Guidance Document on the Technical Requirements for SARS-CoV-2 Rapid Antigen Test Kits

Guidance Document

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September 2020

1. BACKGROUND

In early 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing novel coronavirus disease 2019 (COVID-19) as a global pandemic affecting more than 188 countries and regions with at least 29, 279, 316 cases and 928, 403 deaths worldwide as of 15 Sept 2020[1]. In the Philippines, COVID-19 affected over 269, 407 cases with 4,663 deaths as of 15 September, 2020[2]. To date, treatment remains unknown.

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. The current review shall focus on exploring the role of another point-of-care test, the rapid antigen test (RAgT) for diagnosing COVID-19.

2. SCOPE

The minimum specifications contained in this Guidance shall be used to guide the Department of Health, PhilHealth, and all healthcare facilities in ensuring the appropriate use of RAgTs and the reliability of test results during the COVID-19 pandemic.

3. PURPOSE OF THE GUIDANCE DOCUMENT

This Guidance is being issued to:

- set the HTAC-recommended use case for RAgTs
- outline the minimum specifications of RAgTs

The HTAC currently identifies the specific conditions where RAgTs are recommended for use, as well as the desired attributes of RAgTs to guide the healthcare providers in selecting which among the commercially available test kits exhibit the minimum diagnostic performance and operational characteristics for the recommended COVID-19 use case. The document is also meant to provide guidance to test kit developers on the ideal qualities of RAgTs that are being considered by HTAC in the evaluation of kits that are currently available in the market.

It is recognized that current evidence on the diagnostic accuracy of RAgTs is limited and continues to evolve. This guidance therefore is an interim document based on the joint rapid review conducted by the HTA Unit, the UP Institute of Clinical Epidemiology and the Asia Pacific Center for Evidence-based Healthcare, using the best available synthesized evidence at the time of writing. The rapid review is subject to updates and revisions as validation results on the performance of different RAgT brands are done by the RITM, the FDA, other internationally recognized stringent regulatory authorities and research institutions.

4. RAPID ANTIGEN TEST FOR DIAGNOSING COVID -19

Rapid Antigen Tests (RAgTs) belong to a class of rapid diagnostic tests which detects the presence of viral proteins or antigens expressed by the COVID-19 virus in a sample from the respiratory tract of the person[3]. These point-of-care diagnostic tests quickly detect fragment of proteins found on or within the virus by testing samples collected from the nasal cavity using swab[4]. Antigen tests, like nucleic-acid based tests such as the RT-PCR test, are designed to detect active SARS-CoV-2 infection. There are currently eleven approved RAgT brands by the Philippine Food and Drug Administration (PH FDA) as of their latest published list dated 11 September 2020[5]. Table 1 characterizes antigen tests compared to antibody tests and RT-PCR[6-9].

Table 1. Comparison of molecular, antigen, and antibody tests

Parameter	MOLECULAR TEST	ANTIGEN-BASED TESTS	ANTIBODY-BASED TESTS
Time frame	Slow (4-8 hours)	Rapid (15-40) Slow (1-3 hrs)	
Samples obtained	Nasopharyngeal, nasal or oropharyngeal swab, bronchoalveolar fluid	Nasopharyngeal, nasal or oropharyngeal swab; potentially oral fluid stool	Fingerstick blood, venous blood; potentially oral fluid
Type of infection detected	Current		Past
Ideal use case	Diagnosis/ monitoring		Seroprevalence Epidemiological purposes
What technique is used	Based on polymerase chain reaction (PCR) which makes millions of copies of a specific section of the viral genome, amplifying small amounts to detectable levels	Based on a technique called enzyme-linked immunosorbent assay (ELISA), in which molecules attach to the antibodies or antigen in the sample and produce a detectable signal	
Where does the testing take place	Performed in a laboratory (BSL 2) due to equipment requirements	May be laboratory-based (BSL 2 or higher) or performed at point of care, depending on test design	
Where and who performs?	Trained healthcare workers, wearing appropriate personnel protective equipment (PPE) at decentralized points of needs		
A positive result means	Confirms a current SARS-CoV-2 infection	Confirms a current SARS-CoV-2 infection or suggests a potential infection (depending on test design)	Indicates a recent or past infection, and could be used to screen for current infection (tests may not be reliable in early phase of infection)

5. CURRENT NATIONAL POLICIES ON DIAGNOSIS OF COVID-19

In recognition of the need for accelerated expansion of testing coverage, the DOH developed Guidelines on Expanded Testing for COVID-19 with its latest version issued as *Department Memorandum 2020-0258: Updated Interim Guidelines on Expanded Testing for COVID-19 (29 May 2020)* to set the guidelines on risk-based testing for COVID-19 in covering all individuals who are at-risk of contracting the disease[10]. 'COVID-19 Expanded Testing' was defined in this guideline as the testing of all individuals who are at-risk for contracting COVID-19 infection. Regardless of the presence or absence of symptoms, there are two populations that are considered suspect cases; individuals with relevant history of exposure or travel, and healthcare workers with possible exposure. They are grouped according to the severity of clinical presentation and exposure risk, patients that have the most severe symptoms are given the highest priority in testing.

Currently, RT-PCR is the sole confirmatory test for diagnosing COVID-19 in the Philippines, and the DOH has no existing guidance yet on the use of antigen test as diagnostic test for COVID-19. In the context of the rapid review conducted, diagnosis was defined per WHO FIND definition: *the intended use is to diagnose a symptomatic individual with a SARS CoV-2 infection in an epidemic or endemic setting. Sites include locations where individuals commonly present seeking primary care, such as primary healthcare facilities, ambulatory and urgent care clinics, emergency rooms, hospitals or where individuals are referred for advanced care[11]. Examples may include: using a positive serological testing result to diagnose a probable or suspect patient of COVID-19 as a standalone test, irrespective of RT-PCR result; or, using RAgT as an adjunct to diagnosis of patients who present late (i.e., greater than or equal to 15 days).*

6. HTAC 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 and 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.
- 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 (refer to section 7 for guidance), and **pass the acceptance testing** by RITM at the cost of the winning supplier**.**

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**

	WITH history of exposure	**WITHOUT history of exposure**
WITH symptoms	HIGH index of suspicion: Recommended for rapid antigen testing	HIGH index of suspicion: Recommended for rapid antigen testing
WITHOUT symptoms	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*	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.

WHAT DO THE RECOMMENDATIONS MEAN?

The interim HTAC recommendation on rapid antigen tests gives general guidance to front-liners and policymakers on how current rapid antigen tests can be deployed and used in conjunction with other diagnostic tools for the detection and diagnosis of COVID-19.

Similar to other diagnostics for COVID-19, proper timing of the use of antigen tests and correct interpretation of results based on what is currently known on the natural history of the disease must be observed to optimize their use in the management of patients and as a tool for surveillance as well as outbreak containment and response. While antigen tests are generally less sensitive than RT-PCR, rapid antigen tests may be helpful in particular situations such as in immediately identifying and triaging COVID-19 patients where access to RT-PCR is limited or turnaround times are too slow to inform clinical and public health decision-making.

The HTAC emphasizes that antigen tests perform best when proper timing is observed (i.e. during the acute stage of the disease) as well as the importance of adhering to the recommendations on the specific purposes and situations mentioned above for identifying potentially infected individuals.

What does a positive antigen test result mean?
A positive result in an individual who is symptomatic and/or who has a known exposure to a confirmed case means that the person is infected with SARS-CoV-2 and is most likely in the acute phase of the disease during which the viral load is highest and therefore viral antigens can be collected from throat and nasal swabs. Because of the generally high concordance of rapid antigen tests with RT-PCR and its high levels of specificity, a positive antigen test is said to be generally reliable in detecting a COVID-19 case. Individuals who are highly suspected to have COVID-19 and who test positive thru rapid antigen test should be isolated and properly managed according to current protocols in treating and managing COVID-19.

What does a negative rapid antigen test result mean?
A negative result may mean any of the following:

- that the individual truly has no COVID-19 disease

- that the individual may have COVID-19 disease but may not have high enough viral load at the time of testing to detect viral antigens
- that the brand of rapid antigen test used is not sensitive enough to detect viral antigen

Because of the lower sensitivity of existing rapid antigen tests when compared with molecular testing, those administering the test should be properly guided on the performance limitations of currently available antigen test kits and the potential for having false negative results. In all cases, rapid antigen test results must be correlated with the clinical picture, exposure history and other laboratory and imaging findings suggestive of COVID-19. A negative result in an individual highly suspected to have COVID 19 should have confirmatory testing and must also be isolated until the negative result is confirmed using RT- PCR.

7. MINIMUM REQUIREMENTS FOR RAPID ANTIGEN TESTS FOR THE RECOMMENDED CONDITIONS FOR USE

The *Health Technology Assessment Council* has set minimum regulatory, technical, and operational requirements to guide purchasing decisions of the Department of Health and its accredited COVID-19 testing laboratories.

a. Regulatory Requirements

All products allowed for use in public health facilities must obtain the necessary marketing authorization from the Philippine FDA, which is the national authority mandated to ensure the safety, efficacy and quality of medical products and devices such as those for use against COVID-19.[12] For rapid antigen test kits for COVID-19, a certificate of product registration (CPR) or special certification must have been obtained by suppliers.

b. Technical Requirements

The technical requirements include minimally acceptable clinical specifications for diagnostic performance given the **emergency situation** and the national objective to expand testing capacity and at the same time reliably diagnose and profile COVID-19 cases.

HTAC recognizes the importance of RAgTs for COVID-19 in various settings depending on the recommended use, hence it is important that the test can be done without the need of BSL-2 or higher facilities anymore. However, there must still be evidence that the live virus was deactivated early in the process[13]. In addition, a physician must always be available to evaluate the patient's health status and clinically correlate results with patient context and history. This is to avoid diagnostic errors such as false negative and false positive results from RAgTs usage. It is still important to properly implement infection prevention and control protocols when using RAgTs.

Furthermore, RAgTs must be independently validated by a local or international third-party reputable government or private research institution including but not limited to the Research Institute for Tropical Medicine, UP National Institutes of Health, US Food and Drug Administration, World Health Organization, Foundation for Innovative New Diagnostics (FIND), Therapeutic Goods Administration (Australia), Medicines and Healthcare products Regulatory Agency (MHRA, UK), and the Pharmaceuticals and Medical Devices Agency (PMDA, Japan).

In addition, HTAC recommends that for validating RAgT kits, the validation/ reference standards to be used must be the test kits used by reputable institutions, such as in-house laboratory RT-PCR tests. If a commercial RT-PCR test is to be used as reference standard, the specifications must adhere to the Guidance Document for RT-PCR test kits released by the HTA Council due to inherent variations in performance even among PCR test kits[14].

HTAC recommends minimum values for clinical sensitivity and specificity for the results of the laboratory validation studies. Clinical sensitivity refers to the proportion of subjects with the target condition in whom the index test (RAgTs) is positive while clinical specificity refers to the proportion of subjects without the target condition in whom the index test (RAgTs) is negative.

The HTAC recommends that rapid antigen tests should have a minimum sensitivity and specificity of 80% and 97%, respectively. This recommendation was adapted from the UK-Medicines & Healthcare products Regulatory Agency and the World Health Organization Interim Guidance.[13,15]

The HTAC recognizes the critical role of accurate testing both in terms of disease management and public health decisions made by policy makers. A test with low sensitivity will inaccurately diagnose a COVID-19 patient as negative which consequently leads to incorrect clinical management and further harm to the patient. This may also lead to a false sense of security for a misdiagnosed COVID-19 patient potentially exposing others especially vulnerable populations to the disease. Likewise, a test with low specificity will inaccurately diagnose a non-COVID patient as positive which may misallocate scarce healthcare resources.

In testing for clinical sensitivity and specificity, a validation test must be submitted based on a minimum of 30 positive and 30 negative clinical samples, using the abovementioned reference test.

To facilitate independent appraisal of the submitted validation studies, the following information will be requested from the manufacturer:

- The complete manuscript of the validation study,
- A table containing the following details for each specimen
    - the specimen type,
    - the specimen collection date,
    - date of onset of symptoms (if present),
    - date of RT-PCR testing, and results
    - severity of symptoms (if known),
    - tests used to identify COVID19 patients, etc.

c. Operational requirements and cost efficiency

HTAC considers the health system and cost implications of adopting health technologies and therefore also sets minimum operational requirements to ensure the ease of use of different RAgTs by laboratory personnel.

Operational requirements include minimum standards on the stability of the products and storage requirements. It must not require more than the basic competency of personnel

equipped with skills on specimen collection and infection prevention and control (IPC) procedures. The detailed requirements can be seen in the next section.

MINIMUM REQUIREMENTS FOR RAPID ANTIGEN TEST KITS FOR COVID-19

Parameter	Requirement
Regulatory Requirement	Must have a certificate of product registration (CPR) or emergency 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.
Result output	Qualitative, result must be read visually or with a reader but must be operable using batteries
Human resource training	Less than half a day to no additional training needed for healthcare professionals to be able to optimize performance
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
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)
Clinical Specificity	At least 97% specificity
Processing Time	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
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 • severity of symptoms (if known) • tests used to identify COVID19 patients, etc.
Requirement for Independent Validation	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
Transport and Storage Requirements	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 12 months at the time of delivery
Calibration Requirement	If calibration is required, it can be done onsite
Cost of test kit	The cost of the RAgT kit should be significantly less than the cost of the RT-PCR test kit

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