Use of Rapid Antibody-based Test Kits (RATs) for Various Use Cases for COVID-19

Evidence Summary

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Section 1.

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 more than 188 countries and regions with at least 16,199,931 cases and 647,910 deaths worldwide as of July 27, 2020. Locally, there are over 80,448 cases and 1,932 deaths as of July 26, 2020.

As a response to this pandemic, the Department of Health issued testing policy guidelines seeking the conduct of an evidence appraisal of the Health Technology Assessment (HTA) Council on the use of rapid antibody-based kits (RATs) for the diagnosis of COVID-19. RATs belong to a class of diagnostic tests called antibody-based-serologic tests which measures immune response by detecting antibodies (e.g., IgG, IgM) present in the blood when the body responds to a specific infection. Serologic tests for COVID-19, as compared to nucleic-acid based tests such as real time reverse transcriptase polymerase chain reaction (RT-PCR) test, is not designed to detect active SARS-CoV-2 infection. The strength of antibody response is dependent on several factors such as age, nutritional status, and severity of the disease. 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 proteins of SARS-CoV-2, not live virus. Tests that detect binding antibodies fall into two broad categories: the *laboratory-based tests* such as enzyme-linked immunosorbent assay (ELISA) and chemiluminescence immunoassay (CLIA); and, the *point-of-care (POC) tests* or RATs or Lateral Flow Immunoassay (LFIA) which includes and colloidal gold immunoassay (CGIA) and fluorescence-labelled immunochromatographic assays (FIA). As of 24 June 2020, the Food and Drug Administration Philippines (FDA) has approved 69 brands of RATs. Meanwhile, neutralizing antibody detection tests such as plaque-reduction neutralization test (PRNT) and microneutralization 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. (CDC, 2020d) The Philippine FDA has not approved neutralizing antibody detection tests as of 10 July 2020.

The two major antigenic targets of SARS-CoV-2 virus against which antibodies are detected include the ***spike glycoprotein (S)*** and ***nucleocapsid phosphoprotein (N).*** 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. (CDC, 2020d) 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. Further, Premkumar et al, 2020 suggests 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.

According to Senthuraman, et al. (2020), 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. 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.

Two relevant recommendations have been issued by the HTAC, both of which have stated that there is insufficient evidence for the use of RATs as sole screening and diagnostic tool for COVID-19 and diagnosis of mild and asymptomatic COVID-19 infections. Their recommendation 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.

However, given the need to expand testing coverage, the DOH has 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 to cover all individuals who are at-risk of contracting the disease. 'COVID-19 Expanded Testing' was defined in this guideline as the testing of all individuals who are at-risk for contracting COVID-19 infection; these are the suspect cases; individuals with relevant history or travel of exposure, whether symptomatic or asymptomatic; and healthcare workers with possible exposure, whether symptomatic or asymptomatic.

The guidelines also state conditions under which conditions RT-PCR tests and RATs are to be used. Currently, RT-PCR remains the standard 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 not to be recommended in the Philippine testing guidelines as a standalone test to definitively diagnose or rule out COVID-19, and they must be used in conjunction with RT-PCR. It is also important to note that the current DOH testing guidelines has restricted the use of RATs to only those 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).

Another issued policy by DOH is *Department Memorandum 2020-0200: Omnibus Interim Guidelines for the Quarantine and Testing Procedures for all Arriving Overseas Filipino (OFs) and Foreign Nationals During COVID-19 Pandemic* (01 May 2020) which states that "all OFs and foreign nationals classified for Mandatory Quarantine shall undergo rapid antibody COVID-19 testing upon arrival as baseline, and 14-day Mandatory Quarantine at an OWWA (Overseas

Workers Welfare Administration)-designated Mandatory Quarantine Facility. Mandatory Quarantine shall refer to quarantine protocols imposed upon all other OFs and foreign nationals who are not classified for Stringent Quarantine (i.e., sea-based OFs coming from a ship or vessel classified as high-risk by DOH; land-based OFs and foreign nationals who are coming from a high-risk place of origin; and, any individual OF or foreign national who has been assessed to have influenza-like signs and symptoms upon arrival at a port of entry).

In addition, the DOH also issued *Department Memorandum 2020-0220: Interim Guidelines on the Return-to-Work* (11 May 2020) which provides the use of FDA-approved RATs as alternative testing option for the testing among representative samples of asymptomatic returning employees. The issuance noted that the cost of the test not covered by PhilHealth shall be borne by the employer.

Currently, there are various use cases of RATs in the DOH testing guidelines. A *use case* refers to the purpose of using a particular test, which in the context of RATs in the DOH testing guidelines refer to: (1) diagnosis of COVID-19, (2) determination of previous exposure to SARS-CoV-2, and (3) epidemiologic surveillance of COVID-19.

In light of the rapidly evolving evidence on COVID-19 testing, **an update of the previous rapid review will be conducted to search for and synthesize information on approved use case/s of RATs from selected regulatory agencies,** existing **guidelines on the use of RATs from selected healthcare systems** as well as existing **evidence on the performance of RATs for the diagnosis of COVID-19, determination of previous exposure to SARS-CoV-2, and epidemiologic surveillance of COVID-19.** In the context of this review, we will be setting the definitions of these use cases of interest based on the definitions used by the *Foundation for Innovative New Diagnostics (FIND).*

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: o *[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;* o *[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 of immune 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;

Policy Question

Which use case and for what population should the Philippine DOH consider the use of RATs?

Research Questions

1. Regulatory Approval

1.1. What is/are the approved use case/s of RATs by selected regulatory agencies?
1.2. What are the validation testing requirements of selected regulatory agencies?
1.3. What are the performance standards used by selected regulatory agencies?

2. Testing guidelines and evidence synthesis on use of RATs

2.1. Which country/countries have implemented testing strategies using RATs for diagnosis, determination of previous exposure, or epidemiologic surveillance of COVID-19?
2.2. What is the current position/ recommendation of HTA agencies regarding the use of RATs for diagnosis, determination of previous exposure, or epidemiologic surveillance of COVID-19?

3. Diagnostic Performance:

What is the accuracy of RATs in the following use cases?

3.1. Diagnosis of COVID-19 among asymptomatic patients
3.2. Determination of previous exposure to SARS-CoV-2
3.3. Epidemiologic surveillance of COVID-19

Section 2.

Responsiveness to disease magnitude and severity

Globally, COVID-19 has affected more than 160 countries and regions with at least 15,537,513 cases and 634,069 deaths worldwide as of 24 July 2020 (Dong, Du & Gardner, 2020). In the Philippines, COVID-19 affected over 76,444 cases with 1,879 deaths as of 24 July 2020 (DOH, 2020).

COVID-19 can have various clinical manifestations among those infected, ranging from mild pneumonia to having respiratory failure, septic shock, and multiple organ dysfunction or failure (Cascella, Rajnik, Cuomo et al., 2020). In the Philippines, among the active cases, 89.83% are mild cases, 0.49% are severe, 0.42% are critical, and 9.25% are asymptomatic.

Section 3.

Safety and effectiveness

*Note: Refer to **Annex B** for the full report of the **rapid review on the Use of Rapid Antibody-based Test Kits for Various Use Cases for COVID-19**.*

3.1. Regulatory Approval

What is/are the approved use case/s of RATs by selected regulatory agencies? What are the validation testing requirements of selected regulatory agencies? What are the performance standards used by selected regulatory agencies?

Eleven regulatory agencies were checked for any regulatory guidelines for approval and validation testing of COVID-19 RATs. These agencies include the Philippine FDA and 10 countries with stringent regulatory authorities. Of these, we found relevant regulatory agency reports from four countries only (US, UK, Australia and Canada). Based on their regulatory guidelines, RATS are approved mainly for the determination of previous exposure in US, Canada and UK, except in Australia where they are approved for diagnosis through detection at the start of seroconversion.

As with validation testing requirements, despite being approved for the determination of previous exposure, RT-PCR was set as the reference test for the required validation testing of RATs by the regulatory agencies of US, Canada and UK. In the case of Australia, the set reference tests for comparing the performance of RATs are RT-PCR, enzyme immunoassay (EIA) and molecular point-of-care tests (POCTs). The sample size ranges from at least 30 antibody positive samples and 75 antibody negative samples to as high as 200 antibody positive samples and 200 antibody negative samples. As regards their diagnostic performance, only UK and US have explicitly stated their performance testing standards to guide the developers of RATs, as follows:

United Kingdom:

- Clinical sensitivity: Greater than 98% (with 95% confidence intervals of 96-100%) on specimens collected 20 days or more after the appearance of first symptoms.
- Clinical specificity: Greater than 98% (within 95% confidence intervals 96- 100%)
- Analytical specificity: Minimal cross-reactivity with other known coronavirus, or common respiratory pathogens

United States:
The same set parameters apply to the addition of symptomatic population but with addition of at least 100 negative samples
- 95% positive percent agreement (PPA)
- 98% negative percent agreement (NPA)

A total of 15 RATs that were initially listed by US FDA were removed from the notification list due to withdrawal of the manufacturer/distributor or revocation of EUA as of 26 June 2020. Of these 15 RATs that were removed, two are listed in the 59 RAT brands registered in the Philippine FDA as of June 16 2020.

In the Philippines, although regulatory parameters for validation testing were not disclosed by the FDA to the public, the DOH has mandated that prior to the use of any RAT, it has to be FDA-approved and, locally-validated by the RITM or DOST, or those with acceptable performance of >90% sensitivity and >95% specificity validated by WHO-FIND.

3.2. Testing Guidelines and Evidence Synthesis on Use of RATs

3.2.1. Which country/countries have implemented testing strategies using RATs for diagnosis, determination of previous exposure, or epidemiologic surveillance of COVID-19?

3.2.1.1. DIAGNOSIS

Five guidelines are currently using RATs for diagnosis where two (Australia and China) have included the results of serology testing (either laboratory-based or RATs) as part of their national case definitions of laboratory-confirmed COVID-19 cases, while three (Philippines, European CDC and US) are using RATs as an adjunct to RT-PCR testing.

While RT-PCR remains as the primary means of diagnosis during the acute phase of COVID-19 illness in Australia and China, serological testing results showing seroconversion of IgG from negative to positive, or four-fold rise in IgG titer may be used to define a COVID-19 case. This implies the need for testing patients at least two times, with the first being conducted for the purpose of baseline testing and the second for documenting seroconversion. This can be used specifically for: patients with high clinical suspicion who present late (such as in suspected cases that were not able to undergo RT-PCR during the acute phase of illness) based on the guidelines in Australia; and, patients with high clinical suspicion and with a negative RT-PCR result based on the guidelines in China.

Meanwhile, the European CDC recommends the use of validated RATS, with priority for patients at risk for developing severe disease, patients with acute respiratory illness, symptomatic health workers, symptomatic individual in prison or nursing care facility. In the Philippines, testing using RATs have only been explicitly mentioned for symptomatic patients and should be done only when there is no available RT-PCR test. Their guidelines also require RATs to be locally-validated or to have acceptable performance of >90% sensitivity and >95% specificity for those validated by WHO-FIND prior to use. It is also noted that the national health insurance scheme does not currently cover use of RATs for this use case. Lastly, the US CDC, recognizes the use of RATs for patients with late presentation specifically those who present at day 9-14 from symptom onset.

On the other hand, five countries (Canada, Germany, Italy, Switzerland, and the UK) and one international agency (WHO) do not recommend the use of RATs for diagnosis.

3.2.1.2 DETERMINATION OF PREVIOUS EXPOSURE

Four countries (China, Indonesia, Malaysia and the Philippines) have been using RATs for determining previous exposure. China uses either RATs or laboratory-based serological testing for determining past exposure and for serologic surveys. In Indonesia, a negative RAT result is required prior to entry into the country. Meanwhile, Malaysia and Taiwan use RATs to monitor the recovery and convalescence of RT-PCR-confirmed cases, and to guide the decision on the release of asymptomatic patients from home quarantine. The Philippines permits testing using RATs as part of entry to country and return to work guidelines. Regardless of the RATs result, however, people entering the country shall still need to undergo a 14-day quarantine. Note that their national health insurance scheme does not also currently cover the use of RATs for this use case.
In addition, five countries (Canada, Japan, Singapore, Taiwan, and the US (CDC) and US (AMA)) declared using serologic testing (not specified if laboratory-based or RATs) to conduct seroprevalence studies in their population. Meanwhile, five countries (Germany, Italy, Switzerland, UK, Philippines) implement or recommend antibody testing for seroprevalence surveys but use laboratory-based tests and not RATs.

The WHO and the US AMA, however, cautions against the use of antibody testing as “immunity passports” or “risk-free certificate” as this may increase the risks of continued transmission as people who received a positive test result, having a false assumption that being positive for antibodies will confer immunity to a second infection, may ignore public health advisories. Further, the US CDC, US AMA, and US IDSA do not recommend the use of RATs to guide return-to-work decisions.

3.2.1.3. EPIDEMIOLOGIC SURVEILLANCE

Only the Philippines currently allows use of antibody tests in general (which includes RATs) for surveillance purposes in areas with suspected COVID-19 community transmission, provided that these are properly validated by RITM, DOST, and FIND.
Meanwhile, three countries (Australia, Canada, and the US) use serology testing as part of their contract tracing and outbreak investigations, although these countries did not specify

whether RATS or laboratory-based tests will be used. Furthermore, two countries (Germany and UK) recommended laboratory-based serologic testing for epidemiologic surveillance. In Germany, the Robert Koch Institute will be using ELISA or CLIA laboratory-based serological testing to help monitor the spread of the virus. In the UK, the country uses laboratory-based serological testing for screening donated blood, however it is undefined if it is ELISA or CLIA-based.

While the WHO is currently not explicitly recommending RATs for surveillance, it encourages the conduct of studies to establish the usefulness of RATs for this use case.

3.2.2. What is the current position/ recommendation of HTA agencies regarding the use of RATs for diagnosis, determination of previous exposure, or epidemiologic surveillance of COVID-19?

Of the sixteen (16) HTA agencies reviewed on their assessment recommendations on RATs, none has reviewed the evidence and provided their recommendations specifically on RATs alone but for serology tests in general. We found, however, existing and ongoing HTA reviews for COVID-19 serology tests in general - five agencies [Canada's Canadian Agency for Drugs and Technologies in Health CADTH), University of Oxford's Center for Evidence-Based Medicine (CEBM), Europe's European Network for Health Technology Assessment (EUNetHTA), France's Haute Autorité de Santé (HAS), and Malaysia's Malaysian Health Technology Section (MaHTAS)] which have published a review; and one agency [and Switzerland's Federal Office of Public Health (FOPH)] with on-going reviews. Below are their key recommendations:

3.2.2.1. DIAGNOSIS

All five HTA agencies which published a review on serological tests do not recommend its use for early diagnosis of COVID-19 due to high likelihood of false negative results as antibody production starts roughly after the first week of infection. Further, false positive results may also emerge because of cross-reactivity from a previous or current infection with other coronaviruses. CADTH, one of the said agencies, mentioned though that these tests, when used in combination with RT-PCR, can enhance the accuracy the detection of infection. Another report made by CEBM added that once validated serological assays become available, antibody-based tests can support diagnosis in cases where molecular tests are negative.

3.2.2.2 DETERMINATION OF PREVIOUS EXPOSURE

While all the reviews recognize that COVID-19 serological tests may be better suited for determining previous exposure, the results of these tests are only limited to indication of immune response to the virus which is not synonymous to protective immunization against reinfection with the same virus. Considering time as a factor for presence of antibodies, EUNetHTA said that the presence of IgM antibodies may imply a recent or potentially active infection while the presence of IgG antibodies could identify past exposures. There remains no evidence, however, that the presence of these antibodies to SARS-CoV-2 confers immunity to subsequent infection.

3.2.2.3. EPIDEMIOLOGIC SURVEILLANCE

Finally, serological testing can play a role in surveillance which may not just provide insight to the extent of the infection but may also provide inputs to policies on PPE use and distribution, social distancing relaxation, vaccination, and drug development.

3.3. Diagnostic Performance of RATs

A total of 29 references were included in the qualitative synthesis. Of these, 17 references were studies assessing the accuracy of RATs for use case diagnosis, 1 reference assessed the accuracy of RATs for use case determination of previous exposure, 1 reference assessed the accuracy of RATs for both use case diagnosis and determination of previous exposure, and 10 references assessed accuracy of RATs for epidemiologic surveillance. Overall, this review detected many studies assessing the performance of RATs for use case diagnosis in comparison to the limited/few evidence detected for the other use cases. There is limited evidence to establish the accuracy of RATs for the determination of previous exposure. Meanwhile, there were ten studies which assessed the performance of RATs for epidemiologic surveillance.

3.3.1. DIAGNOSIS

Among the studies on use case diagnosis, the comparators were either RT-PCR using different PCR test kit brands or microneutralization test (MNT). We note that most of the evaluations used RT-PCR as comparator for this use case. Majority did not classify the population being studied in terms of presence of symptoms. There were only few studies among symptomatic and asymptomatic study populations; hence, there is limited evidence to strongly establish and conclude the performance of RATs for diagnosis for symptomatic or for asymptomatic cases. There were also more studies which have assessed and reported the diagnostic performance of RATs in terms of sensitivity than specificity.

Generally, the accuracy of RATs for diagnosis is highly varied based on wide ranges of both the point estimates and confidence intervals reported in the studies. Further, among studies which assessed the performance of RATs (versus RT-PCR) for use case diagnosis, an increase in the clustered point estimates was observed on the sensitivity data for IgM and IgG (for population with undefined information on the presence of symptoms) as the disease progresses to late stages, with point estimates ranging from < 40% for both IgM and IgG during early onset (≤ 7 days), at least 60% for IgM, 40-80% for IgG during mid onset (8-14 days), and 60-96% for IgM, 60-80% for IgG during late onset (≥15 days). Similar to the trend observed in “undefined cases” versus PT-PCR, there is an observed increase in accuracy data from early to late onset of disease among symptomatic cases. However, due to limited evidence available for this population, strong conclusions for symptomatic cases based on onset of disease cannot be made. As there were no studies reporting specificity data based on onset of illness, we can only estimate the specificity of RATs from studies focusing on populations with undefined presence of symptoms and onset of disease. Across studies reporting specificity, it was observed that majority (i.e., 26 out of 28 studies for IgM; 30 out of 31 studies for IgG) of these point estimates cluster around values greater than 80%.

While relatively higher sensitivity values were observed during the late stages of the disease, there remains to be no conclusive evidence to show that any RAT brand can generally be

recommended for use in diagnosis due to the high variability in their performance (whether the comparator is RT-PCR or MNT). Hence, it is important for RAT brands in the market to undergo validation testing using appropriate study designs to ascertain its 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.

As for the applicability of evidence on this use case, we note that the patient profile of the study sources presented for this use case are generally from Asia and Europe, and hospitalized patients; hence, its performance on patients outside this profile may be deemed variable. Furthermore, since majority of the studies did not define the patient profile in terms of presence of symptoms, it is difficult to establish its generalizability overall.

3.3.2. 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. On the other hand, the specificity shows to be quite higher, although this is based only on one study by Hoffman et al. (2020).

As for the applicability of evidence on this use case, we note that the patient profile of the study sources presented for this use case are generally from Europe, and hospitalized patients; hence, its performance on patients outside this profile may be deemed variable. Furthermore, since the two study sources did not define the patient profile in terms of presence of symptoms and there are no other relevant patient characteristics reported in the studies, it is difficult to establish its generalizability overall.

3.3.3. EPIDEMIOLOGIC SURVEILLANCE

There is limited evidence to establish the accuracy of RATs for use case epidemiologic surveillance. Based on the 10 independent evaluation 10 RAT brands against ELISA, we found varying performance of RATs in terms of sensitivity. The specificity values though were quite higher and point estimates appear to be closer to one another as compared to the sensitivity data.

As for the applicability of evidence on this use case, we note that the patient profile of the two 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.

As for the validity of the studies included in this review, majority of the these critically appraised studies were found to have moderate risk of bias. Some factors that may affect the validity of these studies were noted such as non-independence on the performance of the index test and reference standard due to lack of information on the testing of negative samples using reference standard, and non-independence on the interpretation of the index test and reference standard.

Section 4.

Household financial impact

No evidence available

Section 5.

Cost-effectiveness

No evidence available

Section 6.

Affordability and viability

No evidence available

Section 7.

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:

- *symptomatic patients (greater than or equal to 15 days from symptom onset, AND*
- *tested at least twice negative with RT-PCR, AND*
- 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.

Furthermore, the Council has set the minimum regulatory, technical, and operational requirements for RATs as an adjunct test for COVID-19 to guide purchasing decisions of the Department of Health and its accredited COVID-19 testing laboratories:

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
Results Output	**Qualitative,** result must be read visually, without need for a reader/ additional equipment.
Storage, expiration, and 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 Sensitivity (Gene Targets)	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 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.

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

Section 8.

References

1 World Health Organization (WHO). (2020). *WHO Coronavirus Diseases (COVID-19) Dashboard*. https://covid19.who.int/ (accessed 13 July 2020)

2 Health Technology Assessment Unit - Policy, Planning, and Evaluation (PPE) Team. (2020). *Rapid Review on Use of Rapid Antibody-Based Test Kits for Various Cases for COVID-19*. Department of Health (Philippines), Sta. Cruz, Manila.

3 Health Technology Assessment Unit - Policy, Planning, and Evaluation (PPE) Team. (2020). *Guidance Document on Technical Requirements for SARS-CoV-2 Rapid Antibody Test Kits as an Adjunct Test for COVID-19*. Department of Health (Philippines), Sta. Cruz, Manila.

4. Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation and Treatment Coronavirus (COVID-19) [Updated 2020 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/