japan and WHO currently recommend the use of antigen testing for COVID-19. The US CDC (2020) guidelines currently recommend its use for diagnostic testing of vulnerable patients with high pre-test probability (ie., symptomatic patients or patients with known exposure to a confirmed case), and for screening testing in vulnerable high-risk congregate settings. Meanwhile, in Japan, RAgTs may be used for patients suspected for COVID-19. The WHO (2020) also recommends the use of antigen tests (that meet the minimum performance requirements of  $\geq 80\%$  sensitivity and  $\geq 97\%$  specificity compared to a NAAT reference assay) as a diagnostic test

in a range of settings where NAAT is unavailable or where prolonged turnaround times preclude clinical utility. These include its use 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 supporting outbreak investigations, in monitoring trends in disease incidence in communities, in areas with widespread community transmission, and in testing asymptomatic contacts of cases.

- As diagnostic test, these guidelines consider a positive antigen test to be reliable given the high specificity of approved tests, while a negative test must be considered presumptive and confirmatory test must be conducted when applicable (Japan MHLW, US CDC and WHO). The US CDC (2020) and WHO (2020) 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 (2020) 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. As screening test, the US guidelines for the screening of population with high pre-test probability using RAgT follow the same recommendation as that for the diagnostic testing among population with high pre-test probability using RAgT. However, for the screening of patients with low pre-test 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.
- According to the WHO (2020) guidelines, there are instances in which RAgTs are not recommended for use. These are in settings or populations with low prevalence of disease, in individuals 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.
- On the other hand, Canada does not recommend the use of antigen testing for the diagnosis of COVID-19 due to issues on its sensitivity and possible false negatives. Canada only recommends the use of antigen testing in researching their performance and potential diagnostic utility (Health Canada, 2020b).
- South Korea, Vietnam and UK, Australia, Malaysia, China and Philippines 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. Australia, Malaysia, China and Philippines, however, additionally allows the use of RATs in conjunction with RT-PCR under different circumstances.
- Singapore, Indonesia and Thailand do not have publicly accessible national testing guideline.

### 3.4. HTA Review Recommendations

None of the 10 reviewed HTA agencies (EUnetHTA, USA, UK, Australia, Canada, China, Indonesia, Malaysia, Singapore, South Korea) had any published or on-going assessments or relevant guidance regarding the use of antigen-based serology testing for the diagnosis of COVID-19.

## 4. Safety and effectiveness

### 4.1. Diagnostic Performance

Bayona et al. (2020) noted the following key findings from their rapid review with meta-analysis on the use of RAgTs as screening tool:

- The sensitivity of RAgTs greatly varies, ranging from 0 to 94%. The pooled sensitivity of 49% implies that RAgTs have a high false negative rate. On the other hand, the specificity of RAgTs remained very high at 99% across all studies. Caution should be taken when interpreting the findings especially for pooled estimates for sensitivity as there was substantial heterogeneity noted across studies.
- The sensitivity is highly brand-dependent, possibly due to differences in the reading or interpretation of results or the reagents used. RAgTs that make use of automated readers for determining a positive or negative result, such as the *Bioeasy 2019-nCoV Ag Fluorescence Rapid Test Kit* and *Sofia 2 SARS Antigen FIA*, showed higher sensitivity compared to those which depended on visual readouts.
- Sensitivity estimates were higher among symptomatic compared to asymptomatic participants. However, this warrants further investigation as the number of asymptomatic patients involved in this review was small to allow clear conclusions to be made.
- Testing patients early in the disease process also appeared to increase the sensitivity of RAgTs. This finding appears consistent with previous work showing viral load of SARS-CoV-2 peaks at the onset of symptoms and gradually decreases thereafter (He 2020; To 2020; Zou 2020).
- RAgTs that require the use of an automated reader for interpreting the results appear to have a higher sensitivity as compared to RAgTs that rely on visual interpretation of results.
- RAgT using nasopharyngeal swab specimens had the highest sensitivity but did not significantly differ from those taken via combined nasopharyngeal and oropharyngeal swab. Studies conducted on other respiratory viral infections have shown that the combined nasopharyngeal and oropharyngeal swab showed little added benefit compared to nasopharyngeal swab alone (Dawood 2015). Sampling via oropharyngeal swab alone compared to nasopharyngeal swab had lower sensitivity in detecting COVID-19 (Wang 2020).

Overall, they concluded that based on moderate quality evidence, the use of RAgTs as a screening tool for COVID-19 is limited by its low sensitivity. Because of its overall low sensitivity and the high uncertainty on its accuracy, they recommend its use for diagnosis confirmation for the following conditions: (1) when RT-PCR is not available or with slow turnaround and having immediate test results are vital such as situations where urgent decisions regarding interventions and patient management are needed (e.g., emergency admissions) or for contact tracing; or, (2) for patients with high pre-test probability such as symptomatic cases in hospitals, symptomatic contacts, and patients with anosmia, ageusia, and other related symptoms. High quality validation studies are needed.

## 5. Household financial impact

No evidence available.

## 6. Cost-effectiveness

No evidence available.



## 7. Affordability and viability

### 7.1. Resource Requirements

We found limited guidance documents or references relevant to the resource requirements of RAgTs internationally and locally, hence, we used information from the target product profile by the UK MHRA (2020b) and interim guidance by the WHO (2020). Based on the target profile document, RAgTs must have all materials needed to run the test, but in cases where some materials are not provided, these materials must still be procured by DOH and its accredited laboratories. Meanwhile, the WHO (2020) mentions that contents of the test kit may not necessarily include everything to perform and quality control the test. In terms of power requirements, the test must be operated without the need for a power source, but for tests that require an analyzer for reading the results, the equipment must be operated using a rechargeable and replaceable battery or through a standard power supply. In cases where additional training is needed for users such as healthcare professionals, this must not exceed half a day (MHRA, 2020b). In line with these requirements, the WHO (2020) mentions that the need for a reader or detection system will require additional training to personnel and additional infrastructure such as electricity. The UK MHRA (2020) discussed in their TPP that RAgTs should also have a quick turnaround, must be operable without the need for BSL 2 or 3 laboratory facilities, and in 15 to 30 °C temperature. On the other hand, the WHO (2020) emphasized that RAgTs must not be used if appropriate biosafety and infection control prevention measures such as PPE and ventilation are not in place. Because this information was sourced only from two international documents, it is important to note that some conditions or resource requirements may change depending on local conditions.

## 8. Recommendation

The HTAC reiterates that **RT-PCR remains the gold standard for diagnosis of COVID-19**, and would like to note that the following *interim recommendations on rapid antigen test are subject to change* pending new evidence.

The HTAC **does not recommend the use of rapid antigen tests** for indiscriminate use in mass screening (e.g., returning overseas Filipino workers (OFWs), return-to-work clearance, tourist clearance, land-stranded individuals (LSIs)) and COVID-19 diagnosis in individuals with low index of suspicion (i.e., asymptomatic and no history of exposure).

**Rapid antigen tests, like other diagnostic tests, are used to initiate contact tracing, epidemiological surveillance, and clinical management. Rapid antigen tests have been found to be most useful during the acute phase of the disease** when the viral load is high, that is, within five days after the onset of symptoms. Meanwhile, for asymptomatic contacts, rapid antigen tests can be used from four to 11 days after exposure even before symptoms develop. This is based on the WHO guidelines stating that antigen tests could be used one to three days before the onset of symptoms. Rapid antigen tests are currently recommended **by HTAC only for very specific purposes:**



- For targeted screening and diagnosis of suspect and probable cases of COVID-19 (i.e., with high index of suspicion), meeting the clinical and/or epidemiologic criteria as currently defined by the WHO in the hospital or community settings;
- 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; and,
- For targeted screening and diagnosis of suspect and probable cases of COVID-19 in suspected outbreaks (as currently defined by the DOH – Epidemiology Bureau) of COVID-19 in remote settings, (e.g., geographically isolated areas), where RT-PCR is not immediately available.

**Provided that rapid antigen tests satisfy the following recommended minimum regulatory, technical and operational specifications** set by the HTAC, and **pass the acceptance testing** by RITM at the cost of the winning supplier:

<b>Parameter</b>	<b>Requirement</b>
<b>Regulatory Requirement</b>	Must have a certificate of product registration (CPR) or emergency authorization (EA) from the FDA Philippines
<b>Test kit package content</b>	It is desirable that rapid antigen test kits contain all materials and accessories necessary for the procedure.
<b>Result output</b>	Qualitative, result must be read visually or with a reader but must be operable using batteries
<b>Human resource training</b>	Less than half a day to no additional training needed for healthcare professionals to be able to optimize performance
<b>Biosafety concerns</b>	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
<b>Clinical Sensitivity</b>	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)
<b>Clinical Specificity</b>	At least 97% specificity
<b>Processing Time</b>	Less than 2 hours from sample collection to result
<b>Reference Standard</b>	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
<b>Sample Requirement in Validation Studies</b>	Positive samples: minimum of 30 positive specimens Negative samples: 30 negative specimens  Include details such as: <ul style="list-style-type: none"> <li>• specimen type</li> <li>• specimen collection date</li> <li>• date of onset of symptoms (if present)</li> <li>• date of PCR testing</li> <li>• severity of symptoms (if known)</li> </ul>

	<ul style="list-style-type: none"> <li>tests used to identify COVID19 patients, etc.</li> </ul>
<b>Requirement for Independent Validation</b>	<p>Must have been validated by an independent or a third-party reputable government or private research institution including but not limited to the following:</p> <ul style="list-style-type: none"> <li>Research Institute for Tropical Medicine (RITM)</li> <li>UP National Institutes of Health (NIH)</li> <li>US Food and Drug Administration (US-FDA)</li> <li>World Health Organization, Foundation for Innovative New Diagnostics (WHO-FIND)</li> <li>Therapeutic Goods Administration (TGA, Australia)</li> <li>Medicines and Healthcare products Regulatory Agency (MHRA, UK)</li> <li>Japan Pharmaceuticals and Medical Devices Agency</li> </ul>
<b>Transport and Storage Requirements</b>	The storage and working temperature can be 18 to 30 °C. It should be used in a controlled environment.
<b>Shelf-Life</b>	Shelf-life should not be shorter than twelve (12) months at the time of delivery
<b>Calibration Requirement</b>	If calibration is required, it can be done onsite
<b>Cost of test kit</b>	The cost of the RAgT kit should be significantly less than the cost of the RT-PCR test kit

**Note:** The sensitivity and specificity thresholds using field validation results must be added to the technical requirements once clinical studies are available.

The following are considered individuals with **high index of suspicion**:

- **Symptomatic and with history of exposure OR**
- **Symptomatic and with no history of exposure OR**
- **Asymptomatic and with history of exposure**

	<b>WITH history of exposure</b>	<b>WITHOUT history of exposure</b>
<b>WITH symptoms</b>	HIGH index of suspicion: Recommended for rapid antigen testing	HIGH index of suspicion: Recommended for rapid antigen testing
<b>WITHOUT symptoms</b>	HIGH index of suspicion: Recommended for rapid antigen testing  <i>Applicable to guide patient cohort management to minimize transmission of COVID 19 to healthcare workers and other patients</i>	LOW index of suspicion: NOT recommended for rapid antigen testing

It is recommended that **individuals with positive rapid antigen test results (positive for COVID-19)** be isolated and managed as COVID-19 cases. **Individuals with a high index of suspicion and who tested negative using rapid antigen tests should be quarantined until they can be confirmed negative by RT-PCR results.** The confirmatory RT-PCR test for those who tested with negative rapid antigen test result should be done within two (2) days 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).**

**In areas where RT-PCR is not available to confirm a negative antigen test result,** persons with negative antigen test results but with high index of suspicion for COVID-19 **should undergo the complete 14-day quarantine.**

Finally, the **HTAC recommends research** on the **value of repeated antigen testing** compared to confirmatory RT-PCR and to symptom-based screening, as well as the **value of rapid antigen tests in screening and diagnosing asymptomatic COVID-19 patients.** The studies should aim for validating the performance of the test on diverse groups of people and settings that represent the full spectrum of disease including repeated measures. To be useful, the studies should provide proof of improvement of test performance when applied in clinical settings and field situations or at a minimum simulation models.

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.

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