

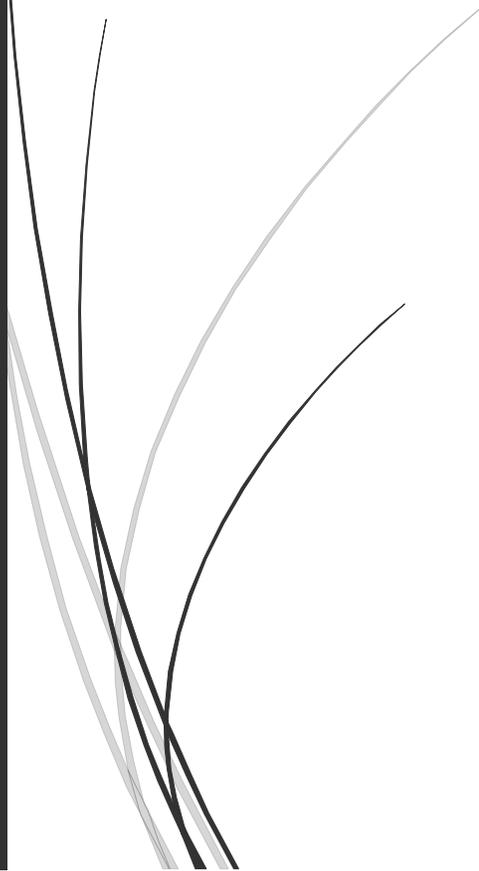


11/9/2020

# COVID-19 Literature Review Group

Prepared by The Ohio State University

## Focus on Antigen Tests



**ODH Literature Review Group**  
THE OHIO STATE UNIVERSITY

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## Important Links

- Interim Guidance for Rapid Antigen Testing for SARS-CoV-2
  - <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html>
- HHS Fact Sheet about Abbott BinaxNOW Antigen Test
  - <https://www.hhs.gov/sites/default/files/abbott-binaxnow-fact-sheet.pdf>
- Abbott BinaxNOW Emergency Use Authorization
  - <https://www.fda.gov/media/141570/download>

## COVID-19 Literature Review

Prepared by Elena McGoey, The Ohio State University  
November 5, 2020

**Title:** Comparison of automated SARS-CoV-2 antigen test for COVID-19 infection with quantitative RT-PCR using 313 nasopharyngeal swabs, including from seven serially followed patients

**Source:** *International Journal of Infectious Diseases*

**Publication:** August 12, 2020

**Link:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7422837/>

**Study Period:** Not given

**Study Location:** Yamanashi Central Hospital, Japan

**Sample Size:** 313 swabs (82 serial samples from 7 infected patients, 231 individual samples from 4 infected patients and 215 non-infected individuals)

**Summary:** This study presented LUMIPULSE SARS-CoV-2 Ag kit, a SARS-CoV-2 antigen test system based on chemiluminescence enzyme immunoassay. When compared to RT-qPCR results for viral load on testing of 313 nasopharyngeal swabs, results for the antigen test showed 55.2% sensitivity and 99.6% specificity, with a 91.4% agreement rate between the antigen test results and the RT-qPCR results (used as the reference). When antigen levels in samples of infected individuals were examined, the antigen test showed 100% agreement with RT-qPCR results when samples had greater than 100 viral copies. Antigen test results showed 85% agreement with RT-qPCR results when samples had between 10 and 100 viral copies, and this percentage of agreement between the antigen test and RT-qPCR results declined further with lower viral loads. Antigen levels showed steady decline in serial samples, as opposed to the abrupt negative-to-positive/positive-to-negative status changes of RT-qPCR testing.

**Key findings most relevant to Ohio's response:** Limitations of the antigen test include: a low sensitivity compared to RT-qPCR and the consideration that the presence of an antigen does not necessarily indicate the presence of viable virus. While the antigen testing detected SARS-CoV-2 accurately in all the samples with a viral load over 100, the antigen test method is not as accurate for lower viral loads and may result in many false-negatives in these instances. The test kit used for this study quantitatively measured antigen levels in samples, and the results showed that SARS-CoV-2 antigen levels steadily declined in these samples. These results support that antigen levels could be used in the future to distinguish between the phases of the COVID-19 infection, which could be very helpful to hospital systems in determining when to release infected patients.

**Title:** Clinical Evaluation of Self-Collected Saliva by Quantitative Reverse Transcription-PCR (RT-qPCR), Direct RT-qPCR, Reverse Transcription-Loop-Mediated Isothermal Amplification, and a Rapid Antigen Test to Diagnose COVID-19

**Source:** *Journal of Clinical Microbiology*

**Publication:** August 24, 2020

**Link:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7448663/>

**Study Period:** February 11, 2020 to May 13, 2020

**Study Location:** Self-Defense Forces Central Hospital, Japan

**Sample Size:** 103 patients with laboratory-confirmed COVID-19

**Summary:** This study used saliva samples of patients with laboratory-confirmed COVID-19 to compare accurate results from the following testing methods: quantitative reverse transcription-PCR (RT-qPCR) lab-developed test, cobas SARS-CoV-2 high-throughput system, three direct RT-qPCR kits, reverse transcription-loop-mediated isothermal amplification (RT-LAMP), and rapid antigen testing. Viral RNA was detected in 50.5-81.6% of the samples when using the molecular

diagnostic tests (the first four testing methods listed), while an antigen was detected in only 11.7% of the samples when using the rapid antigen testing. Detection of viral RNA was significantly higher in samples collected within 9 days of symptom onset than in samples either collected after 10 days of symptom onset or samples from asymptomatic patients.

**Key findings most relevant to Ohio’s response:** These study results support continued self-collected saliva as an option alternative to swabs for diagnosing COVID-19, when the saliva collection is completed as soon as possible after symptom onset. Benefits of rapid antigen testing include faster results and no need for special equipment or highly skilled lab technicians. However, it is important to note that this study does not recommend rapid antigen test for initial COVID-19 diagnoses unless combined with other testing methods, due to the low sensitivity of the rapid antigen test. The other methods listed (molecular diagnostic tests) all showed adequate sensitivities and selectivity and are still recommended over rapid antigen testing in clinical settings for these reasons.

**COVID-19 Literature Review**

**Prepared by Anjali Prabhakaran, The Ohio State University**

**November 5, 2020**

<b>Title</b>	Implementation of rapid SARS-CoV-2 antigenic testing in a laboratory without access to molecular methods: Experiences of a general hospital
<b>Source</b>	Journal of Clinical Virology
<b>Publication Date</b>	08/19/2020
<b>Link</b>	<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7261076/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7261076/</a>
<b>Study Period</b>	04/05/2020 - 05/04/2020
<b>Study Location</b>	Belgium
<b>Sample Size</b>	774 patients
<b>Summary</b>	This study assessed the sensitivity of the COVID-19 Ag (Antigen) Respi-Strip assay and compared it to the values reported by the manufacturer. Patient samples were obtained through performing nasopharyngeal smears with UTM-RT swabs. After antigenic testing, the samples were sent to a university center for qRT-PCR testing. The negative results obtained with the Respi-Strip kit were compared to those obtained from qRT-PCR. Of the 774 patients tested, 714 samples tested negative using the Respi-Strip assay. When these samples were sent for qRT-PCR confirmation, 159 were found to be positive. The median observed sensitivity was 23.9% and the Cohen’s kappa score was 0.35. Furthermore, compared to expected performance, the Respi-Strip assay resulted in 80% more false negative samples and 2.2 times fewer positive samples. The authors also found that the assay does not reduce costs per patient.
<b>Key Findings Relevant to Ohio’s Response</b>	The results of this study will help clinicians decide which antigen test to use and whether or not it would be appropriate for their healthcare facility.

	Furthermore, this study emphasizes the importance of validating the accuracy and efficacy of antigen tests before large-scale implementation.
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<b>Title</b>	Rapid detection and monitoring of human coronavirus infections
<b>Source</b>	New Microbes and New Infections
<b>Publication Date</b>	05/209/2018
<b>Link</b>	<a href="https://www.sciencedirect.com/science/article/pii/S2052297518300350">https://www.sciencedirect.com/science/article/pii/S2052297518300350</a>
<b>Study Period</b>	December 2015 – December 2016
<b>Study Location</b>	Finland
<b>Sample Size</b>	6 patients
<b>Summary</b>	This study used the mariPOC respi test to assess CoV antigen levels in CoV-OC43 positive patients from onset of disease to until disappearance of symptoms. CoV-OC43 was one of the most prevalent coronaviruses in many countries at the time of this study. Samples were obtained from daily nasopharyngeal swabs. After mariPOC analysis, the samples were sent to two different laboratories for RT-PCR verification. All samples with measurable CoV antigen levels in mariPOC were also positive by both RT-PCRs. The antigen secretion levels also correlated relatively well with symptom severity. Since antigen secretion peaked during the third and fourth day after symptom onset, sampling should also be done during this time to ensure maximum accuracy of the antigen test. While antigen positivity lasted 3 to 6 days in secondary infections, it lasted 13 days in primary infections.
<b>Key Findings Relevant to Ohio’s Response</b>	This study provides guidance to clinicians on when to perform antigen testing to ensure accurate results. While this paper focused specifically on the mariPOC test, the recommendations could be applied to other antigen tests focusing on human corona virus (CoV) infections

<b>Title</b>	Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection.
<b>Source</b>	Cochrane Library
<b>Publication Date</b>	08/26/2020
<b>Link</b>	<a href="https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013705/full">https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013705/full</a>
<b>Study Period</b>	Studies up to 05/25/2020
<b>Study Location</b>	n/a
<b>Sample Size</b>	22 articles
<b>Summary</b>	This systematic review evaluated twenty-two publications to assess the diagnostic accuracy of point-of-care antigen and molecular-based SARS-CoV-2

	<p>tests. The publications included in this study were independently assessed by two review authors. The average sensitivity and specificity of antigen tests were 56.2% and 79.8% respectively, and 95.2% and 98.9% for rapid molecular assays. The Xpert Xpress individual test had a sensitivity of 99.4% and specificity of 96.8%, while the ID NOW test had a sensitivity of 76.8% and a specificity of 99.6%. However, the authors indicated that confidence in the evidence is limited since three quarters of the included studies did not follow the test manufacturers' instructions, and a quarter of the included studies were preprints. Furthermore, patient selection was judged to have a high risk of bias in 50% of studies due to the deliberate oversampling of patients with confirmed COVID-19 infection. Additionally, none of the reviewed studies include participants with no symptoms.</p>
<p><b>Key Findings Relevant to Ohio's Response</b></p>	<p>The results of this study highlight the dire need for more research to be performed in the area of rapid point-of-care COVID-19 testing. Based on the results, some individual tests and rapid molecular assays appear to be more accurate than antigen tests. While point-of-care testing may not be accurate enough to replace laboratory based RT-PCR, it can serve as a triage to RT-PCR by allowing earlier detection and rapid management of those testing positive.</p>

## COVID-19 Literature Review

Prepared by Greta Warmbier, The Ohio State University  
November 1, 2020

**Title:** Development of a rapid test kit for SARS-CoV-2: an example of product design

**Source:** Bio-design and Manufacturing

**Publication Date:** May 11, 2020

**Link:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211913/>

**Study Period:** n/a

**Study Location:** n/a

**Sample Size:** n/a

**Summary:** This study explores the development of a rapid test kit to detect SARS-COV-2. Tests are intended for field use and for home use, in the longer term. Tests detect whether a subject is currently infected with the virus and is infectious. To meet these urgent needs, an antigen test based on RT-LAMP with colorimetric readout was chosen for the tests. Direct use of swab sample with no RNA extraction was explored. Tests can be performed on field without the need for a laboratory or specialist equipment. Need-driven product design methodology was used to create tests. A rapid test at the airport can help to decide whether the passenger goes to isolation or quarantine (if they test positive) or pass without concerns (if negative). The key question that needs to be addressed is: “how can we know an individual is carrying the virus and could be infectious?” Rapid tests must: detect SARS-COV-2 (COVID-19) specifically, be portable and able to be used anywhere, take 30 minutes or less, be on-site without transport of samples, have no need for laboratory or special instruments, be easy to operate with no need for skilled technicians, be able to test individuals. and have sufficient throughput for screening. A symptom-based test, like measuring temperature, cannot be used as a robust diagnostic test for COVID-19. SARS-COV-2 is an enveloped single-strand RNA. The virus exists in the upper respiratory system and can be sampled with nasopharyngeal (NP) swabs and oropharyngeal (OP) swabs. RNA detection can be performed using polymerase chain reaction (RT-PCR) or reverse transcription loop-mediated amplification (RT-LAMP). Both are well-established methods for amplifying DNA. RT-PCR test takes 90–120 min per sample set, while LAMP can be completed with 30 min. The successful detection of COVID-19 virus by either method depends on the design of the primers that can specifically bind the viral RNA and its fragments. An antibody test using blood samples (serology-based test) can show whether a person is currently infected or has been in the past. Its limitation lies in its inability to determine whether the person is still infectious. Its success depends on identification of the correct antibody. “How can we test an individual to determine whether she/he is infected and infectious on the spot while she/he waits?” is a question that can only be answered by the antigen test. The RT-PCR method is widely used worldwide. It involves RNA extraction from the patient swab solution followed by reverse transcription of the RNA and then PCR expansion of the cDNA. The process can be automated and high-throughput testing can be performed, which makes it ideal for central test laboratories. However, it is not suitable for field use as it depends on a PCR machine, a laboratory environment for RNA extraction and skilled operators. Additionally, the surge for PCR reagents has created a global shortage of reagents supplies and has limited the test capacities. RT-LAMP can detect both RNA and RNA fragments and can deliver the result much faster with easy operation of isothermal amplification of DNA at 65 °C. Thus, LAMP is an obvious choice for its shorter running time as well as the fact that it usually has a lower detection limit. We could take advantage of this and remove the RNA extraction step. If possible, this would greatly simplify the test. Key features of this specific rapid test kit include: the use of patient swabs directly, does not require complicated instruments, with only needing a heating source to maintain at 65 °C (even works by adding 1 part cold water to 2 parts boiling water if a heating block is not available), displays results with color change, detectable by eye and understandable by lay people. “Needs” will continue to develop as the virus spreads and affects different regions.

**Relevance to Ohio’s COVID-19 Response:** It is important that rapid tests must be readily available and able to identify both whether the virus is present and/or if the individual is infectious. It must also not require the use of laboratory equipment nor medical professionals.

**Topic:** Antigen Testing

**Title:** Evaluation of rapid antigen test for detection of SARS-CoV-2 virus

**Source:** Journal of Clinical Virology

**Publication Date:** August 2020

**Link:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7278630/>

**Study Period:** February 1, 2020 – April 21, 2020

**Study Location:** Hong Kong

**Sample Size:** 368

**Summary:** Rapid antigen detection (RAD) tests detect viral antigen by the immobilized coated SARS-CoV-2 antibody on the device. According to this study, the detection limits between RAD test, viral culture and RT-PCR varied hugely. RAD was  $10^3$  fold less sensitive than viral culture while RAD was  $10^5$  fold less sensitive than RT-PCR. The RAD test detected between 11.1 % and 45.7% of RT-PCR-positive samples from COVID-19 patients. This study demonstrated that the RAD test serves only as adjunct to RT-PCR test because of potential for false-negative results. The purpose of this study is to assess the diagnostic use of the commercially available BIOCREREDIT COVID-19 Ag test. The aim of the first part of the study was to assess the limit of detection (LOD) between RAD test, viral culture and RT-PCR and the second part was to evaluate performance of RAD test in detecting SARS-CoV-2 virus in different types of respiratory samples. From February 1, 2020 to April 21, 2020, respiratory samples from individuals confirmed with SARS-CoV-2 infection by RT-PCR targeting the SARS-CoV-2 virus-specific RdRp gene were retrieved. Samples were placed in viral transport media (VTM) or Phosphate-Buffered Saline (PBS) for RNA extraction. The Public Health Laboratory Services Branch (PHLSB) in Hong Kong has been designated as WHO COVID-19 reference laboratory since April 2020 and all confirmed cases in Hong Kong were either diagnosed or confirmed by PHLSB. 368 confirmed COVID-19 samples were available. The intended use for the BIOCREREDIT COVID-19 Ag kit is for a nasopharyngeal swab sample. The recommended sample volume by the BIOCREREDIT COVID-19 Ag kit was 90–150  $\mu\text{L}$ . To unify the sample volume, 100  $\mu\text{L}$  sample volume was used in this study. Viral culture was conducted by inoculating samples onto Vero E6 cells. When virus-induced cytopathic effect was examined, identification of SARS-CoV-2 virus in culture fluid was confirmed by the RT-PCR. The in-house developed RT-PCR was used to detect the presence of SARS-CoV-2 virus nucleic acid in all samples. It was conducted using NxtScript Enzyme and Master Mix. The LOD of the RAD test was 1000 fold less sensitive than viral culture when 100  $\mu\text{L}$  sample was added directly into a sample well of the device. The fold difference between two RAD sample processing methods seemed to be related to the volume of sample used and the dilution effect in the assay diluent tube. A total of 35 samples each for NPA & TS, NPS & TS were selected to evaluate the RAD test. Since sputum and throat saliva are rarely used for the RAD tests, an additional 10 more samples each for sputum and throat saliva were selected. 160 RT-PCR-positive respiratory samples from 152 different patients were retrospectively tested using the RAD test. All 70 NPA & TS and NPS & TS samples were handled with “less viscous samples” processing method. For the 90 sputum and throat saliva samples, 83 samples were handled with “less viscous samples” processing method, 7 samples were handled with “viscous samples” processing method because of the viscous nature of these respiratory samples. The low prevalence of high viral load samples limits the use of RAD test in clinical setting. At the time of writing this report, among the SARS-CoV-2 positive samples received in PHLSB, only 16.6 % were high viral load.

**Relevance to Ohio’s COVID-19 Response:** The testing of patients suspected of SARS-CoV-2 infection with antigen-based assay may produce more false negative results in clinical practice. An overall sensitivity of 30.2% was found for the 106 SARS-CoV-2 RT-PCR positive samples. Application of such assays alone in clinical settings is not recommended in favor of continued molecular diagnostics.

## COVID 19 Literature Review

Prepared by Amanda Seifferth, The Ohio State University November 9, 2020

**Title:** Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis

**Source:** Journal of Clinical Virology

**Publication Date:** August 2020

**Link:** <https://doi.org/10.1016/j.jcv.2020.104455>

**Study Period:** 4/8/2020 - 4/21/2020 **Study Location:** Brussels, Belgium **Sample Size:** 148

**Summary:** Although RT-qPCR tests are the current recommended diagnostic method for the SARS-CoV-2 virus, insufficient quantities of necessary staff, equipment, and time have prompted the development of easily administered rapid antigen tests in various countries. Recently, researchers sought to measure the relative accuracy of a rapid antigen test known as the Coris COVID-19 Ag Respi-Strip test. They administered 148 nasopharyngeal swabs. One hundred and six came back positive through the recommended RT-qPCR test compared to only 32 positive results through the rapid antigen test. This denotes a 30.2% sensitivity rate of rapid antigen tests, bringing to question their usefulness. All 32 positive results detected by the rapid antigen test were also detected by the RT-qPCR test. Researchers note that higher viral loads increase the probability of detection through rapid antigen tests. Nevertheless, insufficient sensitivity of rapid antigen tests indicate their futility in frontline testing.

**Key Findings Relevant to Ohio's Response:** It is imperative that public health policy employ the most effective strategies for containing Covid-19 transmission. Diagnostic testing is a key component in doing so, and it is crucial that the most accurate yet efficient diagnostic methods are utilized. This study highlights the shortcomings of the rapid antigen test, as its accuracy is largely dependent upon viral load, quality of specimen, and processing of specimen. Moreover, researchers conclude that the test is of little use, as a negative result cannot comprehensively rule-out the virus. Thus, rapid antigen tests should not be used in isolation.

**Title:** The utilization of rapid serological tests in Covid-19 diagnostics - A high risk of false-negative results in outpatient care, with particular emphasis on dental treatment

**Source:** Medycyna Pracy

**Publication Date:** 9/9/2020

**Link:** <https://doi.org/10.13075/mp.5893.01034>

**Study Period:** 1/24/2020 - 5/15/2020

**Study Location:** N/A

**Sample Size:** N/A

**Summary:** Health care professionals in a variety of outpatient settings face a disproportionate risk of contracting SARS-CoV-2. Dental staff in particular experience more frequent exposure due to close interaction with aerosol particles. Researchers recently investigated various Covid-19 diagnostic methods, evaluating their potential for implementation in outpatient settings, specifically dental offices through a systematic literature review. Researchers concluded that molecular diagnostic tests, including the

recommended RT-PCR test, are preferable due to their high sensitivity and specificity, exemplifying 71%-98% sensitivity. However, RT-PCR tests do not present a viable, quick testing option in outpatient settings. In contrast, rapid-antigen tests produce results much faster and with much lower costs.

Nonetheless, evidence depicts a low sensitivity of such tests, indicating their limited effectiveness in outpatient settings. Researchers also evaluated the ELISA method, a serological antibody test. They note its usefulness in indicating the percentage of a population previously infected and now presumably immune. Recently, rapid diagnostic tests based on antibody detection have been tentatively produced and recommended by manufacturers as a screening tool in dental offices. They function similar to pregnancy tests, producing a result through a few droplets of finger blood. However, they show low sensitivity and specificity, with a high false negative result. They also have high potential for false positives through reactions to other coronaviruses. Thus, WHO does not yet recommend the use of these tests in outpatient care, instead emphasizing the need for continued improvement of such technology.

**Key Findings Relevant to Ohio's Response:** This study indicates the unreliability of current rapid testing. It suggests the need for continued research into rapid testing technology before its implementation into outpatient settings, as false negatives may evoke immense consequences amid the Covid-19 pandemic. Furthermore, researchers maintain that the best protective measures for staff in outpatient settings remain epidemiological interviews, temperature checks, and implementation of strict infection mitigation strategies.