ANNEX A

GUIDANCE DOCUMENT ON THE TECHNICAL REQUIREMENTS FOR SARS-COV-2 RAPID ANTIBODY TEST KITS AS AN ADJUNCT TEST FOR COVID-19

Health Technology Assessment Council

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I. BACKGROUND

On March 8, 2020, the national government of the Republic of the Philippines declared a public health emergency due to COVID-19, recognizing that the pandemic has a significant potential to threaten public health and safety as well as affect the country's social and economic security.[1]

The *Health Technology Assessment Council* (HTAC) recognizes the urgency of addressing the current public health emergency by deploying tools such as innovative drugs, vaccines, medical devices, medical procedures and public health interventions which can aid the national government in mounting an effective response against the pandemic. Thus, the HTAC has been constantly seeking evidence on new and existing health technologies and has also responded to urgent requests from the DOH for guidance on the effective and efficient application and use of health technologies in its public health programs and strategies.

On March 25 2020, the HTAC issued a recommendation on the use of COVID-19 rapid antibody tests (RATs) for Mild and Asymptomatic At-Risk COVID-19 cases guided by a rapid review of evidence conducted by the HTA Unit. In view of the results of the review, the Council did not have sufficient evidence to recommend the use of immunoassays in diagnosing COVID-19. Further, they stated that in the event that the government still considers such health technology, its implementation should only be used for validation in the local setting and always in parallel with an RT-PCR diagnostic test. The Council then released another recommendation on 6 April 2020 to reiterate that RATs are still not recommended as a sole screening and diagnostic tool for COVID-19, pending further evidence on its accuracy. Their recommendation also stated that a parallel multi-site clinical trial is highly recommended and that only those who will enroll in such research should have access to RATs procured using government funds. Their recommendations then guided the issuance of *Department Circular 2020-0184* (9 April 2020) which states that RATs will not be financed and reimbursed by DOH and PhilHealth unless in the context of conducting validation studies to be done by the Research Institute for Tropical Medicine (RITM) and for conducting research such as serologic studies by RITM and other designated institutions.[2]

Given the rapidly emerging evidence on rapid antibody tests across different countries and settings, the HTAC is now releasing this Guidance Document to inform policy makers and the public on the appropriate use of rapid antibody test kits based on the current understanding of the human immune response to the SARS-CoV-2 virus and experience across countries and settings. The Guidance Document also draws information from new research reports on the diagnostic performance of different antibody test kits available in current scientific literature and officially recognized sources such as national regulatory authorities, the Research Institute for Tropical Medicine (RITM) and other locally and internationally recognized reference laboratories.

What this Guidance contains:

- Recommended use case of rapid antibody test kits relative to the clinical management of individual COVID-19 patients and public health management during the pandemic

- Desired technical and operational characteristics of rapid antibody test kits for use by DOH-accredited laboratories for COVID-19

II. 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 rapid antibody tests (RATs) and the reliability of test results during the COVID-19 pandemic.

III. PURPOSE OF THE GUIDANCE DOCUMENT

This Guidance is being issued to:

- set the HTAC-recommended use case for RATs
- outline the minimum specifications of rapid antibody tests (RATs) also known as lateral flow kits.

The HTAC recommends the appropriate use case for RATs and the desired attributes of RATs 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 RATs that are being considered by HTAC in the evaluation of kits that are currently available in the market.

It is recognized that evidence is evolving for COVID-19 and that there has been a rapid increase in studies on the diagnostic accuracy of different testing kits based on reliable independent validation by DOH-recognized local and international research laboratories. This guidance therefore is an interim document based on the internal rapid review conducted by the HTA Unit using the best available synthesized evidence at the time of writing. The rapid review is subject to updates and revisions as the post market assessments on the performance of different RATs are done by the RITM, the FDA, other internationally recognized stringent regulatory authorities and research institutions.

IV. SEROLOGIC ASSAYS AND ANTIBODY TEST KITS IN USE FOR COVID -19

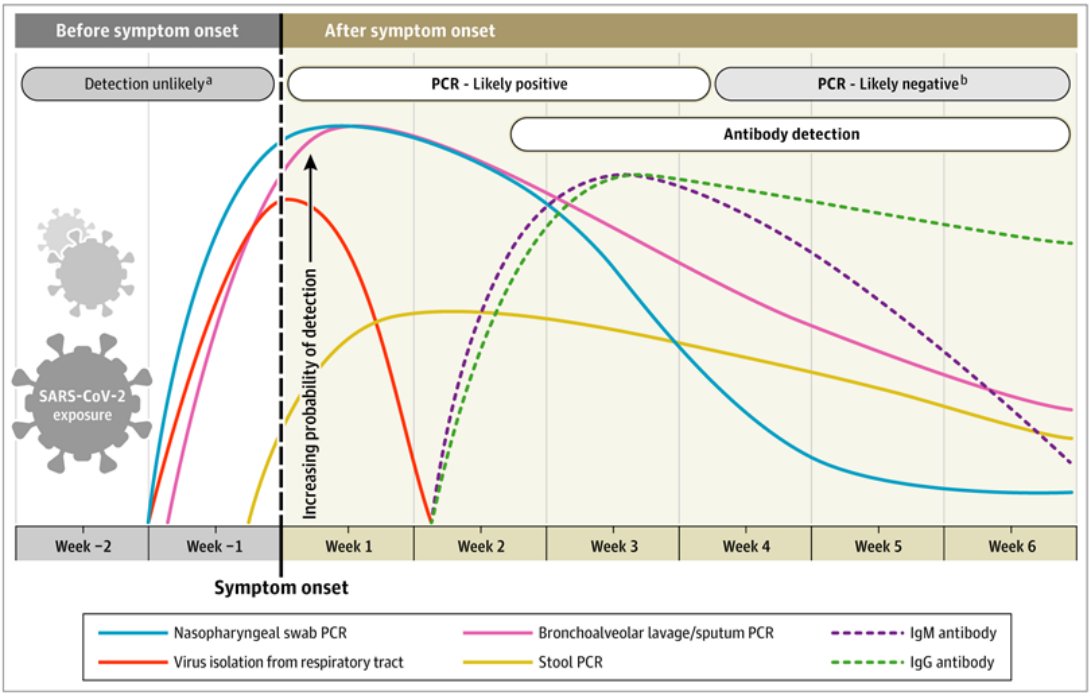
Currently, molecular testing and serologic antibody testing determines the two major ways to detect SARS-CoV-2 infection. Molecular tests, specifically nucleic acid amplification tests are qualitative methods for detecting nucleic acid from SARS CoV-2 in nasal or pharyngeal samples, sputum, bronchoalveolar lavage fluid, and other bodily fluids, including feces and blood collected from suspect cases or individuals with relevant history of travel and exposure.[3] It is the current gold standard in the diagnosis of COVID-19.

Meanwhile, serologic antibody testing detects for the body's immune response to the SARS-CoV-2 infection. Serologic antibody tests, either quantitatively or qualitatively, detect the presence of either

immunoglobulin G or M (IgG, IgM). Aspects of immune response and functionality of antibodies can be determined using different types of assays which can be broadly classified into binding antibody detection tests and neutralizing antibody detection tests. Binding antibody detection tests determine individual antibody types, like IgG, IgM, and IgA using purified protein fragments of SARS-CoV-2, not the whole live virus. Tests that detect binding antibodies fall into two broad categories - the *laboratory-based tests* such as enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA) and neutralization assay; and, the *point-of-care (POC) tests* or RATs such as Lateral Flow Immunoassay (LFIA), and colloidal gold immunoassay (CGIA). Meanwhile, neutralizing antibody detection tests determine the functional ability of antibodies to prevent infection of virus in vitro. The test involves incubating serum or plasma with live virus followed by infection and incubation of cells. The focus of this Guidance is for RATs only. [4]

One important factor affecting performance of antibody tests is the kinetics of antibody production. According to Senthuraman, et al. (2020) (see Figure 1), viral RNA in the nasopharyngeal swab becomes detectable as early as day 1 of symptoms and peaks within the first week of symptom onset in most individuals with symptomatic COVID-19 infection. By week 3, the positivity starts to decline and subsequently becomes undetectable. Further, the timeline of PCR positivity is different in specimens other than nasopharyngeal swab. PCR positivity declines more slowly in sputum and may still be positive after nasopharyngeal swabs are negative. Serological diagnosis, on the other hand, is especially important for patients with mild to moderate illness who may present beyond the first 2 weeks of onset of illness. The levels of total antibodies begin to increase from the second week of symptom onset. The majority of IgM and IgG seroconversion occurs between the third and fourth week of clinical illness onset. IgM begins to decline and reaches lower levels by week 5 and almost disappears by week 7; whereas IgG persists beyond 7 weeks.[5]

Figure 1. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset, Senthuraman et. Al (2020)



In addition to the kinetics, the specific antigen used also plays a role in antibody tests. The two major antigenic targets of SARS-CoV-2 virus against which antibodies are detected include the ***spike glycoprotein (S)*** and ***nucleocapsid phosphoprotein (N)*****.** The S protein is essential for virus entry and is present on the viral surface. Meanwhile, N protein is the most abundantly expressed immunodominant protein that interacts with RNA. Multiple forms of S protein — full-length (S1+S2) or partial (S1 domain or receptor binding domain [RBD]) — are used as antigens. The protein target determines cross-reactivity and specificity because N is more conserved across coronaviruses than S, and within S, RBD is more conserved than S1 or full-length S.[4]

Kontou et al, 2020, found in their meta-analysis of COVID-19 antibody tests that, of the 14 studies which reported diagnostic accuracy results from ELISA-based tests (detecting anti-N or anti-S IgG, IgM antibodies, or both), S-based tests are more sensitive compared to those based on N antigen.[6] Further, Premkumar et al, 2020 suggest that as the receptor-binding domain (RBD) of the spike protein is poorly conserved between SARS-CoVs and other pathogenic human coronaviruses, the RBD represents a promising antigen for detecting CoV-specific antibodies in people. In their study, a marked correlation between the levels of RBD antibodies in patients and the ability of patient sera to neutralize SARS-CoV-2 virus was observed.[7]

While some COVID-19 diagnostic assays have claimed to have high sensitivity and specificity, independent validation studies have been initiated by local and reputable research organizations to provide stronger evidence on their diagnostic performance. The Foundation for Innovative New Diagnostics (FIND), based at the University of Geneva, is a WHO Collaborating Center for Laboratory Strengthening and Diagnostic Technology Evaluation. Aside from performing external verification and validation, FIND also collates independent validation studies on test performance of COVID-19 tests. The institution plans to publish a report on the analytical performance of SARS-CoV-2 immunoassays.[8] Apart from the information publicly available in the FIND website, other stringent regulatory authorities also provide information on standards of validation of serologic assays as well on their test performance such as the US Food and Drug Administration (USFDA), the UK Medicines Health Regulatory Agency (MHRA), and the Australian Therapeutics Good Administration (TGA).

V. 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.[9] '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. The Guidelines further specifies under which conditions RT-PCR tests and RATs are to be used.

Currently, RT-PCR is the sole confirmatory test for diagnosing COVID-19 in the Philippines. While RATs have been considered to help in addressing the limitations of RT-PCR testing, they remain to be not recommended in the Philippine testing guidelines as a standalone test to definitively diagnose or rule out COVID-19. This means RATs must be used in conjunction with RT-PCR, regardless of RATs result. The guidelines noted, however, that RATs can be used among symptomatic patients but only when there is no available RT-PCR test. Furthermore, the current DOH testing guidelines has restricted the use of RATs to only those brands which have been approved by the FDA and locally-validated by the RITM or the Department of Science and Technology (DOST), or those with acceptable performance of >90% sensitivity and >95% specificity validated by WHO-Foundation for Innovative New Diagnostics (WHO-FIND). In addition, the said testing guidelines allows the use of antibody tests in general (including RATs) for surveillance purposes. Properly validated antibody tests by RITM, DOST and FIND can be used in areas with suspected COVID-19 community transmission. All who intend to conduct their own validation studies are requested to do the following: register their studies with DOH; use the protocol for local validation study as provided in the said Guidelines; and report the testing results to DOH.[9]

RATs have also been allowed by the Department of Health as an adjunct to screening of COVID-19, primarily in entry-to-country/ province and return-to-work policies.[10,11] DOH Department Memorandum No. 2020-0200 released last May 1, 2020 details the interim guidelines in the quarantine and testing of all arriving overseas Filipinos (OFs) and foreign nationals during the current pandemic. It specifies that all OFs and foreign nationals shall undergo RATs upon arrival at port-of-entry as baseline, accompanied by a 14-day quarantine at an OWWA-designated mandatory quarantine facility, then a second RAT at the end of the 14-day quarantine. It also mentioned that RT-PCR may be performed once logistics and supplies permit or under the discretion of the NTF COVID-19 Chief Implementer.[10]

For return-to-work policies, DOH DM2020-0220 allows the use of FDA-approved rapid antibody-based test among representative samples of asymptomatic employees returning to work, and the test can be conducted up to every 14 days. Furthermore, it mentions that the cost of testing is not covered by PhilHealth and shall be borne by the employer.[11]

VI. USE CASES OF RATs IN COVID-19

Use cases in the context of this document refer to the purpose to which the rapid antibody tests are to be used. Put simply, this is the intended use of the RATs. Identifying use cases is important to facilitate the classification of who will be tested, by whom, the site of testing, and what types of results will trigger a specific medical response (i.e. a positive test to confirm presence or absence of circulating antibodies specific to COVID-19). In addition, this document also guides designated and independent institutions on the possible objectives of independent validations, appropriate study population, and study designs and methodologies that will be employed.

There are generally three uses of antibody tests based on the expanded testing guidelines released by the Department of Health, and whose definitions were adapted from WHO-FIND.[12]

Use Case	Definition (adapted from FIND)
(1) Diagnosis of COVID-19	• 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. Examples may include: ○ *[Use case 1a] 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.* ○ *[Use case 1b] Using RAT as an adjunct to diagnosis of patients who present late (i.e., greater than or equal to 15 days).* *Probable or suspect COVID-19 patients as defined in the national DOH case definitions.
(2) Determination of previous exposure to SARS-CoV-2	• Intended for use to determine if an individual without symptoms has previously been exposed to SARS-CoV-2. • If the clinical data supports the claims, such an individual would not require quarantining and could associate with uninfected or infected individuals with minimal danger of transmission or new infection. • If possible, it would be quite valuable to use the test to assess protective immunity. • It could be useful to conduct serology studies in a cohort of cured patients to monitor antibody titers and immunity over time. • This may include seroprevalence surveys; return to work and school guidelines; entry to country guidelines; and, checking theimmune status for convalescent plasma donation.
(3) Epidemiologic surveillance of COVID-19	• Intended use is to monitor a local or sentinel population in order to obtain early indications of a COVID-19 outbreak. • If SARS-CoV-2 diagnostics are not in routine use in the location of interest, procedures to test a statistically meaningful subset of the respiratory and febrile disease patient populations would be used. • In most situations, samples from a subset of the respiratory and febrile disease patients or healthcare workers in sentinel clinics would be sent for testing at a remote site. • Positive confirmation would trigger a planned response. • This may include outbreak investigation and contact tracing of cases; surveillance of areas with suspected COVID-19 transmission; and, surveillance of areas with high-risk of COVID-19 transmission;

This review done by the Philippine HTA unit found a significantly higher number of studies regarding the use of RATs in diagnosis compared to other use cases. Majority of the said studies used RT-PCR as a comparator, which is the current gold standard in the diagnosis of COVID-19.

Diagnosis of COVID-19

Majority of the studies did not classify the population being studied in terms of presence of symptoms. In addition, there were more studies which reported the diagnostic performance of RATs in terms of sensitivity than specificity.

Generally, the accuracy of RATs for diagnosis is highly varied across the different stratifications [e.g., 0% to 96% sensitivity for IgM during late onset (beyond 14 days from symptom onset) of disease among undefined cases of symptomatic or asymptomatic; 0-100% sensitivity for IgG during late onset of disease among undefined cases of symptomatic or asymptomatic] when compared to RT-PCR. As for the accuracy of RATs when compared to MNT, a very limited number of studies shows variability of its accuracy as well (e.g. 46 – 81% sensitivity for IgM regardless of onset of disease among undefined cases of symptomatic or asymptomatic; 56% to 72% sensitivity for IgG regardless of onset of disease among undefined cases of symptomatic or asymptomatic). This general observation of highly varied accuracy of RATs for diagnosis is based on wide ranges of both the point estimates and confidence intervals reported in the studies. Furthermore, we note that the RATs assessed by these studies were mostly tested in a laboratory-based setting. Hence, their accuracy performance may be vary in the real-world setting.

While the reported ranges of both IgM and IgG sensitivity and specificity point estimates (versus RT-PCR) do not suggest a trend based on onset of disease, there is noticeable clustering of point estimates (for the population with undefined information on the presence of symptoms) during early onset (≤7 days) (i.e., < 40% for both IgM and IgG), mid onset (8-14 days) (i.e., at least 60% for IgM; 40-80% for IgG), and late onset (≥15 days) (i.e., 60-96% for IgM; 60-80% for IgG) of disease based on the generated forest plots. An increasing clustering of point estimates on the sensitivity data for IgM and IgG (for population with undefined information on the presence of symptoms) as the disease progresses (per week) was observed in the data.

It is also important to note that there were only a few studies detected among defined symptomatic and asymptomatic cases; hence, there is limited evidence to make a positive conclusion on the performance of RATs for diagnosis among these populations.

Overall, based on the evidence gathered, it can be concluded that the RATs being studied for its diagnostic potential for COVID-19. While relatively higher sensitivity values during late onset of the disease were observed, there remains to be no conclusive evidence to show that any RAT can generally be recommended for use in diagnosis due to the consistently high variability observed in the RAT performance (whether the comparator is RT-PCR or MNT). Hence, it is important that RAT brands currently in the market undergo validation testing using appropriate study designs to ascertain their performance in the real-world setting and in the local context, and that specifications for RATs must be set to ensure that only RATs with proven diagnostic accuracy for the intended population shall be used.

Determination of previous exposure

There is limited evidence to establish the accuracy of RATs for use case determination of previous exposure. Based on two studies, we found varying performance of RATs in terms of sensitivity and specificity of 10 RAT brands when compared with RT-PCR. The sensitivity values of IgM and IgG can range from 43% to 91% and 39 to 93%, respectively. On the other hand, the specificity is higher (although based on one study only) with a specificity for IgM at 100% (95% CI: 97%-100%) and for IgG at 99% (95% CI: 96%-100%).

Epidemiologic Surveillance

There is limited evidence to establish the accuracy of RATs for use case epidemiologic surveillance. Based on the independent evaluation of the US National Cancer Institute for 10 rapid antibody test kit brands against ELISA, the sensitivity values of IgM and IgG can range from 27% to 100% and 30 to 97%, respectively. On the other hand, the specificity appears to be much higher than the sensitivity and point estimates appear to be closer to one another, with the ranges for IgM and IgG being 86% to 100% and 91% to 100% respectively.

As for the applicability of the conclusions drawn on use case epidemiologic surveillance, we note that the patient profiles of the ten study sources presented for this use case are generally from the US, and without information on patient characteristics; hence, it is difficult to establish its generalizability overall.

HTAC Recommendation

HTAC DOES NOT RECOMMEND the use of RATs in:

- use case 1a. i.e. as a standalone test, irrespective of RT-PCR result.
- seroprevalence surveys, return-to-work decisions, or entry-to-country/ province policies due to the lack of evidence regarding the link of presence of antibodies and the immunity to subsequent infection AND on the persistence of protection from COVID-19.
- disease surveillance activities (i.e. contact tracing or as part of acute outbreak investigations) to guide public health decisions.

A **validated** rapid antibody test kit **may** be used as an adjunct to diagnosis of patients who satisfy ALL of the following criteria:

a. symptomatic patients (greater than or equal to 15 days from symptom onset, AND
b. tested at least twice negative with RT-PCR, AND
c. with clinical and diagnostic manifestations of COVID-19

Furthermore, the HTAC advises that only licensed medical doctors may request, administer, and interpret results of rapid antibody-based test.

Please be reminded that the result of the testing is only applicable to the health status of the patient at the time of the test, and does not prevent future risk of infection. Following minimum public health standards is still recommended.

What do the recommendations mean?

The rapid antibody tests are unreliable in determining whether or not one has the COVID virus. Timing of the conduct of the test is important. If the test is done too early, i.e., within 14 days from exposure, there is a high probability that the finding will be negative even if the person tested is truly positive for COVID-19 because it takes time for the body to develop antibodies. Moreover, independent tests of these rapid antibody tests show wide variability in performance, and that the accuracy of these tests can depend not only on the test itself, but also on factors such as when the test is conducted and how a user interprets the result. Thus, the HTAC specifically states that rapid antibody tests are not suitable for determining if personnel may return to work, nor for establishing whether people can return to the province. The HTAC only recommends the use of the rapid antibody tests on patients who have symptoms that are highly suggestive of COVID-19 but whose RT-PCR (swab) examinations have turned out to be negative.

What does a positive RAT result mean?

A positive result means that a person was infected with SARS-CoV-2 and the body's immune system has responded by creating antibodies. Due to the way the body responds to the virus, it often takes about 2 to 3 weeks for an infected person to test positive after being infected with SARS-CoV-2. It

means that RATs should not be used to diagnose COVID-19 in the acute phase of the disease. Additionally, there is no evidence that having antibodies for COVID-19 will have a protective effect in the long-term.

What does a negative RAT result mean?

A negative result may mean any of these four things:

- that there was not enough time yet for the body to have an immune response to an ongoing infection
- that the circulating level of antibodies for SARS-CoV-2 is too low to be detected by the particular test
- that the brand of RAT used is not sensitive enough to detect the circulating antibodies
- that the antibodies for SARS-CoV-2 are absent, and the person was not infected

In addition, there has not been enough evidence to prove that either a positive/ negative RAT result can protect a person from future SARS-CoV-2 infection.

VII. MINIMUM REQUIREMENTS FOR RATS AS AN ADJUNCT TEST FOR COVID-19 (USE CASE 1b)

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.[13] For rapid antibody test kits for COVID-19, a certificate of product registration (CPR) or emergency use authorization must have been obtained by suppliers.

b. Technical Requirements

Technical requirements include minimally acceptable analytical and 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.

While the HTAC recognizes the importance of quickly deploying diagnostic tools for COVID-19, it is recommended that RATs are to be used only in accredited laboratories. RATs are not to be used outside of hospital or research laboratories nor to be used by non-healthcare professionals A physician must always be available to evaluate the patient's health status. This is to avoid

diagnostic errors such as false negative and false positive results from RATs usage. It is still important to properly implement infection prevention and control protocols when using RATs.

Furthermore, RATs 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, DOST, 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).

In addition, HTAC recommends that for validating RAT kits, the validation/ reference standards to be used must be the test kits used by reputable institutions, such as the RT-PCR test kits and the ELISA serology test device. 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.

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 (RATs) is positive while clinical specificity refers to the proportion of subjects without the target condition in whom the index test (RATs) is negative.

In a simulation of 1,000 patients that will undergo rapid antibody testing, the number of false positive and false negative results vary as sensitivity and specificity values are changed. There is a significant reduction in the number of false positives and false negatives when sensitivity and specificity is both shifted from 90% to 98. The prevalence values used in the simulation are based on the July 4, 2020 version of the DOH Data Drop data from accredited COVID-19 testing laboratories.

Table 1. Number of false negative and false positive results based on varying values of clinical performance and prevalence

Prevalence	Population	True Positive	True Negative	Sensitivity	Specificity	False Negative	False Positive	PPV	NPV
0.2%	1000	2	998	50	75	1	250	0.68	99.87
				85	85	0	150	1.12	99.96
				90	90	0	100	1.67	99.98
				95	95	0	50	3.29	99.99
				98	98	0	20	7.85	100.00
1%	1000	10	990	50	75	5	248	3.32	99.33
				85	85	2	149	5.41	99.82
				90	90	1	99	7.91	99.89
				95	95	1	50	14.66	99.95
				98	98	0	20	30.04	99.98
4%	1000	40	960	50	75	20	240	12.41	97.30
				85	85	6	144	19.10	99.27
				90	90	4	96	26.15	99.54

				95	95	2	48	41.46	99.78
				98	98	1	19	63.91	99.92
7%	1000	70	930	50	75	35	233	20.38	95.22
				85	85	11	140	29.90	98.69
				90	90	7	93	39.02	99.17
				95	95	4	47	56.13	99.61
				98	98	1	19	76.18	99.85
9%	1000	90	910	50	75	45	228	25.16	93.81
				85	85	14	137	35.92	98.28
				90	90	9	91	45.67	98.91
				95	95	5	46	62.70	99.48
				98	98	2	18	80.78	99.80
20%	1000	200	800	50	75	100	200	45.95	85.71
				85	85	30	120	58.62	95.77
				90	90	20	80	68.00	97.30
				95	95	10	40	80.95	98.70
				98	98	4	16	91.40	99.49

The indicated prevalence rates are based on RT-PCR results of regional testing centers from the DOH Data Drop. The values of prevalence are based on the positivity rate of the said testing center.

Based on this information, the HTAC recommends that rapid antibody tests should have a minimum sensitivity and specificity of 98%, and 98%, and confidence intervals within 96-100% on specimens collected 20 days or more after the appearance of first symptoms. This recommendation was adapted from the UK-Medicines & Healthcare products Regulatory Agency.[14]

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.

Clinical/ diagnostic sensitivity and specificity

In testing for clinical sensitivity and specificity, a validation test must be submitted based on a minimum of 70 positive and 70 negative samples, using RT-PCR or ELISA as a 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 RATs 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.

MINIMUM REQUIREMENTS FOR RAPID ANTIBODY TEST KITS AS AN ADJUNCT TEST FOR COVID-19 (Use Case 1b)

Requirement Domains	Recommendation
Regulatory requirement	Must have a **certificate of product registration (CPR)** or **emergency authorization (EA)** from the FDA Philippines.
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) • Department of Science and Technology (DOST) • 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)
Test format	A test kit that contains the necessary materials for the procedure, such as: the RAT cartridge, the reagent, droppers/ applicators, and the lancet.
Target Analyte	**Immunoglobulin G, and M, with separate indicators** for each immunoglobulin
Sample type	**Capillary whole blood** from fingerstick sample
Result output	**Qualitative,** result must be read visually, without need for a reader/ additional equipment.
Storage, expiration & stability	The expiration date must not be less than **six (6) months** from date of manufacture. The storage and working temperature must be **18 to 30 °C**. It should be used in a controlled environment. Must **pass the acceptance testing** by RITM at the cost of the winning supplier.

Human resource	Must not require more than the **basic competency** of personnel equipped with skills on **sample collection and proper infection prevention and control (IPC)** procedures.
Viral Antigen Targets	Either **N and S protein**, preferably both, plus other protein targets
Analytical Specificity (Cross-Reactivity)	Not specified
Clinical Sensitivity	Must have at least 98% sensitivity at least 2 weeks from symptom onset.
Clinical Specificity	Must have at least 98% specificity
Processing Time	Not more than twenty (20) minutes from sample application.
Reference Standard	Either ELISA or RT-PCR.
Sample Size Requirement in the validation studies	Positive samples: 70 to 100 Negative samples: 70 to 100 Include details such as: • the specimen type, • the 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.

REFERENCES

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