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

Rapid Review

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1. CONTEXT AND POLICY ISSUES

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 (Johns Hopkins Corona Virus Resource Center) In the Philippines, COVID-19 affected over 269, 407 cases with 4,663 deaths as of 15 September, 2020 (DOH, 2020). To date, treatment remains unknown. (Dong, Du & Gardner, 2020; DOH, 2020)

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 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 (WHO, 2020). 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 (FDA, 2020). Antigen tests, like nucleic-acid based tests such as the RT-PCR test, are designed to detect active SARS-CoV-2 infection. Table 1 characterizes antigen tests compared to antibody tests and RT-PCR. (FIND, 2020a) (FIND, 2020b) (WHO, 2004) (Green, et al. 2020)

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	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	

Parameter	MOLECULAR TEST	ANTIGEN-BASED TESTS	ANTIBODY-BASED TESTS
	small amounts to detectable levels		
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)

As of writing this report, the DOH has no existing guidance on the use of antigen test. There are currently eleven approved RAgTs by the Philippine Food and Drug Administration (PH FDA) as of their latest published list dated 11 September 2020.

This **rapid review was performed to search, appraise and synthesize currently existing evidence and information pertaining to the performance standards and validation testing requirements for RAgTs among selected regulatory agencies; guidelines on the use of RAgTs as well as existing recommendations and positions from other HTA agencies; the accuracy of RAgTs for COVID-19 diagnosis; and, the resource requirements for using or implementing RAgTs.** In the context of this review, we will be setting the definition of the use case *diagnosis* based on the definitions used by the WHO FIND which is defined as: *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: 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).*

2. POLICY AND RESEARCH QUESTIONS

POLICY QUESTION
Should the Philippine DOH consider the use of rapid antigen test kits (RAgTs) for the diagnosis of COVID-19?

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

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

3. **Global guidelines and position on use of RATs**
    3.1. *Which countries have implemented testing strategies using RAgTs for diagnosing COVID-19?*
    3.2. *What is the current position of HTA agencies regarding the use of RAgts for diagnosis COVID-19?*

4. **Resource requirements**
    What are the resource requirements needed to use RAgTs?

3. KEY FINDINGS

In exploring the role of RAgTs in diagnosing COVID-19, a rapid review was conducted to search and synthesize existing evidence and information on the regulatory guidance or policies, various national testing guidelines, HTA evidence review recommendations from selected countries, and resource requirements on the use of RAgTs. Evidence on the diagnostic performance of the RAgTs was sourced from the rapid review of Bayona et al. (2020) from the ICE, NIH-UP and the Asia-Pacific Center for Evidence-Based Healthcare Inc.

REGULATORY STANDARDS   Of the eleven regulatory agencies reviewed for any regulatory guidelines for the approval and validation testing of COVID-19 RAgTs, we found relevant information from five regulatory agencies namely Health Canada, Pharmaceutical and Medical Devices Agency (PMDA) of Japan, UK Medicines and Healthcare Products Regulatory Agency (MHRA), US Food and Drug Administration (US FDA), and the PH FDA. Among these five regulatory agencies, only the US FDA, PH FDA and Japan PMDA have issued authorizations for COVID-19 RAgTs and allowed them to be marketed in their respective countries. To date, the number of registered brands of RAgTs are four by the US FDA, eleven by the PH FDA, and two by the Japan PMDA. Both Health Canada and UK MHRA have not registered yet RAgTs in their markets. Health Canada provides information on in vitro diagnostic devices including those which detect the presence of RNA from SARS-CoV-2 or its antigen for point–of-care settings but cites the April 2020 Scientific brief of the WHO on *Advice on the use of point-of-care immunodiagnostic tests for COVID-19* which does not recommend the use of antigen testing, but recommends these tests should only be used in research settings. The UK MHRA, on the other hand, has only provided a target product profile for point-of-care SARS-CoV-2 detection tests.

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

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

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

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

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

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

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

- US, Japan and WHO currently recommend the use of antigen testing for COVID-19.
- The US guidelines currently recommend its use for diagnostic testing of vulnerable patients with high pre-test probability (ie., symptomatic patients or patients with known exposure to a

confirmed case), and for screening testing in vulnerable high-risk congregate settings. Meanwhile, in Japan, RAgTs may be used for patients suspected for COVID-19. The WHO also recommends the use of antigen tests (that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared to a NAAT reference assay) as a diagnostic test in a range of settings where NAAT is unavailable or where prolonged turnaround times preclude clinical utility. These include its use in responding to suspected outbreaks of COVID-19 in remote settings, institutions and semi-closed communities where nucleic acid amplification test (NAAT) is not immediately available; in supporting outbreak investigations; in monitoring trends in disease incidence in communities; for early detection and isolation of positive cases in areas with widespread community transmission, and in testing asymptomatic contacts of cases.

- As diagnostic test, these guidelines consider a positive antigen test to be reliable given the high specificity of approved tests, while a negative test must be considered presumptive and confirmatory test must be conducted when applicable (Japan MHLW, US CDC and WHO). The US CDC and WHO guidelines highlighted that confirmatory testing following a negative antigen test should be done subject to the use case, pretest probability, and clinical context of the patient while the guidelines released by MHLW in Japan states that the physician will decide on the need to conduct PCR test for a negative antigen test. In general, the decision on conducting confirmatory testing for a negative antigen result should be based on the clinical characteristics and history of the patient. As screening test, the US guidelines for the screening of population with high pre-test probability using RAgT follow the same recommendation as that for the diagnostic testing among population with high pre-test probability using RAgT. However, for the screening of patients with low pre-test probability, the US guidelines require patients with positive antigen test to isolate until confirmed by RT-PCR, while a negative antigen test can be considered negative and may not anymore require an RT-PCR confirmatory test.

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

- On the other hand, Canada's guideline, as of writing, still adopts the April 8, 2020 Scientific brief of the WHO on *Advice on the use of point-of-care immunodiagnostic tests for COVID-19* which does not recommend the use of antigen testing, but recommends research into their performance and potential diagnostic utility.

- South Korea, Vietnam and UK, Australia, Malaysia, China and Philippines do not mention the use of antigen testing in their current national testing guidelines and recommend the use of RT-PCR as the standard test in diagnosing COVID-19. Australia, Malaysia, China and Philippines, however, additionally allows the use of RATs in conjunction with RT-PCR under different circumstances.

- Singapore, Indonesia and Thailand do not have publicly accessible national testing guideline.

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

RESOURCE REQUIREMENTS We found limited guidance documents or references relevant to the resource requirements of RAgTs internationally and locally, hence, we used information from the target product profile by the UK MHRA and interim guidance of the WHO. According to MHRA, RAgTs must have all materials needed to run the test, but in cases where sample collection materials are not provided, materials such as swabs must still be procured by DOH and its accredited laboratories. However, the WHO notes that the contents of test kits may not necessarily include everything to perform and quality control the test. Based on the target product profile (TPP) of MHRA, the test must also be operated without the need for a power source, but, if needed specifically for the purposes of having an analyzer for reading the results, the equipment must be operated using a rechargeable and replaceable battery or through a standard power supply. The WHO notes that an additional detection system implies additional training for the operator as well as resources such as electricity. MHRA notes that in cases where additional training is needed for users such as healthcare professionals, this must not exceed half a day. Furthermore, RAgTs are desired to have a turnaround time in less than 30 minutes from sample collection to results, but it is still acceptable to have a turnaround time of less than 2 hours from sample collection to result. In terms of use of the test, RAgTs should be operable without the need for BSL 2 or 3 laboratory facilities and in 15 to 30 ^{0}C temperature. The WHO on the other hand emphasized that RAgTs are not to be used when appropriate biosafety and infection prevention control measures are lacking. Since the information for its operation was sourced only from the UK MHRA and the WHO, it is important to note that some conditions or resource requirements can change depending on local conditions.

Overall, this rapid review found limited evidence and relevant information on existing regulatory standards, guideline and assessment recommendations, and the diagnostic accuracy of RAgTs that conclusively defines its overall performance and role for diagnosing COVID-19. As research on the different facets of COVID-19 is on-going and rapidly evolving, the evidence and findings presented here rapidly change as well. Hence, updating of evidence would be necessary.

4. METHODOLOGY

4.1. Literature Search Methods

Two reviewers performed targeted search on relevant evidence and information on performance standards and validation testing requirements by selected regulatory bodies, selected international or country-specific testing guidelines, positions or assessment recommendations from selected HTA agencies regarding the use of RAgTs in diagnosis and resource requirements. Below are the targeted sources reviewed:

Table 2. List of Countries, Agencies, and Databases Searched

Regulatory standards, validation requirements, and resource requirements	11 Regulatory Agencies - Health Canada, Japan Pharmaceutical and Medical Devices Agency (PMDA), UK Medicines and Healthcare Products Regulatory Agency (MHRA), US Food and Drug Administration (US FDA), and the Philippine Food and Drug Administration (PH FDA), Australia Therapeutic Goods Authority (TGA), European Medicine

	Agency (EMA), The French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Germany Federal Institute for Drugs and Medical Devices (BfArM), The Pharmaceutical Service Ministry of Health Republic of Italy, Swissmedic Switzerland.
National Testing Guidelines	14 National Testing Guidelines – US Center for Disease Control (US CDC), Japan Ministry of Health Labor and Welfare, South Korea Ministry of Health and Welfare, Vietnam Ministry of Health, United Kingdom National Health Service (UK NHS), Australia Therapeutic Goods Authority, Malaysia Ministry of Health, China Center for Disease Control, Philippines Department of Health (PPH DOH), Public Health Canada, Singapore Ministry of Health, Indonesia Ministry of Health, Thailand Ministry of Health and the World Health Organization (WHO)
HTA Agency Reviews	10 HTA agencies - EUnetHTA, US Agency for Healthcare Research and Quality (AHRQ), UK National Institute for Health and Care Excellence (NICE), Australia Medical Services Advisory Committee (MSAC), Canadian Agency for Drugs and Technologies for Health (CADTH), China National Health Economics Institute (NHEI), Indonesian Health Technology Assessment Committee (InaHTAC), Malaysian Health Technology Assessment Section (MAHTAS), Singapore Agency for Care Effectiveness (ACE), South Korea National Evidence-based Healthcare Collaborating Agency (NECA)

There were no language restrictions in the search. Google Translate was used for direct English translation of contents in the websites and issuances which were not originally written in the English language (i.e. Canada, China, Indonesia, Malaysia, Vietnam and South Korea).

For the review of the evidence on the diagnostic performance, while an independent systematic search was intended to be performed, a rapid review on the accuracy of RAgTs was simultaneously being conducted by the Institute of Clinical Epidemiology, National Institutes of Health – University of the Philippines Manila and the Asia Pacific Center for Evidence-Based Healthcare Inc.; hence, we partnered with their research team to adopt and reference their review findings in order to come up with a complementary report that addresses all the set research questions that will guide the development of HTAC's recommendation to DOH on the use of RAgTs.

In their review, literature search for studies published in 2019 to 2020 on MEDLINE was conducted using subject headings combined with text words related to COVID-19 or SARS-CoV-2 and rapid antigen tests/testing, with no language limits or method filters. They searched the Cochrane COVID-19 Study Register using "antigen" as a search term, and the COVID-19 Living Evidence Database using "antigen" as the search term to identify preprint studies. Their final search date was done on 15 August 2020 with full search details available in their report. In addition, they included available data from the FIND SARS-CoV-2 Diagnostic pipeline database (last updated on 30 July 2020) to supplement their search. Relevant clinical trials were searched on clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). (Bayona et al, 2020)

4.2. Selection Criteria and Methods

For the review of the performance standards and validation requirements by selected regulatory bodies, country guidelines, the positions/recommendations from HTA agencies, and the resource requirements, two reviewers screened the documents which were included in our review.

For the review of evidence on the diagnostic performance of RAgTs conducted by Bayona et al. (2020), two researchers independently screened study titles and abstracts. Disagreements were resolved by consensus or by consulting a third review author. Below are their inclusion criteria for their review:

Table 3. Criteria for considering studies for review (Bayona et al, 2020)	
Type of studies	published and preprint studies (diagnostic cross-sectional, cohort, or case-control study designs) that reported the diagnostic performance data of any rapid antigen test for SARS-CoV-2 and used RT-PCR as reference standard; other study types included as long as they provided data that allowed computation of diagnostic accuracy measures.
Participants	studies that recruited participants of any age, COVID-19 status, symptom severity, risk of exposure, and setting. Studies that used stored laboratory specimens from patients were also included.
Intervention (index test)	novel, RAgTs detecting recombinant SARS-CoV-2 antigens that were listed in the FIND SARS-CoV-2 Diagnostic Pipeline or have obtained regulatory approval from the PH FDA
Target Conditions	mild to moderate COVID-19, COVID-19 pneumonia, suspected or confirmed current SARS-CoV-2 infection, past SARS-CoV-2 infection, or asymptomatic infection with SARS-CoV-2
Comparator (reference standard)	RT-PCR, regardless of whether it was used alone or in combination with imaging (e.g., chest CT), clinical evaluation, or current WHO case definitions. No restrictions were applied in terms of specimen used or brand/manufacturer or diagnostic threshold (cycle threshold or Ct value).

4.3. Data extraction and Management
We extracted the following information from the included studies/guidelines/references for the following characteristics:

Table 4. Extracted Information (Testing Guidelines, Regulatory Agencies, and HTA Reports)

Regulatory Approval	- Country of Origin - Approved use case/s of RAT - Performance standards - Validation requirements - population, sample size, reference test/s
National Testing Guidelines	- Country of Origin - Originating agency of the guidelines - Use case/s of RAT - Target population of RAT - Recommendation Reviews
Reviews from HTA agencies	- Country of Origin - Originating agency of the guidelines

	• Use case/s of RAT
	• Target population of RAT
	• Recommendation Reviews

Meanwhile, for the studies on diagnostic accuracy, two researchers independently performed data extraction on the following information for all included studies in the study of Bayona et al. (2020):

Table 5. Extracted Information (Diagnostic Accuracy Studies)

Diagnostic performance	• Study information: country, test setting, date, funding source
	• Population: number, symptom severity, onset of symptoms
	• Reference standard: RT-PCR brand, specimen used, diagnostic threshold
	• Index test: name of antigen test, manufacturer, test use case, specimen used, method of interpretation, target antigen
	• Diagnostic performance data: true and false positives, true and false negatives, sensitivity, specificity, etc.
	Authors were contacted by email in case of missing information or to clarify details.

4.4. Assessment of Methodological Quality

For the assessment of the methodological quality of the included studies on the diagnostic performance conducted by Bayona et al. (2020), two review authors independently assessed the risk of bias of the included studies and applicability concerns using the QUADAS-2 tool (Whiting 2011). Their disagreements were resolved by discussion until a consensus rating was obtained.

4.5. Data Synthesis

We employed qualitative synthesis to present the current evidence and information on the regulatory standards, guideline and HTA agency recommendations and resource requirements on the use of RAgTs.

Meanwhile for the diagnostic performance, Bayona et al. (2020) performed a quantitative synthesis by pooling the sensitivity and specificity estimates using a bivariate mixed-effects binary regression model (Dwamena 2007). They determined the presence of heterogeneity using visual inspection of the forest plots. In anticipation of the presence of heterogeneity across studies, they pooled the sensitivity and specificity estimates according to test brand, type of specimen used, and participant characteristics using a univariate random-effects model due to the limited number of studies (< 4) available per brand (Takwoingi 2015). Further, they also performed sensitivity analysis by removing studies rated as low methodologic quality. All statistical analyses were performed using Stata 15.0. (TX, USA: StataCorp LLC, 2019). Data were organized using Review Manager (RevMan) 5.4 (Cochrane Collaboration, 2020).

5. SUMMARY OF EVIDENCE

5.1. Regulatory Standards on RAgTs

Of the eleven regulatory agencies, we found relevant information from five regulatory agencies namely Health Canada, Pharmaceutical and Medical Devices Agency (PMDA) of Japan, UK Medicines and Healthcare Products Regulatory Agency (MHRA), US Food and Drug Administration (US FDA), and the PH FDA.

Among these five regulatory agencies, only the US FDA, PH FDA and Japan PMDA have issued authorizations to RAgTs and allowed to be marketed in their respective countries (PH FDA, 2020b; US FDA, 2020b; PMDA, 2020a). To date, the number of registered brands of RAgTs are four by the US FDA, eleven by the PH FDA, and two by the Japan PMDA. Meanwhile, Health Canada provides information on in vitro diagnostic devices including those which detect the presence of RNA from SARS-CoV-2 or its antigen for point–of-care settings but cites the April 2020 Scientific brief of the WHO on *Advice on the use of point-of-care immunodiagnostic tests for COVID-19* which does not recommend the use of antigen testing, but recommends these tests should only be used in research settings (Health Canada, 2020b). Furthermore, while the UK provides a target product profile for point-of-care SARS-CoV-2 detection tests, no antigen tests have been approved yet as of writing of this report, based on their list (MHRA, 2020a).

For the US, emergency use authorizations were given to approved RAgTs for diagnosis among symptomatic patients while the PH FDA provides special certification. Meanwhile the approved antigen test in Japan has underwent the regular review scheme (PMDA, 2020b; PH FDA, 2020a).

The US FDA has provided a template submission form for manufacturers of antigen tests and recommends that validation studies on analytical sensitivity, analytical specificity, microbial interference, and clinical agreement be conducted (US FDA, 2020c). For the clinical agreement study, US FDA requires the use of natural clinical specimens for the evaluation, collected either prospectively or retrospectively. Contrived specimens are not allowed and a minimum of 30 positive specimens and 30 negative specimens must be used, with the testing done in a randomized and blinded fashion. For the comparator, the US FDA recommends the use of a high sensitivity EUA RT-PCR test. Furthermore, the test should be able to demonstrate a minimum sensitivity of greater than or equal to 80% for all sample types. No information on the minimum specificity required was mentioned in the document. In addition, the US FDA suggests providing studies supporting point-of-care claim such as data to demonstrate that non-laboratory personnel can perform the test in the intended use environment claimed by the manufacturer (US FDA, 2020a). The full information requirements for EUA submission of antigen tests can be seen in this document: https://www.fda.gov/media/137907/download.

For the Philippines, the PH FDA only requires the product registration of the COVID-19 test kit by a regulatory agency or accredited third party from countries with established regulations (PH FDA, 2020a).

Meanwhile, in Japan, the regular review scheme involves evaluation by reviewers who possess expertise in medical engineering, biological engineering, and biomaterials, specialists with degrees in medicine, dentistry, pharmaceutical science, and other fields in non-clinical, clinical, and biostatistical evaluations. In addition, the reviewers also exchange opinions with external experts in the process of Expert Discussions for highly specialized reviews (PMDA, 2020c). No specific validation requirements were presented for antigen tests, but the review summary

for one of the approved antigen test by the regulatory agency can provide information on their basis of approval (https://www.pmda.go.jp/files/000235116.pdf). According to this document, the agency considers the clinical performance, cross-reactivity, stability, and precautions required for using the product.

On the other hand, while no antigen tests have been registered yet, the UK MHRA has provided specifications and requirements for POC SARS-CoV-2 detection tests as mentioned above. Based on the document, the point-of-care SARS-CoV-2 detection test is desired to aid in triage of current SARS-CoV-2 infection by detection of nucleic acids or antigens in samples from people of all ages at any point during the active infection but detection during acute phase of infection is acceptable. In addition, it is desirable that the test be applicable for use in people with or without clinical signs and symptoms associated with SARS-CoV-2 but it is also acceptable if the test can be used only for people with clinical signs and symptoms. In terms of the performance characteristics, it is desirable that the test has a sensitivity of greater than 97% (within 93-100% C.I.) and specificity of greater than 99% (within 97-100% C.I.) while it is acceptable to have a sensitivity of greater than 80% (within 95% C.I. of 70-100) and specificity of greater than 95% (within 95% C.I. of 90-100) (MHRA, 2020b). The full target profile can be seen here: https://www.gov.uk/government/publications/how-tests-and-testing-kits-for-coronavirus-covid-19-work/target-product-profile-antibody-tests-to-help-determine-if-people-have-recent-infection-to-sars-cov-2-version-2.

Appendix 1 shows the summary of the regulatory agencies and the information related to validation and approval of RAgTs.

5.2. Performance Characteristics

This section shall only highlight the key results of Bayona et al. (2020) on the diagnostic performance of RAgTs. Kindly refer their full report for the complete details of their study (Accessible via: https://www.psmid.org/should-rapid-antigen-tests-be-used-as-a-screening-tool-for-covid-19/)

5.2.1. Quantity and Characteristics of Included Studies (Completed Studies)

According to the study of Bayona et al. (2020), search of MEDLINE, Cochrane COVID-19 Study Register, and the COVID-19 Living Evidence Database yielded a total of 331 records while an additional 77 records were retrieved from the FIND SARS-CoV-2 Diagnostic Pipeline, clinicaltrials.gov, and WHO ICRTP. After removing 86 duplicates, 322 records underwent independent screening, leaving a total of 18 articles for full-text screening. Among these, only 9 were deemed to fit the research question and thus were included in the final analysis. Six of the nine studies were published articles while the remaining three are preprint articles. (Bayona et al., 2020)

Of the nine included studies, seven involved symptomatic or suspected COVID-19 patients while three included both symptomatic and asymptomatic patients. Two studies analyzed diagnostic accuracy according to onset of symptoms. Seven brands of RAgTs were evaluated, with two producing results that were automatically read by a fluorescence immunoassay analyzer and the rest relying on visual interpretation by reader. Of the seven

brands, two have authorizations from the PH FDA. All the included studies used RT-PCR as the reference standard. Two studies only used SARS-CoV-2 positive samples; hence only sensitivity estimates are available for these studies. In terms of geographic distribution, three studies were from Europe, two from Chile, two from China and Hong Kong, one from Japan and one from USA. (Bayona et al., 2020)

5.2.2. Methodological Quality of Included studies

Based on the appraisal of included studies by Bayona et al. (2020), the overall methodological quality of included studies appears moderate. Among the included studies, only one was rated to be of high quality while 4 studies were found to be of moderate quality. Two studies were rated to have low to moderate quality and two studies were rated to be of low quality. About half of the studies (56%; 5/9) had issues in the participant selection domain due to use of convenience sampling for selecting specimens for testing, while two studies were found to have high risk of bias in the index test domain since they applied RAgTs that depend on subjective interpretation of visual readouts among samples that were all known to be positive for SARS-CoV-2 on RT-PCR. On the other hand, only three studies had low risk of bias in terms of the flow and timing domain.

5.2.3. Diagnostic Accuracy Findings

Meta-analysis was conducted for nine studies and the pooled sensitivity of RAgTs was found to be 49% (95%CI: 28,70; I^2=97.33, 95%CI: 96.54, 98.12) while the pooled specificity was found to be 99% (95%CI: 98, 100; I^2=0, 95%CI: 0, 87.51). Substantial heterogeneity was observed for estimates of sensitivity, hence, subgroup analysis was conducted to explore the factors affecting sensitivity. However, it must be noted that heterogeneity is typically expected for diagnostic test accuracy reviews. (Bayona et al., 2020)

Subgroup analysis by brand
Two test kits had sensitivity of higher than 75%, with the *Bioeasy 2019-nCoV Ag Fluorescence* having a pooled sensitivity of 82.3% (95%CI: 66, 98.5; I^2=94.9%; 3 studies) and the *Sofia 2 SARS Antigen FIA,* one of the two locally-registered brands, having a sensitivity of 76.7% (95%CI: 72.6, 80.3; 1 study). The five other brands of RAgT had sensitivities below 50%, which includes the other locally-authorized brand *Biocredit COVID-19 Ag* (41.3%, 95%CI: 35.3, 47.3; 2 studies).

Subgroup analysis by presence symptoms
Seven studies were pooled for the symptomatic group and the resulting sensitivity was found to be 50.3% (95%CI: 20, 80.7; I^2=99.8), which is already the highest among the subgroup. In the asymptomatic group, two studies were pooled, and the resulting sensitivity was found to be 18.6% (95%CI: 4.7, 32.5). There were two studies that did not report on presence of symptoms among patients enrolled in the study, and the resulting pooled sensitivity was found to be 38% (95%CI: 32.1, 43.9).

Subgroup analysis by phase of the disease

Sensitivity estimates were found to be higher in the early phase (0-7 days) with a pooled sensitivity of 43.1% (95%CI: 6.3, 79.8; 4 studies) as compared to the late phase of disease (8-14 days) with a pooled sensitivity of 12.7% (95%CI: 3.2, 22.3; 2 studies). There were five studies with undefined characteristic in terms of phase of disease and the resulting pooled sensitivity was reported to be 57% (95% CI: 40.2, 73.7).

Subgroup analysis by type of specimen used
In this subgroup, the highest sensitivity was observed for RAgTs that used nasopharyngeal swab samples with a pooled sensitivity of 56.7% (95%CI: 40.8, 72.7; 5 studies). For the other specimens used, the pooled sensitivity for nasopharyngeal and oropharyngeal swab is 50.5.9% (95%CI: 6.4, 94.7) while the pooled sensitivity for saliva samples is 16.1% (95%CI: 10.4, 21.8; 2 studies). Only one study each reported the use of sputum, and nasopharyngeal aspirate and throat swab samples and their corresponding sensitivities are 11.1% (95%CI: 4.8, 23.5) and 34.3% (95%CI: 20.8, 50.8), respectively (Bayona et al., 2020).

Subgroup analysis by reading method
The highest sensitivity for this subgroup was observed among test kits that have an automated reader, having a pooled estimate of 81% (95% CI: 70, 91.7) from four studies. Two of the RAgT brands in this review require an automated reader for interpreting the results which includes the *Bioeasy 2019-nCoV Ag fLuorescence Rapid Test Kit* and the locally-authorized *Sofia 2 SARS Antigen FIA*. On the other hand, the RAgT group that relies on visual interpretation of results only had a pooled sensitivity of 32% (95% CI: 14.2, 50.4) which was obtained from six studies. The remaining five brands in the review rely on visual interpretation of the results and this includes the locally authorized *BIOCREDIT COVID-19 Ag* test.

Other factors
The cycle threshold value for RT-PCR (reference standard) may also have an influence on the sensitivity of RAgTs, with one study reporting that changing Ct value threshold for a positive result from ≤ 40 to ≤ 30 increased the sensitivity of the index test from 68% (95%CI: 61, 74) to 98% (95%CI: 90, 100). (Bayona et al., 2020)

Sensitivity Analysis
Upon removal of 4 studies rated with low methodologic quality, the overall sensitivity estimate (49%) increased to 57% (95% CI: 23, 93) but still remained low.

Applicability of findings to the review question
Post-test probabilities were computed for RAgTs among asymptomatic patients, symptomatic patients who are mild cases, and symptomatic patients with moderate to severe symptoms. The pre-test probabilities of 0.4%, 10%, and 40% were used for the asymptomatic patients, the symptomatic patients (mild cases), and the symptomatic patients (moderate to severe symptoms), respectively. Using the pooled sensitivity of 49% for the three scenarios above, the resulting positive post-test probabilities were 17%, 85%, and 97%. On the other hand, the negative post-test probabilities will not change for asymptomatic patients but will decrease to 5% among

symptomatic patients (mild cases) and to 25% among symptomatic patients (moderate to severe symptoms).

Implications for practice

Bayona et al. (2020) highlighted that because of the overall low sensitivity and the high uncertainty on the accuracy of RAgTs, they do not recommend these tests for screening asymptomatic disease (e.g., mass screening, or return to work clearance). They noted that RAgTs may have some use though for confirming diagnosis for the following conditions or target uses:

- For patients with high pre-test probability (e.g., symptomatic patients in hospital settings, cases of anosmia or ageusia, etc.).
- Situations when RT-PCR is not available –can allow faster tracing of contacts of positive cases and can be useful in situations where immediate decisions regarding interventions and patient management are needed (e.g., emergency admissions).

Lastly, they noted that for these cases, a negative result would still require confirmation with RT-PCR due to high false negative rate of RAgT, and would also need to be correlated with clinical (symptoms) and epidemiological parameters (exposure history).

5.2.4. Characteristics of Ongoing Studies

Bayona et al. (2020) found 12 ongoing clinical validation studies for RAgTs from trial registries and FIND. Seven of the validation studies are trials that aim to evaluated the diagnostic accuracy of RAgTs as compared to RT-PCR among symptomatic adults with suspected or confirmed COVID-19 disease while the remaining pertain to the independent validation of FIND for 5 RAgT brands, of which no results have been released yet as of writing (Bayona et al., 2020).

5.3. Testing Guideline Recommendations and HTA Evidence Reviews on RAgTs

5.3.1 Review of Testing Guideline Recommendations

A total of fourteen testing guidelines for the diagnosis of COVID-19 from thirteen selected countries and the WHO were checked for their current guideline recommendations on the use of RAgTs. Among these, only three (Japan, US and WHO) currently recommend the use of antigen testing for the diagnosis of COVID-19.

In Japan, the national testing guideline released last June 2020 states that a RAgT (conducted using nasopharyngeal swab) can be used as diagnostic testing of patients suspected for COVID-19 (subject to decision of physician and public health center). A positive antigen test is considered a definitive diagnosis for COVID-19. Meanwhile, a negative antigen test, upon the recommendation of a physician, requires an RT-PCR confirmatory test (MHLW, 2020).

In the US, the CDC notes that RAgTs are particularly helpful if the person is tested in the early stages of infection with SARS-CoV-2 when viral load is generally at its highest. They noted the role of RAgT for the following conditions or applications for use:

- For diagnostic testing situations in which the vulnerable person has a known exposure to a confirmed case of COVID-19
- For screening testing in vulnerable high-risk congregate settings in which repeat testing could quickly identify persons with SARS-CoV-2 infection to inform infection prevention and control measures, thus preventing transmission throughout the congregate setting. In this case, there may be value in providing immediate results with antigen tests even though they may have lower sensitivity than RT- PCR tests, especially in settings where a rapid turnaround time is required.

On the other hand, the US CDC finds limited data to guide the use of RAgTs on the following conditions or applications for use:
- As a screening test on asymptomatic persons;
- To determine whether a previously confirmed case is still infectious;
- To make decisions about discontinuing isolation

As the US CDC still considers the RT-PCR test as the gold standard, they noted that it may be necessary to confirm a RAgT result with a nucleic acid test, especially if the result of the antigen test is inconsistent with the clinical context. Generally, clinicians can rely upon a positive diagnostic antigen test because the specificity of current US FDA-authorized antigen test is high. The sensitivity of the current US FDA-authorized antigen test varies, and thus in most cases, negative antigen diagnostic test results are considered only presumptive.

Hence, the US CDC has recommended the following conditions that will require and not require a confirmatory test with an RT-PCR test:

- When RAgT is used for diagnostic testing:
  - Confirmatory nucleic acid (RT-PCR) testing following a negative antigen test results should be done especially when the pretest probability is relatively high (vulnerable patient is symptomatic or has a known exposure to a person confirmed to have COVID-19). Ideally, confirmatory RT-PCR testing should take place within two days of the initial antigen testing. If RT-PCR testing is not available, clinical discretion can be used in whether to recommend the patient to isolate. Currently, the two RAgTs that have received EUAs from the US FDA are limited to diagnostic testing on symptomatic persons within the first five days of symptom onset.
  - While the guideline did not explicitly state that a positive result will not require confirmatory nucleic acid testing, they generally stated that clinicians can rely upon a positive diagnostic antigen test result because of the high specificity of current FDA-authorized antigen tests. However, in cases where the result is inconsistent with clinical context, it is still necessary to do confirmatory RT-PCR testing.

- When RAgT is used for screening testing in congregate settings:
  - Confirmatory nucleic acid testing following a positive antigen test may not be necessary when the pretest probability is high, especially if the person is symptomatic or has a known exposure. When the pretest probability is low, those persons who receive a positive antigen test should isolate until they can be confirmed by RT-PCR.

o On the other hand, confirmatory nucleic acid testing following a negative antigen test may not be necessary if the pretest probability is low, the person is asymptomatic, has no known exposures, or is part of a cohort that will receive rapid antigen tests on a recurring basis.

According to the WHO interim guidelines published on Sept 11, 2020, RAgTs that meet the minimum performance requirements of ≥80% sensitivity and ≥97 specificity compared to a nucleic acid amplification test (NAAT) reference assays can be used to diagnose SARS-COV-2 infection in a range of settings where NAAT is unavailable or where prolonged turnaround times preclude clinical utility. Appropriate scenarios for use of RAgTs include the following:

1. **To respond to suspected outbreaks of COVID-19 in remote settings, institutions and semi-closed communities where NAAT is not immediately available.**
   - A positive result from multiple suspects is highly suspicious of a COVID-19 outbreak and would allow for early implementation of infection control measures
   - Where possible, all samples giving positive RAgT result should be transported to laboratories with NAAT capability for confirmatory testing.
2. **To support outbreak investigations (e.g. in closed or semi-closed groups including schools, care homes, cruise ships, prisons, work places and dormitories, etc)**
   - In a NAAT-confirmed COVID-19 outbreaks, RAgTs could be used to screen at-risk individuals and rapidly isolate positive cases and prioritize sample collection from RDT-negative individuals for NAAT.
3. **To monitory trends in disease incidence in communities, and particularly among essential workers and health workers during outbreaks or in regions of widespread community transmission where PPV and NPV of rapid antigen result is sufficient to enable effective infection control**.
4. **Where there is widespread community transmission, RAgTs may be used for early detection and isolation of positive cases in health facilities, COVID-19 testing centers/ sites, care homes, prisons, schools, front-line and health-care workers and for contact tracing.**
   - Safe management of patients with negative samples will depend on RAgTs performance and the community prevalence of COVID-19
   - A negative result cannot completely exclude an active COVID-19 infection, and, therefore, repeat testing or preferably confirmatory testing using NAAT should be performed whenever possible, particularly in symptomatic patients
5. **Testing of asymptomatic contacts of cases may be considered even if the RAgTs is not specifically authorized for this use, since asymptomatic cases have been demonstrated to have viral loads similar to asymptomatic cases.**
   - Though, in these situations, a negative result should not remove a contact from quarantine requirements

The WHO recommends that for initial introduction of RAgTs into clinical use, countries should consider selecting some settings where in NAAT confirmatory testing is currently available so that staff can gain confidence in assays, confirm performance of selected RAgTs, and troubleshoot any implementation issues encountered. Whenever NAAT will be used for

confirmatory testing in patients screened using a RAgTs, the samples for the two tests should be collected at roughly the same time, or at most within a period of less than 2 days.

In addition, the WHO cautions that in any situations where confirmatory testing with NAAT is not feasible, any indications that results may be incorrect should raise suspicions about validity. These include the following:

- A positive test result, but clinical manifestations are not consistent with COVID-19.
- A positive test detected in a low-prevalence setting. In a low prevalence setting, the positive predictive value is low, which makes the risk of false positives high.
- A negative test result, but have a classical syndrome, are close contacts of a case or are tested in a high-prevalence setting. In such situations, considerations should be given to repeating the test, especially if there is also uncertainty about the visual result or adequacy of sampling.

On the other hand, the WHO does not recommend the use of RAgTs in **settings** or **populations with low prevalence of disease** (e.g. screening at points of entry, blood donation, elective surgery), **especially where confirmatory testing by NAAT is not readily available especially where confirmatory testing by NAAT is not readily available.** They further explained that such use will not be possible until there are more data from high-quality studies confirming high specificity (>99%) of one or more of the commercialized RAgTs. The specific situations where RAgTs should not be used based on current evidence according to the WHO are as follows:

1. **In individuals without symptoms unless the person is a contact of a confirmed case**
   - Pretest probability is low
2. **Where there are zero or only sporadic cases**
   - RAgTs are not recommended for routine surveillance purposes or case management in this setting.
   - Positive test results would likely be false positives
   - Molecular testing is preferred.
3. **Appropriate biosafety and infection prevention and control measures are lacking**
   - To safeguard health workers, respiratory sample collection for any test from patients with suspected COVID-19 requires that operators wear gloves, gown, mask and face shield or goggles
4. **Management of the patient does not change based on the result of the test**
   - If treatment/ management is the same because of unknown or low PPV or NPV, then there is no benefit in testing.
5. **For airport or border screening at points of entry**
   - Prevalence of COVID-19 will be highly variable among travellers, and therefore not possible to determine PPV and NPV of test results. Confirmatory testing is required to increase PPV and NPV for decision making.
6. **In screening prior to blood donation**
   - A positive RDT result would not necessarily correlate with presence of viremia. Asymptomatic blood donors do not meet the definition of a suspect case

Meanwhile, Canada's guideline, as of writing, still adopts the April 8, 2020 Scientific brief of the WHO on *Advice on the use of point-of-care immunodiagnostic tests for COVID-19*

which does not recommend the use of antigen testing, but recommends research into their performance and potential diagnostic utility.

Seven countries (South Korea, Vietnam, UK, Australia, Malaysia, China and the Philippines) reviewed do not mention the use of antigen testing in their currently published national testing guidelines. These countries currently recommend the use of RT-PCR as the standard test in diagnosing COVID-19; however, Australia, Malaysia, China and Philippines additionally allow the use of RATs in conjunction with RT-PCR under different circumstances. Australia allows the use of RATs for patients who present late (suspected case that were not able to undergo RT-PCR during the acute phase of illness). Malaysia allows the use of RATs in screening for close contact of confirmed case. RT-PCR must be used if the close contact develops any symptoms. China allows the use of RATs in patients who tested persistently negative using RT-PCR but have strong clinical suspicion of SARS-CoV-2. In the Philippines, RATs may be used if patients 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 manifestation of COVID-19.

Meanwhile, the remaining, three countries (Singapore, Indonesia, Thailand) do not have publicly accessible national testing guidelines.

Appendix 2 shows more details on the different guidelines reviewed.

5.3.2 Review recommendations of HTA agencies

None of the ten HTA agencies (EUnetHTA, US Agency for Healthcare Research and Quality [AHRQ], UK National Institute for Health and Care Excellence [NICE], Australia Medical Services Advisory Committee [MSAC], Canada Canadian Agency for Drugs and Technologies for Health [CADTH], China National Health Economics Institute (NHEI), Indonesian Health Technology Assessment Committee [InaHTAC], Malaysian Health Technology Assessment Section [MAHTAS], Singapore Agency for Care Effectiveness [ACE], South Korea National Evidence-based Healthcare Collaborating Agency [NECA]) searched and reviewed had any published or on-going assessments or relevant guidance regarding the use of antigen-based serology testing for diagnosing COVID-19.

5.4. Resource Requirements

This review found very limited available guidance documents or relevant references on the resource requirements of RAgTs internationally and locally. Hence, the resource requirements discussed in this section were based on the target product profile provided by the UK Medicines & Healthcare Products Regulatory Agency (MHRA, 2020b) as well as the interim guidance for rapid antigen tests by the World Health Organization (2020).

The RAgT kit must contain all materials for the procedure including controls, reagents, and instructions for use as well as accessories needed for sample collection; however, it is acceptable for the accessories for sample collection be provided separately. In the case where the accessories for sample collection are not provided, the accessories or equipment needed must use those that are currently being procured by DOH and its accredited laboratories (i.e. sterile swabs) (MHRA, 2020b). The WHO on the other hand mentions that contents of the test kit may not necessarily include everything to perform and quality control the test (WHO, 2020).

In terms of power requirement, ideally, the test should run with no power source or the test can be done through a rechargeable and replaceable battery. When this requirement cannot be met, it may be acceptable if the test can be done using a standard power supply. This is particularly important for rapid antigen tests that come with an equipment to read the results, where power is important to run the machine. In addition, the test must be suitable for use by trained healthcare professionals, where minimal (less than half day of training) to no additional training is required (MHRA, 2020b). The WHO (2020) notes however that use of instrumented detection systems will require additional training requirements such as use and calibration of the instrument and other additional resources like sufficient infrastructure particularly a reliable source of electricity. In addition, specimen collection requirements of testing kits will also influence the extent of training and supervision required (WHO, 2020).

In terms of the turnaround time, it is desired that the test kit produces the result in less than 30 minutes from sample collection, but it is still acceptable to have tests that have less than 2 hours from sample to result. In terms of biosafety concerns, personnel doing the antigen test kits must still use standard personal protective equipment (PPE) and follow safety procedures but without the need for biosafety level (BSL) 2 or 3 laboratory facilities, provided that there is evidence that the live virus was deactivated early in the process. In addition, as mentioned above, it is important that healthcare professionals can use the antigen test at the point of care both in healthcare and non-healthcare settings (MHRA, 2020b). In line with the biosafety considerations, the WHO states that RAgTs are not to be used when appropriate biosafety and infection and prevention control measures are lacking as health workers must still wear the basic PPE and must have the biohazard waste bag and good ventilation for their safety.

For the operational characteristics, it is desirable for the test kits to not require a cold chain or can be stored at 15 to 30^{0}C but it is acceptable for test kits and reagents to require storage at 2-8^{0}C for at least 12 months, with stability for 12 hours when removed from the cold storage. Nevertheless, the antigen test kits must be viable for use at 15 to 30^{0}C (MHRA, 2020b). On the other hand, the WHO (2020) states that shelf-life must be at least 12-18 months at 30^{0}C and ideally 40^{0}C. In addition, requiring a cold chain for shipping or storage would increase the cost and complexity of procurement and distribution of the test kits.

From the aforementioned resource requirements for use of RAgTs, it is expected that running a test would cost much less as compared to RT-PCR tests because there is no need for BSL 2 or 3 laboratory facilities and the lesser equipment and materials would be required. Furthermore, since RAgTs take a significantly shorter amount of time from specimen collection to results as compared to PCR, it is expected that more tests can be conducted within a specified amount of time.

However, as the above information were sourced from the UK Medicines & Healthcare Products Regulatory Agency (2020b) and the WHO (2020) interim guidance, it is important to note that some conditions or resource requirements may change based on local context, such as the power requirements and cold storage which may not be stable or available in rural or geographically isolated and disadvantaged areas.

6. LIMITATIONS

This review recognizes the following limitations. First, as this is a rapid review, targeted search for evidence in the review of regulatory standards, testing guidelines, HTA agencies recommendation and

resource requirements was employed because of the need to urgently produce evidence while ensuring the quality of the synthesis methodology is our primary priority.

In addition, we note the following limitation of Bayona et al. (2020), as follows: Since most studies only focused on evaluating the diagnostic accuracy of one test brand, the effect of confounding factors should be considered when attempting to compare the accuracy of different test brands. While a bivariate model should have been used in pooling diagnostic test accuracy, a univariate model was used due to limited studies found, which may have resulted in imprecise pooled estimates. The overall pooled estimate may be inaccurate due to high heterogeneity across studies. While we identified possible causes of heterogeneity, further studies are needed to verify their effect on sensitivity of RAgTs.

Lastly, as research on the different facets of COVID-19 is on-going and rapidly evolving, the evidence presented here can rapidly change as well. Hence, updating of evidence would be necessary.

7. CONCLUSION

REGULATORY STANDARDS ON RAgTs
We found limited information on the current regulatory standards for RAgTs. From the five regulatory agencies with relevant information on RAgTs, only the US FDA, PH FDA and Japan PMDA have so far authorized COVID-19 RAgTs in their respective countries. Both Health Canada and UK MHRA have not registered yet RAgTs in their markets. Health Canada provides information on in vitro diagnostic devices including those which detect the presence of RNA from SARS-CoV-2 or its antigen for point–of-care settings but cites the April 2020 Scientific brief of the WHO on *Advice on the use of point-of-care immunodiagnostic tests for COVID-19* which does not recommend the use of antigen testing, but recommends these tests should only be used in research settings. The UK MHRA, on the other hand, has only provided a target product profile for point-of-care SARS-CoV-2 detection tests.

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

What are the validation testing requirements of selected regulatory agencies for COVID-19 RAgTs?
Only the US FDA has published details on the validation requirements. For the clinical agreement study, the use of natural clinical specimens for the evaluation, collected either prospectively or

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

Meanwhile, the UK MHRA target product profile for point-of-care SARS-CoV-2 detection tests has indicated that it is desirable that the test has a sensitivity of greater than 97% (within 93-100% C.I.) and specificity of greater than 99% (within 97-100% C.I.) while it is acceptable to have a sensitivity of greater than 80% (within 95% C.I. of 70-100) and specificity of greater than 95% (within 95% C.I. of 90-100).

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

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

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

GUIDELINE RECOMMENDATION AND EVIDENCE SYNTHESIS FROM HTA AGENCIES ON USE OF RAgTs

Which countries have implemented testing strategies using RAgTs for diagnosing COVID-19?

Of the fourteen guidelines reviewed, there are only three guidelines (US, Japan, WHO) that currently recommend the use of RAgTs, one country (Canada) that explicitly do not recommend the use of RAgTs, seven countries that did not mention RAgT in their current testing guidelines, and the remaining three countries (Singapore, Indonesia and Thailand) had no accessible guidelines that can be reviewed.

- US, Japan and WHO currently recommend the use of antigen testing for COVID-19.
  - The US guidelines currently recommend its use for diagnostic testing of patients with high pre-test probability (ie., symptomatic patients or vulnerable patients with known exposure to a confirmed case), and for screening testing in high-risk congregate settings. Meanwhile, in Japan, RAgTs may be used for patients suspected for COVID-19. The WHO also recommends the use of antigen tests (that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared to a NAAT reference assay) as a diagnostic test in a range of settings where NAAT is unavailable or where prolonged turnaround times preclude clinical utility. These include its use in responding to suspected outbreaks of COVID-19 in remote settings, institutions and semi-closed communities where NAAT is not immediately available, in supporting outbreak investigations, in monitoring trends in disease incidence in communities, in areas with widespread community transmission, and in testing asymptomatic contacts of cases.
  - As diagnostic test, these guidelines consider a positive antigen test to be reliable given the high specificity of approved tests, while a negative test must be considered presumptive and confirmatory test must be conducted when applicable (Japan MHLW, US CDC, WHO). The US CDC and the WHO guidelines highlighted that confirmatory testing following a negative antigen test should be done subject to the use case, pretest probability, and clinical context of the patient while the guidelines released by MHLW in Japan states that the physician will decide on the need to conduct PCR test for a negative antigen test. In general, the decision on conducting confirmatory testing for a negative antigen result should be based on the clinical characteristics and history of the patient.
  - As screening test, the US guidelines for the screening of population with high pre-test probability using RAgT follow the same recommendation as that for the diagnostic testing among population with high pre-test probability using RAgT. However, for the screening of patients with low pre-test probability, the US guidelines require patients with positive

antigen test to isolate until confirmed by RT-PCR, while a negative antigen test can be considered negative and may not anymore require an RT-PCR confirmatory test.

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

- On the other hand, Canada does not recommend the use of antigen testing for diagnosis of COVID-19 due to sensitivity issues and possibility of false negatives. Canada's guideline, as of writing, still adopts the April 8, 2020 Scientific brief of the WHO on *Advice on the use of point-of-care immunodiagnostic tests for COVID-19* which does not recommend the use of antigen testing, but recommends research into their performance and potential diagnostic utility.

- South Korea, Vietnam and UK, Australia, Malaysia, China and the Philippines do not mention the use of antigen testing in their current national testing guidelines and recommend the use of RT-PCR as the standard test in diagnosing COVID-19. Australia, Malaysia, China and the Philippines, however, additionally allows the use of RATs in conjunction with RT-PCR under different circumstances.

What is the current position of HTA agencies regarding the use of RAgTs for diagnosis COVID-19?

None of the 10 reviewed HTA agencies had any published or on-going assessments or relevant guidance regarding the use of antigen-based serology testing for the diagnosis of COVID-19.

RESOURCE REQUIREMENTS

What are the resource requirements needed to use RAgTs?

We found limited guidance documents or references relevant to the resource requirements of RAgTs internationally and locally, hence, we used information from the target product profile by the UK MHRA and interim guidance by the WHO. Based on the target profile document, RAgTs must have all materials needed to run the test, but in cases where some materials are not provided, these materials must still be procured by DOH and its accredited laboratories. Meanwhile, the WHO mentions that contents of the test kit may not necessarily include everything to perform and quality control the test. In terms of power requirements, the test must be operated without the need for a power source, but for tests that require an analyzer for reading the results, the equipment must be operated using a rechargeable and replaceable battery or through a standard power supply. In cases where additional training is needed for users such as healthcare professionals, this must not exceed half a day. In line with these requirements, the WHO mentions that the need for a reader or detection system will require additional training to personnel and additional infrastructure such as electricity. The UK MHRA discussed in their TPP that RAgTs should also have a quick turnaround, must be operable without the need for BSL 2 or 3 laboratory facilities, and in 15 to 30 ^{0}C temperature. On the other hand, the WHO emphasized that RAgTs must not be used if appropriate biosafety and infection control prevention measures such as PPE and ventilation are not in place. Because this information was sourced only from two international documents, it is important to note that some conditions or resource requirements may change depending on local conditions.

Overall, this rapid review found limited evidence and relevant information on existing regulatory standards, guideline and assessment recommendations, and the diagnostic accuracy of RAgTs that conclusively defines its overall performance and role for diagnosing COVID-19. As research on the different facets of COVID-19 is on-going and rapidly evolving, the evidence and findings presented here rapidly change as well. Hence, updating of evidence would be necessary.

8. DECLARATION OF CONFLICT OF INTERESTS

The reviewers declare that they no competing interests.

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10. APPENDICES

Appendix 1. Summary of Regulatory Agencies and Information on Validation and Approved Rapid Antigen Tests

Country of Origin	Agency	# of Registered RAgTs	Minimum Standards for Diagnostic Performance	Validation Requirements		
				Population	Reference Test	Sample size
Philippines	Food and Drug Administration	11	None mentioned	Registration or issuance of certificate dependent on product approval from other countries with stringent regulatory agencies		
Australia	Therapeutic Goods Administration	No information				
Canada	Health Canada	0	No information			
European Union	European Medicines Agency	No information				
France	National Drug and Health Products Safety Agency	No information				
Germany	Federal Institute for Drugs and Medical Devices	No information				
Italy	Italian Medicines Agency	No information				
Japan	Pharmaceutical and Medical Devices Agency	2	None mentioned	No information but may refer to review summary of the first registered antigen test kit in this document for basis of approval: https://www.pmda.go.jp/files/000235116.pdf		
Switzerland	Swiss Agency for Therapeutic Products	No information				
United Kingdom	Medicines and Healthcare Products Regulatory Agency	0	Sensitivity: Greater than 80% (within 95% C.I. of 70-100) Specificity: Greater than 95% (within 95% C.I. of 90-100)	People with or without clinical signs and symptoms associated with SARS-CoV-2 infection, if testing is appropriate	A validated CE-marked laboratory method in current clinical use, against which the Negative/Positive Percent Agreement is calculated	At least 150 positive clinical samples and at least 250 negative clinical samples

Country of Origin	Agency	# of Registered RAgTs	Minimum Standards for Diagnostic Performance	Validation Requirements		
				Population	Reference Test	Sample size
United States	Food and Drug Administration	4	Sensitivity: Greater than or equal to 80% Specificity: none mentioned	None mentioned	High sensitivity EUA RT-PCR test which uses a chemical lysis step followed by solid phase extraction of nucleic acid (e.g., silica bead extraction)	minimum of 30 positive specimens and 30 negative specimens

Appendix 2. Country Guidelines on the Use of RAgTs

Country	Use of Antigen Tests	References
United Kingdom	**UK does not mention the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines only recommend the use of RT-PCR.** The preferred screening/testing is molecular diagnosis of COVID-19 using real-time RT-PCR (RdRp gene) assay based on oral swabs, which Public Health England (PHE) laboratories have been using to confirm this disease.	National Health Service (2020) Guidance and Standard Operating Procedure on Covid-19 Virus Testing in NHS Laboratories. Retrieved August 13, 2020 from: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/guidance-and-sop-covid-19-virus-testing-in-nhs-laboratories-v1.pdf
United States	**USA recommends the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines allow the use of RT-PCR, Antigen Tests and Rapid antibody tests.** Molecular diagnostic and antigen tests can yield false-negative results. In people with a high likelihood of infection based on exposure history and/or clinical presentation, a single negative test result does not completely exclude SARS-CoV-2 infection, and repeat testing should be considered. When a person who is strongly suspected to have SARS-CoV-2 infection has a negative result on an initial antigen test, repeat testing using a molecular diagnostic test may be warranted. ***General Guidance*** Antigen tests are immunoassays that detect the presence of a specific viral antigen, which implies current viral infection. Antigen tests are currently authorized to be performed on nasopharyngeal or nasal swab specimens placed directly into the assay's extraction buffer or reagent. The currently authorized antigen tests are not restricted to use on persons of a certain age.	National Institute of Health (2020). Covid-19 treatment guidelines. Retrieved August 17, 2020 from: https://files.covid19treatmentguidelines.nih.gov/guidelines/archive/covid19treatmentguidelines-07-24-2020.pdf Center for Disease Control (2020). Interim Guidance for Rapid Antigen Testing for SARS-CoV-2. Retrieved August 24, 2020 from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html#table1,

Antigen tests are relatively inexpensive and can be used at the point-of-care. The currently authorized devices return results in approximately 15 minutes. Antigen tests for SARS-CoV-2 are generally less sensitive than viral tests that detect nucleic acid using reverse transcription polymerase chain reaction (RT-PCR). Proper interpretation of antigen test results is important for accurate clinical management of patients with suspected COVID-19, or for identification of potentially infected persons when used for screening.

The clinical performance of rapid antigen diagnostic tests largely depends on the circumstances in which they are used.

Rapid antigen tests are particularly helpful if the person is tested in the early stages of infection with SARS-CoV-2 when viral load is generally highest. They also may be informative in diagnostic testing situations in which the person has a known exposure to a confirmed case of COVID-19. Rapid antigen tests can be used for screening testing in high-risk congregate settings in which repeat testing could quickly identify persons with a SARS-CoV-2 infection to inform infection prevention and control measures, thus preventing transmission throughout the congregate setting. In this case, there may be value in providing immediate results with antigen tests even though they may have lower sensitivity than RT-PCR tests, especially in settings where a rapid turnaround time is required.

There are limited data to guide the use of rapid antigen tests as screening tests on asymptomatic persons to detect or exclude COVID-19, or to determine whether a previously confirmed case is still infectious.

Clinicians should understand antigen test performance characteristics in order to recognize potentially false negative or false positive results and to guide patient management. Laboratory and testing professionals who perform rapid antigen tests should also understand the factors that affect the accuracy of antigen testing, as described in this guidance.

Performance of Rapid Antigen Tests for SARS-CoV-2

The "gold standard" for clinical diagnostic detection of SARS-CoV-2 remains RT-PCR. Thus, it may be necessary to confirm a rapid antigen test result with a nucleic acid test, especially if the result of the antigen test is inconsistent with the clinical

context. When confirming an antigen test result with a RT-PCR test, it is important that the time interval between the two sample collections is less than two days, and there have not been any opportunities for new exposures between the two tests. If more than two days separates the two tests, or there have been opportunities for new exposures between the two tests, the nucleic acid test should be considered a separate test – not a confirmatory test.

The sensitivity of rapid antigen tests is generally lower than RT-PCR. The first two antigen tests that have received FDA EUAs demonstrate sensitivity of 84% and 97% compared to RT-PCR. Studies have shown that antigen levels in some patients who have been symptomatic for more than five days may drop below the limit of detection of the test. This may cause the test to return a negative result, while a more sensitive test, such as RT-PCR, may return a positive result.

The specificity of rapid antigen tests is generally as high as RT-PCR – the first two antigen tests that have received FDA EUAs have specificity of 100% – which means that false positive results are unlikely. Positive and negative predictive values of all in vitro diagnostic tests vary depending upon the pretest probability of the patient being tested. Pretest probability is impacted by the prevalence of the target infection in the community as well as the clinical context of the recipient of the test.

CDC recommends that laboratory and testing professionals who perform rapid antigen testing should determine infection prevalence based on a rolling average of the positivity rate of their own SARS-CoV-2 testing over the previous 7–10 days. Infection prevalence at the time of testing, as well as the clinical context of the recipient of the test, impacts pretest probability. If a specific testing site, such as a nursing home, has a positivity rate near zero, the prevalence of disease in the community (e.g., cases per population) should instead be used to help determine pretest probability. Rapid antigen tests should be interpreted in the context of the prevalence of infection or disease, the device's performance characteristics and instructions for use, and the patient's clinical signs, symptoms, and history.

Evaluating the Results of Rapid Antigen Testing for SARS-CoV-2

Evaluating the results of a rapid antigen test for SARS-CoV-2 should take into account the performance characteristics (e.g. sensitivity, specificity), instructions for use of the FDA-authorized assay, the prevalence of COVID-19 in that particular

community (positivity rate over the previous 7–10 days or cases per population), and the clinical and epidemiological context of the person who has been tested.

The evaluation of a diagnostic antigen test result should consider the length of time the patient has experienced symptoms. Generally, clinicians can rely upon a positive diagnostic antigen test result because the specificity of current FDA-authorized antigen tests is high.

The sensitivity of current FDA-authorized antigen tests varies, and thus negative diagnostic testing results should be handled differently depending on the testing device and its stated performance characteristics. In most cases, negative antigen diagnostic test results are considered presumptive. CDC recommends confirming negative antigen test results with an RT-PCR test when the pretest probability is relatively high, especially if the patient is symptomatic or has a known exposure to a person confirmed to have COVID-19. Ideally, confirmatory RT-PCR testing should take place within two days of the initial antigen testing. If RT-PCR testing is not available, clinical discretion can be used in whether to recommend the patient isolate. CDC does not recommend using antigen tests to make decisions about discontinuing isolation.

Currently, the two rapid antigen tests that have received EUAs from FDA are limited to *diagnostic testing* on symptomatic persons within the first five days of symptom onset. Serial antigen testing within a closed congregate setting, such as a long-term care facility or a correctional facility, could quickly identify someone with a SARS-CoV-2 infection and prevent further transmission. Modeling evidence external icon shows that outbreak control depends largely on the frequency of testing and the speed of reporting and is only marginally improved by high test sensitivity. For this reason, serial antigen testing may have benefits for early identification and controlling outbreaks in some situations, such as congregate living, compared to RT-PCR tests in settings with prolonged turnaround times.

When used for *screening testing* in congregate settings, test results for SARS-CoV-2 should be considered presumptive. Confirmatory nucleic acid testing following a *positive* antigen test may not be necessary when the pretest probability is high, especially if the person is symptomatic or has a known exposure. When the pretest probability is low, those persons who receive a positive antigen test should isolate until they can be confirmed by RT-PCR.

	Confirmatory nucleic acid testing following a *negative* antigen test used for screening testing may not be necessary if the pretest probability is low the person is asymptomatic or has no known exposures, or is part of a cohort that will receive rapid antigen tests on a recurring basis. Nucleic acid testing is also considered presumptive when screening asymptomatic persons, the potential benefits of confirmatory testing should be carefully considered in the context of person's clinical presentation.		
Australia	**Australia does not mention the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines still recommend the use of RT-PCR as the primary means of diagnosis; however, RATs are acceptable to be used in patients who present late (suspected cases that were not able to undergo RT-PCR during the acute phase of illness)** Tests for COVID-19 aim to detect the causative virus, SARS-CoV-2, or an immune response to SARS-CoV-2. The reliability of COVID-19 tests is uncertain due to the limited evidence base. Available evidence mainly comes from symptomatic patients, and their clinical role in detecting asymptomatic carriers is unclear. The two main types of SARS-CoV-2 tests are: Nucleic acid detection tests - using qPCR to detect SARS-CoV-2 viral (Ribonucleic acid) RNA; and Serology tests - to detect IgM and/or IgG antibodies against SARS-CoV-2. A Confirmed case is a person who:	Therapeutic Goods Authority (2020). Covid-19 testing in Australia- information for health professionals. Retrieved: August 13, 2020 from: https://www.tga.gov.au/covid-19-testing-australia-information-health-professionals	

	i. tests positive to a validated specific SARS-CoV-2 nucleic acid test; OR
	    ii. ii. has the virus isolated in cell culture, with PCR confirmation using a validated method; OR
	    iii. iii. undergoes a seroconversion to or has a significant rise in SARS-CoV-2 neutralizing or IgG antibody level (e.g. fourfold or greater rise in titer).
	
	Serology does not currently have a role in the diagnosis of COVID-19 during the acute illness but can be helpful for the diagnosis of past cases, such as for public
		Communicable Diseases Network Australia. (2020, May 29). CDNA National guidelines for public health units. Retrieved August 17, 2020, from https://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-novel-coronavirus.htm	

	health follow up of suspected cases who either did not undergo nucleic acid testing (NAT) during the acute illness or were NAT negative. Serology will also be important for broad-based surveillance, vaccine efficacy and research activities.		

Canada	**Canada does <u>not recommend</u> the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines only allow the use of RT-PCR.**
	
	The Canadian Public Health Laboratory Network released a statement on point-of-care serology testing for COVID-19 in May 2020. It recommended that serology could be used to inform public health responses. However, **near patient serological assays for SARS-CoV-2** should not be used for clinical testing in any capacity at this time.
	
	The World Health Organization (WHO) recently provided advice on the use of point-of-care immunodiagnostic tests for COVID-19. The WHO recommended against using either antigen-detecting or antibody-detecting rapid diagnostic tests for clinical decision-making. It also suggested that new point-of-care immunodiagnostic tests should be used **only** in research settings. The WHO also noted the need to further validate these tests in appropriate populations and settings. It stated that the use of inadequate tests could hinder overall efforts to control the disease.
	
	A near patient in vitro diagnostic device (IVDD) is used for:
	
	   • *point-of-care testing in a health care setting (for example, doctor's office, pharmacy, at the bedside) or*
	   • *home testing (self-testing)*
	
	Typically, these rapid test devices are simple to use and provide visual results within a short time period.
	
	A near patient IVDD used for COVID-19 could include:
	
	   • *a device that can detect the presence of RNA from the SARS-CoV-2 virus that causes COVID-19 or its antigens* **or**
	   • *a serological test that can detect the presence of antibodies developed against the virus in the blood of people who have already been infected*
		Public Health Canada. (2020) Testing devices for Covid-19. Retrieved August 14, 2020 from https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/medical-devices/testing/home-devices.html	

	To be useful in reducing the spread of COVID-19, near patient IVDDs must produce accurate and reliable results. It is also critical that the test results be made available to health authorities so they can connect patients to medical care and provide guidance to prevent transmission of additional infections.	
Singapore	**National testing guidelines for COVID-19 are not publicly available.**	
Malaysia	**Malaysia does not mention the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines still recommend the use of RT-PCR as the primary means of diagnosis; however, RATs are acceptable to be used in screening patients who are close contact of a confirmed case. RT-PCR test is warranted if a close contact develops symptoms.** 	Malaysia Ministry of Health (2020). Guidelines testing. Retrieved August 14, 2020 from : http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_5a_Guidelines_on_Lab_Testing_COVID_22032020.pdf on laboratory Malaysia Ministry of Health (2020). Guidelines on laboratory testing. Retrieved August 14, 2020 from: http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_5b_Laboratory_Testing_for_Patients_22032020.pdf

GUIDELINES ON LABORATORY TESTING FOR COVID-19

Clinical Specimens To Be Collected From Asymptomatic Contacts

Category	Test	Type of sample	Timing	Storage and transportation
Asymptomatic contacts	**RT-PCR**	Nasopharyngeal **AND** oropharyngeal swabs	Within 14 days of last documented contact – to collect on first encounter.	If transportation of samples is within 72 hours, store at 2- 8°C. If transportation of samples is more than 72 hours, store at - 80°C and transport in ice.
	RTK Serology IgM test (POCT)	Whole Blood Serum	Day 13 of Home surveillance	Not Applicable (Point of care testing)

- Repeat sample by PCR if symptoms develop (Annex 2a)
- If negative by PCR, to take serology test at day 13 of last exposure.
- If serology positive (IgM only or both IgM & IgG); to proceed with OPS & NPS swab for PCR.
- If PCR positive to admit patient
- If serology IgM negative, he / she will be given Release From Undergoing Supervision and Observation Order at Home

Malaysia Ministry of Health (2020). Guidelines on management of closed contact of confirmed case. Retrieved August 17, 2020 from: http://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_12a_Management_of_Close_Contacts_of_Confirmed_Case_23032020.pdf

Indonesia	**National testing guidelines for COVID-19 are not publicly available.**	
Thailand	**National testing guidelines for COVID-19 are not publicly available.**	
Vietnam	**Vietnam does not mention the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines only recommend the use of RT-PCR.** According to the Ministry of Health, the test method suitable to the prevention and control conditions in Vietnam is the RT-PCR test with test kits produced by the Military Medical Academy, ensuring the ability of domestic supply, regardless of the	Vietnam Ministry of Health (2020). Urgent Guidelines issued over COVID-19 testing. Retrieved August 17, 2020 from: https://vietnam.vnanet.vn/english/urgent-guidelines-issued-over-covid-19-testing/442926.html

	supply from the outside. The ministry is appraising and licensing several units that have registered.	

China	**China does not mention the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines still recommend the use of RT-PCR as the primary means of diagnosis; however, RATs are acceptable to be used in patients who are persistently negative in RT-PCR but have high clinical suspicion of SARS-CoV-2**
	
	Confirmation of cases
	
	    Laboratory confirmation of positive cases requires one of the following two conditions:
	
	    1. The real-time fluorescence-based RT-PCR assay of 2019-nCoV in the same specimen shows that the two targets, ORF1ab and Protein N, are both positive. In case of the result showing positive for one target, then samples shall be re-collected for another test. If it is still positive for a single target, the result should be deemed positive.
	
	    2. The real-time fluorescence-based RT-PCR assay of two types of specimens show one single target as positive at the same time, or one target as positive in two samples of the same type, the result should be deemed positive.
	
	    Negative nucleic acid results cannot rule out 2019-nCoV infections. Factors leading to false negatives shall be precluded including: poor quality of samples, for instance the respiratory tract samples of the oropharynx and other parts; samples collected too early or too late; samples that are improperly stored, transported, or processed; technical reasons such as virus mutations, PCR inhibition, etc.
	
	Serum Antibody Tests
	
	    Serum antibody tests (colloidal gold, magnetic particle chemiluminescence, ELISA) are used as supplementary tests for cases of negative 2019-nCoV nucleic acid tests, used in conjunction with nucleic acid tests in the diagnosis of suspected cases, or used in serological surveys and past exposure surveys of concerned population groups. Laboratory confirmed positive cases need to meet one of the following two conditions:
	
	    1. Serum IgM antibodies and/or IgG antibodies to 2019-nCov are positive;
		China Center for Disease Control (2020). Technical Guidelines for COVID-19 Laboratory Testing. Retrieved August 14, 2020 from: http://weekly.chinacdc.cn/en/article/doi/10.46234/ccdcw2020.085

	2. Serum IgG antibodies to 2019-nCov turn from negative to positive or the IgG antibody titers of recovery period are 4 times or more higher than that of acute phase. Using serum in the acute phase within 7 days after the onset of disease detects IgM and IgG, if the test result is negative, repeat collection for testing within 10 days after the onset of disease is recommended. Convalescent serum specimens within 3−4 weeks after the onset of illness should be used for detecting IgG. Instructions from the manufacturer's manual should be followed for commercial testing kits. *China uses serum antibody tests (both laboratory-based and RATs) are used as supplementary tests for cases of negative 2019nCoV nucleic acid tests but with high clinical suspicion of COVID-19.*	
South Korea	**South Korea does not mention the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines only recommend the use of RT-PCR.** Confirmed case - a person confirmed to be infected with COVID-19 according to the diagnostic test standard*, regardless of clinical manifestation *diagnostic test: COVID-19 genetic (PCR) test, virus isolation*	South Korea Ministry of Health and Welfare (2020). Guideline for the operation of COVID-19 screening clinic. Retrieved August 14, 2020 from: http://ncov.mohw.go.kr/en/guidelineView.do?brdId d=18&brdGubun=181&dataGubun=&ncvContSeq= 2937&contSeq=2937&board_id=&gubun=#
Japan	**Japan recommends the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines allow the use of RT-PCR, and antigen tests** Since an antigen test detects the SARS-CoV-2 antigen that is specifically produced in cells infected with SARS-CoV-2, a positive result leads to an accurate diagnosis. Together with PCR tests, the antigen test can be used to provide a definitive diagnosis (May 13, 2020). - Positive antigen test: Definitive diagnosis of COVID-19 - Negative antigen test: Physician decides whether to conduct a PCR test. In Japan, etiological tests including the antigen test are conducted when a patient is suspected by the physician to have COVID-19 or for patients with symptoms such as fever. In general, the decision to test is still subject to the discretion of the examining physician and the public health center, based on the guidelines of Japan. For these patients suspected of having COVID-19, virus isolation, sARS-CoV-2 genome detection or antigen detection is conducted using sputum, respiratory tract secretions, alveolar lavage fluid, nasopharyngeal swab, saliva or autopsy material.	Ministry of Health, Labor and Welfare (2020). Clinical Management of Patients with COVID-19. Retrieved August 17, 2020 from: https://www.mhlw.go.jp/content/000646531.pdf

	This provides a definitive diagnosis if the result is positive. (An antigen test should be conducted using a nasopharyngeal swab). There is a sensitivity limit to etiological tests so the test results should be comprehensively combined with the clinical features to achieve a proper diagnosis.		
WHO	**WHO recommends the use of RAgTs under the following scenarios:** General recommendations for the use of SARS-CoV-2 Ag-RDTs 1. **SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared to a NAAT reference assays can be used to diagnose SARS-CoV-2 infection in a range of settings where NAAT is unavailable or where prolonged turnaround times preclude clinical utility.** To optimize performance, testing with Ag-RDTs should be conducted by trained operators in strict accordance with the manufacturer's instructions and within the first 5-7 days following the onset of symptoms. *NAAT- Nucleic Acid Amplification Tests* 2. **Appropriate scenarios for use of COVID-19 Ag-RDTs include the following**: i) **To respond to suspected outbreaks of COVID-19 in remote settings, institutions and semi-closed communities where NAAT is not immediately available.** Positive Ag-RDT results from multiple suspects is highly suggestive of a COVID-19 outbreak and would allow for early implementation of infection control measures. Where possible, all samples giving positive Ag-RDT results (or at least a subset) should be transported to laboratories with NAAT capability for confirmatory testing. ii) **To support outbreak investigations (e.g. in closed or semi-closed groups including schools, care-homes, cruise ships, prisons, work-places and dormitories, etc.)** In NAAT-confirmed COVID-19 outbreaks, Ag-RDTs could be used to screen at-risk individuals and rapidly isolate positive cases	World Health Organization (2020) Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays, Interim Guidance. Retrieved Sept 14, 2020 from: https://www.who.int/publications-detail-redirect/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays	

(and initiate other contact tracing efforts) and prioritize sample collection from RDT-negative individuals for NAAT.

iii) **To monitor trends in disease incidence in communities, and particularly among essential workers and health workers during outbreaks or in regions of widespread community transmission** where the positive predictive value and negative predictive value of an Ag-RDT result is sufficient to enable effective infection control.

iv) **Where there is widespread community transmission, RDTs may be used for early detection and isolation of positive cases in health facilities, COVID-19 testing centres/sites, care homes, prisons, schools, front-line and health-care workers and for contact tracing**. Note that the safe management of patients with RDT-negative samples will depend on the RDT performance and the community prevalence of COVID-19. A negative Ag-RDT result cannot completely exclude an active COVID-19 infection, and, therefore, repeat testing or preferably confirmatory testing (NAAT) should be performed whenever possible, particularly in symptomatic patients.

v) **Testing of asymptomatic contacts of cases may be considered even if the Ag-RDT is not specifically authorized for this use, since asymptomatic cases have been demonstrated to have viral loads similar to symptomatic cases**, though in that situation, a negative Ag-RDT should not remove a contact from quarantine requirements.

3. **For initial introduction of Ag-RDTs into clinical use, countries should consider selecting some settings where NAAT confirmatory testing is currently available so that staff can gain confidence in the assays, confirm performance of the selected RDT, and troubleshoot any implementation issues encountered.** Wherever NAAT will be used for confirmatory testing in patients screened using an Ag-RDT, the samples for the two tests should be collected at roughly the same time, or at most within a period of less than 2 days.

4. **In situations where confirmatory testing with NAAT is not feasible, any indications that results may be incorrect should raise suspicions about validity.** Examples would include patients who are test-positive but have a

clinical syndrome not consistent with COVID-19, or patients with a positive test detected in a low-prevalence setting (where the predictive value of a positive test is low and the risk of false-positives high).

Other warning signals might include patients who are test-negative but have a classical syndrome, are close contacts of a case or are tested in a high-prevalence setting. In such situations, considerations should be given to repeating the test, especially if there is also any uncertainty about the visual result (faint bands) or adequacy of sampling.

5. **Use of Ag-RDTs is not recommended in settings or populations with low expected prevalence of disease (e.g. screening at points of entry, blood donation, elective surgery), especially where confirmatory testing by NAAT is not readily available**. Such use will not be possible until there are more data from high-quality studies confirming high specificity (>99%) of one or more of the commercialized Ag-RDT test kits.

WHO does NOT recommend the use of RAgTs under the following scenarios:

Do not use SARS-CoV-2 Ag-RDTs:	Explanation
In individuals without symptoms unless the person is a contact of a confirmed case	Pre-test probability (the likelihood, before testing, that the patient has the disease based on epidemiology, case contact, clinical findings) is low.
Where there are zero or only sporadic cases	Ag-RDTs are not recommended for routine surveillance purposes or case management in this setting. Positive test results would likely be false positives. Molecular testing is preferred.
Appropriate biosafety and infection prevention and control measures (IPC) are lacking	To safeguard health workers, respiratory sample collection for any test from patients with suspected COVID-19 requires that operators wear gloves, gown, mask and face shield or goggles.
Management of the patient does not change based on the result of the test	If test-positive and test-negative patients will be treated the same way because of unknown or low PPV and/or NPV, then there is no benefit to testing.

		For airport or border screening at points of entry	Prevalence of COVID-19 will be highly variable among travellers, and it is therefore not possible to determine PPV and NPV of test results. Positive and negative tests would require confirmatory testing to increase PPV and NPV for decision making.	
		In screening prior to blood donation	A positive RDT result would not necessarily correlate with presence of viremia. Asymptomatic blood donors do not meet the definition of a suspect case	
Philippines	**Philippines does not mention the use of antigen testing in their national testing guideline for COVID-19. Testing guidelines still recommend the use of RT-PCR as the primary means of diagnosis; however, RATs are acceptable to be used in patients who meet all of the following criteria:** 　i.　**Symptomatic patients (greater than or equal to 15 days from onset of symptoms, AND** 　ii.　**Tested atleast twice negative RT-PCR, AND** 　iii.　**With clinical and diagnostic manifestation of COVID-19.** Department Memo 2020-0258: 　-　Based on current available evidence, real-time polymerase chain reaction (RT-PCR) testing is the confirmatory test for diagnosis. In the Philippines, this pertains to using rT-PCR test kits that are approved by the Food and Drug Administration (FDA), and validated by the Research Institute of Tropical Medicine (RITM) 　-　Rapid antibody-based test kits shall not be used as standalone tests to definitively diagnose or rule out COVID-19. Because these must be used in conjunction with RT-PCR, care must be exercised to not unduly consume RT-PCR test kits for the sake of confirmation. 　-　Reporting of confirmed cases shall continue to be based on rT-PCR testing, in accordance with Administrative Order 2020-0013.			https://www.doh.gov.ph/sites/default/files/health-update/dm2020-0258.pdf